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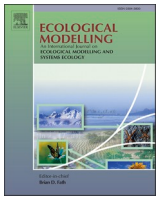

The effect of landscape, transmission mode and social behavior on disease transmission: Simulating the transmission of chronic wasting disease in white-tailed deer (*Odocoileus virginianus*) populations using a spatially explicit agent-based model

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ABSTRACT

We developed a spatially explicit agent-based model (ABM), DeerLandscapeDisease (DLD), to investigate the effects of landscape structure, disease transmission, and management alternatives on dynamics of chronic wasting disease (CWD) in white-tailed deer (*Odocoileus virginianus*). We fitted biased random walk models to data from GPS-collared deer to simulate movements of individual deer and deer groups in an agricultural landscape with fragmented forest patches and a forest-dominated landscape. We estimated behavioral and demographic parameters from field data and published literature of deer ecology. We considered both direct and indirect transmission routes and assumed that bioavailability of infectious pathogens deposited in the environment decreased exponentially over time. We tuned transmission parameters to match observed trajectories of CWD prevalence in Wisconsin, and assumed that infection probability during an encounter was equal for all age classes. Thus, infection prevalence varied with sex- and age-specific behavior.

DLD simulations demonstrated significant effects of landscape structure, social behavior and transmission mode on temporal changes in prevalence. Prevalence rose faster and reached higher levels in fragmented forest landscapes due to aggregation of deer within small forest patches. Furthermore, simulation results suggested that CWD might be driven through a mix of frequency- and density-dependent processes, potentially facilitating coexistence of CWD and deer populations. These results demonstrate the utility of ABMs and the importance of including spatial and behavioral heterogeneity when modeling disease transmission.

1. Introduction

Wildlife epizootics are challenging to predict or control, and any hope of doing so requires understanding of the routes and patterns of transmission. Epizootiological models can inform predictions of disease and impacts and the success of control efforts, based on observed or hypothesized transmission patterns. Classical mathematical models assume that force of infection is dependent on either the proportion of infected hosts (frequency-dependent transmission) or the population density of infected hosts (density-dependent transmission, (May and Anderson, 1979; O'Keefe, 2005) yet many diseases may not fit well within this strict dichotomy. In addition, the establishment and transmission of disease within a population are both stochastic and intrinsically spatial, affected by demography, population dispersion, and habitat heterogeneity (Drake, 2005; Fa et al., 2001; Gudelj and White, 2004; Parratt et al., 2016; Rees et al., 2013). An animal may die before it can transmit the disease, extinguishing an epizootic before it can begin. Once the disease is established, an infected animal might become spatially isolated or surrounded by other infected animals, thus reducing the transmission of disease to susceptible hosts. Spatially explicit, agent-based models (ABMs) are advantageous because they can reproduce stochastic spatio-temporal segregation of infected and uninfected individuals (Fa et al., 2001; Gudelj and White, 2004) and can incorporate detailed spatio-temporal variables, individual variations,

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and demographic stochasticity (Conner et al., 2007; Rees et al., 2013; Wilson, 1998).

Most ABMs on epizootiology only incorporate direct transmission pathways and do not base individual behaviors on empirical movement data (e.g. rabbit viral hemorrhagic disease, Fa et al., 2001, bovine tuberculosis in badgers, Smith et al., 2001, and chronic wasting disease, Belsare et al., 2018; Belsare and Stewart, 2020). Several diseases, such as bovine tuberculosis and chronic wasting disease (CWD) may be spread through both direct and indirect contact (Palmer and Whipple, 2006; Williams et al., 2002). Furthermore, disease transmission is dependent on contact rates that in turn are determined by how animals move within their environment (indirect contact) and in relation to other animals (direct contact). Previous models on CWD transmission have not incorporated empirical-based movement (Gross and Miller, 2001) nor indirect transmission of the disease (Belsare et al., 2018; Belsare and Stewart, 2020), but the effect of animal movement on contact rates and thus disease transmission indicates that incorporating realistic movement behaviors into models of disease transmission may be of great importance.

We developed DeerLandscapeDisease (DLD), a spatially explicit ABM to simulate disease transmission in white-tailed deer using published data on CWD and empirical data on deer behavior and movement. CWD is the only transmissible spongiform encephalopathy found in free-ranging wildlife, affecting deer (*Odocoileus hemionus, Odocoileus virginianus*), elk (*Cervus Canadensis*, Miller et al., 2000; Saunders et al., 2012; Williams et al., 2002), reindeer (*Rangifer tarandus*, Benestad et al., 2016) and moose (*Alces alces*, Baeten et al., 2007; Colorado Division of Wildlife, 2012). CWD affects the central nervous tissue and is characterized by behavioral changes such as excessive salivation, tremors, lack of coordination, difficulty swallowing and increased drinking and urination, followed by loss of body condition and ultimately death (Miller et al., 2000). The prion agent causing CWD has been found in saliva, blood, urine, and feces (Haley et al., 2009a; C.K. Mathiason et al., 2006) and can remain infective in the environment for years (Mathiason et al., 2009; Miller and Williams, 2003; Williams et al., 2002), thus both direct and indirect transmission of CWD may occur. However, little is known about the strength of each infection route and the subsequent long-term effect of CWD on population densities within wild animal populations. The animal model in DLD specifically simulates behavior of white-tailed deer thought to influence population dynamics and disease transmission, such as movement, mating and grouping behavior. The disease component in DLD allows for pathogen build-up in the environment, and contacts between individual deer, either direct or indirect, are modeled as a stochastic process depending on movement of the animals involved. We used DLD to investigate the following research questions: (1) how does landscape composition affect deer behavior and movement and thus CWD transmission?, (2) how will different transmission pathways (direct vs. indirect transmission) affect long-term host-disease dynamics (frequency- vs. density-dependent transmission)?, and (3) will deer removal aid in controlling CWD in wildlife populations? Our description of DLD follows the ODD (Overview, Design concepts, Details) protocol (Grimm et al., 2006, 2010, 2020), detailing methods for modeling individual- and group movement within home ranges based on GPS collar locations in appendices.

2. Materials and methods

2.1. Programming platform

DLD was created using the Repast Simphony platform (North et al., 2013, 2007, 2005) and Java programming language (Arnold et al., 2005). We chose Repast Simphony due to its user friendly graphical user interface, its ability to incorporate raster files and shape files, the versatility of the Java programming language, and the ability to run from standalone batch files. Furthermore, Repast Simphony is free and open-source.

2.2. Landscape data

The landscapes in DLD are based on two study sites in Illinois, USA (Fig. 1). One is a predominantly forested landscape in southern Illinois, whereas the east-central Illinois study site is dominated by agricultural fields and fragmented forest patches (Table 1). In DLD, we refer to the southern Illinois landscape as the contiguous forest landscape, and the east-central Illinois landscape as the fragmented forest landscape.

2.3. Model overview

DLD is a stochastic spatio-temporal simulation model that runs with 2-hour time steps. The model is agent-based and incorporates demographic processes of white-tailed deer such as birth and death, mating, grouping, as well as a detailed empirically based movement model. DLD furthermore includes a disease component, simulating the transmission of CWD both directly via animal-to-animal contact, and indirectly as CWD prion build-up and decay in the environment.

2.4. Summary ODD

A complete, detailed model description, following the ODD protocol (Grimm et al., 2020, 2010, 2006) is provided in Appendix A, and a summary ODD following the template by Grimm et al. (2020) follows.

The overall *purpose* of DLD is to understand the transmission dynamics and long-term impacts of CWD in white-tailed deer populations. We are specifically addressing how landscape structure and transmission mode affect population level CWD dynamics in white-tailed deer (frequency- vs. density-dependent transmission) under realistic movement and social behaviors. In addition, we aim to assess the effectiveness of alternative culling strategies for disease control. To consider our model realistic enough for its purpose, we use *patterns* in mortality, reproduction, mating, age, home range, grouping and movement.

The model comprises the following *entities*: individual deer (adult females, adult males and fawns), landscape (square grid cells of 25 $\times$ 25 m, referred to as pixels), time, and disease. Individual deer are characterized by the state *variables*: identity number, age, sex, identity of the home range where the individual lives, group membership, and disease status. Individual deer are assigned specific behavioral states that are dependent on season, age, and sex of the animal. Each behavioral state is associated with state-specific movement and behavior, and transitions between states are triggered by events such as dispersing or mating. States in the model are: normal, dispersal, mating, and exploratory behavior (Fig. 2).

As for the *spatial* and *temporal* resolution and extent: each time step in the model is 2 h and simulations are run for 50 years. DLD is spatially explicit, but landscape structure and habitat types are held constant within the model.

The most important *processes* of the model, which are repeated every *time step*, are the update of indirect and direct contacts produced by moving deer agents as well as the update of the landscape pixels regarding build up and decay of CWD prions (indirect contact). Furthermore, the following deer behaviors and attributes heavily influence the above processes: 1) Individual movement at each time step, as it is dependent on the age, sex, and behavioral state of the agent - whether it is member of a group, tending to a fawn (female movement only), following a female during the mating season (male movement only), dispersing or conducting exploratory behavior (See Appendix A and C for details on modeling movement based on empirical data), 2) CWD status, as direct infectivity rates, prion deposition rates, and mortality rates due to CWD are modeled as functions of time resulting in infected agents becoming more infectious with time, shedding more prions in the environment with time, and mortality increasing as the disease progresses (See Appendix A and B for details). As we allow for CWD prions to accumulate in a landscape pixel, we added prion decay to simulate an exponential decline over time of prions in a pixel (Appendix

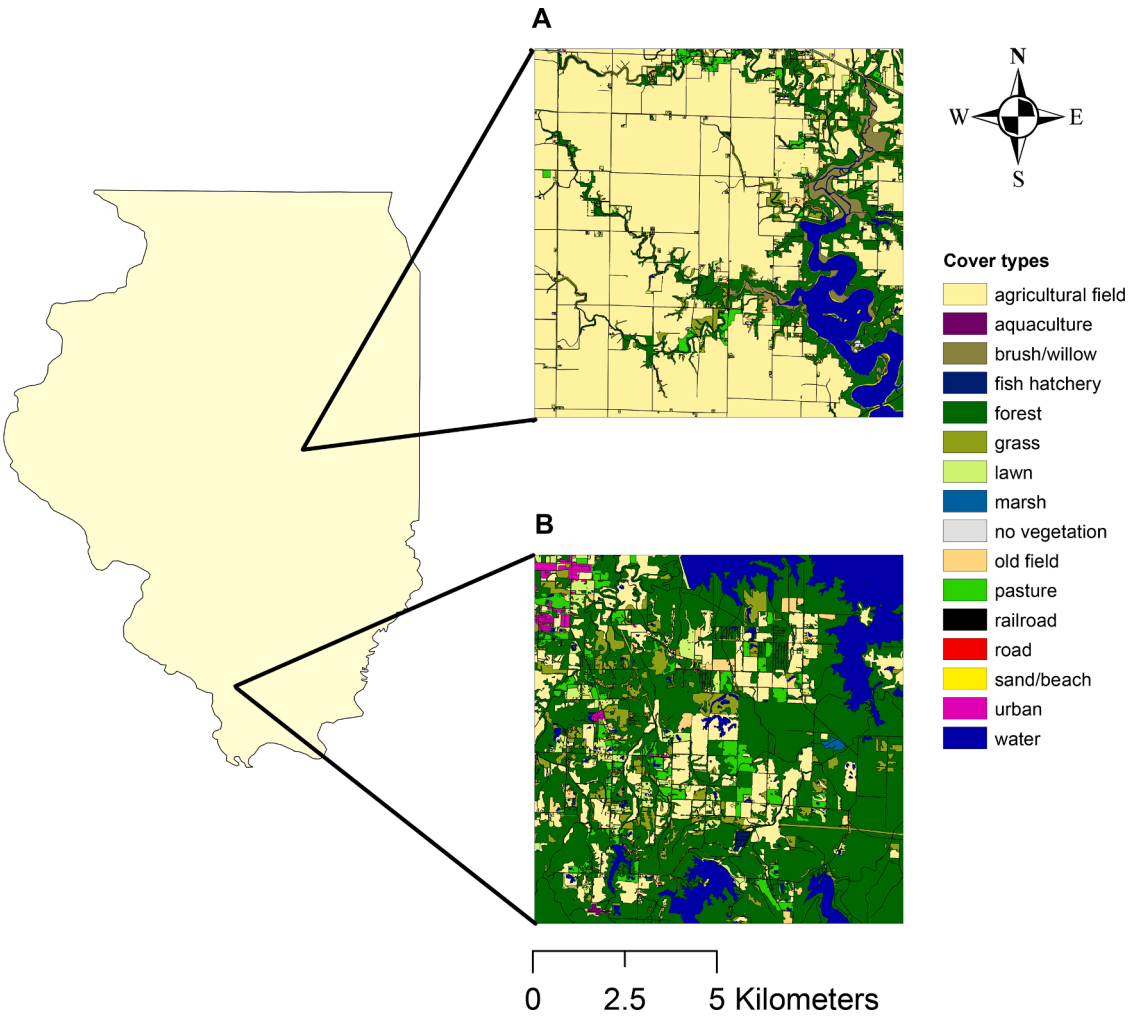

Fig. 1. Maps of the two study sites. Land cover composition of 10 × 10 km areas of the southern Illinois and east-central Illinois study sites, respectively.

Table 1
Landcover types in the 10 × 10 km raster maps used in DeerLandscapeDisease for the contiguous forest landscape (CFL) and the fragmented forest landscape (FFL). Percentages can be obtained by dividing total areas by 100.

Landcover code	CFL Total area (ha)	FFL Total area (ha)	Description
Agricultural field	1405.6	6984.0	Agricultural fields, mainly corn and soybeans
Aquaculture	7.5	N/A	Aquaculture center
Brush/willow	N/A	252.4	Mainly brush and willow
Fish hatchery	16.0	N/A	Fish hatchery
Forest	5565.2	1380.5	Forest consisting mainly of oak-hickory
Grass	609.9	264.6	Native grasses, not mowed
Lawn	427.9	203.0	Mowed and tended lawns
Marsh	13.9	N/A	Marsh
No vegetation	N/A	12.4	No vegetation, driveways, parking lots etc.
Old field	136.7	49.9	Field in late successional state, with brush and trees
Pasture	442.6	106.5	Grassy fields, grazed by livestock
Railroad	N/A	2.1	Railroad
Road	80.0	72.5	Highways, roads and gravel roads
Sand/beach	N/A	29.1	Sandy areas and beach
Urban	117.7	15.7	Buildings and houses
Water	1181.2	630.9	Lakes, ponds and rivers

A), a decay that is also updated at each time step (See Appendix A and B for details). Empirical data on the bioavailability of prions in the environment is not available, so we set a half-life of 6 months as a starting point (See Appendix A and B).

The most important *design concepts* of the model are the way DLD incorporates behavior-dependent deer movement based on empirical data from field studies (movement sub-model, Appendix A and C) and the incorporation of a CWD sub-model governing direct- and indirect contact rates, and CWD prion build up and decay in the landscape pixels. These components allow for emergent patterns of disease dynamics based on individual behaviors and movements within DLD.

2. 5. DLD scenarios

We created 6 different scenarios to investigate the importance of landscape structure, mode of transmission, and deer removal on disease transmission and host population dynamics. We ran direct and indirect transmission scenarios separate for both the fragmented forest landscape and the contiguous forest landscape (4 scenarios). We separated the two transmission modes, as the contribution of each transmission pathway in nature is unknown, and we wanted to assess how different transmission modes can affect long-term disease dynamics. We explored the efficacy of general (e.g., increased public harvest) as opposed to localized culling (e.g., sharpshooting entire groups) by reducing maximum group sizes to half of the default values (female group size: 2, male group size: 5) at the same overall population size (for default groups sizes, see Appendix B). We only reduced group sizes given direct transmission, because we

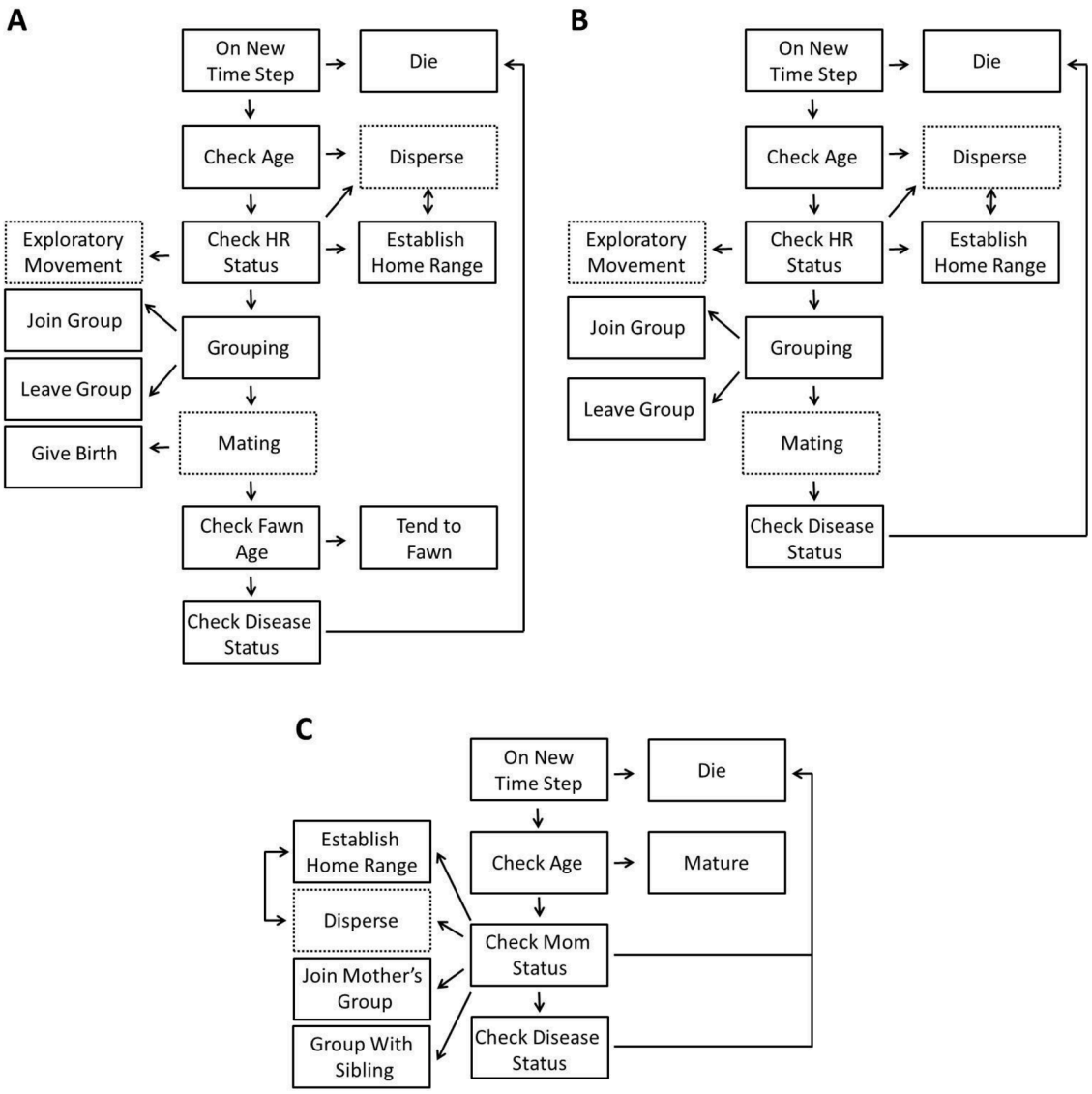

Fig. 2. Behavioral phases in the model. Diagram of behaviors/behavioral phases for (A) female agents, (B) male agents, and C) fawn agents. Broken square boxes depict actual states. As soon as the agent is done with a state (usually triggered by some event or by time), the agent returns to the state "normal" (not depicted but all other behaviors belong to this state). Some of the behaviors/behavioral phases are processed at each time step whereas some are dependent on time of year. In DLD individuals and their behavior/behavioral phases are processed in random order, unless behaviors/phases are dependent on other behaviors/phases.

expected the effect of reduced groups to be higher for direct contacts (Schauber et al., 2007). We also ran each landscape without any disease present, and thus ended up with 8 scenarios total. We ran 500 replicates of each scenario for 50 simulation years (including a 5 year burn-in period) and checked for convergence.

2.6. Data analysis

2.6.1. CWD prevalence and force of infection

We first checked if 500 replicate runs were adequate to reach convergence of the standard deviation for prevalence. Then, we compared temporal patterns of prevalence (arcsine square root transformed) among scenarios using repeated measures ANOVA (omitting year 1–5 to avoid initial transient dynamics). We used the same analysis to compare prevalence between males, females, and fawns within scenarios. We also compared prevalence between young (≤ 3 years) and old (> 3 years) males and females to examine how prevalence changes with age. To investigate whether differences between observed prevalence patterns in our model and prevalence found in field studies could be attributed to difficulties in detecting early disease infection, we re-analyzed our data using only animals infected for at least 6 months (infectious prevalence) using same methods as above.

To assess whether transmission patterns that emerged in our model corresponded better to density-dependent or frequency-dependent concepts, we used a power-law regression to compare how strongly force of infection (ζ, proportion of susceptible in year i surviving to year $i+1$ that became infected during that year) was related to the density of infectious (infected $>$ 6 months) animals in year i (I, density dependence) versus infectious prevalence in year i (I/N, frequency dependence)

$$\zeta = e^{b0} * I^{b1} * (I/N)^{b2} \rightarrow ln(\zeta) = b0 + b1ln(I) + b2ln(I/N) \quad (1)$$

If ζ is linearly density-dependent, then b1 should $= 1$ and b2 should $= 0$, and vice versa for linear frequency dependence. Nonlinearity can be handled by exponents different from 1. We only included animals infected $>$ 6 months in I and I/N, because CWD in DLD is modeled as having a latent period with animals at an advanced disease stage assumed to be more infectious.

To account for delays in prion accumulation in the indirect-

transmission scenarios, we also used power law regression to model ζ in year *i* against I and I/N in year *i* and prior years:

$$Lag1 : \cdot ln(\zeta_i) = b0 + b1ln(I_i) + b2ln(I/N_i) + b3ln(I_{i-1}) + b4ln(I/N_{i-1}) \quad (2)$$

$$Lag2 : ln(\zeta_i) = b0 + b1ln(I_i) + b2ln(I/N_i) + b3ln(I_{i-1}) + b4ln(I/N_{i-1}) + b5ln(I_{i-2}) + b6ln(I/N_{i-2}) \quad (3)$$

To account for collinearity of I and I/N, we used standard linear regression to compare the fit of the above models with models involving either I alone or I/N alone, and calculated the Partial R^2 for each predictor:

$$PartialR^2[B] = \left(R^2[AandB] - R^2[Aonly]\right) / \left(1 - R^2[Aonly]\right) \quad (4)$$

All analyses were conducted in R.3.5.2 (R Development Core Team, 2018), and we omitted year 1 to 7 for all power-law analyses to avoid initial transient dynamics and account for time lags up to 2 years.

2.6.2. Sensitivity analysis

We conducted a one-factor-at-a-time local sensitivity analysis on prion half-life by decreasing and increasing it by 2 months (half-life of 4 and 8 months, respectively). The half-life of prion proteins is largely unknown, thus we varied our default half-life of 6 months by ±33.33% to assess how different magnitudes of this parameter would impact prevalence. The analysis was carried out for indirect scenarios and run for 50 years with the same initial parameters as the original runs. During the transmission coefficient calibration process to fit our prevalence patterns to observed prevalence patterns in Wisconsin (see Appendix A), we observed a very high sensitivity of the model to this parameter, both for the direct and indirect scenarios, thus we did not conduct sensitivity analysis on this parameter.

3. Results

3.1. DLD simulation runs

Convergence of prevalence standard deviations was reached with 500 replicates of each scenario (Appendix D, Fig. D1), indicating that 500 replicates were enough to distinguish between scenarios and to perform statistical hypotheses testing on the simulation results.

All repeated measures analyses of total infection prevalence and infectious prevalence (proportion infected > 6 months) indicated significant scenario*time (all $F_{220,134730}$ >100, $P < 0.0001$) and age/sex category*time interactions (all $F_{176,673650}$ >10, $P < 0.0001$).

3.1.1. Landscape effects and transmission mode

Without the disease component, populations grew at an average rate of ca. 3% per year and population sizes after 50 years averaged ca. 4500 animals for both landscapes (not depicted). Adding the disease component to the model caused population decline in all of the fragmented forest scenarios (where effective population densities were higher because less of the landscape was suitable for home ranges). The direct transmission runs showed an average peak population decline (average of peak declines of all replicates, omitting year 1–5) of 11.3%, with an average population size of ca. 502 in year 50 of the simulation run (Fig. 3A). In the indirect transmission scenario, the average peak population decline was 11.3%, with an average population size of ca. 546 in year 50. For the contiguous forest landscape, populations also decreased in the direct transmission scenarios with default group sizes with an average peak decline of 7.8% and a population size of ca. 884 in year 50 of the simulation runs. For the continuous indirect transmission

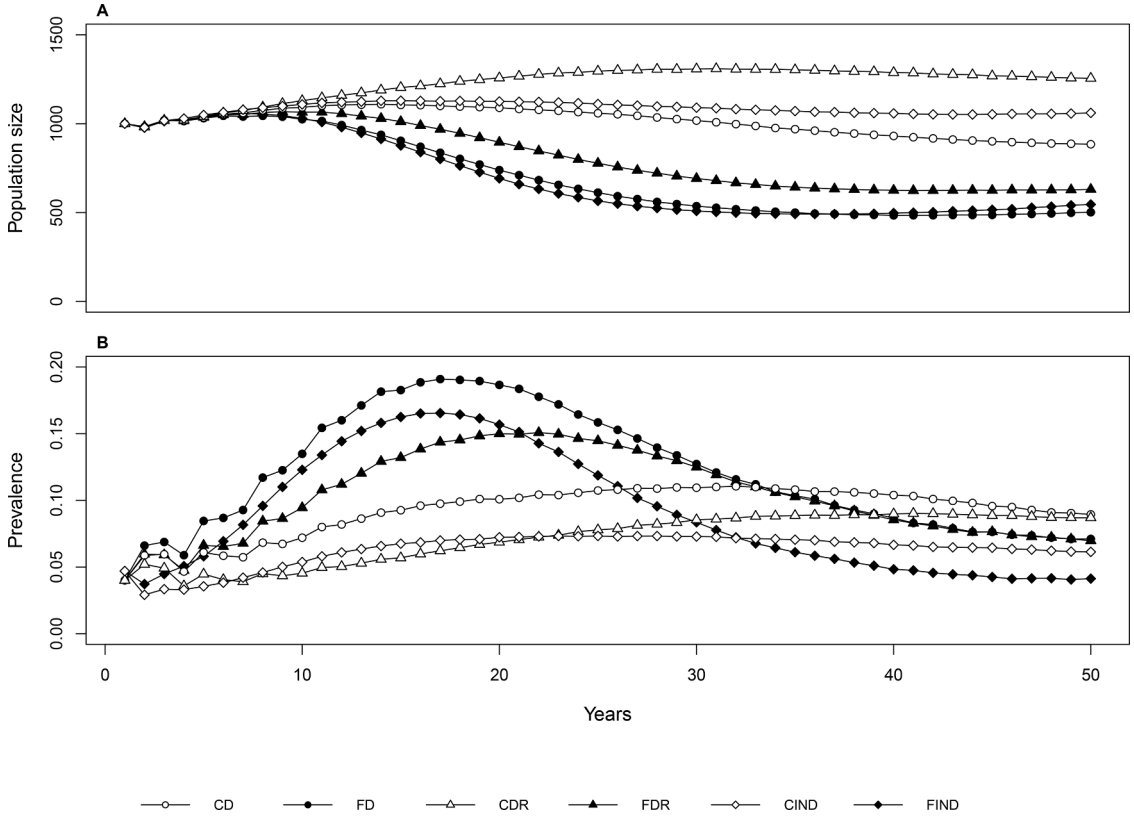

Fig. 3. Deer population size and prevalence in DLD scenarios. A) Average deer population sizes in the different DLD scenarios, B) average prevalence in the different DLD scenarios. C = contiguous forest, *F* = fragmented forest, *D* = direct transmission, *R* = reduced group size, and IND = indirect transmission. *N* = 500 replicates for each scenario.

scenario, the average peak decline was 7.3% with an average population size of ca. 1061 in year 50 of the simulation runs (Fig. 3A).

For both direct and indirect transmission, CWD prevalence reached higher values and peaked earlier in the fragmented forest landscape, where the deer population was compressed into less space, than the contiguous forest landscape (Fig. 3B). In both landscapes, direct transmission resulted in higher prevalence than did indirect transmission.

With direct transmission, prevalence was higher in males, whereas prevalence values in fawns, females and old females were similar (Fig. 4). When only including animals infected longer than 6 months, the difference between age and sex groups in the direct scenarios was mainly due to higher prevalence in males and lower prevalence in fawns (Fig. 5). Prevalence in old males was higher than in young males for the direct scenarios. For the indirect scenarios the differences in prevalence levels were mainly due to lower prevalence in fawns (Fig. 4 and Fig. 5).

3.1.2. Deer removal

Population size for the direct fragmented forest scenario with reduced group size showed an average peak decline of 9.9%, and ended with an average size of ca. 631 in year 50 (Fig. 3A). The contiguous forest scenarios generally increased in population size but had an average peak decline of 6.5% and an average population size of ca. 1255 in year 50 (Fig. 3A) .

Reducing group sizes produced lower prevalence and later epizootic peaks than with default group sizes for both the fragmented and contiguous forest scenarios (Fig. 3B). As with default group size, we found that CWD prevalence was higher in males with similar prevalence for fawns and females for both the fragmented and contiguous forest scenarios (Fig. 4). When looking at animals infected longer than 6 months, we found higher prevalence in males and lower prevalence in fawns (Fig. 5).

3.1.3. Force of infection and host-disease dynamics

Force of infection (ζ) showed similar relationships with the density of infectious individuals (I, those infected >6 months) and infectious prevalence (I/N) across the different scenarios (Fig. 6). The density and frequency of infected animals (I and I/N, respectively) tracked similar trajectories over time (Fig. 6), making it difficult to determine which was the stronger driver of changes in force of infection. However, power-law regression of output with direct transmission lent more support for frequency-dependent than density-dependent transmission (Tables 2-4). Whether comparing the relative sizes of the coefficients representing density dependence and frequency dependence (Table 2), the percentage of runs where each coefficient was statistically significant (Table 3), or their partial R^2 values (Table 4), frequency dependence received about twice the support or more than density dependence across scenarios with direct transmission. In contrast, results from indirect transmission scenarios yielded balanced support for density- and frequency-dependent transmission in the contiguous landscape, and greater support for density dependence in the fragmented landscape (Tables 2–4). Output from simulations with indirect transmission yielded little evidence for lagged effects of I or I/N on ζ (Tables 2–4). Adding lagged predictors did not substantially improve R^2 (Table 4), and resulted in unstable coefficient estimates (Table 2) that achieved statistical significance in less than 11% of replicate runs (Table 3).

3.2. Prion half-life

Sensitivity analysis performed on prion half-life showed that disease prevalence was highly sensitive to this parameter. Compared to the original 6 month half-life, a shorter half-life of 4 months resulted in lower prevalence for both the contiguous and fragmented forest scenarios, where at the prevalence peak, prevalence for both scenarios were

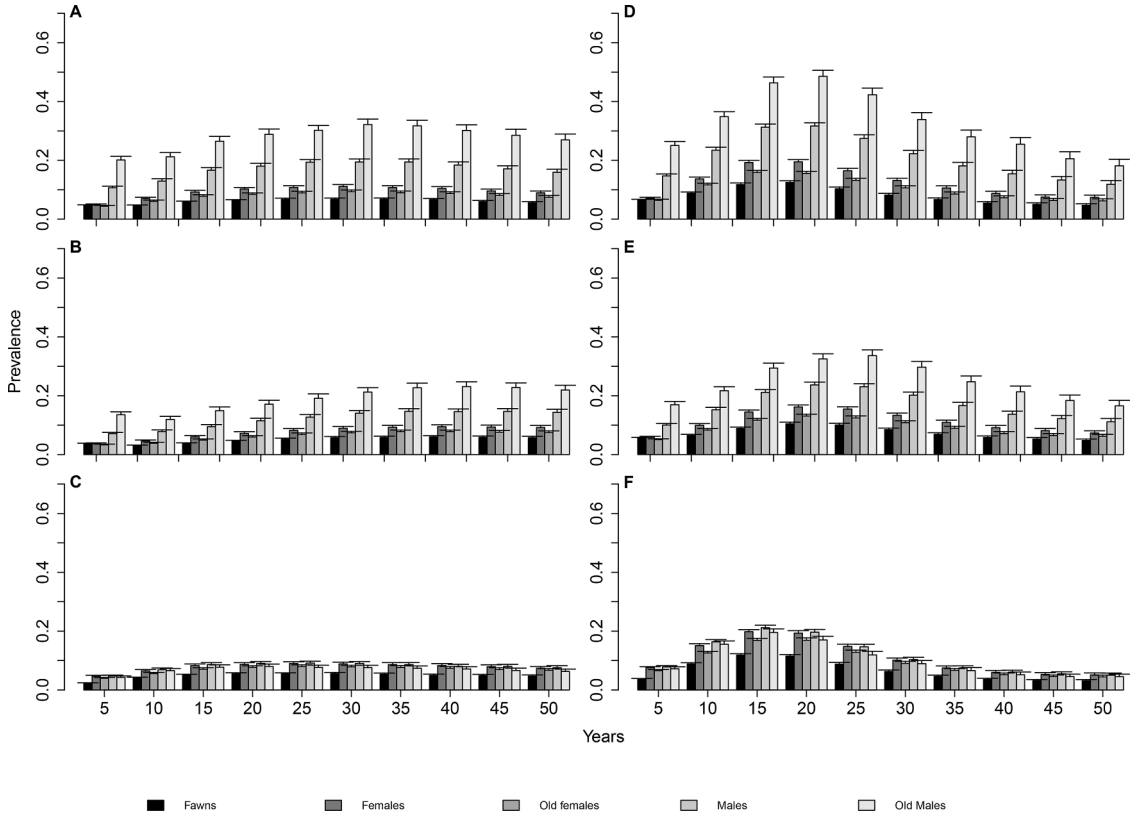

Fig. 4. Age- and sex-specific infection prevalence in DLD scenarios. CWD infection prevalence divided into age- and sex groups in A) direct transmission, contiguous forest landscape, B) direct transmission, reduced group size, contiguous forest landscape, C) indirect transmission, contiguous forest landscape, D) direct transmission, fragmented forest landscape, E) direct transmission, reduced group size, fragmented forest landscape, F) indirect transmission, fragmented forest landscape. Error bars are standard errors. For illustrative purpose, only years 5, 10, 15, 20, 25, 30, 35, 40, 45 and 50 are depicted.

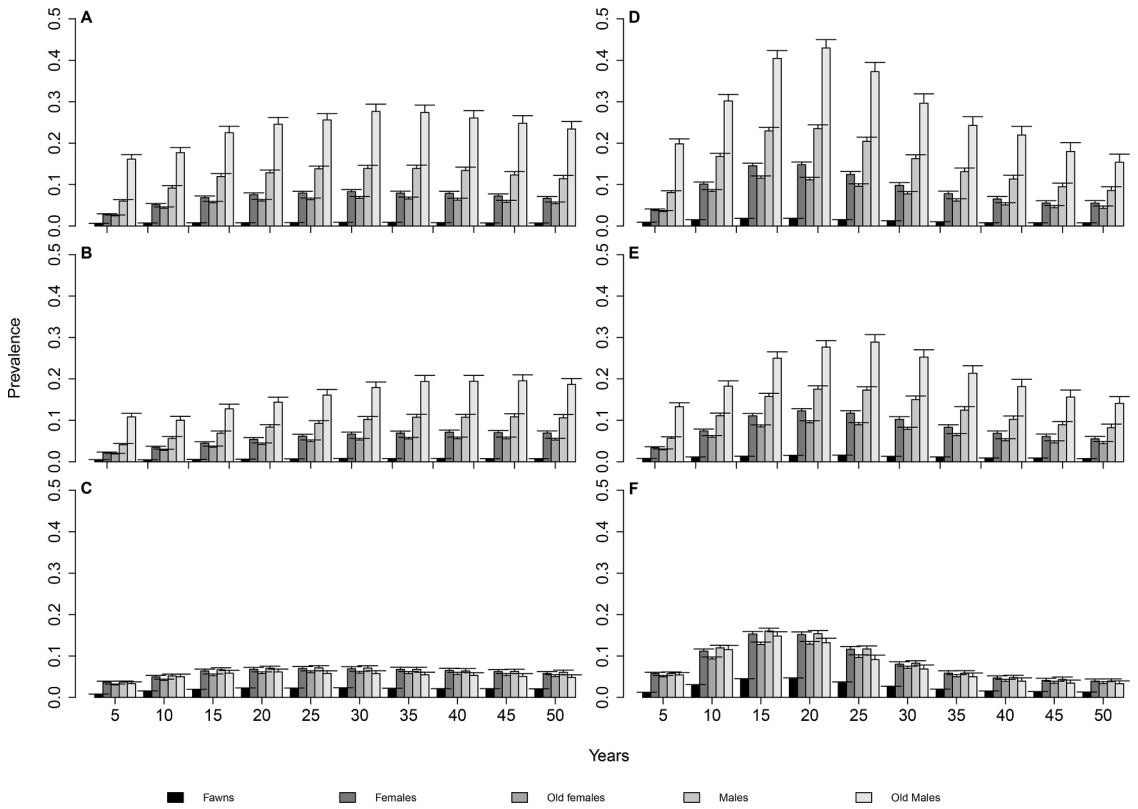

Fig. 5. Age- and sex-specific infection prevalence of infectious individuals. CWD prevalence of infectious individuals (infected longer than 6 months) divided into age- and sex groups in A) direct transmission, contiguous forest landscape, B) direct transmission, reduced group size, contiguous forest landscape, C) indirect transmission, contiguous forest landscape, D) direct transmission, fragmented forest landscape, E) direct transmission, reduced group size, fragmented forest landscape, F) indirect transmission, fragmented forest landscape. Error bars are standard errors. For illustrative purpose, only years 5, 10, 15, 20, 25, 30, 35, 40, 45 and 50 are depicted.

almost half of the prevalence produced by a 6 month half-life (Appendix D, Fig. D2). This resulted in a higher deer population size than in the original scenarios, with a still increasing population for the contiguous forest landscape (Appendix D, Fig. D3). A half-life of 8 months resulted in almost a doubling of the prevalence at the prevalence peak for both the contiguous and fragmented forest scenarios compared to scenarios with a 6 month half-life (Appendix D, Fig. D2). Population size for these scenarios were much lower than for the original scenarios, with a much earlier decrease in deer numbers (Appendix D, Fig. D3).

4. Discussion

We developed an agent-based spatially explicit model on CWD transmission in white-tailed deer to investigate how landscape and transmission mode may affect overall and sex-specific CWD prevalence and subsequently host-disease dynamics. We simulated culling, by reducing group sizes to investigate whether deer removal could aid in controlling CWD in white-tailed deer. We furthermore used force of infection to assess whether the emerging transmission patterns corresponded better to density-dependent or frequency-dependent concepts.

4.1. Landscape effects on CWD transmission

CWD transmission and mortality were sufficient to cause deer population declines in both contiguous and fragmented landscapes, but disease spread more rapidly and produced earlier and more severe population impact in the fragmented landscape. These population impacts can be explained by differences in effective population density between the two landscapes. White-tailed deer need a component of forest cover within their home range (Marchington and Hirth, 1984), concentrating and increasing the local density of deer in landscapes with small forest patches and thus the potential for both direct and indirect contacts. Farnsworth et al. (2005) found that destruction of suitable habitat due to development might cause a concentration of mule deer (*O. hemionus*) in suitable fragmented patches, increasing local population density and thus accelerating transmission of CWD. Storm et al. (2013) found CWD incidence in Wisconsin to be positively related to forest edge density (length of edge relative to the total area analyzed), and in Canada, Norbert et al. (2016) found high CWD risk in high deer density riparian forest patches surrounded by agriculture. As simulated population sizes decreased in DLD, prevalence in the fragmented forest landscape still increased for multiple years when transmission was both direct and indirect, until the host-disease system somewhat approached a stable equilibrium by the end of the simulations. This could be due to landscape configuration, where deer in the fragmented scenario would be aggregated in forest patches with local densities being still high enough to drive prevalence until a certain threshold. A different pattern is found in the contiguous forest scenarios, where direct transmission scenarios show a more concomitant relationship between population size and prevalence. These results highlight that CWD control efforts may need to be both more intensive (due to enhanced transmission) and more spatially extensive to be effective in landscapes where deer habitat is highly fragmented, such as in much of the Midwest and Great Plains. Urbanization and agricultural expansion are continuously causing forest fragmentation in the US and elsewhere (Fynn and Campbell, 2018). High effective density of deer within small strips and patches of forest cover, combined with the greater dispersal tendency and distance of white-tailed deer in open landscapes (Kelly et al., 2014; Long et al., 2005; Lutz et al., 2015; Nixon et al., 2007), amplify the challenge. In Illinois, where CWD is found within agriculture-dominated areas in the

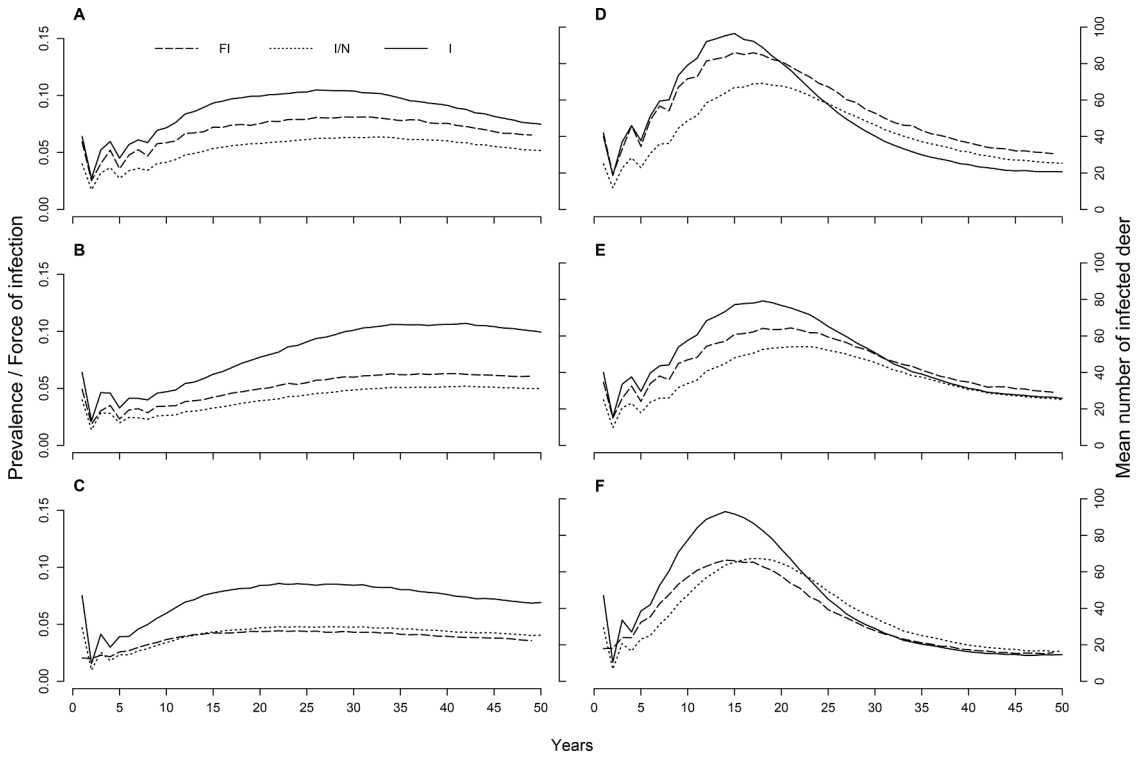

Fig. 6. Force of infection (FI) plotted with mean infectious prevalence (I/N infected > 6 months) and mean number of infected individuals (I). A) direct transmission, contiguous forest landscape, B) direct transmission, reduced group size, contiguous forest landscape C) indirect transmission, contiguous forest landscapes, D) direct transmission, fragmented forest landscape, E) direct transmission, reduced group size, fragmented forest landscape, and F) indirect transmission, fragmented forest landscape.

Table 2
Mean (SD) power-law regression coefficients for the relationship between force of infection and density of infected individuals (I) and infectious prevalence (I/N). C = contiguous forest, *F* = fragmented forest, *D* = direct transmission, *R* = reduced group size, IND = indirect transmission. For IND scenarios, *i*-1 and *i*-2 depict indicate time lags between force of infection and I and I/N in the power law regression Eqs. 2 and (3). A coefficient value of 1.0 indicates a linear, proportional relationship.

Scenario	I	I/N
CD	0.20 (0.29)	0.67 (0.30)
CDR	0.25 (0.95)	0.62 (0.90)
CIND	0.46 (0.98)	0.42 (0.96)
$CIND_{i\text{-}1}$	0.71 (1.49)	-0.41 (1.55)
$CIND_{i\text{-}2}$	0.27 (1.54)	-0.29 (1.61)
FD	0.28 (0.15)	0.58 (0.23)
FDR	0.26 (0.19)	0.62 (0.22)
FIND	0.52 (0.21)	0.33 (0.28)
$FIND_{i\text{-}1}$	0.63 (1.49)	-0.33 (1.57)
$FIND_{i\text{-}2}$	0.36 (1.55)	-0.21 (1.60)

Table 3
Fraction of replicates for each scenario with significant power-law regression coefficients indicating the relationship between force of infection and either density of infected individuals (I) or infectious prevalence (I/N). C = contiguous forest, *F* = fragmented forest, *D* = direct transmission, *R* = reduced group size, IND = indirect transmission. For IND scenarios, *i*-1 and *i*-2 depict indicate time lags between force of infection and I and I/N in the power law regression Eqs. 2 and (3).

	Fraction of significant replicates ($P < 0.05$)	
Scenario	I	I/N
CD	0.068	0.620
CDR	0.072	0.430
CIND	0.276	0.246
$CIND_{i\text{-}1}$	0.092	0.074
$CIND_{i\text{-}2}$	0.056	0.066
FD	0.372	0.712
FDR	0.258	0.720
FIND	0.700	0.284
$FIND_{i\text{-}1}$	0.106	0.082
$FIND_{i\text{-}2}$	0.092	0.094

northern tier of the state, efforts to control CWD have arguably been successful in slowing the rise in prevalence (Manjerovic et al., 2014; Mateus-Pinilla et al., 2013) but continual geographic spread is straining capacity. When CWD is first detected in a fragmented landscape, there may be a unique opportunity to locally suppress or even eradicate the disease but only with intensive effort around the area of initial discovery (Varga et al., 2021)

4.2. Transmission mode of CWD and host-disease dynamics

4.2.1. Direct and indirect transmission

CWD can be transmitted through both direct animal contact and environmental sources (Haley et al., 2009a; Mathiason et al., 2009; C.K. 2006; Miller and Williams, 2003; Williams and Miller, 2003), but the strength of each pathway and how much they each contribute to the transmission and persistence of CWD in free-living populations are unknown. We chose to separate the different modes of transmission in our model runs, to investigate possible effects on model outcome. The difference in prevalence could be due to direct transmission being more stochastic, as contacts are very time-dependent and there is a higher chance of disease extinction, due to death of diseased animals. Indirect transmission can continue even after the death of the diseased individual, due to accumulation of prions in the environment, thus disease transmission is more reliably dependent on duration of exposure. Schauber et al. (2007; 2015) found that indirect contact rates among female deer were much less strongly influenced by social group membership than were direct contact rates, with indirect contacts being

Table 4
Partial R^2 for each scenario and predictor – what fraction of the variance not explained by A is explained by B (see text for details). C = contiguous forest, *F* = fragmented forest, *D* = direct transmission, *R* = reduced group size, IND = indirect transmission.

Scenario	Mean R^2			Fraction of Replicates with R^2[I Only] > R^2[I/N Only]	Fraction of Replicates with Partial R^2 > 0.1		Mean Partial R^2	
	I Only	I/N Only	Both		I	I/N	I	I/N
CD	0.656	0.709	0.718	0.186	0.066	0.598	0.033	0.178
CDR	0.715	0.735	0.744	0.290	0.060	0.400	0.037	0.107
CIND	0.706	0.706	0.725	0.530	0.252	0.232	0.070	0.068
$CIND_{i\text{-}1}$	0.734	0.723	0.755	0.678	0.532	0.294	0.129	0.081
$CIND_{i\text{-}2}$	0.743	0.732	0.770	0.686	0.644	0.424	0.157	0.106
FD	0.699	0.739	0.759	0.254	0.348	0.700	0.082	0.191
FDR	0.675	0.734	0.749	0.234	0.232	0.718	0.065	0.217
FIND	0.792	0.775	0.807	0.770	0.678	0.282	0.150	0.079
$FIND_{i\text{-}1}$	0.816	0.793	0.835	0.820	0.842	0.416	0.214	0.107
$FIND_{i\text{-}2}$	0.825	0.802	0.848	0.812	0.902	0.530	0.246	0.135

driven mainly by the amount of shared space.

Transmission mode greatly affected age- and sex specific prevalence patterns. For the direct transmission scenarios, the observed patterns roughly reflected those seen in wild deer populations impacted by CWD. The higher prevalence in male deer, especially older males, is also observed in empirical studies of CWD, potentially due to differences in behavior or physiology (Farnsworth et al., 2005; Grear et al., 2006; Miller and Conner, 2005; Osnas et al., 2009; Samuel and Storm, 2016). In our model, males are part of larger groups and move around more than females, leaving and joining new groups. Furthermore, we model males to follow females around during the rut, which could potentially add to infection exposure. Infection prevalence was very similar in fawns and adult females when we included all infected animals. In empirical studies, however, observed CWD prevalence is generally lower in fawns than adults (Grear et al., 2006; Wisconsin Department of Natural Resources, 2012). This discrepancy could be explained by difficulties in detecting early stage infection with standard diagnostic tests (Haley et al., 2009b; Mathiason et al., 2009). Our results, when including only animals infected longer than 6 months, mirror the lower apparent prevalence in fawns compared to all other age classes.

Although indirect transmission is dependent on how animals move and overlap in habitat and space use, it does not require simultaneous space use, which could explain similar prevalence across adult sex- and age classes in the indirect scenarios. The observed lower prevalence in fawns could be explained by transmission not being a result of contact between individuals but being a question of time of exposure to the pathogen. Fawns would have had less time to be exposed to prions in the environment.

These results suggest that the age- and sex specific differences in CWD prevalence observed in wild deer populations may mostly be driven by direct transmission (given no evidence of increased genetic CWD susceptibility in males, Rogers et al., 2022), as they could be a result of differences in behavior. The higher prevalence in males, along with greater male mobility (Hawkins et al., 1971; Nixon et al., 2007, 1994; Rosenberry et al., 1999), could lead managers to conclude that CWD control may be better applied focusing on males . However, with indirect transmission or if transmission is primarily from females to males, this form of male-focused culling may only work in areas where CWD has not yet been established. Recent simulation models on harvest-based CWD management have suggested that higher disease prevalence in males may not necessarily indicate that male deer are more responsible for disease transmission, only that they may experience higher exposure or susceptibility (Rogers et al., 2022). These models showed that for management interventions to be efficient in limiting CWD epidemics, harvest of both male and female deer is required (Rogers et al., 2022), emphasizing how sex-selective harvest based on prevalence alone might be misleading.

4.2.2. *Host-disease dynamics – density- or frequency-dependent transmission of CWD*

The force of infection measures the rate of disease spread within a population, and our results varied between landscapes and transmission modes. Within a landscape, direct transmission seemed to produce a higher force of infection than indirect transmission except when group sizes were reduced. Force of infection was better predicted by infectious prevalence than density of infected animals (infected >6 months) in the direct transmission scenarios, whereas the pattern was unclear or leaned toward density dependence for the indirect transmission scenarios. These statistical results are in contrast to the overall epizootic dynamics that are strongly consistent with density-dependent transmission, namely the fact that the CWD epizootic peaked earlier and at higher prevalence in the fragmented forested landscape scenarios (where local population density was greater) than in the contiguous landscape. Overall, these findings suggest that disease transmission of CWD may be dependent on the combination of transmission mode and landscape structure. Also, the true nature of CWD transmission, whether through direct or indirect contacts, may be intermediate between density- and frequency-dependent transmission but unlikely to destabilize host populations. In a CWD study from Wisconsin, Storm et al. (2013) found that models with intermediate transmission modes performed better than strictly density- or frequency-dependent transmission models when predicting incidence rates in harvested yearling deer, also suggesting that mode of transmission may not be completely linear. Both density-dependent transmission and an intermediate of density- and frequency-dependent transmission could potentially result in co-existence of CWD and deer, but the lack of long term empirical data prevents us from validating our findings.

In studies from both Wisconsin and Illinois, Samuel and Storm (2016) found that although estimated values for force of infection varied across years and states, they report average yearly increases in the force of infection rate of 26.8%, 6.3% and 2.5% for males, females and yearlings respectively. This suggests an increase over time in the rates of CWD transmission across the areas. For our scenarios, force of infection decreased or leveled over time as the numbers of susceptible host were decreasing. The discrepancy between our model results and the above-mentioned study suggests that more studies are needed to estimate force of infection rates in CWD endemic areas and if possible relate them to population density and prevalence rates to determine transmission patterns of CWD.

4.3. *Deer removal to control CWD in wildlife populations*

Transmission of disease within social groups has often been used as a justification to assume frequency-dependent transmission, as group composition and number of encounters between or among individuals may be more or less constant despite variations in population size (May and Anderson, 1979; O'Keefe, 2005). However, some species may exhibit more flexible group structures with varying group sizes, and this

pattern is especially seen in white-tailed deer male bachelor groups (Halls, 1984; Hirth, 1977; Marchington and Hirth, 1984; Nixon et al., 1994). Our results showed that reduction of deer group sizes affected prevalence levels in the direct transmission scenarios for both landscapes. This reduction of group sizes in the model reduced the transmission potential within groups and thus affected disease transmission between groups as well. We explored these scenarios to compare increased hunting pressure or unselective culling (which would increase mortality generally) to strategies where entire groups are culled (which would reduce the number of groups, but not group size). Both selective and non-selective culling have been the preferred means of CWD management in free-ranging populations (Uehlinger et al., 2016; Wasserberg et al., 2009; Williams and Miller, 2002). Uncertainties about mode of transmission can hinder choosing management strategies for disease eradication (Uehlinger et al., 2016; Wasserberg et al., 2009). Assuming direct transmission, culling and reduction of populations could result in population thresholds below which the disease is not able to persist in the population (Anderson and May 1978). Using a multi-state computer simulation model, Wasserberg et al. (2009) found that hunted deer populations exhibited lower CWD prevalence than non-hunted populations, suggesting that population density and turnover affect CWD transmission and that culling may be a suitable strategy for CWD management. Lower population densities might reduce joint space use and chance of indirect contacts. However, the potential for re-colonization and subsequent reemergence of the disease caused by environmental contaminants poses a challenge to disease management, and further research is needed to expand our understanding of environmental prion accumulation as a route of disease transmission.

4.4. Long-term effects of CWD

CWD has only recently been discovered in wildlife populations and is of great concern to wildlife managers and public alike. The need to understand and predict CWD dynamics is evident and developing models to make predictions and pinpoint areas of interest in CWD research could be of great value. Gross and Miller (2001) developed a mechanistic ABM, simulating CWD transmission in mule deer populations. Their model failed to predict long-term co-existence of disease and deer populations, but their model lacked spatial components and assumed fixed contact rates. Publications of the agent-based CWD model developed by Belsare et al. (Belsare et al., 2020; Belsare and Stewart, 2020) do not investigate long-term effect of CWD on deer populations, but are focused on surveillance and detection, and thus we cannot compare our results to predictions from this model. This model however, uses fixed contact rate matrices with direct transmission only.

DLD incorporates spatial- and temporal stochasticity and imposes no top-down assumptions regarding contact rates – in this model contact rates, both indirect and direct, are emergent properties of the movement behavior of agents within the model. Gross and Miller (2001) acknowledge that the limited amount of data from long-term surveillance can complicate making long-term predictions. Because of this limitation, we chose to run DLD for a maximum of 50 years, since further predictions would need to be validated by field studies. In areas where CWD has been occurring for a prolonged time, evidence exists that CWD does affect population dynamics of wild cervids. In northern Colorado, Miller et al. (2008) found prevalence levels in mule deer ranging from 20 to 40% in a population that had been declining over the last 20 years, and this decline coincided with the emergence of CWD in the population. Edmunds et al. (2016) reported an annual decline of 10.4% in white-tailed deer populations in CWD-positive areas in Wyoming, where prevalence levels ranged from 28.8% in males to 42% in females. Also in Wyoming, DeVivo et al. (2017) found average annual CWD prevalence in mule deer to be 24% coinciding with annual population declines of 21%. Our model scenario prevalence patterns showed increasing prevalence levels and decreasing deer populations, particularly in the fragmented forest scenarios. Still, prevalence and population sizes seemed to reach a relatively stable equilibrium for all scenarios by year 50, suggesting a potential for co-existence of CWD and deer. However, as with any model, caution must be taken not to rely too heavily on projected scenarios. Many aspects of CWD dynamics are still unknown and we strongly support further surveillance of CWD and research into the underlying factors promoting prion transmission. More extensive research into infectivity, prion decay and environmental pathways is needed to improve on predictive modeling.

4.5. Model utility

DLD provides an excellent tool for investigating how different disease transmission pathways and control efforts can affect epizootic dynamics within a population. Our results indicate that indirect transmission produces dynamics more consistent with density-dependent transmission, despite posing a greater challenge to disease eradication or control (Potapov et al., 2012). Furthermore, prevalence levels in the model with indirect transmission were less affected by behavioral differences between the sexes and age groups, as well as current population density, than with direct transmission. However, conclusion is tentative, as some age- and sex-specific behaviors (e.g., scraping and other marking behaviors, or fighting) were not included in the model.

DLD is adaptable to simulate most diseases in deer. Disease parameters can be altered to fit the disease under investigation, and landscapes can be imported to fit the desired habitat of interest. DLD is still being developed and fine-tuned, and the current version does not include density dependence in survival and recruitment rates in the model, but density dependence could prevent or reduce decreases in population size due to disease (Gross and Miller, 2001). Density dependence could be incorporated into later versions of DLD. We also did not include the potential for infected carcasses to stay in the landscape and add to environmental contamination (Miller et al., 2004; Williams and Miller, 2002) nor did we add scraping sites of bucks that may also serve as a potential hot spot for indirect disease transmission (Alexy et al., 2017). Furthermore, we did not remove home range fidelity at end stages of the disease to simulate behavioral anomalies caused by CWD (Edmunds et al., 2018; Miller and Wild, 2004; Williams and Miller, 2000). These aspects might have an effect on transmission levels and may be incorporated in later versions of DLD.

5. Conclusions

DLD simulations of chronic wasting disease transmission in white-tailed deer showed that landscape structure, social behavior and mode of transmission all affected prevalence within deer populations. Furthermore, DLD results suggest that CWD-transmission may be driven by a mixture of density- and frequency-dependent processes, which can potentially lead to co-existence of CWD and deer populations. These results emphasize the importance of spatial, temporal and behavioral heterogeneity in disease modeling, and demonstrate the utility of ABMs in incorporating spatio-temporal variables as well as animal behavior when predicting and modeling disease spread.

Software availability

Model name: DeerLandscapeDisease (DLD)

Availability: Javadocs and entire DLD program code have been uploaded to figshare: https://figshare.com/articles/online_resource/DeerLandscapeDisease_zip/17430101

Language: Java

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CRediT authorship contribution statement

Lene J. Kjær: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Eric M. Schauber:** Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The model code has been uploaded to figshare and a link is provided

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ecolmodel.2022.110114.

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