LANDSCAPE ECOLOGY OF CHRONIC WASTING DISEASE IN VIRGINIA, USA

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ABSTRACT

Wildlife diseases often occur under quantifiable and consistent patterns, which can be understood to statistically predict their occurrence and spread across landscapes. Chronic wasting disease (CWD) is a neurodegenerative disease in the deer family Cervidae caused by a prion, a pathogenic and misfolded variant of a naturally occurring protein. Managing and controlling CWD is imperative for conservation of ecologically and economically important cervid species, but unclear transmission mechanisms within landscapes complicate evidence-based management. Gaps of information in the landscape ecology for CWD are particularly pronounced for areas with recent disease emergence and spread, such as within the CWD cluster in the Mid-Atlantic United States. Thus, I identified current gaps in information and sought to fill neglected areas of research, specifically focusing on landscape determinants for CWD occurrence and spread in the state of Virginia. In chapter 2, I conducted a scoping study that collected and synthesized decades of CWD research and identified trends with respect to statistical and mathematical modeling methods used, connectivity within the CWD research community, and the geographic areas from which studies were performed. In chapter 3, I investigated landscape determinants for CWD in Virginia using remote sensing landscape data and an epidemiological dataset from Virginia Department of Wildlife Resources (DWR) using diverse algorithms and model evaluation techniques. Finally, in chapter 4, I modeled landscape connectivity between confirmed CWD cases to examine potential paths and barriers to CWD spread across landscapes. My results indicate that landscape ecology was rarely incorporated throughout CWD's 50+ year history. I provide evidence that remotely-sensed landscape conditions can be used to predict the likelihood of CWD occurrence and connectivity in Virginia landscapes, suggesting plausible CWD spread. I suggest areas of future work by explicitly identifying gaps in CWD research and diagnostic methods from which models are based, and encourage further consideration of host's ecology in modeling. By integrating remotely-sensed data into my modeling framework, the workflow should be easily adaptable to new study areas or other wildlife diseases.

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GENERAL AUDIENCE ABSTRACT

Understanding why diseases occur in some locations and not others can be a critical challenge for disease ecologists. One disease that has received significant attention from the media and scientific community is chronic wasting disease (CWD), which is caused by a misfolded protein called a prion. Virginia Department of Wildlife Resources (DWR) has identified a stark increase in the number of CWD cases since first discovered in 2009, which threatens white-tailed deer populations and a 500 million dollar industry used for conservation of Virginia wildlife species. Previous research found that CWD does not occur randomly on the landscape, but otherwise little is known about the landscape ecology of CWD. To provide insight on Virginia's CWD outbreak, I assessed methods used to investigate other CWD outbreaks in both space and time. Also, I used landscape data collected from satellites and data from CWD cases in Virginia, and applied statistical tools to identify patterns in the landscape that were linked with CWD cases. My results suggest that landscapes were rarely examined to understand CWD, and instead, researchers focused on understanding how populations will respond to the disease. I also provide evidence that, at least in Virginia, researchers can use satellite information with disease data to predict CWD on the landscape and estimate its spread. This information can be used by wildlife managers to control the disease. For example, disease surveillance can be increased in areas where CWD has been predicted, or herd sizes can be reduced in areas likely to promote disease spread. This information could also be used to tailor wildlife health regulations aimed to minimize the risk of other deer populations acquiring the disease. Ultimately, the landscape plays an important role in CWD, but research on this topic is limited; therefore, additional research is needed to understand and eventually control this disease affecting ecologically and culturally important game species.

DEDICATION

I dedicate this thesis to my whole family, best of friends, and many mentors that have enabled, supported, and inspired me in my career pursuits. We may not always be a quick drive away from each other (some with an ocean separating us), but I've always felt your love and support.

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ATTRIBUTION

Committee chair Dr. Luis E. Escobar (LEE) and committee members Drs. Megan S. Kirchgessner (MSK) and Emmanuel A. Frimpong (EAF) each contributed significantly to this thesis. LEE acted as the project design supervisor, and contributed to the writing of thesis chapters for publication. MSK provided guidance in research directions to enhance direct utility for disease management purposes, and additionally provided epidemiological surveillance data from Virginia Department of Wildlife Resources as well as assistance in editions. EAF provided guidance and support in statistical analyses and additionally served as an editor. Some chapters have minor redundancies related to literature review given they are intended for peer-reviewed publications. Most chapters are formatted to reflect guidelines for *Journal of Wildlife Diseases*; however, formatting variations in Chapter 3 reflect guidelines for submission to Landscape Ecology.

Chapter 2 of this thesis has appeared in published form in the *Journal of Wildlife Diseases*, with co-authors, and appears here with permission from the Wildlife Disease Association.

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Parts of Chapters 3 and 4 are currently submitted and in review with the journal *Landscape Ecology* in a combined publication, under the title: *A landscape epidemiological approach for chronic wasting disease: A case study in Virginia, US*, and was co-authored with Megan S. Kirchgessner, Emmanuel A. Frimpong, and Luis E. Escobar.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

CHAPTER 1: INTRODUCTION

Steven N. Winter

Chronic wasting disease (CWD) is a contagious and invariably fatal transmissible spongiform encephalopathy (TSE) caused by a misfolded protein called a prion (Williams and Young 1980; Prusiner 1982). Consistent with other TSEs and prion diseases, CWD-infected cervids experience cognitive decline and neurodegeneration from infectious prion (PrPSc) manifestation in neurons. Due to CWD's transmissibility, prevalence can reach 40-50% in wild cervid populations (Edmunds et al. 2016; Carlson et al. 2018), and 80-100% in captive populations (Keane et al. 2008). These epidemiological characteristics make CWD management a priority for wildlife managers and conservationists responsible for species of economic and conservation concern (Wisconsin Department of Natural Resources 2010; Texas Parks and Wildlife and Texas Animal Health Commission 2015). Currently there is no vaccine or treatment for CWD that provides complete protection (Goñi et al. 2015); thus, managers depend on culling host species to mitigate disease spread in local (Wasserberg et al. 2009; Manjerovic et al. 2014; Wolfe et al. 2018) or more severe regional scales (i.e., population eradication; Mysterud and Rolandsen 2018; Rolandsen et al. 2019).

Chronic wasting disease is an emerging wildlife disease worldwide. Initially, CWD was observed in 1967 in a captive deer facility in Colorado, USA, classified as a TSE in 1979 (Williams and Young 1980), and discovered to be emergent in wild cervids in western US States in 1981 (Spraker et al. 1997). Chronic wasting disease's origin is unknown, but has been speculated to emerge from contact and possible spillover from scrapie-infected sheep (*Ovis spp.*), which were held in the same facility with the first cervids that developed CWD (Williams and Young 1980; Miller and Fischer 2016). Wildlife managers found CWD in white-tailed deer herds

(*Odocoileus virginianus*) in Wisconsin in 2002 (Joly et al. 2003), which served as the impetus for CWD surveillance programs in many states east of the Mississippi River. More recently, enhanced CWD surveillance resulted in the discovery of CWD in Mid-Atlantic States (i.e., Maryland, Pennsylvania, Virginia, and West Virginia) in 2005 in West Virginia. Soon thereafter, CWD surveillance efforts resulted in the confirmation of CWD in Virginia (2009), Maryland (2010), and Pennsylvania (2012) (Evans et al. 2014). By late 2020, CWD was confirmed in wild cervid populations in 24 US states, two Canadian provinces, and areas of Norway, Sweden (Statens Veterinärmedicinska Anstalt 2019; USGS 2020), and Finland, as well as in captive facilities in 17 US states, four Canadian provinces, and two South Korean provinces (Kim et al. 2005; Dubé et al. 2006; USGS 2020).

Considering the diversity of landscapes and host species affected, a main question in the study of CWD is the degree to which the landscape can explain its geographic distribution. This question is largely connected to prion's unusual properties to remain infective in the environment for prolonged periods (i.e., possibly decades; Georgsson et al. 2006; Almberg et al. 2011), and the pathogen's close relationship with its host relative to other diseases (e.g., vector-borne diseases). Previous research suggests geomorphology and landscape features (e.g., forests, rivers; O'Hara Ruiz et al. 2013; Nobert et al. 2016) can influence CWD's distribution. Nevertheless, much remains unknown about the landscape ecology of CWD.

This thesis is an effort to synthesize research and apply methods from landscape ecology to elucidate CWD-landscape relationships in the CWD outbreak in Virginia. In Chapter 2, I compiled decades of CWD research to characterize the state of modeling in a scoping study framework that addresses landscape modeling approaches used, focal study species, and collaboration structures among CWD researchers in Virginia and worldwide. Subsequent

chapters address the CWD outbreak in Virginia more explicitly. In Chapter 3, I utilize remote sensing and CWD epidemiological data to determine the extent to which CWD can be quantifiably predicted from landscape conditions. Finally, in Chapter 4, I seek to examine connectivity between current CWD cases identified in Virginia, and between this known area and an additional susceptible cervid population within Virginia for disease management consideration.

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CHAPTER 2: TRENDS IN CHRONIC WASTING DISEASE LANDSCAPE ECOLOGY RESEARCH USING A SCOPING STUDY ANALYSIS

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Abstract

Chronic wasting disease (CWD) is an infectious and fatal prion disease occurring in the Cervidae family. To update the research community regarding the status quo of CWD epidemiological models, we conducted a meta-analysis on CWD research. We collected data from peer-review articles published since 1980, when CWD was first diagnosed, until December 2018. We explored the analytical methods used historically to understand CWD. We used 14 standardized variables to assess overall analytical approaches of CWD research communities, data used, and the modeling methods employed. We found that CWD modeling initiated in the early 2000s and has increased since then. Connectivity of the research community was heavily reliant on a cluster of CWD researchers. Studies focused primarily on regression and compartment model-based models, population-level approaches, and host species of game management concern. Similarly, CWD research focused on single populations, species, and locations, neglecting modeling using community ecology and biogeographic approaches. Chronic wasting disease detection relied on classic diagnostic methods with limited sensitivity for most stages of infection. Overall, we found that past modeling efforts generated a solid baseline for understanding CWD in wildlife, and increased our knowledge on infectious prion ecology. Future analytical efforts should consider more sensitive diagnostic methods to quantify uncertainty and broader-scale studies to elucidate CWD transmission beyond population-level approaches. Considering that infectious prions may not follow biological rules of well-known wildlife pathogens (i.e., viruses, bacteria, fungi), assumptions employed when modeling other infectious disease may not apply for CWD. Chronic wasting disease is a new challenge in wildlife epidemiology.

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Introduction

Chronic wasting disease (CWD) is an invariably fatal neurological disorder caused by a misfolded protein called prion (Prusiner 1982). It has recently received considerable attention from the public and scientific community. It is a transmissible spongiform encephalopathy (TSE; Williams and Young 1980). Cervids experience cognitive decline and neurodegeneration as a result of infectious prion (PrP^{CWD}) replication in neurons. Chronic wasting disease was first observed in 1967 in a captive deer facility in Colorado, USA, classified as a TSE in 1979 (Williams and Young 1980), and discovered in wild herds in 1981 (Spraker et al. 1997). By late 2019, the disease was detected in wild cervid populations in 24 US states, two Canadian provinces, and areas of Norway, Sweden (Statens Veterinärmedicinska Anstalt 2019), and Finland, as well as in captive facilities in 17 US states, four Canadian provinces, and two South Korean provinces (Kim et al. 2005; Dubé et al. 2006; USGS 2019). Naturally susceptible Cervidae species include white-tailed deer (*Odocoileus virginianus*), mule deer (*Odocoileus hemionus*), elk (*Cervus canadensis*), red deer (*Cervus elaphus*), caribou (*Rangifer tarandus*), moose (*Alces alces*), black-tailed deer (*Odocoileus hemionus hemionus*), and sika deer (*Cervus nippon*) to date (Spraker et al. 1997; Baeten et al. 2007; Benestad et al. 2016; Centers for Disease Control and Prevention 2019a). Due to its highly contagious nature, CWD prevalence can reach 40-50% in wild cervid populations (Edmunds et al. 2016; Carlson et al. 2018), and 80-100% in captive populations (Keane et al. 2008). These epidemiological characteristics make CWD management a priority for wildlife managers and conservationists responsible for species of economic and conservation concern (Wisconsin Department of Natural Resources 2010; Texas Parks and Wildlife and Texas Animal Health Commission 2015).

Despite traditionally concerning wildlife professionals, new emphasis on CWD's spillover potential has garnered attention from the US Centers for Disease Control and Prevention (Centers for Disease Control and Prevention 2019b) and the European Food Safety Authority (EFSA Panel on Biological Hazards 2018). Experimental challenge via intra-cranial prion inoculation demonstrates other wildlife, such as raccoons (*Procyon lotor*; Moore et al. 2019), common livestock species including sheep (*Ovis aries*) and cattle (Bos taurus; (Hamir et al. 2006, 2007), and non-human primates (Marsh et al. 2005) can be susceptible to prion infection. Similarly, swine (*Sus scrofa*) have shown susceptibility to PrPCWD after consuming prion-infected tissues (Moore et al. 2017). While there are no reports of CWD infecting humans, public health experts discourage consuming CWD-positive cervids (Centers for Disease Control and Prevention 2019b) and posit that CWD's ever-increasing spread and exposure warrants action (Osterholm et al. 2019).

To determine which measures of surveillance, control, and prevention for infectious diseases are appropriate, epidemiologists work to comprehend the phenomena and mechanisms that trigger and facilitate disease spread. Since the mid-1700s, epidemiologists have utilized statistical and mathematical models for describing epidemiological data and complex infection processes (Heesterbeek et al. 2015). Models are often valued for their abilities to simplify complex biological systems, describing and forecasting infectious disease events, and evaluating control methods under diverse, what-if, scenarios (Garner and Hamilton 2011). A plethora of studies have examined diverse epidemiological modeling approaches for infectious diseases caused by viruses (Gambhir et al. 2015; Herzog et al. 2017), protozoa (Wallace et al. 2014), fungi (Maanen and Xu 2003), bacteria, and nematodes (Hollingsworth et al. 2015; Lou and Wu 2017).

Like other wildlife diseases, research on the ecology of CWD has relied on modeling of epidemics. For example, models have found associations between deer demographics and CWD infection, typically with highest CWD prevalences in older males followed by older females, and then yearling males (Grear et al. 2006; Heisey et al. 2010), which led to development and testing of demographically-weighted harvesting systems for disease control (Walsh and Miller 2010; Jennelle et al. 2018). Other studies have expanded knowledge on CWD transmission mechanisms, prion dynamics, and host population dynamics (Mejía-Salazar et al. 2016; Samuel and Storm 2016). Recent landscape epidemiological studies have identified factors that explain roles of the landscape in CWD prevalence (Walter et al. 2011a; O'Hara Ruiz et al. 2013; Edmunds et al. 2018). Similarly, physical landscape features like geomorphology (Mateus-Pinilla et al. 2013), and rivers and roads (Robinson et al. 2013) have shown linkages with CWD transmission (Rees et al. 2012) and modify the shape of CWD epidemics (Robinson et al. 2013).

Identifying trends in research is commonly employed to identify promising approaches, gaps of knowledge, and guide additional efforts in epidemiology (Allen et al. 2012; Heesterbeek et al. 2015; McCallum 2016; Herzog et al. 2017). Chronic wasting disease is of interest for wildlife and veterinary professionals, livestock industries, and public health agencies, and has therefore been the subject of previous assessment of its trends (Schauber and Woolf 2003; Conner et al. 2008). A recent assessment of sixteen articles found that models support the role of management interventions (i.e., selective and non-selective culling, seasonal hunting, and vaccination), and identify uncertainty in models (Uehlinger et al. 2016). We used a broad definition of modeling in the epidemiological sense (statistical or mathematical). Our aim was to explore past trends in CWD epidemiology. We identified analytical approaches, diagnostic

methods applied, collaboration structure among researchers, model parameterizations, and gaps of information.

Methods

Search and screening approach

We collected articles from Web of Science (Clarivate Analytics, Philadelphia, Pennsylvania, USA) in January 2019. Keywords included chronic wasting disease, prion, model*, landscape, and spatial, combined to capture articles published from January 1980 to December 2018, encompassing more than 35 years of CWD research since its formal recognition in Colorado (Williams and Young 1980). We conducted an initial screening of titles and abstracts to retain online peer-reviewed research manuscripts (i.e., non-literature reviews) related to statistical or mathematical modeling. We applied the following selection criteria: 1) articles written in English language, 2) models applied were statistical or mathematical (i.e., not animal models), 3) articles that were not clinical or pathogenetic, 4) CWD infection accounted for in models (i.e., not loosely implied), and 5) model approaches accounted for cervid ecology (i.e., CWD reservoirs explicitly considered in models). Next, the bibliographies of articles were inspected manually to identify articles not detected in our initial search and falling within our inclusion criteria.

Data collection

Articles were reviewed, and data were extracted and assembled in four major groups: article title, publication year, journal name, and authors, to address what, when, where, and by whom, articles were published. Additionally, we extracted epidemiological data from articles using a content analysis (Hsieh and Shannon 2005) considering different research approaches.

More specifically, research approaches were defined based on biological organizational levels as: 1) individual-level studies (i.e., focused on individual or cohort pathogenesis/survival); 2) population-level studies (i.e., one or more cervid populations defined by the article were the dependent variables of the modeling application); 3) community-level (i.e., models integrating multiple species from diverse taxa), 4) ecosystem-level (i.e., models integrating environmental features and epidemiological data); and 5) biogeographic-level studies (i.e., coarse-scale, broad-extent studies). We also collected the geographic location, host species involved in the modeling, data source (i.e., primary or secondary), sample size and CWD prevalences, and diagnostic methods used to detect CWD infection. We categorized between studies based on empirical and simulated data (i.e., virtually created populations and/or environments). Finally, we identified the modeling algorithms used, model evaluation methods, type of modeling (predictive vs. descriptive), and variables assessed. Variables included in the modeling were characterized in 11 categories: 1) control/management method (i.e., exploration of methods for management control, such as harvest); 2) demographic (i.e., population-centric variables); 3) epidemiological (i.e., characteristics of pathogens or hosts); 4) landscape (e.g., land cover types); 5) life cycle (e.g., functions of population viability); 6) location, 7) sampling method (e.g., route of data collection); 8) time; 9) sampling effort; 10) trophic-related variables; and 11) spatial- following Auchincloss et al. (2012).

Data analyses

We organized, summarized, and visualized data with R software (R Core Team 2020) using *ggplot2* and *dplyr* packages in the tidyverse platform (Wickham and RStudio 2018). Additionally, we used ArcMap 10.5 (Environmental Systems Research Institute, Redlands, California, USA) for choropleth map generation to show geographic distribution of studies by

state. We used a social network analysis to describe the structure of the CWD modeling community (Newman 2004). We compiled an adjacency matrix containing the number of selected publications written by and between authors. We extracted each authors' affiliations listed in the articles, and categorized affiliations as: 1) state wildlife agencies; 2) academia, 3) federal science agencies; and 4) other governmental agencies (e.g., city government). Finally, I used Gephi 0.9.2 network analysis software (Bastian et al. 2009) to quantify author influence in connectivity and affiliation-based structures of the research community.

Results

The search strings yielded a total of 679 articles. After removing duplicates, 589 unique articles remained. Following our selection criteria, 79 research articles were found, including eight additional articles not captured by the search on Web of Science but recovered from articles' bibliography (Joly et al. 2003, 2006; Johns and Mehl 2006; Miller et al. 2008; Al-Arydah et al. 2012; Edmunds et al. 2016; Galloway et al. 2017; Schuler et al. 2018). The 79 articles and their corresponding metadata can be found in Table A1.

The number of articles on CWD modeling has steadily increased since 2000 (Fig. 2.1), with a mean of 4.2 (SD=2.2) publications being published per year. Miller et al. (2000) and Conner et al. (2000) published the first research articles applying analytical modeling to CWD. The first article integrating spatial statistics across scales was published in 2003 (Joly et al. 2003). Ecological modeling including environmental covariates started in 2005 (Farnsworth et al. 2005; Krumm et al. 2005). Integrating genetics in CWD epidemic modeling started in 2008 (Miller et al. 2008).

A total of 37 journals contained the articles collected. Of these, the *Journal of Wildlife Diseases*, *PLoS One*, *Journal of Wildlife Management*, and *Ecological Applications* contained

about half of the articles (Fig. A1). Articles were published mainly in journals related to ecology (e.g., *Ecology, Journal of Applied Ecology, Ecosphere*), and biomathematics (e.g., *Journal of Mathematical Biology, Bulletin of Mathematical Biology, ISRN Biomathematics*), with a limited presence in veterinary journals (e.g., *Preventative Veterinary Medicine, Veterinaria Italiana*). A total of 180 individual authors participated in the 79 research articles. The social network of the CWD community revealed that a few specific researchers (nodes) occurred in most modeling studies (Fig. 2.2). Additionally, individual authors' level of influence in overall network connectivity (eigenvector centrality) was unevenly distributed among the CWD-modeling community, with a small number being the most influential in connectivity. State and federal agencies (e.g., natural resource departments and US Geological Survey) comprised a considerable number of connections with other researchers (Fig. 2.3a), and with academic institutions (Fig. 2.3b). About 18% articles were generated by isolated groups of authors (i.e., mathematicians), while authors from other disciplines were generally well-connected to the major network. Only one researcher was not affiliated with a STEM (science, technology, engineering, and mathematics) department.

The research approaches employed were not evenly distributed across the pool of articles. For example, two articles were performed at the individual-level, in studies of cohort survival and transmission (Monello et al. 2017; Davenport et al. 2018). Population-level studies were the most common scale studied (n=48), followed by ecosystem-level (n=20). The number of population-level articles remained relatively constant over time but ecosystem-level analyses became more frequent during the 2010s. Six community-level articles explored predator populations directly or indirectly through predation-associated mortality on cervids and infection status (Miller et al. 2008; Walsh and Miller 2010; Wild et al. 2011; Monello et al. 2014; DeVivo

et al. 2017; Maji et al. 2018). Nine articles mixed methods by including cervid genetics, spatial-analyses, and landscape-level variables (Blanchong et al. 2008; Miller et al. 2008; Grear et al. 2010; Cullingham et al. 2011b, 2011a; Rogers et al. 2011; Robinson et al. 2013; Kelly et al. 2014; Mejía-Salazar et al. 2017). We did not identify studies using biogeographic level approaches or studies across large study areas.

Thirteen studies used artificial, simulated environments for modeling (Gross and Miller 2001; Diefenbach et al. 2004; Johns and Mehl 2006; Nusser et al. 2008; Almberg et al. 2011; Wild et al. 2011; Al-Arydah et al. 2012; Potapov et al. 2012; Cortez and Weitz 2013; Oraby et al. 2014; Sun et al. 2015; Vasilyeva et al. 2015; Maji et al. 2018). Excluding aspatial simulations, all modeling studies were conducted in the US and Canada (Fig. 2.4). Wisconsin (n=25) and Colorado (n=21), US, were the most represented states in the literature, followed by neighboring states of Wyoming (n=10) and Illinois (n=7). In Canada, provinces with most articles were Saskatchewan (n=7) and Alberta (n=6). Similarly, cervid species used in the pool of research articles were unevenly represented. Articles modeled white-tailed deer (n=39) and mule deer (n=37) most frequently (88%), followed by elk, which were rarely the target species (n=5). Five studies did not report the host species studied (Wild et al. 2011; Oraby et al. 2014; Sun et al. 2015; Vasilyeva et al. 2015; Maji et al. 2018). We did not find studies focused on other known CWD-susceptible host species (i.e., moose, sika deer, red deer, or caribou).

Most articles (n=54) relied on secondary data sources for modeling (i.e., published data collected from surveillance or literature), while primary-sourced data (original field or experimental data) studies were less common (n=25). Excluding simulation-based studies with artificial populations, articles using secondary data sources (e.g., statewide surveillance programs) had sample sizes that accounted for >96% of cervids used in models. These secondary

sources typically revealed higher CWD prevalences and larger sample sizes across articles (μ=11.7%; range=0 to 94.7% and μ=12,405; range=39 to 152,133, respectively). Reported prevalences and number of cervids sampled in articles at the year of their publication was highly variable (Fig. 2.5).

Regarding CWD prion diagnostic or detection, nearly all studies (72/79) relied on immunohistochemical (IHC) and/or enzyme-linked immunosorbent assay (ELISA). These methods were used directly or indirectly for determining CWD infection status in cervids. Five studies did not report diagnostic methods used or assumed for CWD detection (Diefenbach et al. 2004; Almberg et al. 2011; Cullingham et al. 2011a; Galloway et al. 2017; Maji et al. 2018). Only one study (Davenport et al. 2018) incorporated real-time quaking induced conversion (RT-QuIC) and no studies reported use of protein-misfolding cyclic amplification (PMCA).

Analytical methods

Phenomenological models, like regression analyses, and mechanistic models, such as compartmental models using differential equations (i.e., S-I-R), were the most common analytical approaches, followed by hierarchical Bayesian models, population matrix models, and descriptive statistics (Fig. 2.6). Less common methods included diffusion models, machine learning (i.e., boosted regression trees and Maxent), and network models, among others (Table A2). Additionally, 32% (25/79) studies were descriptive, aiming to reconstruct past epidemics, while 58% (46/79) relied on modeling algorithms that were predictive in nature, aiming to forecast unknown CWD scenarios.

From the 79 modeling articles, 49 relied on time explicitly (e.g., prevalence over time) or implicitly (e.g., in compartment model timesteps), 40 articles incorporated spatial information (e.g., Game Management Unit, geographic coordinates, or Township-Region-Section; Conner

and Miller 2004; Krumm et al. 2005; Kelly et al. 2014, respectively). Four studies explored sampling effort in CWD research (Joly et al. 2009; Walsh and Miller 2010; Rees et al. 2012; Mateus-Pinilla et al. 2013) and six examined trophic variables as top-down effects of predation on cervids and infection status (Miller et al. 2008; Walsh and Miller 2010; Wild et al. 2011; Monello et al. 2014; DeVivo et al. 2017; Maji et al. 2018). No studies investigated bottom-up effects, and a few explored cervid body condition (Edmunds et al. 2016; DeVivo et al. 2017) and consumption rates (Potapov et al. 2013) as functions of movement habits and prion deposition, respectively. Common landscape variables of ecosystem-level studies included characteristics of forest composition, agricultural habitat, and soils, while wetlands and riparian habitats were rarely incorporated (Table 2.1). Demographic variables including sex and age of cervids, and epidemiological variables like prevalence were the most frequent in CWD modeling (Fig. 2.7).

Discussion

Using 79 research articles, our research revealed trends in epidemiological modeling of CWD. We collected and standardized metadata using methods comprehensible and accessible for both epidemiologists and wildlife professionals. We offer a synthesis of analytical modeling of CWD, the prion disease with the highest spillover potential (Escobar et al. 2020). The articles we outlined have generated valuable findings to guide current and future management actions and efforts from the research community remain critical in understanding this emerging infectious disease. We note the following patterns: 1) population-level studies were predominant, 2) models relied on diagnostic tests of limited sensitivity, 3) the research community is collaborative among professions and institutions, and 4) the data collected are geographically clustered, representing portions of CWD's distribution.

Our review indicated that the first modeling applications began over 30 yr after the initial detection of CWD. This lag is likely a result of the timeline of the diagnosis of CWD as a TSE and identification in wild herds in the early 1980s (Spraker et al. 1997). Also, delays in publication are subject to lengths of surveillance periods, data cleaning and analysis, and other practical limitations. Still, in less than two decades, the magnitude of CWD modeling research has increased consistently along with the number of researchers.

The CWD modeling community is tightly linked with major researchers at federal and state agencies. In academia, veterinary scientists and ecologists possess strong ties expressed as co-authorship across academic realms. Supportively, publications in ecological and veterinary journals featured authors with larger collaboration networks, while isolated clusters of authors often published in specialized journals. The fact that the community of researchers was well connected, with a few isolated clusters, suggest strong collaboration among disciplines and agencies, and multidisciplinarity in the study of CWD. A deficiency of social science researchers suggests little input from experts in human-dimension, economics, and policy, which could limit the use of CWD model for management.

Research approaches focused on population-level modeling that has revealed demographic patterns on CWD infection (Miller and Conner 2005; Grear et al. 2006) useful for testing epidemiological control at the local level, including culling practices to reduce prevalence (Wasserberg et al. 2009; Potapov et al. 2012). Whether CWD transmission is frequency- or density-dependent (or a hybrid of the two) is still in debate and models show mixed results (Grear et al. 2010; Cortez and Weitz 2013; Storm et al. 2013; Jennelle et al. 2014; Oraby et al. 2014). We found that population-level models that incorporate spatial analysis revealed that CWD is not randomly distributed, rather it is observed in geographic clusters (Joly et al. 2003,

2006). These clusters result in hotspots of infection that could serve as a source for posterior CWD spread to other regions (Nusser et al. 2008; Heisey et al. 2010). Population-level studies incorporating genetics identified heterogeneous transmission risk (Matsumoto et al. 2013), allelic selection (Monello et al. 2017), impacts of genetic relatedness on probability of transmission (Grear et al. 2010; Mejía-Salazar et al. 2017), and patterns of geographic spread (Blanchong et al. 2008; Cullingham et al. 2011a, 2011b; Rogers et al. 2011; Robinson et al. 2013; Kelly et al. 2014).

Community-level studies often determined the roles of cervid predation in CWD spread. These studies were generally empirically-based (Miller et al. 2008; Walsh and Miller 2010; Monello et al. 2014; DeVivo et al. 2017) and theoretical applications were less common (Wild et al. 2011; Maji et al. 2018). Ecosystem-level studies revealed the importance of landscape features for CWD spread (Garlick et al. 2011; Nobert et al. 2016; Hefley et al. 2017b). For example, landscape epidemiology identified positive associations between CWD prevalence and specific variables such as urban (Farnsworth et al. 2005), forested (O'Hara Ruiz et al. 2013; Storm et al. 2013) and riverine landscapes (Edmunds et al. 2018), while soil composition had limited effects (O'Hara Ruiz et al. 2013; Storm et al. 2013; Manjerovic et al. 2014) in contrast to (Walter et al. 2011b). One individual-level study determined cohort pathogenesis and transmission (Davenport et al. 2018), while the other investigated survival in relation to genotype (Williams et al. 2014).

Most studies were conducted in regions severely afflicted by CWD (USGS 2019). For example, modeling studies were conducted in 11 of the 26 CWD-affected US states and in two out of the five countries in which CWD has been detected in wild cervids. This is probably a result of available funding in CWD endemic areas, low detection of prions outside foci of

infection, and limited data available for modeling other regions. Most articles in our review used study areas selected pragmatically or based on political boundaries, which has been cautioned against, considering the lack of biological support and artifactual results of such study designs (Barve et al. 2011). Interestingly, some study areas were defined through Game Management Units, delineations of which can vary in their accommodation to wildlife-populations (Miller and Conner 2005), landscape, and human associated variables, such as land cover types and infrastructure (Wisconsin Department of Natural Resources 1998; Joly et al. 2009). Fortunately, despite traditional wildlife management operating within political boundaries, recent recommendations from wildlife managers are now promoting CWD management and monitoring across state and provincial boundaries (Western Association of Fish and Wildlife Agencies 2018).

Many susceptible cervid species (e.g., moose, caribou, red deer) were neglected in the revised modeling studies. The three species generally included in models (i.e., white-tailed deer, mule deer, and elk) are highly economically valued as game species (Koontz and Loomis 2005; Wisconsin Department of Natural Resources 2010; Mule Deer Working Group 2015), which may suggest an implicit economic bias in the species selection. Alternatively, the lack of modeling studies for moose, caribou, red deer could reflect either lower prevalences detected in these species, or a deficiency of journal publications of the research conducted on these species.

Sample sizes of studies showed a tendency to increase, but CWD prevalences were considerably variable across time. This may suggest an increased sampling effort, but inconsistent sampling designs. Also, it is unclear if prevalence estimations represented different stages of CWD epidemics. In addition, it is possible that variability of prevalence across time and studies is linked to inclusion (or not) of samples from passive surveillance (e.g., road-killed

deer) that may have different prevalences than samples from active epidemiological surveillance (e.g., hunting for sampling). The high variability in prevalences reveals the increase in research teams studying CWD prevalence in wildlife using non-standardized methods for estimations, making studies hard to compare. For example, some studies rely on decade-long surveillance data and others across years. Unfortunately, efforts to elucidate correction of prevalence values by sampling bias as well as controlling for expanding geographic coverage has been limited. Indeed, geographic areas and temporal periods, which are critical units to estimate CWD prevalence, varied considerably among studies. I call for more informed, standardized reports of CWD prevalence that include the sample size (e.g., number of animals tested), sampling period (e.g., annual basis, duration since local discovery, or stage of epidemic), and study area extent (e.g., hectares). This will make metadata more reliable as a baseline to facilitate prevalence comparison across regions, periods, and populations.

Most CWD data originated from two diagnostic tests: IHC and ELISA. These tests are considered the gold standard for CWD diagnosis (Haley and Richt 2017). Routine procedure uses ELISA for initial screening, followed by IHC for confirmation. Strikingly, recent studies showed that IHC has questionable sensitivity when detecting low concentrations of prions in the asymptomatic phase of infection. For example, IHC could fail to detect PrP^{CWD}-infected individuals in controlled, transgenic mice (McNulty et al. 2019). Similarly, ELISA fails to detect low concentrations of CWD prions in brain homogenate (McNulty et al. 2019), which may be consistent with earlier stages of the disease. Therefore, considering that diagnostic methods used in CWD modeling produce false negatives, previous epidemiological models could be underestimating CWD prevalences. In the US, IHC and ELISA are the only accepted methods for CWD diagnosis officially (US Department of Agriculture 2014). Thus, state agencies in the

US are restricted from using other non-US Department of Agriculture validated tests (i.e., ultra-sensitive methods like PMCA or RT-QuIC) in routine CWD surveillance. This could influence understanding of CWD in wildlife, including increased temporal lags in detecting the effects of management intervention. Future research should consider developing corrector parameters to account for uncertainties in CWD detection. Such parameters could be estimated by estimating CWD detection error using other diagnostic methods with elevated sensitivity (e.g., PMCA, RT-QuIC) of subsets of samples tested using conventional diagnostic tests. I note that this approach may be impractical for large sample sizes but could help detect the circulation of lower prion concentrations otherwise missed, which may be specifically crucial in early stages of CWD invasion when outbreak control could be more effective.

Analytical methods to analyze CWD were dominated by regression and compartment-based models. These models have generated a baseline to guide management efforts and build new research hypotheses. Nevertheless, the quality of compartment models is subject to the robustness and biological realism of specific parameters, and is context-, population, and time-specific (Uehlinger et al. 2016). Regression models chiefly identified linkages between CWD infection and environmental features (Mateus-Pinilla et al. 2013). This empirical work can help guide experimental work to assess CWD transmission under specific landscape features (e.g., plant species) to build upon preliminary work with scrapie prions (Pritzkow et al. 2015, 2018). This will elucidate mechanisms of causation of CWD environmental transmission and will guide evidence-based interventions based on landscape modification for CWD control (Goñi et al. 2015). Additional research could include exploring the effects of more sensitive CWD detection on parameter estimation for SI, hierarchical, and matrix models as it pertains to prion transmission dynamics and demographic trends in wild cervids. For example, environmental

prion loads may be better quantified with accurate detection of cervids in the preclinical phase of infection (Henderson et al. 2017). Finally, hunter-sourced data has been invaluable in CWD surveillance programs, however, these data can be biased (Conner et al. 2000) or incomplete compared to active epidemiological sampling. Future research could include assessing bias mitigation strategies for the epidemiological surveillance derived from samples obtained opportunistically from hunters.

Model evaluation and field validation remain barely explored; current models only focus on calibration. That is, CWD descriptive models prioritize model-fit to the data available (e.g., Akaike information criteria). For predictive models, evaluation approaches should split data to ensure temporal and spatial independence among datasets. We found that current evaluation methods do not assure statistical independence between calibration and evaluation datasets (e.g., cross-validation) and require accurate detection of positive and negative individuals (e.g., evaluations based on sensitivity and specificity), which is not a robust approach considering the CWD detection capacities of major diagnostic methods employed (i.e., IHC and ELISA).

Few modeling studies incorporated sampling effort and no studies integrated biogeographic approaches in models (e.g., continental geomorphology), which are often starting points in which infectious diseases are generally explored (Emmanuel et al. 2011; Peterson 2014). Instead, models were restricted to finer-scale population-level variables and localized geomorphology (i.e., soil composition). Considering resistance and environmental transmissibility of prions (Zabel and Ortega 2017) and recent experiments showing potential of prion deactivation from natural weathering processes (Yuan et al. 2018) research on CWD based on landscape epidemiology warrants further investigation.

A new frontier in CWD modeling research includes addressing the detection, quantification, and mitigation of sampling biases in surveillance. Biases could be linked to the geographic areas studied, species inspected, and diagnostic approaches employed. Specifically, broad-scale biogeographic models are encouraged to account for the roles of environmental variation on past CWD epidemics (Evans et al. 2016). Such coarse-scale studies will allow researchers to reconstruct patterns in CWD spread, establishment, and maintenance in novel areas and populations, as has been proven useful for other infectious disease agents including worms, bacteria, and viruses (Reisen 2010; Cadavid Restrepo et al. 2016). Continental-level assessment of CWD surveillance will elucidate whether current CWD distributions are driven by sampling effort, specifically in more probabilistic areas for CWD infection (e.g., CWD-free counties neighboring endemic CWD areas).

Chronic wasting disease and other prion diseases remain a challenge in wildlife disease modeling. Prion diseases may not follow traditional rules and assumptions derived from other pathogens for which more information is available. For example, unlike most diseases, hosts fail to demonstrate immune responses to prion infection, and prions lack genetic identity necessary for coevolution (Zabel and Avery 2015). Additionally, prions remain resilient in extreme conditions otherwise fatal to other pathogens (Jung et al. 2003), and their unclear origins further complicate CWD tracking. More importantly, CWD is the only prion disease affecting free-ranging wildlife, it has no treatment, and its zoonotic potential cannot be discredited, limiting the scientific community's abilities to develop experimental work in basic laboratory settings. Our overview of CWD modeling could serve as a baseline for future CWD research.

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Table 2.1: Landscape variables used in chronic wasting diseases research published in journals from 1980-2018. From ecosystem-level studies in meta-analysis, columns show categorized landscape variables, how often they appeared in articles, an example of the variable or its description, and their respective sources. Variables related to forests, urbanization, and agriculture were more common, while riparian and broad-scale variables (e.g., ecoregions) were seldom examined. Note that climactic variables are absent.

	Number			
Variable	**CO[a]**	**LCT[b]**	**Example**	**Sources**
Forest	11	8	Forest size, percent forested area, edge size, proportion deciduous forest	Joly et al. 2006; Nusser et al. 2008; Skuldt et al. 2008; Garlick et al. 2011; Rees et al. 2012; Mateus-Pinilla et al. 2013; O'Hara Ruiz et al. 2013; Robinson et al. 2013; Storm et al. 2013; Garlick et al. 2014; Kelly et al. 2014; Manjerovic et al. 2014; Evans et al. 2016; Mejía-Salazar et al. 2016; Nobert et al. 2016; Hefley et al. 2017b, 2017a; Edmunds et al. 2018
Soil characteristics	6	0	Percent clay, pH, average organic matter	Mateus-Pinilla et al. 2013; O'Hara Ruiz et al. 2013; Robinson et al. 2013; Storm et al. 2013; Manjerovic et al. 2014; Evans et al. 2016
Terrain	6	0	Topographic variability, ruggedness, elevation, slope	Rees et al. 2012; Mateus-Pinilla et al. 2013; O'Hara Ruiz et al. 2013; Kelly et al. 2014; Evans et al. 2016; Edmunds et al. 2018
Agriculture	4	7	Percent cropland, pasture, cultivated crops	Joly et al. 2006; Nusser et al. 2008; Skuldt et al. 2008; Garlick et al. 2011; Rees et al. 2012; O'Hara Ruiz et al. 2013; Garlick et al. 2014; Kelly et al. 2014; Mejía-Salazar et al. 2016; Nobert et al. 2016; Edmunds et al. 2018
Development	5	5	Amount or percent of developed land	Farnsworth et al. 2005, 2006, 2007; Garlick et al. 2011; O'Hara Ruiz et al. 2013; Kelly et al. 2014; Evans et al. 2016; Hefley et al. 2017b, 2017a; Edmunds et al. 2018
Rivers	4	5	Proximity, density	Blanchong et al. 2008; Cullingham et al. 2011b; Rees et al. 2012; O'Hara Ruiz et al. 2013; Robinson et al. 2013; Kelly et al. 2014; Nobert et al. 2016; Hefley et al. 2017b; Edmunds et al. 2018
Private land	2	0	Proportion, percentage	Farnsworth et al. 2005, 2006
Streams	2	0	Proximity, density	Rees et al. 2012; O'Hara Ruiz et al. 2013
Human population	2	0	Average density	Mateus-Pinilla et al. 2013; O'Hara Ruiz et al. 2013

Roads	2	5	Proximity, density	Krumm et al. 2005; Blanchong et al. 2008; Rees et al. 2012; Robinson et al. 2013; Kelly et al. 2014; Nobert et al. 2016; Edmunds et al. 2018
Riparian	2	3	Proportion, percentage	Garlick et al. 2014; Evans et al. 2016; Edmunds et al. 2018
Shrubland	1	4	Area (hectares)	Joly et al. 2006; Rees et al. 2012; Mejía-Salazar et al. 2016; Nobert et al. 2016; Edmunds et al. 2018
Wetlands	1	1	Area (hectares)	Joly et al. 2006
Fragmentation	1	0	Connectivity, size	Kelly et al. 2014
Grassland	0	7	Proximity, presence	Joly et al. 2006; Garlick et al. 2011, 2014; Rees et al. 2012; Kelly et al. 2014; Mejía-Salazar et al. 2016; Edmunds et al. 2018
Waterbodies	0	2	Relating to motility functions	Garlick et al. 2011, 2014
Ecoregions	0	2	Southeast glacial plains, Great lakes, Southwest savanna	Rogers et al. 2011; Robinson et al. 2013
Scrubland	0	2	Foothill, saltbrush, salt desert scrub	Garlick et al. 2011, 2014

[a] CO= quantitative covariate, [b] LCT= qualitative land cover type.

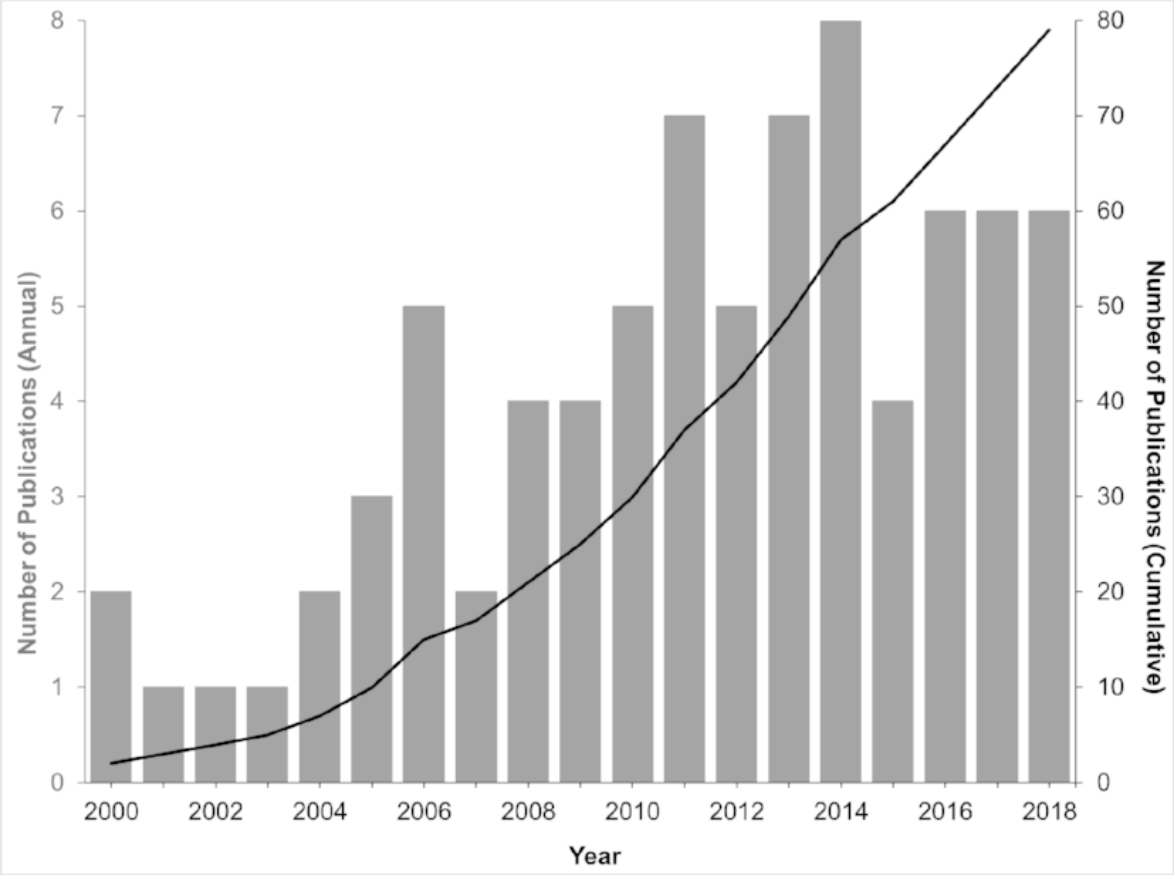

Figure 2.1: Selected chronic wasting disease modeling studies published from 2000–2018 ($\bar{x}$=4.2 publications/year, SD=2.2). Modeling studies started in 2000. Bar plots (gray) show number of publications (left) by year. The solid line represents cumulative number of articles (right) across years.

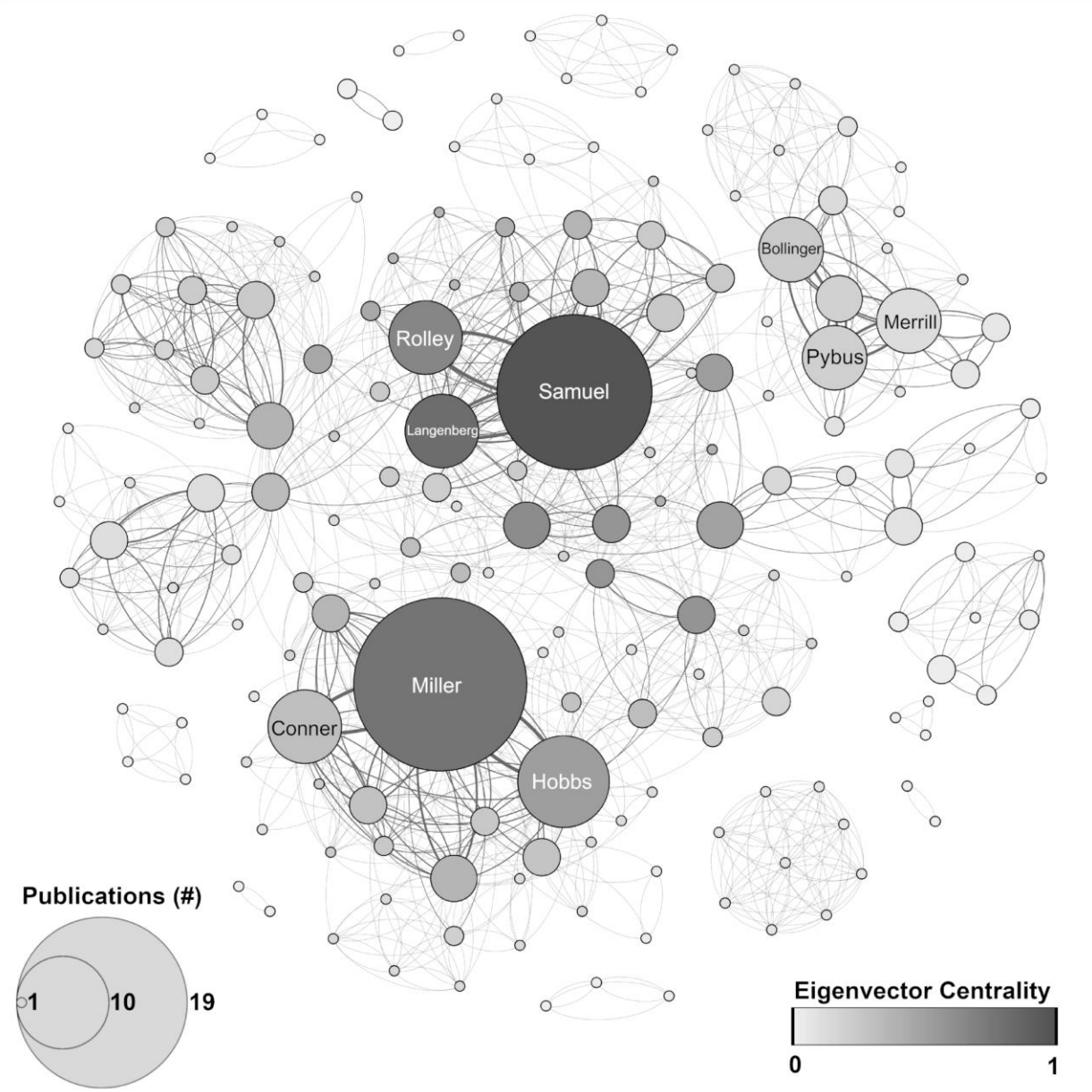

Figure 2.2: Collaboration network of chronic wasting disease modeling research. Nodes (circles) represent authors having between one (small circle) and 19 publications (largest circle). Edge (connecting lines) thickness represents magnitude of collaboration between authors in terms of shared publications and vary from low (thin lines) to high (thick lines). The influence of authors for connectivity (eigenvector centrality) is denoted as showing in decreasing densities of shades from high (dark gray) to low influence (light gray). Note that a few authors have been central to connect CWD research in the community (large circles) and a few isolated clusters reflect research conducted independently. Inset the last name of high-influence authors in the network.

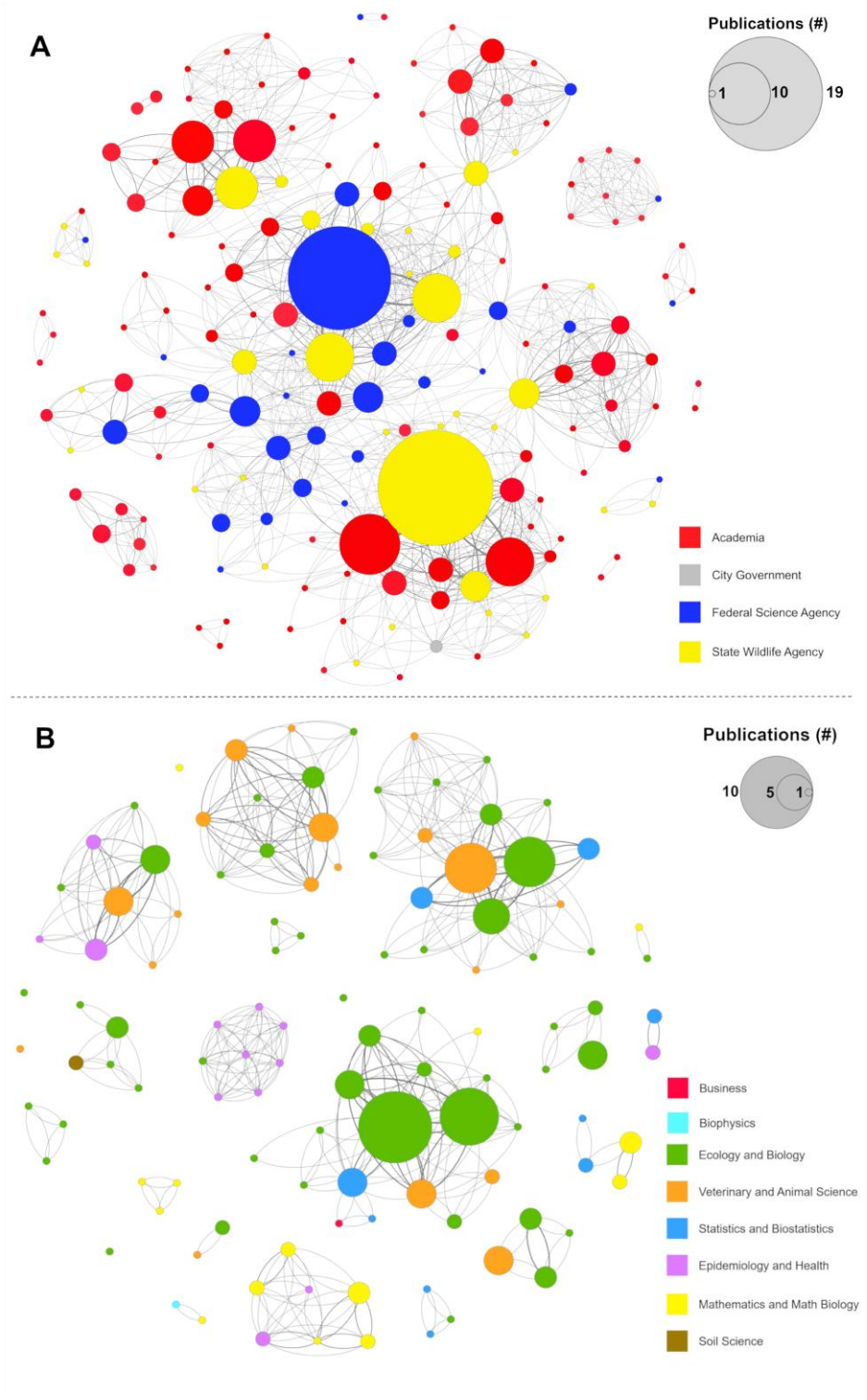

Figure 2.3: Network of CWD researchers' affiliations. Network models showing individual authors and their number of publications (node size), while edge (connecting line) thickness denotes strength of collaboration via number of papers written between authors. Author affiliations recorded from authors'

publications. A) Collaboration among state wildlife agencies (yellow), federal science agencies (blue), other government (gray), and academia (red). Note the apparent role of state and federal science agencies in connecting academia. B) Academia-affiliated authors categorized as biological and ecologically based departments (green), veterinary and animal science (orange), epidemiology and health (pink), mathematics and mathematical biology (yellow), statistics and biostatistics (blue), biophysics (turquoise), soils (brown), and business (red). Note the strong connection (large nodes) between ecology (green) and veterinary fields (orange).

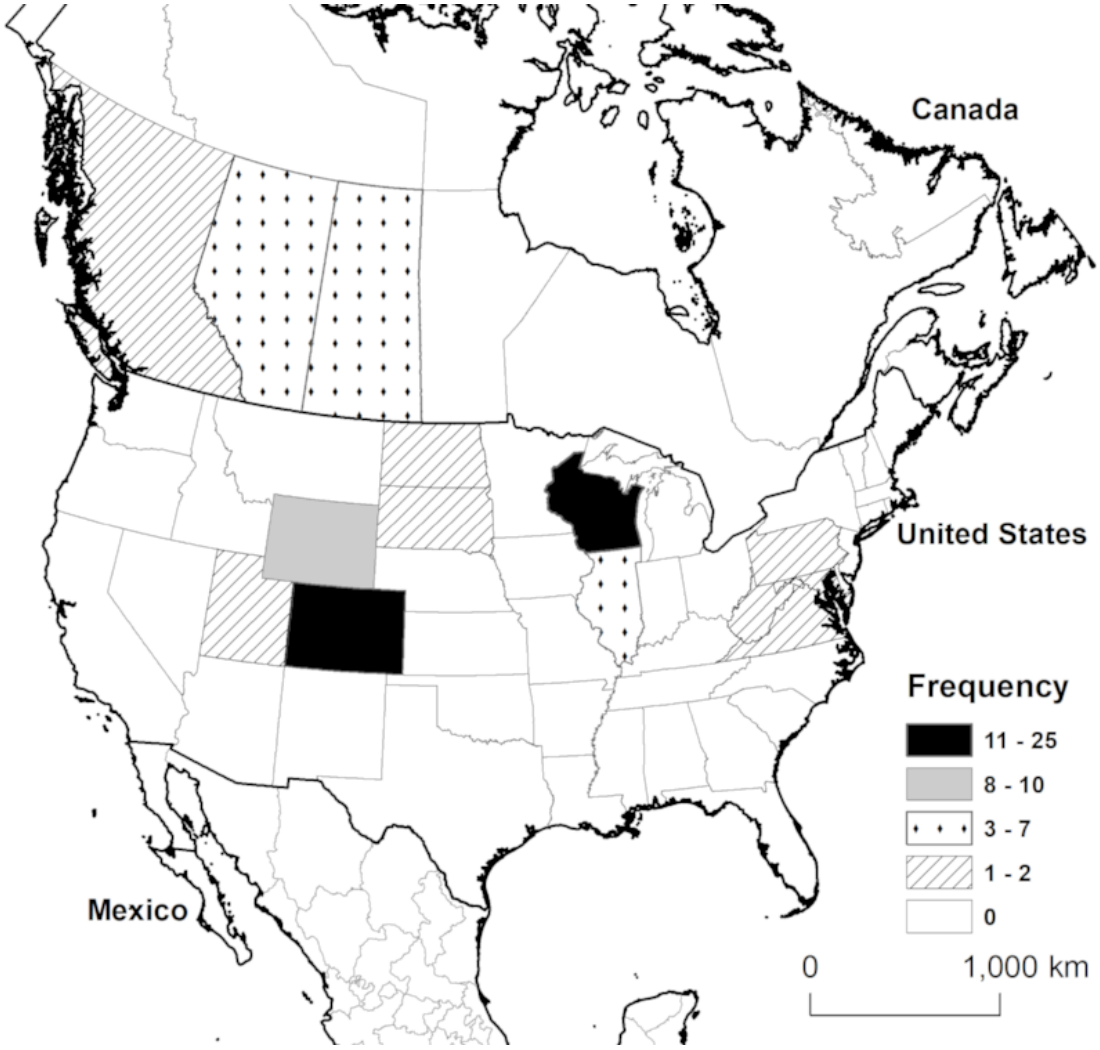

Figure 2.4: Spatial distribution of chronic wasting disease modeling studies by administrative area. In the United States, studies were conducted in Wisconsin, Illinois, Colorado, Wyoming, Utah, Maryland, Virginia, Pennsylvania, West Virginia, North Dakota and South Dakota. In Canada, studies occurred in the provinces of Saskatchewan Alberta, and British Columbia. No modeling studies were conducted in other states, provinces, or countries (white). Research articles based on artificial, simulated data were excluded (n=13), and we retained the remaining articles (n=66).

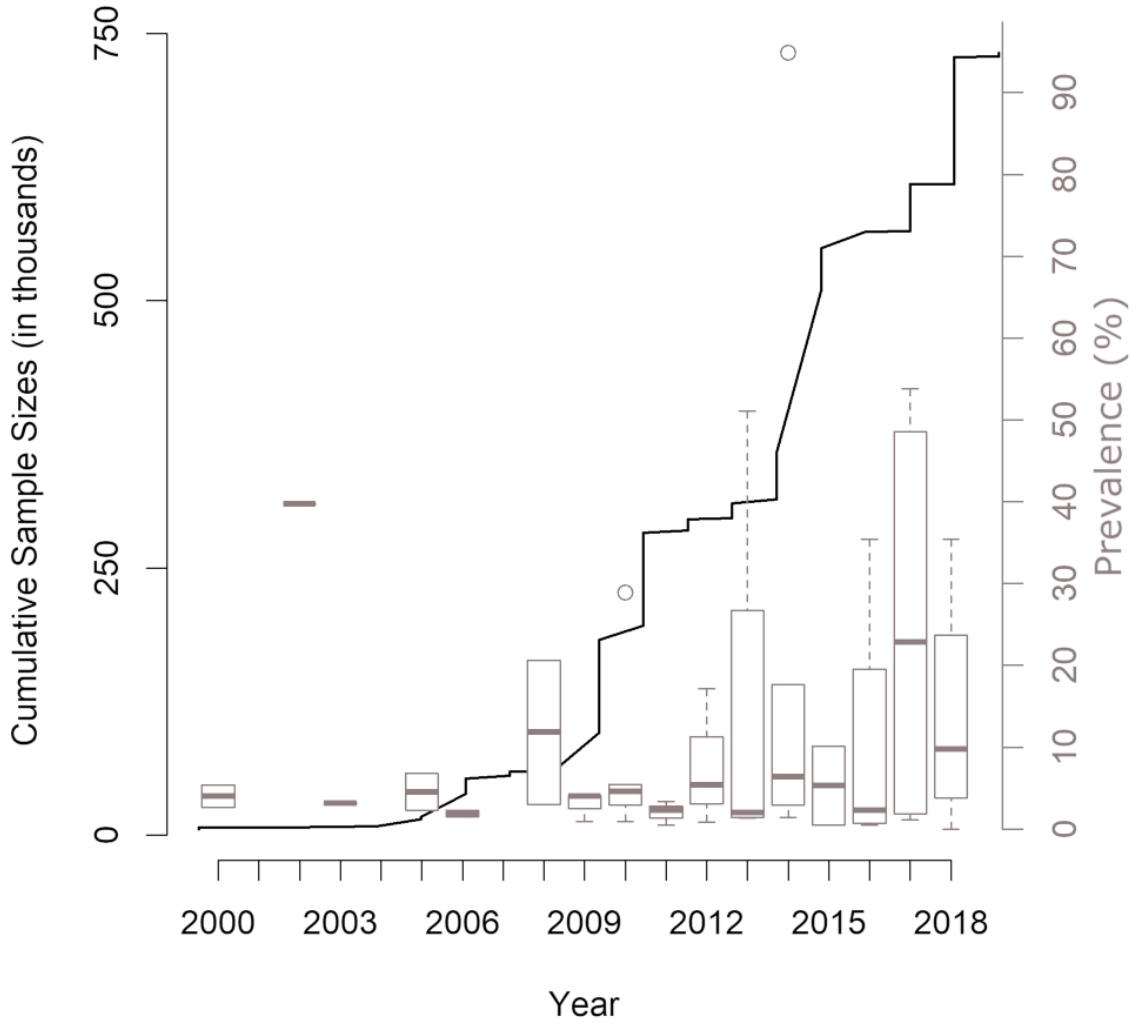

Figure 2.5: Reported prevalences and sampling sizes of chronic wasting disease modeling studies by year for published articles. The cumulative sample sizes ($\times 10^3$; black line) and reported prevalence in percent (grey boxes). Note the variability of prevalence values among studies. No published articles reported prevalences in 2001 and 2003. Studies using simulated data were omitted.

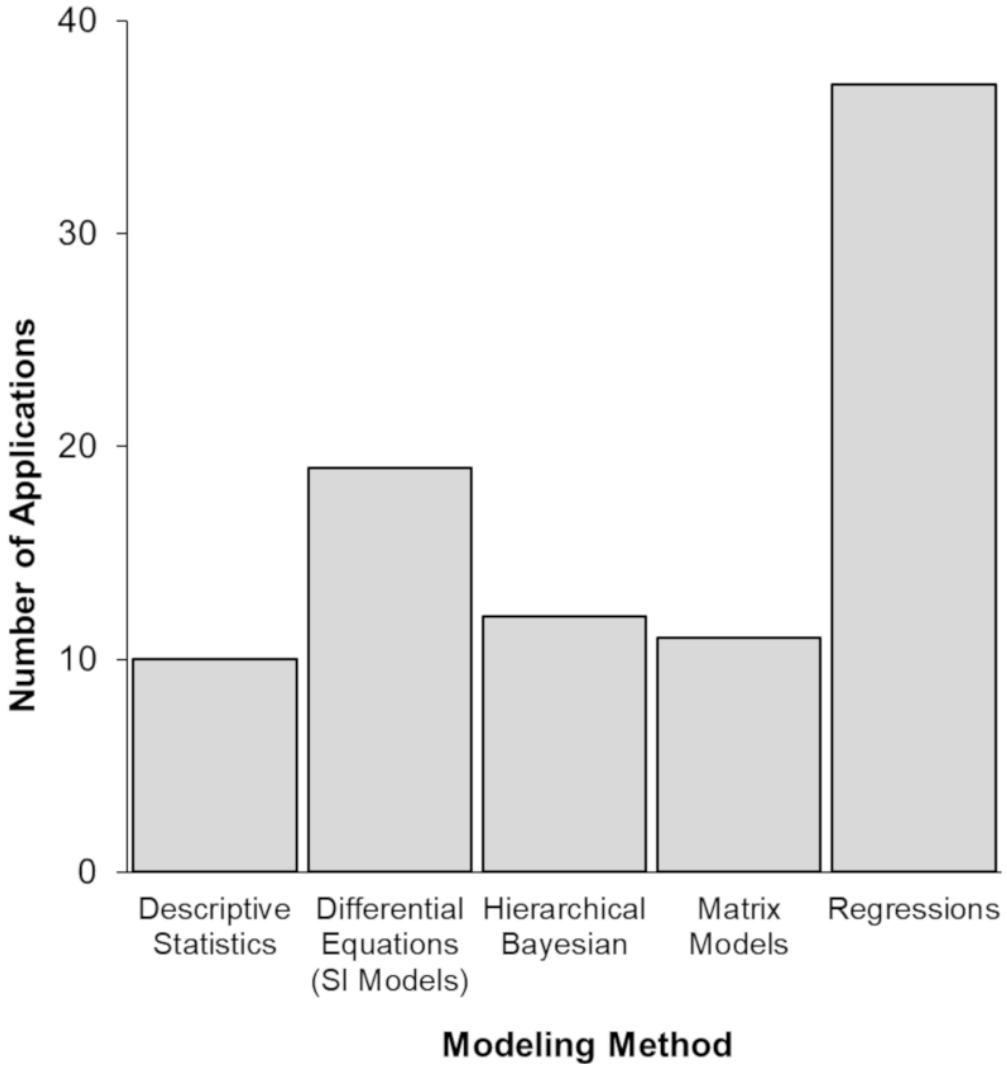

Figure 2.6: Modeling methods used in chronic wasting disease research. Regressions (e.g., logistic, linear, GLMM, negative binomial) were the most commonly used models, followed by compartment models using differential equations (e.g., SIR models), Hierarchical Bayesian, matrix population models, and descriptive statistics, respectively. Less common methods were omitted from the figure and are described in Appendix A.

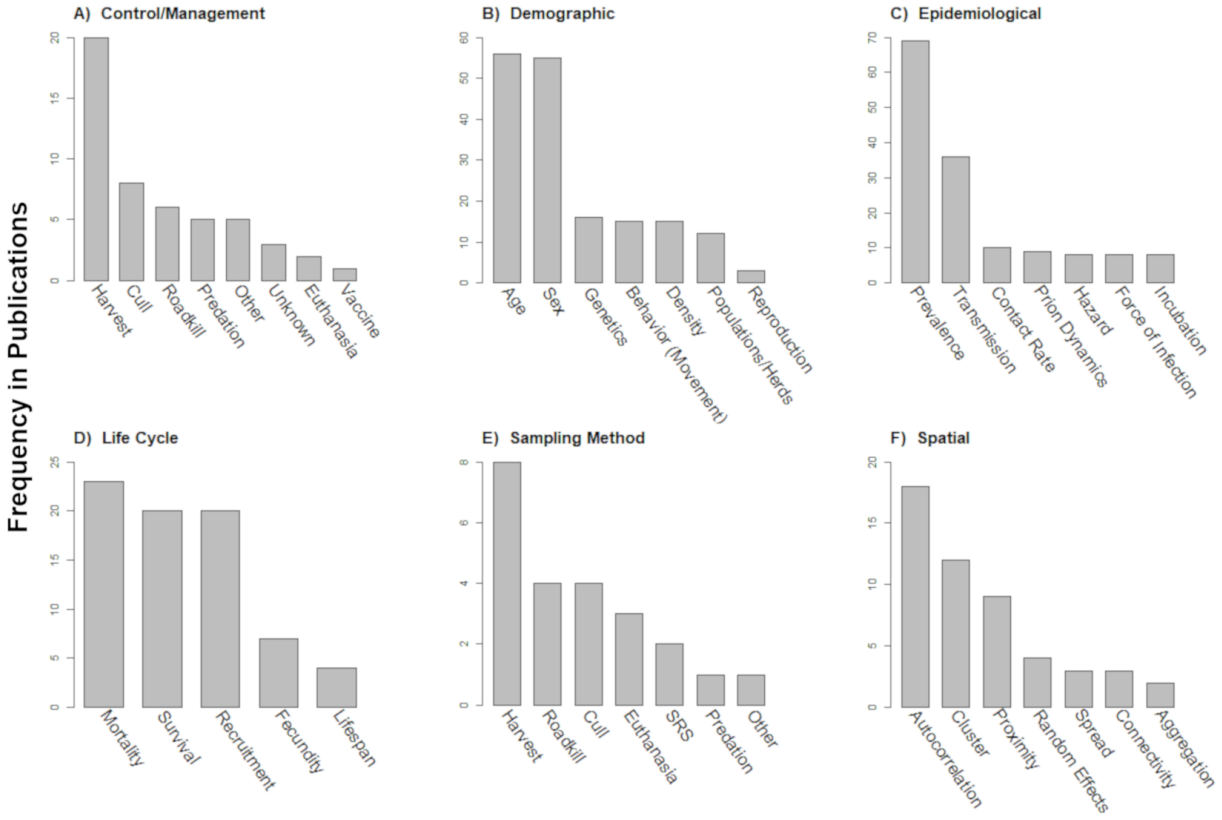

Figure 2.7: Variables used for model parameterization in chronic wasting disease modeling research. Demographic variables (e.g., sex and age) and epidemiological variables (e.g., prevalence and transmission rate) were frequently included in the models. Variables relating to sampling methods, effort, or control measures were less common. Landscape variables are presented in Table 2.1.

CHAPTER 3: INVESTIGATE THE LANDSCAPE DETERMINANTS OF CHRONIC WASTING DISEASE IN VIRGINIA USING LONG-TERM REMOTE SENSING AND EPIDEMIOLOGICAL DATA

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Abstract

Context

Many infectious diseases in wildlife occur under quantifiable landscape ecological patterns useful in facilitating epidemiological surveillance and management, though little is known about prion diseases. Chronic wasting disease (CWD), a fatal prion disease of the deer family Cervidae, currently affects white-tailed deer (*Odocoileus virginianus*) populations in the Mid-Atlantic United States (US), and challenges disease ecologists with its unclear mechanisms and associations within landscapes.

Objective

We aimed to provide guidance for wildlife disease management by identifying the extent to which CWD can be reliably predicted from landscape conditions.

Methods

Using the CWD outbreak in Virginia (US), as a case study system, we used diverse algorithms (e.g., support vector machines, kernel density estimation, and principal components logistic regression) and data partitioning methods to quantify remotely-sensed landscape conditions associated with CWD cases in using both presence-only and presence-absence approaches. We used various model evaluation tools (e.g., partial receiver operating characteristic, cumulative binomial probability testing, coefficients of determination) to assess predictions of disease

transmission risk using independent CWD data. We further examined presence-only model variation in the context of uncertainty.

Results

We provided significant support that landscape conditions can predict and map CWD transmission risk. Presence-only model predictions improved when incorporating inferred home ranges instead of raw hunter-reported coordinates. Different data availability scenarios identified variation among models. Compensating for zero-inflation in presence-absence models had mixed performance, and associated projected probability maps appear biased towards significant parameters.

Conclusion

By showing that CWD could be predicted and mapped, our project adds to the limited information regarding the landscape ecology of CWD transmission risk in free-ranging populations and natural conditions. Our presence-only modeling framework and use of widely-available landscape data could be replicated for other infectious wildlife diseases and study areas.

Introduction

Effective wildlife disease management and control depends upon epidemiological surveillance, though identifying geographic locations where surveillance should be deployed can be challenging. Recent advances in landscape epidemiology have identified likely areas for pathogen presence from associations between disease occurrence and landscape characteristics using correlative methods (Peterson 2008; Peterson et al. 2011). Comprehensive protocols and conceptual bases in landscape epidemiology are well developed for domestic animals (Pfeiffer 2010), but are still in development for wildlife.

Prions are infectious pathogens that cause neurodegenerative diseases in humans and animals (Prusiner 1982). Landscape epidemiology approaches remain limited for infectious prions in general (Winter and Escobar 2020), which may be due, at least in part, to unclear origins of prion biology and the atypical biological properties of prions with respect to other pathogens (Zabel and Avery 2015). Because of their inextricable connection with hosts and the unclear role of other animals in their propagation, prion diseases are the new challenge in wildlife epidemiology (Escobar et al. 2020).

Chronic wasting disease (CWD) is a prion disease of wildlife (Williams and Young 1980). Identified in wild cervid populations in the western United States (US) since the 1980s (Spraker et al. 1997), CWD was not detected in eastern portions of the US until the early 2000s (Evans et al. 2014). High CWD prevalences have been shown to diminish wild cervid population viability (Edmunds et al. 2016; Carlson et al. 2018); therefore, monitoring and surveilling for the highly contagious and invariably fatal disease is crucial for wildlife management. Direct contact between susceptible and infected cervids can transmit prions causing CWD (Davenport et al. 2018; Kramm et al. 2019). Also, prion contamination of the landscape through infected hosts' bodily fluids and tissues (Zabel and Ortega 2017; Escobar et al. 2020) can indirectly transmit the pathogen and complicate CWD control.

Many transmission mechanisms related to environmental exposure to CWD prions remain unclear. Experimental work with scrapie prions show that plants can effectively bind, absorb, and uptake the pathogen, suggesting a potential method of indirect CWD prion transmission (Pritzkow et al. 2015). Also, common environmental materials (e.g., wood, plastic, rocks, cement) and specific soil minerals can serve as substrate for infectious prions and potentially alter their infectivity (Johnson et al. 2007; Pritzkow et al. 2018). Recent work with

CWD prions identified that pathogen infectivity varies with soil type (Kuznetsova et al. 2018), but not with time; only prion recovery within soil decreases with longer binding duration, which suggests that failing to detect prions in the environment may not totally negate transmission risk (Kuznetsova et al. 2020). Recent research focused on the CWD cluster in the Mid-Atlantic US (i.e., Maryland, Pennsylvania, Virginia, West Virginia) identified forested landscapes to be negatively related to CWD occurrence (Evans et al. 2014, 2016), contradicting patterns in disease distributions found in the Midwestern US where CWD was found to be positively related to forested landscapes (O'Hara Ruiz et al. 2013; Storm et al. 2013). Evans et al. (2016) postulated that reduced CWD occurrence in forested landscapes could be indicative of the early stages of an outbreak, or that this CWD-landscape relationship is unique to the Mid-Atlantic. Most modeling efforts to reconstruct and predict CWD transmission have prioritized finer-scale population-level transmission models to generate useful findings for management (Winter and Escobar 2020). The role of the landscape, however, has seen less attention in CWD epidemiology. This is potentially due to the unclear role of the landscape in CWD transmission, and limited protocols to study the landscape epidemiology of prion diseases.

Black-box approaches in landscape epidemiology use locations of known disease outbreaks as occurrence data for model calibration and predicting distributions when specific transmission mechanisms are not entirely known, as is the case of CWD (Peterson 2014; Johnson et al. 2019). Often, data collected from remote sensing technologies facilitate black-box landscape epidemiology by acquiring environmental variables at local scales that may otherwise be unattainable in situ, or were not collected at the time of disease emergence (Horning et al. 2010; He et al. 2015; Quiner and Nakazawa 2017). Often in black-box analyses, recorded locations of occurrences are used to draw relationships between landscape characteristics and

disease presence, similar to landscape genetics (Graves et al. 2012). Likewise, most CWD-landscape models rely on environmental conditions at harvest locations of CWD-infected individuals (Winter and Escobar 2020). However, hunter bias and the cryptic nature of chronic diseases can obscure forensic efforts to identify local sources of infection from occurrence points (Conner et al. 2000; Wobeser 2007), which could restrict our understanding of CWD-landscape relationships.

Presently, CWD is actively spreading in the Mid-Atlantic US and refined guidance on CWD surveillance is critically needed. For example, sustained active and passive surveillance and monitoring efforts throughout the state of Virginia have identified increasing CWD burden over the last two decades (Fig. 3.1). We hypothesized that a black-box landscape epidemiology approach can significantly predict areas suitable for CWD transmission to guide prioritization of surveillance. In this study we attempt to test our hypothesis by utilizing a long-term epidemiological dataset from the state of Virginia, USA, and remote sensing vegetation phenology data to identify the extent at which CWD in Virginia can be reliably predicted using: i) only samples with CWD positive diagnosis in presence-only models, and ii) all samples (i.e., CWD positive and negative diagnosis) in presence-absence models. This analysis intends to facilitate management decisions (e.g., disease management area delineation), guide CWD surveillance, and assess landscape epidemiology methods to predict a wildlife disease.

Methods

CWD in Virginia

Virginia Department of Wildlife Resources (DWR) began testing deer for CWD in 2002; however, active surveillance was not formally initiated until 2005, after a white-tailed deer (*Odocoileus virginianus*) tested positive for CWD in neighboring West Virginia (DWR 2014).

Active, systematic epidemiological monitoring has largely occurred in Virginia's disease management areas, which have been created in response to CWD confirmations (Fig. 3.1A). On the West Virginia border, DWR detected the first CWD-positive deer in Virginia in 2009. Disease Management Area 1 (DMA1) in northwestern Virginia is delineated by the political boundaries of Frederick, Shenandoah, Clarke, and Warren counties (Fig. 3.1A) (DWR 2019). Subsequently, DWR has identified increasing CWD incidence (i.e., number of new CWD positive deer) over time (Fig. 3.1B). Similarly, increasing prevalence (i.e., ratio of CWD-positive deer to total deer tested) has been detected in localized, CWD-endemic areas within DMAs (Fig. 3.1C), and within portions of counties. Sampling to date has been achieved through diverse sampling methods (e.g., active surveillance via hunter harvest and roadkill sampling, passive surveillance via the testing of clinically ill deer) (Fig. 3.1D). In 2019, a second Disease Management Area (DMA2) was developed in Culpeper, Madison, and Orange counties in response to a CWD confirmation in Culpeper County.

Epidemiological and landscape data

Surveillance data consisted of 11,201 individual white-tailed deer tested for CWD via postmortem extraction of medial retropharyngeal lymph nodes (DWR 2014). By March 2020, DWR identified 88 confirmed cases of CWD in Virginia (Fig. 3.1B). These data largely originated from DMA1 hunting grids at 2.59 km^2 spatial resolution. DWR also investigated exact hunting locations for each CWD-positive deer with hunters to reduce spatial uncertainty. Preliminary CWD-testing was accomplished via using either enzyme-linked immunosorbent assay (ELISA) or immunohistochemistry (IHC). All confirmatory testing was accomplished via IHC (DWR 2014; Haley and Richt 2017).

We used vegetation indices as surrogates of landscape characteristics across space and time. Vegetation indices are versatile remotely-sensed metrics of photosynthetically active radiation and vegetative evapotranspiration that consistently identify and correlate with landscape patterns (Pettorelli 2013). More specifically, we used the enhanced vegetation index (EVI) due to its strong relationship with vegetative productivity, elevation, temperature, precipitation, and soil characteristics (Zhang et al. 2009; Pettorelli et al. 2011), which have associations to CWD distribution. Enhanced vegetation index also corrects for soil and atmospheric interferences, and remains sensitive to canopy-structured evapotranspiration (i.e., forested land cover types; Huete et al. 2002, Horning et al. 2010, Pettorelli 2013). We collected EVI data at 250 meter spatial resolution and 16-day temporal resolution from the MODIS sensor in NASA's Terra satellite (Didan 2015; Busetto and Ranghetti 2016). We collected EVI data from 2005 to 2019, assuming CWD circulation at least four years before the first detected case in Virginia (i.e., 2009), which corresponds to the maximum incubation period in white-tailed deer (Williams 2005).

Landscape data preparation

Spatial models in general are affected by the study area extent, and should be meaningful in the context of the focal species (Barve et al. 2011). Thus, we confined the case study area based on the estimated movement potential (i.e., possible area accessible) of CWD reservoirs (Poo-Muñoz et al. 2014). More specifically, we used dispersal (i.e., permanent movement away from a place of origin) due to its role in extreme bouts of deer movement (Oyer et al. 2007). Because the maximum dispersal distance observed for white-tailed deer in Mid-Atlantic US is 45 km (Long et al. 2005), we used this distance as a radius around CWD-positive cases, and took

the dissolved union of circular buffers to define the extent of the study area (Fig. 3.2). Next, we averaged individual 16-day rasters to monthly pairs to reduce gaps in data caused by cloud obstruction and cropped rasters to the study area extent (Fig. 3.3A).

We performed principal components analysis (PCA) on the EVI raster data to reduce multicollinearity and dimensionality (Fig. 3.3B). Principal components analysis ensures orthogonality in predictor variables by normalizing and transforming correlations found within data into new dimensions called principal components (PCs), which summarize both magnitude and direction of variance by generating eigenvalues and eigenvectors, respectively. Principal components differ in the amount of variance they explain, where the first PC explains the majority of variance and subsequent PCs characterize decreasing amounts of variance (Gotelli and Ellison 2013). Based on the long-term nature of the remote sensing data, the PCA resulted in 176 PCs, which were reduced to those deemed statistically significant using the broken-stick method (Jackson 1993). Significance is determined by whether the observed eigenvalues exceed those generated from null theoretical components (Jackson 1993; Barros et al. 2016; Jarvis et al. 2019). The broken-stick methods' reduction resulted in the inclusion of the first four PCs (explaining 67% of total variance) to be used in modeling as rasterized dimensions in environmental space.

Epidemiological data preparation

Our black-box model used a data-driven identification of landscape conditions occupied by CWD cases (n = 88) in environmental space (Qiao et al. 2017). To validate models, we divided data into calibration (model construction) and evaluation (model testing) sets in a 50:50 ratio (Fig. 3.3C). We partitioned data geographically rather than relying on random selection to

avoid artificially inflating models' predictive performance (Radosavljevic and Anderson 2014). By partitioning CWD cases into geographic quadrants using their reported coordinates (i.e., NE = northeast, NW = northwest, SE = southeast, SW = southwest; Fig. 3.2), we reduced spatial autocorrelation by ensuring spatial independence between quadrants used in calibration and evaluation (Muscarella et al. 2014). We tested all six combinations of paired quadrant arrangements.

We investigated two scales from which we extracted landscape data, referred to as Harvest Location and Home Range scales. For the Harvest Location scale, we extracted CWD-associated landscape data from the principal components at the precise reported coordinates of CWD-positive deer for Harvest Location models (Fig. 3.3D). Yet, we assumed that simple harvest locations might fail to encompass the range of landscape conditions that motile white-tailed deer experienced, which could underrepresent CWD-landscape relationships. In the Home Range scale (i.e., named after the area most commonly inhabited for foraging, mating, and parental care; Burt 1943), we constructed buffers of 1.2 km2 surrounding the same coordinates of CWD cases to represent local home ranges (Campbell et al. 2004) to capture a more generalized representation of landscape relationships (Fig. 3.3D). Then, we averaged the PCA raster values found within the buffers constructed to generalize variation at a broader scale, and used these averages at each dimension as landscape data in Home Range models.

Model calibration

We estimated the environmental conditions occupied by CWD infected deer based on detailed delineation of environmental space occupied by cases (i.e., hypervolume), which can then be projected onto geography (Blonder 2018). Hypervolume estimation performance

improves with use of a low number of continuous, uncorrelated variables to avoid constraining its shape (Blonder et al. 2014), making the PCA analysis compatible with this black-box approach of identifying areas of disease transmission risk with only positive cases. We determined the environments occupied by CWD cases using the *hypervolume* package in R (Blonder 2019; R Core Team 2020).

We used the PCA data extracted at the two scales (i.e., Harvest Locations and Home Ranges) from all six possible combinations of paired quadrants to be later evaluated with their complementary evaluation datasets (Fig. 3.3D). We developed hypervolume models with two algorithms: Gaussian kernel density estimation (KDE) and one-class support vector machines (SVM). In general, KDE performs a density analysis in environmental space to delineate areas in the hypervolume model with higher probability given the data available, while SVM uses cluster analysis to fit a boundary around data in environmental space that classifies conditions (i.e., "in" and "out" of the hypervolume) that should be similarly classified, but potentially unobserved (Blonder et al. 2018) (Fig. 3.3E). Both algorithms for hypervolumes delineate environmental conditions where CWD transmission would be more likely, influenced by the parameters for each algorithm (i.e., KDE uses kernel bandwidth, weighting of the data, and quantile threshold; SVM uses smoothing parameter, γ, and error rate, ν) (Blonder et al. 2018). Bandwidth selection in KDE determines how tightly the estimated probability density function fits the data in multivariate space (e.g., small bandwidth values yield high fit to the data). We followed previous efforts supporting the use of smoothed cross-validation to determine KDE bandwidth for four dimensional data (Duong and Hazelton 2005), which also has been reported to reduce predictive error in hypervolumes (Blonder et al. 2018). Additionally, based on DWR's comprehensive surveillance, we allowed even weighting of the data because we assumed each CWD case was

equally probable in describing environmental conditions. We assumed a consistent quantile threshold of 95% ($\alpha = 0.05$) to curtail the KDE probability density to give the hypervolume its shape (Peterson et al. 2011; Blonder et al. 2018). Further, we relied on the default SVM parameters of $\gamma = 0.5$ and $\nu = 0.1$, based on their support found in literature (Blonder et al. 2018). Finally, we projected each of the 24 hypervolumes generated from all quadrant combinations, algorithms, and scales (i.e., six quadrant combinations at two scales for two algorithms) from environmental space onto geographic space (Fig. 3.3F) in the form of risk maps for CWD transmission to evaluate models.

Model evaluation

We evaluated predictive abilities in the 24 hypervolumes by testing the hypothesis that, when projected in the form of risk maps, hypervolume models are predicting CWD transmission in landscapes that were independent of model calibration (i.e., evaluation quadrants) better than a random expectation. For example, when the NE and SW quadrants were used for model calibration, the NW and SE quadrants were used for evaluation, and model predictions would be deemed statistically significant if risk maps for evaluation quadrants appropriately predict risk where known CWD cases have occurred (adopting $\alpha = 0.05$) (Fig. 3.3G). We restricted risk map projections to the quadrants independent of model calibration because model evaluation methods that rely on the quantification of the proportion of areas predicted as "suitable" for high risk (Peterson et al. 2008) would be inherently inflated in model calibration quadrants.

Evaluation methods were specific to type of geographic map generated when projecting hypervolumes. For example, binary outputs (i.e., no risk = 0, risk = 1) were the only option in SVM-delineated hypervolumes due to the nature of classification; however, we selected a fixed

95% threshold to generate binary maps for hypervolumes delineated with KDE. For all binary maps, we used a cumulative binomial probability distribution accounting for the proportion of area predicted as "suitable" for risk and the number of independent occurrence records successfully being predicted by the map (Anderson et al. 2002; Peterson et al. 2011). For model projections of continuous probability from KDE, we used the partial receiver operating characteristic (partial ROC) in the *ntbox* package (Osorio-Olvera et al. 2020). Partial ROC evaluates the relationship between model sensitivity in relation to varying thresholds of proportional area predicted with a user-defined error rate assumed from false-negatives (Peterson et al. 2008). Specifically, we used 500 bootstrapping samples using 50% of the models' complementary evaluation data resampled with replacement, accounting for a 5% error rate in omission presumed from any errors in diagnostic methods. We based model interpretations on ratios between the model's area under the partial ROC curve (AUC) and a null model (AUC=0.50), whereby ratio values greater than one suggest model performance in predicting independent data is better than a random expectation (Peterson et al. 2008).

Uncertainty estimation

To examine whether CWD was occurring in consistent and quantifiable vegetation phenology conditions, we examined variation in hypervolume models from different data availability scenarios as a proxy of uncertainty (Barros et al. 2016; Carmona et al. 2016; Verhoeven et al. 2020). That is, we generated models with different magnitudes of CWD data to determine whether CWD occurred in consistent environmental conditions. This was determined by measuring the change in position and size of hypervolume models relative to changes in CWD data. For both scales (Harvest Locations and Home Ranges), we used a jackknife (i.e.,

leave-one-out) approach by building multiple hypervolume models iteratively removing single occurrence records (i.e., n – 1), which is generally used in statistics to assess model variation and bias (Gotelli and Ellison 2013) (Fig. 3.4A). To assess variation in hypervolume models, we compared all leave-one-out hypervolume models against a model using the full CWD dataset as a baseline. Model comparison was done using the Jaccard similarity index, which calculates intersection of two hypervolume models (i.e., full data vs. leave-one-out) relative to their union, where values of 0 indicate dissimilar models and 1 indicate identical models (Mammola 2019) (Fig. 3.4B). Also, to examine variation in hypervolume model size, we calculated the volume for each leave-one-out hypervolume in environmental space. Finally, leave-one-out hypervolume models were assembled (i.e., averaged) to generate single continuous risk maps at each scale to identify areas where high risk predictions were consistent among all data availability scenarios.

Presence-absence modeling

Addressing our second aim, we examined contrasting landscape determinants between deer samples diagnosed with CWD and those without prion detection. Some geographic locations (i.e., hunting grids) over the study period yielded mixed disease statuses (i.e., spatial and temporal co-occurrence of CWD-positive and CWD negative (i.e., non-detection in the sample suing immunohistochemistry). Given the nature of prions to remain infectious for long periods following deposition from cervid tissues and fluids, and possible imperfect sampling (Conner et al. 2000; Georgsson et al. 2006), we omitted from analyses 92 samples of CWD negative (undetected) cases that also occurred in locations where CWD was detected. Next, we controlled for potential bias in CWD non-detect landscape conditions driven by sampling effort by filtering remaining data to a uniform distribution, ensuring only unique reported coordinates

are used. This resulted in a working dataset for presence-absence model construction containing 1328 samples (i.e., 1240 negatives and 88 positives).

We used reported coordinates of harvest locations from deer samples to extract environmental data from the four principal components (*see Landscape data preparation section above*). These data were used to model the relationship between diagnosed disease status: 1 = CWD-positive, 0 = CWD non-detect) and extracted values from principal components (Aguilera et al. 2006). Specifically, we constructed principal components logistic regression (PCLR) models, which evaluated principal components' relationships with a response variable without concern for multicollinearity influencing models (Aguilera et al. 2006). We developed one PCLR model using the full dataset (i.e., coordinates from all spatially unique locations), and ten PCLR models adjusting for zero-inflation by using a 1:1 ratio of CWD-positive to different sets of CWD negative samples (i.e., 88 CWD non-detect samples). Most CWD-positive cases occurred in the northwestern tip of the state where surveillance becomes jurisdictionally constrained, and CWD non-detect cases were predominant in southern areas relative to most CWD cases (Fig. 3.5). Therefore, purely random selection of CWD non-detects in the 1:1 ratio models would disproportionately under-represent CWD non-detect environmental conditions in northern latitudes. We compensated for this by developing geographic quadrants (Muscarella et al. 2014), and building models such that equal number of CWD-positives and negatives were sampled with replacement from all quadrants (i.e., 22 CWD positives and 22 CWD negatives; Fig. 3.5).

We evaluated models using analysis of deviance and obtaining levels of significance (i.e., *p*-values representing evidence of differences in PCLR models to null models) and coefficients of determination (R^2 values) to identify whether sufficient evidence suggests PCA values' relationship with disease status is not due to chance and to understand the effect sizes of

relationships, respectively. We converted all statistically significant models into pixel-level probability ($\hat{p}$) maps of CWD positivity using the following equation modified from Fletcher and Fortin (2019):

$$\hat{p} = \exp(b_0 + b_1x_1 + b_2x_2 + \cdots b_nx_n) / (1 + \exp(b_0 + b_1x_1 + b_2x_2 + \cdots b_nx_n)) \quad \text{(Eq. 1)}$$

where b_0 is the coefficient for the logistic regression model intercept, b_1 is coefficient for the first principal component raster layer, b_2 is coefficient for second principal component raster layer, etc. x_1 is the first principal component raster layer, x_2 is second principal component raster layer, etc. We complied summary statistics (i.e., mean, standard deviation, range) on the converted probability maps to identify areas with consistently higher probability of CWD positivity.

Results

Under both KDE and SVM algorithms, we found similarly statistically significant predictions of CWD cases according to cumulative binomial probability testing (Table 1). Notably, models were statistically significant at both scales despite the proportion of area projected as suitable being higher in hypervolumes delineated from Harvest Locations (Table 1). When evaluating KDE-delineated hypervolume projections of continuous risk outputs, partial ROC and bootstrapping manipulations identified that most data resampling resulted in models with AUC ratios > 1 in all paired quadrant combinations signifying statistically significant predictive abilities (Fig. 3.5). Hypervolume models calibrated from Home Ranges yielded significantly higher AUC ratios to those from Harvest Locations (μ = 1.318 and 1.305, respectively; $t(5531) = 3.949$, $p < 0.001$). The lowest AUC ratios observed were calibrated with NE and NW quadrants at the Harvest Locations scale, but still had a mean AUC ratio greater

than 1 (μ = 1.1). Nevertheless, this model as a whole did not predict better than random expectation ($p > 0.05$) as > 5% of the AUC ratios from bootstrapping were less than 1 (Fig. 3.6).

Uncertainty estimation

We found considerable Jaccard similarity among hypervolume models with different magnitudes of CWD data (μ = 0.94 for Harvest Locations and μ = 0.95 for Home Ranges; Fig. 3.7A). Still, Jaccard values were variable among iterations of data availability scenarios (i.e., n-1) both within and between scales, where Jaccard values from Home Ranges were significantly higher than Harvest Locations ($t(87) = 3.632$, $p < 0.001$). We also observed differences in calculated volumes in environmental space (Fig. 3.7B). Size (i.e., volume) from models built using Home Ranges were generally smaller in volume ($t(87) = –246.38$, $p < 0.001$) compared to Harvest Locations (Fig. 3.7B). Finally, maps assembled from the leave-one-out hypervolume models revealed areas of consistent predicted CWD transmission risk was heterogeneous across the study area and between scales (Fig. 3.8). In general, mapped hypervolume models delineated with data at Harvest Locations predicted CWD transmission risk across broader geographic areas (Fig. 3.6).

Presence-absence modeling

Results indicated that the majority (60%) of models using a 1:1 ratio of CWD-positives to CWD non-detects were statistically significant ($p < 0.05$) and possessed generally low, but varying degrees of variance explained expressed in R^2 values (range: 0.040–0.107; Table 3.2). Additionally, the model containing the full dataset was statistically significantly different from a null model ($p = 0.008$), but yielded a low R^2 value (0.008). The averaged probability map from

1:1 significant models identified higher relative probability of CWD-positive disease status occurring in central Frederick County, as well as in eastern Loudon County (Fig. 3.9A), with little variation noted in the study area (Fig. 3.9B). These areas of higher probability for positive CWD status appeared consistent even in the lowest range of values observed (Fig. 3.9C); values at the highest range identified widespread high probability (Fig. 3.9D).

Discussion

Predicting where wildlife diseases may occur next is a challenging pursuit that relies on careful collection of predictor variables, epidemiological data, and consideration of the host species' ecology. Here, our black-box analysis demonstrated that using remotely sensed vegetation phenology data alone can predict CWD transmission risk with statistical significance. Furthermore, we highlighted that consideration of the host species' ecology (i.e., home range) and can enhance understanding for a free-ranging wildlife disease. Finally, we showed that incorporating both CWD positive and CWD negative samples in presence absence modeling provides less robust results than presence-only using identical predictor variables.

By using a method that accounts for independent evaluation data and the area predicted with respect to the area available (i.e., AUC ratio), we found strong quantitative support for the use of landscape information to trace CWD transmission risk. We quantified the extent to which CWD could be reliably predicted on the landscape using our data-driven hypervolume models delineated with both KDE and SVM. This was determined using the proportion of areas predicted as risky under both binary and continuous risk projections. We found that models that acknowledged the host species' ecology (i.e., Home Range models) generated significantly different outcomes in performance (i.e., AUC ratios) than those developed from landscape

determinants at Harvest Locations. Specifically, Home Range models yielded higher AUC ratios. We suspect this finding is a result of summarizing the heterogeneity in EVI surrounding each CWD case in a manner compatible with the landscape ecology of chronic diseases.

In the context of CWD in Virginia, our jackknife analysis identified that every CWD case influences the amount of risk predicted. Never reaching a Jaccard index value of 1 could suggest that variation seen in environmental space with new CWD cases could stem from disease non-equilibrium (i.e., CWD current distribution may not be exhausting its potential occupancy of environmental conditions; Pili et al. 2020). Under this finer-population scale, this would not be surprising given the range of landscape conditions that CWD has been identified worldwide (e.g., Scandinavia; Benestad et al. 2016), and the environmental hardiness of prions in general. Results from our uncertainty analysis identify that landscape conditions associated with higher CWD transmission risk have been observed consistently in portions of DMA1 and DMA2, where DWR has conducted comprehensive sampling. Consistently high risk areas distant from known CWD cases could suggest new landscapes for potential CWD establishment assuming host dispersal is plausible, though human-associated movement of infected cervids or tissues still threaten unpredicted areas (Carlson et al. 2018). Notably, we identified EVI variation associated with higher CWD risk consistently in Rappahannock County, which remained outside disease management area delineation during the study period and has seen historically lower surveillance effort relative to neighboring counties within DMAs by the time of the study (μ=6 samples per year from 2007–2019). In light of these results, we suggest that increased surveillance during future harvest seasons, or promoting convenience sampling (e.g., roadkill deer) in risky counties could be prudent for management consideration (Nusser et al. 2008).

The results from our presence-absence modeling identified that adjusting for zero-inflation yielded mixed results in model performance. Pixel-level probability maps from presence-absence models show statistically significant models were generally consistent (i.e., the highest values in rasters were found in mostly identical locations). Interestingly, maps show landscape conditions associated with higher probability for positive CWD diagnosis in different regions from our presence-only modeling. For example, we noted higher relative probabilities for CWD positivity in central Frederick County and eastern Loudon County, and along riparian corridors. We suspect that this finding may be an artifact of predictor variables (principal components raster values) characterizing similar variation (e.g., lower overall signatures of EVI consistent with urbanization or water bodies) proximate to some CWD cases, relative to the broader sampling available for CWD non-detects. Overall, despite revealing a statistically significant relationship, the lowest R^2 value from the "full" dataset relative to models adjusted for zero-inflation indicate that less variance is explained in the full dataset model than the 1:1 models.

The strength of black-box approaches lies in their nature of modeling the disease outbreaks *sensu stricto*, which can elucidate landscape relationships for poorly known diseases in humans and animals. Critical starting points in landscape epidemiology of orthopoxviruses and filoviruses (Pigott et al. 2015; Quiner and Nakazawa 2017) have relied on black-boxes to support public health interventions, for example. Still, despite the unclear ecology of prions in the environment relative to other pathogens (Escobar et al. 2020), we found analysis of CWD epidemics were surprisingly withheld from black-box approaches (see Chapter 2). This is likely related to our finding that landscape ecological approaches in general are historically under-represented in CWD research (Winter and Escobar 2020). Similarly, the use of n-dimensional

hypervolumes have remained largely absent from both landscape ecological and landscape epidemiological research despite their functionality in ecological modeling of species distributions and niches (Blonder 2018).

Our work presents methodology that is novel to CWD and prion diseases in general. Yet we recognize some inherent limitations to our modeling. For example, hypervolume models are data-driven, therefore additional data from new CWD cases could identify different, and possibly improved patterns. Relative to other algorithms (i.e., Maxent), hypervolume algorithms also do not provide strong extrapolation capabilities to landscape conditions outside of the study area. Nevertheless, our methodology selection permits a reduced number of parameters and their respective assumptions compared with approaches (e.g., presence-background). Further, CWD data are reliant on diagnostic tests with sensitivity and specificity noted for false negatives (Haley and Richt 2017), which could clearly influence the results in our presence-absence approach. Although false-negatives in the current dataset are more likely than false-positives (i.e., by DWR ensuring confirmatory diagnostic testing), the solution of using ultra-sensitive diagnostic tests would be unfeasible for extensive sampling. The current data yield patterns that can facilitate management decisions and emphasize the utility of a presence-only modeling protocol. Next, we recognize the assumption of inferring home range sizes surrounding CWD cases for model construction may be simplistic relative to empirical data (e.g., GPS-collaring cervids, integrating demographic differences in home ranges). Clearly, such data demand resources, logistics, and ethical considerations that may be prohibitive, sensitive to seasonality and restricted to finer-scale landscapes, and contradictory to management objectives (e.g., permitting CWD-infected cervids on the landscape to understand changes in home range sizes and dispersal; Edmunds et al. 2018).

Past CWD landscape ecology research utilized numerous, often static data sources for associating disease risk factors (e.g., national land cover datasets, human population densities) (Winter and Escobar 2020). In contrast, our study serves to utilize a dataset spanning over one decade with corresponding high spatial and temporal resolution remote sensing data to predict CWD transmission risk among dimensions of variation in environmental predictors. Our finding of model performance improving from testing broader scale landscape conditions associated with a chronic and cryptic disease (i.e., conditions present in potential home ranges) suggests an avenue for future research. For instance, the occurrence of spatial "outlier" cases in CWD epidemics could possess similar spatiotemporal conditions in environmental space, or landscape models calibrated from harvest locations may harbor bias in landscape relationships similarly found in population-level studies (e.g., prevalence estimates; Conner et al. 2000). We show here that CWD was able to be mapped using tools effective for other infectious diseases, even though CWD is caused by a very misunderstood and poorly known pathogen. Our project shows the capacities of widely available and standardized satellite-derived landscape data to reconstruct CWD transmission risk in free-ranging populations under natural conditions.

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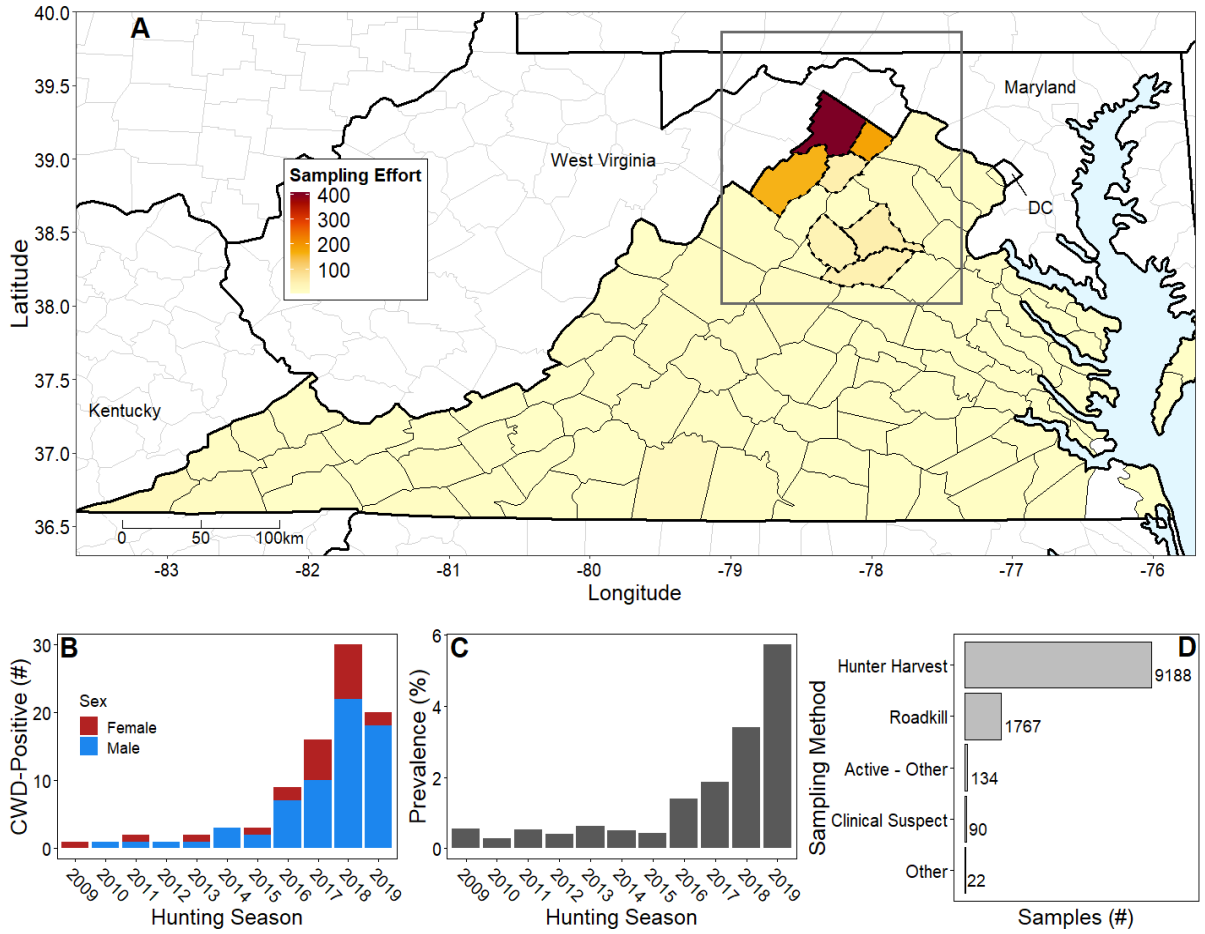

Figure 3.1: Natural history of chronic wasting disease in Virginia, US from 2007 to 2020. A – Virginia county colors represent average annual number of deer samples ranging from: no samples (white) to highest sampling intensity in Frederick County (dark red; ~400 deer per year); mean cumulative number of samples is 143 white-tailed deer per county. In response to CWD detections, DWR increased sampling intensity and delineated disease management areas (dotted county lines). Our case study area (dark gray rectangle) focused on the northern tip of Virginia and portions of Maryland, Pennsylvania, and West Virginia. B – Stacked bar chart shows sex-ratios of CWD positive cases from 2009 – 2019 hunting seasons. The apparent drop in number of cases in 2019 is attributed to reallocation of DWR resources to prioritize sampling in non-CWD endemic counties. C – Bar chart shows prevalence in CWD endemic Frederick County from DMA1 increasing over time. Details of higher prevalence values in some regions are lost due to administrative boundaries. D – Horizontal bar chart shows hunter harvest as the predominant sampling method, followed by testing roadkill and clinical suspect cases.

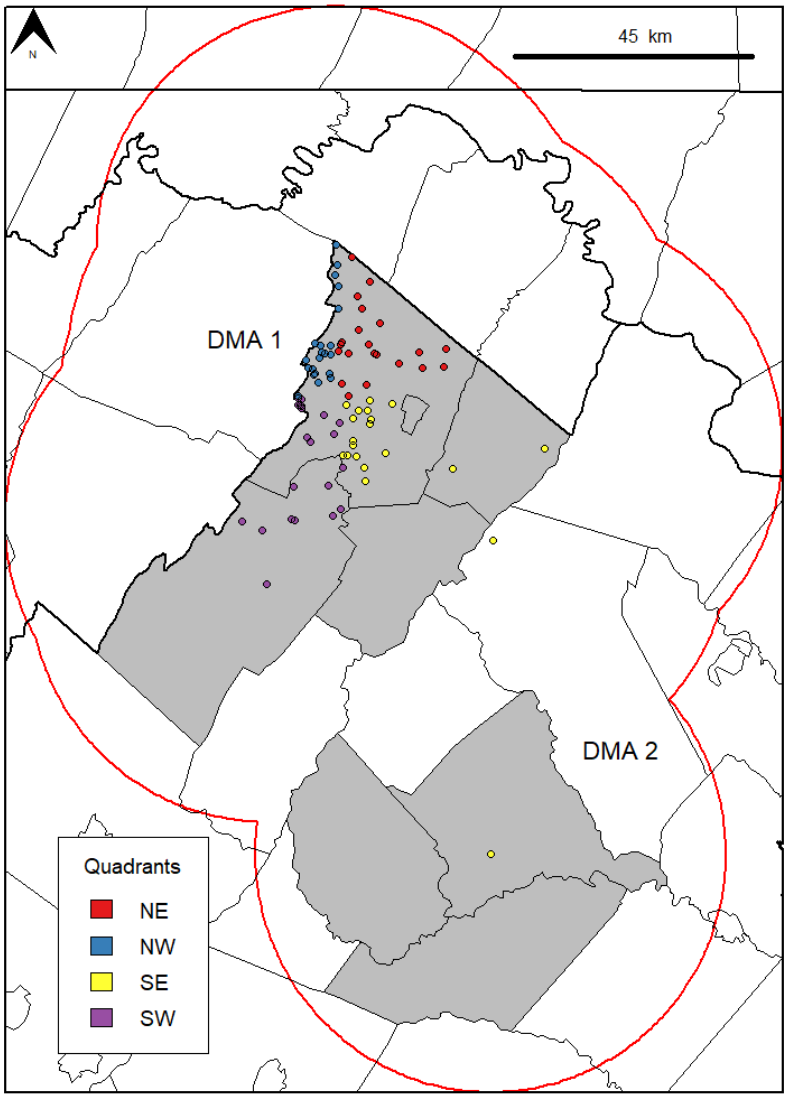

Figure 3.2: Case study area delineation and current CWD distribution. Map shows the study area outline (gray rectangle, as in Fig. 3.1) determined using dissolved buffers (red line) of maximum dispersal distance of deer (45km; Long et al. 2005) around positive cases (circles). Colored circles show quadrant organization of CWD-positives (n=88) used in modeling in Virginia Department of Wildlife Resources Disease Management Areas (DMA) 1 and 2 (gray polygons). This case study area was used for acquiring landscape information (see modeling workflow in Fig. 3.3).

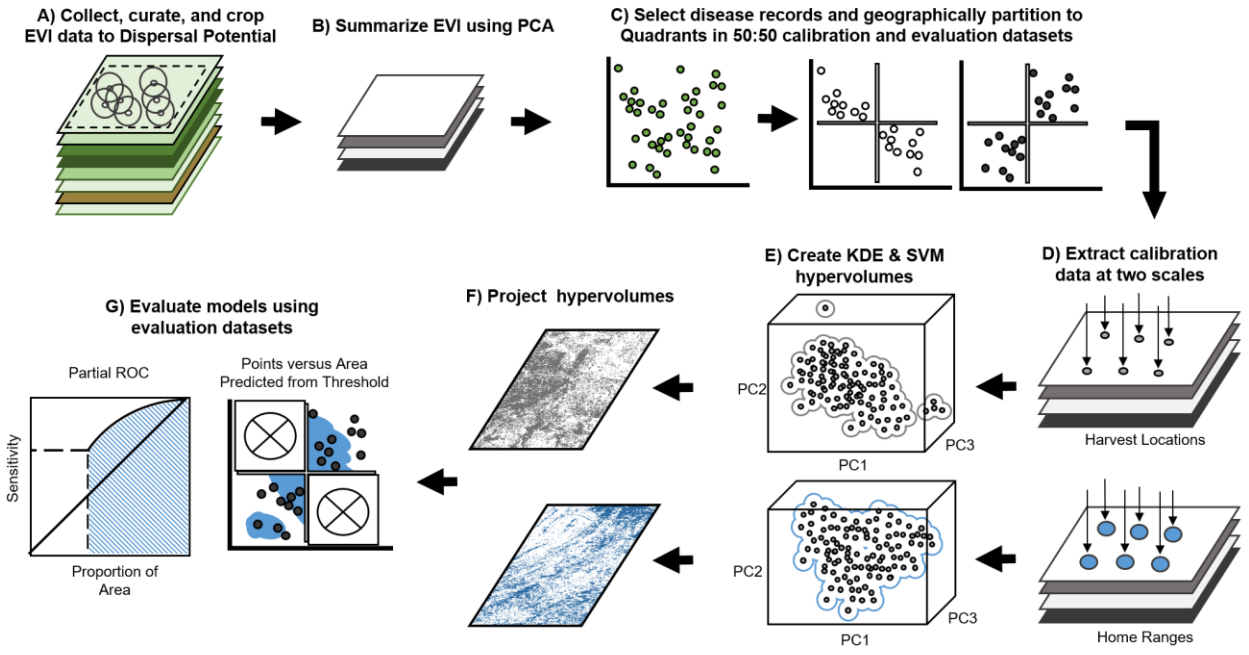

Figure 3.3: Workflow of black-box landscape epidemiology analysis. Workflow displays black-box modeling and evaluation procedure. A – We collected remotely sensed enhanced vegetation index (EVI), and cropped rasters to the extent of the maximum dispersal potential for our focal species as radii about disease records (for details see Fig. 3.2). B – We performed a principal component analysis on the EVI data to reduce multicolinearity and generate dimensions in analysis. C – Next, we selected only disease occurrence locations, and partitioned data into geographic quadrants for calibration and evaluation datasets. D – We extracted data at both Harvest Location and Home Range scales (the latter inferred from focal species' home range size). E – WE developed 24 hypervolumes using Gaussian kernel density estimation and a one-class support vector machine for all six quadrant combinations and both scales. F – Each hypervolume was projected onto geography in the form of binary risk maps, but KDE hypervolumes were additionally projected into continuous risk maps. G – We used models to generate maps of likely CWD transmission risk and evaluated models using methods appropriate for the projection: cumulative binomial probability testing (for binary maps; Anderson et al. 2002) and partial ROC (for continuous maps; Peterson et al. 2008). To more rigorously test models, we penalized suitability inherent to calibration data and restricted each map to evaluation dataset quadrants (represented by "×").

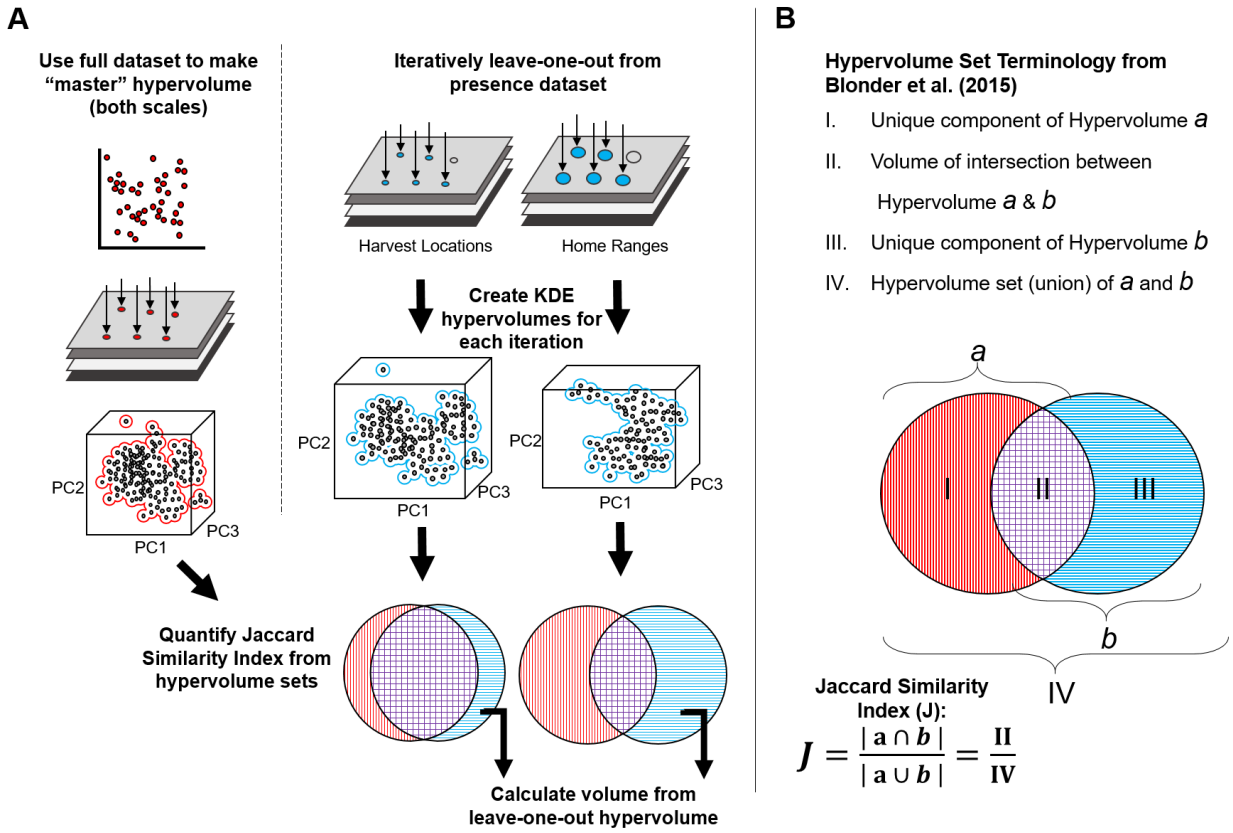

Figure 3.4: Workflow for hypervolume uncertainty analysis. A – Environmental variation determined by iteratively removing one CWD-positive case from total dataset, creating KDE hypervolumes for each iteration and examining overlap between total dataset (n=88) and subset (n=87). B – Key to terminology and equations used in calculating hypervolume overlap statistics including components that comprise Jaccard similarity index, adapted from Blonder et al. (2015).

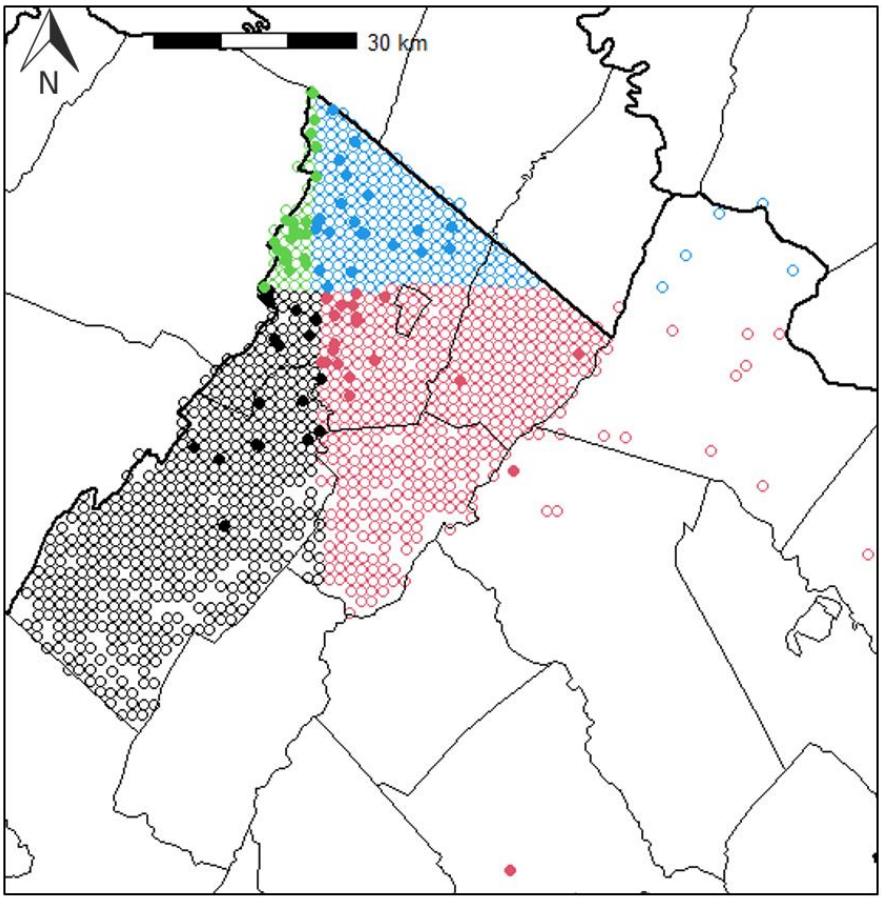

Figure 3.5: Geographic distribution of CWD surveillance. CWD-positive cases (filled circles) cluster in the northwestern-most tip of the state of Virginia, while CWD non-detect cases (hollow circles) were more evenly distributed, emblematic of DWR's comprehensive surveillance. We used geographic quadrants (colors) to evenly partition CWD positives and negatives to avoid under-representing northern environmental conditions.

Table 3.1: Evaluation of binary suitability maps generated from both algorithms under all quadrant and scale combinations. Cumulative binomial testing (following Anderson et al. 2002) use the number of Successes (i.e., number of CWD cases' coordinates that successfully occur within modeled suitable landscapes for transmission risk), Trials (i.e., total number of CWD cases' coordinates being tested from quadrants found in "Testing Quad"), and proportion of the area suitable for transmission risk relative to the overall area to generate significance levels (i.e., *p*-values). Results from models that were delineated using two algorithms: kernel density estimation (KDE) and one-class support vector machines (SVM) can be found within their respective columns. Note that all combinations of quadrants (rows) from data partitioning yielded statistically significant predictions better than by random expectation ($p < 0.05$). Scale specifies whether models were delineated from data at specific *Harvest Locations* (HARVEST) or generalized *Home Ranges* (RANGE), which describe conditions from the exact reported locations that hunters harvested deer, or conditions within a home range buffer surrounding these locations.

Calibration Quad.[1]	**Evaluation Quad.**	**Scale**[2]	**Successes**[3]		**Trials**[4]	**Proportion of Suitable Area**		***p*-value**	
			KDE	*SVM*		*KDE*	*SVM*	*KDE*	*SVM*
NE and NW	SE and SW	HARVEST	38	19	44	0.675	0.167	0.001	<0.001
NE and SW	NW and SE	HARVEST	40	21	44	0.707	0.251	<0.001	<0.001
NE and SE	NW and SW	HARVEST	42	17	44	0.711	0.234	<0.001	0.007
NW and SW	NE and SE	HARVEST	38	27	44	0.767	0.260	0.038	<0.001
NW and SE	SW and NE	HARVEST	41	21	44	0.715	0.208	<0.001	<0.001
SW and SE	NW and NE	HARVEST	44	22	44	0.710	0.289	<0.001	<0.001
NE and NW	SE and SW	RANGE	35	10	44	0.458	0.070	<0.001	<0.001
NE and SW	NW and SE	RANGE	33	15	44	0.527	0.147	0.001	<0.001
NE and SE	NW and SW	RANGE	34	13	44	0.495	0.127	<0.001	<0.001
NW and SW	NE and SE	RANGE	36	20	44	0.599	0.176	0.001	<0.001
NW and SE	SW and NE	RANGE	34	12	44	0.443	0.111	<0.001	<0.001
SW and SE	NW and NE	RANGE	34	13	44	0.467	0.133	<0.001	0.001

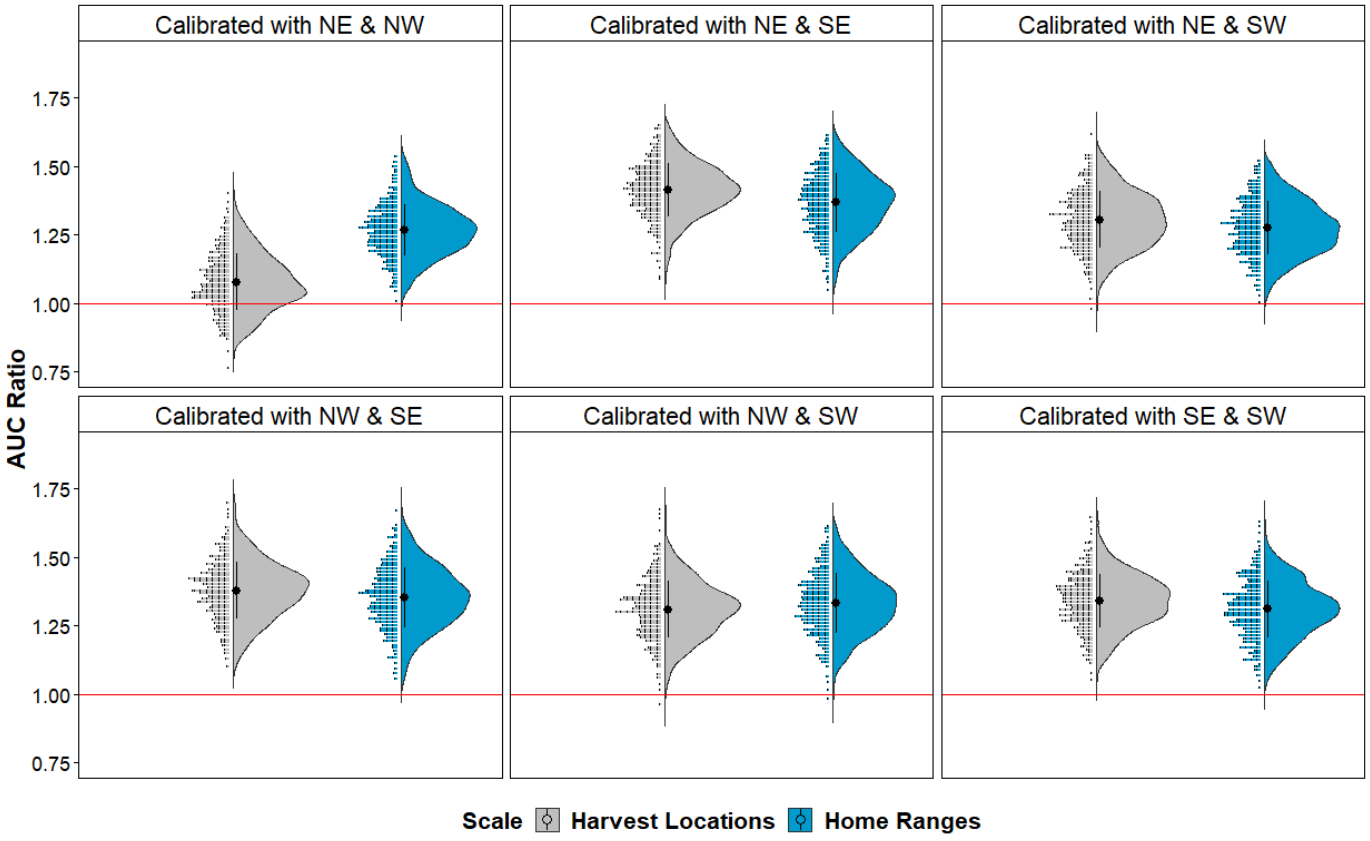

Figure 3.6: AUC ratio evaluation from partial ROC of continuous suitability maps in each geographic partition. Model evaluation according to different quadrants configuration used for calibration. Half violin and raw data distribution plots denote bootstrapped AUC ratios obtained from the evaluation quadrants (not used in model calibration) for models based on *Harvest Locations* (gray) and *Home Ranges* (blue). Note that most configurations have AUC ratios > 1, which is above the threshold for random expectation (red line; $p < 0.001$), except for one *Harvest Location* model calibrated with the northeast and northwest quadrants with non-significant predictions ($p > 0.05$). Ribbon abbreviations follow cardinal directions (i.e., NE = northeast, NW = northwest, SE = southeast, SW = southwest).

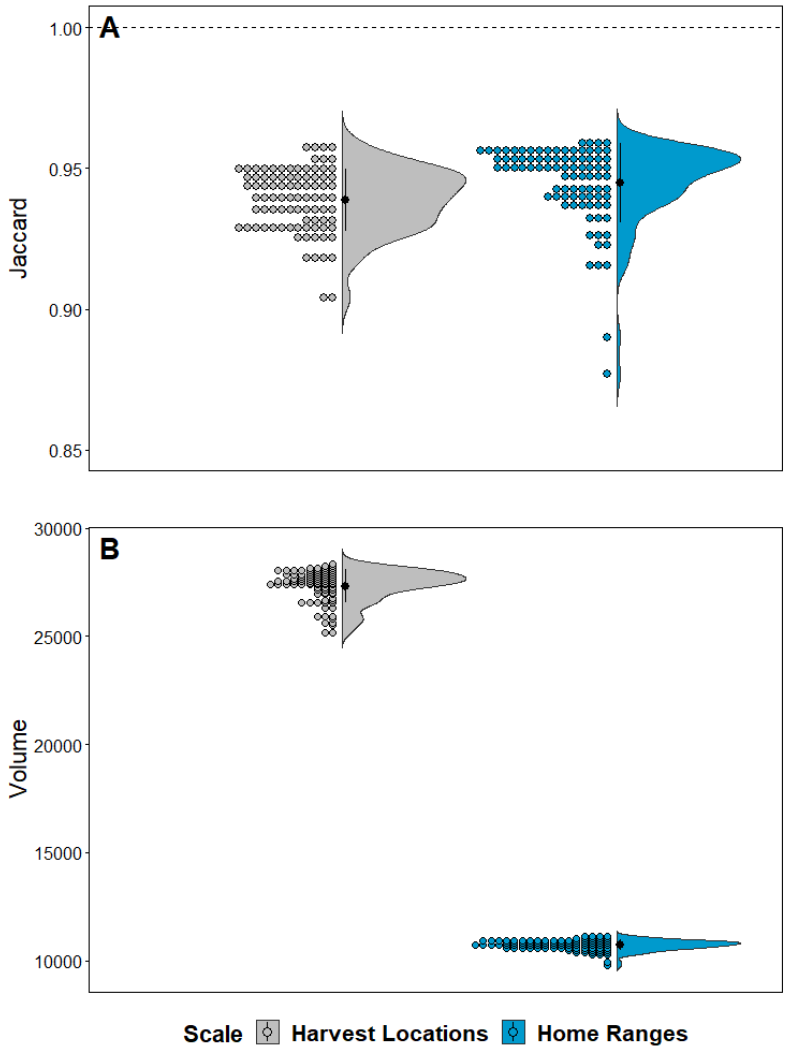

Figure 3.7: Hypervolume variation and characteristics by scale. A – Plots show Jaccard's similarity index between hypervolume sets of the full CWD-positive dataset (*n* = 88) and those created from iteratively removing one occurrence record (leave-one-out). Note that the models never reach a Jaccard similarity index values at 1 denoted with dashed horizontal line, which would indicate complete overlap and identical position and size in environmental space. B – Half violin plots and raw data distribution represent volumes extracted from hypervolumes created from leave-one-out iterations. Colors represent the scale for whether models were delineated from data at *Harvest Locations* (gray) or *Home Ranges* (blue). Note that hypervolumes from *Home Ranges* generally occupied smaller volumes in environmental space despite equal sample sizes.

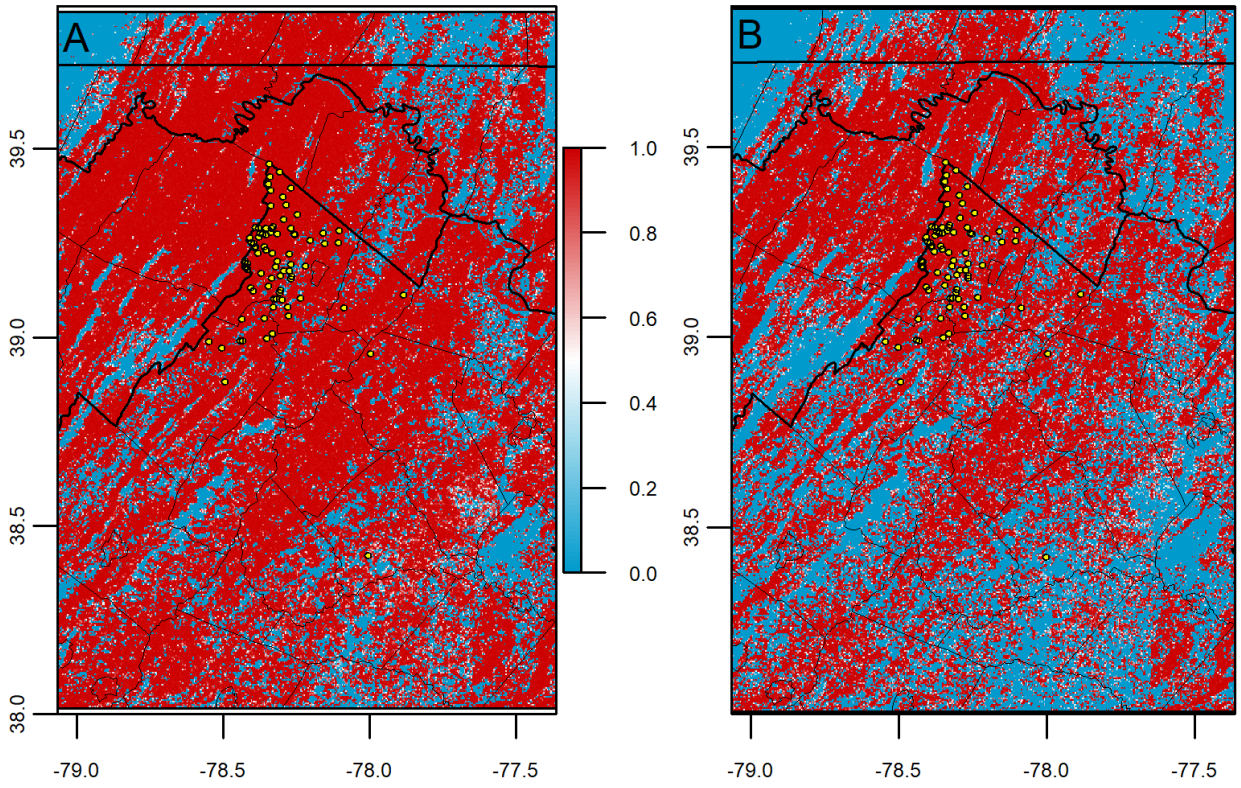

Figure 3.8: Maps of projected CWD transmission risk from variation analysis. Risk maps identify areas determined with more (red) or less (blue) consistent risk for CWD transmission from jackknife analysis. We found more homogenous and widespread transmission risk being consistent among models using A – *Harvest Locations* compared to B – *Home Ranges*. Note counties with considerable transmission risk include Rappahannock County. Lines indicate boundaries of states (thick white) and counties (thin white), while points (white circles) represent known CWD cases (n = 88). Overall, the amount of area predicted as consistently risky was higher in models generated from *Harvest Locations*.

Table 3.2: Evaluation results for presence-absence principal components logistic regression models. First ten models used an equal weighting of CWD-positive and non-detect cases, while the final "Full" model used all spatially unique absences (n = 1240) with presences (n = 88). Statistically significant models are denoted with an asterisk (*). Coefficients for determination (R^2) were generally low for all models, but more pronounced in the model using full dataset.

Model	***p-value***	***R^2***
1	0.112	0.042
2	0.066	0.046
3	0.028*	0.059
4	0.020*	0.061
5	0.018*	0.059
6	0.012*	0.071
7	0.109	0.040
8	<0.001*	0.107
9	0.067	0.046
10	0.021*	0.063
Full	0.008*	0.008

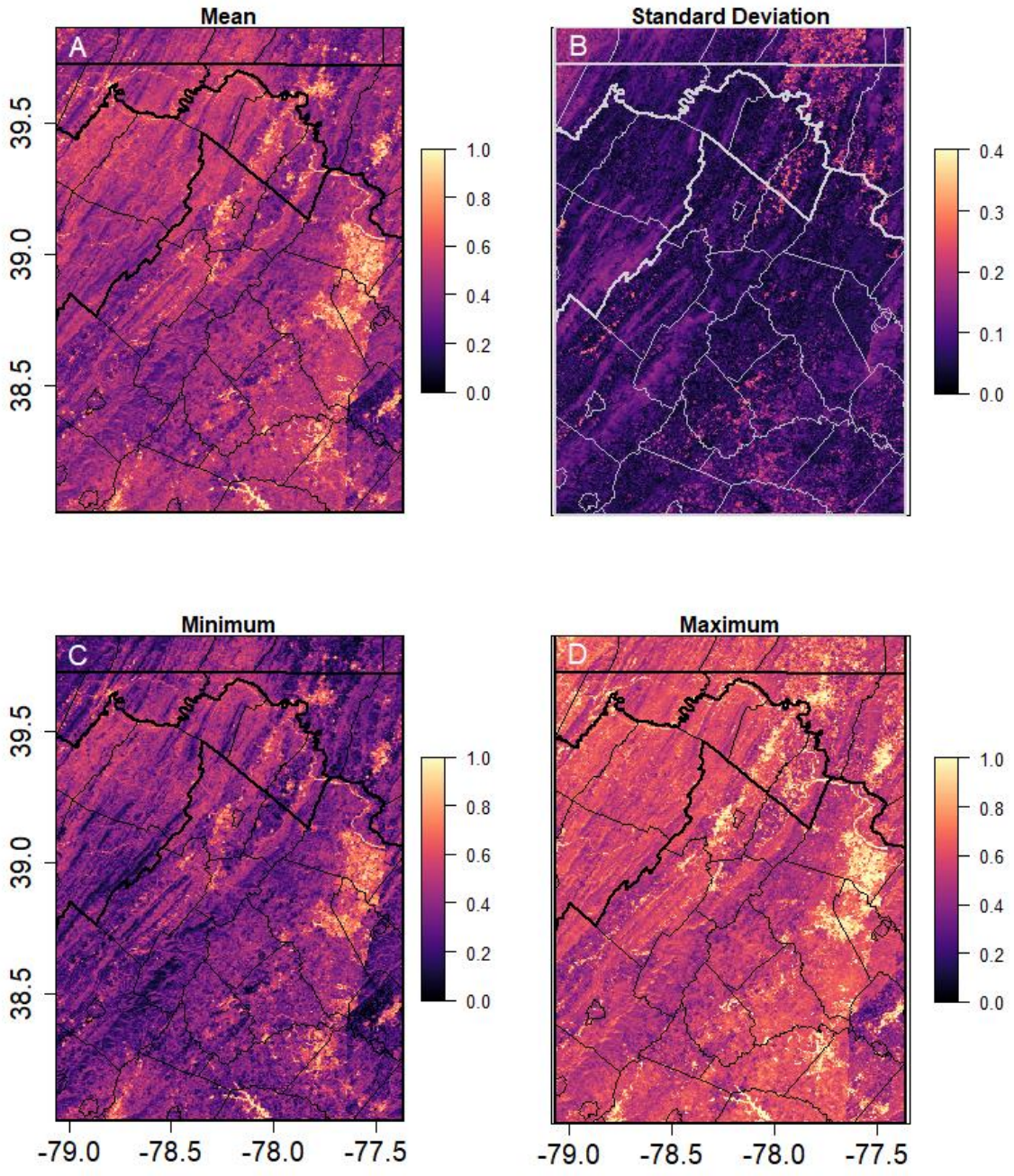

Figure 3.9: Maps showing summary statistics of probability of CWD positivity from statistically significant models adjusted for even weighting of CWD-positive and CWD non-detect cases. A – Mean probability values observed from statistically significant models highlight hotspots of higher relative probability in central Frederick County and eastern Loudon County. B – Standard deviation observed between statistically significant models identify low variation in the northern tip of Virginia. C – Lowest range of values observed in models resemble similar patterns as mean values, albeit with generally lower values ($\mu = 0.378$). D – Higher range of probabilities observed indicate similar areas of highest probability, but otherwise widespread probability greater than 0.5 ($\mu = 0.589$).

CHAPTER 4: LANDSCAPE CONNECTIVITY AND CHRONIC WASTING DISEASE CASES IN VIRGINIA: POTENTIAL FOR SPREAD

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Abstract

In wildlife, landscape connectivity often facilitates disease spread, as evidence suggests is the case for the emerging neurological prion disorder called chronic wasting disease (CWD). Electrical circuit theory has been be adapted for ecological purposes as a widely-regarded tool for understanding landscape connectivity, and identifying areas where movement between locations of interest are more likely. Recent research validated the use of species distribution model outputs to complement other methods used in inferring landscape resistance to movement, such as individual deer movement data or genetics. Thus, in this chapter, we utilized hypervolume model outputs from Chapter 3 to calibrate circuit theory models testing different assumptions of risk-delineated resistance to CWD spread. We examined connectivity between known cases of CWD-positive white tailed deer (*Odocoileus virginianus*) between established disease management areas in the northwestern portion of Virginia, USA. In an additional practical application, we also examined statewide connectivity between known CWD areas and a recently established and susceptible elk population (*Cervus canadensis*) located in southwestern Virginia. Our results indicate there were few barriers to connectivity between most known CWD cases in Virginia, though pathways for spread in distant cases become less clear given the data available. Model outputs varied among different transformation functions used in both disease management area- and statewide-level study areas. Our local connectivity models complement recent broader scale research focusing on connectivity between deer populations in the Mid-Atlantic CWD cluster (Maryland, Pennsylvania, Virginia, and West Virginia). Models serve as an initial attempt in relatively fine-scale population connectivity modeling, and thus, caution should be exercised when interpreting results from statewide analyses. Nevertheless, our work highlights important trends that may be useful for managers in controlling an invariably fatal disease of free-ranging cervids.

Introduction

Anthropogenic land use change has resulted in ever-increasing landscape fragmentation, disruption of natural processes (e.g., migration; Berger et al. 2006), and division of wildlife populations (Hilty et al. 2019) for which conservation of high priority areas for connectivity is critical (Grafius et al. 2017; Dickson et al. 2018). Paradoxically, landscape fragmentation can both promote infectious diseases in some systems (Allan et al. 2003), and impede host and

parasite movement, resulting in reduced disease spread aligning with conservation efforts (Huang et al. 2015). For example, creating adaptive barriers to disrupt connectivity and halt disease spread to susceptible populations has been proposed by managers to control chronic wasting disease (CWD), a neurodegenerative disease in deer species (Williams and Young 1980; Mysterud et al. 2020). Distributed worldwide, CWD is caused by a pathogenic and misfolded protein, called a prion (Williams and Young 1980; Prusiner 1982). Despite the contagious and fatal nature of CWD, promoting fragmentation begets additional concerns for wildlife (e.g., genetic bottlenecking), and understanding how focal species respond to barriers on the landscape is imperative (Mysterud et al. 2020)

Currently no method is regarded as a "silver bullet" for modeling disease connectivity because understanding disease spread across landscapes depend on focal species and populations and quality and amount of data available to researchers (Zeller et al. 2012). For example, landscape genetics studies often assume similarity in genetic structures from sympatric or interconnected populations, while observed heterogeneities are inferred as potential presence of barriers to dispersal, and thus pathogen spread (Biek and Real 2010). While there are benefits from empirical landscape genetics approaches, such as defining trends in allelic structures among populations, resources required for sampling and genotyping populations may be potentially prohibitive for managers. Further, these studies require careful interpretation because animal movement and gene flow have been noted to be non-synonymous (Spear et al. 2010). Ecological diffusion models are another method useful for understanding disease spread. In general, diffusion models use random walks to model stochastic movements of populations across the landscape, and can provide detailed spatiotemporal forecasts of biological processes (Okubo and Levin 2001). Random walks in diffusion models require calibration using imported or observed

motility and transmission coefficients to estimate rates of pathogen diffusion in discrete time (Garlick et al. 2011; Hefley et al. 2017a). Diffusion models can be useful in ecological contexts (Okubo and Levin 2001); yet, such detailed parameterizations and intensive computations often require simplification of landscapes and theoretically-derived values (Garlick et al. 2011), which are generally not available for poorly understood wildlife diseases.

Circuit theory is a widely-regarded connectivity modeling method that relies on principles from electrical circuit theory to model movement across gradients of resistance inferred from landscape features (McRae et al. 2008). In circuit theory, effective resistance coefficients are derived through matrix selection functions to create a two-dimensional raster as proxy of a circuit (McRae et al. 2008). Then, electrical nodal analysis from Kirchhoff's and Ohm's laws passes current (i.e., simulated animal movement via random walks) simultaneously between nodes (i.e., sources and destinations of interest for which connectivity is examined). Simulated random walks travel through resistance-defined raster cells in matrix form and observed current between each pair of nodes are recorded to identify all general pathways between them (Shah and McRae 2008). Software created for circuit theory modeling (e.g., Circuitscape; McRae et al. 2009) records observed currents across raster cells, where high cumulative current density indicate a higher relative probability of a random walker passing through the cell, therefore emphasizing the cell's importance in connectivity (Dickson et al. 2018).

While conceptually simple, circuit theory approaches are critically dependent on understanding how to infer resistance values from different landscape features, which can be a complex task. For example, although common, inferring resistance values from expert opinion has been exceedingly cautioned against due to lower performance and mixed results across

studies (Zeller et al. 2012; Reed et al. 2017). Alternatively, empirical resistance surface creation has historically relied on genetic data from which relationships are based using allelic structures (i.e., isolation by distance using pairwise Fst values; McRae 2006) and fine-scale movement data generated from collaring individuals (i.e., step selection functions). Additionally, recent work validated using outputs from correlative distribution models for inferring empirical resistance surfaces, whereby suitability is inversely related to landscape resistance (Keeley et al. 2016; Zeller et al. 2018).

In addition to elucidating evolutionary processes and priority areas for biodiversity conservation (McRae et al. 2008; Brodie et al. 2015; Dutta et al. 2016), circuit theory has recently been used to model disease spread critical for wildlife health. For example, circuit theory characterized elevated risk areas for transmission of CWD among white-tailed deer (*Odocoileus virginianus*) and mule deer (*O. hemionus*) in CWD-endemic areas in Canada (Nobert et al. 2016). The landscape ecology of prions remains poorly understood (Winter and Escobar 2020), and modeling studies examining CWD spread through potential connectivity of cervid populations have predominantly used landscape genetics (Blanchong et al. 2008; Robinson et al. 2013; Kelly et al. 2014) and diffusion models (Garlick et al. 2011; Hefley et al. 2017a, 2017b). These models, however, are focused on longer established CWD areas, such as Illinois and Wisconsin, United States (US), where area-specific modeling parameters can be used directly (Winter and Escobar 2020).

In contrast, the contiguous CWD cluster in the Mid-Atlantic US (i.e., Maryland, Pennsylvania, Virginia, West Virginia) remains largely understudied due to its more recent establishment and limited and inconsistent available funding for disease surveillance (Evans et al. 2014; Winter and Escobar 2020). A recent assessment in the Mid-Atlantic cluster identified

landscape connectivity between CWD-affected subpopulations, supporting cervid dispersal as a driver for CWD spread (Miller et al. 2020), which is consistent with other regions (e.g. Colorado and Wisconsin, US and Alberta, Canada; Conner and Miller 2004; Skuldt et al. 2008; Nobert et al. 2016). Nevertheless, connectivity remains unexplored at a finer scale within populations experiencing expansions of CWD outbreaks, as is the case within the state of Virginia (US). The Virginia Department of Wildlife Resources (DWR) has recently documented a stark increase in the magnitude and extent of confirmed annual CWD cases. Previous regional analyses utilized dataset containing significantly fewer data points (i.e., five cases analyzed in Evans et al. 2016). For several years after the initial confirmation of CWD in Virginia in 2009, the disease was only detected in western Frederick County and northwestern Shenandoah County (DWR 2014, 2019). Subsequently, CWD was confirmed in a deer sampled from Culpeper County in November 2018, >70 km southeast from the next geographically proximate case in disease management area 1 (DMA1). In the next deer hunting season after the initial CWD detection in Culpeper County (i.e., late 2019 to early 2020), DWR prioritized sampling in the edge counties of DMA1 (i.e., Clarke, Warren, Shenandoah Counties) and within DMA2 (i.e., Culpeper, Madison, and Orange Counties). In addition to more CWD-positive confirmations in previously established endemic areas, in 2020 new CWD cases were confirmed in two new counties for the first time (i.e., Clarke and Fauquier Counties).

To prioritize CWD surveillance, DWR seeks to understand potential connectivity within and between DMAs; however, fine-scale deer movement and state-wide genetic data of highly admixed Virginia white-tailed deer populations (McDonald and Miller 2004) is absent in Virginia. Therefore, in this chapter we hypothesized that rasters of suitability for CWD transmission risk (Chapter 3) could characterize potential transmission pathways for CWD in

Virginia, but would provide limited clarity on isolated cases due to predicted widespread suitability for prion transmission. We calibrated circuit theory models to understand connectivity between known CWD cases within and between DMAs. Additionally, we provide a practical application modeling connectivity between known CWD areas and a susceptible population of management interest.

Methods

Resistance data

We used correlative distribution models (i.e., hypervolume outputs) that characterized consistent CWD transmission risk to create resistance surfaces for connectivity analysis both within and between DMAs. Due to differences in geographic predictions (i.e., risk areas predicted) and evaluations (i.e., predictive performance), we used both maps of projected hypervolumes generated from an uncertainty analysis, calculated from data extracted at precise locations of harvest and inferred home ranges surrounding harvest locations (i.e., *Harvest Location* and *Home Range* scales; *details in Chapter 3*). The use of correlative distribution modeling outputs to infer resistance across the landscape assumes that pathways between suitable patches have more resistance when separated by unsuitable landscapes, rather than contiguous landscapes of equal or higher suitability (Keeley et al. 2016). These assumptions were expressed through different mathematical functions that transform values of consistent suitability of transmission risk to the inverse of resistance. Specifically, previous work commonly use two negative exponential functions (i.e., referred to as C4 and C8) and one negative linear function (i.e., referred to as negative linear) to describe resistance (Fig. 4.2; Keeley et al. 2016; Zeller et al. 2018). Past research evaluating these functions have found mixed results in which function performs best on independent data. For example, Keeley et al. (2016)

suggested that C4 and C8 perform better for habitat generalist species, while negative linear functions performed better for specialist species with less widespread suitability. In contrast, Zeller et al. (2018) identified that a negative linear function outperformed both C4 and C8 functions when modeling connectivity using correlative distribution models' outputs for a generalist species. Therefore, we transformed the values from hypervolume outputs using all mathematical functions given their mixed results in published literature.

Nodal data preparation

We used DWR's CWD surveillance and monitoring dataset, which contained geographic coordinates for CWD positive cases detected in the state of Virginia (n=88). We rasterized these spatial points to an identical resolution and geographic projection as resistance surfaces. These rasterized points (cells) were used as nodes from which pairwise currents were calculated to understand connectivity.

DMA connectivity modeling

We performed a resistance-based connectivity analysis to estimate potential routes of current between CWD cases that fall within and between DMAs established in Virginia. Specifically, we normalized our risk map projections from both *Harvest Location* and *Home Range* scales (i.e., converted probabilities to a range of values from 0 to 1). Next, we transformed probabilities representing consistent transmission risk to resistance using all three functions described above (i.e., negative linear, C4, and C8). We employed our circuit-based analysis using Circuitscape (version 4.0.5; McRae et al. 2009) called in the R programming environment (R Core Team 2020) to examine pairwise connectivity between CWD cases.

Cumulative (summed) current maps are often used for connectivity model interpretations; therefore, we created the six cumulative (summed) current maps to represent all three transformation functions (i.e., negative linear, C4, and C8) for both *Harvest Location* and *Home Range* scales. Due to all pixels within the study area being used in the circuit and having values, we obtained more probable pathways by selecting the upper 50% quantile of cumulative (sum) current density values, which represent pixels that have more probability of a random walker traveling through them (McRae et al. 2008). Finally, we transformed pathways with log10 to improve visualizations, which is commonly used in connectivity modeling interpretations (Pelletier et al. 2014).

Virginia statewide connectivity modeling

In a practical application, we applied similar methods described in detail in Chapter 3 to a broader study area to encompass the state of Virginia and a susceptible population of elk (*Cervus canadensis*) in Buchanan County. We modeled statewide CWD transmission risk by constructing six support-vector machine (SVM) delineated hypervolumes to represent all combinations of paired quadrants from geographic partitioning of CWD-associated environmental data (Muscarella et al. 2014; Blonder et al. 2018). That is, we created hypervolume models from all paired quadrant combinations (adopting a 50:50 division of data similar to Chapter 3), and projected hypervolumes in the form of binary maps. These binary risk maps were averaged to identify areas that were consistently within SVM hypervolumes.

Next, as above, statewide suitability for transmission risk maps were transformed using all three functions (i.e., negative linear, C4, and C8) to infer resistance. Using these outputs, we examined risk-delineated connectivity between the CWD outbreak in northern Virginia and a

recently established elk population in Buchanan County. To achieve this, we calculated two centroids of minimum convex polygons: one from reported elk locations in Buchanan County (unpublished data; Quinlan and Ford 2020), and the second from all CWD-positive deer in northern Virginia. Centroid points were rasterized as above to be used as nodes in circuit-based connectivity calculations. All analyses were conducted in the native spatial grain from hypervolume risk maps (250 meter spatial resolution) given their predictive abilities identified in Chapter 3. Finally, as above, cumulative (sum) statewide current maps were restricted to the upper 50% quantile of values to obtain more likely pathways, and values were transformed with log10 and used for connectivity modeling interpretations.

Results

Circuit-based connectivity modeling identified considerable current density passing through high risk areas connecting CWD cases in Virginia (Fig. 4.3). Cumulative current maps revealed that pairwise connections between cases were often not directly related to the shortest available Euclidian distance. We found little differences between current maps from *Harvest Location* and *Home Range* scales (Fig. 4.3). The two negative exponential functions yielded different connectivity maps, where the function inferring lower transmission risk with the highest proportional resistance (i.e., C8) generated maps showing little evidence of direct pathways between CWD cases (Fig. 4.4). The other negative exponential (i.e., C4) and the negative linear function generated relatively similar connectivity maps. For all functions, relative to other pairwise connections, we found current density to be lower and more diffuse for distant CWD cases found along the peripheries of DMA1 and within DMA2. We found more clarity for potential pathways when a single pairwise connection was isolated from the overall cumulative current density map (Fig. B1).

Statewide transmission risk maps identified transmission risk throughout Virginia, with some similarities in projected risk found in the northernmost tip of Virginia (Fig. 4.5); however, models more broadly delineated landscapes as "outside" of hypervolumes (seen in black coloration in Fig. 4.5). We found that different transformation functions produced differences in pathways (Fig. 4.5). For example, we noted more concentrated current densities using the C8 transformations, with currents being less clear in the negative linear transformation (Fig. 4.6).

Discussion

Overall, our results indicated that using hypervolume model outputs to infer resistance can identify pathways of connectivity. We found that the different mathematical functions used to infer resistance influenced currents passing between known CWD-positive deer. Similarly, functions' influence were more pronounced in our practical application with a larger study area connecting CWD-affected areas with a potentially susceptible elk population. The results from our study can guide management and surveillance; however, we note some caveats to our results with respect to the pathogenic agent causing CWD.

As expected, we found higher densities of pairwise currents between CWD cases that were more closely arranged, suggesting plausible connectivity and between most CWD cases in Virginia. We observed that currents connecting some CWD cases did not follow the shortest Euclidean distance, indicating some pathways were driven by resistance. The results of our analysis did not clearly identify pathways connecting isolated cases (i.e., cases in the periphery of the DMA1 and the geographically isolated case in Culpeper County); however, CWD cases detected in future surveillance efforts surrounding DMAs may provide insight on pathways.

In congruence with other studies emphasizing the importance of topographic features in CWD spread (Mateus-Pinilla et al. 2013; Robinson et al. 2013), our statewide connectivity

application identified higher current densities falling within valleys and along the interstate I-81 highway corridor. Current pathways were seemingly more pronounced in the C8 transformation in statewide connectivity, opposite of outputs generated in DMA modeling. We note that this is more likely a result of the differences seen in the hypervolume outputs. The statewide hypervolume more broadly delineated landscapes as "outside" the landscape conditions where CWD is currently found. When the C8 function is applied to outputs with a matrix of unsuitability interrupted with patchy areas of suitability, more distinct pathways are created because the least amount of relative resistance is inferred in these rarer highly suitable areas, effectively funneling currents through them. This contrasts with generally more diffuse currents found in the statewide map using the negative linear transformation because there is less resistance being inferred in unsuitable areas.

Connectivity modeling for CWD in the Mid-Atlantic remains in its infancy, with Miller et al. (2020) serving as only published study that focused on CWD transmission between Mid-Atlantic deer populations. In Virginia, Miller et al. (2020) identified two distinct subpopulations through genetic evaluation that appear divided near the I-81 highway corridor (see Figure 1 from Miller et al. 2020), but connectivity between these populations was not explicitly examined. Our analyses complement their work by identifying connectivity within Virginia's CWD outbreak. We found that the I-81 corridor rarely impeded currents passing through, which is likely a result of the coarse resolution and transformation of landscape data (i.e., principal components analysis of 250 meter EVI; Didan 2015).

To date, all approaches examining connectivity for CWD have relied on landscape variables of static seasonality with often correlated predictor variables (Nobert et al. 2016; Miller et al. 2020). In contrast, our DMA connectivity modeling used statistically significant predictions

of CWD risk that were derived from orthogonal variables characterizing long-term variation and seasonality in landscape features (i.e., principal components of EVI) in Chapter 3. Nevertheless, we note that despite serving as practical application of our methods, statewide connectivity maps should be taken with caution with respect to the data-driven nature of our models. That is, projected hypervolume models show limited transmission risk in the southeastern and coastal Virginia. We caution that these results are likely more caused by our limited understanding of CWD. For example, differences in risk could be due to differences in landscape conditions between where CWD cases have occurred and coastal Virginia, rather than these areas being completely inhospitable for prion transmission (i.e., EVI conditions in northern Virginia are presumably just different from the coast). Additionally, we recognize that the resistance model lacks empirical validation; therefore, caution should be taken when interpreting modeling outputs. Presently, connectivity evaluation methods remain in development without consensus (McClure et al. 2016). Nevertheless, common connectivity evaluation practices use secondary locations of known individuals to test paths and corridors against random expectation or using model fit (McClure et al. 2016; Zeller et al. 2018), assuming that either re-captured or new individuals will be present in areas of high current density and high-risk areas (Wade et al. 2015). In the context of CWD, however, hunter harvest-based sampling makes re-locations for movement validation impossible. Finally, we note the assumption of landscape resistance being inversely related to suitability for transmission risk does not explicitly model movement capabilities of the host species, which is more common among resistance-based connectivity modeling (Zeller et al. 2012, 2018). Other than the limited availability of data to inform such models, we intentionally disregarded movement considering this area empirical research remains unexplored. That is, important discrepancies in cervid movement as CWD progresses is currently

unknown in general, much less across different landscape features found in CWD's distribution. This topic, however, has seen attention in the western US (Edmunds et al. 2018) and warrants additional experimentation in more species and regions.

The hardy nature of prions to remain infectious in conditions inhospitable for their hosts (i.e., extreme heat; Jung et al. 2003) may suggest that prion transmission risk is driven by hosts' capacity for movement and prion deposition. These two drivers emphasize the overall importance in understanding connectivity in the context of CWD, cervid hosts, and other wildlife (Escobar et al. 2020). Unfortunately, data required for detailed calibration of movement-related models may depend on observing infected cervids on the landscape, which would clearly undermine management objectives and defy stakeholder interests. Therefore, we suggest that future studies should investigate deer movement in the context of prion disease progression.

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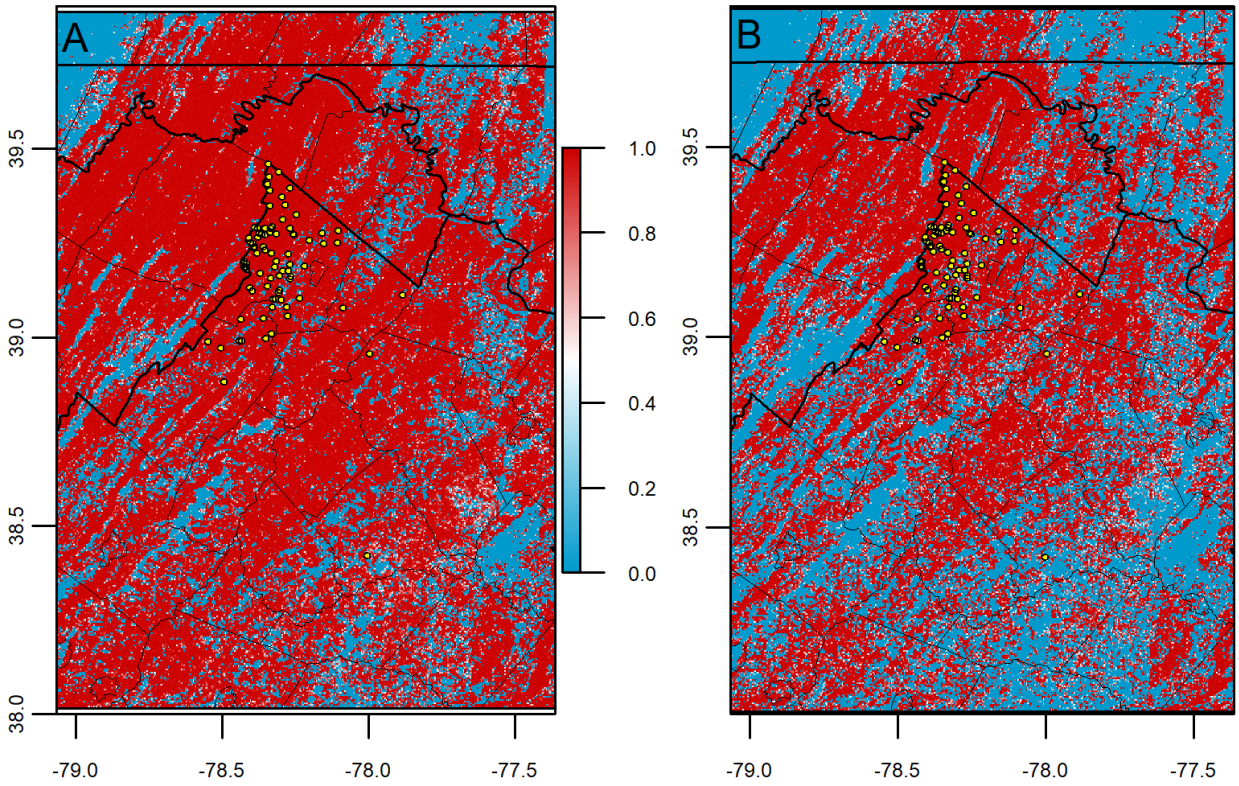

Figure 4.1: Hypervolume risk maps used in DMA connectivity modeling. Risk maps identify areas determined with more consistent probable risk for CWD transmission from jackknife analysis. We found more homogenous and widespread transmission risk being consistent among models using A – *Harvest Locations* compared to B – *Home Ranges*. Note counties with considerable transmission risk include Rappahannock County. Lines indicate boundaries of states (thick white) and counties (thin white), while points (white circles) represent known CWD cases (*n*=88). Overall, the amount of area predicted as consistently risky was higher in models generated from *Harvest Locations*.

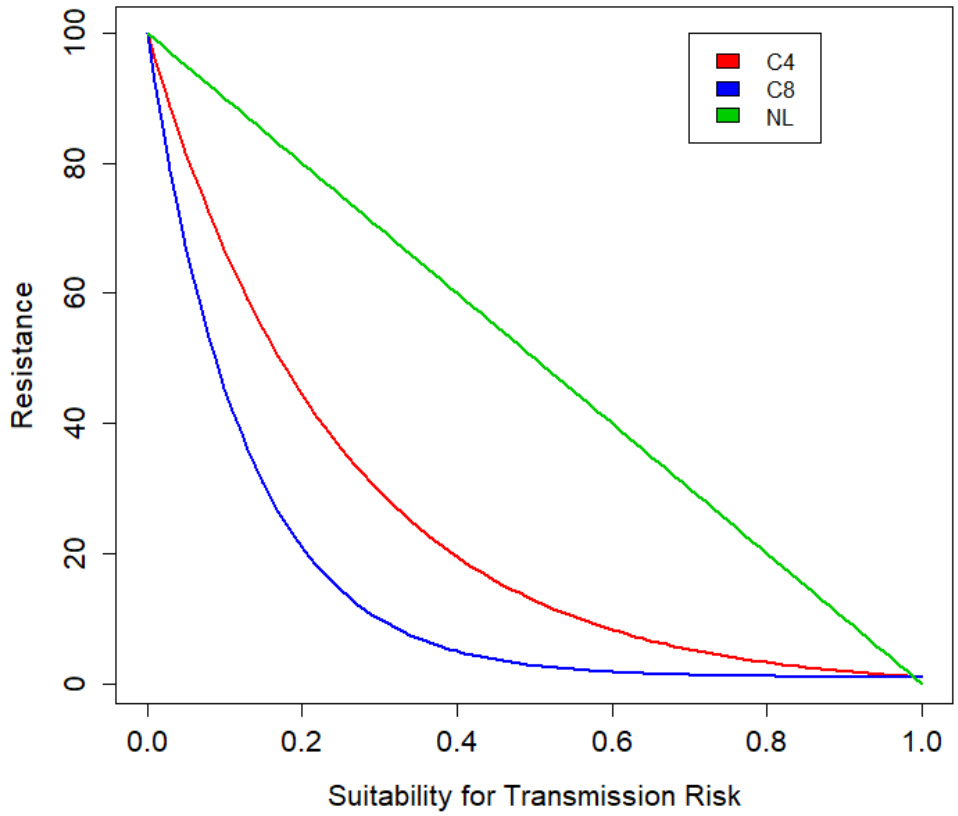

Figure 4.2: Functions used for transforming suitability to landscape resistance. The negative linear function (green line) assumes the simple inverse of suitability is resistance. Negative exponential functions (i.e., C4 and C8 shown as red and blue curves) attribute higher resistance with lower values for suitability in different magnitudes (i.e., Resistance = 100-99*((1 – exp(-C*X))/(1 –exp(-C))), where C corresponds to either 4 or 8 depending on the function and X is are suitability for transmission risk values from correlative distribution modeling (i.e., hypervolume) outputs, reproduced from Keeley et al. (2016) and Zeller et al. (2018).

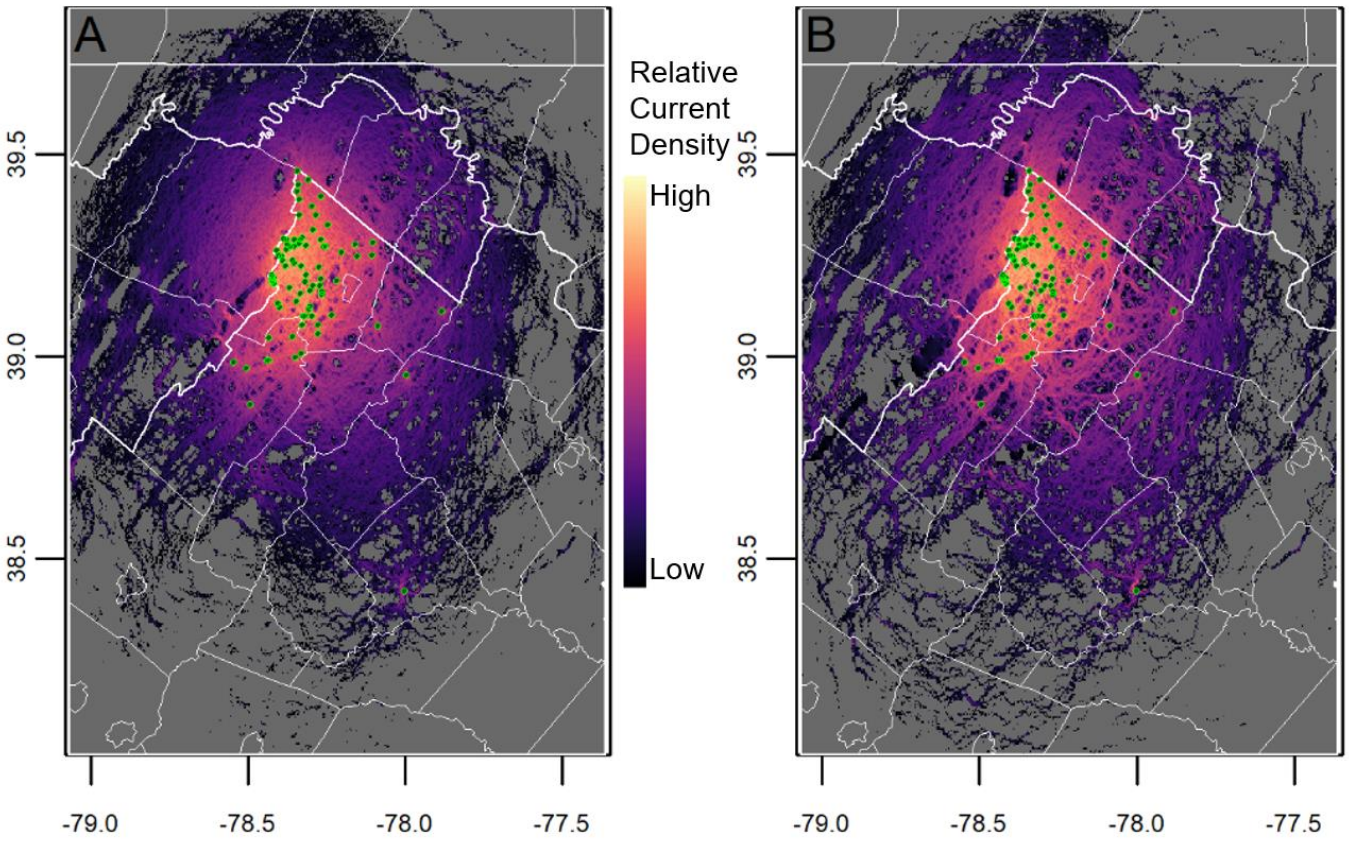

Figure 4.3: Circuitscape maps showing current density between CWD cases**.** Risk values from variation analysis (*see Fig. 5*) were used to infer a negative linear relationship to resistance values for connectivity modeling. We found little differentiation between connectivity models derived from projected CWD transmission risk using A – *Harvest Locations* compared to B – *Home Ranges*. Despite higher relative current density (light pink color) being found between most cases, low current densities were found surrounding many isolated cases (dark purple to black colors). Lines indicate boundaries of states (white) and counties (light gray), while points (green circles) represent known CWD cases (*n*=88).

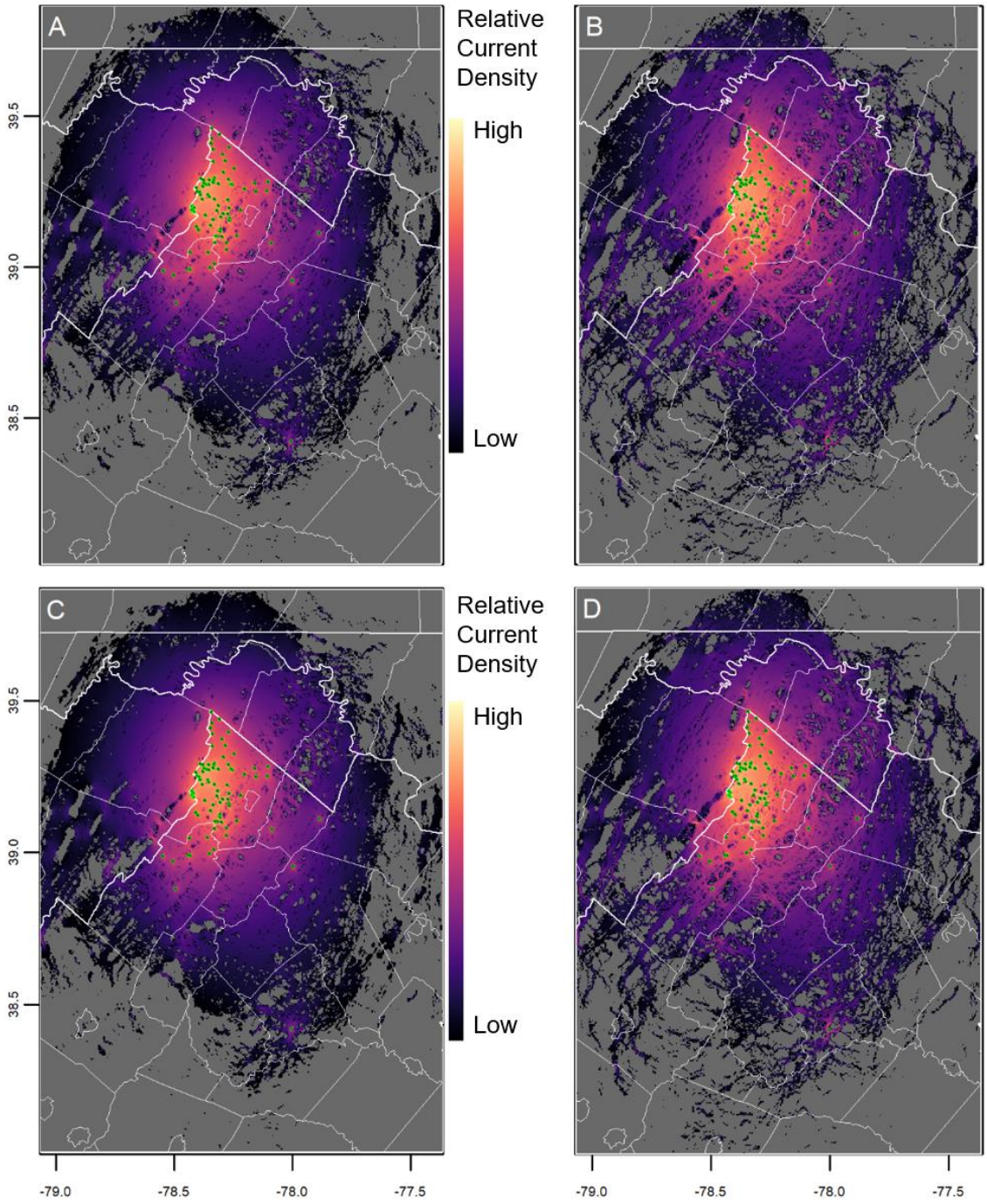

Figure 4.4: Current maps from negative exponential functions between known CWD cases. Panels represent different scales (i.e., *Harvest Locations* and *Home Ranges*) and resistance transformations, following Keeley et al. 2016; Zeller et al. 2018. A – C4 transformation from Harvest Location models; B – C4 transformation from Home Range models. C – C8 transformation from Harvest Location models; D – C8 transformation from Home Range models. Relative to the negative linear function, C4 and C8 infer a stronger negative relationship between resistance and suitability for transmission risk. Current density maps shows high concentrations of current (pink color) passing between most CWD cases (green circles), with differentiation among transformations and scales being noted in less-likely pathways (currents in black coloration) along the periphery of the study area.

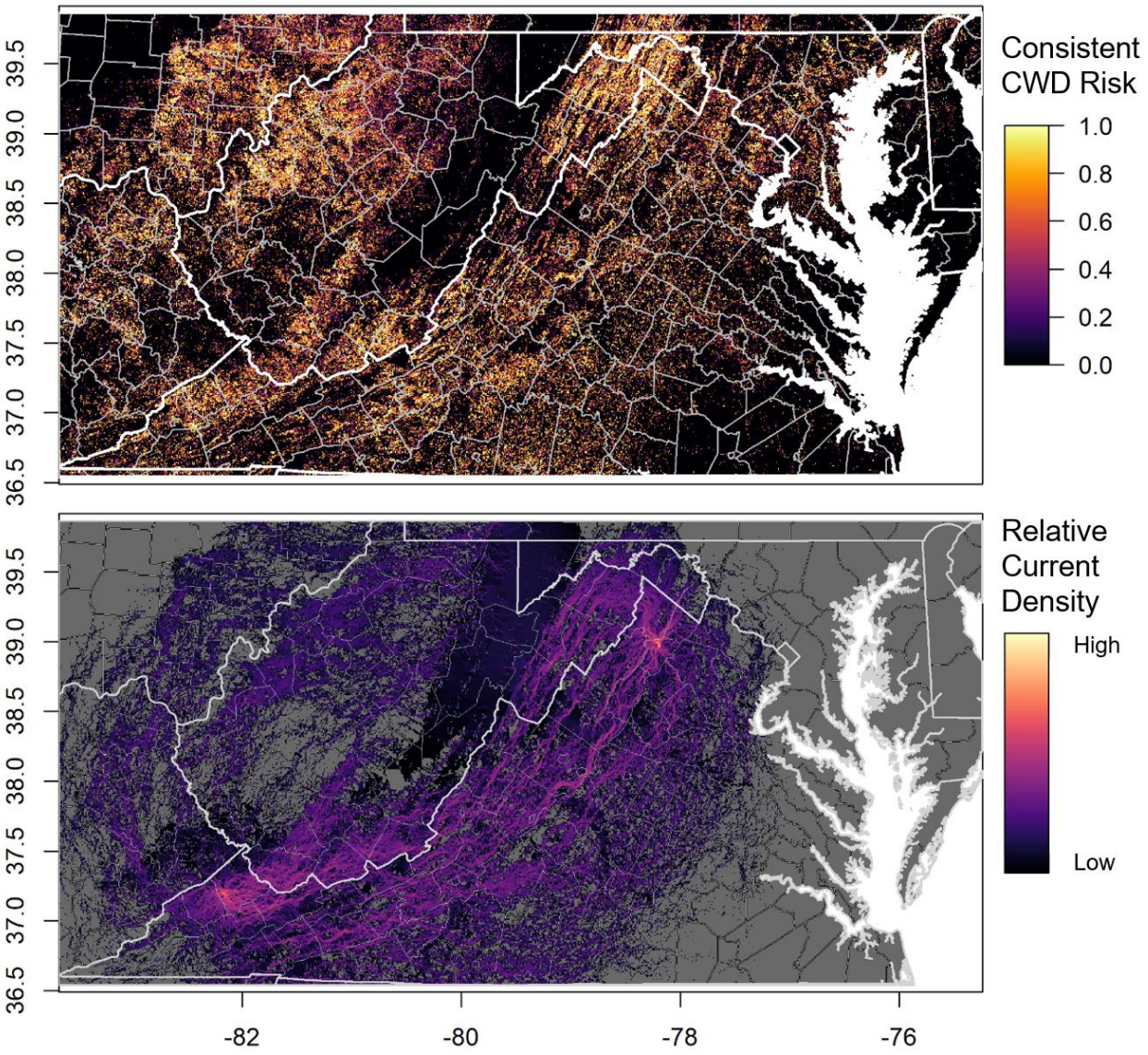

Figure 4.5: Statewide CWD risk map and current density map between CWD areas to elk population. Risk values from SVM analysis (top) were used to infer a C8 transformation to resistance values for connectivity modeling (bottom). We found higher relative current density (light pink colors) in areas near Charlottesville, VA, with low current density (dark purple colors) traveling along coastal Virginia. Lines indicate boundaries of states (white) and counties (gray).

CHAPTER 5: CONCLUSIONS

Steven N. Winter

Studies have identified that CWD prevalence in wild cervid populations can reach upwards of 40-50%, which can reduce population viability by 10-20% (Edmunds et al. 2016; DeVivo et al. 2017; Carlson et al. 2018). Understanding how landscape conditions influence the distribution of CWD is a crucial first step in controlling prions in the environment indirectly transmitting CWD in wild cervid species. Limited information on the role of landscape on CWD spread, however, challenges wildlife managers and disease ecologists (Miller et al. 2004). The importance of the landscape has been emphasized in seldom researched directions examining prion dynamics, where modeling scenarios identified that future population reductions and extinctions could be dependent on the duration of prion persistence in the environment, and should CWD spread remain unabated, management interventions could eventually lose their efficacy (Almberg et al. 2011). Indeed, future research understanding population-level effects of prions remaining infective over time (Georgsson et al. 2006), evading detection both within environments and hosts (McNulty et al. 2019; Kuznetsova et al. 2020), and spreading throughout the ecosystem (Pritzkow et al. 2015, 2018; Escobar et al. 2020) will demand innovative and evolving scientific investigation building upon previous research studying CWD epidemics across space and time. Nevertheless, knowing similarities exist between epidemics in different areas is needed prior to more advanced research.

General gaps in knowledge and discovery of novel tools for surveillance could be particularly important for conservation measures in areas experiencing rampant outbreaks of CWD, such as Virginia (US). In addition to previous efforts reviewing the state of CWD modeling neglecting research performed in the Mid-Atlantic US, they also spared landscape-

level modeling and, instead, focused on population management (Conner et al. 2008; Uehlinger et al. 2016). Thus, the objectives of my thesis were to 1) synthesize and identify trends in the history of CWD modeling research, and 2) elucidate CWD-landscape relationships within the CWD outbreak in Virginia by applying methods from landscape ecology, based on evidence of their success in other ecological systems (Blonder et al. 2014; Nobert et al. 2016).

Chronic wasting disease's documented history began when it was first identified in 1967 in a captive cervid facility in Colorado, and within two decades would be identified in wild herds (Williams and Young 1980; Spraker et al. 1997). My examination of the historical trends in CWD research revealed that the methods by which ecologists understand disease systems (i.e., statistical or mathematical modeling) did not reach published form until the 2000s, but quickly proliferated in the following two decades. Additionally, most researchers concentrated on the effects of the disease in the context of single species, single populations and within a single study area (Winter and Escobar 2020). In fact, investigating the landscape's influence with CWD only began in 2005 (Farnsworth et al. 2005), and received relatively less attention only until recent years (i.e., the mid to late-2010s). Nevertheless, modeling research has generated invaluable findings in understanding the effects of adaptive management tools (e.g., harvest, culling, and selective predation; Wild et al. 2011; Mateus-Pinilla et al. 2013; Manjerovic et al. 2014), and inspires future research in developing corrections for commonly used diagnostic tests and applying broad scale (i.e., biogeographic) analyses to understand continental patterns in CWD spread.

Remote sensing technologies are useful for modeling landscape relationships for many diseases of humans and wildlife (Allen et al. 2017), and my work supports its use for CWD as well. My work directly examined vegetation values that relate to CWD transmission risk at high

temporal and spatial resolutions. Directly using vegetation values builds on previous work that found utility from indirectly using satellite-derived vegetation data in temporally coarse-grained categorical land cover classifications in past CWD landscape modeling (Mateus-Pinilla et al. 2013; Storm et al. 2013; Evans et al. 2016). My work serves the CWD community by showing that satellite-derived vegetation phenology data (i.e., enhanced vegetation index) could serve as another reliable tool in future landscape modeling for CWD. Patterns in landscape conditions within Virginia were quantifiable to the extent that CWD could be predicted using independent data, and used to understand landscape connectivity for characterizing how CWD may have spread. My results can inform state wildlife managers on where locations for CWD check stations warrant reinforcement (i.e., Rappahannock County) either based on having similar landscape conditions associated with CWD transmission risk, or because connectivity modeling identified hypothetical pathways important for concentrating and facilitating disease spread. Management interventions to increase hunter participation are urgently needed in high risk areas because CWD emergence may reduce hunter participation (Erickson et al. 2020), which could lead to even higher CWD prevalences (Miller et al. 2020). Additionally, my results show that to date, CWD has not occurred in identical landscape conditions within Virginia according to different data availability scenarios, which according to theory, would suggest that establishment in new environments may be likely (Peterson et al. 2011). Indeed, CWD establishment in novel environments in Virginia may also have few impediments based on limited evidence for barriers to disease spread between known disease cases.

Finally, my work provokes several future research directions. My identification that models' predictions improved from incorporating aspects of deer ecology, such as home ranges, encourages empirically assessing home ranges in detail for at-risk CWD areas, and within the

context of disease progression. For instance, whether home ranges contract or expand with CWD progression remains barely explored, and only in western US (Edmunds et al. 2018). Also, preliminary research has revealed that landscape connectivity promotes CWD risk in longer-established epidemics (Garlick et al. 2014; Nobert et al. 2016), which was also supported by my identification of little barriers to disease spread between CWD cases in Virginia. Yet, studies collecting empirical (i.e., collared deer) data used to calibrate movement and contact rates predominantly rely on healthy deer and remove individuals once diagnosed as infected (Schuler 2006) in agreement with management objectives. Importantly, studies examining movement-related changes from neurodegeneration found mixed results (i.e., both increased and decreased deer movement) in clinical experiments and more recent field settings (Williams and Young 1993; DeVivo 2015; Edmunds et al. 2018), emphasizing that the movement potential for CWD-infected deer remains unclear. Finally, future CWD research directions in Virginia's outbreak could benefit from characterization of fine-scale deer densities across the state. Current deer density estimates in Virginia are based on harvest of male deer, and are only available at the county level. Present deer density reporting limits our abilities to understand the severity of CWD prevalence in some areas because deer subpopulations are undefined, thus restricting modeling abilities to forecast the efficacy of management interventions (i.e., reducing deer density via harvest or culling). These gaps in research are crucial for estimating rates and potential of CWD spread across the landscape, which will aid in understanding the exposure of other species to CWD-infected deer that may serve as potential vectors for prion movement, predators removing infected hosts, or opportunities for potential prion spillover (Escobar et al. 2020).

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APPENDICES

Appendix A: Scoping study metadata and supplemental figures.

Table A1: Metadata from manuscripts included in this study. Data collected from 79 articles includes article identifiers (such as article title, authors, journal title, and year of publication), epidemiological variables, modeling-associated variables, and characteristics of the data used for modeling.

Article Citation	Variables Assessed[1-6]	Diag. Test[7-10]	Methods[11-20]	Data Origin; Nature of Modeling	Sample Size (Infected : Total) OR Total	Prevalence (NA if # Infected Missing OR Simulation)	State(s) or Province, Country	Major Approach
Miller MW, Williams ES, McCarty CW, Spraker TR, Kreeger TJ, Larsen CT, Thorne ET. 2000. Epizootiology of chronic wasting disease in free-ranging cervids in Colorado and Wyoming. *J Wildl Dis* 36:676–690.	Dem: Sex; Age. Time. Location: Unit (Game). Epi: Prevalence; Transmission; Contact Rate. Life Cycle: Survival, Recruitment	IHC	Diff. Eq./SI Models	Primary; Predictive	145 : 5513	2.6%	Colorado; Wyoming, USA	Population
Conner MM, McCarty CW, Miller MW. 2000. Detection of bias in harvest-based estimates of chronic wasting disease prevalence in mule deer. *J Wildl Dis* 36:691–699.	Dem: Sex; Age. Time. Sampling Method: Harvest. Epi: Prevalence.	IHC	Log. Reg.	Primary; Predictive	74 : 1370	5.4%	Colorado, USA	Population
Gross JE, Miller MW. 2001. Chronic wasting disease in mule deer: Disease dynamics and control. *J Wildl Manage* 65:205–215.	Dem: Sex; Age. Epi: Prevalence; Transmission; Contact Rate. Life Cycle: Mortality; Recruitment; Survival. Control, Mortality, Management: Harvest	IHC	Diff. Eq./SI Models	Secondary; Predictive	1000	NA	Simulation	Population
Wolfe LL, Conner MM, Baker TH, Dreitz VJ, Burnham KP, Williams ES, Hobbs NT, Miller MW. 2002. Evaluation of antemortem sampling to estimate chronic wasting disease prevalence in free-ranging mule deer. *J Wildl Manage* 66:564.	Dem: Age; Populations/Herds. Epi: Prevalence. Sampling Method: Harvest; Cull; Clinical	IHC	Desc. Stats	Primary; Descriptive	64 : 161	39.8%	Colorado, USA	Population
Joly DO, Ribic CA, Langenberg JA, Beheler K, Batha CA, Dhuey BJ, Rolley RE, Bartelt G, Van Deelen TR, Samuel MD. 2003. Chronic wasting disease in free-ranging Wisconsin white-tailed deer. *Emerg Infect Dis* 9:599–601.	Dem: Sex; Age. Location: TRS. Epi: Prevalence. Spatial: Cluster	IHC	Log. Reg.; Spatial scan statistic	Secondary; Both	15 : 476	3.2%	Wisconsin, USA	Population
Diefenbach DR, Rosenberry CS, Boyd RC. 2004. From the field: Efficacy of detecting chronic wasting disease via sampling hunter-killed white-tailed deer. *Wildl Soc Bull* 32:267–272.	Location: GMU. Sampling Method: Harvest. Epi: Prevalence.	NS	Sampling Simulations; Desc. Stats	Primary; Predictive	2-60 : 2000-6000	NA	Pennsylvania, USA; Simulation	Population
Conner MM, Miller MW. 2004. Movement patterns and spatial epidemiology of a prion disease in mule deer population units. *Ecol Appl* 14:1870–1881.	Dem: Age; Populations/Herds; Behavior (Movement). Location: UTM. Time. Epi: Prevalence; Contact Rate. Spatial: Cluster.	IHC	Hierarchical Cluster Analysis; Desc. Stats; Matrix Model	Primary; Descriptive	363	NA	Colorado, USA	Population

Farnsworth ML, Wolfe LL, Hobbs NT, Burnham KP, Williams ES, Theobald DM, Conner MM, Miller MW. 2005. Human land use influences chronic wasting disease prevalence in mule deer. *Ecol Appl* 15:119–126.	Dem: Sex; Populations/Herds. Location. Epi: Prevalence. Landscape: LCT (Urban; Non-Urban).	IHC; ELISA	Log. Reg.	Primary; Predictive	NS	NA	Colorado, USA	Ecosystem
Miller MW, Conner MM. 2005. Epidemiology of chronic wasting disease in free-ranging mule deer: Spatial, temporal, and demographic influences on observed prevalence patterns. *J Wildl Dis* 41:275–290.	Dem: Sex; Age; Populations/Herds. Location: Unit (Game). Time. Epi: Prevalence; Transmission.	IHC; ELISA	Log. Reg.	Secondary; Predictive	470 : 6925	6.8%	Colorado, USA	Population
Krumm CE, Conner MM, Miller MW. 2005. Relative vulnerability of chronic wasting disease infected mule deer to vehicle collisions. *J Wildl Dis* 41:503–511.	Dem: Sex; Age. Location: UTM; Unit (Study). Epi: Prevalence. Landscape: Roads	IHC; ELISA	GLM	Secondary; Predictive	198 : 2488	2.3%	Colorado, USA	Ecosystem
Grear DA, Samuel MD, Langenberg JA, Keane D. 2006. Demographic patterns and harvest vulnerability of chronic wasting disease infected white-tailed deer in Wisconsin. *J Wildl Manage* 70:546–553.	Dem: Age; Sex. Epi: Prevalence.	IHC; ELISA	Log. Reg.; Desc. Stats	Secondary; Both	316 : 21285	1.5%	Wisconsin, USA	Population
Johns CJ, Mehl CH. 2006. A dynamic spatial model for chronic wasting disease in Colorado. *J Data Sci* 4:21–37.	Dem: Behavior (Movement). Location: Unit (Study). Epi: Prevalence; Transmission. Time.	IHC	Hier. Bayes.; Difference Equations; Matrix Model	Secondary; Predictive	25000	NA	Simulation	Population
Farnsworth ML, Hoeting JA, Hobbs NT, Miller MW. 2006. Linking chronic wasting disease to mule deer movement scales: A Hier. Bayes. approach. *Ecol Appl* 16:1026–1036.	Dem: Sex; Age; Behavior (Movement). Location. Epi: Prevalence; Transmission. Spatial: Random Effects; Connectivity. Landscape: LCT (Developed; Undeveloped); CO (Private Land; Habitat)	IHC; ELISA	Log. Reg.; GLM; Hier. Bayes.	Secondary; Predictive	3855	NA	Colorado, USA	Ecosystem
Joly DO, Samuel MD, Langenberg JA, Blanchong JA, Batha CA, Rolley RE, Keane DP, Ribic CA. 2006. Spatial epidemiology of chronic wasting disease in Wisconsin white-tailed deer. J Wildl Dis 42:578–588.	Dem: Sex; Age. Location. Time. Epi: Prevalence. Spatial: Direction/Distance of Spread. Landscape: CO (Forest; Shrubland; Wetland; Agriculture; Grassland).	IHC; ELISA	Desc. Stats; Spatial Scan Statistic; Gaussian Geostatistical Model	Primary; Both	246 : 10678	2.3%	Wisconsin, USA	Ecosystem
Miller MW, Hobbs NT, Tavener SJ. 2006. Dynamics of prion disease transmission in mule deer. *Ecol Appl* 16:2208–2214.	Dem: Density. Time. Epi: Prevalence; Incubation; Contact Rate; Transmission. Life Cycle: Mortality; Recruitment.	IHC	Diff. Eq./SI Models	Secondary; Predictive	Not Specified	NA	Colorado; Wyoming, USA	Population
Conner MM, Miller MW, Ebinger MR, Burnham KP, Applications SE, Jan N. 2007. A meta-BACI approach for evaluating management intervention on chronic wasting disease in mule deer. *Ecol Appl* 17:140–153.	Dem: Sex; Age. Epi: Prevalence. Location. Time. Control, Mortality, Management: Culling; Harvest	IHC; ELISA	Desc. Stats; Meta-analysis; Before-and-After Control Impact (BACI)	Secondary; Descriptive	2414	NA	Colorado, USA	Population

Farnsworth ML, Hoeting JA, Hobbs NT, Conner MM, Burnham KP, Wolfe LL, Williams ES, Theobald DM, Miller MW. 2007. The role of geographic information systems in wildlife landscape epidemiology: models of chronic wasting disease in Colorado mule deer. Vet Ital 43:581–593.	Location. Epi: Transmission; Prevalence. Landscape: Land Use Type (Developed; Undeveloped); CO (Private land; Habitat). Spatial: Connectivity. Dem: Sex; Age; Behavior (Movement)	IHC	Log. Reg.; GLM; Hier. Bayes.	Secondary; Predictive	3855	NA	Colorado, USA	Ecosystem
Nusser SM, Clark WR, Otis DL, Huang L. 2008. Sampling considerations for disease surveillance in wildlife populations. *J Wildl Manage* 72:52–60.	Epi: Prevalence. Sampling Method: SRS; Cull; Harvest; Road-kill. Dem: Density. Time. Landscape: LCT (Agriculture; Forest; Other).	IHC	Sampling Simulations; Desc. Stats	Secondary; Predictive	105 : 7000	NA	Simulation	Ecosystem
Miller MW, Swanson HM, Wolfe LL, Quartarone FG, Huwer SL, Southwick CH, Lukacs PM. 2008. Lions and prions and deer demise. *PLoS One* 3:e4019.	Dem: Age; Sex; Genetics. Epi: Prevalence; Hazard. Life Cycle: Survival. Trophic: Predation	IHC	Log. Reg.	Primary; Predictive	27 : 131	20.6%	Colorado, USA	Mixed
Skuldt LH, Mathews NE, Oyer AM. 2008. White-tailed deer movements in a chronic wasting disease area in south-central Wisconsin. *J Wildl Manage* 72:1156–1160.	Dem: Sex; Age; Density; Behavior (Movement). Epi: Prevalence. Time. Location. Landscape: CO (Forest; Agriculture). Control, Mortality, Management: Harvest	IHC	Log. Reg.; GLMM	Primary; Predictive	5 : 165	3.0%	Wisconsin, USA	Ecosystem
Blanchong JA, Samuel MD, Scribner KT, Weckworth B V, Langenberg JA, Filcek KB. 2008. Landscape genetics and the spatial distribution of chronic wasting disease. *Biol Lett* 4:130–133.	Dem: Genetics. Location: Unit (Study). Epi: Prevalence. Landscape: Roads; Rivers.	IHC; ELISA	Lin. Reg.	Secondary; Predictive	886	NA	Wisconsin, USA	Mixed
Joly DO, Samuel MD, Langenberg JA, Rolley RE, Keane DP. 2009. Surveillance to detect chronic wasting disease in white-tailed deer in Wisconsin. *J Wildl Dis* 45:989–997.	Location: Township; Unit (Game). Epi: Prevalence. Spatial: Aggregation. Sampling Effort. Sampling Method: Harvest.	IHC; ELISA	Sampling Simulations; Desc. Stats	Secondary; Predictive	35080	NA	Wisconsin, USA	Population
Wasserberg G, Osnas EE, Rolley RE, Samuel MD. 2009. Host culling as an adaptive management tool for chronic wasting disease in white-tailed deer: A modelling study. *J Appl Ecol* 46:457–466.	Dem: Age; Sex; Density. Time. Epi: Force of Infection; Prevalence; Transmission. Life Cycle: Fecundity; Survival; Mortality. Control, Mortality, Management: Cull; Harvest.	IHC; ELISA	Matrix Model	Secondary; Predictive	401 : 10065	4.0%	Wisconsin, USA	Population
Osnas EE, Heisey DM, Rolley RE, Samuel MD. 2009. Spatial and temporal patterns of chronic wasting disease: Fine-scale mapping of a wildlife epidemic in Wisconsin. *Ecol Appl* 19:1311–1322.	Dem: Sex; Age. Time. Location. Epi: Prevalence; Transmission. Spatial: Regression; Random Effects.	IHC; ELISA	Hier. Bayes.	Secondary; Predictive	501 : 12164	4.1%	Wisconsin, USA	Population
Song HR, Lawson A. 2009. Space-time Bayesian survival modeling of chronic wasting disease in deer. *Prev Vet Med* 91:46–54.	Dem: Age; Sex. Time. Spatial: Cluster; Random Effects; Regression. Life Cycle: Survival. Epi: Hazard; Prevalence.	IHC; ELISA	Hier. Bayes.	Secondary; Predictive	618 : 65085	0.9%	Wisconsin, USA	Population

Heisey DM, Osnas EE, Cross PC, Joly DO, Langenberg JA, Miller MW. 2010. Linking process to pattern: Estimating spatiotemporal dynamics of a wildlife epidemic from cross-sectional data. *Ecol Monogr* 80:221–240.	Dem: Age; Sex. Location. Spatial: Regression. Time. Epi: Prevalence; Transmission.	IHC; ELISA	Bayesian Spatial Regression; Lexis Diagram; Partial Diff. Eq.	Secondary; Predictive	596 : 13101	4.5%	Wisconsin, USA	Population
Grear DA, Samuel MD, Scribner KT, Weckworth B V, Langenberg JA. 2010. Influence of genetic relatedness and spatial proximity on chronic wasting disease infection among female white-tailed deer. *J Appl Ecol* 47:532–540.	Dem: Age; Sex; Genetics. Time. Location. Spatial: Proximity. Epi: Transmission; Prevalence.	IHC; ELISA	Log. Reg.	Secondary; Descriptive	75 : 1387	5.4%	Wisconsin, USA	Mixed
Dulberger J, Hobbs NT, Swanson HM, Bishop CJ, Miller MW. 2010. Estimating chronic wasting disease effects on mule deer recruitment and population growth. *J Wildl Dis* 46:1086–1095.	Demographics: Age; Behavior (Recruitment). Life Cycle: Recruitment; Survival. Epi: Prevalence.	IHC	Matrix Model	Primary; Predictive	15 : 52	28.8%	Colorado, USA	Population
Lawson A, Song HR. 2010. Semiparametric space-time survival modeling of chronic wasting disease in deer. *Environ Ecol Stat* 17:559–571.	Dem: Sex; Age. Epi: Prevalence; Transmission; Hazard. Life Cycle: Survival. Location. Spatial: Regression; Random Effects.	IHC; ELISA	Hier. Bayes.	Secondary; Predictive	618 : 65085	0.9%	Wisconsin, USA	Population
Walsh DP, Miller MW. 2010. A weighted surveillance approach for detecting chronic wasting disease foci. *J Wildl Dis* 46:118–135.	Dem: Age; Sex. Epi: Prevalence; Incubation. Sampling Effort. Sampling Method: Cull; Harvest; Roadkill; Predation; Euthanasia. Trophic: Predation.	IHC; ELISA	Sampling Simulations; Desc. Stats	Secondary; Predictive	595 : 20400	2.9%	Colorado, USA	Community
Cullingham CI, Merrill EH, Pybus MJ, Bollinger TK, Wilson GA, Coltman DW. 2011. Broad and fine-scale genetic analysis of white-tailed deer populations: Estimating the relative risk of chronic wasting disease spread. *Evol Appl* 4:116–131.	Dem: Sex; Age; Genetics; Populations/Herds. Location. Epi: Prevalence. Spatial: Proximity; Cluster.	NS	Network Model; Moran's I Statistic; Bayesian Clustering; Matrix Model	Primary; Descriptive	47 : 2088	2.3%	Alberta; British Columbia; Sask., CA	Mixed
Cullingham CI, Nakada SM, Merrill EH, Bollinger TK, Pybus MJ, Coltman DW. 2011. Multiscale population genetic analysis of mule deer (*Odocoileus hemionus hemionus*) in western Canada sheds new light on the spread of chronic wasting disease. Can J Zool 89:134–147.	Dem: Sex; Age; Genetics; Populations/Herds. Location. Epi: Prevalence. Spatial: Proximity; Cluster. Landscape: Rivers.	IHC; ELISA	Matrix Model; Moran's I Statistic; Bayesian Clustering	Primary; Descriptive	85 : 2535	3.4%	Alberta; British Columbia; Sask., CA	Mixed
Wild MA, Hobbs NT, Graham MS, Miller MW. 2011. The role of predation in disease control: A comparison of selective and nonselective removal on prion disease dynamics in deer. *J Wildl Dis* 47:78–93.	Epi: Transmission; Prevalence. Life Cycle: Recruitment. Trophic: Predation. Time.	IHC	Diff. Eq./SI Models	Secondary; Predictive	1000	NA	Simulation	Community
Rogers KG, Robinson SJ, Samuel MD, Grear DA. 2011. Diversity and distribution of white-tailed deer mtDNA lineages in chronic wasting disease (CWD) outbreak areas in southern Wisconsin, USA. *J Toxicol Env Heal - Part A Curr Issues* 74:1521–1535.	Dem: Genetics; Populations/Herds. Location. Landscape: Ecoregions. Spatial: Cluster.	IHC; ELISA	Anselin's LISA; Network Model	Secondary; Descriptive	359	NA	Wisconsin, USA	Mixed

Almberg ES, Cross PC, Johnson CJ, Heisey DM, Richards BJ. 2011. Modeling routes of chronic wasting disease transmission: Environmental prion persistence promotes deer population decline and extinction. *PLoS One* 6:e19896.	Epi: Force of Infection; Transmission; Prevalence; Prion Dynamics. Life Cycle: Recruitment; Survival. Time.	NS	Diff. Eq./SI Models	Secondary; Predictive	15000	NA	Simulation	Population
Sharp A, Pastor J. 2011. Stable limit cycles and the paradox of enrichment in a model of chronic wasting disease. *Ecol Appl* 21:1024–1030.	Life Cycle: Recruitment; Mortality. Epi: Prion Dynamics; Prevalence; Transmission.	IHC	Diff. Eq./SI Models	Secondary; Predictive	NS	NA	Colorado; Wyoming, USA	Population
Garlick MJ, Powell JA, Hooten MB, McFarlane LR. 2011. Homogenization of large-scale movement models in ecology. *Bull Math Biol* 73:2088–2108.	Life Cycle: Mortality. Dem: Density; Behavior (Movement). Time. Epi: Prevalence; Transmission. Landscape: LCT (Rock; Scrub; Forest; Grassland; Agriculture; Development; Open Water; Wetlands).	IHC	Diff. Eq./SI Models; Diffusion Model	Secondary; Predictive	38 : 7400	0.5%	Utah, USA	Ecosystem
Robinson SJ, Samuel MD, Johnson CJ, Adams M, McKenzie DI. 2012. Emerging prion disease drives host selection in a wildlife population. *Ecol Appl* 22:1050–1059.	Dem: Sex; Age; Genetics. Location. Epi: Force of Infection; Prevalence; Transmission. Life Cycle: Fecundity; Mortality; Survival. Time.	IHC; ELISA	Hier. Bayes.; Moran's I Statistic; Leslie Matrix Model	Secondary; Predictive	192 : 1119	17.2%	Wisconsin; Illinois, USA	Population
Al-Arydah M, Smith RJ, Lutscher F. 2012. Modeling gender-structured wildlife diseases with harvesting: Chronic wasting disease as an example. *ISRN Biomath* 2012:802450.	Epi: Force of Infection; Transmission; Prevalence; Incubation; Contact Rate. Life Cycle: Mortality; Fecundity; Lifespan. Dem: Sex; Age. Time. Control, Mortality, Management: Harvest.	IHC	Diff. Eq./SI Models; Matrix Model; Latin Hypercube	Secondary; Predictive	120000	NA	Simulation	Population
Blanchong JA, Grear DA, Weckworth B V, Keane DP, Scribner KT, Samuel MD. 2012. Effects of chronic wasting disease on reproduction and fawn harvest vulnerability in Wisconsin white-tailed deer. *J Wildl Dis* 48:361–370.	Dem: Sex; Age; Genetics. Location. Epi: Prevalence. Time.	IHC	Log. Reg.	Secondary; Descriptive	96 : 1798	5.3%	Wisconsin, USA	Population
Rees EE, Merrill EH, Bollinger TK, Hwang YT, Pybus MJ, Coltman DW. 2012. Targeting the detection of chronic wasting disease using the hunter harvest during early phases of an outbreak in Saskatchewan, Canada. *Prev Vet Med* 104:149–159.	Dem: Age; Sex. Location. Epi: Prevalence; Transmission. Sampling Effort. Time. Spatial: Proximity. Landscape: LCT (Agriculture; Forest; Shrubland; Grassland); CO (Cover Type; Ruggedness; Rivers; Roads; Streams; Drainages)	IHC	Log. Reg.; GLMM	Secondary; Predictive	102 : 11932	0.9%	Sask., CA	Ecosystem
Potapov A, Merrill E, Lewis MA. 2012. Wildlife disease elimination and density dependence. *Proc R Soc B Biol Sci* 279:3139–3145.	Dem: Sex; Age. Life Cycle: Recruitment; Survival; Mortality. Epi: Prevalence; Transmission. Control, Mortality, Management: Harvest; Vaccine.	IHC; ELISA	Diff. Eq./SI Models	Secondary; Predictive	NS	NA	Simulation	Population
Storm DJ, Samuel MD, Rolley RE, Shelton P, Keuler NS, Richards BJ, Van Deelen TR. 2013. Deer density and disease prevalence influence transmission of chronic wasting disease in white-tailed deer. *Ecosphere* 4:1–14.	Dem: Age; Sex; Density. Location. Epi: Prevalence; Transmission. Landscape: CO (Soil Characteristics ; Forest; Edge)	IHC; ELISA	Log. Reg.; Moran's I Statistic	Secondary; Predictive	95 : 3901	2.4%	Wisconsin, USA	Ecosystem

Matsumoto T, Samuel MD, Bollinger T, Pybus M, Coltman DW. 2013. Association mapping of genetic risk factors for chronic wasting disease in wild deer. *Evol Appl* 6:340–352.	Dem: Sex; Age; Genetics. Location.	IHC; ELISA	Log. Reg.; Bayesian Clustering	Secondary; Predictive	192 : 376	51.1%	Wisconsin, USA; Sask., CA	Population
Cortez MH, Weitz JS. 2013. Distinguishing between indirect and direct modes of transmission using epidemiological time series. *Am Nat* 181:E43–E52.	Epi: Transmission; Contact Rate; Prevalence; Prion Dynamics. Time. Life Cycle: Mortality; Recruitment; Fecundity. Dem: Density.	IHC	Diff. Eq./SI Models; Latin Hypercube	Secondary; Predictive	NS	NA	Simulation	Population
Potapov A, Merrill E, Pybus M, Coltman D, Lewis MA. 2013. Chronic wasting disease: Possible transmission mechanisms in deer. *Ecol Model* 250:244–257.	Dem: Density; Sex; Age. Life Cycle: Mortality; Recruitment. Epi: Force of Infection; Prevalence; Transmission; Prion Dynamics. Control, Mortality, Management: Harvest. Time.	IHC	Diff. Eq./SI Models	Secondary; Predictive	NS	NA	Alberta, CA	Population
Mateus-Pinilla N, Weng HY, Ruiz MO, Shelton P, Novakofski J. 2013. Evaluation of a wild white-tailed deer population management program for controlling chronic wasting disease in Illinois, 2003-2008. *Prev Vet Med* 110:541–548.	Dem: Sex; Age. Time. Sampling Effort. Epi: Prevalence. Control, Mortality, Management: Cull; Harvest; Roadkill; Other. Landscape: CO (Terrain; Soil Characteristics; Forest; Human Population Density)	IHC	Log. Reg.; GLMM	Secondary; Descriptive	226 : 14650	1.5%	Illinois, USA	Ecosystem
O'Hara Ruiz M, Kelly AC, Brown WM, Novakofski JE, Mateus-Pinilla NE. 2013. Influence of landscape factors and management decisions on spatial and temporal patterns of the transmission of chronic wasting disease in white-tailed deer. Geospat Health 8:215–227.	Time. Location: TRS. Dem: Sex; Age. Epi: Prevalence. Spatial: Cluster; Proximity. Landscape: CO (Forest; Agriculture; Development; Terrain; Soil Characteristics; Human Population Density; Rivers; Streams; Water body)	IHC; ELISA	ML; Ecological Niche Modeling; Moran's I Statistic; Kulldorff Spatial Scan Statistic; Neg. Binom. Reg.	Secondary; Both	382 : 28954	1.3%	Wisconsin; Illinois, USA	Ecosystem
Robinson SJ, Samuel MD, Rolley RE, Shelton P. 2013. Using landscape epidemiological models to understand the distribution of chronic wasting disease in the midwestern USA. *Landsc Ecol* 28:1923–1935.	Demographics: Genetics. Location: Townships. Epi: Prevalence. Spatial: Proximity; Cluster. Landscape: Ecoregion; CO (Soil Characteristics; Forest; River; Road)	IHC; ELISA	GLM; Moran's I Statistic; Diffusion Model	Secondary; Both	NS	NA	Wisconsin; Illinois, USA	Mixed
Manjerovic MB, Green ML, Mateus-Pinilla N, Novakofski J. 2014. The importance of localized culling in stabilizing chronic wasting disease prevalence in white-tailed deer populations. *Prev Vet Med* 113:139–145.	Epi: Prevalence. Location: State. Control, Mortality, Management: Harvest; Cull. Time. Landscape: CO (Forest; Soil Characteristics)	IHC; ELISA	GLM	Secondary; Descriptive	2179 : 152133	1.4%	Wisconsin; Illinois, USA	Ecosystem
Oraby T, Vasilyeva O, Krewski D, Lutscher F. 2014. Modeling seasonal behavior changes and disease transmission with application to chronic wasting disease. *J Theor Biol* 340:50–59.	Dem: Density. Time. Epi: Transmission. Life Cycle: Recruitment; Mortality.	IHC; ELISA	Diff. Eq./SI Models; Latin Hypercube	Secondary; Predictive	NS	NA	Simulation	Population
Monello RJ, Powers JG, Hobbs NT, Spraker TR, Watry MK, Wild MA. 2014. Survival and population growth of a free-ranging elk population with a long history of exposure to chronic wasting disease. *J Wildl Manage*	Dem: Age. Epi: Prevalence; Transmission. Life Cycle: Survival; Recruitment; Mortality. Time. Trophic: Predation. Control, Mortality, Management: Harvest; Predation; Roadkill; Unknown; Disease.	IHC	Hier. Bayes.	Primary; Descriptive	24 : 136	17.6%	Colorado, USA	Community

78:214–223.								
Jennelle CS, Henaux V, Wasserberg G, Thiagarajan B, Rolley RE, Samuel MD. 2014. Transmission of chronic wasting disease in Wisconsin white-tailed deer: Implications for disease spread and management. *PLoS One* 9:e91043.	Dem: Age; Sex; Density. Epi: Transmission; Prevalence. Spatial: Direction/Distance of Spread. Life Cycle: Fecundity; Survival. Time. Control, Mortality, Management: Harvest.	IHC; ELISA	Matrix Model; GLM; Latin Hypercube	Secondary; Predictive	958 : 16773	5.7%	Wisconsin, USA	Population
Heisey DM, Jennelle CS, Russell RE, Walsh DP. 2014. Using auxiliary information to improve wildlife disease surveillance when infected animals are not detected: A Bayesian approach. *PLoS One* 9:e89843.	Dem: Sex; Age. Sampling Method: SRS; Harvest; Other; Euthanasia. Epi: Prevalence.	IHC; ELISA	Bayesian Log. Reg.	Secondary; Descriptive	595 : 20400	2.9%	Colorado, USA	Population
Kelly AC, Mateus-Pinilla NE, Brown W, Ruiz MO, Douglas MR, Douglas ME, Shelton P, Beissel T, Novakofski J. 2014. Genetic assessment of environmental features that influence deer dispersal: Implications for prion-infected populations. Popul Ecol 56:327–340.	Dem: Sex; Age; Genetics; Density. Location: Unit (Study); TRS. Epi: Prevalence. Spatial: Cluster; Proximity. Landscape: LCT (Development; Slope; Forest; Grassland; Agriculture; Roads; Rivers); CO (Cover Types; Fragmentation; Connectivity; Cohesion; Clustering; Shape)	IHC; ELISA	Kriging; Bayesian Clustering; Lin. Reg.	Secondary; Descriptive	141 : 1988	7.1%	Wisconsin; Illinois, USA	Mixed
Williams AL, Kreeger TJ, Schumaker BA. 2014. Chronic wasting disease model of genetic selection favoring prolonged survival in Rocky Mountain elk (*Cervus elaphus*). *Ecosphere* 5:60.	Dem: Age; Sex; Genetics. Time. Epi: Incubation. Life Cycle: Survival; Mortality; Fecundity. Control, Mortality, Management: Harvest; Other (Non-Harvest); Disease.	IHC; ELISA	Stochastic Simulation	Primary; Both	37 : 39	94.9%	Wyoming, USA	Individual
Garlick MJ, Powell JA, Hooten MB, MacFarlane LR. 2014. Homogenization, sex, and differential motility predict spread of chronic wasting disease in mule deer in southern Utah. *J Math Biol* 69:369–399.	Epi: Transmission; Prevalence; Contact Rate; Prion Dynamics. Life Cycle: Recruitment; Mortality. Control, Mortality, Management: Cull; Disease. Dem: Age; Sex; Density; Behavior (Movement). Time. Landscape: LCT (Forest; Open water; Agriculture; Scrubland; Desert; Grassland)	IHC	Diff. Eq./SI Models; Diffusion Model	Secondary; Predictive	0-38600 : 19500-38600	NA	Utah, USA; Simulation	Ecosystem
Vasilyeva O, Oraby T, Lutscher F. 2015. Aggregation and environmental transmission in chronic wasting disease. *Math Biosci Eng* 12:209–231.	Time. Epi: Force of Infection; Transmission; Prevalence; Prion Dynamics; Contact Rate. Life Cycle: Mortality; Lifespan; Recruitment. Control, Mortality, Management: Disease.	IHC	Diff. Eq./SI Models; Latin Hypercube	Secondary; Predictive	NS	NA	Simulation	Population
Potapov A, Merrill E, Pybus M, Lewis MA. 2015. Empirical estimation of R0 for unknown transmission functions: The case of chronic wasting disease in Alberta. *PLoS One* 10:1–15.	Epi: Force of Infection; Prevalence; Transmission. Life Cycle: Survival; Mortality. Time. Dem: Sex; Behavior (Movement). Control, Mortality, Management: Cull; Harvest.	IHC	Matrix Model	Secondary; Predictive	77 : 15038	0.5%	Alberta, CA	Population

Geremia C, Miller MW, Hoeting JA, Antolin MF, Hobbs NT. 2015. Bayesian modeling of prion disease dynamics in mule deer using population monitoring and capture-recapture data. *PLoS One* 10:1–20.	Dem: Age; Populations/Herds. Epi: Prevalence; Hazard. Life Cycle: Recruitment; Survival; Mortality; Lifespan. Time. Spatial: Aggregation; Cluster.	IHC	Matrix Model; Leslie Matrix Model	Primary; Both	22 : 217	10.1%	Colorado,; Wyoming, USA	Population
Sun L, Lee C, Hoeting JA. 2015. Parameter inference and model selection in deterministic and stochastic dynamical models via approximate Bayesian computation: Modeling a wildlife epidemic. *Environmetrics* 26:451–462.	Epi: Transmission; Prion Dynamics; Prevalence. Time. Life Cycle: Mortality; Recruitment.	IHC	Diff. Eq./SI Models; Hier. Bayes.	Secondary; Predictive	NS	NA	Simulation	Population
Al-arydah M, Croteau MC, Oraby T, Smith RJ, Krewski D. 2016. Applications of mathematical modeling in managing the spread of chronic wasting disease (CWD) in wild deer under alternative harvesting scenarios. J Toxicol Env Heal - Part A Curr Issues 79:690–699.	Epi: Incubation; Transmission; Contact Rate. Life Cycle: Lifespan; Mortality; Fecundity. Control, Mortality, Management: Disease; Harvest. Dem: Sex; Age; Density. Time.	IHC; WB	Diff. Eq./SI Models; Latin Hypercube	Secondary; Predictive	24 : 650	3.7%	Alberta, CA	Population
Edmunds DR, Kauffman MJ, Schumaker BA, Lindzey FG, Cook WE, Kreeger TJ, Grogan RG, Cornish TE. 2016. Chronic wasting disease drives population decline of white-tailed deer. *PLoS One* 11:e0161127.	Epi: Prevalence; Hazard; Incubation. Life Cycle: Recruitment; Survival. Dem: Sex; Age; Health; Behavior (Movement); Pregnancy. Time. Control, Mortality, Management: Predation; Roadkill; Unknown; Disease; Other; Harvest; Euthanasia.	IHC; ELISA	Log. Reg.; Leslie Matrix Model	Primary; Descriptive	57 : 161	35.4%	Wyoming, USA	Population
Evans TS, Kirchgessner MS, Eyler B, Ryan CW, Walter WD. 2016. Habitat influences distribution of chronic wasting disease in white-tailed deer. *J Wildl Manage* 80:284–291.	Dem: Sex; Age; Behavior (Movement). Epi: Location. Sampling Method: (Roadkill; Harvest; Cull). Landscape: LCT (Forest; Development; Open); CO (LCTs; Soil Characteristics; Elevation; Riparian Corridors). Spatial: Cluster.	IHC; ELISA	Hier. Bayes.; Log. Reg.	Secondary; Descriptive	69 : 7427	0.9%	Maryland; West Virginia; Virginia, USA	Ecosystem
Mejía-Salazar MF, Waldner C, Stookey J, Bollinger TK. 2016. Infectious disease and grouping patterns in mule deer. *PLoS One* 11:e0150830.	Dem: Age; Sex; Populations/Herds. Landscape: LCT (Grassland; Forest; Shrubland; Agriculture). Time.	IHC	GLMM	Primary; Descriptive	365	NA	Sask., CA	Ecosystem
Nobert BR, Merrill EH, Pybus MJ, Bollinger TK, Hwang YT. 2016. Landscape connectivity predicts chronic wasting disease risk in Canada. *J Appl Ecol* 53:1450–1459.	Dem: Sex; Behavior (Movement). Location. Epi: Prevalence. Landscape: LCT (Forest; Shrubland; Agriculture); Rivers; Roads. Time. Spatial: Connectivity; Direction/Distance of Spread; Cluster.	IHC	Log. Reg.; Circuit Theory	Secondary; Predictive	94 : 19546	0.5%	Alberta; Sask., CA	Ecosystem
Samuel MD, Storm DJ. 2016. Chronic wasting disease in white-tailed deer: Infection, mortality, and implications for heterogeneous transmission. *Ecology* 97:3195–3205.	Dem: Sex; Age. Epi: Force of Infection; Hazard; Prevalence; Transmission; Contact Rate. Location: State. Life Cycle: Mortality. Control, Mortality, Management: Disease; Harvest.	IHC; ELISA	Bayesian WAIFW Matrix Model	Secondary; Descriptive	16257	NA	Wisconsin; Illinois, USA	Population

Mejía-Salazar MF, Goldizen AW, Menz CS, Dwyer RG, Blomberg SP, Waldner CL, Cullingham CI, Bollinger TK. 2017. Mule deer spatial association patterns and potential implications for transmission of an epizootic disease. *PLoS One* 12:e0175385.	Dem: Sex; Age; Behavior (Reproduction; Movement); Populations/Herds; Genetics. Spatial: Proximity. Epi: Prevalence. Time.	IHC	GLMM	Primary; Descriptive	32 : 74	43.2%	Sask., CA	Mixed
Hefley TJ, Hooten MB, Russell RE, Walsh DP, Powell JA. 2017. When mechanism matters: Bayesian forecasting using models of ecological diffusion. *Ecol Lett* 20:640–650.	Location. Time. Spatial: Landscape: CO (Forest; Development; Rivers). Dem: Sex; Age; Behavior (Movement).	IHC; ELISA	Diff. Eq./SI Models; GLMM; BRT; ML; Hier. Bayes.; GAM; Diffusion Model	Secondary; Predictive	2562 : 103256	2.5%	Wisconsin, USA	Ecosystem
Galloway NL, Monello RJ, Brimeyer D, Cole E, Hobbs NT. 2017. Model forecasting of the impacts of chronic wasting disease on the Jackson elk herd. Biological Research Division, National Park Service, Washington, DC, USA 32 pp.	Dem: Sex; Age. Control, Mortality, Management: Harvest; Disease. Epi: Prevalence; Transmission. Time. Life Cycle: Survival; Recruitment; Mortality.	NS	Matrix Model	Primary; Both	NS	NA	Wyoming, USA	Population
Monello RJ, Galloway NL, Powers JG, Madsen-Bouterse SA, Edwards WH, Wood ME, O'Rourke KI, Wild MA. 2017. Pathogen-mediated selection in free-ranging elk populations infected by chronic wasting disease. *Proc Natl Acad Sci U S A* 114:12208–12212.	Dem: Genetics; Populations/Herds. Location. Epi: Prevalence; Incubation.	IHC; ELISA	Hier. Bayes.; Log. Reg.	Secondary; Descriptive	1018	NA	Wyoming; Colorado; North Dakota, USA	Population
Hefley TJ, Hooten MB, Hanks EM, Russell RE, Walsh DP. 2017. Dynamic spatio-temporal models for spatial data. *Spat Stat* 20:206–220.	Dem: Sex; Age; Behavior (Movement); Density. Time. Location: Lat/Long. Landscape: CO (Forest; Development). Epi: Prevalence.	IHC; ELISA	GLMM; Diffusion Model; Diff. Eq./SI Models; Hier. Bayes.	Secondary; Predictive	168 : 14648	1.1%	Wisconsin, USA	Ecosystem
DeVivo MT, Edmunds DR, Kauffman MJ, Schumaker BA, Binfet J, Kreeger TJ, Richards BJ, Schätzl HM, Cornish TE. 2017. Endemic chronic wasting disease causes mule deer population decline in Wyoming. *PLoS One* 12:e0186512.	Dem: Age; Sex; Health; Pregnancy; Genetics. Life Cycle: Recruitment; Survival. Epi: Prevalence; Hazard; Transmission. Time. Control, Mortality, Management: Harvest; Disease; Predation; Roadkill; Other. Trophic: Predation.	IHC; ELISA	Matrix Model	Primary; Descriptive	77 : 143	53.8%	Wyoming, USA	Community
Edmunds DR, Albeke SE, Grogan RG, Lindzey FG, Legg DE, Cook WE, Schumaker BA, Kreeger TJ, Cornish TE. 2018. Chronic wasting disease influences activity and behavior in white-tailed deer. *J Wildl Manage* 82:138–154.	Dem: Sex; Age; Behavior (Movement); Health. Location. Epi: Prevalence. Spatial: Proximity. Time. Landscape: LCT (Development; Riparian; Grassland; Agriculture; Shrubland; Forest; Rivers; Road); CO (Curvature; Surface Area Ratio; Slope; Surface Relief Ratio; Compound Topographic Index; Heat Load Index; Circular Aspect Transformation).	IHC	Brownian-Bridge Movement Model; GLM	Primary; Descriptive	57 : 161	35.4%	Wyoming, USA	Ecosystem

Davenport KA, Mosher BA, Brost BM, Henderson DM, Denkers ND, Nalls A V, McNulty E, Mathiason CK, Hoover EA. 2018. Assessment of chronic wasting disease prion shedding in deer saliva with occupancy modeling. *J Clin Microbiol* 56:e01243-17.	Dem: Genetics; Sex. Time. Epi: Incubation; Prion Dynamics; Transmission.	RT-QuIC; IHC; WB	Occupancy Modeling	Primary; Descriptive	45	NA	Colorado, USA	Individual
Maji C, Mukherjee D, Kesh D. 2018. Deterministic and stochastic analysis of an eco-epidemiological model. *J Biol Phys* 44:17–36.	Dem: Density. Life Cycle: Mortality; Recruitment; Survival. Epi: Transmission; Prion Dynamics. Control, Mortality, Management: Predation; Disease. Trophic: Predation.	NS	Diff. Eq./SI Models; Hopf Bifurcation	Secondary; Predictive	NS	NA	Simulation	Community
Wolfe LL, Watry MK, Sirochman MA, Sirochman TM, Miller MW. 2018. Evaluation of a test and cull strategy for reducing prevalence of chronic wasting disease in mule deer (*Odocoileus hemionus*). *J Wildl Dis* 54:511–519.	Dem: Age; Sex; Populations/Herds. Location. Time. Epi: Prevalence. Control, Mortality, Management: Cull.	IHC	Desc. Stats	Primary; Descriptive	269 : 3566	7.5%	Colorado, USA	Population
Jennelle CS, Walsh DP, Samuel MD, Osnas EE, Rolley R, Langenberg J, Powers JG, Monello RJ, Demarest ED, Gubler R, et al. 2018. Applying a Bayesian weighted surveillance approach to detect chronic wasting disease in white-tailed deer. J Appl Ecol 55:2944–2953.	Dem: Age; Sex. Location. Time. Epi: Prevalence; Hazard. Sampling Method (Roadkill; Euthanasia). Control, Mortality, Management: Disease; Harvest; Cull; Roadkill; Other.	IHC; ELISA	Bayesian Log. Reg.	Primary; Descriptive	0 : 80	0.0%	Virginia, USA	Population
Schuler KL, Jenks JA, Klaver RW, Jennelle CS, Bowyer RT. 2018. Chronic wasting disease detection and mortality sources in semi-protected deer population. *Wild Biol* 2018:wlb.00437.	Dem: Sex; Age. Control, Mortality, Management: Predation; Roadkill; Harvest; Unknown; Euthanasia. Epi: Prevalence. Life Cycle: Survival; Mortality.	IHC	MARK Survival Model	Primary; Descriptive	8 : 67	11.9%	South Dakota, USA	Population

[1] LCT = Land Cover Type, [2]CO = Covariate, [3]Dem = Demographic variables, [4]Epi = Epidemiological variables, [5]TRS = Township-region-section, [6]UTM = Universal transverse Mercator

[7]IHC = Immunohistochemistry, [8]ELISA = Enzyme-linked immunosorbent assay, [9]WB = Western blot, [10]RT-QuIC = Real-time quaking induced conversion

[11]GLM = Generalized linear model, [12]GLMM = Generalized linear mixed model, [13]Log. Reg. = Logistic regression, [14]Lin. Reg. = Linear regression, [15]WAIFW = "Who-acquired-infection-from-whom", [16]BRT = Boosted regression trees, [17]GAM = Generalized additive model, [18]Diff. Eq/SI Models = Differential equations and/or SI models, [19]Desc. Stats = Descriptive statistics, [20]Hier. Bayes = Hierarchical Bayesian modeling, [21]ML = Machine learning

NS = Not specified.

Table A2: Less common modeling methods. Type of modeling method and number of uses (*n*) in CWD research. Includes methods with <5 uses in publications.

Modeling Method	***n***
Anselin's LISA	1
Bayesian Clustering	4
Bayesian Spatial Regression	1
Bayesian WAIFW Matrix Model	1
Before-and-After Control Impact (BACI)	1
Boosted Regression Trees	1
Brownian-Bridge Movement Model	1
Circuit Theory	1
Difference Equations	1
Diffusion Model	4
Ecological Niche Modeling	1
Gaussian Geostatistical Model	1
Generalized Additive Model	1
Hierarchical Cluster Analysis	1
Hopf Bifurcation	1
Kriging	1
Kulldorff Spatial Scan Statistic	1
Leslie Matrix Model	3
Lexis Diagram	1
Machine Learning	2
MARK Survival Model	1
Meta-analysis	1
Network Model	2
Occupancy Modeling	1
Partial Differential Equations	1
Sampling Simulations	4
Spatial Scan Statistic	2

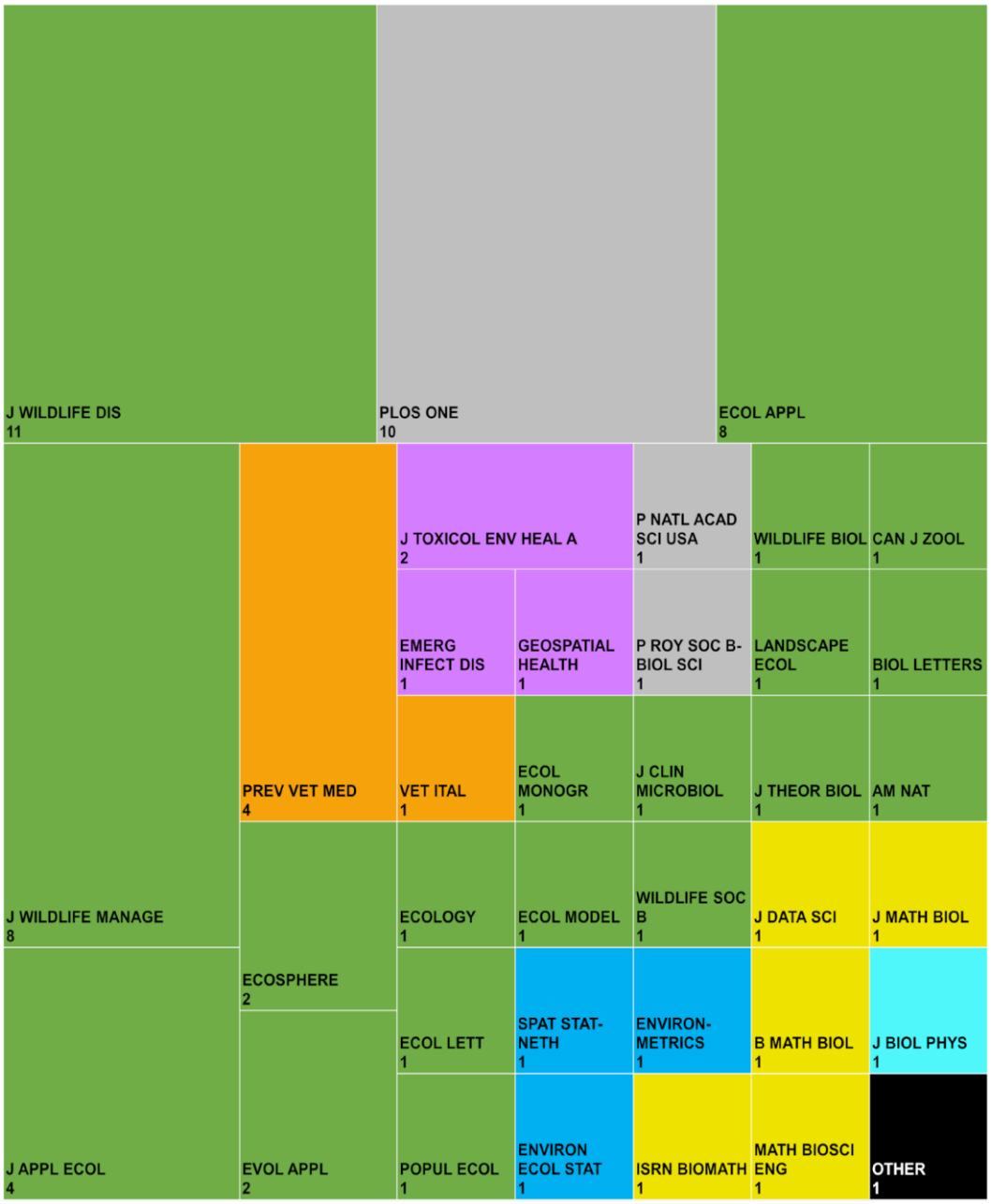

Fig. A1: Distribution of chronic wasting disease modeling studies across scientific journals. Modeling studies were published largely in journals publishing in the areas of wildlife and ecology (green; *n*=48 articles), mathematical biology (yellow; *n*=5 articles), multidisciplinary (gray; *n*=12 articles), epidemiology (magenta; *n*=4 articles), spatial analyses (blue; *n*=3 articles), veterinary sciences (orange; *n*=5 articles), biophysical sciences (light blue; *n*=1 article), and other technical reports (black; *n*=1 article).

Appendix B: Supplementary circuit theory connectivity maps.

Figure B1: Maps showing current density connecting two CWD cases. Panels show hypothetical connections between a single CWD case in Frederick County and the isolated Culpeper case under different scales and resistance transformations (i.e., C4, C8, and Negative Linear). Overall, many pathways indicate the hypothetical routes of spread still largely remain unclear.