

Modelling Travelling Waves in Spatially Constrained Environments

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Abstract

This paper concerns on the travelling waves phenomenon modelled on crowded environments. Here, we used the Fractional Reaction Diffusion Partial Differential Equations (FRDPDEs) to get the results. We applied our model to a real biological problem known as Hirschsprung's disease. By applying our model for modelling the Hirschsprung's disease, allowing us to establish an interesting result for the mobility of the cellular processes under crowded environments. This model also help us to understand the potential action of Hirschsprung's Disease which is linked to neural crest cells migration.

Contents

1	Introduction	2
2	Numerical Method	3
3	Case Study:Modelling Hirschsprung's Disease	4
3.1	Numerical experiments	4
3.2	Results	6
4	Summary	9

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1 Introduction

The identification and analysis of travelling waves in chemical reactions was first reported by Luther [1] and since then researchers have been captivated by the existence of wave phenomena exhibited in chemical and biological systems. Thirty years after Luther's result, Fisher analysed in detail reaction-diffusion waves for modelling the spatial spread of favoured genes in a population [2]. Later, Semenov described cool flames in combustion, proposed a model containing cubic non-linearity and developed an analytical form for the front velocity. Travelling waves in system biology was also described by Fall et al. [3] and Murray [4].

Much work has recently been done on developing numerical methods to describe travelling waves. Gubernov et al. [5] consider shooting and relaxation methods to investigate propagating waves in solutions of reaction diffusion equations. Landman et al. [6, 7] have written a number of papers describing cell migration by diffusion and chemotaxis using phase plane and the perturbation technique. Mendez et al. [9] studied reaction diffusion equations in heterogeneous media and derived analytic expressions for the speed of front based on perturbation and Hamilton-Jacobi methods. Agrawal [10] presents a finite sine and Laplace transforms methods for fractional diffusion wave equations defined in a bounded space domain.

Based on recent progress and published literature in areas such as genetic sequencing and microscopy and also advances in scientific method, it shows that cell membrane possesses a highly complex structure [11]. Therefore, how is diffusion and chemical kinetics wave affected due to the crowdedness in the biological media? In this paper, we have provided models for enabling the use of fractional derivatives models for modelling dynamical processes on living cell. In particular, we considered the class of continuous spatial modelling to portray the diffusion wave behaviour in complex environments. This work uses fractional order differential equations (FDEs) in one dimensional systems with varying obstacle densities as a tool to model chemical reactions within constrained environments.

This paper is organized as follows. In the next section, the model of fractional differential equation will be introduced. Then, we proceed with the numerical experiments based on Hirschsprung's Disease in section 3. The results of the experiments will be displayed in section 3.2 and summary will be presented at the end of the section.

2 Numerical Method

Consider the fractional differential equation of the form

$$\begin{aligned} \frac{dy(t)}{dt} &= D_t^{1-\alpha} f(y(t)) + g(y(t)), & t \in [0, T], \\ y(0) &= y_0, y_0 \in \mathbf{R}^m, \end{aligned} \quad (1)$$

where $0 < \alpha < 1$. $D_t^{1-\alpha} f$ denotes the Riemann-Liouville fractional derivative of the function f , defined by [14]

$$D_t^{1-\alpha} f(t) = \frac{1}{\Gamma(\alpha)} \frac{d}{dt} \int_0^t \frac{f(s)}{(t-s)^{1-\alpha}} ds. \quad (2)$$

Here $\Gamma(\alpha)$ is the Gamma function defined by

$$\Gamma(\alpha) = \int_0^\infty e^{-t} t^{\alpha-1} dt.$$

The Caputo fractional derivative is given by

$$\widehat{D}_t^{1-\alpha} f(t) = \frac{1}{\Gamma(\alpha)} \int_0^t \frac{f'(s)}{(t-s)^{1-\alpha}} ds. \quad (3)$$

If $f(t)$ is continuous and $f'(t)$ is integrable in the interval $[0, T]$, then for every $0 < \alpha < 1$ the Riemann-Liouville and the Caputo fractional derivatives satisfy the following relation [14]

$$D_t^{1-\alpha} f(t) = \widehat{D}_t^{1-\alpha} f(t) + \frac{t^{\alpha-1}}{\Gamma(\alpha)} f(0), \quad t > 0. \quad (4)$$

A number of authors, for example Ford et al. [15], consider the numerical solution of so-called Caputo FDEs that take the form

$$\widehat{D}_t^\alpha y(t) = f(y(t)),$$

but we prefer the form (1) as it is more naturally allied to problems in systems biology arising from the anomalous diffusion and chemical kinetics of molecular species in a crowded environment [16, 17].

To solve problem (1), we consider a numerical method, namely the fractional Trapezoidal method written as

$$y_{n+1} = y_n + \frac{h}{2} (D_t^{1-\alpha} (f(y_n) + f(y_{n+1}))) + \frac{h}{2} (g(y_n) + g(y_{n+1})). \quad (5)$$

3 Case Study:Modelling Hirschsprung's Disease

In this section, we investigate the travelling waves phenomenon with respect to a common developmental disorder problem, known as Hirschsprung's Disease. More details related to Hirschsprung's Diseases can be found on [18, 19, 20].

3.1 Numerical experiments

The model was used by Simpson et al. [8] in a non-growing gut system and later Landman et al. [12] extends the system by including the gut growth to the existing system.

The one-dimensional donor-host system as a fractional equation, is given as

$$\begin{aligned}\frac{\partial \mathbf{D}}{\partial t} &= D_t^{1-\alpha} \left(K_{\mathbf{D}} \frac{\partial^2 \mathbf{D}}{\partial x^2} + \sigma_{\mathbf{D}} \mathbf{D} \left[1 - \frac{\mathbf{D} - \mathbf{H}}{C} \right] \right) - \frac{\partial v \mathbf{D}}{\partial x}, \quad x \in [0, L], \quad t > 0, \\ \frac{\partial \mathbf{H}}{\partial t} &= D_t^{1-\alpha} \left(K_{\mathbf{H}} \frac{\partial^2 \mathbf{H}}{\partial x^2} + \sigma_{\mathbf{H}} \mathbf{H} \left[1 - \frac{\mathbf{D} - \mathbf{H}}{C} \right] \right) - \frac{\partial v \mathbf{H}}{\partial x},\end{aligned}\quad (6)$$

where \mathbf{D} and \mathbf{H} are the donor and host cell types densities in space and time. Here, x represent the invasion axis or the position along the gut, $K_{\mathbf{D}}, K_{\mathbf{H}}$ are the diffusivities of the donor and host cell types and $\sigma_{\mathbf{D}}, \sigma_{\mathbf{H}}$ represent the mitotic indices for the donor and host cell types respectively. C is a carrying capacity density of the tissue and v represent the velocity field associated with the growth of the gut.

If we set $v = 0$, then (6) is written as

$$\begin{aligned}\frac{\partial \mathbf{D}(x, t)}{\partial t} &= D_t^{1-\alpha} \left(K_{\mathbf{D}} \frac{\partial^2 \mathbf{D}}{\partial x^2}(x, t) + \sigma_{\mathbf{D}} f(\mathbf{D}(x, t), \mathbf{H}(x, t)) \right), \\ \frac{\partial \mathbf{H}(x, t)}{\partial t} &= D_t^{1-\alpha} \left(K_{\mathbf{H}} \frac{\partial^2 \mathbf{H}}{\partial x^2} + \sigma_{\mathbf{H}} g(\mathbf{D}(x, t), \mathbf{H}(x, t)) \right).\end{aligned}\quad (7)$$

The functions $f(\mathbf{D}(x, t), \mathbf{H}(x, t))$ and $g(\mathbf{D}(x, t), \mathbf{H}(x, t))$ or $f(\mathbf{D}, \mathbf{H})$ and $g(\mathbf{D}, \mathbf{H})$ represent the effects of chemical reactions and are

$$\begin{aligned}f(\mathbf{D}, \mathbf{H}) &= \mathbf{D} \left(1 - \frac{\mathbf{D} - \mathbf{H}}{C} \right), \\ g(\mathbf{D}, \mathbf{H}) &= \mathbf{H} \left(1 - \frac{\mathbf{D} - \mathbf{H}}{C} \right).\end{aligned}$$

We apply no-flux boundary conditions which can be written as

$$\begin{aligned}\mathbf{D}(L+1, t) &= \mathbf{D}(L, t); & \mathbf{D}(-1, t) &= \mathbf{D}(0, t); \\ \mathbf{H}(L+1, t) &= H(L, t); & \mathbf{H}(-1, t) &= \mathbf{H}(0, t).\end{aligned}\tag{8}$$

To solve (7) numerically, we divide the interval into m equal parts. We restrict our computations to a finite interval given as $0 \leq x \leq m$. As t is not discretized, the grid comprises the x values at which the solution is to be found and is given as $x_i = i\Delta x$; $i = 0, 1, 2, \dots, m$; $\Delta x = \frac{L}{m}$ and

$$\begin{aligned}\mathbf{D}_{m+1}(t) &= \mathbf{D}_m(t); & \mathbf{D}_{-1}(t) &= \mathbf{D}_0(t); \\ \mathbf{H}_{m+1}(t) &= H_m(t); & \mathbf{H}_{-1}(t) &= \mathbf{H}_0(t).\end{aligned}\tag{9}$$

We denote

$$\mathbf{D}_i(t) \approx \mathbf{D}(x_i, t), \quad \mathbf{H}_i(t) \approx \mathbf{H}(x_i, t).$$

By discretizing $\frac{\partial^2 \mathbf{D}}{\partial x^2}$ and $\frac{\partial^2 \mathbf{H}}{\partial x^2}$ from (7) using the *method of lines*, we get

$$\begin{aligned}\frac{\partial^2 \mathbf{D}}{\partial x^2} &\approx \frac{1}{(\Delta x)^2} \left(\mathbf{D}_{i+1}(t) - 2\mathbf{D}_i(t) + \mathbf{D}_{i-1}(t) \right), \\ \frac{\partial^2 \mathbf{H}}{\partial x^2} &\approx \frac{1}{(\Delta x)^2} \left(\mathbf{H}_{i+1}(t) - 2\mathbf{H}_i(t) + \mathbf{H}_{i-1}(t) \right).\end{aligned}\tag{10}$$

Using (10), we now arrive at the system of FDEs for equations (6)

$$\begin{aligned}\frac{d\mathbf{D}_i(t)}{dt} &= D_t^{1-\alpha} \left(K_{\mathbf{D}} \left[\frac{\mathbf{D}_{i+1}(t) - 2\mathbf{D}_i(t) + \mathbf{D}_{i-1}(t)}{(\Delta x)^2} + \sigma_{\mathbf{D}} f(\mathbf{D}_i(t), \mathbf{H}_i(t)) \right] \right), \\ \frac{d\mathbf{H}_i(t)}{dt} &= D_t^{1-\alpha} \left(K_{\mathbf{H}} \left[\frac{\mathbf{H}_{i+1}(t) - 2\mathbf{H}_i(t) + \mathbf{H}_{i-1}(t)}{(\Delta x)^2} + \sigma_{\mathbf{H}} g(\mathbf{D}_i(t), \mathbf{H}_i(t)) \right] \right).\end{aligned}\tag{11}$$

Hence, we find the fractional differential equation system as

$$\frac{d\mathbf{U}}{dt} = D_t^{1-\alpha} (\mathbf{J}\mathbf{U} + \mathbf{H}),$$

Second initial conditions

$$\mathbf{D}(x, 0) = \begin{cases} 1.2, & 90 \mu m \leq x \leq 95 \mu m, \\ 0, & \textit{elsewhere}. \end{cases}$$

$$\mathbf{H}(x, 0) = \begin{cases} 0.2, & 0 \mu m \leq x \leq 70 \mu m, \\ 0, & \textit{elsewhere}. \end{cases}$$

Third initial conditions.

$$\mathbf{D}(x, 0) = \begin{cases} 1.3, & 80 \mu m \leq x \leq 90 \mu m, \\ 0, & \textit{elsewhere}. \end{cases}$$

$$\mathbf{H}(x, 0) = \begin{cases} 0.75, & 60 \mu m \leq x \leq 80 \mu m, \\ 0, & \textit{elsewhere}. \end{cases}$$

Parameters used for the simulations are $\sigma_a = 2.25$, $\sigma_b = \sigma_a$, and $K_a = 0.25$, $K_b = K_a$. Numerical results based on these three initial conditions are shown in Figure (1), Figure (2) and Figure (3).

For Figure (1), the donor cells were placed into the host cells region or behind the host cells wavefront. Initially, the donor cells densities are at 1.8 and host cells are 1.4. Note that the gut carrying capacity density is 1. First, we discuss the variation of behaviour at $\alpha = 1$. We see that the cells at the donor-host interface are above the limit of gut carrying capacity. At $t = 50$, these donor cells do not proliferate but spread in either side of the donor-host interface. Meanwhile, host cells at the donor-host interface also not able to proliferate. Some donor and host cells migrated into the uninvaded region on either side of the donor-host interface. Both cells which are still at the donor-host interface ceased until they have achieved the carrying capacity density. The host cells which move on either side of the donor-host interface will proliferate to reach carrying capacity. Meanwhile, some donor cells which are moving on either side of the donor-host interface cease.

In the constrained environments, we see that both cells have slowed their movements due to increases in obstacles. At $t = 50$, some of the host cells which are moving to uninvaded region on either side of donor-host interface are slower to proliferate and still not reaching the carrying capacity density. After some times $t \geq 300$, then we can see the host cells at either side of the donor-host interface are able to reach the carrying capacity density. The effect of crowdedness is getting more severe, for instance at $\alpha = 0.5$, because during this time, the migration and proliferation of donor and host cells are slowing down. The process of spreading to either side of donor-host interface by donor cells also slows and needs longer time frames.

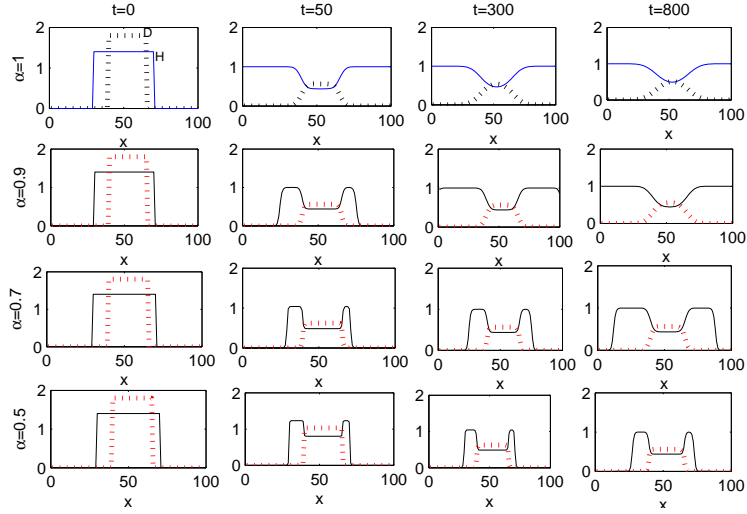


Figure 1: Simulation of donor (dotted) and host (solid) cell types with different α parameters at $t = 0, 50, 300$ and $t = 800$ based on the first initial condition.

Figure (2) investigates the effect of locating the donor cell in a region of unoccupied tissue. In this case, the cells from the donor tissue migrate in both rostral and caudal directions. At $t = 50$, we see that once the rostrally moving donor wave and caudally moving host wave travel towards each other, the waves coalesce. After coalescence, the cells at the donor-host interface cease proliferation since the total cell density is already reaching the capacity density. Looking at the behaviour of these cells in crowded environments, we see that the presence of obstacles have obstructed the movement of both cells to move rostrally and caudally. The time for each cells to coalesce is also slowing down. The slowing down of these cells is getting more severe when $\alpha = 0.5$.

In Figure (3), the donor cells were located at the front of the host cells leading edge. The behaviour of these cells are much similar to the results in Figure (2). Describing the system during normal diffusion, we see that donor cells form an invasion wave moving in both directions. As the donor cells migrate caudally, the host cells also migrate rostrally. These cells will invade until coalesce. After coalescence, cells at donor-host interface will cease proliferation in order to control gut carrying capacity. At $t=800$, we see that both cells mingling by diffusion resulting in a much slower rate of advance. As we increase the level of crowdedness in the system, obstacles scattered around the unoccupied area have impeded the migration of donor

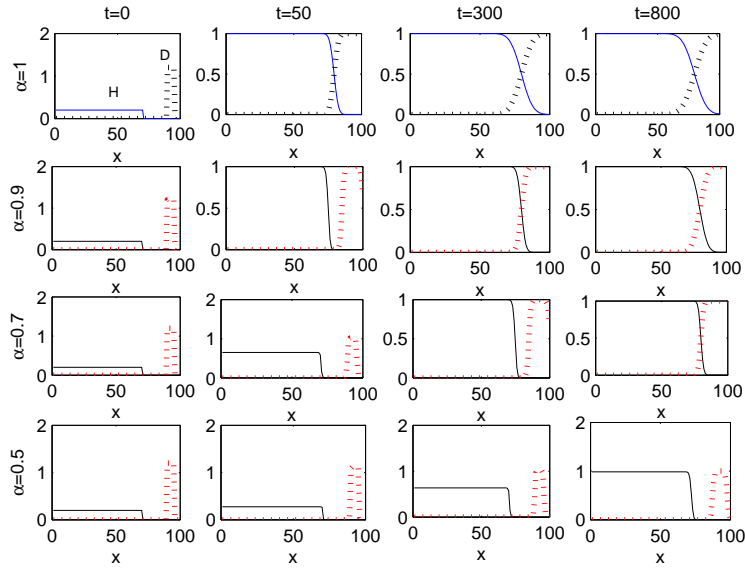


Figure 2: Mathematical simulation of donor (dotted) and host (solid) cell types with different α parameters at $t = 0, 50, 300$ and $t = 800$ based on the second initial condition.

and host cells. Both cells also need longer time frame before can invade each other.

4 Summary

In these numerical results, based on Figures (2) and (3), we can conclude that if the host Neural Crest derived cells and donor Neural Crest derived cells migrate in an opposite direction, both of these cells vanguards might impede with each other [13]. Another important results derived from these experiments is that at the donor-host interface, neither donor nor host neural crest cells proliferate once the total density reached maximum capacity. All results confirmed that immobile structures and barriers have caused the diffusion and proliferation of NC cells to slow down and sometimes the processes halt. Therefore the growing gut is not able to fully colonize within a specific time frame which has resulted in the syndrome such as Hirschsprung's Disease.

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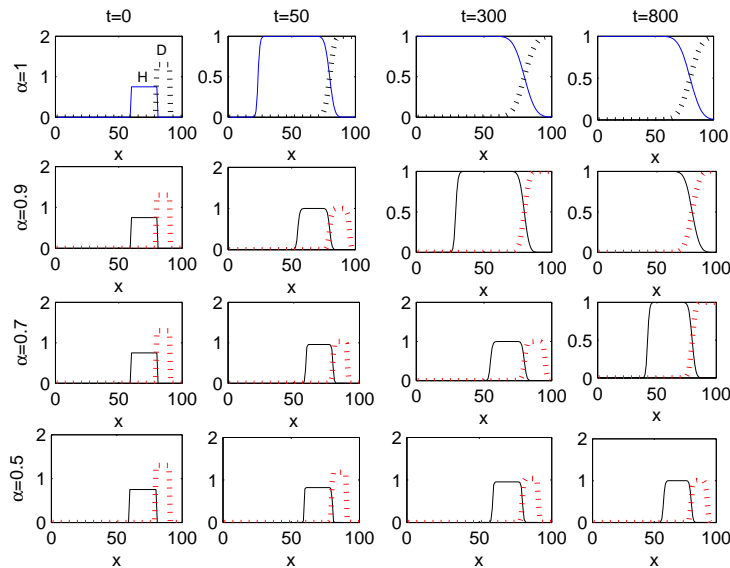


Figure 3: Mathematical simulation of donor (dotted) and host (solid) cell types with different α parameters at $t = 0, 50, 300$ and $t = 800$ on the third initial condition.

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References

- [1] R. Luther, *Propagation of chemical reactions in space*, *Elektrochem.*, 12, (1906), 596.
- [2] R. A. Fisher, The wave of advance advantageous genes, *Ann. Eugen.*, 7, (1937), 355–369.
- [3] C. P. Fall, E. S. Marland, J. M. Wagner and J. J. Tyson, Computational Cell Biology, *Interdisciplinary Applied Mathematics*, New York: Springer-Verlag, 2002.
- [4] J. D. Murray, Mathematical Biology - I. An Introduction, *Interdisciplinary Applied Mathematics*, 3rd ed. New York: Springer-Verlag, 2002.
- [5] V. Gubernov, G. N. Mercer, H. S. Sidhu and R. O. Weber, Numerical methods for the travelling waves solutions in reaction-diffusion equations, *ANZIAM J.*, 44(E), (2003), C271–C289. <http://anziamj.austms.org.au/v44/CTAC2001/Gube>

- [6] K. A. Landman, M. J. Simpson, J. L. Slater and D. F. Newgreen, Diffusive and Chemotactic Cellular Migration: Smooth and Discontinuous Travelling Wave Solutions, *SIAM J. Appl. Math.*, 65(4), (2005), 1420–1442. DOI: 10.1137/040604066
- [7] K.A. Landman, G.J. Pettet and D.F. Newgreen, Chemotactic Cellular Migration: Smooth and Discontinuous Travelling Wave Solutions, *SIAM J. Appl. Math.*, 63(5), (2003), 1666–1681. DOI: 10.1137/S0036139902404694
- [8] M.J. Simpson, K.A. Landman, B.D. Hughes and D.F. Newgreen, Looking inside an invasion wave of cells using continuum models: Proliferation is the key, *Journal of Theoretical Biology*, 243, (2006), 343–360. DOI: 10.1016/j.jtbi.2006.06.021
- [9] V. Mendez, J. Fort, G. H. Rotstein and S. Fedotov, Speed of reaction-diffusion fronts in spatially heterogeneous media, *Phys. Rev. E.*, 68, (2003) 041105. DOI:10.1103/PhysRevE.68.041105
- [10] O. M. Agrawal, Solution for A Fractional Diffusion-Wave Equation Defined In A Bounded Domain, *Nonlinear Dynam.*, 29, (2002) 145–155.
- [11] M. Edidin, The state of lipid rafts : from model membranes to cells. *Annu. Rev. Biophys. Biomol. Struct.*, 32, (2003), 257-283.
- [12] K.A. Landman, M.J. Simpson and D.F. Newgreen, Mathematical and experimental insights into the development of enteric nervous system and Hirschsprung’s Disease, *Develop. Growth Differ.*, 49, (2007), 277–286. DOI: 10.1111/j.1440-169x.2007.00929.x
- [13] M.J. Simpson, D.C. Zhang, M. Mariani, K.A. Landman and D.F. Newgreen, Cell proliferation drives neural crest cell invasion of the intestine, *Dev. Biol.*, 302, (2007), 553–568. DOI: 10.1016/j.ydbio.2006.10.017
- [14] K. B. Oldham and J. Spanier, The Fractional Calculus, 111, *Mathematics in Science and Engineering*, Academic Press, New York, 1974.
- [15] N. J. Ford and C. Simpson, Numerical approaches to the solution of some fractional differential equations, *Proceedings of Herma*, (2001), 100-107.
- [16] S.B. Yuste and K. Lindenberg, Subdiffusion limited A+A reactions, *Phys. Rev. Lett.*, 87, (2001), 1–4. ISSN: 0031-9007

- [17] S. B. Yuste and K. Lindenberg, Subdiffusion-limited reactions, *Chem. Phys.*, 284, (2002), 169–180. ISSN: 0301-0104
- [18] P. Ferreti, A. Copp, C. Tickle and G. Moore, Embryos, Genes and Birth Defects, 2nd ed., John Wiley and Sons, UK, 2006.
- [19] R. Skaba, Historic milestones of Hirschsprung’s disease (commemorating the 90th anniversary of Professor Harald Hirschsprung’s death), *J. Pediatr. Surg.*, 42, (2007), 249-251. DOI: 10.1016/j.jpedsurg.2006.09.024
- [20] E. Passarge, Dissecting Hirschsprung disease, *Nature Genet.*, 31, (2002), 11–12. DOI: 10.1038/ng878