Turing Patterns from Dynamics of Early HIV Infection

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Received: 4 September 2012 / Accepted: 12 March 2013 / Published online: 2 April 2013
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Abstract We have developed a mathematical model for in-host virus dynamics that includes spatial chemotaxis and diffusion across a two-dimensional surface representing the vaginal or rectal epithelium at primary HIV infection. A linear stability analysis of the steady state solutions identified conditions for Turing instability pattern formation. We have solved the model equations numerically using parameter values obtained from previous experimental results for HIV infections. Simulations of the model for this surface show hot spots of infection. Understanding this localization is an important step in the ability to correctly model early HIV infection. These spatial variations also have implications for the development and effectiveness of microbicides against HIV.

Keywords HIV · Turing patterns · In-host viral dynamics · Chemotaxis · Reaction–diffusion

1 Introduction

The normal response in an individual after being infected by a virus is activation of the immune system, driving infection levels down. If the immune response is sufficiently potent then the disease can be completely eradicated from the body, but in many instances this does not occur. Instead, over the course of time, an eventual balance of disease replication and immune clearance is established leading to chronic

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Springer
infection. These steady state outcomes, clearance versus chronic infection, are suggestive of simple dynamics, but this ignores spatial variations, including possible hot spots of infection (Haase et al. 1996), which confound the dynamics in both transient and long time behaviours. Although there has been some mathematical modelling of acute HIV infection (Murray et al. 1998; De Boer 2007; Ribeiro et al. 2010), current mathematical models of HIV infection mainly focus on response to antiretroviral therapy of HIV viral levels after the viral setpoint (Perelson et al. 1996; Wei et al. 1995). Moreover, these models assume a well-mixed environment with no real spatial behaviour. This is very different to what happens at the very earliest stages of infection at the vaginal or rectal epithelium during sexual transmission of HIV from an infected man to his partner. A single lineage usually expands in the new host, even though the genetically heterogeneous inoculum contains numerous infectious units. The dynamics of high HIV seminal loads leading to sporadic infection and the establishment of single foci of infection (Keele et al. 2008), are difficult to understand biologically and completely fall outside the sphere of usual mathematical modelling of infectious diseases with simple ordinary differential equations.

Spatially heterogeneous outcomes may arise from underlying spatial heterogeneity possibly due to tissue architecture or damage from other sexually transmitted infections (Haase 2010), but it is also possible to have such non-uniformities spontaneously arise from the infection dynamics. One of the archetypical manners in which this occurs is through the existence of a Turing instability in a set of partial differential equations (PDEs). Turing’s seminal work in 1952 (Turing 1952) showed that for some non-linear reaction–diffusion equations the steady state solution of the system is not spatially uniform. The Turing instability occurs when a spatially homogeneous steady state of the reaction dynamics, which is linearly stable in the absence of diffusion, becomes linearly unstable when the reactions are coupled with the diffusion. This can occur when there are two or more nonlinearly interacting species with different diffusivities. The resultant inhomogeneous spatial pattern is called a Turing pattern. Turing patterns have been proposed to explain patterning in numerous physical, chemical, and biological systems (Cooper and Maini 2012), including models of morphogenesis (Murray 2002; Edelstein-Keshet 2005; Maini et al. 2012; Meinhardt 2012) and some chemical reactions (Ouyang and Swinney 1991). Turing pattern formation has also been investigated in an SIR model to predict the spatial transmission of diseases in a population (Liu and Zhen 2007).

In order to investigate the impact of spatial dynamics in a simple mathematical model of HIV infection, we extended an SIR model for in-host virus dynamics (Nowak et al. 1996; Nowak and May 2000) to include spatially random diffusion and spatially directed chemotaxis (Jin et al. 2008). The spatio-temporal behaviour of this system is investigated within the framework of Turing instability-induced pattern formation (Turing 1952), and is shown to result in spatial hot spots of infection for certain ranges of the parameter values. We further explored the behaviour of the model system through numerical simulations, which reveals complicated spatial dynamics persisting through transient and long time behaviours. These spatial variations have implications for the development and effectiveness of microbicides against HIV (Klasse et al. 2006).
2 Model Equations

The standard SIR-based model for in-host virus dynamics is given by (Wei et al. 1995; Nowak and May 2000; Perelson et al. 1996)

\[
\begin{align*}
\frac{dT}{dt} &= s - kVT - \mu T, \\
\frac{dI}{dt} &= kVT - \delta I, \\
\frac{dV}{dt} &= NI - cV.
\end{align*}
\]  

(1)

In these equations, the dependent variables are: \(T\), the population of uninfected target cells; \(I\), the population of infected cells; and \(V\), the population of free virions, where these all vary with time \(t\), but not space. It is assumed that the target cells are supplied at a constant rate \(s\) and they are removed either through cell death with death rate \(\mu\) or by becoming infected by virions. The parameter \(k\) represents the rate of infection of target cells per virion; \(N\) represents the number of virions produced per unit time, per infected cell; \(\delta\) is the death rate of the infected cells and \(c\) is the clearance rate of virions.

Extending this model to also include spatial aspects so that the independent variables are now \((t, x)\) produces the following model:

\[
\begin{align*}
\frac{\partial T}{\partial t} &= s - kVT - \mu T + D_T \nabla^2 T - \chi \nabla(T \nabla I), \\
\frac{\partial I}{\partial t} &= kVT - \delta I + D_I \nabla^2 I, \\
\frac{\partial V}{\partial t} &= NI - cV + D_V \nabla^2 V,
\end{align*}
\]  

(2)

where \(T\), \(I\), and \(V\) are now concentrations of target cells, infected cells, and virus respectively, with appropriate units according to the space dimension (e.g. cells/mm for 1D or cells/mm\(^2\) for 2D). In this model, it is assumed that the target CD4+ T cells, infected cells, and free virions all diffuse with diffusion constants \(D_T\), \(D_I\), and \(D_V\), respectively. We have also included a spatial chemotaxis term \(-\chi \nabla(T \nabla I)\) to represent the chemotactic attraction of target immune cells driven by the concentration gradient of cytokines from inflammation at sites of infection. The random walk diffusive motion of these T cells has been well established both \textit{in vitro} and \textit{in vivo} (Miller et al. 2003) with some evidence for an anomalous component to the diffusion (Harris et al. 2012), although in this work, for simplicity, we will assume a purely Brownian diffusion. The chemotaxis of T cells is more difficult to establish but careful experiments have clearly demonstrated the chemotaxis of T cells in response to gradients of chemokines in microfluidic \textit{in vitro} studies (Lin and Butcher 2006). The vaginal or rectal epithelium will be represented by a 2-dimensional surface so that our space component is given by \(\mathbf{x} = (x_1, x_2)^T\).
3 Turing Patterns

We are interested in whether the dynamics of the spatially extended model allow for formation of spatial patterns. The system of partial differential equations (2) may be classified as a reaction–chemotaxis–diffusion system. Patterns may occur in this system in the neighbourhood of a spatially homogeneous steady state provided the conditions for a Turing instability are met, namely that this spatially homogeneous steady state is:

(T1) linearly stable in the absence of diffusion and chemotaxis; and
(T2) linearly unstable in the presence of diffusion and chemotaxis.

4 Steady States

The spatially extended system (2), has the same (spatially) homogeneous steady states as the standard model (1): the disease-free state

\[ T_0^* = \frac{s}{\mu}, \quad I_0^* = 0, \quad V_0^* = 0, \]

and the endemic state

\[ T^* = \frac{c\delta}{kN}, \quad I^* = \frac{skN - c\delta\mu}{Nk\delta}, \quad V^* = \frac{skN - c\delta\mu}{ck\delta}. \]

5 Non-dimensional Equations

In order to reduce the number of parameters and simplify some of the analysis, it is useful to work with a non-dimensional version of the system (2). Let the non-dimensional dependent variables be given by

\[ u_1 = \frac{T}{T_c}, \quad u_2 = \frac{I}{I_c}, \quad u_3 = \frac{V}{V_c} \]

and the non-dimensional independent space and time variables be given by

\[ X_1 = \frac{x_1}{L}, \quad X_2 = \frac{x_2}{L}, \quad \tau = \frac{t}{t_c} \]

where the values of \( T_c, I_c, V_c, L, \) and \( t_c \) shall be chosen later in such a way to minimise the total number of parameters. We substitute the non-dimensional variables into (2) and obtain

\[ \frac{\partial u_1}{\partial \tau} = \left( \frac{s}{T_c} \right) - \frac{V_c t_c k u_3 u_1}{(\mu t_c)u_1} + \left( \frac{D_T t_c}{L^2} \right)^2 u_1 - \left( \frac{t_c I_c \chi}{L^2} \right) \nabla (u_1 \nabla u_2), \]
\[
\frac{\partial u_2}{\partial \tau} = \left( \frac{kV_c T_c}{I_c} \right) u_1 u_3 - (\delta t_c) u_2 + \left( \frac{D_t I_c}{L^2} \right) \nabla^2 u_2,
\]

\[
\frac{\partial u_3}{\partial \tau} = \left( \frac{N I_c t_c}{V_c} \right) u_2 - (c t_c) u_3 + \left( \frac{D V t_c}{L^2} \right) \nabla^2 u_3.
\]

There is now freedom in setting the scaling factors and simplifying the equations. To this end set \(T_c, I_c, \) and \(V_c\) to the corresponding values of the endemic homogeneous steady state \(T^*, I^*, V^*.\) The non-dimensional equations then become

\[
\frac{\partial u_1}{\partial \tau} = t_c \left( \frac{skN}{c \delta} \right) (1 - u_3 u_1) - t_c \mu u_1 (1 - u_3) + \left( \frac{D_T t_c}{L^2} \right) \nabla^2 u_1
\]

\[
- t_c \left( \frac{(skN - c \delta \mu) \chi}{N k \delta L^2} \right) \nabla (u_1 \nabla u_2),
\]

\[
\frac{\partial u_2}{\partial \tau} = (\delta t_c) u_1 u_3 - (\delta t_c) u_2 + \left( \frac{D_t I_c}{L^2} \right) \nabla^2 u_1,
\]

\[
\frac{\partial u_3}{\partial \tau} = (c t_c) u_2 - (c t_c) u_3 + \left( \frac{D V t_c}{L^2} \right) \nabla^2 u_3.
\]

We may further simplify (4) by choosing \(t_c := \frac{1}{\mu}\) and \(L^2 := \frac{D_T}{\mu}.\) Then we set the new non-dimensional parameters to be the following:

\[
\xi := \frac{skN}{c \delta \mu}, \quad d_I := \frac{D_I}{D_T}, \quad d_V := \frac{D_V}{D_T},
\]

\[
d_\chi := \frac{s \chi}{\delta D_T} \left( 1 - \frac{1}{\xi} \right), \quad \alpha := \frac{\delta}{\mu}, \quad \beta := \frac{c}{\mu}.
\]

Finally, we arrive at the non-dimensional version of (2):

\[
\frac{\partial u_1}{\partial \tau} = \xi - (\xi - 1) u_1 u_3 - u_1 + \nabla^2 u_1 - d_\chi \nabla (u_1 \nabla u_2),
\]

\[
\frac{\partial u_2}{\partial \tau} = \alpha (u_1 u_3 - u_2) + d_I \nabla^2 u_2,
\]

\[
\frac{\partial u_3}{\partial \tau} = \beta (u_2 - u_3) + d_V \nabla^2 u_3.
\]

It is straightforward to check that in the absence of spatial variation this system admits the following two equilibria:

(E1) The endemic spatially homogeneous steady-state at \((u_1^*, u_2^*, u_3^*) = (1, 1, 1).\)

(E2) The disease-free spatially homogeneous steady state at \((u_1^*, u_2^*, u_3^*) = (\xi, 0, 0).\)

Observe also that the value of \(\xi\) in (5) determines one of two distinct scenarios:

(i) When \(\xi < 1,\) we have \(I, V < 0\) whenever \(u_2, u_3 \geq 0,\) hence the endemic homogeneous steady state is not physically relevant as it corresponds to negative concentrations of infected cells and free virus. The only spatially homogeneous steady state is the state free of disease, \((\xi, 0, 0).\)
(ii) When \( \xi > 1 \), both of the spatially homogeneous steady states, \((\xi, 0, 0)\) and \((1, 1, 1)\), are physically relevant.

In order to explore the possibility of Turing pattern formation, we shall consider the stability of (5) linearised about each of the two steady states.

6 Linearising About the Endemic Spatially Homogeneous Steady State

Let us assume for this section that \( \xi > 1 \) as we have already established above that this is a necessary condition for a physically relevant endemic homogeneous steady state. We perturb this equilibrium \((u_1^*, u_2^*, u_3^*) = (1, 1, 1)\) by writing \( u_i = u_i^* + \Delta u_i \) for each \( i \in \{1, 2, 3\} \). The linearised form of (5) for the perturbations \( \Delta u_i \) is given by

\[
\frac{\partial}{\partial \tau} \begin{bmatrix}
\Delta u_1 \\
\Delta u_2 \\
\Delta u_3
\end{bmatrix} = \begin{bmatrix}
-\xi & 0 & -(\xi - 1) \\
\alpha & -\alpha & \alpha \\
0 & \beta & -\beta
\end{bmatrix} \begin{bmatrix}
\Delta u_1 \\
\Delta u_2 \\
\Delta u_3
\end{bmatrix} + \begin{bmatrix}
1 & -d\chi & 0 \\
0 & dI & 0 \\
0 & 0 & dV
\end{bmatrix} \nabla^2 \begin{bmatrix}
\Delta u_1 \\
\Delta u_2 \\
\Delta u_3
\end{bmatrix}.
\]

(6)

It shall be convenient to carry out Fourier transforms with respect to the spatial variables in (6). This yields

\[
\frac{\partial}{\partial \tau} \begin{bmatrix}
\Delta U_1 \\
\Delta U_2 \\
\Delta U_3
\end{bmatrix} = \begin{bmatrix}
(-\xi - q^2) \alpha & d\chi q^2 & -(\xi - 1) \\
0 & (-\alpha - dI q^2) \alpha & \alpha \\
0 & \beta & (-\beta - dV q^2)
\end{bmatrix} \begin{bmatrix}
\Delta U_1 \\
\Delta U_2 \\
\Delta U_3
\end{bmatrix},
\]

(7)

where \( \Delta U_i \) denote the Fourier transform of \( \Delta u_i \) and \( q^2 := q^T q \) where \( q \in \mathbb{R}^d \) is the Fourier variable, with \( d \) the spatial dimension. The conditions for Turing instabilities are determined from the eigenvalue spectrum of the coefficient matrix in (7). The requirement that the homogeneous steady state is stable in the absence of diffusion and chemotaxis is met if all eigenvalues have negative real parts when \( q^2 = 0 \). A Turing instability may then occur if one or more eigenvalues have positive real parts for some \( q^2 > 0 \).

The characteristic polynomial of the matrix in (7) is

\[
\lambda^3 + \lambda^2 (\xi + \alpha + \beta + (1 + dI + dV) q^2) \\
+ \lambda \left\{ \xi \alpha + \xi \beta + (\alpha dV + \beta dI + \xi dI + \alpha + \xi dV + \beta - \alpha d\chi) q^2 \\
+ (dI dV + dI + dV) q^4 \right\} \\
+ \left\{ \xi \alpha dV + \xi \beta dI - \alpha \beta d\chi \right\} q^6 \\
+ \left\{ \xi \alpha dV + \xi \beta dI + \xi dI + \alpha + \xi dV + \beta dI - \alpha d\chi dV \right\} q^4 \\
+ (dI dV) q^6 + (\xi - 1) \alpha \beta \right] .
\]

(8)

To check for stability, recall that a cubic polynomial \( \lambda^3 + a\lambda^2 + b\lambda + c \) has all roots in the left half complex plane if and only if \( a, b, c > 0 \) and \( ab > c \) (Ruth–Hurwitz stability criterion for a cubic polynomial (Hurwitz 1964)). Below we consider the characteristic polynomial for different values of \( q^2 \).
6.1 Case of No Spatial Variation

In the absence of diffusion and chemotaxis \((q^2 = 0)\), the characteristic polynomial (8) simplifies to

\[
\lambda^3 + \lambda^2(\alpha + \beta + \xi) + \lambda(\alpha\beta + \beta\xi) + (\xi - 1)\alpha\beta. \tag{9}
\]

Since we have assumed that \(\xi > 1\), all the coefficients of (9) are positive. Thus, the remaining condition

\[
(\alpha + \beta + \xi)(\alpha + \beta)\xi > (\xi - 1)\alpha\beta \tag{10}
\]

is necessary and sufficient for all roots of (9) to be in the left half-plane.

Since \(\alpha\) and \(\beta\) are positive and \(\xi > 1\), Eq. (10) is always true:

\[
(\alpha + \beta + \xi)(\alpha + \beta)\xi > (\alpha + \beta)^2\xi > 2\alpha\beta\xi > (\xi - 1)\alpha\beta.
\]

Thus, the endemic steady state is stable in the absence of diffusion and chemotaxis and the first Turing condition (T1) is satisfied.

6.2 Case of Spatial Variation

Now we investigate the nature of the roots of (5) in the presence of diffusion and chemotaxis \((q^2 > 0)\).

Firstly, consider the case for large \(q^2\). Then the characteristic polynomial (8) will have all its coefficients positive (as in each term the largest power of \(q^2\) has a positive coefficient). Moreover, the coefficient of \(\lambda^2\) tends to \((1 + d_I + d_V)q^2\), the coefficient of \(\lambda\) tends toward \((d_I d_V + d_I + d_V)q^4\) while the constant coefficient is dominated by \((d_I d_V)q^6\). It is then straightforward to show that the product of the former two is larger than the latter, hence for sufficiently large \(q^2\) all roots of (8) are in the left half complex plane and the system is stable.

Even though for large values of \(q^2\) the system becomes stable, there may still be sufficiently large values of \(d_\chi\) and an appropriate range of values of \(q^2\) for which instabilities occur. To determine the threshold on \(d_\chi\) (or \(\chi\)) above which instabilities may be possible, let us first write the polynomial (8) in the following form:

\[
\lambda^3 + \lambda^2(a_1 + a_2q^2) + \lambda(b_1 + b_2q^2 + b_3q^4) + (c_1 + c_2q^2 + c_3q^4 + c_4q^6) \tag{11}
\]

for appropriate values of coefficients \(a_1, a_2, b_1, b_2, b_3, c_1, c_2, c_3, \) and \(c_4\). Note that all these coefficients are positive except for possibly \(b_2, c_2\) and \(c_3\). If we assume that these too are positive then:

(S1) \(a_1b_1 > c_1\).
(S2) \(a_1b_2 + a_2b_1 > c_2\).
(S3) \(a_1b_3 + a_2b_2 > c_3\).
(S4) \(a_2b_3 > c_4\).
The proof of this is straightforward but tedious, and is shown in the Appendix. Now, (S1)–(S4) imply that

\((a_1 + a_2q^2)(b_1 + b_2q^2 + b_3q^4) > c_1 + c_2q^2 + c_3q^4 + c_4q^6,\)

for all \(q\), therefore by the Ruth–Hurwitz stability criterion, all roots of (11) (and (8)) are in the left half complex plane, and thus (7) is stable.

We conclude that the only way the system in (7) may become unstable is if at least one of \(b_2, c_2, \) or \(c_3\) becomes non-positive. Therefore, the necessary (but not sufficient) condition for Turing condition (T2) to hold is that either

\[
\begin{align*}
\text{(C1)} \quad & b_2 \leq 0, \quad \text{that is} \quad d\chi \geq dV + (\beta + \xi)dI /\alpha + 1 + \xi + 1/\alpha, \\
\text{(C2)} \quad & c_2 \leq 0, \quad \text{that is} \quad d\chi \geq \xi dV /\beta + \xi dI /\alpha; \text{or} \\
\text{(C3)} \quad & c_3 \leq 0, \quad \text{that is} \quad d\chi \geq \xi dI /\alpha + 1 + \beta dI / (\alpha dV).
\end{align*}
\]

Using \(d\chi = s\chi \delta DT (1 - 1/\xi)\), we see that (C1), (C2), and (C3) are equivalent to

\[
\begin{align*}
\text{(C1')} \quad & \chi \geq \frac{s\delta DT}{s(1-1/\xi)} (dV + (\beta + \xi)dI /\alpha + 1 + \xi + 1/\alpha), \\
\text{(C2')} \quad & \chi \geq \frac{s\delta DT}{s(1-1/\xi)} (\xi dV /\beta + \xi dI /\alpha), \text{or} \\
\text{(C3')} \quad & \chi \geq \frac{s\delta DT}{s(1-1/\xi)} (\xi dI /\alpha + 1 + \beta dI / (\alpha dV))
\end{align*}
\]

respectively. Given a set of parameters, for the purpose of determining a possible existence of a Turing instability, we shall only consider the weakest condition of the three.

7 Linearising About the Disease-Free Spatially Homogeneous Steady State

Similar to our approach for the endemic equilibrium in the previous section, we may linearise (5) about the disease-free spatially homogeneous steady state \((u^*_1, u^*_2, u^*_3) = (\xi, 0, 0)\). Since this state is always physically relevant, for the time being we need not assume any additional conditions on \(\xi\) (apart from positivity). After performing a Fourier transform of (5) linearised about \((\xi, 0, 0)\), we get

\[
\frac{\partial}{\partial \tau} \begin{bmatrix} \Delta U_1 \\ \Delta U_2 \\ \Delta U_3 \end{bmatrix} = \begin{bmatrix} -1 - q^2 & d\chi \xi q^2 & -\xi(\xi - 1) \\ 0 & -\alpha - d_1q^2 & \alpha \xi \\ 0 & \beta & -\beta - dV q^2 \end{bmatrix} \begin{bmatrix} \Delta U_1 \\ \Delta U_2 \\ \Delta U_3 \end{bmatrix}.
\]

(12)

In the spatially homogeneous setting \((q^2 = 0)\), it is easy to check that the disease-free steady state is stable if and only if \(\xi < 1\).

The matrix in (12) has \(-1 - q^2 < 0\) as one of its eigenvalues. The remaining two are given by the eigenvalues of the \(2 \times 2\) lower-right submatrix

\[
\begin{bmatrix} -\alpha - d_1q^2 & \alpha \xi \\ \beta & -\beta - dV q^2 \end{bmatrix}.
\]

It is easy to check that if \(\xi < 1\) the eigenvalues of this matrix lie in the left half complex plane (e.g. observe that the matrix has negative trace and positive determinant),
and this holds for all values of $q^2$. So, (T1) and (T2) cannot both be true, and we conclude that the Turing conditions cannot be satisfied in a neighbourhood of the disease-free steady state.

8 Regularisation of Chemotaxis

It is well known that in two spatial dimensions chemotaxis above a certain threshold results in a finite time blow up of solutions to the governing equations (see, e.g. Horstmann 2003). The standard approach to deal with this non-realistic phenomenon is to introduce a regularisation term to (5). We shall use a density-dependent sensitivity regularisation, studied in Velasquez (2004), based on the assumption that with increasing cell density, their advective velocity reduces. For other forms of regularisation, see the survey article by Hillen and Painter (2009). Our new governing equations become:

\[
\frac{\partial u_1}{\partial \tau} = \xi - (\xi - 1)u_1 u_3 - u_1 + \nabla^2 u_1 - (1 + \varepsilon) d_\chi \nabla \left( \frac{u_1}{1 + \varepsilon u_1} \nabla u_2 \right),
\]

\[
\frac{\partial u_2}{\partial \tau} = \alpha (u_3 u_1 - u_2) + d_I \nabla^2 u_2,
\]

\[
\frac{\partial u_3}{\partial \tau} = \beta (u_2 - u_3) + d_V \nabla^2 u_3
\]

(13)

for some dimensionless regularisation parameter $\varepsilon \geq 0$ such that in the limit as $\varepsilon \to 0$ we recover the original non-regularised model.

Let us introduce the notion of effective chemotaxis:

\[
\tilde{d}_\chi(u_1; \varepsilon) := \frac{1 + \varepsilon}{1 + \varepsilon u_1} d_\chi.
\]

Then $\tilde{d}_\chi = d_\chi$ at the endemic steady state ($u_1 = 1$), and the linearised equations (6) and (7) remain unchanged, therefore, in this case our stability analysis and conditions for Turing patterns formation from previous sections also apply in the regularised setting. Also, note that $\tilde{d}_\chi \to 0$ as $u_1 \to \infty$.

9 Parameters, Units, and Dimensions

There has been considerable investigation of parameter values for variants of the SIR model, based on trials in HIV-infected individuals (Perelson et al. 1996, 1997; Murray et al. 2007, 2011) and from SIV infected macaques (Mandl et al. 2007), and it is reasonable to assume that these parameter values provide useful starting approximations for variants of the model (1) that also includes a spatial component.

We assume the original HIV model (1) has parameter estimates given by $N = 480$ virions cell$^{-1}$ day$^{-1}$, $k = 3.43 \times 10^{-5}$ ml virions$^{-1}$ day$^{-1}$, $\delta = 0.5$ day$^{-1}$, $c = 3$ day$^{-1}$, $s = 10$ cells mm$^{-3}$ day$^{-1}$, $\mu = 0.03$ day$^{-1}$. These parameter estimates,
which are taken from Nelson et al. (2000), are characteristic of typical parameter values (Haase et al. 1996; Reilly et al. 2007; Chen et al. 2007; Ramratnam et al. 1999). The following simulations show representative behaviours of spatial variations with the above parameter values.

We will perform numerical simulations in both one and two spatial dimensions. Note that the constants $k$ and $s$ given above are volume-based. In order to adapt them to two or one spatial dimensions, let us assume that the region in which we are solving the PDE is either a thin rectangular sheet of thickness $h$ or a thin wire with a square $h \times h$ cross-section. Thus, the new dimension-specific values of $k$ and $s$ become $\tilde{k} = kh^{3-d}$ and $\tilde{s} = sh^{3-d}$, respectively, where $d \in \{1, 2\}$ is the number of spatial dimensions. Note that by changing $d$ the only non-dimensional parameter that changes is $d\chi$. For all of the numerical simulations, we shall take $h = 0.1$ mm.

The diffusion of T cells in lymphatic tissue has been estimated at (Miller et al. 2002)

$$D_T = 1.1 \mu m^2 s^{-1} = 0.09504 \text{ mm}^2 \text{ day}^{-1}. \quad (14)$$

It can be assumed that the uninfected ($T$) and infected ($I$) CD4+ T cells will have similar diffusion coefficients. The diffusion of virions has been measured in different studies (Ewers et al. 2007; Boukari et al. 2009) and in the case of standard diffusion the diffusion coefficient is of the order of 0.0088 $\mu m^2 s^{-1}$. The only parameters without experimental bounds are the effective chemotaxis term $\chi$ and the regularisation constant $\epsilon$. For the above stated parameters, the weakest necessary (but not sufficient) condition for Turing instability is $(C2)$, requiring $d\chi > 219.8$, that is $\chi > 10.4 \text{ mm}^4 \text{ cell}^{-1} \text{ day}^{-1}$ in two spatial dimensions and $\chi > 104 \text{ mm}^3 \text{ cell}^{-1} \text{ day}^{-1}$ in one spatial dimension. These are our lower bounds on the chemotactic threshold. Changing the parameters, $N, c, k, s, \delta, \mu$, will alter the lower bounds on the chemotactic threshold. However, the spatial patterning will be similar for different choices of the parameters; albeit at different values of $\chi$.

Figure 1 shows the real part of the leading eigenvalue of the matrix of the linearised system (7) for the parameters stated above as a function of spatial frequency. Note that even though $\chi = 110 \text{ mm}^3 \text{ cell}^{-1} \text{ day}^{-1}$ is above our calculated lower bound on the chemotactic threshold, the system remains stable for all spatial frequencies. Turing conditions are only met for $\chi$ somewhere between 110 and 120 mm$^3$ cell$^{-1}$ day$^{-1}$.

Recall that we set the scaling factors for independent variables to $t_c = 1/\mu$ and $L^2 = D_T/\mu$. With the given parameters, this results in values $t_c \approx 33.3$ days and $L \approx 1.78$ mm.

10 Numerical Solutions in One Spatial Dimension

The model PDE, (13), is solved numerically on a one-dimensional domain of length $L$ with zero-flux boundary conditions. In one-dimension, the chemotaxis term need not be regularised, thus unless otherwise stated, we shall use $\epsilon = 0$ in this section. We used MATLAB’s built in 1D PDE solver pdepe. The initial conditions are taken as either a small random or deterministic perturbation around the endemic steady state.
Fig. 1 Leading eigenvalues of the linear model, (7), in one spatial dimension as a function of spatial frequency for several values of $\chi$. Empty squares correspond to $\chi = 100 \text{ mm}^3 \text{ cell}^{-1} \text{ day}^{-1}$; empty circles to $\chi = 110 \text{ mm}^3 \text{ cell}^{-1} \text{ day}^{-1}$; empty triangles to $\chi = 120 \text{ mm}^3 \text{ cell}^{-1} \text{ day}^{-1}$; filled squares to $\chi = 130 \text{ mm}^3 \text{ cell}^{-1} \text{ day}^{-1}$; filled circles to $\chi = 150 \text{ mm}^3 \text{ cell}^{-1} \text{ day}^{-1}$; and filled triangles to $\chi = 170 \text{ mm}^3 \text{ cell}^{-1} \text{ day}^{-1}$.

For $\chi$ below 104 mm$^3$ cell$^{-1}$ day$^{-1}$ (our lower bound on the chemotactic threshold for a Turing instability), the solutions become flat with no spatial features as time progresses. This can be seen in Fig. 2.

For $\chi$ above this threshold, we see Turing pattern formation in the form of three uniformly separated peaks. This pattern remains and the peaks do not blow up in time; see Fig. 3.

As the strength of chemotaxis increases, we see that the spikes become steeper. However, the solutions are still finite for all time; see Fig. 4.

Increasing the length of the domain results in proportionally more spikes; see Fig. 5. It should also be noted that in this case it takes a longer length of time for the solutions to settle to a steady state and the spikes to become uniform in height.

Starting with a random initial condition of $u_2$ (e.g. uniform on $(0.975, 1.025)$), the oscillations are initially at a higher frequency than for a smooth initial condition. However, these oscillations quickly settle and produce a pattern similar to the case with normal initial distribution; see Fig. 4.

10.1 Dependence on Initial Conditions

The spatial frequency of the steady state solution may depend on the initial conditions for long domains. Figure 6 shows density profiles for two solutions with different initial distributions of infected cells—the first one concentrated on the left border and
Fig. 2 Solution of (13) for $\chi = 100$ mm$^3$ cell$^{-1}$ day$^{-1}$. The solid blue line represents $u_1$ (left axis), the non-dimensional version of concentration of healthy cells and the dashed red line is $u_2$ (right axis), the concentration of infected cells. The concentration of infected cells $u_2$ is initially normally distributed. The concentration of free virus (not shown in the graph) is initially constant at $u_3 = 1$ and changes similarly to $u_2$ (Color figure online).

Fig. 3 Solution of (13) for $\chi = 130$ mm$^3$ cell$^{-1}$ day$^{-1}$ with same initial conditions as those in Fig. 2. The solid blue line represents $u_1$ (left axis), the non-dimensional version of concentration of healthy cells and the dashed red line is $u_2$ (right axis), the concentration of infected cells (Color figure online)
Fig. 4 Solution of (13) for $\chi = 220 \text{ mm}^3 \text{ cell}^{-1} \text{ day}^{-1}$ with $u_1 = u_3 = 1$ initially constant and $u_2$ taken from a uniform random distribution in $(0.975, 1.025)$. Note that the size of the domain has been doubled compared to the preceding figures. The solid blue line represents $u_1$ (left axis), the non-dimensional version of concentration of healthy cells and the dashed red line is $u_2$ (right axis), the concentration of infected cells (Color figure online).

Fig. 5 Solution of (13) for $\chi = 130 \text{ mm}^3 \text{ cell}^{-1} \text{ day}^{-1}$ on a longer domain. The speed of propagation of the pattern is estimated to be $0.36 \text{ mm day}^{-1}$. The solid blue line represents $u_1$ (left axis), the non-dimensional version of concentration of healthy cells and the dashed red line is $u_2$ (right axis), the concentration of infected cells (Color figure online).
second one concentrated in the middle of the region. The resulting final states contain a different number of peaks—16 and 17, respectively.

10.2 Solutions with Initial Conditions Near the Disease-Free Steady State

We have already shown that the disease-free homogeneous steady-state is unstable when \( skN > c\delta\mu \). Hence, we can expect any disturbance of this state (i.e. the introduction of virus or infected cells) to result in system transitioning to the endemic steady state.

Because we are considering global behaviour of the system, it is more useful to draw plots in terms of re-dimensionalised variables (for example, it enables one to compare the number of infected cells to the number of healthy cells). In the absence of spatial variation a typical transition to the endemic steady state is shown in Fig. 7.
Fig. 7 A typical transition from disease-free steady state to endemic steady state in the absence of spatial variation (Color figure online)

Fig. 8 A typical transition from the disease-free steady state to the endemic steady state in the presence of spatial variation. The chemotaxis parameters are $\chi = 130 \text{ mm}^3 \text{ cell}^{-1} \text{ day}^{-1}$ and $\varepsilon = 1.0$. Target cells $T$ (blue solid lines), infected cells $I$ (red dashed lines) (Color figure online)

Figures 8 and 9 show the transition to the endemic steady state from a small random disturbance around the disease-free steady state, and a spatially localized disturbance, respectively. The chemotaxis, $\chi = 130 \text{ mm}^3 \text{ cell}^{-1} \text{ day}^{-1}$, is above the critical threshold, regularised with $\varepsilon = 1.0$. The resulting Turing pattern is identical to the
Fig. 9  Initial stage of infection with the distribution of infected cells localised near $X_1 = 0$. Chemotaxis was regularised with $\chi = 130 \text{ mm}^3 \text{ cell}^{-1} \text{ day}^{-1}$ and $s = 1.0$. The infection spreads at the rate of approximately 5 mm per day. Target cells $T$ (blue solid lines), infected cells $I$ (red dashed lines) (Color figure online)

Fig. 10  Change in Turing patterns after clearance rate changes from $c = 3 \text{ day}^{-1}$ to $c = 4 \text{ day}^{-1}$. The dotted lines indicate the initial densities and the solid lines indicate the final densities of non-infected cells ($T$) and infected cells ($I$) (Color figure online)

pattern produced starting from a perturbation of the endemic steady state (see, e.g. Fig. 3).

10.3 Consequences of Changing the Virus Clearance Rate

Figure 10 shows the change in the Turing pattern after the rate of virus clearance increases from $c = 3 \text{ day}^{-1}$ to $c = 4 \text{ day}^{-1}$. Even though the overall number of infected cell reduces, the maximum density of infected cells remains roughly the same as with
the lower rate of clearance. Note that increasing \( c \) in this way will result in a lower chemotactic threshold for Turing pattern formation.

11 Numerical Solutions in Two Spatial Dimensions

The two-dimensional model exhibits a blow up of solutions in finite time for sufficiently strong chemotactic attractions. For this reason, we have employed a regularisation as described in (13). Setting the thickness of the surface on which we are modelling the infection to \( h = 0.1 \) mm, results in the critical value for chemotaxis \( \chi \) to lie somewhere between 11 and 12 mm\(^4\) cell\(^{-1}\) day\(^{-1}\).

The governing PDE was solved numerically on a square domain with sides of length \( L \approx 1.78 \) mm (i.e. \( X_1 = X_2 = 1 \)). The method of lines was used, which involved semi-discretising (13) in both space variables on a uniform rectangular grid and solving the resulting ODE system in time using MATLAB’s implementation of the Runge–Kutta method, \texttt{ode45}. The results for the endemic steady state are shown in Figs. 11 and 12.

While the two-dimensional model is more difficult to solve numerically and some form of chemotactic regularisation is required, we did not observe any qualitative behaviour that was different from the setting of only one dimension in space.
Fig. 12 Density of target cells at different points in time for $\chi = 12 \text{ mm}^4 \text{ cell}^{-1} \text{ day}^{-1}$, $\varepsilon = 10$. The initial conditions are taken as a random perturbation of the endemic steady state (Color figure online)

12 Discussion

We have shown analytically and numerically that HIV infection does not need a spatial heterogeneous tissue structure to exhibit spatially heterogeneous infection patterns. The patterns can only occur if (i) the conditions for existence of an infected steady state hold ($skN > c\delta\mu$), and (ii) the chemotactic attraction is strong enough. With the parameter values as outlined in Sect. 9, the estimated time for transition to the non-homogeneous endemic state to occur locally (i.e. on a small patch of tissue) is around 14 days (see Fig. 7).

Larger chemotactic attraction results in a larger range of possible spatial frequencies for the Turing patterns as well as higher amplitudes of the peaks. While the resulting pattern may depend on the initial state of the infection, we found that in most cases it does not. However, different initial states may significantly affect the speed at which the pattern is established, with small random perturbations of the endemic state enabling faster settling to a Turing pattern than localised perturbations, which in turn settle faster than from a perturbation of the disease-free steady state.

We found that if the initial perturbation is local, the pattern tends to get established near the perturbation, and then propagates outwards, whereas for random initial perturbations the patterns emerge more or less simultaneously across the whole region.
Upon getting infected by HIV it typically takes 1–2 months (Murray et al. 1998) for the body’s immune system to respond by increasing the rate at which the virus is cleared. This is enough time for the initial Turing pattern to form. After the clearance rate is increased, it is possible for new, more prominent and less frequent Turing patterns to form. Also, even if the system was in a state that does not admit any patterns and the infection becomes spatially homogeneous, such a response from the immune system may give rise to pattern formation.

This analysis indicates that foci of HIV infection that are observed in tissue, can be established as a result of the dynamics of the system irrespective of any spatial heterogeneity in the tissue. These foci may provide an environment where new infection of cells outweighs immune clearance and hence supports the maintenance of infection despite an expanding immune response. Our analysis indicates that these patterns are established over a longer time scale than would be relevant for the impact of a microbicide which acts at the very earliest stages of infection. This analysis, however, assumes that the surface itself representing the vaginal or rectal epithelium, is homogeneous. This is not the case, however, and further work to assess the impact of the generation of Turing patterns in a more realistic environment is required. For example, spatial heterogeneities may cause Turing patterns to occur within a time period that overlaps the effectiveness of microbicides, and spatial variation in levels of infection may impact on the effectiveness of microbicidal barriers. However, further knowledge on the earliest stages of HIV infection in mucosa, including interactions between microbicides and the virus, are needed before more realistic mathematical models of microbicidal barriers in HIV can be developed.

Acknowledgements We greatly acknowledge discussions with T.A.M. Langlands and P.J. Klasse on aspects of this work. This research was assisted through the support from the Australian Commonwealth Government (ARC DP1094680) and the UNSW Goldstar Scheme.

Appendix: Showing Conditions for Turing Instability

Proposition 1 Consider the characteristic polynomial (11). Provided $a_1, a_2, b_1, b_2, b_3, c_1, c_2, c_3, \text{ and } c_4$ are all positive, conditions (S1)–(S4) hold.

Proof We demonstrate each of the conditions in turn below.

(S1)

\begin{align*}
a_1b_1 &= (\xi + \alpha + \beta)(\xi\alpha + \xi\beta) \\
&> \xi\alpha\beta \\
&> (\xi - 1)\alpha\beta = c_1;
\end{align*}

(S2)

\begin{align*}
a_1b_2 + a_2b_1 &= (\xi + \alpha)b_2 + \beta b_2 + (1 + d_I)b_1 + d_V b_1 \\
&= (\xi + \alpha)b_2 + (1 + d_I)b_1
\end{align*}
\[ + \beta(\alpha dV + \beta dI + \xi dI + \alpha + \xi dV + \beta - \alpha d\chi) + \xi \alpha dV + \xi \beta dV \\
= (\xi + \alpha)b_2 + (q + dI) b_1 + \beta(\alpha dV + \beta dI + \alpha + \xi dV + \beta) \\
+ \xi \beta dV + (\xi \alpha dV + \xi \beta dI - \alpha \beta d\chi) \\
> \xi \alpha dV + \xi \beta dI - \alpha \beta d\chi = c_2; \]

(S3)

\[ a_1 b_3 + a_2 b_2 = (\xi + \alpha + \beta)(dI dV + dI + dV) \\
+ (1 + dI + dV)(\alpha dV + \beta dI + \xi dI + \alpha + \xi dV + \beta - \alpha d\chi) \\
> \xi dI dV + \alpha dV + \beta dI \\
+ (1 + dI)b_2 + dV(b_2 + \alpha d\chi) - \alpha d\chi dV \\
> \xi dI dV + \alpha dV + \beta dI + \alpha d\chi dV = c_3; \]

(S4)

\[ a_2 b_3 = (1 + dI + dV)(dI dV + dI + dV) \\
> dI dV = c_4. \]

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