Applied Mathematics and Computation 286 (2016) 232–249

Contents lists available at ScienceDirect

Applied Mathematics and Computation

journal homepage: www.elsevier.com/locate/amc

Stochastic methods for epidemic models: An application to the 2009 H1N1 influenza outbreak in Korea

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ARTICLE INFO

MSC:
65-09
68-13
92-09
92-11

Keywords:
Epidemic models
Stochastic computation
Moment closure method

ABSTRACT

In this paper, we present stochastic methods for computation of influenza transmission models. First, SEIR type deterministic epidemiological models are revisited and stochastic modeling for those models are introduced. The main motivation of our work is to present computational methods of the stochastic epidemic models. In particular, the moment closure method (MCM) is developed for some influenza models and compared with the results under the standard stochastic simulation algorithm (SSA). All epidemic outcomes including the peak size, the peak timing and the final epidemic size of both methods are in a good agreement, however, the MCM has reduced the computational time and costs significantly. Next, the MCM has been employed to model the 2009 H1N1 influenza transmission dynamics in South Korea. The influenza outcomes are compared under the standard deterministic approach and the stochastic approach (MCM). Our results show that there is a considerable discrepancy between the results of stochastic and deterministic models especially when a small number of infective individuals is present initially. Lastly, we investigate the effectiveness of control policies such as vaccination and antiviral treatment under various scenarios.

1. Introduction

There have been a number of influenza outbreaks in the world since the 20th century and some of them were very severe such as 1918 Spanish flu pandemic which killed about 50 million people. The 1957 Asian influenza (H2N2) had spread worldwide within a short period of time and the number of infective people was about 250 thousands. In the early 1968, a new virus (H3N2) emerged in Hong Kong and mortality was about 34,000 people. Recently, a novel H1N1 pandemic influenza was back in 2009 all around the world but it turned out to be mild. The case fatality rate was estimated as 30 per 100,000 cases [1]. A pandemic influenza has the unpredictable timing and severity and a new pandemic influenza causes many casualties and economic losses, although there has been much medical advance. Hence, it is very challenging to prepare effective countermeasures or intervention strategies to reduce the negative impact of a novel pandemic influenza.

Various mathematical models have been developed for predicting and preventing the spread of influenza, in that such models can be used for simulating the transmission dynamics of the infectious disease even when real experiments are difficult or impossible. Moreover, the analysis of the models is useful for understanding the mechanism of the spread

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http://dx.doi.org/10.1016/j.amc.2016.04.019
0096-3003/

of infectious disease. The deterministic compartment model was firstly proposed by McKendrick [2] and Kermack and McKendrick [3]. They used deterministic differential equations (so called SIR models) that assume that the population is divided into three compartments, susceptible (S), infectious (I), and recovered (R). Let $S(t)$, $I(t)$ and $R(t)$ denote the number of individuals at time t in the corresponding compartments. Let $N(t) = S(t) + I(t) + R(t)$ denote the total population size. The simple SIR model using ordinary differential equations can be written as

$$\frac{dS}{dt} = -\beta(N)SI$$
$$\frac{dI}{dt} = \beta(N)SI - \gamma I$$
$$\frac{dR}{dt} = \gamma I$$

where γ is the recovery rate and $\beta(N)$ is the rate of new infections. More precisely, $\beta_0 = \beta(N)N$ is the average number of the individuals who make contacts with an infective, which lead to an infection per unit time, and each susceptible can have contact with anyone in the population with the rate β_0, encountering a proportion I/N of the infectives. For convenience of notation, hereafter we use β instead of $\beta(N)$.

On the other hand, the mechanism of the spread of infectious diseases is probabilistic in nature and the intrinsic fluctuation or noise occurs in the time evolution of the number in each compartment. This fluctuation can play a critical role in the transmission dynamics of infectious diseases, especially when the size of the population is small. While the deterministic epidemic models can successfully describe the dynamics of the spread of epidemic diseases for models with a large population size, they cannot capture the intrinsic fluctuations when the size of population is small. To capture the fluctuation, one has to employ a stochastic approach (random processes) rather than a deterministic approach. In particular, at the initial stage of an epidemic spread, the number of the infectious people is usually small and few infectious individuals may initiate the infection. In this case, the stochastic modeling should be used for an accurate description of the disease transmission.

There have been some works on stochastic models for the transmission dynamics of infectious diseases. A good introduction for stochastic epidemic models can be found in [4–6]. The stochastic epidemic models require heavy and intensive computations for simulation since the variables of the models generally have huge dimensions. Therefore, there have been works in order to reduce computational costs significantly and one of them is the moment closure method. It is one of approximate methods to overcome the difficulty in the computation of stochastic models [7–12]. Moment closure methods have been used to approximate the equilibrium distribution of stochastic logistic models [7,8] and to estimate the variability of average behavior in stochastic models for some recurrent epidemics [9]. A second-order moment closure approximation was applied to stochastic SI and SIS models [10]. In [11], the authors developed a moment closure method in a rigorous way, which will be applied to stochastic epidemic models in this paper.

The aim of this paper is to present computational methods for stochastic epidemic models such as a stochastic simulation algorithm (SSA) and a moment closure method (MCM). First, the results are compared under these two methods and next, the MCM is employed to an H1N1 influenza model. Also, we show that there is a considerable quantitative difference between results from stochastic and deterministic models, especially if there is a small number of the infective people at the initial stage.

The outline of the paper is as follows; in Section 2, we introduce deterministic models of influenza dynamics such as SEIR and SLIAR models. Also, we describe the stochastic modeling of the epidemic models and present computational methods for the time evolution of stochastic models. In Section 3, we apply the stochastic methods to an H1N1 influenza model with control policies and numerical results are presented. Moreover, we investigate the impact of various vaccination and antiviral treatment intervention scenarios on the influenza dynamics.

2. Epidemic modeling

2.1. Deterministic modeling

In this paper, we focus on the epidemiological models for a pandemic influenza which ends within a year (a short term dynamics). Therefore, the demographic effect is negligible so that the birth and death rates are ignored. The SIR can be extended to the SEIR model which includes the latent or exposed state by adding the new compartment E. Here, the latent state means the individual has been infected but is not yet infectious. Transmission from S to E only occurs when the infectious individuals have effective contact with susceptible individuals. After the latent period, the exposed individuals move to the infective stage and then enter the recovered stage when recovered from the disease. The compartment of the individuals who died of the disease is denoted by D. The governing equation of the SEIR model with death is written as

$$\frac{dS}{dt} = -\beta SI$$
$$\frac{dE}{dt} = \beta SI - \kappa E$$

$$\begin{aligned}\frac{dI}{dt} &= \kappa E - \alpha I \\ \frac{dR}{dt} &= f\alpha I, \\ \frac{dD}{dt} &= (1-f)\alpha I,\end{aligned} \tag{1}$$

where β is the new infection rate, κ is the progression rate of individuals from E to I, and α is the recovery rate of infectious individuals [13]. $(1-f)$ is the fatality rate of infectious individuals.

Next, the SLIAR model has five epidemiological classes which are susceptible (S), latent (L), infectious and symptomatic (I), asymptomatic but infectious (A), and recovered (R). The governing equation of the SLIAR model with death is written as follows [14,15];

$$\begin{aligned}\frac{dS}{dt} &= -\beta S(I+\delta A) \\ \frac{dL}{dt} &= \beta S(I+\delta A) - (1-p)\kappa L - p\kappa L \\ \frac{dI}{dt} &= p\kappa L - f\alpha I - (1-f)\alpha I \\ \frac{dA}{dt} &= (1-p)\kappa L - \eta A \\ \frac{dR}{dt} &= f\alpha I + \eta A \\ \frac{dD}{dt} &= (1-f)\alpha I.\end{aligned} \tag{2}$$

Here, the parameter δ quantifies the fraction of reduced transmissibility of the asymptomatic infectious class. A fraction p of latent individuals progresses to the class I at the rate κ and the rest $(1-p)$ proceeds to the class A at the same rate. The parameters α and η indicate the recovery rates from I and A to R, respectively. f is the fraction recovering from the disease of the individuals leaving I and $(1-f)$ is given as a fatality. This SLIAR model is extended to the model with treatment in Section 3.

The basic reproduction number, denoted by R_0, measures the average number of secondary infections by a single infectious individual introduced into an entirely susceptible population. For the above SLIAR model, R_0 can be computed by using the next generation matrix described in [13,16];

$$R_0 = \beta_0\left[\frac{p}{\alpha} + \frac{\delta(1-p)}{\eta}\right]. \tag{3}$$

The value of R_0 reflects the stability of the disease-free equilibrium. If $R_0 < 1$, then the disease-free equilibrium is locally asymptotically stable, and if $R_0 > 1$, the disease-free equilibrium is unstable [17,18].

2.2. Stochastic modeling

It is known that there is a quantitative discrepancy between the solution of deterministic models and the mean of the stochastic models except for the linear models [4]. One of the main reasons is that the expected value of the product of random variables is generally not the same as the product of the expected values of the random variables.

In Fig. 1, results from stochastic and deterministic models for the SLIAR model are compared. In Fig. 1(a), four realizations of the stochastic model of the SLIAR system (2) are compared with the deterministic solution. Fig. 1(b) compares the solution of the deterministic SLIAR model with the stochastic solutions based on 10,000 realizations by the stochastic simulation algorithm (SSA). One sees that the dynamical behaviors of the two models are similar, but there is about 10% discrepancy between the deterministic solution and the stochastic mean at the peak. This indicates that the deterministic solution overestimates the epidemic peak size.

Here, we briefly present the stochastic formulation of the epidemic compartment model. If there are s distinct compartments and r reactions, we write the form

$$\sum_{i=1}^{s} \nu_{ij}^{a} M_i \to \sum_{i=1}^{s} \nu_{ij}^{b} M_i, \quad j = 1, \ldots, r,$$

where ν_{ij}^{a} and ν_{ij}^{b} are the coefficients of change of the compartment i involved in the jth reaction. We let $\nu_{ij} = -\nu_{ij}^{a} + \nu_{ij}^{b}$ and define a matrix V whose (i,j)th entry is ν_{ij}. Then, the (i,j)th entry of V denotes change of the number of population in the ith compartment by the jth reaction and the jth column V_j of V is the change in the number of the population of compartments by the occurrence of jth reaction.

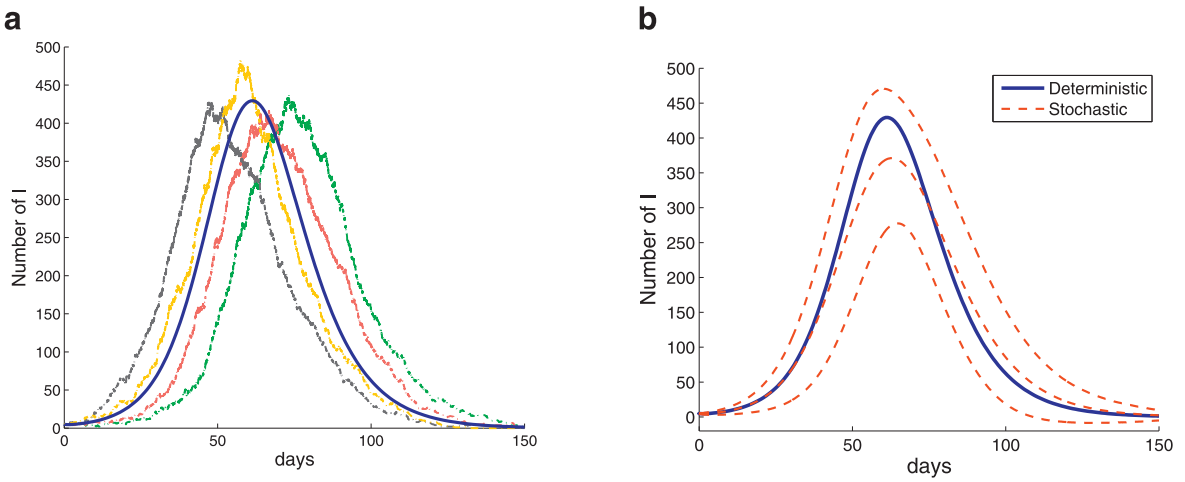


Fig. 1. Comparison of simulation results of deterministic and stochastic SLIAR models. (a) Comparison of the deterministic solution (blue solid curve) and four sample paths (black, red, green, yellow dashed curves) of the stochastic model by the SSA. (b) Comparison of the deterministic solution (blue) and the mean + standard deviation (upper red), mean (middle red), mean − standard deviation (lower red) of the stochastic model. Initial conditions are $S(0) = 5000, I(0) = 5, L(0) = A(0) = R(0) = 0$ and parameter values are $p = 0.67, \delta = 0.5, \alpha = \eta = 1/7, \kappa = 1/1.4, f = 0.999$ and $\beta_0 = 0.3422$ ($R_0 = 2.0$). The stochastic results are based on 10,000 realizations of the SSA. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

For example, in the SIR model

$$S + I \to 2I, \quad I \to R,$$

if we denote $M_1 = S, M_2 = I, M_3 = R$, then the coefficients of change are

$$v_{11}^a = 1, \quad v_{21}^a = 1, \quad v_{31}^a = 0, \quad v_{11}^b = 0, \quad v_{21}^b = 2, \quad v_{31}^b = 0,$$

$$v_{12}^a = 0, \quad v_{22}^a = 1, \quad v_{32}^a = 0, \quad v_{12}^b = 0, \quad v_{22}^b = 0, \quad v_{31}^b = 1,$$

and the matrix V is

$$V = \begin{bmatrix} -1 & 0 \\ 1 & -1 \\ 0 & 1 \end{bmatrix}.$$

If $p(\mathbf{x}, t)$ denotes the probability that the number of population of compartments is $\mathbf{x}$ at time t, the governing equation for the stochastic epidemic model is written as

$$\frac{dp(\mathbf{x}, t)}{dt} = \sum_{k=1}^{n} [a_k(\mathbf{x} - V_k)p(\mathbf{x} - V_k, t) - a_k(\mathbf{x})p(\mathbf{x}, t)] \tag{4}$$

where V_k is the kth column of V and a_k is the propensity function for the kth reaction which is determined by mass action kinetics. More precisely, a_k is

$$a_k(\mathbf{x}) = c_k g_k(\mathbf{x}), \tag{5}$$

where c_k is the probability constant such that $c_k \Delta t$ is the probability that the kth reaction occurs during the time interval $(t, t + \Delta t)$ and $g_k(\mathbf{x})$ is the product of the numbers of population of the compartments involved in the kth reaction.

For example, in the SEIR model (1), if we denote the number of S, E, I, R and D by $\mathbf{x}(t) = (x_1(t), x_2(t), x_3(t), x_4(t), x_5(t))$ at time t, respectively, we write the stochastic governing equation of the model

$$\begin{aligned} \frac{dp(x_1, x_2, x_3, x_4, x_5, t)}{dt} &= c_1(x_1 + 1)x_3 p(x_1 + 1, x_2 - 1, x_3, x_4, x_5, t) + c_2(x_2 + 1)p(x_1, x_2 + 1, x_3 - 1, x_4, x_5, t) \\ &\quad + c_3(x_3 + 1)p(x_1, x_2, x_3 + 1, x_4 - 1, x_5, t) + c_4(x_3 + 1)p(x_1, x_2, x_3 + 1, x_4, x_5 - 1, t) \\ &\quad - (c_1 x_1 x_3 + c_2 x_2 + c_3 x_3 + c_4 x_3)p(x_1, x_2, x_3, x_4, x_5, t). \end{aligned}$$

where $c_1 = \beta, c_2 = \kappa, c_3 = f\alpha, c_4 = (1 - f)\alpha$.

Alternatively, if one finds all possible states of $\mathbf{x}$ and transition rates between them, one can also write the governing equation in the linear form

$$\frac{d\mathbf{p}}{dt} = A\mathbf{p}(t), \tag{6}$$

where $\mathbf{p}(t)$ is the vector of $p_i(t)$ which is the probability that the value of $\mathbf{x}(t)$ is the ith state and A is the transition rate matrix or Markov chain generator matrix which is obtained by the values of a_k between different states [19].

Since it is difficult to solve the governing equations (4) and (6) analytically for most real models due to high dimensionality of variables, one should rely on the numerical computation based on stochastic algorithm. One of the well-known computational algorithms is the stochastic simulation algorithm (SSA) as follows; [20].

Step 1. Set initial condition $\mathbf{x}(0) = \mathbf{x}_0$.

Step 2. Calculate

- the function $a_k(\mathbf{x})$ for each k
- $a_T = \sum_{k=1}^{n} a_k(\mathbf{x})$

Step 3. Generate two random numbers r_1 and r_2 from the uniform distribution (0, 1). Set $\tau = -\frac{\log(r_1)}{a_T}$ and choose l such that

$$\sum_{k=1}^{l-1} a_k(\mathbf{x}) < r_2 a_T \le \sum_{k=1}^{l} a_k(\mathbf{x}).$$

Step 4. Update $t + \tau \to t$.

Step 5. Let $\mathbf{x} + V_l \to \mathbf{x}$. Go to Step 2.

2.3. Moment closure method (MCM)

One of the shortcomings of the stochastic simulation algorithm is that one needs intensive computations for simulating the system stochastically especially if the system is large or the infection processes are fast. To overcome the shortcoming, we use the moment closure method, an approximation method for finding the moments. In [11], the authors presented the way of the recursive computations of moments followed by the truncation of higher order moments and the estimation of the error generated by the truncation. In this section, we apply this method to an H1N1 influenza model and compare the results from the deterministic and stochastic models.

Here, we first describe the moment closure method briefly [11] under the assumption that the order of reaction is second-order, so that the function a_k is at most quadratic. This assumption is true for most of epidemic compartment models such as SIR, SEIR and SLIAR models that we consider in this paper. From the master Eq. (4), one can obtain

$$\frac{d\mu_i}{dt} = \sum_k \nu_{ik}\left(a_k(\mu) + \frac{1}{2}\sum_{l,m}\frac{\partial^2 a_k(\mu)}{\partial x_l \partial x_m}\sigma_{l,m}\right) \tag{7}$$

$$\begin{aligned}\frac{d\sigma_{i,j}}{dt} = &\sum_k \left[\nu_{ik}\sum_\ell \frac{\partial a_k(\mu)}{\partial x_\ell}\sigma_{j,\ell} + \nu_{jk}\sum_\ell \frac{\partial a_k(\mu)}{\partial x_\ell}\sigma_{i,\ell} + \nu_{ik}\nu_{jk}\left(a_k(\mu) + \frac{1}{2}\sum_{\ell,m}\frac{\partial^2 a_k(\mu)}{\partial x_\ell \partial x_m}\sigma_{\ell,m}\right)\right.\\ &\left. + \nu_{ik}\frac{1}{2}\sum_{\ell,m}\frac{\partial^2 a_k(\mu)}{\partial x_\ell \partial x_m}\sigma_{j,\ell,m} + \nu_{jk}\frac{1}{2}\sum_{\ell,m}\frac{\partial^2 a_k(\mu)}{\partial x_\ell \partial x_m}\sigma_{i,\ell,m}\right],\end{aligned} \tag{8}$$

where $\mu_i = E[x_i]$, $\sigma_{i,j} = E[(x_i - \mu_i)(x_j - \mu_j)]$ and $\sigma_{i,j,k} = E[(x_i - \mu_i)(x_j - \mu_j)(x_k - \mu_k)]$.

Furthermore, after some computations, we can obtain the equation for general nth central moments denoted by

$$M_{i_1,\dots,i_s} = E[(x_1 - \mu_1)^{i_1} \dots (x_s - \mu_s)^{i_s}],$$

for $n = i_1 + \cdots + i_s \ge 3$, as follows;

$$\frac{dM_{i_1,i_2,\dots,i_s}}{dt} = \frac{d}{dt}E[(x_1 - \mu_1)^{i_1} \cdots (x_s - \mu_s)^{i_s}] \tag{9}$$

$$\begin{aligned}&= \sum_k a_k(\mu)\sum_{\mathcal{L}}\binom{i_1}{\ell_1}\cdots\binom{i_s}{\ell_s}(\nu_{1k})^{i_1-\ell_1}\cdots(\nu_{sk})^{i_s-\ell_s}M_{\ell_1,\dots,\ell_s}\\ &\quad + \sum_k\sum_q \frac{\partial a_k(\mu)}{\partial x_q}\sum_{\mathcal{L}}\binom{i_1}{\ell_1}\cdots\binom{i_s}{\ell_s}(\nu_{1k})^{i_1-\ell_1}\cdots(\nu_{sk})^{i_s-\ell_s}M_{\ell_1,\dots,\ell_q+1,\dots,\ell_s}\\ &\quad + \frac{1}{2}\sum_k\sum_{q,r}\frac{\partial^2 a_k(\mu)}{\partial x_q \partial x_r}\sum_{\mathcal{L}}\binom{i_1}{\ell_1}\cdots\binom{i_s}{\ell_s}(\nu_{1k})^{i_1-\ell_1}\cdots(\nu_{sk})^{i_s-\ell_s}M_{\ell_1,\dots,\ell_s+e_q+e_r} - \sum_{j=1}^{s} i_j \mu'_j M_{i_1,\dots,i_j-1,\dots,i_s}\end{aligned} \tag{9}$$

where the index set $\mathcal{L} = \{\ell_1, \dots, \ell_s \ge 0 : 0 \le \ell_1 + \cdots + \ell_s \le n-1\}$, the notation $\binom{i}{\ell} = \frac{i!}{\ell!(i-\ell)!}$ and the subscript $\ell_1, \dots, \ell_s + e_q + e_r$ denotes adding 1's to qth and rth entries of $\ell_1, \dots, \ell_s$, respectively. Note that the term $M_{\ell_1,\dots,\ell_s+e_q+e_r}$ is $(n+1)$st moment when $\ell_1 + \cdots + \ell_s = n-1$. Thus, the system of the moment Eqs. (7), (9) and (10) is infinite dimensional, that is, the system is not closed, since equations for any nth moments include at least one of $(n+1)$st moments. Therefore, we

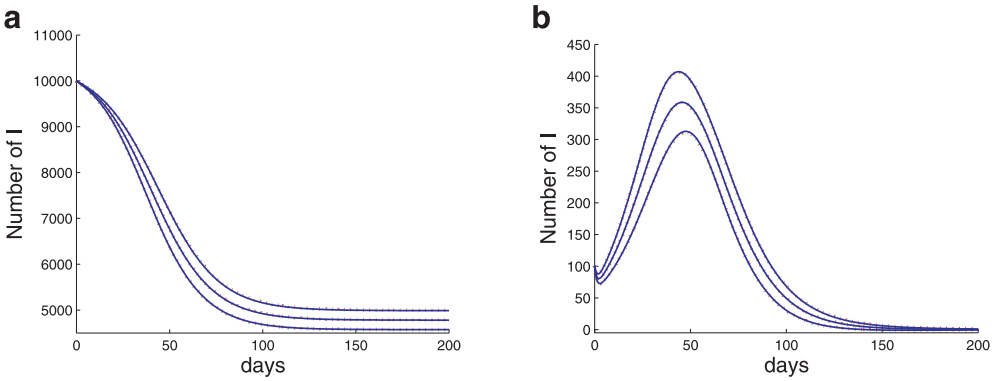


Fig. 2. Simulation results of a stochastic SEIR model. Comparison of the mean + standard deviation (upper curve), mean (middle curve) and mean − standard deviation (lower curve) by MCM (blue solid curves) and SSA (red dots). The initial condition is $(S, E, I, R) = (10000, 0, 100, 0)$ and parameter values are $\kappa = 1/1.9, \alpha = 1/4.1,\ f = 0.98,\ \beta_0 = 0.3422$. The results by SSA are based on 10,000 realizations. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

cannot find the exact solution of the system analytically or numerically. However, if we truncate the system by letting the $(n+1)$st moments be zero, then Eq. (10) is changed into an equation with at most nth moment terms as follows;

$$\frac{dM_{i_1,i_2,\ldots,i_s}}{dt} = \sum_k a_k(\mu) \sum_{\substack{\ell_1,\ldots,\ell_s \\ \sum_i \ell_i \neq n}} \binom{i_1}{\ell_1} \cdots \binom{i_s}{\ell_s} (\nu_{1k})^{i_1-\ell_1} \cdots (\nu_{sk})^{i_s-\ell_s} M_{\ell_1,\ldots,\ell_s}$$
$$+ \sum_k \sum_q \frac{\partial a_k(\mu)}{\partial x_q} \sum_{\substack{\ell_1,\ldots,\ell_s \\ \sum_i \ell_i \neq n}} \binom{i_1}{\ell_1} \cdots \binom{i_s}{\ell_s} (\nu_{1k})^{i_1-\ell_1} \cdots (\nu_{sk})^{i_s-\ell_s} M_{\ell_1,\ldots,\ell_q+1,\ldots,\ell_s} - \sum_{j=1}^{s} i_j \mu'_j M_{i_1,\ldots,i_j-1,\ldots,i_s}. \quad (10)$$

Thus, by the truncation, the original infinite dimensional system of (7),(9) and (10) is reduced to a solvable finite dimensional system of (7), (9) and (11).

If we use a numerical scheme to solve the truncated finite system of (7), (9) and (11) numerically, we will have the error generated from truncation and numerical integration. The formal error estimation and numerical consistency of the method have been shown in [11] as follows;

Theorem 1. *Suppose that we truncate the system (7), (9) and (10) by letting* nth *central moment be zero at any* t *in a time interval* $[0, h]$. *Then the error between the exact mean and the approximated mean obtained from the truncated Eqs. (7), (9) and (11) is* $O(h^{n-1})$ *and the error in second central moments is* $O(h^{n-2})$, *for any* $t \in [0, h]$.

Although the truncation at a higher order moment can give a more accurate approximation, the truncation at the third moment is practically useful, because it gives a decent approximation to important stochastic quantities such as first and second moments and also it is computationally more efficient than the truncation at the higher order moments. The system of the moment equations obtained by the truncation at the third moment is written as

$$\frac{d\mu_i}{dt} = \sum_k \nu_{ik} \left(a_k(\mu) + \frac{1}{2} \sum_{l,m} \frac{\partial^2 a_k(\mu)}{\partial x_l \partial x_m} \sigma_{l,m} \right) \quad (11)$$

$$\frac{d\sigma_{i,j}}{dt} = \sum_k \left[\nu_{ik} \sum_\ell \frac{\partial a_k(\mu)}{\partial x_\ell} \sigma_{j,\ell} + \nu_{jk} \sum_\ell \frac{\partial a_k(\mu)}{\partial x_\ell} \sigma_{i,\ell} + \nu_{ik}\nu_{jk} \left(a_k(\mu) + \frac{1}{2} \sum_{\ell,m} \frac{\partial^2 a_k(\mu)}{\partial x_\ell \partial x_m} \sigma_{\ell,m} \right) \right]. \quad (12)$$

As an example, we apply the system of (11) and (12) to the SEIR model with parameters from [21,22] and compare the simulation results obtained by SSA and MCM in Fig. 2. One can see that the results of MCM and SSA are in good agreement and the MCM captures the time-evolution of mean and standard deviation accurately. For the computational efficiency of the MCM, we observe that the MCM takes about 0.5 s for obtaining the mean and variance, but the SSA takes more than 0.5 h. Thus, the MCM computes the solution much faster than the SSA, while its accuracy is good enough.

3. Application: H1N1 influenza model in Korea

3.1. Mathematical transmission model with interventions

In this section, we construct a mathematical model for the spread of H1N1 influenza prevailed in Korea from 2009 through 2010 for an application of the stochastic methods. The SLIAR model described in the previous section is extended

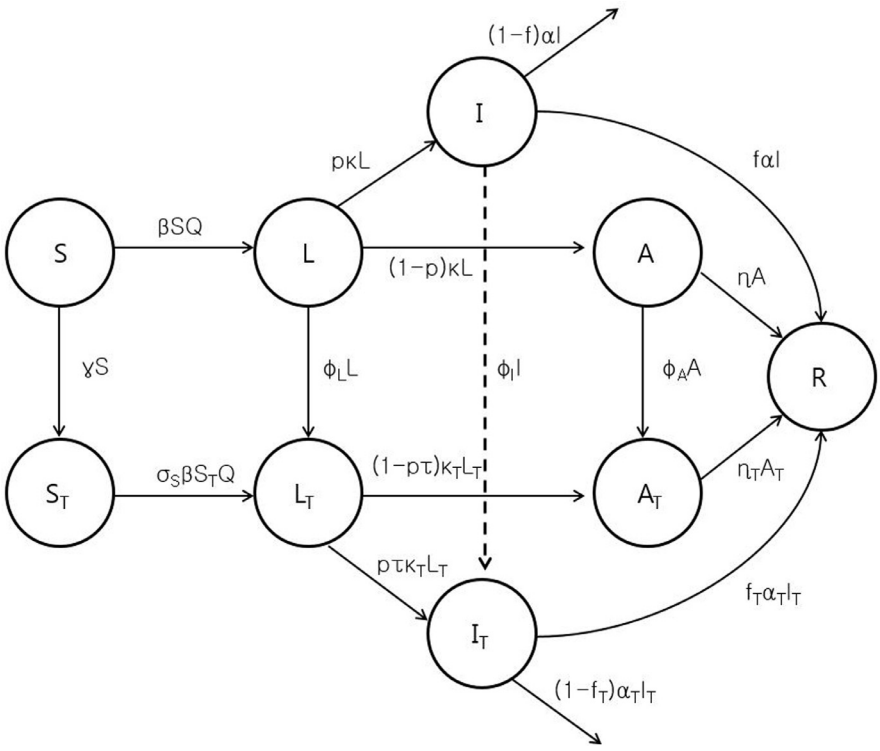


Fig. 3. SLIAR with treatment model.

to the one with treatment compartments which is based on the model in [15]. This model includes the control parameters such as vaccination and antiviral treatment implemented by the government's interventions. We have modified the model in [15] to incorporate more realistic scenarios for the 2009 Korean influenza pandemic. First, the relapse terms from treated individuals to untreated individuals are removed in order to focus on the short term dynamics of the 2009 influenza pandemic. Second, vaccination was implemented during the epidemic (not at the beginning of the influenza outbreak) since the vaccine was available after six months. We denote the number of individuals in the treated susceptible (or vaccinated susceptible), treated latent, treated infectious and treated asymptomatic classes by $S_T(t)$, $L_T(t)$, $I_T(t)$ and $A_T(t)$, respectively. The diagram for our compartment model is described in Fig. 3.

In general, there are non-pharmaceutical and pharmaceutical interventions for countermeasures. Non-pharmaceutical interventions are administrative controls including the isolation of diagnosed infective individuals and quarantine of suspected individuals. Pharmaceutical interventions include the antiviral treatment and vaccination. The vaccination also reduces the susceptibility to the pandemic influenza. The antiviral treatment has an effect on the reduction in the infectivity for the influenza. Early in the spread of the disease, when no vaccine is available, the antiviral treatment such as Tamiflu is important in mitigating the spread of the virus. Therefore, the following intervention strategies for controlling the spread of influenza are included in our model;

(i) The isolation and quarantine lead to a reduction of the contact rate by a control parameter x, i.e. the contact rate is $\beta(1-x)$.
(ii) The parameters ϕ_I and ϕ_A denote the control parameters representing the a fraction per unit time (one day) of the antiviral treatment that decreases the infectivity of I and A, respectively. We assume that there is no treatment in the latent state because it is highly likely that individuals do not receive treatment during the latent period, i.e., $\phi_L = 0$. The parameters ϕ_I and ϕ_A are assumed as the function $-\ln(1-r_a)/d_a$ where r_a and d_a are the rate and the duration of the antiviral treatment, respectively. More details for this formula can be found in the references [23,24].
(iii) Vaccination reduces susceptibility. A factor σ_S in the infection rate of S_T means that the vaccination has a perfect effect if $\sigma_S = 0$, and it has no effect if $\sigma_S = 1$. We assume that it takes about 90 days or more until vaccine is available. Similar to the parameters ϕ_I and ϕ_A for the antiviral treatment, the parameter γ for the vaccination is assumed as $-\ln(1-r_v)/d_v$, where r_v and d_v are the rate and the duration of vaccination, respectively.

Furthermore, we put the following assumptions for parameters related to the treatment compartment; the fraction $p\tau$ of treated latent members proceeds to the compartment I_T with the mean infectious period of $1/\alpha_T$, while the remainder goes to A_T with the mean infectious period of $1/\eta_T$. Here, κ_T is the rate of departure from L_T. α_T and η_T are recovery rates for I_T

Table 1
Parameters for the 2009 H1N1 influenza model in Korea.

Parameter	Description	Value	Reference
p	Fraction of L that progress to I	0.67	[23]
$(1-f)$	Fatality fraction for I	0.001	[23]
$(1-f_T)$	Fatality fraction for I_T	0	[23]
α	Recovery rate for I	0.2/day	[22]
η	Recovery rate for A	0.2/day	[22]
κ	Rate of departure from L	0.59/day	[22]
α_T	Recovery rate for I_T	0.22/day	[22]
η_T	Recovery rate for A_T	0.22/day	[22]
κ_T	Rate of departure from L_T	0.59/day	[22]
τ	Fraction of progression rate for L_T	0.38	[22]
δ	Infectivity reduction constant for A, A_T	0.5	[22]
q	Contact reduction constant for I, I_T	0.3	[23]
σ_S	Reduction constant for susceptibility of S_T	0.2	[23]
σ_I, σ_A	Infectivity reduction constant for I_T, A_T	0.2	[15]

and A_T with infectivity reduced by factors σ_I and σ_A, respectively. Infective individuals have the contact rate reduced by a fraction q. $(1-f)$ and $(1-f_T)$ are fatality fractions for I and I_T, respectively. All parameters are summarized in Table 1.

Using the model described above, one can write the governing equation as follows;

$$\begin{aligned}
\frac{dS}{dt} &= -\beta SQ - \gamma S\\
\frac{dS_T}{dt} &= -\sigma_s\beta S_T Q + \gamma S\\
\frac{dL}{dt} &= \beta SQ - \kappa L\\
\frac{dL_T}{dt} &= \sigma_s\beta S_T Q - \kappa_T L_T\\
\frac{dI}{dt} &= p\kappa L - \alpha I - \phi_I I\\
\frac{dI_T}{dt} &= p\tau\kappa_T L_T - \alpha_T I_T + \phi_I I\\
\frac{dA}{dt} &= (1-p)\kappa L - \eta A - \phi_A A\\
\frac{dA_T}{dt} &= (1-p\tau)\kappa_T L_T - \eta_T A_T + \phi_A A\\
\frac{dR}{dt} &= f\alpha I + f_T\alpha_T I_T + \eta A + \eta_T A_T\\
\frac{dD}{dt} &= (1-f)\alpha I + (1-f_T)\alpha_T I_T\\
Q &= (1-q)I + (1-q)\sigma_I I_T + \delta A + \delta\sigma_A A_T,
\end{aligned} \tag{13}$$

where $S(0) = S_0 > 0, S_T(0) = 0, I(0) = I_0 > 0, L(0) = L_T(0) = A(0) = A_T(0) = I_T(0) = R(0) = D(0) = 0$.

One can compute the disease-free equilibrium $X_0 = (S_0, S_{T0}, 0, 0, 0, 0, 0, 0, 0, 0)$ and the controlled reproduction number as follows;

$$R_c = \beta S_0\left[\frac{(1-q)p}{(\alpha+\phi_I)} + \frac{(1-q)\sigma_I p\phi_I}{\alpha_T(\alpha+\phi_I)} + \frac{\delta(1-p)}{(\eta+\phi_A)} + \frac{\delta\sigma_A\phi_A(1-p)}{\eta_T(\eta+\phi_A)}\right] + \sigma_s\beta S_{T0}\left[\frac{(1-q)\sigma_I p\tau}{\alpha_T} + \frac{\delta\sigma_A(1-p\tau)}{\eta_T}\right].$$

Note that R_c becomes R_0 in the absence of controls and the detailed derivation of R_c is given in Appendix A. Moreover, the controlled (basic) reproduction number is computed using the parameter values in Section 3.3.

3.2. Stochastic influenza model

In this section, we present a stochastic model for the H1N1 influenza pandemic. Let us denote the numbers of S, S_T, L, L_T, I, I_T, A, A_T, R, D at time t by $\mathbf{x}(t) = (x_1(t), x_2(t), x_3(t), x_4(t), x_5(t), x_6(t), x_7(t), x_8(t), x_9(t), x_{10}(t))$, respectively. The master equation of the model is obtained as

$$\frac{dp(\mathbf{x},t)}{dt} = (c_1(x_1+1)x_5 + c_2(x_1+1)x_6 + c_3(x_1+1)x_7 + c_4(x_1+1)x_8)\cdot p(\mathbf{x}+\mathbf{e}_1-\mathbf{e}_3,t) + (c_5(x_2+1)x_5$$

$$
\begin{aligned}
&+ c_6(x_2+1)x_6 + c_7(x_2+1)x_7 + c_8(x_2+1)x_8) \cdot p(\mathbf{x}+\mathbf{e}_2-\mathbf{e}_4,t) + c_9(x_3+1)p(\mathbf{x}+\mathbf{e}_3-\mathbf{e}_5,t)\\
&+ c_{10}(x_3+1)p(\mathbf{x}+\mathbf{e}_3-\mathbf{e}_7,t) + c_{11}(x_4+1)p(\mathbf{x}+\mathbf{e}_4-\mathbf{e}_6,t) + c_{12}(x_4+1)p(\mathbf{x}+\mathbf{e}_4-\mathbf{e}_8,t)\\
&+ c_{13}(x_5+1)p(\mathbf{x}+\mathbf{e}_5-\mathbf{e}_6,t) + c_{14}(x_5+1)p(\mathbf{x}+\mathbf{e}_5-\mathbf{e}_9,t) + c_{15}(x_5+1)p(\mathbf{x}+\mathbf{e}_5-\mathbf{e}_{10},t)\\
&+ c_{16}(x_6+1)p(\mathbf{x}+\mathbf{e}_6-\mathbf{e}_9,t) + c_{17}(x_6+1)p(\mathbf{x}+\mathbf{e}_6-\mathbf{e}_{10},t) + c_{18}(x_7+1)p(\mathbf{x}+\mathbf{e}_7-\mathbf{e}_8,t)\\
&+ c_{19}(x_7+1)p(\mathbf{x}+\mathbf{e}_7-\mathbf{e}_9,t) + c_{20}(x_8+1)p(\mathbf{x}+\mathbf{e}_8-\mathbf{e}_9,t) + c_{21}(x_1+1)p(\mathbf{x}+\mathbf{e}_1-\mathbf{e}_2,t)\\
&- (c_1x_1x_5 + c_2x_1x_6 + c_3x_1x_7 + c_4x_1x_8 + c_5x_2x_5 + c_6x_2x_6 + c_7x_2x_7 + c_8x_2x_8 + c_9x_3 + c_{10}x_3\\
&+ c_{11}x_4 + c_{12}x_4 + c_{13}x_5 + c_{14}x_5 + c_{15}x_5 + c_{16}x_6 + c_{17}x_6 + c_{18}x_7 + c_{19}x_7 + c_{20}x_8 + c_{21}x_1)\Big)p(\mathbf{x},t)
\end{aligned}
\tag{15}
$$

where each $\mathbf{e}_i, i = 1,\ldots,10$ denotes the 10 dimensional unit vector containing 1 at the ith entry and 0 elsewhere and parameters are as follows;

$$
\begin{aligned}
&c_1 = \beta(1-q), \quad c_2 = \beta(1-q)\sigma_I, \quad c_3 = \beta\delta, \quad c_4 = \beta\delta\sigma_A, \quad c_5 = \sigma_S\beta(1-q),\\
&c_6 = \sigma_S\sigma_I\beta(1-q), \quad c_7 = \sigma_S\beta\delta, \quad c_8 = \sigma_S\beta\delta\sigma_A, \quad c_9 = p\kappa, \quad c_{10} = (1-p)\kappa,\\
&c_{11} = p\tau\kappa_T, \quad c_{12} = (1-p\tau)\kappa_T, \quad c_{13} = \phi_I, \quad c_{14} = f\alpha, \quad c_{15} = (1-f)\alpha,\\
&c_{16} = f_T\alpha_T, \quad c_{17} = (1-f_T)\alpha_T, \quad c_{18} = \phi_A, \quad c_{19} = \eta, \quad c_{20} = \eta_T, \quad c_{21} = \gamma.
\end{aligned}
$$

The SSA requires heavy computational loads and would be computationally infeasible if the large number of population is involved in the system such as the above stochastic model. As described in Section 2.3, the MCM is an efficient approximate method which is much more efficient than the SSA. Especially it is very useful when one wants to investigate the effectiveness of various intervention scenarios and obtain fast simulation results. In this work, we apply the MCM for simulating the stochastic model (15) instead of the SSA, since Eq. (15) has high dimensional variables and a large number of population is involved in the model. If we derive the moment equations and truncate them at the third moments, we obtain the system of 65 equations for the first moments $\mu_i = E[x_i]$ and second moments $\sigma_{i,j} = E[(x_i-\mu_i)(x_j-\mu_j)]$. The full system of the 65 equations are given in Appendix B.

3.3. Numerical simulations

We present the influenza outcomes of deterministic and stochastic models by applying intervention strategies. The first infective individual in Korea was a women who returned from Mexico, and she was diagnosed as the index case on May 2, 2009, which we set as day 0. The total population size of South Korea in 2009 is 47,800,896 estimated from [25] and we assume the number of initial infective people is 10 [23]. Numerical simulations of the model accounting for government's control strategies are carried out from day 0 to day 400 to estimate the incidence curve. The epidemic duration is divided into four different periods, day 0–79 (period P_1), day 80–110 (P_2), day 111–176 (P_3) and day 177–400 (P_4). These countermeasures in the four periods implemented by South Korean government are summarized below, which are taken from [22,23,26].

(i) In the period P_1, the government's main purpose of strategies was to prevent the propagation of the disease. Infected individuals voluntarily restricted their activity out of school or work. It leads to reduce the contact rate by about 60%. Also, 60% of the confirmed cases received antiviral treatment and 30% of asymptomatic infectious who contact with a confirmed case also received antiviral treatment for prophylaxis.

(ii) One of aims of the policies in the period P_2 was to minimize the outbreak of serious cases and mortalities for reducing the social and economic damage. A majority of Koreans adopted the public recommendations such as washing hands or using hand sanitizer more frequently and wearing a flu mask. Due to these behavioral responses, the contact rate was reduced by 20%. Antiviral agents were used for confirmed patients.

(iii) In the period P_3, the antiviral treatment rates were increased since antiviral drugs were widely available. The vaccination was not available during the periods P_1, P_2 and P_3, i.e., $\gamma = 0$.

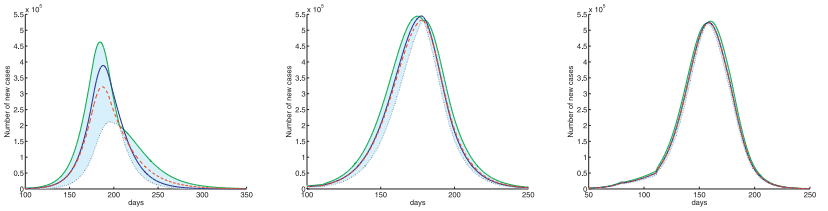
(iiii) During the period P_4, the vaccination policy started implementing. According to the KCDC [27], we estimate that the vaccination rate between day 177 and day 400 is 0.28. We assume that most people were vaccinated within 20 days after providing vaccine and so the duration of vaccination d_v is 20 days. For the values of control parameters described, refer to Table 2.

For all simulations, the influenza outcomes include the peak time, the peak size and the final attack ratio. The peak size is defined as the maximum value of the incidence during the epidemic duration. The peak time is measured as the time when the peak size occurs. The final attack ratio is defined as $1 - \lim_{t\to\infty}(S(t)+S_T(t))/N$. Using the parameters in the first period P_1 given in Tables 1 and 2, the controlled (basic) reproduction number is computed as $R_c = 1.55$ and $R_0 = 3.09$.

First, Fig. 4 and Table 3 show quantitative differences between the solutions of the two models for different initial numbers of the infective individuals such as 10, 50 and 250. One can see that the difference between the solutions of the two models decreases as the initial number of the infectives increases. Especially, if the initial number of the infective people is as small as 10, there is a significant difference between the results of deterministic and stochastic models and even the deterministic solution is out of the interval between mean − standard deviation and mean + standard deviation of the

Table 2
Summary of response to the 2009 H1N1 influenza in South Korea. Here, d_i denotes the duration of the P_i period.

Period	Response strategies	Control parameters
P_1	• The contact rate of I is reduced by 60% i.e. $q = 0.6$.	$\beta_0 = 0.7390$
	• Antiviral treatment for I and A is given as 60% and 30%.	$\phi_I = \frac{-ln(1-0.6)}{d_1}$ $\phi_A = \frac{-ln(1-0.3)}{d_1}$
P_2	• The contact rate is reduced by 20% by washing hands and wearing a mask.	$\beta_0 = 0.4038$
	• Antiviral treatment for I are given as 20%.	$\phi_I = \frac{-ln(1-0.2)}{d_2}$
P_3	• Antiviral treatment for I and A is given as 40%, 20%.	$\phi_I = \frac{-ln(1-0.4)}{d_3}$ $\phi_A = \frac{-ln(1-0.2)}{d_3}$
P_4	• Antiviral treatment for I and A is given as 20%, 20%.	$\phi_I = \frac{-ln(1-0.2)}{d_4}$ $\phi_A = \frac{-ln(1-0.2)}{d_4}$
	• The vaccination was implemented from Oct. 27, 2009.	$\gamma = \frac{-ln(1-0.28)}{20}$



(a) I(0)=10 (b) I(0)=50 (c) I(0)=250

Fig. 4. Comparison of the incidence curves from the deterministic model (blue solid) and the mean + standard deviation (green dash-dot), mean (red dash) and mean − standard deviation (black dotted) of the stochastic SLIAR treatment model. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 3
Comparison of the incidence curves between the deterministic model and the stochastic model under different initial numbers $I(0)$ when the total population size (N) is fixed as 47, 800, 896. The relative L^2 error is defined as $\sqrt{\sum_t (x(t)-y(t))^2}/\sqrt{\sum_t x(t)^2}$, where $x(t)$, $y(t)$ are the solutions of the MCM and ODE at time t, respectively.

Model	Epidemic outcomes	Initial infectives ($I(0)$)		
		10	50	250
Deterministic	Peak time	187.94	177.49	158.44
	Peak size	388810	544922	524894
	Final attack ratio	0.3963334	0.5219399	0.5828409
Stochastic	Peak time	187.02	177.78	158.59
	Peak size	321812	531516	522856
	Final attack ratio	0.3735441	0.5173449	0.5825586
	Relative L^2 error	0.1810354	0.0274155	0.0060483

stochastic solution in the time interval between 200 and 230 days as in Fig. 4(a). If the initial numbers get larger as 50 and 250, quantitative discrepancies between the two models get smaller. If the deterministic model is used in case that the initial number of the infectives is small enough, it is highly likely that the model would generate a significant error in time-dependent prediction of the number of the infectives.

Next, we investigate the impact of various control policies on the influenza outcomes using the stochastic method (MCM). First, the impact of the starting time for vaccination is illustrated. This shows the effectiveness of the hypothetical vaccination starting time which would start earlier than the actual first date (Oct. 27) of the vaccination in Korea. Fig. 5 shows the comparison of the effect of the vaccination according to its initial vaccination dates. The initial vaccination dates are set to be day 167, day 147, day 117, day 87, which are 10 days, 30 days, 60 days and 90 days earlier than the actual initial date (day 177) of the vaccination, respectively. Table 4 shows that the peak sizes are reduced by about 31.2% if vaccination starts 10 days earlier than the actual initial date. Likewise, starting the vaccination 1 month, 2 months and 3 months earlier leads to 75.7%, 97% and 99.7% reduction of the peak size, respectively, resulting in a dramatic reduction in the incidence. This result implies that, although it may be obvious, the earlier the vaccination starts, the more effective it is.

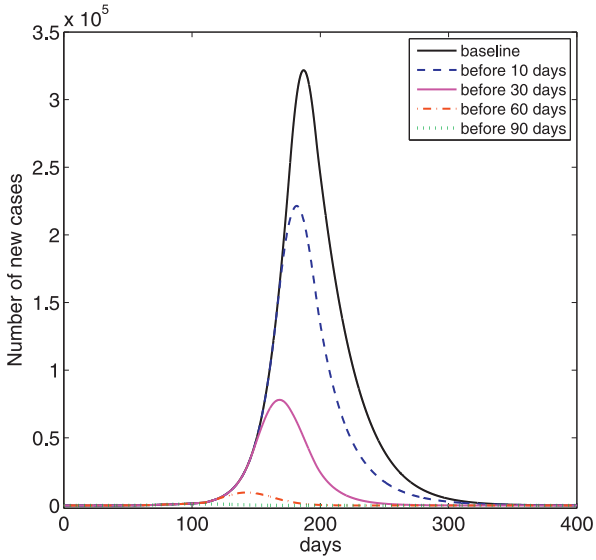


Fig. 5. Comparison of the incidence curves under different starting dates of vaccination. The baseline curve (black solid) is based on the actual parameter in Table 1.

Table 4
Comparison of the peak time, the peak size and the final attack ratio using different starting dates of vaccination for the results in Fig. 5.

Vaccination date	Baseline (day 177)	Day 167	Day 147	Day 117	Day 87
Peak time	187.02	181.60	168.30	142.60	99.00
Peak size	321812	221464	78080	9593	1121
Final attack ratio	0.3735441	0.2468626	0.0842707	0.0108695	0.0015369

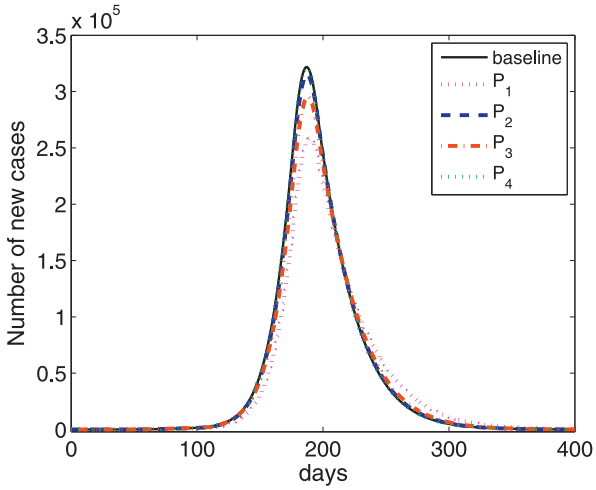


Fig. 6. Comparison of the incidence curves when the antiviral treatment rate ϕ_I is increased 50% times more than the actual amount administered by the governmental policy for each period.

Lastly, we investigate how the incidence curve is affected by increasing amounts of antiviral treatment. In Fig. 6, we assume that the antiviral treatment for infectious individuals are given 50% more than the actual amount spent in each period. Table 5 shows that in the periods P_1 and P_3, the peak size decreases by about 19.7% (about 63,400 cases) and 8.2% (about 26,400 cases), respectively and also the peak day is delayed by about 2.5 days and 1 day, respectively. Now, we focus antiviral treatment for infectious individuals on the third period only. Fig. 7 and Table 6 illustrate the impact of the amount of ϕ_I on the epidemic outcomes. If we increase 20%, 50% and 100% more than the actual amount of antiviral treatment

Table 5
Comparison of the peak time, the peak size and the final attack ratio for the results in Fig. 6.

Period	P_1	P_2	P_3	P_4
Peak time	189.48	187.35	188.06	186.99
Peak size	258437	314946	295393	320793
Final attack ratio	0.3369820	0.3694439	0.3596954	0.3723046

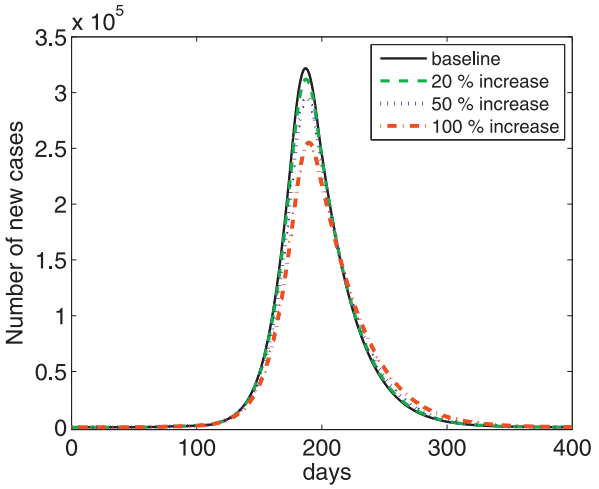


Fig. 7. Comparison of the incidence curves under different treatment rates ϕ_I for the third period (P_3).

Table 6
Comparison of the peak time, the peak size and the final attack ratio for the results in Fig. 7.

Increased amount	20% increase	50% increase	100% increase
Peak time	187.40	188.06	189.71
Peak size	312037	295393	255180
Final attack ratio	0.3685485	0.3596954	0.3381703

of the infective individuals by the governmental policy, we see that the peak time is slightly delayed and the peak sizes decrease to 3%, 8.2% and 20.7% of the actual infective cases, respectively.

4. Conclusion

In this paper, we presented stochastic methods for simulating the epidemic models and applied it to the SLIAR model with treatment for the 2009 H1N1 influenza in South Korea. For the SLIAR model with treatment, we observed that if the initial number of the infective people is relatively large (e.g. the government agents notice an outbreak of an epidemic disease when a considerable number of people have already been infected), then the solution of the deterministic model is very close to that of the stochastic model. But, if the initial number of the infective people is small like the case of the H1N1 spread in Korea, there is a significant quantitative difference between the two solutions. One reason for the difference might be that since there is a small number of the infective people at the initial stage, the infection process should be considered as a probabilistic event between discrete individuals, but the deterministic model assumes continuous changes of population, which can generate some errors in the initial stage of the infection. In such cases, we suggest to use the stochastic modeling.

Computational efficiency is an important issue for stochastic modeling when one tries to simulate several scenarios with different assumptions and parameters. In general, the exact stochastic simulation algorithm (SSA) requires intensive and expensive computations especially when there is a large number of population. In that case, the moment closure approximation is a good alternative way for computation. For example, for the SEIR model based on the parameters in [22], the moment closure approximation takes less than 1 s to obtain the results, but the SSA takes about 0.5 h to obtain the meaningful statistical quantities such as mean and variance based on 10,000 realizations. Of course, when we perform less number of realizations, the SSA takes less time, but the result may have large errors and fluctuations in mean and variance due to the insufficient number of realizations. When one simulates the stochastic epidemic models, we suggest to use the moment closure method rather than the stochastic simulation algorithm, since the moment closure method can capture the important statistical quantities such as mean and variance accurately and more efficiently. Especially, if one wants to see quickly

the simulation results of stochastic epidemic models with different scenarios and various control parameters, the moment closure method is a very useful and efficient computational method.

Acknowledgments

This work was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2014R1A1A2054976).

Appendix A. The controlled and basic reproduction number

The controlled reproduction number R_c is defined as the number of secondary infections by a single infectious individual in only susceptible population with the control measures. In our model with control measures, R_c can be calculated as follows;

$$\begin{aligned}
\frac{dL}{dt} &= \beta SQ - \kappa L - \phi_L L \\
\frac{dL_T}{dt} &= \sigma_s \beta S_T Q - \kappa_T L_T + \phi_L L \\
\frac{dI}{dt} &= p\kappa L - \alpha I - \phi_I I \\
\frac{dI_T}{dt} &= p\tau\kappa_T L_T - \alpha_T I_T + \phi_I I \\
\frac{dA}{dt} &= (1-p)\kappa L - \eta A - \phi_A A \\
\frac{dA_T}{dt} &= (1-p\tau)\kappa_T L_T - \eta_T A_T + \phi_A A \\
\frac{dS}{dt} &= -\beta SQ - \gamma S \\
\frac{dS_T}{dt} &= -\sigma_s \beta S_T Q + \gamma S \\
Q &= (1-q)I + (1-q)\sigma_I I_T + \delta A + \delta\sigma_A A_T
\end{aligned} \tag{16}$$

System (16) has the disease-free equilibrium either $x_0 = ((S_0, S_{T0}, 0, 0, 0, 0, 0, 0)$ with $\gamma = 0$. Let $X = (L, L_T, I, I_T, A, A_T, S, S_T)$, the model (16) can be written as $X' = \mathcal{F}(X) - \mathcal{V}(X)$, where

$$\mathcal{F}(X) = \begin{pmatrix} \beta SQ \\ \sigma_s \beta S_T Q \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \mathcal{V}(X) = \begin{pmatrix} (\kappa + \phi_L)L \\ -\phi_L L + \kappa_T L_T \\ -p\kappa L + (\alpha + \phi_I)I \\ -p\tau\kappa_T L_T - \phi_I I + \alpha_T I_T \\ -(1-p)\kappa L + (\eta + \phi_A)A \\ -(1-p\tau)\kappa_T L_T - \phi_A A + \eta_T A_T \\ \beta SQ + \gamma S \\ \sigma_s \beta S_T Q - \gamma S \end{pmatrix}.$$

Under the assumption, let $\phi_L = 0$. The Jacobian matrices of $\mathcal{F}(X)$, $\mathcal{V}(X)$ at the disease free equilibrium x_0 are partitioned as

$$D\mathcal{F}(x_0) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix}, \qquad D\mathcal{V}(x_0) = \begin{pmatrix} V & 0 \\ J_3 & J_4 \end{pmatrix}, \quad \text{where } J_4 = \begin{pmatrix} \gamma & 0 \\ -\gamma & 0 \end{pmatrix}$$

(The eigenvalues of J_4 have positive real part.) If we assume that $\gamma = 0$, then system (16) has the disease-free equilibrium $x_0 = (S_0, S_{T0}, 0, 0, 0, 0, 0, 0)$. Here, F and V are 6×6 matrices given by

$$F = \begin{pmatrix} 0 & 0 & \beta S_0(1-q) & \beta S_0(1-q)\sigma_I & \beta S_0\delta & \beta S_0\delta\sigma_A \\ 0 & 0 & \sigma_s\beta S_{T0}(1-q) & \sigma_s\beta S_{T0}(1-q)\sigma_I & \sigma_s\beta S_{T0}\delta & \sigma_s\beta S_{T0}\delta\sigma_A \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

$$V = \begin{pmatrix} \kappa+\phi_L & 0 & 0 & 0 & 0 & 0 \\ -\phi_L & \kappa_T & 0 & 0 & 0 & 0 \\ -p\kappa & 0 & \alpha+\phi_I & 0 & 0 & 0 \\ 0 & -p\tau\kappa_T & -\phi_I & \alpha_T & 0 & 0 \\ -(1-p)\kappa & 0 & 0 & 0 & \eta+\phi_A & 0 \\ 0 & -(1-p\tau)\kappa_T & 0 & 0 & -\phi_A & \eta_T \end{pmatrix} \tag{17}$$

FV^{-1} is the next generation matrix of system (13). Especially, since the matrix F has rank 1, the spectral radius of FV^{-1} is equal to the trace of FV^{-1}. For simplicity of calculation we assume mass action incidence $\beta = \beta_0/S_0$ for some constant β_0 in [15]. Thus, the controlled reproduction number of system (13) with $\gamma = 0$ is given by

$$\begin{aligned} R_c &= \varrho(FV^{-1}) \\ &= \beta S_0\left[\frac{(1-q)p}{(\alpha+\phi_I)} + \frac{(1-q)\sigma_I p\phi_I}{\alpha_T(\alpha+\phi_I)} + \frac{\delta(1-p)}{(\eta+\phi_A)} + \frac{\delta\sigma_A\phi_A(1-p)}{\eta_T(\eta+\phi_A)}\right] + \sigma_s\beta S_{T0}\left[\frac{(1-q)\sigma_I p\tau}{\alpha_T} + \frac{\delta\sigma_A(1-p\tau)}{\eta_T}\right]. \end{aligned}$$

Appendix B. Moment equations for SLIAR model

For the moments $\mu_i = E[x_i]$ and $\sigma_{i,j} = E[(x_i-\mu_i)(x_j-\mu_j)]$, we have

$$\begin{aligned}
\frac{d\mu_1}{dt} &= -c_{21}\mu_1 - c_1\sigma_{1,5} - c_2\sigma_{1,6} - c_3\sigma_{1,7} - c_4\sigma_{1,8} - c_1\mu_1\mu_5 - c_2\mu_1\mu_6 - c_3\mu_1\mu_7 - c_4\mu_1\mu_8 \\
\frac{d\mu_2}{dt} &= c_{21}\mu_1 - c_5\sigma_{2,5} - c_6\sigma_{2,6} - c_7\sigma_{2,7} - c_8\sigma_{2,8} - c_5\mu_2\mu_5 - c_6\mu_2\mu_6 - c_7\mu_2\mu_7 - c_8\mu_2\mu_8 \\
\frac{d\mu_3}{dt} &= c_1\sigma_{1,5} + c_2\sigma_{1,6} + c_3\sigma_{1,7} + c_4\sigma_{1,8} - c_{10}\mu_3 - c_9\mu_3 + c_1\mu_1\mu_5 + c_2\mu_1\mu_6 + c_3\mu_1\mu_7 + c_4\mu_1\mu_8 \\
\frac{d\mu_4}{dt} &= c_5\sigma_{2,5} + c_6\sigma_{2,6} + c_7\sigma_{2,7} + c_8\sigma_{2,8} - c_{11}\mu_4 - c_{12}\mu_4 + c_5\mu_2\mu_5 + c_6\mu_2\mu_6 + c_7\mu_2\mu_7 + c_8\mu_2\mu_8 \\
\frac{d\mu_5}{dt} &= c_9\mu_3 - c_{13}\mu_5 - c_{14}\mu_5 - c_{15}\mu_5 \\
\frac{d\mu_6}{dt} &= c_{11}\mu_4 + c_{13}\mu_5 - c_{16}\mu_6 - c_{17}\mu_6 \\
\frac{d\mu_7}{dt} &= c_{10}\mu_3 - c_{18}\mu_7 - c_{19}\mu_7, \quad \frac{d\mu_8}{dt} = c_{12}\mu_4 + c_{18}\mu_7 - c_{20}\mu_8 \\
\frac{d\mu_9}{dt} &= c_{14}\mu_5 + c_{16}\mu_6 + c_{19}\mu_7 + c_{20}\mu_8, \quad \frac{d\mu_{10}}{dt} = c_{15}\mu_5 + c_{17}\mu_6 \\
\frac{d\sigma_{1,1}}{dt} &= c_{21}\mu_1 + c_1\sigma_{1,5} - 2c_1\mu_1\sigma_{1,5} + c_2\sigma_{1,6} - 2c_2\mu_1\sigma_{1,6} + c_3\sigma_{1,7} - 2c_3\mu_1\sigma_{1,7} + c_4\sigma_{1,8} - 2c_4\mu_1\sigma_{1,8} \\
&\quad + c_1\mu_1\mu_5 - 2c_{21}\sigma_{1,1} - 2c_1\mu_5\sigma_{1,1} + c_2\mu_1\mu_6 - 2c_2\sigma_{1,1}\mu_6 + c_3\mu_1\mu_7 - 2c_3\sigma_{1,1}\mu_7 + c_4\mu_1\mu_8 - 2c_4\sigma_{1,1}\mu_8 \\
\frac{d\sigma_{2,2}}{dt} &= c_{21}\mu_1 + 2c_{21}\sigma_{1,2} + c_5\sigma_{2,5} - 2c_5\mu_2\sigma_{2,5} + c_6\sigma_{2,6} - 2c_6\mu_2\sigma_{2,6} + c_7\sigma_{2,7} - 2c_7\mu_2\sigma_{2,7} + c_8\sigma_{2,8} - 2c_8\mu_2\sigma_{2,8} \\
&\quad + c_5\mu_2\mu_5 - 2c_5\mu_5\sigma_{2,2} + c_6\mu_2\mu_6 - 2c_6\sigma_{2,2}\mu_6 + c_7\mu_2\mu_7 - 2c_7\sigma_{2,2}\mu_7 + c_8\mu_2\mu_8 - 2c_8\sigma_{2,2}\mu_8 \\
\frac{d\sigma_{3,3}}{dt} &= c_1\sigma_{1,5} + c_2\sigma_{1,6} + c_3\sigma_{1,7} + c_4\sigma_{1,8} + 2c_1\mu_1\sigma_{3,5} + c_{10}\mu_3 + c_9\mu_3 + 2c_2\mu_1\sigma_{3,6} + 2c_3\mu_1\sigma_{3,7} + 2c_4\mu_1\sigma_{3,8} \\
&\quad + c_1\mu_1\mu_5 + 2c_1\sigma_{1,3}\mu_5 - 2c_{10}\sigma_{3,3} - 2c_9\sigma_{3,3} + c_2\mu_1\mu_6 + 2c_2\sigma_{1,3}\mu_6 + c_3\mu_1\mu_7 \\
&\quad + 2c_3\sigma_{1,3}\mu_7 + c_4\mu_1\mu_8 + 2c_4\sigma_{1,3}\mu_8 \\
\frac{d\sigma_{4,4}}{dt} &= c_5\sigma_{2,5} + c_6\sigma_{2,6} + c_7\sigma_{2,7} + c_8\sigma_{2,8} + 2c_5\mu_2\sigma_{4,5} + 2c_6\mu_2\sigma_{4,6} + 2c_7\mu_2\sigma_{4,7} + 2c_8\mu_2\sigma_{4,8} + c_{11}\mu_4 + c_{12}\mu_4 \\
&\quad + c_5\mu_2\mu_5 + 2c_5\sigma_{2,4}\mu_5 - 2c_{11}\sigma_{4,4} - 2c_{12}\sigma_{4,4} + c_6\mu_2\mu_6 + 2c_6\sigma_{2,4}\mu_6 + c_7\mu_2\mu_7 + 2c_7\sigma_{2,4}\mu_7 \\
&\quad + c_8\mu_2\mu_8 + 2c_8\sigma_{2,4}\mu_8 \\
\frac{d\sigma_{5,5}}{dt} &= 2c_9\sigma_{3,5} + c_9\mu_3 + c_{13}\mu_5 + c_{14}\mu_5 + c_{15}\mu_5 - 2c_{13}\sigma_{5,5} - 2c_{14}\sigma_{5,5} - 2c_{15}\sigma_{5,5} \\
\frac{d\sigma_{6,6}}{dt} &= 2c_{11}\sigma_{4,6} + c_{11}\mu_4 + 2c_{13}\sigma_{5,6} + c_{13}\mu_5 + c_{16}\mu_6 + c_{17}\mu_6 - 2c_{16}\sigma_{6,6} - 2c_{17}\sigma_{6,6} \\
\frac{d\sigma_{7,7}}{dt} &= c_{10}\mu_3 + 2c_{10}\sigma_{3,7} - 2c_{18}\sigma_{7,7} - 2c_{19}\sigma_{7,7} + c_{18}\mu_7 + c_{19}\mu_7 \\
\frac{d\sigma_{8,8}}{dt} &= 2c_{12}\sigma_{4,8} + c_{12}\mu_4 + 2c_{18}\sigma_{7,8} - 2c_{20}\sigma_{8,8} + c_{18}\mu_7 + c_{20}\mu_8
\end{aligned}$$

$$\frac{d\sigma_{9,9}}{dt} = 2c_{14}\sigma_{5,9} + 2c_{16}\sigma_{6,9} + c_{14}\mu_5 + 2c_{19}\sigma_{7,9} + 2c_{20}\sigma_{8,9} + c_{16}\mu_6 + c_{19}\mu_7 + c_{20}\mu_8$$

$$\frac{d\sigma_{10,10}}{dt} = 2c_{15}\sigma_{5,10} + 2c_{17}\sigma_{6,10} + c_{15}\mu_5 + c_{17}\mu_6$$

$$\begin{aligned}\frac{d\sigma_{1,2}}{dt} = {} & -c_{21}\mu_1 - c_{21}\sigma_{1,2} - c_5\sigma_{1,5}\mu_2 - c_6\sigma_{1,6}\mu_2 - c_7\sigma_{1,7}\mu_2 - c_8\sigma_{1,8}\mu_2 \\ & - c_1\mu_1\sigma_{2,5} - c_2\mu_1\sigma_{2,6} - c_3\mu_1\sigma_{2,7} - c_4\mu_1\sigma_{2,8} - c_1\sigma_{1,2}\mu_5 - c_5\sigma_{1,2}\mu_5 \\ & + c_{21}\sigma_{1,1} - c_2\sigma_{1,2}\mu_6 - c_6\sigma_{1,2}\mu_6 - c_3\sigma_{1,2}\mu_7 - c_7\sigma_{1,2}\mu_7 - c_4\sigma_{1,2}\mu_8 \\ & - c_8\sigma_{1,2}\mu_8\end{aligned}$$

$$\begin{aligned}\frac{d\sigma_{1,3}}{dt} = {} & -c_{10}\sigma_{1,3} - c_{21}\sigma_{1,3} - c_9\sigma_{1,3} - c_1\sigma_{1,5} + c_1\mu_1\sigma_{1,5} - c_2\sigma_{1,6} + c_2\mu_1\sigma_{1,6} \\ & - c_3\sigma_{1,7} + c_3\mu_1\sigma_{1,7} - c_4\sigma_{1,8} + c_4\mu_1\sigma_{1,8} - c_1\mu_1\sigma_{3,5} - c_2\mu_1\sigma_{3,6} \\ & - c_3\mu_1\sigma_{3,7} - c_4\mu_1\sigma_{3,8} - c_1\mu_1\mu_5 - c_1\sigma_{1,3}\mu_5 + c_1\mu_5\sigma_{1,1} - c_2\mu_1\mu_6 \\ & - c_2\sigma_{1,3}\mu_6 + c_2\sigma_{1,1}\mu_6 - c_3\mu_1\mu_7 - c_3\sigma_{1,3}\mu_7 + c_3\sigma_{1,1}\mu_7 - c_4\mu_1\mu_8 \\ & - c_4\sigma_{1,3}\mu_8 + c_4\sigma_{1,1}\mu_8\end{aligned}$$

$$\begin{aligned}\frac{d\sigma_{1,4}}{dt} = {} & -c_{11}\sigma_{1,4} - c_{12}\sigma_{1,4} - c_{21}\sigma_{1,4} + c_5\sigma_{1,5}\mu_2 + c_6\sigma_{1,6}\mu_2 + c_7\sigma_{1,7}\mu_2 \\ & + c_8\sigma_{1,8}\mu_2 - c_1\mu_1\sigma_{4,5} - c_2\mu_1\sigma_{4,6} - c_3\mu_1\sigma_{4,7} - c_4\mu_1\sigma_{4,8} + c_5\sigma_{1,2}\mu_5 \\ & - c_1\sigma_{1,4}\mu_5 + c_6\sigma_{1,2}\mu_6 - c_2\sigma_{1,4}\mu_6 + c_7\sigma_{1,2}\mu_7 - c_3\sigma_{1,4}\mu_7 + c_8\sigma_{1,2}\mu_8 \\ & - c_4\sigma_{1,4}\mu_8\end{aligned}$$

$$\begin{aligned}\frac{d\sigma_{1,5}}{dt} = {} & c_9\sigma_{1,3} - c_{13}\sigma_{1,5} - c_{14}\sigma_{1,5} - c_{15}\sigma_{1,5} - c_{21}\sigma_{1,5} - c_2\mu_1\sigma_{5,6} - c_3\mu_1\sigma_{5,7} \\ & - c_4\mu_1\sigma_{5,8} - c_1\sigma_{1,5}\mu_5 - c_2\sigma_{1,5}\mu_6 - c_1\mu_1\sigma_{5,5} - c_3\sigma_{1,5}\mu_7 - c_4\sigma_{1,5}\mu_8\end{aligned}$$

$$\begin{aligned}\frac{d\sigma_{1,6}}{dt} = {} & c_{11}\sigma_{1,4} + c_{13}\sigma_{1,5} - c_{16}\sigma_{1,6} - c_{17}\sigma_{1,6} - c_{21}\sigma_{1,6} - c_1\mu_1\sigma_{5,6} - c_3\mu_1\sigma_{6,7} \\ & - c_4\mu_1\sigma_{6,8} - c_1\sigma_{1,6}\mu_5 - c_2\sigma_{1,6}\mu_6 - c_2\mu_1\sigma_{6,6} - c_3\sigma_{1,6}\mu_7 - c_4\sigma_{1,6}\mu_8\end{aligned}$$

$$\begin{aligned}\frac{d\sigma_{1,7}}{dt} = {} & c_{10}\sigma_{1,3} - c_{18}\sigma_{1,7} - c_{19}\sigma_{1,7} - c_{21}\sigma_{1,7} - c_1\mu_1\sigma_{5,7} - c_2\mu_1\sigma_{6,7} - c_1\sigma_{1,7}\mu_5 \\ & - c_4\mu_1\sigma_{7,8} - c_2\sigma_{1,7}\mu_6 - c_3\mu_1\sigma_{7,7} - c_3\sigma_{1,7}\mu_7 - c_4\sigma_{1,7}\mu_8\end{aligned}$$

$$\begin{aligned}\frac{d\sigma_{1,8}}{dt} = {} & c_{12}\sigma_{1,4} + c_{18}\sigma_{1,7} - c_{20}\sigma_{1,8} - c_{21}\sigma_{1,8} - c_1\mu_1\sigma_{5,8} - c_2\mu_1\sigma_{6,8} - c_1\sigma_{1,8}\mu_5 \\ & - c_3\mu_1\sigma_{7,8} - c_2\sigma_{1,8}\mu_6 - c_4\mu_1\sigma_{8,8} - c_3\sigma_{1,8}\mu_7 - c_4\sigma_{1,8}\mu_8\end{aligned}$$

$$\begin{aligned}\frac{d\sigma_{1,9}}{dt} = {} & c_{14}\sigma_{1,5} + c_{16}\sigma_{1,6} + c_{19}\sigma_{1,7} + c_{20}\sigma_{1,8} - c_{21}\sigma_{1,9} - c_1\mu_1\sigma_{5,9} - c_2\mu_1\sigma_{6,9} \\ & - c_1\sigma_{1,9}\mu_5 - c_3\mu_1\sigma_{7,9} - c_4\mu_1\sigma_{8,9} - c_2\sigma_{1,9}\mu_6 - c_3\sigma_{1,9}\mu_7 - c_4\sigma_{1,9}\mu_8\end{aligned}$$

$$\begin{aligned}\frac{d\sigma_{1,10}}{dt} = {} & c_{15}\sigma_{1,5} + c_{17}\sigma_{1,6} - c_{21}\sigma_{1,10} - c_1\mu_1\sigma_{5,10} - c_2\mu_1\sigma_{6,10} - c_1\sigma_{1,10}\mu_5 \\ & - c_3\mu_1\sigma_{7,10} - c_4\mu_1\sigma_{8,10} - c_2\sigma_{1,10}\mu_6 - c_3\sigma_{1,10}\mu_7 - c_4\sigma_{1,10}\mu_8\end{aligned}$$

$$\begin{aligned}\frac{d\sigma_{2,3}}{dt} = {} & c_{21}\sigma_{1,3} - c_{10}\sigma_{2,3} - c_9\sigma_{2,3} + c_1\mu_1\sigma_{2,5} + c_2\mu_1\sigma_{2,6} + c_3\mu_1\sigma_{2,7} + c_4\mu_1\sigma_{2,8} \\ & - c_5\mu_2\sigma_{3,5} - c_6\mu_2\sigma_{3,6} - c_7\mu_2\sigma_{3,7} - c_8\mu_2\sigma_{3,8} + c_1\sigma_{1,2}\mu_5 - c_5\sigma_{2,3}\mu_5 \\ & + c_2\sigma_{1,2}\mu_6 - c_6\sigma_{2,3}\mu_6 + c_3\sigma_{1,2}\mu_7 - c_7\sigma_{2,3}\mu_7 + c_4\sigma_{1,2}\mu_8 - c_8\sigma_{2,3}\mu_8\end{aligned}$$

$$\begin{aligned}\frac{d\sigma_{2,4}}{dt} = {} & c_{21}\sigma_{1,4} - c_{11}\sigma_{2,4} - c_{12}\sigma_{2,4} - c_5\sigma_{2,5} + c_5\mu_2\sigma_{2,5} - c_6\sigma_{2,6} + c_6\mu_2\sigma_{2,6} \\ & - c_7\sigma_{2,7} + c_7\mu_2\sigma_{2,7} - c_8\sigma_{2,8} + c_8\mu_2\sigma_{2,8} - c_5\mu_2\sigma_{4,5} - c_6\mu_2\sigma_{4,6} \\ & - c_7\mu_2\sigma_{4,7} - c_8\mu_2\sigma_{4,8} - c_5\mu_2\mu_5 - c_5\sigma_{2,4}\mu_5 + c_5\mu_5\sigma_{2,2} - c_6\mu_2\mu_6 \\ & - c_6\sigma_{2,4}\mu_6 + c_6\sigma_{2,2}\mu_6 - c_7\mu_2\mu_7 - c_7\sigma_{2,4}\mu_7 + c_7\sigma_{2,2}\mu_7 - c_8\mu_2\mu_8 \\ & - c_8\sigma_{2,4}\mu_8 + c_8\sigma_{2,2}\mu_8\end{aligned}$$

$$\begin{aligned}\frac{d\sigma_{2,5}}{dt} = {} & c_{21}\sigma_{1,5} + c_9\sigma_{2,3} - c_{13}\sigma_{2,5} - c_{14}\sigma_{2,5} - c_{15}\sigma_{2,5} - c_6\mu_2\sigma_{5,6} - c_7\mu_2\sigma_{5,7} \\ & - c_8\mu_2\sigma_{5,8} - c_5\sigma_{2,5}\mu_5 - c_6\sigma_{2,5}\mu_6 - c_5\mu_2\sigma_{5,5} - c_7\sigma_{2,5}\mu_7 - c_8\sigma_{2,5}\mu_8\end{aligned}$$

$$\begin{aligned}\frac{d\sigma_{2,6}}{dt} = {} & c_{21}\sigma_{1,6} + c_{11}\sigma_{2,4} + c_{13}\sigma_{2,5} - c_{16}\sigma_{2,6} - c_{17}\sigma_{2,6} - c_5\mu_2\sigma_{5,6} - c_7\mu_2\sigma_{6,7} \\ & - c_8\mu_2\sigma_{6,8} - c_5\sigma_{2,6}\mu_5 - c_6\sigma_{2,6}\mu_6 - c_6\mu_2\sigma_{6,6} - c_7\sigma_{2,6}\mu_7 - c_8\sigma_{2,6}\mu_8\end{aligned}$$

$$\begin{aligned}
\frac{d\sigma_{2,7}}{dt} &= c_{21}\sigma_{1,7} + c_{10}\sigma_{2,3} - c_{18}\sigma_{2,7} - c_{19}\sigma_{2,7} - c_5\mu_2\sigma_{5,7} - c_6\mu_2\sigma_{6,7} - c_5\sigma_{2,7}\mu_5 \\
&\quad - c_8\mu_2\sigma_{7,8} - c_6\sigma_{2,7}\mu_6 - c_7\mu_2\sigma_{7,7} - c_7\sigma_{2,7}\mu_7 - c_8\sigma_{2,7}\mu_8 \\
\frac{d\sigma_{2,8}}{dt} &= c_{21}\sigma_{1,8} + c_{12}\sigma_{2,4} + c_{18}\sigma_{2,7} - c_{20}\sigma_{2,8} - c_5\mu_2\sigma_{5,8} - c_6\mu_2\sigma_{6,8} - c_5\sigma_{2,8}\mu_5 \\
&\quad - c_7\mu_2\sigma_{7,8} - c_6\sigma_{2,8}\mu_6 - c_8\mu_2\sigma_{8,8} - c_7\sigma_{2,8}\mu_7 - c_8\sigma_{2,8}\mu_8 \\
\frac{d\sigma_{2,9}}{dt} &= c_{21}\sigma_{1,9} + c_{14}\sigma_{2,5} + c_{16}\sigma_{2,6} + c_{19}\sigma_{2,7} + c_{20}\sigma_{2,8} - c_5\mu_2\sigma_{5,9} - c_6\mu_2\sigma_{6,9} \\
&\quad - c_5\sigma_{2,9}\mu_5 - c_7\mu_2\sigma_{7,9} - c_8\mu_2\sigma_{8,9} - c_6\sigma_{2,9}\mu_6 - c_7\sigma_{2,9}\mu_7 - c_8\sigma_{2,9}\mu_8 \\
\frac{d\sigma_{2,10}}{dt} &= c_{21}\sigma_{1,10} + c_{15}\sigma_{2,5} + c_{17}\sigma_{2,6} - c_5\mu_2\sigma_{5,10} - c_6\mu_2\sigma_{6,10} - c_5\sigma_{2,10}\mu_5 \\
&\quad - c_7\mu_2\sigma_{7,10} - c_8\mu_2\sigma_{8,10} - c_6\sigma_{2,10}\mu_6 - c_7\sigma_{2,10}\mu_7 - c_8\sigma_{2,10}\mu_8 \\
\frac{d\sigma_{3,4}}{dt} &= -c_{10}\sigma_{3,4} - c_{11}\sigma_{3,4} - c_{12}\sigma_{3,4} - c_9\sigma_{3,4} + c_5\mu_2\sigma_{3,5} + c_6\mu_2\sigma_{3,6} + c_7\mu_2\sigma_{3,7} \\
&\quad + c_8\mu_2\sigma_{3,8} + c_1\mu_1\sigma_{4,5} + c_2\mu_1\sigma_{4,6} + c_3\mu_1\sigma_{4,7} + c_4\mu_1\sigma_{4,8} + c_1\sigma_{1,4}\mu_5 \\
&\quad + c_5\sigma_{2,3}\mu_5 + c_2\sigma_{1,4}\mu_6 + c_6\sigma_{2,3}\mu_6 + c_3\sigma_{1,4}\mu_7 + c_7\sigma_{2,3}\mu_7 \\
&\quad + c_4\sigma_{1,4}\mu_8 + c_8\sigma_{2,3}\mu_8 \\
\frac{d\sigma_{3,5}}{dt} &= -c_{10}\sigma_{3,5} - c_{13}\sigma_{3,5} - c_{14}\sigma_{3,5} - c_{15}\sigma_{3,5} - c_9\sigma_{3,5} - c_9\mu_3 + c_2\mu_1\sigma_{5,6} \\
&\quad + c_3\mu_1\sigma_{5,7} + c_4\mu_1\sigma_{5,8} + c_1\sigma_{1,5}\mu_5 + c_9\sigma_{3,3} + c_2\sigma_{1,5}\mu_6 + c_1\mu_1\sigma_{5,5} \\
&\quad + c_3\sigma_{1,5}\mu_7 + c_4\sigma_{1,5}\mu_8 \\
\frac{d\sigma_{3,6}}{dt} &= c_{11}\sigma_{3,4} + c_{13}\sigma_{3,5} - c_{10}\sigma_{3,6} - c_{16}\sigma_{3,6} - c_{17}\sigma_{3,6} - c_9\sigma_{3,6} + c_1\mu_1\sigma_{5,6} \\
&\quad + c_3\mu_1\sigma_{6,7} + c_4\mu_1\sigma_{6,8} + c_1\sigma_{1,6}\mu_5 + c_2\sigma_{1,6}\mu_6 + c_2\mu_1\sigma_{6,6} + c_3\sigma_{1,6}\mu_7 \\
&\quad + c_4\sigma_{1,6}\mu_8 \\
\frac{d\sigma_{3,7}}{dt} &= -c_{10}\mu_3 - c_{10}\sigma_{3,7} - c_{18}\sigma_{3,7} - c_{19}\sigma_{3,7} - c_9\sigma_{3,7} + c_1\mu_1\sigma_{5,7} + c_2\mu_1\sigma_{6,7} \\
&\quad + c_1\sigma_{1,7}\mu_5 + c_4\mu_1\sigma_{7,8} + c_{10}\sigma_{3,3} + c_2\sigma_{1,7}\mu_6 + c_3\mu_1\sigma_{7,7} + c_3\sigma_{1,7}\mu_7 \\
&\quad + c_4\sigma_{1,7}\mu_8 \\
\frac{d\sigma_{3,8}}{dt} &= c_{12}\sigma_{3,4} + c_{18}\sigma_{3,7} - c_{10}\sigma_{3,8} - c_{20}\sigma_{3,8} - c_9\sigma_{3,8} + c_1\mu_1\sigma_{5,8} + c_2\mu_1\sigma_{6,8} \\
&\quad + c_1\sigma_{1,8}\mu_5 + c_3\mu_1\sigma_{7,8} + c_2\sigma_{1,8}\mu_6 + c_4\mu_1\sigma_{8,8} + c_3\sigma_{1,8}\mu_7 + c_4\sigma_{1,8}\mu_8 \\
\frac{d\sigma_{3,9}}{dt} &= c_{14}\sigma_{3,5} + c_{16}\sigma_{3,6} + c_{19}\sigma_{3,7} + c_{20}\sigma_{3,8} - c_{10}\sigma_{3,9} - c_9\sigma_{3,9} + c_1\mu_1\sigma_{5,9} \\
&\quad + c_2\mu_1\sigma_{6,9} + c_1\sigma_{1,9}\mu_5 + c_3\mu_1\sigma_{7,9} + c_4\mu_1\sigma_{8,9} + c_2\sigma_{1,9}\mu_6 + c_3\sigma_{1,9}\mu_7 \\
&\quad + c_4\sigma_{1,9}\mu_8 \\
\frac{d\sigma_{3,10}}{dt} &= c_{15}\sigma_{3,5} + c_{17}\sigma_{3,6} - c_{10}\sigma_{3,10} - c_9\sigma_{3,10} + c_1\mu_1\sigma_{5,10} + c_2\mu_1\sigma_{6,10} \\
&\quad + c_1\sigma_{1,10}\mu_5 + c_3\mu_1\sigma_{7,10} + c_4\mu_1\sigma_{8,10} + c_2\sigma_{1,10}\mu_6 \\
&\quad + c_3\sigma_{1,10}\mu_7 + c_4\sigma_{1,10}\mu_8 \\
\frac{d\sigma_{4,5}}{dt} &= c_9\sigma_{3,4} - c_{11}\sigma_{4,5} - c_{12}\sigma_{4,5} - c_{13}\sigma_{4,5} - c_{14}\sigma_{4,5} - c_{15}\sigma_{4,5} + c_6\mu_2\sigma_{5,6} \\
&\quad + c_7\mu_2\sigma_{5,7} + c_8\mu_2\sigma_{5,8} + c_5\sigma_{2,5}\mu_5 + c_6\sigma_{2,5}\mu_6 + c_5\mu_2\sigma_{5,5} \\
&\quad + c_7\sigma_{2,5}\mu_7 + c_8\sigma_{2,5}\mu_8 \\
\frac{d\sigma_{4,6}}{dt} &= c_{13}\sigma_{4,5} - c_{11}\sigma_{4,6} - c_{12}\sigma_{4,6} - c_{16}\sigma_{4,6} - c_{17}\sigma_{4,6} - c_{11}\mu_4 + c_5\mu_2\sigma_{5,6} \\
&\quad + c_7\mu_2\sigma_{6,7} + c_8\mu_2\sigma_{6,8} + c_5\sigma_{2,6}\mu_5 + c_{11}\sigma_{4,4} + c_6\sigma_{2,6}\mu_6 + c_6\mu_2\sigma_{6,6} \\
&\quad + c_7\sigma_{2,6}\mu_7 + c_8\sigma_{2,6}\mu_8 \\
\frac{d\sigma_{4,7}}{dt} &= c_{10}\sigma_{3,4} - c_{11}\sigma_{4,7} - c_{12}\sigma_{4,7} - c_{18}\sigma_{4,7} - c_{19}\sigma_{4,7} + c_5\mu_2\sigma_{5,7} + c_6\mu_2\sigma_{6,7} \\
&\quad + c_5\sigma_{2,7}\mu_5 + c_8\mu_2\sigma_{7,8} + c_6\sigma_{2,7}\mu_6 + c_7\mu_2\sigma_{7,7} + c_7\sigma_{2,7}\mu_7 + c_8\sigma_{2,7}\mu_8 \\
\frac{d\sigma_{4,8}}{dt} &= c_{18}\sigma_{4,7} - c_{11}\sigma_{4,8} - c_{12}\sigma_{4,8} - c_{20}\sigma_{4,8} - c_{12}\mu_4 + c_5\mu_2\sigma_{5,8} + c_6\mu_2\sigma_{6,8} \\
&\quad + c_5\sigma_{2,8}\mu_5 + c_7\mu_2\sigma_{7,8} + c_{12}\sigma_{4,4} + c_6\sigma_{2,8}\mu_6 + c_8\mu_2\sigma_{8,8}
\end{aligned}$$

$$
\begin{aligned}
&+ c_7\sigma_{2,8}\mu_7 + c_8\sigma_{2,8}\mu_8\\
\frac{d\sigma_{4,9}}{dt} &= c_{14}\sigma_{4,5} + c_{16}\sigma_{4,6} + c_{19}\sigma_{4,7} + c_{20}\sigma_{4,8} - c_{11}\sigma_{4,9} - c_{12}\sigma_{4,9} + c_5\mu_2\sigma_{5,9}\\
&+ c_6\mu_2\sigma_{6,9} + c_5\sigma_{2,9}\mu_5 + c_7\mu_2\sigma_{7,9} + c_8\mu_2\sigma_{8,9} + c_6\sigma_{2,9}\mu_6 + c_7\sigma_{2,9}\mu_7\\
&+ c_8\sigma_{2,9}\mu_8\\
\frac{d\sigma_{4,10}}{dt} &= c_{15}\sigma_{4,5} + c_{17}\sigma_{4,6} - c_{11}\sigma_{4,10} - c_{12}\sigma_{4,10} + c_5\mu_2\sigma_{5,10} + c_6\mu_2\sigma_{6,10}\\
&+ c_5\sigma_{2,10}\mu_5 + c_7\mu_2\sigma_{7,10} + c_8\mu_2\sigma_{8,10} + c_6\sigma_{2,10}\mu_6\\
&+ c_7\sigma_{2,10}\mu_7 + c_8\sigma_{2,10}\mu_8\\
\frac{d\sigma_{5,6}}{dt} &= c_9\sigma_{3,6} + c_{11}\sigma_{4,5} - c_{13}\sigma_{5,6} - c_{14}\sigma_{5,6} - c_{15}\sigma_{5,6} - c_{16}\sigma_{5,6} - c_{17}\sigma_{5,6}\\
&- c_{13}\mu_5 + c_{13}\sigma_{5,5}\\
\frac{d\sigma_{5,7}}{dt} &= c_{10}\sigma_{3,5} + c_9\sigma_{3,7} - c_{13}\sigma_{5,7} - c_{14}\sigma_{5,7} - c_{15}\sigma_{5,7} - c_{18}\sigma_{5,7} - c_{19}\sigma_{5,7}\\
\frac{d\sigma_{5,8}}{dt} &= c_9\sigma_{3,8} + c_{12}\sigma_{4,5} + c_{18}\sigma_{5,7} - c_{13}\sigma_{5,8} - c_{14}\sigma_{5,8} - c_{15}\sigma_{5,8} - c_{20}\sigma_{5,8}\\
\frac{d\sigma_{5,9}}{dt} &= c_9\sigma_{3,9} + c_{16}\sigma_{5,6} + c_{19}\sigma_{5,7} + c_{20}\sigma_{5,8} - c_{13}\sigma_{5,9} - c_{14}\sigma_{5,9} - c_{15}\sigma_{5,9}\\
&- c_{14}\mu_5 + c_{14}\sigma_{5,5}\\
\frac{d\sigma_{5,10}}{dt} &= c_9\sigma_{3,10} + c_{17}\sigma_{5,6} - c_{13}\sigma_{5,10} - c_{14}\sigma_{5,10} - c_{15}\sigma_{5,10} - c_{15}\mu_5 + c_{15}\sigma_{5,5}\\
\frac{d\sigma_{6,7}}{dt} &= c_{10}\sigma_{3,6} + c_{11}\sigma_{4,7} + c_{13}\sigma_{5,7} - c_{16}\sigma_{6,7} - c_{17}\sigma_{6,7} - c_{18}\sigma_{6,7} - c_{19}\sigma_{6,7}\\
\frac{d\sigma_{6,8}}{dt} &= c_{12}\sigma_{4,6} + c_{11}\sigma_{4,8} + c_{13}\sigma_{5,8} + c_{18}\sigma_{6,7} - c_{16}\sigma_{6,8} - c_{17}\sigma_{6,8} - c_{20}\sigma_{6,8}\\
\frac{d\sigma_{6,9}}{dt} &= c_{11}\sigma_{4,9} + c_{14}\sigma_{5,6} + c_{13}\sigma_{5,9} + c_{19}\sigma_{6,7} + c_{20}\sigma_{6,8} - c_{16}\sigma_{6,9} - c_{17}\sigma_{6,9}\\
&- c_{16}\mu_6 + c_{16}\sigma_{6,6}\\
\frac{d\sigma_{6,10}}{dt} &= c_{11}\sigma_{4,10} + c_{15}\sigma_{5,6} + c_{13}\sigma_{5,10} - c_{16}\sigma_{6,10} - c_{17}\sigma_{6,10} - c_{17}\mu_6 + c_{17}\sigma_{6,6}\\
\frac{d\sigma_{7,8}}{dt} &= c_{10}\sigma_{3,8} + c_{12}\sigma_{4,7} - c_{18}\sigma_{7,8} - c_{19}\sigma_{7,8} - c_{20}\sigma_{7,8} + c_{18}\sigma_{7,7} - c_{18}\mu_7\\
\frac{d\sigma_{7,9}}{dt} &= c_{10}\sigma_{3,9} + c_{14}\sigma_{5,7} + c_{16}\sigma_{6,7} + c_{20}\sigma_{7,8} - c_{18}\sigma_{7,9} - c_{19}\sigma_{7,9} + c_{19}\sigma_{7,7}\\
&- c_{19}\mu_7\\
\frac{d\sigma_{7,10}}{dt} &= c_{10}\sigma_{3,10} + c_{15}\sigma_{5,7} + c_{17}\sigma_{6,7} - c_{18}\sigma_{7,10} - c_{19}\sigma_{7,10}\\
\frac{d\sigma_{8,9}}{dt} &= c_{12}\sigma_{4,9} + c_{14}\sigma_{5,8} + c_{16}\sigma_{6,8} + c_{19}\sigma_{7,8} + c_{18}\sigma_{7,9} - c_{20}\sigma_{8,9} + c_{20}\sigma_{8,8}\\
&- c_{20}\mu_8\\
\frac{d\sigma_{8,10}}{dt} &= c_{12}\sigma_{4,10} + c_{15}\sigma_{5,8} + c_{17}\sigma_{6,8} + c_{18}\sigma_{7,10} - c_{20}\sigma_{8,10}\\
\frac{d\sigma_{9,10}}{dt} &= c_{15}\sigma_{5,9} + c_{14}\sigma_{5,10} + c_{17}\sigma_{6,9} + c_{16}\sigma_{6,10} + c_{19}\sigma_{7,10} + c_{20}\sigma_{8,10}
\end{aligned}
$$

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