



A spatially explicit agent-based modeling approach for the spread of Cutaneous Leishmaniasis disease in central Iran, Isfahan



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ABSTRACT

Cutaneous Leishmaniasis (CL) is an endemic vector-borne disease in the Middle East and a worldwide public health problem. The spread of CL is highly associated with the socio-ecological interactions of vectors, hosts and the environment. The heterogeneity of these interactions has hindered CL modeling for healthcare preventive measures in endemic areas. In this study, an agent-based model (ABM) is developed to simulate the dynamics of CL spread based on a Geographic Automata System (GAS). A Susceptible-Exposed-Infected-Recovered (SEIR) approach together with Bayesian modeling has been applied in the ABM to explore the spread of CL. The model is then adapted locally for Isfahan Province, an endemic area in central Iran. The results from the model indicate that desertification areas are the main origin of CL, and riverside population centers have the potential to host more sand fly exposures and should receive more preventive measures from healthcare authorities. The results also show that healthcare service accessibility prevented exposures from becoming infected and areas with new inhabitants experienced more infections from same amount of sand fly exposures.

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1. Introduction

Leishmaniasis is caused by protozoan *Leishmania* parasites and is strongly associated with victims' living conditions, e.g. poverty, malnutrition, famine, illiteracy, and migrations. (Kumar, 2013). The disease has three major forms with different clinical manifestations (Handman, 2001), with Cutaneous Leishmaniasis (CL) being the most common type. CL can be transmitted by the bite of a female *Phlebotomus* sand fly (Swaminath et al., 2006), and considered to be a zoonosis which mostly has a gerbil specie as reservoir host (WHO, 1990). The disease is characterized by skin lesions, which typically develop within several weeks or months after exposure and results in severe scarring. No vaccine or drugs are available neither to prevent the infection nor to erase the scars. Even though the disease is treatable and preventable via reducing contacts with sand flies by using preventive measures, it remains a health hazard in many developing countries where such prevention is not possible.

WHO reports have indicated that 1.5–2.0 million new cases of CL occurs each year worldwide (WHO, 2010). Among these cases, nearly 90% of CL cases currently occur in Iran, Syria, Saudi Arabia, Afghanistan, Algeria, Peru, and Brazil (Desjeux, 2004; Kumar, 2013, Gramiccia and Gradoni, 2005).

CL is the most frequent vector-borne disease in Iran, with an average of more than 22,000 cases in the last decade (Oshaghi et al., 2010). Isfahan province, at the center of Iran, has long been known as one of the most important endemic areas of CL (Arjmand et al., 2014; Nadim and Faghieh, 1968) and still experiences a large number of annual infections, with approximately 2200 occurrence in 2013. CL resulting from *Leishmania major* and *Leishmania tropica* protozoa currently has epidemic status in Isfahan. *Rhombomys opimus*, a domestic rodent, is the main reservoir host and *Phlebotomus papatasi* is the most common CL sand fly vector in Isfahan (Emami et al., 2009). Despite numerous preventive measures of healthcare authorities and frequent research efforts during the last 30 years, the number of infections in Isfahan has remained prominent and the disease recently began spreading to the non-endemic regions of the province (Emami et al., 2009; Arjmand et al., 2014).

The spatial distribution of CL as a vector-borne disease is

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associated with the geographic range of its vectors and their habitat preferences (Kitron, 1998). Sampling of sand flies and determining the presence and abundance of intermediate host species is costly and time consuming (Kassem et al., 2012). The dispersion of sandflies and consequently the geographical distribution of CL can be influenced by environmental factors (Ferreira et al., 2001; Rispaill et al., 2002; Kassem et al., 2012) and environmental and man-made changes such as fast-growing urbanization, development of new projects e.g., road building, mining, farming, forestry development, military activities and deterioration in social and economic conditions in the poor suburbs of cities (Desjeux, 2004; Dujardin, 2006; Adegboye and Kotze, 2012). Hence, the modeling of CL spread should comprise various environmental factors and also the interactions between the environment, sand flies and humans. Agent based models (ABMs), have the flexibility and capacity to incorporate these components. By simulating the individual behaviors, ABMs operate at a scale at which disease dynamics are based. Spatial analysis techniques can be applied with these simulation models to identify environmental patterns associated with CL vectors and are very helpful for identifying control strategies in unsampled areas (see Section 2). Hence, a spatial epidemiological approach was conducted in this study to analyze and evaluate the spread of CL by using an agent-based modeling method. The agent based method was chosen in this research because properly complied with requirements of such disease modeling problem (see Section 2 for details). The study area is mainly focused on Isfahan province in the central part of Iran (Fig. 1).

The rest of this paper is organized as follows. In Section 2, previous studies in modeling CL spread and the applicability of

agent-based models in disease modeling are explored. In Section 3, the local survey and data collection processes are described briefly. In Section 4, the model used for modeling CL dynamics is presented. The results are expressed in Section 5. Discussions and ideas for further work are represented in Section 6, and a short summary of the paper and the conclusions are presented in Section 7.

2. Background

The impact of spatial analysis approaches on existing knowledge regarding CL spread and incidence cannot be ruled out. Previously, Nadim and Faghih (1968) considered geography in the epidemiology of CL. Lysenko (1971) presented one of the first attempts at CL mapping, in which the geographical distribution of CL cases was illustrated using cartographic maps. It took a while for researchers to consider spatial analysis as an explorative tool for CL epidemiology rather than as a visualization tool. Mott et al. (1995) introduced the application of geographical analysis for epidemiology and predictive modeling of Leishmaniasis. Thereafter, spatial analysis was used to identify and evaluate the underlying environmental precondition factors that influence the CL epidemic (Seid et al., 2014; Garni et al., 2014; Ali-Akbarpour et al., 2012). Resurfacing of Geographic information systems (GIS) highlighted the significant role of space when exploring the spread of CL. GIS has frequently been combined with statistical and cluster analysis methods to identify new CL epidemiological patterns (Salah et al., 2007; Rodríguez et al., 2013; Mollalo et al., 2015; Adegboye and Kotze, 2012). Spatial analysis methods have been utilized to generate CL risk maps (Seid et al., 2014; Garni et al., 2014; Ali-

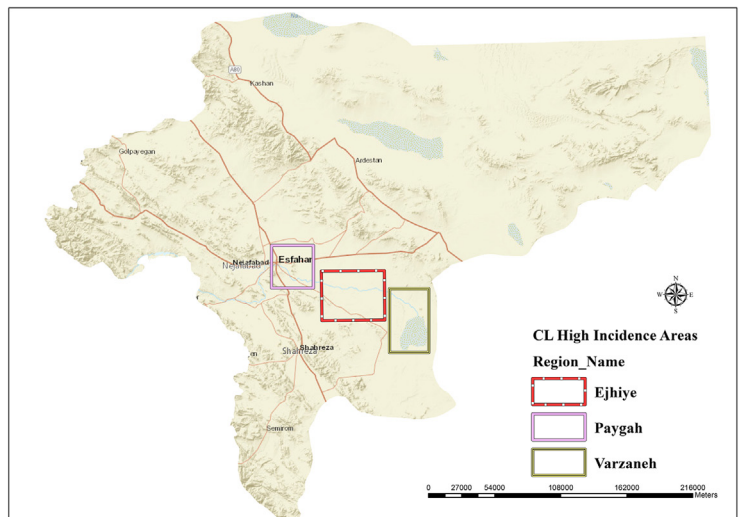


Fig. 1. Study area, Isfahan province, Iran.

Akbarpour et al., 2012). In addition, entomological researchers have conducted studies in which GIS is used to understand the ecology of CL sand flies (Karimi et al., 2014; Gálvez et al., 2010; Abdel-Dayem et al., 2012; Kassem et al., 2012).

Although CL has been discussed in several spatial and non-spatial themes, CL spread modeling and the impacts of the interactions between the environment, vectors and hosts on the spread have been briefly explored. Nevertheless, CL spread modeling has been performed using mathematical modeling approaches (Chaves and Hernandez, 2004; Rabinovich and Feliciangeli, 2004) and time series analysis methods (Lewnard et al., 2014; Chaves et al., 2014; Chaves and Pascual, 2006). In addition, in several studies, CL dynamics have been modeled by considering only one of the potential factors. For example, Barhoumi et al. (2015) highlighted the impacts of irrigating arid regions in Tunisia on the population of CL sand fly vectors. Mollalo et al. (2014) developed a model to discuss the relationships between vegetation cover and the incidence of CL. Garmi et al. (2014) explored the influences of land cover changes on the occurrence of CL using GIS and remote sensing analysis.

Although the models mentioned above can be applied to CL spread modeling, researchers have criticized them. For example, although the interactions between the environment, hosts and vectors in specific locations play important roles in the development of an epidemic from an outbreak, the mentioned models do not consider socio-ecological complex relations and individual behavioral factors for epidemic progression modeling (Epstein, 2009). Moreover, the interactions between the key epidemiological factors could not be realistically simulated using conventional methods (e.g., differential equations) (Bonabeau, 2002). In addition, most classical models neglect the population heterogeneity (Bonabeau, 2002) and consider uniform mixing assumptions for the spread of disease (Eubank et al., 2004). Classical models also tend to smooth out fluctuations, making them susceptible to large perturbations (Bonabeau, 2002). Accordingly, treating all components of an epidemic as largely homogeneous entities is another criticism of these models (Crooks and Heppenstall, 2012). Subsequently, modeling the disease dynamics in the mentioned models is performed by focusing on the local interactions and ignoring the complex situations of the environment (Birkin and Wu, 2012).

Agent-based modeling approaches have recently been used to overcome the above mentioned shortcomings of conventional models such as the heterogeneity problem and the complex interactions problem (Crooks and Heppenstall, 2012). Using diverse interactions between individual agents or between an individual agent and the environment, ABMs provide a realistic simulation of processes and their impacts (Crooks and Heppenstall, 2012; Crooks and Hailegiorgis, 2014). Moreover, agents can make decisions based on the knowledge they gain from the environment. This knowledge enables ABMs to simulate dynamic situations (Birkin and Wu, 2012). These simulations are more similar to reality and capable of better representing the socio-ecological interactions of environment than other modeling approaches (Van Dyke Parunak et al., 1998; Crooks and Heppenstall, 2012).

The specifications mentioned above, make ABMs a proper approach for simulating problems such as epidemics that comprise landscape and natural resources. The mobility of ABMs make them more appropriate for geospatial modeling which includes spatially explicit variables and parameters (Crooks and Heppenstall, 2012). In this regard, integrating ABM and spatial analysis has been noticed as a powerful approach for evaluating and analyzing the spread of diseases (Perez and Dragicevic, 2009) and has been increasingly used in many spatial epidemiology applications for different diseases (Crooks and Hailegiorgis, 2014; Lourenço and Recker, 2013; Patlolla et al., 2006; Simoes, 2012; Linard et al.,

2009; Dion et al., 2011; Ajelli and Merler, 2009; Rao et al., 2009; Perez and Dragicevic, 2009). However, the spread of CL using ABM approaches has not been explored yet, which constructs the main objective of this research.

Furthermore, with respect to vector-borne diseases, little work has been carried out using ABMs and by analyzing habitat vectors and reservoir hosts. For example, Linard et al. (2009) explored the potential biting rate of malaria vectors in a land use/cover map using a multi-agent simulation. Arifin et al. (2013) developed a model to simulate the resource-seeking process of malaria vectors. In this paper, an agent based modeling approach will be represented for CL spread modeling in which the mentioned drawbacks of the current studies are covered along with four common challenges of ABMs in such applications (Filatova et al., 2013). First, the behaviors of agents will be simulated using dynamic interactions between environments, vectors and hosts. Accordingly, the ABM for CL should provide knowledge of the socio-ecological interactions of its three main actors, the environment, vectors and reservoir hosts. Second, the simulation will be validated and verified using a relevant uncertainty and sensitivity analysis. Third, the model will be coupled with various socio-ecological factors to make it more realistic. Fourth, different types of agents will be defined in a spatially explicit environment to perform a habitat analysis of vectors, hosts and the environment relative to CL spread.

3. Study area

The explorations and field survey of the authors in the study region indicated that the infested area is a semi-arid plain located at an altitude of 1400–1600 m. Several desertification areas exist within the infested area, and Haloxylon plants are the most popular species for desertification in Isfahan. The long roots of the plants under the ground contain moisture and provide a suitable habitat for local rodents, which host the CL parasite (Nilforoushzhadeh et al., 2014). These rodents live in large colonies composed of many subgroups and create networks of underground burrows in their favorite habitats (i.e., Haloxylons). The rodents are only active during the spring and summer (April to October) and only appear during the night and in the early morning outside of their burrows. Their activities decrease significantly when the temperature decreases in the fall and winter. The underground burrows have suitable and stable weather and provide rodent blood for phlebotomine sand flies in the study area. Within these burrows, sand flies can survive at temperatures of 35°–45° in the Isfahan summer. Once the sand flies obtain rodent blood meal, they become a vector for the CL disease. The (female) sand flies spread the disease by biting humans during the night and in the early morning. Riverbeds and embankments are also favorite habitats for the rodents (Abai et al., 2010). Accordingly, several active colonies have been observed in these areas in Isfahan province. Further explorations indicated that a significant number of ancient underground water transmission networks (Qanat) exist in the study area. These areas were also considered as suitable habitats for the rodents because several rodent activities were identified around these facilities. Moreover, the registered CL cases in healthcare authorities indicated that people working at livestock or poultry facilities have one of the highest infection rates (approx. 50 annual incidences). Accordingly, poultry and livestock facilities are considered as another favorite place for rodents. Therefore, desertification, rivers, embankments, Qanat, livestock and poultry are considered in this study as the main habitats of rodents in the Isfahan province (Fig. 2). These habitat layers together with the human demography data provided the information framework for the model in this study.

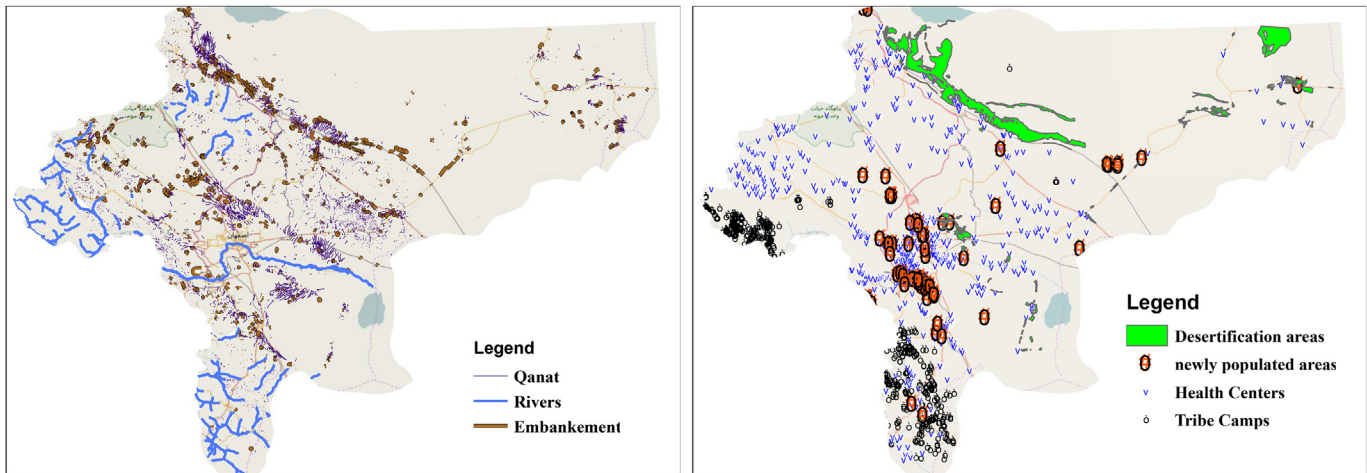


Fig. 2. Input data for the agent based model in this study.

4. Model

A Java-based simulation environment called Repast (North et al., 2005) was used to implement the algorithms developed in this study. The model description follows the ODD (Overview, Design concepts, Details) protocol for describing individual- and agent-based models (Grimm et al., 2010). In the remainder of this section and after a brief overview of the model components and processes (see section 4.1), the key concepts of model design, including observations, sensing, interactions and stochasticity, are described (see Section 4.2). Next, the details of model implementation are presented (Section 4.3).

4.1. Overview

4.1.1. Purpose

This model was developed to provide a spatiotemporal simulation of the spread of CL in Isfahan Province, Iran. The main source of the epidemic is the interaction between humans (host), sand flies (vectors) and rodents (reservoir host) through the environment. The model includes ecological factors that influence these interactions and generate the simulation system of CL spread in the study area. To skip complexities that result in the deviation of the model from its defined purpose, some simplifying assumptions have been made, which are detailed in the following sections.

4.1.2. State variable and scales

Fig. 3 represents a unified modeling language (UML) class diagram of the components constructing the model. There are two types of agents in the model, mobile agents and cell agents. Mobile agents are divided in two classes, sand flies and humans. In addition it is worth to mention that rodents cannot transmit CL without the sand fly intervention and have not been defined as mobile agents in this study. Rodent habitats are assumed to remain unchanged during model processes and the habitat information is available for all agents in each field unit.

The mobile agents of this study are designed based on the epidemiology of a zoonotic CL in which each infection is a result of a transmission cycle between an infected rodent as the reservoir, a sand fly that has bitten an infected rodent as the vector, and humans who have been bitten by infected sandflies (Yaghoobi-Ershadi et al., 2001; Nadim and Faghih, 1968; Reithinger et al., 2007). Even though there might be both non-infected rodents,

and non-vector sand flies in the study area, they have no role in CL transmission cycle because non-vector transmission is rare (Reithinger et al., 2007) and *P. papatasi* sand flies which maintain the *L. major* parasite among rodents are known to be the main CL vector in study area (Yaghoobi-Ershadi et al., 1994). Accordingly, in this study only infectious *Leishmania* protozoa vectors are simulated, and are considered as the main mobile agent of the study, which represents a group of CL vectors that seek suitable habitat locations. Sand fly agents have two behaviors, foraging and biting humans.

Human agents are mobile and have four different states, susceptible, exposed, infected, and recovered. When human health is not threatened by any sand fly group, humans are susceptible and have no direct role in the model. Once a human has been bitten, they become exposed and the environment is used to calculate their probability of becoming infected or recovering.

Accordingly, cell agents generate a risk value based on the number of infections for each location, which is calculated based on their observations. Environmental parameters in each field unit are assumed to be constant. They reflect the habitat suitability and thus serve as a proxy for rodents, the main CL reservoir host in the study area.

Two 12-h time periods were modeled to represent CL vector-human interactions: (i) one hour after sunrise until one hour before sunset and (ii) one hour before sunset until one hour after sunrise. These two periods are simulated using two temporal resolutions: hour and day. Human and vector activities are impacted by the temporal periods and resolutions. The main purpose of choosing this timeframe was to represent the sand fly appearance outside and inside the rodent burrows during spring and summer seasons, with an average sunrise at 05:00, and sunset at 19:00 thorough the study area. Even though the sand fly exposure might differ in different parts of study area during weekdays, the model has been designed apathetic to weekdays here, because CL infections occur a few weeks after sand fly's bites. CL has a long and variant incubation period (Reithinger et al., 2007) and infection symptoms might start a few days or weeks after a sand fly bite. This indicates the infection could occur in any weekdays nevertheless the occurrence date of exposure was in a weekend or in any weekdays. With this in mind and in order to reduce the complexity and increase the performance of the model, all risky activities of humans in this study have been adjusted in a daily timeframe with no discrimination between weekdays (see Section 4.3.2).

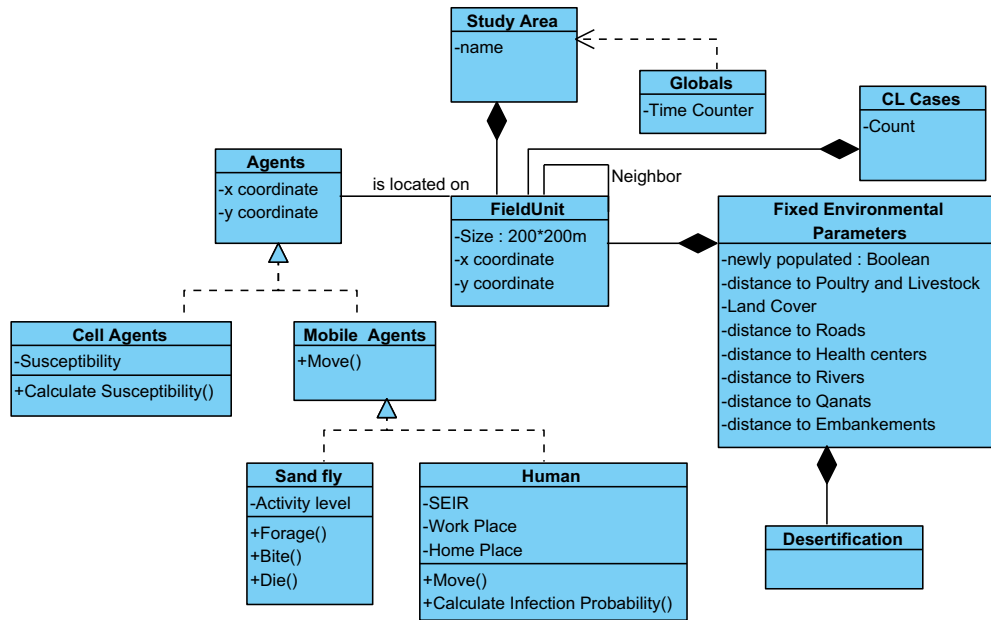


Fig. 3. Representation of the CL model using the UML class diagram.

4.1.3. Process overview and scheduling

The model simulates the interactions between sand flies and humans across the landscape over time. The processes running during each time step and their relations are illustrated in a UML sequence diagram (Fig. 4). This diagram presents an outline of the sequence of processes and the schedule of interactions between the different agents at each discrete time step. Each process is defined based on a certain class of agents according to the UML class diagram.

First, the time counter is updated at each time step. Then, the field unit values are updated according to environmental parameters and the CL infection history. Next, cell agents are located in the study area. Then, sand flies appear in the landscape at different random locations and start seeking suitable habitats. Finally, humans appear in the study area and movements occur according to suitable target locations. At each step, agents of the same type are processed using a random sequence. Some processes are only activated under particular conditions, e.g., the infection probability calculation only starts after a sand fly bites a human. Although sand flies bite one of the humans within their perception range randomly, the CL infection process is designed based on a susceptible, exposed, infected, recovered process (SEIR) (see Sections 4.3.2.2 and 4.3.2.3).

4.2. Design concepts

4.2.1. Observation

Spatial and temporal variations in individual and population-level processes have been observed in the model. These included the number of biting sand flies, the number of susceptible, exposed, infected and recovered humans, and the exposure sites. Moreover, the location of mobile agents and the value of cell agents have been tracked by recording the position, (x, y), of each mobile agent, and the value of each cell agent at each time step.

4.2.2. Sensing

Mobile agents can calculate the distance to their desired locations and should know their underlying and neighboring cell agents based on the Moore neighborhood (Weisstein, 2005).

Moreover, mobile agents know how to identify suitable habitats within the environment. CL susceptibility has been addressed by considering cell agents that can perceive the interactions among hosts and vectors through their environment. Human agents sense the population pattern, landscape and facility availability.

4.2.3. Interactions

The interactions between agents and between agents and the environment are the main basis for the dynamics of the model. Rodent habitats attract sand flies and sand flies transmit the CL disease by biting humans. The environment provides all of the mobile agents with their required resources and the spatiotemporal dynamics of interactions are influenced by the landscape characteristics at each location. Accordingly, the interactions vary within the study area and the agents will behave heterogeneously.

4.2.4. Stochasticity

There are several stochastic processes within the model to present landscape heterogeneity and natural variations. The initial locations of the agents, the infection probability of humans, the movement of humans and foraging of sand flies all include elements of stochasticity. See Section 4.3.2 for details.

4.3. Details

4.3.1. Initialization

The model initializes with the landscape information of the study area, including the spatial and non-spatial data. Grid cells were assigned initial values of infection history, population pattern (existence of new population), population, access to healthcare services, land cover class, proximity to poultry and livestock facilities, roads, rivers, Qanats and embankments.

The input data were extracted from reliable official data sources as follows. The CL-related healthcare data were generated from ministry of health records. The landscape data were prepared using 1:25,000 national cartographic center topographic data. The census and demographic data were extracted from the records of national statistic organizations. All of the parameters and data are summarized in Table 1.

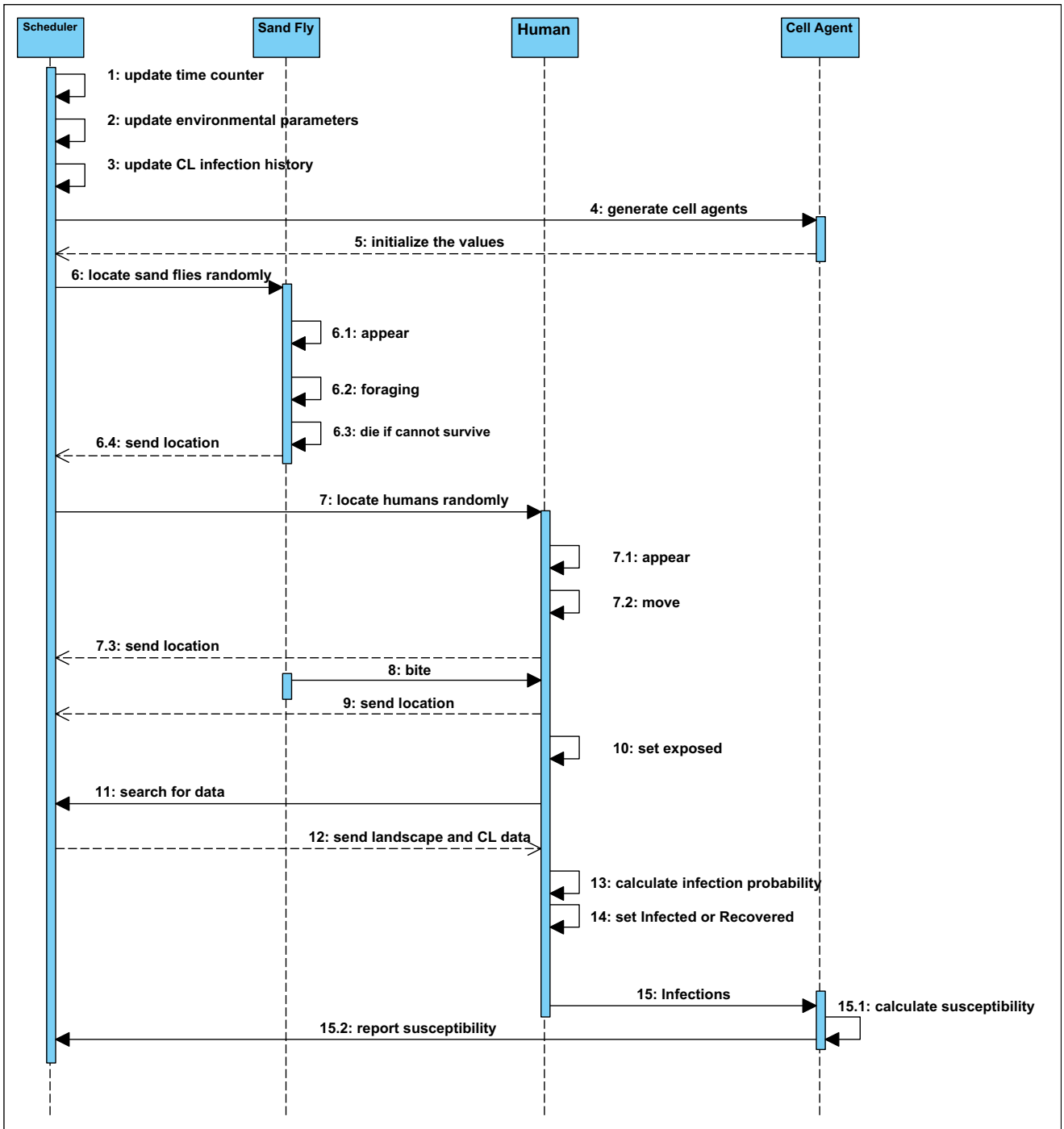


Fig. 4. UML sequence diagram of the CL model.

4.3.2. Sub models

4.3.2.1. Spatially explicit environment. A geographic automata system (GAS) (Torrens and Benenson, 2005) was used to take advantage of both cellular automata and agent-based techniques for CL spread modeling. The broader objective was to provide a spatial approach for modeling the CL epidemic as a geographically complex system comprised of landscape data (land cover, accessibility, demography, etc.) and agent objects (CL vector, CL host). Thus, the model is enabled to consider the heterogeneity of space and spatial behaviors explicitly. According to Torrens and Benenson (2005), a GAS consists of the following seven components:

$$GAS \sim \{K; S, T_s; L, M_L; N, R_N\} \tag{1}$$

where K indicates a set of automata types in GAS. The first pair denotes a set of states, S, and state transition rules, T_s, that are associated with GAS. In the second pair, L dictates the location of automata in the system and M_L denotes the movement rules for automata. In the third pair, N represents the neighbors of automata and R_N represents the rules that govern changes of the automata relative to other automata.

According to GAS, two automata types (K), exist in the CL model

Table 1
Summary of input parameters and variables.

Parameters and data	(Default) Values	Reference/source
Population centers	Type (cities, districts, villages) Population Population pattern (new inhabitants: (yes/No)	Ministry of Interior, National Statistical Center
Accessibility	Proximity to health centers Proximity to roads Proximity to rivers Proximity to livestock and poultry Proximity to Qanats Proximity to embankments	(Abai et al., 2010)/(NCC ^a)
Land Cover	Desertification Dry farming Irrigated farming and orchards Urban and rural areas	(Nilforoushzhadeh et al. (2014), Mollalo et al. (2014))/(Forest and Rangeland Organization)
CL notification	CL incidences from 2007 to 2013 CL endemic areas	(MOH, 2013), Field data collected by authors with the collaboration of CCDC ^b
Population in living areas	Villages: 28%, cities: 52%, nomadic villages: 10%, other: 10%	(MOH, 2013)
Population in working areas	Military: 18%, farmer: 27%, poultry and livestock 2.5%, Other:52.5	(MOH, 2013)
Sand fly perception range	1000 m	Authors estimation
Maximum sand fly flight range	2500 m	Linard et al. (2009)
Neighborhood to desertification areas	2500 m	Authors estimation

^a National Cartographic Center, NCC, 1:25,000 Maps.

^b Center for Communicable Diseases Control of Ministry Of Health (MOH).

within this study, including mobile agents and cell agents. The geometries of both humans and sandflies are rigid (both are point objects), their state is variable and they are both enabled to move. Hence, according to Goodchild et al. (2007) they are modeled as the same automata type in this study. The states of both mobile and cell agents change over time. The states of cell agents include their susceptibility value which changes according to rules designed in the susceptibility mapping (Section 4.3.2.6). The state of sand fly agents refers to their activity level and changes through their foraging behavior (Section 4.3.2.4). The state of human agents indicates their SEIR situation and changes according to the SEIR model and Bayesian modeling (Section 4.3.2.2, Section 4.3.2.3). Although both types of agents are located in a certain location within the study area, only the locations of mobile agents change over time. Mobile agents can move and explore the entire study area according to their desired habitats and designated rules. The movement of sandflies is based on their foraging and the movements of humans are according to their home and work places (Section 4.3.2.4 and Section 4.3.2.5). Cell agents are static and have no movements. All cell agents know their neighbors according to the Moore neighborhood and recognize other automata types (i.e., mobile agents) and their interactions in their neighborhood. Sand flies use the Moore neighborhood for their foraging and movements. Human agents perceive their work place and home places through the study area and use the Moore neighborhood when roaming around these targets. The applied GAS in this study has one additional component which allows creating a network between all of the automata types that are associated with each other through interactions. This allows the cell agents to track the results obtained from each interaction even after a few time steps when the agent is no longer in their vicinity (Section 4.3.2.6) (Fig. 5).

4.3.2.2. CL SEIR model. An explicit representation of the interactions between the CL host and the environment has been generated using a Susceptible-Exposed-Infected-Recovered (SEIR) model. The main objective was to model the infection process from when a human is exposed to a CL vector until CL symptoms are shown. The population is assumed susceptible to CL. The exposure

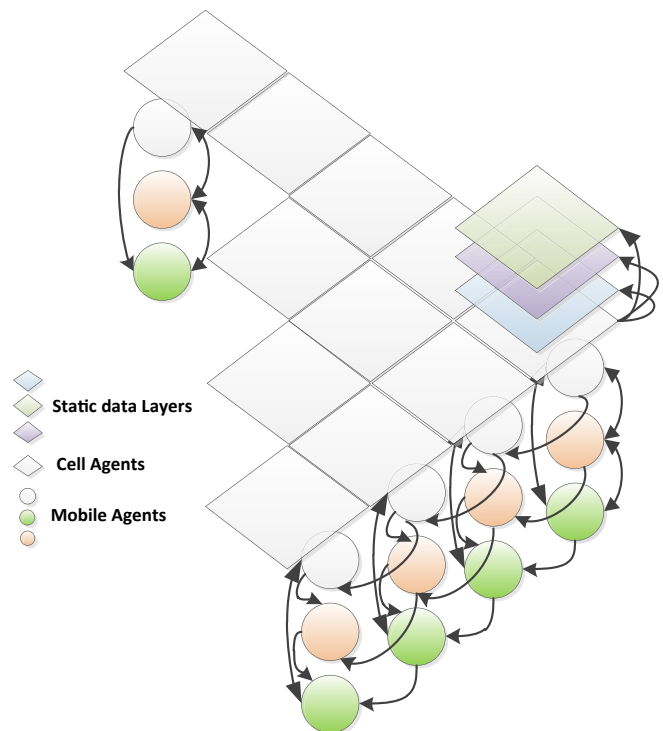


Fig. 5. Geographic automata system for CL spread.

of a victim to CL is assumed to be associated with the existence of sand fly agents in the underlying field unit.

An exposed agent preserves its state for a predefined incubation period and then becomes infected based on a set of predefined conditions. The collected qualitative and quantitative data from the field surveys revealed that 98.31% of infected local people only infected by CL once (MOH, 2013). Although they continued their behavior and appeared in risky rodent habitat neighborhoods after infection, they never became infected again. Thus, new inhabitants

are more vulnerable to CL infection, and this influence has been modeled using a population pattern parameter. For example, 17.71% of all CL reported cases during the years 2010–2013 originated from Paygah, a military base that attracts several new inhabitants annually (MOH, 2013). New inhabitants are usually poorly informed about CL vectors and have high vulnerability. Military bases and nomadic tribal camps have been considered as newly populated areas within Isfahan province. This parameter is influential at this stage, which can make the exposed agent, infectious.

Healthcare authorities have been informing local people about the protection against CL vectors. Well-informed domestic people use window screens, repellent sprays, clothes with adequate coverage, etc., to increase their protection level. In addition, well-informed people refuse to visit risky areas in the early morning or during the night. We have considered these educational activities as a dissuasive factor for human agents to be infected by CL. This parameter was calculated directly based on the access level to health-centers in the study area. Consequently, infection results from CL exposures vary considerably according to healthcare accessibility and the population patterns of geographical regions.

We have assumed that the infected human populations are not a CL reservoir host. Accordingly, a susceptible or recovered agent cannot spread any *L. major* parasites. The infectious agents pass into the recovery stage after a predefined lag.

4.3.2.3. Infection probability. As mentioned in Section 4.3.2.2, the probability that an exposed agent becomes infected depends on the population pattern and access to healthcare services. From a geographical viewpoint, the probability that an exposed human agent (E) becomes infected (I) is also associated with the landscape characteristics of the area (i.e., field units). Various methods exist to estimate the probability of the occurrence of a phenomenon based on patterns of mapped socio-economic, environmental and demographic data. Bayes' conditional probability theorem is a

$$P(A_I|\{V_0(r), V_1(r), \dots, V_m(r)\}) = \frac{P(\{V_0(r), V_1(r), \dots, V_m(r)\}|A_I) \times P(A_I)}{P(V_0(r), V_1(r), \dots, V_m(r))} \quad (2)$$

powerful method that is used to estimate the probabilities of occurrence of such events within a unit area. Bayesian probabilistic modeling first assumes that an event can occur anywhere within the study area by providing a prior probability for the event. Next, various indicator map patterns are used to update the prior probability by using Bayes' rule to estimate the posterior probability for each unit area. These posterior probabilities are calculated by exposed human agents to complete the SEIR process. Given the uncertainty associated with CL incidence as a phenomenon and its relationships with landscape, agents have adopted conditional probability in their decision making process to assess the nearby CL susceptibility.

The indicator pattern maps for the Bayesian conditional probability are considered according to three main classes, (i) demography (ii) healthcare facilities and (iii) main CL host habitats. The demographic pattern contains areas with newly migrated or nomadic populations. These areas contain the military bases and temporary camps of nomads. The second class includes healthcare centers, and the third class includes five maps that indicate the candidate areas with most rodent colonies: desertification areas, poultry and livestock areas, rivers, ancient water transmission facilities (Qanat) and embankment areas. Exposed agents use Bayes' rule in a spatially explicit framework with landscape data and

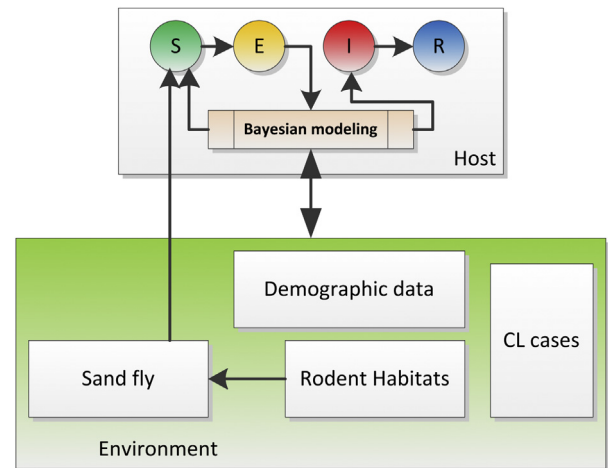


Fig. 6. Bayesian modeling for infection probability.

information about healthcare services, population patterns and previous CL incidences to calculate their infection probability (Fig. 6).

In this study, Bayesian modeling to extract the infection probability of an exposed agent consists of three steps. First, the exposed agent explores the spatial database, which contains all of the evidence layers and highly infected villages as training points. Second, the relationships between the training points and the evidence are explored to determine which evidence layers are predictive. Third, the weights are calculated. Finally, the evidence values will be combined to produce posterior probability. When applied to assess CL infections, Bayes' theorem is used to determine the probability that sandflies in an exposure site will generate infections given the local environmental conditions, as expressed in Eq. (2):

Where A_I denotes that an infection will occur in field unit r , for which $\{V_0(r), V_1(r), \dots, V_m(r)\}$ independent environmental conditions are known.

4.3.2.4. Sand fly foraging. Sand flies randomly appear in the study area. Next, they begin to search for their favorite places where the rodent colonies are. Sand fly foraging is a two-stage process that includes random flight when the habitat is not within the sand fly's perception range and directional flight to the habitat when it is perceived. Accordingly, sand flies skim in their habitats neighborhood looking for blood meals. When they reach population centers, they can expose human agents in their neighborhood; thus, these humans' status becomes exposed. The sand fly perception and flight range varies according to their activity level. During the day they have their activity in a minimum level (first time period) and during the night their activity level reach maximum (second time period). The model also defines a mortality procedure for the sand flies. The sand flies die following a certain number of time steps if they are roaming (or lost) in a non-habitat neighborhood.

4.3.2.5. Human movement. Each human agent is assigned two attributes which determines its movement scenario. First, an

attribute in relation to where it lives which can be (i) city, (ii) village, (iii) nomadic camp, (iv) other. Second, an attribute in relation to where it works including (i) farms (ii) military bases (iii) poultry and livestock (iv) other. At the first time step human agents are initialized according to the attributes. The population of humans is assigned according to approximate proportion of CL infections in ministry of health records during 2007–2013 (MOH, 2013) and also mentioned in Table 1. The correlation between a living area and a working place has been set based on demographic data acquired from the National Statistical Center. Hence, most of the villagers are considered to work on their nearby farms (i.e. 70%), some of them are assigned poultry and livestock workplace (i.e. 20%) and the rest will go to the other working places (i.e.10%). Similarly, most of the inhabitants of nomadic camps are considered to work on the nearby farm lands (i.e. 90%), and the rest will choose other work places. In addition, most of the workers in military and poultry and livestock are considered to be city inhabitants (i.e. 80%). As mentioned before, there are two time periods in the model: period 1, period 2. In period 1, agent looks for its assigned work place and goes towards it. In period 2, agents finish their work and move towards their homes. When a work place or living place for an agent is considered as “other”, the agent will appear randomly in vicinity of roads, rivers and parks.

4.3.2.6. Susceptibility mapping. The susceptibility of a cell agent depends on the abundance of sand fly exposures that result in infections. Once an exposed agent changes its state to infected, the underlying cell agent where the agent was exposed is identified using the network attribute of the GAS. This cell updates its infection information and also updates the susceptibility map. Areas with more susceptibility indicate the most probable risky cells where a sand fly will find vulnerable victims. Sand fly behaviors are assumed anthropophagous. Accordingly, sand flies prefer to bite humans rather than other hosts.

4.3.3. Model outputs

The main outputs from the model include the number of agents that are susceptible, exposed, infected and recovered in each model iteration and the susceptibility of each field unit. Through such outputs, the spread of CL can be traced throughout the study area.

5. Results

5.1. Global sensitivity and uncertainty analysis (GSUA)

Uncertainty and sensitivity of the implemented ABM for CL is here investigated using a two-step GSUA method: a screening method proposed by Morris (1991), and a variance-based method proposed by Sobol' (1990). The Morris method (Morris, 1991) assesses the importance of each input factor qualitatively while the Sobol' method (Sobol', 1990) evaluates the sensitivity and uncertainty quantitatively. This two-step method has been applied in several environmental studies for model evaluation and investigations (Convertino et al., 2014; Chu-Agor et al., 2011, 2012). The twofold application of GSUA using Morris and Sobol' methods is ideally suited for models that (i) have uncertain factors, (ii) are complex and expensive to run, and (iii) have unknown structure (in terms of factor importance and interaction) (Convertino et al., 2014).

The GSUA in this study is based on a set of uncertain input factors selected from the implemented ABM (see Table 2). These factors are selected because of their association with CL host, vector and reservoir host, thus the uncertainty is related to the location of CL incidence with respect to these factors. However, no CL-related uncertainty was identified for some of the ABM input factors

including: proximity to roads, rivers, Qanats, embankments and health centers. For the uncertain land cover classes the uncertainty is assigned as a discrete probability that represents the error in classification of each land cover pixel. Since there were no previous GSUA regarding the CL disease, or land cover of study area a field survey was conducted to acquire a rough approximation of land cover uncertainties. For example, according to the local field surveys a desertification pixel whose class is 2 can be classified as 3 (Dry farming) or 4 (urban and rural areas) with a 15% probability. Considering these uncertainty values, the categorical land cover becomes a continuous variable in GSUA. For the population factors a triangular distribution was assigned to them in order to represent their variability. The triangular distribution is based on a minimum value, a most probable (default) value and maximum value acquired from national statistics organization and MOH official records. The uncertainty of areas with new inhabitants has been considered as a discrete distribution with 0 and 1 values. The CL infection parameter has been considered as one of the uncertainties of the model with a uniform distribution. The minimum and maximum for the distribution range was assigned using the minimum and maximum infection per 1000 people in the MOH registered records thorough Isfahan. Lastly, sand fly perception range was also assigned a uniform distribution with the maximum value of 2500 m, equal to its flight range. The outputs considered in GSUA are the CL susceptibility throughout the study region in two situations: (i) human agents can freely explore the whole study area, (ii) there is no human movement around a 2500 neighborhood of desertification areas.

The Morris method is performed in this study in five steps: (1) the probability distribution functions (pdfs) are assigned (Table 2); (2) sample points are generated; (3) ABM is executed using each of the sample points to generate a set of outputs; (4) global sensitivity analysis is performed; and, (5) the important input factors are identified for the Sobol' variance-based analysis. Next, the Sobol' method is carried out according to the same steps 1 to 4 of the Morris method (Morris, 1991) except that sample points are generated using the Sobol' method (Sobol', 1990). SimLab 2.2 designed for Monte Carlo-based uncertainty and sensitivity analysis (Saltelli et al., 2004) is used to perform GSUA of the ABM in this study. In this case study ABM is executed with 130 Morris simulations and 6656 Sobol' simulations.

5.1.1. Uncertainty analysis using Morris method

The Morris method (Morris, 1991) enables the qualitative assessment of the each uncertain input factor of a model. It determines the effects of input factors (i.e., negligible, linear, additive, non-linear and interactive effects), based on the elementary effect analysis (Saltelli et al., 2008). Morris method calculates, two sensitivity measures for each input factor: (1) the mean elementary effect, μ ; and (2) the standard deviation of the elementary effects, σ . These measures estimate the overall effect (i.e. the importance) and the interaction with other factors respectively. The results of the Morris method are presented here by plotting σ on the vertical axis and μ on the horizontal axis for each input factor (Fig. 7). The results show that most of the input factors with high variability effect on the CL susceptibility (Fig. 7) are interactive factors. Accordingly, the standard deviation of the elementary effect, σ is predominant over the mean of the elementary effect, μ . Thus all points in Fig. 7 that correspond to ABM input factors are above or around the diagonal line. Moreover, this indicates the non-linearity of the ABM implemented in this study for CL. The results show that PF (Population of farmers) is the most important input factor of the model when movements are restricted. It is surprising the importance of PF over other input factors. This happens due to the important role of farmers (human agents) in the SEIR model that largely affect the

Table 2

Input factors for GSUA and probability distributions assumed for the global sensitivity and uncertainty analysis. The adopted probability distributions for the input factors are: discrete (“D”); uniform (“U”); and triangular (“T”) distributions.

No.	Description	Notation	Range	Distribution	Default value
1	Areas with New inhabitants	NI	(0,1)	D (0.3,0.7)	1
2	Desertification	DE	(2,3,5)	D (0.7,0.15,0.15)	2
3	Dry farming	DR	(3,4,5)	D (0.7,0.15,0.15)	3
4	Irrigated farming and orchards	IO	(3,4,5)	D (0.15,0.7,0.15)	4
5	Urban and rural areas	UR	(3,4,5)	D (0.15,0.15,0.7)	5
6	CL notification (per 1000)	CL	(0,100)	U	No default value
7	Population in villages	PV	(20,35)	T	28%
8	Population in cities	PC	(40,60)	T	52%
9	Population of nomads	PN	(5,15)	T	10%
10	Population working in military	PM	(5,25)	T	18%
11	Population working in farms	PF	(15,35)	T	27%
12	Population working in poultry and livestock	PP	(1,5)	T	2.5%
13	Sand fly perception range	SP	(500,2500)	U	1000 m

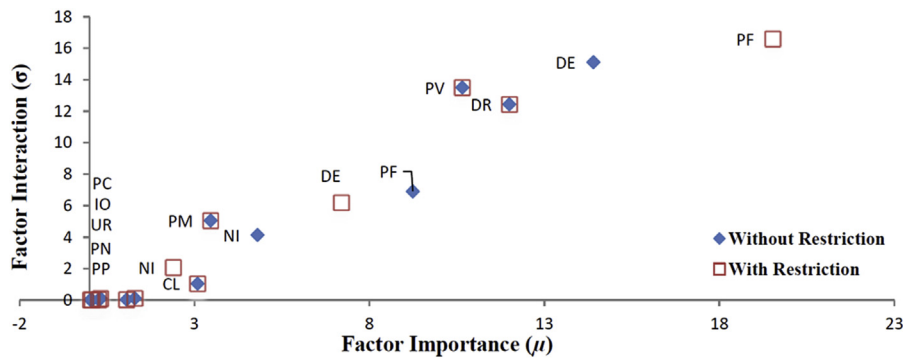


Fig. 7. Morris factor importance and interaction.

model output especially with the confined movements.

Factors UR, IO, PP, SP and PC have low importance considering the Morris index pair (μ, σ) and also contributed almost equally (very low) to the final output (Fig. 7). The input factors selected after the Morris screening for the variance-based sensitivity analysis are CL, DE, PF, PV, PM, PN, NI, and DR, because their overall importance for the CL susceptibility. The selection is performed on the basis of a “visual inspection” of the Morris index pair (μ, σ) of input factors. Morris index pairs close to the origin of the plots haven’t been considered important, and other pairs along the diagonal or pairs large μ or σ are important. The population of nomads, PN, and CL factors have lower importance than expected for the model output and errors in these parameters do not affect the output of ABM significantly. The low importance of CL factor is a reflection of both the stochastic behavior of ABM but also of the static design of the CL reservoir host in the model. Considering Fig. 7, desertification and dry farming areas, population of villagers result very important in the predicted CL susceptibility.

5.1.2. Sensitivity analysis using Sobol’ method

The Sobol’ method (Sobol’, 1990) performs a quantitative analysis of model sensitivity based on the principle of variance decomposition using variance based analysis (Chu-Agor et al., 2011). Hence, the total variance of the model output is given by the sum of the variances of all input factors (Saltelli et al., 2008). The Sobol’ method provides the ability to assess the influence of the full range of variation of each input factor on the model output by quantifying sensitivity measures which summarize the model’s behavior. The most common measure of sensitivity is the first-order sensitivity index, S, that represents the main effect (direct contribution) of each factor to the variance of the model output

(Convertino et al., 2014).

The results of the global sensitivity analysis are reported in Fig. 8. The Sobol’ first order index S, is calculated for the most important input factors, after the Morris screening. The Sobol’ first order index measures the contribution of each input factor to the uncertainty of the model (Convertino et al., 2014). The Sobol’ analysis reveals more variability of input factors than the Morris method. The plots in Fig. 8 allow one to visually detect the most important factors for each movement situation on the model predictions. The input factors DE, PF, DR AND PM are the most important factors when there is no movement restriction. On the other side, with movement restriction around the desertification areas, the PF factor influences significantly model outputs (Fig. 8).

5.2. Model results

This section presents results based on the hypothesis focused on spreading CL from the potential habitats of local rodents towards humans based on the interactions between different disease components (see Section 4.3.2). The results are discussed and explored to investigate the infection process using the SEIR model. Initial model explorations revealed that the model outputs agree with the opinions of local CL experts and do not produce counter-intuitive outputs.

Figs. 9 and 10 show the dynamics of susceptible, exposed, infected and recovered human agents within the Isfahan province with different population sizes. In addition, Figs. 9 and 10 show how sensitive the model is to different population sizes. Two different movement rules are used in the simulation. First, humans can appear in different parts of the study area according to their desired activities and landscape properties (Fig. 9). Second, humans

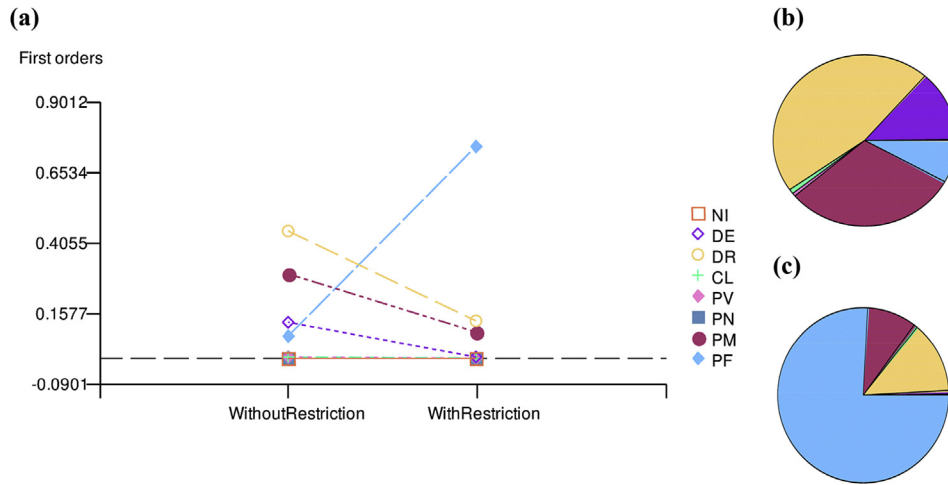


Fig. 8. (a) Sobol' first order index for the most important factors after Morris screening method. (b) Direct contribution of factors to the variance of model output when there is no restriction on the movement of human agents (c) direct contribution of factors to the variance of model output when the movement of human agents is restricted.

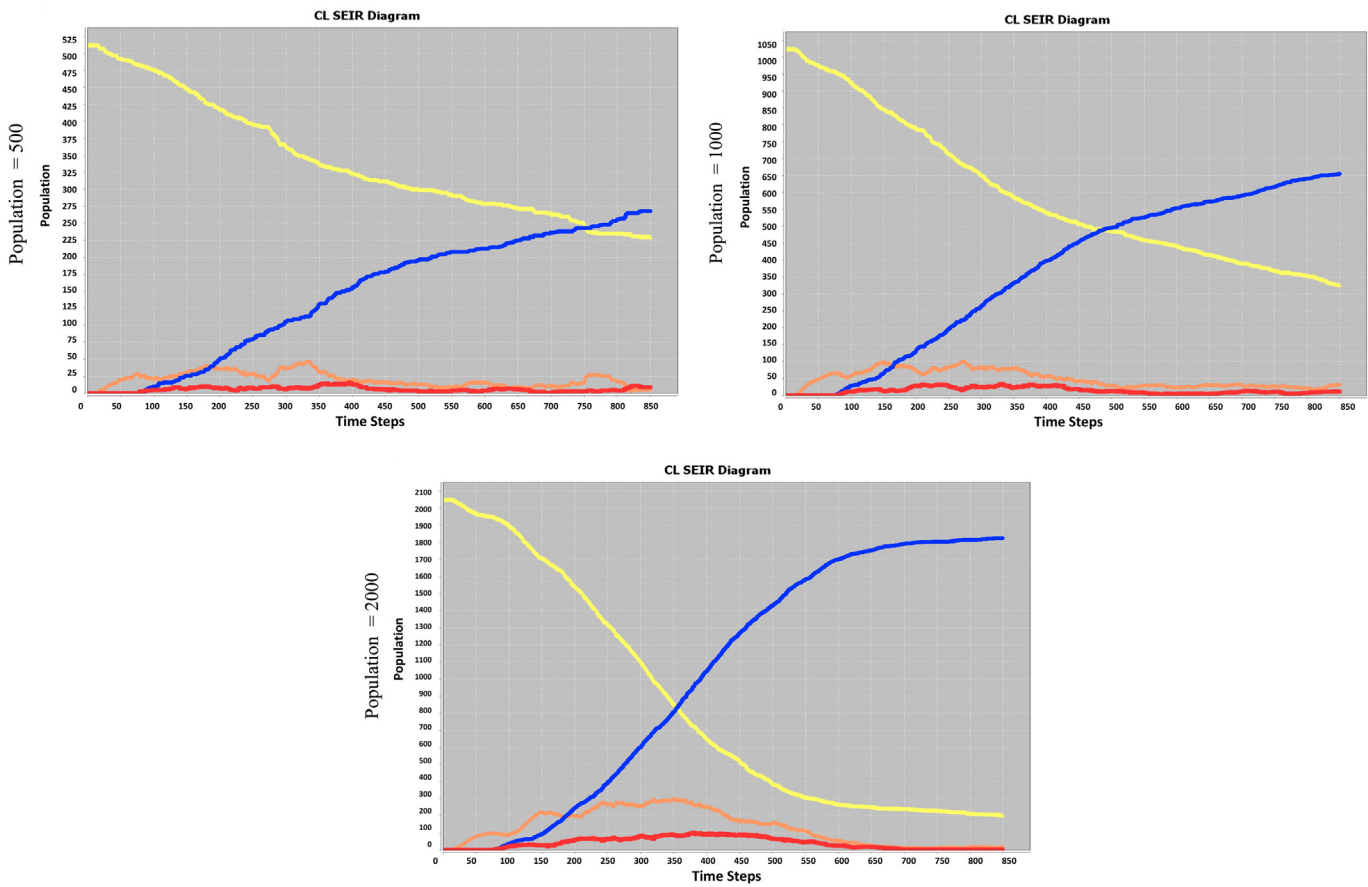


Fig. 9. SEIR results. Without any restrictions. Each time step represents a 12-h period.

cannot appear in a 2.5 km neighborhood in desertification areas where most of the active rodent colonies are located (Fig. 10). The 2.5 km neighborhood is considered for the restriction area since it is the maximum distance the CL vectors can fly in this model. In both figures, the CL spread follows a traditional epidemiological curve. Sand flies that have access to inhabitants rapidly increase the exposure of the population to CL parasites. Without any movement restrictions, the exposure results in a high exposure peak during

the first time steps that gradually decreases by the next time steps (Fig. 9). During this spike, approximately 10–30% of the susceptible populations are infected.

The results indicate that by increasing the population from 500 to 2000, the proportion of infected humans remains approximately constant when human agents do not appear around desertification areas (Fig. 10). However, without any movement restrictions, CL infections have been changed increasingly as the population has

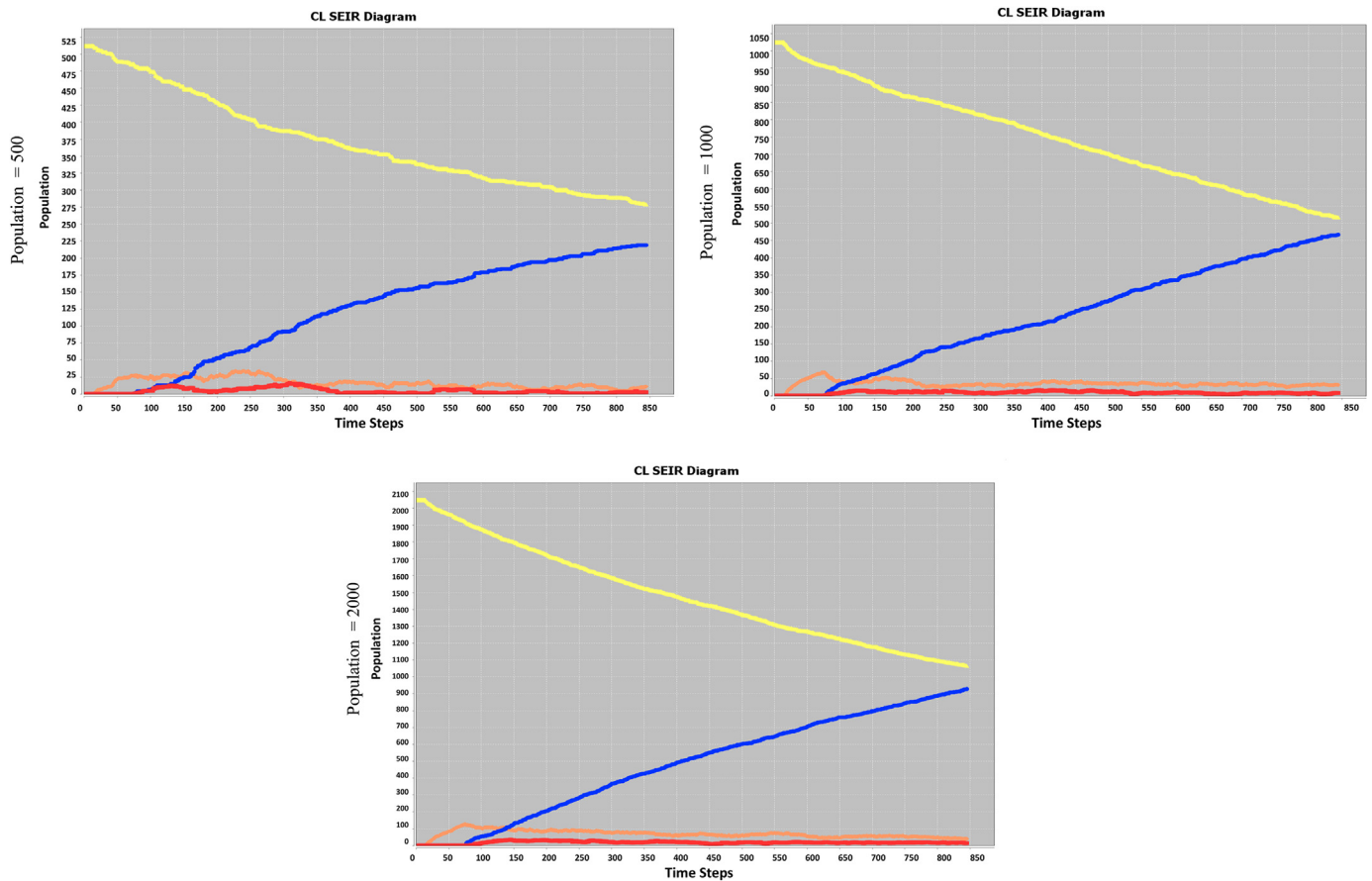


Fig. 10. SEIR results. With restriction in the movement. Each time step represents a 12-h period.

increased. While the number of sand flies and desertification areas were constant, this is not the case for people who appear within sand fly territories. The number of people with access to areas within sand fly vision ranges increases as people are allowed to appear in risky neighborhoods of areas undergoing desertification. According to Fig. 9, the appearance of people in these areas will result in longer infection periods after the initial peak, and restricting movements can result in a 24% decrease in the total infected population.

Three highly infected areas in Isfahan province, including Paygah, Varzaneh and Ejhiye, have been explored separately using the model results (Fig. 11). More areas of desertification are located around the cities of Paygah and Varzaneh, which makes them more exposed to CL from sand flies. Moreover, various well-equipped health centers are located in Paygah relative to other cities, mainly because it is closer to Isfahan, which is the capital of the province. Although more CL infections occur in Paygah, many exposures in Paygah do not result in infection. However, a larger portion of the population is infected in Varzaneh, where most of exposures resulted in infection. This result potentially occurs because of the non-usage of sprays and mosquito nets in Varzaneh due to less access to medical education and equipment. The comparison of SEIR in Paygah and Varzaneh indicates that the accessibility to healthcare services and proper preventive equipment, decreased 17% the probability of being infected from an exposure in Paygah. In Ejhiye, the story is different, despite existence of several desertification sites, the infections is still lower than other two cities. It could be due to high proportion of once infected inhabitants which makes them resistance to CL exposures. Restriction

of sand fly movements in this area resulted in approximately 45% decrease in the peak of infections; However the infection process lasted in a longer time period than before (Fig. 11).

Fig. 11 illustrates that restricting movements significantly decreases the number of infections in Varzaneh and has a slightly significant influence on CL infections in Ejhiye. According to Fig. 11, restricting movements does not change the infection rate in Paygah, which can be interpreted as the influence of a large number of new uninformed inhabitants. Because Paygah is a military base, its population pattern changes each year, which makes it highly vulnerable to CL infections. The results from different model runs indicated an average increase of 15% in Paygah infections compared with cities in similar landscapes because of its population pattern.

Figs. 12 and 13 show the results of a typical run of the model where the infection risk of field units has been calculated while tracking CL infections. Areas with more risk value show a high probability of CL exposure and infection. The spatial pattern of CL is much more confined to desertification areas when there is no restriction to movement (Fig. 12). Accordingly, the spatial spread of CL infections indicates that access to desertification areas affects the pattern and extent of CL. As shown in Fig. 13, when agents are not allowed to roam around desertification areas, CL is more localized around nomadic villages south and west of the study area. In this situation, CL infection is localized around areas with new inhabitants (more nomads and new inhabitants) and begins to spread along rivers (Fig. 13). A comparison of the maps in Figs. 12 and 13 show that the spatial patterns for Paygah are alike in both situations and that various highly infected areas occur in this area for

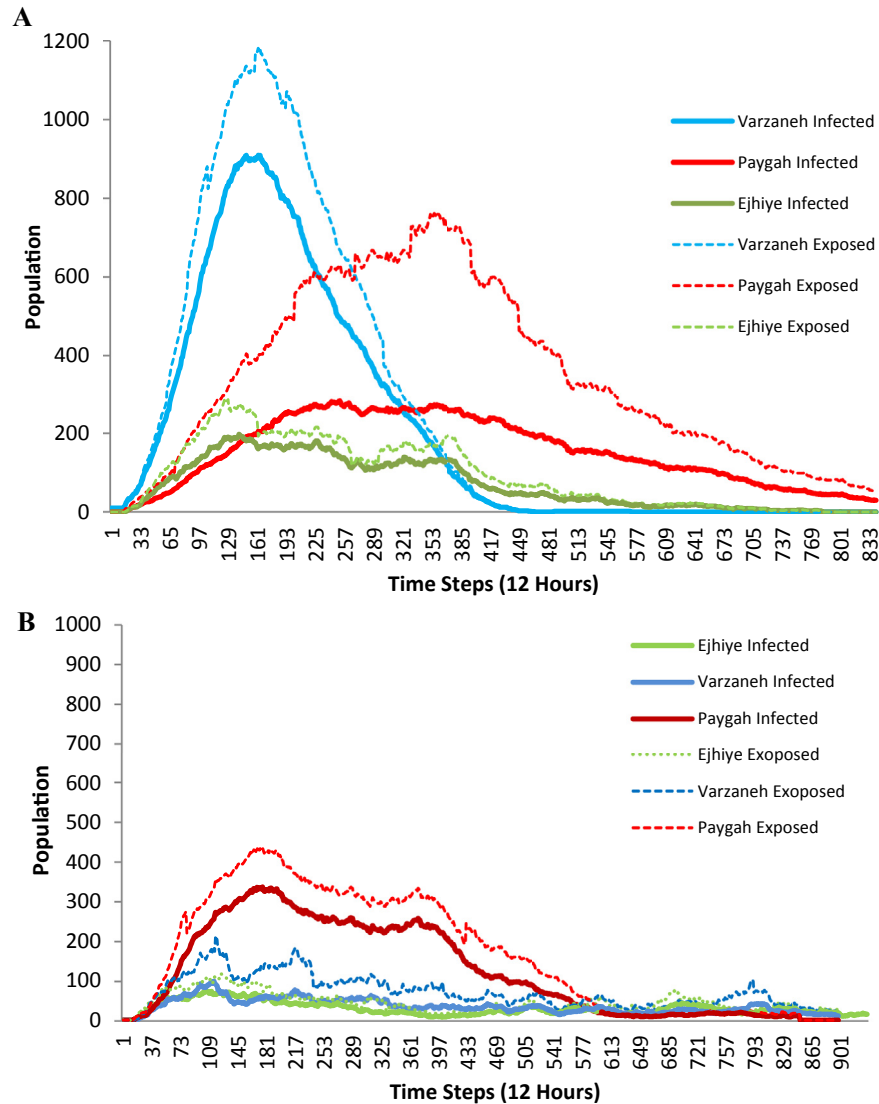


Fig. 11. Number of infections in three endemic areas in Isfahan Province. A. Without any restricted movement. B. With restricted movement.

both movements. However, the spatial patterns for Ejhiye and Varzaneh are completely different in Figs. 12 and 13. In Ejhiye, infections still occur in the area but have moved to the river neighborhood and the southern villages with lower access to health centers. By restricting movements in Varzaneh, most infections are transmitted to the northern part of the city where the river passes.

From a disease control point of view, a lot can be done to reduce the exposures around risky areas regarding the components of CL transmission cycle. Since the sand flies' larvae are located mostly in underground burrows, elimination of them is an expensive and a long-term process which also needs receiving permissions from higher-level organizations. Hereby, the most appropriate way to control sand flies is to identify their exposure sites and do healthcare measures by informing local people, providing relevant preventive equipment, etc. The model simulations showed that vector-human interactions occur not only near desertification areas but also on riversides, extending up to 2 km from the river. This indicates the importance of riverside population centers to receive preventive measures while they had been noticed with less priority before. Following desertification areas, the most frequent contact area is that near the Zayande River, an important perennial river

flowing inside Isfahan. Contact mainly occurs in farmlands, parks, and nomad camps and through poultry and livestock. Less contact occurs in urban settlements, bush lands and woodlands, which was an unexpected result. This interesting result which also was confirmed by later field surveys showed the ability of the underlying system to simulate the interactions between environment and the agents.

The outputs from simulation experiments were mainly consistent with field observations, which increased the confidence of the model although the availability of reliable validation data was limited. The comparison between the field data and model predictions was restricted to highly infected areas that were not used for training so they could be used for validation. The visual evaluation of the predicted risks and validation data showed a consistency between them.

6. Discussion

The results of this study revealed that the spatial situation of the main contact places between humans and CL vectors is the most important factor for exploring the spread of CL. This factor depends

Time step: 200

Time step: 400

Time step: 600

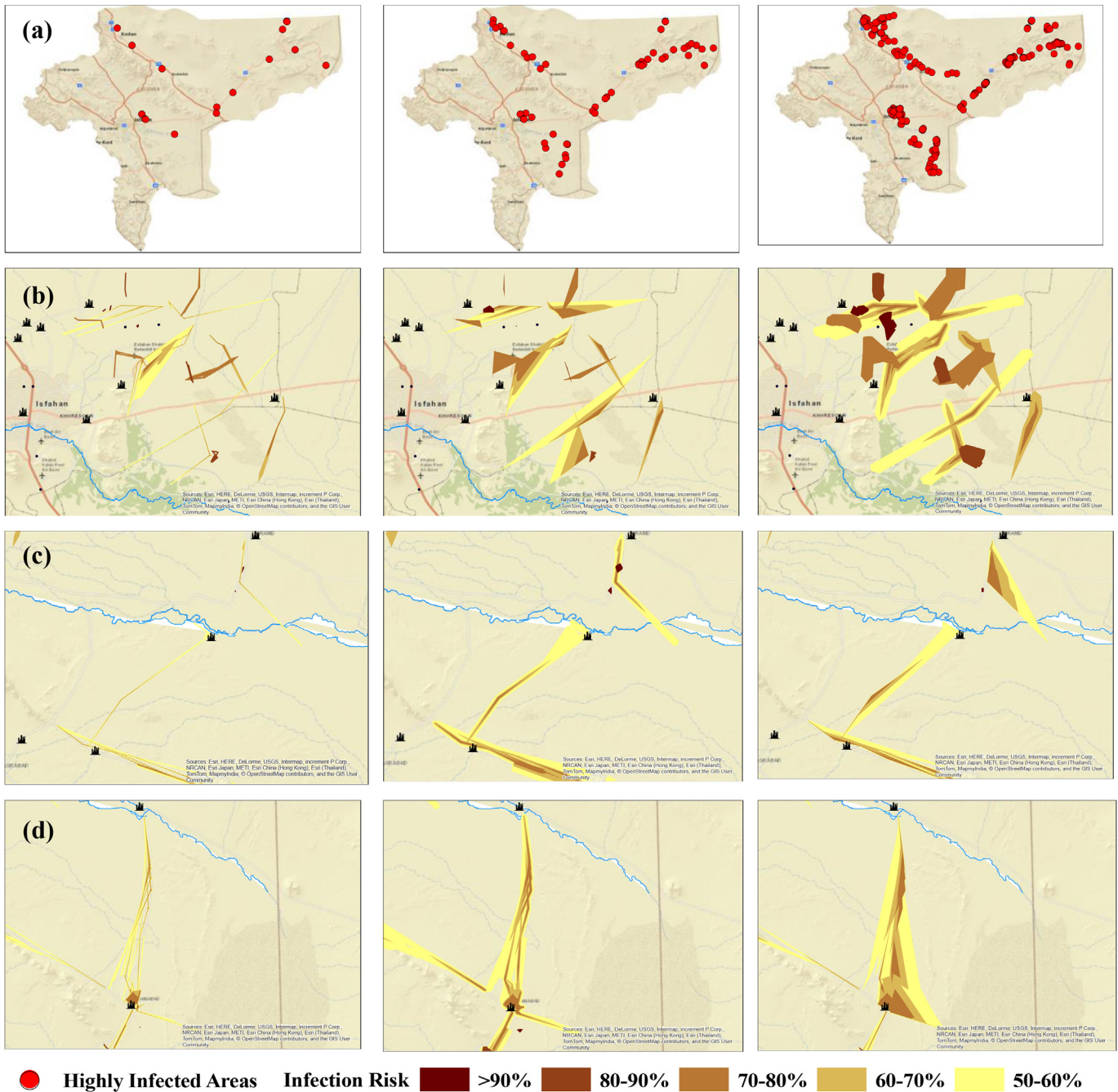


Fig. 12. Identification of CL risky areas when there is no movement restriction around desertification areas. (a) Isfahan Province (b) Paygah region (c) Ejhiye region (d) Varzaneh region.

on the socio-ecological configuration of the landscapes in each region. In this study, the physical and social characteristics of the environment in Isfahan province were simulated to explore the dynamics of these critical contacts by using an ABM. The model developed in this study addresses the four challenges in spatial ABMs mentioned by (Filatova et al. (2013)) including: (1) design of agent decision models, (2) verification, validation and sensitivity analysis, (3) integration of socio-demographic, ecological, and biophysical models and (4) spatial representation. First, the agents' behaviors were designed and parameterized using a SEIR model for the human agents and by considering the ecological characteristics

of the sand fly agents. Second, the sensitivity of models to different human populations was investigated using the epidemiological curve and also a global sensitivity and uncertainty analysis was performed to investigate the model uncertainties. Third, environmental and demographic data and ecological information from the CL vector and reservoir host were coupled in the CL ABM model to provide a realistic vision for preventive measures of healthcare authorities. Finally, a geographic automata system (GAS) was adapted to the CL problem to represent the spatial heterogeneity of the landscape in the model.

The main limitation of the developed CL model was a lack of

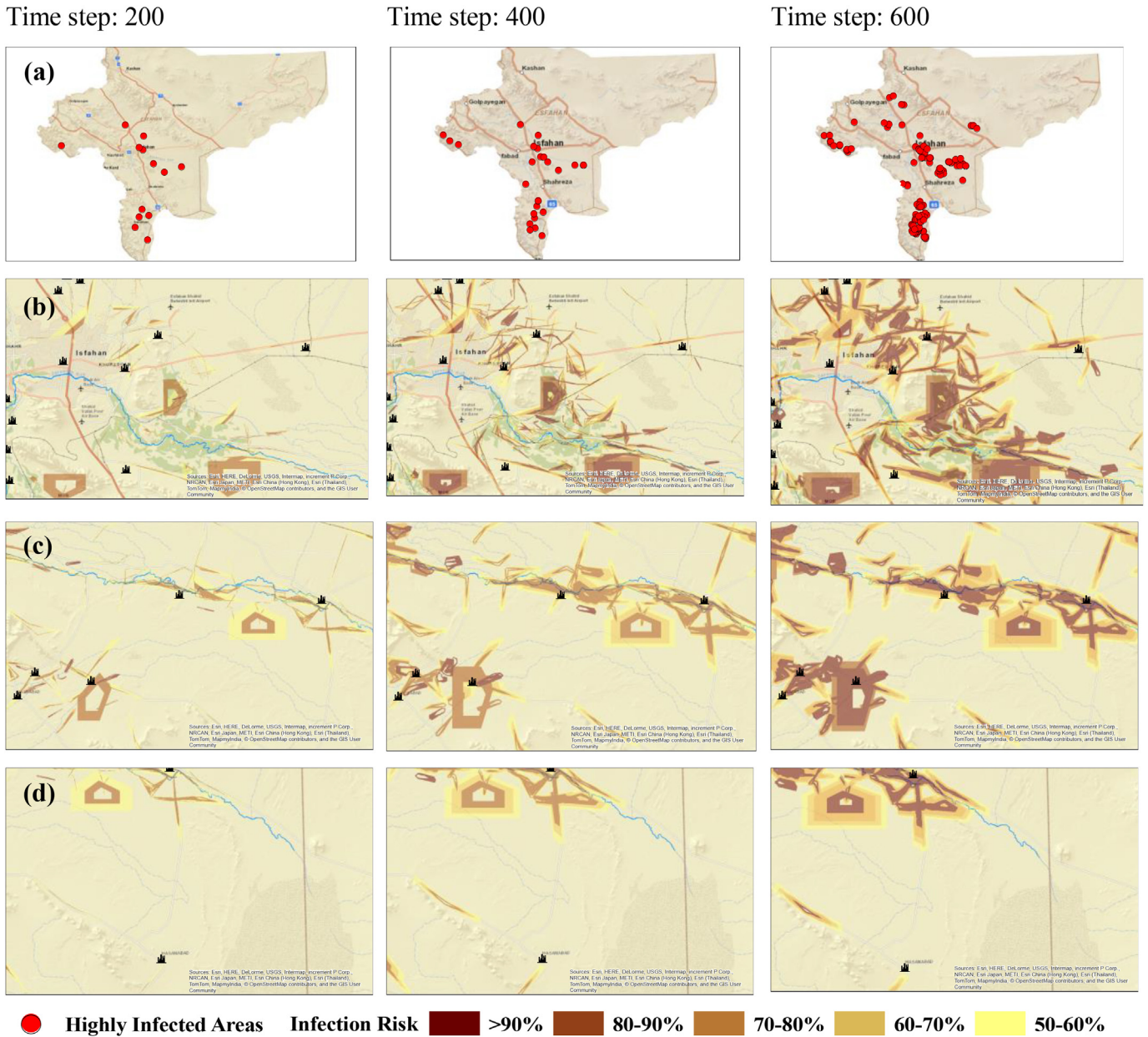


Fig. 13. Identification of CL risky areas when there is movement restriction around desertification areas. (a) Isfahan Province (b) Paygah region (c) Ejhiye region (d) Varzaneh region.

calibration data. Moreover, the ecology of *Rhombomys opimus* behaviors and its habitats in Isfahan are not well understood. Consequently, the model only represents risky areas based on the assumed rodent habitats. Although several studies have proven the roles of this rodent as the main CL reservoir host in Isfahan (Yaghoobi-Ershadi et al., 1996; Nadim and Faghih, 1968; Akhavan et al., 2010), the habitat analysis and rodent behaviors have not been sufficiently explored. By resolving these issues, they can easily be integrated into the model and improve the simulation performance.

In a follow-up work from the authors of this study, the rodent behaviors will be simulated with their ecological characteristics and the CL agent-based model developed in this study will be extended to explore various intervention scenarios based on the dynamics of contacts between rodents, sand flies and landscape configurations. We will explore hypotheses that include environmental and human made changes (e.g., urban growth, land use

change) and healthcare authority interventions.

To our knowledge the CL ABM model is one of the first studies to model the spread of CL based on interactions between hosts and vectors considering socio-ecological attributes. This model provides a robust basis for exploring the transmission of CL through the environment and possible healthcare measures for preventing further infections.

7. Conclusions

In this paper, a spatially explicit agent-based model was used to explore the spread of CL within a highly endemic area in central Iran. The spread of disease was modeled by explicitly representing the socio-ecological interactions between sand fly vectors, humans, and their environment. An ABM was developed to simulate the spatiotemporal dynamics of such interactions as components of a complex system. The ABM approach allowed these components to

behave based on socioeconomic and landscape factors. Moreover, the ABM was integrated with a SEIR model here to provide the ability to explore the spread of disease realistically.

Through simulations, the model showed how CL could spread in different parts of study area with different healthcare availability, population pattern, and environmental characteristics. The results indicated that the spread of CL mainly originates from desertification areas and that restricting human activities around desertification areas could reduce the intensity of infections. However, even with restrictions around desertification areas, the model results indicated significant infections in riverside population centers where haven't been noticed before. The results also confirmed that availability of health centers can result in more protection against sand flies and more resistance against CL exposures when there is no possibility for restricting activities. Moreover, the results indicated that places with new inhabitants are more vulnerable to sand fly exposures and this raises serious concerns for a new wave of CL infection regarding the new housing activities in Isfahan suburbs.

One pragmatic approach to control such vector-borne diseases is to limit vector-host interactions. A better understanding of the factors that influence the interactions can improve the quality of preventive measures of healthcare authorities. The ABM developed for CL within this study can be used to integrate and investigate multiple factors and explore their interactions in a spatiotemporal environment with spatial representation capabilities. The CL ABM could be easily adapted to areas other than Isfahan and to other vector-borne diseases by changing a few landscape and socioeconomic variables.

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