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Discrete-time Non-Standard Finite Difference schemes for antimicrobial resistance models

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ABSTRACT

Antimicrobial resistance (AMR) remains one of the most pressing global health challenges, with significant implications for human, animal, and environmental health. While numerous mathematical models have been developed to describe the dynamics of AMR, most are formulated in continuous time. In contrast, discrete-time models, particularly those based on Non-Standard Finite Difference (NSFD) schemes, offer important advantages, such as preserving key dynamical properties including nonnegativity, equilibrium points, and stability for arbitrary time steps. In this work, we analyze a family of discrete-time models for intra-host AMR dynamics, derived from continuous-time formulations via NSFD discretization. In particular, we consider four NSFD-based numerical schemes and investigate their qualitative properties. Moreover, we evaluate the performance of the discrete-time models through numerical simulations under various scenarios and conduct a comparative analysis of the four schemes from a numerical perspective. Additionally, we use one of the proposed schemes to construct a discrete-time representation of a more complex AMR model, which incorporates both mutation and horizontal gene transfer via plasmids. This modeling framework not only fills a methodological gap in the study of AMR dynamics, but also provides a foundation for computer simulations in several contexts where discrete-time analysis is more suitable.

1. Introduction

Antimicrobial resistance (AMR) refers to the phenomenon by which certain microorganisms, such as bacteria, viruses, or fungi, develop resistance to chemical compounds designed either to kill them or inhibit their growth. As a result, the uncontrolled spread of resistant microbial populations can lead to severe medical complications and diseases that are extremely difficult to treat. For instance, resistant strains of *Mycobacterium tuberculosis* [1], *Plasmodium falciparum* (malaria) [2], *Helicobacter pylori* [3], and *Staphylococcus aureus* [4,5] have been well documented. AMR is not limited to human medicine; it also extends to animals [6], and its community-wide implications have placed it within the scope of the One Health framework [7]. The continued misuse and overuse of antibiotics in both human medicine and the livestock and food production sectors constitute a major driver of AMR [8]. In 2019, it was estimated that AMR was directly responsible for 1.27 million deaths and contributed to an additional 4.95 million deaths [9]. The outlook for the coming decades is no better: by 2050, the number of direct deaths is projected to reach 1.9 million, with AMR-related deaths rising to 8.2 million [10], making it one of the leading causes of mortality worldwide. Beyond the intrinsic health challenge, AMR also places a significant economic burden on healthcare systems, due to the need for more expensive,

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prolonged treatments and extended hospital stays. The World Bank estimates that AMR could generate a global economic cost of up to 2 trillion USD by 2050 [11]. For these reasons, combating AMR has become a priority for governments, with the development of dedicated national programs (e.g., US National Action Plan for Combating Antibiotic-Resistant Bacteria [12], UK Five-Year National Action Plan on Tackling Antimicrobial Resistance [13], Australia's National Antimicrobial Resistance Strategy [14], Singapore's National Strategic Action Plan (NSAP) on AMR [15], European One Health Action Plan against AMR [16], among others). A multifaceted approach is essential to address the challenge of AMR: the development of new antibiotics, improved usage of the current antimicrobial arsenal, and a deeper understanding of the emergence and transmission of resistance.

Mathematical modeling has become, in recent decades, a valuable tool in the understanding and mitigation of AMR [17]. Modeling allows us to explore the underlying mechanisms of resistance emergence and spread, identify knowledge gaps, design intervention strategies, and serve as a testing ground for policies, thus supporting decision-makers in the effective fight against AMR [18]. In this regard, mathematical models have been used to estimate and forecast the burden of resistant strains (for surveillance and prevention), to determine the community-level spread of resistant infections, to design efficient drug administration strategies, and to understand mechanisms of resistance emergence and bacterial transmission. For example, [19] uses a statistical model to estimate latent tuberculosis cases caused by multidrug-resistant strains, and [20] provides a review of models for AMR burden prediction. A continuous deterministic model is used in [5] to describe the spread of methicillin-resistant *Staphylococcus aureus* in a population. In [21], a transmission model for resistant *Neisseria gonorrhoeae* is analyzed, while [22] employs an agent-based stochastic model to study the spread of colistin-resistant *Acinetobacter baumannii* in Valencia, Spain. The work in [23] applies a Markov model to describe the spread of antibiotic resistance in a small hospital population. A deterministic compartmental model is used in [24] to study the propagation of Influenza A in the presence of antiviral resistance, and [25] investigates resistant meningitis. In addition, some works focus on optimal drug administration to enhance treatment efficacy under AMR conditions. For instance, [26] proposes optimal dosing strategies, while [27] explores drug cycling approaches. Additionally, [28] introduces a model that integrates antibiotics, debridement, and an anti-adhesion therapy to block bacterial tissue adherence.

Intra-host emergence of AMR can occur either via person-to-person transmission of resistant bacteria (a community-level process, as modeled by the works cited above), or within an individual due to mutations or selective pressure induced by antibiotic usage. Resistance genes may be acquired via mutation or horizontal gene transfer (HGT), the latter being the process by which microorganisms acquire genetic material from others. HGT involves plasmids, transposons, or integrons and operates via three primary mechanisms: transformation, transduction, and conjugation. Among these, conjugation is the most relevant for the spread of resistance genes in hospital settings under antibiotic pressure [29].

There is a substantial body of literature on mathematical models describing AMR emergence through mutation and HGT. A comprehensive review is provided in [30]. The work [31] analyzes a model for the growth, resistance acquisition, and immune response of *Helicobacter pylori*, determining the conditions under which sensitive and resistant populations are cleared or persist. In [32], a continuous-time logistic model describes resistant bacterial dynamics due to mutation and plasmid-mediated HGT. In [33], the focus shifts to bacteria concurrently exposed to multiple antibiotics, with resistance acquired through mutation. Similar phenomena are studied in [34] for *Mycobacterium tuberculosis* and *Pseudomonas aeruginosa*. A fractional model is introduced in [35], accounting for antibiotic exposure, immune response, and mutation-driven resistance emergence. [36] develops a continuous deterministic model with mutation and HGT in the presence of antibiotics, with optimal control strategies to combat AMR. In [37], a model for the temporal evolution of AMR in microbial communities is proposed, incorporating competition between two bacterial strains, antibiotic-driven mutation, and host immune dynamics. [38,39] introduce a model with a continuous resistance spectrum, which differs from the common binary approach, and is described by integro-differential equations. [40] explores a Darwinian evolution model of resistance using a continuous compartmental framework. [41] analyzes resistant and susceptible bacterial populations in agricultural waste with HGT while [42] studies similar dynamics in wastewater. Furthermore, the loss of resistance due to selective pressures (AMR reversal) has also been modeled. In [43], deterministic, stochastic, and fractional models are introduced to study AMR reversal caused by fitness disadvantages in resistant *Escherichia coli* strains.

Although the literature on the topic is extensive, the majority of existing models have been formulated in continuous time. However, discrete-time models offer notable advantages. They can represent a wide variety of dynamic behaviors, are easier to simulate computationally, have greater numerical efficiency, and allow for more straightforward parameter estimation from experimental data. Therefore, the development of discrete-time models to capture intra-host AMR emergence is of significant value, particularly for the design of simulation platforms to support understanding, control strategy testing, and decision-making. Thus, the aim of this work is to introduce and analyze systematic procedures for constructing such discrete models. Two approaches are available: direct discrete-time modeling or discretization of existing continuous models. While direct discrete modeling has been extensively applied in the study of epidemic spread [44–48], its application to intra-host AMR dynamics appears, to the best of the authors' knowledge, to remain largely unexplored. Given the vast number of existing continuous-time models, this work adopts a discretization-based approach, transforming existing continuous-time intra-host AMR models into discrete-time formulations.

Discretization methods provide a way to transform continuous models into discrete ones. The resulting discrete system should preserve both the qualitative and quantitative features of the original model. Ideally, if the continuous system possesses properties such as positivity or stability of solutions, the discrete counterpart should also exhibit them regardless of the integration step size (also referred to as sampling period). Likewise, the discrete solutions are expected to approximate the continuous ones uniformly with respect to step size. This has motivated extensive research into discretization schemes possessing these properties, among which Non-Standard Finite Difference (NSFD) methods, introduced by Mickens in the 1980s [49,50], stand out. NSFD methods use non-local approximations for nonlinear terms, enabling the construction of discrete schemes that preserve the dynamic properties of the continuous system independently of the integration step. For this reason, NSFD schemes have been widely applied to

derive discrete models from continuous biological systems. They have demonstrated excellent performance in preserving key features of epidemic models. Several studies have applied NSFD methods to compartmental-type epidemic models for typhoid [51], HIV [52], dengue [53], Zika [54], malaria [55,56] and COVID-19 [57], showing that such schemes maintain positivity, stability, and boundedness of solutions for arbitrary step sizes. Other works, such as [58–60] apply NSFD to species interaction and predator–prey models, confirming the preservation of qualitative properties under different modeling scenarios. Comparisons with other discretization techniques, such as Euler or Runge–Kutta methods, reveal the superiority of NSFD schemes in terms of structural preservation and numerical stability [51,53,55,60,61]. Some studies have also extended NSFD techniques to fractional epidemic models (e.g., Ebola and Zika) [62,63], and to control and optimization strategies [54,64]. Altogether, this body of work highlights the robustness and flexibility of NSFD methods in modeling a wide variety of biological systems [57,65–69].

This work applies NSFD techniques to derive discrete models for intra-host AMR emergence that retain most of the qualitative properties of the underlying continuous models and are consistent with the continuous-time solution, providing a good numerical performance for a wide range of step sizes. The main contributions are:

- Derivation of discrete models describing intra-host AMR emergence due to mutations in the presence of antibiotics using various NSFD schemes.
- Qualitative analysis of the proposed models, including nonnegativity, existence and stability of equilibrium points.
- Comparative assessment of the NSFD schemes in terms of numerical accuracy and structural properties.
- Application of one NSFD scheme to a model incorporating human immunity and AMR emergence due to both mutation and through HGT via plasmids.

The proposed discrete models serve as efficient computational tools for simulating AMR emergence processes, offering insight into underlying mechanisms and potential mitigation strategies. Although NSFD methods have been extensively used in modeling epidemic spread, most studies have focused on comparing them with classical schemes such as Euler or Runge–Kutta [53,55,70,71], while fewer works have compared different NSFD approaches directly [61,72].

The remainder of this paper is structured as follows. Section 2 presents the continuous intra-host AMR model that forms the basis for discretization. Section 3 introduces the NSFD discretization approach and the proposed schemes. Section 4 establishes the qualitative properties of the discrete models and their correspondence with the continuous model. Section 5 presents numerical simulations while Section 6 applies one numerical scheme to a model incorporating human immunity, horizontal gene transmission and mutation. Finally, Section 7 provides the conclusions.

2. Model description and problem formulation

The starting point is the bacterial resistance model given by Eqs. (2.1)–(2.3) [73] where, for the sake of clarity, the temporal dependence of the variables has been omitted. This model has been chosen in contrast to more complex formulations [4,32], in order to keep the presentation and core ideas transparent. Moreover, the methods introduced in this section are extendable to more comprehensive models capable of capturing additional types of phenomena. The model describes the temporal evolution of the population of bacteria sensitive to an antibiotic, denoted by $S(t)$, and its resistant variant, $R(t)$, in the presence of an antibiotic concentration represented by $C(t)$. Both the sensitive and resistant bacterial populations grow logistically with a constant carrying capacity K , and respective reproduction rates β_s and β_r , with $\beta_r \leq \beta_s$. The sensitive bacteria have a constant mortality rate denoted by μ_s , while the resistant bacteria die at a rate given by μ_r . In addition, sensitive bacteria are killed by the antibiotic at a rate proportional to the product of S and C , with proportionality constant α_S . Furthermore, a fraction of resistant bacteria emerges due to mutations of sensitive bacteria in the presence of the antibiotic. This fraction is represented by $q\alpha_S C S$. Finally, the antibiotic is administered at a constant rate Λ and degrades at a rate given by μ_c .

$$\frac{dS}{dt} = \beta_s S \left(1 - \frac{S+R}{K}\right) - \alpha_S C S - \mu_s S \quad (2.1)$$

$$\frac{dR}{dt} = \beta_r R \left(1 - \frac{S+R}{K}\right) + q\alpha_S C S - \mu_r R \quad (2.2)$$

$$\frac{dC}{dt} = \Lambda - \mu_c C \quad (2.3)$$

In order to reduce the number of parameters and simplify both the structure of the equations and that of the corresponding discrete counterparts to be derived, the following change of variables is introduced:

$$s = \frac{S}{K}, \quad r = \frac{R}{K}, \quad c = \frac{C}{\Lambda/\mu_c}, \quad \alpha_s = \alpha_S \frac{\Lambda}{\mu_c}, \quad (2.4)$$

which leads to the system of Eqs. (2.5)–(2.7) in the normalized variables,

$$\frac{ds}{dt} = \beta_s s (1 - (s+r)) - \alpha_s c s - \mu_s s, \quad (2.5)$$

$$\frac{dr}{dt} = \beta_r r (1 - (s+r)) + q\alpha_s c s - \mu_r r, \quad (2.6)$$

$$\frac{dc}{dt} = \mu_c - \mu_c c. \quad (2.7)$$

Since the Eqs. (2.5)–(2.7) biologically represent a population of bacteria, the variables s and r must be nonnegative, and their sum must not exceed the carrying capacity of the environment. Additionally, the antibiotic concentration, c , must neither be negative nor exceed the administered amount. Therefore, the set of interest, Ω , is given by (2.8):

$$\Omega = \{(s, r, c) \in \mathbb{R}_+^3 : 0 \leq s + r \leq 1, 0 \leq c \leq 1\}. \quad (2.8)$$

The constraint $0 \leq s + r \leq 1$ will be referred to in the following as the *biological property*. Moreover, Assumption 1 is made regarding the model parameters:

Assumption 1. The model parameters satisfy:

1. $\alpha_S, \beta_r, \beta_s, \mu_s, \mu_r, \mu_c, K, \Lambda > 0$
2. $0 < q < 1$
3. $\beta_r \leq \beta_s$

In [73], the following properties of the system (2.5)–(2.7) are proven.

Theorem 2.1 (Nonnegativity of Solutions). The set Ω defined by (2.8) is a positively invariant set for the system of Eqs. (2.5)–(2.7).

Theorem 2.2 (Existence of Equilibrium Points). The system (2.5)–(2.7) always has the trivial equilibrium point $E_0 = (0, 0, 1)$. If $R_r := \frac{\beta_r}{\mu_r} > 1$, in addition to E_0 , there exists the equilibrium point $E_1 = (0, \frac{R_r - 1}{R_r}, 1)$. If $S_0 := \frac{\beta_s}{\alpha_s + \mu_s} > 1$ and $S_0 > R_r$, there also exists the equilibrium point $E_2 = (s^*, r^*, 1)$ where:

$$s^* = \frac{S_0 - 1}{S_0} \frac{\mu_r \left(1 - \frac{R_r}{S_0}\right)}{q\alpha_s + \mu_r \left(1 - \frac{R_r}{S_0}\right)} \quad (2.9)$$

$$r^* = \frac{q\alpha_s(S_0 - 1)}{(q\alpha_s + \mu_r) \left(S_0 - \frac{\mu_r}{\mu_r + q\alpha_s} R_r\right)} \quad (2.10)$$

Theorem 2.3 (Stability of Equilibrium Points). The following items hold:

- (i) If $S_0 < 1$ and $R_r < 1$, then the trivial equilibrium E_0 is globally asymptotically stable in Ω . If $S_0 > 1$ or $R_r > 1$, then E_0 is unstable.
- (ii) If $S_0 < R_r$ and $R_r > 1$, then the equilibrium E_1 is locally asymptotically stable in Ω . If $S_0 > R_r$, then E_1 is unstable.
- (iii) If $S_0 > 1$ and $S_0 > R_r$, then E_2 is locally asymptotically stable in Ω .

Theorems 2.1–2.3 prove the main qualitative properties of the system, which are the nonnegativity of the solutions (for any nonnegative initial condition), the conditions under which the equilibrium points exist, and their stability. This work aims to study and compare different NSFD-based discretization schemes by examining their ability to preserve the qualitative dynamics of the continuous model and assessing their numerical performance under varying step sizes. The discretization schemes considered in this work are presented in Section 3.

3. Non-standard finite difference (NSFD) discretization of the model

Discretization methods for continuous dynamical systems aim to construct a discrete model that accurately approximates the solution of the original continuous dynamics. To this end, let us consider the time instants given by $t_k = kh$ with $k \in \mathbb{N}_0$, where $h > 0$ represents the integration step (also referred to as the sampling period in some contexts such as Control or Signal Processing). The goal is to find sequences s_k , r_k , and c_k that approximate the solutions $s(t)$, $r(t)$, and $c(t)$ of the system (2.5)–(2.7) at $t_k = kh$. To achieve this, we will use the NSFD methods proposed by Mickens [50].

Remark 1. (Fundamental Assumptions of the NSFD Scheme) For a numerical method to be classified as non-standard, its construction must be based on at least one of the following two core assumptions [61]:

- *Denominator function:* In the discretization of the first derivative, the traditional denominator h is replaced by a nonnegative function $\phi(h)$ that satisfies $\phi(h) = h + \mathcal{O}(h^2)$ as $h \rightarrow 0$.
- *Non-local approximation:* Nonlinear terms on the right-hand side of the differential equations are approximated in a non-local way, distributing their evaluation across several points of the discretization mesh. For example, the term $u(t)^2$ could be approximated by $u_k u_{k+1}$ rather than strictly evaluating at a single point, u_k^2 .

Four different NSFD schemes are applied to the system (2.5)–(2.7) in order to obtain discrete-time models of AMR system. The Schemes are given by:

Scheme 1

$$\frac{s_{k+1} - s_k}{\phi(h)} = \beta_s s_k - \beta_s s_{k+1} (s_k + r_k) - \alpha_s c_k s_{k+1} - \mu_s s_{k+1} \quad (3.1)$$

$$\frac{r_{k+1} - r_k}{\phi(h)} = \beta_r r_k - \beta_r r_{k+1}(s_k + r_k) + q\alpha_s c_k s_{k+1} - \mu_r r_{k+1} \quad (3.2)$$

$$\frac{c_{k+1} - c_k}{\phi(h)} = \mu_c - \mu_c c_{k+1} \quad (3.3)$$

Scheme 2

$$\frac{s_{k+1} - s_k}{\phi(h)} = \beta_s s_k - \beta_s s_k(s_{k+1} + r_{k+1}) - \alpha_s c_k s_{k+1} - \mu_s s_{k+1} \quad (3.4)$$

$$\frac{r_{k+1} - r_k}{\phi(h)} = \beta_r r_k - \beta_r r_k(s_{k+1} + r_{k+1}) + q\alpha_s c_k s_{k+1} - \mu_r r_{k+1} \quad (3.5)$$

$$\frac{c_{k+1} - c_k}{\phi(h)} = \mu_c - \mu_c c_{k+1} \quad (3.6)$$

Scheme 3

$$\frac{s_{k+1} - s_k}{\phi(h)} = \beta_s s_{k+1} - \beta_s s_{k+1}(s_k + r_k) - \alpha_s c_k s_{k+1} - \mu_s s_{k+1} \quad (3.7)$$

$$\frac{r_{k+1} - r_k}{\phi(h)} = \beta_r r_{k+1} - \beta_r r_{k+1}(s_k + r_k) + q\alpha_s c_k s_{k+1} - \mu_r r_{k+1} \quad (3.8)$$

$$\frac{c_{k+1} - c_k}{\phi(h)} = \mu_c - \mu_c c_{k+1} \quad (3.9)$$

Scheme 4

$$\frac{s_{k+1} - s_k}{\phi(h)} = \beta_s s_{k+1} - \beta_s s_k(s_{k+1} + r_{k+1}) - \alpha_s c_k s_{k+1} - \mu_s s_{k+1} \quad (3.10)$$

$$\frac{r_{k+1} - r_k}{\phi(h)} = \beta_r r_{k+1} - \beta_r r_k(s_{k+1} + r_{k+1}) + q\alpha_s c_k s_{k+1} - \mu_r r_{k+1} \quad (3.11)$$

$$\frac{c_{k+1} - c_k}{\phi(h)} = \mu_c - \mu_c c_{k+1} \quad (3.12)$$

It is important to notice that all the previous Schemes are implicit, in the sense that the values of the state variables at the sampling instant t_{k+1} are not expressed independently of their values at t_k , this is, the values at t_{k+1} are merged with the values at t_k . In order to facilitate symbolic manipulation and to derive an explicit formulation, we proceed to rewrite the previous Schemes as follows:

$$\mathcal{A}_n y_{k+1} = D_n y_k + b \quad (3.13)$$

with $n = 1, 2, 3, 4$ representing Schemes 1, 2, 3 and 4, respectively, and $y_k^T = [s_k \ r_k \ c_k]$. The matrices $\mathcal{A}_n$ and D_n are given by:

$$\mathcal{A}_1 = \begin{pmatrix} 1 + \beta_s \phi(s_k + r_k) + \alpha_s \phi c_k + \mu_s \phi & 0 & 0 \\ -q\alpha_s \phi c_k & 1 + \beta_r \phi(s_k + r_k) + \mu_r \phi & 0 \\ 0 & 0 & 1 + \mu_c \phi \end{pmatrix} \quad (3.14)$$

$$\mathcal{A}_2 = \begin{pmatrix} 1 + \beta_s \phi s_k + \alpha_s \phi c_k + \mu_s \phi & \beta_s \phi s_k & 0 \\ \beta_r \phi r_k - q\alpha_s \phi c_k & 1 + \beta_r \phi r_k + \mu_r \phi & 0 \\ 0 & 0 & 1 + \mu_c \phi \end{pmatrix} \quad (3.15)$$

$$\mathcal{A}_3 = \begin{pmatrix} 1 + \beta_s \phi(s_k + r_k) + \alpha_s \phi c_k + (\mu_s - \beta_s) \phi & 0 & 0 \\ -q\alpha_s \phi c_k & 1 + \beta_r \phi(s_k + r_k) + (\mu_r - \beta_r) \phi & 0 \\ 0 & 0 & 1 + \mu_c \phi \end{pmatrix} \quad (3.16)$$

$$\mathcal{A}_4 = \begin{pmatrix} 1 + \beta_s \phi s_k + \alpha_s \phi c_k + (\mu_s - \beta_s) \phi & \beta_s \phi s_k & 0 \\ \beta_r \phi r_k - q\alpha_s \phi c_k & 1 + \beta_r \phi r_k + (\mu_r - \beta_r) \phi & 0 \\ 0 & 0 & 1 + \mu_c \phi \end{pmatrix} \quad (3.17)$$

while

$$D_1 = D_2 = \begin{pmatrix} 1 + \beta_s \phi & 0 & 0 \\ 0 & 1 + \beta_r \phi & 0 \\ 0 & 0 & 1 \end{pmatrix} \quad (3.18)$$

$$D_3 = D_4 = I_3 \quad (3.19)$$

and

$$b = \begin{pmatrix} 0 \\ 0 \\ \mu_c \phi \end{pmatrix}. \quad (3.20)$$

With this notation, the above Schemes can be explicitly written (whenever the inverse matrices exist) as:

$$y_{k+1} = \mathcal{A}_n^{-1} D_n y_k + \mathcal{A}_n^{-1} b \quad (3.21)$$

for $n = 1, 2, 3, 4$. The four presented schemes will be compared numerically but, initially, some of their theoretical properties are studied in the next Section.

4. Qualitative properties of the discrete models

In this section, the qualitative properties of the numerical schemes introduced earlier will be presented, particularly the consistency with respect to the continuous-time solution, the nonnegativity of the solutions, the existence and location of equilibrium points, and their stability. Initially, following the methodological framework presented in [55], the consistency of the proposed numerical schemes is verified by analyzing their Local Truncation Error (LTE) via Taylor series expansions. This fundamental result is formally stated in the following theorem.

Theorem 4.1 (Consistency of Numerical Schemes). *The four NSFD schemes (3.1)–(3.3), (3.4)–(3.6), (3.7)–(3.9), and (3.10)–(3.12) are consistent with the continuous-time system (2.5)–(2.7) provided that the denominator function $\phi(h)$ satisfies the condition $\lim_{h \rightarrow 0} \frac{\phi(h)}{h} = 1$.*

Proof. To prove consistency, we must show that the discrete scheme recovers the continuous-time system as the step size $h \rightarrow 0$, which is equivalent to demonstrating that the Local Truncation Error (LTE) vanishes. To achieve this, we substitute the exact smooth solutions $s(t)$, $r(t)$, and $c(t)$ of the continuous system into the discrete scheme. For the discrete derivative terms, we utilize Taylor series expansions around $t = t_k = kh$. The exact solutions at $t_{k+1} = t_k + h$ can be expanded as:

$$\begin{aligned} s(t_{k+1}) &= s(t_k) + h \frac{ds}{dt}(t_k) + \mathcal{O}(h^2), \\ r(t_{k+1}) &= r(t_k) + h \frac{dr}{dt}(t_k) + \mathcal{O}(h^2), \\ c(t_{k+1}) &= c(t_k) + h \frac{dc}{dt}(t_k) + \mathcal{O}(h^2). \end{aligned}$$

Let us analyze Scheme 1. For the discrete derivative on the left-hand side, we substitute the Taylor expansion while keeping the denominator function $\phi(h)$. Factoring out h , for any variable $y \in \{s, r, c\}$, we obtain:

$$\frac{y(t_{k+1}) - y(t_k)}{\phi(h)} = \frac{h \frac{dy}{dt}(t_k) + \mathcal{O}(h^2)}{\phi(h)} = \frac{h}{\phi(h)} \left(\frac{dy}{dt}(t_k) + \mathcal{O}(h) \right).$$

Substituting the continuous solutions into the first equation of Scheme 1, replacing only the derivative term with its Taylor expansion, we obtain:

$$\frac{h}{\phi(h)} \left(\frac{ds}{dt}(t_k) + \mathcal{O}(h) \right) = \beta_s s(t_k) - \beta_s s(t_k + h)(s(t_k) + r(t_k)) - \alpha_s c(t_k) s(t_k + h) - \mu_s s(t_k + h).$$

To demonstrate consistency, we evaluate the limit as $h \rightarrow 0$. On the left-hand side, we apply the fundamental property $\lim_{h \rightarrow 0} \frac{\phi(h)}{h} = 1$ (which trivially implies $\lim_{h \rightarrow 0} \frac{h}{\phi(h)} = 1$) and note that the $\mathcal{O}(h)$ term vanishes. On the right-hand side, since the exact solutions are continuous functions, $\lim_{h \rightarrow 0} y(t_k + h) = y(t_k)$. Thus, taking the limit yields:

$$1 \cdot \frac{ds}{dt}(t_k) = \beta_s s(t_k) - \beta_s s(t_k)(s(t_k) + r(t_k)) - \alpha_s c(t_k) s(t_k) - \mu_s s(t_k)$$

$$\frac{ds}{dt}(t_k) = \beta_s s(t_k)(1 - s(t_k) - r(t_k)) - \alpha_s c(t_k) s(t_k) - \mu_s s(t_k).$$

This perfectly recovers the first differential equation of the continuous system (2.5) evaluated at t_k , confirming that the LTE for this equation approaches zero.

Applying the exact same procedure to the equations for r and c in Scheme 1 yields:

$$\frac{h}{\phi(h)} \left(\frac{dr}{dt}(t_k) + \mathcal{O}(h) \right) = \beta_r r(t_k) - \beta_r r(t_k + h)(s(t_k) + r(t_k)) + q \alpha_s c(t_k) s(t_k + h) - \mu_r r(t_k + h)$$

$$\frac{h}{\phi(h)} \left(\frac{dc}{dt}(t_k) + \mathcal{O}(h) \right) = \mu_c - \mu_c c(t_k + h).$$

Taking the limit $h \rightarrow 0$ utilizing continuity and the condition $\lim_{h \rightarrow 0} \frac{h}{\phi(h)} = 1$, we identically recover Eqs. (2.6) and (2.7). Thus, Scheme 1 is consistent.

For Schemes 2, 3, and 4, the nonlinear approximations involve different combinations of variables evaluated at t_{k+1} and t_k . However, taking the limit $h \rightarrow 0$ invokes the continuity of the solutions for all cross-terms, seamlessly recovering the exact continuous nonlinear terms. Evaluating the limits under the condition $\lim_{h \rightarrow 0} \frac{h}{\phi(h)} = 1$ confirms that the LTE vanishes for all proposed schemes. $\square$

Remark 2. The proposed NSFD schemes inherently exhibit a first-order rate of convergence, $\mathcal{O}(h)$, which is a standard feature for classic formulations based on Mickens' nonstandard rules. Although NSFD methods generally prioritize structural and qualitative stability over high-order algebraic accuracy, enhancing their rate of convergence remains an active area of research. For instance, the numerical precision of nonstandard schemes can be improved by coupling them with Richardson extrapolation techniques [53]. Additionally, recent advances have led to the design of explicit second-order [74] and general high-order nonstandard methods [75] tailored to preserve specific dynamical properties of continuous systems.

Theorem 4.1 guarantees that the proposed numerical schemes are able to recover the solution of the continuous-time system as the step size (sampling time) tends to zero. However, from a practical perspective, it is interesting to show how the schemes behave for finite and arbitrary values of h . These properties are studied in the sequel.

Theorem 4.2 (Properties of c_k). For all the discrete-time Schemes 1–4, the concentration of antibiotic, c_k , satisfies $0 \leq c_k \leq 1$ for all $k > 0$ provided that $0 \leq c_0 \leq 1$ and [Assumption 1](#) holds.

Proof. All four schemes provide the same discrete-time evolution equation for c_k :

$$c_{k+1} = \frac{1}{1 + \mu_c \phi} c_k + \frac{\mu_c \phi}{1 + \mu_c \phi}. \quad (4.1)$$

The solution to (4.1) with initial condition c_0 is given by:

$$c_k = 1 - \left(\frac{1}{1 + \mu_c \phi} \right)^k (1 - c_0). \quad (4.2)$$

Since [Assumption 1](#) holds, the sequence $\left\{ \left(\frac{1}{1 + \mu_c \phi} \right)^k \right\}_{k=0}^{\infty}$ satisfies $0 \leq \left(\frac{1}{1 + \mu_c \phi} \right)^k \leq 1$ for all $k \geq 0$. Thus, $c_0 \leq c_k \leq 1$ for all $k \geq 0$ implying $0 \leq c_k \leq 1$. $\square$

Theorem 4.3 (Well-Posedness of Schemes and Nonnegativity of Sequences s_k and r_k). Assume that [Assumption 1](#) holds and $s_0, r_0, c_0 \geq 0$. Then,

- (i) Scheme 1 is well-posed¹ and the state variables s_k and r_k remain nonnegative for all $k \geq 0$.
- (ii) Scheme 2 is well-posed and the state variables s_k and r_k remain nonnegative for all $k \geq 0$ provided that $\beta_s = \beta_r$.
- (iii) Scheme 3 is well-posed and the state variables s_k and r_k remain nonnegative for all $k \geq 0$ provided that $\mu_s \geq \beta_s$, $\mu_r \geq \beta_r$.
- (iv) Scheme 4 is well-posed and the state variables s_k and r_k remain nonnegative for all $k \geq 0$ provided that $\mu_s = \beta_s = \mu_r = \beta_r$.

Proof. It will be proved by complete induction. Since [Assumption 1](#) holds, [Theorem 4.2](#) also holds and $0 \leq c_k \leq 1$. Thus, the nonnegativity is true for s_0, r_0, c_0 and it is assumed to be true for a finite k . We will prove now that $s_{k+1}, r_{k+1} \geq 0$. The proof is split for the different Schemes:

(i) Scheme 1.

The determinant of $\mathcal{A}_1$ at any $k \geq 0$ is given by:

$$\det(\mathcal{A}_1) = (1 + \beta_s \phi(s_k + r_k) + \alpha_s \phi c_k + \mu_s \phi)(1 + \beta_r \phi(s_k + r_k) + \mu_r \phi)(1 + \mu_c \phi) \quad (4.3)$$

which is positive at k since $s_k, r_k, c_k \geq 0$ and all the parameters are positive by [Assumption 1](#). Consequently, $\mathcal{A}_1$ is invertible and the explicit formulation of the discrete-time system is possible at time $t_k = kh$ as:

$$y_{k+1} = \mathcal{A}_1^{-1} (\mathcal{D}_1 y_k + b), \quad (4.4)$$

with

$$\mathcal{A}_1^{-1} = \begin{pmatrix} \hat{\mathcal{A}}_1^{-1} & \mathbf{0} \\ \mathbf{0} & \frac{1}{1 + \mu_c \phi} \end{pmatrix} \quad (4.5)$$

and

$$\hat{\mathcal{A}}_1^{-1} = \begin{pmatrix} \frac{1}{1 + \mu_s \phi + \alpha_s c_k \phi + \beta_s \phi r_k + \beta_s \phi s_k} & 0 \\ \frac{\alpha_s c_k \phi q}{(1 + \mu_r \phi + \beta_r \phi r_k + \beta_r \phi s_k)(1 + \mu_s \phi + \alpha_s c_k \phi + \beta_s \phi r_k + \beta_s \phi s_k)} & \frac{1}{1 + \mu_r \phi + \beta_r \phi r_k + \beta_r \phi s_k} \end{pmatrix}. \quad (4.6)$$

Since all the elements of the right-hand side of (4.4) are nonnegative so will be s_{k+1} , r_{k+1} and c_{k+1} .

(ii) Scheme 2.

At step time $t_k = kh$, the determinant of $\hat{\mathcal{A}}_2$ is given by Eq. (4.7),

$$\begin{aligned} \det(\mathcal{A}_2) = 1 + & (\mu_r + \mu_s + \alpha_s c_k + \beta_r r_k + \beta_s s_k) \phi \\ & + (\mu_r \mu_s + \alpha_s c_k \mu_r + \beta_r \mu_s r_k + \beta_s \mu_r s_k + \alpha_s \beta_r c_k r_k + \alpha_s \beta_s c_k q s_k) \phi^2, \end{aligned} \quad (4.7)$$

which is positive due to the induction hypothesis. Therefore, $\mathcal{A}_2^{-1}$ exists and Scheme 2 can be explicitly written as $y_{k+1} = \mathcal{A}_2^{-1} (\mathcal{D}_2 y_k + b)$. Moreover, s_{k+1} and r_{k+1} are explicitly given by:

$$s_{k+1} = \frac{\beta_s \mu_r s_k \phi^2 + s_k (\beta_s + \mu_r + \underbrace{(\beta_r - \beta_s) r_k}_{(*)}) \phi + s_k}{\det(\mathcal{A}_2)}, \quad (4.8)$$

¹ In the sense that the explicit formulation of the discrete-time system given by (3.21) is possible.

and

$$r_{k+1} = \frac{\eta_{11}\phi^2 + \eta_{12}\phi + r_k}{\det(\mathcal{A}_2)}, \quad (4.9)$$

with

$$\eta_{11} = \beta_r \mu_s r_k + \alpha_s \beta_r c_k r_k + \alpha_s \beta_s c_k q s_k \quad (4.10)$$

$$\eta_{12} = \beta_r r_k + \mu_s r_k + \alpha_s c_k r_k + \underbrace{(\beta_s - \beta_r) r_k s_k}_{(*)} + \alpha_s c_k q s_k. \quad (4.11)$$

If $\beta_s = \beta_r$, then the terms $(*)$ are zero and η_{11} , η_{12} are positive. Therefore, (4.8) and (4.9) are positive for all $\phi(h) > 0$ leading to $s_{k+1}, r_{k+1} \geq 0$.

(iii) Scheme 3.

The determinant of $\mathcal{A}_3$ is given by (4.12):

$$\det(\mathcal{A}_3) = (1 + \beta_s \phi(s_k + r_k) + \alpha_s \phi c_k + (\mu_s - \beta_s) \phi)(1 + \beta_r \phi(s_k + r_k) + (\mu_r - \beta_r) \phi)(1 + \mu_c \phi). \quad (4.12)$$

If $\mu_s \geq \beta_s$ and $\mu_r \geq \beta_r$ hold, then $\det(\mathcal{A}_3) > 0$ and the inverse matrix $\mathcal{A}_3^{-1}$, which exists and is given by:

$$\mathcal{A}_3^{-1} = \begin{pmatrix} \hat{\mathcal{A}}_3^{-1} & \mathbf{0} \\ \mathbf{0} & \frac{1}{1 + \mu_c \phi} \end{pmatrix}, \quad (4.13)$$

with

$$\hat{\mathcal{A}}_3^{-1} = \frac{1}{\det(\hat{\mathcal{A}}_3)} \begin{pmatrix} \phi(\mu_r - \beta_r + \beta_r r_k + \beta_r s_k) + 1 & 0 \\ \alpha_s c_k \phi q & \phi(\mu_s - \beta_s + \alpha_s c_k + \beta_s r_k + \beta_s s_k) + 1 \end{pmatrix}. \quad (4.14)$$

$$\det(\hat{\mathcal{A}}_3) = (\phi(\mu_r - \beta_r + \beta_r r_k + \beta_r s_k) + 1)(\phi(\mu_s - \beta_s + \alpha_s c_k + \beta_s r_k + \beta_s s_k) + 1) \quad (4.15)$$

has positive entries. Thus, since all the elements in the right-hand side of (3.21) are positive, so will be s_{k+1} , r_{k+1} and c_{k+1} .

(iv) Scheme 4.

When $\mu_s = \beta_s = \mu_r = \beta_r = \beta$, the determinant of $\mathcal{A}_4$ reads:

$$\begin{aligned} \det(\mathcal{A}_4) &= 1 \\ &+ (\mu_c + \alpha_s c_k + \beta r_k + \beta s_k) \phi \\ &+ (\alpha_s c_k \mu_c + \beta \mu_c r_k + \beta \mu_c s_k + \alpha_s \beta c_k r_k + \alpha_s \beta c_k q s_k) \phi^2 \\ &+ (\alpha_s \beta c_k \mu_c r_k + \alpha_s \beta c_k \mu_c q s_k) \phi^3, \end{aligned} \quad (4.16)$$

which is positive under the assumptions in (iv). Thus, the inverse matrix $\mathcal{A}_4^{-1}$ exists and the system is well-posed. Moreover, the values of s_{k+1} and r_{k+1} are given by:

$$\begin{aligned} s_{k+1} &= \frac{s_k}{(\alpha_s \beta c_k r_k + \alpha_s \beta c_k q s_k) \phi^2 + (\alpha_s c_k + \beta r_k + \beta s_k) \phi + 1}, \\ r_{k+1} &= \frac{(\alpha_s c_k r_k + \alpha_s c_k q s_k) \phi + r_k}{(\alpha_s \beta c_k r_k + \alpha_s \beta c_k q s_k) \phi^2 + (\alpha_s c_k + \beta r_k + \beta s_k) \phi + 1}, \end{aligned}$$

which are positive as well. Thus, it is proved that the discrete-time Schemes 1–4 are well-posed and remain nonnegative for all $k \geq 0$ and any nonnegative initial condition regardless the value of step size h , under the mentioned assumptions. $\square$

It is worth noting that the nonnegativity of the solutions is not guaranteed in a general case under Schemes 2, 3 and 4, since either the determinant or the inverse matrix of $\mathcal{A}_n$ possess negative components that might lead to negative values for the next-step state for certain combinations of parameters and current state values. Thus, for Scheme 2 we have:

$$\mathcal{A}_2^{-1} = \begin{pmatrix} \hat{\mathcal{A}}_2^{-1} & \mathbf{0} \\ \mathbf{0} & \frac{1}{1 + \mu_c \phi} \end{pmatrix}, \quad (4.17)$$

with

$$(\hat{\mathcal{A}}_2)^{-1} = \frac{1}{\det(\hat{\mathcal{A}}_2)} \begin{pmatrix} \mu_r \phi + \beta_r \phi r_k + 1 & -\beta_s \phi s_k \\ \alpha_s c_k \phi q - \beta_r \phi r_k & \mu_s \phi + \alpha_s c_k \phi + \beta_s \phi s_k + 1 \end{pmatrix}, \quad (4.18)$$

and $\det(\hat{\mathcal{A}}_2)$ given by (4.7). At the induction hypothesis, s_k , r_k and c_k are nonnegative implying that $\det(\mathcal{A}_2)$ is positive. However, Eq. (4.18) exhibits some negative entries. As a result, for some parameter combinations, the solutions might attain negative values and the nonnegativity of the solutions cannot be directly guaranteed for arbitrary step sizes. Something similar happens to Scheme

3, since the presence of differences $(\mu_s - \beta_s)$ and $(\mu_r - \beta_r)$ in matrix $\mathcal{A}_3$ may cause some terms to be negative. This fact is observed in the value of $\det(\mathcal{A}_3)$ in (4.12). On the other hand, for Scheme 4 we have in the general case:

$$\det(\mathcal{A}_4) = 1 + A\phi + B\phi^2 + C\phi^3, \quad (4.19)$$

with

$$\begin{aligned} A &= \mu_c + \mu_r + \mu_s - \beta_s - \beta_r + \alpha_s c_k + \beta_r r_k + \beta_s s_k, \\ B &= \mu_c \mu_r + \mu_c \mu_s + \mu_r \mu_s + \beta_r \beta_s - \mu_c \beta_r - \mu_c \beta_s - \mu_r \beta_s - \mu_s \beta_r \\ &\quad - \alpha_s \beta_r c_k + \alpha_s c_k \mu_c + \alpha_s c_k \mu_r + \beta_r \mu_c r_k + \beta_r \mu_s r_k + \beta_s \mu_c s_k + \beta_s \mu_r s_k \\ &\quad + \alpha_s \beta_r c_k r_k + \alpha_s \beta_s c_k q s_k - \beta_r \beta_s (r_k + s_k), \\ C &= \mu_c \mu_r \mu_s + \beta_r \beta_s \mu_c - \beta_r \beta_s \mu_c r_k - \beta_r \beta_s \mu_c s_k - \beta_s \mu_c \mu_r - \beta_r \mu_c \mu_s \\ &\quad + \beta_r \mu_c \mu_s r_k + \beta_s \mu_c \mu_r s_k + \alpha_s \beta_r c_k \mu_c r_k + \alpha_s \beta_s c_k \mu_c q s_k + \alpha_s c_k \mu_c \mu_r \\ &\quad - \alpha_s \beta_r c_k \mu_c + \alpha_s \beta_r c_k \mu_c r_k, \end{aligned}$$

for which the coefficients A , B and C may be positive or negative depending on the combination of parameters and states. However, under certain circumstances, given by Theorem 4.3, some sufficient conditions can guarantee the nonnegativity of the schemes.

Moreover, the biological property satisfied by the original continuous system, namely, $0 \leq s(t) + r(t) \leq 1$, can be guaranteed to be preserved by the proposed numerical schemes under certain circumstances.

Theorem 4.4 (Biological Property of the Discrete Model, $0 \leq s_k + r_k \leq 1$). Assume that Assumption 1 holds and $0 \leq s_0 + r_0 \leq 1$. Then,

- (i) For Scheme 1, if $\beta_s = \beta_r$, then $0 \leq s_k + r_k \leq 1$ for all $k \geq 0$.
- (ii) For Scheme 1, if $q \leq \frac{\beta_r}{\beta_s}$, then $0 \leq s_k + r_k \leq 1$ for all $k \geq 0$.
- (iii) For Scheme 2, if $\beta_s = \beta_r$, then $0 \leq s_k + r_k \leq 1$ for all $k \geq 0$.
- (iv) For Scheme 3, if $\beta_s = \mu_s$ and $\beta_r = \mu_r$, then $0 \leq s_k + r_k \leq 1$ for all $k \geq 0$.
- (v) For Scheme 4, if $\beta_s = \mu_s = \beta_r = \mu_r$, then $0 \leq s_k + r_k \leq 1$ for all $k \geq 0$.

Proof. The proof proceeds by induction. The base case $s_0 + r_0 \leq 1$ holds by hypothesis, and we assume that $s_k + r_k \leq 1$ at some time step $t_k = kh$. We will show that $s_{k+1} + r_{k+1} \leq 1$.

(i) Scheme 1. Case $\beta_s = \beta_r$.

We proceed by contradiction. Suppose that $s_{k+1} + r_{k+1} > 1$. Adding Eqs. (3.1)–(3.3), we obtain:

$$\frac{(s_{k+1} + r_{k+1}) - (s_k + r_k)}{\phi(h)} = \beta_s s_k + \beta_r r_k - (\beta_s s_{k+1} + \beta_r r_{k+1})(s_k + r_k) + (q - 1)\alpha_s c_k s_{k+1} - \mu_s s_{k+1} - \mu_r r_{k+1}. \quad (4.20)$$

Denoting $\delta_k = s_k + r_k$ and assuming $\beta_s = \beta_r = \beta$, Eq. (4.20) simplifies to:

$$\frac{\delta_{k+1} - \delta_k}{\phi(h)} = \beta \delta_k (1 - \delta_{k+1}) + (q - 1)\alpha_s c_k s_{k+1} - \mu_s s_{k+1} - \mu_r r_{k+1}. \quad (4.21)$$

Since $\delta_{k+1} > 1$ and $\delta_k \leq 1$ by hypothesis, the left-hand side of (4.21) is positive. However, the right-hand side is negative, because $(1 - \delta_{k+1}) < 0$, $\delta_k > 0$, and $0 < q < 1$, which yields a sum of strictly negative terms, a contradiction. Hence, δ_{k+1} cannot exceed one. The induction step is complete, and we conclude that $s_k + r_k \leq 1$ for all $k \geq 0$.

(ii) Scheme 1. Case $q \leq \frac{\beta_r}{\beta_s}$.

The value of the sum $s_{k+1} + r_{k+1}$ is given by:

$$s_{k+1} + r_{k+1} = \frac{\eta_{21}\phi^2 + \eta_{22}\phi + r_k + s_k}{\eta_{31}\phi^2 + \eta_{32}\phi + 1}, \quad (4.22)$$

with

$$\eta_{21} = \beta_r \mu_s r_k + \beta_s \mu_r s_k + \beta_r \beta_s r_k^2 + \beta_r \beta_s s_k^2 + 2\beta_r \beta_s r_k s_k + \alpha_s \beta_r c_k r_k + \alpha_s \beta_s c_k q s_k, \quad (4.23)$$

$$\eta_{22} = \beta_r r_k + \beta_s s_k + \mu_s r_k + \mu_r s_k + \beta_s r_k^2 + \beta_r s_k^2 + \alpha_s c_k r_k + \beta_r r_k s_k + \beta_s r_k s_k + \alpha_s c_k q s_k, \quad (4.24)$$

$$\eta_{31} = (\mu_r + \beta_r r_k + \beta_r s_k)(\mu_s + \alpha_s c_k + \beta_s r_k + \beta_s s_k), \quad (4.25)$$

$$\eta_{32} = \mu_r + \mu_s + \alpha_s c_k + \beta_r r_k + \beta_s r_k + \beta_r s_k + \beta_s s_k. \quad (4.26)$$

Since all the terms (4.23)–(4.26) are positive, the condition $s_{k+1} + r_{k+1} < 1$ holds if:

$$(\eta_{31} - \eta_{21})\phi^2 + (\eta_{32} - \eta_{22})\phi + 1 - r_k - s_k > 0, \quad (4.27)$$

for all $\phi(h) > 0$, which in turn is satisfied if:

$$\eta_{31} - \eta_{21} = \underbrace{\mu_r \mu_s + \alpha_s c_k \mu_r + \beta_s \mu_r r_k + \beta_r \mu_s s_k + \alpha_s c_k s_k (\beta_r - \beta_s q)}_{(*)} > 0, \quad (4.28)$$

$$\eta_{32} - \eta_{22} = \mu_r(1 - s_k) + \mu_s(1 - r_k) + \alpha_s c_k(1 - r_k - q s_k) + \beta_s r_k(1 - r_k - s_k) + \beta_r s_k(1 - s_k - r_k) > 0. \quad (4.29)$$

If $q \leq \frac{\beta_r}{\beta_s}$, then the term (*) is positive and all the parameters in (4.28) are positive. On the other hand, since $s_k + r_k < 1$, then $s_k < 1$, $r_k < 1$, $1 - s_k - r_k > 0$, $1 - r_k - q s_k > 0$, (4.29) holds and the positiveness condition holds. Thus, (ii) is proved.

(iii) Scheme 2.

The value of the sum $s_{k+1} + r_{k+1}$ is given by:

$$s_{k+1} + r_{k+1} = \frac{\eta_{41}\phi^2 + \eta_{42}\phi + r_k + s_k}{\eta_{51}\phi^2 + \eta_{52}\phi + 1}, \quad (4.30)$$

with

$$\eta_{41} = \beta_r \mu_s r_k + \beta_s \mu_r s_k + \alpha_s \beta_r c_k r_k + \alpha_s \beta_s c_k q s_k, \quad (4.31)$$

$$\eta_{42} = \beta_r r_k + \beta_s s_k + \mu_s r_k + \mu_r s_k + \alpha_s c_k r_k + \alpha_s c_k q s_k, \quad (4.32)$$

$$\eta_{51} = \mu_r \mu_s + \alpha_s c_k \mu_r + \beta_r \mu_s r_k + \beta_s \mu_r s_k + \alpha_s \beta_r c_k r_k + \alpha_s \beta_s c_k q s_k, \quad (4.33)$$

$$\eta_{52} = \mu_r + \mu_s + \alpha_s c_k + \beta_r r_k + \beta_s s_k. \quad (4.34)$$

Since all the terms (4.31)–(4.34) are positive, the condition $s_{k+1} + r_{k+1} < 1$ holds if:

$$(\eta_{51} - \eta_{41})\phi^2 + (\eta_{52} - \eta_{42})\phi + 1 - r_k - s_k > 0, \quad (4.35)$$

for all $\phi(h) > 0$, which in turn is satisfied if:

$$\eta_{51} - \eta_{41} = \mu_r \mu_s + \alpha_s c_k \mu_r > 0, \quad (4.36)$$

$$\eta_{52} - \eta_{42} = \mu_r(1 - s_k) + \mu_s(1 - r_k) + \alpha_s c_k(1 - r_k - q s_k) > 0. \quad (4.37)$$

All the parameters in (4.36) are positive, and, since $s_k + r_k < 1$, then $s_k < 1$, $r_k < 1$, $1 - s_k - r_k > 0$, $1 - r_k - q s_k > 0$, (4.37) holds and (iii) is proved.

(iv) Scheme 3. Case $\beta_s = \mu_s$ and $\beta_r = \mu_r$.

The value of the sum $s_{k+1} + r_{k+1}$ is given by:

$$s_{k+1} + r_{k+1} = \frac{\eta_{62}\phi + r_k + s_k}{\eta_{71}\phi^2 + \eta_{72}\phi + 1}, \quad (4.38)$$

so that the condition $s_{k+1} + r_{k+1} < 1$ holds if:

$$\eta_{71}\phi^2 + (\eta_{72} - \eta_{62})\phi + 1 - r_k - s_k > 0, \quad (4.39)$$

for all $\phi(h) > 0$, which in turn is satisfied if:

$$\eta_{71} = (\mu_r - \beta_r + \beta_r r_k + \beta_r s_k)(\mu_s - \beta_s + \alpha_s c_k + \beta_s r_k + \beta_s s_k) > 0, \quad (4.40)$$

$$\begin{aligned} \eta_{72} - \eta_{62} &= \mu_r - \beta_r + \mu_s - \beta_s + (\beta_s - \mu_s)r_k + (\beta_r - \mu_r)s_k + \alpha_s c_k(1 - r_k - q s_k) + \beta_r r_k \\ &\quad + \beta_r s_k(1 - r_k - s_k) + \beta_s s_k + \beta_s r_k(1 - r_k - s_k) > 0. \end{aligned} \quad (4.41)$$

If $\beta_r = \mu_r$ and $\beta_s = \mu_s$, then (4.40) and (4.41) hold and the biological property is preserved.

(v) Scheme 4.

The value of the sum $s_{k+1} + r_{k+1}$ is given when $\beta_s = \mu_s = \beta_r = \mu_r = \beta$ by:

$$s_{k+1} + r_{k+1} = \frac{\eta_{82}\phi + r_k + s_k}{\eta_{91}\phi^2 + \eta_{92}\phi + 1}, \quad (4.42)$$

so that the condition $s_{k+1} + r_{k+1} < 1$ holds if:

$$\eta_{91}\phi^2 + (\eta_{92} - \eta_{82})\phi + 1 - r_k - s_k > 0, \quad (4.43)$$

for all $\phi(h) > 0$, which in turn is satisfied if:

$$\eta_{91} = \alpha_s \beta c_k r_k + \alpha_s \beta c_k q s_k > 0, \quad (4.44)$$

$$\eta_{92} - \eta_{82} = \beta r_k + \beta s_k + \alpha_s c_k(1 - r_k - q s_k) > 0. \quad (4.45)$$

Since (4.44) and (4.45) hold under the assumed conditions, then $s_{k+1} + r_{k+1} < 1$ and the biological property is preserved. $\square$

Remark 3. Theorems 4.3 and 4.4 establish sufficient conditions to ensure the well-posedness, nonnegativity, and preservation of the biological property for the discrete-time schemes. However, these conditions are somewhat conservative, and such properties may still hold under weaker or alternative assumptions. In particular, in the cases studied, these properties are guaranteed for arbitrary time step sizes.

Remark 4. When $\beta_s > \beta_r$, we can write $\beta_s = \beta_r + \eta$ with $\eta > 0$. In such a case, Eq. (4.20) can be re-written in terms of η as:

$$\frac{\delta_{k+1} - \delta_k}{\phi(h)} = \delta_k [\beta_r(1 - \delta_{k+1}) - \eta s_{k+1}] + \eta s_k + (q-1)\alpha_s c_k s_{k+1} - \mu_s s_{k+1} - \mu_r r_{k+1}. \quad (4.46)$$

Now, the positive term ηs_k appears in the right-hand side of (4.46), so that if η is big, the right-hand side could potentially be positive for certain combinations of variables and states. Therefore, in the general case, the biological property of $s_k + r_k \leq 1$ cannot be proved with the current approach for numerical Scheme 1, although it may still hold. The numerical examples shown in Section 5 will explicitly consider the biological case when there is a large difference between the values of β_s and β_r .

Theorem 4.5 (Preservation of Equilibrium Points). *The numerical Schemes 1, 2, 3 and 4 possess the same equilibrium points as the continuous-time system (2.5)–(2.7).*

Proof. All numerical Schemes yield the same set of equilibrium equations, namely:

$$\beta_s s - \beta_s(s+r)s - \alpha_s cs - \mu_s s = 0, \quad (4.47)$$

$$\beta_r r - \beta_r(s+r)r + q\alpha_s cs - \mu_r r = 0, \quad (4.48)$$

$$\mu_c - \mu_c c = 0, \quad (4.49)$$

which is the same set obtained for the original continuous-time system (2.5)–(2.7). It follows that the four numerical schemes preserve the location of the equilibrium points. $\square$

Theorem 4.6 (Preservation of Stability Under NSFD Discretization). *Numerical Schemes 1, 2, 3, and 4 preserve the stability properties of the equilibrium points E_0 , E_1 , and E_2 as described in Theorem 2.3. In particular, the schemes reproduce the same asymptotic stability or instability of these equilibria under the corresponding parameter conditions.*

Proof. We provide the proof for Scheme 1, as the procedure is identical for the other Schemes. To show that the equilibrium points maintain their stability characteristics under discretization via Scheme 1, we use the explicit form of the discrete system $y_{k+1} = \mathcal{A}_1^{-1} \mathcal{D}_1 y_k + \mathcal{A}_1^{-1} b_1$. Local asymptotic stability is guaranteed if the Jacobian of the map $\mathcal{A}_1^{-1} \mathcal{D}_1 y_k + \mathcal{A}_1^{-1} b_1$ at the equilibrium point has all its eigenvalues strictly inside the unit circle. The Jacobian of Scheme 1 at the equilibrium point E_0 is given by:

$$\left(\frac{\partial (\mathcal{A}_1(y_k)^{-1} \mathcal{D}_1 y_k + \mathcal{A}_1^{-1} b_1)}{\partial y_k} \right)_{E_0} = J(E_0) = \begin{pmatrix} \frac{\beta_s \phi + 1}{\alpha_s \phi + \mu_s \phi + 1} & 0 & 0 \\ \frac{\alpha_s \phi q (\beta_s \phi + 1)}{(\mu_r \phi + 1)(\alpha_s \phi + \mu_s \phi + 1)} & \frac{\beta_r \phi + 1}{\mu_r \phi + 1} & 0 \\ 0 & 0 & \frac{1}{\mu_c \phi + 1} \end{pmatrix}. \quad (4.50)$$

The eigenvalues of this matrix are:

$$\lambda_1 = \frac{\beta_s \phi + 1}{\alpha_s \phi + \mu_s \phi + 1},$$

$$\lambda_2 = \frac{\beta_r \phi + 1}{\mu_r \phi + 1},$$

$$\lambda_3 = \frac{1}{\mu_c \phi + 1}.$$

Clearly, $\lambda_3 < 1$ for all positive values of the parameters and ϕ . The other two eigenvalues should satisfy:

$$\frac{\beta_s \phi + 1}{\alpha_s \phi + \mu_s \phi + 1} < 1, \quad (4.51)$$

and

$$\frac{\beta_r \phi + 1}{\mu_r \phi + 1} < 1. \quad (4.52)$$

Inequality (4.51) is satisfied if $S_0 := \frac{\beta_s}{\alpha_s + \mu_s} < 1$, while (4.52) holds if $R_r := \frac{\beta_r}{\mu_r} < 1$, which are the same stability conditions as those established in Theorem 2.3. The same analysis applies to the equilibrium point E_1 , for which the Jacobian is:

$$J(E_1) = \begin{pmatrix} \frac{\beta_s \phi + 1}{\phi \frac{\beta_s}{S_0} + \frac{\beta_s \phi (R_r - 1)}{R_r} + 1} & 0 & 0 \\ \frac{\alpha_s \phi q (\beta_s \phi + 1)}{(\beta_r \phi + 1) \left(\phi \frac{\beta_s}{S_0} + \frac{\beta_s \phi (R_r - 1)}{R_r} + 1 \right)} - \frac{\mu_r \phi (R_r - 1)}{\beta_r \phi + 1} & 1 - \frac{\mu_r \phi (R_r - 1)}{\beta_r \phi + 1} & 0 \\ 0 & 0 & \frac{1}{\mu_c \phi + 1} \end{pmatrix}. \quad (4.53)$$

The eigenvalues are:

$$\lambda_1 = \frac{\beta_s \phi + 1}{\phi \frac{\beta_s}{S_0} + \frac{\beta_s \phi (R_r - 1)}{R_r} + 1}, \quad (4.54)$$

$$\lambda_2 = 1 - \frac{\mu_r \phi (R_r - 1)}{\beta_r \phi + 1}, \quad (4.55)$$

$$\lambda_3 = \frac{1}{\mu_c \phi + 1}.$$

Clearly, $0 < \lambda_3 < 1$ for all positive values of the parameters. The conditions for λ_1 and λ_2 become:

$$-1 < \frac{\beta_s \phi + 1}{\phi \frac{\beta_s}{S_0} + \frac{\beta_s \phi (R_r - 1)}{R_r} + 1} < 1, \quad (4.56)$$

and

$$-1 < 1 - \frac{\mu_r \phi (R_r - 1)}{\beta_r \phi + 1} < 1. \quad (4.57)$$

Condition (4.57) holds if $R_r > 1$, while condition (4.56) is equivalent to $S_0 < R_r$, which again match the stability conditions of the continuous system. Finally, for the equilibrium point E_2 , the Jacobian is given by:

$$\left(\frac{\partial (\mathcal{A}_1(y_k)^{-1} \mathcal{D}_1 y_k + \mathcal{A}_1^{-1} b_1)}{\partial y_k} \right)_{E_2} = J(E_2) = \begin{pmatrix} \hat{J}_{E_2} & \mathbf{B} \\ \mathbf{0} & \frac{1}{1 + \mu_c \phi} \end{pmatrix}. \quad (4.58)$$

The eigenvalues of this matrix are given by those of $\hat{J}_{E_2}$ and $\lambda_3 = \frac{1}{1 + \mu_c \phi}$. However, the block $\hat{J}_{E_2}$ has a very intricate expression in terms of system's parameters and its eigenvalues cannot be calculated explicitly. Therefore, the following conditions (4.59)–(4.61), [76], will be used to assess its stability as an alternative to the direct calculation approach:

$$1 - \text{Tr}(\hat{J}_{E_2}) + \det(\hat{J}_{E_2}) > 0, \quad (4.59)$$

$$1 + \text{Tr}(\hat{J}_{E_2}) + \det(\hat{J}_{E_2}) > 0, \quad (4.60)$$

$$|\det(\hat{J}_{E_2})| < 1. \quad (4.61)$$

The condition (4.59) reads:

$$1 - \text{Tr}(\hat{J}_{E_2}) + \det(\hat{J}_{E_2}) = \frac{a_{11} \phi^2}{b_{11} \phi^2 + b_{12} \phi + \beta_s}, \quad (4.62)$$

where:

$$\begin{aligned} a_{11} &= \underbrace{(\beta_s \mu_r - \alpha_s \beta_r - \beta_r \mu_s)}_{>0} \underbrace{(\beta_s - \alpha_s - \mu_s)}_{>0} > 0, \\ b_{11} &= \beta_s (\beta_r \beta_s + \underbrace{\beta_s \mu_r - \beta_r \mu_s - \alpha_s \beta_r}_{>0}) > 0, \\ b_{12} &= \beta_r \beta_s + \beta_s^2 + \underbrace{\beta_s \mu_r - \alpha_s \beta_r - \beta_r \mu_s}_{>0} > 0. \end{aligned}$$

In order to establish the sign of the above coefficients, the relationships $S_0 = \frac{\beta_s}{\alpha_s + \mu_s} > R_r = \frac{\beta_r}{\mu_r}$ and $\beta_s > \alpha_s + \mu_s$ have been used, implying $\beta_s \mu_r - \alpha_s \beta_r - \beta_r \mu_s > 0$ and $\beta_s - \alpha_s - \mu_s > 0$, respectively. These conditions are the ones that allow guaranteeing the stability of the E_2 equilibrium point in continuous-time (Theorem 2.3). Consequently, all the coefficients are positive and since $\phi(h) > 0$, so is the right-hand side of (4.62) and condition (4.59) is fulfilled. Moreover, the condition (4.60) reads:

$$1 + \text{Tr}(\hat{J}_{E_2}) + \det(\hat{J}_{E_2}) = \frac{a_{21} \phi^2 + a_{22} \phi + a_{23}}{b_{21} \phi^2 + b_{22} \phi + b_{23}}, \quad (4.63)$$

with:

$$\begin{aligned} a_{21} &= -(\alpha_s + \beta_s + \mu_s) \underbrace{(\beta_s \mu_r - \alpha_s \beta_r - \beta_r \mu_s + \alpha_s \beta_s q)}_{>0} \underbrace{(\beta_s \mu_r - \alpha_s \beta_r - \beta_r \mu_s + 2\beta_r \beta_s)}_{>0} < 0, \\ a_{22} &= -2 \underbrace{(\beta_s \mu_r - \alpha_s \beta_r - \beta_r \mu_s)}_{>0}^2 - 2\beta_s^2 \underbrace{(\beta_s \mu_r - \alpha_s \beta_r - \beta_r \mu_s)}_{>0} \\ &\quad - 2\beta_s \underbrace{(\beta_s \mu_r - \alpha_s \beta_r - \beta_r \mu_s)}_{>0} (\alpha_s + 2\beta_r + \mu_s) - 2q \alpha_s \beta_s^2 (2\beta_s + \beta_r + \mu_r) < 0, \end{aligned}$$

$$\begin{aligned}
a_{23} &= -4\beta_s \underbrace{(\beta_s \mu_r - \alpha_s \beta_r - \beta_r \mu_s)}_{>0} - 4\alpha_s \beta_s^2 q < 0, \\
b_{21} &= -\beta_s \left(\underbrace{\beta_s \mu_r - \alpha_s \beta_r - \beta_r \mu_s}_{>0} + \beta_r \beta_s \right) \left(\underbrace{\beta_s \mu_r - \alpha_s \beta_r - \beta_r \mu_s + \alpha_s \beta_s q}_{>0} \right) < 0, \\
b_{22} &= - \left(\underbrace{\beta_s \mu_r - \alpha_s \beta_r - \beta_r \mu_s + \alpha_s \beta_s q}_{>0} \right) \left(\underbrace{\beta_s^2 + \beta_r \beta_s + \beta_s \mu_r - \alpha_s \beta_r - \beta_r \mu_s}_{>0} \right) < 0, \\
b_{23} &= -\beta_s \underbrace{(\beta_s \mu_r - \alpha_s \beta_r - \beta_r \mu_s)}_{>0} - \alpha_s \beta_s^2 q < 0.
\end{aligned}$$

Since all the coefficients are negative and $\phi(h) > 0$ the right-hand side of (4.63) is the quotient of two negative numbers and therefore, positive, satisfying as a consequence the condition (4.60). Finally, for the condition (4.61) we calculate $\det \hat{J}_{E_2}$ to get:

$$\det \hat{J}_{E_2} = \frac{a_{31}\phi^2 + a_{32}\phi + a_{33}}{b_{31}\phi^2 + b_{32}\phi + b_{33}}, \quad (4.64)$$

where:

$$\begin{aligned}
a_{31} &= -\beta_s \left(\underbrace{\alpha_s \beta_r (\beta_s \mu_r - \alpha_s \beta_r - \beta_r \mu_s + \beta_s q \alpha)}_{>0} + \beta_r \mu_s \underbrace{(\beta_s \mu_r - \alpha_s \beta_r - \beta_r \mu_s)}_{>0} + \alpha \beta_r \beta_s q \mu_s \right) < 0, \\
a_{32} &= -\beta_s \left((\alpha_s + \mu_s + \beta_r) \underbrace{(\beta_s \mu_r - \alpha_s \beta_r - \beta_r \mu_s)}_{>0} + \alpha_s^2 \beta_r q + \alpha_s \beta_s^2 q + \alpha_s \beta_r \mu_s q \right) < 0, \\
a_{33} &= b_{33} = -\beta_s \left(\underbrace{\beta_s \mu_r - \alpha_s \beta_r - \beta_r \mu_s + \alpha_s \beta_s q}_{>0} \right) < 0, \\
b_{31} &= -\beta_s \underbrace{(\beta_s \mu_r - \alpha_s \beta_r - \beta_r \mu_s + \beta_r \beta_s)}_{>0} \underbrace{(\beta_s \mu_r - \alpha_s \beta_r - \beta_r \mu_s + \alpha_s \beta_s q)}_{>0} < 0, \\
b_{32} &= -(\beta_s^2 + \beta_r \beta_s + \underbrace{\beta_s \mu_r - \alpha_s \beta_r - \beta_r \mu_s}_{>0}) \underbrace{(\beta_s \mu_r - \alpha_s \beta_r - \beta_r \mu_s + \alpha_s \beta_s q)}_{>0} < 0.
\end{aligned}$$

Since the right-hand side of (4.64) is the ratio of negative numbers, it is indeed positive and $\det \hat{J}_{E_2} > 0$. Thus, condition (4.64) becomes $\det(\hat{J}_{E_2}) < 1$ which can be written as:

$$\phi(K\phi + Q) > 0, \quad (4.65)$$

with

$$\begin{aligned}
K &= \beta_s \underbrace{(\beta_s \mu_r - \alpha_s \beta_r - \beta_r \mu_s + \beta_r (\beta_s - \alpha_s - \mu_s))}_{>0} \underbrace{(\beta_s \mu_r - \alpha_s \beta_r - \beta_r \mu_s + \alpha \beta_s q)}_{>0} > 0, \\
Q &= \underbrace{(\beta_s \mu_r - \alpha_s \beta_r - \beta_r \mu_s)^2}_{>0} + \underbrace{(\beta_s \mu_r - \alpha_s \beta_r - \beta_r \mu_s)}_{>0} \beta_s (q\alpha + \underbrace{(\beta_s - \alpha_s - \mu_s)}_{>0}) \\
&\quad + \alpha \beta_s \beta_r q \underbrace{(\beta_s - \alpha_s - \mu_s)}_{>0} > 0.
\end{aligned}$$

Hence, since K and Q are positive, (4.65) holds and $\det(\hat{J}_{E_2}) < 1$. Consequently, conditions (4.59)–(4.61) hold under the same assumptions as in the continuous-time case and the stability properties of E_2 are also preserved under NSFD discretization. The same arguments apply for the remaining Schemes. $\square$

Remark 5. Since Theorem 4.6 imposes no restrictions on the step size h or the function $\phi(h)$, the stability properties are preserved for any value of h . This is one of the key advantages of using Non-Standard Finite Difference (NSFD) methods, which are designed to retain essential qualitative features of the continuous system regardless of the discretization step.

Remark 6. For numerical Schemes 2, 3 and 4, the local stability of the equilibrium points is preserved provided that the associated inverse matrices exist. In this case, stability is ensured even if the schemes do not preserve the positivity or the biological property of the solutions.

Table 1
Summary of structural features of the numerical schemes.

	Scheme 1	Scheme 2	Scheme 3	Scheme 4
Consistency	✓	✓	✓	✓
Nonnegativity	✓	$\beta_s = \beta_r$	$\mu_r \geq \beta_r, \mu_s \geq \beta_s$	$\beta_s = \beta_r = \mu_s = \mu_r$
Bio. Condition	$\beta_s = \beta_r$ or $q \leq \frac{\beta_r}{\beta_s}$	$\beta_s = \beta_r$	$\beta_s = \mu_s, \beta_r = \mu_r$	$\beta_s = \beta_r = \mu_s = \mu_r$
Eq. points	✓	✓	✓	✓
Stability	✓	✓	✓	✓

Table 2
Interpretation and values of the parameters used, [73].

Parameter	Definition	Value
α_S	Elimination of S by the antibiotic	$0.3960 \text{ (min mg)}^{-1}$
K	Carrying capacity of S and R	10^{12} bacteria
q	Fraction of S that acquire resistance	4×10^{-3}
μ_s	Natural death rate of S	0.2 min^{-1}
μ_r	Natural death rate of R	0.09 min^{-1}
μ_c	Degradation rate of the antibiotic (C)	0.0083 min^{-1}
Λ	Constant dose supply of the antibiotic	0.8328 mg/min

Table 3
Description of numerical experiments.

	Initial conditions		
	$0.6 = s_0 > r_0 = 0.1$	$0.4 = s_0 = r_0 = 0.4$	$0.2 = s_0 < r_0 = 0.5$
$\beta_s > \beta_{r1}$	Exp. 1	Exp. 2	Exp. 3
$\beta_s \gg \beta_{r2}$	Exp. 4	Exp. 5	Exp. 6

Table 1 summarizes the qualitative properties established for the numerical schemes.

After analyzing some theoretical aspects of the proposed schemes, the next Section 5 is devoted to their numerical evaluation.

5. Numerical simulations

This Section contains some numerical simulation examples concerning the discrete-time schemes introduced previously. To this end, we consider the continuous-time system (2.1)–(2.3) parameterized by the values showed in Table 2, which are taken from [73]. The growth rate of sensitive bacteria, β_s , and that of resistant bacteria, β_r , are not included in the table because different values of these parameters will be considered throughout the simulations. The parameter set in Table 2 is chosen so that the continuous-time system admits the equilibrium point E_2 , whose components are all strictly positive. This equilibrium represents the coexistence of all populations involved in the model and therefore corresponds to the most biologically relevant nontrivial scenario. By contrast, the other equilibrium points involve the extinction of at least one population, since one or more of their components are equal to zero. Multiple initial conditions are also considered. Table 3 contains the descriptions and labels of the numerical experiments that will be conducted, which run from number 1 to 6.

In Table 3, $\beta_s = 0.4 \text{ min}^{-1}$ and $\beta_{r1} = 0.1 \text{ min}^{-1}$, $\beta_{r2} = 0.01 \text{ min}^{-1} \ll \beta_{r1}$. In this way, the case when there is a large difference between both rates is studied. This case, as discussed in Section 4, may cause problems in guaranteeing the biological property in some of the discrete-time models. The discretization function, $\phi(h)$, is given in all cases by:

$$\phi(h) = \frac{1 - e^{-\lambda h}}{\lambda}. \quad (5.1)$$

The value of λ is selected as $\lambda = \mu_c$ since this value minimizes the distance of the sampled function $c(t)$ at $t_k = kh$ ($c(t_k) = c(kh)$) with respect to the discrete-time solution c_k , which is the same for the four schemes. Thus, λ is tuned to best approximate the discrete-time output c_k to the continuous-time one, $c(t)$. This function satisfies:

$$\lim_{h \rightarrow 0} \frac{1 - e^{-\lambda h}}{\lambda} = 0,$$

$$\lim_{h \rightarrow 0} \frac{1 - e^{-\lambda h}}{\lambda h} = 1,$$

as required theoretically for this function in order to define a NSFD scheme and make the discrete-time system consistent with the continuous-time system. It is important to notice that all the four schemes provide the same equation for c_k , so that the comparison between schemes will be performed by using only the susceptible and resistant strains, and not the concentration of antibiotic. The true solution of the system is considered to be the solution of the continuous-time equation with Matlab method *ode15s*. All the

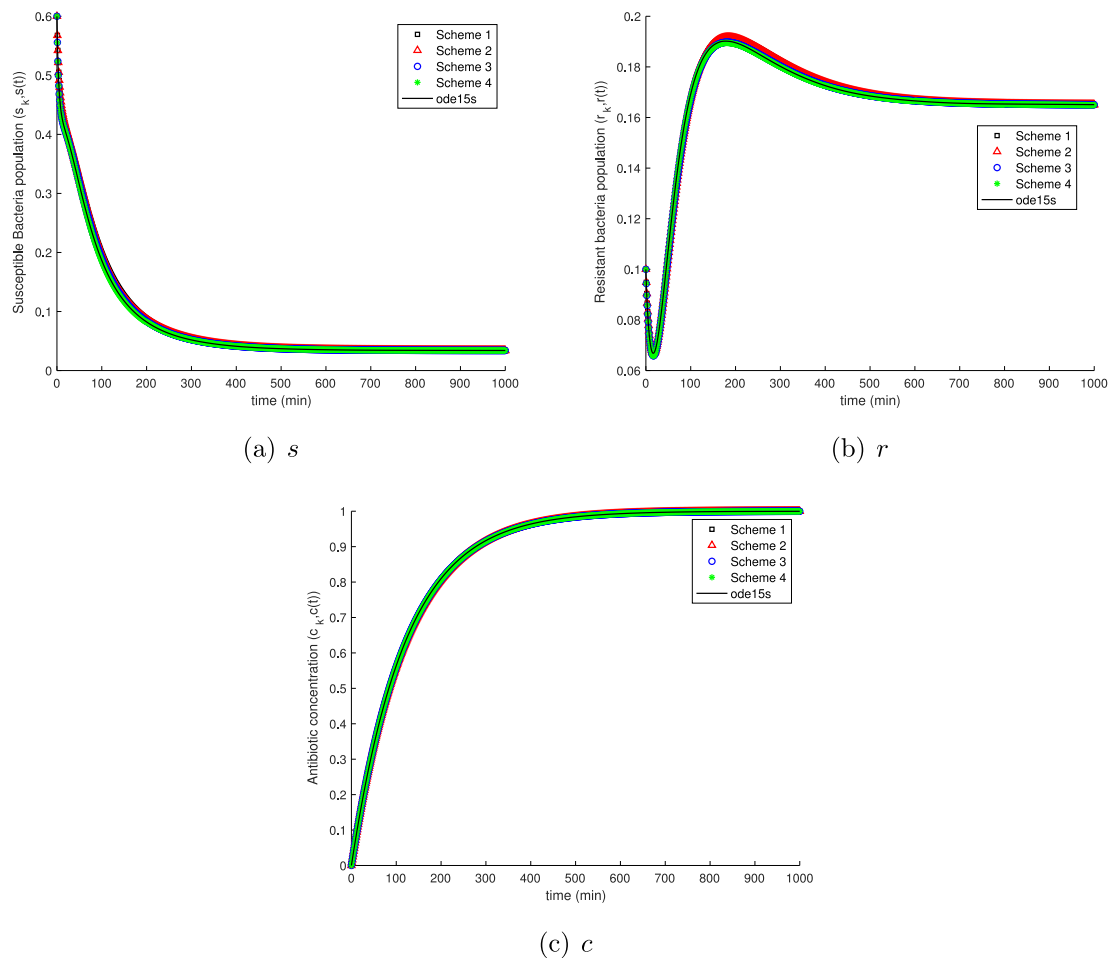


Fig. 1. Results of Experiment 1 for the four discrete-time schemes in s , r and c for $h = 1$ min.

discrete-time models are compared with respect to this solution, that is regarded as the true one. The simulation time is 1000 min and the discrete-time output is computed for three sampling times, namely, 1, 5 and 10 min. Fig. 1 shows that the four schemes are capable of recovering the true solution of the system when the step size is small. However, as the step size increases, Scheme 4 performs poorly in most experiments when compared to the other three proposed (as seen in Fig. 2 with a sampling time of 10 min). The same behavior is exhibited in most of the experiments, and therefore only the first three schemes are shown for the remainder of the results.

Figs. 3–15 display the results for the different numerical experiments. In particular, Fig. 5 shows that the value of c_k is identical for all three main schemes. Therefore, this variable is omitted from further comparison. In all scenarios, it can be concluded that for small step sizes, all three schemes closely approximate the continuous-time reference solution. This behavior is expected, as all numerical schemes are consistent and recover the continuous-time solution as the step size $h \rightarrow 0$. Conversely, as the step size increases, a quantitative discrepancy between the continuous “true” solution and the discrete-time approximations becomes apparent. Thus, the accuracy of the proposed NSFD schemes is inherently linked to the step size h . As h increases, the Local Truncation Error (LTE), which scales as $\mathcal{O}(h)$, grows proportionally. This degradation in accuracy is a characteristic feature of first-order schemes (as previously discussed in Remark 2), where the discrete derivative provides a poorer approximation of the continuous rate of change. While NSFD methods are primarily designed to preserve structural stability and qualitative dynamics, quantitative precision is inevitably reduced as the discretization step deviates significantly from zero. Furthermore, Scheme 3 consistently outperforms the other two alternatives across all tested situations, providing a discrete-time trajectory closer to the actual solution of the continuous-time system. Moreover, although the parameter values used in these simulations fall outside most of the sufficient cases identified in Theorems 4.3 and 4.4 for ensuring well-posedness and nonnegativity, the numerical results indicate that the discrete-time models nevertheless continue to exhibit the expected qualitative behavior. This suggests that the sufficient conditions derived in the analysis are not sharp, and that a larger admissible parameter region may exist.

Moreover, a numerical comparison is performed by means of the square error of the difference between the continuous-time output and the output of each corresponding discrete-time scheme. The numerical results are given in Tables 4–15 corresponding

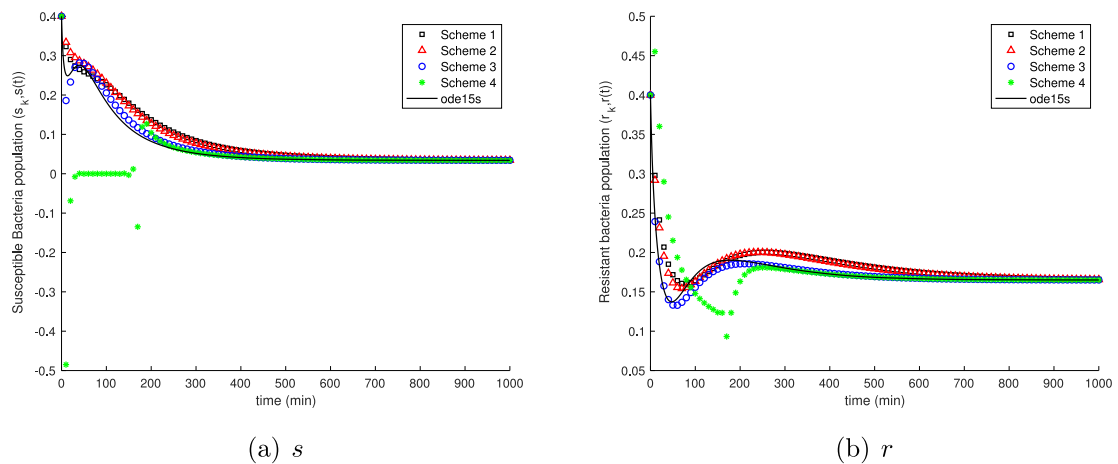


Fig. 2. Results of Experiment 2 for the four discrete-time schemes in s and r for $h = 10$ min.

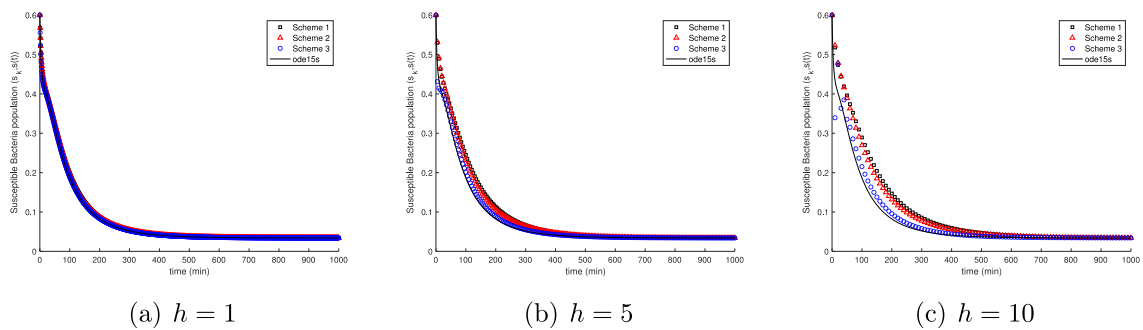


Fig. 3. Results of Experiment 1 in s for different values of the sampling time h (in minutes).

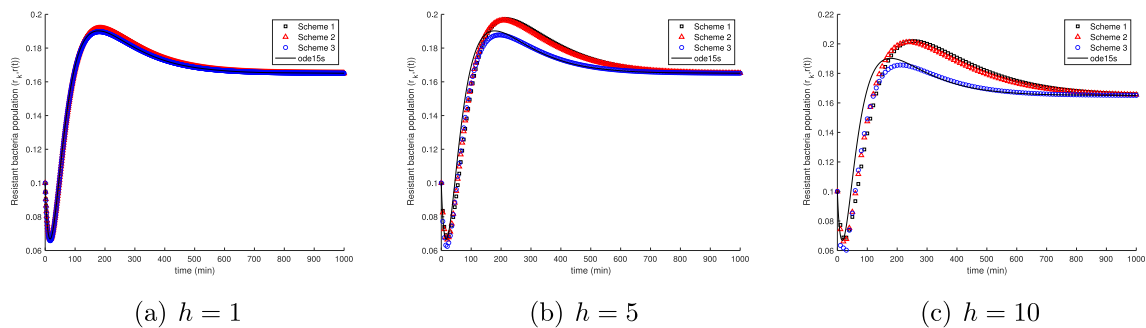


Fig. 4. Results of Experiment 1 in r for different values of the sampling time h (in minutes).

to each experiment from Table 3. The lowest value in each column is highlighted in yellow. As can be observed in the numerical results, Scheme 3 outperforms the other two (Schemes 1 and 2) in all the conducted experiments. As a conclusion, if a small step size is to be used, any of the presented schemes can be used. However, if a larger step size is preferred, the Scheme 3 would be the recommended option since it is able to generate better numerical results.

6. Discretization applied to a mutation–conjugation resistance model

In this Section, an approach based on Scheme 3 is used to generate a discrete-time model based on a system including mutation and horizontal gene transfer (HGT) through plasmid transmission. Alongside the effect of antibiotics, the process of bacterial conjugation can take place and resistant plasmids may be donated by resistant bacteria to susceptible ones. Moreover, the effect of host's immune system is also included in the model. The model is extensively discussed in [32] and given by Eqs. (6.1)–(6.4). The

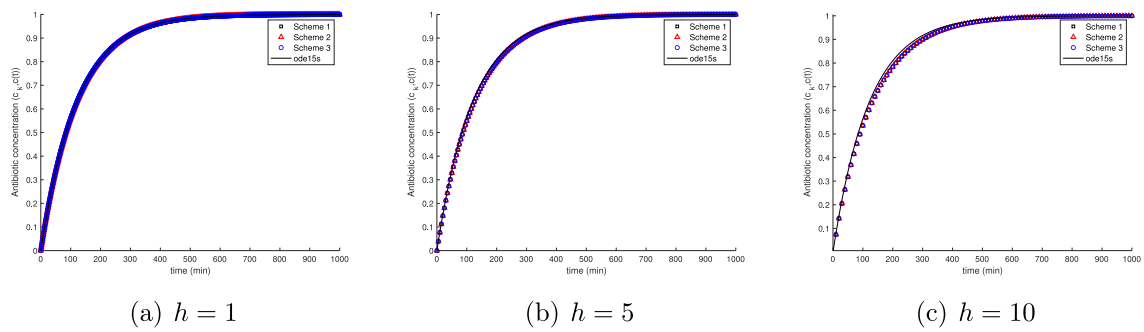


Fig. 5. Results of Experiment 1 in c for different values of the sampling time h (in minutes).

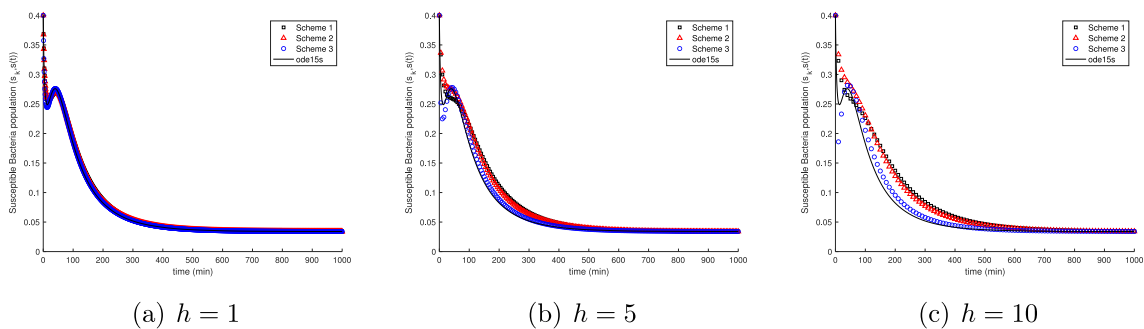


Fig. 6. Results of Experiment 2 in s for different values of the sampling time h (in minutes).

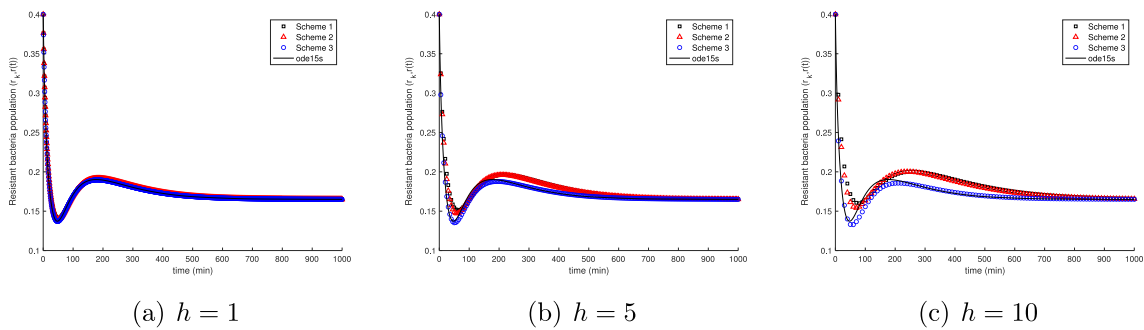


Fig. 7. Results of Experiment 2 in r for different values of the sampling time h (in minutes).

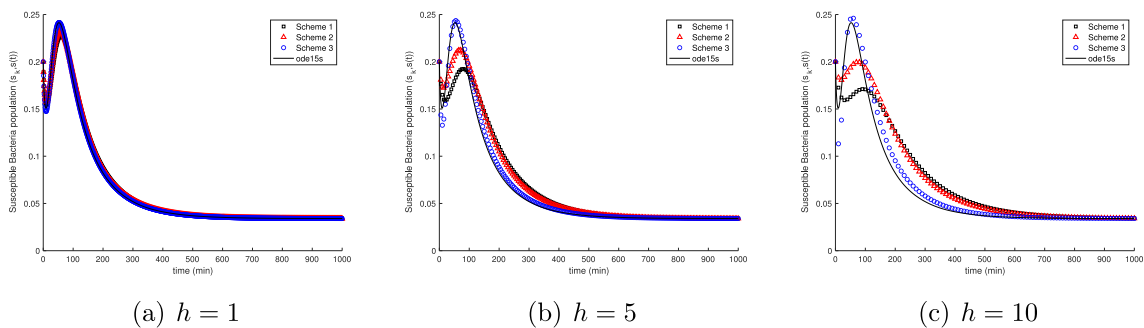


Fig. 8. Results of Experiment 3 in s for different values of the sampling time h (in minutes).

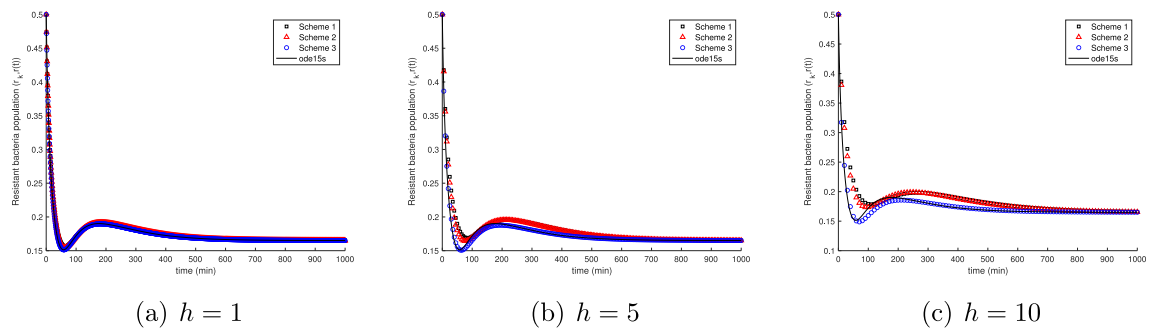


Fig. 9. Results of Experiment 3 in r for different values of the sampling time h (in minutes).

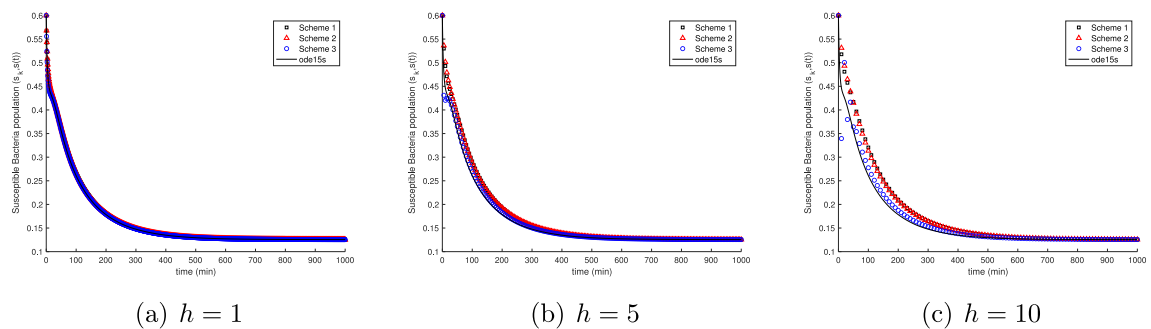


Fig. 10. Results of Experiment 4 in s for different values of the sampling time h (in minutes).

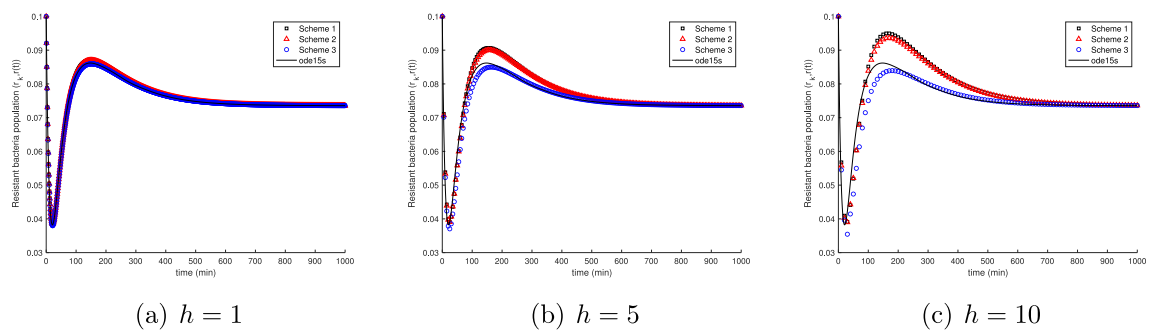


Fig. 11. Results of Experiment 4 in r for different values of the sampling time h (in minutes).

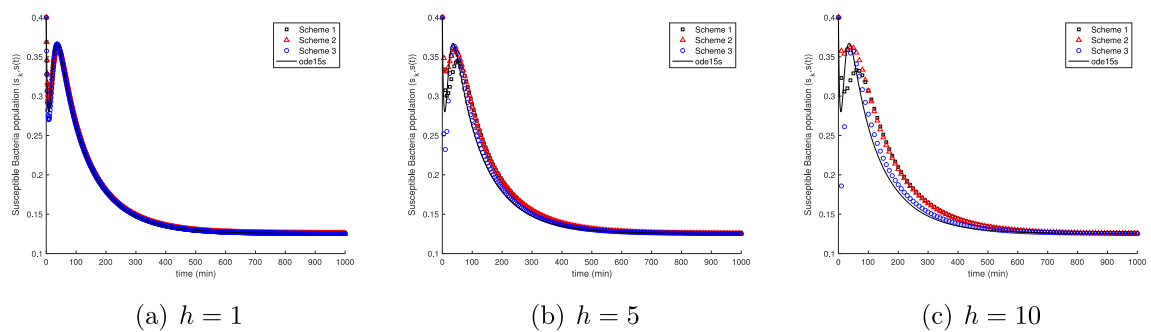


Fig. 12. Results of Experiment 5 in s for different values of the sampling time h (in minutes).

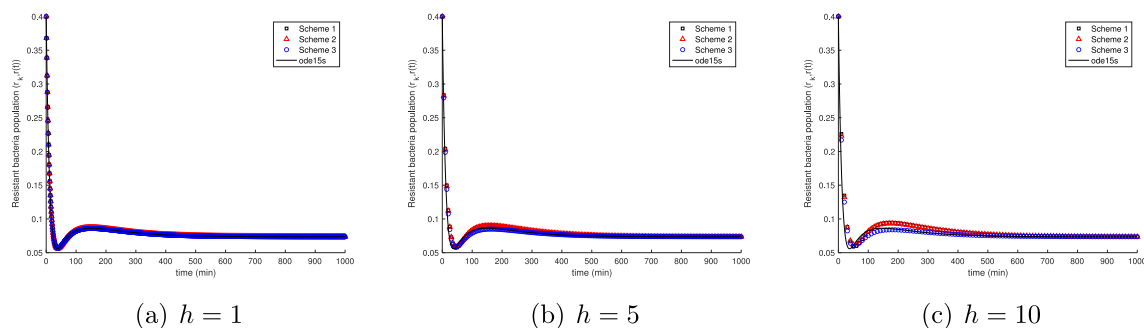
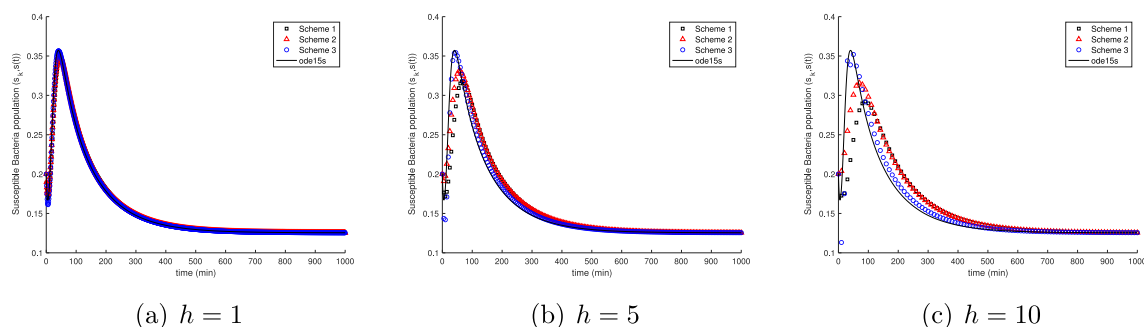
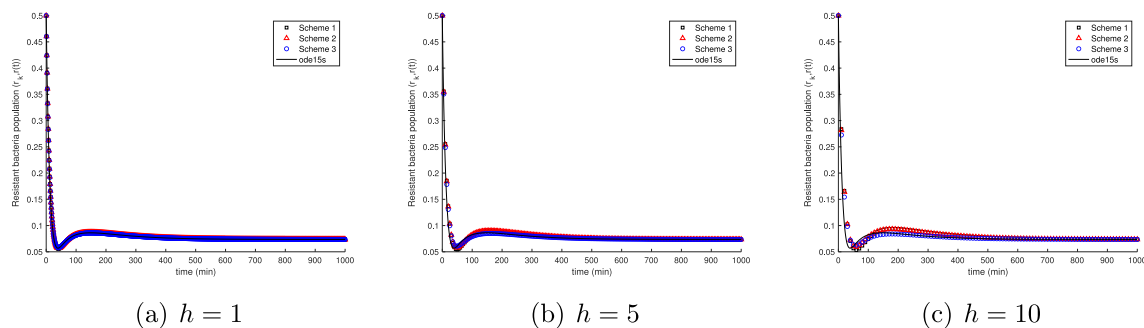
Fig. 13. Results of Experiment 5 in r for different values of the sampling time h (in minutes).Fig. 14. Results of Experiment 6 in s for different values of the sampling time h (in minutes).Fig. 15. Results of Experiment 6 in r for different values of the sampling time h (in minutes).

Table 4
Comparative results between schemes for the variable s in Experiment 1.

	$\sum_{k=1}^N (s_k - s(t_k))^2$		
	$h = 1 \text{ min}$	$h = 5 \text{ min}$	$h = 10 \text{ min}$
Scheme 1	0.0254	0.1071	0.1802
Scheme 2	0.0168	0.0725	0.1247
Scheme 3	0.0014	0.0080	0.0264

same notation as in the model described in Section 2 is used, except that the new state variable $P(t)$ denotes the concentration of extracellular plasmids at time t , which mediate horizontal gene transfer from resistant to susceptible bacteria. In addition to the previously-defined parameters, $\bar{q}$ is the mutation rate of susceptible bacteria, $\bar{\delta}$ is the rate of transfer of resistant plasmids among bacteria and γ is the rate at which susceptible and resistant bacteria are eliminated by the host's immune system. Also, σ_p denotes the rate of plasmid release, proportional to the population of resistant bacteria, and μ_p is the degradation rate of extracellular plasmids. The formulation of mutation in this extended model differs from that in Eq. (2.2), where it is coupled to the interaction term $\alpha_S C S$ through the factor q . In the present model, mutation is instead represented independently via the parameter $\bar{q}$, in accordance with

Table 5Comparative results between schemes for the variable r in Experiment 1.

	$\sum_{k=1}^N (r_k - r(t_k))^2$		
	$h = 1 \text{ min}$	$h = 5 \text{ min}$	$h = 10 \text{ min}$
Scheme 1	0.0021	0.0102	0.0187
Scheme 2	0.0014	0.0068	0.0130
Scheme 3	5.6970×10^{-4}	0.0026	0.0050

Table 6Comparative results between schemes for the variable s in Experiment 2.

	$\sum_{k=1}^N (s_k - s(t_k))^2$		
	$h = 1 \text{ min}$	$h = 5 \text{ min}$	$h = 10 \text{ min}$
Scheme 1	0.0143	0.0481	0.0705
Scheme 2	0.0100	0.0381	0.0605
Scheme 3	0.0011	0.0057	0.0115

Table 7Comparative results between schemes for the variable r in Experiment 2.

	$\sum_{k=1}^N (r_k - r(t_k))^2$		
	$h = 1 \text{ min}$	$h = 5 \text{ min}$	$h = 10 \text{ min}$
Scheme 1	0.0030	0.0136	0.0229
Scheme 2	0.0021	0.0093	0.0162
Scheme 3	2.3856×10^{-4}	0.0011	0.0021

Table 8Comparative results between schemes for the variable s in Experiment 3.

	$\sum_{k=1}^N (s_k - s(t_k))^2$		
	$h = 1 \text{ min}$	$h = 5 \text{ min}$	$h = 10 \text{ min}$
Scheme 1	0.0209	0.0545	0.0596
Scheme 2	0.0095	0.0298	0.0395
Scheme 3	8.5448×10^{-4}	0.0041	0.0080

Table 9Comparative results between schemes for the variable r in Experiment 3.

	$\sum_{k=1}^N (r_k - r(t_k))^2$		
	$h = 1 \text{ min}$	$h = 5 \text{ min}$	$h = 10 \text{ min}$
Scheme 1	0.0070	0.0270	0.0418
Scheme 2	0.0043	0.0181	0.0301
Scheme 3	2.1037×10^{-4}	8.9085×10^{-4}	0.0016

Table 10Comparative results between schemes for the variable s in Experiment 4.

	$\sum_{k=1}^N (s_k - s(t_k))^2$		
	$h = 1 \text{ min}$	$h = 5 \text{ min}$	$h = 10 \text{ min}$
Scheme 1	0.0085	0.0366	0.0647
Scheme 2	0.0082	0.0348	0.0606
Scheme 3	8.7505×10^{-4}	0.0053	0.0230

the formulation adopted in [32]. The model is given by:

$$\frac{dS}{dt} = \beta_s S \left(1 - \frac{S+R}{K}\right) - (\bar{q} + \alpha_S)CS - \bar{\delta}PS - \gamma S - \mu_s S, \quad (6.1)$$

$$\frac{dR}{dt} = \beta_r R \left(1 - \frac{S+R}{K}\right) + \bar{q}CS + \bar{\delta}PS - \gamma R - \mu_r R, \quad (6.2)$$

Table 11Comparative results between schemes for the variable r in Experiment 4.

	$\sum_{k=1}^N (r_k - r(t_k))^2$		
	$h = 1 \text{ min}$	$h = 5 \text{ min}$	$h = 10 \text{ min}$
Scheme 1	1.8289×10^{-4}	9.5298×10^{-4}	0.0020
Scheme 2	1.5670×10^{-4}	7.9080×10^{-4}	0.0016
Scheme 3	1.1004×10^{-4}	5.0073×10^{-4}	9.2824×10^{-4}

Table 12Comparative results between schemes for the variable s in Experiment 5.

	$\sum_{k=1}^N (s_k - s(t_k))^2$		
	$h = 1 \text{ min}$	$h = 5 \text{ min}$	$h = 10 \text{ min}$
Scheme 1	0.0083	0.0265	0.0375
Scheme 2	0.0066	0.0229	0.0353
Scheme 3	0.0022	0.0098	0.0173

Table 13Comparative results between schemes for the variable r in Experiment 5.

	$\sum_{k=1}^N (r_k - r(t_k))^2$		
	$h = 1 \text{ min}$	$h = 5 \text{ min}$	$h = 10 \text{ min}$
Scheme 1	0.0010	0.0045	0.0077
Scheme 2	9.5877×10^{-4}	0.0041	0.0068
Scheme 3	6.0448×10^{-4}	0.0026	0.0043

Table 14Comparative results between schemes for the variable s in Experiment 6.

	$\sum_{k=1}^N (s_k - s(t_k))^2$		
	$h = 1 \text{ min}$	$h = 5 \text{ min}$	$h = 10 \text{ min}$
Scheme 1	0.0237	0.0710	0.0867
Scheme 2	0.0096	0.0297	0.0398
Scheme 3	0.0021	0.0092	0.0164

Table 15Comparative results between schemes for the variable r in Experiment 6.

	$\sum_{k=1}^N (r_k - r(t_k))^2$		
	$h = 1 \text{ min}$	$h = 5 \text{ min}$	$h = 10 \text{ min}$
Scheme 1	0.0016	0.0074	0.0127
Scheme 2	0.0016	0.0068	0.0113
Scheme 3	0.0011	0.0046	0.0076

$$\frac{dP}{dt} = \sigma_p R - \mu_p P, \quad (6.3)$$

$$\frac{dC}{dt} = \Lambda - \mu_c C. \quad (6.4)$$

If we define now $s = \frac{S}{K}$, $r = \frac{R}{K}$, $p = \frac{P}{K\sigma_p}$ and $c = \frac{C}{\Lambda/\mu_c}$, the above system can be rewritten in a normalized way as:

$$\frac{ds}{dt} = \beta_s s (1 - (s + r)) - (q + \alpha_s)cs - \delta ps - \gamma s - \mu_s s, \quad (6.5)$$

$$\frac{dr}{dt} = \beta_r r (1 - (s + r)) + qc s + \delta ps - \gamma r - \mu_r r, \quad (6.6)$$

$$\frac{dp}{dt} = r - \mu_p p, \quad (6.7)$$

$$\frac{dc}{dt} = \mu_c - \mu_c c, \quad (6.8)$$

Table 16
Interpretation and values of the parameters, [32].

Parameter	Definition	Value
α_s	Elimination of S by the antibiotic	$0.9617 \text{ (min mg)}^{-1}$
K	Carrying capacity of S and R	10^{12} bacteria
$\bar{q}$	Mutation rate of S	$0.00063785 \text{ (min mg)}^{-1}$
μ_s	Natural death rate of S	0.16 min^{-1}
μ_r	Natural death rate of R	0.16 min^{-1}
μ_c	Degradation rate of the antibiotic (C)	0.0083 min^{-1}
Λ	Constant dose supply of the antibiotic	0.8328 mg/min
γ	Elimination rate of S and R by the Immune System	0.04 min^{-1}
σ_p	Release rate of P	1.2 rep/bac/min
μ_p	Degradation rate of Plasmids	0.012 min^{-1}

with $q = \bar{q} \frac{\Lambda}{\mu_c}$, $\alpha_s = \alpha_s \frac{\Lambda}{\mu_c}$ and $\delta = \bar{\delta} \sigma_p K$. The following NSFD discrete-time model based on the previously outperforming Scheme 3 is proposed as:

$$\frac{s_{k+1} - s_k}{\phi(h)} = \beta_s s_{k+1} (1 - (s_k + r_k)) - (q + \alpha_s) c_k s_{k+1} - \delta p_k s_{k+1} - \gamma s_{k+1} - \mu_s s_{k+1}, \quad (6.9)$$

$$\frac{r_{k+1} - r_k}{\phi(h)} = \beta_r r_{k+1} (1 - (s_k + r_k)) + q c_k s_{k+1} + \delta p_k s_{k+1} - \gamma r_{k+1} - \mu_r r_{k+1}, \quad (6.10)$$

$$\frac{p_{k+1} - p_k}{\phi(h)} = r_{k+1} - \mu_p p_{k+1}, \quad (6.11)$$

$$\frac{c_{k+1} - c_k}{\phi(h)} = \mu_c - \mu_c c_{k+1}. \quad (6.12)$$

Eqs. (6.9)–(6.12) can be cast into the form $\mathcal{A}_c y_{k+1} = D_c y_k + b_c$, with $y_k^T = [s_k \ r_k \ p_k \ c_k]$, and:

$$\mathcal{A}_c = \begin{pmatrix} \mathcal{A}_{c11} & 0 & 0 & 0 \\ -q\phi c_k - \delta\phi p_k & \mathcal{A}_{c22} & 0 & 0 \\ 0 & -\phi & 1 + \mu_p\phi & 0 \\ 0 & 0 & 0 & 1 + \mu_c\phi \end{pmatrix}, \quad (6.13)$$

with

$$\mathcal{A}_{c11} = 1 - \beta_s \phi (1 - s_k - r_k) + (q + \alpha_s) \phi c_k + (\mu_s + \gamma) \phi + \delta \phi p_k, \quad (6.14)$$

$$\mathcal{A}_{c22} = 1 - \beta_r \phi (1 - s_k - r_k) + (\mu_r + \gamma) \phi, \quad (6.15)$$

$$D_c = I_4, \quad (6.16)$$

and,

$$b_c = \begin{pmatrix} 0 \\ 0 \\ 0 \\ \mu_c \phi \end{pmatrix}, \quad (6.17)$$

so that, whenever $\mathcal{A}_c^{-1}$ exists, we have $y_{k+1} = \mathcal{A}_c^{-1} D_c y_k + \mathcal{A}_c^{-1} b_c$. The NSFD scheme for this model is evaluated numerically in the next Subsection.

6.1. Numerical simulation of the mutation–conjugation resistance model

This section presents some numerical experiments on the behavior of the discrete-time system (6.9)–(6.12) for parameters describing the population dynamics of *Staphylococcus aureus*, with a particular focus on the emergence and proliferation of antibiotic-resistant strains. While *Staphylococcus aureus* is commonly found in healthy individuals, it can also cause severe infections. The widespread use of antibiotics has led to the evolution of resistance, first to penicillin and later to methicillin, giving rise to multi-resistant strains such as MRSA. The numerical values employed in simulations are described in Table 16, sourced from [32]. The values of β_s and β_r are varied to obtain different experiments, and are indicated in the caption of each figure.

Fig. 16 displays the behavior of the four state variables of the model for the parameters contained in Table 16. It can be observed that the system is stiff and exhibits two time scales: a fast one related to the population dynamics of bacteria, and a slow one related to plasmids and antibiotic dynamics. Since the dynamics of susceptible bacteria is very fast and the evolution of the antibiotic concentration follows a first order equation, we will focus on how the discrete model behaves with respect to the resistant bacteria dynamics and plasmid concentration.

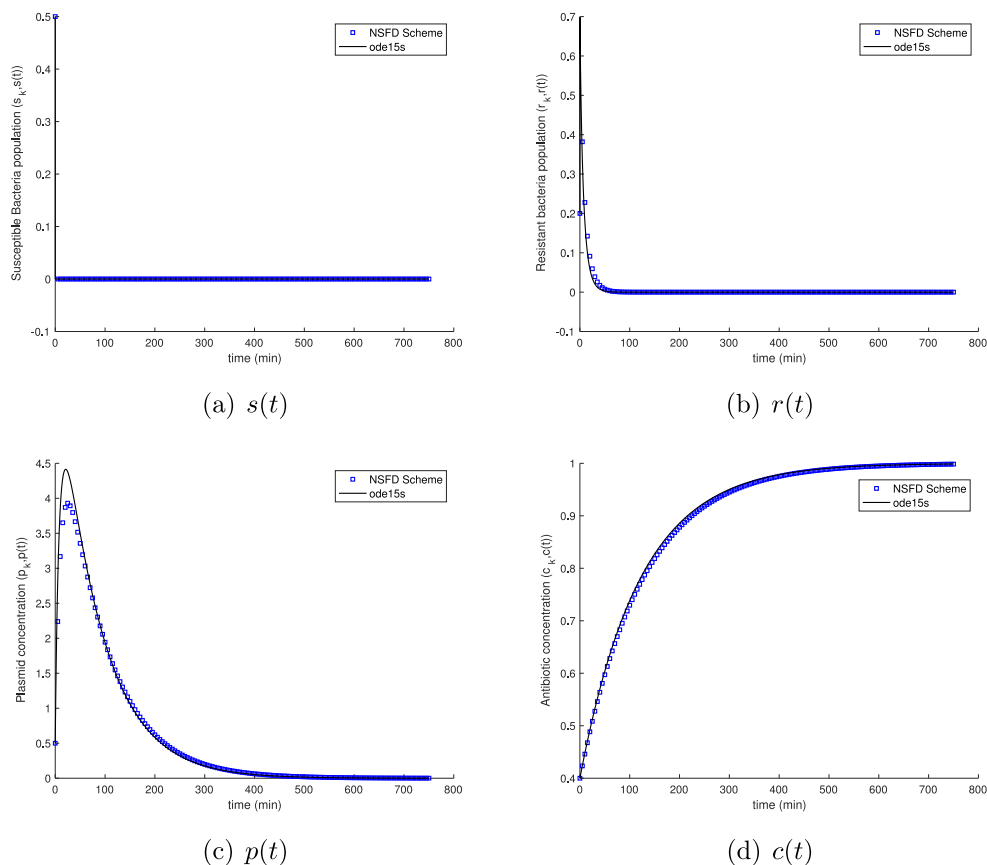


Fig. 16. State variables evolution for $h = 5$ min. The initial conditions are $s_0 = 0.5$, $r_0 = 0.2$, $p_0 = 0.5$ and $c_0 = 0.4$. $\beta_s = 0.4$ and $\beta_r = 0.1$.

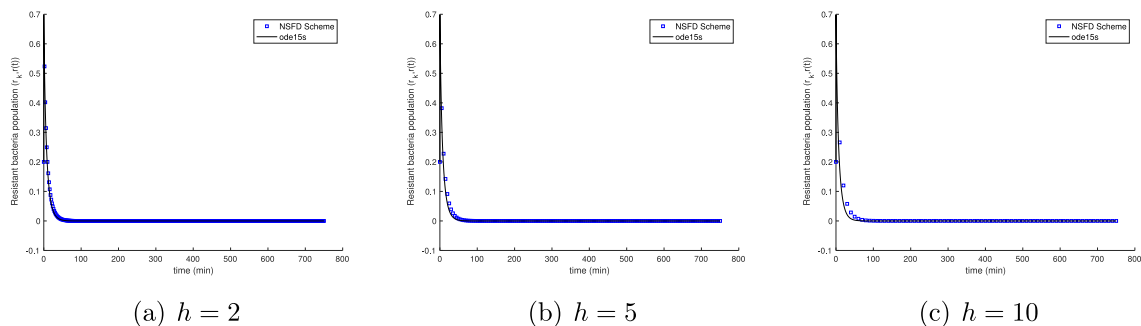


Fig. 17. Value of $r(t)$ when $\beta_s = 0.4$ and $\beta_r = 0.1$, for various sampling times, h (in minutes). The initial conditions are $s_0 = 0.5$, $r_0 = 0.2$, $p_0 = 0.5$ and $c_0 = 0.4$.

Figs. 17–22 display the numerical behavior of the discrete-time model for various time step sizes (2, 5 and 10 min). As before, the true solution is regarded to be the solution of the continuous-time system by using Matlab *ode15s* method. As expected, the discrete-time output is close to the actual solution of the system for small values of the step size. As the step size increases, a difference emerges between the continuous and discrete-time outputs. However, the scheme is stable and remains close to the original output.

The discrete system remains stable and closely matches the continuous model within parameter ranges that correspond to biologically realistic situations. In conclusion, the NSFD approach has proven to be a suitable tool for modeling antimicrobial resistance.

Remark 7 (Comparison with Runge–Kutta Methods). Runge–Kutta methods are well known for producing accurate numerical approximations for non-stiff differential equations. However, they are generally not suitable for stiff problems, such as the bacterial resistance model involving mutation and conjugation considered here. In this case, Runge–Kutta methods fail to produce numerically

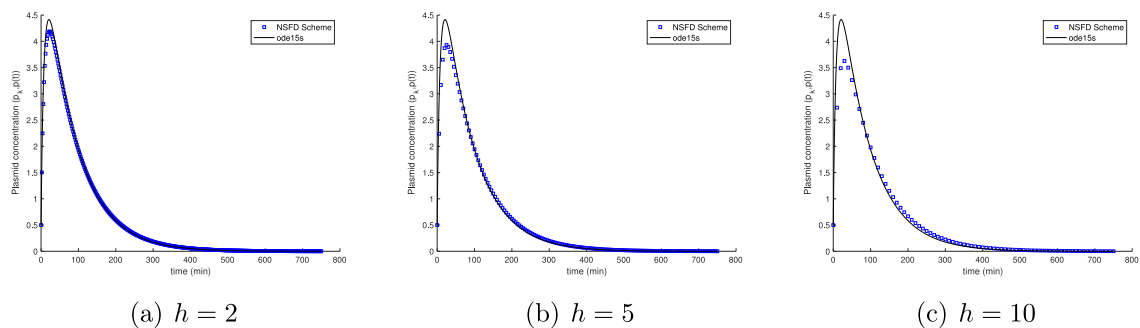


Fig. 18. Value of $p(t)$ when $\beta_s = 0.4$ and $\beta_r = 0.1$, for various sampling times, h (in minutes). The initial conditions are $s_0 = 0.5$, $r_0 = 0.2$, $p_0 = 0.5$ and $c_0 = 0.4$.

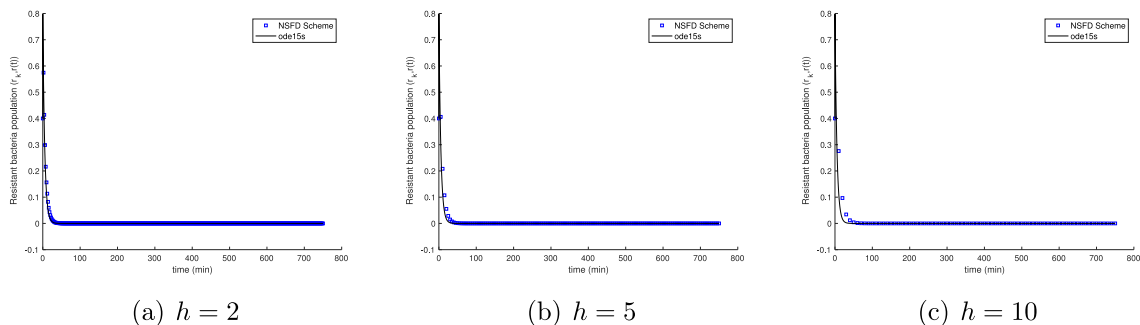


Fig. 19. Value of $r(t)$ when $\beta_s = 0.4$ and $\beta_r = 0.01$, for various sampling times, h (in minutes). The initial conditions are $s_0 = 0.4$, $r_0 = 0.4$, $p_0 = 0.5$ and $c_0 = 0.4$.

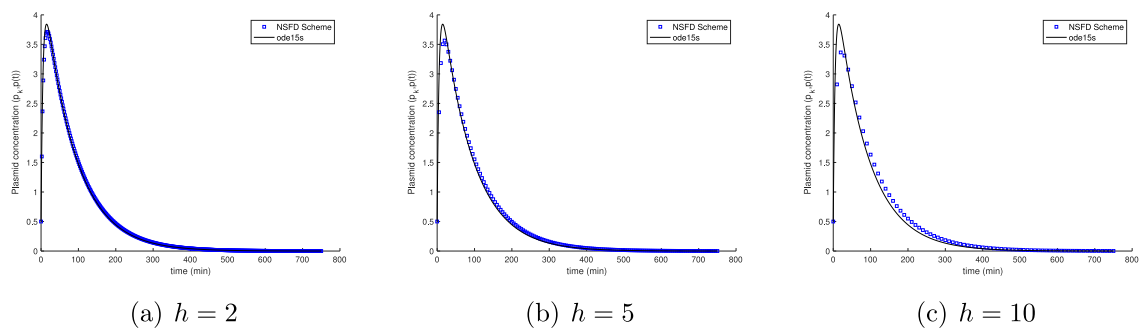


Fig. 20. Value of $p(t)$ when $\beta_s = 0.4$ and $\beta_r = 0.01$, for various sampling times, h (in minutes). The initial conditions are $s_0 = 0.4$, $r_0 = 0.4$, $p_0 = 0.5$ and $c_0 = 0.4$.

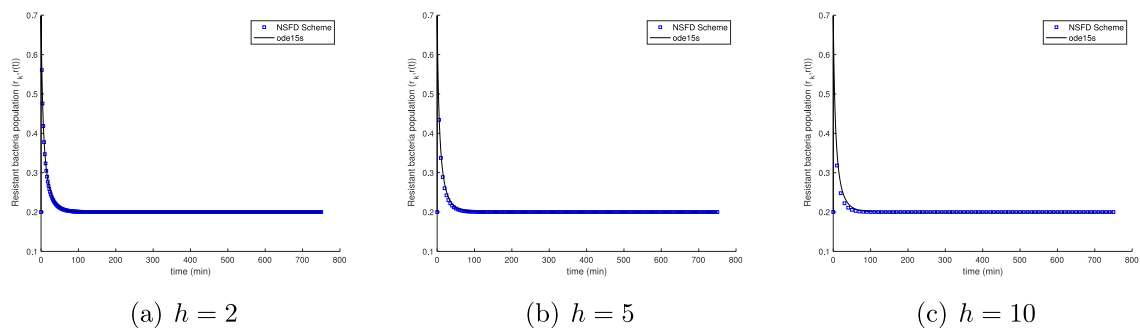


Fig. 21. Value of $r(t)$ when $\beta_s = 0.4$ and $\beta_r = 0.25$, for various sampling times, h (in minutes). The initial conditions are $s_0 = 0.5$, $r_0 = 0.2$, $p_0 = 0.5$ and $c_0 = 0.4$.

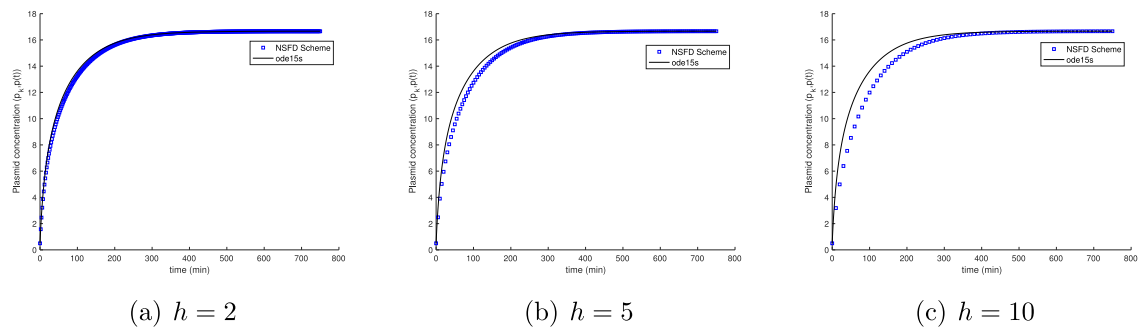


Fig. 22. Value of $p(t)$ when $\beta_s = 0.4$ and $\beta_r = 0.25$, for various sampling times, h (in minutes). The initial conditions are $s_0 = 0.5$, $r_0 = 0.2$, $p_0 = 0.5$ and $c_0 = 0.4$.

stable solutions for any integration step size. Although Runge–Kutta methods may offer better local accuracy than the NSFD method for the scenario described in Section 5, they do not yield a closed discrete system that captures the qualitative behavior of the underlying biological process. As such, they are less suitable for tasks such as parameter fitting or structural analysis. In contrast, NSFD schemes not only exhibit acceptable numerical performance but also provide a discrete model that is self-contained and consistent with the original dynamics.

7. Conclusions

This work has compared four numerical schemes based on Non-Standard Finite Difference (NSFD) methods, applied to a continuous-time logistic-type model describing the intra-host emergence of antimicrobial resistance (AMR). The model consists of two bacterial populations, one susceptible to an antibiotic and another resistant, evolving within a single host under the effect of antibiotic treatment. This interaction drives the emergence of resistance in a portion of the bacterial population, and is formulated through a system of logistic differential equations. The four discretization schemes were applied to the model, and their main qualitative properties were analyzed. Although all four schemes are consistent with the continuous-time formulation and reproduce the expected behavior for sufficiently small time steps, their ability to preserve the qualitative properties of the continuous model has only been rigorously established under specific sufficient conditions. These conditions, while ensuring well-posedness, nonnegativity and the biological property, are rather conservative and are only sufficient. Indeed, numerical simulations indicate that these properties may still hold under broader circumstances. A natural direction for future work is to obtain more general and less restrictive conditions under which the qualitative behavior of the discrete schemes is ensured to be preserved, as well as performing a formal numerical stability and error-propagation analysis to fully characterize the step-size dependence. The schemes were also compared numerically. As expected, for small time steps, all four methods produce results that closely match the continuous-time solution. However, as the time step increases, Scheme 3 consistently outperforms the others in terms of accuracy and qualitative fidelity. Although the analytical techniques employed in this work do not allow us to rigorously establish all theoretical properties for Scheme 3, extensive numerical evidence indicates that it remains stable and biologically consistent. Accordingly, Scheme 3 is recommended as the most reliable option when a finite (large) step size is required. This scheme was subsequently applied to a more complex AMR model incorporating not only mutation but also horizontal gene transfer via plasmids. The resulting system of differential equations exhibits stiffness, with distinct time scales emerging in the solution dynamics. Numerical experiments demonstrate that the NSFD approach provides a stable and reliable discrete-time representation over a wide range of time steps, remaining robust even in cases where classical Runge–Kutta methods fail, such as in the model incorporating horizontal gene transmission. We additionally note that NSFD schemes applied to logistic-type equations present greater challenges in preserving and proving qualitative properties such as nonnegativity, boundedness, and stability, compared to their application in classical epidemic models. This may be due to the intrinsic nonlinearity of logistic dynamics, which can lead to discrete-time models where these properties cannot be directly inferred from the continuous-time counterparts.

CRedit authorship contribution statement

Asier Ibeas: Writing – original draft, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Nakul Chitnis:** Writing – review & editing, Supervision.

AI use declaration

ChatGPT Turbo 4 was used to perform grammatical and stylistic correction of the English in this article and to generate $\text{\LaTeX}$ code for tables and equations. Also, in addition to ChatGPT, Gemini 2.5 Pro and Perplexity were used to manipulate the algebraic expressions that appear in the proof of Theorem 4.6. These expressions were then checked out by a computer algebra system. The authors retain full responsibility for the content of this manuscript.

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