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Diffusion-Chemotaxis Model of Effects of Cortisol on Immune Response to Human Immunodeficiency virus

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Abstract: In quest to contain and subsequently eradication Human Immunodeficiency virus (HIV) in the society, mathematical modelling remains an important research tool. In this paper, we formulated a mathematical model to study the effects of cortisol on immune response to HIV capturing the roles played by dendritic cells, T helper cells, regulatory T cells and cytotoxic T cells in the virus replication dynamics. The primary source of concentration of cortisol in this work is through psychological stress. Numerical experiments are performed to examine the effect of cortisol on selective inhibition of antigen presentation activities and up-regulation of naive cytotoxic T cells activation in the case of acute and persistent stressful conditions.

Keywords: chemotaxis system, radial basis functions, cortisol

MSC: 93A30, 92B08, 65P10, 65P35

1 Introduction

In last three and a half decades, there is all fronts battle against human immunodeficiency virus (HIV) disease due to its devastating consequences on the infected individual and the society. Researchers have been working hard to unravel the mysteries behind the virus pathogenesis, immune response and other possible parameters that may influence the progress of the disease but it is still not completely understood [1, 2]. For example, chronic immune activation and viral latency are among major factors that

favour the persistence of virus. Also, HIV attack is mainly on the command centre of the immune system called $CD4^+$ T-cells [3]. Though, it can also infect other immune cells with low level CD4 expression such as macrophages and dendritic cells [4].

There are convincing evidences that, chronic or persistence stress impact negatively on the immune system. The stimulation of sympathetic fibres releases hormones that bind to receptors on white blood cells [5–7]. Particularly, the hypothalamic–pituitary–adrenal (HPA), the sympathetic–adrenal–medullary (SAM), and the hypothalamic–pituitary–ovarian (HPO) axes secrete the adrenal hormones such as epinephrine, norepinephrine, and cortisol which regulate the immune cells distribution and function [8].

Cortisol inhibits the production of interleukin (IL)-12, interferon (IFN)-gamma, IFN-alpha, and tumor-necrosis-factor (TNF)-alpha by antigen-presenting cells (APCs) and T helper (Th)1 cells, but upregulates IL-4, IL-10, and IL-13 secreted by Th2 cells which results in a shift toward a Th2 immune response [9]. It also prevents proliferation of T-cells by rendering the interleukin-2 producer T-cells unresponsive to IL-1, and unable to produce the T-cell growth factor (IL-2) [10].

Several mathematical models have been formulated to study the HIV growth dynamics [11–16], drug therapy [17–20] and the rate of generation of HIV variants that escape immune responses [21–25]. Presently, just handful models of immune responses to HIV are found in literature [26, 27]. These models capture only the time evolution while little or no attention is given to spatial distribution of interacting cells and proteins. In this paper, we proposed a mathematical model of immune response to HIV under the influence of cortisol which captures the time evolution of the viral load, as in previous models, the potential effect of cell-to-cell transmission of HIV [28–33]. The rest of the paper is organized thus: model formulation is done in Section 2 while the analysis of the model is presented in Section 3. The numerical scheme is explained in Section 4 alongside with the results while Section 5 concludes the paper with important remarks.

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2 The Mathematical Model

In order to examine the effects of cortisol on immune response to HIV, the time evolution of viral load, dendritic cells, T helper cells, regulatory T cells, cytotoxic T cells, intercellular messengers and concentration of cortisol are modelled as a system of nonlinear partial differential equations, over a square domain Ω . Here, dendritic cells play two roles; viral particles carried by exposed dendritic cells are taken to CD4 T-cells for antigen presentation process and also transmit the virus to CD4 T-cells [34–37]. The symbols representing the state variables are described thus: c_1 : Concentration chemokine secreted by dendritic cells; c_2 : Concentration of cytokine secreted by T helper cells signalling attack on virus infected immune cells; c_3 : Concentration of cytokine secreted by T helper cells signalling self-regulation; c_4 : Concentration of cortisol in lymph node; p_1 : Average population naive immature dendritic cells; p_2 : Average population partially mature dendritic cells; p_3 : Average population fully mature dendritic cells; q_1 : Average population of naive regulatory T-cells; q_2 : Average population of activated regulatory T-cells; q_3 : Average population of naive cytotoxic T-cells; q_4 : Average population of activated cytotoxic T-cells; u_1 : Average population of naive T helper cells; u_2 : Average population of activated T helper cells; u_3 : Average population of latently infected T helper cells; u_4 : Average population of actively infected T helper cells; v : Average population density of HIV.

The immune cells release diverse intercellular messengers to communicate and direct the movement of both innate and adaptive immune system [38, 39]. The immune system communication processes are very complex which comprises of several chemical messengers secreted by different immune cells for specific functions but for the sake of simplicity, we only consider c_1, c_2, c_3 as described above. All the components have diffusion, secretion and decay terms as given in equations (1)–(3) below

$$\frac{\partial c_1}{\partial t} = \mathcal{D}_1 \Delta c_1 + a_1 p_3 - \sigma_1 c_1, \quad (1)$$

$$\frac{\partial c_2}{\partial t} = \mathcal{D}_2 \Delta c_2 + a_2 u_2 - \sigma_2 c_2, \quad (2)$$

$$\frac{\partial c_3}{\partial t} = \mathcal{D}_3 \Delta c_3 + a_3 u_2 - \sigma_3 c_3, \quad (3)$$

$$c_1(x, y, 0) = 0, \quad c_2(x, y, 0) = 0, \quad c_3(x, y, 0) = 0 \text{ in } \Omega,$$

$$\frac{\partial c_1}{\partial n} = \frac{\partial c_2}{\partial n} = \frac{\partial c_3}{\partial n} = 0 \text{ on } \partial\Omega.$$

There is strong evidence that adrenal hormones induced by stress, selectively inhibits or activates the response of immune cells [40]. Particularly, cortisol is known to inhibit

the production of chemokines responsible for antigen presentation process but upregulates the cytokines responsible for activation of naive cytotoxic T cells [41]. Experimental results show cortisol suppression of interleukin-12 (IL-12) synthesis and an increase in IL-10 production [42]. This model captures the two roles played by cortisol amongst several others. In equation (4) below, c_4 denotes concentration of cortisol with diffusion, secretion, decay and source terms.

$$\frac{\partial c_4}{\partial t} = \mathcal{D}_4 \Delta c_4 + a_4 c_4 - \sigma_4 c_4 + g(x, t), \quad (4)$$

$$c_4(x, y, 0) = C_{40}, \text{ in } \Omega, \quad \frac{\partial c_4}{\partial n} = 0 \text{ on } \partial\Omega.$$

Next, the population of dendritic cells is divided into three subpopulation. Equation (5) models rate of change of the density of the immature dendritic cells which have a source term ρ_1 while $b_1 p_1 v$ describes a portion of dendritic cells that successfully bind viral particle and die at the rate y_1 . Equation (6) describes the rate of change of the density of immature dendritic cells with viral particle ready for presentation in this case called partially matured. They move randomly at the rate $\mathcal{D}_5$ while they also move towards naive CD4 T-cells at the rate of $\chi_1(u_1) = \frac{d_1}{(d_1+u_1)^2}$ with dissociation constant d_1 . The rate at which they mature is b_2 and also experience death at rate y_2 . Equation (7) stand for rate of change of the density of mature dendritic cells with effective chemotaxis $\chi_2(p_2) = \frac{d_2}{(d_2+p_2)^2}$ with dissociation constant d_2 and diffusion term $\mathcal{D}_5 \Delta p_3$, and natural death rate of y_3 . Thus the following equations:

$$\frac{\partial p_1}{\partial t} = \mathcal{D}_5 \Delta p_1 + \rho_1 - b_1 p_1 v - y_1 p_1, \quad (5)$$

$$\frac{\partial p_2}{\partial t} = \mathcal{D}_5 \Delta p_2 - \nabla \cdot (\chi_1(u_1) p_2 \nabla u_1) + b_1 p_1 v - \frac{\omega b_2 p_2}{\omega + c_4} - y_2 p_2, \quad (6)$$

$$\frac{\partial p_3}{\partial t} = \mathcal{D}_5 \Delta p_3 + \nabla \cdot (\chi_2(p_2) p_3 \nabla p_2) + \frac{\omega b_2 p_2}{\omega + c_4} - y_3 p_3, \quad (7)$$

$$p_1(x, y, 0) = p_1^0, \quad p_2(x, y, 0) = 0, \quad p_3(x, y, 0) = 0 \text{ in } \Omega,$$

$$\frac{\partial p_1}{\partial n} = \frac{\partial p_2}{\partial n} = \frac{\partial p_3}{\partial n} = 0 \text{ on } \partial\Omega.$$

Regulatory T cells down-regulate the proliferation of T helper cells to check excessive reaction of the immune system [43]. According to Sakaguchi et al [43] regulatory T cells suppress the proliferation of naive T cells and their differentiation to effector T cells in vivo. They can also suppress effector activities of differentiated CD4⁺ and CD8⁺ T cells and the function of natural killer cells, natural killer T cells, B cells, macrophages, osteoclasts, and dendritic cells [44–47]. Once intercellular signal for this purpose is received, the naive regulatory T cells are activated and directed towards the immune cells that need regulation with

sensitivity function $\chi_3(q_4) = \frac{d_3}{(d_3+q_4)^2}$ with dissociation constant d_3 .

$$\frac{\partial q_1}{\partial t} = \mathfrak{D}_6 \Delta q_1 + \rho_2 - r_1 c_3 q_1 - \gamma_4 q_1, \quad (8)$$

$$\frac{\partial q_2}{\partial t} = \mathfrak{D}_6 \Delta q_2 - \nabla (\chi_3(q_4) q_2 \nabla q_4) + r_1 c_3 q_1 - \gamma_5 q_2, \quad (9)$$

$$q_1(x, y, 0) = q_1^0, \quad q_2(x, y, 0) = 0 \text{ in } \Omega,$$

$$\frac{\partial q_1}{\partial n} = \frac{\partial q_2}{\partial n} = 0 \text{ on } \partial\Omega.$$

Cytotoxic T cells kill the HIV infected immune cells to maintain the integrity of the immune system [48]. The activation of naive cytotoxic T cells is upregulated by cortisol concentration [f43]. In equation (10), ρ_3 is the source term for naive cytotoxic T cells, $r_2 \left(1 + \frac{c_4}{\omega}\right) c_2 q_3$ is the cortisol enhanced activation term and $\gamma_6 q_3$ is the portion of dead naive cytotoxic T cells. In equation (11) the activated cytotoxic T cells (q_4) tend to move towards the infected T helper cells (u_4) with a chemoattraction function $\chi_4(u_4) = \frac{d_4}{(d_4+u_4)^2}$ with dissociation constant d_4 while $k_2 q_2 q_4$ is the regulation term; $\gamma_7 q_4$ is the death term. To minimize the complexity of the model, it is assumed that, the HIV target cells are T helper cells while we neglect other immune cells with low CD4 expression.

$$\frac{\partial q_3}{\partial t} = \mathfrak{D}_7 \Delta q_3 + \rho_3 - r_2 \left(1 + \frac{c_4}{\omega}\right) c_2 q_3 - \gamma_6 q_3, \quad (10)$$

$$\frac{\partial q_4}{\partial t} = \mathfrak{D}_7 \Delta q_4 - \nabla (\chi_4(u_4) q_4 \nabla u_4) + r_2 \left(1 + \frac{c_4}{\omega}\right) c_2 q_3 - k_2 q_2 q_4 - \gamma_7 q_4, \quad (11)$$

$$q_3(x, y, 0) = q_3^0, \quad q_4(x, y, 0) = 0 \text{ in } \Omega,$$

$$\frac{\partial q_3}{\partial n} = \frac{\partial q_4}{\partial n} = 0 \text{ on } \partial\Omega.$$

Human Immunodeficiency virus (HIV) attack is largely directed at the command centre of the immune system [49–53]. In equations (12)–(15), $\mathfrak{D}_8$ is common diffusion coefficients of respective naïve, activated, latently infected and actively infected T helper cells for the sake of simplicity. During antigen presentation by the dendritic cells, the naive T helper cells are activated at the rate k_1 . The infection of both naive and activated T helper cells is considered in four ways: (i) during antigen presentation by the immature dendritic cells. (ii) After antigen presentation, mature dendritic cells migrate with viral particles to lymph node crowded with CD4 T-cells. (iii) Free viral particles (iv) Cell-to-cell transfer of virus by T helper cells. These four possible transmission avenues are captured by $(\delta_1 p_2 + \delta_2 p_3 + \delta_3 u_4 + \delta_4 v) u_1$ and $(\delta_1 p_2 + \delta_2 p_3 + \delta_3 u_4 + \delta_4 v) u_2$. In equation (12) naive T helper cells have constant source ρ_4 and death rate of μ_1 , the term $k_1 c_1 u_1$ represents the proportion of activated T helper cells which experience death at rate μ_2

as in equation (13). Equation (14) models the subpopulation of latently infected T helper cells in which the term $(\delta_1 p_2 + \delta_2 p_3 + \delta_3 u_4 + \delta_4 v) (u_1 + u_2)$ tells about infection of both naive and activated T helper cells and subsequently graduate into a group of actively infected T helper cells at the rate k_3 and die at the rate μ_3 . In equation (15), the actively infected T helper cells undergo lysing at the rate k_4 , they are also killed by the activated cytotoxic T cells at the rate r_3 and die at rate μ_4 .

$$\begin{aligned} \frac{\partial u_1}{\partial t} &= \mathfrak{D}_8 \Delta u_1 + \rho_4 - k_1 c_1 u_1 \\ &\quad - (\delta_1 p_2 + \delta_2 p_3 + \delta_3 u_4 + \delta_4 v) u_1 - \mu_1 u_1, \end{aligned} \quad (12)$$

$$\begin{aligned} \frac{\partial u_2}{\partial t} &= \mathfrak{D}_8 \Delta u_2 + k_1 c_1 u_1 - (\delta_1 p_2 + \delta_2 p_3 + \delta_3 u_4 + \delta_4 v) u_2 \\ &\quad - \mu_2 u_2, \end{aligned} \quad (13)$$

$$\begin{aligned} \frac{\partial u_3}{\partial t} &= \mathfrak{D}_8 \Delta u_3 + (\delta_1 p_2 + \delta_2 p_3 + \delta_3 u_4 + \delta_4 v) (u_1 + u_2) \\ &\quad - k_3 u_3 - \mu_3 u_3, \end{aligned} \quad (14)$$

$$\frac{\partial u_4}{\partial t} = \mathfrak{D}_8 \Delta u_4 + k_3 u_3 - r_3 q_4 u_4 - k_4 u_4 - \mu_4 u_4, \quad (15)$$

$$u_1(x, y, 0) = u_1^0, \quad u_2(x, y, 0) = 0, \quad u_3(x, y, 0) = 0,$$

$$u_4(x, y, 0) = 0 \text{ in } \Omega,$$

$$\frac{\partial u_1}{\partial n} = \frac{\partial u_2}{\partial n} = \frac{\partial u_3}{\partial n} = \frac{\partial u_4}{\partial n} = 0 \text{ on } \partial\Omega.$$

Finally, the actively infected T helper cells are lysed to produce N number of free virions per cell. The free virions are cleared from the system naturally at the rate μ_5 and also by infecting the target cells at the rate δ_4 as in equation (16).

$$\frac{\partial v}{\partial t} = \mathfrak{D}_9 \Delta v + N k_4 u_4 - \delta_4 (u_1 + u_2) v - \mu_5 v, \quad (16)$$

$$v(x, y, 0) = v^0 \text{ in } \Omega, \quad \frac{\partial v}{\partial n} = 0 \text{ on } \partial\Omega.$$

The parameter values of the model are presented in Table 1 below.

3 Kinetics System

When the mobility of the cells is considered very small to be neglected, this results into the kinetic system of the model given below:

$$\frac{dc_1}{dt} = a_1 p_3 - \sigma_1 c_1, \quad (17)$$

$$\frac{dc_2}{dt} = a_2 u_2 - \sigma_2 c_2, \quad (18)$$

$$\frac{dc_3}{dt} = a_3 u_2 - \sigma_3 c_3, \quad (19)$$

$$\frac{dc_4}{dt} = a_4 c_4 - \sigma_4 c_4 + g(t), \quad (20)$$

Table 1: Model Parameters.

Symbol	Description	Value/Reference
a_1	Rate of secretion chemokine by mature dendritic cells for antigen presentation	0.04 pg/cell/day
a_2	Rate of secretion of cytokine by activated T helper cells signalling attack on virus infected immune cells	0.06 pg/cell/day [54]
a_3	Rate of secretion of cytokine by activated T helper cells signalling for self-regulation	0.06 pg/cell/day [55]
a_4	Secretion rate of cortisol	0.04 [56]
b_1	Rate of activation of dendritic cells	0.3/day [57]
b_2	Rate of maturation of dendritic cells	0.4 /day [57, 58]
k_1	Rate of activation of naive T helper cells	0.4/day [57]
k_2	Rate of down-regulation by regulatory T-cells	0.3/cell/day [58]
k_3	Rate of activation of latently infected T helper cells into actively infected T helper cells	1.2×10^{-4} [59]
k_4	Rate of lysing actively infected T helper cells	0.25 /day [59]
r_1	Rate of activation of naive cytotoxic T-cells	0.3/day
r_2	Rate of activation of naive regulatory T-cells	0.4/day
r_3	Rate of killing of infected T helper cells by cytotoxic T-cells	0.00001 /day
δ_1	Antigen presentation enhanced infection rate	0.01vironsmm ³ /day[60]
δ_2	Mature dendritic cells enhanced infection rate	0.02vironsmm ³ /day[60]
δ_3	Cell-to-cell infection rate	0.3/day [59]
δ_4	Free virus-to-cell infection rate	0.05 vironsmm ³ /day[59]
N	Number of viruses produced by lysing an infected T helper cells	1500 virons/cell [60]
ω	Normal body concentration of cortisol	0.28mol/mm ³ [56]
ρ_1	Source term for naive immature dendritic cells	1.25×10^2 cells[60]
ρ_2	Source term for naive regulatory T-cells	3.63×10^2 cells[60]
ρ_3	Source term for naive cytotoxic T-cells	3.63×10^2 cells[60]
ρ_4	Source term for naive T helper cells	2.1×10^2 cells[60]
σ_1	Decay rate of chemokine secreted by dendritic cells	2.0/day
σ_2	Decay rate of cytokine secreted by T helper cells signalling attack on virus infected immune cells	2.16/day [61, 62]
σ_3	Decay rate of cytokine secreted by T helper cells signalling self-regulation	3.70/day [55]
σ_4	Decay rate of cortisol	0.1/day [56]
γ_1	Death rate of immature dendritic cells	0.35/day [63]
γ_2	Death rate of partially mature dendritic cells	0.25/day [63]
γ_3	Death rate of fully mature dendritic cells	1.0 /day [63]
γ_4	Death rate of naive regulatory T-cells	0.3/day [64]
γ_5	Death rate of activated regulatory T-cells	0.3/day [58]
γ_6	Death rate of naive cytotoxic T-cells	0.3/day [58]
γ_7	Death rate of activated cytotoxic T-cells	0.3/day [58]
μ_1	Death rate of naive T helper cells	0.06/day
μ_2	Death rate of activated T helper cells	0.06/day
μ_3	Death rate of latently infected T helper cells	0.06/day
μ_4	Death rate of actively infected T helper cells	0.24/day
μ_5	Death rate of free HIV	3/day
$\mathfrak{D}_1$	Diffusion rate of chemokine secreted by dendritic cells	0.0049 mm ² /day [65]
$\mathfrak{D}_2$	Diffusion rate of cytokine secreted by T helper cells signalling attack on virus infected immune cells	0.0042 mm ² /day [66]
$\mathfrak{D}_3$	Diffusion rate of cytokine secreted by T helper cells signalling self-regulation	0.0042 mm ² /day [67]
$\mathfrak{D}_4$	Diffusion rate of cortisol in lymph node	0.0049 mm ² /day
$\mathfrak{D}_5$	Diffusion rate of dendritic cells	0.0028 mm ² /day [68]
$\mathfrak{D}_6$	Diffusion rate of regulatory T-cells	0.0021 mm ² /day [69]
$\mathfrak{D}_7$	Diffusion rate of cytotoxic T-cells	0.0056 mm ² /day [69]
$\mathfrak{D}_8$	Diffusion rate of T helper cells	0.0045 mm ² /day [70]
$\mathfrak{D}_9$	Diffusion rate of HIV	0.0008mm ² /day
d_1	Chemotaxis rate of partially mature dendritic cells	0.0028 mm ² /day [69]
d_2	Chemotaxis rate of fully mature dendritic cells	0.0028 mm ² /day [69]
d_3	Chemotaxis rate of activated regulatory T-cells	0.0045 mm ² /day [70]
d_4	Chemotaxis rate of activated cytotoxic T-cells	0.0045 mm ² /day[70]

$$\frac{dp_1}{dt} = \rho_1 - b_1 p_1 v - y_1 p_1, \quad (21)$$

$$\frac{dp_2}{dt} = b_1 p_1 v - \frac{\omega b_2 p_2}{\omega + c_4} - y_2 p_2, \quad (22)$$

$$\frac{dp_3}{dt} = \frac{\omega b_2 p_2}{\omega + c_4} - y_3 p_3, \quad (23)$$

$$\frac{dq_1}{dt} = \rho_2 - r_1 c_3 q_1 - y_4 q_1, \quad (24)$$

$$\frac{dq_2}{dt} = r_1 c_3 q_1 - y_5 q_2, \quad (25)$$

$$\frac{dq_3}{dt} = \rho_3 - r_2 \left(1 + \frac{c_4}{\omega}\right) c_2 q_3 - y_6 q_3, \quad (26)$$

$$\frac{dq_4}{dt} = r_2 \left(1 + \frac{c_4}{\omega}\right) c_2 q_3 - k_2 q_2 q_4 - y_7 q_4, \quad (27)$$

$$\frac{du_1}{dt} = \rho_4 - k_1 c_1 u_1 - (\delta_1 p_2 + \delta_2 p_3 + \delta_3 u_4 + \delta_4 v) u_1 - \mu_1 u_1, \quad (28)$$

$$\frac{du_2}{dt} = k_1 c_1 u_1 - (\delta_1 p_2 + \delta_2 p_3 + \delta_3 u_4 + \delta_4 v) u_2 - \mu_2 u_2, \quad (29)$$

$$\frac{du_3}{dt} = (\delta_1 p_2 + \delta_2 p_3 + \delta_3 u_4 + \delta_4 v) (u_1 + u_2) - k_3 u_3 - \mu_3 u_3, \quad (30)$$

$$\frac{du_4}{dt} = k_3 u_3 - r_3 q_4 u_4 - k_4 u_4 - \mu_4 u_4, \quad (31)$$

$$\frac{dv}{dt} = N k_4 u_4 - \delta_4 (u_1 + u_2) v - \mu_5 v, \quad (32)$$

$$c_1(0) = 0, \quad c_2(0) = 0, \quad c_3(0) = 0, \quad c_4(0) = c_4^0,$$

$$p_1(0) = p_1^0, \quad p_2(0) = 0, \quad p_3(0) = 0,$$

$$q_1(0) = q_1^0, \quad q_2(0) = 0, \quad q_3(0) = q_3^0, \quad q_4(0) = 0,$$

$$u_1(0) = u_1^0, \quad u_2(0) = 0, \quad u_3(0) = 0,$$

$$u_4(0) = 0, \quad v(0) = v^0$$

3.1 The Equilibrium Points

The spatially homogeneous equilibrium point is gotten by setting the kinetic parts of (17)-(32) to zero and solving, we have

$$c_1^* = \frac{a_1 b_2 \omega}{\sigma_1}, \quad c_2^* = \frac{\rho_3 - y_6 y_7}{r_2 y_7 \xi_1}, \quad c_3^* = \frac{\rho_2 - y_4 y_5}{r_1 y_5},$$

$$c_4^* = \frac{g(t)}{\sigma_4 - a_4}, \quad p_1^* = \frac{\rho_1 - \omega b_2 - y_2 y_3 \xi_2}{y_1},$$

$$p_2^* = y_3 \xi_2, \quad p_3^* = \omega b_2, \quad q_1^* = y_5, \quad q_2^* = \frac{\rho_2 - y_4 y_5}{y_5},$$

$$q_3^* = \frac{k_2 \rho_2 - k_2 y_4 y_5}{y_5} + y_7, \quad q_4^* = \frac{\rho_3 - y_6 y_7}{y_7},$$

$$u_1^* = \frac{\rho_4 - \mu_2 u_2 - (k_3 + \mu_3) u_3}{\mu_1},$$

$$u_2^* = \frac{r_1 y_5 (\rho_3 - y_6 y_7) + (\rho_2 - r_2 y_4 y_5 y_7) \xi_1}{r_1 r_2 y_5 y_7 \xi_1},$$

$$u_3^* = \frac{r_3 (\rho_3 - y_6 y_7) - y_7 (k_4 + \mu_4)}{y_7},$$

$$u_4^* = k_3, \quad v^* = \frac{y_1 y_2 y_3 \xi_2 + \omega b_2 y_1}{b_1 \rho_1 - \omega b_1 b_2 - b_1 y_2 y_3 \xi_2}, \quad (33)$$

where $\xi_1 = \left(1 + \frac{g}{\omega(\sigma_4 - a_4)}\right)$, $\xi_2 = \left(\omega + \frac{g}{\sigma_4 - a_4}\right)$ and $\sigma_4 > a_4$.

3.2 Linearized System Eigenvalues

Here, the kinetic system (17)-(32) of the model is linearized using the Jacobian matrix method [71]. Simple algebra yields the eigenvalues of the Jacobian matrix given below:

$$\lambda_1 = -\sigma_1, \quad \lambda_2 = -\sigma_2, \quad \lambda_3 = -\sigma_3, \quad \lambda_4 = a_4 - \sigma_4,$$

$$\lambda_5 = -b_1 v^* - y_1, \quad \lambda_6 = -\frac{\omega b_2}{\omega + c_4^*} - y_2, \quad \lambda_7 = -y_3,$$

$$\lambda_8 = -r_1 c_3^* - y_4, \quad \lambda_9 = -y_5,$$

$$\lambda_{10} = -r_2 \left(1 + \frac{c_4^*}{\omega}\right) c_2^* - y_6, \quad \lambda_{11} = -y_7,$$

$$\lambda_{12} = -k_1 c_1^* - (\delta_1 p_2^* + \delta_2 p_3^* + \delta_3 u_4^* + \delta_4 v^*) - \mu_1,$$

$$\lambda_{13} = -(\delta_1 p_2^* + \delta_2 p_3^* + \delta_3 u_4^* + \delta_4 v^*) - \mu_2,$$

$$\lambda_{14} = -k_3 - \mu_3, \quad \lambda_{15} = -r_3 q_4^* - k_4 - \mu_4,$$

$$\lambda_{16} = -\delta_4 (u_1^* + u_2^*) - \mu_5. \quad (34)$$

Since all the eigenvalues are negative, the kinetic system is uniformly and asymptotically stable.

4 Model Solution

4.1 Numerical Method

Firstly, we observed that the system (1)-(16) can be grouped into diffusion ((1)-(5), (8), (10), (12)-(16)) and chemotaxis ((6), (7), (9), (11)) equations thereby expressing the system in the general form of Keller–Segel equations [72] thus:

$$\frac{\partial u}{\partial t} = \overbrace{D_1 \Delta u}^{\text{Diffusion}} - \overbrace{\nabla \cdot (\chi u \nabla v)}^{\text{Chemotaxis}} + \overbrace{f(u, v)}^{\text{Kinetic Terms}}, \quad (35)$$

$$\frac{\partial v}{\partial t} = \overbrace{D_2 \Delta v}^{\text{Diffusion}} + \overbrace{f(u, v)}^{\text{Kinetic Term}}, \quad (36)$$

In this work, we use Radial Basis Functions-Pseudospectral (RBF-PS) method [73] to solve the model numerically. Other numerical techniques such as the finite difference methods (FDMs), finite element methods (FEMs), and finite volume methods (FVMs) can also be applied. The pseudospectral (PS) techniques are superior to FDMs and FEMs because of its spectral accuracy i.e. PS methods achieve a desired accuracy with lesser number of

spatial grid-points than FDMs and FEMs [74]. Analytical methods such as homotopy methods proved to be useful in case of systems of few equations but become cumbersome and sometimes impossible with a system of large number of equations. RBF-PS method is implemented by formation of differentiation matrix associated with spectral method using RBF instead of orthogonal polynomial such as chebyshev or hermite. The time partial derivatives are usually discretized by appropriate time stepping scheme. Here, we use the forward finite difference scheme given as

$$\frac{\partial u}{\partial t} \approx \frac{u(x, y, \Delta t + t) - u(x, y, t)}{\Delta t} = \frac{U^{n+1} - U^n}{\Delta t}, \quad (37)$$

$$\frac{\partial v}{\partial t} \approx \frac{v(x, y, \Delta t + t) - v(x, y, t)}{\Delta t} = \frac{V^{n+1} - V^n}{\Delta t}. \quad (38)$$

In case of spatial derivatives, we use RBF $\Psi(\|x - x_i\|)$ for a set of data points $x_i \in R^2$, $i = 1, \dots, N$ such that the interpolations of u and v are given as

$$U(x) = \sum_{i=1}^N \alpha_{1i} \Psi(\|x - x_i\|), \quad V(x) = \sum_{i=1}^N \alpha_{2i} \Psi(\|x - x_i\|), \quad (39)$$

where $\|\cdot\|$ is the Euclidean norm, α_{1i} and α_{2i} are the coefficients respectively. The required derivatives of RBF are given by

$$\begin{aligned} U_{xx}^n(x) &= \sum_{i=1}^N \alpha_{1i}^n \frac{\partial^2}{\partial x^2} \Psi(\|x - x_i\|), \\ V_{xx}^n(x) &= \sum_{i=1}^N \alpha_{2i}^n \frac{\partial^2}{\partial x^2} \Psi(\|x - x_i\|), \\ U_x^n(x) &= \sum_{i=1}^N \alpha_{1i}^n \frac{\partial}{\partial x} \Psi(\|x - x_i\|), \\ V_x^n(x) &= \sum_{i=1}^N \alpha_{2i}^n \frac{\partial}{\partial x} \Psi(\|x - x_i\|). \end{aligned} \quad (40)$$

Now, equations (39)–(41) can be written in matrix form as

$$U = A\alpha_1, \quad V = A\alpha_2, \quad (42)$$

$$U_{xx} = A_{xx}\alpha_1, \quad V_{xx} = A_{xx}\alpha_2, \quad U_x = A_x\alpha_1, \quad V_x = A_x\alpha_2, \quad (43)$$

where $U = [u_1, u_2, \dots, u_N]^T$, $V = [v_1, v_2, \dots, v_N]^T$, $A_{i,j} = \Psi(\|x_i - x_j\|)$, $A_{xxi,j} = \frac{\partial^2}{\partial x^2} \Psi(\|x_i - x_j\|)$, $A_{xi,j} = \frac{\partial}{\partial x} \Psi(\|x_i - x_j\|)$, $\alpha_1 = [\alpha_{11}, \alpha_{12}, \dots, \alpha_{1N}]^T$, $\alpha_2 = [\alpha_{21}, \alpha_{22}, \dots, \alpha_{2N}]^T$ while x_j are centres. Here, we used the following RBFs

$$\Psi(x_i, y_i) = \sqrt{(x - x_i)^2 + (y - y_i)^2 + c^2} \quad \text{Multiquadric(MQ)} \quad (44)$$

$$\Psi(x_i, y_i) = \exp\left(-c(x - x_i)^2 - c(y - y_i)^2\right) \quad \text{Gaussian(GA)} \quad (45)$$

where c is the shape parameter. More on RBFs solution of PDEs can be found in [75–78].

In view of (37), (38) and (43), the approximate solutions of (35) and (36) at every time step $t^n = n\Delta t$ with zero boundary conditions at the collocation points $\{x_i\}_{i=1}^N$ and $\{y_i\}_{i=1}^N$ is leads to a system of vector equations

$$U^{n+1} = U^n + \Delta t \{D_1 (U_{xx}^n + U_{yy}^n) - X + f(U^n, V^n)\}, \quad (46)$$

$$V^{n+1} = V^n + \Delta t \{D_2 (V_{xx}^n + V_{yy}^n) + f(U^n, V^n)\}, \quad (47)$$

where we use $\cdot^*$ to represent element-wise multiplication of matrices and

$$\begin{aligned} X &= \chi(V^n) \cdot^* (U_x^n \cdot^* V_x^n + U_y^n \cdot^* V_y^n) \\ &+ \chi(V^n) \cdot^* U^n \cdot^* (V_{xx}^n + V_{yy}^n) \\ &+ U^n \cdot^* (\chi_x(V^n) \cdot^* V_x^n + \chi_y(V^n) \cdot^* V_y^n), \\ U^n &= \{U^n(x_i, y_i)\}_{i=1}^N, \quad U_x^n = A_x A^{-1} U^n, \quad U_y^n = A_y A^{-1} U^n, \\ U_{xx}^n &= A_{xx} A^{-1} U^n, \quad U_{yy}^n = A_{yy} A^{-1} U^n. \end{aligned}$$

Consequently, using the same approach, the discretized form of system (1)–(16) is given as

$$C_1^{n+1} = C_1^n + \Delta t \{D_1 (C_{1xx}^n + C_{1yy}^n) + a_1 P_3^n - \sigma_1 C_1^n\}, \quad (48)$$

$$C_2^{n+1} = C_2^n + \Delta t \{D_2 (C_{2xx}^n + C_{2yy}^n) + a_2 U_2^n - \sigma_2 C_2^n\}, \quad (49)$$

$$\begin{aligned} C_3^{n+1} &= C_3^n + \Delta t \{D_3 (C_{3xx}^n + C_{3yy}^n) + a_3 U_2^n - \sigma_3 C_3^n\}, \quad (50) \\ C_4^{n+1} &= C_4^n \\ &+ \Delta t \{D_4 (C_{4xx}^n + C_{4yy}^n) + a_4 C_4^n - \sigma_4 C_4^n + g(x_i, y_j, t^n)\}, \end{aligned} \quad (51)$$

$$\begin{aligned} P_1^{n+1} &= P_1^n \\ &+ \Delta t \{D_5 (P_{1xx}^n + P_{1yy}^n) + \rho_1 - b_1 P_1^n \cdot^* V^n - y_1 P_1^n\}, \quad (52) \\ P_2^{n+1} &= P_2^n \\ &+ \Delta t \left\{ D_5 (P_{2xx}^n + P_{2yy}^n) - \theta_1 + b_1 P_1^n \cdot^* V^n - \frac{\omega b_2 P_2^n}{\omega + C_4^n} - y_2 P_2^n \right\}, \end{aligned} \quad (53)$$

$$\begin{aligned} P_3^{n+1} &= P_3^n \\ &+ \Delta t \left\{ D_5 (P_{3xx}^n + P_{3yy}^n) - \theta_2 + \frac{\omega b_2 P_2^n}{\omega + C_4^n} - y_3 P_3^n \right\}, \quad (54) \\ Q_1^{n+1} &= Q_1^n \\ &+ \Delta t \{D_6 (Q_{1xx}^n + Q_{1yy}^n) + \rho_2 - r_1 C_3^n \cdot^* Q_1^n - y_4 Q_1^n\}, \quad (55) \\ Q_2^{n+1} &= Q_2^n \\ &+ \Delta t \{D_6 (Q_{2xx}^n + Q_{2yy}^n) - \theta_3 + r_1 C_3^n \cdot^* Q_1^n - y_5 Q_2^n\}, \quad (56) \\ Q_3^{n+1} &= Q_3^n + \Delta t \{D_7 (Q_{3xx}^n + Q_{3yy}^n) + \rho_3 \\ &- r_2 \left(1 + \frac{C_4^n}{\omega}\right) \cdot^* C_2^n \cdot^* Q_3^n - y_6 Q_3^n\}, \quad (57) \\ Q_4^{n+1} &= Q_4^n + \Delta t \{D_7 (Q_{4xx}^n + Q_{4yy}^n) - \theta_4 \\ &+ r_2 \left(1 + \frac{C_4^n}{\omega}\right) \cdot^* C_2^n \cdot^* Q_3^n - k_2 Q_2^n \cdot^* Q_4^n - y_7 Q_4^n\}, \quad (58) \end{aligned}$$

$$U_1^{n+1} = U_1^n + \Delta t \left\{ \mathfrak{D}_8 (U_{1xx}^n + U_{1yy}^n) + \rho_4 - k_1 C_1^n \cdot * U_1^n - \Theta_5 \cdot * U_1^n - \mu_1 U_1^n \right\}, \quad (59)$$

$$U_2^{n+1} = U_2^n + \Delta t \left\{ \mathfrak{D}_8 (U_{2xx}^n + U_{2yy}^n) + k_1 C_1^n \cdot * U_1^n - \Theta_5 \cdot * U_2^n - \mu_2 U_2^n \right\}, \quad (60)$$

$$U_3^{n+1} = U_3^n + \Delta t \left\{ \mathfrak{D}_8 (U_{3xx}^n + U_{3yy}^n) + \Theta_5 \cdot * (U_1^n + U_2^n) - k_3 U_3^n - \mu_3 U_3^n \right\}, \quad (61)$$

$$U_4^{n+1} = U_4^n + \Delta t \left\{ \mathfrak{D}_8 (U_{4xx}^n + U_{4yy}^n) + k_3 U_3^n - r_3 Q_4^n \cdot * U_4^n - k_4 U_4^n - \mu_4 U_4^n \right\}, \quad (62)$$

$$V^{n+1} = V^n + \Delta t \left\{ \mathfrak{D}_9 (V_{xx}^n + V_{yy}^n) + N k_4 U_4^n - \delta_4 (U_1^n + U_2^n) V^n - \mu_5 V^n \right\}, \quad (63)$$

where $\cdot *$ denotes element wise multiplication of matrices and

$$\begin{aligned} \Theta_1 &= \chi_1 (U_1^n) \cdot * (P_{2x}^n \cdot * U_{1x}^n + P_{2y}^n \cdot * U_{1y}^n) \\ &\quad + \chi_1 (U_1^n) \cdot * P_2^n \cdot * (U_{1xx}^n + U_{1yy}^n) \\ &\quad + P_2^n \cdot * (\chi_{1x} (U_1^n) \cdot * U_{1x}^n + \chi_{1y} (U_1^n) \cdot * U_{1y}^n) \\ \Theta_2 &= \chi_2 (P_2^n) \cdot * (P_{2x}^n \cdot * P_{3x}^n + P_{2y}^n \cdot * P_{3y}^n) \\ &\quad + \chi_2 (P_2^n) \cdot * D_3^n \cdot * (P_{2xx}^n + P_{2yy}^n) \\ &\quad + P_3^n \cdot * (\chi_{2x} (P_2^n) \cdot * P_{2x}^n + \chi_{2y} (P_2^n) \cdot * P_{2y}^n) \\ \Theta_3 &= \chi_3 (Q_4^n) \cdot * (Q_{2x}^n \cdot * Q_{4x}^n + Q_{2y}^n \cdot * Q_{4y}^n) \\ &\quad + \chi_3 (Q_4^n) \cdot * Q_2^n \cdot * (Q_{4xx}^n + Q_{4yy}^n) \\ &\quad + Q_2^n \cdot * (\chi_{3x} (Q_4^n) \cdot * Q_{4x}^n + \chi_{3y} (Q_4^n) \cdot * Q_{4y}^n) \\ \Theta_4 &= \chi_4 (U_4^n) \cdot * (Q_{4x}^n \cdot * U_{4x}^n + Q_{4y}^n \cdot * U_{4y}^n) \\ &\quad + \chi_4 (U_4^n) \cdot * Q_4^n \cdot * (U_{4xx}^n + U_{4yy}^n) \\ &\quad + Q_4^n \cdot * (\chi_{4x} (U_4^n) \cdot * U_{4x}^n + \chi_{4y} (U_4^n) \cdot * U_{4y}^n) \\ \Theta_5 &= (\delta_1 P_2^n + \delta_2 P_3^n + \delta_3 U_4^n + \delta_4 V^n) \end{aligned}$$

4.2 Numerical Results

The above numerical scheme (48)-(63) is coded using MATLAB R2013a (see Appendix A.1.). The simulation is primarily to examine the effect of cortisol on dendritic cells activation and antigen presentation. The experiments also, tend to examine up-regulation of naive cytotoxic T cells $q_3(x, y, t)$ activation by cortisol concentration $c_4(x, y, t)$. The domain of simulation is a rectangle $[-2, 2] \times [-2, 2]$ while the parameter values are taken from Table 1. Source

term for cortisol concentration $g(t)$ is considered (i) transient, representing acute stress; (ii) constant, representing persistent stress, i.e.

$$g(t) = \begin{cases} 0.02 \cos(0.1\pi x) \cos(0.05\pi y) e^{-0.2t}, & \text{acute - stress} \\ 0.2, & \text{persistent - stress} \end{cases} \quad (64)$$

and the initial conditions are given as

$$\begin{aligned} c_4(x, y, 0) &= 2.8, \quad p_1(x, y, 0) = 200e^{-0.75(x+1)^2 - 0.75(y+1)^2}, \\ q_1(x, y, 0) &= 200e^{-0.75(x-1)^2 - 0.75(y-1)^2}, \\ q_3(x, y, 0) &= 300e^{-0.75(x+1)^2 - 0.75(y+1)^2}, \\ u_1(x, y, 0) &= 400e^{-0.75(x-1)^2 - 0.75y^2}, \quad v(x, y, 0) = 10. \end{aligned} \quad (65)$$

For simplicity, we used the chebyshev points

$$-\frac{1}{2} \left((b+a-2\Delta x) + (b-a-2\Delta x) \cos \left(\frac{(2k-1)\pi}{2N} \right) \right), \quad k = 1, 2, \dots, N; \quad \Delta x = \frac{b-a}{N} \quad (66)$$

to generate centres within the square domain $[a, b]^2$.

The numerical experiments are presented below in Figures 1–8. It is deduced from the plots below that, the diffusion of concentration of chemokines secreted by dendritic cells is much faster in persistent stress scenario (Figure 2(a), Figure 6 (a)) than the acute stress (Figure 1(a), Figure 5 (a)) thereby inducing the activation of naive T helper cells $u_1(x, y, t)$ in the same proportion (Figure 6(d), Figure 8(d)). Furthermore, the up-regulation effect of cortisol on naive cytotoxic T cells $q_3(x, y, t)$ activation was also observed but the activation is much faster in the case of persistent stress (Figure 6(c), Figure 8(c)).

5 Conclusion

In this work, we study a 2-dimensional chemotaxis system of immune response to HIV in the presence of cortisol concentration high than normal in lymph organ. The homogeneous endemic equilibrium point of the system are evaluated, examined and found to be uniformly and asymptotically stable. The model is solved numerically in MATLAB using RBFs-PS method where the temporal derivative is discretized by forward finite difference scheme while the spatial derivatives are discretized using radial basis functions.

Fig. 1: Plots of concentration gradients of (a) chemokine secreted by dendritic cells, (b) cytokine secreted by T helper cells signalling attack on virus infected immune cells, (c) cytokine secreted by T helper cells signalling self-regulation and (d) cortisol; during acute stress for $t = 2.5$ days

Fig. 2: Plots of concentration gradients of (a) chemokine secreted by dendritic cells, (b) cytokine secreted by T helper cells signalling attack on virus infected immune cells, (c) cytokine secreted by T helper cells signalling self-regulation and (d) cortisol; during persistent stress for $t = 2.5$ days

Fig. 3: Plots of concentration gradients of (a) chemokine secreted by dendritic cells, (b) cytokine secreted by T helper cells signalling attack on virus infected immune cells, (c) cytokine secreted by T helper cells signalling self-regulation and (d) cortisol; during acute stress for $t = 5$ days

Fig. 4: Plots of concentration gradients of (a) chemokine secreted by dendritic cells, (b) cytokine secreted by T helper cells signalling attack on virus infected immune cells, (c) cytokine secreted by T helper cells signalling self-regulation and (d) cortisol; during persistent stress for $t = 5$ days

Fig. 5: Plots of density distribution of (a) partially mature dendritic cells, (b) mature dendritic cells, (c) activated cytotoxic T cells and (d) activated T helper cell; during acute stress for $t = 2.5$ days

Fig. 6: Plots of density distribution of (a) partially mature dendritic cells, (b) mature dendritic cells, (c) activated cytotoxic T cells and (d) activated T helper cell; during persistent stress for $t = 2.5$ days

Fig. 7: Plots of density distribution of (a) partially mature dendritic cells, (b) mature dendritic cells, (c) activated cytotoxic T cells and (d) activated T helper cell; during acute stress for $t = 5$ days

Fig. 8: Plots of density distribution of (a) partially mature dendritic cells, (b) mature dendritic cells, (c) activated cytotoxic T cells and (d) activated T helper cell; during persistent stress for $t = 5$ days

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A.1. Matlab Codes

```

1 clear all
2 clc
3 Tf=15;a=-2; b=2; nx=21; ny=21; dx=(b-a)/nx;dy=(b-a)/ny;
4 x=a:dx:b; y=a:dy:b; dt=0.005; N=Tf/dt;
5 %Constants
6 a1=0.04; a2=0.06; a3=0.06; a4=0.04; b1=0.3; b2=0.4; k1=0.4; k2=0.3;
7 k3=0.00012; k4=0.25; Nv=150; r1=0.3; r2=0.4; r3=0.00001;
8 sigma1=2.0; sigma2=2.16; sigma3=3.7; sigma4=0.1; gamma1=0.35;
9 gamma2=0.25; gamma3=1.0; gamma4=0.3; gamma5=0.3; gamma6=0.3;
10 gamma7=0.3; rho1=1.25e+02; rho2=3.63e+02; rho3=3.63e+02; rho4=2.10e+02;
11 delta1=0.001; delta2=0.002; delta3=0.3; delta4=0.005; mu1=0.06;
12 mu2=0.06; mu3=0.06; mu4=0.24; mu5=3.0; omega=0.28;
13
14 %Preallocation
15 c1t=zeros(nx+1,ny+1);      c2t=zeros(nx+1,ny+1);      c3t=zeros(nx+1,ny+1);
16 c4t=zeros(nx+1,ny+1);      p1t=zeros(nx+1,ny+1);      p2t=zeros(nx+1,ny+1);
17 p3t=zeros(nx+1,ny+1);      q1t=zeros(nx+1,ny+1);      q2t=zeros(nx+1,ny+1);
18 q3t=zeros(nx+1,ny+1);      q4t=zeros(nx+1,ny+1);      u1t=zeros(nx+1,ny+1);
19 u2t=zeros(nx+1,ny+1);      u3t=zeros(nx+1,ny+1);      u4t=zeros(nx+1,ny+1);
20 vt=zeros(nx+1,ny+1);
21 %
22 c1=zeros(nx+1,ny+1);      c2=zeros(nx+1,ny+1);      c3=zeros(nx+1,ny+1);
23 c4=zeros(nx+1,ny+1);      p1=zeros(nx+1,ny+1);      p2=zeros(nx+1,ny+1);
24 p3=zeros(nx+1,ny+1);      q1=zeros(nx+1,ny+1);      q2=zeros(nx+1,ny+1);
25 q3=zeros(nx+1,ny+1);      q4=zeros(nx+1,ny+1);      u1=zeros(nx+1,ny+1);
26 u2=zeros(nx+1,ny+1);      u3=zeros(nx+1,ny+1);      u4=zeros(nx+1,ny+1);
27 v=zeros(nx+1,ny+1);
28 % IC
29 for i=1:nx
30     for j=1:ny
31         wao=0.75;
32         c1t(i,j)=0;
33         c2t(i,j)=0;
34         c3t(i,j)=0;
35         c4(i,j)=5.8;
36         p1t(i,j)=200*exp(-wao*(x(i)-1).^2-wao*(y(j)+1).^2);
37         p2t(i,j)=0;
38         p3t(i,j)=0;
39         q1t(i,j)=200*exp(-wao*(x(i)-1).^2-wao*(y(j)-1).^2);
40         q2t(i,j)=0;
41         q3t(i,j)=300*exp(-wao*(x(i)+1).^2-wao*(y(j)+1).^2);
42         q4t(i,j)=0;
43         u1t(i,j)=400*exp(-wao*(x(i)-1).^2-wao*(y(j)).^2);
44         u2t(i,j)=0;
45         u3t(i,j)=0;
46         u4t(i,j)=0;
47         vt(i,j)=10;
48     end
49 end
50 %%
51 for n=1:N
52     %%
53     c1=c1t; c2=c2t; c3=c3t; c4=c4t; p1=p1t; p2=p2t; p3=p3t; q1=q1t;
54     q2=q1t; q3=q3t; q4=q4t; u1=u1t; u2=u2t; u3=u3t; u4=u4t; v=vt;
55     [xp,yp]=meshgrid(x);
56     kk=1:nx+1;

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57 x0=-0.5*(b+a-2*dx)-0.5*(b-a-2*dx)*cos(((2*kk-1)*pi)/(2*nx));
58 [xc,yc]=meshgrid(x0);
59 for i=2:nx
60     for j=2:ny
61         % Spatial Derivatives
62         c=0.45;
63         GA(i,j) = exp(-c*((xp(i,j)-xc(i,j)).^2+(yp(i,j)-yc(i,j)).^2));
64         GI(i,j)=(GA(i,j))^-1;
65         %
66         GAx(i,j) = -2*c*(xp(i,j)-xc(i,j)).*GA(i,j);
67         GAY(i,j) = -2*c*(yp(i,j)-yc(i,j)).*GA(i,j);
68         GAXX(i,j)=-2*c*exp(-c*(xp(i,j)-xc(i,j)).^2 - c*(yp(i,j)-yc(i,j)).^2)+...
69             4*c^2*exp(-c*(xp(i,j)-xc(i,j)).^2 - c*(yp(i,j)-yc(i,j)).^2).*(xp(i,j)-xc(i,j))
70             .^2;
71         GAYY(i,j) = -2*c*exp(-c*(xp(i,j)-xc(i,j)).^2 - c*(yp(i,j)-yc(i,j)).^2)+...
72             4*c^2*exp(-c*(xp(i,j)-xc(i,j)).^2 - c*(yp(i,j)-yc(i,j)).^2).*(yp(i,j)-yc(i,j))
73             .^2;
74
75         % First Oder x direction
76         c1x(i,j)=GAx(i,j)*GI(i,j);
77         c2x(i,j)=GAx(i,j)*GI(i,j);
78         c3x(i,j)=GAx(i,j)*GI(i,j);
79         c4x(i,j)=GAx(i,j)*GI(i,j);
80         p1x(i,j)=GAx(i,j)*GI(i,j);
81         p2x(i,j)=GAx(i,j)*GI(i,j);
82         p3x(i,j)=GAx(i,j)*GI(i,j);
83         q1x(i,j)=GAx(i,j)*GI(i,j);
84         q2x(i,j)=GAx(i,j)*GI(i,j);
85         q3x(i,j)=GAx(i,j)*GI(i,j);
86         q4x(i,j)=GAx(i,j)*GI(i,j);
87         u1x(i,j)=GAx(i,j)*GI(i,j);
88         u2x(i,j)=GAx(i,j)*GI(i,j);
89         u3x(i,j)=GAx(i,j)*GI(i,j);
90         u4x(i,j)=GAx(i,j)*GI(i,j);
91         vx(i,j)=GAx(i,j)*GI(i,j);
92
93         % firt oder y direction
94         c1y(i,j)=GAY(i,j)*GI(i,j);
95         c2y(i,j)=GAY(i,j)*GI(i,j);
96         c3y(i,j)=GAY(i,j)*GI(i,j);
97         c4y(i,j)=GAY(i,j)*GI(i,j);
98         p1y(i,j)=GAY(i,j)*GI(i,j);
99         p2y(i,j)=GAY(i,j)*GI(i,j);
100        p3y(i,j)=GAY(i,j)*GI(i,j);
101        q1y(i,j)=GAY(i,j)*GI(i,j);
102        q2y(i,j)=GAY(i,j)*GI(i,j);
103        q3y(i,j)=GAY(i,j)*GI(i,j);
104        q4y(i,j)=GAY(i,j)*GI(i,j);
105        u1y(i,j)=GAY(i,j)*GI(i,j);
106        u2y(i,j)=GAY(i,j)*GI(i,j);
107        u3y(i,j)=GAY(i,j)*GI(i,j);
108        u4y(i,j)=GAY(i,j)*GI(i,j);
109        vy(i,j)=GAY(i,j)*GI(i,j);
110
111        % Second order x direction
112        c1xx(i,j)=GAXX(i,j)*GI(i,j);
113        c2xx(i,j)=GAXX(i,j)*GI(i,j);
114        c3xx(i,j)=GAXX(i,j)*GI(i,j);
115        c4xx(i,j)=GAXX(i,j)*GI(i,j);
116        p1xx(i,j)=GAXX(i,j)*GI(i,j);

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115 p2xx(i,j)=GAXx(i,j)*GI(i,j);
116 p3xx(i,j)=GAXx(i,j)*GI(i,j);
117 q1xx(i,j)=GAXx(i,j)*GI(i,j);
118 q2xx(i,j)=GAXx(i,j)*GI(i,j);
119 q3xx(i,j)=GAXx(i,j)*GI(i,j);
120 q4xx(i,j)=GAXx(i,j)*GI(i,j);
121 u1xx(i,j)=GAXx(i,j)*GI(i,j);
122 u2xx(i,j)=GAXx(i,j)*GI(i,j);
123 u3xx(i,j)=GAXx(i,j)*GI(i,j);
124 u4xx(i,j)=GAXx(i,j)*GI(i,j);
125 vxx(i,j)=GAXx(i,j)*GI(i,j);
126
127 % second order y direction
128 c1yy(i,j)=GAYy(i,j)*GI(i,j);
129 c2yy(i,j)=GAYy(i,j)*GI(i,j);
130 c3yy(i,j)=GAYy(i,j)*GI(i,j);
131 c4yy(i,j)=GAYy(i,j)*GI(i,j);
132 p1yy(i,j)=GAYy(i,j)*GI(i,j);
133 p2yy(i,j)=GAYy(i,j)*GI(i,j);
134 p3yy(i,j)=GAYy(i,j)*GI(i,j);
135 q1yy(i,j)=GAYy(i,j)*GI(i,j);
136 q2yy(i,j)=GAYy(i,j)*GI(i,j);
137 q3yy(i,j)=GAYy(i,j)*GI(i,j);
138 q4yy(i,j)=GAYy(i,j)*GI(i,j);
139 u1yy(i,j)=GAYy(i,j)*GI(i,j);
140 u2yy(i,j)=GAYy(i,j)*GI(i,j);
141 u3yy(i,j)=GAYy(i,j)*GI(i,j);
142 u4yy(i,j)=GAYy(i,j)*GI(i,j);
143 vyy(i,j)=GAYy(i,j)*GI(i,j);
144
145 %COMPLETE SYSTEM
146 %Random and chemotaxis Constants
147 Df1=0.0049; Df2=0.0042; Df3=0.0042; Df4=0.0049; Df5=0.0028; Df6=0.0021;
148 Df7=0.0056; Df8=0.0045; Df9=0.0008; t=n*dt;
149 d1=2.8; d2=2.8; d3=4.5; d4=4.5;
150 c1t(i,j)= c1(i,j)+ dt*(Df1*(c1xx(i,j)+c1yy(i,j))...
151 +a1*p3(i,j)-sigma1*c1(i,j));
152 c2t(i,j)=c2(i,j)+dt*(Df2*(c2xx(i,j)+c2yy(i,j))...
153 +a2*u2(i,j)- sigma2*c2(i,j));
154 c3t(i,j)=c3(i,j)+dt*(Df3*(c3xx(i,j)+c3yy(i,j))...
155 +a3*u2(i,j)- sigma3*c3(i,j));
156 c4t(i,j)=c4(i,j)+dt*(Df4*(c4xx(i,j)+c4yy(i,j))...
157 +a4*c4(i,j)-sigma4*c4(i,j)+ ...
158 0.02*cos(0.1*pi*x(i)).*cos(0.05*pi*y(j)).*exp(-0.2*t));
159 %DENDRITIC CELLS SUBGROUP
160 p1t(i,j)=p1(i,j)+dt*(Df5*(p1xx(i,j)+p1yy(i,j))...
161 +rho1-b1*p1(i,j).*v(i,j)-gamma1*p1(i,j));
162 p2t(i,j)= p2(i,j)+dt*(Df5*(p2xx(i,j)+p2yy(i,j))-...
163 ((d1*p2(i,j))./((d1+u1(i,j)).^2).*(u1xx(i,j)+u1yy(i,j))...
164 +(d1/(d1+u1(i,j)).^2).*(p2x(i,j).*u1x(i,j)+p2y(i,j).*u1y(i,j))...
165 -(2*d1*p2(i,j))./((d1+u1(i,j)).^3).*((u1x(i,j)).^2 ...
166 +(u1yy(i,j)).^2))+b1*p1(i,j).*v(i,j)...
167 -(omega*b2*p2(i,j))./(omega+c4(i,j))-gamma2*p2(i,j));
168 p3t(i,j)= p3(i,j)+dt*(Df5*(p3xx(i,j)+p3yy(i,j))-...
169 ((d2*p3(i,j))./((d2+p2(i,j)).^2).*(p2xx(i,j)+p2yy(i,j))...
170 +(d2/(d2+p2(i,j)).^2).*(p3x(i,j).*p2x(i,j)+p3y(i,j).*p2y(i,j))...
171 -(2*d2*p3(i,j))./((d2+p2(i,j)).^3).*((p2x(i,j)).^2 ...
172 +(p2yy(i,j)).^2))+ (omega*b2*p2(i,j))./(omega+c4(i,j))...
173 -gamma3*p3(i,j));
174 %REGULATORY T-CELLS SUBGROUP

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175 q1t(i,j)=q1(i,j)+dt*(Df6*(q1xx(i,j)+q1yy(i,j))...
176 +rho2-r1*c3(i,j).*q1(i,j)-gamma4*q1(i,j));
177 q2t(i,j)=q2(i,j)+dt*(Df5*(q2xx(i,j)+q2yy(i,j))...
178 -((d3*q2(i,j))./((d3+q4(i,j)).^2).*(q4xx(i,j)+q4yy(i,j))...
179 +(d3/(d3+q4(i,j)).^2).*(q2x(i,j).*q4x(i,j)+q2y(i,j).*q4y(i,j))...
180 -(2*d3*q2(i,j))./((d3+q4(i,j)).^3).*(q4x(i,j)).^2 ...
181 +(q4yy(i,j)).^2))+r1*c3(i,j).*q1(i,j)-gamma5*q2(i,j));
182 %CYTOTOXIC T-CELLS SUBGROUP
183 q3t(i,j)=q3(i,j)+dt*(Df7*(q3xx(i,j)+q3yy(i,j))...
184 +rho3-r2*(1+c4(i,j)/omega).*c2(i,j).*q3(i,j)-gamma6*q3(i,j));
185 q4t(i,j)=q4(i,j)+dt*(Df5*(q4xx(i,j)+q4yy(i,j))-...
186 ((d4*q4(i,j))./((d4+u4(i,j)).^2).*(u4xx(i,j)+u4yy(i,j))...
187 +(d4/(d4+u4(i,j)).^2).*(q4x(i,j).*u4x(i,j)+q4y(i,j).*u4y(i,j))...
188 -(2*d4*q4(i,j))./((d4+u4(i,j)).^3).*(u4x(i,j)).^2 ...
189 +(u4yy(i,j)).^2))+r2*(1+c4(i,j)/omega).*c2(i,j).*q3(i,j)...
190 -k2*q2(i,j).*q4(i,j)-gamma7*q4(i,j));
191 % T HELPER CELLS
192 u1t(i,j)=u1(i,j)+dt*(Df8*(u1xx(i,j)+u1yy(i,j))...
193 +rho4-k1*c1(i,j).*u1(i,j)-(delta1*p2(i,j)+delta2*p3(i,j)...
194 +delta3*u4(i,j)+delta4*v(i,j)).*u1(i,j)-mu1*u1(i,j));
195 u2t(i,j)= u2(i,j)+dt*(Df8*(u2xx(i,j)+u2yy(i,j))...
196 +k1*c1(i,j).*u1(i,j)-(delta1*p2(i,j)+delta2*p3(i,j)...
197 +delta3*u4(i,j)+delta4*v(i,j)).*u2(i,j)-mu2*u2(i,j));
198 u3t(i,j)=u3(i,j)+dt*(Df8*(u3xx(i,j)+u3yy(i,j))...
199 +(delta1*p2(i,j)+delta2*p3(i,j)+delta3*u4(i,j)...
200 +delta4*v(i,j)).*(u1(i,j)+u2(i,j))-k3*u3(i,j)-mu3*u3(i,j));
201 u4t(i,j)=u4(i,j)+dt*(Df8*(u4xx(i,j)+u4yy(i,j))...
202 +k3*u3(i,j)-r3*q4(i,j).*u4(i,j)-k4*u4(i,j)-mu4*u4(i,j));
203 % HIV
204 vt(i,j)= v(i,j)+dt*(Df9*(vxx(i,j)+vyy(i,j))+Nv*k4*u4(i,j)...
205 -delta4*(u1(i,j)+u2(i,j)).*v(i,j)-mu5*v(i,j));
206
207 %BC
208 c1(1,j)=0; c1(nx+1,j)=0;
209 c2(1,j)=0; c2(nx+1,j)=0;
210 c3(1,j)=0; c3(nx+1,j)=0;
211 c4(1,j)=0; c4(nx+1,j)=0;
212 p1(1,j)=0; p1(nx+1,j)=0;
213 p2(1,j)=0; p2(nx+1,j)=0;
214 p3(1,j)=0; p3(nx+1,j)=0;
215 q1(1,j)=0; q1(nx+1,j)=0;
216 q2(1,j)=0; q2(nx+1,j)=0;
217 q3(1,j)=0; q3(nx+1,j)=0;
218 q4(1,j)=0; q4(nx+1,j)=0;
219 u1(1,j)=0; u1(nx+1,j)=0;
220 u2(1,j)=0; u2(nx+1,j)=0;
221 u3(1,j)=0; u3(nx+1,j)=0;
222 u4(1,j)=0; u4(nx+1,j)=0;
223 v(1,j)=0; v(nx+1,j)=0;
224
225 c1(i,1)=0; c1(i,nx+1)=0;
226 c2(i,1)=0; c2(i,nx+1)=0;
227 c3(i,1)=0; c3(i,nx+1)=0;
228 c4(i,1)=0; c4(i,nx+1)=0;
229 p1(i,1)=0; p1(i,nx+1)=0;
230 p2(i,1)=0; p2(i,nx+1)=0;
231 p3(i,1)=0; p3(i,nx+1)=0;
232 q1(i,1)=0; q1(i,nx+1)=0;
233 q2(i,1)=0; q2(i,nx+1)=0;
234 q3(i,1)=0; q3(i,nx+1)=0;

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```

235         q4(i,1)=0; q4(i,nx+1)=0;
236         u1(i,1)=0; u2(i,nx+1)=0;
237         u3(i,1)=0; u3(i,nx+1)=0;
238         u4(i,1)=0; u4(i,nx+1)=0;
239         v(i,1)=0; v(i,nx+1)=0;
240
241     end
242 end
243 %% Plotting Results
244 if mod(n,250)==0
245     xx=x(2:end-1);
246     yy=y(2:end-1);
247     figure
248     subplot(2,2,1)
249     hd1 = surf(xx,yy,c1(2:end-1,2:end-1));
250     set(hd1,'edgecolor','none');
251     title('(A) Conc. of Dendritic Cells Chemokine')
252     zlabel('c_1(x,y, t)');
253     xlabel('x');
254     ylabel('y');
255     axis([-2 2 -2 2])
256     %caxis([-10,15]);
257     shading interp
258     view(-40,55);
259     %colorbar;
260     subplot(2,2,2)
261     hd2 = surf(xx,yy,c2(2:end-1,2:end-1));
262     set(hd2,'edgecolor','none');
263     title('(B) Conc. of Effector Cytokine')
264     %title('B');
265     zlabel('c_2(x,y,t)');
266     xlabel('x');
267     ylabel('y');
268     axis([-2 2 -2 2])
269     %caxis([-10,15]);
270     shading interp
271     view(-40,55);
272     %colorbar;
273     subplot(2,2,3)
274     hd3 = surf(xx,yy,c3(2:end-1,2:end-1));
275     set(hd3,'edgecolor','none');
276     axis([-2 2 -2 2])
277     title('(C) Conc. of Regulatory Cytokine')
278     zlabel('c_3(x,y,t)');
279     xlabel('x');
280     ylabel('y');
281     %caxis([-10,15]);
282     shading interp
283     view(-40,55);
284     %colorbar;
285     subplot(2,2,4)
286     hd4 = surf(xx,yy,c4(2:end-1,2:end-1));
287     set(hd4,'edgecolor','none');
288     axis([-2 2 -2 2])
289     title('(D) Conc. of Cortisol')
290     zlabel('c_4(x,y,t)');
291     xlabel('x');
292     ylabel('y');
293     %caxis([-10,15]);
294     shading interp

```

```

295     view(-40,55);
296     %colorbar;
297     Shikaa = ['nlegA', int2str(n), '.tiff'];
298     print(Shikaa, '-dtiff', '-r350')
299     %% figure 2
300     figure
301     subplot(2,2,1)
302     hd5 = surfc(xx,yy,p2(2:end-1,2:end-1));
303     set(hd5,'edgecolor','none');
304     title('(A) Partially Matured Dendritic Cells');
305     zlabel('p_2(x,y,t)');
306     xlabel('x');
307     ylabel('y');
308     axis([-2 2 -2 2])
309     %caxis([-10,15]);
310     shading interp
311     view(-40,55);
312     %colorbar;
313     subplot(2,2,2)
314     hd6 = surfc(xx,yy,p3(2:end-1,2:end-1));
315     set(hd6,'edgecolor','none');
316     title('(B) Matured Dendritic Cells');
317     zlabel('p_3(x,y,t)');
318     xlabel('x');
319     ylabel('y');
320     axis([-2 2 -2 2])
321     %caxis([-10,15]);
322     shading interp
323     view(-40,55);
324     %colorbar;
325     subplot(2,2,3)
326     hd11 = surfc(xx,yy,q4(2:end-1,2:end-1));
327     set(hd11,'edgecolor','none');
328     axis([-2 2 -2 2])
329     title('(C) Activated Cytotoxic T Cells');
330     zlabel('q_4(x,y,t)');
331     xlabel('x');
332     ylabel('y');
333     %caxis([-10,15]);
334     shading interp
335     view(-40,55);
336     %colorbar;
337     subplot(2,2,4)
338     hd13 = surfc(xx,yy,u2(2:end-1,2:end-1));
339     set(hd13,'edgecolor','none');
340     title('(D) Activated T Helper Cells');
341     axis([-2 2 -2 2])
342     zlabel('u_2(x,y,t)');
343     xlabel('x');
344     ylabel('y');
345     %caxis([-10,15]);
346     shading interp
347     view(-40,55);
348     %colorbar;
349     Shikaab = ['nlegB', int2str(n), '.tiff'];
350     print(Shikaab, '-dtiff', '-r350')
351     %%
352     fprintf('Time t = %f\n',n*dt);
353     ch = input('Hit enter to continue :','s');
354     if (strcmp(ch,'k') == 1)

```

```
355         keyboard;  
356     end  
357 end  
358 end
```