ENHANCING MODELS FOR GRADIENT SENSING BY CHEMOTAXIS AND CELL COMMUNICATION

BRIAN FROST-LAPLANTE AND COLLIN VICTOR

ADVISOR: JUAN RESTEPO
OREGON STATE UNIVERSITY

ABSTRACT. Gradient sensing for cells is crucial to understanding many biological processes, including prenatal development and wound healing. We seek to generalize a currently relevant mathematical model for gradient sensing through cellular communication by extending the communication method for an arbitrary kernel in arbitrary dimension. By replacing specific matrix multiplication with n-dimensional convolution, we find that we can use Taylor polynomials and properties of the communication process to derive better approximations for our newly generalized model. Numerical simulations are then used in order to qualify the differences between these approximations of communication. We find that substantial differences exist between methods at short scales, but find that for larger groups of cells in large time-scale, the general method is incredibly close to the current model while being simpler to compute via Fourier transforms.

1. INTRODUCTION

Chemotaxis is the ability for groups of cells to move according to a chemical gradient. Essentially, chemotactic cells are able to sense the changing concentration of attractant and/or repellent and move accordingly. For a given gradient, it has been shown that cells behave differently depending on the size of the group of cells. That is, single cells are known to do random walks, but when a large enough collection has gathered, the cells move according to the gradient. Due to behaviour, it is theorized that cells are able to communicate with one another.

The Local Excitation, Global Inhibition (LEGI) model is a well-established model for gradient sensing developed initially by **?**. The model is a system of four equations that describes, for a one-dimensional chain of cells, the concentration of some chemical $\tilde{c}$, the number of active receptors $\tilde{r}$ on each cell, and the amount of active local $\tilde{x}$ and global $\tilde{y}$ molecules in each cell. The number of $\tilde{r}$ for each cell is dependent on the concentration of $\tilde{c}$ around that cell, and while a cell has receptors it activates $\tilde{x}$ and $\tilde{y}$ at a rate of $\tilde{\beta}$. $\tilde{x}$ is a local molecule, it will never leave the cell, while $\tilde{y}$ is a global molecule that is passed

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between cells at a rate of $\tilde{\gamma}$. Both $\tilde{x}$ and $\tilde{y}$ are activated and deactivated at the same rates, but the exchange of $\tilde{y}$ between cells leads to differences in $\tilde{x}$ and $\tilde{y}$. This difference between $\tilde{x}$ and $\tilde{y}$ is how each cell senses the local gradient.

This study serves to analyze and improve upon the standard LEGI model by implementing a general communication via a convolution term into a nondimensionalized version of the model, as well as generalizing the model into higher dimensions. By implementing numerical simulations in MATLAB we have tested differences between various approximations of this convolution model under a variety of conditions. This report outlines the development of our generalized nondimensional model from the original LEGI model and details simulations for a fixed system of cells with different communication methods and concentration gradients.

2. Problem Statement

2.1. **Original Model.** The LEGI model is described by a system of four differential equations, presented by **?** as follows:

$$\frac{\partial \tilde{c}}{\partial \tilde{t}} = D\nabla^2 \tilde{c} - \sum_{n=1}^{m} \delta\left(\frac{\vec{\tilde{z}}}{L} - \frac{\vec{\tilde{z}}_n}{L}\right)\frac{d\tilde{r}_n}{d\tilde{t}}, \tag{1}$$

$$\frac{d\tilde{r}_n}{d\tilde{t}} = \tilde{\alpha}\tilde{c}_n - \tilde{\mu}\tilde{r}_n + \tilde{\eta}_n, \tag{2}$$

$$\frac{d\tilde{x}_n}{d\tilde{t}} = \tilde{\beta}\tilde{r}_n - \tilde{\nu}\tilde{x}_n + \tilde{\xi}_n, \tag{3}$$

$$\frac{d\tilde{y}_n}{d\tilde{t}} = \tilde{\beta}\tilde{r}_n + \sum_{n'=1}^{m} \tilde{M}_{nn'}\tilde{y}_{n'} + \tilde{\chi}_n, \tag{4}$$

$$\tilde{M} = \delta_{n,n'}(-\tilde{\nu} - 2\tilde{\gamma}) + (\delta_{n-1,n'} + \delta_{n+1,n'})(\tilde{\gamma}). \tag{5}$$

Here, $\vec{\tilde{z}}$ is a position variable, $\tilde{t}$ is a time variable, $\tilde{D}$ is the diffusion constant, m is the number of cells, δ is the discrete impulse function, $\tilde{\alpha}$ and $\tilde{\mu}$ are the binding and unbinding rates of receptors (the number of which is given by $\tilde{r}$) respectively, and $\tilde{\beta}$ and $\tilde{\nu}$ are the activation and deactivation rates of both $\tilde{x}$ and $\tilde{y}$, respectively. $\tilde{M}$ is a communication matrix for $\tilde{y}$, and $\tilde{\gamma}$ is the rate at which $\tilde{y}$ is transferred between cells. Lastly, $\tilde{\eta}$, $\tilde{\xi}$ and $\tilde{\chi}$ are zero-mean Gaussian white noise terms given by

$$\tilde{\eta}_n = \tilde{\alpha}\bar{\tilde{c}}_n \delta F_n, \tag{6}$$

$$< \tilde{\xi}_n(t), \tilde{\xi}_{n'}(t') >= \delta_{n',n}(\tilde{\beta}\bar{\tilde{r}}_n + \tilde{\nu}\bar{\tilde{x}}_n)\delta(t-t'), \tag{7}$$

$$\begin{aligned} < \tilde{\chi}_n(t), \tilde{\chi}_{n'}(t') > = & [\delta_{n',n}(\tilde{\beta}\bar{\tilde{r}}_n + \tilde{\nu}\bar{\tilde{y}}_n + 2\tilde{\gamma}\bar{\tilde{y}}_n + \tilde{\gamma}\bar{\tilde{y}}_{n-1} + \tilde{\gamma}\bar{\tilde{y}}_{n+1}), \\ & - \delta_{n',n-1}(\tilde{\gamma}\bar{\tilde{y}}_{n-1} + \tilde{\gamma}\bar{\tilde{y}}_n), \\ & - \delta_{n',n+1}(\tilde{\gamma}\bar{\tilde{y}}_{n+1} + \tilde{\gamma}\bar{\tilde{y}}_n)]\,\delta(t-t'). \end{aligned} \tag{8}$$

Where F is the free energy associated with unbinding **? ?**.

We now nondimensionalize these equations. In these new dimensionless equations, a is the length of a cell, c_0 is the average value of $\tilde{c}$ and $L = ma$ is the total length of the cell chain. These dimensionless terms are defined as follows:

$$z = \frac{\tilde{z}}{L}, t = \frac{\tilde{t}D}{L^2}, c = \frac{\tilde{c}}{c_0},$$

$$\alpha = \frac{\tilde{\alpha}a^2}{D}, \mu = \frac{\tilde{\mu}a^2}{D}, \beta = \frac{\tilde{\beta}a^2}{D}, \nu = \frac{\tilde{\nu}a^2}{D},$$

$$r = \frac{\tilde{r}}{c_0}, x = \frac{\tilde{x}}{c_0}, y = \frac{\tilde{y}}{c_0}.$$

We now look to rewrite equations **??** through **??** using these dimensionless terms. Doing so rescales the equations and results in the below dimensionless equations, where $\lambda = \frac{L^2}{a^2} = m^2$ and $\varepsilon = \frac{L^2}{Dc_0}$:

$$\frac{\partial c}{\partial t} = \frac{\partial^2 c}{\partial z^2} - \sum_{n=1}^{m} \delta(\vec{z} - \vec{z_n})\frac{dr_n}{dt}, \tag{9}$$

$$\frac{dr_n}{dt} = \lambda\alpha c_n - \lambda\mu r_n + \varepsilon\eta_n, \tag{10}$$

$$\frac{dx_n}{dt} = \lambda\beta r_n - \lambda\nu x_n + \varepsilon\xi_n, \tag{11}$$

$$\frac{dy_n}{dt} = \lambda\beta r_n + \lambda\sum_{n'=1}^{m} M_{nn'}y_{n'} + \varepsilon\chi_n. \tag{12}$$

$$M = \delta_{n,n'}(-\nu - 2\gamma) + (\delta_{n-1,n'} + \delta_{n+1,n'})(\gamma) \tag{13}$$

2.2. **Problem Summary.** We look to analyze a generalized version of this non-dimensionalized LEGI model in the case of very large clusters of cells and in arbitrary dimension. To do this, we generalize the model to a continuous one, i.e. where there are infinitely many cells. We show the extent to which this model agrees with the LEGI model, as well as the cases in which it disagrees. We hope to provide an accurate and computationally simple model for gradient sensing in arbitrary dimension.

3. Cell Communication Generalized and in Higher Spatial Dimensions

Our next step, was to generalize the LEGI model, using a discrete convolution-based communication term in place of the matrix M from (**??**). This is due to the matrix M allowing only for communication between each cell and its immediate neighbors. For a process that is modeled in discrete time, the previous model may not be physically accurate for a given time step. To compensate for this, we introduce the ability for cells to communicate further in a single time step.

Equation (**??**) features the matrix M, which regards both deactivation of y at rate ν and communication at rate γ. In order to generalize this term using convolution, we need to change parts of the differential equation itself. While deactivation continues to happen at the same rate, the communication term requires a fundamental change. We propose a new model for communication by replacing M with a convolution with kernel w. The resulting differential equation without noise looks as follows:

$$\frac{dy_n}{dt} = \lambda(\beta r_n - \nu y_n + \gamma(w * y)_n). \tag{14}$$

This equation holds for all n, barring those on the boundary. In this case, we have found properties that this convolution must satisfy and, as a result, realistic properties of the kernel w.

The convolution must be such that there is no net change in system-wide y as a result of communication. That is to say, the kernel of this convolution must sum to zero across all spatial indices once boundary conditions have been accounted for. This said, there should not be disproportionate communication in either direction, so for the average cell not affected by boundary conditions, w should have even symmetry about 0. The original model can be replicated by such a w that looks like

$$w = -2\delta(n) + \delta(n-1) + \delta(n+1). \tag{15}$$

Where δ is the discrete impulse function. Other simple ideas for w are now more easily considered. For example, if you want a possibility of two-cell-long communication, where it is much more common for communication to occur at a one-cell distance, you may come up with

$$w = -2\delta(n) + \frac{4}{5}(\delta(n-1) + \delta(n+1)) + \frac{1}{5}(\delta(n-2) + \delta(n+2)). \tag{16}$$

We now wish to look at the natural extension of this discrete convolution model to a continuous one, allowing also for arbitrary dimension.

The one-dimensional LEGI model is presented as (**??**) - (**??**). The first three of these differential equations are of little interest in this generalization, as they are not specific to any dimension and are trivially extended to continuous space. Equation **??**, however, is of interest as it only allows for a very specific kind of one-dimensional communication. We have, as a result, altered only (**??**) yielding

$$\frac{dy_n}{dt} = \lambda(\beta r_n - \nu y_n + (w * y)_n) + \varepsilon\chi_n. \tag{17}$$

Where w is a kernel satisfying the following properties:

- w is an even function in all spatial dimensions,
- w has a small support relative to the length of the system,
- w integrates (or sums, in the discrete case) to zero over its support.

This convolution in spacial dimension z, in the continuous case, is defined as

$$w * y = \int_{-\infty}^{\infty} w(u)y(z-u)\,du. \tag{18}$$

Following the method used in **?**'s *Mathematical Biology*, we now expand y into a Taylor series centered at z. Because the support of w is relatively small, we are justified in using a rather small order approximation for y. Here, we specifically choose a second order approximation:

$$\int_{-\infty}^{\infty} w(u)y(z-u)\,du \approx \int_{-\infty}^{\infty} w(u)\left(y(z) - uy'(z) + \frac{u^2}{2}y''(z)\right)du. \tag{19}$$

Breaking this up into three integrals and taking the u-independent terms out, we get

$$y(z)\int_{-\infty}^{\infty} w(u)\,du - y'(z)\int_{-\infty}^{\infty} uw(u)\,du + y''(z)\int_{-\infty}^{\infty} \frac{u^2}{2}w(u)\,du. \tag{20}$$

From the properties of w, we know this first integral is zero. We also know that w is even, so its product with u is odd, meaning its integral over a symmetric interval is also zero. This leaves only the second order term. The final integral will also evaluate to a single number dependent only on the kernel. We call this number Ω_1, allowing us to simply write

$$w * y \approx y''(z) \int_{-\infty}^{\infty} \frac{u^2}{2} w(u)\, du = \Omega_1 y''(z), \tag{21}$$

and (**??**) generalizes to

$$\frac{\partial y}{\partial t} \approx \lambda(\beta r(z,t) - \nu y(z,t) + \Omega_1 y''(z)) + \varepsilon\chi. \tag{22}$$

We can apply the same general method to generate the LEGI model's natural extension to two dimensions. This means we must use the two-dimensional definition of convolution in space dimensions x_1 and x_2 given by

$$w * y = \iint_{\mathbb{R}^2} w(u_1,u_2) y(z_1 - u_1, z_2 - u_2)\, du_1 du_2. \tag{23}$$

We also must use the multivariable Taylor expansion about (z_1, z_2), which is given to order two by

$$y(\vec{z}) - \vec{u} \cdot \nabla y(\vec{z}) + \frac{1}{2} \vec{u}^T H(y(\vec{z})) \vec{u}. \tag{24}$$

Where $H(y(\vec{z}))$ is the Hessian matrix of y. Note that the first and second terms here vanish similar to (**??**). Only the last term survives, leaving

$$w * y \approx \frac{1}{2} \iint_{\mathbb{R}^2} w(\vec{u}) \left(u_1^2 y_{z_1 z_1} + u_2^2 y_{z_2 z_2} + 2 u_1 u_2 y_{z_1 z_2} \right) d\vec{u}. \tag{25}$$

It is of interest that this can be split into three separate integrals, the first to of which vanish simply by the fact that in one dimension they integrate as w alone. The last term also does not survive, as the integral in either spatial dimension is that of an odd function multiplied by an even one. As a result, order two is not enough. We must have a term with an even power of u factor that also has representation of each spatial dimension. This can only be achieved by a third order term or higher. However, all third order terms also vanish due to the even symmetry of w. This means we must look at a fourth order Taylor approximation. Most of these terms will drop out, and only terms with two z_1 derivatives and two z_2 derivatives remain. This reduces our problem to a combinatorial one used to determine which terms exist and remain. That work is spared here, but results in

$$\frac{1}{4!} \iint_{\mathbb{R}^2} w(\vec{u}) \left(6 u_1^2 u_2^2 y_{z_1 z_1 z_2 z_2} \right) = \Omega_2 y_{z_1 z_1 z_2 z_2}. \tag{26}$$

This leads to a final equation:

$$\frac{\partial y}{\partial t} \approx \lambda(\beta r(\vec{z},t) - \nu y(\vec{z},t) + \Omega_2 y_{z_1 z_1 z_2 z_2}) + \varepsilon\chi. \tag{27}$$

When looking at an m-dimensional system, it follows from the two-dimensional reasoning that one must expand y to at least the $2m^{th}$ term of its Taylor series. As all terms prior to this term integrate to zero, as do a portion of the $2m^{th}$ terms. These terms must have exactly two derivatives of each of the spatial dimensions, and as these mixed partials are all equal, we can represent them by $y_{z_1 z_1 \ldots z_m z_m}$. The number of terms that look like this are determined by the multinomial coefficient:

$$\binom{2m}{2,2,\ldots,2} = \frac{2m!}{2!2!\ldots 2!} = \frac{2m!}{2^m}. \tag{28}$$

If one accounts for the fact that these Taylor series terms are preceded by a $\frac{1}{2m!}$, it is clear that, for arbitrary dimension m,

$$\Omega_m = \frac{1}{2^m} \int \cdots \int_{\mathbb{R}^m} w(\vec{u}) u_1^2 \ldots u_m^2 \, d\vec{u}. \tag{29}$$

This gives us a very simple general estimation for arbitrary dimension:

$$\frac{\partial y}{\partial t} \approx \lambda(\beta r(\vec{z},t) - \nu y(\vec{z},t) + \Omega_m y_{z_1 z_1 \ldots z_m z_m}) + \varepsilon\chi. \tag{30}$$

Naturally, the fact that we are truncating a Taylor series leads to the question of error. Clearly we are being inexact, but under what conditions is this error small enough to be disregarded?

It is also important to note that we are also creating another source of error in how we compute the derivatives of y. If one takes Equation **??**, applies a central second order finite difference approximation to y, and takes Ω_1 to be γa^2, then one retrieves (refnormy) exactly. However, is this a sufficient approximation? If we expand the Taylor series further, this question must be asked for each extra term.

For simplicity, we look at the second question in the one-dimensional case first. It is true that, for $a \longrightarrow 0$,

$$y''(z) = \frac{y(z+a) - 2y(z) + y(z-a)}{a^2} + O(a^2). \tag{31}$$

However, we can take better finite difference approximations to minimize error. For example:

$$y''(z) = \frac{\frac{-1}{12}y(z+2a) + \frac{4}{3}y(z+a) - \frac{5}{2}y(z) + \frac{4}{3}y(z-a) - \frac{1}{12}y(z-2a)}{a^2} + O(a^4). \tag{32}$$

3.1. **Fourth Derivative Term.** The approximation of the convolution term can always be improved by adding more terms from the Taylor expansion. The next interesting addition is the fourth derivative term:

$$\frac{\partial y}{\partial t} \approx \lambda(\beta r(z,t) - \nu y(z,t) + \Omega_1 y''(z) + \phi y^{(4)}(z)) + \varepsilon\chi, \tag{33}$$

$$\phi = \frac{1}{4!}\int_{-\infty}^{\infty} w(u)u^4 du. \tag{34}$$

This term is significant in any conditions that result in a large $y^{(4)}(z)$. This can be due to noise or a sharp change in the concentration gradient. In cases where this term is significant, one can approximate $y^{(4)}(z)$ using centered finite difference:

$$y^{(4)}(z) = \frac{y(z+2a) - 4y(z+a) + 6y(z) - 4y(z-a) + y(z-2a)}{a^4} + O(a^2). \tag{35}$$

The constant ϕ is dependent on the convolution kernel w. As w is an arbitrary kernel, we are unable to determine the value of ϕ, relative to Ω.

4. Results

Should one generalize y communication to the aforementioned convolution model, one may naturally ask what are the differences are between this general convolution and the original communication method (**??**). We look at the differences between the communication (**??**), the higher order finite difference approximation for the second derivative (**??**), and lastly observe the effect of adding a fourth derivative term ().

As the kernel w is not determined, we look at a range of values for ϕ with relation to an experimentally realistic γ value. This value was set to $\frac{\gamma}{4}$ for the sake of our simulations. We examine at the effect it has on the noiseless system first.

Should the initial concentration be linear, we expect that the addition of a higher order approximation or a fourth derivative term is highly inconsequential for any number of cells. This is due to the fact that y tends to quickly become linear, making for zero second and fourth derivatives.

Thus, initial concentrations most affected by this change are expected to be ones with large derivatives, especially in the case of a low diffusion constant. This motivated the use of initial concentrations such as e^{5z} and z^5.

We use a simulation with details provided in Appendix **??** to attain the behavior of the three communication methods for one-dimensional cell chains. The initial concentration

and number of cells were varied. We looked to compare, specifically, methods of communication based on the maximum difference between y values, the only differing term. We also look to scale these maximums relative to the maximum value of y for the system, as this is consistent between all communication methods for a fixed d and number of cells. This also gives a relative size of the difference as compared to y itself. We define two new terms,

$$S_2 = 100\,\frac{max|y_1 - y_2|}{max(y_1)},$$
$$S_3 = 100\,\frac{max|y_1 - y_3|}{max(y_1)},$$

where y_1 is y computed by second order finite difference second derivative communication, y_2 is y computed by fourth order finite difference second derivative communication, and y_3 is y computed with a second and fourth derivative communication term. These terms state the maximum difference between these alternative communication models and the original LEGI model. They are multiplied by 100 as to present the data in percentages. The data for S_2 and S_3 are presented in Tables **??** through **??**.

We find that in the cases of linear initial concentration, there is very little difference between the three possible methods of communication, should there be no noise. If, however, the concentration is given by a function with larger high-order derivatives, such as e^z, it is clear that the difference in method does, in fact, make a difference in the communication between cells. Specifically, it makes the greatest difference towards the ends of a one-dimensional cell chain, although there is an existent difference between the methods throughout space.

The greatest of these differences was seen between the standard method and the fourth derivative method for initial concentration z^5, followed very closely by e^{5z} and lastly $\frac{1}{2}z$. As y changes in space in a manner that depends in some way on this concentration, it is intuitively clear that a high fourth derivative in the initial concentration would make for a larger difference between the standard and fourth derivative method. A linear y has no second nor fourth derivative, thereby diffusion-influenced slight changes in y accounts for all of the difference between methods.

As should be expected, the better second derivative approximation does affect, in some manner, the value of y, but it is not nearly as large of a contribution as a higher order term.

We also see that this difference is highly dependent on the number of cells in either case. This is very much expected mathematically, as the size of a cell a relative to L becomes very small as the number of cells increases. We know that our convolution approximations become much closer to the actual convolution's value as this occurs.

We see that a smaller diffusion constant allows for larger differences between these methods, than higher diffusion constants. This is likely due to the fact that in the case of

higher D, y is affected more substantially by the changing concentration than the communication between cells.

While this data gives us insight into the maximum long-time effects of differing methods of communication on the system, we also take interest in short-time effects of this communication. As such, we look at the setup in which the concentration is initialized to zero everywhere. We then, initialize y to be begin with an initial value of zero in each cell, except the center cell, denoted z_0, which has an initial value of one. Since c and r are zero everywhere for every timestep, the only manners in which y changes are by deactivation and communication. In the very earliest timesteps, this change is heavily dominated by communication, as γ is 100 times larger than ν. In the early moments, we look to see the properties of communication between cells with respect to both distance and time.

To do this, we look at the autocorrelation of a certain method's y in space at each point in time. This is done by application of the Wiener-Kinchin theorem, which is justified by the finite length of y. That is

$$r_1 = \mathcal{F}^{-1}(\mathcal{F}(y_1)\overline{\mathcal{F}(y_1)}),$$
$$r_2 = \mathcal{F}^{-1}(\mathcal{F}(y_2)\overline{\mathcal{F}(y_2)}),$$
$$r_3 = \mathcal{F}^{-1}(\mathcal{F}(y_3)\overline{\mathcal{F}(y_3)}),$$

where $\bar{(\cdot)}$ denotes the complex conjugate. Graphs of r_1, r_2 and r_3 at the third timestep (9ms into simulation) is shown in Figure **??**. This serves, qualitatively, as a way to see the relative size of the differences between the three communication methods in early stages of communication.

From this, we find a correlation length at each time by stating that the autocorrelation is nearly proportional to $exp(-(z-z_0)/C)$ and we find a C such that the autocorrelation at z_0+C is closest e^{-1}. We look at C for each method of communication as a function of time, and we are able to determine some differences between them. This data can be seen in Figure **??**.

We find from this that the correlation lengths for the three methods are remarkably close, and in fact never different by more than one cell length to the nearest cell length. At moments where they are different, however, it is always true that the higher order second derivative approximation method has the highest C, followed by the standard method, and lastly by the fourth derivative approximation method. With this in mind, we look to see what direct effect this has on early stage spread of y.

To do this we look at the first 50 timesteps of our simulation in which one timestep is 3 milliseconds, where the differences are most apparent. We look to see, at these times, how many cells contain a higher y value than a certain tolerance T. We find that, in fact, the fourth derivative method provides y to the most cells at all times (for T of varying sizes), with the standard method behind it and the higher order second derivative method

in last; this is the opposite order to the sizes of the correlation length. We see that the largest differences occur very early in the simulation, with as many as ten more cells communicating with the fourth derivative approximation than the standard method very early on. These differences persist long after 20 timesteps but become less obvious for all T. This data for a given T is shown in Figure **??**.

5. Discussion and Concluding Remarks

Motivated by this work is similar work in higher dimensions with this general model, as well as potentially the use of this general model when predicting behavior of higher numbers of cells. This is justified by the fact that a convolution is much faster for the purpose of simulation due to the ability to apply fast Fourier Transforms. It also motivates the question as to whether this general model better describes small chains of cells than the standard LEGI model. This noted, these differences may only be seen in cases with high noise and shallow initial concentrations of an exponential or high degree polynomial variety, as the differences between y values for these methods of communication are quite small relative to the values of y itself in most cases.

We also see that the most notable difference between communication methods; the number of cells aware of communicant y as a function of time; is most affected in the short timescale. Long-term effects are of a smaller scale, and it is likely always valid to use any convolution method or approximation for a high number of cells, and long-term gradient sensing model. There may be motivation now for determination of which of these methods is most accurate in very rapid gradient modulation scenarios for actual cells.

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APPENDIX A. APPENDIX 1: NUMERICAL METHODS

We solved Equation **??** using the Crank-Nicolson method, while Heun's method was used for the remaining three equations. These methods were then interfaced in a loop using a different time step for both methods, with a smaller time step for the Heun's method iterations. We use $a = 10\mu m$, $\tilde{\alpha} = .1s^{-1}$, $\tilde{\mu} = \tilde{nu} = 1s^{-1}$, $\tilde{\beta} = \tilde{\gamma} = 100s^{-1}$.

LIST OF FIGURES

APPENDIX B. TABLES AND FIGURES

Initial Concentration	$D(\mu m^2 s^{-1})$	S_2	S_3
$\frac{1}{2}z$	50	0.0993	0.3077
	500	0.0576	0.1770
	5000	0.0169	0.0520
z^5	50	0.2989	0.9914
	500	0.1453	0.4646
	5000	0.0411	0.1313
e^{5z}	50	0.2459	0.8108
	500	0.1218	0.3879
	5000	0.0347	0.1104

TABLE 1. Deterministic Communication differences for 10 cells

Initial Concentration	$D(\mu m^2 s^{-1})$	S_2	S_3
$\frac{1}{2}z$	50	0.0228	0.0765
	500	0.0174	0.0591
	5000	0.0112	0.0394
z^5	50	0.1098	0.3519
	500	0.0778	0.2497
	5000	0.0426	0.1402
e^{5z}	50	0.0968	0.3108
	500	0.0673	0.2167
	5000	0.0357	0.1182

TABLE 2. Deterministic Communication differences for 50 cells

Initial Concentration	$D(\mu m^2 s^{-1})$	S_2	S_3
$\frac{1}{2}z$	50	0.0100	0.0339
	500	0.0074	0.0255
	5000	0.0043	0.0156
z^5	50	0.0517	0.1685
	500	0.0376	0.1235
	5000	0.0212	0.0719
e^{5z}	50	0.0479	0.1557
	500	0.0343	0.1124
	5000	0.0186	0.0632

TABLE 3. Deterministic Communication Differences for 100 cells

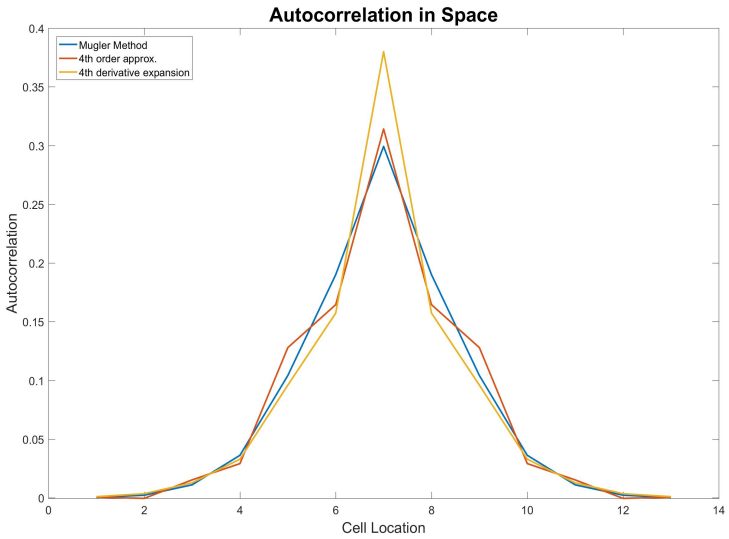

FIGURE 1. Autocorrelation on the third timestep

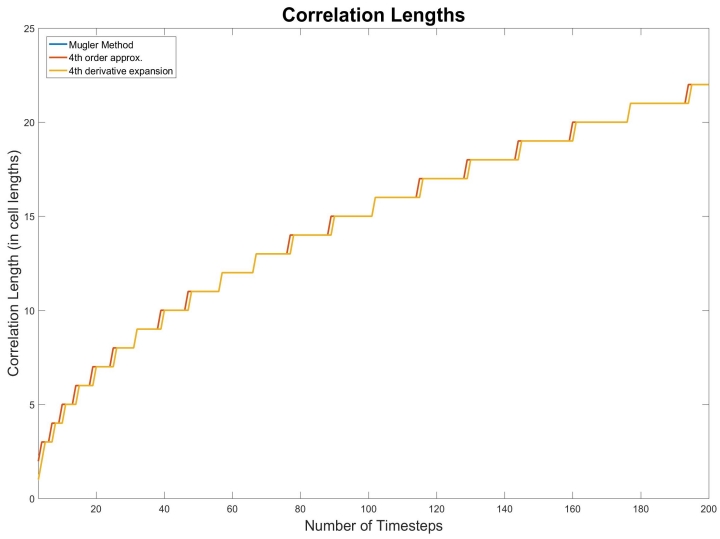

FIGURE 2. Correlation length over time

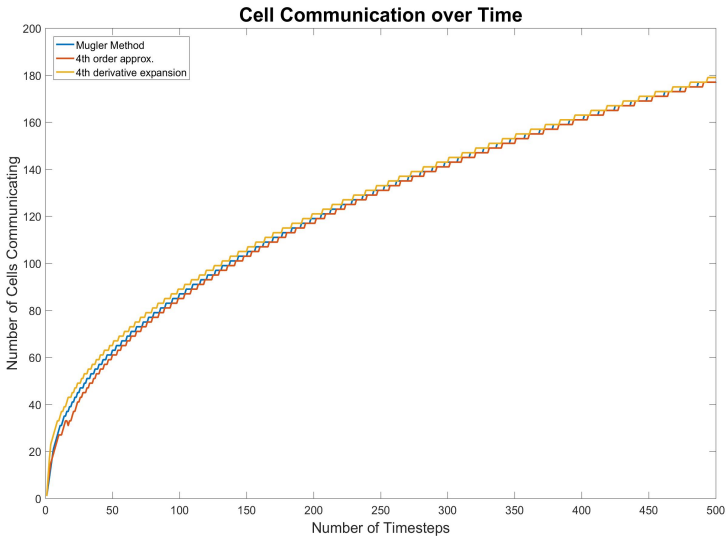

FIGURE 3. Number of cells over tolerance level of $T = 1E-8$

COOPER UNION
E-mail address: brianfrost97@gmail.com

UNIVERSITY OF NEBRASKA-LINCOLN
E-mail address: cvictor@cse.unl.edu