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On the nonlocal discretization of the simplified Anderson-May model of viral infection[1]

Abstract We present five nonstandard finite difference methods designed for the numerical simulation of the simplified Anderson-May model of viral infection. The proposed methods, based solely on the principle of nonlocal discretization, are able to preserve all of the essential qualitative features of the original model: the non-negativity of the solutions and local stability of the equilibrium points, along with their stability conditions. One of the proposed methods preserves the types of the equilibrium points (*i.e.* the presence and absence of oscillations) as well. All of these results are independent of the chosen step-size of the simulation.

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1. Introduction. The nonstandard finite difference methods (or NSFD methods / schemes) are numerical methods dedicated for mathematical models based on systems of differential equations [3, 4, 6]. The main idea that lies behind this approach is that the continuous model should be discretized in such a manner that the dynamics of the obtained difference equations are qualitatively consistent with the dynamics of the original continuous model. This is achieved by a combination of two discretization strategies: (1) introduction of a special function of the step-size in the denominator of the discrete derivative, and (2) nonlocal discretization of the model equations.

In this paper, we present five examples of NSFD methods designed for the numerical simulation of the simplified (*i.e.* two dimensional) Anderson-May model of viral infection [1, 5]. This model is very significant for the mathematical modeling of the immune response, as it is often used as a basis for more complicated descriptions of virus - immune system dynamics, see *e.g.* [7].

There exist several general NSFD methods that may be applied to the simplified Anderson-May model (*e.g.* [2, 8]). All of these approaches preserve the non-negativity of the solutions and the stability of the equilibria. What makes our examples stand out among other approaches is that our NSFD

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methods are based solely on the principle of nonlocal discretization of the mathematical model. The qualitative properties of the simplified Anderson-May model are preserved without restrictions on the step-size, and therefore there is no need for modification of the denominator of the discrete derivative.

As it turns out, one of the presented nonlocal discretization methods also preserves the presence (or absence) of oscillations around the asymptotically stable equilibrium point. This qualitative feature (the preservation of the types of equilibrium points) is rarely investigated. As a consequence, in many discretization methods, the choice of certain parameter values may lead to qualitative inconsistencies with the original mathematical model.

2. The simplified Anderson-May model of viral infection. The simplified Anderson-May model of viral infection describes the interactions of the uninfected target cells (x) and infected cells (y). The model is a system of two ordinary differential equations:

$$\dot{x} = \lambda - dx - \beta xy, \tag{1a}$$

$$\dot{y} = \beta xy - ay, \tag{1b}$$

with a non-negative initial condition and positive values of the parameters.

Parameter λ denotes the constant inflow of the uninfected cells (x). These cells become infected by virus particles at a rate proportional to concentrations of both uninfected (x) and infected cells (y) with proportionality parameter β. The death rate of uninfected and infected cells is denoted by d and a, respectively. For a more detailed biological interpretation of system (1) and its parameters, see *e.g.* [1] or [7].

The qualitative properties of the simplified Anderson-May model are well known. The solutions of system (1) are non-negative. The model has two equilibrium points. The observed outcome is governed by the basic reproductive ratio of the virus (the average number of newly infected cells produced by a single infected cell at the beginning of the infection):

$$R_0 = \frac{\beta\lambda}{ad}. \tag{2}$$

The first (*virus-free*) equilibrium is observed in the absence of infection ($y(0) = 0$) or when the viral replication is too low to establish a long term infection ($R_0 < 1$). In these cases solutions of system (1) converge to:

$$\left(x_{vf}, y_{vf}\right) = \left(\frac{\lambda}{d}, 0\right). \tag{3}$$

In the case of $R_0 > 1$, on the other hand, a successful infection is established and solutions of system (1) converge to the following *infection* equilibrium:

$$\left(x_{inf}, y_{inf}\right) = \left(\frac{a}{\beta}, \frac{\lambda}{a} - \frac{d}{\beta}\right). \tag{4}$$

The local stability analysis reveals that the *virus-free* equilibrium is always a stable node, *i.e.* there are no oscillations around point (3). The type of the *infection* equilibrium depends on the discriminant of the characteristic equation:

$$\Delta_c = \left(\frac{\beta\lambda}{a}\right)^2 - 4(\beta\lambda - ad). \tag{5}$$

In the case of $\Delta_c \geq 0$, point (4) is a stable node and no oscillations should be observed. In the opposite case ($\Delta_c < 0$), point (4) is a stable focus, therefore fading oscillations should always be present in the numerical simulations of this case.

3. The nonlocal discretization. We start the discretization of system (1) by replacing the left-hand sides of equations with discrete derivatives. We use a standard form of the discrete derivative, the same as in forward Euler or Runge-Kutta methods:

$$\dot{x} \longrightarrow \frac{x_{n+1} - x_n}{h}, \quad \dot{y} \longrightarrow \frac{y_{n+1} - y_n}{h},$$

where $h > 0$ is the step-size of the simulation. Next, the variables on the right-hand sides of equations (1) have to be replaced with their present (local) or future (nonlocal) discrete approximations. There are many ways of how this can be done. For convenience, we only consider the cases which do not put restrictions on the step-size h for the non-negativity of x_{n+1} and y_{n+1}.

After some additional analyses, we arrive at the following five easiest possibilities of nonlocal discretization of system (1):

$$x_{n+1} - x_n = h(\lambda - dx_{n+1} - \beta x_{n+1}\hat{y_1}), \tag{6a}$$

$$y_{n+1} - y_n = h(\beta\hat{x}\hat{y_2} - ay_{n+1}), \tag{6b}$$

where the triple $(\hat{y_1}, \hat{x}, \hat{y_2})$ is equal to one of the following:

$$(y_n, x_n, y_n), \tag{7a}$$

$$(y_n, x_{n+1}, y_n), \tag{7b}$$

$$(y_{n+1}, x_n, y_n), \tag{7c}$$

$$(y_{n+1}, x_{n+1}, y_n), \tag{7d}$$

$$(y_{n+1}, x_{n+1}, y_{n+1}). \tag{7e}$$

Each of the discretization methods given by Eqs. (6) - (7) preserves the qualitative properties of system (1) independently of the chosen step-size $h > 0$ (see Theorems 3.1 - 3.4 below). Please note that we provide proofs only for the most complicated discretization case (7e). The proofs of Theorems 3.1 - 3.4 in four other cases (7a) - (7d) are either analogous or easier.

THEOREM 3.1 For a non-negative initial condition (x_0, y_0) there exists a unique and nonnegative solution of system (6) with $(\hat{y_1}, \hat{x}, \hat{y_2})$ given by any of formula (7).

PROOF (case (7e)) It is sufficient to show that if $x_n, y_n \geq 0$ then there exist unique and nonnegative x_{n+1}, y_{n+1}. From Eq. (6a), we have:

$$x_{n+1} = \frac{x_n + h\lambda}{1 + hd + h\beta y_{n+1}}, \tag{8}$$

which substituted into Eq. (6b) yields:

$$A(h)y_{n+1}^2 + B(h, x_n, y_n)y_{n+1} + C(h, y_n) = 0, \tag{9}$$

where:

$$A(h) = \beta h(1 + ha),$$
$$B(h, x_n, y_n) = 1 + (-\beta x_n - \beta y_n + a + d)h + (ad - \beta\lambda)h^2,$$
$$C(h, y_n) = -y_n(1 + hd).$$

For any $h > 0$ and $y_n \geq 0$, we have $A(h) > 0 \geq C(h, y_n)$, and thus quadratic equation (9) has two real roots, one of which is non-negative. Therefore we choose y_{n+1} to be the larger root of Eq. (9). The non-negativity of y_{n+1} yields that x_{n+1} has to be non-negative as well (see Eq. (8)). ∎

THEOREM 3.2 The fixed points of discrete system (6) are equal to equilibrium points (3) - (4) of continuous system (1).

PROOF Each fixed point $(\bar{x}, \bar{y})$ of system (6) satisfies:

$$0 = \bar{x} - \bar{x} = h(\lambda - d\bar{x} - \beta\bar{x}\bar{y}),$$
$$0 = \bar{y} - \bar{y} = h(\beta\bar{x}\bar{y} - a\bar{y}).$$

Therefore, for all $h > 0$ the fixed points of system (6) are the same as equilibrium points of system (1). ∎

THEOREM 3.3 The *virus-free* fixed point (3) of system (6) is a locally asymptotically stable node as long as $R_0 < 1$, where R_0 is given by (2).

PROOF (case (7e)) The Jacobi matrix for (x_{vf}, y_{vf}) is equal to:

$$\mathbf{J}(x_{vf}, y_{vf}) = \begin{bmatrix} \frac{1}{1+hd} & \frac{-\beta\lambda h}{(1+hd)(d+(ad-\beta\lambda)h)} \\ 0 & \frac{d}{d+(ad-\beta\lambda)h} \end{bmatrix},$$

and thus the eigenvalues of system (6) are:

$$L_1 = \frac{1}{1 + hd}, \quad L_2 = \frac{d}{d + (ad - \beta\lambda)h}.$$

Under the assumption $R_0 < 1$, we obtain that $L_1, L_2 \in (0, 1)$ for any step size $h > 0$. Therefore (x_{vf}, y_{vf}) is locally asymptotically stable. Moreover, it is a node. ∎

Note that the converse assumption $R_0 > 1$ makes the fixed point (x_{vf}, y_{vf}) unstable (since $L_2 > 1$, see the proof of Theorem 3.3). This result is consistent with the qualitative behavior of system (1).

THEOREM 3.4 The *infection* fixed point (4) of system (6) is locally asymptotically stable as long as $R_0 > 1$, where R_0 is given by (2).

PROOF (case (7e)) The Jacobi matrix for (x_{inf}, y_{inf}) is equal to:

$$\mathbf{J}(x_{inf}, y_{inf}) = \frac{1}{a + \beta\lambda h + a(\beta\lambda - ad)h^2} \begin{bmatrix} a & -a^2 h \\ (\beta\lambda - ad)h & a + \beta\lambda h \end{bmatrix},$$

thus the characteristic polynomial of system (6) takes the following form:

$$\chi(L) = L^2 - \frac{2a + \beta\lambda h}{a + \beta\lambda h + a(\beta\lambda - ad)h^2} L + \frac{a}{a + \beta\lambda h + a(\beta\lambda - ad)h^2}. \quad (10)$$

It can easily be shown that under the assumption $R_0 > 1$, the following inequalities hold for all $h > 0$:

$$0 < \chi(0) < 1, \quad 0 < \chi(1), \quad \frac{2a + \beta\lambda h}{a + \beta\lambda h + a(\beta\lambda - ad)h^2} < 2. \quad (11)$$

Inequalities (11) guarantee that the characteristic polynomial (10) either has two complex roots with magnitude less that one (since $\chi(0) < 1$) or two real roots within the range $(0, 1)$. We conclude that the eigenvalues of system (6) satisfy $|L_1|, |L_2| < 1$, which entails the local stability of (x_{inf}, y_{inf}). ∎

Apart from ensuring the stability of the *infection* equilibrium, inequalities (11) play a major role in the preservation of oscillations around the point (x_{inf}, y_{inf}). They yield that the real roots of characteristic polynomial (10) have to be positive. Therefore, the presence of oscillations in discrete system (6) is governed solely by the sign of the discriminant Δ_{dis} of the characteristic polynomial $\chi(L)$. As it turns out, in the case of (7e) we obtain:

$$\Delta_{dis} = \left(\frac{ah}{a + \beta\lambda h + a(\beta\lambda - ad)h^2} \right)^2 \Delta_{con}, \quad (12)$$

where Δ_{con} (5) is the discriminant of the characteristic polynomial of system (1). Since the signs of Δ_{con} and Δ_{dis} are responsible for the presence (or absence) of oscillations around the point (x_{inf}, y_{inf}), we arrive at the following conclusion.

COROLLARY 3.5 The discretization method given by Eqs. (6) and (7e) preserves the type of the *infection* equilibrium point (4) independently of the chosen step-size. Oscillations around the point (x_{inf}, y_{inf}) are simultaneously present (or absent) in systems (1) and (6).

Finally, we have to point out that although inequalities (11) hold true for every considered discretization case (7), property (12) is unique for case (7e). In other cases, it is possible to chose parameter values and step-size h in such a way that the qualitative oscillatory properties of systems (1) and (6) are different. For example, the choice of $a = d$ and $\beta\lambda = 2d^2$ in the case (7a) gives $\Delta_{dis} < 0 = \Delta_{con}$ for all step-sizes $h > 0$, and therefore spurious oscillations may be observed in the discrete system.

4. Numerical simulations In order to illustrate the results from Section 3, we simulate the simplified Anderson-May model (1) using the discretization method given by (6) and (7e) (the explicit equations for this approach are (8) - (9)).

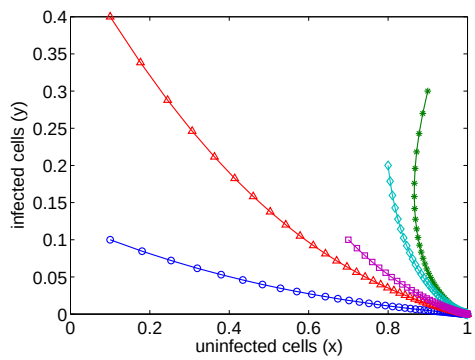

Figure 1: Stability of the *virus-free* equilibrium: node (13a).

We arbitrarily chose the following three parameter sets:

$$\lambda = 1, \quad d = 1, \quad \beta = 1, \quad a = 2, \tag{13a}$$

$$\lambda = 1, \quad d = 1, \quad \beta = 10, \quad a = 1, \tag{13b}$$

$$\lambda = 1, \quad d = 1, \quad \beta = 10, \quad a = 5. \tag{13c}$$

Parameter sets (13) correspond to different qualitative outcomes for system (1). The simulations are started from five initial points, with step-size $h = 0.1$ and time span $t \in [0, 20]$. The obtained results are presented in Figs. 1 - 2.

Parameter values (13a) correspond to the case of $R_0 < 1$ (see Eq. (2)), and therefore the *virus-free* equilibrium point (3) is a locally asymptotically stable node, as seen in Fig. 1.

The choice of either (13b) or (13c) gives $R_0 > 1$ (2), and thus entails the instability of the *virus-free* equilibrium point (3) and local asymptotic stability of the *infection* equilibrium (4). Depending on the parameter values, this equilibrium point may be a stable node (13b) or a stable focus (13c). Our numerical simulations (Fig. 2) are consistent with these mathematical results.

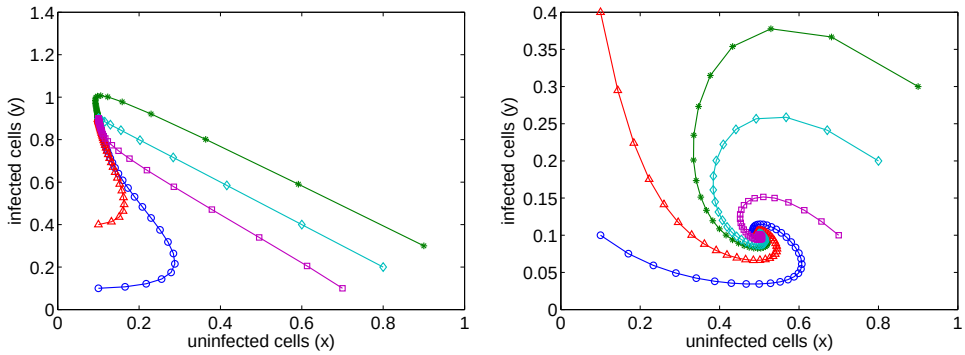

Figure 2: Stability of the *infection* equilibrium: (i) node (13b), (ii) focus (13c).

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O nielokalnej dyskretyzacji uproszczonego modelu Andersona-Maya infekcji wirusowej.

Adam Korpusik, Marek Bodnar

Streszczenie Przedstawiono pięć niestandardowych metod różnic skończonych zaprojektowanych do symulacji numerycznych uproszczonego (dwuwymiarowego) modelu infekcji wirusowej Andersona-Maya. Proponowane przez nas metody są oparte wyłącznie na zasadzie nielokalnej dyskretyzacji układu. Dzięki temu wszystkie wyniki dotyczące zachowania przez nie własności jakościowych uproszczonego modelu Andersona-Maya są niezależne od wybranego kroku symulacji. Prezentowane metod zachowują istotne cechy jakościowe wyjściowego modelu ciągłego, tzn. nieujemność rozwiązania i lokalną stabilność punktów stacjonarnych, wraz z warunkami ich stabilności. Jedna z proponowanych metod zachowuje również typy punktów stacjonarnych, co przekłada się na obecność lub brak oscylacji w ich otoczeniu.

Klasyfikacja tematyczna AMS (2010): 65L12; 65L20.

Słowa kluczowe: niestandardowa metoda różnic skończonych, metoda NSFD, nielokalna dyskretyzacja, model Andersona-Maya, infekcja wirusowa.

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