Modelling the distribution in Hawaii of *Angiostrongylus cantonensis* (rat lungworm) in its gastropod hosts

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Abstract

Angiostrongylus cantonensis (rat lungworm), a parasitic nematode, is expanding its distribution. Human infection, known as angiostrongyliasis, may manifest as eosinophilic meningitis, an emerging infectious disease. The range and incidence of this disease are expanding throughout the tropics and subtropics. Recently, the Hawaiian Islands have experienced an increase in reported cases. This study addresses factors affecting the parasite's distribution and projects its potential future distribution, using Hawaii as a model for its global expansion. Specimens of 37 snail species from the Hawaiian Islands were screened for the parasite using PCR. It was present on five of the six largest islands. The data were used to generate habitat suitability models for *A. cantonensis*, based on temperature and precipitation, to predict its potential further spread within the archipelago. The best current climate model predicted suitable habitat on all islands, with greater suitability in regions with higher precipitation and temperatures. Projections under climate change (to 2100) indicated increased suitability in regions with estimated increased precipitation and temperatures, suitable habitat occurring increasingly at higher elevations. Analogously, climate change could facilitate the spread of *A. cantonensis* from its current tropical/subtropical range into more temperate regions of the world, as is beginning to be seen in the continental USA.

Introduction

Eosinophilic meningitis caused by infection with *Angiostrongylus cantonensis*, the rat lungworm, is an emerging infectious disease, with increasing numbers of cases and recent expansion to new geographic areas (Wang *et al.*, 2008; Lv *et al.*, 2011; Cowie, 2013a; Flerlage *et al.*, 2017; Stockdale Walden *et al.*, 2017). *Angiostrongylus cantonensis* is a parasitic nematode with a complex life cycle (Alicata, 1965). Various species of rats are the definitive hosts (Yong and Eamsobhana, 2015) and numerous gastropod species from widely different taxonomic groups have been recorded as intermediate hosts (Kim *et al.*, 2014). Accidental hosts such as humans and other mammals, as well as birds, are infected in the same manner as the definitive rat hosts, primarily by ingesting infected intermediate or paratenic hosts (Cowie, 2013b; Burns *et al.*, 2014). However, in these accidental hosts, most larvae do not complete their natural life cycle. Instead they remain in the central nervous system and eventually die, primarily in the brain (Cowie, 2013a). Humans are usually infected through inadvertent consumption of infected snails on produce or wilful eating of raw or undercooked snails (Cowie, 2013b).

The first known human case of eosinophilic meningitis caused by *A. cantonensis* was in 1945 in Taiwan (Beaver and Rosen, 1964). However, it was not until reports of cases in French Polynesia (Rosen *et al.*, 1961) and Hawaii (Horio and Alicata, 1961) that the link between the disease and infection by *A. cantonensis* became widely understood. Since then, cases have been reported in about 30 countries: in Asia, Australasia, Africa, South America and North America, and including many cases in the islands of the Pacific and the Caribbean (Wang *et al.*, 2008). With increasing international trade and travel facilitating further spread of infected definitive and intermediate hosts, the range of *A. cantonensis* is likely to continue to expand, and although it is generally restricted to tropical and subtropical regions (Wang *et al.*, 2008), global climate change may permit it to spread into currently more temperate areas (Lv *et al.*, 2011; York *et al.*, 2014, 2015).

Angiostrongylus cantonensis was first observed in the Hawaiian Islands in 1960 (Ash, 1962), and the first definitive case of eosinophilic meningitis caused by *A. cantonensis* in Hawaii was in the same year (Horio and Alicata, 1961). Since then there have been cases on five of the six largest Hawaiian Islands (Kauai, Oahu, Maui, Lanai, Hawaii), with a possible increase in the frequency of cases since around 2004 (Hochberg *et al.*, 2007; Cowie, 2017). Although there have been several studies identifying the intermediate hosts of *A. cantonensis* (Kim *et al.*, 2014), little is known about the factors affecting its distribution (e.g. Lv *et al.*, 2011).

Species distribution models (SDMs) that quantify patterns of habitat suitability by comparing species occurrences with environmental factors have been widely used to project future distributions (Guisan and Zimmermann, 2000; Elith and Leathwick, 2009). To inform management and adaptive responses, habitat suitability models are critical tools (Crase *et al.*, 2015). Determining how possible predictors such as temperature and precipitation may affect the distribution of *A. cantonensis* will permit better forecasting of its potential spread and facilitate better targeted public health intervention. The objectives of this study were to: (1) document the geographic distribution of *A. cantonensis* across the Hawaiian Islands; (2) develop a current habitat suitability model to estimate the probability of occurrence of *A. cantonensis* under current climate conditions; and (3) project future potential range shifts for *A. cantonensis* under climate change. We hypothesized that: (1) areas with higher precipitation will support higher levels of *A. cantonensis* than will drier areas, as the intermediate gastropod hosts are more abundant and active in such areas; (2) lower elevation areas will support higher levels of *A. cantonensis* than higher elevation areas, first because globally *A. cantonensis* is restricted to regions with tropical and subtropical climates and areas at higher elevations in Hawaii would be too cold, and second because of the greater numbers of rats at lower elevations (Amarasekare, 1994); and (3) as the climate changes, higher areas and areas in which precipitation increases will become suitable for *A. cantonensis* as well as for their snail hosts.

Materials and methods

Mollusc specimens and study area

As part of a survey of gastropods across the Hawaiian Islands starting in 2004, over 8000 live snails were collected from the six largest Hawaiian Islands and preserved in 75–95% ethanol. From these collections, 1271 specimens from 182 sites, encompassing all six islands, were selected to provide a broad coverage of species and locations. Geographical coordinates were recorded using hand-held global positioning system devices (Rino 520HCx; Garmin International, Olathe, Kansas, USA), and in some cases were estimated using Google Earth.

Total DNA was extracted from gastropod foot tissue, and the presence of *A. cantonensis* was determined following Qvarnstrom *et al.* (2007, 2010), as described by Kim *et al.* (2014).

Environmental data and exploratory analysis

We compiled and explored Geographic Information Systems (GIS) environmental grid layers for vegetation index (http://glcf.umd.edu/data/vcf/), soil type (http://sdmdataaccess.nrcs.usda.gov/), mean annual precipitation (Giambelluca *et al.*, 2013) and mean annual surface temperature (Giambelluca *et al.*, 2014). From the Hawaiian Regional Climate Model (HRCM) based on Zhang *et al.* (2012), we explored mean annual precipitation, mean annual surface temperature, precipitation seasonality (coefficient of variation), precipitation of coldest quarter, precipitation of warmest quarter, temperature of coldest quarter and temperature of warmest quarter. Elevation was not included in the models as it is strongly correlated with temperature in the Hawaiian Islands. Some of the variables did not provide sufficient coverage of the study areas, nor support suitable class size and model complexity relative to the number of collection sites. Following exploratory investigations of all variables, only mean annual surface temperature and mean annual precipitation appeared to offer any predictive power, and only these two variables were used in the final analysis presented here.

For current climate variables, we used temperature (Giambelluca *et al.*, 2014) and precipitation (Giambelluca *et al.*, 2013) estimates

with 250 m grid cell resolution. For future climate, we used the 2100 projections of the HRCM from Zhang *et al.* (2012), based on the Weather Research and Forecasting model V3.3. Original spatial resolution was 3 km for all islands except Maui, with 1 km resolution. The HRCM is a regional dynamical downscaling of climate changes based on averaging multiple CMIP3 global circulation models (GCMs) and future climate forcing of the Special Report on Emissions Scenarios (SRES) A1B (Nakicenovic and Swart, 2000), a conservative emission pathway. New future forcing scenarios have been developed to replace SRES. CMIP5 Representative Concentration Pathways (RCPs) are designed to cover a wider range of possible magnitudes of climate change in models (Collins *et al.*, 2013). However, for small, extremely diverse climate regions with steep precipitation gradients and trade wind inversions such as Hawaii, GCM projections may be unsuitable. All environmental variables were resampled to a consistent projection (geographic WGS1984) with 250 m grid cell resolution in ArcGIS 10.0. Final resolution used for modelling was 250 m.

SDMs and forecasting change

SDMs were generated based on the detected presence and absence of *A. cantonensis* in the gastropod specimens screened, with mean annual surface temperature and mean annual precipitation as the explanatory variables. We developed SDMs with two correlative approaches, generalized linear models (GLMs) and boosted regression tree (BRT) models, and compared their performance.

GLMs have great utility in statistical analyses either when variances are not equal, when error structure is non-normal or both (Crawley, 2007). For the logistic regression framework, we built models using binomial error distributions and default link logit functions (Agresti, 1996; Manning, 2007) to predict habitat suitability as probability of occurrence. We used a backward simplification approach from a full model with all predictors, generating seven models in the glmulti package (Calcagno, 2013) in R version 3.2.0. We first compared individual model fit using the relative Akaike information criterion and model weight. We tested model performance using area under the curve (AUC) of the receiver operating characteristic. An AUC score above 0.7 may indicate model performance as fair, and above 0.9 as excellent (Swets, 1988). With the package cvAUC (LeDell *et al.*, 2013) in R ver 3.2.0, we performed 10-fold cross-validation (cv) on each of the seven models to calculate cvAUC scores and standard errors. Goodness of fit between modelled and observed values was evaluated by deviance explained, D^2, as null deviance minus residual deviance, divided by null deviance (Guisan and Zimmermann, 2000). Mean cvAUC scores with mean standard errors and deviance explained were compared to select the optimal predictive model.

BRT models (De'ath, 2007; Elith *et al.*, 2008) are machine-learning approaches that automatically model multiway interactions among explanatory variables and can capture complex, non-linear response curves that are often more representative of species responses (Gaston, 2003). We compared BRT models with tree complexity from 1 to 5, varying learning rates and constant bag fractions (0.75) using the gbm functions in the dismo package (Ridgeway, 2015) in R ver 3.2.0 and code from Elith *et al.* (2008). To assess the predictive performance of BRT modelling strategies and to select optimal models, we used 10-fold cv to compare cvAUC scores and standard error with the gbm functions (Lu *et al.*, 2011; Crase *et al.*, 2015). Goodness of fit between modelled and observed values was evaluated by deviance explained (D^2).

We selected the best model generated between the GLM and BRT approaches by comparing cvAUC scores and D^2. We used the best model to estimate the probabilities of *A. cantonensis* occurrence across the study area and generate a current habitat suitability

Table 1. *Angiostrongylus cantonensis* (rat lungworm) infection rates in gastropod species screened and distribution of positive infection among the Hawaiian Islands

Species	Number of snails screened	Number (%) of snails positive	Number of sites positive (total sites)	Islands with positive specimens
Non–native species				
Achatina fulica[a]	62	7 (11)	4 (21)	K, O, M
Arion intermedius	20	0	0 (8)	
Arion subfuscus	8	0	0 (4)	
Bradybaena similaris[a]	65	0	0 (16)	
Bulimulus guadalupensis	10	0	0 (2)	
Cornu aspersum	25	0	0 (8)	
Cyclotropis sp.	13	1 (8)	1 (3)	H
Deroceras laeve[a]	79	0	0 (27)	
Deroceras reticulatum[a]	61	2 (3)	1 (23)	Mo
Euglandina rosea[a]	39	8 (21)	5 (16)	K, H
Fossaria viridis	18	0	0 (4)	
Gonaxis kibweziensis	11	0	0 (5)	
Laevicaulis alte[a]	44	13 (30)	11 (21)	K, O, M, Mo, H
Lehmannia valentiana[a]	11	1 (9)	1 (6)	K
Liardetia doliolum	8	0	0 (5)	
Limax flavus[a]	8	0	0 (4)	
Limax maximus[a]	11	3 (27)	2 (4)	M, H
Melanoides tuberculata[a]	17	0	0 (5)	
Milax gagates	22	0	0 (7)	
Ovachlamys fulgens[a]	10	1 (10)	1 (4)	M
Oxychilus alliarius	69	10 (14)	6 (17)	K, M, Mo, H
Parmarion martensi[a]	19	13 (68)	5 (8)	O, H
Paropeas achatinaceum[a]	73	3 (4)	2 (18)	K, H
Planorbella duryi	20	0	0 (6)	
Pomacea canaliculata[a]	56	1 (2)	1 (15)	K
Physa spp.	27	0	0 (6)	
Subulina octona[a]	54	2 (4)	1 (13)	H
Succinea tenella	25	0	0 (6)	
Veronicella cubensis[a]	159	4 (3)	3 (45)	M, H
Zonitoides arboreus	18	0	0 (5)	
Native species				
Auriculella spp.	31	0	0 (8)	
Elasmias spp.	18	0	0 (9)	
Kaala subrutila	2	0	0 (1)	
Lamellidea spp.	25	0	0 (13)	
Philonesia sp.	31	1 (3)	1 (11)	H
Succinea caduca	12	0	0 (4)	
Tornatellides spp.	90	1 (1)	1 (30)	H
Total	1271	71 (6)	47	

K, Kauai; O, Oahu; M, Maui; Mo, Molokai; H, Hawaii.
[a]Previously recorded as a host in the Hawaiian Islands and/or elsewhere (Kim *et al.*, 2014).

map. We forecasted potential suitability changes under one future projected climate scenario for mean annual surface temperature and mean annual precipitation (2100) using the HRCM CMIP3 SRES A1B emission scenario (based on Zhang *et al.*, 2012), in R ver 3.2.0 using the raster package (Hijmans *et al.*, 2015).

Results

Of the 37 gastropod species screened, 16 (71 specimens) tested positive for *A. cantonensis* (Table 1). Of the 182 sites, 40 sites located on five of the six islands (not Lanai) had infected gastropods (Fig. 1). Kauai and Hawaii had the highest percentages of
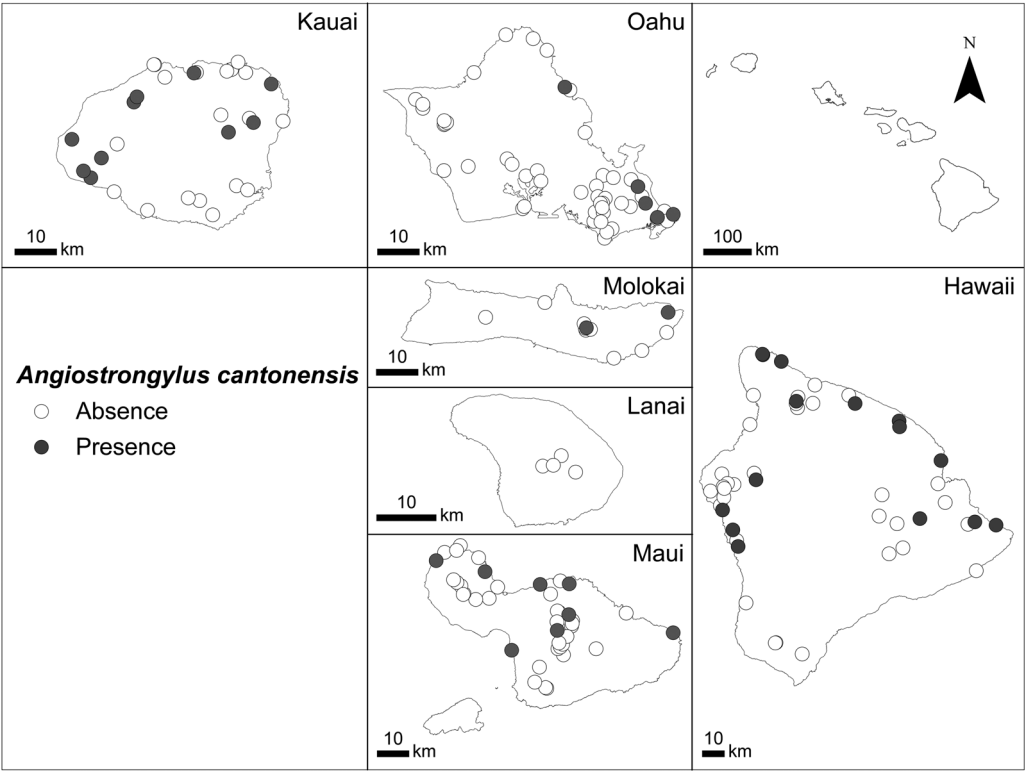
Fig. 1. The presence (grey, 40 sites) and absence (white, 142 sites) of *Angiostrongylus cantonensis* (rat lungworm) at the study sites in the Hawaiian Islands. Dots for some sites overlap and may not be visible.

sites with *A. cantonensis* (34 and 33%, respectively), followed by Molokai, Maui and Lanai combined as Maui Nui (18%) and Oahu (10%) ($\chi^2 = 10.6$, D.F. = 5, $P = 0.014$). More windward sites (northern and eastern sites influenced by the trade winds and therefore with higher precipitation) had more *A. cantonensis* than leeward (southern and western sites with generally less precipitation) (28 and 16%, respectively; $\chi^2 = 4.0$, D.F. = 1, $P = 0.047$).

Individuals that were negative for *A. cantonensis* did not occur at sites with mean annual surface temperatures as low as 10.3 °C, whereas positive specimens occurred at sites with temperatures only as low as 15.2 °C, essentially being restricted to warmer, lower elevation sites than negative specimens (Fig. 1). Both negative and positive specimens occurred at sites with temperatures up to 23.9 °C. Specimens that were negative for *A. cantonensis* were from sites with mean annual precipitation of 224–8615 mm (Fig. 1), whereas those testing positive were from sites with a narrower range of mean annual rainfall (291–5960 mm). The average mean annual temperature for sites with *A. cantonensis* was higher (21.3 °C) than for sites where it was absent (20.5 °C). Sites with *A. cantonensis* also had higher mean annual precipitation (1816 mm) than sites without it (1699 mm).

Among the seven habitat suitability models produced with the GLM approach (Table 2), the optimal model was precipitation + (precipitation × temperature) with coefficients as follows: intercept, −3.846; precipitation, $-1.096e^{-03}$; precipitation × temperature, $8.206e^{-05}$. This model had the highest mean cvAUC score (0.633) though not the lowest cvAUC standard error (±0.036). The cvAUC score indicates poor model performance. The model shared the highest D^2 (0.047); however, this value is very low compared with BRT values.

Of the five models generated with the BRT approach (Table 2), the optimal model had a tree complexity of 5, learning rate of 0.025 and bag fraction of 0.75. This model had the highest mean cvAUC score (0.727), though not the lowest cvAUC

Table 2. Model performance metrics for models of *Angiostrongylus cantonensis* habitat suitability

Model	Model performance metrics		
	AUC	S.E.	D^2
GLM			
HS = T + P + (P × T)	0.629	0.036	0.047
HS = P + (P × T)	**0.633**	**0.036**	**0.047**
HS = T + (P × T)	0.632	0.034	0.042
HS = T + P	0.615	0.034	0.032
HS = P × T	0.623	0.035	0.027
HS = P	0.608	0.035	0.011
HS = T	0.503	0.028	0.003
BRT			
Tree complexity 5	**0.727**	0.041	**0.302**
Tree complexity 4	0.715	0.033	0.299
Tree complexity 3	0.714	0.040	0.295
Tree complexity 2	0.713	0.045	0.281
Tree complexity 1	0.690	0.040	0.285

AUC, 10-fold cross-validated area under the curve; S.E., standard error of the mean; D^2, deviance explained; GLM, generalized linear models; HS, habitat suitability; *T*, mean annual surface temperature; *P*, mean annual precipitation; BRT, boosted regression tree models. Boldface indicates the optimal model in each approach. Underline indicates the optimal scores for each statistic.

standard error (±0.041). The cvAUC score indicates fair model performance. The model had the highest D^2 (0.302). This BRT model was selected as best overall and used to generate habitat suitability maps for current and future projected climates in 2100.
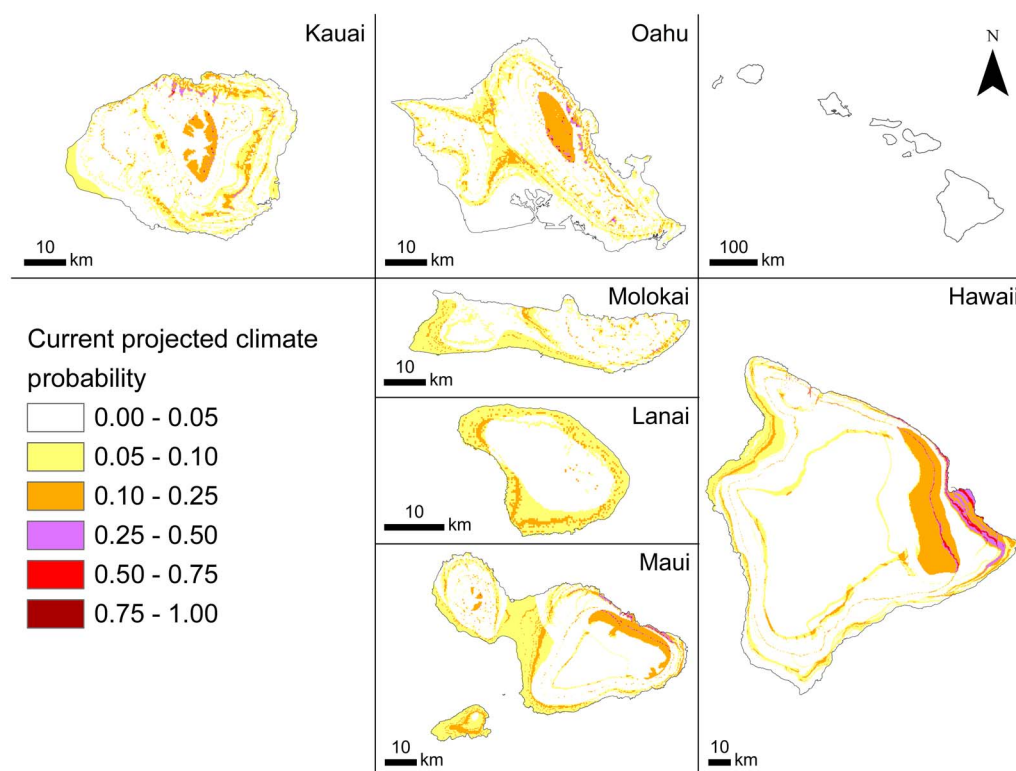
Fig. 2. *Angiostrongylus cantonensis* (rat lungworm) habitat suitability projected by BRT (tree complexity 5) in current climate conditions in the main Hawaiian Islands.

The current probability of occurrence (Fig. 2) ranged between 0.006 and 0.740 (habitat suitability), indicating that although some areas are not suitable for *A. cantonensis*, many areas are somewhat suitable (Fig. 2). The model predicted higher habitat suitability in windward areas where precipitation is greater than in leeward areas. Higher elevation areas that experience lower temperatures also seem to be less suitable than lower elevation areas, especially on the leeward (western and south-western) sides of the islands. The probability of occurrence for our 2100 climate prediction was forecasted as being between 0.006 and 0.845 (habitat suitability) with range expansion projected for windward regions and slight increases with elevation (Fig. 3).

Discussion

Infected snails were found on five of the six largest Hawaiian Islands. They were not found on Lanai, although a human case of infection has been recorded on that island (Hochberg *et al.*, 2007). It is possible that produce regularly shipped from Maui to Lanai was contaminated and the victim was infected through consumption of such produce, or that the victim became infected while on another island.

The parasite was found predominantly at lower elevation sites with warmer temperatures and higher precipitation, which supports the original hypotheses and predictions of the current model. These patterns are reasonable considering the parasite's generally tropical and subtropical range (York *et al.*, 2014), which is related to the threshold temperature for larval development in its intermediate mollusc hosts (Lv *et al.*, 2006), and its susceptibility to dry conditions (Richards and Merritt, 1967). Higher precipitation may also facilitate transfer of the parasite to hosts by keeping rat faeces hydrated and able to support the first-stage larvae, as well as providing suitable conditions for greater numbers and diversity of intermediate hosts.

Kauai and Hawaii are the two islands with the highest proportions of positive sites. Most positive leeward sites on Kauai are clustered around a landfill, where there may be higher rat densities that could facilitate higher rates of infection in nearby areas. The island of Hawaii, the largest island, has the greatest area of highly suitable current habitat (Fig. 2), which is reflected not only in the high proportion of positive sites but also in the high incidence of human infection on that island (Hochberg *et al.*, 2007; Cowie, 2017; Howe and Jarvi, 2017). Oahu had the lowest proportion of positive sites, possibly because of the higher proportions of freshwater species and native species sampled from this island. Freshwater snails are less likely to encounter rat faeces and are less likely to be eaten by rats than terrestrial snails, and native snails are generally found at higher elevations than non-native species. Overall, freshwater snails in the Hawaiian Islands have lower infection rates than terrestrial gastropods, as do native compared with non-native gastropods (Kim *et al.*, 2014).

The south-eastern part of the island of Hawaii has been the area with most human infections (Howe and Jarvi, 2017). The optimal current model (BRT, tree complexity 5, learning rate 0.025, bag fraction 0.75) predicted that this area is highly suitable for *A. cantonensis*, perhaps because of its particularly wet conditions. In contrast, current habitat suitability is generally low across the island of Lanai, which has relatively low precipitation.

Habitat suitability by 2100 was projected under a single climate scenario, a regional downscaled HRCM based on CMIP3 SRES A1B emission scenario. This scenario probably underestimates future conditions as the current trajectory has far surpassed the defining estimates (Schröder and Schmidt, 2014). However, GCM projections may have limited value for interpolated applications in the Hawaiian Islands.

The range of *A. cantonensis* is constrained within the range of its hosts. High elevation sites (e.g. the summits of Mauna Kea and Mauna Loa on the island of Hawaii, ∼4200 m) are cold, dry and barren and support no intermediate gastropod hosts. In addition,
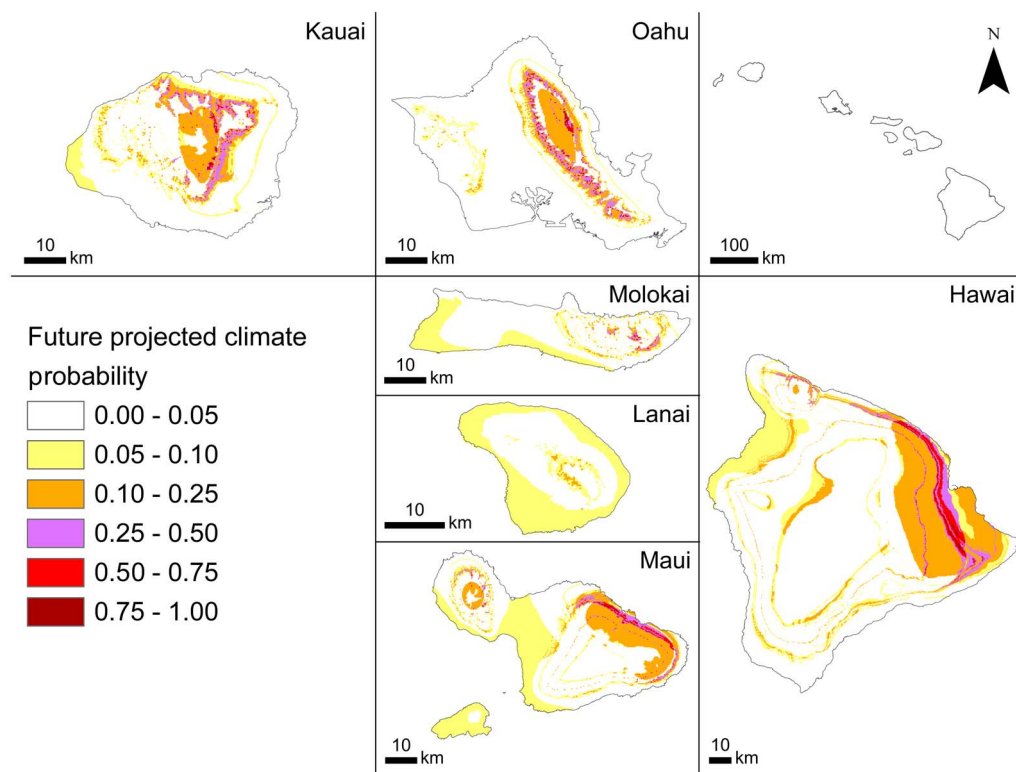
Fig. 3. *Angiostrongylus cantonensis* (rat lungworm) habitat suitability projected by BRT (tree complexity 5) in future projected climate conditions for 2100 in the main Hawaiian Islands based on HRCM (from Zhang *et al.*, 2012).

other factors such as soil type, soil moisture, vegetation type, aspect and habitat connectivity may be involved in habitat suitability for the gastropod hosts (some of which were investigated but the data available were unsatisfactory for the analysis; see Materials and methods section). Factors such as proximity to human settlements or agricultural land may have higher densities of definitive rat hosts and consistent levels of moisture from artificial irrigation.

Laevicaulis alte exhibits a high frequency of infection and the highest individual parasite load (Kim *et al.*, 2014). It is currently found on all six of the largest Hawaiian Islands. However, *Parmarion martensi*, recorded on the islands of Oahu and Hawaii (Cowie *et al.*, 2008), and more recently on Maui (Cowie *et al.*, 2018), exhibited the highest frequency of infection as well as a high parasite load (Kim *et al.*, 2014). *Parmarion martensi* was first recorded in the Hawaiian Islands in the 1990s but quickly became widespread and abundant in the south-eastern part of the island of Hawaii. It has been suggested that this species may be connected with many of the recent cases of angiostrongyliasis (Howe and Jarvi, 2017). These and other species may well have been introduced and spread *via* the horticulture industry, which plays a major role in the spread of snails throughout the Hawaiian Islands (Cowie *et al.*, 2008) and globally (Cowie and Robinson, 2003; Bergey *et al.*, 2014) and may contribute to the continued emergence of this disease.

Significant advances in preventing the spread of pathogenic diseases to human populations can be achieved by integrating rapid molecular genetic methods with field epidemiology and habitat suitability models to estimate the pathogenic range and its potential expansion under climate change (Kim *et al.*, 2014; York *et al.*, 2014, 2015; Stockdale Walden *et al.*, 2017). Globally, York *et al.* (2014) suggested that the centre of the range of *A. cantonensis* will move northwards approximately 100 km per decade during the 21st century. The analogous change of temperature

with both elevation and latitude means that a 1000 m change in elevation is roughly equivalent to a 1000 km change in latitude, or a 1 °C change in temperature occurs over roughly 150 m elevation or 150 km of latitude (Jump *et al.*, 2009). Thus, in Hawaii, an elevational microcosm of wide latitudinal change, we have shown that in general suitable habitat will occur increasingly at higher elevations.

Habitat suitability models may provide valuable information for the application of prevention and management strategies. Across the main Hawaiian Islands, our forecasted habitat suitability maps indicate an increase in both range and probability of *A. cantonensis* occurrence by 2100. If the definitive and intermediate hosts are present in such areas, spread of *A. cantonensis* appears likely and may have negative impacts on public health. Using a framework for infectious disease modelling coupled with ecological and social network models (e.g. Haak, 2015) may facilitate a better understanding of disease transmission and further inform resource management and policy.

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