Sains Malaysiana 42(5)(2013): 661–666

Simulations of Hirschsprung's Disease Using Fractional Differential Equations

(Simulasi Penyakit Hirschsprung Menggunakan Persamaan Pembezaan Pecahan)

F.A. ABDULLAH*

ABSTRACT

In this paper, we examined a model of cell invasion focusing on the wavefront of the neural crest (NC) cells in the case of Hirschsprung's disease (HSCR). Hirschsprung's disease (HSCR) is a congenital defect of intestinal ganglion cells and causes patients to have disorders in peristalsis. This simulation model was performed using the fractional differential equations (FDEs) based upon two basic cell functions. Here, we simulated the mathematical model in a one-dimensional setting, based on the fractional trapezoidal numerical scheme and the results showed an interesting outcome for the mobility of the cellular processes under crowded environments.

Keywords: Fractional differential equation; Hirschsprung disease; simulation

ABSTRAK

Dalam penyelidikan ini, kami mengkaji model berkaitan penyerangan sel dan fokus kajian adalah pada gelombang penyerangan sel neural dalam penyakit Hirschsprung (HSCR). Penyakit Hirschsprung (HSCR) adalah penyakit yang berkaitan dengan kecacatan semasa lahir atau sebelum lahir dan berpunca daripada sel ganglion sehingga menyebabkan proses periltalsis menjadi tidak normal. Model simulasi adalah berdasarkan persamaan pembezaan pecahan (FDES) ke atas dua sel asas. Kajian ini mensimulasikan model matematik dalam satu dimensi berpandukan kepada kaedah berangka trapezoid pecahan. Hasil keputusan daripada simulasi ini menunjukkan wujud hasil yang menarik daripada pergerakan sel dalam keadaan bersesak.

Kata kunci: Penyakit Hirschsprung; persamaan pembezaan pecahan; simulasi

INTRODUCTION

Hirschsprung's disease or HSCR is the name given to intestinal motility disorder (Ferreti et al. 2006; Skaba 2007). The main cause of the disease was discovered by Swenson (Ferreti et al. 2006), although HSCR was first described more than 50 years earlier by Harald Hirschsprung (Ferreti et al. 2006; Passarge 2002; Skaba 2007). Since then, the surgical treatments recommended for HSCR has been described, giving hope to its sufferers. In order to understand the underlying nature of HSCR, it is necessary to understand the enteric nervous system (ENS), which is part of the human peripheral nervous system that controls the gastrointestinal (GI) tract (Ferreti et al. 2006).

The ENS is present in all vertebrates and is important for regulating normal digestive activity of the digestion system. The ENS is established by rostral-to-caudal migration of neural crest (NC) cells along the GI tract (Yntema & Hammond 1954). During normal development, NC cells migrate from the oral (rostral) end of the developing vertebrate gut to the anal (caudal) end, in order to colonize the developing gut. However, under certain circumstances, NC cells fail to reach the caudal part of the gut, resulting in a lack of enteric ganglia in the caudal part of the gut. The gross reduction in intrinsic nerve cells also causes defects in the digestive system.

Details relating to cell migration along the developing gut are important as they provide understanding of ENS dysmorphologies, such as Hirschsprung's disease and cleft palate. Recently, there has been increased interest in studying the dynamic behaviour of these cells as they migrate through the gut. Landman et al. (2005) described cell migration based upon diffusion and chemotaxis mechanisms. Their model showed the existence of a travelling wave solution, regardless of whether the migration is purely diffusion, chemotaxis or a combination of both processes and showed that diffusion masks the influence of chemotaxis more effciently than chemotaxis masks diffusion. Simpson et al. (2006) later developed a population-scale mathematical model by including various cell mechanisms, as well as proliferation by logistic growth. Landman et al. (2007) combined and updated the work described by Simpson et al. (2006, 2007), stating that the relative contributions of cell motility, cell proliferation and gut growth determine NC cell invasion of the intestine in the growing gut. Their model also supports the hypothesis that an imbalance between gut growth and NC cell migration may also give rise to HSCR disease.

On observation, it seems that the majority of papers describing cell invasion or migration processes are based upon partial differential equations (PDE). Although these models agree with the experimental hypothesis, there is

a need to consider other approaches, so as to understand cell migration in the presence of molecular crowding. Previous research has discovered the effects of diffusion when biological environments have high densities and viscosities due to macromolecular crowding (Yuste & Lindenberg 2001, 2002; Yuste et al. 2004). Even though many numerical methods related to PDEs have been developed, their application to biological modelling has not, as yet, been given much attention. This motivated the application of the fractional differential equation (FDE) approach to modelling of Hirschsprung's disease (Landman et al. 2005, 2007; Simpson et al. 2006), since cell proliferation can block cell migration.

The structure of the paper is as follows. In the next section, we introduce the notion of fractional differentiation and later applied this differentiation to a physical problem. Finally, the results of this simulation are presented in the last section.

Numerical Method

Consider the fractional differential equation of the form:

$$\frac{dy(t)}{dt} = D_t^{1-\alpha} f\ (y(t) + g(y(t)), t \in [0, T],$$
$$y(0) = y_0, y_0 \in \mathbb{R}^m, \tag{1}$$

where $0 < \alpha < 1$. $D_t^{1-\alpha} f$ denotes the Riemann-Liouville fractional derivative (Oldham & Spanier 1974) of the function f, defined by:

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

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

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

The Caputo fractional derivative is given by:

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

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 (Oldham & Spanier 1974):

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

A number of authors, for example Diethelm et al. (2002, 2004), Ford and Simpson (2001), considered the numerical solution of so-called Caputo FDEs that take the form:

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

but here the preferred form is (1), as it is more naturally allied to problems discussed in this paper (Abdullah 2009). This form also appears when solving problems in systems biology arising from anomalous diffusion and chemical kinetics of molecular species in a crowded environment (Yuste & Lindenberg 2001, 2002).

To solve problem (1), we use the implicit fractional trapezoidal method written as:

$$y_{n+1} = y_n + \frac{h}{2}\left(D_t^{1-\alpha}\left(f(y_n) + f(y_n)\right)\right) + \frac{h}{2}\left(g(y_n) + g(y_{n+1})\right), \tag{5}$$

where h refers to the time stepsize.

In order to implement this method, numerical approximations to the fractional derivative operator are required. Here, the approximation by Diethelm et al. (2005) is used when approximating the Caputo fractional derivative operator:

$$D_t^{1-\alpha} f(y_n) \approx \frac{h^{\alpha-1}}{\Gamma(1+\alpha)} \sum_{j=0}^{n} C_{jn} f(y_j), \tag{6}$$

where $h = T/n$ is the integration stepsize, $t_j = jh, j = 0,1,2,\ldots, n$, y_n is an approximation to exact solution $y(t_n)$.

$$C_{jn} = \begin{cases} \alpha n^{\alpha-1} - n^{\alpha} + (n-1)^{\alpha}, & \text{if } j = 0, \\ (n-j+1)^{\alpha} - 2(n-j)^{\alpha} + (n-j-1)^{\alpha}, & \text{if } j = 1,2,3,\ldots,n-1, \\ 1, & \text{if } j = n. \end{cases} \tag{7}$$

Numerical Experiments

The system of partial differential model for donor and host population density was used by Simpson et al. (2006) in a non-growing gut system and later by Landman et al. (2007), who extend the system by including gut growth into the existing system.

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

$$\frac{\partial D}{\partial t} = D_t^{1-\alpha}\left(K_D \frac{\partial^2 D}{\partial x^2} + \sigma_D D\left(1 - \frac{D-H}{C}\right)\right) - \frac{\partial vD}{\partial x}, x \in [0, L], t > 0,$$
$$\frac{\partial H}{\partial t} = D_t^{1-\alpha}\left(K_H \frac{\partial^2 H}{\partial x^2} + \sigma_H H\left(1 - \frac{D-H}{C}\right)\right) - \frac{\partial vH}{\partial x}, \tag{8}$$

where D and H are the densities of donor and host cell types in space and time. Here, x represents the invasion axis or the position along the gut, K_D, K_H are the diffusivities of the donor and host cell types and σ_D, σ_H represent mitotic indicesfor the donor and host cell types, respectively. C is the carrying capacity density of the tissue and v represents the velocity field associated with growth of the gut.

If we set $\nu = 0$, then (8) is written as:

$$\frac{\partial D(x,t)}{\partial t} = D_t^{1-\alpha} = \left(K_D \frac{\partial^2 D(x,t)}{\partial x^2} + \sigma_D f\left(D(x,t), H(x,t)\right) \right),$$
$$\frac{\partial H(x,t)}{\partial t} = D_t^{1-\alpha} = \left(K_H \frac{\partial^2 H(x,t)}{\partial x^2} + \sigma_H g\left(D(x,t), H(x,t)\right) \right). \tag{9}$$

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

$$f(D,H) = D\left(1 - \frac{D-H}{C}\right),$$
$$g(D,H) = H\left(1 - \frac{D-H}{C}\right).$$

Values at the 'ghost points' are found using a discretized version of the boundary conditions $\partial D/\partial x\big|_{x=0,L} = 0$, $\partial H/\partial x\big|_{x=0,L} = 0$.

To solve (9) numerically, the interval is divided into m equal parts. Computations were restricted to a finite interval, given as $0 \le x \le m$. As t is not discretized, the grid comprises the x values at which the solution is to be found and is given as $x_i = i\Delta x;\ i = 0,1,2, \ldots, m$; $\Delta x = \frac{L}{m}$ and

$$D_{m+1}(t) = D_m(t);\ D_{-1}(t) = D_0(t);$$
$$H_{m+1}(t) = H_m(t);\ H_{-1}(t) = H_0(t). \tag{10}$$

We denote:

$$D_i(t) \approx D(x_i,t),\ H_i(t) \approx H(x_i,t).$$

By discretizing $\frac{\partial^2 D}{\partial x^2}$ and $\frac{\partial^2 H}{\partial x^2}$ from (9) using the method of lines, we get:

$$\frac{\partial^2 D}{\partial x^2} \approx \frac{1}{(\Delta x)^2}\left(D_{i+1}(t) - 2D_i(t) + D_{i-1}(t)\right),$$
$$\frac{\partial^2 H}{\partial x^2} \approx \frac{1}{(\Delta x)^2}\left(H_{i+1}(t) - 2H_i(t) + H_{i-1}(t)\right). \tag{11}$$

Using (11), we now arrive at the system of FDEs for (8):

$$\frac{dD_i(t)}{dt} = D_t^{1-\alpha}\left(K_D\left[\frac{D_{i+1}(t) - 2D_i(t) + D_{i-1}(t)}{(\Delta x)^2}\right] + \sigma_D f\left(D_i(t), H_i(t)\right)\right),$$
$$\frac{dH_i(t)}{dt} = D_t^{1-\alpha}\left(K_H\left[\frac{H_{i+1}(t) - 2H_i(t) + H_{i-1}(t)}{(\Delta x)^2}\right] + \sigma_H g\left(D_i(t), H_i(t)\right)\right). \tag{12}$$

Hence, we find the fractional differential equation system, as:

$$\frac{d\mathrm{U}}{dt} = D_t^{1-\alpha}\left(\mathrm{JU+H}\right),$$

where the discretisation matrix J is defined as:

$$\mathrm{J} = \frac{K}{(\Delta x)^2}\left[\begin{array}{ccccc|ccccc}
-1 & 1 & & & & & & & & \\
1 & -2 & 1 & & & & & & & \\
 & \ddots & \ddots & \ddots & & & & & & \\
 & & 1 & -2 & 1 & & & & & \\
 & & & 1 & -1 & & & & & \\
\hline
 & & & & & -1 & 1 & & & \\
 & & & & & 1 & -2 & 1 & & \\
 & & & & & & \ddots & \ddots & \ddots & \\
 & & & & & & & 1 & -2 & 1 \\
 & & & & & & & & 1 & -1
\end{array}\right] \tag{13}$$

and the vectors U and H are defined by:

$$\mathrm{U} = \left[\begin{array}{c} D_0(t) \\ D_1(t) \\ \vdots \\ \vdots \\ D_m(t) \\ \hline H_0(t) \\ H_1(t) \\ \vdots \\ \vdots \\ H_m(t) \end{array}\right];\ \mathrm{H} = \left[\begin{array}{c} \sigma_D f_0(t) \\ \sigma_D f_1(t) \\ \vdots \\ \vdots \\ \sigma_D f_m(t) \\ \hline \sigma_H g_0(t) \\ \sigma_H g_1(t) \\ \vdots \\ \vdots \\ \sigma_H g_m(t) \end{array}\right]. \tag{14}$$

In simulations, the donor and host cell populations are plotted at various time points $t = 0s$, $50s$, $300s$, $800s$ and the length of the axis $L = 100$ μm. Parameter L represents the invasion axis or gut length.

Here, the progress of these cells at different times is observed and the results are illustrated with different α parameters. These simulations are able to relate to the rostro-caudal (left to right) or caudo-rostal (right to left) progression wave during cell invasion of a growing gut. The initial conditions of these simulations are based on three conditions constructed to establish details of the rules of migration for the rostro-caudal wave of NC cells. From these results, several important questions about the nature of the behaviour of the NC cell invasion wave in crowded environments can be answered.

The first initial conditions:

$$D(x,0) = \begin{cases} 1.8, & 40\ \mu\mathrm{m} \le x \le 65\ \mu\mathrm{m}, \\ 0, & \text{elsewhere}, \end{cases}$$
$$H(x,0) = \begin{cases} 1.4, & 30\ \mu\mathrm{m} \le x \le 70\ \mu\mathrm{m}, \\ 0, & \text{elsewhere}, \end{cases}$$

The second initial conditions:

$$D(x,0) = \begin{cases} 1.2, & 90\ \mu\mathrm{m} \le x \le 95\ \mu\mathrm{m}, \\ 0, & \text{elsewhere}, \end{cases}$$
$$H(x,0) = \begin{cases} 0.2, & 0\ \mu\mathrm{m} \le x \le 70\ \mu\mathrm{m}, \\ 0, & \text{elsewhere}, \end{cases}$$

The third initial conditions:

$$D(x,0)=\begin{cases}1.3, & 80\ \mu\text{m} \le x \le 90\ \mu\text{m},\\ 0, & \text{elsewhere},\end{cases}$$

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

Parameters used for the simulations are $\sigma_D = 2.25$, $\sigma_H = \sigma_D$ and $K_D = 0.25$, $K_H = K_D$. Numerical results based on these three initial conditions are shown in Figures 1, 2 and 3.

Figure 1 shows the donor cells were placed into the host cell region or behind the host cell wavefront. Initially, donor cell density is 1.8 and that of host cells is 1.4. Note that the gut carrying capacity density is 1. First, the behaviour at $\alpha = 1$, is investigated and it can be seen that cells at the donor-host interface are above the limit of gut carrying capacity. At t = 50 s, these donor cells do not proliferate but spread to either side of the donor-host interface. Meanwhile, host cells at the donor-host interface are also unable to proliferate. Some donor and host cells migrate into the uninvaded regions on either side of the donor-host interface.The host cells that move to either side of the donor-host interface will proliferate to reach the carrying capacity. Meanwhile, some donor cells that are moving on either side of the donor-host interface die.

In constrained environments, we see that both types of cells show slower movements. At t = 50 s, some of the host cells that are moving to the uninvaded region on either side of donor-host interface are slower to proliferate and do not reach the carrying, capacity density. After $t \ge 300$ s we can see that host cells at either side of the donor-host interface are able to reach the carrying capacity density. The effect of crowdedness accentuates these effects. Figure 2 shows the effect of locating donor cells in a region of unoccupied tissue. In this case, cells from the donor tissue migrate in both rostral and caudal directions. At t = 50 s, we see that once the rostrally-moving donor wave and caudally-moving host wave meet each other, the waves coalesce. After coalescence, cells at the donor-host interface cease proliferation, since the total cell density already reaches the density capacity. In crowded environments the time for each cell to coalesce also slows down. In Figure 3, the donor cells were located ahead of the host cells' leading edge. The behavior of these cells is similar to the results in Figure 2. Describing the system during normal diffusion, it can be seen that donor cells form an invasion wave moving in both directions. As donor cells migrate caudally, host cells also migrate rostrally. These cells will invade until they coalesce. After coalescence, cells at the donor-host interface will cease proliferation in order to control the gut carrying capacity. At t = 800 s, we see that both cells are mingling by diffusion, resulting in a much slower rate of advance. As the level of crowdedness in the system is increased, both cell types also require longer time frames before they can invade each other.

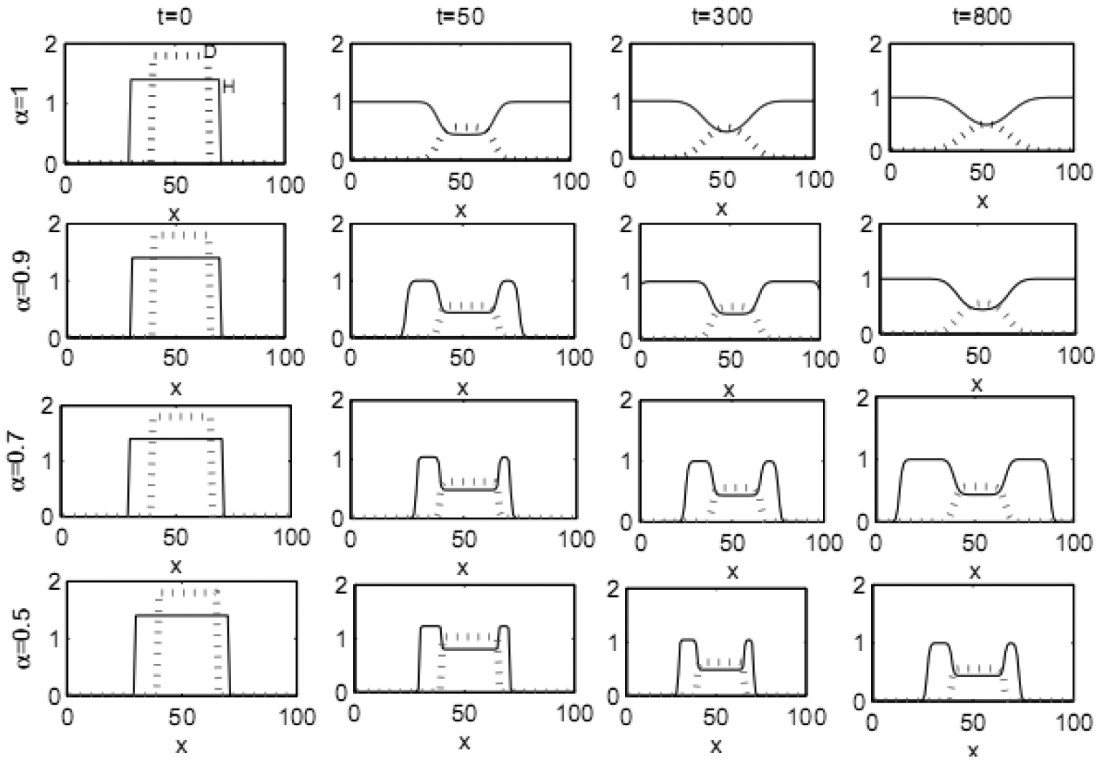

FIGURE 1. Simulation of donor (dotted) and host (solid) cell types with various α parameters at $t = 0s$, $50s$, $300s$ and $t = 800s$ based on the initial condition

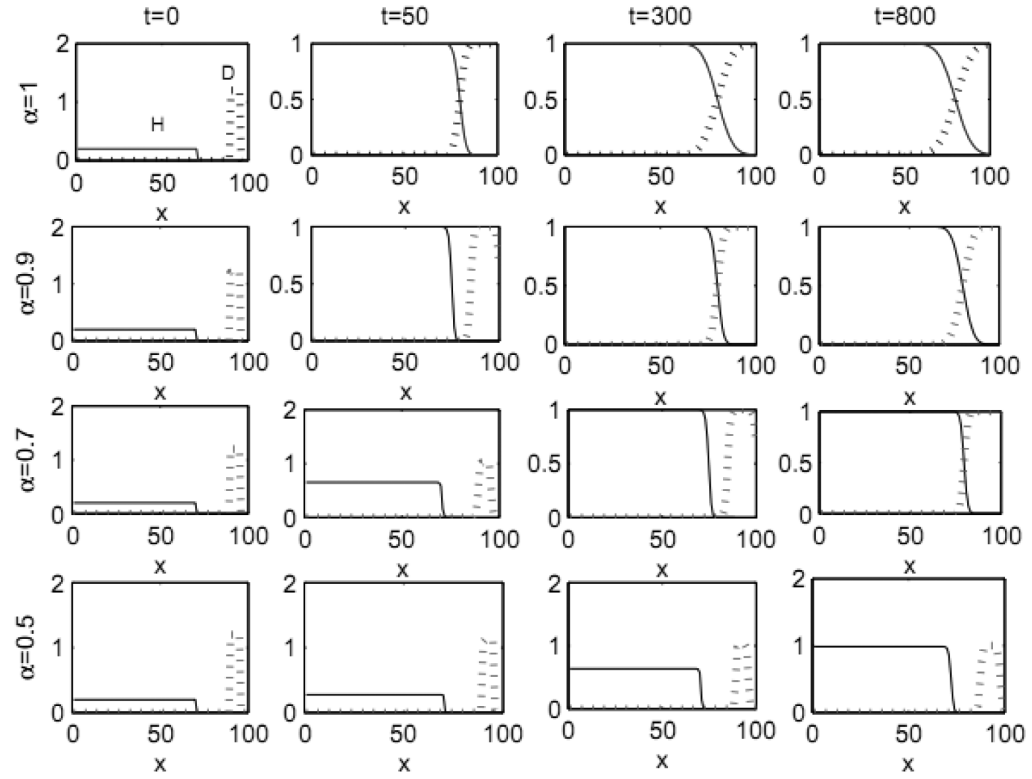

FIGURE 2. Mathematical simulation of donor (dotted) and host (solid) cell types with different α parameters at t = 0 s, 50 s, 300 s and t = 800 s based on the second initialcondition

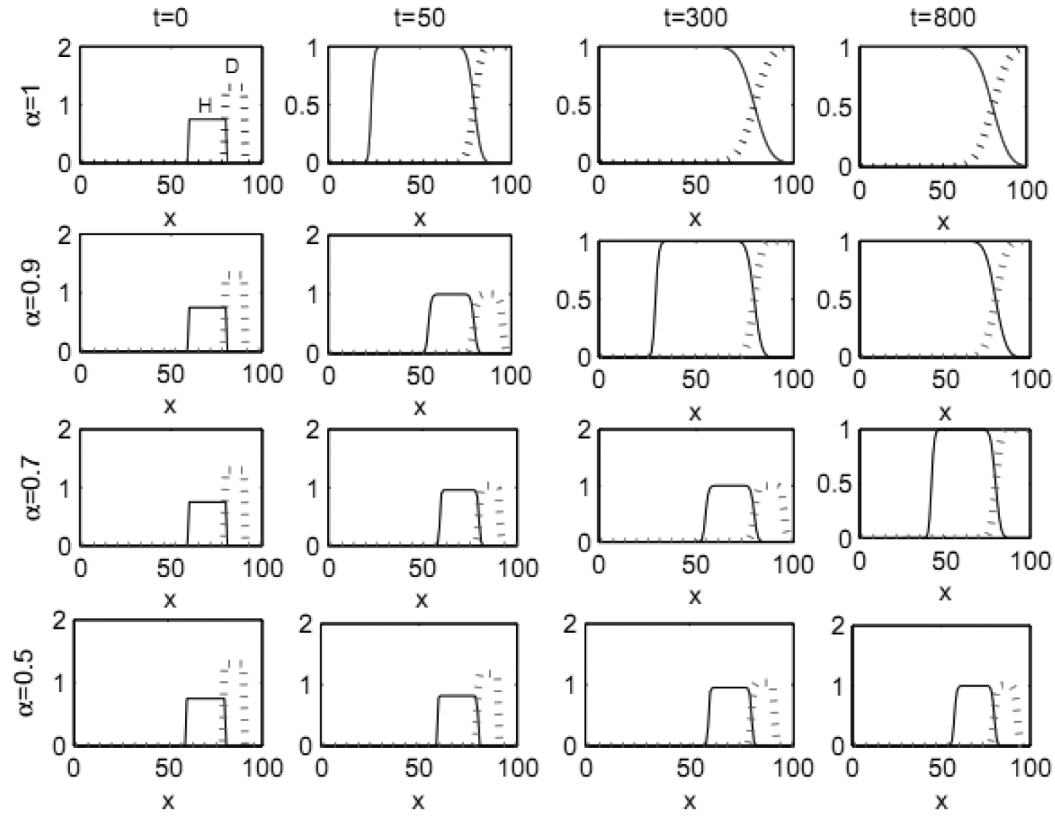

FIGURE 3. Mathematical simulation of donor (dotted) and host (solid) cell typeswith different α parameters at t = 0 s, 50 s, 300 s and t = 800 s on the third initialcondition

CONCLUSION

From these numerical results, based on Figures 2 and 3, it can be concluded that, if host NC-derived cells and donor NC-derived cells migrate in opposite directions, these cell vanguards might impede each other (Simpson et al. 2007). Another important result derived from these experiments is that, at the donor-host interface, neither donor nor host NC cells proliferate, once maximum capacity is reached. All results confirmed that anomalous diffusion caused the proliferation of NC cells to slow down and sometimes these processes halt. Therefore, the growing gut is not able to fully colonize within a specific time frame, resulting in a Hirschsprung's disease-like scenario.

ACKNOWLEDGEMENTS

The research was supported by the Incentive Grant from Universiti Sains Malaysia (Grant No:T174756/ MATHS6310072). The author thanks Professor Kevin Burrage of the Institute of Molecular Bioscience, University of Queensland, Australia for the valuable and useful discussion. The authors would also like to thank the reviewers for their comments that help improved the manuscript.

REFERENCES

Abdullah, F.A. 2009. Numerical methods for fractional differential equations and their applications to system biology. PhD Thesis, School of Physical Sciences, University of Queensland, Brisbane, Australia (unpublished).

Diethelm, K., Ford, N.J. & Freed, A.D. 2002. A Predictor-corrector approach for the numerical solution of fractional differential equations. *Nonlinear Dynam*. 29: 3-22.

Diethelm, K., Ford, N.J. & Freed, A.D. 2004. Detailed error analysis for a fractional Adams method. *Numerical Algorithms* 36: 31-52.

Diethelm, K., Ford, N.J., Freed, A.D. & Luchko, Y. 2005. Algorithms for the fractional calculus: A selection of numerical methods. *Comput. Methods Appl. Mech. Engrg*. 194: 743-773.

Ferreti, P., Copp, A. Tickle, C. & Moore, G. 2006. *Embryos, Genes and Birth Defects*. 2nd ed. UK: John Wiley and Sons.

Ford, N.J. & Simpson, C. 2001. Numerical approaches to the solution of some fractional differential equations. *Proceedings of HERCMA* 100-107.

Landman, K.A., Simpson, M.J. & Newgreen, D.F. 2007. Mathematical and experimental insights into the development of enteric nervous system and Hirschsprung's disease. *Develop. Growth Differ.* 49: 277-286.

Landman, K.A., Simpson, M.J., Slater, J.L. & Newgreen, D.F. 2005. Diffusive and chemotactic cellular migration: Smooth and discontinous travelling wave solutions. *SIAM J. Appl. Math*. 65(4): 1420-1442.

Oldham, K.B. & Spanier, J. 1974. *The Fractional Calculus, 111, Mathematics in Science and Engineering*. New York: Academic Press.

Passarge, E. 2002. Dissecting Hirschsprung disease. *Nat. Genet*. 31: 11-12.

Simpson, M.J., Landman, K.A., Hughes, B.D. & Newgreen, D.F. 2006. Looking inside an invasion wave of cells using continuum models: Proliferation is the key. *J. Theor. Biol*. 243: 343-360.

Simpson, M.J., Zhang, D.C., Mariani, M., Landman, K.A. & Newgreen, D.F. 2007. Cell proliferation drives neural crest cell invasion of the intestine. *Dev. Biol*. 302: 553-568.

Skaba, R. 2007. Historic milestones of Hirschsprung's disease (commemorating the 90th anniversary of Professor Harald Hirschsprung's death). *J. Pediatr. Surg*. 42: 249-251.

Yntema, C.L. & Hammond, W.S. 1954. The origin of intrinsic autonomic ganglia of trunk viscera in the chick embryo. *J. Comp. Neurol*. 101: 515-541.

Yuste, S.B., Acedo, L. & Lindenberg, K. 2004. Reaction front in an A+B→C reaction- subdiffusion process. *Phys. Rev. E* 69: 036126.

Yuste, S.B. & Lindenberg, K. 2001. Subdiffusion limited A+A reactions. *Phys. Rev. Lett*. 87: 118301.

Yuste, S.B. & Lindenberg, K. 2002. Subdiffusion-limited reactions. *Chem. Phys*. 284: 169-180.

School of Mathematical Sciences
Universiti Sains Malaysia
11800 USM, Pulau Pinang
Malaysia

*Corresponding author; email: farahaini@usm.my

Received: 20 July 2011
Accepted: 20 October 2012