**A Network Model of H5N1 Avian Influenza Transmission Dynamics in Domestic Cats**

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**Impacts**

- Natural occurrence of H5N1 influenza in cats combined with a cat reservoir of H5N1 in the United States could provide an environment for zoonotic disease spread to humans.
- A predictive network model, coupling cat–cat interactions with biological properties of the H5N1 virus, was developed to demonstrate possible H5N1 epidemic dynamics in a cat population.
- The roaming behaviour of cats significantly influenced epidemic dynamics, as demonstrated by different model simulations.

**Summary**

Naturally occurring cases of influenza in cats owing to the H5N1 strain have been reported in several countries. A cat reservoir of H5N1 in the United States could provide an environment for zoonotic disease spread to humans. This scenario was the impetus to develop a model to study potential transmission of H5N1 virus in domestic cats utilizing information on cat ownership and cat–cat interaction patterns, in addition to biological properties of the virus. The roaming behaviour of cats significantly influenced epidemic dynamics, as demonstrated by the simulation results from this model. A better understanding of the behaviour of domestic cats and the H5N1 influenza virus can be used to predict epidemic dynamics following the introduction of H5N1 virus into the United States and to develop effective strategies to prevent virus transmission to both cats and humans.
(Myers et al., 2007). The widespread occurrence of H5N1 in wild birds, high probability of contact between cats and wild birds, and the ability of H5N1 to undergo genetic changes naturally formed the impetus to develop an epidemiological model to study and predict the transmission of the virus should it enter the pet cat population in the United States.

**Rationale**

Models for the spread of infectious diseases (both epidemic and endemic) among human and animal populations are mostly deterministic in nature (Mollison, 1995). They generally employ difference equations to explain transmission dynamics of infectious agents assuming a fully mixed population in which each individual is equally likely to interact with another. This assumption however ignores the relevant connectivity structure that exists among individuals and is a poor representation of reality when such interactions are far from random (Anderson and May, 1992). Another approach would be to use interaction patterns of individuals in the population for epidemic modelling and analysis. This approach would be stochastic in nature and merges graph theory of mathematics and modern network science with epidemiology (Moreno and Vázquez, 2003; Newman, 2003; Barthelemey et al., 2004). Similar approaches have been applied to such diverse areas as the spread of viruses on the internet (Pastor-Satorras and Vespignani, 2001), analysis of protein interactions (Jeong et al., 2001) and the national air transportation network (DeLaurentis et al., 2008). While these models have been used in the study of epidemics and control strategies in human populations (Wasserman and Faust, 1994; Pourbohloul et al., 2005), none has addressed the interactions among domestic animals and how they relate to human exposures.

**Methods**

**Fully mixed model**

The widely employed fully mixed model assumes that, in a given population containing infected and uninfected members, all individuals have an equal likelihood of interacting with every other individual, resulting in a complete ‘mixing’ of individuals. Fully mixed models can be categorized into the susceptible-infective-removed (SIR) (e.g. the well-known Reed–Frost model, named after its proponents) and the susceptible-infective-susceptible (SIS) types (Bailey, 1975). As the name suggests, the SIR model is applicable when an individual is initially susceptible to an infection, becomes infected and finally recovers or dies, in either case being ‘removed’ from the population of susceptible individuals. A recovered individual is never susceptible again. Individuals infected with an influenza virus are typically considered to follow this pattern. The SIS model differs in that an infected individual who recovers is again susceptible to infection owing to a lapse in immunity.

**Network-based model**

In contrast to fully mixed models, network-based models incorporate the physical connectivity of individuals within a population. For the present application, this approach consisted of forming a network representing interactions among domestic cats and then applying the SIR model to analyse influenza infection dynamics within this network. The network was formed with individual cats as ‘nodes’ and geographic interactions between cats as ‘links’. The network modified the SIR model dynamics by restricting transmission only to the linked nodes.

**Contact network**

Influenza in a cat population was assumed to spread only by direct physical contact between cats. Therefore, a network of structured cat–cat interactions was constructed to provide the substrate for modelling the transmission of infection from one cat to another.

Nodal positions in the network were assigned randomly following a uniform distribution of the coordinates of cat households in a hypothetical geographic area (Fig. 1a). The cat density for any specific region in the United States can be estimated using human census data and pet domestic demographic data (cats per household) (United States Census Bureau, 2007). For this study, census data for Marion County, IN, (comprising Indianapolis) was used. A sample area from this region was estimated to have 62 cat households per square kilometre (~160 cat households per square mile).

Each node in the network represents one cat living in a household, and a link between two nodes represents the possibility of direct physical contact between two cats (Fig. 1b). As links in the network indicate direct contact between cats, the network is referred as ‘contact network.’ The cats were assumed to travel from their household within a circular region or ‘domain circle’, which defines the maximum distance a cat travels from its household. A link was formed between two nodes when their domain circles intersected. For all the analyses, a 1600-node contact network with a cat-household density of 62 cat households per square kilometre (~160 cat households per square mile) was used. This size was chosen as it was large enough to capture the dynamics of infection, yet of manageable computational complexity.

The contact network belongs to a class of networks known as random geometric graphs (RGG) whose general
connectivity characteristics have been studied (Dall and Christensen, 2002). Our interests with this type of network lay in its application to study the cat-infection dynamics in the context of H5N1 influenza virus, for which it is well suited.

Analysis of contact-network properties

Three different domain-circle radii were chosen [0.16 km (~0.1 mile), 0.81 km (~0.5 mile), and 1.61 km (~1.0 mile)] and their network topologies generated (Fig. 2). The statistical properties of these three networks were computed (Table 1; see Appendix for a glossary of terms). As anticipated, the number of links increased with the radius, as a cat wandering farther from its household interacts with more cats than one traversing closer distances. Hence, network density increased.

The degree distributions of the networks (Fig. 3) for the three radii indicated the type of topology present. The topology for the smallest radius was a sparse network, with only a handful of links. As the domain-circle radius was increased to 0.81 km (~0.5 mile), the topology shifted to resemble a random network with a typical node having a degree of about 5. At the largest radius, the mean and variance of the degree distribution increased (average degree of 19), indicating an increase in the diversity of cat–cat interactions. While a much larger radius would produce a network tending towards the theoretical limit of a fully connected network, such a case is unlikely in practice. The random network for the 0.81 km (~0.5 mile) radius was chosen as a baseline for all simulations and analyses.

Simulations from the Reed–Frost model and the network-based model were compared to evaluate the relative merits. Further, sensitivity analyses were performed to understand the influence of the domain-circle radius, number of initial infections and rate of infection transmission on infection dynamics.

Results and Sensitivity Analysis

Reed–Frost model versus network-based SIR model

A transmission rate of $P = 0.3$ and five initial infections entering at $t = 0$ were assumed (Fig. 4). The Reed–Frost model predicted about 1325 infections in the first-time step (~83% of the population) followed by a rapid ‘die-out’ within two time steps (Fig. 4a). A time step for this model would represent 3 days, the latent period from H5N1 infection to virus shedding in cats (Rimmelzwaan et al., 2006). The propagation of infection from this model was not affected by the structure of connectivity or the location of initially infected individuals. The network-based SIR simulation produced substantially different results: maximum number of infections at any given time step never exceeded seven, while the infection persisted for a much longer time (about 24 time steps compared with two time steps for the Reed–Frost model) (Fig. 4b). The result from the network-based model was a composite average of 500 simulations, as there was some

Fig. 1. Cat contact network for a representative area of 2.59 sq. km (~1.0 square mile) with 160 nodes and a density of 62 cat households per square kilometre (~160 cat households per sq. mile). (a) Distribution of cat households in a 2.59 sq. km (~1.0 square mile) area. Circle centres (●) represent the location of each household, and thus, the location of each cat belonging to that household. The cats were assumed to travel in a circular region from their household. Circles represent the distance each cat travels from its household, referred as ‘domain circles’; the domain circles were assumed to be 0.81 km (~0.5 mile) in radius for this figure. While there could be more than one cat in each household, only one cat was modelled from each household. (b) Contact network of cats in the specified region. ‘Node’ (●) represents the location of a cat while a ‘link’ (—) indicates direct physical contact between two cats (i.e. when the corresponding domain circles intersect). All coordinate distances were measured in kilometres.
variability in the probability of infection transmission for any two linked cats among individual runs. Essentially, the network topology at time $t_i$ was dependent on the state of the topology at $t_{i-1}$. Variation in each of the 500 individual trajectories was bounded and represented by the composite average. For identical initial conditions, the Reed–Frost model showed a rapid spread of infection while the network-based model indicated that this was an unlikely scenario.

Sensitivity analysis

Effect of domain-circle radius

A change in domain-circle radius for a cat had marked effect on the structure of contact network (Figs 2 and 3, Table 1). The dependence of infection spread on the radius of cat domain circle was examined for contact networks with three different radii (Fig. 5a). The network with the largest domain-circle radius [1.61 km (~1.0 mile)] had the highest average degree and density of links, and thus, the highest number of infections for any time step (~170 infections at time step 8). A possible explanation for this phenomenon would be that the network provided many relatively short pathways for the infection to quickly spread from one node to another, consequently increasing the number of infections. On the other hand, the contact network formed using a radius of 0.16 km (~0.1 mile) had a very low number of links and network density, i.e. there were insufficient routes for the infection to spread even with relatively high transmission rates. Consequently, infection died out rapidly [the peak number barely rose over the initial five infections and was ‘extinguished’ after three time steps as compared with about 15 time steps for 0.81 km (~0.5 mile) and 23 for 1.61 km (~1.0 mile)]. These sensitivities are manifestations of the nature of the contact network as an RGG; RGG can exhibit features of both regular lattices and random graphs. At low values of domain-circle radius, the
contact network resembled a lattice, and diseases do not spread effectively on lattices as infected individuals mostly interact only with other infectives (Watts, 2003). As the domain-circle radius was increased, the network topology resembled a random graph with higher probability of reaching the epidemic threshold.

The network formed using the intermediate radius of 0.81 km (~0.5 mile) represented a scenario where cats formed into relatively small groups or ‘clusters’ with a high average degree for the nodes within these clusters (large number of links between these nodes). However, these clusters had fewer links to the other clusters, reducing the average degree of the entire network, thereby reducing the number of routes for infection spread across the network. As a result, infection dynamics on this network was not easily understood solely on the basis of its average degree. This suggested that factors like transmission rate and the number and positions of initial infections may play a larger role. Furthermore, the clustering coefficient measured the local cohesiveness of a node in its neighbourhood. As the coefficient increased, so did the speed of transmission through the network.

Effect of number of initial infections

Three scenarios for the initial number of infections were studied – low (0.125% of the population, or two infections), moderate (0.3125%, or five infections) and high (0.625%, or 10 infections). Node positions of the initial infections were randomly selected and then fixed for all simulation runs in order to clarify the role of the number of initial infections on the dynamics of infection. For the sensitivity study, the network with a 0.81-km (~0.5-mile) domain-circle radius was used with a constant transmission rate of 0.3 (Fig. 5b). Results were generated for infections with two, five and 10 initial infections, averaged over 200 simulations. The results showed that increasing the number of initial infections increased both the maximum number of infections at a time step and the total number of infections and the ‘life’ of infection. Although this could be anticipated even without the network-based model, the Reed–Frost model was incapable of predicting these results (Fig. 4).

Effect of infection transmission rate

A sensitivity analysis was conducted for infection spread with regard to the infection transmission rate. The contact network with 0.81 km (~0.5 mile) domain-circle radius and five initial infections (0.3125% of the population) was utilized (Fig. 5c). As the actual transmission rate of H5N1 influenza was unknown, the rates explored spanned the range of values for other viral diseases. The results indicated that even with a low transmission rate ($P = 0.01$), the infection persisted for at least three time steps before declining as opposed to the one time step of Reed–Frost model even after a higher transmission rate
was used (Fig. 4). In the absence of field or laboratory data, this observation suggested the dependence of H5N1 viral transmission between cats on population structure and interactions between individuals.

**Effect of infection latency period**

The infection spread was simulated for three latency periods of the infection. The contact network with 0.81 km (~0.5 mile) domain-circle radius with a transmission rate of 0.3 was utilized (Fig. 5d). In addition, the number of initial infections was varied as 2, 5 and 10. The results generated were an average of 200 simulations. The results indicated that the rate of infection spread was higher for smaller latency periods (shown by a steeper slope of the curves for a latency period of 1 day), but the infection persisted for longer time for larger latency periods (almost 120 days for a latency period of 5 days as against 20 and 60 days for latency periods of 1 and 2 days, respectively). These results were generated to study the infection dynamics in lieu of varying laboratory data on the exact latency period of H5N1 infection in cats.

**Discussion**

The model developed in this study was based on certain important assumptions: a randomized network model was utilized as the main construct to evaluate H5N1 virus transmission in the cat contact network; dynamics of the network structure (e.g. addition and removal of links) were not accounted during simulation; the infection spread from cat to cat via direct contact; the cats’ roaming range spanned only within a circular region from their household (domain circle); the links in the network were unweighted, hence the extent of overlap between domain circles was not accounted.

These assumptions were necessary as very little is known about the clinical features and dynamics of H5N1 infection in cats in a natural setting. While these assumptions likely simplify the (largely unknown) real-world population dynamics, the model nevertheless is still useful for understanding the sensitivity to transmission characteristics and the role of population configurations in the spread of infections. Similar to other epidemiological models, the incubation period or time-to-infectivity for this or another disease is handled in the network model as a time ‘step’. For diseases with shorter incubation times, a single time step represents as a shorter calendar period and a greater number of steps will occur in a defined calendar period, e.g. 30 days. Improvements in the realism of the model are expected as more information becomes available from the field. This includes infusing more realistic scenarios and possibly other network models.
While the network was developed for a hypothetical cat-household population, it could easily be applied to any region of interest using human census data and pet demographic data for that region. This was another important reason for the present study: the easy availability of data on pet demographics, pet ownership, pet care etc. in the United States made the creation of a more realistic epidemiological model than the Reed–Frost model. Further realism could be enabled by information on actual cat movements over time, allowing for the dynamics of network structure to be studied simultaneously with disease dynamics. The present use of a fixed network in which the links persist as the disease progresses in the population represents a worse case. Such adaptability and flexibility afforded by this approach makes it suitable to develop intervention and prevention strategies for a wide variety of diseases. For example, using the present study, when an infection is

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**Fig. 5.** Sensitivity analysis of infection dynamics using a network-based model with respect to domain-circle radius (a), number of initial infections (b), infection transmission rate (c) and latency period of infection (d). (a) Simulation results for 0.16 km (~0.1 mile), 0.81 km (~0.5 mile) and 1.61 km (~1.0 mile) domain-circle radii with five initial infections and transmission rate $P = 0.3$. (b) Simulation results for two, five and 10 initial infections with 0.81 km (~0.5 mile) domain-circle radius and transmission rate $P = 0.3$. (c) Simulation results for three transmission rates with 0.81 km (~0.5 mile) domain-circle radius and five initial infections: $P = 0.01$, 0.1 and 0.3. Each time step represented a latent period of 3 days. (d) Simulation results for two, five and 10 initial infections with 0.81 km (~0.5 mile) domain-circle radius and transmission rate $P = 0.3$ for three different latency periods of infection: one, three and five days. All results were an average of 200 simulations for a population of 1600 cats.
detected, the health authorities can be advised on the dynamics of the infection and suitable action can be planned: isolate the infected cats or, in the worst case, euthanize them and all cats that were in contact with them. Further, additional co-factors meriting further investigation in future studies include immunodeficiency or immunocompromise, e.g. feline immunodeficiency virus (FIV) and/or feline leukemia virus (FeLV) infection, in certain cats within the population.

Although infection dynamics depend on both the number of initial infections and their position in the network, only the former was investigated. A sensitivity analysis using the latter on infection spread would further the understanding of infection characteristics and enhance the model. Owing to their highly mobile behaviour, modelling a feral cat population along with domestic cats poses a major challenge. While feral cats can be modelled as ‘mobile’ nodes in the contact network, lack of sufficient data on their behaviour currently restricts construction of such models.

Conclusions

While the human population in the United States is unlikely to directly interact with infected birds and poultry, domestic cats could provide a pathway for H5N1 influenza from birds to humans. The commonly used SIR model (Reed–Frost model) assumes a fully mixed population which is a poor representation of realistic interactions among domestic cats. To better understand the dynamics of H5N1 influenza infection in cats, the Reed–Frost model was ‘superimposed’ on the cat population network (contact network). The network-based model yielded insights not provided by the SIR model. For the same population configuration and infection conditions, the network-based model suggested that infection persisted for longer periods in the population than for the Reed–Frost model, although the total number of infections was less compared with the Reed–Frost model.

The dependence of infection dynamics on connectivity patterns among cats was evaluated by varying the radius of domain circles, number of initial infections and rate of infection transmission. The results indicated that the structure of the contact network was important in understanding infection dynamics, and that the domain-circle radius was an important determinant of network behaviour.

References


## Appendix

### Glossary of Network Theory Terminology

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<th>Network property</th>
<th>Equation and sample calculation</th>
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<td>Degree (<strong>k</strong>)</td>
<td>Number of links connected to a node.</td>
</tr>
<tr>
<td>Network density</td>
<td>Ratio of the actual number of links to the number of all possible connections; it is dimensionless.</td>
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**Sample network**

![Sample network](image)

\[ k_A = 3 \]

Network density = 5/6

Degree distribution: quantifies the fraction of nodes with \(k\) links. Alternatively, it can depict the actual number of nodes instead of the fraction.

Degree distribution of sample network

![Degree distribution](image)

\[ C_i = \frac{\text{number of triangles connected to node } i}{\text{number of triples centered on node } i} \]

e.g.: \(C_A = 2/3; C_B = 1/1 = 1\)

\[ l = \frac{1}{n(n-1)} \sum_{i<j} l_{ij} \]

where, \(l_{ij}\) = length of shortest path between nodes \(i\) and \(j\). For the sample network: \(l = 7/6\)

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Appendix

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<th>Network property</th>
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<td>Typical degree distributions of a random network and a near-ordered lattice*</td>
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*All nodes in an ordered lattice have the same degree. As a result, the degree distribution for such a network would be a single point. The typical degree distribution shown represents an approximate ordered lattice, wherein almost all nodes have the same degree while a few nodes have a smaller and/or larger degree, leading to the spread in the degree distribution.