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A FRACTIONAL-ORDER MATHEMATICAL MODEL OF THE SPREAD OF INFLUENZA

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ABSTRACT

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Keywords:

Influenza; Fractional-Order Model; Caputo Derivative; Stability; Sensitivity Analysis; Numerical Simulation; Influenza is an infectious disease that has become a public health concern and affects millions of people every year. In Indonesia, 1,527 people were recorded as being infected with influenza from May 2013 to April 2016. In this article, a fractional-order $\alpha \in (0, 1]$ mathematical model of influenza spread was formulated in the sense of Caputo derivative. Based on the model analysis, we obtained two equilibrium points: the disease-free and endemic equilibria. The disease-free equilibrium point is locally asymptotically stable if the basic reproduction number is less than one. Meanwhile, the endemic equilibrium point exists and tends to be asymptotically stable whenever the basic reproduction number is greater than one. Next, a sensitivity analysis was carried out to determine whether changes in parameter values affect the increase or decrease in the value of the basic reproduction number. Lastly, the numerical simulation of the fractional-order model is demonstrated to support the analytical results.



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1. INTRODUCTION

Influenza is an acute respiratory infection caused by the influenza virus and is common worldwide. Influenza disease is caused by negative-strand RNA viruses from the Orthomyxoviridae family [1]. In Indonesia, 1,527 people were recorded as being infected with influenza from May 2013 to April 2016. Overall, the estimated annual incidence of influenza ranges from 13 to 19 for every 100,000 population. The highest incidence rate occurs in children aged 0 - 4 years, namely 82 - 114 for every 100,000 population, followed by children aged 5 - 14 years, namely 22 - 36 for every 100,000 population [2]. Common symptoms of influenza include fever, cough, headache, etc. These symptoms usually start about two days after being infected by someone with the virus [3]. Vaccination programs, isolation, quarantine, etc can be used to prevent the spread of influenza [4].

Mathematical modeling is a field of mathematics used to formulate a real problem into a mathematical model [5]. Several researchers have studied the dynamics of the spread of influenza using mathematical modeling, namely Khanh [6], who described the transmission of influenza virus with disease resistance in humans. Erdem et al. [7] have studied the influenza model with the assumption that everyone has the same opportunity to contact other individuals. Next, Erdem et al. [7] developed the model by adding a quarantine class, assuming the latency period (inactive virus) is negligible and immunity is permanent. Kanyiri et al. [8] have constructed a model for the spread of influenza by dividing the infected subpopulation into two types, namely infected with the wild-type strain and the resistant strain. Rosyada et al. [9] discussed mathematical modeling that explains the model of influenza virus transmission with the SEIR Model in a case study in Pekalongan City. Baba et al. [10] have constructed a mathematical model by assuming a functional response of type I Holling for urban areas and type II Holling for rural areas on the rate of infection transmission. Guan et al. [12] have established an influenza epidemic model with vaccinated and asymptomatic patients. Chen [13] has developed a model for the spread of influenza stratified by age.

Fractional order mathematical modeling is a mathematical technique used to formulate natural phenomena into models involving fractional order. Fractional order refers to a form of differential equation that contains derivatives of non-integer order, namely derivatives with fractional powers. This order adds information from classical theory with a more accurate description so that it can explain natural phenomena better [14]. One of the researchers who has studied the development of influenza spread using a fractional model approach is Ebenezer [15] who examined the fractional order of influenza using an epidemic model. Yaro et al. [16] have studied respiratory epidemic models, one of which is caused by the influenza virus, using Caputo's fractional order derivative. Cui and Liu [17] have formulated a fractional model that governs the dynamical properties of bi-strains of influenza. Evirgen et al. [18] have constructed a fractional-order influenza using the Atangana-Baleanu Caputo fractional-order derivative operator in place of the standard operator. Khan et al. [20] have investigated the coexistence of two influenza strains. Alsubaje et al. [21] have modeled the transmission dynamic of influenza using a deterministic SEIHR-V model under Caputo fractional-order Calculus.

Based on the description above, we proposed a fractional-order mathematical model of influenza spread using the Caputo fractional approach proposed by Ojo et al. [4]. We also modified the basic model in [4] by eliminating the influenza vaccination compartment, considering that in Indonesia, influenza vaccination is given from the age of 6 months through an immunization program. By using fractional ordinary differential equations, we hope that the fractional order mathematical model can accommodate the actual phenomenon of the spread of influenza.

2. RESEARCH METHODS

In this section, we will provide the mathematical theory used and the research methods carried out in this research.

2.1 Caputo Derivative

The Caputo fractional derivative is defined as follows [22]:

Definition 1. Let f(t) is a function that is differentiable to the m^{th} derivative. The Caputo derivative of f(t) of order $\alpha \in (0, 1]$ can be defined as follows:

$$D^{\alpha}f(t) = \frac{d^{\alpha}f(t)}{dt^{\alpha}} = \begin{cases} \frac{1}{\Gamma(m-\alpha)} \int_{0}^{t} \frac{f^{(m)}(\tau)}{(t-\tau)^{\alpha-m+1}} d\tau, \ m-1 < \alpha < m \\ f^{(m)}(t), \ \alpha = m \end{cases}$$

where t > 0 and $m \in \mathbb{N}$.

Caputo fractional derivative of a constant *C* is zero, namely
$$\frac{d^{\alpha}c}{dt^{\alpha}} = 0$$
 and holds:
$$\frac{d^{\alpha}t^{m}}{dt^{\alpha}} = \begin{cases} 0, \ m \le \alpha - 1 \\ \frac{\Gamma(m+1)}{\Gamma(m-\alpha+1)} t^{m-\alpha}, \ m > \alpha - 1 \end{cases}$$

If $\alpha = 1$, then the Caputo fractional derivative is an ordinary derivative. Thus, the Caputo fractional derivative is a generalization of the ordinary derivative [23].

2.2 Systems of Nonlinear Fractional-order Differential Equation

The following are the definition and theorem regarding systems of nonlinear fractional-order differential equations [23]:

Definition 2. Consider a system of fractional-order nonlinear differential equations using the Caputo approach as follows:

$$D^{\alpha}x(t) = f(x) \tag{1}$$

where $x \in \mathbb{R}^n$ and $\alpha \in (0, 1]$.

Theorem 1. The equilibrium point of Equation (1) is the solution to f(x) = 0. An equilibrium point is locally asymptotically stable if all eigenvalues (λ_i) of the Jacobian matrix $J = \partial f / \partial x$ evaluated at the equilibrium point satisfy $|\arg(\lambda_i)| > \alpha \pi/2$.

2.2 Research Methods

The steps used to analyze the fractional-order mathematical model of the spread of influenza are as follows:

- a. Modifying the mathematical model of the spread of influenza as referred to by Ojo et al. [4], namely by only taking the influenza spread model, adding fractional order to the model, and modifying the model by eliminating the vaccination compartment.
- b. Analyze the stability of the equilibrium points in the fractional-order mathematical model of the spread of influenza with the following steps:
 - i. Determining the equilibrium point in a fractional-order mathematical model of the spread of influenza.
 - ii. Calculating the basic reproduction number (\mathcal{R}_0) using the next-generation matrix method.
 - iii. Linearize the fractional-order mathematical model of the spread of influenza using the Jacobian matrix.
 - iv. Testing the local stability of the equilibrium point of the fractional-order mathematical model of the spread of influenza using the Routh-Hurwitz criterion.
- c. Carrying out numerical simulations on fractional-order mathematical models of the spread of influenza using MATLAB software.

3. RESULTS AND DISCUSSION

In this section, we propose a fractional-order mathematical model of the spread of influenza, analysis of the model, and conduct numerical simulations of the model to support the analytical results.

3.1 Model Formulation

A fractional-order mathematical model of the spread of influenza is constructed under the following assumptions:

- The population is divided into four compartments: the susceptible subpopulations (S), the exposed a. subpopulations (E), the infected subpopulations (I), and the recovered subpopulations (R). Moreover, the total population is given by N = S + E + I + R.
- b. All newborn individuals are considered susceptible to influenza.
- c. The rate of disease spread begins with a saturation incidence rate.
- d. Immunity in individuals who have recovered from influenza may decrease, so individuals who recover can become susceptible to the disease again.
- e. Individuals who are vaccinated against influenza are still considered individuals who are susceptible to the disease.
- All parameter values have positive values. f.

A description of the parameters in the mathematical model of the spread of influenza can be seen in Table 1 as follows:

No	Parameter	Description	
1	π	Rate of influx of susceptible individuals	
2	μ	Rate of natural death	
3	κ	Rate of decline in immunity of recovered individuals	
4	β	Rate of transmission	
5	ρ	Rate of saturation	
6	σ	Rate of influenza progression from exposure to infection	
7	γ	Recovery rate of individuals infected	
8	δ	Influenza death rate	

 Table 1. Description of the Parameters

Based on these assumptions and parameters, the compartment diagram of the influenza spread model can be formed in Figure 1 as follows:



Figure 1. Compartment Diagram for Mathematical Model of the Spread of Influenza

Based on Figure 1, a mathematical model of the spread of influenza can be formed as follows:

$$\frac{dS}{dt} = \pi + \kappa R - (\mu + r)S,$$

$$\frac{dE}{dt} = rS - (\sigma + \mu)E,$$
 (2)

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$$\frac{dI}{dt} = \sigma E - (\gamma + \mu + \delta)I,$$
$$\frac{dR}{dt} = \gamma I - (\kappa + \mu)R,$$

where $r = \frac{\beta I}{1 + \rho I}$. The solution of Equation (2) is defined for every $t \ge 0$ in the set of positive invariants, with:

$$\Omega = \left\{ (S, E, I, R) \in \mathbb{R}^4_+ \left| S, E, I, R \ge 0, 0 \le N \le \frac{\pi}{\mu} \right\}.$$
(3)

Next, we consider a fractional-order model of **Equation (3)**. The fractional-order mathematical model of the spread of influenza is as follows:

$$\frac{d^{\alpha}S}{dt^{\alpha}} = \pi + \kappa R - (\mu + r)S,$$

$$\frac{d^{\alpha}E}{dt^{\alpha}} = rS - (\sigma + \mu)E,$$

$$\frac{d^{\alpha}I}{dt^{\alpha}} = \sigma E - (\gamma + \mu + \delta)I,$$

$$\frac{d^{\alpha}R}{dt^{\alpha}} = \gamma I - (\kappa + \mu)R,$$
(4)

where $\alpha \in (0, 1]$ is the order of the fractional derivative. The fractional derivative used in Equation (4) is the Caputo approach.

3.2 Model Analysis

Based on **Theorem 1**, the equilibrium point is obtained by making the right side of **Equation (4)** zero. The disease-free equilibrium point in **Equation (4)** is:

$$x^{0} = (S^{0}; E^{0}; I^{0}; R^{0}) = \left(\frac{\pi}{\mu}; 0; 0; 0\right).$$
 (5)

Then, the basic reproduction number (\mathcal{R}_0) of model **Equation** (5) is computed using the nextgeneration matrix method. The basic reproduction number is defined as the number of secondary cases of primary cases during the infectious period due to the type of infection [24]. Based on **Equation** (5), there are two compartments with infected compartments, namely *E* and *I*. The Jacobian matrices *F* and *V* for the new infection acquired from susceptible individuals and the rate of individual movement from one subpopulation to another subpopulation evaluated at the free equilibrium point x^0 are given by:

$$F = \begin{bmatrix} 0 & \pi\beta_I \\ 0 & 0 \end{bmatrix}, V = \begin{bmatrix} \sigma + \mu & 0 \\ -\sigma_I & \gamma + \mu + \delta \end{bmatrix}.$$
(6)

The basic reproduction number of Equation (6) is obtained by determining the spectral radius of the matrix FV^{-1} , so that it is obtained:

$$\mathcal{R}_0 = \frac{\pi\beta\sigma}{\mu(\sigma+\mu)(\gamma+\mu+\delta)}.$$
(7)

The following theorem provides the local stability of the disease-free equilibrium point.

Theorem 2. The disease-free equilibrium point x^0 is locally asymptotically stable if $\mathcal{R}_0 < 1$.

Proof. The Jacobian matrix of Equation (4) around the disease-free equilibrium point x^0 is given by:

$$J(x^{0}) = \begin{bmatrix} -\mu & 0 & -\frac{\pi\beta}{\mu} & \kappa_{I} \\ 0 & -(\sigma+\mu) & \frac{\pi\beta}{\mu} & 0 \\ 0 & \sigma_{I} & \frac{\pi\beta}{\mu} & 0 \\ 0 & 0 & -(\gamma+\mu+\delta) & -(\kappa+\mu) \\ & & \gamma_{I} \end{bmatrix}.$$
 (8)

Based on Equation (8), the eigenvalues of Jacobian matrix *J* are $\lambda_1 = -\mu$, $\lambda_2 = -(\kappa + \mu)$, and the roots of quadratic equation:

$$\lambda^2 + a_1 \lambda + a_2 = 0, \tag{9}$$

where $a_1 = (\sigma + \mu) + (\gamma + \mu + \delta)$ and $a_2 = (\sigma + \mu)(\gamma + \mu + \delta) - \pi\beta\sigma_i/\mu$. Using the Routh-Hurwitz criterion, the roots of **Equation (9)** have a positive real part if and only if $a_1 > 0$ and $a_2 > 0$, which obtained when $\mathcal{R}_0 < 1$. Ahmed et al. [25] showed that for every $n \in \mathbb{N}$, $a_n > 0$ is a necessary condition for $|\arg(\lambda_i)| > \frac{\alpha\pi}{2}$, where i = 1, 2, ..., n. Thus, it is proven that the disease-free equilibrium point x^0 is locally asymptotically stable for $\alpha \in (0, 1]$ if $\mathcal{R}_0 < 1$.

Next, the endemic equilibrium point x^* of Equation (4) will be determined. The endemic equilibrium point x^* of Equation (3) is:

$$x^* = (S^*; E^*; I^*; R^*), \tag{10}$$

where

$$S^{*} = \frac{\pi(1+\rho I^{*})}{\mu \mathcal{R}_{0}},$$

$$E^{*} = \frac{\gamma + \mu + \delta}{\sigma} I^{*},$$

$$I^{*} = \frac{\mu(\sigma + \mu)(\gamma + \mu + \delta)(\kappa + \mu)(\mathcal{R}_{0} - 1)}{\mu \rho(\sigma + \mu)(\gamma + \mu + \delta)(\kappa + \mu) + \beta((\sigma + \mu)(\gamma + \mu + \delta)(\kappa + \mu) - \sigma \kappa \gamma)},$$

$$R^{*} = \frac{\gamma}{\kappa + \mu} I^{*}.$$

The endemic equilibrium point x^* exists if $\mathcal{R}_0 > 1$.

The following theorem provides the local stability of the endemic equilibrium point.

Theorem 3. The endemic equilibrium point x^* is locally asymptotically stable if $\mathcal{R}_0 > 1$.

Proof. The Jacobian matrix of Equation (4) around the disease-free equilibrium point x^0 is given by:

$$J(x^*) = \begin{bmatrix} -(\mu + r^*) & 0 & -p_1 & \kappa \\ r^* & -(\sigma + \mu) & p_1 & 0 \\ 0 & \sigma_l & -(\gamma + \mu + \delta) & 0 \\ 0 & 0 & \gamma_l & -(\kappa + \mu) \end{bmatrix},$$
(11)

where $p_1 = \frac{\beta}{(1+\rho I^*)^2}$. Based on Equation (11), the eigenvalues of Jacobian matrix *J* are the roots of the characteristic equation:

$$\lambda^4 + b_1 \lambda^3 + b_2 \lambda^2 + b_3 \lambda + b_4 = 0, \tag{12}$$

where $b_1 = j_1 + j_4 + j_6 + j_7$, $b_2 = j_4 j_6 - j_5 \sigma_I + (j_1 + j_7)(j_4 + j_6) + j_1 j_7$, $b_3 = (j_1 + j_7)(j_4 j_6 - j_5 \sigma_I) + j_1 j_7 (j_4 + j_6) + j_2 j_3 \sigma_I$, dan $b_4 = j_1 j_7 (j_4 j_6 - j_5 \sigma_I) + j_3 \sigma_I (j_2 j_7 - \kappa_I \gamma_I)$. Due to the complexity of the coefficient expression in the characteristic equation, the analytical proof is difficult to carry out, so the proof will be shown numerically. Numerical simulations to determine the stability of the endemic equilibrium point x^* are carried out by taking two order α values, namely $\alpha = 0.75$ and $\alpha = 1$. The initial values and parameter values used in this numerical simulation are given in **Table 2** and **Table 3** as follows:

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Initial Values	S	Ε	Ι	R
<i>z</i> ₁	200,000	90,000	500	400
<i>Z</i> ₂	225,000	60,000	450	350
<i>Z</i> ₃	250,000	35,000	400	300

Table 2. Initial Values in Phase Portrait Simulation

Table 3. Parameter Values in Fractional-order Mathematical Model of the Spread of Influenza

Parameter	Value	Reference
π	100	Assumed
μ	3.516×10^{-4}	[4]
κ	0.088	[4]
β	5.03×10^{-6}	Assumed
ρ	0.7	Assumed
σ	0.4	[4]
γ	0.1998	[4]
δ	0.021	[4]

The results of the numerical simulation can be seen in Figure 2 by taking three different initial values.



Based on the numerical simulation results in **Figure 2**, the solution of (4) with three different initial values given converges to the endemic equilibrium point x^* , where $\mathcal{R}_0 = 6.4623 > 1$. Thus, the endemic equilibrium point x^* tend to be locally asymptotically stable for $\alpha \in (0, 1]$ if $\mathcal{R}_0 > 1$.

3.3 Sensitivity Analysis

In this sub-section, we present the sensitivity analysis of the reproduction number (\mathcal{R}_0) to the parameters in Equation (4). The aim of this analysis was to measure the parameters that have the most effects on \mathcal{R}_0 . The index of each parameter involved in \mathcal{R}_0 can be formulated as follows:

$$e_m^{\mathcal{R}_0} = \frac{\partial \mathcal{R}_0}{\partial m} \frac{m}{\mathcal{R}_0},\tag{13}$$

where e_m is the sensitivity index of the parameter *m* and *m* is the parameter to be analyzed. The sensitivity index of \mathcal{R}_0 with respect to each parameter, such as π , β , σ , μ , γ , and δ can be computed using (13). For example, the sensitivity index of \mathcal{R}_0 with respect to β and γ are:

$$e_{\beta}^{\mathcal{R}_{0}} = \frac{\partial \mathcal{R}_{0}}{\partial \beta} \frac{\beta}{\mathcal{R}_{0}} = 1, e_{\gamma}^{\mathcal{R}_{0}} = \frac{\partial \mathcal{R}_{0}}{\partial \gamma} \frac{\gamma}{\mathcal{R}_{0}} = -0.9035.$$

The results of calculating the sensitivity index on the parameters of the fractional-order mathematical model of the spread of influenza can be seen in **Table 4** as follows:

Parameter	Sensitivity index
π	1
β	1
σ	8.7823×10^{-4}
μ	-1.0025
γ	-0.9035
δ	-0.095

 Table 4. Parameter Sensitivity Index Calculation Results

Based on **Table 4**, a sensitivity index with a positive value indicates that an increase in the parameter value will cause an increase in the basic reproduction number, while a sensitivity index with a negative value indicates that an increase in the parameter value will cause a decrease in the basic reproduction number. For example, sensitivity index $e_{\beta}^{\mathcal{R}_0} = 1$, increasing the β value by 10% will increase \mathcal{R}_0 by 10% and for $e_{\gamma}^{\mathcal{R}_0} = -0.9035$, increasing the γ value by 10% will decrease \mathcal{R}_0 by 9.035%.

Based on the parameter values in Table 3, we also perform sensitivity simulations to verify our sensitivity analysis of β with respect to \mathcal{R}_0 in Figure 3 as follows:



Figure 3. Sensitivity of \mathcal{R}_0 with respect to (a) β and (b) γ for Different Values of π

Based on the sensitivity simulation results in **Figure 3**, it can be seen that if the β value increases, the resulting \mathcal{R}_0 value will increase monotonically, and if the γ value increases, the resulting \mathcal{R}_0 value will decrease monotonically. Next, we perform sensitivity simulations of β and γ with respect to *I* in **Figure 4** as follows:



Figure 4. Sensitivity of β with respect to *I* when (a) $\alpha = 1$ and (b) $\alpha = 0.75$



Based on Figure 4, it can be seen that the number of infected individuals will be more significant if the rate of the spread of influenza is greater. Based on Figure 5, the number of infected individuals will decrease if the rate of the spread of influenza is greater. Apart from that, sensitivity analysis of β and γ with high order α have faster convergence speeds compared to smaller α .

Based on the description above, it can be seen that the level of influenza transmission significantly impacts the spread of influenza. This indicates that preventive measures are needed to control the spread of influenza, such as maintaining cleanliness, wearing masks, maintaining distance, and so on. In addition, the recovery rate of influenza also has a major impact on reducing the spread of influenza. Therefore, effective influenza treatments can reduce the number of infected individuals.

3.4 Numerical Simulation

In this sub-section, we conduct several numerical simulations of **Equation (4)**. Numerical simulations were carried out using MATLAB software. The initial values used in these simulations are (S(0); E(0); I(0); R(0)) = (200,000; 90,000; 500; 400). Here, we take 500 days for the time horizon. Simulations were carried out with varying fractional derivative order values $\alpha \in (0.5, 1]$.

Now, we will perform a numerical simulation for the disease-free equilibrium point x^0 . The parameter values used in this numerical simulation are $\beta = 2.03 \times 10^{-7}$ and other parameter values are taken in **Table** 2. In this case, the value of \mathcal{R}_0 is $\mathcal{R}_0 = 0.0026 < 1$, which means there is no disease spread in a population. The results of the numerical simulation of the disease-free equilibrium point in **Equation (4)** can be seen in **Figure 6** and **Figure 7** as follows:



Figure 6. Numerical Solution of Equation (4) when $\mathcal{R}_0 < 1$ for (a) Susceptible Population and (b) Exposed Population



Figure 7. Numerical Solution of Equation (4) when $\mathcal{R}_0 < 1$ for (a) Infected Population and (b) Recovered Population

Based on the numerical simulation results in **Figure 6** and **Figure 7**, we observe that the solution of **Equation (4)** converges to disease-free equilibrium when $\mathcal{R}_0 < 1$. Apart from that, numerical simulation with high-order α have faster convergence speeds compared to smaller α .

Next, we will perform a numerical simulation for the endemic equilibrium point x^* . The parameter values used in this numerical simulation are taken in **Table 2**. In this case, the value of \mathcal{R}_0 is $\mathcal{R}_0 = 6.4632 > 1$, which means that disease spreads in a population. The results of the numerical simulation of the endemic equilibrium point in **Equation (4)** can be seen in **Figure 8** and **Figure 9** as follows:



Figure 8. Numerical Solution of Equation (4) when $\mathcal{R}_0 > 1$ for (a) Susceptible Population and (b) Exposed Population



Figure 9. Numerical Solution of Equation (4) when $\mathcal{R}_0 > 1$ for (a) Infected Population and (b) Recovered Population

Based on the numerical simulation results in Figure 8 and Figure 9, we observe that the solution of Equation (4) converges to endemic equilibrium when $\mathcal{R}_0 > 1$. Apart from that, numerical simulation with high-order α have faster convergence speeds compared to smaller α .

4. CONCLUSIONS

In this article, we have investigated a fractional-order mathematical model of the spread of influenza as a generalization of the integer-order model proposed by Ojo et al. [4]. The basic model in [4] is modified by simply taking the influenza spread model, removing the influenza vaccination compartment, and generalizing the model by adding a fractional order. We have calculated the basic reproduction number (\mathcal{R}_0) and proven the equilibrium point stability of a fractional-order mathematical model of the spread of influenza. Based on mathematical analysis, a disease-free equilibrium point is locally asymptotically stable if $\mathcal{R}_0 < 1$, which means there is no disease spread in a population. Numerically, the endemic equilibrium point tends to be locally asymptotically stable when $\mathcal{R}_0 > 1$, which means that disease spreads in a population. We also studied sensitivity analysis analytically and numerically to measure parameters that have a high impact of \mathcal{R}_0 . Finally, we have performed numerical simulations for different order (α) values of the fractional derivative. The numerical simulation results show that solutions with high-order α have faster convergence than those with smaller α .

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