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Estimating wildlife disease dynamics in complex systems using an Approximate Bayesian Computation framework

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Abstract. Emerging infectious diseases of wildlife are of increasing concern to managers and conservation policy makers, but are often difficult to study and predict due to the complexity of host–disease systems and a paucity of empirical data. We demonstrate the use of an Approximate Bayesian Computation statistical framework to reconstruct the disease dynamics of bovine tuberculosis in Kruger National Park's lion population, despite limited empirical data on the disease's effects in lions. The modeling results suggest that, while a large proportion of the lion population will become infected with bovine tuberculosis, lions are a spillover host and long disease latency is common. In the absence of future aggravating factors, bovine tuberculosis is projected to cause a lion population decline of ~3% over the next 50 years, with the population stabilizing at this new equilibrium. The Approximate Bayesian Computation framework is a new tool for wildlife managers. It allows emerging infectious diseases to be modeled in complex systems by incorporating disparate knowledge about host demographics, behavior, and heterogeneous disease transmission, while allowing inference of unknown system parameters.

Key words: *African buffalo,* Syncerus caffer; *Approximate Bayesian Computation, ABC; bovine tuberculosis, bTB; disease modeling; emerging disease; Kruger National Park, South Africa; lion,* Panthera leo; *multi-host system;* Mycobacterium bovis; *wildlife epidemiology*

Introduction

Emerging infectious diseases in wildlife can potentially reduce biodiversity, threaten human health, and cause economic losses (Daszak 2000), but wildlife management decisions are often necessary before the disease dynamics are fully understood. Although mathematical models can help to estimate disease dynamics and impacts, simple models may not accurately capture complex dynamics, and complex models may be challenging to parameterize. Data collection on wild populations can be difficult owing to logistical challenges, expense, and risks of handling, both to individual animals and to veterinary staff. A modeling approach is needed that can incorporate disparate information about populations and disease in complex systems, while leaving some parameters unspecified.

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An example of such an emerging infectious disease is the bovine tuberculosis (bTB, *Mycobacterium bovis*) outbreak in the lion (*Panthera leo*) population of Kruger National Park (KNP), South Africa. Exotic to sub-Saharan Africa, bTB probably was introduced to KNP around 1960, when free-roaming African buffalo (*Syncerus caffer*) contracted the disease from domestic cattle in the southeast part of the park (Bengis et al. 1996, De Vos et al. 2001, Hofmeyr et al. 2006). Buffalo continue to be the primary maintenance host, although greater kudu (*Tragelaphus strepsiceros*) may also be a maintenance host under some conditions (Renwick et al. 2007). An additional dozen species in KNP have tested positive for bTB and are thought to be spillover hosts (de Garine-Wichatitsky et al. 2013).

In 1995, a lion in KNP was discovered to be infected with bTB (Keet et al. 1997). The discovery of bTB in lions caused concern among park management for multiple reasons. The KNP lion population is one of only a handful of large lion populations left in the world, and the potential of bTB to significantly reduce

the population was unknown. Additionally, lions move across park borders, raising the possibility of spreading the disease among wildlife and domestic livestock and threatening key transboundary initiatives in southern Africa, such as the Great Limpopo Transfrontier Conservation Area (Wolmer 2003), which includes KNP as well as other national parks, communal land, and conservancies in South Africa, Mozambique, and Zimbabwe.

A disease assessment workshop was convened in 2009 to assess the current state of knowledge about bTB in KNP's lion population, to identify gaps in knowledge for future research, and to conduct predictive simulation modeling (Keet et al. 2009). The resultant model paired lion demography with disease dynamics, in which all disease parameters were estimated from known data where possible and by expert opinion where data were scarce or absent. Although the workshop successfully compiled available information about bTB in KNP's lions, parameterized simulation models erroneously predicted major declines in the lion population that have not occurred (Appendix S2: Fig. S21). The conclusion from this effort was that a different type of model was needed in which several key parameters could be left unspecified.

Classical infectious disease models can sometimes provide insight into disease dynamics (Anderson and May 1991, Keeling and Rohani 2007), but must make simplifying assumptions about the host and disease to be analytically tractable. Host populations are thus assumed to be well mixed and of fixed size, and disease transmission rates between individuals must be uniform. However, many wildlife disease systems do not conform to these assumptions and classical models can be misleading (e.g., Eisinger and Thulke 2008), especially in group-living species like lions, where population contact structure has important ramifications for disease spread (Tompkins et al. 2011).

To address these limitations, more complex wildlife disease models include details about wildlife population spatial structure and contact patterns (e.g., Snäll et al. 2008, Craft et al. 2009, Hamede et al. 2009), using simulation and Monte Carlo methods to investigate disease dynamics in heterogeneous networks of individuals. However, these models typically require extensive empirical data specific to the study system. When such data are not available, educated guesses and expert opinion are needed to specify parameters that cannot be excluded from the models.

The Approximate Bayesian Computation (ABC) modeling framework can address complex disease systems without specifying all system parameters or relying on educated guesses. ABC generates an approximate likelihood function, allowing statistical parameter estimation when an explicit likelihood function is not available. This enables analysis of realistic stochastic models that incorporate nonlinear dynamics and disparate information about host population structure, movement, behavior, and heterogeneous transmission rates. When empirical data are limited, ABC explores the logically complete space of the unspecified parameters.

The ABC framework grew out of simple rejection algorithms that generate samples from probability distributions using large amounts of simulated data and summary statistics (Tavaré et al. 1997, Pritchard et al. 1999). It has since been adopted and refined in the fields of population genetics (Hamilton et al. 2005), human epidemiology (Shriner et al. 2006, Tanaka et al. 2006, McKinley et al. 2009), livestock epidemiology (Bekara et al. 2014), and ecology (Jabot and Chave 2009, Scranton et al. 2014). An ABC technique using sequential Monte Carlo (ABC-SMC) is more computationally efficient than its predecessors (Sisson et al. 2007, Beaumont et al. 2009, Toni et al. 2009, Beaumont 2010, Csilléry et al. 2010), and has recently been used to investigate costs to drug resistance in *Mycobacterium tuberculosis* (Luciani et al. 2009) and to estimate disease parameters for Ebola virus (McKinley et al. 2009), a macroparasite infection of domestic cats (Drovandi and Pettitt 2011*b*), hospital-acquired staph infections (Drovandi and Pettitt 2011*a*), and Severe Acute Respiratory Syndrome, SARS (Walker et al. 2010).

We demonstrate the use of ABC-SMC to determine the disease dynamics of bTB in lions in KNP based on spatial data of lions, population size, and disease prevalence across the park. We assumed little prior knowledge about the model's disease parameters and investigated the full range of their possible values. In particular, we address whether bTB spreads primarily from buffalo to lion or from lion to lion, the long-term effect of bTB on lion population size and disease prevalence, and the implications for management of KNP's lion population.

Methods

Kruger National Park (KNP) is a 19,485-km^2 wildlife reserve located in the northeastern part of South Africa (22°19′–25°32′ S, 30°52′–32°03′ E) and is part of the Great Limpopo Transfrontier Conservation Area, a protected area that also comprises national parks and limited-use lands in Mozambique and Zimbabwe. Two major permanent rivers, the Sabie and the Olifants, cut across KNP from west to east and reduce animal movements northward and southward, effectively dividing the park into three sectors: the northern, central, and southern regions.

Bovine tuberculosis (bTB) has spread from the south of the park northward via the buffalo population, and genomic analysis indicated that lions originally contracted bTB from buffalo (Keet et al. 1997). Lions are also suspected of transmitting bTB from one to another via aerosol transmission while in close proximity or via wounds during fights (Kaneene and Pfeiffer

2006, Keet et al. 1998). Lions exhibiting symptoms of bTB usually die within several years (Keet et al. 2000, Renwick et al. 2007, Trinkel et al. 2011). Emergent bTB has raised concerns about lion population viability in KNP because diseases have been implicated in declines of lions in protected areas elsewhere (Munson et al. 2008).

Lion demographic simulation

We modified an existing individual-based lion stochastic simulation model called SimSimba (Whitman et al. 2004, 2007) to incorporate bTB disease dynamics. Individual lions stochastically progress in half-year time steps through life stages, including birth, maturation, dispersal, reproduction, and death. The modeled lions form prides and coalitions that mimic the social patterns of actual lions by moving around on a user-defined spatial lattice of territories and interacting with one another; males fight to compete for access to females and commit infanticide when they take over a pride with cubs. Parameterization of lion demographics in SimSimba used KNP data when available and was supplemented with data on lions from the Serengeti (see Appendix S1). Parameterization was validated by running the model without disease and comparing lion age structure, sex ratios, and population size to known demographic values in KNP. Ignoring the disease component was deemed reasonable for parameterizing the demographic model, as bTB has had little documented effect on lions at the population level (Ferreira and Funston 2010).

A landscape map of model territories was created to mimic the geography and lion density of Kruger National Park (Fig. 1). The lion territories were distributed by dividing the estimated number of actual lions in each of six regions of the park (northeast, northwest, central east, central west, southeast, and southwest; Ferreira and Funston 2010) by estimated pride sizes, and were arranged in a honeycomb pattern in proportion to the physical dimensions of the park.

Disease model

Each modeled lion exists in one of three disease states: susceptible, exposed, or infectious. All lions begin as susceptible and stochastically transition to exposed, whereupon they are considered to have a latent form of the disease that has no effect on mortality or fecundity. Exposed lions then stochastically transition to infectious, transmit the disease to susceptibles, and suffer increased mortality. We made the explicit assumption that lions in the latent state could not transmit the disease, based on *Mycobacteria*

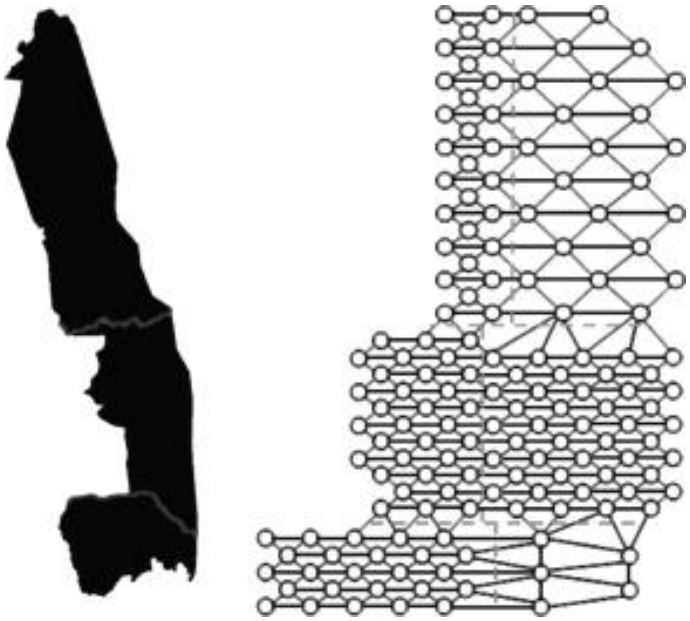

FIG. 1. The geographic shape of Kruger National Park, South Africa (left), trisected by the Olifants and Sabie Rivers (light lines). Model schematic of Kruger National Park (right); each circle represents a lion territory and potential pride, while lines indicate physical connectance of those territories.

tuberculosis pathogenesis in humans (Bates 1984). We also assumed that exposed and infectious lions never returned to the susceptible state nor entered an immune state.

The transition from susceptible to exposed is based on three parameters: B defines the probability of transmission from the infected buffalo population to a susceptible lion; L defines the probability of transmission from an infected lion to a susceptible lion; O defines the probability of an encounter between two lions each time step. Two lions within the same social group have a 100% probability of encounter. Lions in neighboring groups have a probability of encounter between 0 and 1, as do nomadic lions passing through resident lions' territories. Resident lions from non-adjacent territories are assumed not to encounter each other.

The transition from exposed to infectious at each time step is governed by parameter E, which is comparable to the transition parameter of classical SIR disease models. The increased mortality of infectious lions was modeled with parameter I, which describes the exponential probability of dying from disease each time step and is additive to the background mortality imposed by demographic specifications. Formally, for each lion in each time step:

$$\text{pr}(\text{susceptible} \rightarrow \text{exposed}) = B \cdot \text{prev}_{\text{buff}} + \left[1 - (1 - L)^{i+jO}\right]$$

$$\text{pr}(\text{exposed} \rightarrow \text{infectious}) = E$$

$$\text{pr}(\text{infectious} \rightarrow \text{dead}) = I$$

where $\text{prev}_{\text{buff}}$ is the prevalence of bTB in buffalo in the area, i is the number of infectious lions in the same social group, and j is the number of infectious lions in neighboring groups and local nomads. The disease dynamics parameters (B, L, O, E, and I) are summarized in Fig. 2.

We set the prevalence of bTB in buffalo to follow logistic curves fitted to match the observed prevalence in each region of the park in 1991–1992 and 1998, with an asymptote of 0.67; Appendix S3: Fig. S31 (De Vos et al. 2001, Rodwell et al. 2001). These curves were then used as input to the lion demographic disease model to compute the probability of disease transmission to a lion from infectious buffalo; the rate that lions become exposed to bTB from buffalo in a given region at a given time is the product of the prevalence in buffalo in that region at that time and parameter B.

Observed field data

The field data used to compare results from the ABC-SMC simulations (Table 1) consist first of a set bTB prevalence data (Keet et al. 2000) that were obtained by tuberculin testing 125 "repeat-offender" lions in good physical condition. These lions have caused park management repeated problem, such as killing cattle or leaving the park, and are brought to the park veterinarians for euthanizing. Although not a perfect random sample, these lions provide the best available estimates, as tuberculin testing requires repeated handling of lions three days apart. We excluded prevalence data on sick and emaciated lions because they would have biased our data toward high prevalence rates. The tuberculin test for lions has a very high rate of detection in animals in good condition (Keet et al. 2010).

The second set of field data consists of lion population surveys, conducted using call-up stations. The surveys were conducted in the 1970s and again in 2005–2006 (Ferreira and Funston 2010). There was no

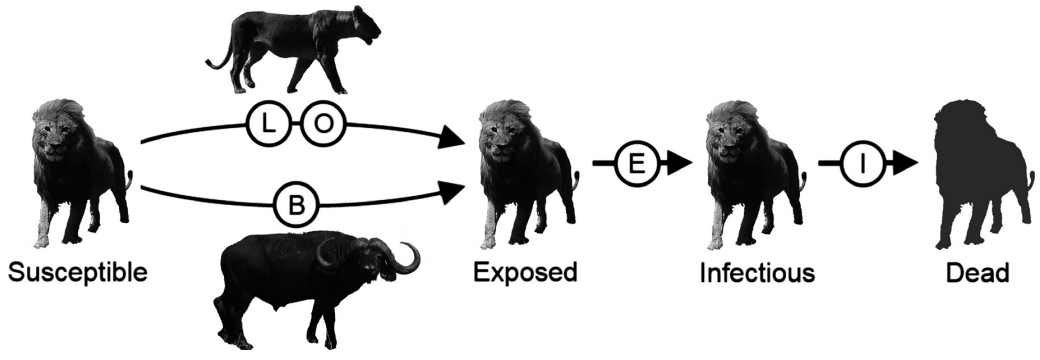

FIG. 2. Disease dynamics model parameters: L is the probability of transmission of bovine tuberculosis to a lion from another lion; O indicates the rate of contact between lions not in the same pride; B describes the probability of bovine tuberculosis transmission from the buffalo population; E is the transition rate of an exposed lion to the infectious state; and I is the mortality rate of infectious lions.

TABLE 1. Observational data on bovine tuberculosis prevalence and lion population size.

Data	Value	Method	Reference
bTB prevalence in lions		single cervical intradermal testing of repeat offender lions in good condition	Keet et al. (2000, 2010)
South region (1998–2000)	78.1% (50/64)		
Central region (1998–2000)	46.2% (18/39)		
North region (1998–2000)	0.0% (0/22)	full-park survey using call-up stations	Ferreira and Funston (2010)
Change in lion population size between 1976–1978 and 2005–2006	no detectable change		

detectable change in lion population size between the 1970s surveys and those conducted in 2005–2006 (Ferreira and Funston 2010).

ABC-SMC algorithm

We used ABC-SMC to determine posterior distributions of the disease dynamics parameters in the Kruger lion system. The algorithm searched the space of all possible disease parameters (B, L, O, E, I) by choosing a set of random parameter values, and then iteratively running the SimSimba-Disease model. Model results were compared against field data (Table 1) to find the parameter sets with highest likelihood, and then these parameter values were perturbed to obtain new values for the next round.

In Bayesian methods, a posterior distribution $f(\theta|x_0)$ of model parameters θ is taken from a parameter space Θ given the observed data x_0. Through Bayes' theorem, $f(\theta|x_0)$ is proportional to $f(x_0|\theta)\ \pi(\theta)$, where $f(x_0|\theta)$ is the likelihood function and $\pi(\theta)$ is the prior distribution of model parameters. The posterior $f(\theta|x_0)$ is approximated with Monte Carlo techniques to draw a large number of possible samples from $f(x_0|\theta)\ \pi(\theta)$. This is done by repeatedly drawing a candidate parameter set, θ^*, from the prior density and simulating data, x^*, using a model $g(x^*|\ \theta^*)$. In ABC, if the simulated data sufficiently match the observed data x_0, θ^* is accepted and becomes part of the sampled posterior distribution (Sisson et al. 2007).

In SMC, each parameter set is termed a "particle." A population of particles $\theta_1, \ldots, \theta_N$ is drawn from the parameter space Θ according to the parameters' prior distribution. Data x^* are simulated for each particle, as in all ABC methods, and distance measure D, a measure of closeness between the simulated data, x^*, and the observed data, x_0, is calculated. The tolerance, ε, is defined as the maximum value of D that will allow the particle's acceptance. The tolerance is reduced at each iteration, improving the fit between the resulting distribution and the posterior distribution. The set of accepted particles is weighted and smoothed to form the prior distribution for the next iteration, whereupon a new set of particles is drawn, ε is decreased, and the process is repeated until the desired tolerance is reached. This process explores complex parameter spaces more quickly than previous ABC algorithms in which particles are correlated with one another (Sisson et al. 2007).

We used a modified version of the original ABC-SMC algorithm that selects a fixed fraction of the best particles in each round to determine the value of ε for that round. This modification speeds up posterior distribution convergence that might otherwise stall with poorly chosen a priori ε values (Drovandi and Pettitt 2011*a*).

Our algorithm runs as follows:

1) Our parameter space consists of the disease parameters $\Theta = \{B, L, O, E, I\}$ and each particle is a point in that space. We assign flat priors for B, L, O, E, and I from uniform distributions on [0,1]. We draw 50,000 independent particles from Θ.
2) We set the parameter values in SimSimba according to the particle's associated values and run the model from 1960 to 2006 (46 years, 92 time steps).
3) For each run of SimSimba, we randomly sample 22, 39, and 64 lions in the north (n), central (c), and south (s) regions, respectively, in the year 1999. We record the number of exposed or infectious lions in each sample as F_n, F_c, and F_s. We also record the simulated population size of the north, central, and south region in 1960 and in 2006, denoting the difference in population sizes as N_n, N_c, and N_s, respectively. The output from each run is therefore $x^* = (F_n, F_c, F_s, N_n, N_c, N_s)$.
4) We compare observed data $x_0 = (0, 18, 50, 0, 0, 0)$ (from Table 1) and x^* for each run, transforming both x_0 and x^* with partial least squares regression so as to more equally consider all six components (Wegmann et al. 2009). We then calculate D as the Euclidean distance between the transformed x_0 and the transformed x^*.
5) We sort the 50,000 particles by D and accept the 1000 particles with the least difference between simulated outcomes and our observed data. For each of the 1000 accepted particles, we calculate

weights $w^{(i)}$. In the first round, each particle is weighted equally. Subsequently,

$$w_t^{(i)} = \frac{1}{\sum_J w_{t-1}^{(j)} K_t\left(\theta_{t-1}^{(j)}, \theta_t^{(i)}\right)}$$

where t represents the current round, $t-1$ the previous round, and K_t is the kernel, or transition density function, for round t. This equation computes a current particle's weight based on the distribution of the previous round's particles and the probability that it derived from each of those particles. We then normalize the weights to sum to 1.

6) We generate 50,000 new particles from the weighted distribution of the 1000 particles accepted in the prior round. For each new particle, we randomly choose an accepted particle and perturb it using the uniform perturbation kernel $K_t = \alpha U(-1,1)$ with α as one standard deviation of each parameter value. This perturbation smoothes and spreads the accepted distribution to explore nearby parameter space.
7) We return to Step 2 and repeat until the new distribution no longer departs significantly from the previous iteration, which is defined as a change between rounds in the mean and standard deviation of each parameter of less than 0.05 (Lenormand et al. 2013).
8) We examine the marginal probabilities of the joint distribution on our five parameters.

We report results as means, medians, and 95% credible intervals of the posterior distributions. Credible intervals are analogous to the confidence intervals of frequentist statistics; there is a 95% certainty that the true value lies within a 95% credible interval (Edwards et al. 1963).

SimSimba simulations were run at the University of Minnesota Supercomputing Institute. Transformation, weighting, and perturbation of parameter sets was performed in R on a laptop computer using packages *MASS, car*, and *pls* (Venables and Ripley 2002, Fox and Weisberg 2011, Mevik et al. 2011, R Core Team 2012).

After running the ABC-SMC algorithm, we performed a cross-validation using the "cv4abc" function in the R package *abc* (Csilléry et al. 2012). This procedure used the simulation results from the first round of particles, which were evenly distributed across the parameter space, to determine whether the modeling framework can accurately estimate parameter values. See Appendix S4 for details.

To check for the possibility of additional solutions, we excluded the region of parameter space containing the first solution and reran the ABC-SMC algorithm on the reduced parameter space. For efficiency, we ran only 20,000 particles per round instead of 50,000. If a good match to the observed data was found, we reran the ABC-SMC algorithm, until the model converged on another solution or until there was no convergence.

For each valid solution, we took the 1000 parameter sets from the posterior distribution of the ABC-SMC algorithm and ran them in SimSimba from 1960 to 2060 (100 years, 200 time steps) to forecast the impact of bTB on disease prevalence and lion population size. To determine equilibrium impact of the disease, we ran the simulations from 1960 to 2260 (300 years, 600 time steps).

To determine whether lions are maintenance or spillover hosts, we repeated the forecasting procedure while removing all disease from the buffalo from 2010 onward by eliminating buffalo-to-lion transmission and only allowing the disease to be transmitted from lion to lion.

To see how lion-to-lion transmission affects disease spread and population size, we took the 1000 parameter sets from the posterior distribution and set L to zero. We compared the results for simulations with $L > 0$ and $L = 0$ for six replicates for each parameter set, using t tests blocked by parameter set.

Code for the SimSimba disease model (in C++) and for performing the ABC-SMC algorithm and cross-validation (in R) is *available online*.[7]

Results

Our analysis revealed that two parameters, L and O, were not identifiable with this model (see Appendix S4 for details). L, the rate of lion-to-lion transmission of bovine tuberculosis (bTB), plays little role in model dynamics when very few individuals are infectious and transmitting the disease. The value of L is also irrelevant when almost all individuals are infectious and transmitting the disease. Further, buffalo-to-lion spread of the disease dominates disease dynamics when L is small and B, the rate of transmission from buffalo to lions, is relatively large. In all other cases, the population of lions goes extinct, and L is not identifiable. Because O, the contact rate among non-pride lions, modifies the effect of L, O is also not identifiable. Although our model cannot determine rates of lion-to-lion transmission of bTB or the contact rate between non-pride lions, we can still infer the other three disease parameters and characterize disease dynamics of the system as a whole.

In our initial run of the ABC-SMC algorithm, parameter distributions converged after five rounds (Appendix S3: Fig. S32), with observed data values falling into the middle of model summary statistics distributions (Appendix S3: Figs. S33 and S34). After excluding this area of parameter space and rerunning

[7] http://dx.doi.org/10.6084/m9.figshare.1418430

the algorithm, we discovered another region with equally low distance measures (Appendix S5: Figs. S53 and S54). When we excluded both solutions and reran the algorithm a third time, the model converged on an area of parameter space where distance scores were markedly higher (Appendix S5: Fig. S55), indicating a poor match to observed data (Appendix S5: Fig. S56).

Solution 1

Mirroring buffalo prevalence patterns, lion prevalence showed a logistic increase in each region of the park (Fig. 3), while lion population size decreased slightly (Fig. 4). Disease dynamics in this system were largely driven by two parameters. The transmission rate between an infected buffalo and a susceptible lion, B, drove the disease prevalence in lions (Appendix S3: Table S31, Figs. S35 and S36). ABC-SMC converged on a stable posterior distribution for B with mean 0.60, median 0.61, and 95% credible interval of [0.17–0.91] (Fig. 5). Assuming a contact rate of one buffalo per six-month period and a stably infected buffalo population, this translates to an average annual exposure rate of 0.64 per individual lion from buffalo consumption (95% CI [0.21–0.85]).

The rate that lions transition from exposed to infectious, E, drove changes in lion population size (Appendix S3: Table S32, Figs. S37 and S38). ABC-SMC converged on a stable distribution for E with mean 0.0068 (median 0.0056, 95% CI [0.0003–0.0188]; Fig. 5). This is equivalent to an annual per lion rate of transition from exposed to infectious state of 0.014 (95% CI [0.0006–0.037%]) and a mean duration of latency of 74 years (95% CI [27–1670 years]), much longer than a lion's lifespan. The mean fraction of exposed individuals that transitioned to infectious in their lifetimes was 0.051 (95% CI [0.002–0.143]; Appendix S3: Fig. S39).

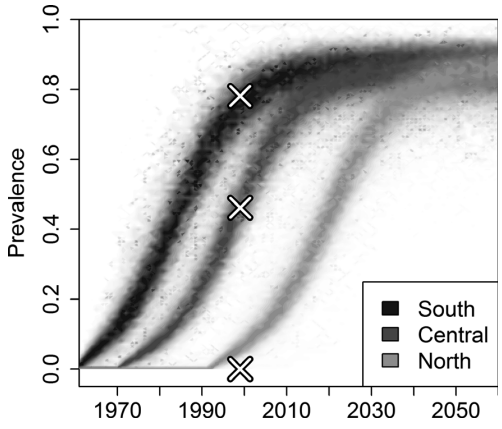

FIG. 3. Modeled prevalence of bovine tuberculosis in the lion population for the south, central, and north regions shows that prevalence across the park asymptotes at around .08 by 2050. Prevalence values are shaded by likelihood density, with highest likelihood shaded dark and lowest likelihood pale. White X's indicate observed prevalence in the south, central, and north regions, respectively (Keet et al. 2010).

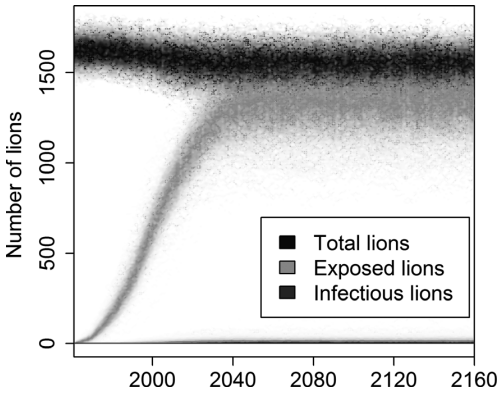

FIG. 4. Modeled number of total adult and subadult lions in the population, those that are exposed, and those that are infectious. Values are shaded by likelihood density, with highest likelihood shaded dark and lowest likelihood pale.

Parameter I, the rate at which infectious lions die of bTB, averaged 0.58 (95% CI [0.07–0.97]). This is equivalent to an average annual disease mortality rate of 82% (95% CI [14–100%]). Parameter L's posterior distribution had mean 0.44 (95% CI [0.02–0.93]) and parameter O had mean 0.46 (95% CI [0.02–0.95]); both retained fairly flat posterior distributions and are, in any case, not identifiable (Fig. 5).

Solution 2

When we excluded the region of parameter space that contained the first solution ($E < 0.15$), we found a second solution (Appendix S5: Figs. S53 and S54). The algorithm converged with very low L values (mean 0.008, median 0.006, 95% CI [0.000–0.0226]). B values (mean 0.227, median 0.143, 95% CI [0.003–0.804]) were higher than L values, indicating that the spread of bTB was again governed primarily by buffalo-to-lion transmission.

Parameter E had a posterior distribution of mean 0.494, median 0.467, and 95% CI [0.164–0.948]. The posterior distribution for I (mean 0.035, median 0.017, 95% CI [0.001–0.163]) indicated low mortality from bTB for this solution, equivalent to a 6.9% mortality rate per year (95% CI [0.2–29.9%]) and a mean duration of infectiousness of 14.3 years (95% CI [3.1–500]), on par with the maximum lifespan of wild lions. Parameter O had posterior distribution

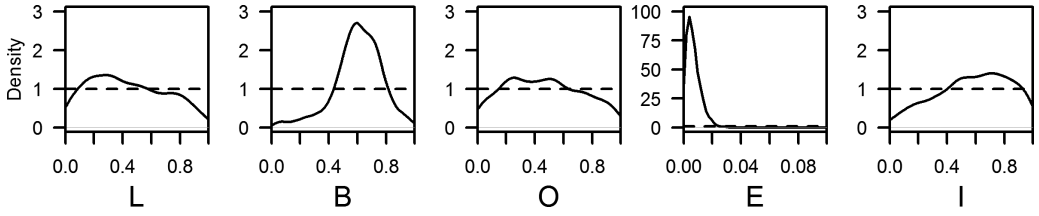

FIG. 5. Posterior density distributions for the five model disease parameters. Horizontal dashed lines indicate initial parameter distributions ("priors"). Parameters *B* (bovine tuberculosis transmission rate from buffalo to lion) and *E* (transition rate of an exposed lion to the infectious state) show a peaked distribution that deviates substantially from their priors, indicating that these parameters are most informed by the data, whereas parameters *L* (transmission rate from lion to lion), *O* (contact rate between lions not of the same pride), and *I* (disease mortality rate) do not deviate as much from their priors.

of mean 0.323, median 0.256, and 95% CI [0.013–0.905].

Due to the biological infeasibility of such low mortality from bTB (see *Discussion*), we did not conduct further analyses or forecasting of solution 2.

Forecasting

The forecasting simulations for solution 1 suggest that the lion population is not in danger of crashing from the introduction of bTB alone (Fig. 4). Results suggest a 3% decline over the next 50 years due to increased mortality from bTB (95% CI [−0.09–0.14]). The long-term forecast indicates that the lion population will reach a new long-term carrying capacity at this slightly depressed level.

Mirroring the rise of bTB in buffalo, disease prevalence in lions increased logistically in all three regions. Most lions were exposed to the disease by the mid-2020s, and 85% of all lions were exposed by 2060 (Fig. 3; 95% CI [74–92%]).

When we simulated a disease-eradication program in buffalo, there was an immediate steep drop in lion prevalence (Fig. 6), and the disease was eradicated from lions within 20 years. The lion population size declined slightly as the disease continued to progress in previously exposed individuals but then recovered to pre-disease levels (Fig. 6).

When infectious lions were allowed to transmit the disease to susceptible lions, bTB prevalence was slightly higher than when transmission was strictly from buffalo to lion (mean difference in 1999 = 0.0474, SEM = 0.0022, $P < 0.0001$) and the total lion population size showed a minor decline (mean difference in 2006 = 3.78 individuals, SEM = 1.20, $P < 0.0001$).

DISCUSSION

Using ABC-SMC, we made important inferences about bovine tuberculosis (bTB) dynamics in the lion population in Kruger National Park (KNP), despite lacking empirical knowledge about the transmission and progression of the disease.

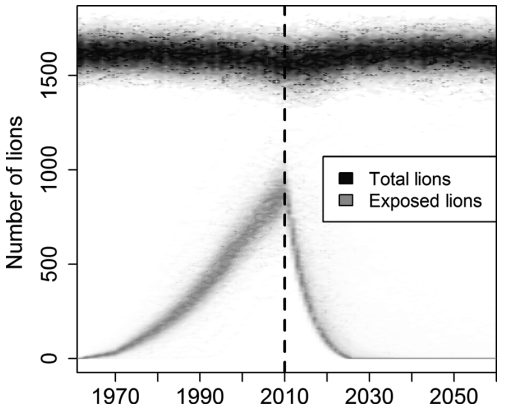

FIG. 6. Modeled number of total adult and subadult lions in the population, and those that are exposed. The prevalence of bovine tuberculosis in buffalo is set to 0 in the year 2010. Subsequently, the disease clears from lions and the lion population rebounds. Values are shaded by likelihood density, with highest likelihood shaded dark and lowest likelihood pale.

Solutions found by ABC-SMC

We identified two areas in our parameter space where model simulations matched lion population and bTB prevalence data. The first solution describes a situation in which latency of bTB in lions is long. Most lions that are exposed to the disease remain in this latent state in which they neither experience symptoms of the disease nor transmit it to others. Only about 5% of lions that become exposed eventually develop symptoms and become contagious; the rest die from other causes while still in the latent stage.

Because so few lions are contagious at any point in time, lion-to-lion transmission is unimportant for disease spread at the population level. Even if a single infectious lion exposed all of its pridemates and all neighboring pride lions to the disease, the prolonged latency of the disease would likely prevent more than one other lion from becoming infectious. Note that because the lion-to-lion transmission rate, *L*, is

unidentifiable in our model, we cannot deduce the actual rate, or efficiency, of lion-to-lion transmission. bTB might be extremely contagious in infectious lions, or it might be relatively non-contagious. The model suggests that the actual lion-to-lion transmission rate is unimportant for disease dynamics because the vast majority of lions exposed to the disease never progress to infectious.

This solution also describes a high mortality rate for lions in the infectious state. An 82% annual disease mortality is equivalent to an expected lifespan of 10–15 months following onset of bTB symptoms and contagiousness. Thus the few lions that do become infectious die before they can spread the disease extensively.

Because lion-to-lion transmission of bTB is infrequent, transmission results primarily from infected prey, and we estimate that a lion has a 64% chance per year of becoming exposed to the disease by consuming infected buffalo. Consistent with this finding, the bTB prevalence patterns in lions reflect those in buffalo, with highest prevalence in the south and lowest in the north.

The second solution describes a situation in which disease latency is shorter and disease mortality is very low. Lions progress from the exposed to the infectious state at a rate of 0.74 per year, spending 1–2.5 years in the exposed state. Each lion that becomes infectious has just a 6.9% chance of dying each year and remains infectious for an average of 14.3 years, longer than most wild lions' lifespans, meaning that lions showing symptoms of the disease usually die from causes other than bTB. At the same time, lion-to-lion transmission rates in solution 2 are very low: a lion that comes into contact with a contagious lion has just a 1.6% chance each year of becoming exposed to the disease. Over a 10-year period, an infectious lion would expose a susceptible pridemate just 15% of the time. Exposure of lions to bTB from eating infected buffalo is estimated to be 40.2% per year. Thus, as with solution 1, the disease dynamics are dominated by buffalo-to-lion transmission in solution 2.

Although both solutions 1 and 2 describe statistically valid sets of disease parameters that are consistent with lion population size and bTB prevalence, solution 2 does not agree with additional empirical data about bTB-induced lion mortality. Solution 2 is characterized by a very low mortality rate of bTB after transitioning to the infectious state. However, veterinary data show that once lions begin to show symptoms of bTB, they deteriorate quickly, and typically die within five years (Keet et al. 2000, Renwick et al. 2007, Trinkel et al. 2011). Even at the top of the 95% credible interval for disease mortality in solution 2, annual mortality is 29.9% per year, and about one-sixth of infectious lions would survive past five years. As a result, solution 1 describes the most biologically reasonable set of disease parameters for bTB dynamics in KNP's lion population.

Our multi-step approach to find successive solutions in the parameter space is not a pure ABC algorithm. A more elegant method would use a single ABC algorithm that converges on a multimodal distribution, which in this case would have identified two modes. Three algorithmic choices contributed to our finding only a single mode at a time. First, we chose a uniform prior on the principle of "insufficient reason" (Kass and Wasserman 1996). We potentially could have specified a prior such that areas of high nonlinearity received greater weight, but we had no reason to believe that the area of solution 2 was more nonlinear than other parts of parameter space. Second we chose the perturbation kernel as a uniform distribution. A distribution with a more central tendency, such as a Gaussian, would reduce the spread of particles from round to round and might have allowed the algorithm to converge on a bimodal distribution, albeit more slowly. Third, we accepted only 2% of particles in each round (1000/50,000), which sped convergence, but quickly eliminated particles in solution 2 that would have benefitted from additional exploration. The first round contained ~3000 particles in solution 2. But only 16 made it into the second round based on the 2% cut-off, and no particles in solution 2 survived from the second round to the third round. Unfortunately, there is no known way to estimate when decisions that accelerate computation will risk excluding a secondary solution spanning a relatively small fraction of parameter space. Finally, an ABC Markov chain Monte Carlo (MCMC) algorithm might also have identified a bimodal distribution, but it, too, may have only found the first solution.

Implications of model results

The workshop model (Keet et al. 2009) that predicted an unobserved crash in the lion population (Fig. S21) appears to have overestimated the rate of transition from the exposed (latent) state to the infectious state. This overestimation resulted from personal observations of dying lions and one small-scale study, suggesting that expert opinion must be used cautiously when combined with complex models.

By contrast, we assumed nothing about the rate of transition from the exposed to the infectious state (E) and instead explored all possible rates. In the most biologically reasonable solution, only small values of E resulted in dynamics that matched empirical observations, so we can reasonably conclude that E must be small. In fact, while lifetime transition probabilities of tuberculosis are unknown for wildlife, the observed rate of 0.051 in our model is comparable to the rate of 1 out of 10 in untreated humans (Appendix S3: Fig. S39); Bates 1984.

Our model also suggests that bTB is primarily transmitted from buffalo to lions, whereas transmission from one lion to another is infrequent. This result is consistent with veterinary findings that infected lions only occasionally show pulmonary lesions, implying infrequent aerosol transmission (Keet et al. 2000). Prior studies have been inconclusive as to whether lions are maintenance or spillover hosts of bTB (Michel et al. 2006), but our model suggests that lions constitute a spillover host, in agreement with other studies (Renwick et al. 2007, Maas et al. 2012).

We forecast that most lions will be exposed to bTB over the next few decades. However, the disease will remain latent in the majority of lions because of the low transition rate from exposed to infectious. The number of sick lions will increase in the central and northern regions, where the disease has not yet reached equilibrium. However, even at equilibrium, we predict that only about a dozen lions will die from bTB across the park annually (Fig. 4). In total, the lion population size will only decrease by about 3% over the next 50 years, but such a small effect will be difficult to detect from short-term monitoring (Jolles et al. 2005, Ferreira and Funston 2010).

In addition to revealing disease patterns, the results from our model can be used to infer the primary driving variables of a system. In the case of the KNP lions, we found that parameter E, the rate of transition from exposed to infectious, was the primary driver of lion population size. With this knowledge, we further infer that changes to the system that increase E, such as coinfection with new diseases, might cause greater bTB mortality. In humans, for example, coinfection with the human immunodeficiency virus (HIV) causes an increase in the transition rate from the latent stage of tuberculosis (*M. tuberculosis*) to the infected state (Lawn and Zumla 2011). While coinfection with the related feline immunodeficiency virus (FIV) does not appear to have a similar effect on bTB progression in lions (Maas et al. 2012), other combinations of disease are known to increase lion mortality (Munson et al. 2008).

Parameter B, the rate of disease transmission from buffalo to lions, was the primary driver of disease prevalence in lions. Changes in the system that increase B may also increase the incidence of bTB in the lion population. Drought, for example, causes the fraction of infectious buffalo in the park to increase, as buffalo are stressed by food limitation and increased endoparasite load (Caron et al. 2003). As a result, lionesses kill four times as many buffalo during droughts (Funston and Mills 2006). We therefore expect that the increase in bTB prevalence in lions in the central and northern areas of KNP to accelerate during droughts.

Information on driving variables also allows for practical management recommendations. Because our model shows that buffalo are the primary source of bTB in lions, recommendations for controlling the disease in lions should focus on reducing buffalo-to-lion transmission. In KNP, culling and quarantining buffalo is not feasible, and so the development of a vaccine for buffalo might be one recommendation. Given the limited impact of the disease on the lion population, however, the expense of vaccine development for the sole purpose of protecting lions may not be justified. On the other hand, vaccination might be warranted when considering the combined effects of bTB on the KNP system, such as the risk of bTB spread to other wildlife and livestock populations and policy implications for management agreements among South Africa, Mozambique, and Zimbabwe, the co-managers of the Great Limpopo Transfrontier Conservation Area.

Testing model results

The results of our modeling efforts might be seen as hypotheses that can now be empirically tested. In particular, we hypothesize that most (>95%) lions that have been exposed to the disease are not symptomatic or contagious. We hypothesize that once a lion becomes symptomatic, the mortality rate is high, with lions typically dying an average of less than year and a half after symptom onset. We also hypothesize that transmission from infected buffalo to lions is fairly efficient, with a 64% chance that a lion feeding on infected buffalo becomes exposed in a given year.

To test the fraction of exposed lions that show symptoms of bTB, it is first necessary to identify individuals that test positive for the disease. The best method for determining exposure to bTB in lions is a skin test, similar to that in humans, that requires the injection of tuberculin with a follow-up observation 72 hours later (Keet et al. 2010). This test requires the immobilization and confinement of each wild lion to an enclosure, where it is kept for three days, immobilized again, then moved and released. In the process, lions can be assessed for bTB symptoms: weight loss, swollen joints, hygromas at the elbows, and poor healing (Renwick et al. 2007). A high fraction of bTB-positive lions without bTB symptoms would support the hypothesis of a low rate of transition from the exposed to the infectious state.

To measure the mortality rate of lions that have entered the infectious state, an intensive ground effort would be needed to systematically monitor the condition of a large number of lions. Once an individual exhibited symptoms of bTB, it should be observed repeatedly until death. But because so few lions are likely to become infectious and because symptoms of bTB in live lions are nonspecific, regular surveys should include hundreds of lions to ensure observations of the complete duration of infectiousness.

To ascertain the rate of bTB transmission from buffalo to lions, lions could be sampled for disease exposure in areas of contrasting prevalence in buffalo,

focusing on young lions, so as to estimate the time between the onset of meat eating and infection.

Our model also predicts that the prevalence of bTB in lions will slowly rise in the central and northern parts of KNP and level off around 2020 and 2040, respectively. Data published subsequent to the analysis in this paper support this increase in the north, with a 0.13 prevalence (n = 31) by 2003 and 0.41 (n = 17) by 2009 (Maas et al. 2012). Prevalence rates for the central region were unavailable. By comparison, our model predicted that prevalence in the north would reach 0.12 (95% CI [0.05–0.26]) in 2003 and 0.21 (95% CI [0.11–0.39]) in 2009.

Model assumptions

We acknowledge that our results rely on implicit assumptions arising from the demographic simulation model and the disease model. SimSimba uses a number of parameters (Appendix S1) that describe lion demography and social behavior and affect our results. It is likely, however, that the model and parameter values provide a reasonable interpretation of KNP lion dynamics. SimSimba was developed to realistically mimic Serengeti lion population dynamics, age structure, and sex ratios that have been observed in detail in ~5000 lions over four decades (Whitman et al. 2004). It was modified to incorporate as much KNP data as possible and was validated by comparison with static KNP demographic data. Lion model parameters have previously been altered to describe specific demographic and ecological conditions of various different lion populations and feline species, and SimSimba outputs have repeatedly been found to be robust (Whitman et al. 2007, Packer et al. 2009, Brink 2010). Most parameters are based on extensive empirical data, and conclusions do not appear to be overly sensitive to modifications of any of the unmeasured variables.

Our disease model makes several assumptions. We assume that once lions become infectious, they subsequently die without any chance of developing immunity. We also assume that the timing of infectiousness of bTB in lions corresponds with the timing of their increased mortality from the disease. These assumptions are based on the epidemiology and pathogenesis of tuberculosis in humans and other animals (Bates 1984). We also assume that there was no feedback between lions and buffalos; in particular, the prevalence of bTB in buffalo was not affected by lion population size in our model. Buffalo population size in KNP is believed to be controlled both by predation and availability of food (Funston and Mills 2006), so a future decrease in lion population size could cause an increase in buffalo population. However, it is unclear whether a change in buffalo population size would have a measurable effect on bTB prevalence in buffalo.

We assume a uniform prevalence of bTB in buffalo in each region of KNP, although herds differ in their levels of infection (Rodwell et al. 2001). We also assume that lion contact with buffalo remains constant through time and that buffalo are the only prey species important for transmitting bTB to lions. We have no evidence that differential disease prevalence in buffalo herds follows any pattern that would increase or decrease transmission to lions. The KNP buffalo population has grown over the past two decades (Cross et al. 2009), but lion populations respond very slowly to increases in prey availability, as social and territorial mechanisms are at least as important as prey density in determining lion density (Packer et al. 2005, Ferreira and Funston 2010). Further, KNP lions preferentially prey upon wildebeest and zebra in periods of above-average rainfall (Mills et al. 1995), as seen in the past two decades in Kruger (Cross et al. 2009). Of the two known maintenance hosts for bTB, buffalo are a major lion prey, while the greater kudu are not (Mills et al. 1995); wildebeest and zebra have not yet been found to be infected with bTB.

We also acknowledge that estimates of disease prevalence in the KNP lions were determined from a nonrandom sample: most individuals were "repeat offenders" that had killed cattle or escaped the park. However, these lions were equally likely to be male or female and were not obviously skewed toward subadults or adults (Maas et al. 2012), and there is no reason to believe that they were more or less likely to eat buffalo than other lions. If the prevalence rates in these sampled lions were somewhat higher or lower than that of the whole population, we would expect any bias to be similar across regions of the park. Thus, the precise parameter estimates would change, but the general pattern and implications would remain.

Despite the assumptions in model structure and parameterization, simplification of the ecological system, and imperfect observational data, we suggest that our demographic simulation and disease model reasonably reflect the dynamics of bTB in lions in KNP. Our model yields reasonable results that corroborate veterinary findings, that are in accord with similar dynamics in humans, and that lead to predictions consistent with subsequent system observations.

Applicability of ABC to other systems

The main strength of the ABC framework is to clarify the dynamics of complex stochastic systems in which the likelihood cannot be captured by analytic expressions. ABC efficiently explores the full distribution of posterior parameter probabilities (Hartig et al. 2011), can determine when measurements are insufficient to constrain parameter estimates, and can identify the most relevant data for closing these gaps (e.g., Jabot 2010, Csilléry et al. 2012).

Two components are needed when using the ABC framework to investigate wildlife disease systems: (1) empirical data describing one or (preferably) more patterns in the target population or community; and (2) a stochastic simulation model that describes the system, with one or more unknown parameters whose precise measurements would yield insight into system dynamics. The patterns serve to constrain the parameter space, and as such, variation over space and/or time in the number of individuals, size or age classes, sex ratios, disease prevalence, or mortality rate are useful (Wiegand et al. 2003). The existence of more than one pattern is typically necessary to constrain the parameter space enough to find a meaningful solution (Grimm et al. 2005). However if initial attempts indicate that empirical measurements are inadequate to constrain the parameter space, cross-validation techniques can elucidate the data that should be collected in the future (e.g., Jabot 2010, Csilléry et al. 2012).

When using the ABC framework, a set of summary statistics must be selected. For systems with little observational data, such as described here, options may be limited, but summary statistics for more comprehensively studied systems may need to reduce the dimensionality of the associated data. See Hartig et al. (2011) for a discussion of minimally sufficient summary statistics. Before proceeding with the ABC algorithm, artificially created data can be used to test whether the summary statistics are sufficient and efficient (e.g., Jabot and Chave 2009).

Computational demands must also be considered, because stochastic simulation models must be run repeatedly over a potentially large parameter space. The approximate time required to conduct an ABC analysis is the product of the average simulation runtime, the number of particles used in each round, and the number of rounds necessary to reach posterior convergence. Currently, R packages *abc* and *EasyABC* make implementing ABC algorithms straightforward and provide tools for post-processing (Csilléry et al. 2012, Jabot et al. 2013).

Alternatives to ABC exist. For the lion and bTB system, we could have employed synthetic likelihoods that matched model results with observed data (Wood 2010), and we might have considered optimization methods such as simulated annealing or genetic algorithms to search the parameter space for the best parameter sets. However, we wanted to infer the breadth of the likely parameters as well as the mean and median.

Emerging infectious diseases are an increasing challenge for wildlife management (Daszak 2000) and for international conservation policy. However, wildlife disease dynamics are often difficult to study due to a paucity of data and the expense and logistical difficulties associated with their collection. Classical analytic disease models are of limited use in complex systems where disease dynamics depend on host social structure, behavior, and heterogeneous contact rates. Complex simulation and network models often require large amounts of empirical data that are not always available. The ABC modeling framework can employ data on population structure together with observed patterns of disease to constrain the set of all possible combinations of unmeasured parameters. In the case of the KNP lions, we knew little about the disease itself, but were able to infer disease patterns based on lion demographics and social structure, spatiotemporal spread of disease in buffalo, and just one set of observations of disease prevalence in lions. The ABC framework is a next step in wildlife disease modeling, making it possible to estimate essential disease dynamics in complex systems with limited field data in order to inform management decision making.

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Supporting Information

Additional supporting information may be found in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1890/14-1808.1/suppinfo

Data Availability

Data output from the model is available online: http://dx.doi.org/10.6084/m9.figshare.1418428

Code for running model simulations, the ABC-SMC algorithm, and the cross-validation is available online: http://dx.doi.org/10.6084/m9.figshare.1418430