MEDINFO 2010
C. Safran et al. (Eds.)
IOS Press, 2010

doi:10.3233/978-1-60750-588-4-457

Towards A Multi-Level Game Model for Influenza Epidemics

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Abstract

Although game theory has been first invented to reason with economic scenarios with rational agents, it has since been extended into many other fields including biological and medical sciences. In this paper we propose to model the interactions between virus and human in an influenza epidemic in a two player, adversarial game scenario with multiple levels of abstraction. As conventional game representations are inadequate in this complex problem domain, we propose Object Oriented Multi-Agent Influence Diagrams (OO-MAID), a novel graphical representation for multi-level games, which takes advantage of both organizational information and probabilistic independence in the problem domain. The OO-MAID representation can be readily applied in similar medical situations exhibiting hierarchical and probabilistic independent characteristics. We demonstrate the feasibility of this novel approach with sample models in the domain.

Keywords:

Game theory, Influenza, Knowledge representation

Introduction

Influenza or "flu" is one of the most common diseases found in both developed and developing countries, causing tens of thousands of deaths and huge financial losses each year. The damages are even greater in the case of a flu epidemic, e.g., the recent spread of H1N1 virus. While it is one of the most studied diseases, we have yet to be able to effectively deploy various management strategies to control the spread of seasonal or epidemic influenza.

The current modeling techniques for influenza can be classified into three categories: deterministic dynamics functions [1,2], complex network theory [3,4], and stimulation based on mathematical spreading models and population distribution [5]. Most of these approaches assume fixed virus characteristics, known consequences of policies, and/or unbound resources, which are often unrealistic. In addition, most of the research emphasizes on the epidemiological impact, without details on lower level interactions, such as clinical and microscopic interactions. In this paper, we propose to model the holistic interactions between influenza viruses and human populations in a game theoretic framework.

Game theory provides a mathematical framework for determining what strategies are, according to pre-defined utilities, most beneficial for agents interacting with each other in a partially observed environment. While it was first proposed to analyze rational behavior in economics, its adaptation in the biological domains, i.e., evolutionary game theory [6], enables reasoning with populations under revolutionary pressure, instead of rational agents. In this context, players are individuals in a large population engaging in a series of independent game play. Strategies may be any phenotypic characteristics, such as tail length in certain bird species; or behaviors, such as the instinct of defending territory. Payoffs, or utilities, for the players are additional or reduced "fitness" a player receives after each game play, using some set of strategies. The concept of Nash Equilibrium is replaced by a similar concept of revolutionary stability, and the associated concept Evolutionary Stable Strategies, defined as the set of strategies that, under the current circumstances, cannot be "invaded" by mutant strategies [6].

Modeling Influenza as a Game Scenario

In any game, there are three essential components: players, strategies and payoffs. In addition, there may exist random variables in the problem domain that are beyond the control of the players, who may however observe some of their values. In this section we identify the three components as well as possible random factors in the proposed influenza game scenario, and examine potential challenges and issues in modeling and reasoning in the game.

As the interactions between influenza virus and human society is a complicated process involving a large number of random variables in multiple levels of abstraction, we divide the possible factors and interactions into three levels of different granularities: microscopic, clinical, and epidemiological. In all three levels, the players would be influenza virus and human. The strategies, utilities and other factors, however, may differ.

At the microscopic level, the infection of influenza in a human host is the interactions between influenza virus and human body cells. In general, systematic infection of a host by influenza virus depends on factors [7,8] such as: matching hemagglutinin receptors on the host cell surfaces, availability of protease for virus post-entry cleavage, cleavage properties of virus surface protein precursor (the above three factors facilitate the entry of virus into a host cell, in a process called endocytosis), suitability of the host cell for viral replication, and release of replicated viruses into bloodstream for further infection, which is related to virus neuraminidase surface protein. The immune system responds to virus infection by two mechanisms: innate response, which respond to infections in general; and adaptive immune response, which keys specifically to some particular virus strain after an infection. The acquired adaptive immune response against a specific influenza virus strain is temporary, waning with time. In response to immune anti-viral mechanisms, influenza virus may evolve to acquire mutant genes that can suppress the immune response [9].

In a game model for the microscopic level, strategies for player virus are characteristics such as HA and NA configurations, while strategies for human player are characteristics such as immune responses. The payoff at this level is the extent of the infections, which can be modeled as average virus count in the infected host.

At the clinical level, we consider medical intervention in influencing infection cases. Treatments for infected cases usually aim for symptom relief and do not directly target viruses, although anti-viral treatments may be necessary in immno-compromised patients. Therefore, for the population at large, the most important step taken during a flu season is prevention. Clinical prevention of influenza can be divided into two categories: vaccination and prophylactic use of anti-viral drugs. Vaccination is highly effective when the vaccine matches with the circulating virus strand. However, the fast mutation of influenza virus means that there is usually a genetic drift of the circulating virus strand. Prophylaxis with anti-viral drugs is less sensitive to genetic drift; still, drug resistance may arise from its usage. We show a sample game models the interaction in Table 1.

Table 1- Sample game model in the clinical level

	Drug-resistant	Non-resistant
Anti-viral	$c\beta$	$(1-\theta)\beta$
Vaccination	$c(1-\lambda)\beta$	$(1-\lambda)\beta$

Let β be the baseline transmissibility of influenza virus, c be the factor of change in transmissibility after drug-resistant mutation, λ be the efficacy of the vaccine, and θ be the efficacy of prophylaxis. The human player may choose using anti-viral prophylaxis or vaccination. And virus may mutate to become drug-resistant. The four possible scenarios are:

1) Anti-viral prophylaxis is chosen; virus strain mutates to become drug-resistant. In this case, the prophylaxis would be ineffective. However, studies also show that mutated drug-resistant virus strains have lower transmissibility than wild-type virus strains [5]. Therefore, the transmissibility in this case is reduced to $c\beta$. c may be as low as 10% [5].

2) Anti-viral prophylaxis is chosen and virus strain does not mutate. In this case the transmissibility is reduced by effective prophylaxis measure. The payoff in terms of transmissibility is $(1-\theta)\beta$. Currently θ (for neuraminidase inhibitors) is around 70% [10].

3) Vaccination is chosen; virus strain mutates to become drug-resistant. The payoff as transmissibility is $c(1-\lambda)\beta$.

4) Vaccination is chosen and virus strain does not mutate. The payoff in this case is $(1-\lambda)\beta$.

This simple model may help to explain the low level of emerging drug-resistant strains <1% [11], as strategy “non-resistant” dominates “drug-resistant” for virus player. A complete model would include many more factors and provide a clearer picture of the interactions.

At the epidemiological level, the factors relevant to the extent and severity of an influenza epidemic are well studied. Some of these factors are: transmissibility, a characteristic of the virus strain, which determines how easily the virus can spread in a population; infectious period, the duration that an infected case continues virus shedding (Combined, transmissibility and infectious period can be modeled as a function of infectiousness over time.); regeneration number, which is defined as the number of secondary infections generated from a primary infection case; contact rate, the number of people a person gets into contact in a fixed time unit; quarantine efficacy, which can be defined as either the portion of infected people being quarantined, or the degree that their infectiousness is reduced.

At this level, payoff for the human player may be defined as a cost function consisting of disease management cost and extent of virus infection in the population. For the virus player, the payoff may be a similar function of the extent of infection.

From the proposed modeling approach, we observe that a complete game model consisting of all three levels and all the important factors is a very complex scenario. Therefore, neither of the traditional game representations, including the normal form, which is a table listing payoffs according to different combination of strategies; and the extensive form, which is a game tree with payoffs at the leaf nodes, is feasible. They both suffer from the curse of dimensionality and omit potentially important structural information in the problem domain. A new game representation is needed to address the characteristics in this specific problem domain.

Graphic Representation for Multi-Level Games

A related work that addresses part of the complexity is the Multi-Level Games representation proposed by Hausken [12]. It provides a framework for analyzing game situations where there are different levels of organization. However, at each level, the strategies and payoffs in the sub-game are still represented in either normal or extensive forms. Therefore it is unable to take advantage of any locality features that often exist in complex game domain such as the proposed influenza game scenario.

A representation that does utilize potential probabilistic independencies in the problem domain is the Multi-Agent Influence Diagram (MAID) [13], a probabilistic graphical game representations. It takes advantages of the Influence

Diagrams' ability to represent structural dependencies in the problem domain. However, when dealing with problem domains with multiple levels of organization, the MAID approach requires all hierarchies to be flattened into a single level structure. While this is theoretically possible, it is often inefficient or even intractable when the number of players or levels of organizations are large.

While neither approach alone can satisfy the requirements for the proposed influenza game scenario, a combination of the two addresses both organization and probabilistic independencies issues. Therefore, we propose the Object-oriented Multi-Agent Influence Diagrams (OO-MAID), which is based on the multi-level game concept and the MAID formulation. An OO-MAID is probabilistic graph segment that models an uncertain game situation with multiple levels and multiple agents. Each segment has a set of well defined input and output, which appear as chance nodes in other graphs. In the next section, we formally describe the syntax and semantics of OO-MAID.

Definitions and Semantics

We base our definition of multi-level games on an adaptation of Hausken's work [12]. In this formalism, a multi-level game consists of three components – multi-Level game structure, multi-level game form and finally, multi-level game. All three components are extended in the OO-MAID representation as follows:

Multi-Level game structure, which is a recursively defined directed graph $G = (N, A)$, where N is a set of nodes and A is a set of arcs. Three types of nodes are allowed in set N - chance nodes, decision nodes and utility nodes. We assume that there exists one and only one utility node for each player at each level. The outermost graph (level 0) is labeled G^0, which organizes players. Player A^{L}_{i} at level L plays the game with other players at the same level. In the proposed influenza game scenario, the game structure represents the factors in the whole problem domain, with decision nodes denoting strategies, chance nodes denoting random variables and utility nodes denoting payoffs. The arcs between the nodes share the established semantic meaning in the Influence Diagrams, namely, an arc pointing into a chance node or utility node represents conditional dependence, while an arc point to a decision node represents information availability.

Multi-Level game form, which is a combination of multi-game structure and feasible (pure) strategies S. Therefore, player A^{L}_{i} has strategy domain S^{L}_{i}. This corresponds to the set of possible values for the decision nodes at level L. A decision rule for node D is a function that maps each instantiation pa of Pa(D) (set of parents of D) into a probability distribution. For agent A^{L}_{i} at level L, the assignment of a decision rule to each decision node is called a strategy. In the influenza game scenario, S denotes the possible "strategies" that the virus or the human player may use in the game play in a certain level. Each player may choose to use single strategy or a set of different strategies with different probabilities.

Multi-Level game, which is a multi-game form together with defined payoff structure. In Hausken's definition, each player's (at any arbitrary level) payoff consists of two components: a "within-group" payoff, coming from the sub-game at the player's level, and a fraction of payoff distributed downwards from higher level games. Here, we adopt a simplified case where only "within-group" payoffs are considered. Payoff in the influenza game scenario differs between levels, e.g., for the human player, the payoff in the clinical level may be an individual's well-being after being infected with flu virus, but the in the epidemiological level, the payoff could be a cost function involving the studied population.

With our definition, the basis of modeling a multi-level game starts with building the game structure, which is a directed acyclic graph consisting of basic nodes and complex nodes. There are three types of basic nodes, the chance nodes, decision nodes, and utility nodes, with conditional probabilistic table (CPT), decision rule and utility function, respectively. A complex node is a self-contained OO-MAID segment that models a sub-game in the problem domain and has a set of input nodes and output nodes. Each agent is represented by its corresponding decision nodes in the graph, and may have multiple utility nodes. The overall utility for the agent is simply the summation of all his utility nodes U_{a}^{L} at level L.

An example of a simple multi-level game segment is given in Figure 1, which shows a simplified influenza game model at the clinical level. M denotes the game play in microscopic level, which is an OO-MAID segment contained in the graph. The output of M is observed by both players at the clinical level and has an effect on their utilities. We further define the "output" of an OO-MAID segment below.

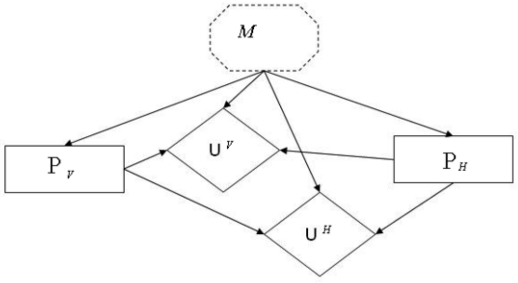

Figure 1- A sample OO-MAID model

We consider an OO-MAID segment to be a stochastic function that converts a set of input to a set of output variables. It is recursively defined as follows: for each complex OO-MAID node X^L at game level L, it consists of

Input: a set of chance nodes or decision nodes in(X^L) defined in X^{L-1}, i.e. for node v in in(X^L), Pa(v) are in graph X^{L-1}. However, they may have children nodes in graph X^L. In addition, v is considered chance nodes in graph X^L.

Output: strategy profile σ, expected payoff EU(X), output chance nodes Out(X^L). The output nodes are defined in X^L, and may be decision nodes or utility nodes in X^L. But they are treated as chance nodes in X^{L-1}.

To map the distribution of input node set to distributions of output nodes, a complex OO-MAID node is itself a complete OO-MAID which may contain basic nodes and complex nodes.

A complex OO-MAID node that contains only basic nodes is simply a MAID. Its correctness is established from the work on Multi-Agent Inference Diagrams. Between levels, we show below that nodes inside a complex are independent of nodes outside, give the input and output nodes set.

Let X^{L-1} be a complex OO-MAID node containing complex node X^L, we prove that node set N^L in X^L are independent of node set $N^{L-1} - N^L$, given the input/output set of X^L.

Proof: First we consider node types in the input/output set of X^L. In the previous section, we have defined the decision rule to be a function that maps each instantiation of D's parents into a probability distribution for node D, therefore it has the same form as a conditional probability distribution. For utility nodes, the utility function also may be considered conditional probability distribution with probabilities of 1 and 0. Therefore, we may treat both decision nodes and utility nodes in similar ways to chance nodes.

Now, consider any path between X^L and $X^{L-1} - X^L$, which contains adjacent nodes n_1 in X^L and n_2 in $X^{L-1} - X^L$. There are two possibilities for the arc direction between n_1 and n_2. If there is an edge from n_1 to n_2, then n_1 is in the output set of X^L. And n_1 does not have converging arrows centered on itself. Applying Baye's Balls rule [15], the path is blocked when conditioning on n_1.

If there is an edge from n_2 to n_1, then n_2 is in the input set of X^L. And n_2 does not have converging arrows. The path is blocked when conditioning on n_2.

With the definition we may now extend the complex node in Figure 1. An example is shown in Figure 2. This is a segment that has one input node and two output nodes.

Computing Nash Equilibrium

The main computation task in any game form is the calculation of the Nash equilibrium. In multi-level games, the definition of the Nash equilibrium can be tricky considering the players and payoffs in all the sub-games. A definition of multilevel Nash Equilibrium is given in [12]. In our proposal, because of the simplification of the "within group" payoff structure and the probabilistic independence proved in previous section, we can use the conventional definition of a single player achieving no benefit from changing strategy, given the strategy of the other players being fixed.

In the single level representation of MAID, the concept of strategy relevance and *s-reachability* is central in the computation of Nash equilibrium [13]. These two concepts both hold for the OO-MAID framework. By definition of the OO-MAID complex node, which maps each instantiated set of pa for Pa(X), the mapping then has the same form of conditional probabilistic distribution. Therefore a complex node can be collapsed into the output node set, with pre-computed distribution function. In addition, as the output nodes are all considered chance nodes in higher level graph, they do not change the topological order of the decision nodes in the higher level.

For games consisting of only basic nodes, e.g., the microscopic level, we may break up the problem domain according to strategic relevance, the sub-graph, consisting of decision nodes that are strategically relevant (denoted as a component graph), is then converted to a regular game tree and standard game solver may be applied [13]. As finding a Nash Equilibrium for a game tree is super-linear, this reduces the computational time. A straightforward "divide and conquer" algorithm and an approximate algorithm have been proposed [14].

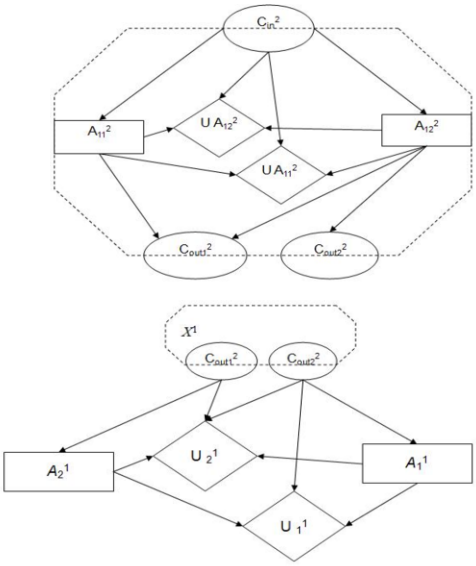

Figure 2- The expanded graph for X' in Figure 1, and an encapsulated X' viewed from the higher level.

For games consisting of both basic and complex nodes, we propose a recursive inference algorithm, enabled by probabilistic independence of a complex OO-MAID node given its input and output node set. The algorithm below makes use of the algorithm proposed for MAID [14], denoted as ComputeMAID. An extra step at the end of ComputeMAID is added to return updated probability distribution of the nodes defined in the output node set of a complex OO-MAID node, after applying the strategy profile calculated from ComputeMAID.

Algorithm

```
ComputeOO-MAID (OO-MAID $X$)
    If $X$ contains only basic nodes
        ComputeMAID ($X$)
    Else
        For each complex node $X_i$' in $X$
            ComputeOO-MAID ($X_i$')
            Update distributions of output node in $X_i$'
        // $X$ now contains only basic nodes
        ComputeMAID ($X$)
```

Comparing OO-MAID with MAID, while both take advantage of the "divide and conquer" concept, the built-in conditional independent complex nodes in OO-MAID simplify the topological ordering process by encapsulating decision nodes from sub-games, and also enables pre-computation.

Towards A Complete Influenza Game Scenario

With the introduction of OO-MAID, each level in the proposed influenza game can be modeled in one or more OO-MAID segments, with the graphical representation at each level able to utilize any structural independencies among the random variables at that level.

A complete model with all three levels and most of the relevant factors is currently in progress. Firstly the three different levels will be constructed separately, each with its own in-level strategy set, random variable set and payoff function. The connection between levels will be made possible with relevant input/output nodes. For example, a "strategy" chosen by the virus in the microscopic level, the extent of mutation, or deviation from prevailing strain, will be reflected as averaged virulence in the general population in the clinical level. Further domain knowledge will be elicited in later stages of the model construction.

Conclusion

In this paper we show the potential and feasibility of modeling an influenza epidemic as a game situation involving influenza virus and human society. As the problem domain is highly complex with multiple levels of granularities and large number of random variables in each level, the conventional game representations are inadequate in this situation. To address both the "multiple levels" and "potential structural independency" nature of the scenario, we propose OO-MAID, a novel probabilistic graphical representation for multi-level games. This framework has the potential of taking advantages of possible conditional independences as well as organizational hierarchies in a problem domain. It is based on single level probabilistic graphical game representations, with extensions to allow modeling of a game scenario in different levels of abstraction. Although it's motivated from the influenza game scenario, it is a general game representation that may be applied to other program domains exhibiting both characteristics.

To complete the proposed game model, further domain knowledge on influenza epidemics must be solicited from healthcare experts.

Future work also includes extension of the payoff definition. Currently we only consider localized payoff (or utility) for each agent within his own game level. While this greatly simplifies computation and probabilistic independence analysis, it is a very restricted assumption that may not be satisfied in many real life complex game scenarios. In the influenza game scenario, for example, an individual's payoff is also associated with the payoff in the general population, as one of the factors, percentage of the population infected, greatly influences an individual's chance of being infected.

Acknowledgement

This work was partially supported by Academic Research Council grant R252-000-327-112 and grant R-252-000-309-112 from the Ministry of Education in Singapore.

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