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On a multi-order fractional SIRC model for Influenza

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Abstract

Since influenza is a seasonal mutating disease, in this paper, we propose and analyze a multi-fractional version of the SIRC model (which relates the S-susceptible, I-Infected, R-recovered, and C-cross-immune individuals in the population N) to capture the immunological memory gained by individuals that have previous contact Influenza strains.

We show the well-posedness and consistency of the proposed multi-fractional dynamics and analyze the stability of stationary points with an analytical/numerical strategy.

The simulated scenarios show that the proposed model describes more precisely reported Influenza H1N1 data, from the State of Rio Grande do Sul, in the year 2010. Moreover, it shows that the memory enhanced by the fractional dynamics (that model the immunological memory) implies a substantial decrease of susceptibility of re-infection by strain mutations in long-running diseases, but is larger in the beginning.

Keywords: multi-fractional SIRC model. Influenza. cross-immunity.

1 Introduction

Infectious diseases are among the leaders in the suffering and mortality of populations. Although the transmission mechanism from an infective to susceptible is known, the large-scale spread dynamics of the infection through the populations are very complex. Therefore, your understanding becomes almost impossible without help from a formal mathematical model. Such models might have limitations due to the lack of data to accurately estimate the underline parameters. However, on the other hand, it has capabilities that must be recognized, since models can be used to predict the macroscopic behavior of disease spread through a population.

Even though vaccines are available for many infectious diseases, the rapid mutation or by the only body partial immunity against the causing agents, many diseases remain uncontrolled or re-incident. Influenza is one example of such diseases that causes thousands of death every season (PEASE, 1987).

Influenza A (among the three different types A, B and C) is the epidemiologically the most important cause of infection for humans, due to its capability of genes recombination with those of strains circulating in animal populations (birds, swine and horses), giving rise to new viral subtypes, every few decades, via the so called antigenic shift mechanism (KUSZEWSKI; BRYDAK, 2000).

Such subtypes, originated for the genes encoding the viral surface proteins (HA and NA) (SHAO et al., 2017), are usually antigenic. It means that they are different from their ancestors and gain the capability of escape completely the defenses of the immune system of the previously infected hosts, who can be associated with severe Influenza pandemics. The Spanish flu in 1918 or the Hong Kong influenza in 1968 was caused by the genesis of the H1N1 and H3N2 subtypes respectively, see (NETO; PORTO, 2019). Moreover, influenza viruses are also capable of performance point mutations (with faster time scale concerning shifts) in the HA and NA genes. These minor mutations are associated with every year influenza epidemics that we experience (COBEY; PASCUAL, 2011).

Some works show strong evidences that the antigenic distance between two different strains influences in the degree of partial immunity (cross-immunity) (ADAMS; SASAKI, 2009), conferred to a host already infected by one of the strains regarding the other.

Review of the literature: Many mathematical models have been proposed to describe the dynamics of influenza and its mutations in the population (see (DIEKMANN; HEESTERBEEK; METZ, 1995) for a review). A typical approach uses multiple SIR models (susceptibles-infectives-recovered originally proposed by Kermack and McKendrick (HETHCOTE, 1989)), connected via some cross-immunity parameters, for modeling the interactions between individuals that are (or have been) infected by different viral strains (ANDREASEN; LIN; LEVIN, 1997). The analysis of these models has shown that multiple strains of influenza can persist in the human populations and that their prevalence can exhibit self-sustained oscillations through time.

In (PEASE, 1987), the author suggested the introduction into the model of a loss of immunity by the host, as an alternative to incorporate the emergence of new viral strains. In (GOMES; WHITE; MEDLEY, 2004), the authors proposed 'temporary partial immunity' for the individuals in the R compartment to account for the influenza virus mutation. In (CASAGRANDI et al., 2006), a cross-immune compartment C was incorporated into the SIR-model, to design an intermediate state between the fully susceptible state (S) and the fully protected one (R). Such extension to the SIR-model (now called SIRC) allows to account for exposition to mutate strain, their pre-existing immune responses are boosted (CASAGRANDI et al., 2006). In (GOMES; DE CEZARO, 2017), the authors propose a fractional-order dynamics for the SIRC model (here called (F)-SIRC). The introduction of such dynamics is to account for the memory (in this propose, memory can be interpreted as a

distinct time scale) in the immune system.

In this contribution, we advance a step further in the generalization of the SIRC model, studying a multi-fractional version of it called (MF)-SIRC. Such generalization allows accounting for distinct effects in time scales (immunological memory) of each compartment of the SIRC model. Moreover, generalizing theoretical/numerical approach for the SIRC model for Influenza disease. We also analysis the (MF)-SIRC models with a vaccination strategy. From the theoretical point of view, we prove the well-posedness of the proposed model and some theoretical/numerical results for stability. We also present a particular choice for the model parameters (and fractional derivatives) that numerically shows a better agreement of the (MF)-SIRC compared with (F)-SIRC and SIRC, regarding Influenza data from the year of 2010, from the State of Rio Grande do Sul (Brazil). Furthermore, the numerical finds suggest that pre-existing immunological memory (given, for example, by vaccination, and modeled by the (MF)-SIRC) helps in decreasing the susceptibility to new strains by decreasing cross-immunity after some time (corresponding to one year in our simulations).

Outline: In Section 2, we presented the (MF)-SIRC model with pulse vaccination. In Subsection 2.1, we discuss the Well-posedness for the proposed (MF)-SIRC model. In Subsection 2.2, we analyze the theoretical/numerical stability of equilibrium points for the proposed model. In Section 3, we present and discuss numerical simulations that compare some scenarios with real data from Influenza. Finally, in Section 4, we draw some conclusions and future direction.

2 A (MF)-SIRC model with pulse vaccination

In this manuscript, we assume that a human community $N(t)$ can be subdivided, at any time t, into four compartments concerning the dominant circulating strain of influenza subtypes: the population of susceptible $S(t)$, i.e., those who have a "memory immune" defenses against that particular strain that, eventually, accumulates during the time. The fraction of the population $I(t)$ of those individuals infected by the current dominant strain. We also assume that $I(t)$ eventually heredity the "memory immune" of previews strains, but remain infective. Further, there are other two classes of those who are totally or partially immune to that strain. The recovered $R(t)$ and cross-immune $C(t)$ that also have a "memory immune" from previous strains. The interpretation of $C(t)$ is that the individuals in the $R(t)$ class are those who have recovered from the dominant strain currently circulating, but its immune vanishes with time. Hence, a proportion of the recovering individuals move to the $C(t)$ class. Since the individuals in $C(t)$ have only partial immunity to a new dominant strain that has emerged since they were last infected. Hence, $N(t) = S(t) + I(t) + R(t) + C(t)$. Figure 1 show the schematic representation of the SIRC model.

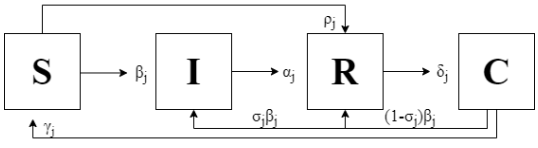

Figure 1: Schematic representation of the SIRC model.

Finally, we assume that the "memory immune" of all the classes can be modeled by the "memory"[1] effects of a fractional-order operator of Caputo-type (DIETHELM, 2010). Let $\theta_j \in]0, 1]$ and η_j the

[1]See Remark 6.4 in (DIETHELM, 2010).

smallest integer greater than or equal to θ_j. For any function $U(t) \in L_1[a,b]$ we define the Caputo fractional derivative operator.

$$D_*^{\theta_j}[U(t)] := J^{\eta_j-\theta_j} D_j^{\eta} U(t), \tag{1}$$

where $J^{\eta_j-\theta_j}$ denotes the Riemann-Liouville fractional integral operator is defined by

$$J_a^{\theta_j} U(t) = \frac{1}{\Gamma(\theta_j)} \int_a^t (t-s)^{(\theta_j-1)} U(s) ds \quad for \quad a \le t \le b.$$

In other words, the dynamics of the diseases is modeled by the multi-fractional (MF)-SIRC model

$$D_*^{\theta_j}[U(t)] = F(t, U(t)) + \xi V(U(t)), \quad \text{for} \quad j = 1, ..., 4\,, \tag{2}$$

where $D_*^{\theta_j}[U(t)] := [D_*^{\theta_1} u_1(t), \cdots, D_*^{\theta_4} u_4(t)]^T$.Moreover, $\theta_j \in]0,1]$, for $j, j = 1, \cdots, 4$, $U(t) = [S(t), I(t), R(t), C(t)]^T$, $F : [0, \infty[\times \mathbb{R}^4 \to \mathbb{R}$ is given by

$$F(t, U(t)) = \begin{bmatrix} \mu^{\theta_1}(N(t) - S(t)) - \beta^{\theta_1} S(t) I(t) + \gamma^{\theta_1} C(t) \\ \beta^{\theta_2} S(t) I(t) + \sigma^{\theta_2} \beta^{\theta_2} C(t) I(t) - (\mu^{\theta_2} + \alpha^{\theta_2}) I(t) \\ (1 - \sigma^{\theta_3}) \beta^{\theta_3} C(t) I(t) + \alpha^{\theta_3} I(t) - (\mu^{\theta_3} + \delta^{\theta_3}) R(t) \\ \delta^{\theta_4} R(t) - \beta^{\theta_4} C(t) I(t) - (\mu^{\theta_4} + \gamma^{\theta_4}) C(t) \end{bmatrix},$$

and $V : [0, \infty[\quad \times \quad \mathbb{R}^4 \to \mathbb{R}^4$ defined as

$$V(U(t)) = \begin{bmatrix} -\xi \rho^{\theta_1} S(t) \\ 0 \\ +\xi \rho^{\theta_3} S(t) \\ 0 \end{bmatrix}, \tag{3}$$

is the vaccination pulse. The parameter $\xi = 1$ (or $\xi = 0$) means that there (do not) exists a vaccination campaign. For $\theta_i = \theta_j$, for $i, j = 1, \cdots, 4$ we call the model (2) as (F)-SIRC. For $\theta_j = 1$, for $j = 1, \cdots, 4$ we have the SIRC model originally proposed in (CASAGRANDI et al., 2006). In that case, the parameters α, δ and γ are the inverses of the average time spent by the individuals in each of the three compartments I, R and C respectively. μ is the birth and mortality rates. The parameter σ can be viewed as the average reinfection probability of a cross-immune individual. The parameter β is the rate of infectivity. Hence, the quantities $\alpha^{\theta_j}, \delta^{\theta_j}$ and $\gamma^{\theta_j}, \sigma^{\theta_j}$, for $\theta_j \in]0,1]$ can be interpreted as the proportion of the gained by the memory heredity immunity. Moreover, μ^{θ_j} means that the birth and mortality rates are not even, for θ_j distinct. In particular, is the diseases is highly transmissible ($\beta > 1$) as the Influenza, then $\beta^{\theta_j} < \beta$, for any $\theta_j \in \quad]0,1]$, meaning that the "memory immunity" acts as a decreasing factor of contagious.

The following initial conditions

$$S(0) = S_0 > 0\,, I(0) = I_0 \ge 0\,, R(0) = R_0 \ge 0 \text{ and } C(0) = C_0 \ge 0\,, \tag{4}$$

complete the multi-fractional order initial value problem (MF)-SIRC (2).

Remark 2.1 *Notice that the original SIRC model proposed in (CASAGRANDI et al., 2006) is equivalent to the model* (2) *with* $\theta_j = 1$*, for* $j = 1, \cdot, 4$ *and* $\xi = 0$*. In SIRC the parameters in the system of equation in* (2) *corresponds to a* $(time)^{-1}$*-dimension. On the other hand the (MF)-SIRC model* (2)*, the parameters corresponds to a* $(time)^{-\theta_j}$ *dimension for* $j = 1, ..., 4$*, e.g., (ALMEIDA et*

al., 2019). An alternative to keep the time-dimension compatible is described by $F(t, U(t))$ defined above.

Since the parameters in the model (2) *are anti-symmetric (for $\theta_i \neq \theta_j$ with $i, j \in \{1, \cdots, 4\}$), we might not expect that the total population $N(t)$ remains constant, as usually assumed in the SIRC model. It implies some major difficulties in the analysis of the model* (2)*. Therefore, in this contribution, we assume that $N(t)$ remains constant at finite interval of time $[0, T]$, for any $T > 0$.*

2.1 Well-posedness of (MF)-SIRC model

In this subsection, we analyze the well-posedness of the initial value (MF)-SIRC model with pulse vaccination (2)-(4).

In remaining of this manuscript, we assume the following general assumption.

H1) The parameters in the system (2) are time-independent. Moreover, $U : [0, \infty[\to \mathbb{R}^4$, is continuous.

The first auxiliary result is the following lemma.

Lemma 2.1 *Let the assumption H1) be satisfied and $T > 0$. Then, the function $F(t, U(t))$ is continuous with relation to t and Lipschitz continuous with relation to $U(t)$, for $t \in [0, T]$.*

Proof: The continuity follows from assumption H1) and the definition of $F(t, U(t))$. Moreover, it is straightforward to show that the Jacobian is given by $J(t, U(t)) =$

$$\begin{bmatrix} \mu^{\theta_1} - \beta^{\theta_1} I(t) - \xi\rho^{\theta_1} & -\beta^{\theta_1} S(t) & 0 & \gamma^{\theta_1} \\ \beta^{\theta_2} I(t) & \beta^{\theta_2}(S(t) + \sigma^{\theta_2} C(t)) - (\mu^{\theta_2} + \alpha^{\theta_2}) & 0 & \sigma^{\theta_2}\beta^{\theta_2} I(t) \\ \xi\rho^{\theta_3} & (1 - \sigma^{\theta_3})\beta^{\theta_3} C(t) + \alpha^{\theta_3} & -(\mu^{\theta_3} + \delta^{\theta_3}) & (1 - \sigma^{\theta_3})\beta^{\theta_3} I(t) \\ 0 & -\beta^{\theta_4} C(t) & \delta^{\theta_4} & -\beta^{\theta_4} I(t) - (\mu^{\theta_4} + \gamma^{\theta_4}) \end{bmatrix}.$$

Hence, it follows from assumption H1) and Weierstrass's Theorem (SOTOMAYOR, 2011), the existence of a constant M, independent of $t \in [0, T]$ and $U(t)$, such that $\|J(t, U(t))(t)\| \leq M$. Therefore, the Lipschitz continuity follows from the Mean Value Theorem (SOTOMAYOR, 2011). □

Next, we prove the well-posedness of the multi-fractional initial value problem (2)-(4).

Theorem 2.1 *Let the assumptions on Lemma 2.1 holds true. Then, there exists a unique solution $U \in C([0, h(T)], \mathbb{R}^4)$ of the (MF)-SIRC model* (2)-(4)*, for some $h(T) > 0$. Moreover, the solution $U(t)$ depends continuously for the initial data* (4)*, from the model parameters and from the fractional derivatives $\theta_j \in]0, 1]$, for $j = 1, \cdots, 4$.*

Proof: It follows from Lemma 2.1 that $F(t, U(t))$ is continuous and Lipschitz continuous w.r.t. the second variable for any $t \in [0, T]$. Therefore, it follows similarly to (DIETHELM, 2010, Theorems 8.7 - 8.11), the existence and uniqueness of a solution $U \in C([0, h(T)], \mathbb{R}^4)$ for the (MF)-SIRC model (2)-(4), for some $h(T) > 0$, as claimed. The continuously dependence of $U(t)$ on the initial conditions, model parameters and fractional derivatives follows arguing similarly to (DIETHELM, 2010, Theorems 8.7 - 8.11). □

Next, we prove the consistency of the solution of the system (2), in the sense that, all its components remains non-negative, as the application suggest. For that reason, define the region $\Omega_+ := \{U(t) := (S(t), I(t), R(t), C(t))^T : \text{ all components of } U(t) \text{ are non-negative}\}$. We will use a similar argument presented in (SANTOS; MONTEIRO; VIEIRA, 2017) to prove that Ω_+ is an invariant region, i.e., whenever the initial conditions (4) belongs to Ω_+, then the solution $U(t)$ of (2) remains in Ω.

Proposition 2.1 *Let the assumptions of Theorem 2.1 holds true and $\xi = 0$. Then, the region Ω_+ is a positive invariant set for the solution of the system* (2).

Proof: Let denote H_+^j the j coordinate[2] subset of Ω_+, for $j = 1, \cdots, 4$. Notice that, the vector field from the model (2) confined in the H_+^j assume the form

$$\begin{aligned} f_1(S(t), I(t), R(t), C(t)) &= (\mu^{\theta_1}(N - S(t)), 0, 0, 0) \\ f_2(S(t), I(t), R(t), C(t)) &= (0, -(\mu^{\theta_2} + \alpha^{\theta_2})I(t), 0, 0) \\ f_3(S(t), I(t), R(t), C(t)) &= (0, 0, -(\mu^{\theta_3} + \delta^{\theta_3})R(t), 0) \\ f_4(S(t), I(t), R(t), C(t)) &= (0, 0, 0, -(\mu^{\theta_4} + \gamma^{\theta_4})C(t)), \end{aligned}$$

for $j = 1 \cdots, 4$, respectively.

Using the properties of the Laplacian transforms applied to the fractional calculus and the definitions of Mittag-Leffler functions e.g., (DIETHELM, 2010), we obtain that the solutions

$$(S(t), 0, 0, 0) = (t^{\theta_1} E_{\theta_1, \theta_1+1}(-\mu_1 N t^{\theta_1})\mu^{\theta_1} N + E_{\theta_1,1}(-\mu_1 N t^{\theta_1})S(0), 0, 0, 0) \tag{5}$$

$$(0, I(t), 0, 0) = (0, E_{\theta_2,1}(-(\mu^{\theta_2} + \alpha^{\theta_2})t^{\theta_2})I(0), 0, 0) \tag{6}$$

$$(0, 0, R(t), 0) = (0, 0, E_{\theta_3,1}(-(\mu^{\theta_3} + \alpha^{\theta_3})t^{\theta_3})R(0), 0) \tag{7}$$

$$(0, 0, 0, C(t)) = (0, 0, 0, E_{\theta_4,1}(-(\mu^{\theta_4} + \alpha^{\theta_4})t^{\theta_4})C(0), \tag{8}$$

remains in H_+^j, whenever the initial conditions (4) belongs to H_+^j, for $j = 1 \cdots, 4$, respectively. This allows the conclusion that H_+^j are positive invariant sets.

Suppose, by contradiction that the solution $(S(t), I(t), R(t), C(t))^T$ is not in Ω_+, for some $t_* \in [0, T]$. Since the solution is continuous w.r.t. t (see Theorem 2.1), there exist a small interval around t_* such that, at least one of the four coordinates shall not be in Ω_+. There are four possibilities:

i) The solution $(S(t), I(t), R(t), C(t))^T$ escapes by the plan because $S(t) < 0$. Then Theorem (2.1), there exist a $t_0 > 0$, such that $S(t_0) = 0$ and $R(t_0) \geq 0$, $I(t_0) \geq 0$ and $C(t_0) \geq 0$ and $S(t) < 0$ for t sufficient near to t_0. On the other hand, $D^{\theta_1} S(t)|_{t=t_0} = \mu_1^{\theta} N(t_0) + \gamma^{\theta_1} C(t_0) \geq 0$. It follows from the Mean Value Theorem for fractional order derivatives (ODIBAT; SHAWAGFEH, 2007) that $S(t) \geq S(t_0) \geq 0$, for t sufficiently near to t_0. An absurd.

ii) The solution $(S(t), I(t), R(t), C(t))^T$ escapes by the plan because $I(t) < 0$. Then Theorem (2.1), there exist a $t_0 > 0$, such that $I(t_0) = 0$ and $S(t_0) \geq 0$, $R(t_0) \geq 0$ and $C(t_0) \geq 0$ and $I(t) < 0$ for t sufficient near to t_0. On the other hand, $D^{\theta_2} I(t)|_{t=t_0} = 0$. It follows from the Mean Value Theorem for fractional order derivatives (ODIBAT; SHAWAGFEH, 2007) that $I(t) = I(t_0) = 0$, for t sufficiently near to t_0. An absurd.

iii) The solution $(S(t), I(t), R(t), C(t))^T$ escapes by the plan because $R(t) < 0$. Then Theorem (2.1), there exist a $t_0 > 0$, such that $R(t_0) = 0$ and $S(t_0) \geq 0$, $I(t_0) \geq 0$ and $C(t_0) \geq 0$ and $R(t) < 0$ for t sufficient near to t_0. On the other hand, $D^{\theta_3} R(t)|_{t=t_0} = (1-\sigma)^{\theta_3}\beta^{\theta_3} C(t_0) I(t_0) + \alpha^{\theta_3} I(t_0) \geq 0$. It follows from the Mean Value Theorem for fractional order derivatives (ODIBAT; SHAWAGFEH, 2007) that $R(t) \geq R(t_0) \geq 0$, for t sufficiently near to t_0. An absurd.

[2] In particular, $H_+^1 := \{(S(t), 0, 0, 0) : S(t) \geq 0\}$.

iv) The solution $(S(t), I(t), R(t), C(t))^T$ escapes by the plan because $C(t) < 0$. Then Theorem (2.1), there exist a $t_0 > 0$, such that $C(t_0) = 0$ and $S(t_0) \geq 0$, $I(t_0) \geq 0$ and $R(t_0) \geq 0$ and $R(t) < 0$ for t sufficient near to t_0. On the other hand, $D^{\theta_4} C(t)|_{t=t_0} = \delta^{\theta^4} R(t_0) \geq 0$. It follows from the Mean Value Theorem for fractional order derivatives (ODIBAT; SHAWAGFEH, 2007) that $C(t) \geq C(t_0) \geq 0$, for t sufficiently near to t_0. An absurd.

Therefore, the solution $U(t) \in \Omega_+$, for all $t \geq 0$.

□

2.2 Stability analysis for the multi-fractional SIRC model for Influenza

In this subsection, we analyze the stability analysis of equilibrium points $U^* = (S^*, I^*, R^*, C^*)^T$ for the (MF)-SIRC model (2). The analysis of stability is carried out in this manuscript is based on linear stability (DIETHELM, 2010).

Since the Caputo derivative of a constant is zero, then we interpret the equilibrium point as follows:

Definition 2.1 *A point $U^* = (S^*, I^*, R^*, C^*)^T \in \mathbb{R}^4$ is a equilibrium point for (MF)-SIRC model* (2) *if*[3] $F(t, U^*) = \vec{0}$.

Assumption 2.1 *Assume that the equilibrium of the system is attained for t large enough such that the total population $N(t) = N$, where N is a constant.*

Let the Assumption 2.1 holds. It follows from Definition 2.1 that any equilibrium point for the (MF)-SIRC model (2) shall satisfies

$$
\begin{aligned}
0 &= \mu^{\theta_1}(N - S^*) - \beta^{\theta_1} S^* I^* + \gamma^{\theta_1} C^* - \xi\rho^{\theta_1} S^* && (9)\\
0 &= \beta^{\theta_2} S^* I^* + \sigma^{\theta_2}\beta^{\theta_2} C^* I^* - (\mu^{\theta_2} + \alpha^{\theta_2}) I^* && (10)\\
0 &= (1 - \sigma^{\theta_3})\beta^{\theta_3} C^* I^* + \alpha^{\theta_3} I^* - (\mu^{\theta_3} + \delta^{\theta_3}) R^* + \xi\rho^{\theta_3} S^* && (11)\\
0 &= \delta^{\theta_4} R^* - \beta^{\theta_4} C^* I^* - (\mu^{\theta_4} + \gamma^{\theta_4}) C^* . && (12)
\end{aligned}
$$

From equation (10), it follows that

$$
I^*.(\beta^{\theta_2} S^* + \sigma^{\theta_2}\beta^{\theta_2} C^* - (\mu^{\theta_2} + \alpha^{\theta_2})) \quad = 0\,, \tag{13}
$$

resulting in $I^* = 0$ or $I^* \neq 0$.

The point $P_0 := (S_0^*, 0, R_0^*, C_0^*)$ $(I^* = 0)$ is called the diseases-free equilibrium point.

Lemma 2.2 *Let Assumption 2.1 holds. Then, the diseases-free equilibrium point $P_0 = (S_0^*, 0, R_0^*, C_0^*)$ is given by*

$$
S_0^* = \frac{-\mu^{\theta_1} N(\mu^{\theta_4} + \gamma^{\theta_4})(\mu^{\theta_3} + \delta^{\theta_3})}{-(\mu^{\theta_1} + \xi\rho^{\theta_1})(\mu^{\theta_4} + \gamma^{\theta_4})(\mu^{\theta_3} + \delta^{\theta_3}) + \gamma^{\theta_1}\delta^{\theta_4}\xi\rho^{\theta_3}}\,, \tag{14}
$$

$$
R_0^* = \frac{-\xi\rho^{\theta_3}\mu^{\theta_1} N(\mu^{\theta_4} + \gamma^{\theta_4})}{-(\mu^{\theta_1} + \xi\rho^{\theta_1})(\mu^{\theta_4} + \gamma^{\theta_4})(\mu^{\theta_3} + \delta^{\theta_3}) + \gamma^{\theta_1}\delta^{\theta_4}\xi\rho^{\theta_3}}\,, \tag{15}
$$

[3] Here, $\vec{0} = (0, 0, 0, 0)^T$.

and

$$C_0^* = \frac{-\mu^{\theta_1} N \delta^{\theta_4} \xi \rho^{\theta_3}}{-(\mu^{\theta_1} + \xi\rho^{\theta_1})(\mu^{\theta_4} + \gamma^{\theta_4})(\mu^{\theta_3} + \delta^{\theta_3}) + \gamma^{\theta_1}\delta^{\theta_4}\xi\rho^{\theta_3}}. \tag{16}$$

In particular, is no vaccination is under way, i.e. $\xi = 0$*, then, the diseases-free equilibrium point is* $P_0^* = (N, 0, 0, 0)$.

Proof: It follows from equations (9)-(12), that P_0 satisfies

$$\mu^{\theta_1} N - (\mu^{\theta_1} + \xi\rho^{\theta_1}) S_0^* + \gamma^{\theta_1} C_0^* = 0 \tag{17}$$

$$-(\mu^{\theta_3} + \delta^{\theta_3}) R_0^* + \xi\rho^{\theta_3} S_0^* = 0 \tag{18}$$

$$\delta^{\theta_4} R_0^* - (\mu^{\theta_4} + \gamma^{\theta_4}) C_0^* = 0 \tag{19}$$

From (18), we get

$$-(\mu^{\theta_3} + \delta^{\theta_3}) R_0^* + \xi\rho^{\theta_3} S_0^* = 0 \Rightarrow R_0^* = \frac{\xi\rho^{\theta_3} S_0^*}{\mu^{\theta_3} + \delta^{\theta_3}}. \tag{20}$$

By replacing equation (20) in (19), we obtain

$$C_0^* = \frac{\delta^{\theta_4} R_0^*}{\mu^{\theta_4} + \gamma^{\theta_4}} = \frac{\delta^{\theta_4}\xi\rho^{\theta_3} S_0^*}{(\mu^{\theta_4} + \gamma^{\theta_4})(\mu^{\theta_3} + \delta^{\theta_3})}. \tag{21}$$

Replacing (21) into (17), we get

$$\mu^{\theta_1} N - (\mu^{\theta_1} + \xi\rho^{\theta_1}) S_0^* + \gamma^{\theta_1} \frac{\delta^{\theta_4}\xi\rho^{\theta_3} S_0^*}{(\mu^{\theta_4} + \gamma^{\theta_4})(\mu^{\theta_3} + \delta^{\theta_3})} = 0, \tag{22}$$

from with, we conclude that S_0^* satisfies (14). Now, the lemma assertion follows from replacing (14) into (20) and (21), respectively. □

Next, we present a preliminary result into the direction of the stability for the diseases-free equilibrium point P_0, given in Lemma 2.2.

Lemma 2.3 *Let the assumptions on Lemma 2.2 holds. The eigenvalues of the Jacobian matrix* $J(t, P_0)$ *are real and given by*

$$\begin{aligned} \lambda_1 &= -\mu^{\theta_1} - \xi\rho^{\theta_1}, \quad \lambda_2 = -\gamma^{\theta_4} - \mu^{\theta_4}, \quad \lambda_3 = -\delta^{\theta_3} - \mu^{\theta_3} \\ \lambda_4 &= (\alpha^{\theta_2} + \mu^{\theta_2}) \left[\mu^{\theta_1} \frac{\beta^{\theta_2} N}{(\alpha^{\theta_2} + \mu^{\theta_2})} \left(\frac{(\delta^{\theta_3} + \mu^{\theta_3})(\gamma^{\theta_4} + \mu^{\theta_4}) - \xi\rho^{\theta_3}\delta^{\theta_4}\sigma^{\theta_2}}{(\delta^{\theta_3} + \mu^{\theta_3})(\gamma^{\theta_4} + \mu^{\theta_4})(\mu^{\theta_1} + \xi\rho^{\theta^1}) - \xi\rho^{\theta_3}\delta^{\theta_4}\gamma^{\theta_1}} \right) - 1 \right]. \end{aligned} \tag{23}$$

Proof: It follows from direct calculations that that the characteristic equation of $J(t, P_0)$ is given by

$$(-\mu^{\theta_1} - \xi\rho^{\theta_1} - \lambda)(\beta^{\theta_2} S_0^* + \sigma^{\theta_2}\beta^{\theta_2} C_0^* - (\mu^{\theta_2} + \alpha^{\theta_2}) - \lambda)(-(\mu^{\theta_3} + \delta^{\theta_3}) - \lambda)(-(\mu^{\theta_4} + \gamma^{\theta_4}) - \lambda)) = 0. \tag{24}$$

Hence, the assertion follows by obtaining the roots of (24). □

Our next step guarantees the conditions for the stability of the disease-free equilibrium point P_0. We shall first introduce the basal reproductive number (rate) $\mathcal{R}_0^{(\xi=0)}$ for the model (2), without a vaccination strategy, i.e., when $\xi = 0$. In this contribution, we define it as

$$\mathcal{R}_0^{(\xi=0)} = \frac{\beta^{\theta_2} N}{\mu^{\theta_2} + \alpha^{\theta_2}} \,. \tag{25}$$

Whiting the above results, we have:

Theorem 2.2 *Let the assumptions of Lemma 2.3 holds. Then, the diseases-free equilibrium point P_0 for the (MF)-SIRC model* (2) *with no vaccination strategy ($\xi = 0$) is asymptotically stable if $\mathcal{R}_0^{(\xi=0)} < 1$ and a saddle point otherwise.*

Proof: It follows from Lemma 2.3 that the eigenvalue that can change signal is

$$\lambda_4 = (\sigma^{\theta_2} + \mu^{\theta_2})(R_0^{(\xi=0)} - 1) \,.$$

Hence, the desired result follows from the theorem assumptions and (DIETHELM, 2010, Theorem 7.20). □

Since the disease-free equilibrium point P_0 given in Lemma 2.3 might not be asymptotic stable, the remained question is: There exists a vaccination strategy ($\xi = 1$) such that the disease is controlled? If yes, what shall be the proportion of the population to be vaccinated (strategy to choose ρ) ?

Notice that, differently form the case where the fractional derivatives are the same ($\theta_1 = \cdots, \theta_4$), as already discussed in (GOMES; DE CEZARO, 2018), critical proportional of the population to be vaccinated shall satisfies $\rho \geq 1 - \frac{1}{\mathcal{R}_0^{\xi=0}}$. Such choice does not seems to feet the desired result of keeping $\lambda_4 < 0$ in Lemma 2.3.

On the other hand, since

$$\left(\frac{(\delta^{\theta_3} + \mu^{\theta_3})(\gamma^{\theta_4} + \mu^{\theta_4}) - \xi\rho^{\theta_3}\delta^{\theta_4}\sigma^{\theta_2}}{(\delta^{\theta_3} + \mu^{\theta_3})(\gamma^{\theta_4} + \mu^{\theta_4})(\mu^{\theta_1} + \xi\rho^{\theta^1}) - \xi\rho^{\theta_3}\delta^{\theta_4}\gamma^{\theta_1}}\right) \leq \left(\frac{(\delta^{\theta_3} + \mu^{\theta_3})(\gamma^{\theta_4} + \mu^{\theta_4})}{(\delta^{\theta_3} + \mu^{\theta_3})(\gamma^{\theta_4} + \mu^{\theta_4})(\mu^{\theta_1} + \xi\rho^{\theta^1}) - \xi\rho^{\theta_3}\delta^{\theta_4}\gamma^{\theta_1}}\right)$$

it follows that the following nonlinear strategy for choosing ρ

$$\mathcal{R}_0^{\xi=0} + \frac{\rho^{\theta_3}\delta^{\theta_4}\gamma^{\theta_1}}{\mu^{\theta_1}(\delta^{\theta_3} + \mu^{\theta_3})(\gamma^{\theta_4} + \mu^{\theta_4})} < 1 + (\rho/\mu)^{\theta_1} \,, \tag{26}$$

is enough to keep P_0 asymptotically stable. In particular, for the parameter choices in the numerical simulations in Table 1, it follows that ρ satisfying (26) is anything biggest that 20%, while, in the standard case where $\theta_j = 1$ for $j = 1, \cdots, 4$, one need $\rho > 30\%$.

Now we follow the analysis for the equilibrium point $I^* \neq 0$.

Lemma 2.4 *The equilibrium point $P_1 = (S_1^*, I_1^*, R_1^*, C_1^*)$, (with $I_1^* \neq 0$) is given by*

$$S_1^* = \frac{\mu^{\theta_2} + \alpha^{\theta_2}}{\beta^{\theta_2}} - \frac{\sigma^{\theta_2}(\beta^{\theta_1}\beta^{\theta_2}\mu^{\theta_2} I_1^* + \alpha^{\theta_2}\beta^{\theta_1} I_1^* + \alpha^{\theta_2}\mu^{\theta_1} + \beta^{\theta_2}\mu^{\theta_1}\mu^{\theta_2} - \mu^{\theta_1}\beta^{\theta_2} N + \beta^{\theta_2}\xi\rho^{\theta_1}\sigma^{\theta_2})}{\beta^{\theta_2}(\gamma^{\theta_1} + \beta^{\theta_1} I_1^*\sigma^{\theta_2} + \mu^{\theta_1}\sigma^{\theta_2})},$$

$$C_1^* = \frac{\beta^{\theta_1}\beta^{\theta_2}\mu^{\theta_2} I_1^* + \alpha^{\theta_2}\beta^{\theta_1} I_1^* + \alpha^{\theta_2}\mu^{\theta_1} + \beta^{\theta_2}\mu^{\theta_1}\mu^{\theta_2} - \mu^{\theta_1}\beta^{\theta_2} N + \beta^{\theta_2}\xi\rho^{\theta_1}\sigma^{\theta_2}}{\beta^{\theta_2}(\gamma^{\theta_1} + \beta^{\theta_1} I_1^*\sigma^{\theta_2} + \mu^{\theta_1}\sigma^{\theta_2})}$$

and

$$R_1^* = \frac{((\gamma^{\theta_4}+\beta^{\theta_4}I_1^*+\mu^{\theta_4})(\alpha^{\theta_2}(\beta^{\theta_1}I_1^*+\mu^{\theta_1}+\xi\rho^{\theta_1})+\beta^{\theta_2}(\beta^{\theta_1}I_1^*\mu^{\theta_2}+\mu^{\theta_1}\mu^{\theta_2}-\mu^{\theta_1}N+\mu^{\theta_2}\xi\rho^{\theta_1})))}{(\beta^{\theta_2}\delta^{\theta_4}(\gamma^{\theta_1}+(\beta^{\theta_1}I_1^*+\mu^{\theta_1}+\xi\rho^{\theta_1})\sigma^{\theta_2}))}$$

and I_1^* is given by any positive roots of the polynomial

$$a(I_1^*)^2 + bI_1^* + c = 0\,, \tag{27}$$

where

$$\begin{aligned}
a &= (-\beta^{\theta_1}(\beta^{\theta_2}(\beta^{\theta_4}\mu^{\theta_2}(\delta^{\theta_3}+\mu^{\theta_3})+\delta^{\theta_4}(-\alpha^{\theta_3}\sigma^{\theta_2}+\beta^{\theta_3}\mu^{\theta_2}(-1+\sigma^{\theta_3})))\\
&\quad+\alpha^{\theta_2}(\beta^{\theta_4}(\delta^{\theta_3}+\mu^{\theta_3})+\beta^{\theta_3}\delta^{\theta_4}(-1+\sigma^{\theta_3}))))\\
b &= (\alpha^{\theta_3}\beta^{\theta_2}\delta^{\theta_4}(\gamma^{\theta_1}+(\mu^{\theta_1}+\xi\rho^{\theta_1})\sigma^{\theta_2})-\alpha^{\theta_2}(\beta^{\theta_1}(\delta^{\theta_3}+\mu^{\theta_3})(\gamma^{\theta_4}+\mu^{\theta_4})\\
&\quad+(\mu^{\theta_1}+\xi\rho^{\theta_1})(\beta^{\theta_4}(\delta^{\theta_3}+\mu^{\theta_3})+\beta^{\theta_3}\delta^{\theta_4}(-1+\sigma^{\theta_3})))\\
&\quad-\beta^{\theta_2}(\beta^{\theta_1}(\gamma^{\theta_4}\mu^{\theta_2}\mu^{\theta_3}+\mu^{\theta_2}\mu^{\theta_3}\mu^{\theta_4}+\delta^{\theta_3}\mu^{\theta_2}(\gamma^{\theta_4}+\mu^{\theta_4})-\delta^{\theta_4}\xi\rho^{\theta_3}\sigma^{\theta_2})\\
&\quad+(\mu^{\theta_1}(\mu^{\theta_2}-N)+\mu^{\theta_2}\xi\rho^{\theta_1})(\beta^{\theta_4}(\delta^{\theta_3}+\mu^{\theta_3})+\beta^{\theta_3}\delta^{\theta_4}(-1+\sigma^{\theta_3}))))\\
c &= -\alpha^{\theta_2}(\delta^{\theta_3}+\mu^{\theta_3})(\gamma^{\theta_4}+\mu^{\theta_4})(\mu^{\theta_1}+\xi\rho^{\theta_1})\\
&\quad-\beta^{\theta_2}(\mu^{\theta_1}\mu^{\theta_2}\mu^{\theta_3}\mu^{\theta_4}-\mu^{\theta_1}\mu^{\theta_3}\mu^{\theta_4}N+\mu^{\theta_2}\mu^{\theta_3}\mu^{\theta_4}\xi\rho^{\theta_1}+\delta^{\theta_3}(\gamma^{\theta_4}+\mu^{\theta_4})(\mu^{\theta_4}(\mu^{\theta_2}-N)+\mu^{\theta_2}\xi\rho^{\theta_1})\\
&\quad+\gamma^{\theta_4}\mu^{\theta_3}(\mu^{\theta_1}\mu^{\theta_2}-\mu^{\theta_1}N+\mu^{\theta_2}\xi\rho^{\theta_1})-\delta^{\theta_4}\gamma^{\theta_1}\xi\rho^{\theta_3}-\delta^{\theta_4}\mu^{\theta_1}\xi\rho^{\theta_3}\sigma^{\theta_2}-\delta^{\theta_4}\xi\rho^{\theta_1}\xi\rho^{\theta_3}\sigma^{\theta_2})\,,
\end{aligned}$$

if it exist.

Proof: From $I_1^* \neq 0$ and (10), we have

$$S_1^* = \frac{\mu^{\theta_2}+\alpha^{\theta_2}}{\beta^{\theta_2}} - \sigma^{\theta_2}C_1^*\,. \tag{28}$$

Replacing (28) into (10) implies in (27) been satisfied. Hence, replacing (27) into (28), we have . Now, (27) follows by replacing (27) into (12).

Finely, replacing (27)-(2.2) and (27) into (11), we conclude that I_1^* is given the polynomial equation (27). □

Given the number of parameters, the analysis of the existence of a positive root for the polynomial (27), as well as the stability analysis will be done numerically, using the numerical parameters in Table 1 in Section 3.

Theorem 2.3 *Let the assumption in Lemma 2.4 holds true. Furthermore, assume $\rho = 0,4$ and $\xi = 1$. Then we analyze three numerical cases: i) the SIRC model with $\theta_j = 1$, for $j = 1,\cdots,4$; ii) the (F)-SIRC model with $\theta_j = 0,9$, for $j = 1,\cdots,4$ and iii) the (MF)-SIRC model with $\theta_1 = 0,95$, $\theta_2 = 0.75$, $\theta_3 = 0.7$ and $\theta_4 = 0.6$. In all the three cases we have the existence of a unique positive equilibrium point as in Lemma 2.4 given by:*

i) SIRC model - we have $a = -0.194217$, $b = 1.16642$ and $c = 0.155526$, implying in $P_1 = (0.980805, 6.13627, 275.694, 23.5609)^T$. The associated eigenvalues are $\lambda_1 = -9.56518 - 5.31304i$, $\lambda_2 = -9.56518 + 5.31304i$, $\lambda_3 = -1.81193$ and $\lambda_4 = 2.793$.

ii) (F)-SIRC - we have $a = -0.231198$, $b = 1.00734$ and $c = 0.210719$, implying in $P_1 = (1.00471, 4.55706, 133.164, 15.7586)^T$. The associated eigenvalues are $\lambda_1 = -7.20051 - 4.42999i$, $\lambda_2 = -7.20051 + 4.42999i$, $\lambda_3 = -1.61275$, and $\lambda_4 = 2.40509$.

iii) (MF)-SIRC model - we have $a = -0.274299$, $b = 0.144672$ *and* $c = 0.280341$ *imply in* $P_1 = (1.37268, 1.3085, 19.33616.80666)^T$. *The associated eigenvalues are* $\lambda_1 = -2.734 - 2.48699i$, $\lambda_2 = -2.734 + 2.48699i$, $\lambda_3 = -1.11869$, *and* $\lambda_4 = 1.40562$.

Therefore, P_1 *is unstable in all numerical scenarios.*

Proof: Follows directly from the computation. □

A more sophisticated analysis for the stationary points as well as the phase portrait shall be investigated in future contributions.

3 Numerical simulations

In this section, we analyze the (MF)-SIRC model (2)-(4) numerically. We also present some numerical simulations involving the infected reported cases of influenza H1NI, obtained in the DATASUS (DATASUS,), from the state of Rio Grande do Sul, Brazil, in 2010.

Since our system does not have exact analytic solutions, approximation and numerical techniques must be used. Several numerical methods have been proposed to solve problems with Fractional differential equations e.g. (DIETHELM, 2010; EL-SHAHED; ALSAED, 2011; GARRAPPA, 2018, 2015) and references therein. In the simulations below, we follow the ideas in (GARRAPPA, 2018, 2015), where an adaptation of the Trapezoidal Method for fractional differential equations is proposed and analyzed. The mesh-size $h = 10^{-4}$ is adopted in all the simulations. Since h is associated with the time scale, in the numerical simulations with real data, the necessary re-scaling of the parameters shall be done, reflecting the time scale of the observed data.

3.1 Parameters and case study

In all the simulations, the total population N is assumed to be constant. With this assumption, the system 2 is normalized in such way that $N = 50$ in the simulations. The initial conditions are set as $S(0) = 49, I(0) = 1, R(0) = 0$ and $C(0) = 0$.

In our case study, the data from DATASUS[4] of infected reported cases of influenza H1NI, at the state of Rio Grande do Sul, Brazil, in 2010, is considered. The parameters choices proposed in (CASAGRANDI et al., 2006) are adjusted (see Table 1) to represent the observed data. We did not strive to obtain the optimal values for the adjustment and is a point for future work.

Table 1: List of parameters for case study

Parameter	Description	Value
μ	The mortality and birth rate	$0,02$
α	Recovery rate of infected	$5,14$
δ	The average time of appearance of new dominant clusters	$0,75$
γ	Cross-immune period	$0,35$
σ	The average reinfection probability of $C(t)$	$0,12$
β	Contact (transmission) rate of susceptible to be infected	$1,355$

[4]DATASUS (DATASUS,) is an information technology system that provides information from many diseases in Brazil.

Case study: Influenza H1N1 the state of RS in 2010 Our case study corresponds to the epidemiological week reported data of Influenza H1N1 collected on the DATASUS (DATASUS,) in the year of 2010, for the state of Rio Grande do Sul - RS (Brazil). They are represented as o in the Figure 2. Figure 2 show also simulated infected population $I(t)$ in the SIRC model (2) with the multi-fractional order $\theta_1 = 0,95$, $\theta_2 = 0.75$, $\theta_3 = 0.7$ and $\theta_4 = 0.6$ in red, with the same fractional order $\theta_j = 0,9$ in green and $\theta_j = 1$ in black (standard SIRC), for $j = 1, \cdots, 4$, respectively. It shows the same situation described above in a scenario with vaccination ($\rho = 0,4$), plotted as discontinuous lines[5].

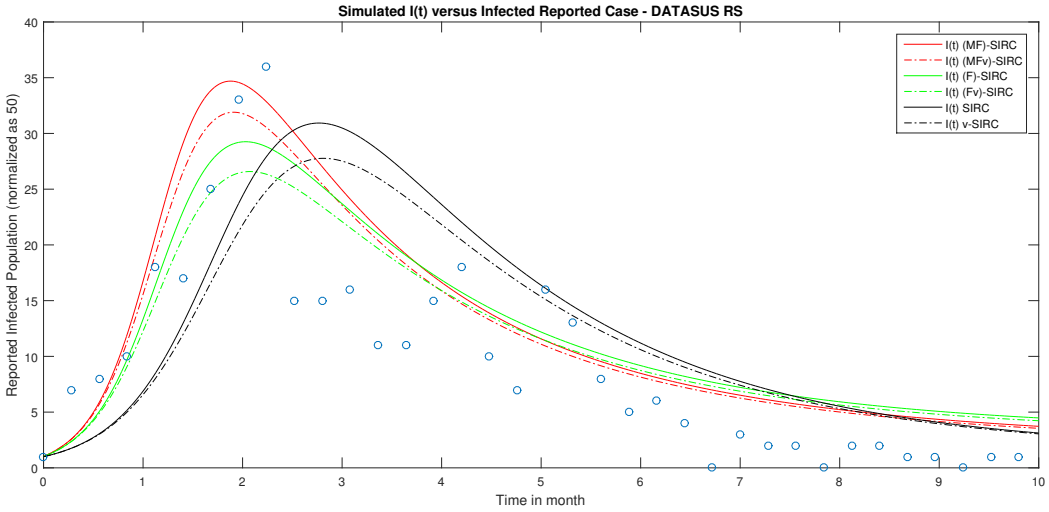

Figure 2: The continuous (discontinuous) lines shows the simulated infected population $I(t)$ with (MF)-SIRC, (F)-SIRC and SIRC models (with vaccination strategy with $\rho = 0,4$ indicated with -v), respectively.

The results presented in Figure 2 shows that the (MFO)-SIRC model has better agreement with the reported infected cases of Influenza H1N1, from the state of Rio Grande do Sul (Brazil) when compared with the simulated results from the (F)-SIRC or SIRC models. In particular, the (MFO)-SIRC describes very well the critical phase of the H1N1 epidemics. It shows also that vaccination can reduce the cases in all the simulated scenarios, even with a percentage of only $\rho = 40\%$. A more interesting scenario emerges in the long-running of the dynamics presented in Figure 3.

In Figure 3, we show the same simulated scenarios presented in Figure 2, for a longer time (5 years), for each of the classes S, I, R, C, respectively.

The simulated scenarios in Figure 3 suggest the following conclusions that might have profound impacts on the epidemiological interpretation, that, for now, we do not have enough data to validate. They are:

- i) The existence of immunological memory increases the possibility of re-infection from new strains of the virus in the earliest time of the diseases. It is because cross-immunity for the (MF)-SIRC is larger than the one from the SIRC model before one year (see the figure corresponding $C(t)$ in Figure 3). On the other hand, the situation is in reverse after one year (small cross-immunity implies less susceptibility to a new strain of the virus). Hence, we can conjecture two reasons for adopting the earliest vaccination strategy: a) Early contact

[5]Identified with a v in the captions.

with the strain by vaccination implies benefits for the long-term diminution of susceptibility to strain mutation; b) Increasing the probability of having immunological memory after the strain mutation. The gain with the immunological memory appears after the first year in our simulated scenario.

- ii) The stability of the disease's critical points is attained early in (MF)-SIRC than for the other simulated scenarios. It coincides with numerical finds for the critical points in Theorem 2.3.

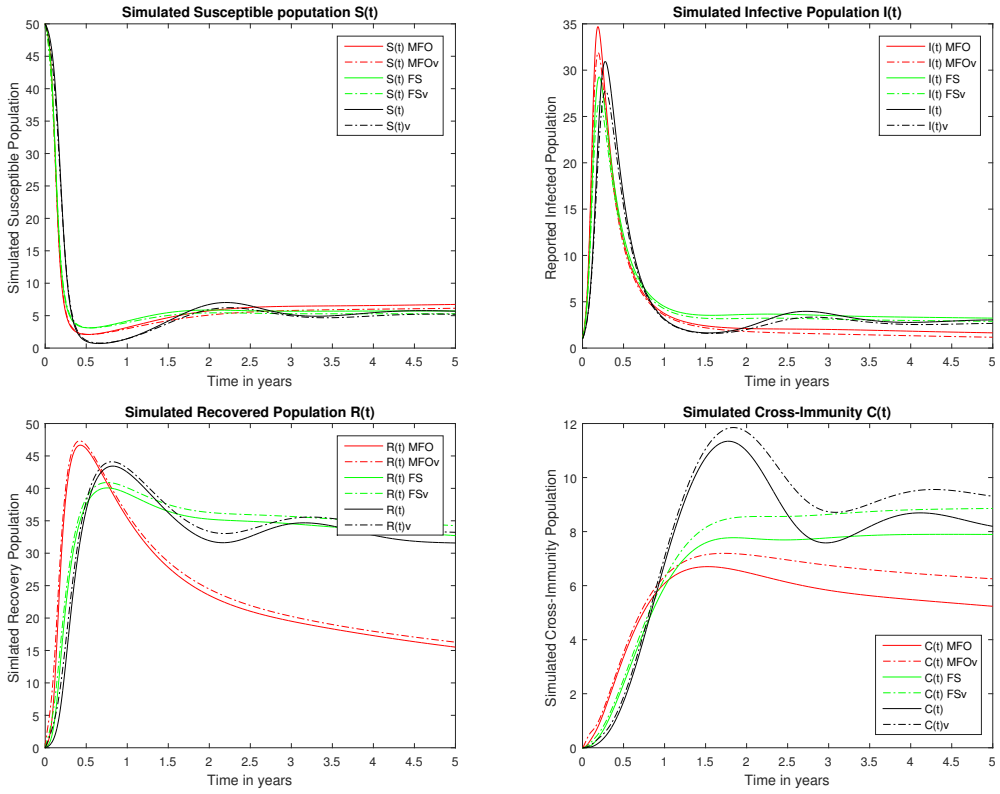

Figure 3: Simulated scenarios for the S, I, R, C, with a time spend of 5 years.

4 Conclusions and future directions

We proposed a generalized SIRC model (named (MF)-SIRC) that is a multi-fractional version of the one proposed by (CASAGRANDI et al., 2006). Such generalization uses the memory enhanced by the fractional derivatives for modeling the immunological memory of diseases that have mutation over time. In this case, influenza.

We proved the well-posedness and consistency of the model (indeed, that $U(t) \in \Omega_+$, for $t \in [0, T]$.). Furthermore, we analyze the existence and linearized stability of equilibrium points using analytical/numerical arguments for the influenza parameters.

Moreover, we compare simulated scenarios with the (MF)-SIRC, (F)-SIRC, and SIRC models, against reported data of Influenza H1N1 for the year of 2010 of the state of Rio Grande do Sul - RS (Brazil). We present a specific configuration for the fractional-order of the derivatives for the (MF)-SIRC that shows a better agreement with the reported data (see Figure 2).

A more intriguing and surprising result of simulated scenarios (presented in Figure 3) shows that the existing immunological memory implies, in a short time, more susceptibility to a new strain of the virus (larger $C(t)$). But, its susceptibility of been infected by stain mutations decreases for longer-running periods (one year in our numerical findings). Our numerical findings also show that the stability of the disease's critical points is attained early in (MF)-SIRC, than in the other simulated scenarios.

The complete analysis of equilibrium points and phase portrait for the (MF)-SIRC model, as well as the applicability to describe other sets of observed Influenza data (other mutating diseases as COVID-19) shall be investigated carefully in future contributions.

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