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B. Zubik-Kowal
Boise State University

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Solutions for the cell cycle in cell lines derived from human tumors

B. ZUBIK–KOWAL*

Department of Mathematics, Boise State University, 1910 Boise University Drive, Boise, Idaho 83725, USA

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The goal of the paper is to compute efficiently solutions for model equations that have the potential to describe the growth of human tumor cells and their responses to radiotherapy or chemotherapy. The mathematical model involves four unknown functions of two independent variables: the time variable t and dimensionless relative DNA content x. The unknown functions can be thought of as the number density of cells and are solutions of a system of four partial differential equations. We construct solutions of the system, which allow us to observe the number density of cells for different t and x values. We present results of our experiments which simulate population kinetics of human cancer cells *in vitro*. Our results show a correspondence between predicted and experimental data.

Keywords: Human tumor cells; Cell cycle dynamics; Mathematical model; Population kinetics of human cancer cells *in vitro*

2000 Mathematics Subject Classification codes: 92C50; 65N22

1. Introduction

The cancer cell division cycle can be divided into four distinct phases, namely the G_1-phase, DNA synthesis or S-phase, G_2-phase and mitosis or M-phase; see figure 1 of Ref. [1], which expresses the accumulation of cells in each of the phases and the movement of cells between them. For earlier studies on cell cycle dynamics, see Refs. [2–6]. Many mathematical models describing the behavior of cell populations have been developed in Refs. [1,7–18]. The goal of this paper is the analysis of human cell cycle dynamics, using the model of Ref. [1] and observing the G_1, S, G_2, M-phases.

The transitions between the G_1, S, G_2, M-phases are controlled by stochastic processes. The mathematical model, which is developed in Ref. [1], describes these phases and the transition rates between them. The model equations of Ref. [1] are:

$$\begin{cases} \frac{\partial G_1(x,t)}{\partial t} = 4bM(2x,t) - (k_1 + \mu_{G_1})G_1(x,t), \\ \frac{\partial S(x,t)}{\partial t} = D\frac{\partial^2 S(x,t)}{\partial x^2} - \mu_S S(x,t) - g\frac{\partial S(x,t)}{\partial x} + k_1 G_1(x,t) - I(x,t;T_S), \\ \frac{\partial G_2(x,t)}{\partial t} = I(x,t;T_S) - (k_2 + \mu_{G_2})G_2(x,t), \\ \frac{\partial M(x,t)}{\partial t} = k_2 G_2(x,t) - bM(x,t) - \mu_M M(x,t). \end{cases} \tag{1}$$

*Email: zubik@math.boisestate.edu

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Here, $t \geq 0$ is time (measured in hours) and x is the dimensionless relative DNA content. The dependent variables, $G_1(x,t)$, $S(x,t)$, $G_2(x,t)$ and $M(x,t)$ can each be thought of as the number density of cells. For the dispersion term $D(\partial^2 S(x,t)/\partial x^2)$, we refer the reader to Ref. [1], section 1. The term $I(x,t;T_S)$ is given by

$$\begin{cases} I(x,t;T_S) = \int_0^\infty k_1 G_1(y, t-T_S)\gamma(T_S,x,y)\,\mathrm{d}y, & t \geq T_S, \\ I(x,t;T_S) = 0, & t < T_S, \end{cases} \tag{2}$$

where $\gamma(T_S,x,y)$ is a given weight function and T_S is a constant representing the time in the S-phase, see Ref. [1].

The parameters μ_{G_1}, μ_S, μ_{G_2} and μ_M are the death rates in G_1, S, G_2 and M-phases, respectively. The parameters k_1 and k_2 are the transition probabilities of cells from G_1 to S-phase and from G_2 to M-phase, respectively; b is the division rate; D is the dispersion coefficient; and g is the average growth rate of DNA in the S-phase. In this paper, we consider constant parameters, like in Ref. [1], but they all may be functions of either x or t, or both of these variables.

The system (1) is incomplete and should be supplemented with initial and boundary conditions. These side conditions, which are chosen according to experimental evidence, take the form

$$\begin{aligned} G_1(x,0) &= \frac{a_0}{\sqrt{2\pi\theta_0^2}} \exp\left(-\frac{(x-1)^2}{2\theta_0^2}\right), \quad 0 < x < \infty, \\ S(x,0) &= 0, \;\; G_2(x,0) = 0, \;\; M(x,0), \quad 0 < x < \infty, \end{aligned} \tag{3}$$

$$D\frac{\partial S(0,t)}{\partial x} - gS(0,t) = 0, \quad t > 0. \tag{4}$$

Here, a_0 is the total number of cells in G_1-phase at time $t = 0$ and the average DNA content is 1.

The goal of this paper is to compute quickly the dependent variables $G_1(x,t)$, $S(x,t)$, $G_2(x,t)$ and $M(x,t)$ at arbitrary values of x and t. When discretizing system (1) with respect to the variable x, one arrives at a large system of differential equations. Then, the large system needs to be integrated in time t. When using explicit time integrators for equation (1), we have to deal with stability restrictions, which depress the time step-size Δt. The explicit methods are straightforward in implementation, but they need depression of the time step-size to avoid instabilities. However, small step-sizes Δt mean very intensive computations. Unfortunately, since the G_1, S, G_2 and M-phases need to be controlled over long time intervals, integrating model (1) in small step-sizes Δt leads to serious problems with the computational time. Therefore, model (1) needs unconditionally stable implicit time integrators so that no restrictions are imposed on the time step-size Δt. Using such methods allows the choice of Δt only according to accuracy needs and without fulfilling any stability conditions.

Although, using unconditionally stable implicit time integrators has the advantage of using arbitrary time steps Δt, they need additional computations because of their implicitness, which produces additional systems of algebraic equations. Moreover, these additional algebraic systems need to be solved step by step at each time grid over the whole interval of

time integration. This increases the computational time especially for long time intervals. Therefore, we propose a different approach.

In this paper, we use implicit time integrators for equation (1) and take the advantage of their good stability properties. However, since implicit methods require the extra cost of solving algebraic systems per each time step, our goal is to change semi-discrete systems for equation (1) into simple triangular systems of differential equations. Since triangular systems of differential equations can be solved by implicit integrators in a straightforward way before their actual implementation, our method does not need any algebraic system to be solved in any time step.

To have simple triangular systems of differential equations for (1), we construct iterations (section 2), which differ from classical iterations as their successive iterates are functions of time instead of sets of discrete unknowns. The convergence of the iterations is studied in section 3. The triangular form of the newly-constructed differential systems for equation (1) allows the use of the advantages of the implicit integrators without dealing with their disadvantages. This saves the computational time for equation (1), which gives easy access to the solution curves for the G_1, S, G_2, M-phases.

In section 4, we compute the dependent variables $G_1(x,t)$, $S(x,t)$, $G_2(x,t)$ and $M(x,t)$ using our iterative technique and compare them with the experimental data, which are presented in Ref. [1]. The data correspond to the population kinetics of human cancer cells *in vitro*. Our computed approximations for $G_1(x,t)$, $S(x,t)$, $G_2(x,t)$ and $M(x,t)$ resolve the experimental data. A good correspondence between the predicted and the experimental data is confirmed by our solutions.

2. Solving the model problem

To compute $S(x,t)$, the DNA synthesis or S-phase, we first discretize the second equation of (1) in the variable x. We apply the κ-scheme of Ref. [19] for the advection part and the central finite difference operator for the diffusive part of the second equation in system (1). This results in the following system of differential equations:

$$\begin{cases} \frac{\mathrm{d}G_1(t)}{\mathrm{d}t} = 4bM_2(t) - (k_1 + \mu_{G_1})G_1(t), \\ \frac{\mathrm{d}S(t)}{\mathrm{d}t} = AS(t) - \mu_S S(t) + R(t), \\ \frac{\mathrm{d}G_2(t)}{\mathrm{d}t} = I(t;T_S) - (k_2 + \mu_{G_2})G_2(t) \\ \frac{\mathrm{d}M(t)}{\mathrm{d}t} = k_2 G_2(t) - (b + \mu_M)M(t) \end{cases} \tag{5}$$

with the unknown vectors:

$$S(t) = \begin{bmatrix} S_1(t) \\ \cdots \\ S_i(t) \\ \cdots \\ S_n(t) \end{bmatrix}, \quad G_l(t) = \begin{bmatrix} G_1^{(l)}(t) \\ \cdots \\ G_i^{(l)}(t) \\ \cdots \\ G_n^{(l)}(t) \end{bmatrix}, \quad M(t) = \begin{bmatrix} M_1(t) \\ \cdots \\ M_i(t) \\ \cdots \\ M_n(t) \end{bmatrix}, \quad M_2(t) = \begin{bmatrix} M_2(t) \\ \cdots \\ M_{2i}(t) \\ \cdots \\ M_{2n}(t) \end{bmatrix},$$

for $l = 1, 2$, $i = 1, \ldots, n$ and $t \geq 0$. Here, $S_i(t)$, $G_i^{(l)}(t)$, $M_i(t)$ and $M_{2i}(t)$ are approximations to $S(x_i, t)$, $G_l(x_i, t)$, $M(x_i, t)$, $M(x_{2i}, t)$, respectively. The approximations are computed at the grid points $x_i = ih$, which are determined by $h > 0$, the parameter of the finite-difference discretization in x. Moreover, A is the n by n matrix defined by

$$A = \begin{bmatrix} p_3 & p_4 & 0 & 0 & 0 & \ldots & 0 & 0 & 0 & 0 \\ p_2 & p_3 & p_4 & 0 & 0 & \ldots & 0 & 0 & 0 & 0 \\ p_1 & p_2 & p_3 & p_4 & 0 & \ldots & 0 & 0 & 0 & 0 \\ 0 & p_1 & p_2 & p_3 & p_4 & \ldots & 0 & 0 & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \ldots & \vdots & \vdots & \vdots & \vdots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \ldots & \vdots & \vdots & \vdots & \vdots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \ldots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & 0 & 0 & \ldots & p_1 & p_2 & p_3 & p_4 \\ 0 & 0 & 0 & 0 & 0 & \ldots & 0 & p_1 & p_2 & p_3 \end{bmatrix} \tag{6}$$

with

$$p_1 = \frac{-g(1-\kappa)}{4h}, \quad p_2 = \frac{g(5-3\kappa)}{4h} + \frac{D}{h^2}, \quad p_3 = \frac{-g(3-3\kappa)}{4h} - \frac{2D}{h^2}, \\ p_4 = \frac{-g(1+\kappa)}{4h} + \frac{D}{h^2}. \tag{7}$$

The term $I(t; T_S)$, for $t > 0$, is a column vector of n components $I_i(t; T_S)$, $i = 1, \ldots, n$, approximating the values of $I(x_i, t; T_S)$ defined by equation (2) at the grid points x_i. To deal with the infinite domain of the integration in equation (2), we investigate the kernel $\gamma(T_S, x, y)$. An important property of $\gamma(T_S, x, y)$ is that it has significant values for computing the product $G_1(x, t - T_S)\gamma(T_S, x, y)$ (within the machine precision) only over a short y-interval whose width is 1. Therefore, we apply the composite trapezoidal rule over this interval to compute the approximations $I_i(t; T_S)$. These approximations are also used to compute the term $R(t)$, for $t > 0$, which is a column vector of n components defined by the inhomogeneous term $k_1 G_1(x, t) - I(x, t; T_S)$ from the second equation in (1) and the zero flux boundary condition (4). System (5) is supplemented by initial conditions determined by equation (3).

The functions $S(t)$, $G_l(t)$, $M(t)$ and $M_2(t)$ give approximations to the solutions of the problems (1)–(4), only at the grid points x_i for the variable x. These approximations are more accurate for smaller step sizes h. However, we also need to compute approximations for $S(t)$, $G_l(t)$, $M(t)$ and $M_2(t)$ at some grid points for the variable t. Therefore, the system (5) needs to be integrated in t by using some time step Δt. Applying explicit methods to integrate equation (5) requires stability conditions, which depress the size of Δt to avoid instabilities. Moreover, the smaller h values we take (for improving x-discretization), the more restrictive stability conditions we are forced to deal with.

To avoid this problem, we introduce the sequence of successive iterates $S^k(t)$, for $k = 0, 1, \ldots$. The iterates are functions of t and converge to the solution $S(t)$, that is

$$\lim_{k\to\infty} S^k(t) = S(t). \tag{8}$$

Our goal is to construct an iteration process in such a way that it starts from an arbitrary function $S^0(t)$, then converges fast, and the iterates $S^k(t)$ are computed by solving a new simple triangular system of differential equations, which performs the same x-discretization process as system (5) does. Since the newly constructed differential system has a triangular form, applying unconditionally stable implicit methods (which do not need any depression of Δt) is as simple as applying explicit methods.

Our computational process for equations (1)–(4) is composed of two steps:

Step 1: we first compute approximations for the functions $G_2(t)$, $M(t)$, $G_1(t)$ by integrating the system

$$\begin{cases} \frac{\mathrm{d}G_2(t)}{\mathrm{d}t} = I(t; T_S) - (k_2 + \mu_{G_2})G_2(t), \\ \frac{\mathrm{d}M(t)}{\mathrm{d}t} = k_2 G_2(t) - (b + \mu_M)M(t), \\ \frac{\mathrm{d}G_1(t)}{\mathrm{d}t} = 4bM_2(t) - (k_1 + \mu_{G_1})G_1(t), \end{cases} \tag{9}$$

sequentially from up to down. Application of implicit methods to equation (9) is straightforward as the function $I(t; T_S)$ has the retarded time argument $t - T_S$ and it can be computed by using the values of $G_1(t - T_S)$, which are known from either the initial condition (3) or from the values computed for previous temporal grid points.

Step 2: we use the values of $R(t)$, obtained from Step 1, and compute the successive iterates $S^k(t)$ from the scheme

$$\frac{\mathrm{d}S^k(t)}{\mathrm{d}t} = A_1 S^k(t) + A_2 S^{k-1}(t) - \mu_S S^k(t) + R(t). \tag{10}$$

for $k = 1, 2, \ldots$. The iteration process (10) is started from an arbitrary starting function $S^0(t)$. Here, $A = A_1 + A_2$ and

$$A_1 = \begin{bmatrix} p_3 & 0 & 0 & 0 & 0 & \ldots & 0 & 0 & 0 & 0 \\ p_2 & p_3 & 0 & 0 & 0 & \ldots & 0 & 0 & 0 & 0 \\ p_1 & p_2 & p_3 & 0 & 0 & \ldots & 0 & 0 & 0 & 0 \\ 0 & p_1 & p_2 & p_3 & 0 & \ldots & 0 & 0 & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \ldots & \vdots & \vdots & \vdots & \vdots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \ldots & \vdots & \vdots & \vdots & \vdots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \ldots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & 0 & 0 & \ldots & p_1 & p_2 & p_3 & 0 \\ 0 & 0 & 0 & 0 & 0 & \ldots & 0 & p_1 & p_2 & p_3 \end{bmatrix},$$

$$A_2 = \begin{bmatrix} 0 & p_4 & 0 & 0 & 0 & \dots & 0 & 0 & 0 & 0 \\ 0 & 0 & p_4 & 0 & 0 & \dots & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & p_4 & 0 & \dots & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & p_4 & \dots & 0 & 0 & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \dots & \vdots & \vdots & \vdots & \vdots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \dots & \vdots & \vdots & \vdots & \vdots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \dots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & 0 & 0 & \dots & 0 & 0 & 0 & p_4 \\ 0 & 0 & 0 & 0 & 0 & \dots & 0 & 0 & 0 & 0 \end{bmatrix}.$$

Since equation (10) is linear, equation (8) is satisfied. Moreover, since the matrix A_1 is triangular, we can solve system (10) sequentially from up to down by implicit methods and no algebraic system needs to be solved in any time step. Note that application of implicit methods to system (5) needs an algebraic system per each time step to be solved, which significantly increases the computational cost due to the large number of temporal grid points especially for long time intervals. There is no such cost if equation (5) is changed into equations (9) and (10) and implicit methods are applied to equations (9) and (10) instead of to equation (5).

To find fast iterates $S^k(t)$ for equations (1)–(4), in the next section, we analyze how the convergence equation (8) depends on the coefficients of the system (10).

3. Analysis of the sequence $S^k(t)$

In this section, we analyze the influence of the coefficients from equation (10) on the rate of convergence in equation (8). We show that the convergence of the sequence $S^k(t)$ is faster if the previous iterates $S^{k-1}(t)$ are multiplied by coefficients closer to zero than if $S^{k-1}(t)$ are multiplied by coefficients which are further from zero. We then use this analysis in section 4 to apply such coefficients p_4, of the matrix A_2, for which the iterates $S^k(t)$ converge in one iteration.

Theorem 3.1. Let $r \neq 0$ be a real number, M_1, M_2, N be n by n real matrices and $y, z : [-T_S, T] \to R^n$ be solutions to the initial value problems:

$$\begin{cases} \frac{\mathrm{d}}{\mathrm{d}t} y(t) = (M_1 + M_2) y(t) + N y(t - T_S) + p(t), \\ y(t) = y_0(t), \quad -T_S \leq t \leq 0, \text{ and} \end{cases}$$

$$\begin{cases} \frac{\mathrm{d}}{\mathrm{d}t} z(t) = (M_1 + rM_2) z(t) + rN z(t - T_S) + q(t), \\ z(t) = z_0(t), \quad -T_S \leq t \leq 0, \end{cases}$$

respectively. Here, p, q:$[0,T] \to R^n$ and y_0, z_0:$[-T_S, 0] \to R^n$. Let y^k and z^k, $k = 1, 2, \ldots$, be the successive iterates defined by the schemes:

$$\begin{cases} \frac{\mathrm{d}}{\mathrm{d}t} y^k(t) = M_1 y^k(t) + M_2 y^{k-1}(t) + N y^{k-1}(t - T_S) + p(t), & 0 < t \le T, \\ y^k(t) = y_0(t), & -T_S \le t \le 0, \text{and} \end{cases}$$

$$\begin{cases} \frac{\mathrm{d}}{\mathrm{d}t} z^k(t) = M_1 z^k(t) + rM_2 z^{k-1}(t) + rN z^{k-1}(t - T_S) + q(t), & 0 < t \le T, \\ z^k(t) = z_0(t), & -T_S \le t \le 0, \end{cases}$$

respectively. Suppose that the schemes are started with some initial functions y^0 and z^0, respectively, whose initial errors are the same.

Then

$$z^k(t) - z(t) = r^k\big(y^k(t) - y(t)\big),$$

for $t \in [0, T]$.

Proof. Let $e_y^k = y^k - y$ and $e_z^k = z^k - z$ over $[-T_S, T]$. Then

$$\begin{cases} \frac{\mathrm{d}}{\mathrm{d}t} e_y^k(t) = M_1 e_y^k(t) + M_2 e_y^{k-1}(t) + N e_y^{k-1}(t - T_S), & 0 < t \le T, \\ e_y^k(t) = 0, & -T_S \le t \le 0, \end{cases}$$

$$\begin{cases} \frac{\mathrm{d}}{\mathrm{d}t} e_z^k(t) = M_1 e_z^k(t) + rM_2 e_z^{k-1}(t) + rN e_z^{k-1}(t - T_S), & 0 < t \le T, \\ e_z^k(t) = 0, & -T_S \le t \le 0. \end{cases}$$

Let $M^*(t,s) = \exp((t-s)M_1)$. From the above, we have

$$\begin{aligned} e_y^k(t) &= \int_0^t M^*(t,s)\Big[M_2 e_y^{k-1}(s) + N e_y^{k-1}(s - T_S)\Big]\mathrm{d}s, \\ e_z^k(t) &= r\int_0^t M^*(t,s)\big[M_2 e_z^{k-1}(s) + N e_z^{k-1}(s - T_S)\big]\mathrm{d}s. \end{aligned} \tag{11}$$

Since the starting errors are the same, $e_y^0 = e_z^0$, by equation (11), we have $re_y^1 = e_z^1$. From this and from equation (11), by induction, we have $r^k e_y^k = e_z^k$, which finishes the proof. □

The next theorem compares iterative schemes represented by matrices for which all entries differ by the coefficient r.

Theorem 3.2. Let $M = M_1 + M_2$ and N be n by n real matrices, $\|\cdot\|$ be an arbitrary vector norm in R^n and $r \neq 1$. Let y:$[-T_S, T] \to R^n$ and z:$[-T_S/r, T] \to R^n$ be the solutions to the initial value problems:

$$\begin{cases} \frac{\mathrm{d}}{\mathrm{d}t} y(t) = My(t) + Ny(t - T_S) + p(t), \\ y(t) = y_0(t), \quad -T_S \le t \le 0, \end{cases} \qquad \begin{cases} \frac{\mathrm{d}}{\mathrm{d}t} z(t) = rMz(t) + rNz(t - T_S/r) + q(t), \\ z(t) = z_0(t), \quad -T_S/r \le t \le 0, \end{cases}$$

respectively. Here, $p, q : [0, T] \to R^n$, $y_0 : [-T_S, 0] \to R^n$ and $z_0 : [-T_S/r, 0] \to R^n$. Suppose that y^k and z^k, $k = 1, 2, \ldots$, solve the corresponding schemes

$$\begin{cases} \frac{\mathrm{d}}{\mathrm{d}t} y^k(t) = M_1 y^k(t) + M_2 y^{k-1}(t) + N y^{k-1}(t - T_S) + p(t), \quad 0 \le t \le T, \\ y^k(t) = y_0(t), \quad -T_S \le t \le 0, \end{cases}$$

$$\begin{cases} \frac{\mathrm{d}}{\mathrm{d}t} z^k(t) = rM_1 z^k(t) + rM_2 z^{k-1}(t) + rN z^{k-1}(t - T_S/r) + q(t), \quad 0 \le t \le T, \\ z^k(t) = z_0(t), \quad -T_S \le t \le 0, \end{cases}$$

with some starting functions $y^0, z^0 : [0, T] \to R^n$ such that

$$\begin{aligned} y^0(t) - y(t) &= z^0(t/r) - z(t/r), \quad 0 < t \le T, \\ y^0(t) &= y_0(t), \quad z^0(t/r) = z_0(t/r), \quad -T_S \le t \le 0; \end{aligned}$$

that is, both schemes start with the errors which are the same over the intervals $[-T_S, T]$ and $[-T_S/r, T/r]$, respectively.

If $r \ge 1$ then

$$\max_{t \in [0, \bar{t}]} \|y^k(t) - y(t)\| \le \max_{t \in [0, \bar{t}]} \|z^k(t) - z(t)\|, \tag{12}$$

for $k = 0, 1, \ldots$ and $0 \le \bar{t} \le T$. The opposite inequality holds if $r \le 1$.

Proof. Let $e_y^k = y^k - y$ and $e_z^k = z^k - z$ over $[-T_S, T]$. Then

$$\begin{cases} \frac{\mathrm{d}}{\mathrm{d}t} e_y^k(t) = M_1 e_y^k(t) + M_2 e_y^{k-1}(t) + N e_y^{k-1}(t - T_S), \quad 0 < t \le T, \\ e_y^k(t) = 0, \quad -T_S \le t \le 0, \end{cases}$$

$$\begin{cases} \frac{\mathrm{d}}{\mathrm{d}t} e_z^k(t) = rM_1 e_z^k(t) + rM_2 e_z^{k-1}(t) + rN e_z^{k-1}(t - T_S/r), \quad 0 < t \le T, \\ e_z^k(t) = 0, \quad -T_S/r \le t \le 0. \end{cases}$$

Let $\mathrm{e}^k(s) = e_z^k(s/r)$, for $-T_S \le s \le T$ and $k = 0, 1, \ldots$. Then

$$\begin{aligned} \frac{\mathrm{d}}{\mathrm{d}s} \mathrm{e}^k(s) &= \frac{1}{r} \frac{\mathrm{d}}{\mathrm{d}t} e_z^k\left(\frac{s}{r}\right) = M_1 e_z^k\left(\frac{s}{r}\right) + M_2 e_z^{k-1}\left(\frac{s}{r}\right) + N e_z^{k-1}\left(\frac{s - T_S}{r}\right) \\ &= M_1 e^k(s) + M_2 e^{k-1}(s) + N e^{k-1}(s - T_S), \end{aligned}$$

for $0 < s \le T$ and

$$e^k(s) = 0,$$

for $-T_S \le s \le 0$. Since $e_y^0(t) = e_z^0(t/r)$ for $-T_S \le t \le T$, $e_y^0(t) = e^0(t)$ for $-T_S \le t \le T$. Therefore,

$$\begin{cases} \frac{\mathrm{d}}{\mathrm{d}t} e^1(t) = M_1 e^1(t) + M_2 e^0(t) + N e^0(t - T_S), \quad 0 < t \le T, \\ e^1(t) = 0, \quad -T_S \le t \le 0, \end{cases}$$

and e_y^1 and e^1 solve the same initial value problem on $[-T_S, T]$. By uniqueness, $e_y^1(t) = e^1(t)$ for $-T_S \le t \le T$. It can be shown by induction that $e_y^k(t) = e^k(t)$ for $-T_S \le t \le T$ and $k = 0, 1, 2, \ldots$. We now take an arbitrary $0 \le \bar{t} \le T$ and have

$$\max_{t\in[0,\bar{t}]} \left\| e_y^k(t) \right\| = \max_{t\in[0,\bar{t}]} \left\| e^k(t) \right\| \le \max_{s\in[0,r\bar{t}]} \|e^k(s)\| = \max_{s\in[0,r\bar{t}]} \left\| e_z^k(s/r) \right\| = \max_{t\in[0,\bar{t}]} \left\| e_z^k(t) \right\|.$$

The proof of the opposite inequality is similar. □

Assuming that N is the zero matrix and the present iterates are multiplied by the main diagonal entries of M, we can derive an exact formula for the error $y^k(t) - y(t)$. Note that iterative schemes, which iterate only along the main diagonal entries, allow using parallel computing environments, as all equations of the iterative schemes can be solved separately at the same time. This saves the computational time especially when dealing with systems which contain large numbers of equations.

Theorem 3.3. Let $m \in R$, $M_1 = \operatorname{diag}\{m\}$ and $M = M_1 + M_2$ be n by n real matrices. Let $y : [-T_S, T] \to R^n$ be the solution to the initial value problem:

$$\begin{cases} \frac{\mathrm{d}}{\mathrm{d}t} y(t) = My(t) + p(t), \\ y(t) = y_0(t), \quad -T_S \le t \le 0. \end{cases}$$

Here, $p{:}[0, T] \to R^n$ and $y_0{:}[-T_S, 0] \to R^n$. Let y^k be the successive iterates defined by the scheme:

$$\begin{cases} \frac{\mathrm{d}}{\mathrm{d}t} y^k(t) = M_1 y^k(t) + M_2 y^{k-1}(t) + p(t), \quad 0 < t \le T, \\ y^k(t) = y_0(t), \quad -T_S \le t \le 0, \quad k = 1, 2, \ldots \end{cases}$$

started with an arbitrary function y^0.

Then smaller values of m make the error $e^k(t) = y^k(t) - y(t)$ closer to zero and

$$e^{k+1}(t) = M_2^{k+1} e^0(\xi^k) \frac{1}{k!} \int_0^t s^k \exp(ms)\, \mathrm{d}s$$

with some $\xi^k \in [0, t]$, for $k = 0, 1, \ldots$.

Proof. It can be proved that

$$e^{k+1}(t) = \int_0^t \int_0^{t_2} \ldots \int_0^{t_k} \int_0^{t_{k+1}} \exp(m(t - t_{k+2})) M_2^{k+1} e^0(t_{k+2})\, \mathrm{d}t_{k+2}\, \mathrm{d}t_{k+1} \ldots \mathrm{d}t_3\, \mathrm{d}t_2.$$

By the mean value theorem, we have

$$\begin{aligned} e^{k+1}(t) &= M_2^{k+1} e^0(\xi^k) \int_0^t \int_0^{t_2} \ldots \int_0^{t_k} \int_0^{t_{k+1}} \exp(m(t - t_{k+2}))\, \mathrm{d}t_{k+2}\, \mathrm{d}t_{k+1} \ldots \mathrm{d}t_3\, \mathrm{d}t_2 \\ &= M_2^{k+1} e^0(\xi^k) \frac{1}{k!} \int_0^t s^k \exp(ms)\, \mathrm{d}s. \end{aligned}$$

Therefore, the errors $e^k(t)$ approach zero with decreasing m, which finishes the proof of the theorem. □

The equations in (9) and (10) create a family of h-dependent problems which change with the changing parameter h. Theorems 3.1, 3.2 and 3.3 describe strategies for the selection of such parameters h which result in fast convergence in equation (8). We use the strategies of section 4 when computing solutions for problems (1)–(4).

4. Computing solutions to the model problem

To compute solutions for problems (1)–(4), we first compute G_2, M and G_1 from equation (9) and then we compute the successive iterates S^k from equation (10). To integrate equations (9) and (10) in time, we apply the backward differentiation formula of order 3 (BDF3) with $\Delta t = 0.1$. Although BDF methods are implicit, their application to equations (9) and (10) is straightforward due to the fact that equations (9) and (10) are written in triangular forms, which allows to integrate them sequentially from up to down and no algebraic system needs to be solved in any time step.

For the iteration process (10), we aim to find such values of the entries of the matrix A_2 which make the sequence $S^k(t)$ fastly convergent to $S(t)$. We use Theorem 3, from which we conclude that smaller values of $|p_4|$ result in faster convergence in equation (8). We take $\kappa = 1/3$ in equation (7) and as in Ref. [1], we take the interval $[0, 2.5]$ for the domain of the variable x. We use $n+2$ equidistant grid points x_i and investigate the values of the coefficients p_i defined by equation (7). Three values of n, their corresponding numbers of iterations k and approximations to their corresponding values of h and p_i, are listed in table 1. The successive iterates $S^k(t)$ computed with the values, which are listed in table 1, are presented in figures 1 and 2.

Figures 1 and 2 show a correspondence between predicted and experimental data. The graphs of figure 1 correspond to the experimental data presented in Ref. [1, graph (b) of figure 4]. The graphs of figure 2 correspond to the experimental data presented in Ref. [1, graph (b) of figure 5]. In all of the graphs from figures 1 and 2, the solutions G_1, S, G_2 and M are presented by solid, dashed, dash-dotted and dotted lines, respectively. The curves by the dashed lines are obtained with $k \geq 8$ in the (a) graphs, with $k \geq 4$ in the (b) graphs, and with $k \geq 1$ in the (c) graphs of both figures. Further iterations (with k larger than 8, 4 and 1, respectively) provide the same curves as the curves obtained with $k = 8$, $k = 4$ and $k = 1$, respectively.

For graphs (a) and (b) of figures 1 and 2, the curves which were obtained with $k = 1$ are different to the curves which were obtained with $k \geq 8$ in (a) and with $k \geq 4$ in (b). Graphs (a) of figures 1 and 2 were prepared with $n = 950$. For this choice, iterations with $k = 1, 2, \ldots, 7$ give curves different to the curve obtained with $k \geq 8$. Graphs (b) were prepared with $n = 945$. For this choice, iterations with $k = 1, 2, 3$ give curves different to the curve obtained with $k \geq 4$. However, the same curves and regions are obtained with all $k \geq 1$ for

Table 1. Selection of the number n.

n	Iterations	h	p_4	p_3	p_2	p_1
940	1	2.6567×10^{-3}	3×10^{-3}	-50	57	-7
945	4	2.6427×10^{-3}	8×10^{-2}	-50	57	-7
950	8	2.6288×10^{-3}	2×10^{-1}	-50	57	-7

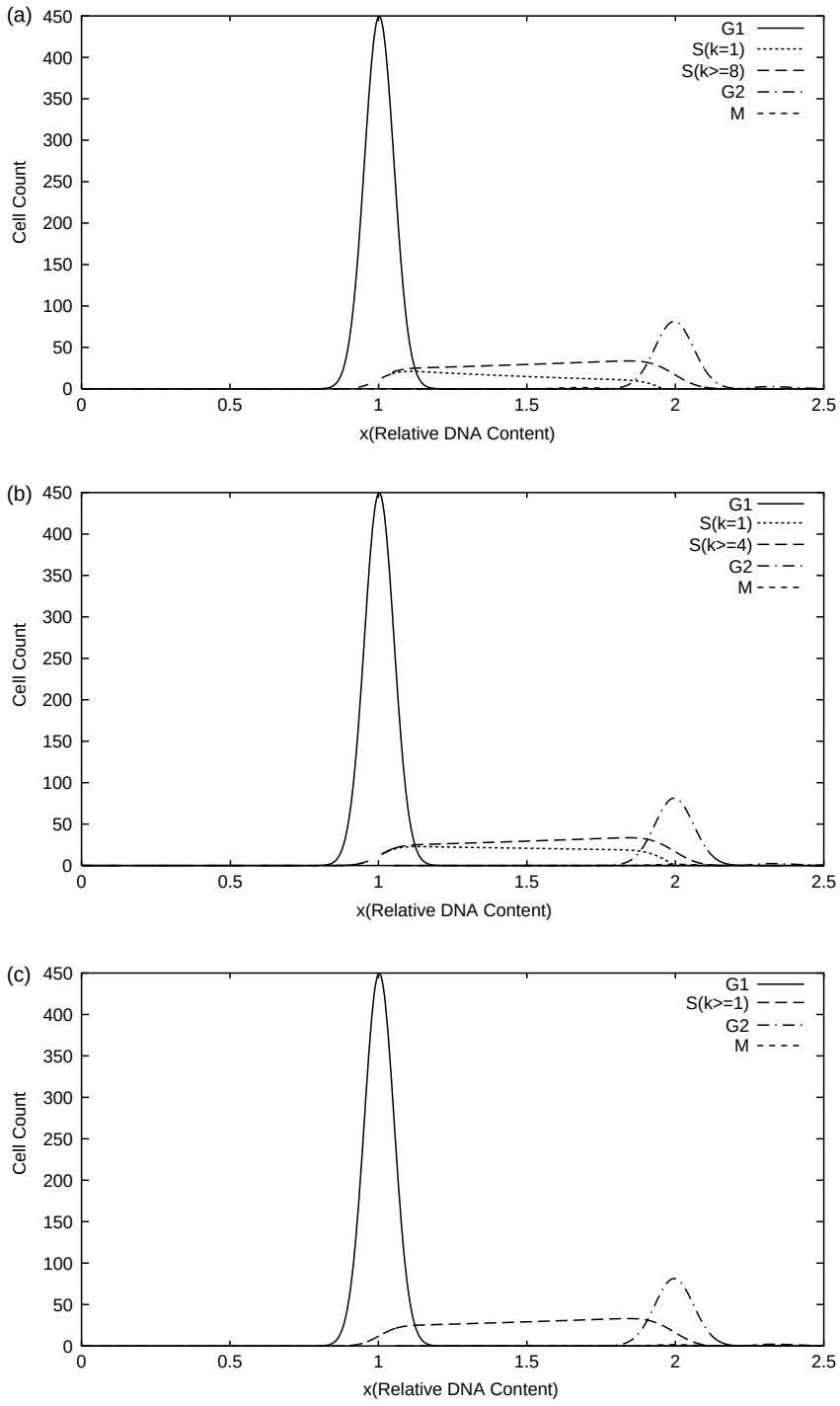

Figure 1. Approximations to $G_1(x,t)$ (solid), $S(x,t)$, the DNA synthesis (dashed), $G_2(x,t)$ (dash-dotted) and $M(x,t)$ (dotted) as functions of x, at $t = 12$ in 8 iterations with $n = 950$ (a), 4 iterations with $n = 945$ (b), and 1 iteration with $n = 940$ (c).

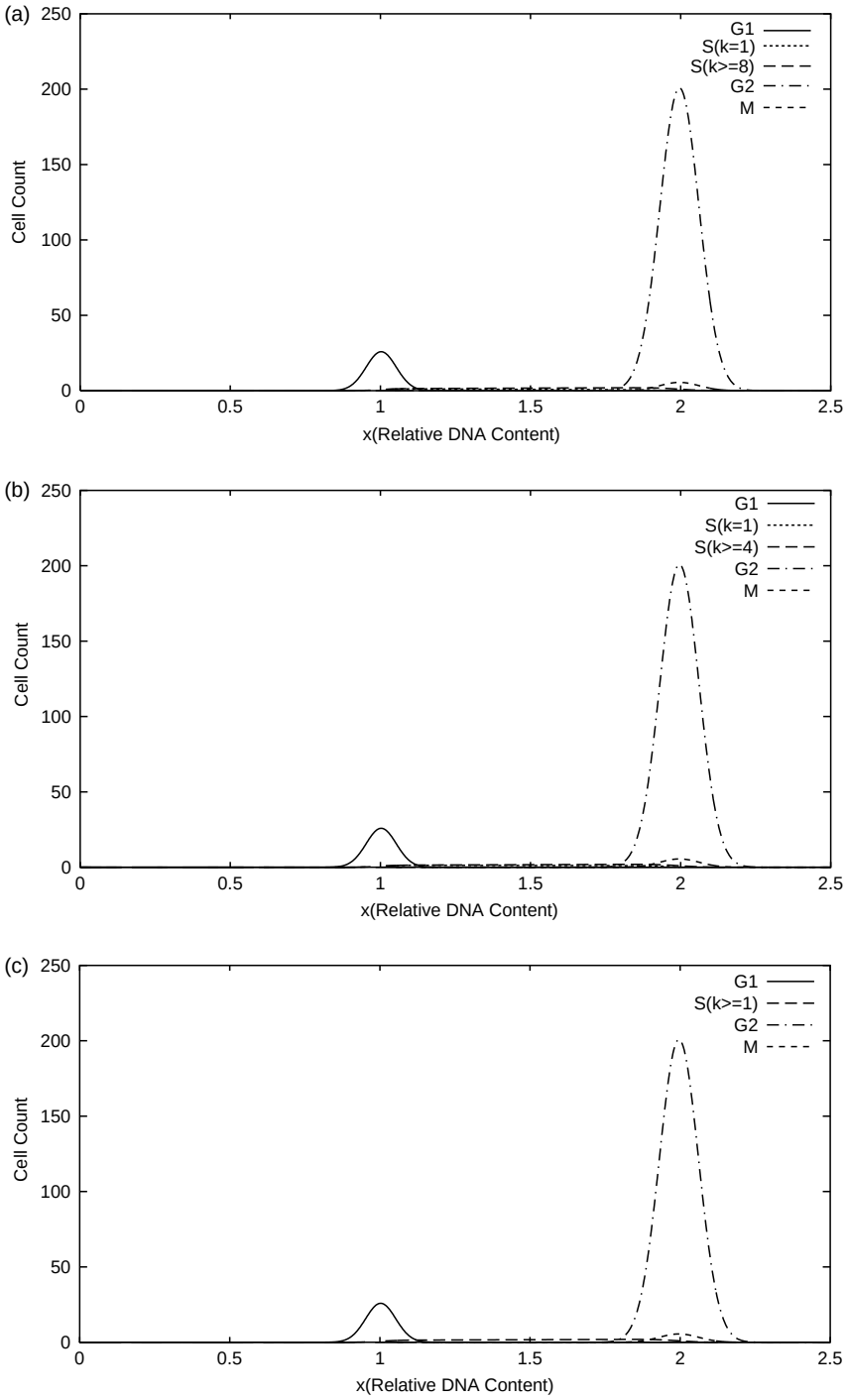

Figure 2. Approximations to $G_1(x,t)$ (solid), $S(x,t)$, the DNA synthesis (dashed), $G_2(x,t)$ (dash-dotted) and $M(x,t)$ (dotted) as functions of x, at $t = 72$ in 8 iterations with $n = 950$ (a), 4 iterations with $n = 945$ (b), and 1 iteration with $n = 940$ (c).

graphs (c) of figures 1 and 2, which shows that the iterations used for graphs (c) are faster than the iterations used for graphs (a) and (b).

Note that the numbers of iterations listed in the second column of table 1 increase and the values of h listed in the third column decrease. These relations are explained by Theorem 3.2 in the following way. Since the matrix A defined by equation (6) can be thought of as $h^{-2}\tilde{A}$, with $\tilde{A}$ having nearly constant entries (when h is small), we can apply Theorem 3.2 with $r = h^{-2}$ and N being the zero matrix. Using Theorem 3.2, we can conclude that smaller values of r (larger h) result in faster iterations (smaller k). Table 1 confirms this conclusion. Moreover, the same conclusion can be derived from equation (12) which shows that for fixed k, the errors of the successive iterates are decreasing with decreasing r, that is, with increasing h.

5. Concluding remarks

We applied iterative techniques to the mathematical model of Ref. [1] and computed densities of cells as functions of relative DNA content x and time t. The iterative techniques, which we studied in this paper, saved the computational time because of three reasons. Firstly, the iterative schemes allowed for straightforward integration in time of the finite difference semi-discrete systems by implicit methods, which are not demanding with respect to stability. Secondly, since we applied iterative schemes, no algebraic system needed to be solved in any time step. Thirdly, we computed the numerical solution to the mathematical model of Ref. [1] in only one iteration.

Because of the computational savings, the iterative schemes are useful for the optimisation procedures applied in Refs. [1,20]. The procedures allow the discovery of the coefficients b, D, g, μ_{G_1}, μ_{G_2}, μ_S, μ_M, k_1 and k_2 needed for the models of Refs. [1,20]. The solutions presented in Ref. [1] and in this paper were computed with $\mu_{G_1} = \mu_{G_2} = \mu_S = \mu_M = 0$. However, since the iterative techniques improve the computational time, introducing the nonzero coefficients μ_{G_1}, μ_{G_2}, μ_S, μ_M together with the techniques for the optimization procedures would result in additional savings in the computational time, which is needed for finding the least square errors between the experimental DNA distributions used in Refs. [1,20] and total DNA distributions predicted by the models. Savings in computational time are also important when solving the models over long time intervals.

Future work will address the model of Ref. [20] with a new A-phase, in which DNA is degraded with time. The model of Ref. [20] is composed of five partial differential equations and is an extension of the model of Ref. [1]. The model shows the action of an anticancer drug used for the treatment of cancer. We will also address the related models of Refs. [21–23] for modeling cancer cell populations.

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