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Investigation of random and Stochastic models for CD8-T cell immune response

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Abstract: In this study, a mathematical model of pathogen-specific CD8 T Cell immune response has been investigated from a random perspective. The equation system presented by Crauste et al. has been modified for modeling the random nature of T Cell immune responses. Stochastic noise and random effects have been added to the deterministic system and the results have been analyzed for investigating the dynamics of the immune response. Randomness of the event has been interpreted by comparison of the results for the deterministic, random and stochastic cases.

Keywords: Random differential equation, Stochastic differential equation, Milstein scheme, random effect, simulation.

1 Introduction

Random modeling of real life events has been gaining more attraction in the last few decades, since the numbers of random studies in biology, engineering and medicine have increased noticeably. The use of mean-square calculus for the analysis of random differential equations and approximation methods such as Euler-Maruyama and Milstein schemes for stochastic differential equations provide reliable basis for the investigation of randomness in nature.

Health-related models in the fields of medicine, biology, biochemistry and etc. have an important role in understanding diseases and improving the health status of communities. Another research area in mathematical modeling is the modeling of immune system-related issues [8, 9]. Immunological memory is a crucial point in understanding and modeling the dynamics of the immune response. In this study, a random modeling approach will be used for modeling CD8 T cell (or CD8+ T Cell) immune response.

The dynamics of acquiring T-cell memory to a pathogen consists of several stages. After infection by a virus or bacteria, the existing naive CD8 T cells are rapidly transformed into effector T cells. The pathogen is encountered by the effector T cells. Once the infection is cleared, the effector CD8 T cells differentiate and become memory T cells, which act as the key for a swift response to an infection by the same pathogen [1]. There are several mathematical models in the literature for analyzing CD8 T Cell immune response prediction [2–4].

In this study, the equation system given by Crauste et al. [5], which model the evolution of CD8 T cell numbers for an infection by three pathogens will be used for analyzing the random dynamics of the immune response. The random analysis will enable the investigation of the effects of natural fluctutations through the infection process. This random modeling approach has been proposed by the authors and has been used for analyzing disease dynamics such as Polio [6] and Hepatitis C [7]. Using these previous studies as a motivation, a random perspective for T cell immune responses will

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be investigated in this study. Random and stochastic differential equations will be obtained by using random effects and stochastic noise terms in the model and the results will be compared for these two cases along with the results from the deterministic system. The second section contains the deterministic model given in the referred study. The third and fourth sections contain the random and stochastic models along with their results, respectively. A comparison of the results and conclusions are given as a final remark of the study.

2 The deterministic model

The study of Crauste et al. contains predictions from a sytem consisting of four ordinary differential equations for modeling T Cell immune response to simultaneous infections by multiple pathogens [5]. The model is given as:

$$\begin{aligned}
\frac{d}{dt}N(t) &= -\mu_N N - \delta_{NE} PN, \\
\frac{d}{dt}E(t) &= \delta_{NE} PN + \rho_E PE - \mu_E E^2 - \delta_{EM} E, \\
\frac{d}{dt}M(t) &= -\mu_M M + \delta_{EM} E \\
\frac{d}{dt}P(t) &= \rho_P P^2 - \mu_P EP - \mu_P^0 P.
\end{aligned} \tag{1}$$

Here, $N(t)$ denotes the number of naive CD8 T cells, $E(t)$ denotes the number of effector CD8 T cells and $M(t)$ denotes the number of memory CD8 T cells while $P(t)$ is the amount of pathogen presented to CD8 T cells. The variable t denotes the time which is the number of days. This model is the modified verison of the original system scaled to an initial pathogen amount of $P(0) = 1$. Hence, the initial values of the system are given as follows, modeling the correspoding numbers of the naive, effector and memory CD8 T cells at the beginning of the infection with the inital pathogen number as,

$$N(0) = 5000, E(0) = 0, M(0) = 0, P(0) = 1. \tag{2}$$

The parameters of the model are given as follows:

Table 1: The descriptions, units and values of the parameters in (1)

Parameter	Description	Value	Unit
μ_N	Naive cells death rate	10^{-2}	$\frac{1}{day}$
δ_{NE}	Naive cells differentiation rate	10^{-3}	$\frac{1}{day}$
ρ_E	Effector cells proliferation rate	1	$\frac{1}{day}$
μ_E	Effector cells death rate	10^{-8}	$\frac{1}{day}$
δ_{EM}	Effector cells differentiation rate	10^{-5}	$\frac{1}{day}$
μ_M	Memory cells death rate	0	$\frac{1}{day}$
ρ_P	Pathogen proliferation rate	10^{-4}	$\frac{1}{day}$
μ_P	Effector dependent Pathogen death rate	10^{-8}	$\frac{1}{day}$
μ_P^0	Pathogen natural death rate	10^{-4}	$\frac{1}{day \times gene}$

The values of the parameters have been obtained from the referred study [5]. Using these parameters and initial conditions, the model (1) will be analyzed under random effects. It should be noted that any of the existing models in the literature can also be used for analyzing the random dynamics of CD8 T cell immune response.

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2.1 Deterministic results for CD8 T cell model

Equation system (1) is analyzed deterministically with the parameter values in Table 1 and the initial conditions (2) using the lower order numerical schemes in MATLAB. The results are shown in the figure below (Figure 1). The maximum and minimum values of the model variables $N(t)$, $E(t)$, $M(t)$ and $P(t)$ are given in the following table (Table 2).

Table 2: Extremum values of variables

Variable	(Max. Value, Time)	(Min. Value, Time)
$N(t)$	$(5000, 0)$	$(1805, 100)$
$M(t)$	$(3.684 \times 10^7, 18.1)$	$(0, 0)$
$E(t)$	$(5965, 100)$	$(0, 0)$
$P(t)$	$(1, 0)$	$(0.002529, 100)$

The deterministic model shows that through the 100 days investigation period, the number of naive CD8 T cells decreases constantly from its initial maximum value of 5000 to its minimum value of 1805 at $t = 100$. It is seen that the number of effector cells get their maximum value 3.684×10^7 at $t = 18.1$ whereas the maximum number of memory T cells is obtained at $t = 100$ with 5965. The number of effector cells at the end of the process ($t = 100$) is 1.526×10^6. The number of pathogens vary between its minimum value 0.002529 at $t = 100$ and its initial maximum number.

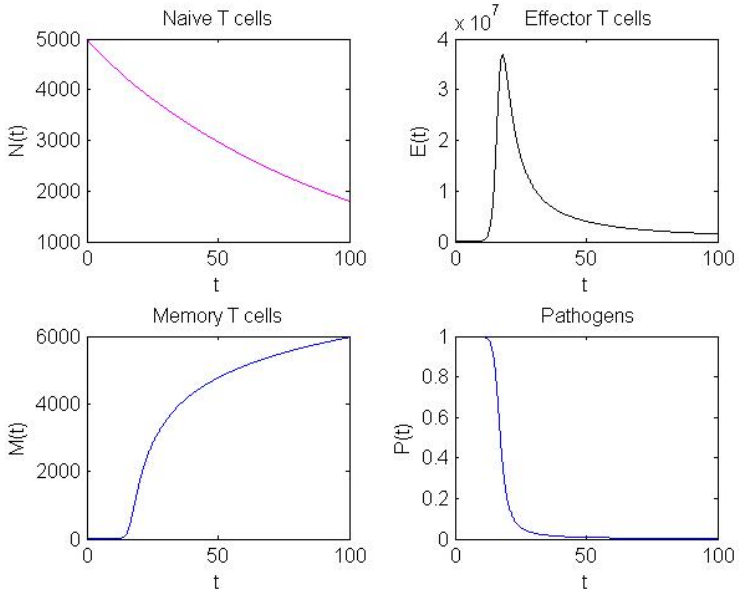

Fig. 1: Deterministic results for (1)

3 Random model of CD8 T cell immune response

The rates for cell death, differentiation, proliferation etc. are not independent from the conditions in which the human body exists and hence, the varying environment conditions such as the climate, geography and etc. may mean a fluctutation for

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these rates as well. Altough these fluctutations may sometimes be ignorable, in some cases a modeling approach which takes the variability of these rates into consideration is more appropriate. In this study, the parameters of system (1) will be transformed into random variables with normal distribution to model the random nature of CD8 T cell immune response. Rates for cell death, differentiation etc. will be considered as random values to analyze the statistical characteristics of the event. The newly defined random parameters are given as follows,

$$\begin{aligned}
&\mu_N \sim N(a_1, s_1^2),\ \delta_{NE} \sim N(a_2, s_2^2),\ \rho_E \sim N(a_3, s_3^2),\\
&\mu_E \sim N(a_4, s_4^2),\ \delta_{EM} \sim N(a_5, s_5^2),\ \mu_M \sim N(a_6, s_6^2),\\
&\rho_P \sim N(a_7, s_7^2),\ \mu_P \sim N(a_8, s_8^2),\ \mu_P^0 \sim N(a_9, s_9^2).
\end{aligned}$$

Here, $a_i, i = \overline{1,9}$ and $s_i^2, i = \overline{1,9}$ are the means and variances of the distributions assumed for the parameters, respectively. Normal distribution is used for the random parameters since the exact distributions of the parameters are unknown and normal distribution is the most suitable choice for random variables with unknwon distributions that are affected by many external factors. The random parameters will be assigned mean values and standard deviations such that their expectation will be equal to their deterministic values and their coefficients of variation will be 5%. Hence, $a_i, i = \overline{1,9}$ and $s_i^2, i = \overline{1,9}$ will be assigned as below ($\chi_i, i = \overline{1,9}$ are independent standard normal random variables),

$$\begin{aligned}
&\mu_N = 10^{-2} + 5\times 10^{-4}\chi_1,\ \delta_{NE} = 10^{-3} + 5\times 10^{-5}\chi_2,\ \rho_E = 1 + 0.05\chi_3,\\
&\mu_E = 10^{-8} + 5\times 10^{-10}\chi_4,\ \delta_{EM} = 10^{-5} + 5\times 10^{-7}\chi_5,\ \mu_M = 0 + 0\times\chi_6,\\
&\rho_P = 10^{-4} + 5\times 10^{-6}\chi_7,\ \mu_P = 10^{-8} + 5\times 10^{-10}\chi_8,\ \mu_P^0 = 10^{-4} + 5\times 10^{-6}\chi_9.
\end{aligned}$$

Using these random parameters, (1) becomes (note that the parameter μ_M have been included in the model as well since it can assume a value other than 0 if another set of values are used for the model),

$$\begin{aligned}
\frac{d}{dt}N(t) =& -(10^{-2} + 5\times 10^{-4}\chi_1)N - (10^{-3} + 5\times 10^{-5}\chi_2)PN,\\
\frac{d}{dt}E(t) =& (10^{-3} + 5\times 10^{-5}\chi_2)PN + (1 + 0.05\chi_3)PE\\
&- (10^{-8} + 5\times 10^{-10}\chi_4)E^2 - (10^{-5} + 5\times 10^{-7}\chi_5)E,\\
\frac{d}{dt}M(t) =& -(0 + 0\times\chi_6)M + (10^{-5} + 5\times 10^{-7}\chi_5)E\\
\frac{d}{dt}P(t) =& (10^{-4} + 5\times 10^{-6}\chi_7)P^2 - (10^{-8} + 5\times 10^{-10}\chi_8)EP\\
&- (10^{-4} + 5\times 10^{-6}\chi_9)P.
\end{aligned} \tag{3}$$

3.1 Random results

The random model (3) was simulated in MATLAB using a number of repititions. Using the results of these simulations, statistical characteristics of the random model are given below.

3.1.1 Solution Curves

The solution curves of the random model (3) denote the results for a single trial of the random event. The solution curves are given below (Figure 2). Minimum and maximum values for the variables of (3) in this particular realization are given in the following table below (Table 3).

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Table 3: Extremum values of variables

Variable	(Max. Value, Time)	(Min. Value, Time)
$N(t)$	$(5000,0)$	$(1750,100)$
$M(t)$	$(3.227\times10^7,20)$	$(0,0)$
$E(t)$	$(5819,100)$	$(0,0)$
$P(t)$	$(1,0)$	$(0.003659,100)$

The similarity between Figures 1 and 2 underlines the accurate modeling performance of the random model. This accuracy can also be seen from the extremum values given in Tables 2 and 3.

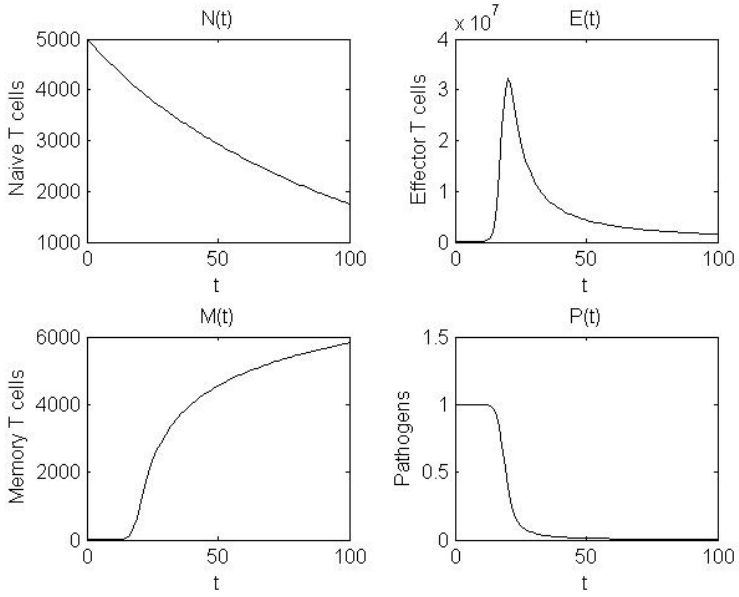

Fig. 2: Solution curves for a realization of (3)

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3.1.2 Expected values

Using the simulations of the random model (3), the expectations of the variables are shown in the figure below (Figure 3).

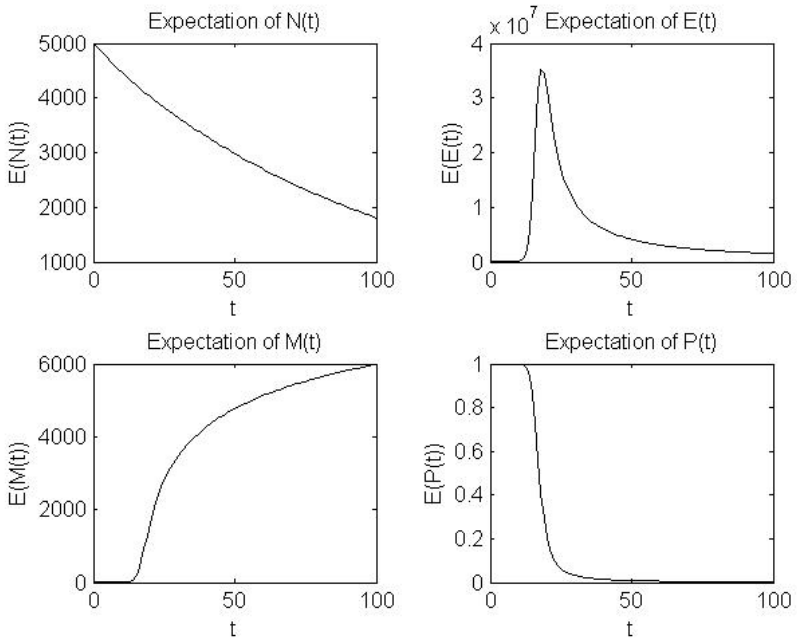

Fig. 3: Expectations of the random model

Extremum values of the model components can be seen in the following table (Table 4).

Table 4: Extremum values of the expectations

Variable	(Max. Value, Time)	(Min. Value, Time)
$E(N(t))$	$(5000,0)$	$(1807,100)$
$E(M(t))$	$(3.516\times 10^7,18)$	$(0,0)$
$E(E(t))$	$(5984,100)$	$(0,0)$
$E(P(t))$	$(1,0)$	$(0.002595,100)$

The expected values represent the expectations of the number of naive CD8 T cells, effector CD8 T cells, memory CD8 T cells and pathogens for the random model (3). A correspondance with the results in Tables 2 and 4 suggest that the random model is just as capable for modeling the CD8 T cell immune response. However, the random model also enables the researcher to analyze the variations, standart deviations and other tools for analyzing the distribution of data in real life occurences, which can not be made with the deterministic model. The random model also shows the constant decrease in $N(t)$, the early increases in $E(t)$ and $M(t)$ and the early decrease in $P(t)$, just like the deterministic model.

3.1.3 Variances

The results for the variances in model (3) have been achieved by using the results of the simulations. The results are shown in the following figure (Figure 4).

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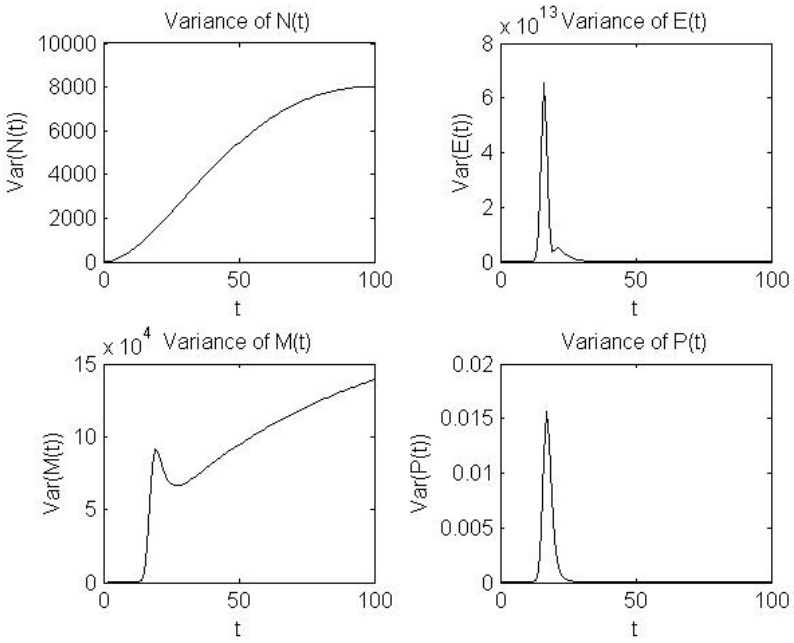

Fig. 4: Variances of the random model

Extremum values of the variations are also given in the following table (Table 5).

Table 5: Extremum values of the expectations

Variable	(Max. Value, Time)	(Min. Value, Time)
$E(N(t))$	$(5000,0)$	$(1807,100)$
$E(M(t))$	$(3.516\times 10^7,18)$	$(0,0)$
$E(E(t))$	$(5984,100)$	$(0,0)$
$E(P(t))$	$(1,0)$	$(0.002595,100)$

The minimum variations are all achieved in the beginning of the process whereas the maximum variations are obtained at $t = 100$ for $N(t)$ and $M(t)$, and at $t = 16$ for $E(t)$ and $t = 17$ for $P(t)$.

3.1.4 Confidence Intervals

The confidence intervals for the expected values of the components of the random model (3) are given in the following figure and have been obtained from the simulation results (Figure 4).
The confidence intervals for the expected values are demonstrated for 3 standard deviations around the mean value of the random variables. This shows aa approximately 99% confidence interval for a random variable with normal distribution. The dahsed line below and above the bold inner line shows the upper and lower limits of the confidence intervals, whereas the solid line shows the expected values.
The extremum values for the expectations of the model components within the 99% confidence intervals are shown in the following table (Table 6).

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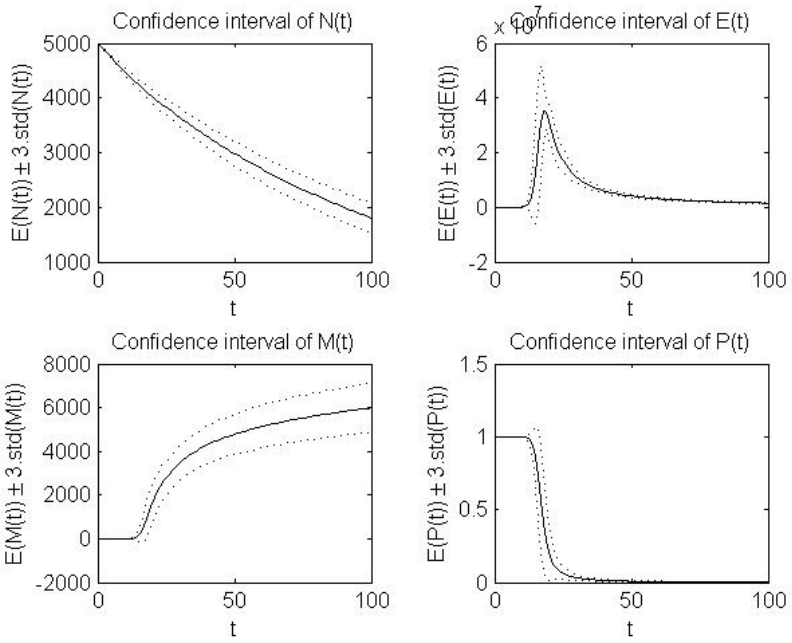

Fig. 5: Confidence intervals of the random model

Table 6: Extremum values of the expectations within the confidence intervals

Variable	(Max. Value, Time)	(Min. Value, Time)
$CI: E(N(t))$	$(5000, 0)$	$(1538, 100)$
$CI: E(M(t))$	$(5.174 \times 10^7, 17)$	$(0, 0)$
$CI: E(E(t))$	$(7102, 100)$	$(0, 0)$
$CI: E(P(t))$	$(1.069, 15)$	$(0.0008456, 100)$

The random behaviour of CD8 T cell immune response can be analyzed by using the random model (3), which both shows the deterministic behaviour of the model through the analysis of expectations and also shows the dispersion of data for different trials of the event through the analysis of variances and confidence intervals.

4 Stochastic Model of CD8 T Cell Immune Response

Another option for the random analysis of CD8 T cell immune response model is using stochastic differential equations (SDE). Stochastic noise will be added to the deterministic differential equations of (1) to obtain equations of the form

$$dX_t = a(t, X_t)dt + b(t, X_t)dW_t.$$

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These SDEs with Ito integration will be analyzed by the popular Euler-Maruyama and Milstein stochastic approximation schemes [10]. If stochastic noise is added to the equations of (1), we get,

$$\begin{aligned} dN(t) &= [-\mu_N N - \delta_{NE} PN]dt + \gamma_1 N(t)dW_1 t, \\ dE(t) &= [\delta_{NE} PN + \rho_E PE - \mu_E E^2 - \delta_{EM} E]dt + \gamma_2 E(t)dW_2 t, \\ dM(t) &= [-\mu_M M + \delta_{EM} E]dt + \gamma_3 M(t)dW_3 t, \\ dP(t) &= [\rho_P P^2 - \mu_P EP - \mu_P^0 P]dt + \gamma_4 P(t)dW_4 t. \end{aligned} \tag{4}$$

where $W_i(t), i = 1,2,3,4$ are independent Wiener processes and $\gamma_i, i = 1,2,3,4$ are the diffusion coefficients of the stochastic differential equations. The same initial conditions in (2) will be used for the stochastic model.

4.1 Stochastic results

In a similar manner, the stochastic model (4) is simulated in MATLAB and the following results are obtained by using the approximation methods mentioned above.

4.1.1 Euler-Maruyama Results

Using Euler-Maruyama scheme, the expected values of the stochastic model (4) are obtained as below (Figure 6).

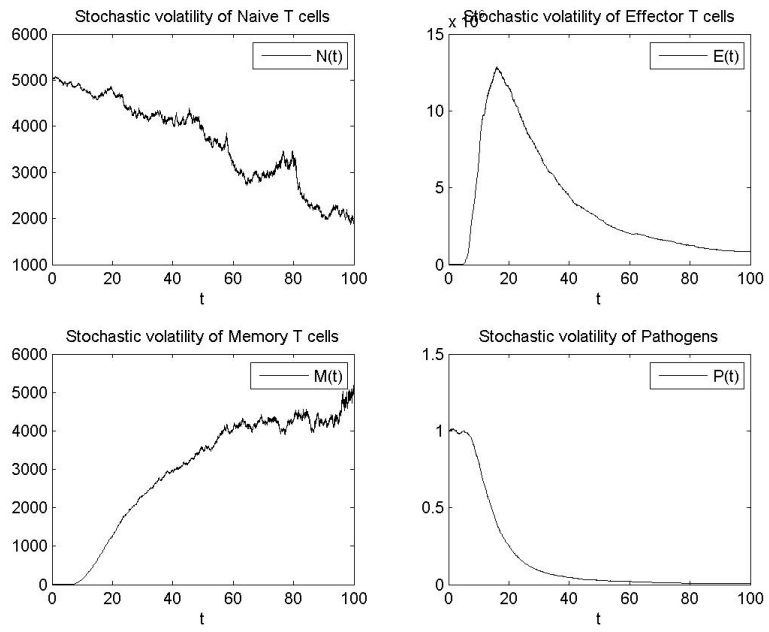

Fig. 6: Realizations of the approximate solutions of the stochastic model (with Euler-Maruyama)

The maximum and minimum values of the stochastic model are given below for a diffusion coefficient of $\gamma_i = 0.25, i = 1,2,3,4$ (Table 7).

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Table 7: Extremum values of the realizations for the stochastic case

Variable	(Max. Value, Time)	(Min. Value, Time)
$E(N(t))$	$(5074, 1.2)$	$(1865, 98.98)$
$E(M(t))$	$(1.286 \times 10^7, 16.03)$	$(0,0)$
$E(E(t))$	$(5190, 99.98)$	$(0,0)$
$E(P(t))$	$(1.013, 1.43)$	$(0.007356, 96.31)$

4.1.2 Milstein results

Extremum values of the results for Milstein method are given below (Table 8).

Table 8: Extremum values of the realizations (with Milstein)

Variable	(Max. Value, Time)	(Min. Value, Time)
$E(N(t))$	$(5000, 1.2)$	$(1491, 98.95)$
$E(M(t))$	$(1.381 \times 10^7, 15.91)$	$(0,0)$
$E(E(t))$	$(4637, 98.98)$	$(0,0)$
$E(P(t))$	$(1.015, 1.89)$	$(0.007232, 99.87)$

Results from both schemes show that the stochastic model (with a considerable amount of stochastic noise) roughly follows the path foreshown by the random model. A much more similar graph can be seen for the two models if a smaller stochastic noise is used for the SDEs.

5 Conclusion

Results for the deterministic, random and stochastic models are compared for the minimum and maximum values of the model components in the following tables (Tables 9 and 10).
It is seen that the extremum values in the results of the stochastic analysis are far more volatile than the expected results of the random analysis. This is due to the difference between the amounts of stochastic and random noise used in these two models. A considerable amount of stochastic noise ($\gamma_i = 0.25, i = 1,2,3,4$) was used in (4) whereas only 5% random effects (random noise in the parameters) were used in the random model (3).

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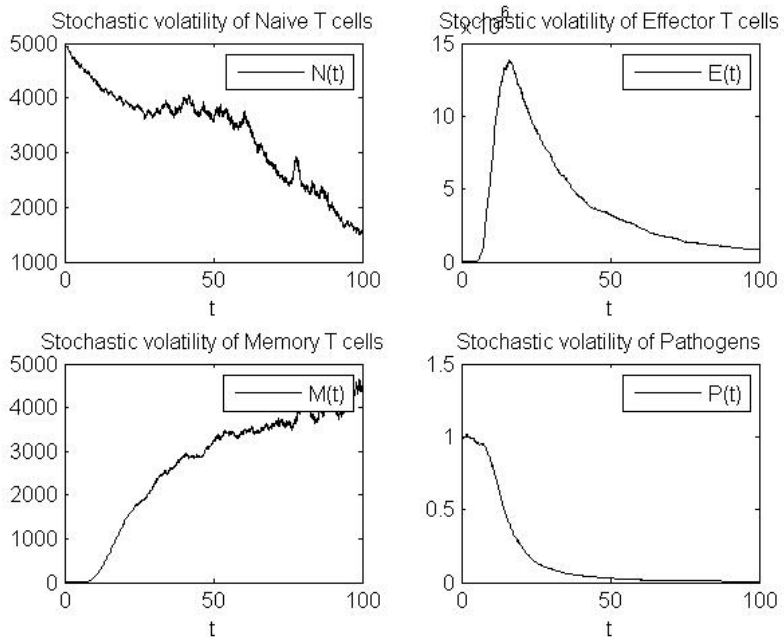

Fig. 7: Approximate solutions of the stochastic model (with Milstein)

Table 9: Comparison of minimum values for the three models

	Deterministic	Random	Stochastic
$N(t)$	$(1805, 100)$	$(1807, 100)$	$(1865, 98.98)$
$M(t)$	$(0, 0)$	$(0, 0)$	$(0, 0)$
$E(t)$	$(0, 0)$	$(0, 0)$	$(0, 0)$
$P(t)$	$(0.002529, 100)$	$(0.002595, 100)$	$(0.007356, 96.31)$

Table 10: Comparison of maximum values for the three models

	Deterministic	Random	Stochastic
$N(t)$	$(5000, 0)$	$(5000, 0)$	$(5074, 1.2)$
$M(t)$	$(3.684 \times 10^7, 18.1)$	$(3.516 \times 10^7, 18)$	$(1.286 \times 10^7, 16.03)$
$E(t)$	$(5965, 100)$	$(5984, 100)$	$(5190, 99.98)$
$P(t)$	$(1, 0)$	$(1, 0)$	$(1.013, 1.43)$

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Note that results from stochastic results from Euler-Maruyama method have been used for the final comparison and a correspondance between the variability from stochastic diffusion coefficients and random parameters would result in a better accordance of the results. Tables 9 and 10 show that the random model is an accurate modeling alternative for the analysis of CD8 T Cell immune response with the 5% random noise. An alternative method for randomizing the parameters would be to obtain medical data to model the random behavior of these values, instead of assigning hypothetical statistical characteristics, which could result in a more realistic analysis. The approach of random modeling can be generalized to any compartmental models used in biology, medicine and related fields since the methodology is based on a straightforward modification of the deterministic models that are available in the literature.

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