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PARTICLE FILTERING IN A SEIRV SIMULATION MODEL OF H1N1 INFLUENZA

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ABSTRACT

Numerous studies have been conducted using simulation models to predict the epidemiological spread of H1N1 and understand intervention trade-offs. However, existing models are generally not very accurate in H1N1 model predictions. In this report, we examine the impact of using particle filtering in a compartmental SEIRV (susceptible, exposed, infected, recovered and vaccinated) model which considers the impact of vaccination on the outbreak in the province of Manitoba. For the purpose of evaluating the performance of the particle filtering method, this work further compares the ability of particle filtering and traditional calibration to anticipate the evolution of the outbreak. Preliminary simulated results indicate that the particle filtering approach outperforms the calibration method in terms of the discrepancy between empirical data and model data.

1 INTRODUCTION

The emergence and subsequent spread of pandemic H1N1 presents several challenges to public health professionals and policy makers, including as planning vaccination schedules and clinical resource

constraints. Epidemiological time series by themselves fail offer much assistance for these tasks. This reflects the fact that they are not only extremely noisy, but – more importantly – fail to provide insight into counterfactuals, such as how an outbreak will play out in the absence of further intervention. Dynamic modeling for outbreak analysis plays a significant role in the planning of the public health reaction to infectious disease outbreaks. Statistical and mathematical models aid in understanding the role of social distancing measures such as school closure and in evaluating the value of the vaccination programs and establishing priorities to target populations for vaccination, prioritizing data collection, addressing application of antiviral therapy and in easing collaboration between policy-makers and analysts. One of the most essential planning tools is to anticipate outbreak progression in light of empirical time series data. While models offer strong benefits, there is the inevitable need to omit or approximate some processes and factors. Inevitably – and particularly for fast-breaking outbreaks of emerging pathogens – this leads to simplification and misestimation of the dynamic models. These shortcomings – together with stochastic transitions associated with human and economic behavior – inevitably lead the model forecasts to diverge from empirical data (Lee and Shin 2014, Ong et al. 2010, Chyi 2011).

This quandary has attracted many and diverse studies from the research community. Seasonal influenza viruses, including H1N1, cause 3 to 5 million cases resulting severe illness each year with between 250,000 and 500,000 deaths (according to the WHO reports). Each year the vaccine is modified to include currently circulating strains thought to present the greatest risk to public health. Antiviral drugs can also be used to limit the severity of complications and risk of death. However, the virus is constantly changing and is an ongoing source of uncertainty in public health. Simulation modeling is an important tool in predicting the behavior of the virus and planning intervention strategies. Hence, (Manchanda et al. 2004) proposed an immune system mathematical modeling methodology that focuses on the explanation of variations in influenza kinetics caused by virus strains in mice. Using ordinary differential equations, the authors' model considers several variables and parameters to conduct sensitivity and identifiability analysis. The model is able to predict the outcome of infection, and simulate and interpret the cause of outcomes. However, the work offers little contribution at the epidemiological level, such as with regards to the impact of vaccination, and the spread of infection with exposure to the virus and so on. Furthermore, the need to understand influenza H1N1's transmission motivated by (Chao et al. 2014) to model a colony of agents representing virtual humans termed the "artificial community". The authors defined connections between the agents at three ordinal levels, such that the agents can be described as having strong ties, ordinary ties, and weak ties with each other. By adopting the SEIR model, the authors seek to pay attention to critical flow constraints, such as the natural history characterized by a latent period and treatment-receiving period. The authors, however, did not compare the model results with any empirical data and the sensitivity analysis is not sufficiently detailed to guarantee reproducibility of the model outcome. Moreover, the global spread of the H1N1 virus caught the attention of (Shubin et al. 2013) who studied the impact of the outbreak of H1N1 in Finland. The work considered prior and posterior distributions factors such as severity. The model predictions show that the severity of the outbreak in the second season is almost half of the first epidemic. Although the authors in this case looked into the effect of vaccination, their primary model is the susceptible, infective, and recovered (SIR) model, rather than focusing on secondary infection risks. Also, (Pongsumpun and Tang 2014) have seen the need to study the impact of H1N1 virus transmission using the SEIQR (susceptible, exposed, infected, quarantine, and recovered) model. The proposed model also took into account the incidents of death in the population and the impact of repetitive contacts. The work showed that when the repetitive contacts increase, the number of susceptible people decreases. The authors, however, did not consider vaccination and its impact on the population. Particularly for diseases with nonspecific symptoms, several factors obstruct the tracing and prediction of emerging epidemics: the disconnect between transparent epidemic dynamics and what is discernible from noisy and incomplete surveillance data and the imperfectly observed system. Also, behavior changes compound this through altering both true dynamics and

reporting patterns. (Birrell et al. 2011), seek to unravel these effects to resolve the hidden dynamics of the 2009 influenza A/H1N1 pandemic in London. To disclose significant changes in contact patterns and health-seeking behavior, they embed an age-structured model into a Bayesian synthesis of multiple evidence sources. As the result, this approach is capable of real-time learning about model parameters during the epidemic progress, and provides a sequence of nested projections to reflect the epidemic. (Conway et al. 2009) in their model, represented the Greater Vancouver Regional District and surrounding residential areas with a population of 2 million and investigated the effect of timing of different vaccination strategies in estimating the transmission of the pandemic H1N1. With the development of a compartmental susceptible-infected-recovered (SIR)-type epidemic model, different distribution strategies were initiated. For each vaccination strategy, the effect of varying the vaccination strategy under various baseline transmission parameter values were tested. It was found that the model output was consistent with provincial surveillance data and that vaccine efficacy had an important impact on depleting the size of the susceptible population and consequently reducing the outbreak size. Their work could further be improved by considering the addition of a vaccination stock in their compartmental model. (Tuite et al. 2010) developed a compartmental model of influenza transmission in the Canadian population and sought to obtain the optimal strategy for prioritization of vaccine distribution in order to minimize morbidity and mortality rates.

To yield a more accurate consensus estimate (Osgood et al. 2014) used sequential Monte Carlo methods in the form of particle filtering to combine intuitions from dynamic models containing systematic errors and noisy empirical data, and to aid in parameter estimation. To demonstrate the advantages from particle filtering, parameters and variables in an aggregate systematically biased SEIR model, they compared particle filtering against synthetic ground truth produced by an agent-based model. In this work, in addition to introducing a model of H1N1 in which vaccinated percentage has been considered, we use clinical data from the Midwestern Canadian province of Manitoba for H1N1 pandemic 2009 to evaluate the application of particle filtering approach, using a temporally-based cross-validation approach. Specifically, we compare the performance of the particle filter with a traditional calibration method in anticipating the future evolution of counts of reported cases.

2 MOTIVATION FOR CALIBRATION AND PARTICLE FILTERING

For emergent conditions such as H1N1, there is an acute need to plan and mathematical modeling through outbreak analysis plays a significant role in the planning. The corresponding parameter values, the current situation, and even the natural history of the infection, are frequently unknown or poorly known in the early stages of an emergent condition. In this context, a model that supports a wide range of interpretations is particularly valuable. In our model we sought to obtain empirical estimates for various parameters, for example, Contacts per week multiplied by Probability of Infection Transmission Given Exposure ($c\beta$), Mean Latent Time (τ), Fraction Reported Incidence (f), Fraction Initially Susceptible, Fraction Initially Exposed, Fraction Initially Infective and Fraction Initially Recovered by calibrating the model to the empirical data obtained by Manitoba Health, Healthy Living and Seniors. To predict shorter-term projection of the existing conditions or intervention scenarios, well-calibrated dynamic models are frequently accurate, but for longer term projections they tend to diverge from empirical patterns and also, generally, there exist a shortage of reliable and automated means of keeping current with the latest in empirical data. Particle Filtering was introduced as a method that builds on well-studied statistical techniques to join together dynamic models and empirical data, while decreasing the inherent weakness of both. While calibration processes often require much time and typically entail manual oversight and intervention, the particle filtering process was executed in considerable less time and proved to be more accurate in model predictions. Particle filtering however, has been applied to comparatively few previous applications in the public health area, specifically in predicting infectious diseases.

3 SCHEME OF THE MODEL

We present the formulation of a compartmental model, which includes Susceptible, Exposed, Infectious, Recovered and Vaccinated stocks (SEIRV). We present here a comparison between the applications of a particle filter and a calibration method for a System Dynamics transmission model for H1N1 influenza, and then evaluate the performance of that particle filter compared to that of traditional calibration when operating using empirical data from Manitoba Health, Healthy Living and Seniors.

3.1 Empirical Data

The empirical data obtained from Manitoba Health, Healthy Living and Seniors indicated weekly confirmed cases of pandemic H1N1 and vaccine delivery rates for the period of October 6th ,2009-January 18th ,2010.

3.2 Dynamic Model

We describe here our dynamic model to be used with the particle filter and calibration. Figure 1 demonstrates all stocks, flows and parameters.

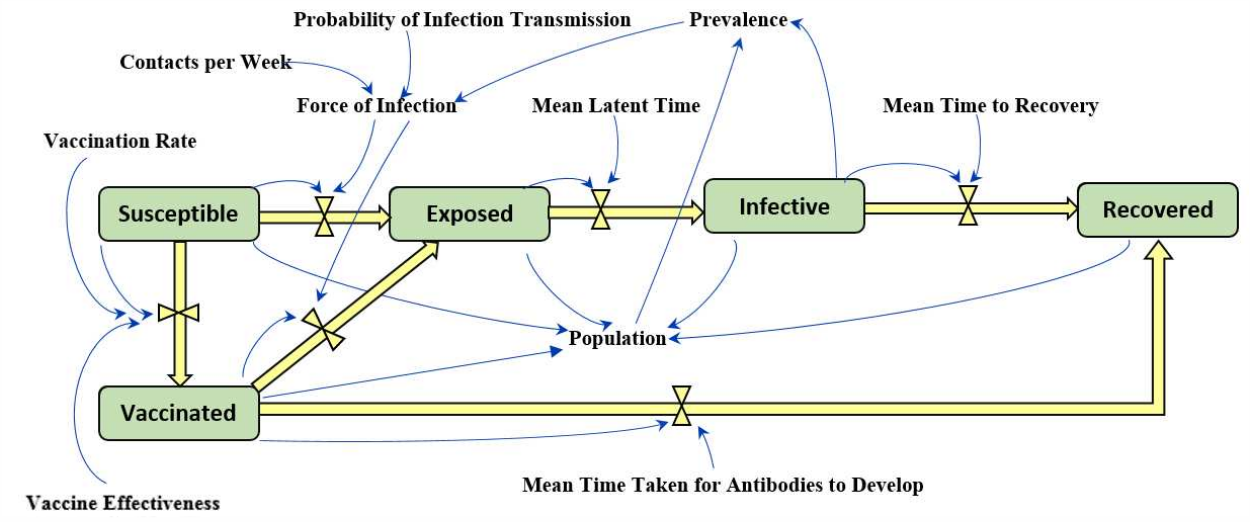

Figure 1: System Dynamics Model.

The aggregate compartmental state equations for the model are given as follows:

$$\dot{S} = -c\beta \frac{I}{S+E+I+R+V} S - abS$$

$$\dot{E} = c\beta \frac{I}{S+E+I+R+V} S + c\beta \frac{I}{S+E+I+R+V} \mathrm{V} - \frac{E}{\tau}$$

$$\dot{I} = \frac{E}{\tau} - \frac{I}{\mu}$$

$$\dot{R} = \frac{I}{\mu} + \frac{V}{v_a}$$

$$\dot{V} = abS - \frac{V}{v_a} - c\beta \frac{I}{S+E+I+R+V}\mathrm{V}$$

In comparison with the previous work, we have developed a novel H1N1 model by adding a vaccinated stock to the previous SEIR model. We have defined the input of this stock as the multiplication of Susceptible, vaccine effectiveness parameter (*b*) and the per-capita vaccination rate (*a*), where the vaccine effectiveness parameter refers to the ability of the vaccine to bring about the intended beneficial effects on vaccinated individuals and the vaccination rate (*a*) is defined to be the fraction of new vaccinated people taken over the entire population per unit time (*i.e.*, the vaccination rate parameter is a variable of time). For this parameter (*a*), we made use of the empirical data obtained from the province of Manitoba. The outputs of the "Vaccinated" stock are the number of people vaccinated divided by mean time taken for antibodies to develop (v_a) which enter "Recovered" stock and number of people vaccinated multiplied by force of infection which enter "Exposed" stock. The model runs for 15 weeks and the primary model output examined here are reported infectives which is a multiplication of the size of "Infective" stock and the fraction of reported incidence. The compartmental parameters are specified in Table 1:

Table 1: Table showing parameters.

Variable Name	Notation	Value	Units
Probability of Infection Transmission Given Exposure	β	0.06	Unit
Mean Time to Recovery	μ	1	Weeks
Vaccine Effectiveness	b	0.9	Unit
Mean Time Taken for Antibodies to Develop	v_a	2	Weeks
Total Population Size	N	1214403	Person
Mean Latent Time	τ	Uniformly Distributed (0.4, 0.8)	Weeks
Vaccination Rate	a	Extracted from Empirical Vaccinated Percentage	Unit
Fraction of Reported Incidents	f	Different Strategies for estimating it in Calibration and Particle Filter	Unit
Contacts per Week	c	Different Strategies for estimating it in Calibration and Particle Filter	1/Week

It is notable that the model includes a stochastic process associated with Contacts per Week and Fraction of Reported Incidents. In the particle filtering model, these parameters are initially uniformly distributed between maximum and minimum parameter values, however these parameters are calibrated in the calibration model.

3.3 Particle Filter and its Characteristics in Proposed Model

Particle filtering is a sequential Monte Carlo method for performing inference in state-space models. For these models, the state of a system evolves across time *t* and information about the state is obtained via noisy measurements. We assume for simplicity that measurements are received only at integer boundaries in time. We further assume a Markovian system, where the probability distribution for the state of a system at time x_t depends only on the state at time *t*-1, that is $\mathrm{p}(x_t|x_{t-1}, x_{t-2}, \ldots x_1) = \mathrm{p}(x_t|x_{t-1})$. The

state vector x_t is assumed to be latent or unobservable. Information about x_t is obtained through noisy observations y_t, which are governed by the observation component for the probabilistic model conditional on the state variable x_t, denoted by $g(y_t|x_t)$. The general particle filter algorithm leverages the approach of importance sampling which utilizes the fact that if one wishes to sample from a target distribution *p(x)* but is unable to do so directly, one can sample instead from an importance proposal distribution *q(x)* which holds the key features of *p(x)*. By maintenance of a series of weights together with corresponding samples from *q(x)*, the net effect of sampling from *p(x)* can be obtained. The algorithm can be summarized as follows: Let N be the number of particles.

1. At time $t = 1$, for $i = 1, 2, ..., N$

(i). Sample $X_1^{(i)}$ from $q_1(x_1|y_1)$.

(ii). Compute a weight for each particle $w_1^{(1)} = \frac{p(x_1)g(y_1|x_1)}{q\left(x_1^{(i)}\middle|\, y_1\right)}$.

2. At time $t \geq 2$, perform a recursive update as follows:

(i) Advance the sampled state by sampling $X_t^{(i)} \sim q_i(x_t|\, y_t, x_{1:t-1})$ and set $X_{1:t}^{(i)} = X_{1:t-1}, X_t^{(i)}$.

(ii) Update the weights to reflect the probabilistic and state update models

$$w_t^{(i)} = w_{t-1}^{(1)} \frac{p\left(x_t^{(i)}\middle|\, x_{t-1}^{(i)}\right) g\left(\mathrm{y_t}\middle|x_t^{(i)}\right)}{q\left(x_t^{(i)}\middle|\, \mathrm{y_t}, x_{t-1}^{(i)}\right)}$$

Normalize the weights

$$w_t^{(i)} = \frac{w_t^{(i)}}{\sum_{i=1}^{N} w_t^{(i)}}$$

3. Resampling step

For any time *t*, if the effective sample size is too small (i.e., if the variance of the weights is too high, $\frac{1}{\sum_{i=1}^{N}(w_t^{(i)})^2} < k$), resample $X_t^{(i)}$ and set $w_t^{(i)} = \frac{1}{N}$. Here *k* is a threshold value for the variation of the weights (Osgood and Liu, 2014). In our model, we use the simplest and most widely used proposal distribution, $\mathrm{q}\left(x_t\middle|y_t, x_{t-1}\right) = \mathrm{p}(x_t|x_{t-1})$, and the weight update simplifies to $w_t^{(i)} = w_{t-1}^{(i)} g\left(y_t\middle|x_t^i\right)$. Here the weights are not restricted to being updated by considering later measurements but are obtained for a given observation point *t* by multiplying the weight associated with each particular particle at *t* by the likelihood of observing the measured data conditional on the state of that particle. This approach, used in our model and the termed condensation algorithm, does possess some vulnerabilities but is a well-established and highly popular sub-type of particle filtering (Murphy 2012).

In our model, each particle at a point in time *t* is associated with all state variables (*S, E, I, R,V*). Moreover, the suggested dynamic model includes parameters such as contact rate and fraction of reported incidents which are associated with state variables evolving over time. To use particle filtering to adapt to values of such parameters, we further associate each particle with a value for the parameters *c* and *f*. Each particle is thus associated with a vector [*S, E, I, R, V, c, f*].

In estimating the likelihood formulation for observing y_t individuals per week given an estimated weekly count of i_t becoming cases, we employ the negative binomial distribution $\mathrm{p}\left(y_t\middle|i_t\right) = \binom{y_t + r - 1}{y_t} p^{y_t}(1-p)^r$, where $\mathrm{p} = \frac{i_t}{i_t + r}$, *r* is a dispersion parameter and $i_t = \frac{E}{\tau}$. The negative binomial was preferred as being a more robust distribution than the binomial distribution for the particle filtering methodology. This was due to the fact that for situations where all particles are associated with

rates of completing latency smaller than the empirical data observed, weights identically equal to zero would be triggered across all such particles, causing a singularity during weight renormalization (Osgood and Liu 2014).

3.4 Comparison between Particle Filtering and Calibration

In this contribution, we investigate the degree to which the model is efficient in robust estimation and prediction of model states with and without particle filtering. Since the knowledge of the situation is imperfect there is frequently a need to estimate model parameters based on available empirical data regarding phenomena that are emergent within the model.

In this article, we investigate the capabilities of particle filter and calibration methodologies in mitigating the effects of aggregation and prognosticating model states in the context of data from a real-world outbreak. We defined a variable, "Check Time" T^*,which indicates the time t up to which the particles' weights are updated based on observation, where $0 \leq t \leq T^*$. After $t = T^*$, the particle filtering ceases, in that particle weights is no longer updated using the empirical data, and no further resampling occurs. The equivalent T^* in calibration methodology is the time t up to which empirical data has been used for tuning the model.

In this experiment, we utilized the parameter "fraction reported incidence" to account for the fact that reported counts only included a subset of the persons infected. For uncertain parameters such as "probability of transmission given exposure" and "mean latent time", we define a function that takes a range of uniformly distributed values from minimum to a maximum. For the calibration method, we ran the model for 20,000 iterations. In order to ensure robustness in the context of the stochastic evolution of model parameters *c* and *f*, we further ran 10 realizations (replications) per iteration. For this optimization experiment, the objective function involved minimizing the average of squared difference between linearly interpolated data sets which are model data and empirical data. The integration range is the intersection of argument ranges of data sets. In calibration, we considered the empirical data up to time $t = T^*$ and after calibrating the parameters, we were able to obtain simulation results for the entire time range (including time points $t>T^*$) for the model based on those parameters. Specifically, we assess particle filter and calibration by comparing their estimates of reported new infections against corresponding quantities from empirical data.

4 RESULTS

According to Figures 2-5 we have demonstrated the performance of particle filter and calibration for $T^*= 14$ and $T^*= 6$. Figure 2 presents calibration curve fitting historic data and figure 3 illustrates the particles from particle filtering methodology pursuing empirical data up to $T^*= 14$. From these two figures, it can be concluded that although calibration methodology performs properly to match historic data, but particle filtering surpasses this traditional technique in terms of discrepancy between real data and simulation data. For $T^*<14$, we have defined the discrepancy as a function which focuses on the average per-time-unit error during the time $t > T^*$. In this case, we are only considering how accurate it is in predicting data about which it has not been told (a form of cross-validation). Besides, we have divided the discrepancy over the time period $t>T^*$ by the length of that time period to have comparability of results. The function below calculates the value for discrepancy found for the particle filtering process. This function was defined as $\frac{\sum_{i=T^*+1}^{T_f}(x_i^M - x_i^E)^2}{T_f - T^*}$ for the calibration process, where T_f is the end time, x_i^M is the data extracted from the model at time i and x_i^E is the respective empirical data.

For the particle filtering methodology, by sampling *n* particles with larger weights, the discrepancy value is obtained via below formula while x_{ij}^p is data pertaining sampled particle *j* at time *i.*

$$\frac{\sum_{i=\mathrm{T}^*+1}^{\mathrm{T}_f}\left(\frac{\sum_{j=1}^{n}(x_{ij}^{p}-x_i^{E})^2}{n}\right)}{\mathrm{T}_f-\mathrm{T}^*}$$

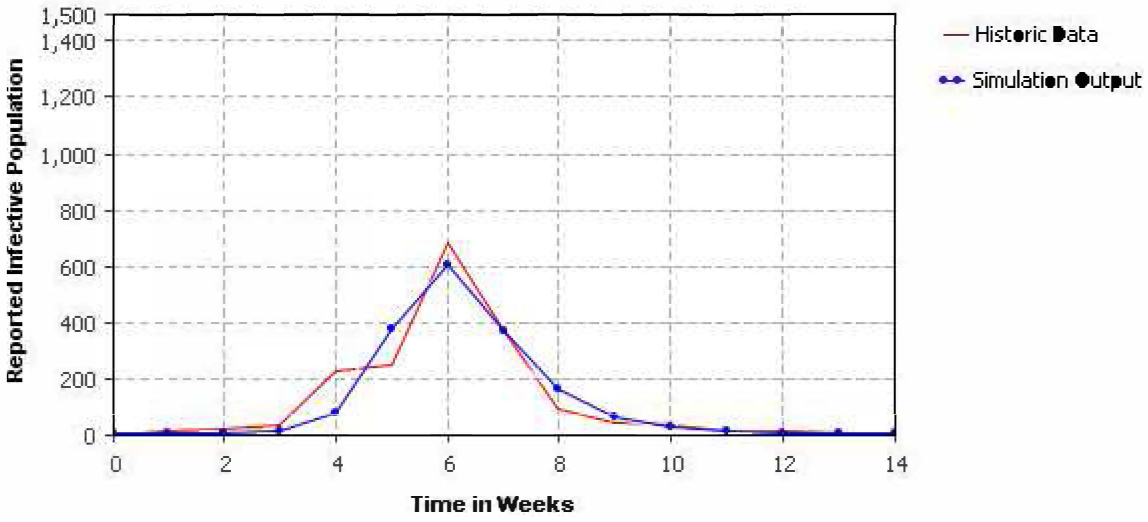

Figure 2: Calibration results for 20,000 iterations and for T^*= 14.

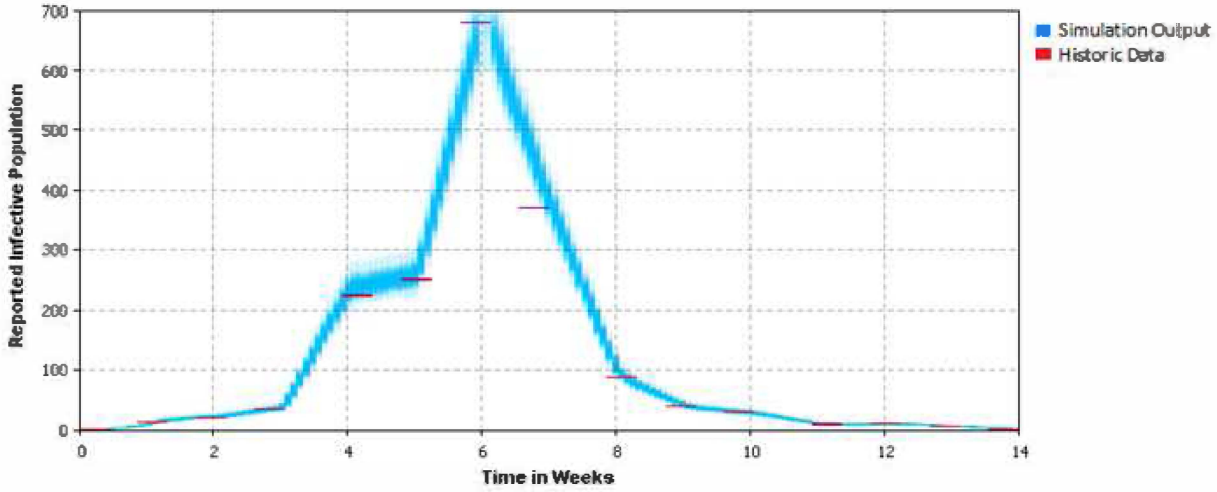

Figure 3: Particle filtering results for T^*= 14.

Figures 4 and 5 present, respectively, the capability of calibration and particle filtering in projecting future outcome based on current historic data. It can be observed that while calibration method fails to predict future outcomes, particle filtering tracks future data accurately.

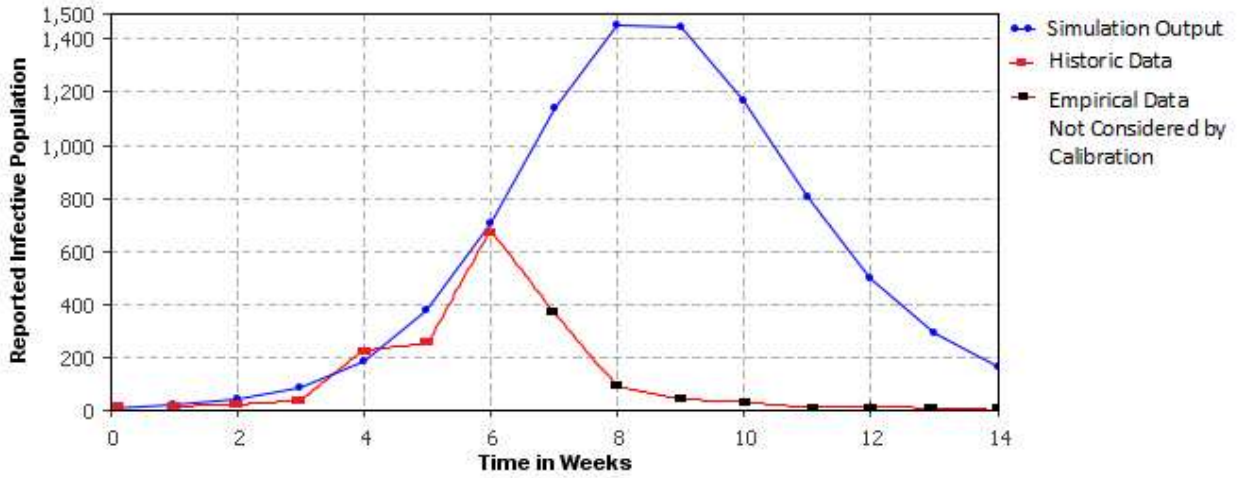

Figure 4: Calibration results for 20,000 iterations and for T^*= 6.

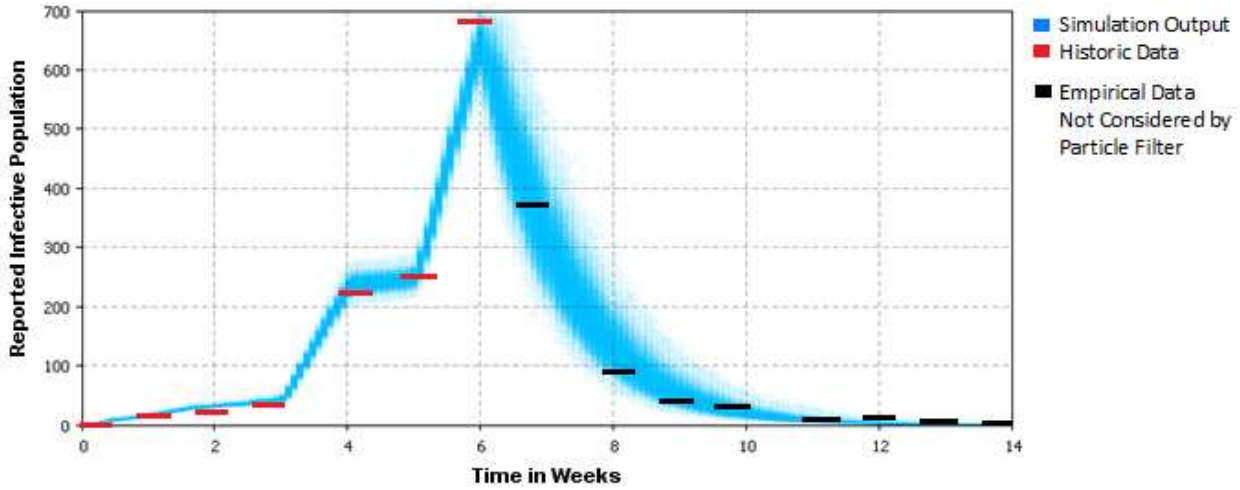

Figure 5: Particle filtering result for T^*= 6.

Figure 6 presents a histogram showing the discrepancies from Particle Filter and Calibration for T^*= 6, 7, 8, 9 and 10. For all values of t = T^*, the discrepancy from particle filter is less than the discrepancy from calibration. However for both the particle filter and calibration methods, the discrepancy increases as the value of T^* decreases. Put another way, as the window of empirical data considered by both the particle filter and calibration methods grow in size, the accuracy of those approaches in predicting the entire time series rises.

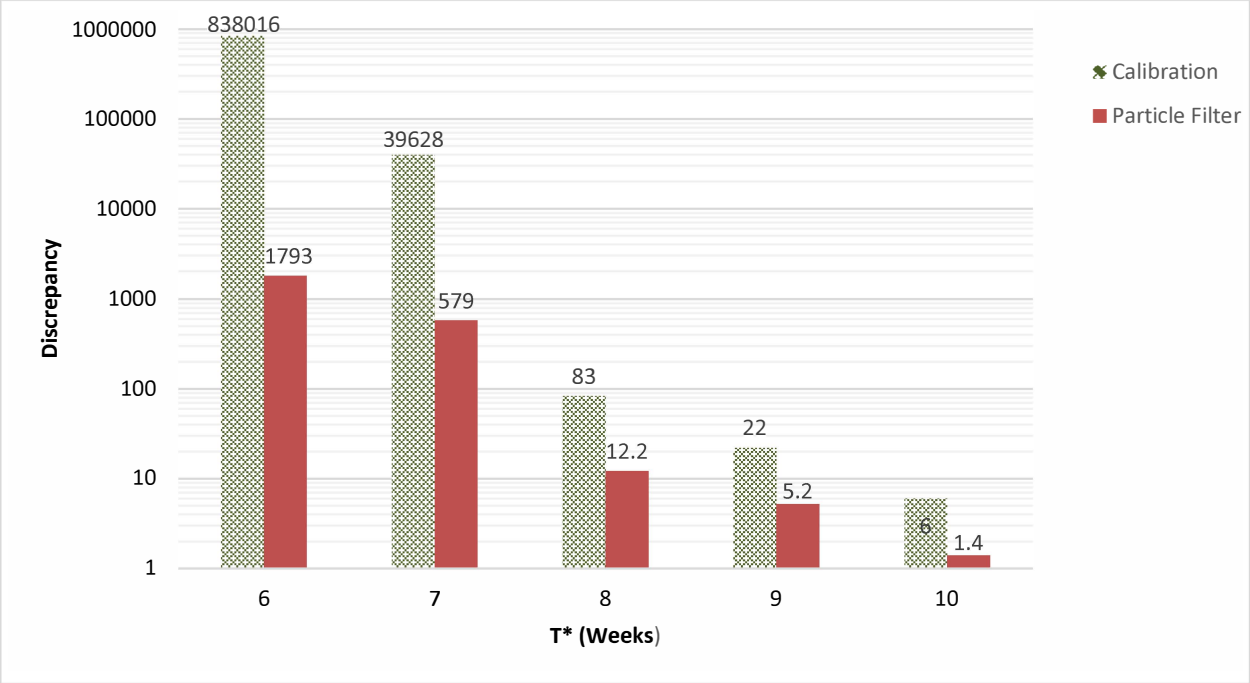

Figure 6: Logarithmic graph showing discrepancy for calibration and particle filtering vs check time (T*).

5 CONCLUSIONS

In this work, we explored the performance of particle filtering and calibration in a System Dynamics model against empirical data from an H1N1 outbreak. The particle filtering was put forward to readily read data and further correct the model output using historic data. In addition to particle filtering contributing to the estimation of model states, particle filtering also aided in estimating the model parameters. It was well adapted to evolution in the effective value of dynamic parameters that would otherwise be treated as static. For example, by applying a distribution to the Contacts per week parameter, a more accurate estimate was achieved during the model simulation.

The work examines the SEIRV (susceptible, exposed, infected, recovered and vaccinated) model and provides an extension to many existing SEIR models. Moreover, the proposed model is similar in structure to the models that do consider the effects of vaccination. The discrepancy for the particle filtering was found to be less than the discrepancy associated with the calibration method when compared to existing empirical data. In addition to this phenomenon being true for different time scenarios, the particle filtering methodology was observed to better predict the model outcome when using observable data. The calibrated parameters and their values for check time 14 are specified in Appendix 1. We suspect that much of the favorable character of the particle filter results derives from the flexibility in evolving the parameter values over time to be sure, but also the fact that the particle filter estimates not only the parameter values, but also the latent state of the stocks.

The main contributions of our work include the proposal of the SEIRV model, the comparison of particle filtering and calibration methodologies and the prediction of future outcome based on current empirical data. Many priorities remain for future work. It will be important to incorporate heterogeneity within our model by observing various age groups and also anti-viral treatments. We further hope to investigate the impact of relaxing the constraints of the condensation algorithm on model accuracy.

APPENDIX A

The Calibrated Values of Parameters are shown as bellow:

Variable Name	Value	Unit
Probability of Infection Transmission Given Exposure Multiplied by Contacts per Week	4.8	1/Week
Mean Latent Time	0.278	Week
Fraction of Reported Incidents	0.001	Unit
Fraction Initially Susceptible	0.993	Unit
Fraction Initially Exposed	9.2 E-8	Unit
Fraction Initially Infective	1.59 E -5	Unit
Fraction Initially Recovered	0.005	Unit

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