CHAPTER 18

Mathematical Models for Rabies

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Abstract

Rabies virus and its associated host–pathogen population dynamics have proven a remarkable model system for developing mathematical models of infectious disease emergence and spread. Beginning with simple susceptible-infectious-removed (SIR) compartment models of fox rabies emergence and spread across Western Europe, mathematical models have now been developed to incorporate dynamics across heterogeneous landscapes, host demographic variation, and environmental stochasticity. Model structures range from systems of ordinary differential equations (ODEs) to stochastic agent-based computational simulations. We
have reviewed the variety of mathematical approaches now available for analyzing dynamics in different host populations; most notably rabies virus spread in raccoon hosts.

I. INTRODUCTION

There has been a long history of mathematical models associated with the study of rabies, and in many ways the timeline of model development for rabies over the last 30 years has closely followed the development of mathematical methods within the analysis of the ecology of infectious diseases in general.

Early models of rabies dynamics were similar to early models for most other diseases and followed the basic “SEIR” framework where populations are subdivided into specific classes corresponding to susceptible (S), exposed (E), infectious (I), and recovered/removed (R) individuals (Anderson and May, 1979, 1981). The dynamics are encapsulated through the construction of a system of ordinary differential equations (ODEs) representing either single populations or linked metapopulations from which a variety of predictions can be drawn concerning temporal and spatial pattern.

Although these foundational models may have lacked the level of mathematical sophistication, we see in models today, there was really no need for highly complicated mathematical representations since data itself were rather limited. For instance, some recent models for describing rabies dynamics incorporate explicit spatial interactions and can account for events that are discrete in time and space. These spatially explicit models may not have provided much improvement over the earliest ODE models used 30 years ago by Anderson and May (1981), since early in the epidemic, detailed temporal history was not yet available and spatial resolution was limited to densities of individuals within large regions. At present, even though the mathematical toolkit for studying the ecological and evolutionary dynamics of a variety of infectious diseases is very robust, it is the availability of data that lags behind.

In addition to asking the question of what modeling approach works best with one’s data, it is also necessary to consider what the overall goal of the modeling approach will be. With rabies systems, in general, the goals of researchers are often very different. They can range from models that are predictive, which could be used to assess the quality of different management regimes or understand spillover risks, to models that are focused on providing insights into ecological and evolutionary processes that could possibly improve parameter estimations. Although many modeling approaches can address aspects of all of these concerns, certain
modeling approaches are more appropriate when properly considering the available data and the primary questions.

From a modeling perspective, rabies is particularly interesting in that the virus can infect a wide variety of mammalian hosts with different species associations in different ecological regions. In Europe, rabies has been primarily restricted to spread within the red fox (Vulpes vulpes), whereas in North America, rabies infects a wide range of terrestrial carnivores including raccoons (Procyon lotor), skunks (Mephitis mephitis), arctic and red foxes (Vulpes lagopus and V. vulpes), and coyotes (Canis latrans). Rabies virus also circulates among domesticated animals (especially dogs and cats) and among various bat species. Despite geographic and ecological overlap in the ranges of many of these species, the implications of multispecies host susceptibility and the community ecology of rabies has rarely been examined (Real and Childs, 2006).

Most models for rabies virus transmission have been confined to single species dynamics and, although the general framework for models across these species is similar, ecological and biological constraints between species can often make it difficult to form generalizations about dynamics. Nonetheless, there has been a distinct history associated with the structure of models applied to individual systems, which provides a general conceptual framework for understanding the biological mechanisms driving temporal and spatial pattern.

II. THE DEVELOPMENT OF THE MATHEMATICAL APPROACH TO RABIES DYNAMICS

The past decade has seen substantive developments in both mathematical and computational approaches to studying rabies virus dynamics, particularly raccoon rabies within North America. In this chapter, we will focus our discussion on these more recent developments in modeling approaches. However, in order to put contemporary analysis into an appropriate context, we will also review historical approaches.

Most of the earliest models for rabies virus transmission were developed to understand the epizootic expansion of rabies virus in red fox (V. vulpes) populations into Western Europe from a focus of origin in Eastern Europe following World War II. These early models utilized the basic SEIR compartmental framework and these models were used to derive several critical features of disease emergence and spread. Most importantly, the models were used to calculate the critical threshold for epidemic emergence and the basic reproductive number ($R_0$) for the virus. The value of $R_0$ expresses the number of secondary infections generated
from a single infection in an entirely susceptible population. When $R_0$ is greater than 1, the infection will spread and an epidemic will result. Using $R_0$, it is possible to determine a threshold density of foxes ($S_t$) below which an epizootic cannot occur. By determining a threshold density, it could then be possible to suggest what level of population culling would be necessary in order to bring threshold density below the epizootic level.

The flowchart in Fig. 1 illustrates the basic compartmental framework similar to ones utilized for early fox rabies models.

Although the construction of the model illustrated in Fig. 1 follows the SEIR compartmental framework, we have omitted the inclusion of the $R$ class in order to follow the convention of many of the early rabies models, since there is little or no evidence of natural recovery or the development of natural immunity where no vaccination is considered, which translates susceptibles into the removed category.

The dynamics portrayed in the flowchart can be translated into the following set of ODEs:

$$\frac{dS}{dt} = rS - \gamma SN - \beta SI \quad (1)$$
$$\frac{dE}{dt} = \beta SI - (\sigma + b + \gamma N)E \quad (2)$$
$$\frac{dI}{dt} = \sigma E - (\alpha + b + \gamma N)I \quad (3)$$
$$N = S + E + I \quad (4)$$

where $S$, $E$, and $I$ represent densities of susceptible hosts, exposed, and infectious individuals, respectively. The intrinsic per capita growth is $r = a - b$, where $a$ is the per capita birth rate and $1/b$ is the mean life expectancy. The rate at which individuals are exposed to rabies ($E$) in the

![FIGURE 1](image.png)  
**FIGURE 1** Compartment diagram of basic SEIR framework used in early ODE formulations for rabies. Arrows represent the directionality of each process.
population is proportional to the densities of susceptible and infectious individuals, \( \beta SI \). Here \( \beta \) is the disease transmission parameter. The average length of time a fox remains in the exposed class before becoming infectious is \( 1/\sigma \). Infectious or rabid individuals have greater risk for mortality, such that \( (\alpha + b) \) is the mortality rate for infectious individuals.

In order to parameterize their model for red foxes, Anderson et al. (1981) utilized the available estimates from then recent descriptive studies (MacDonald, 1980). The situation they considered in their models was the introduction of a few rabid foxes into a naive population. In order to determine \( R_0 \) and the corresponding minimum density of foxes \( (S_t) \) necessary for rabies to spread, they also assumed that the host population prior to the introduction of rabies was at a stable equilibrium. From Eqs. (1) to (4), this equilibrium is simply \( K = a/b \). So at the onset of the epidemic at time \( t = 0 \), the population size of susceptibles is then \( S(t = 0) = K \).

By solving Eqs. (1)–(4) simultaneously, they determined that the criteria for an epidemic \( (dI/dt > 0) \), for the equilibrium population size \( K \), at the onset of the first infections is \( K > S_t \), where \( S_t \) is

\[
S_t = (\sigma + a)(\alpha + a)/\beta\sigma
\]

and the relationship between \( K \) and \( S_t \) can be reformulated to define \( R_0 \):

\[
R_0 = \frac{K}{S_t} = \frac{K\beta\sigma}{(\sigma + a)(\alpha + a)}
\]

Based on the available data, Anderson et al. (1981) determined that the minimum threshold density of foxes was \( S_t \sim 0.99 \) foxes/km\(^2\). Subsequent to their analysis, it was confirmed that almost all areas of Europe that had seen outbreaks had densities in excess of this number. Oral vaccines for rabies had not yet been developed, so the recommended control strategy was culling of fox populations in areas with densities above the threshold, \( S_t \).

III. MODELING APPROACHES USING REACTION DIFFUSION METHODS

Concurrent to the development of the models by Anderson et al. (1981), fox rabies was continuing to advance southwesterly into France and Switzerland. Earlier descriptive studies had begun to investigate ecological factors that could influence the spatial propagation of virus, such as habitat quality or fox densities (MacDonald, 1980; MacDonald et al., 1981). Subsequent to these descriptive studies, Murray et al. (1986) developed a reaction-diffusion model to describe the behavior of this propagating wave. Most importantly, this model allowed predictive modeling of
how a transmission barrier might be implemented at the wave front in order to halt the expansion of the epizootic. The construction of a transmission barrier or “break” was akin to that of firebreaks used to arrest the advance of major wildfires.

From the work of Anderson et al. (1981), a minimum density for preventing epizootics within a population had already been determined. From a practical standpoint, implementation of such large-scale culling or vaccine distribution across Europe ahead of the wave front would not be possible. However, the model developed by Murray et al. (1986) allowed for the estimation of movement rates for rabid foxes. It was now possible to suggest how wide and where a break could be implemented in order to halt the spatial propagation of the epidemic. The framework of the reaction diffusion formulation used by Murray et al. (1986) consisted of the following coupled partial differential equations (PDEs):

$$\frac{\partial S(x,t)}{\partial t} = r(1 - N/K)S - \beta SI$$

$$\frac{\partial E(x,t)}{\partial t} = \beta SI - (\sigma + b + rN/K)E$$

$$\frac{\partial I(x,t)}{\partial t} = \sigma E - (\alpha + b + rN/K)I + D \frac{\partial^2 I}{\partial x^2}$$

$$N = S + E + I$$

This one-dimensional reaction diffusion framework is almost identical to the model of Anderson et al. (1981); however, there are two important differences. First, Eqs. (7)–(10) implement density dependence in terms of an environmental carrying capacity $K$, rather than the parameter $\gamma$, which determined the strength of density dependence. However, these terms are interchangeable if we consider $\gamma = r/K$. Second, the reaction diffusion framework incorporates the diffusion term at the end of Eq. (9) that describes the movement of infectious foxes across the landscape. Here $D$ is the diffusion coefficient that specifies the rate of movement of rabid foxes. Utilizing this type of framework, it was estimated that the rate of movement for rabid foxes was $D \sim 50 \text{ km}^2/\text{year}$ (Andral et al., 1982; Murray et al., 1986). The diffusion coefficient $D$ tells part of the story, but in order to describe the velocity $v$ of the traveling waves associated with the epidemic, other model parameters also have to be considered.

Similar to ODEs, the reaction diffusion formulation is composed of a system of coupled equations. In this case, the equations are PDEs. Although these equations can describe the basic properties of spatial progression, they make assumptions similar to that of ODEs, mainly that the population is well mixed and homogeneous and that the rates for process such as infection or birth, etc., can be considered to be constant.
during the course of the epidemic. An epidemic wave propagating at a velocity \( v \) in a homogenous environment will maintain the same shape as it traverses space. Mathematically this allows us to consider a solution in the form \( f(x,t) = f(x - vt) \), for Eqs. (7)–(10), solving these equations simultaneously can be nontrivial; additionally, several solutions for wave velocities may be recovered, so it is necessary to evaluate all solutions. Some solutions may describe unrealistic biological scenarios, whereas others may describe the oscillations of standing waves that occur after a significant time has passed. Although the dynamics of secondary oscillations may be important, particularly for predicting recurrent epidemics, it is often possible in reaction diffusion systems to simply estimate the velocity of the initial epidemic wave by applying some assumptions that will allow us to reduce Eqs. (7)–(10) into a more tractable form. For instance, if we consider that over a small time period, \( \Delta t \) at the forefront of the epidemic wave, population size is relatively constant such that \( a = b = 0 \), it is possible to simplify Eqs. (7)–(9):

\[
\frac{\partial S(x,t)}{\partial t} = -\beta SI \tag{11}
\]

\[
\frac{\partial E(x,t)}{\partial t} = \beta SI - \sigma E \tag{12}
\]

\[
\frac{\partial I(x,t)}{\partial t} = \sigma E - aI + D \frac{\partial^2 I}{\partial x^2} \tag{13}
\]

Additionally, since the initial epidemic process must be driven by the movement of infectious individuals into a region, we can assume that \( \frac{\partial E(x,t)}{\partial t} \sim 0 \) over \( \Delta t \). This allows us to combine Eqs. (12) and (13), by setting \( \beta SI = \sigma E \). Equation (13) now becomes

\[
\frac{\partial I(x,t)}{\partial t} = (\beta S - a)I + D \frac{\partial^2 I}{\partial x^2} \tag{14}
\]

Equation (14) now has the same form as the well-known Fisher–Kolmogoroff Equation:

\[
\frac{\partial u}{\partial t} = f(u) + D \frac{\partial^2 u}{\partial x^2} \tag{15}
\]

which has solutions for the wave velocity \( v = 2[f'(u)D]^{1/2} \); from this relation, the wave velocity from Eq. (14) is

\[
v = 2[(\beta S_0 + a)D]^{1/2} \tag{16}
\]

where \( S_0 \) is the initial density of susceptibles prior to the arrival of the first rabid foxes.
The derived relation in Eq. (16) illustrates how one might investigate the roles played by host density and fox dispersal in driving the epidemic process. From a management standpoint, $S_0$ can suggest the level of culling or vaccination necessary to halt the epidemic wave, and $D$, which is related to the movement rate of infectious foxes, can suggest how wide an area in front of the epidemic should be managed. These were some of the primary relationships that Murray et al. (1986) had investigated. A more comprehensive derivation of the wave speed, including a two-dimensional formation, can be found in Murray et al. (1986). Additionally, a detailed review of early ODE and PDE frameworks in European fox rabies can also be found in Shigesada and Kawasaki (1997).

IV. METHODS FOR INCORPORATING LANDSCAPE HETEROGENEITIES

These early models by Anderson et al. (1981) and Murray et al. (1986) were important and helped illustrate the utility of basic mathematical models in analyzing disease dynamics in ecological systems. However, despite the fact that the use of these deterministic ODE and PDE frameworks in disease ecology was in many ways pioneering at that time, the methods themselves had been available for centuries, particularly in other disciplines such as physics where use of these methods was commonplace for understanding the behaviors of dynamical systems under ideal conditions. These early deterministic models yielded a number of important insights into the dynamics of the rabies virus in wildlife populations. However, due to several simplifying assumptions about the nature of the ecological interactions, several aspects of the observed dynamics remained unexplained and poorly understood. ODE and PDE approaches assume that all ecological interactions occur over a homogenous landscape and at constant rates, and that events occur continuously through time. Given that the spatial distribution of rabies often occurs over large regions, landscape heterogeneity is likely to be important. As data with finer spatial resolution became available, the importance of considering heterogeneity became evident. For instance, data describing the movement of fox rabies across Europe illustrated that the spread of the virus, particularly in areas near Switzerland and northward, was characterized by rapid movement deep into valleys and then a slower percolation of the virus into the areas neighboring those valleys (Steck et al., 1982). Similarly, in North America landscape heterogeneities drove patterns of irregular spread during the epidemic spread of the rabies virus that started in mid-1970s. These patterns became most evident in the northern United States, when the rabies virus began to enter areas of New York and Connecticut.
in the early 1990s. Subsequent modeling and data revealed that rivers were effective barriers to transmission, and drove close to sevenfold delays in the advance of the epidemic wave (Russell et al., 2004; Smith et al., 2002).

Extensions to these early models such as multidimensional reaction diffusion or optimal control have allowed the ODE and PDE frameworks to remain relevant. Extensions can be made to the traditional ODE and PDE frameworks that allow for some consideration of parameter variation, stochasticity, and even some environmental heterogeneity. Mollison and Kuulasmaa (1985) incorporated a stochastic dispersal process, which showed good agreement with estimated velocities for fox rabies. Shigesada and Kawasaki (1997) considered not only variation in rates of diffusion between classes of individuals in a reaction diffusion model but also the effect of two habitat types on those rates of diffusion.

Despite these inroads, it is difficult to fully incorporate the effects of landscape level heterogeneities or stochastic variation among all model parameters without moving to other (mostly computational) approaches, such as network models, cellular automata, interacting particle systems, or percolation-based techniques. A number of recent models have utilized these types of computational approaches to study the roles of environmental heterogeneity and stochastic effects.

Some of the earliest work to incorporate these techniques employed agent-based simulation approaches. In these models, the fate of individual hosts is tracked during the course of transmission generating overall population level dynamics over a landscape. Voigt et al. (1985) utilized this type of model where they considered landscape and habitat heterogeneity specific to Ontario, Canada. By using a model of the rabies virus tailored specifically to a region of interest, they were able to gain important insights into the epidemic process in Ontario and then implement specific management strategies for that region (Macinnes et al., 1988; Voigt et al., 1985). The effectiveness of this agent-based approach in Ontario may beg the question as to why these types of agent-based models are not more predominant. However, the effectiveness of the agent-based or individually based approach depends very much on the scale at which we are interested. This is important in terms of “scale” as applied to not only the size of the overall landscape in which one is interested but also “scale” as measure of coarseness or degree of resolution at which we need to investigate that landscape. An important work by Thulke et al. (1999) investigated this type of question directly by looking for differences in dynamics between models that explored rabies virus dynamics at different scales.

Smith et al. (2002) developed an interactive network model that incorporated local heterogeneities in an attempt to better understand the irregular spread of the rabies wave front across Connecticut in the
early 1990s. Figure 2 details the algorithm they utilized in implementing their model.

The model used by Smith et al. (2002) considered the landscape as a network of connected townships where habitat differences among townships could be approximated as variation in local transmission rates between neighboring townships ($\lambda_{i,j}$) and global transmission among all townships ($\mu_i$). The parameters $\mu_i$ and $\lambda_{i,j}$ were fixed throughout the course of any simulation, but some degree of stochasticity was implemented since the order in which townships were chosen was based on a uniform random distribution. Smith et al. (2002) showed convincingly that landscape heterogeneity could help explain the irregular spread of the raccoon rabies virus across Connecticut, something which reaction diffusion frameworks had difficulty achieving. The initial application of the network approach developed for modeling spread of rabies in Connecticut involved subdividing the landscape into $N$ populations. The parameters $\mu_i$ and $\lambda_{i,j}$ are rates for processes that connect populations; here $\mu_i$ describes the rate at which long distance translocation occurs in a particular population $i$, and $\lambda_{i,j}$ describes local movement of the virus from population $i$ to $j$. The flowchart ($a \rightarrow f$) illustrates the sequence followed for iterating and updating the model over time.

**FIGURE 2** Diagram of network model used by Smith et al. (2002). The landscape is subdivided into $N$ populations. The parameters $\mu_i$ and $\lambda_{i,j}$ are rates for processes that connect populations; here $\mu_i$ describes the rate at which long distance translocation occurs in a particular population $i$, and $\lambda_{i,j}$ describes local movement of the virus from population $i$ to $j$. The flowchart ($a \rightarrow f$) illustrates the sequence followed for iterating and updating the model over time.
Connecticut used the observed pattern of spread across that State to parameterize the network simulation. Russell et al. (2004) then used the parameterized model to predict the pattern of spread in a novel geographic region and demonstrated a remarkable correspondence between the observed and predicted spatial pattern of appearance across New York.

V. STOCHASTIC MODELS

Stochastic effects in model behavior can be explored using a variety of techniques, the simplest being the use of one or more distributions to describe a rate process (or processes) in an ODE or PDE. In these cases, the ODE or PDE is implemented algorithmically and a rate process such as *birth* (a) or *death* (d) would be sampled from an appropriate distribution. For instance, from Eq. (1) the expected number of new susceptibles in the interval \( dt \) could be implemented using a Poisson distribution with rate parameter \( rS(t) \)\( dt \). This approach is similar to the one used by Smith et al. (2002) who implemented the waiting time for townships to become infected as an exponential distribution.

Unless there are pertinent ecological or computational reasons to consider the use of specific distributions for stochastic implementations, it may make more sense to implement a fully stochastic model based on the methodology developed by Gillespie (1977). In the most straightforward implementation of the Gillespie method, equations are transformed into a stochastic simulation algorithm, which allows any processes \( \mu \), in a system of equations (such as *birth, death, infection*, etc.), to occur relative to its statistical weight at a particular time \( t \). That is, the probability of any specific event such as *birth* or *death* occurring at a specific time \( t \) is relative to the likelihood of all events that could occur at time \( t \). Gillespie’s insight, which allowed the development of his well-known “direct method,” stems from a reformulation of how the probability of an event occurring in an ODE or PDE system can be expressed. Earlier work by van Kampen (2001) had illustrated that in most interacting systems, a “Master Equation” could be formulated that expressed the exact probability of any process occurring at a specific time and location within the system. By evaluating the spatial component of the “Master Equation” over the entire region or area of interest, Gillespie defined a probability distribution similar to the one below.

\[
P(\mu, \tau) d\tau = a_\mu \exp\left(-\tau \sum_{i} |a_i| \right) d\tau
\]  
(17)
Equation (17) represents the probability that a process $\mu$ will occur at a specific time $\tau$ within the entire region being modeled by an ODE or PDE. For instance, the rate at which the process of infection, $\beta$, occurs in Eq. (8) would be dependent on the densities of $S$ and $I$ at time $\tau$, so in this case, $a_{\mu=\beta} = \beta S(\tau)I(\tau)$. Following from this, the summation of $a_i$ in Eq. (17) is over the total number of processes $k$, in the entire system of coupled equations. This defines the sum probability of any processes (inclusive of the processes $\mu$ being considered) occurring at the time $\tau$. Gillespie noted that the probability distribution expressed in Eq. (17) was a joint probability distribution, such that $P(m, \tau) = P(m)P(\tau)$. If we consider this, then the probability of a specific event occurring in the time interval $d\tau$, around $\tau$ is $a_m(\tau) / \sum a_i(\tau)$ and the time $\tau$, at which the event occurs is exponentially distributed.

Since the probability of an event’s occurrence and the time at which the event occurs is joint, and therefore independent, Gillespie’s algorithm is implemented by sampling two random numbers $r_1$ and $r_2$ from a uniform distribution. Then using the following relations, the algorithm sequentially updates the population dynamics event by event in increments of time $\tau$.

$$\tau = (1/a_0) \ln(1/r_1)$$  \hspace{1cm} (18)

$$\sum_{i=1}^{\mu-1} a_i < r_2 a_0 \leq \sum_{i=1}^{\mu} a_i$$  \hspace{1cm} (19)

The relationship in Eqs. (18) and (19) describe how to implement a stochastic algorithm for almost any system of deterministic equations. Whereas in traditional deterministic equations, events and population densities are continuous, the implementation of the Gillespie method discretizes our system of ODEs, such that densities only take on and change in integer increments and all events happen at discrete times (no events occur simultaneously), which adds further realism and utility to this approach.

VI. INCORPORATING STOCHASTICITY AND SPATIAL HETEROGENEITY

Using the framework of an interacting network and the Gillespie method, it is possible to go one step further and consider that each subpopulation within a network can be described by a specific set of stochastically implemented ODEs. Here, similar to Smith et al. (2002), parameters describing local spread or long distance translocation act to couple each set of ODEs. A stochastic $SEIR$ model formulated in this way simulates
the discrete changes in the number of susceptible, exposed, infectious, and vaccinated individuals produced by births, deaths, infections, and movement within all subpopulations. This system of coupled ODEs allows the model to be easily scaled to different ecological units, promoting flexibility in employing the model for hypothesis testing using data reported at different ecological scales. In many ways, this type of approach leverages many of the best qualities of the models discussed earlier. Here we will use this framework to formulate a more sophisticated model that attempts to incorporate a high degree of biological realism based on much of the current knowledge of the rabies virus infection in raccoons in North America. The flowchart in Fig. 3 illustrates how rates and transitions between classes are specified in this type of coupled stochastic SEIR model.

A spatial component is easily incorporated in this model if we consider that the index $i$ on all classes in Fig. 3 corresponds to populations distributed across a lattice. At each location in the lattice, the local dynamics are then based upon the following set of ODE's:

**FIGURE 3** Flowchart illustrating interactions in the model. Here “Movement” is represented as a class, but simply indicates how the process allows for the rearrangement of individuals spatially.
\[
\frac{dS}{dt} = aA_i - bN_iS_i - \beta I_iS_i - vS_i - (\phi + \phi_{LDT})S_i + \sum_{j \neq i} \left( \phi k_{ij} + \phi_{LDT} \hat{k}_{ij} \right) S_j \\
\frac{dE}{dt} = \beta I_iS_i - bN_iE_i - \sigma E_i - (\phi + \phi_{LDT})E_i \sum_{j \neq i} \left( \phi k_{ij} + \phi_{LDT} \hat{k}_{ij} \right) E_j \\
\frac{dI}{dt} = \sigma E_i - \alpha I_i - (\psi + \psi_{LDT})I_i + \sum_{j \neq i} \left( \psi k_{ij} + \psi_{LDT} \hat{k}_{ij} \right) I_j \\
\frac{dR}{dt} = vS_i - bN_iR_i - (\phi + \phi_{LDT})R_i + \sum_{j \neq i} \left( \phi k_{ij} + \phi_{LDT} \hat{k}_{ij} \right) R_j \\
A_i = S_i + E_i + R_i \\
N_i = S_i + E_i + I_i + R_i
\]

Parameterization of Eqs. (20)–(25) is similar to that of earlier models presented here. In these equations, \(S_i, E_i, I_i,\) and \(R_i\) are the number of susceptible, exposed, infectious, and vaccinated individuals at location \(i,\) respectively; \(A_i\) is the total number of noninfectious individuals (Eq. (24)); and \(N_i\) is the local population size (Eq. (25)). Individuals are born into the susceptible class at a per capita rate, \(a.\) In the absence of rabies, the population is only subject to the density-dependent mortality rate, \(b,\) resulting in logistic population growth and a carrying capacity, \(K = a/b.\) In the presence of viral transmission, the rate at which susceptibles are infected is \(\beta I_iS_i,\) where \(\beta\) is the transmission rate. Infection with rabies is followed by a latency period during which the virus reproduces and infection moves toward the central nervous system and salivary glands. Latently infected individuals comprise the exposed class, \(E_i,\) and newly infected individuals enter this class at the rate of infection \(\sigma E_i,\) where \(1/\sigma\) is the expected length of the latency period. The latency period ends when the virus enters the brain and salivary glands at which point an individual becomes infectious. Individuals become infectious at the rate \(\sigma E_i\) and are removed at a rate \(\alpha I_i,\) where \(1/\alpha\) is the life expectancy once infectious.

Equations (20)–(25) also introduce several new interactions and parameters. Individuals transition into a vaccinated class, \(R_i,\) in our model at a rate, \(vS_i,\) and vaccinated individuals die from nondisease-related, density-dependent sources of mortality \(\left(bN_iR_i\right).\) Local populations are linked by local dispersal of individuals from all classes. Noninfectious individuals \(\left(S_i, E_i, R_i\right)\) emigrate from their local population at a per capita rate \(\phi\) and
immigrate to other locations at rate $\phi k_{ij}$, where $i$ and $j$ are location indices. The $k_{ij}$ terms are dispersal coefficients giving the fraction of individuals migrating from location $j$ to location $i$ and characterize the pattern of dispersal. We include the effects of long distance translocation (LDT) by adding a separate term to Eqs. (20)–(23). The per capita rate of translocation is $\phi_{LDT}$ and $\psi_{LDT}$ for the noninfectious ($S_i, E_i, R_i$) and infectious classes ($I_i$), respectively. LDT represents a different process and pattern of movement and we provide separate coefficients, $\hat{k}_{ij}$, quantifying the fraction of individuals that are moved from location $j$ to location $i$ by LDT.

Initial estimates for parameter values (Table I) are drawn from published values and USDA sources or can be estimated indirectly based on fitting our model to epidemiological patterns.

Recently, the approach described here was used to investigate the role of seasonality in dynamics of the rabies virus in raccoon hosts along the East coast in North America. Using this type of model, Duke-Sylvester et al. (2010) implemented a north–south latitudinal gradient in the seasonal demography of raccoon birth rates. Specifically, the implementation of the gradient allowed Duke-Sylvester et al. (2010) to simulate the variation in timing associated with birth pulses for raccoons in the southern United States versus further north. In their model, the larger variance around the timing of spring births associated with southern populations drove spatial synchronization of southern epidemics. However, in northern populations, where the birth pulse is often narrow, epidemics were irregular and not spatially synchronized across the landscape (Fig. 4).

These types of differences between northern and southern populations may be important, particularly in terms of surveillance strategies.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Standard value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$a$</td>
<td><em>Per capita</em> birth rate</td>
<td>2.67 kits/female/year</td>
</tr>
<tr>
<td>$b$</td>
<td>Natural, density-dependent death rate</td>
<td>$2.293 \times 10^{-7}$ year$^{-1}$</td>
</tr>
<tr>
<td>$\beta$</td>
<td>Contact rate</td>
<td>$1 \times 10^{-4}$ (animal days)$^{-1}$</td>
</tr>
<tr>
<td>$\nu$</td>
<td>Vaccination rate</td>
<td>Variable</td>
</tr>
<tr>
<td>$1/\sigma$</td>
<td>Latency period</td>
<td>50 days</td>
</tr>
<tr>
<td>$1/\alpha$</td>
<td>Infectious period</td>
<td>14 days</td>
</tr>
<tr>
<td>$\phi$</td>
<td>Noninfectious movement rate</td>
<td>$6 \times 10^{-6}$ day$^{-1}$</td>
</tr>
<tr>
<td>$\phi_{LDT}$</td>
<td>Long distance translocation rate</td>
<td>$6 \times 10^{-7}$ day$^{-1}$</td>
</tr>
<tr>
<td>$\psi$</td>
<td>Infectious movement rate</td>
<td>$6 \times 10^{-6}$ day$^{-1}$</td>
</tr>
<tr>
<td>$\psi_{LDT}$</td>
<td>Long distance translocation rate</td>
<td>$6 \times 10^{-7}$ day$^{-1}$</td>
</tr>
<tr>
<td>$k_{ij}, \hat{k}_{ij}$</td>
<td>Fraction of emigrants from $j$ to $i$</td>
<td>Variable</td>
</tr>
</tbody>
</table>
Importantly, Duke-Sylvester et al. (2010) note that surveillance in the southern states could be reduced relative to northern locations without loss of detection ability since a single spatial location in the south is informative about neighboring spatial locations while northern locations share no common spatial information about neighbors. The potential monetary savings from a reduced surveillance effort without loss of detection is likely to be significant, and would free up more resources for other avenues, such as increased vaccination coverage.

VII. OPTIMAL CONTROL

An important detail, which separates these early ODE and PDE frameworks from contemporary approaches, is the inclusion of a vaccinated class. Once vaccines were developed and then afterward formulated into affordable easily distributed oral forms, the use of oral vaccination as a management approach for controlling rabies became more prevalent than methods associated with the culling of populations.

For diseases like rabies, where the force of infection was based on a density-dependent transmission kernel, traditional solutions for vaccination and culling strategies took the approach of determining what fraction of the population ($V_f$), should be vaccinated (or culled) in order to bring...
For a single population model, the solution for this vaccination fraction, $V_f$ in terms of $R_0$ is trivial and is given as $V_f = 1 - 1/R_0$. If we consider that for rabies in terrestrial mammals $R_0 \sim 2$, this would suggest that around 50% of a population should be vaccinated in order to prevent an epizootic. In reality, this level of control may be relatively easy or difficult to implement depending on a number of factors, such as the density of the host population in a target area, the type of terrain or level of landscape heterogeneity in the region, and of course the amount of monetary resources available and the given cost to develop and distribute the vaccine given all these considerations.

Often a particular management strategy has a defined goal associated with the implementation of that strategy and, consequently, the full range of methods that have been developed in operations research can be employed. For example, optimal control (Lenhart and Workman, 2007) allows a reformulation of an ODE system with a vaccination class in which a specific objective is defined mathematically and the dynamics of host–pathogen transmission act as constraints on the realization of the proposed strategy. This reformulation defines an objective function that can incorporate, for instance, a cost function for vaccine delivery. A solution for the objective function, for example, can provide insight into what management strategies can both minimize costs as well as minimize the number of infected hosts. Similarly, an objective function could also be formulated to explore strategies that minimize cost and maximize the number of susceptibles. In general, the objective function can be tailored so it considers the specific goals and constraints for the management problem. Consider the system of ODEs given below.

\[
\frac{dS}{dt} = -\beta SI - \varepsilon \delta S - bS \\
\frac{dI}{dt} = \beta SI - (b + \alpha)I \\
\frac{dR}{dt} = \varepsilon \delta S - bR
\]

Here Eqs. (26)–(28) are similar to the earlier system described by Eqs. (11)–(13). However, here for the sake of simplicity, we consider a closed population and have dropped the exposed class and now incorporated a vaccinated class, $R$ in Eq. (28). Here the parameter $\varepsilon$ and $\delta$ represent the efficacy and rate of vaccine distribution, respectively. In order to formulate an objective function for determining optimal control, we consider that any control measure must be applied during a finite time interval $[0,T]$ and our goal is to determine the optimal control $\delta$, from among a set of control strategies $U$, such that
\[ U = \{ \delta = (\delta_1, \ldots, \delta_n), \text{ where } 0 \leq \delta_i(t) \leq \delta_{\text{max}} \text{ for } i = 1, 2, \ldots, n \} \]

Here \( \delta \) is a normalized variable representing the density of bait distribution. In such a formulation, the upper bound \( \delta_{\text{max}} \) is usually specified to be 1, which would represent the maximum level of bait distribution that is currently possible, for rabies in North America, this is around 150 baits/km\(^2\) (Asano et al., 2008). Now let us consider that our optimal control problem is to minimize the number of infected hosts as well as the costs of vaccination.

\[
\text{Minimize } J(\delta) = \sum_{i=1}^{n} \int_{0}^{T} \left( I + \frac{\theta}{2} \delta_i^2 \right) dt \tag{29}
\]

Here \( \theta \) represents a weight in the cost of the control. Additionally, we have considered that our cost function is quadratic, but in general, a cost function can be formulated in a variety of ways; combinations of linear and quadratic costs having the form \( A\delta_i + B\delta_i^2 \) are common. Solutions for Eq. (29) require a formulation of the Hamiltonian for our particular system. Although formulating the Hamiltonian itself is often not difficult, solutions are often nontrivial, particularly if one is dealing with a large system of ODEs and/or complicated cost functions. A detailed mathematical description of the processes can be found in Lenhart and Workman (2007), Asano et al. (2008), and Ding et al. (2007).

**VIII. CONCLUSIONS**

Mathematical modeling of rabies is now quite well developed embracing a large number of complexities in biological organization and interaction including the ability to incorporate environmental stochasticity and landscape heterogeneity among coupled subpopulations of hosts linked across season and ecological gradients. The power of these models has been tested against extant data sets and has proven predictive of spread in novel locations. New tools, such as optimal control, now can utilize these developed ecological models to drive management and strategic planning in conjunction with public health agencies and planners.

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