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Special Edition

Immunological memory improves the long-term cross-immunity: An influenza case study

A memória imunológica melhora a imunidade cruzada de longo prazo: Um estudo de caso de influenza

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ABSTRACT

In this contribution, we investigate the effects of the immunological memory in the population against the strain mutation of a disease, assuming that this memory is enhanced by the dynamics that follow a multi-order fractional SIRC model. We use weekly infection data on Influenza H1N1 in the state of Rio Grande do Sul, reported in the year of 2010, as the guide for our simulations and parameter choices. The simulated results suggest that the best scenarios, regarding the Influenza H1N1 data fit and that have a long-term prevention of reinfection for mutated strains of a circulating disease is the one in which the compartment of the population has a distinct level of immunological memory. Hence, any immunization strategy should be applied as early as possible, allowing the individual to acquire immunological memory before the strain can undergo mutations.

Keywords: Fractional dynamics; SIRC; Immunological memory

RESUMO

Nesta contribuição, investigamos os efeitos da memória imunológica na população contra a mutação da cepa de uma doença, assumindo que a memória é aprimorada pela dinâmica que segue um modelo SIRC fracionário multiordem. Utilizamos os dados semanais de infecção por Influenza H1N1 no estado do Rio Grande do Sul, notificados no ano de 2010, como guia para nossas simulações e escolhas de parâmetros. Os resultados simulados sugerem que os melhores cenários em relação aos dados do Influenza H1N1 e que têm uma prevenção a longo prazo da reinfecção por cepas mutantes de uma doença circulante é aquele em que o compartimento da população tem um nível distinto de memória imunológica. Portanto, qualquer estratégia de imunização deve ser aplicada o mais precocemente possível, permitindo que o indivíduo ganhe memória imunológica antes que a cepa seja capaz de sofrer mutações.

Palavras-chave: Dinâmica Fracionária; SIRC; Memória Imunológica

1 INTRODUCTION

Historically, Influenza has been one of the most recurrent diseases in humans due to the virus's capacity for gene recombination, generating mutant strains able to circulate among people and animals. Such characteristics of the Influenza virus imply the emergence of new virus strains that are able to (partially) escape immunological protection acquired by the host from contact with old circulated strains or vaccination, e.g., Kuszewski and Brydak (2000); Casagrandi, Bolzoni, Levin and Andreasen (2006) and references therein.

Getting some insight on the mechanisms of host immunity losses or temporary partial immunity is fundamental for health authorities surveillance of the diseases as well as to propose prevention actions and vaccination strategies to mitigate the disease effect.

Mathematical models have become one of the most important tools for testing interesting biological hypotheses in disease dissemination and the effects of their strains mutations over time, e.g. Diekmann, Heesterbeek and Metz (1995). An approach analyzed in Pease (1987) considers a coupled multiple SIR where the coupling is due to a cross-immunity parameter. The proposed dynamics allow the interactions between individuals exposed to distinct viral strains. The authors conclude that diseases with multiple strains have the ability to persist in circulation through time. An approach considering a host's linear immunity loss is analyzed in Pease (1987). It indicates that the classical SIRS model does not reflect the main behavior of diseases like Influenza. To deal with the virus mutation, Gomes, White and Medley (2004) propose a "temporary partial immunity"for a proportion of the population that has already recovered.

In this manuscript, we concentrate our attention on the so-called SIRC compartmental model, where the total population $N(t)$ is proportionally sub-divided into susceptibles $S(t)$, infected or infectious $I(t)$, removed or recovered $R(t)$ and the cross-immune $C(t)$ as introduced in Casagrandi *et al*. (2006). The compartment $C(t)$ contains the proportion of the population that is in the intermediate stage between

being totally susceptible $S(t)$ and fully protected $R(t)$ due to previous exposure to different strains of the same viral sub-type. In De Cezaro and Gomes (2017); Gomes and De Cezaro (2018), the authors propose and analyze a fractional SIRC model as an alternative to incorporate the memory immune system (immunological memory) that a host acquires from contact with previous infections. They show that the proposed model has better agreement with real data from the H1N1 influenza diseases.

In this paper, we consider a multi-fractional SIRC model ((MF)-SIRC) to examine the effect of immunological memory in each proportion of the population distributed in the S, I, R, and C. In this contribution, our focus is on examining the role of immunological memory in cross-immunity $C(t)$. The simulated scenarios show that the lower cross-immunity is obtained for populations that acquire some immunological memory only after infection (with no previous contact with the circulating strain). However, such scenarios do not agree with the reported data of Influenza H1N1, meaning that such a hypothetical scenario is unrealistic (at least for common circulation strains like Influenza). We also present a specific choice for the immunological memory of each compartment of the model that fits quite well with the reported data (see the **Scenario 7**). In particular, such a scenario has a large cross-immunity at the beginning of the diseases spreading (around 6 months) and then stabilizes as the one with the lower cross-immunity in the long run. Therefore, we can conclude that the existence of some immunological memory improves the cross-immunity of the population, making it less susceptible to mutating strains.

2 THE MULTI-FRACTIONAL SIRC MODELS AND ITS PROPERTIES

In this section, we present the (MF)-SIRC model and its biological meaning. Furthermore, we prove that the proposed fractional dynamics has a unique continuous solution that demonstrates a memory effect.

2.1 The (MF)-SIRC model

We assume that the total population $N(t) := S(t) + I(t) + R(t) + C(t)$ for $t \geq 0$. Furthermore, the dynamics of each proportion of the population S, I, R and C are driven by multi-order fractional dynamics

$$\begin{aligned} D_*^{\theta_1}(S(t)) &= \mu^{\theta_1}(N(t) - S(t)) - \beta^{\theta_1} S(t) I(t) + \gamma^{\theta_1} C(t) \\ D_*^{\theta_2}(I(t)) &= \beta^{\theta_2} S(t) I(t) + \sigma^{\theta_2} \beta^{\theta_2} C(t) I(t) - (\mu^{\theta_2} + \alpha^{\theta_2}) I(t) \\ D_*^{\theta_3}(R(t)) &= (1 - \sigma^{\theta_3}) \beta^{\theta_3} C(t) I(t) + \alpha^{\theta_3} I(t) - (\mu^{\theta_3} + \delta^{\theta_3}) R(t) \\ D_*^{\theta_4}(C(t)) &= \delta^{\theta_4} R(t) - \beta^{\theta_4} C(t) I(t) - (\mu^{\theta_4} + \gamma^{\theta_4}) C(t), \end{aligned} \tag{1}$$

where $D_*^{\theta_j}$, for $j = 1,...,4$ is the Caputo fractional derivative operator of order $\theta_j \in]0,1]$, e.g. Diethelm (2010). The dynamics (1) has the following initial conditions:

$$S(0) = S_0 > 0, I(0) = I_0 \geq 0, R(0) = R_0 \geq 0 \text{ and } C(0) = C_0 \geq 0. \tag{2}$$

All the parameters in the model (1) are time-independent. α, δ and γ are the average inverses of the time spent by individuals in each of the compartments I, R and C, respectively. μ is the birth and mortality rate (considered the same). σ represents the average reinfection probability of an individual in the cross-immunity compartment C. β is the infectiousness rate of the diseases. Therefore, the quantities α^{θ_j}, δ^{θ_j}, γ^{θ_j}, and σ^{θ_j}, for $\theta_j \in]0,1]$, in the model (1) are interpreted as the proportion of immunity acquired by the host due to the hereditary immunological memory.

Furthermore, μ^{θ_j} indicates that birth and mortality are distinct. It worth mentioning that for a highly contagious diseases as Influenza, where $\beta > 1$ (Pease, 1987), the quantity $\beta^{\theta_j} < \beta$, for any $\theta_j \in]0,1]$. Hence, the parameter β^{θ_j} in the model (1) means that the "immunological memory"helps to mitigate the contagious of the susceptible.

It is worth noting that the proposed (MF)-SIRC model (1) is equivalent to the SIRC (see Casagrandi *et al*. (2006)), whenever $\theta_j = 1$, for $j = 1, \cdots, 4$.

2.2 Well-posed, positively and the memory effect of the solution of the (MF)-SIRC model

In the following, we summarize the results of the existence and uniqueness of a positive solution for the (MF)-SIRC model (1) with initial conditions (2). The positive of its solution, in particular, means that the proposed model has a biological meaning. Furthermore, we demonstrate that the solutions of the model (1) have the property of "memory."

Theorem 1. Let the (MF)-SIRC model with initial conditions (2). There exists a unique continuous and positive solution $U(t) := (S(t), I(t), R(t), C(t))^T \in R^4$ for any $t \geq 0$. This solution is continuously dependent on the initial conditions, on the model parameters and on the fractional derivatives $\theta_j \in]0,1]$, for $j = 1, \cdots, 4$.

The proof of the Theorem 1 can be found in Gomes and De Cezaro (2018).

Integrating each line of the model (1) with order θ_j for $j = 1, \cdots, 4$, it results into the Volterra system of equations

$$u_j(t) = \sum_{l=1}^{4} u_j(0)\frac{t^l}{l!} + \frac{1}{\Gamma(\theta_j)}\int_0^t (t-s)^{\theta_j - 1} f_j(s,u_1(s),...,u_4(s))ds. \tag{3}$$

where f_j and $u_j(t)$ represents the j-coordinate of the $F(t,U(t))$, corresponding the right hand side of the model (1). Hence, if $\theta = min_{j=1,\cdots,4}\theta_j$ then the equation (3) can be rewritten as

$$u_j(t) = \sum_{l=1}^{4} u_j(0)\frac{t^l}{l!} + \frac{1}{\Gamma(\theta_j)}\int_0^t (t-s)^{\theta - 1} \widehat{f}_j(s,u_1(s),...,u_4(s))ds. \tag{4}$$

for $j = 1, \cdots, 4$, where, $\widehat{f}_j(s,u_1,...,u_4) := \frac{\Gamma(\theta)}{\Gamma(\theta_j)}(t-s)^{\theta_j - \theta} f_j(s,u_1,\cdots,u_4)$.

According to (4), any of the coordinates $u_j(t)$ of model solution $U(t)$ is such that, for any time $t_1 \leq t_2$,

$$\begin{aligned} u_j(t_2) - u_j(t_2) = &\frac{1}{\Gamma(\theta_j)}\int_0^{t_1} [(t_2-s)^{\theta-1} - (t_1-s)^{\theta-1}]\widehat{f}_j(s,u_1(s),...,u_4(s))ds \\ &+ \frac{1}{\Gamma(\theta_j)}\int_{t_1}^{t_2} (t_2-s)^{\theta-1}\widehat{f}_j(s,u_1(s),...,u_4(s))ds\,. \end{aligned} \tag{5}$$

If all the $\theta_j = 1$, the term between the brackets in (5) is zero, and the first integral in (5) vanishes. Hence, to compute the solution $U(t)$ in t_2, it depends only on the value of $U(t_1)$ and the functions f_j corresponding to the right hand side of (1). However, if some $\theta_j \neq 1$, then the first integral does not vanish in general. As a result, the history of the dynamics from 0 to t_2 must be considered in order to evaluate the solution, $U(t_2)$. This phenomenon we call "memory".

3 SIMULATED SCENARIOS

In this section, we numerically analyze simulated scenarios for the (MF)-SIRC model in parallel to weekly reported data of influenza H1NI from the state of Rio Grande do Sul, Brazil, in 2010, obtained in the DATASUS (Lima, Januário, Lima, & Silva, 2015), plotted as o in the Fig. 3 and 4.

In all the simulations, we used a trapezoidal type method for the convolution operator (see equation (3)), inspired by the ideas in Garrappa (2015), with mesh-size $h = 10^{-4}$, to compute the numerical solution of the model (MF)-SIRC.

The parameters used in the simulated scenarios are presented in the Table 1.

Table 1 – Parameters of the model

Parameter	Description	Value
μ	The mortality and birth rate	0.02
α	Recovery rate of infected	7.8
δ	The average time of appearance of new dominant strain	0.55
γ	Cross-immune period	0.85
σ	The average reinfection probability of $C(t)$	0.12
β	Contact (transmission) rate of susceptible to be infected	1.355

Source:

3.1 Memory's influence on cross-Immunity

The goal of this subsection is to demonstrate the effect of the different values for θ_j choices presented in Table 2 on population dynamics, using simulations of the (MF)-SIRC model (1).

The interpretation of each simulated scenario (regarding the commentaries about memory in Subsection 2.2) can be as follows: **Scenario 1** means that the population does not have immunological memory; Only individual in $C(t)$ develops immunological memory in **Scenario 2** and **Scenario 3**, with the intensity being greater in **Scenario 3**; In **Scenario 4**, **Scenario** 4^{*}, and **Scenario** 4^{**}, the proportion of the population that recovered from the diseases has immunological memory, with the smallest values of memory in the **Scenario** 4^{*} and the biggest in the **Scenario** 4^{**}; In **Scenario 5** the population has the same immunological memory; In the **Scenario 6** each proportion of the population has a distinct immunological memory.

Table 2 – Simulated scenarios

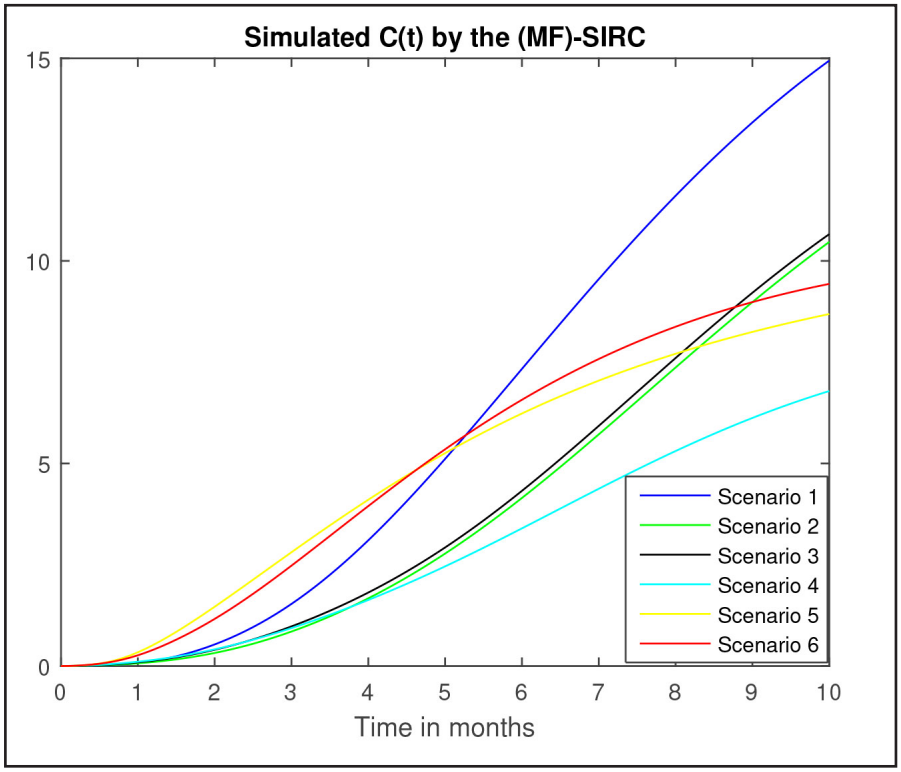
Scenarios	θ_1	θ_2	θ_3	θ_4
Scenario 1:	1	1	1	1
Scenario 2:	1	1	1	0.9
Scenario 3:	1	1	1	0.8
Scenario 4:	1	1	0.8	0.8
Scenario 4*:	1	1	0.9	0.9
Scenario 4**:	1	1	0.7	0.7
Scenario 5:	0.8	0.8	0.8	0.8
Scenario 6:	0.9	0.85	0.8	0.75

Source:

In Fig. 1, we presented the simulated scenarios from Table 2 and the impact of the cross-immunity $C(t)$. It can be seen that **Scenario 4** is the one that presents lower values of cross-immunity, indicating that in a population with no previous contact with any disease sub-type, it will take longer for a reinfection. The long-running simulations, including **Scenarios** 4^{*} **and** 4^{**}, are depicted in Fig. 2. The simulations show that the best scenarios (that present lower cross-immunity) are the ones with memory only in the proportion of the population already recovered (in the compartments $R(t)$ and $C(t)$) and are monotonically with the fractional order - it turns out the continuous dependence of the solution w.r.t. the fractional derivatives presented in Theorem 1. Meanwhile, the **Scenario 5** and **Scenario 6** are comparable in the short run (see Fig.

1), the **Scenario 5** presents a monotonically increasing behavior in the long run of the simulation (see Fig. 2). In particular, **Scenarios 5, 6** present a large cross-immunity in up to 5 months (see Fig. 1) - even larger than the **Scenario 1** - but the **Scenario 6** attains the stability of the cross-immunity after 1 year (see Fig. 2). **Scenarios 1,2,3** show a peak in cross-immunity around 12 months and then oscillating behavior for a longer period of time (see Fig. 2).

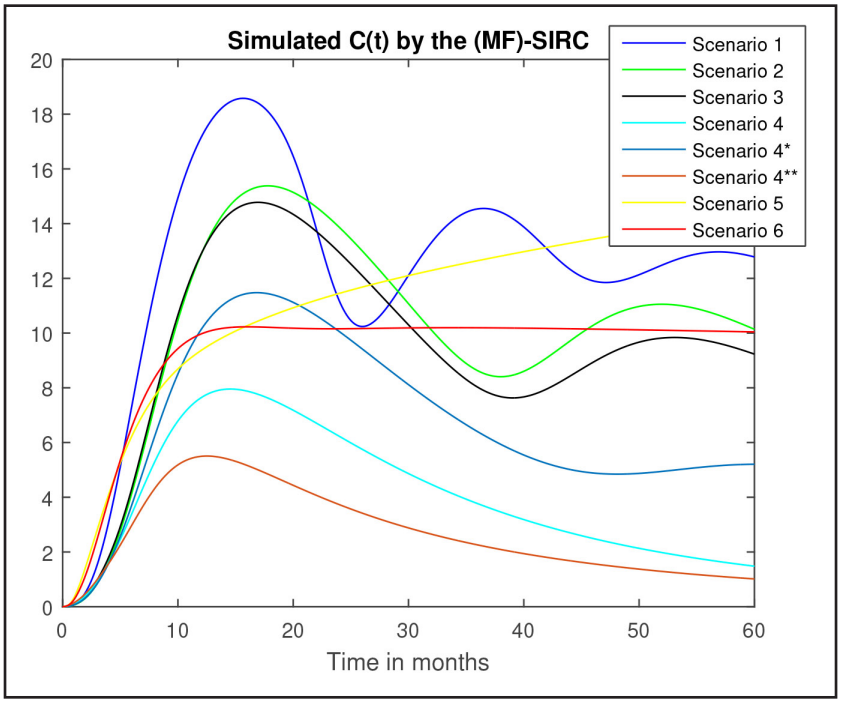
Figure 1 – Cross-Immunity effects in the population simulated with the (MF)-SIRC for choices of the derivatives given in Table 2



Source: Authors

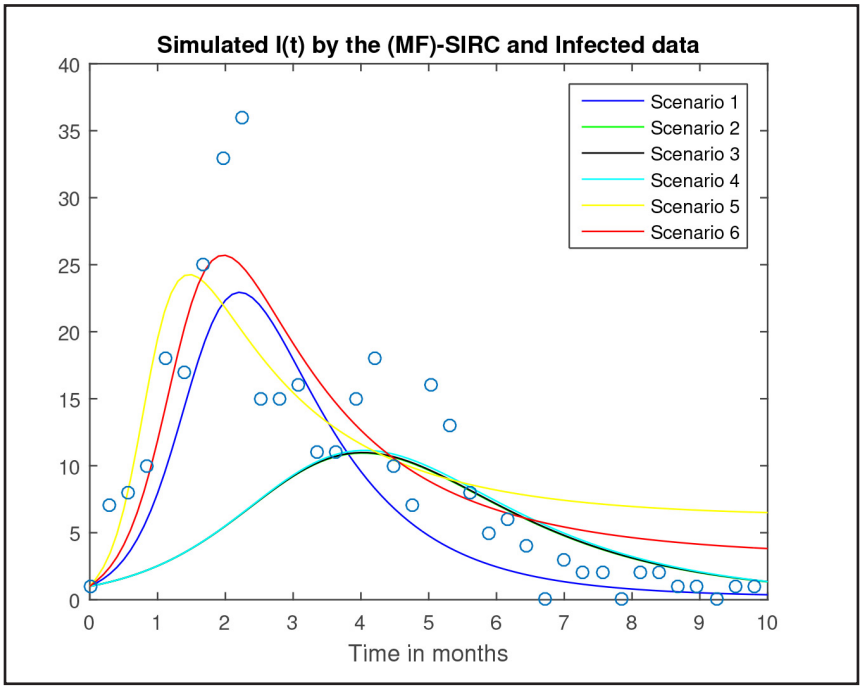
In Fig. 3, we present the simulated scenarios compared with the reported data for Influenza H1N1. The simulated results show that the behavior of the Influenza H1N1 diseases is more compatible with the scenarios where all the sub-populations have some memory (**Scenarios 5, 6**) or there is no immunological memory (**Scenario 1**). In the subsection 3.2 that follows, we investigate the choices for θ_j in more detail.

Figure 2 – Long-run cross-immunity effects in a population simulated with the (MF)-SIRC for the derivatives listed in Table 2



Source: Authors

Figure 3 – Simulations of infected population behavior from the (MF)-SIRC for the derivatives listed in Table 2. In *o* weekly reported data of Influenza H1N1



Source: Authors

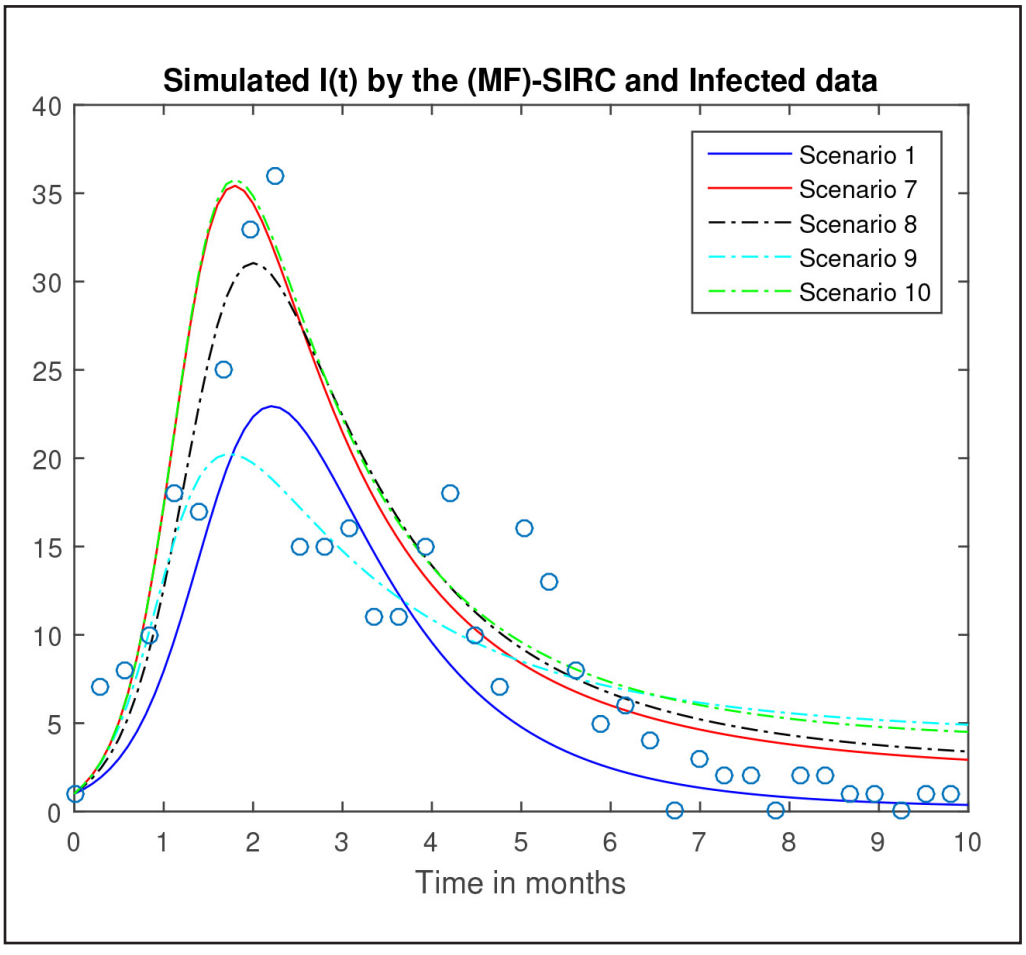
3.2 The effect of memory in comparison with reported data

It follows from the analysis of the simulated scenarios in the Subsection 3.1, that the Influenza H1N1 behavior is more comparable to a scenario with immunological memory in all the sub-populations.

The Fig. 4 compares reported data of Influenza H1N1 with simulated scenarios of the (MF)-SIRC model with θ_j as shown in Table 3.

The results shown in Fig. 4 indicate that the (MF)-SIRC model has better agreement with the weekly reported infected cases of Influenza H1N1 for θ_j values used in **Scenario 7** and **Scenario 10**.

Figure 4 – Simulations of infected population behavior from the (MF)-SIRC for the derivatives listed in Table 3. In *o* weekly reported data of Influenza H1N1



Source: Authors

Table 3 – Simulated scenarios

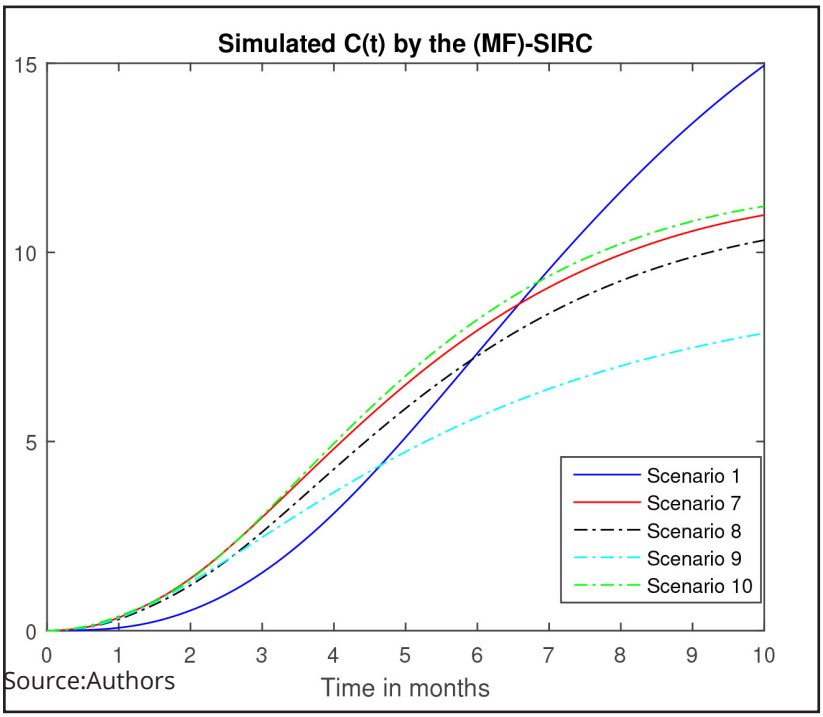
Scenarios	θ_1	θ_2	θ_3	θ_4
Scenario 7:	0.95	0.83	0.8	0.7
Scenario 8:	0.95	0.85	0.8	0.7
Scenario 9:	0.8	0.83	0.85	0.7
Scenario 10:	0.95	0.83	0.85	0.6

Source:Authors

From the dynamics of cross-immunity presented in Fig. 5-6, we can conclude that a population with memory in all of its compartments, according to Table 3, is more susceptible to new strains in a short period of time (first six months - see Fig. 5) and then stabilizes at lower levels as compared with a population with no memory (**Scenario 1**), as presented in Fig. 6.

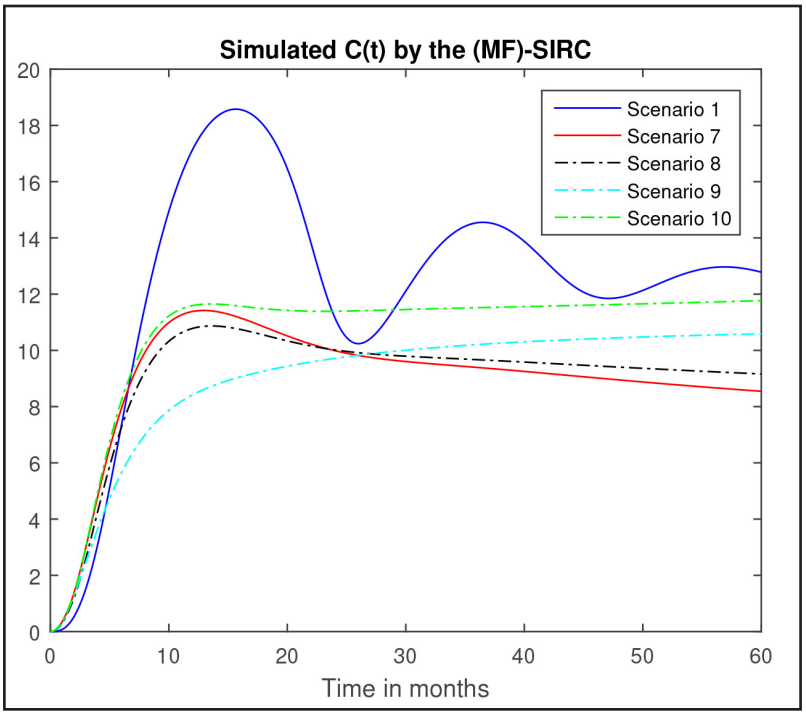
It indicates that the immunization strategy should be given as early as possible such that the population gains immunological memory before the strain is able to mutate. It is common sense among specialists, showing that the proposed (MF)-SIRC model is able to capture important features of the diseases.

Figure 5 – Cross-Immunity effects in the population simulated with the (MF)-SIRC for choices of the derivatives given in Table 3.



Source:Authors

Figure 6 – Long-run cross-immunity effects in a population simulated with the (MF)-SIRC for the derivatives listed in Table



Source: Authors

4 CONCLUSIONS

We used the (MF)-SIRC to simulate the effects of the immunological memory in the population against strains mutation of a disease. The simulated scenarios presented are based on weekly infected data from Influenza H1N1 in the state of Rio Grande do Sul, in 2010.

The simulated scenarios show that for a disease where the population has no previous contact (no immunological memory), the best scenarios for gaining protection from the disease mutation are the ones in which the population acquires memory before infection (simulated **Scenarios 4,** $4^{\square}$**,** $4^{\square\square}$ in Subsection 3.1). On the other hand, such scenarios do not fit the data of Influenza H1N1.

The simulated scenarios where the population does not gain immunological

memory (**Scenario 1** or gain memory only before recovering **Scenarios 2, 3**) show an oscillatory and larger cross-immunity behavior in the long run (see Fig. 2).

The simulated scenarios with multi-fractional order (that corresponds to the situation where all the compartments have distinct levels of immunological memory) show the best fit for the Influenza H1N1 reported data (see **Scenario 7, 10** in Fig. 4) with a lower long-running cross-immunity (see **Scenario 7** in Fig. 6), although it presents a larger probability of reinfection for mutation after 6 months (see Fig. 5).

This study suggests that the best scenario that has a long-term prevention of reinfection for mutated strains of a circulating disease is the one in which the compartment population has a distinct level of immunological memory. It indicates that the immunization strategy should be given as early as possible such that the population gains immunological memory before the strain is able to mutate. It is common sense among specialists, showing that the proposed (MF)-SIRC model is able to capture important features of the diseases.

The applicability of this study to other sets of observed data and mutating diseases such as COVID-19 will be investigated in future contributions.

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