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Ecological Niche Modeling of Lyme Disease Risk in Maine Based on Human Case Data

Elizabeth Dee

ECOLOGICAL NICHE MODELING OF LYME DISEASE RISK IN MAINE BASED ON HUMAN CASE DATA

by

Elizabeth Dee

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(Zoology)

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Advisory Committee:
- Allison Gardner Assistant Professor of Arthropod Vector Biology, Advisor
- R.W. Estela, Preceptor in the Honors College
- Pauline Kamath Assistant Professor of Animal Health
- Brandon Lieberthal, Lecturer in Mathematics
- Angela Mech, Assistant Professor of Forest Entomology

ABSTRACT

Ixodes scapularis, the blacklegged tick, is the primary vector for the Lyme disease-causing bacteria *Borrelia burgdorferi* in the United States. Lyme disease poses a significant concern to the state of Maine, as both the number and geographic distribution of cases across the state have been steadily increasing over the past two decades. In 2001, there were 108 confirmed or probable cases of Lyme disease in Maine compared to 1404 cases in 2018. Using tick-borne disease human case data from the Maine CDC and ArcGIS software, I created three Lyme disease maps for the years 2001, 2009, and 2017. These maps show the number of confirmed and probable cases of Lyme disease in Maine for each town, where case coordinates were randomly assigned within the town boundary that the patient resides in. I used Maxent modeling to locate areas of high-risk for Lyme disease cases in Maine. The land cover variables were taken from the National Land Cover Database and the climate variables were based on Bioclimatic variables from WorldClim. The final variable in this model was the distance from hospital. The findings of this study show that the distribution of Lyme disease cases across the state of Maine increased from 2001 to 2017. The coldest temperature of the coldest month was the best predictor for Lyme disease case prevalence, and land cover was not an important predictor for Lyme disease cases. These findings pose research questions on the causality behind these trends.

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INTRODUCTION

Lyme disease, also known as Lyme borreliosis, is the most common vector borne disease in the United States and poses a significant concern to the state of Maine (Eddens et al., 2019). Lyme disease, transmitted by *Ixodes scapularis* (commonly known as the blacklegged tick)(Feldman et al., 2015), is now the third most reported infectious disease in Maine and is endemic in all sixteen Maine counties (Robinson, 2014). This concern for public health in Maine has led to the development of better insect repellents, education programs, coordinated research efforts through TickNET, and the funding of state health departments to improve surveillance and prevention (Centers for Disease Control and Prevention, 2021). Since currently no Lyme disease vaccine is available to the public (O'Bier, 2021), preventative measures involving determining areas of high risk and educating the public on Lyme disease are highly important.

Ixodes scapularis transmits the Lyme-disease causing bacterial spirochete *Borrelia burgdorferi*, responsible for causing a range of symptoms in North America (Feldman, 2015). After an initial tick bite, a minimum of 24 to 48 hours of tick attachment is typically required to cause infection leading to Lyme disease (Lo Re, 2004). This long window of attachment is necessary for *B. burgdorferi* to migrate from the midgut of the tick to its salivary glands. Symptoms of Lyme disease typically manifest themselves within three to 30 days, with up to 80 percent of cases being characterized by the erythema migrans rash. This rash appears as an oval or circular rash with approximately 19 percent of cases having the characteristic bulls-eye appearance (Wright, 2012). Other non-specific symptoms that can accompany the rash include fever, headache, fatigue, and muscle and joint aches. These are considered early localized Lyme disease symptoms and are primarily brought on by both the innate and adaptive inflammatory immune responses (Glickstein, 2003). Occasionally if Lyme disease is inadequately treated or persists, more severe symptoms including arthritis with severe joint pain and swelling, facial palsy, heart palpitations, and nerve damage can occur (CDC, 2021).

Understanding the life cycle of *I. scapularis* is useful for predicting the risk of tick-human encounters (Nieto, 2018). The life cycle of *I. scapularis* is such that only female nymphs and adults can transmit the Lyme disease causing agent to humans. So, it is important to consider what climate and land cover variables could affect the ability of these life stages to find a host. Warm temperatures could increase desiccation stress, which could lead to low *I. scapularis* population numbers in years with dry, hot temperatures (Ginsberg, 2017). Adult female ticks lay their eggs in the spring, which then hatch as larvae by the following summer and encounter their first blood meal typically in the form of small mammals or birds during the summer or early fall. At this stage, and through additional blood meals, the tick might acquire the bacteria *B. burgdorferi* and becomes able to transmit it to other blood meal hosts for the rest of its life cycle. The tick transitions into its nymphal stage by the following spring at which point it seeks its second blood meal often in the form of another small rodent or in some cases a human. The host of its second blood meal is the first one in the black-legged tick life cycle that could potentially contract *B. burgdorferi* from an infected tick bite. The third and final blood meal occurs when the tick is in its adult life stage during the fall. Adult ticks feed on larger hosts such as deer and humans before laying eggs the following spring when the life cycle repeats (CDC 2020). Tick-host encounter frequencies, and thus cases of tick-borne disease, are influenced by a variety of factors such as climate and land use.

Ixodes scapularis questing behavior is correlated with ambient temperature and humidity, and may have a strong positive relationship with Lyme disease incidence (Schulze, 2003). *Ixodes scapularis* seeks a host through a behavior known as questing. This is where a host-seeking tick climbs up to rest on the tips of grasses and shrubs and holds on to the leaves and grass with their lower legs and keep their upper legs outstretched (Vail, 2002). Since ticks are unable to jump or fly, they wait to climb onto a passing host where they will take a blood meal before dropping off (CDC, 2011). Questing behavior, and thus Lyme disease risk, is largely driven by the time of year and temperature. *Ixodes scapularis* is most active above 4.4 degrees Celsius (Maine CDC, 2021) and has been shown to die in laboratory settings when exposed to temperatures between -18.9 degrees Celsius and -10 degrees Celsius (Department of Conservation and Natural Resources, 2018). This temperature barrier limits tick activity during the harsh winter months in Maine where most ticks are either attached to a host or insulated under leaf litter and snow. High temperatures above 30 °C, and low humidity, can cause decreased questing activity, potentially in part due to dehydration, which could increase tick mortality rates as chances of finding a host go down (Eisen, 2016). Therefore, temperature constraints on questing behavior and probability of obtaining a bloodmeal could be good indicators of tick-human encounter frequencies and thus Lyme disease cases.

The risk of Lyme disease infection is greatest in late spring and summer (Roome, 2018) when *I. scapularis* and human activity are at their peak in Maine. Increased human outdoor activity raises the risk of encountering ticks and thus the risk of Lyme disease transmission (Xu, 2016). In 2018, Mount Desert Island, a popular outdoor Maine tourist destination, received 614,231 recreational visitors in the month of July when nymphal ticks are active. This is compared to the 9,274 recreational visitors in January when cold Maine temperatures limit *I. scapularis* activity (National Park Services U.S. Department of the Interior, 2018). *I. scapularis* has been positively associated with deciduous, dry to mesic forests which can be encountered by tourists doing recreational activities such as hiking in the parks (Guerra, 2002). Along with the increased number of people entering potential tick habitats, the nymph ticks are small, making them hard to spot within the time necessary for transmitting *B. burgdorferi* (Eisen, 2016).

The type of land cover is an important factor when considering *I. scapularis* encounters and Lyme disease. In a habitat suitability model for the distribution of *I. scapularis* in Minnesota, the most influential variable was land cover. Forested habitat, temperate grassland, meadow, and shrubland were all suitable habitats for the establishment of *I. scapularis,* with cool, forested habitat accounting for 67 percent of the predicted habitat in Minnesota (Johnson, 2016). *Ixodes scapularis* abundance has also been shown to be increased in areas with high canopy cover with little shrubland (Talbot, 2019). The type of forest can also have an impact on *I. scapularis* abundance with nymphal tick densities being greater in deciduous forests than in coniferous forests (Ginsberg, 2004).

There may be a strong linkage between the abundance of host-seeking nymphs infected with *B. burgdorferi* and Lyme disease occurrence, and therefore spatial patterns of both the vector and disease occurrence should be studied (Eisen, 2016). One surveillance mechanism open to the public is the Lyme disease incidence data found on the Maine Tracking Network made available by the Maine CDC (Maine Tracking Network, 2021). The University of Maine Cooperative Extension Tick Lab conducts surveillance of ticks and tick-borne pathogens and, for a small fee, accepts tick samples from the public for tick-borne pathogen testing (Rounsville, 2021). This lab conducts a free tick-identification program as well (Rounsville, 2019). While these programs are highly useful and valuable to the current understanding of *I. scapularis* and Lyme disease, a few limitations could be mitigated and explored using a different approach.

The Maine CDC human Lyme disease case dataset that will be used in this model mitigates several biases and limitations of previous passive surveillance tick data . A major limitation of the UMaine Tick Surveillance Program is its reliance on the public's willingness or ability to submit tick samples to be tested and included in the data. This means that for a tick to be reported and tested for tickborne diseases, a member of the public needs to go out of their way to send in the tick sample. This could create bias as individuals who are educated on tickborne diseases and who are knowledgeable about this surveillance program would be more likely to submit a sample (Aenishaenslin, 2016). The method of announcing tick identification services such as through lectures, public health and veterinary newsletters, game biologists, and in the media, has played a significant role in getting submissions from the public in previous surveillance. This mechanism of reporting might also create an inaccurate distribution of ticks and tickborne diseases across the state of Maine as specific outdoor-related groups such as summer camp and hunting camp operators were targeted specifically and given vials and prepaid mailing labels (Rand, 2007). The Maine CDC human Lyme disease case dataset relies on healthcare providers and laboratories to report cases to the state and local health departments. This removes some of the bias since this dataset deals with cases where people have personal interest in seeking medical attention. This dataset shows cases of a patient who meets the clinical definition or has laboratory confirmation of Lyme disease, making this dataset a better candidate for assessing Lyme disease risk across the state of Maine (CDC, 2021). This dataset does has a limitation in that the location associated with each case is the home address of the patient and not necessarily the location where Lyme disease was contracted. It would be impossible to accurately guess where each patient contracted Lyme disease as some do not ever realize that they had been bitten by a tick. This can create some bias as many people can travel to potentially high-risk areas for contracting Lyme disease (Casares, 2020) and then have the case associated with their home address (Bacon, 2008).

The main objective of my research is to create an ecological niche model of Lyme disease risk which can be broken down into three smaller objectives:

1. **Create three Lyme disease case maps** for the years 2001, 2009, and 2017 that show the number of cases of Lyme disease by town in Maine. It is important to understand how the distribution of cases is changing over time, to help predict emerging areas of high risk and help best prepare for them. To do this, the Maine CDC tick-borne disease human case data on Lyme disease for 2001 to 2020 was chosen because it lacks the bias of relying on the public to report tick encounters.
2. **Create an ecological niche model** for Lyme disease risk. An ecological niche model, or ENS, is a correlative model that predicts relative habitat suitability using occurrence data along with environmental data (Warren, 2011). My ENS

uses the Maine CDC tick-borne disease human case data on Lyme disease as the occurrence data along with a series of land cover and climate variables for the environmental data.

3. **Analyze temporal trends** for Lyme disease risk between 2001, 2009, and 2017. I used three different time points to analyze Lyme disease risk to see if the increase in Lyme disease cases, as well as the number of towns affected by Lyme disease, had any influence on my model. I hypothesized that the differences in climate from year to year could have an impact on my model which could be a good launching point for future research.

METHODS

Human Case Data Sources and Visualization

The Maine CDC tickborne disease human case data on Lyme disease was used because it lacks the bias of relying on the public to report tick encounters. The data consists of human case data on tick-borne disease numbers, case status, the report date, and onset date, in Maine between the years of 2001 and 2020. All research involving confidential human case data was conducted in compliance with University of Maine IRB protocol #2017_09_09 and included information such as the type of tick-borne disease, as well as the year of the case and home address of each patient. The four types of tickborne diseases reported in this dataset were Lyme disease, babesiosis, human granulocytic anaplasmosis, and human granulocytic ehrlichiosis. While all these tick-borne diseases can be transmitted by *I. scapularis*, Lyme disease has caused the most concern to public health, so, to create a model that is both relevant and as accurate as possible, I chose to focus on Lyme disease.

The cases of Lyme disease from this Maine CDC human case dataset were reported to the state and local health departments by healthcare providers and laboratories (CDC, 2021). To report a Lyme disease case, a Lyme disease surveillance case report is filled out by a public health official. A patient can be diagnosed with Lyme disease just by having erythema migrans (EM), the characteristic bulls-eye-shaped expanding rash. If the rash is not present, a patient can still be diagnosed with Lyme disease, given at least one late manifestation and a laboratory confirmation of the disease. A variety of late manifestations of Lyme disease affect the musculoskeletal system, the nervous system, and the cardiovascular system. The second part of the diagnosis, the laboratory confirmation, is the isolation of the spirochete *B. burgdorferi* from tissue or body fluid of the patient (CDC 2009).

For this research, Lyme disease cases from the years 2001, 2009, and 2017, were selected. Including a temporal aspect in my model should reveal how potential differences in climate over the span of approximately two decades might affect the change in case numbers and geographic expansion of cases. A temporal variable could also impact the spatial predictors of the occurrence of cases in the model. I also considered compiling a range of years instead of analyzing individual years, however this would compromise the annual climate values in this model. By taking a range of years, I would have needed to average the climate values and ranges for those years. So, if there were two years of mild winter temperatures followed by one year of extremely low temperatures that proved to be an important predictor for Lyme disease risk, that predictor would be lost when the temperatures were averaged together. Key variables such as temperature are vital factors for *I. scapularis* population numbers, and thus Lyme disease numbers, from year to year, so taking the average of these values for a range of years would be detrimental to this model.

To visualize changes in the density of case numbers and their geographic distribution over time, Lyme disease incidence maps were created. Maine's town boundary files from the US census (United States Census Bureau, 2019) were downloaded into ArcMap, a geospatial processing program (ESRI, Inc., Redlands, CA). The Lyme disease case data for each of the three specified years were uploaded into separate maps as CSV files with the town boundary information. The two files were joined in ArcMap, and the map was given a color gradient to symbolize the density of cases in each town. Next, a random points raster was made in ArcMap and set as the list of cases for each year that randomly assigned each case an X and Y coordinate within the town's boundary. This was done to not only protect the identity of the patients in small towns where there might have only been one case, but also because some of the cases did not have an address other than the town listed. To make sure that all cases were being displayed in a uniform manner, they were all randomized within the town boundary they were reported in. Afterwards, the shapefiles for the variables for each year were added to each map. This was done so that the variables could be aligned to the Maine town boundary raster in future steps when exporting into the Maxent model. Some of the shapefiles included data for the entire earth or were at different spatial resolutions which can cause problems in Maxent, so I exported the shapefiles as TIFF files where I could later align them and clip any extraneous data outside of Maine.

Ecological Niche Model Data Sources

To test the hypothesis that different land cover types such as deciduous forests had a higher Lyme disease risk, I included some geographic land cover variables in my model. The land cover data were downloaded from the National Land Cover Database (Multi-Resolution Land Characteristics Consortium, 2011). Land cover may serve as a good indicator for Lyme disease risk because Lyme disease cases are typically associated with the habitat where the infected tick was encountered, unless it is a travel-associated case (Guerra, 2002). The National Land Cover Database is only generated every five years, so no data was available for each year studied in my model. While there are changes in land cover, such as increasing urbanization, the differences between 2001 and 2017 were not drastic enough to pose much significance to my model. For this reason, and because it was the closest to the middle of the years being studied, I chose the land cover data for 2011 to be used in my model for all three years.

This dataset included sixteen separate land cover types for the year 2011. For the purposes of this research, these land cover types (e.g., herbaceous, hay/pasture, cultivated crops …) were grouped together and reclassified as nine different land cover types (Table 1). Many of the land cover types were too narrow and specific for the scope of this study when considering different habitats that might be relevant for contracting Lyme disease. I reclassified the land cover types by considering how both ticks and humans might interact with that land cover; I grouped land cover types together if differences in interaction were minimal, such as with high intensity versus low intensity for developed land cover. For example, the difference between the land cover types Hay/Pasture and Cultivated Crops when considering how humans and ticks might interact or cross paths is too minimal to require separate land cover types. The resolution of this dataset was very fine and created a mosaic effect where every 30 meters there could be a different land type classification. ArcGIS was used to take the dominant land cover type in each town to be used later in the Maxent model. The dominant land cover in each town was used because the Lyme disease cases were all randomized within the town boundary of the patient’s home address. Instead of randomizing only a few cases, they were all randomized which made potential land cover changes every 30 meters within a town irrelevant. By far, across Maine the major land type was deciduous and mixed forest followed by evergreen forest.

Table 1. Reclassified Land Cover Numbers

Reclassified Land Cover Number	Reclassified Land Cover Name	NLDC Land Cover Types
0	Unclassified	Unclassified
1	Open Water	Open Water
2	Developed	Developed, Open Space Developed, Low Intensity Developed, Medium Intensity Developed, High Intensity
3	Barren	Barren Land
4	Deciduous and Mixed Forest	Deciduous Forest Mixed Forest
5	Evergreen Forest	Evergreen Forest
6	Shrub	Shrub/Scrub
7	Agriculture	Herbaceous Hay/Pasture Cultivated Crops
8	Wetlands	Woody Wetlands Emergent Herbaceous Wetlands

Climate variables such as temperature and precipitation are important to consider when thinking about the climate constraints of *I. scapularis*, as well as the impact weather has on human activity. The climate variables, monthly minimum temperature, monthly maximum temperature, and monthly precipitation were downloaded from WorldClim 2.1 (Harris, 2014). The annual average temperature, or tmean, was downloaded from PRISM Climate Group (PRISM, 2021). With these shapefiles, the bioclimatic variables, BIO1-Bio19, could be calculated using cell statistics in ArcMap

(Environment Systems Research Institute, 2020). These variables were based on Worldclim's Bioclimate variables that are derived from the monthly temperature and rainfall values to generate variables that are more biologically meaningful when considering Lyme disease. These bioclimatic variables represent annual trends, seasonality, and extreme or limiting factors (Table 2). To formulate these variables for Maine, I used the equations given on the Worldclim data website by using the monthly maximum and minimum temperatures, monthly precipitation, and the annual mean temperature. Some of these variables, such as annual mean temperature (BIO1), were highly correlated with other variables. If the correlation value between two variables was above 0.80, the variable with the smaller percent contribution was omitted from the model.

Table 2. Bioclim Variable Definitions and Model Inclusion

Variables	**Definitions**	**Included in Model?**
BIO1	Annual Mean Temperature	No
BIO2	Mean Diurnal Range	Yes
BIO3	Isothermality	Yes
BIO4	Temperature Seasonality	No
BIO5	Max Temperature of Warmest Month	Yes
BIO6	Min Temperature of Coldest Month	Yes
BIO7	Temperature Annual Range	No
BIO8	Mean Temperature of Wettest Quarter	No
BIO9	Mean Temperature of Driest Quarter	No
BIO10	Mean Temperature of Warmest Quarter	No

BIO11	Mean Temperature of Coldest Quarter	No
BIO12	Annual Precipitation	Yes
BIO13	Precipitation of Wettest Month	Yes
BIO14	Precipitation of Driest Month	Yes
BIO15	Precipitation Seasonality	Yes
BIO16	Precipitation of Wettest Quarter	Yes
BIO17	Precipitation of Driest Quarter	Yes
BIO18	Precipitation of Warmest Quarter	Yes
BIO19	Precipitation of Coldest Quarter	Yes

The last variable considered in this model was the Maine Hospitals (ESRI 202!) which showed the distance to the nearest hospital. I wanted to include a variable that was related to healthcare infrastructure in my model. Having access to healthcare to get accurately diagnosed and treated for Lyme disease may impact the reporting of Lyme disease cases. The level of knowledge of the signs and symptoms of Lyme disease within a community could influence whether a person sought medical care (as well as knowing how to prevent disease transmission) as most of the early symptoms of Lyme disease such as fatigue, fever, joint and muscle pain, are very similar to the flu and not all patients exhibit the erythema migrans skin lesion (Biesiada, 2012). The level of knowledge of the signs and symptoms of Lyme disease within a community could influence whether a person sought medical care as well as knowing how to prevent disease transmission in the first place. To relate Maine hospitals to the human case dataset, this variable was converted to distance to the nearest hospital in RStudio (RStudio Team, 2020), and saved as a grid file.

The bioclimatic variables and reclassified land cover variables were exported from ArcMap as TIFF files. These files were then converted to grid files using a format raster in RStudio to clip them all to the same size and resolution by using the Maine boundaries file as the template raster.

Ecological Niche Modeling

The Maxent R package (Hijmans, 2020) for maximum entropy modeling was downloaded as well as the following RStudio libraries: biomod2, readr (Wickham, 2020), dplyr (Wickham, 2021), raster (Hijmans, 2020), dismo (Hijmans , 2020), and rgdal (Bivand, 2021). Maxent is a program for modeling species distribution from presence-only species records and is a common tool in ecological niche modeling (Warren, 2011). Maxent takes the geographic point locations of members of a population, or Lyme disease cases for this model, and compares it to all the environments given in that region. Maxent finds the distribution that is most spread out, or closest in uniform within the constraints of the environmental variables in the model. To find this distribution, Maxent calculates two probability densities, one for presence points which characterizes the environment where the species has been found, and one for background points which characterizes the available environment within the study region. What results from the ratio between the two probability densities is the relative environmental suitability for presence of a species for each point in the study area (Elith, 2011). The Maxent model does have some limitations in that it only gives environmental suitability instead of predicted probability of occurrence.

The working directory was set to the location of all the grid files that were just created with the format raster, plus the distance from hospital raster that was created earlier. The relevant raster files were then stacked, and a Pearson correlation matrix was formed to eliminate highly correlated variables that might interfere with the Maxent model. In the case of two variables being highly correlated above 0.8, the variable with the smaller percent contribution to the model was eliminated from the code. This process was done for all three years until three different codes were created.

For each of the three years, a Maxent model report as well as response curve and habitat suitability maps were plotted. The Maxent model included a receiver operating characteristic (ROC) curve with specificity, or true positive rate, on the x-axis and sensitivity, or false positive rate, on the y-axis. The closer the curve reached towards the top-left corner, the better the performance. The area under the ROC curve, or AUC, measures the ability of the model to accurately classify the group being tested where an area of 1 represents a perfect test. Another useful feature of the Maxent model report is the analysis of variable contributions which estimates the relative contributions of the environmental variables in the Maxent model. High percent contributions are associated with better predictors for where Lyme disease cases may be located. The response curves generated by the Maxent model show how each environmental variable affects the Maxent prediction. The response curve shows how the variable changes, such as temperature, on the x-axis and how the probability of a Lyme disease case being present changes in response (Tape 2021). The habitat suitability maps color-code locations of Maine based on the probability of any specific location having a Lyme disease case present with 1 being the highest probability and 0 being the lowest probability.

RESULTS

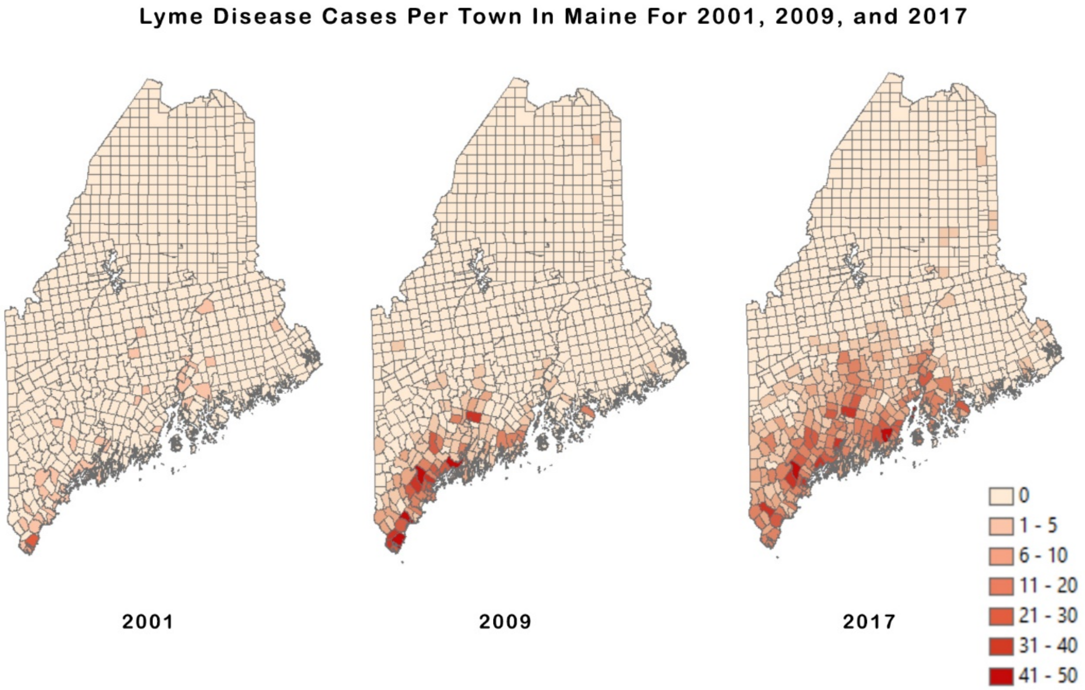

Figure 1: Lyme Disease Cases Per Town In Maine For 2001, 2009, 2017

The three maps (Figure 1) generated in ArcMap show a gradual increase in the number of Lyme disease cases per town, as well as the number of towns with Lyme disease cases, over the three separate years studied. Very few Lyme disease cases are shown in 2001 with the highest number in any town being 23 cases in York, Maine. In 2009, the highest number of Lyme disease cases was also recorded in York, Maine, with a total of 38. In 2017, the highest number of Lyme disease cases was reported in Windham, Maine with a total of 45. For all three years, the most cases were located in the southern region of Maine.

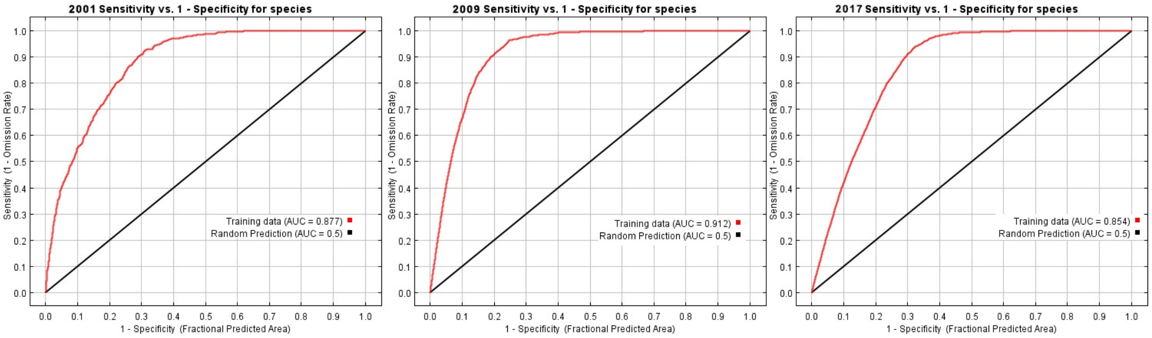

Figure 2: Receiver Operator Characteristic (ROC) Curve

The Receiver Operator Characteristic (ROC) Curve generated for all three years (Figure 2) showed high areas under the curve (AUC). The AUC showed that the model demonstrated good discrimination of positive and negative locations for the presence of a Lyme disease case. The AUC was 0.877 for 2001, 0.912 for 2009, and 0.854 for 2017, indicating a strong model fit.

Table 3: Variable Percent Contributions for Model prediction for 2001, 2009, and 2017. Cells with omitted values indicate the variable was not used for that year due to high correlation with another variable.

Variable	2001 Percent Contribution	2009 Percent Contribution	2017 Percent Contribution
bio2 (Mean Diurnal Range)	2.6		
bio3 (Isothermality)	3.2	1.4	6
bio5 (Max Temperature of Warmest Month)	4	1.5	1.1
bio6 (Min Temperature of Coldest Month)	79.7	85.6	84.6
bio12 (Annual Precipitation)		1.2	
bio13 (Precipitation of Wettest Month)	1.1	0.7	0.3
bio14 (Precipitation of Driest Month)	1.2	1.2	0.5
bio15 (Precipitation Seasonality)	2.4	3.2	0.4
bio16 (Precipitation of Wettest Quarter)		2.4	3
bio17 (Precipitation of Driest Quarter)	2.1		0.3
bio18 (Precipitation of Warmest Quarter)		0	0.1
bio19 (Precipitation of Coldest Quarter)	1.1		0.8
Land Cover	0.7	0.5	0.4
Distance From Hospital	1.9	2.3	2.6

The percent contributions of the variables for 2001, 2009, and 2017 (Table 3) indicate that bio6, the minimum temperature of the coldest month, has the highest contribution in the Maxent model for all three years at 79.7, 85.6, and 84.6 percent for 2001, 2009, and 2017, respectively. The percent contributions table also shows that land cover was not an important predictor with percent contributions of 0.7, 0.5, and 0.4 percent for 2001, 2009, and 2017, respectively. For some years, certain variables have been left out that are included in other years due to a high correlation, 0.80 or higher, with other variables.

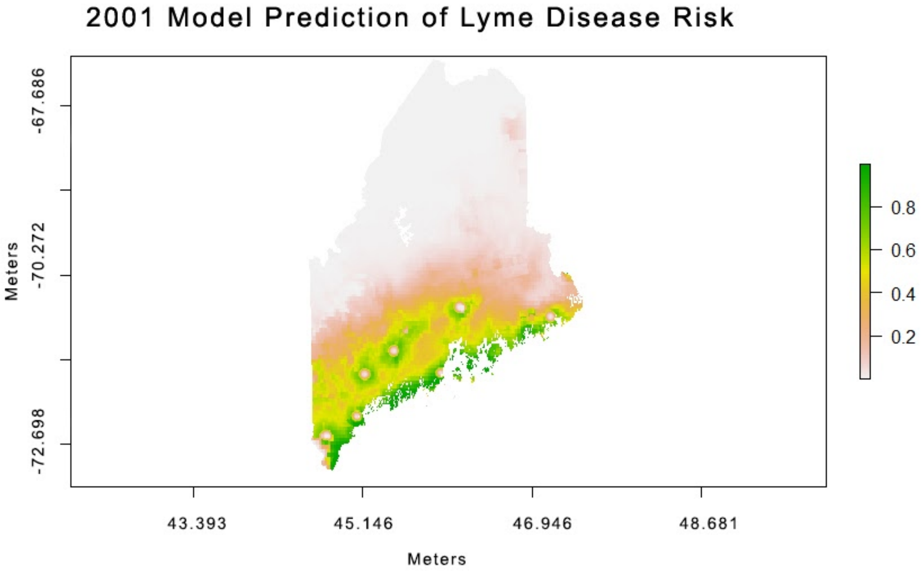

Figure 3: 2001 Model Prediction of Lyme Disease Risk

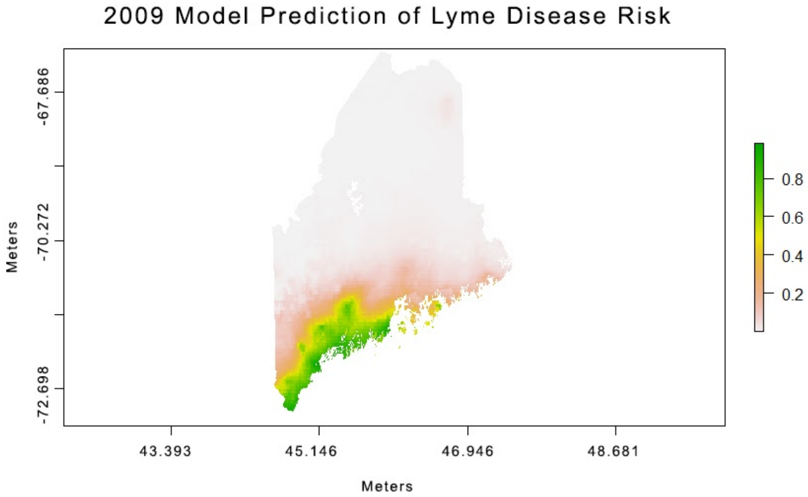

Figure 4: 2009 Model Prediction of Lyme Disease Risk

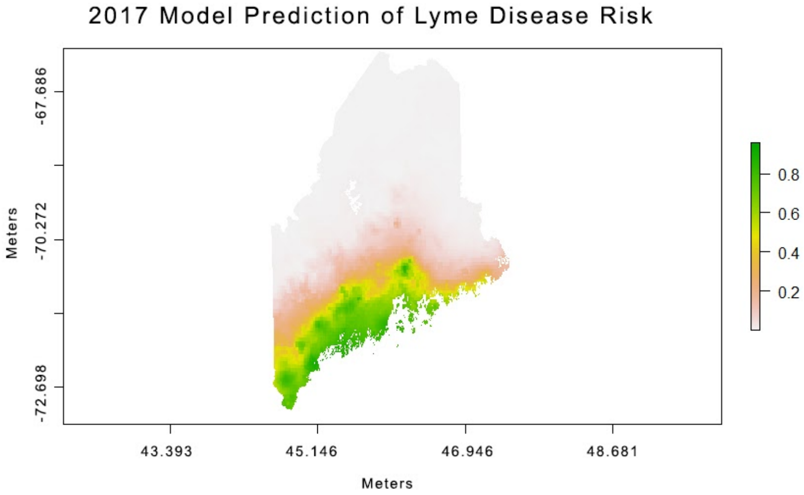

Figure 5: 2017 Model Prediction of Lyme Disease Risk

The color legend on the right of each figure (Figures 3 - 5) represents the probability of a Lyme disease case being in that given area. For all three years, the Lyme disease risk was highest in the southern, coastal region of Maine and gradually decreased traveling north.

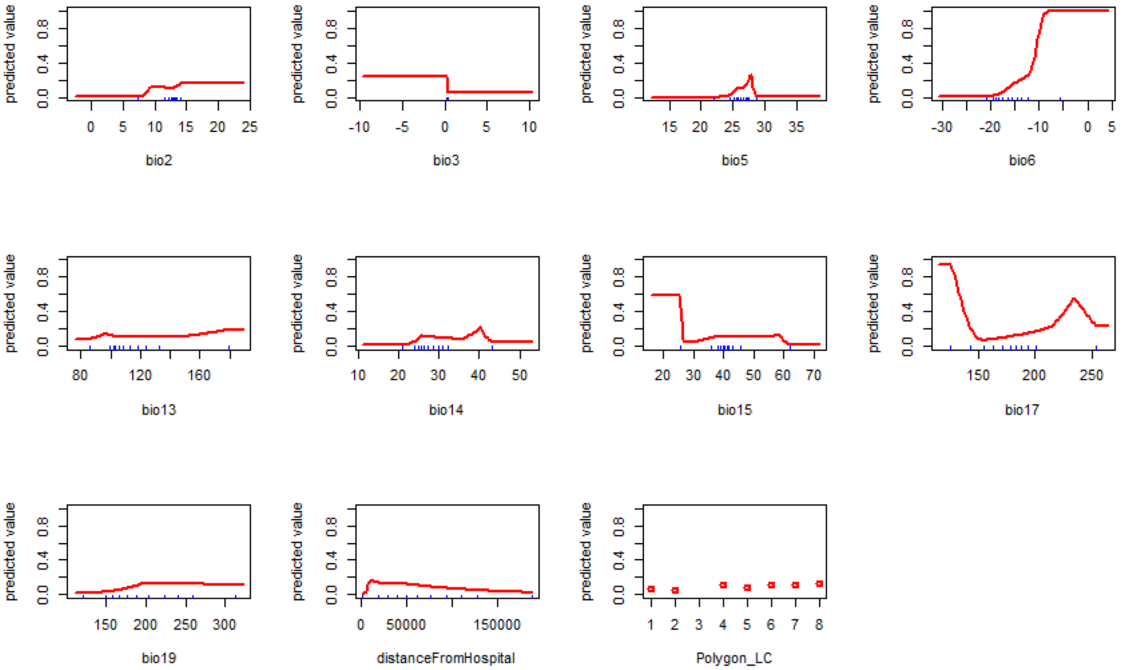

Figure 6: 2001 Response Curve

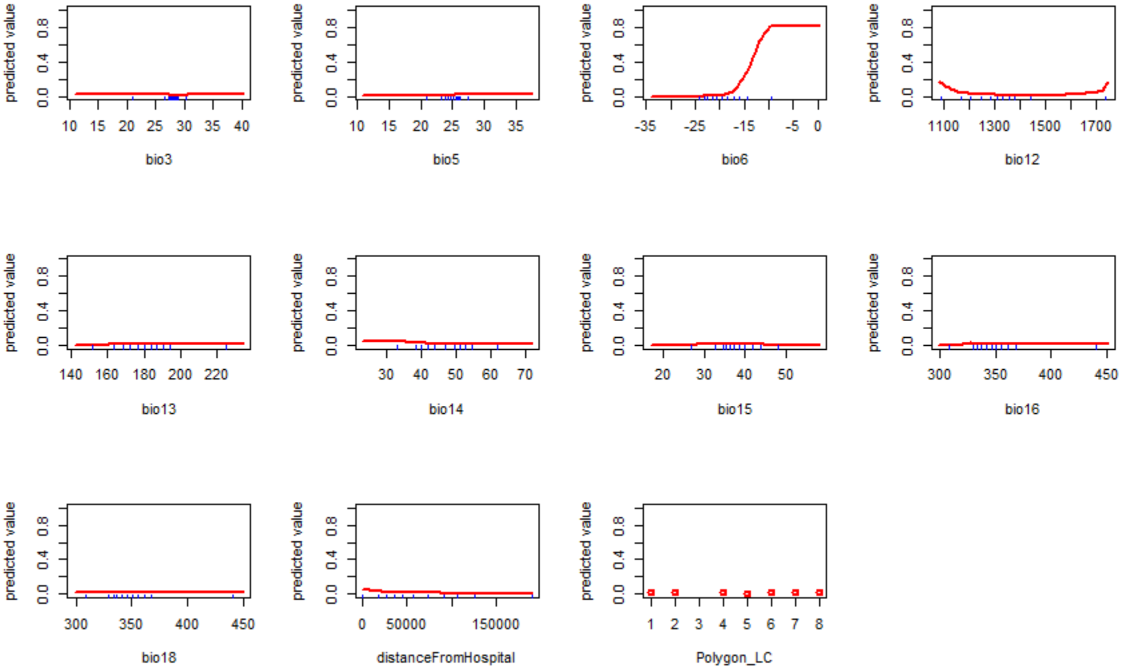

Figure 7: 2009 Response Curve

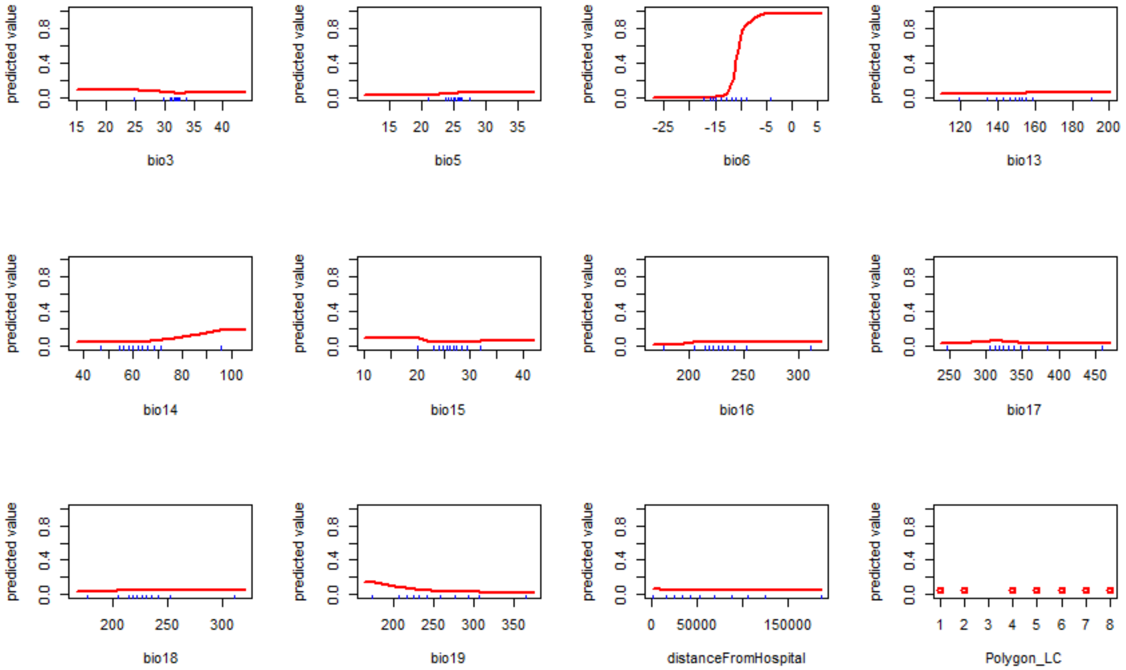

Figure 8: 2017 Response Curve

The response curves (Figure 6 – 8) show the predicted value on the y-axis which is the probability of a Lyme disease case being found in the condition, such as temperature, of the variable on the x-axis. Bio6 (Figure 6 – 8), the minimum temperature of the coldest month, is the main predictor for all three years and shows an S-shaped curve. The first part of the curve between -35 °C and -20 °C show a prediction value of about 0 which indicates that the probability of a Lyme disease case being present at these temperatures is close to zero. This probability increases dramatically between approximately -15 °C and -10 °C before leveling off with a probability of 0.8 to 1.0 at minimum temperatures greater than approximately -10 °C. The land cover, represented as Polygon_LC (Figure 6 – 8), shows the land cover identification number (Table 1) on the x-axis and the probability of a Lyme disease case being present in that land type on the y-axis. All three years show a near-zero probabilities for all land cover types with no value shown for land cover type 3, barren land.

DISCUSSION

The Lyme disease case maps and Maxent model helped form a prediction of Lyme disease risk. The Lyme disease case maps (Figure 1) showed an increase in geographic distribution that expanded north, and an increase in case numbers per town from 2001 to 2017. The percent contributions (Table 3) showed that Bio6, the minimum temperature of the coldest month, was the most important predictor in the model for predicting where Lyme disease cases would be located. Bio6 had percent contributions of 79.7, 85.6, and 84.6 percent for 2001, 2009, and 2017, respectively. The response curves for Bio6 (Figure 6 – 8) indicated a positive association with the probability of a Lyme disease case. As the minimum temperature of the coldest month increased, the probability of a Lyme disease case increased. The percent contribution (Table 3) also showed that land cover was not an important predictor in this model for predicting where Lyme disease cases would be located. Land cover had percent contributions of 0.7, 0.5, and 0.4 percent for 2001, 2009, and 2017, respectively.

The Lyme disease case maps that show the number of Lyme disease cases per town for 2001, 2009, and 2017, are consistent with current data on the increase of Lyme disease cases in Maine over time. Between 2001 and 2017, there is a noticeable increase in geographic distribution and number of cases per town. There is a rising incidence of Lyme disease associated with increasing *I. scapularis* abundance and northward range expansion (Elias, 2020). Lyme disease was first detected in Maine in the late 1980s and has recently risen to more than a thousand cases per year. This rise in cases and geographic range expansion may be caused by a range of factors such as the resurgence of white-tailed deer, attending reforestation, suburbanization of the landscape, and climate change (Smith, 2019). Understanding how the distribution of human cases of Lyme disease is changing over time is important in helping to predict emerging areas of high risk and prepare for them.

The minimum temperature of the coldest month, Bio6, is the most important predictor in this model most likely due to the biological limitations of *I. scapularis*. Figures eight through ten show S-shaped response curves where there are no Lyme disease cases predicted until about -20 °C. A 0.0 to 0.2 predicted value of a Lyme disease case is present at -15 °C and the predicted value continues to rise as the temperature elevates. Between -10 °C and -5 °C, the response curve flattens out with a predictive value between 0.8 and 1. *Ixodes scapularis* populations may be limited by the overwintering conditions that might impact nymphal tick densities and the entomological risk associated with Lyme disease (Hayes, 2015). In one study, the increase of winter temperatures and vegetation vitality, using a Normalized Derived Vegetation Index to measure vegetation stress, switched a habitat from unsuitable to suitable for *I. scapularis* (Estrada-Peña, 2002). In a laboratory setting, engorged female adult ticks died within four hours at -10 °C, and those alternatively exposed to 0 °C survived but did not lay eggs (Ogden, 2004). While these laboratory settings do not mirror the climate and environment variables that *I. scapularis* encounters in its natural habitat, they do give a good indicator of low Maine winter temperatures impacting tick numbers and thus the risk of their transmitting Lyme disease. The presence of leaf litter and snow accumulation is thought to provide some insulation and protection from the harsh winter conditions. In a study on environmental factors for overwintering success of nymphal blacklegged ticks, the ticks where the leaf litter and snow accumulation were undisturbed had significantly greater survival compared to those where the leaf litter was removed or where both leaf litter and snow were removed (Linske, 2019).

Land cover was not an important predictor in this model because Maine is predominantly forested, and the addresses associated with each Lyme disease case weren't linked to the site of human-tick encounter. Forests account for 83% of Maine's surface area, and in the Maxent model, deciduous and mixed forest made up the bulk of land cover (United States Department of Agriculture, 2013). This nearly homogenous landscape, partially a result of only looking at the major land cover type of each town, made land cover a poor predictor for Lyme disease presence. The Maine CDC human Lyme disease case dataset used in this model connects patient home addresses with Lyme disease case locations. A patient might have traveled to Acadia National Park for some outdoor recreational activities and been unknowingly bitten by an infected tick. If the patient is eventually diagnosed with Lyme disease, the home address information will be used instead of Acadia National Park or wherever else Lyme disease might have been contracted. This is partially because it would be impossible for everyone to accurately remember where they were bitten. The model is basing its predictions on home addresses of patients where the land cover type in their town might be completely different from the land cover type that they encountered the infected tick. Even if a patient contracted Lyme disease on their residential property, the land cover majority in a town was used to represent the land cover for the entire town. All the Lyme disease cases were also randomized within town boundaries to prevent patient identification and bias as some patients in the data were not associated with a street-level address.

Other studies have found that a link between tick presence and Lyme disease may explain why the climate variables that influence ticks are good predictors for Lyme disease in my Maxent model. A study in California on the spatial patterns of Lyme disease risk based on disease incidence data found that there was a strong association between areas with high projected acarological risk of exposure to host-seeking *I. pacificus* and Lyme disease incidence at a zip-code scale (Eisen, 2006). This study indicates that high concentrations of nymphal ticks in places where people encounter them, also have a high incidence of Lyme disease. This association between the biological drivers of tick occurrence and human cases of Lyme disease could help explain why the coldest temperature of the coldest month was such a high predictor for Lyme disease. Another model on *I. pacificus* looked at climate suitability and found that cold-season average temperatures below 0 °C created unsuitable habitats for *I. pacificus* (Eisen, 2018). While my model relied on the single coldest temperature of the coldest month of the year instead of the average cold-season temperature, this model further supports that cold temperatures make a habitat unsuitable. A population model for *I. scapularis* that investigated how climate change could affect northward range expansion found that the colder the environment, the greater proportion of ticks die before reproducing (Ogden, 2006).

The Maxent model has a few limitations, one being that it calculates environmental suitability rather than predicted probability of occurrence. This model uses the presence-only Maine CDC human Lyme disease case data and analyzes the climate and land cover types associated with these cases to make predictions on what types of environments are suitable for Lyme disease in Maine. This is in contrast with being able to predict the probability, or chance, of a Lyme disease case occurring in each location. While being able to determine if an environment is suitable for Lyme disease contributes to the understanding of Lyme disease, being able to give percent likelihoods of a Lyme disease case occurring in a location could prove additionally useful in targeting high-risk areas for Lyme disease prevention. Maxent models cannot conclude any causation, rather they are good tools for correlative studies (Elith, 2011). This means that no conclusion can be made if a very low minimum temperature of the coldest month causes a decrease in Lyme disease cases, only that a negative association exists between the minimum temperature of the coldest month and Lyme disease presence. This limits the ability to predict Lyme disease case presence based on the minimum temperature of the coldest month. Further research would need to be done to determine causation between the two which may be useful in further models based on Lyme disease.

Ultimately, this model is a great start at understanding the complex factors involved with Lyme disease risk. Due to its unique land cover and climate, Maine could benefit from its own ecological niche model that is similar to models on Lyme disease in other states. The findings of this model show that cold winter temperatures in Maine may be influencing Lyme disease risk, important when considering the projected climate change in Maine over the next decades (Dumic, 2018). Future research could include using drag cloths at different test locations and testing for *B. burgdorferi* as an indicator for Lyme disease risk to be used in the model instead of the human case data. This could help make land cover more relevant as it would be linked to the tick location. More research on how cold temperatures impact *I. scapularis* would also be beneficial in understanding Lyme disease risk related to tick survival. Some research has been done on how cold temperatures impact ticks in the lab setting as well as outdoors in naturally simulated enclosures with soil, leaves, and snow. However, so many factors impact tick survival in winter conditions such as life stage, if the tick is engorged, amount of snow and detritus covering the tick, and exposure to precipitation and wind, that more research to determine the mechanism of survival in low temperatures should be conducted (Brunner, 2012).

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APPENDIX

APPLICATION COVER PAGE

- ***KEEP THIS PAGE AS ONE PAGE – DO NOT CHANGE MARGINS/FONTS!!!!!!!!!***
- ***PLEASE SUBMIT THIS PAGE AS WORD DOCUMENT***

APPLICATION FOR APPROVAL OF RESEARCH WITH HUMAN SUBJECTS
Protection of Human Subjects Review Board, 400 Corbett Hall

(Type inside gray areas)
PRINCIPAL INVESTIGATOR: Allison Gardner EMAIL: allison.gardner@maine.edu
CO-INVESTIGATOR: EMAIL:
CO-INVESTIGATOR: EMAIL:
FACULTY SPONSOR: EMAIL:
(Required if PI is a student):
TITLE OF PROJECT: The geographic range expansion of Lyme disease in Maine
START DATE: 10/1/2017 PI DEPARTMENT: School of Biology and Ecology
FUNDING AGENCY (if any):

STATUS OF PI: FACULTY/STAFF/GRADUATE/UNDERGRADUATE F (F,S,G,U)

1. If PI is a student, is this research to be performed:

for an honors thesis/senior thesis/capstone? **for a master's thesis?**
for a doctoral dissertation? **for a course project?**
other (specify)

2. Does this application modify a previously approved project? N (Y/N). If yes, please give assigned number (if known) of previously approved project:

3. Is an expedited review requested? Y (Y/N).

**Submitting the application indicates the principal investigator's agreement to abide by the responsibilities outlined in [Section I.E. of the Policies and Procedures for the Protection of Human Subjects](). **

Faculty Sponsors are responsible for oversight of research conducted by their students. The Faculty Sponsor ensures that he/she has read the application and that the conduct of such research will be in accordance with the University of Maine's Policies and Procedures for the Protection of Human Subjects of Research. REMINDER: if the principal investigator is an undergraduate student, the Faculty Sponsor MUST submit the application to the IRB.

Email this cover page and complete application to UMRIC@maine.edu

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FOR IRB USE ONLY Application # 2017-09-06 Review (F/E): E Expedited Category: I.I.3.e.
ACTION TAKEN:

Judged Exempt; category Modifications required? Accepted (date)
X Approved as submitted. Date of next review: by 10/9/2018 Degree of Risk: minimal
Approved pending modifications. Date of next review: by Degree of Risk:
Modifications accepted (date):
Not approved (see attached statement)
Judged not research with human subjects

FINAL APPROVAL TO BEGIN 10/10/2017
Date

01/2017

AUTHOR'S BIOGRAPHY

Elizabeth Xue Dee was born in Jiangxi province, China on September 6, 1998. She was raised in Reading, Massachusetts and graduated from Reading Memorial High School in 2017. Majoring in zoology, Elizabeth has a minor in microbiology and a pre-medical concentration. She was also a member of UMaine's Equestrian Team. Upon graduation, Elizabeth plans on taking a gap year while applying to veterinary medical schools and hopes to become a Doctor of Veterinary Medicine (DVM) after completing a four-year program.