DOI: http://dx.doi.org/10.7551/978-0-262-31709-2-ch005

Simulating Sleeping Sickness: a two host agent-based model

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Abstract

Agent-based modelling is useful for policy evaluation in fields such as epidemiology. The current paper presents a model of Human African Trypanosomiasis (HAT), or sleeping sickness: a disease which is becoming increasingly prominent due to recent epidemics. Associated medication is often scarce, whilst diagnosis through blood screening is not always effective. Current modelling methodology uses simple reaction-diffusion models to predict future epidemics, but this makes policy at the village level difficult to evaluate. Agent-based, object-oriented simulation provides a simple means of adding complexity to models of sleeping sickness, allowing the easy incorporation of spatial and vector data. We present an exploratory two-host agent-based simulation for humans and cattle, applying known values for sleeping sickness infection rate, before evaluating the model's policy implications and suggesting steps for future improvement.

Introduction

Agent-based modelling (ABM) in artificial life has long been used to examine fundamental questions in areas such as the evolution of cooperation or communication. However, ABMs have also been used in a pragmatic way in disciplines such as anthropology (e.g. Gumerman et al., 2003; Lansing and Kremer, 1993), conservation biology (e.g. Watkins et al., 2011), and epidemiology (e.g. Muller et al., 2004; Auchincloss and Diez Roux, 2008). In this latter tradition, we will focus here on an agent-based model of Human African Trypanosomiasis (HAT), also known as sleeping sickness. Our goal is to show how an ABM approach can improve on conventional modelling methods in assessing the likely success of different policies for managing the disease.

HAT is a neglected tropical disease (NTD) (Simarro et al., 2010) and one of the most common conditions affecting the poorest 500 million people living in sub-Saharan Africa (Hotez and Kamath, 2009). Sleeping sickness is a vector-borne, parasitic disease which is transmitted to humans by the bites of the tsetse fly from the genus Glossina. The disease is caused by protozoa of the species Trypanosoma brucei - namely the sub-species *T. b. gambiense* and *T. b. rhodesiense* (Fèvre et al., 2008) and, as of 2005, was responsible for an estimated 100,000 deaths every year (Picozzi et al., 2005).

In recent years, the potential for a spatial cross-over of the two forms of the disease has been heightened due to the continued northward spread of Rhodesian HAT in Uganda (Batchelor et al., 2009). This would be particularly significant as Gambian and Rhodesian HAT require different diagnosis and treatment, and any overlap would compromise previous disease characterisation based on knowledge of the geographical distributions of the diseases.

The resettlement of communities in response to epidemics in the 1900s and 1940s had aided the control of the disease. However, a large volume of uncontrolled movements through tsetse infested bush following a further large outbreak in 1971, combined with a lack of resources and trained personnel, meant that mitigation efforts were hindered in a time of political and economic unrest (e.g. Matovu, 1982; Okiria, 1985). As a result of the poor control measures, the *T. b. rhodesiense* form of the disease spread northwards towards the Tororo district in 1984 (Mbulamberi, 1989), before reaching the Soroti district on the north west shores of Lake Kyoga in 1998 (Fèvre et al., 2004), and the Kaberamaido district in 2004 (Fèvre et al., 2005).

At present, with cases of *T. b. rhodesiense* being diagnosed as far north as the Ugandan district of Lira, there is a distance of only 150 km separating the active foci of Rhodesian sleeping sickness to the north of Lake Kyogo, and the Gambian form of the disease towards the north west of Uganda and south Sudan (Figure 1).

The vector

Mitigation techniques for sleeping sickness in sub-Saharan Africa often focus on the reduction or the removal of the tsetse fly, which carries the disease. For example, while the burning of tsetse infested bush has fallen out of favour due to the associated environmental damage, other effective techniques have incorporated community led 'vector trapping' to reduce the concentration of the flies (Joja and Okoli, 2001). The associated research concluded that the integration of public participation aided community learning and

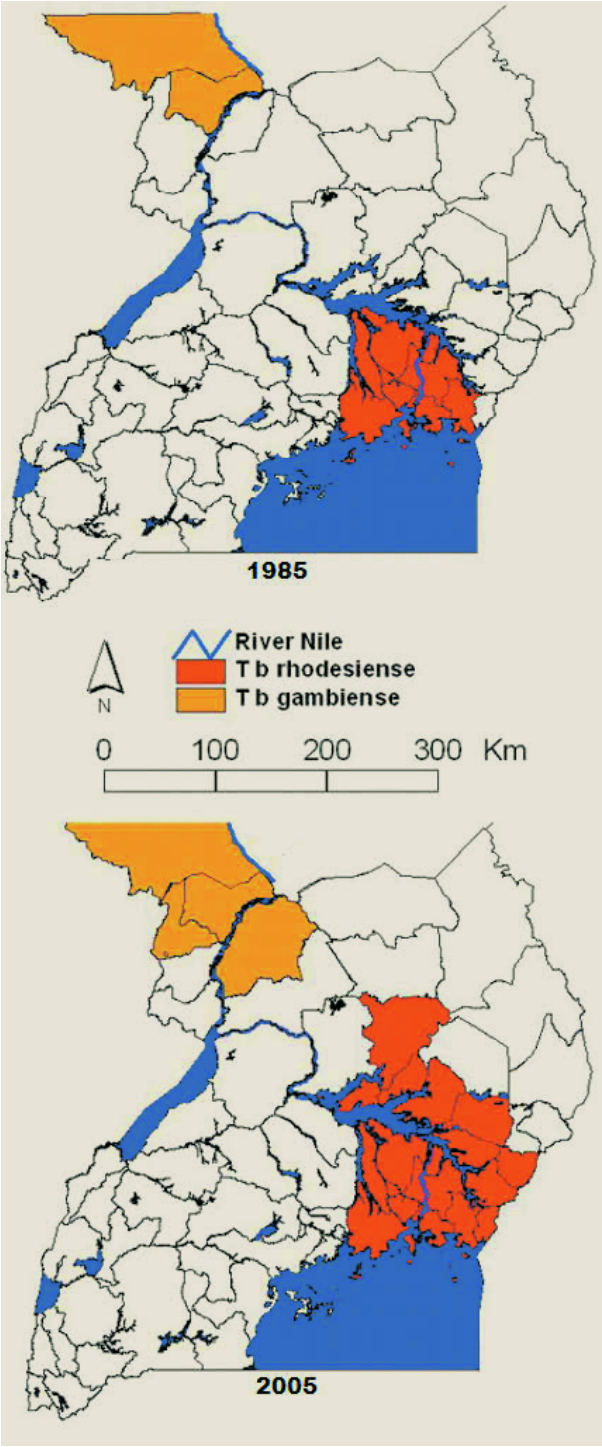

Figure 1: The conversion of Rhodesian (red) and Gambian (orange) sleeping sickness between 1985 and 2005. After Picozzi et al. (2005).

made the volunteers much more open to mass blood screening programmes.

An alternative approach to vector control has been researched in the field of molecular genetics. With the lack of a mammalian vaccine and affordable drugs making disease control difficult, Aksoy (2003) notes that the future of vector control may be the genetic disruption of the parasite transmission cycle in the invertebrate. While this requires a full understanding of the relationship between tsetse and trypanosome, the replacement of susceptible insect phenotypes with anti-pathogenic properties could result in decreased transmission.

Accompany these vastly different mitigation strategies with the application of insecticides such as deltamethrin (e.g. Torr et al., 2007a; Hargrove et al., 2012) to grazing cattle, and a focus on preventative measures which manage tsetse fly population sizes can be identified.

Agent-based modelling

Lambin et al. (2010) review the merits of using multi-agent simulations (MAS) to model disease transmission, concluding that the technique is a good method of acquiring preliminary knowledge of a disease system, and that the representation of the dynamics of people-vector contacts in space and time are ideal to investigate scenarios that have not previously been observed or explored.

Similarly, the modelling of people-vector contacts is of particular significance given that the majority of current mitigation strategies focus on the control of tsetse fly movement and density. Lambin et al. (2010) also consider the incorporation of geographical information in epidemiological models through the use of MAS, such as the impact of land-use and land cover change. The report suggests that the benefits include an increased knowledge of transmission cycles, allowing the construction of 'pathogenic landscapes' which can subsequently provide an early warning of increased transmission risk. The benefits of incorporating geographical data into epidemiological models can be observed widely in the literature. For example, Raffy and Tran (2005) note that landscape features largely control the connectivity between hosts and vector habitats, inhibiting movement, and ultimately modifying disease risk. One of the least well integrated factors in traditional landscape epidemiology is human behaviour (Lambin et al., 2010). Despite this, different risk perception between men and women, and also by permanent and part-time residents of endemic areas, has been shown to influence the adoption of preventative measures and ultimately vary transmission risk (e.g. Stjernberg and Berglund, 2005).

We therefore saw an opportunity to build an ABM that included the disease vector (tsetse flies) and both host species (humans and cattle) interacting in a common geography so that we could assess the likely costs and benefits of widely differing management strategies for HAT.

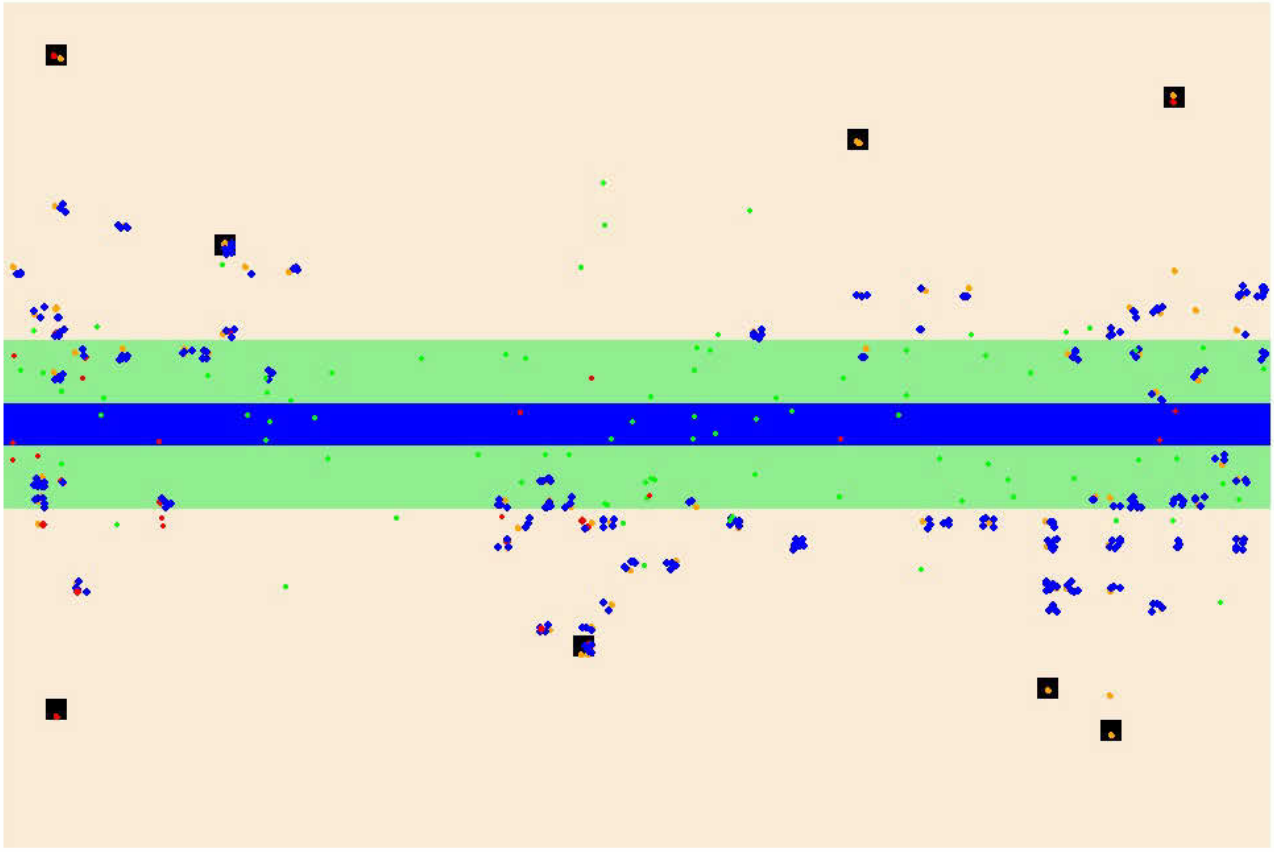

Figure 2: The simulated environment; description in text.

The Model

The simulation incorporates an abstract spatial map and three interacting agents: tsetse flies, humans and cattle, allowing the influence of agent interaction in disease transmission to be explored. The model includes two simple daily tasks for farmer and non-farmer agents: farmers must drive their cattle to the river to drink, before grazing and returning home. Non-farmers must collect water from the river and return it to their settlement. Tsetse flies are assumed to have a natural habitat on, or near the river. Interactions between flies and the ground-based agents occur when the daily tasks take place, and humans and cattle enter the high risk, tsetse infested river area.

We begin with a simple, abstract terrain representing an area of 30 km by 20 km. The simulated land includes a river (blue) at the centre of the canvas, with flood plains either side (green), and the remaining land representing general pasture. Black icons represent small settlements or home bases for human and cattle agents (figure 2).

Within the model, time steps are grouped into the phases 'night' (7 pm - 5 am), 'morning' (5 am - 8 am), 'day' (8 am - 4 pm) and 'evening' (4 pm - 7 pm), simulating a day with 240 time steps. These phases govern agent activity and vary exposure to the disease vector, ensuring that farmers drive their cattle to and from the river each day before grazing and returning to their settlement.

Humans are depicted in the graphical output as orange circles and are divided into farmers and non-farmers. This distinction dictates their movement pattern to and from the river. At setup, all humans are randomly assigned a settlement as a home base, with the initial cattle population randomly assigned a farmer as an owner. During the morning and day phases, all humans are required to have left their home settlements and begun either making a trip to the river to collect water (non-farmers), or driving their cattle to water before grazing (farmers). During the morning phase, there is an initial probability (10%) for each individual leaving their home per time step. When the day phase is reached, any person not to have left home yet is forced to leave.

Movement is governed using a cell desirability function, such that the rows of the map are assigned integer values which are high at the river, and decay to the edges of the

map. People move from home to the river by selecting a desirable cell from a list of their neighbouring locations. When a movement probability is exceeded for each individual, there is a 66% chance they will move to a cell with a higher value (closer to the river), and a 33% chance they will either move closer to the river or make a lateral movement, simulating different routes taken, and the subsequent spreading out of agents.

Non-farmers move directly to their homes when the river has been reached. However, if the people are farmers, a random movement element has been included to simulate the grazing of cattle. Once the cattle have been driven to the river (and whilst still in the day phase) this 'grazing' occurs with a probability per time step of going home (initially 1%). When the evening phase is reached, all remaining farmers drive their cattle to the home settlement. By the 'night' phase, all people and their cattle will have returned to their home settlement and remain there until the next morning phase, when the cycle begins again.

Should people get bitten and become infected with the disease, when they return home, they stay there, and do not resume with the next daily cycle. This simulates the debilitating nature of the disease, preventing people from undertaking their everyday duties.

As previously mentioned, cattle (blue circles) are assigned an owner at initialisation, and are programmed to follow the movement pattern of their keeper. The exception to the rule is when owners become infected and subsequently stay at home for the duration of the simulation. Under these circumstances, the cattle of the infected farmer are redistributed to uninfected people at the same home settlement, during the night phase, so that they can still be driven to the river. The redistributed cattle can be infected or uninfected and this redistribution can continue as more people become ill, until there are no longer any healthy humans in the home settlement. At this point all cattle stay at home, whether infected or not, as there are no healthy human agents to drive the cattle to water.

Tsetse flies are represented as green icons. They stay close to the river and flood plain areas which represent the natural habitat of the species. This behaviour is implemented by assigning each cell on the grid an integer value, with the central 10 rows having a uniformly high value, decaying north and south of the river so that the extreme four rows have values of 0. Tsetse flies have a lower initial movement threshold than humans to simulate faster movement.The random and directed elements of fly movement are not separated to reflect a daily routine as found with humans. Instead, flies are initially set to have a 70% chance of moving using the 'fly suitability rating' of the cells around them (i.e., moving to the neighbouring cell with the highest value). The alternative is a completely random move to any of the agent's 8 neighbouring cells. This movement regime means that, while the majority of flies will stay close to the river and its banks, some spread is observed as stray flies can move away from their natural habitat and towards the settlements.

In this simulation, flies have a 100% chance of contracting the disease if they bite an infected cow or human, however, if the fly does not bite an infected agent for their first blood meal, the fly is re-spawned at the river to represent the removal and replacement of that agent. This action simulates the finding that flies that don't become infected on their first blood meal are much less likely to contract, and therefore, transmit the disease (e.g. Walshe et al., 2011; Aksoy, 2003). Additionally, once a fly has become infected, there is a 15-30 day delay before it becomes infective, incorporated to reflect a real life incubation period for the disease (Muller et al., 2004).

The transmission of the disease between agents is governed by a bite and infection probability, using values extracted from the literature. At the beginning of each simulation, a single fly is infected with sleeping sickness. Transmission occurs from the point of view of the tsetse fly. For every time step, each fly has a 'potential victim' list, made up of all the human and cow agents in the same cell. If this list is populated, and a randomly generated number is less than the chosen bite probability value, the fly randomly chooses one of the agents in the list as a victim.

Whether or not the bite successfully infects the human or cow agent is governed by another pair of probabilities. As humans and cows are widely considered to be differentially susceptible to *T. b. gambiense* and *T. b. rhodesiense* (e.g. Fèvre et al., 2006), different infection probabilities are incorporated for the different types of agents. The values associated with these three probabilities vary in the literature, due in part to the small sample sizes in data collection, and the complexity involved in the transmission of the disease and vector-host interaction. For example, Torr et al. (2007b) find that cattle bite rates vary with cattle age and herd size, suggesting that mean fly feeding probability can increase from 54% to 71% with an increase in herd size from 1 to 12. We take our infection probabilities from the work of Hide (1999), reporting on the dynamics of transmission of sleeping sickness during the 1988 to 1990 sleeping sickness epidemic. Hide (1999) reports a cattle infection probability of 0.0115, and a human infection probability of 0.006, based on data for the frequency of infected hosts in the population during this period in Uganda.

Consequently, the basic bite probability under investigation will be 0.54, while infection rates of 0.115 and 0.06 will be used to reflect the susceptibility of cows and humans respectively. This uses the same ratios as Hide (1999), however the values have been increased by a factor of 10 to compensate for the unrealistically small population sizes we have used (typically 100 humans, 320 cows and 100 flies). Smaller population sizes have been used as it would be computationally inefficient to attempt to simulate every

fly present in an area this size.

To simplify the simulation, and consider worst case epidemic scenarios, recovery from the disease is absent from the model. While an ideal model would incorporate some form of recovery factor, the degree of variability in diagnosis and treatment rates would be a difficult thing to include in a spatially and culturally abstract simulation.

Results

Figure 3 shows the progression of transmission of the disease in this abstract environment with 100 humans (including 80 farmers), 320 cattle, and 100 flies over a 6 month period. 6 months was chosen as, in an environment where there is no recovery, this is how long it takes for the disease to affect the vast majority of the population, given the human infection rate of 0.06, and a cow infection rate of 0.115. Bite rate is set at an intermediate value of 0.54, thought to be significant in cattle herds (after Torr et al., 2007b).

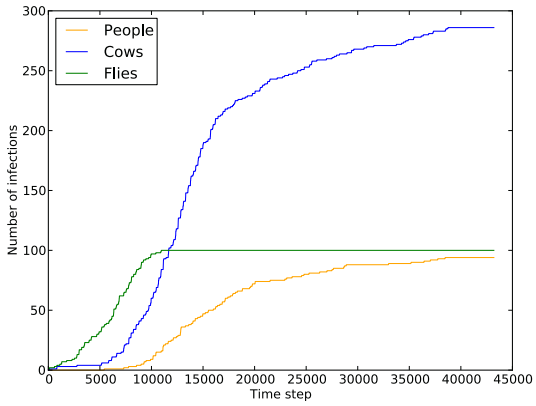

Figure 3: Progression of sleeping sickness over 6 simulated months (240 time step days); from single infected fly to complete epidemic. (Bite probability = 0.54, cow infection probability = 0.115, human infection probability = 0.06).

The six month run of the simulation shows that the fly population is the first to reach complete infection, and as suggested above, the fastest rate of cow infection occurs between months 1 (7200 time steps) and 2 (14400 time steps), once fly infection reaches approximately 50%, and sick humans start to be taken out of the equation by staying at home. The simulation shows that although fly infection occurs for 100% of the population, there are approximately 40 cows and under 10 people which are not infected after 6 months. These remaining cows are at a significantly reduced risk of infection as the simulation progresses as it is possible that all people from a certain settlement become ill, meaning that uninfected cows can be left at home with no fit human to take them to water. Even before this occurs, if it is left to

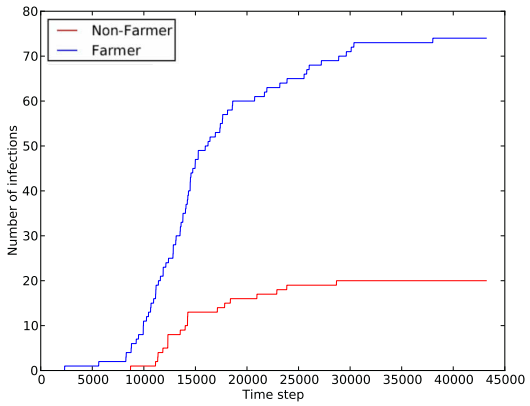

Figure 4: Infection rates of cattle driving farmers and water retrieving children (non-farmers).

one fit person to take an entire settlement's cow population to water, the spatial coverage of this herd is low, the chance of each individual being bitten is low, and a large proportion of the herd may already be infected, reducing the probability of new infections even further. Similarly, the healthy human that drives this large body of cattle is at a significantly reduced risk as the potential victim list for each fly will be more heavily populated. In this sense, even a simple, spatially abstract simulation such as this can help relate to certain theories of transmission, such as that of Torr et al. (2007b), who suggest that although bite probability increases in larger herds, there may be a degree of 'safety in numbers'.

Figure 4 shows the progression of the disease amongst the 80 farmers and 20 non-farmers in the simulation. Prior to running the simulation, one prediction may have been that the infection would propagate at a faster rate among non-farmers than farmers due to the fact that they have no cattle, and therefore when they encounter an infected fly, they are the only potential victim. As the rate of infection for each sub-class appears to be comparable for the first ten victims, this theory appears to be accurate, particularly as there are only 20 non-farmers in the population, compared to 80 farmers.

Figures 5 and 6 show the results from a series of two-month simulations where the ratio of cattle to farmers is systematically increased from 1:1 (80 farmers and cows) up to 1:7 (80 farmers, 560 cows). As before, the infection rates are a scaled representation of those found in the 1988 Ugandan sleeping sickness epidemic (Hide, 1999). These values of 0.115 for cow infection, and 0.06 for human infection, suggest the propagation of a disease which is reflective of the Rhodesian form of sleeping sickness, where cattle are the main reservoir (Batchelor et al., 2009).

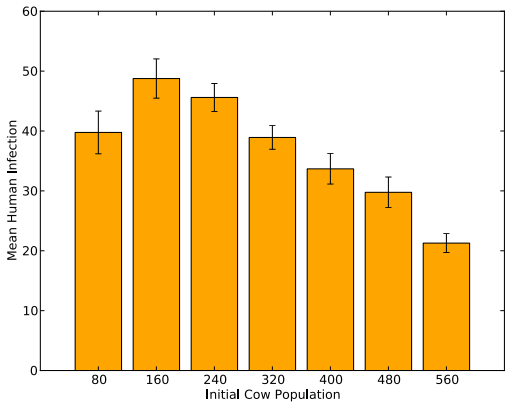

Figure 5: Mean human infection (25 repeat runs) while varying the cow population. *T. b. rhodesiense* infection rate (Bite probability = 0.54, cow infection probability = 0.115, human infection probability = 0.06).

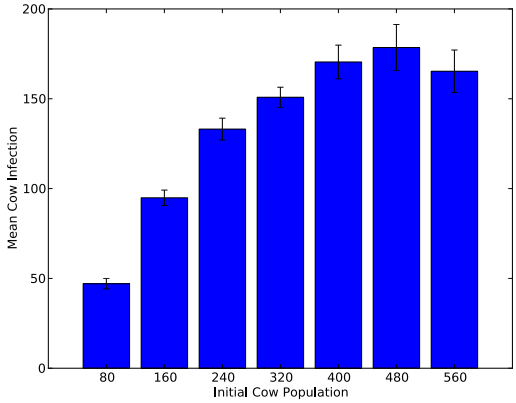

Figure 6: Mean cow infection while varying the cow population. *T. b. rhodesiense* infection rate (as figure 5).

With a 1:1 farmer to cow ratio (80 cows), overall infection is comparable between the two agent types by the end of the two month period. This is likely to be a product of the low total population, and a slower spread of the disease as a result. In a scenario where a fly meets a farmer and his cow in a grid square, there is a 50% chance of selecting either, and the bite probability is the same for both (0.54). Therefore, the only factor promoting infection in cows over humans is the infection rate, which is approximately double, but still only represents a 1 in 10 chance of infection. As a result, flies are less likely to meet infected cows or humans at the earlier stages of this two month simulation and, at this time scale, there is little promoting infection in either agent type

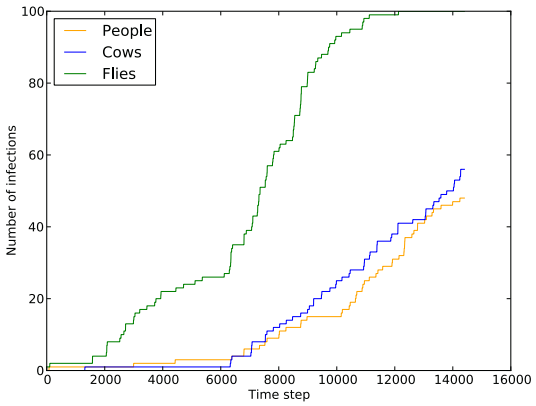

Figure 7: Example of a two month run where human and cow populations are both 80.

(see, for example, figure 7). By the end of the simulation almost all flies are infected (graph not shown) yet the relative sparsity of the human and cow populations means that disease propagation is inhibited.

When the cow population is increased to 160, mean human infection also increases, despite the greater proportion of cows to humans. This is likely to be a result of the increased rate at which the disease is transmitted, given that infection amongst the cow population significantly increases from a mean of 50 infections to a mean of 100. Although the mean increase in human infection is slight, it suggests that the idea of 'safety in numbers' does not apply for this population ratio. However, subsequent increases in the cattle population seem to create this effect, with mean human infection reaching a lower limit of 21 when the human to cow ratio is 1:7. At this point, it appears as though the number of new infections that can occur with an increasing cow population has peaked. This is likely to mean that the cow population is no longer the limiting factor in increasing infection, and instead the fly population is. Indeed, at this point the fly to cow ratio is also 1:7, and therefore a two month period may not be long enough for the vector to have a greater impact on the total population.

Figures 8 and 9 illustrate the results of a similar simulation with the infection probabilities reversed (cows = 0.06, humans = 0.115).

This scenario may be expected to produce infection data representative of the Gambian form of sleeping sickness, where humans are the primary reservoir, and cattle are affected to a lesser extent. While there are on average more infections per 100 of the human population than for the cow population, there are a few interesting points to note. Firstly, the range of mean human infection across all initial cow populations is 30-50 people. Compare this to the human infec-

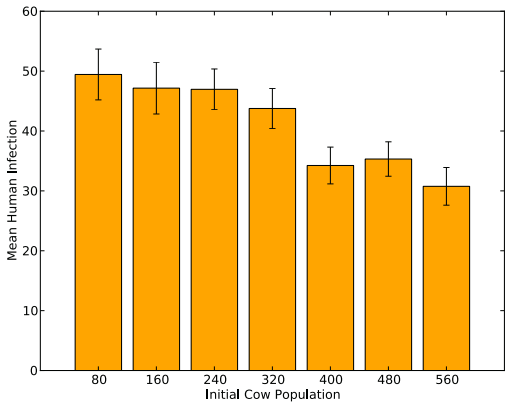

Figure 8: Mean human infection (25 repeat runs) while varying the cow population. Reversed infection rate (Bite probability = 0.54, cow infection probability = 0.06, human infection probability = 0.115).

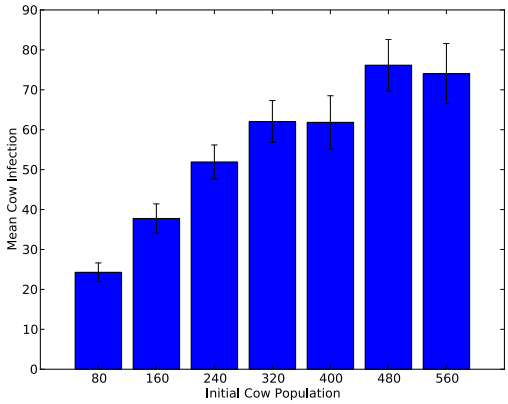

Figure 9: Mean cow infection (25 repeat runs) while varying the cow population. Reversed infection rate (as figure 8).

tion range in figure 5, which is 21-49, and changing the infection rate of humans between simulations appears to have had little effect, particularly as the shape of the plots is very similar. Although there are significantly fewer cow infections observed in figure 9 than figure 6, the data suggests that human to cattle population ratios and human infection numbers alone cannot be used to distinguish between two distinct infection rate scenarios. While only a simple simulation at this point, one can see how this may have some bearing in the real world, where knowledge of cow infection data would be very useful, but may not be widely available, or easy to collect.

Conclusion

This report has outlined a growing problem in sub-Saharan Africa: the re-emergence of sleeping sickness at epidemic levels during the 2000s, and the risk that two distinct forms of the disease, *T.b. rhodesiense* and *T.b. gambiense*, may no longer be spatially discrete in the near future. Combine this with inaccurate diagnosis techniques and scarcely available, outdated treatment, and there are urgent reasons to investigate new means of mitigating the disease. Agent-based modelling appears to be a tool which can aid this mitigation, particularly as a significant amount of focus has been given to controlling the spread and density of the disease vector, the tsetse fly. The results from our model do not yet constitute firm predictions as there are several key parameters on which we would like to get improved data, and we have so far used a spatially abstract simulation. However, the project has conveyed the potential for the technique to incorporate a degree of spatial complexity which would be extremely difficult in a purely traditional epidemiological susceptible-infected-susceptible (SIS) model.

While the future spread of sleeping sickness appears uncertain in the affected areas, the exploration of a number of potential scenarios with agent-based modelling appears to be a sensible step in the future study of the epidemiology of the disease. Improvements that we plan to make in the second iteration of this model include a move away from an abstract gridworld in favour of GIS-derived maps of real Ugandan landscapes, allowing the identification of habitats suitable for tsetse flies, suitable watering holes for cattle, and herding routes for farmers. This incorporation of detailed maps (especially at different times of year) will allow exploration of the connectivity between host and vector habitat, which may vary seasonally due to the drying out of lakes, and the associated modification of the tsetse fly risk zone.

In addition, more attention will be given to the possibilities of ABMs for the rich representation of human daily routine and decision-making on key aspects of behaviour that can affect disease transmission. Parameters to explore may include behaviour towards the sick, the distribution of daily tasks amongst the household, the availability/successful undertaking of preventative measures, and the decision to go to a market town despite the risk of infection.

Acknowledgements

SA was supported by the UK's Engineering and Physical Sciences Research Council via Southampton's Institute for Complex Systems Simulation and doctoral training centre. JN provided support in the construction of the simulation, the interpretation of results, and the formulation of this paper. Thanks to Prof. Peter Atkinson and Prof. Seth Bullock for their constructive feedback on the work.

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