Modeling Chemotaxis with Fractional Step Approaches

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Abstract

Bacteria exhibits a random walk in nature that leads to the formation of special patterns. In [1], this motion is modeled by an advection-diffusion-reaction equation and then solved by a fractional step method. We explore this method and attempt to recreate the 1-dimensional case, learn more about fractional step methods and possibly in 2-dimensions as well.

1 Introduction

Chemotaxis is defined as the motion of an organism in response to a chemical stimulus. This motion is utilized by single celled organism to find food or the escape from poisons. Multicellular organisms also exhibit this phenomenon at some stages like migration of neurons and the motion of the sperm to the egg.

In bacteria, the rotation of the flagella determines its motion. Rotating clockwise and counter-clockwise, the motion involves moving in a straight line before tumbling and thus generating a random walk. In the presence of a chemoattractant, the overall behaviour is to advect towards or away from the chemoattractant gradient. Bacteria generates complex patterns which we seek to recreate by solving advection-diffusion-reaction equations. This is tough to solve and we need fractional steps and implicit methods.

An advection term models the chemotaxis motion while the diffusion term is used to incorporate the random walk. In addition to this, we take a look at the consumption and release of the chemicals involved. We use a reaction term to cover that.

2 Mathematical Background

E.coli and *S.typhimurium* form these complex patterns after feeding on succinate. In response to succinate, the bacteria secretes aspartate which is the chemoattractant. The equations relating the bacteria, aspartate and the succinate are shown below.

$$\frac{\partial n}{\partial t} = D_n \nabla^2 n - \alpha \nabla \Big[\frac{n}{(1+c)^2} \nabla c \Big] + \rho n \Big(\delta \frac{s}{1+s^2} - n \Big)$$

$$\frac{\partial c}{\partial t} = D_c \nabla^2 c + \beta s \frac{n}{\gamma + n^2} - nc$$

$$\frac{\partial s}{\partial t} = D_s \nabla^2 s - \kappa n \frac{s^2}{1+s^2}$$

where:

n is the cell density,

c is the aspartate concentration,

s is the succinate concentration

We see from the first equation that the rate of change of the cell density is determined by the diffusion of the cells, the chemotaxis of the cells and the growth/decay rate of the cells. The aspartate concentraction depends on its diffusion, its production and consumptions by the cells. From the last equation, we see that the succinate concentration is only dependent on its diffusion and its uptake by the cells.

3 Fractional Step Methods

Fractional step or operator-splitting methods present a means to handle non-homogeneous systems of conservation laws that have source terms, where the homogeneous equation is hyperbolic and source terms are functions of the conserved quantities and in some cases position as well. However, for the purposes of this project, all source terms will be considered to be functions purely of the conserved quantities. Given below is the general form of a non-homogeneous conservation law.

$$q_t + f(q)_x = \psi(q)$$

where:

q is the conserved quantities vector

f is the flux vector

ψ is the source term vector

In fractional step methods, this general form is split up into the homogeneous equation, $q_t + f(q)_x = 0$, and $q_t = \psi(q)$. These equations are solved in an alternating fashion to step forward in time. In this manner, each sub-problem may be handled with different methods that suit each equation well.

In order to apply this method, the system of chemotaxis equations are divided up into three separate sub-systems according to the different physical phenomena being modeled as shown below.

$$q_t = \mathscr{A}(q) + \mathscr{D}(q) + \mathscr{R}(q)$$

where:

$$\mathscr{A}(q) = \begin{Bmatrix} -\alpha\nabla\left(\frac{n}{(1+c)^2}\nabla c\right) \\ 0 \\ 0 \end{Bmatrix} \qquad \mathscr{D}(q) = \begin{Bmatrix} D_n\nabla^2 n \\ D_c\nabla^2 c \\ D_s\nabla^2 s \end{Bmatrix} \qquad \mathscr{R}(q) = \begin{Bmatrix} \rho n\left(\frac{\delta s^2}{1+s^2} - n\right) \\ \frac{\beta s n^2}{\gamma+n^2} - nc \\ -\frac{\kappa n s^2}{1+s^2} \end{Bmatrix}$$

are the advection, diffusion, and reaction vectors, respectively.

For the simplest approach, the general equation is split up into three fractional steps, where a step of size Δt is used for the solution of each fractional step equation. These equations are listed below in the sequence they ought to be solved, where the solution of the first uses some initial data $q(x,0) = \mathring{q}(x)$ and that solution becomes the initial state for the next equation in the sequence.

$$q_t = \mathscr{A}(q) \quad \longrightarrow \quad q_t = \mathscr{D}(q) \quad \longrightarrow \quad q_t = \mathscr{R}(q)$$

Each of these steps may combined as a single equation, $q^{n+1} = R(\Delta t)D(\Delta t)A(\Delta t)q^n$, where each sub-step solution has been substituted into the next step, producing the full step from t_n to t_{n+1}. However, this approach, which is known as Lie or Godunov splitting, presents a method that is second order accurate locally (i.e. first order accurate globally), which is undesirably inaccurate.

Thus, for this project the Strang splitting approach, which is a symmetric method that is third order accurate locally (i.e. third order accurate globally), was chosen to improve the accuracy of the results. This method may be written in a similar abbreviated form that combines all steps into one in a symbolic fashion as $q^{n+1} = A(\Delta t/2)D(\Delta t/2)R(\Delta t)D(\Delta t/2)A(\Delta t/2)q^n$.

For a simple linear version of the problem at hand, the governing equation would be $q_t = Aq = (\mathscr{A} + \mathscr{D} + \mathscr{R})q$, which has the solution $q(x, \Delta t) = e^{\Delta t A}\overset{\circ}{q}(x) = e^{\Delta t(\mathscr{A}+\mathscr{D}+\mathscr{R})}\overset{\circ}{q}(x)$, where $q(x, 0) = \overset{\circ}{q}(x)$ is the initial condition of the system. Using the strang splitting approach, the approximate solution would be $q(x, \Delta t) = (e^{\Delta t/2\mathscr{A}} e^{\Delta t/2\mathscr{D}} e^{\Delta t/2\mathscr{R}})(e^{\Delta t/2\mathscr{R}} e^{\Delta t/2\mathscr{D}} e^{\Delta t/2\mathscr{A}})\overset{\circ}{q}(x) = e^{\Delta t/2\mathscr{A}} e^{\Delta t/2\mathscr{D}} e^{\Delta t\mathscr{R}} e^{\Delta t/2\mathscr{D}} e^{\Delta t/2\mathscr{A}}\overset{\circ}{q}(x)$, which is the result of taking two half steps with reversed sequences of solving the three governing equations.

However, for a nonlinear problem, combining all of these steps in one does not make sense, but the application of half steps in reversed order still is the correct approach, which results in the five solution steps listed below.

solve $q_t = \mathscr{A}(q)$ using the IC q^n over the interval $t_n \le t \le t_{n+1/2}$ to find q^*

solve $q_t = \mathscr{D}(q)$ using the IC q^* over the interval $t_n \le t \le t_{n+1/2}$ to find q^{**}

solve $q_t = \mathscr{R}(q)$ using the IC q^{**} over the interval $t_n \le t \le t_{n+1}$ to find q^{***}

solve $q_t = \mathscr{D}(q)$ using the IC q^{***} over the interval $t_n \le t \le t_{n+1/2}$ to find q^{****}

solve $q_t = \mathscr{A}(q)$ using the IC q^{****} over the interval $t_n \le t \le t_{n+1/2}$ to find q_{n+1}

4 Implementation and Development

4.1 Advection Step

Among the three parts, the advection step poses the biggest challenge. The advection arises in response to the chemical stimulus. As a result, we have velocities that depend on the concentration gradient and thus, variable coefficients in our advection equation. The cell density n is modeled by

$$n_t + [un]_x = 0$$

where

$$u = \frac{\alpha}{(1+c)^2}\frac{\partial c}{\partial x}$$

4.1.1 Variable coefficients

At the interface between the cells i and i-1, we have the following.

$$u_{i-1/2} = \frac{\alpha}{(1+c_{i-1/2})^2}\frac{c_i - c_{i-1}}{\Delta x}$$

and

$$u_i = max(u_{i-1/2}, 0) + min(u_{i+s1/2}, 0)$$

For $x < x_{i-1/2}$,

$$q_t + u_{i-1}q_x = 0$$

For $x > x_{i-1/2}$,

$$q_t + u_i q_x = 0$$

So, this cannot be modeled by the regular wave speed traveling with the strength $Q_i - Q_{i-1}$. We try balancing the flux at the interface

$$u_{i-1}Q_{i-1} = u_i Q^*_{i-1/2}$$

$$Q^*_{i-1/2} = \frac{u_{i-1}Q_{i-1}}{u_i}$$

Thus, assuming the velocity is positive, we have

$$A^+\Delta Q_{i-1/2} = s_{i-1/2}W_{i-1/2}$$
$$= u_i(Q_i - Q^*_{i-1/2})$$
$$= u_iQ_i - u_{i-1}Q_{i-1})$$

and

$$A^-\Delta Q_{i-1/2} = 0$$

This is one of many ways to incorporate variable coefficients. However, we use another scheme, the one in [1] which accounts for both positive and negative velocity.

$$A^+\Delta Q = F_{i-1/2} - u_{i-1}n_{i-1}$$

$$A^-\Delta Q = u_in_i - F_{i-1/2}$$

where

$$u_i = max(u_{i-1/2}, 0) + min(u_{i+s1/2}, 0)$$

and

$$F_{i-1/2} = \begin{cases} u_{i-1/2}n_{i-1} & u_{i-1/2} \geq 0 \\ u_{i-1/2}n_i & u_{i-1/2} < 0 \end{cases}$$

4.2 Diffusion Step

For the diffusion step, the Crank-Nicholson method was used due to its similarity to the heat diffusion equation, the equation for which the method was originally developed. Each diffusion equation for the variables in $q = (n, c, s)$ was solved separately in Clawpack using the tri-diagonal system of equations solver *dgtsv*, which is a routine available in LAPACK.

$$Q_i^{n+1} = Q_i^n + \frac{D\Delta t}{2\Delta x^2}\left[\left(Q_{i+1}^n - 2Q_i^n + Q_{i-1}^n\right) + \left(Q_{i+1}^{n+1} - 2Q_i^{n+1} + Q_{i-1}^{n+1}\right)\right] \quad (1)$$

4.3 Reaction Step

For the reaction step, the explicit Forward Euler method was used as per the recommendation of Tyson et al. [2]. The authors compared this simple scheme to a fourth order Runge-Kutta scheme, but were unable to notice any clear difference between the results. However, if rapid oscillations or rapid transients were to arise in the solution due to either the problem parameters and/or initial conditions, then an L-stable method like the TR-BDF2 method would be much better suited to handling such issues.

The Forward Euler method as it was implemented in *src1.f* for the reaction equations is given below.

$$Q_i^{n+1} = Q_i^n + \Delta t\mathscr{R}_i(q) \quad (2)$$

4.4 Clawpack Implementation

When combining all of the steps together into a single solution scheme in Clawpack, two separate source files, *chemo_advection.f90* and *src1.f*, were written, where the first took care of the advection step and the second handled the diffusion followed by the reaction step.

It should be noted that in the actual implementation of the operator-splitting or fractional step methods in Clawpack that the reverse ordering of time steps was not followed explicitly. The analysis driver script, setrun.py, allows for choosing between Godunov and Strang splitting; however, it does not automatically re-order the second set of half time step solutions in the reverse order to the first set as described above. Modifications to the portion of the source code that control the splitting or a

completely user-defined splitting source script would have to be implemented to ensure that the correct order was adhered to for the method. Although the order of the steps is not correct according to Strang's approach, the amount of error accumulated due to this oversight appeared to be negligible in the results, especially relative to the fact that a first order method, Forward Euler, was used for the reaction step of the solution.

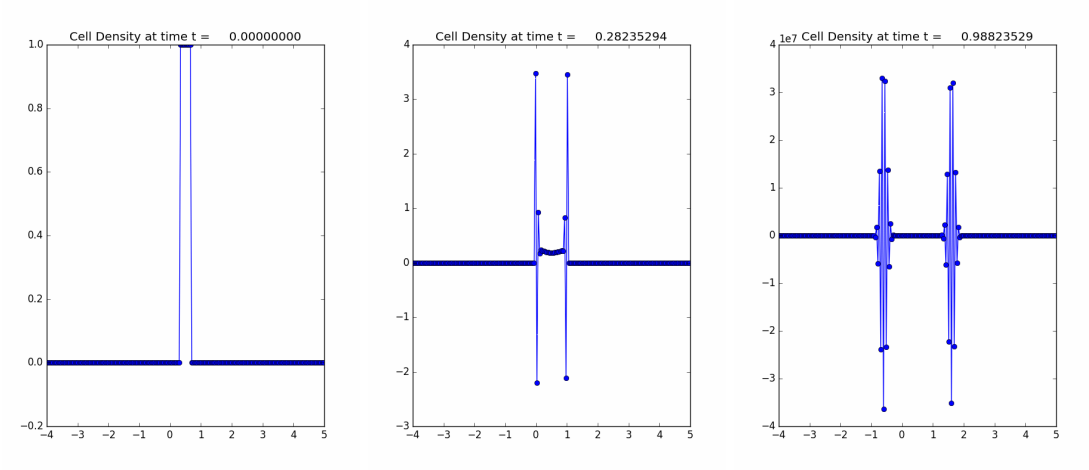
5 Computational Results

5.1 Errors with the second order terms

The advection step is the most complicated step because it is the only step using the finite volume theory and it has variable coefficients. While recreating the scheme from [1], we did not remove a parameter called s which previously the constant velocity.

```
s(i,j) = u;
```

Although we did not use this parameter, it played a huge role by entering the second order correction term and changed the results to those in 1. It blows up quickly around a few points such that the initial condition would not be visible on the scale of the final state.



(a) t=0.0 (b) t=0.28 (c) t=0.98

Figure 1: Advection without second order corrections

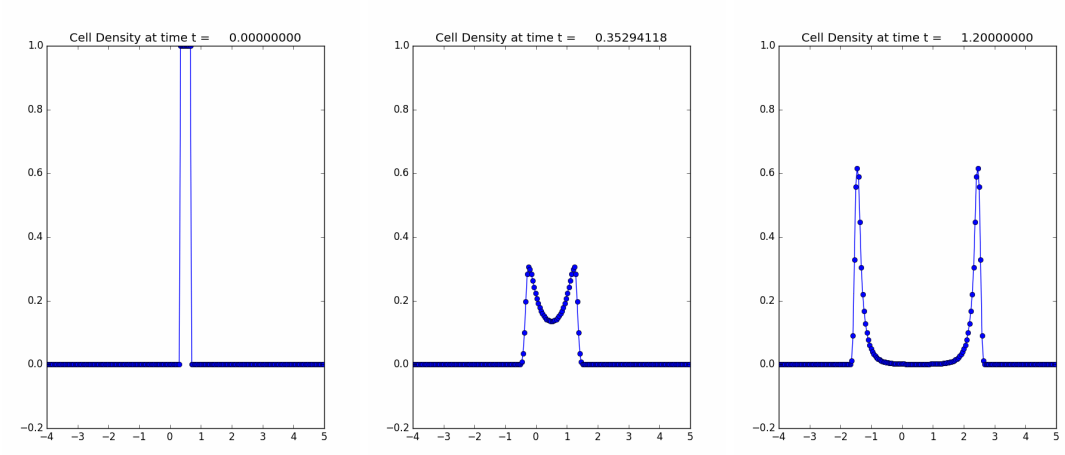
These figures were clearly distinct in their instability. However, with a sufficiently high diffusion term, the instability disappears although the result is not exactly similar.

Correcting this by using a velocity which is more appropriate(like the code below), we get the better results in 2.

```
v = (0.6/((1+((ql(2,i)+qr(2,i-1))/2))**2))*((ql(2,i)-qr(2,i-1))/dx);
s(i,j) = v;
```

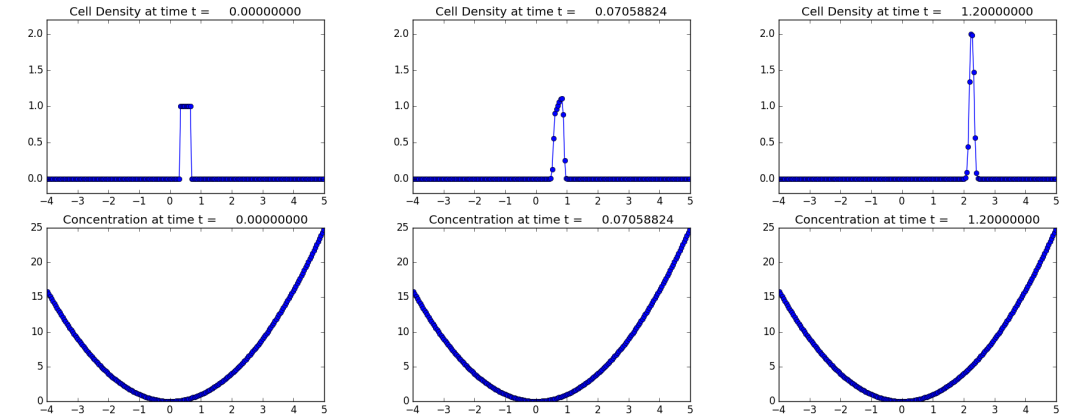
5.2 Different chemoattractant profiles

In response to different chemoattractant profiles, the patterns formed change as well. Using a shifted x^2 profile gives rise to the results in 3



(a) t=0.0 (b) t=0.07 (c) t=1.2

Figure 2: Corrected Advection



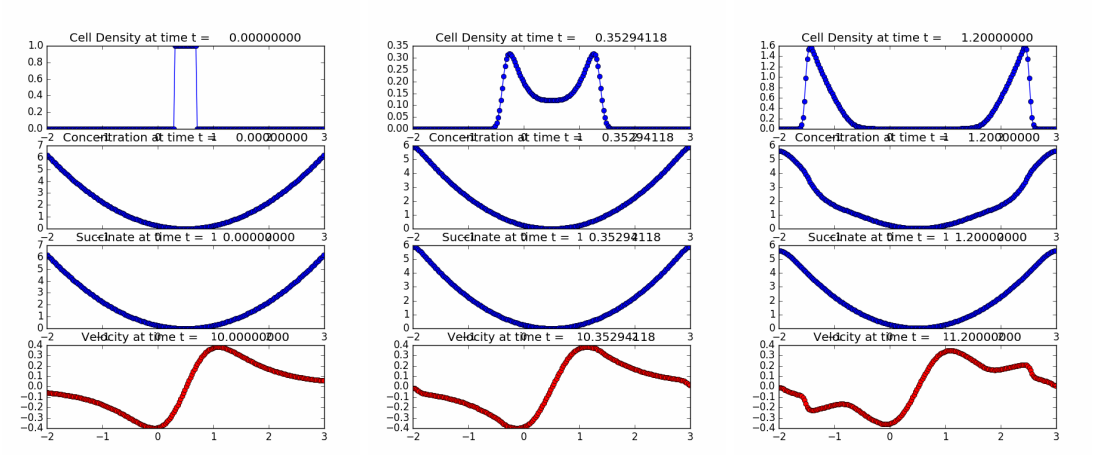
(a) t=0.0 (b) t=0.07 (c) t=1.2

Figure 3: Advection under x^2

Everyone know that boundary conditions are important. They just keep underestimating how important. Choosing the right boundary condition for the advection and diffusion stages is necessary to avoid the formation of a boundary layer which could later blow up. Even with permissible boundary conditions, the nature, the domain used often comes into play. If we used the chemoattractant profile ' $1-cos(x)$ ', the domain must be chosen such that the velocity doesn't turn to zero near the boundaries. This leads to an accumulation of cells near the boundary and ends up blowing up the simulation.

5.3 The dynamics of the advection-diffusion-reaction equation

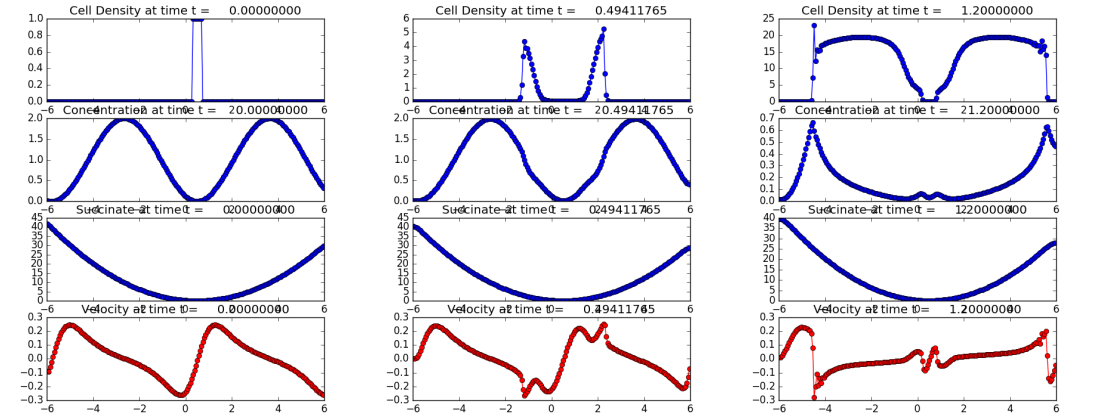
Although the advection step is the toughest to model, the real dynamics lie in the reaction steps . The interplay between the components leads to rapid changes in the solution when we change the coefficients a little.



(a) t=0.0 (b) t=0.35 (c) t=1.2

Figure 4: The Advection-Reaction-Diffusion equation: Case 1

The results in 4 and 5 show have changes in reaction parameters lead to completely different results.



(a) t=0.0 (b) t=0.45 (c) t=1.2

Figure 5: The Advection-Reaction-Diffusion equation: Case 2

6 Summary and Conclusions

This exploration gave us a good look at difficulties that arise while modeling phenomena that are beyond the basic linear constant coefficient cases. It gave us ideas on how to choose domains, test cases and boundary conditions so that we could have a clear analysis. We also gained an understanding of how complex biological processes are. Fundamentally, it gave us insights on how advection, diffusion and reaction work individually and how they change the nature of the solution by changing the shape of the pattern, smoothing it out and bringing new dynamics into the fray.

References

[1] Tyson, Rebecca, L. G. Stern, and Randall J. LeVeque. "Fractional step methods applied to a chemotaxis model." Journal of mathematical biology 41.5 (2000): 455-475.

[2] Clawpack Development Team (2017), Clawpack Version 5.4.0, http://www.clawpack.org, doi:10.5281/zenodo.262111.

[3] Clawpack User Notes available at http://www.depts.washington.edu/clawpack/clawpack-4.3/doc/clawuser.pdf