Iterative operator splitting method for capillary formation model in tumor angiogenesis problem: Analysis and application

Nurcan Gücüyenen* and Gamze Tanoğlu

Izmir Institute of Technology, Department of Mathematics, Gulbahce Campus, Urla, Izmir, 35430

Introduction

Iterative operator splitting method is used to solve numerically the mathematical model for capillary formation in tumor angiogenesis problem. The method is based on first splitting the complex problem into simpler sub-problems. Then each sub-equation is combined with iterative schemes. The algorithms are obtained by applying the proposed method to the given model problem. The explicit local error bounds are derived to show consistency.We also explained the stability by constructing the stability functions. The obtained numerical results show that iterative splitting method provides high accuracy and efficiency with respect to other classical methods in literature.

Capillary formation model in tumor angiogenesis problem

The mathematical model for capillary formation in tumor angiogenesis is originally presented in [1]. In this model , Levine [1] used the cell transport (chemotactic) equations and developed the model by using the theory of reinforced random walk derived by David (see [2]) and this model was recently used by Othmer and Stevens (see [3]) to model fruiting bodies.
In this model, Levine [1] introduces the following initial boundary value problem and this problem describes the endothelial cell movement in capillary.

$$\frac{\partial u}{\partial t} = D\frac{\partial}{\partial x}(u\frac{\partial}{\partial x}(\ln\frac{u}{f(x)})), \quad x \in (0,1), \quad t \in (0,T] \tag{1}$$

Initial condition is given by

$$u(x,0) = 1, \quad x \in (0,1), \tag{2}$$

and boundary conditions are given by

$$Du\frac{\partial}{\partial x}(\ln\frac{u}{f(x)})\mid_{(0,t)} = 0, \quad t \in [0,T], \tag{3}$$

$$Du\frac{\partial}{\partial x}(\ln\frac{u}{f(x)})\mid_{(1,t)} = 0, \quad t \in [0,T], \tag{4}$$

where $f(x)$ is the so-called transition probability function and given by

$$f(x) = (\frac{a + A_1x^k(1-x)^k}{b + A_1x^k(1-x)^k})^{\alpha_1}(\frac{c + 1 - A_2x^k(1-x)^k}{d + 1 - A_2x^k(1-x)^k})^{\alpha_2} \tag{5}$$

and $u(x,t)$ is the concentration of Endothelial Cells, D is the cell diffusion constant and a, b, c, d, A_1, A_2, k, α_1, α_2 are some arbitrary constants.

Iterative operator splitting method

Consider the abstract Cauchy problem

$$u'(t) = (A+B)u(t), \quad t \in [0,T] \tag{6}$$

$$u(0) = u_0 \tag{7}$$

where A and B are bounded linear operators and u_0 is initial condition.
The method is based on iteration by fixing the splitting discretization step size τ on time interval $[t^n, t^{n+1}]$.
The following algorithms are then solved consecutively for $i = 1, 3, \ldots, 2m+1$

$$u_i'(t) = Au_i(t) + Bu_{i-1}(t) \quad \text{with} \quad u_i(t^n) = u^n \tag{8}$$

$$u_{i+1}'(t) = Au_i(t) + Bu_{i+1}(t) \quad \text{with} \quad u_{i+1}(t^n) = u^n \tag{9}$$

where u^n is the known split approximation at time level $t = t^n$ and $u_0 \equiv 0$ is our initial guess.

The split approximation at the time-level $t = t^{n+1}$ is defined as $u^{n+1} = u_{2m+2}(t^n)$, see [6].

Application of Iterative splitting to mathematical model

Consider equation (1), by setting $F(x) = \frac{f'(x)}{f(x)}$ we turn it into simple form

$$u_t = D(u_{xx} - u_xF - F_xu) \tag{10}$$

and after discretizing the space, initial condition becomes

$$u_m = 1, \quad 0 \le m \le N, \tag{11}$$

and boundary conditions are

$$D(\frac{\partial u_0}{\partial x} - u_0F_0) = 0, \quad \text{for} \quad t > 0, \tag{12}$$

$$D(\frac{\partial u_N}{\partial x} - u_NF_N) = 0, \quad \text{for} \quad t > 0 \tag{13}$$

We split the equation

$$u_t = D(u_{xx} - u_xF - F_xu) \tag{14}$$

as diffusion part

$$u_t = Du_{xx} \tag{15}$$

and as advection-reaction part

$$u_t = -Du_xF - DF_xu. \tag{16}$$

Applying the iterative splitting schemes (8), (9) to model problem (14) then we have

$$u_i' = D(u_i)_{xx} - D((u_{i-1})_xF - F_xu_{i-1}) \tag{17}$$

$$u_{i+1}' = D(u_i)_{xx} - D((u_{i+1})_xF - F_xu_{i+1}) \tag{18}$$

where $i = 1, 3, \ldots, 2m+1$.
We use central difference expansions at each discretiazation points (x_m, t) for u_{xx} and u_x terms and have systems $u_{xx} = A_1u$ and $u_x = B_1u$. We also fix the functions $F(x)$ and $F'(x)$ at each discretization points $m = 0, 1, \ldots, N$ and we use central difference approximation for each $F'(x_m)$.
Redefining equations (17),(18) we have

$$u_i' = Au_i + Bu_{i-1} \tag{19}$$

$$u_{i+1}' = Au_i + Bu_{i+1} \tag{20}$$

where $A = DA_1$, $B = -DF(\underline{x})B_1 - DF'(\underline{x})$. We then solve Eqns. (19) and (20) by using midpoint method on each subinterval $[t^n, t^{n+1}], n = 0, 1, ..N.$
We then solve Eqs. (19), (20) by using midpoint method on each subinterval $[t^n, t^{n+1}]$ where $n = 0, 1, ..M.$ Hence, the algorithms can be read as:

$$u_i^{n+1} = (I - \frac{\tau}{2}A)^{-1}((I + \frac{\tau}{2}A)u_i^n + \frac{\tau}{2}B(u_{i-1}^n + u_{i-1}^{n+1})) \tag{21}$$

$$u_{i+1}^{n+1} = (I - \frac{\tau}{2}B)^{-1}((I + \frac{\tau}{2}B)u_{i+1}^n + \frac{\tau}{2}A(u_i^n + u_i^{n+1})) \tag{22}$$

where τ is time discretzation step. We start iteration with $i = 1$, initial guess $u_0(t) = 0$, initial conditions $u_1(t) = u_0$ and $u_2(t) = u_0$.

Error Bound Theorem

Let A, B $\in \mathcal{L}(X)$ be given linear bounded operators. The cauchy problem is in (6). Then the problem has a unique solution. The error bound of the iteration (8), (9) $i = 1, 3, \ldots, 2m+1$ in terms of the operator norm is given by
for i is **odd**

$$||\epsilon_i|| \le (K_1.||A||)^{\frac{i-1}{2}}.(K_2.||B||)^{\frac{i+1}{2}}.||\epsilon_0||\frac{t^i}{i!} \tag{23}$$

for i is **even**

$$||\epsilon_i|| \le (K_1.||A||)^{\frac{i}{2}}.(K_2.||B||)^{\frac{i}{2}}.||\epsilon_0||\frac{t^i}{i!} \tag{24}$$

where $||\epsilon_0||$ is the difference between the exact solution and initial guess, $||exp(At)|| \le K_1$, $||exp(Bt)|| \le K_2$ for $t \ge 0$.

Stability Analysis via stability function bound

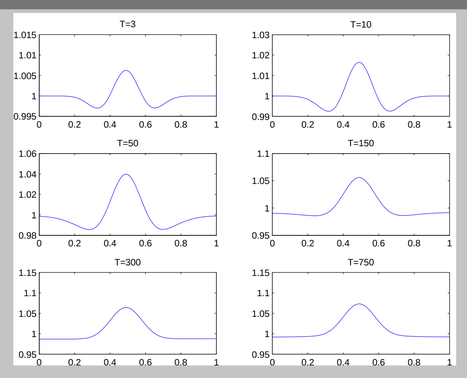
We apply Midpoint rule to the iterative operator splitting methods, then we obtain stable schemes for the linear system with $Z_1 = \tau A$ and $Z_2 = \tau B$ if and only if there exists stable functions $R_i(Z_1, Z_2)$ with:

$$||R_i(Z_1, Z_2)|| \le 1 + K\tau, \qquad \text{for all } Z_1, Z_2 \in X \times X,$$

where K is constant(independent of τ,h), X is a Banach-space, $||\cdot||$ is a matrix norm.

Numerical Results

We present the application of the iterative operator splitting method for the numerical solution of a mathematical model for capillary formation in tumor angiogenesis. For numerical computation we consider the problem (1)-(4) with parameters $D = 0.00025$, $a = 1$, $b = 2$, $c = 10$, $d = 0.1$, $\alpha_1 = \alpha_2 = 1$, $A_1 = 28 \times 10^7$, $A_2 = 0.22 \times 10^9$ and $k = 16$. We write the computer program in Matlab and present our results on graphics which define the concentration of Endothelial Cells at different times. In figure , $u(x,t)$ is plotted for different values of t. It is seen that graphs, in figure, show similar trends as the ones obtained by method of lines in [4] and tau method in [5].



Numerical Results

In Table I and Table II, we compare the errors of different splitting methods and method of lines at times $T = 150$ and $T = 300$. It is shown that iterative splitting method provides very accurate numerical solution for mathematical model in comparison with other classical splitting methods and method of lines.

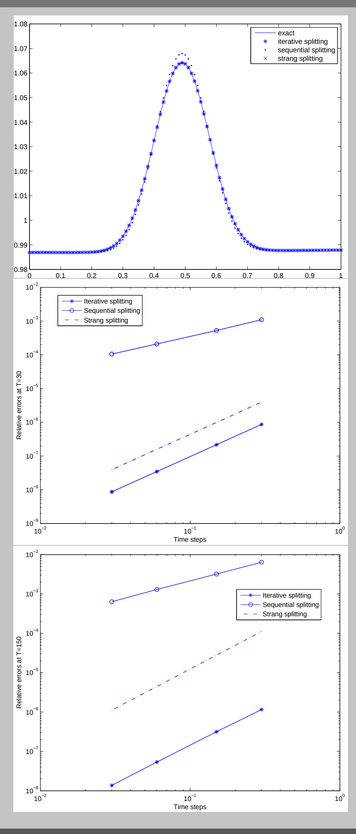
	err_{L_1}	err_{L_2}	$err_{L_{inf}}$
Iterative splitting	4.7701e-007	5.3524e-008	9.4143e-009
Sequential splitting	0.0082	0.0013	3.5973e-004
Strang splitting	2.8190e-005	4.4547e-006	1.1447e-006
Method of lines	9.6361e-004	1.0662e-004	1.6967e-005

Table: The errors of different splitting methods and method of lines for $\Delta x = 0.01$, $\Delta t = 0.3$ at $T = 150$.

	err_{L_1}	err_{L_2}	$err_{L_{inf}}$
Iterative splitting	1.9941e-007	2.2098e-008	3.3364e-009
Sequential splitting	0.0081	0.0013	3.7108e-004
Strang splitting	2.9793e-005	4.5777e-006	1.0991e-006
Method of lines	4.7212e-004	5.2296e-005	7.4543e-006

Table: The errors of different splitting methods and method of lines for $\Delta x = 0.01$, $\Delta t = 0.3$ at $T = 300$.

In the first figure, we simulate the solutions taken with different splitting methods at time $T = 300$. In second and third figures, L_2 errors versus scaled step sizes are represented for $N = 100$, at $T = 30$ and at $T = 150$ times.



Conclusion

In this paper, we have presented iterative operator splitting method to solve the mathematical model for capillary formation in tumor angiogenesis problem. We first study the convergency properties of the method by using matrix analysis. We then compare the performance of the iterative splitting method with traditional operator splitting methods (Lie-Trother, Strang) and non-iterative methods (Method of lines and finite difference). The numerical results reveal that the iterative method is applicable to this model problem and more accurate than the methods we compared.
In our investigation of accuracy and efficiency of iterative splitting method, we found that the iterative splitting method is the best since:

- It keeps the all operators in the equations unlike traditional operator splitting methods. We then obtain the consistent approximations after each inner step because of the exact or approximate starting conditions for previous iterative solution,
- It reduces the local splitting error by using the more iteration steps to obtain higher-order accuracy,
- It has a small constant in the local splitting error with respect to the method of lines.

As a result, this application shows that the iterative operator splitting method gives high convergence and small error and it is quite easy to apply for model problem. The consistency and stability analysis are also studied easily. In future work, we want to apply the method to higher dimensional problems.

References

[1] Levine HA, Pamuk S, Sleeman BD, Nilsen-Hamilton M. Mathematical model of capillary formation and development in tumor angiogenesis: penetration into the stroma. *Bull.Math.Biol.* 2001; 63(5), 801-863.
[2] David D. Reinforced random walks. Probability Theory Related Fields 1990; 84, 203-229.
[3] Othmer HG, Stevens A. Aggregation, blow up and collapse: the ABC's oftaxis and reinforced random walks. SIAM J. Appl. Math., 1997; 57 (4), 1044-1081.
[4] Pamuk S, Erdem A. The method of lines for the numerical solution of a mathematical model for capillary formation: The role of endothelial cells in capillary. Applied Math. and Compt., 2007; 186, 831-835.
[5] Saadatmandi A, Dehghan M. Numerical solution of mathematical model for capillary formation tumor angiogenesis via the tau method. Communications in Numerical Methods in Engineering 2008; 24, 1467-1474
[6] Faragó I, Geiser J. Iterative Operator-Splitting methods for Linear Problems. International Journal of Computational Science and Engineering, 2007; 3, 255-263.

Avaliable: http://onlinelibrary.wiley.com/doi/10.1002/cnm.1435/abstract

nurcangucuyenen@iyte.edu.tr