Derived wave of gradient driven diffusion’s convective flux of efavirenz

T Nemaura
Department of Applied Mathematics, National University of Science and Technology, Zimbabwe
Department of Clinical Pharmacology, University of Zimbabwe, Zimbabwe
E-mail: tnemaura@gmail.com

Abstract
This work gives the description of the derived wave induced by convective diffusive flux of gradient driven diffusion. It makes use of the autonomous system of differential equations. A four compartment system is proposed for the wave produced. The diffusive flux is studied for it is inferred to facilitate transfer of by-products (metabolites) of solution-particle (efavirenz) material. The by-product wave movement is more pronounced in the initial 5 h. The initial 2.5 h indicate a period of a stretching space. The advective movement is the main generator of movement. The interaction of the advective movement’s transient state with its equilibrium potential state gives rise to other movement state-dynamics.

1. Introduction
Efavirenz is a drug used in antiretroviral therapy. It is an important and widely used drug in HIV (human immunodeficiency virus) therapy [1, 2]. Efavirenz is used as part of a first-line treatment and is very effective in suppressing plasma viral load [2, 3]. However, there are concerns over central nervous system (CNS) toxicity related to the drug’s use [1, 3]. The mechanisms responsible for the CNS toxicity of this drug are yet to be resolved. Efavirenz is metabolised by Cytochrome P450 enzymes and has a number of metabolites [2, 4–6]. There are two main metabolites of efavirenz, that is 7- and 8-hydroxefavirenz. Furthermore, there are secondary metabolites associated with products of primary metabolism [4, 5]. A relatively fewer number of studies have attempted to link efavirenz induced CNS toxicity with 8-hydroxefavirenz [6, 7]. A possible metabolites movement carrier in a patient who had been on efavirenz is suggested. The movement carrier of metabolites is characterised by the derived wave of gradient driven diffusion.

There is consideration of a dynamical system model for particle description. It is proposed in modelling the components of a by-product carrier wave. Description of particles is important and several proposals have been made [8–11]. The atomic process has been suggested to be modelled through the use of exterior algebras [12]. In this work there is use of linear dynamical systems to model the particle process. This work continues to support the idea that particles are moments of a vibrational process [13]. This work seeks to characterise the derived wave and project its internal dynamics.

Other researchers define a wave as an organised propagating imbalance [14]. The general understanding of a wave is through modelling its external characterisation [15]. A wave is a dynamically globally unstable movement entity driven internally by an unstable twin-core and a corresponding equal external twin-movement (conductivity and diffusivity processes). Conductivity is an inward movement acquiring process. While diffusivity is the total outward movement acquiring process [16]. Furthermore, the two fluxes are both zero sums of movement.

The total movement flux of a wave is zero. It is a Hamiltonian system, consisting of the total of the two fluxes that is diffusivity and conductivity. Hamiltonian and Lagrangian systems have been used to describe waves [17, 18]. The internal system (anti-solvation) consists of two movements the advective and saturation. However, the external system (pro-solvation) consists of the two movements the passive and convective movements [16].
There is a proposition of the conservative Lagrangian system to describe component fluxes, where the difference between the internal movements \( (I_m) \) and external movements \( (E_m) \) defines diffusivity \( (I_m - E_m) \). Thus, the conductivity and diffusivity fluxes considered are conservative Lagrangian systems in form.

A complete vibrational process lies at the boundary and should include movement fluxes that describe these processes (conductivity and diffusivity). The boundary which is constituted by the two processes’ cores, which are conductivity and diffusivity. The two cores are symmetrical. Space is defined as a particle’s dynamical system saturation field measure. Time is measure of concentration of waves and is driven by the advective, saturation and passive entities [13]. The ideal way to describe space-time boundary is the boundary of active concentration-time. The active concentration-time is a process which has non-zero convective movement. This is because concentration of matter in the solution-particle and the complementary concentration (time) both have the potential to occupy space [13].

In this work, the diffusivity core is considered. It is important to note that the negation of the diffusivity core defines conductivity [19]. The diffusivity core has two main sub-systems. The diffusivity core consists of the three ‘internal’ movements, advective, saturation and passive. Considering the internal movements there is an external movement within, which is the passive movement. In addition, the nullifying/aggregated ‘external’ movement potential balances each core. It establishes local stability of the core. However, the solution particle is globally stable and has a twin stable core with two ‘internal’ movements advective and saturation. It also has a corresponding nullifying entity which establishes local stability, the convective movement. It has zero passive potential. The complete entity of a solution-particle should contain these two processes conductivity and diffusivity.

The fabric that gives rise to concentration (of solution-particle) is defined as a \( \Sigma \)—dominant-fabric and the one that gives rise to time as a \( \Sigma \) — derived-fabric. The \( \Pi \) — dominant is a three dimensional space driven by the advective and saturation components. It consists of three movement entities which are advective, saturation and convective for its apparent system. A saturated system consists of the equality in magnitude of advective component and saturation entity [16]. Furthermore, it has zero convective movement. The \( \Sigma \) — derived-fabric consists of four movement entities that are advective, saturation, passive and convective.

Rather than space-time fabric there is the \( \Pi \) — \( \Sigma \) — fabric. The \( \Sigma \) — complete vibrational entity is a wave-entity with a non-zero passive component. It is driven by the advective, saturation and passive components. In addition, the \( \Pi \) — complete vibrational entity is a solution particle-entity with a zero passive component.

There is consideration of two dynamical systems, that is autonomous, non-autonomous [20, 21] and non-linear regression in modelling waves. The non-autonomous system and non-linear regression models are used to describe primary formation movement in ‘particles’ [13, 16, 19, 22, 23]. Autonomous dynamical systems can be used to characterise stretching-space systems. The generated system give rise to mechanistic system and its space is inferred to expand primarily due to its advective entity (causes the space to ‘warp’). The waves involved in formation/production of a solution particle do not stretch space they are ‘acquiescent’ [13, 22, 23]. However, the by-product waves potentially stretch space. This work gives the potential carrier-wave of by-products of the diffusion process and a phenomenological description of a different type of a wave, that is one that stretches space.

There is investigation of the impact of the parameter changes on state variables in the model using sensitivity analysis. Local sensitivity analysis is used, where the effect of a parameter value in a very small neighbourhood near its nominal value is estimated [24, 25]. The sensitivity analysis is done to observe parameters which are most highly correlated with the state variables and is also used to rank the parameter values, that is which parameter contribute most to state variable variability. Furthermore, consequences resulting from changing given input parameters [26].

2. Methods

Projected PK/PD (Pharmacokinetic/Pharmacodynamic) data of diffusivity convective movement of gradient driven diffusion in a patient on 600 mg of efavirenz is used [23]. Ordinary differential equations are used. The software used, includes Matlab, R, Mathematica.

2.1. Model assumptions

- The convective movement of the gradient driven diffusion generates a derived form of a wave in its neighbourhood.
- The wave consists of four movement variables, advective (A), saturation (S), passive (P), and convective (C), where:
Advective describes the form of movement.

Saturation is the measure of the containing movement of the advective and passive components.

Passive is the measure of internal degree of freedom of movement of the advective entity in saturation (measure of degree of non-localisation of $A$ in $S$).

Convective is the measure of external degree of freedom of the advective movement in the fabric (measure of the degree of non-localisation of $A$ in the fabric).

- There are two internal movements $A$ and $S$ which are such that $I_m = A + S$, and two external movements $P$ and $C$ which are such that $E_m = P + C$.

- A wave consists of two symmetrical processes conductivity ($K = 0$) and diffusivity ($D = 0$). The diffusivity process is the negation of conductivity (each movement moment conserves the flux).

- The diffusivity flux ($D$) is such that,
  \[ 0 = D = I_m - E_m = A + S + \ddot{P} + \ddot{C}, \quad \ddot{P} = -P, \quad \text{and} \quad \ddot{C} = -C, \]
  and the conductivity flux ($K$) is such that,
  \[ 0 = K = E_m - I_m = P + C + \ddot{A} + \ddot{S}, \quad \ddot{A} = -A, \quad \text{and} \quad \ddot{S} = -S. \]

The two fluxes are Lagrangian in form.

- The total movement flux is such that,
  \[ 0 = K + D, \quad \text{a Hamiltonian system.} \]

This system can be observed as a Lagrangian as well in the form,

\[ 0 = K - K, \quad \text{where} \quad -K = D \quad \text{(with respect to conductivity)}, \]

or

\[ 0 = D - D, \quad \text{where} \quad -K = D \quad \text{(with respect to diffusivity)}. \]

### 2.2. Description of the diffusivity part of generated mechanistic wave (Model)

Initially, there is consideration of the wave that is generated from the gradient driven diffusion’s convective movement. There is construction of a system associated with the diffusivity profile of movement. A four dimensional movement process is suggested (figure 1). The equations of the diffusivity wave component are thus given by,

\[
\frac{dA}{dt} = -\alpha A - \gamma_{AS} A - \gamma_{AP} A + \gamma_{SA} S + \gamma_{PA} P = (\alpha + \gamma_{AS} + \gamma_{AP})\ddot{A} + \gamma_{AS} S + \gamma_{PA} \ddot{P}, \tag{1}
\]

\[
\frac{dS}{dt} = \alpha + \gamma_{AS} A - \gamma_{SA} S = \alpha \cdot 1 + \gamma_{AS} A + \gamma_{SA} \ddot{S}, \tag{2}
\]

\[
\frac{dP}{dt} = \gamma_{AP} A - \gamma_{PA} \ddot{P} = \gamma_{AP} A + \gamma_{PA} P, \tag{3}
\]
\[
\frac{dC}{dt} = \alpha A - \alpha = \alpha A + \alpha \cdot \mathbf{I}.
\]  

(4)

The parameters are defined as follows:

\(\alpha\)-stability movement rate proportional constant.

\(\gamma_{AS}\)-movement rate constant of advective movement \((A)\) into saturation \((S)\).

\(\gamma_{AP}\)-movement rate constant of \(A\) into \(P\).

\(\gamma_{PA}\)-response movement rate constant of \(P\) into \(A\).

\(\gamma_{SA}\)-response movement rate constant of \(S\) into \(A\).

Equation (1) describes the acceleration of movement of form. It models the generator of movement. It shares a relation with all state movements. The acceleration field is jointly proportional to \(\mathbf{A}^s(A^s - A)\), and.

Equation (2) represents the ‘container’ (of \(A\) and \(P\) subsequently) movement’s acceleration. The acceleration field is proportional to \(\mathbf{A}^s(A^s - A)\) and \(\mathbf{A}\).

Equation (3) models the derived form’s acceleration. The passive movement \((\bar{P})\) measures the boundary or derived movement of \(A\). It describes \(A\)’s movement limitation in \(S\). The acceleration field is proportional to \(\mathbf{A}\) and \(P\).

Equation (4) models the acceleration of the convective movement. Furthermore, the acceleration field is proportional to \(\mathbf{A}\) and \(\mathbf{A}^s\). It is important to note that convection movement’s acceleration field describes the difference in the form’s (advective) equilibrium potential state and it’s transient state. It ‘balances’ the overall system. It was noted that, sub-conductivity-space is such that \(\mathbf{A}^s, \mathbf{A}^s, \mathbf{A}\) and sub-diffusivity-space (external subspace of diffusivity)

\[
\frac{d\mathbf{C}}{dt} = \alpha A - \alpha = \alpha (A - A^s),
\]

(6)

In addition, the internal subspace has an external component since it forms the following non-conservative Lagrangian system for \(C \neq 0\) and is such that,

\[
D_1 = A + S - P,
\]

(7)

with the internal subsystem,

\[
D_1(I) = A + S,
\]

(8)

and the external subsystem,

\[
D_1(E) = P.
\]

(9)

The advective, passive, and the saturation movements thus form the internal subspace. Additionally, the passive entity form the external entity of the internal system. The convective movement forms the external subspace.

### 2.3. Equilibrium points, eigenvalues and eigenvectors

Setting,

\[
\frac{d\mathbf{A}}{dt} = \frac{dS}{dt} = \frac{dP}{dt} = \frac{dC}{dt} = 0,
\]

(10)

the equilibrium points obtained are such that,

\[
A^* = 1, \ S^* = \frac{\alpha + \gamma_{AS}}{\gamma_{SA}}, \ P^* = \frac{\gamma_{AP}}{\gamma_{PA}}, \ C^* = -\left(1 + \frac{\alpha + \gamma_{AS}}{\gamma_{SA}} + \frac{\gamma_{AP}}{\gamma_{PA}}\right).
\]

The Jacobian matrix for the field inter-system is given by,

\[
J(A^*, S^*, P^*, C^*) = \begin{bmatrix}
-(\alpha + \gamma_{AS} + \gamma_{AP}) & \gamma_{SA} & \gamma_{PA} & 0 \\
\gamma_{AS} & -\gamma_{PA} & 0 & 0 \\
\gamma_{AP} & 0 & -\gamma_{PA} & 0 \\
\alpha & 0 & 0 & 0
\end{bmatrix}
\]

(11)
The characteristic equation of the field system is given by,
\[
0 = \lambda^3 + (\alpha + \gamma_{AS} + 2\gamma_{PA} + \gamma_{AP})\lambda^2 + (-\gamma_{SA}\gamma_{AS} + 2\alpha\gamma_{PA} + 2\gamma_{AS}\gamma_{PA} + \gamma_{PA}\gamma_{AP})\lambda + (\alpha^2\gamma_{PA} + \gamma_{AS}\gamma_{PA} - \gamma_{SA}\gamma_{AS}\gamma_{PA})\lambda,
\]
(12)
thus the eigenvalues are \( \lambda_1 = 0, \lambda_2 = -\gamma_{PA}, \lambda_3 = \frac{1}{2}(-\alpha - \gamma_{AS} - \gamma_{PA} - \gamma_{AP} - \sqrt{-4(-\gamma_{SA}\gamma_{AS} + \alpha\gamma_{PA} + \gamma_{AS}\gamma_{PA}) + (\alpha + \gamma_{AS} + \gamma_{PA} + \gamma_{AP})^2}), \lambda_4 = \frac{1}{2}(-\alpha - \gamma_{AS} - \gamma_{PA} - \gamma_{AP} + \sqrt{-4(-\gamma_{SA}\gamma_{AS} + \alpha\gamma_{PA} + \gamma_{AS}\gamma_{PA}) + (\alpha + \gamma_{AS} + \gamma_{PA} + \gamma_{AP})^2}).
\]
The associated eigenvectors are given by,
\[
\begin{align*}
\frac{1}{2}(-\alpha + \gamma_{AS} + \gamma_{PA} + \gamma_{AP} + \sqrt{-4(-\gamma_{SA}\gamma_{AS} + \alpha\gamma_{PA} + \gamma_{AS}\gamma_{PA}) + (\alpha + \gamma_{AS} + \gamma_{PA} + \gamma_{AP})^2}), \\
\frac{1}{2}(-\alpha + \gamma_{AS} + \gamma_{PA} + \gamma_{AP} - \sqrt{-4(-\gamma_{SA}\gamma_{AS} + \alpha\gamma_{PA} + \gamma_{AS}\gamma_{PA}) + (\alpha + \gamma_{AS} + \gamma_{PA} + \gamma_{AP})^2}), \\
\frac{1}{2}(-\alpha + \gamma_{AS} + \gamma_{PA} + \gamma_{AP} + \sqrt{-4(-\gamma_{SA}\gamma_{AS} + \alpha\gamma_{PA} + \gamma_{AS}\gamma_{PA}) + (\alpha + \gamma_{AS} + \gamma_{PA} + \gamma_{AP})^2}), \\
\frac{1}{2}(-\alpha + \gamma_{AS} + \gamma_{PA} + \gamma_{AP} - \sqrt{-4(-\gamma_{SA}\gamma_{AS} + \alpha\gamma_{PA} + \gamma_{AS}\gamma_{PA}) + (\alpha + \gamma_{AS} + \gamma_{PA} + \gamma_{AP})^2}).
\end{align*}
\]

### 2.4. Sensitivity

The sensitivity matrix \( Q \) is such that an element \( q_{ij} = \frac{\partial y_j}{\partial \theta_i} w_j \), where \( y_j \) is an output variable, \( \theta_i \) is a parameter, \( w_j \) is the scaling of variable \( y_j \), \( w_{ij} \) is the scaling of \( \theta_i, i \in [1, N] \) and \( j \in [1 : k] \). Two important measures

\[
L_1 = \frac{\sum |q_{ij}|}{N}, \quad L_2 = \frac{\sum q_{ij}}{N},
\]

are considered. For any subset of columns of the sensitivity matrix, collinearity \( \rho \) is defined as:
\[
\rho = \frac{1}{\sqrt{\min(EV[Q^TQ])}},
\]
where,
\[
\hat{q}_{ij} = \frac{q_{ij}}{\sqrt{\sum_j q_{ij}^2}}.
\]

Where \( Q \) contains the columns of the sensitivity matrix that correspond to the parameters included in the set, \( EV \) estimates the eigenvalues [24, 25].

### 3. Results

#### 3.1. Numerical solutions: Parameter estimation, equilibrium points, eigenvalues and eigenvectors

The projected hourly convective movement of the diffusivity flux of gradient driven diffusion in a 24 h time period was used [23]. The convective flux was the input variable to obtain the parameter estimates and other variables(table 1) as solutions of equations (1)–(4). The summary statistics (table 2) of parameters were obtained from a generated bootstrap sample with \( n = 1000 \) [27].

The characteristic function using the mean parameter estimates

\[
\hat{\alpha} = 34.83, \hat{\gamma}_{AS} = -54.45, \hat{\gamma}_{SA} = 0.1526, \hat{\gamma}_{PA} = 0.2038, \quad \text{and} \quad \hat{\gamma}_{AP} = 25.92 \text{ was given by},
\]

\[
\begin{align*}
\text{Table 1:} \\
\text{Parameter} & \quad \text{Value} \\
\hat{\alpha} & \quad 34.83 \\
\hat{\gamma}_{AS} & \quad -54.45 \\
\hat{\gamma}_{SA} & \quad 0.1526 \\
\hat{\gamma}_{PA} & \quad 0.2038 \\
\hat{\gamma}_{AP} & \quad 25.92
\end{align*}
\]
with the following eigenvalues,

\[ \lambda_1 = -5.7548, \quad \lambda_2 = -0.749, \quad \lambda_3 = -0.2038, \quad \lambda_4 = 0, \]

and associated eigenvectors,

\[
\begin{align*}
( -0.0802, -0.7862, 0.3743, 0.4851 ), \quad ( -0.0083, -0.8323, 0.3962, 0.3875 ), \\
( 0, 0.8005, -0.5994, 0 ), \quad ( 0, 0, 0, 1 ).
\end{align*}
\]

The equilibrium points were given by,

\[
(A^*, S^*, P^*, \bar{C}) = (1, -128, 127, 0).
\]

### 3.2. Numerical movement rates of the generated mechanistic wave (diffusivity)

The advective movement approached 1 as time increased and the movement was positive for the diffusivity aspect of a wave. However, saturation had positive and negative movements (figure 2). Initially, there is an observed positive direction of movement in the first 2.5 h. As time approached 24 h the state variables were such that \( A \approx A^* \) and \( S \approx S^* \).

The passive movement was positive and opposed the convective movement, it is an external movement of the internal system (figure 3). This is with respect to diffusivity. As time approached 24 h the state variables were such that \( P \approx \bar{P}^* \) and \( \bar{C} \approx \bar{C}^* = 0 \).

### 3.3. Local sensitivity

The effect of parameter estimates on the model is projected. A comprehensive sensitivity analysis was done by assessing the influence and relative importance of each parameter or state variable relationship [26].

#### 3.3.1. Multivariate sensitivity analysis of independent state variables with respect to all parameters

The indicator \( k \) denoted that the parameter was included in the set for sensitivity analysis, and \( k \) the number of parameters in set (table 3). The higher the value of collinearity the larger the linear dependence. The 5 parameter set had a large collinearity with respect to advective movement. The smallest value of collinearity in the five parameter combination was associated with the convective movement. Furthermore, this is an external movement of the system.

#### 3.3.2. Univariate sensitivity analysis

The summary of sensitivity functions of state variables with respect to all parameters was considered (table 4). The contribution to the model is marked by the magnitude of \( L_2 \)-norm. Considering the output variable with least collinearity (This is for identifiability purposes), the order of contribution was given by \( \gamma_{AS} > \alpha > \gamma_{AP} > \gamma_{PA} > \gamma_{SA} \). Furthermore, this matches the order of magnitude of the parameters. The least sensitivity functions ranges were found to be associated with the advective component. Passive movement is least sensitive to \( \gamma_{SA} \) and \( \alpha \). The most contributory parameters to saturation movement are the ones that connect

### Table 1. Parameter estimates in modelling movement rates of equations (1)–(4).

| Parameters | Estimate | Std Error | t value | Pr(>|t|) |
|------------|----------|-----------|---------|----------|
| \( \alpha \) | 33.14 | 0.368 2 | 90 | \( < 2 \times 10^{-16} \) |
| \( \gamma_{AS} \) | -54.98 | 11.40 | -4.824 | 0.000 103 |
| \( \gamma_{AP} \) | 28.16 | 11.69 | 2.409 | 0.023 777 5 |
| \( \gamma_{SA} \) | 0.154 6 | 0.015 03 | 10.28 | 1.99 \( \times 10^{-7} \) |
| \( \gamma_{PA} \) | 0.200 7 | 9.558 \( \times 10^{-4} \) | 209.994 | \( < 2 \times 10^{-16} \) |

### Table 2. Parameter estimates from bootstrap samples for the system of ordinary differential equations.

| Parameters | Mean | Median | (95% CI) |
|------------|------|--------|----------|
| \( \alpha \) | 34.83 | 34.78 | (30.93,39.02) |
| \( \gamma_{AS} \) | 0.152 6 | 0.152 8 | (0.130 1,0.174 7) |
| \( \gamma_{AP} \) | -54.45 | -54.17 | (-60.084 8, -50.244 0) |
| \( \gamma_{PA} \) | 25.92 | 26.07 | (21.082 4,29.742 9) |
| \( \gamma_{SA} \) | 0.203 8 | 0.204 1 | (0.166 64,0.241 2) |

\[
\lambda^4 + 6.7076 \lambda^3 + 5.636 \lambda^2 + 0.8785 \lambda = 0,
\]

(13)
Figure 2. Figure 2(i) shows the effect of increasing time on advective movement, which initially increases to a peak value beyond its equilibrium point $A = 1$, and then decaying steadily approaching its equilibrium state and figure 2(ii) shows that saturation movement initially indicates a stretching movement (positive movement) and then growing steadily in the negative direction to its saturating equilibrium state.

Figure 3. Figure 3(i) shows the effect of increasing time on passive movement, which increases steadily to an equilibrium value. Figure 3(ii) shows the convective movement (and projected data points of convective flux of diffusion), which in magnitude increases steadily to a peak value and then declining steadily to 0 (equilibrium state).

Table 3. Collinearity of each state variable with respect to all parameters.

| Associated state variable | $\alpha$ | $\gamma_{AS}$ | $\gamma_{AP}$ | $\gamma_{SA}$ | $\gamma_{PA}$ | $k$ | Collinearity |
|---------------------------|---------|----------------|----------------|----------------|----------------|----|--------------|
| $A$                       | 1       | 1              | 1              | 1              | 1              | 5  | 1226516      |
| $S$                       | 1       | 1              | 1              | 1              | 1              | 5  | 839          |
| $b$                       | 1       | 1              | 1              | 1              | 1              | 5  | 255          |
| $C$                       | 1       | 1              | 1              | 1              | 1              | 5  | 66           |
Table 4. Univariate sensitivity analysis of all and independent state movement(s) with respect to all parameter values.

| Variables | Parameters | Value | Scale | $L_1$ | $L_2$ | Mean | Min | Max | N |
|-----------|------------|-------|-------|-------|-------|------|-----|-----|---|
| $A$, $S$, $\bar{P}$, $\bar{C}$ | $\alpha$ | 34.83 | 34.83 | 105 | 6.7 | $-0.054$ | $-289$ | 400 | 605 |
|     | $\gamma_{AS}$ | $-54.45$ | $-54.45$ | 165 | 10.5 | 0.085 | $-659$ | 466 | 605 |
|     | $\gamma_{SA}$ | 0.152 6 | 0.152 6 | 46 | 3.1 | $-0.031$ | $-133$ | 165 | 605 |
|     | $\gamma_{AP}$ | 25.92 | 25.92 | 57 | 3.6 | $-0.030$ | $-196$ | 215 | 605 |
|     | $\gamma_{PA}$ | 0.203 8 | 0.203 8 | 45 | 2.9 | 0.030 | $-124$ | 142 | 605 |
| $A$ | $\alpha$ | 34.83 | 34.83 | 0.38 | 0.76 | $-0.27$ | $-2.404$ | 0.20 | 121 |
|     | $\gamma_{AS}$ | $-54.45$ | $-54.45$ | 0.68 | 1.36 | 0.42 | $-0.516$ | 4.41 | 121 |
|     | $\gamma_{SA}$ | 0.152 6 | 0.152 6 | 0.19 | 0.30 | $-0.15$ | $-0.696$ | 0.32 | 121 |
|     | $\gamma_{AP}$ | 25.92 | 25.92 | 0.31 | 0.60 | $-0.15$ | $-2.002$ | 0.33 | 121 |
|     | $\gamma_{PA}$ | 0.203 8 | 0.203 8 | 0.18 | 0.30 | 0.15 | $-0.049$ | 0.73 | 121 |
| $S$ | $\alpha$ | 34.83 | 34.83 | 262.35 | 275.18 | 262.35 | 0.000 | 400.49 | 121 |
|     | $\gamma_{AS}$ | $-54.45$ | $-54.45$ | 410.29 | 433.71 | $-410.29$ | $-659.009$ | 0.00 | 121 |
|     | $\gamma_{SA}$ | 0.152 6 | 0.152 6 | 115.95 | 128.09 | 112.54 | $-21.858$ | 165.46 | 121 |
|     | $\gamma_{AP}$ | 25.92 | 25.92 | 56.67 | 92.50 | 54.10 | $-4.412$ | 214.66 | 121 |
|     | $\gamma_{PA}$ | 0.203 8 | 0.203 8 | 53.22 | 67.75 | $-53.22$ | $-122.803$ | 0.00 | 121 |
| $\bar{P}$ | $\alpha$ | 34.83 | 34.83 | 53.71 | 54.46 | $-34.56$ | $-121.374$ | 0.41 | 121 |
|     | $\gamma_{AS}$ | $-54.45$ | $-54.45$ | 56.67 | 92.50 | 54.10 | $-4.412$ | 466 | 121 |
|     | $\gamma_{SA}$ | 0.152 6 | 0.152 6 | 20.31 | 25.75 | $-19.08$ | $-47.232$ | 214.66 | 121 |
|     | $\gamma_{AP}$ | 25.92 | 25.92 | 92.02 | 103.46 | 81.55 | $-43.485$ | 131.77 | 121 |
|     | $\gamma_{PA}$ | 0.203 8 | 0.203 8 | 61.83 | 77.69 | $-56.38$ | $-124.042$ | 17.47 | 121 |
| $\bar{C}$ | $\alpha$ | 34.83 | 34.83 | 227.52 | 235.34 | $-227.52$ | $-288.861$ | 0 | 121 |
|     | $\gamma_{AS}$ | $-54.45$ | $-54.45$ | 355.76 | 369.95 | 355.76 | 0.000 | 466.24 | 121 |
|     | $\gamma_{SA}$ | 0.152 6 | 0.152 6 | 95.49 | 107.33 | $-93.31$ | $-132.590$ | 13.57 | 121 |
|     | $\gamma_{AP}$ | 25.92 | 25.92 | 135.50 | 141.56 | $-135.50$ | $-195.805$ | 0.00 | 121 |
|     | $\gamma_{PA}$ | 0.203 8 | 0.203 8 | 109.45 | 118.38 | 109.45 | $-0.000$ | 142.22 | 121 |

Where Mean: the mean of the sensitivity functions, Min: the minimal value of the sensitivity functions, Max: the maximal value the sensitivity functions.

it to $A$ and its equilibrium state $A^\alpha$. Generally all the output variables other than the passive movement are most sensitive to $\gamma_{AS}$, followed by the parameter $\alpha$.

Considering figure 4 and table 4, $\gamma_{AS}$ generally had higher sensitivity values compared with other parameters for all the state variables. Adective and passive had relatively similar sensitivity movement profiles. It was important to note that sensitivity in terms of advective (form) movement approach zero for all the parameters. Furthermore, the activity of transportation was mainly in the initial 5 h and the significant parameter was $\gamma_{AS}$.

3.3.3. Bivariate sensitivity analysis (correlation) of parameters of all state variables and convective movement

The bivariate sensitivity analysis for all state variables sensitivity parameters showed a strong negative correlation between $\alpha$ and $\gamma_{AS}$ which had a value of $-1$ (figure 5). This implied that $\gamma_{AS}$ had a negative effect on $\alpha$. Generally the correlation of sensitivity functions with respect to parameters is not linear.

The movement with respect to the convective entity is considered in order to identify parameter relation (figure 6). However, the associated collinearity (convective movement) was relatively large ($66 > 15$) (table 2). A strong correlation ($-1$) between sensitivity functions of $\alpha$ and $\gamma_{AS}$. Furthermore, that of the least contributing parameters or the ‘slower’ parameters $\gamma_{SA}$ and $\gamma_{PA}$, for the correlation between their sensitivity functions was found to be $-0.95$.

3.3.4. Multivariate sensitivity analysis (collinearity) of all state variables with respect to sensitivity of selected parameters

The indicators 1 and 0 denoted the parameter included or not included in the parameter set for sensitivity analysis respectively (table 5). The parameter set that included both $\alpha$, and $\gamma_{AS}$ resulted in a high collinearity index. Any parameter set combination that included these two was not identifiable. These two parameters showed a high level of correlation. A practically identifiable 4-parameter model requires an initially projected value of either $\alpha$ or $\gamma_{AS}$. The two models had collinearity of 9.9 and 10.2 respectively.
4. Discussion

The wave’s diffusivity-system considered in this work had two invariant spaces, a fast subspace corresponding to negative eigenvalues and a slow subspace corresponding to the zero eigenvalue \[21\]. The eigenspace associated with the zero eigenvalue corresponded to an attractive plane of equilibria and was associated with convective movement. Other researchers have suggested, calculations of an atomic field’s electron potential \[28\]. It is inferred that the electron is a moment of the convective movement.

Figure 4. The sensitivity functions with respect to \(, \gamma_{AE}, \gamma_{AS}, \gamma_{AP}, \gamma_{PA}\) corresponding to parameter values in table 5 of (a)-convective, (b)-passive, (c)-saturation, and (d)-advective movement signals of diffusion in time.

Figure 5. The sensitivity functions and parameter correlations of the four-state movements signal of diffusion in time. The correlation values in the lower triangular part of the figure show how the five parameters correlate with each other. A low value, close to 0, means parameters do not correlate and that they are identifiable from one another. A high value in magnitude, close to 1, means they are highly correlated and not independently identifiable.
Figure 6. The sensitivity functions and parameter correlations of the convective movement signal of diffusion in time. The correlation values in the lower triangular part of the figure show how the five parameters correlate with each other. A low value, close to 0, means parameters do not correlate and that they are identifiable from one another. A high value in magnitude, close to 1, means they are highly correlated and not independently identifiable.

Table 5. Collinearity values of all state variables with respect to sensitivity of selected parameters.

| α | γ_{AS} | γ_{AP} | γ_{SA} | γ_{PA} | k | Collinearity |
|---|---|---|---|---|---|---|
| 1 | 1 | 0 | 0 | 0 | 2 | 39.1 |
| 1 | 0 | 1 | 0 | 0 | 2 | 1.8 |
| 1 | 0 | 0 | 1 | 0 | 2 | 2.8 |
| 1 | 0 | 0 | 0 | 1 | 2 | 2.0 |
| 0 | 1 | 1 | 0 | 0 | 2 | 1.9 |
| 0 | 1 | 0 | 1 | 0 | 2 | 2.7 |
| 0 | 1 | 0 | 0 | 1 | 2 | 2.0 |
| 0 | 0 | 1 | 1 | 0 | 2 | 1.3 |
| 0 | 0 | 0 | 1 | 0 | 2 | 3.1 |
| 0 | 0 | 0 | 0 | 1 | 2 | 1.8 |
| 1 | 1 | 1 | 0 | 0 | 3 | 44.2 |
| 1 | 1 | 0 | 1 | 0 | 3 | 56.1 |
| 1 | 1 | 0 | 0 | 1 | 3 | 39.2 |
| 1 | 0 | 1 | 1 | 0 | 3 | 3.9 |
| 1 | 0 | 1 | 0 | 1 | 3 | 3.2 |
| 1 | 0 | 0 | 1 | 1 | 3 | 2.9 |
| 0 | 1 | 1 | 1 | 0 | 3 | 3.7 |
| 0 | 1 | 1 | 0 | 1 | 3 | 3.2 |
| 0 | 1 | 0 | 1 | 1 | 3 | 2.8 |
| 0 | 0 | 1 | 1 | 1 | 3 | 4.4 |
| 1 | 1 | 1 | 1 | 0 | 4 | 57.0 |
| 1 | 1 | 1 | 0 | 1 | 4 | 51.4 |
| 1 | 1 | 0 | 1 | 1 | 4 | 57.4 |
| 1 | 0 | 1 | 1 | 1 | 4 | 10.2 |
| 0 | 1 | 1 | 1 | 1 | 4 | 9.9 |
| 1 | 1 | 1 | 1 | 1 | 5 | 57.7 |
The saturation movement form had negative projections showing possibly extension of space. This was due to the occupation of space by the advection form of movement a possible driver of negative diffusion. These results showed that space is flexible. It was important to note that the advective movement opposed saturation. The passive movement is a positive external movement of the internal movement system. While the the convective movement is the negative external movement. These two movements oppose each other. Other researches, attributes possible drivers of negative diffusion to differences in thermal velocity of particles [29]. In line with the type of wave, if it is a non-stretching space wave the process of negative diffusion leads to occupation of alternative volume spaces by movement [23].

The diffusivity aspect of wave movement and sensitivity of parameters on the model is studied. Sensitivity analysis is done by assessing the influence and relative importance of each parameter or state variable relationship [26]. The passive and advective flux moved in a positive direction. However the convective and saturation opposed movement of advective and passive components. The state movement with the highest index of collinearity was the advective movement. The centre of activity was thus inferred to be the advective component. Inter-state communication in by-product-wave of diffusion began and ended with the two movement variables that is advective and saturation. This was inferred from the parameter rates. With respect to the convective movement, the most contributing parameter was observed to be $\gamma_{AS}$ and the least contributing $\gamma_{SA}$. Furthermore, the bivariate sensitivity analysis showed a strong negative correlation between $\alpha$ and $\gamma_{AS}$.

The metabolites of efavirenz’s transportation was inferred to occur mainly in the initial 18 h. The dosing interval of 24 h was well supported by this work. The most intensive transportation occurs in the initial 2.5 h. This coincided with the stretching of the space in the wave signal, which was observed by the positive movement in saturation. Furthermore, this was inferred from the sensitivity functions of the advective movement.

This work allows for the making of inferences on possible routes for investigation of mechanisms leading to CNS (Central Nervous System) side effects [6]. The potential contribution of efavirenz metabolites to CNS adverse reaction drug reactions of efavirenz needs to be further examined [5]. The majority of efavirenz-induced CNS effects appear early, even after a single dose [6]. A lower dose of less than the 600 mg should be considered [1, 30]. This would reduce the overall volume of drug transported. Negative diffusion takes longer in formation of solution particle ($\leq 5$ h) than for the by-product wave which is 2.5 h [23]. Furthermore, negative diffusion allows for large volumes of the drug to be transported in the initial phase of transportation. If negative diffusion is contributing to CNS toxicity, one can investigate the times of intensity of their occurrences relative to these two waves.

The advective movement is the significant fundamental entity and the passive movement is its derived entity. There are two important states (in case of diffusivity) which are $0 = A + S + \bar{P} + \bar{C}$. transient-state (momentary-equilibrium) and at $A^{+} = 1$ equilibrium-state $(0 = A^{*} + S^{*} + \bar{P}^{*} + \bar{C}^{*})$. The interaction between $A^{+}$ and $A$ gave rise to convective and saturation movements. The internal movement interaction of $A$ and external of its equilibrium state $A^{*} = 1$ produces $\bar{C}$. While the interaction of external movement of $A$ and the internal movement of $A^{+}$ produces $S$. The transient state of $A$ initiated the interaction with its equilibrium state $A^{+}$. The transient state seeks equilibrium in time. Its interaction with its equilibrium state produced other movement states.

If one seeks to infer on the force-fields of these dynamics one can study the acceleration (first derivatives of movement fluxes) of these movement fluxes. A complete vibrational process is a continuous moment to moment description of the two processes conductivity and diffusivity. Waves consists of these vibrational components, furthermore they have an active passive entity (‘fixed spread, an internal degree of spread in time’) [13, 22, 23]. Waves are thus defined as complete $\Sigma$—vibrational entities. While $II$—vibrational entities can be considered to be particles with a zero passive entity (‘fixed point, no internal degree of spread in time’) [13, 16]. Thus, the $II$—particle has a localised internal structure. With respect to the internal subspace, a particle is a representation of a localised wave, while a wave is a representation of a non-localised particle.

Acknowledgments

The author would like to thank the following: C Nhachi, C Masimirembwa, and G Kadzirange, AIBST and The College of Health Sciences, University of Zimbabwe.

ORCID iDs

T Nemaura @ https://orcid.org/0000-0003-4193-2413

References

[1] Dheda M 2017 Efavirenz and neuropsychiatric effects Southern African Journal of HIV Medicine 18 a741
[2] Nightingale S et al on behalf of the PARTITION-Vietnam Study Group 2016 Efavirenz and metabolites in cerebrospinal fluid: relationship with CYP2B6 c.516G?T genotype and perturbed blood-brain barrier due to tuberculous meningitis Antimicrob Agents Chemother 60 4511–8
[3] Sutterlin S, Voge E and Gauggel S 2010 Neuropsychiatric complications of efavirenz therapy: suggestions for a new research paradigm J Neuropsychiatry Clin Neurosci. 22 361–9
[4] Ogburn E T, Jones D R, Masters A R, Xu C, Guo Y and Desta Z 2010 Efavirenz Primary and Secondary Metabolism In Vitro and In Vivo: Identification of Novel Metabolic Pathways and Cytochrome P450 2A6 as the Principal Catalyst of Efavirenz 7–Hydroxylation Drug Metabolism and Disposition 38 1218–29
[5] Aouri M et al. of the Swiss HIV Cohort Study 2016 In vivo profiling and distribution of known and novel phase I and phase II metabolites of efavirenz in plasma, urine, and cerebrospinal fluid Drug Metabolism and Disposition 44 151–61
[6] Apostolova N, Funes H A, Blas-Garcia A, Galindo M J, Alvarez A and Espullagas V 2015 Efavirenz and the CNS: what we already know and questions that need to be answered J. Antimicrob Chemother 70 2693–708
[7] Towar-y-Romo I B, Bumpus N N, Pomerantz D, Avery L B, Sacktor N, McArthur J C and Haughey N J 2012 Dendritic spine injury induced by the 8-hydroxy metabolite of efavirenz J. Pharmacol Exp Ther. 343 696–703
[8] Bohm D 1952 A suggested interpretation of the quantum theory in terms of ‘Hidden’ variables. I Phys. Rev. 85 166–79
[9] Weinberg S 1997 What is an elementary particle? Beam Lane—A Periodical of Particle Physics 27 17–21
[10] Jägielczk B 2009 Elements of the wave–particle duality of light Master Thesis University of Oslo
[11] Woithe J, Wiener G J and Van der Veken F F 2017 Let’s have a coffee with the Standard Model of particle physics! Phys. Educ. 52 034001
[12] Wiley B J and Callaghan R L 2010 The Clifford Algebra Approach to Quantum Mechanics B: The Dirac Particle and its relation to the Bohm Approach arXiv:1011.4033
[13] Nemaura T 2017 The unified description of a solution–particle Journal of Applied Mathematics and Physics 5 991–1000
[14] Scales J A and Snieder R 1999 What is a wave? Nature 401 739
[15] Georgi H 1993 The Physics of Waves (Englewood Cliffs, NJ: Prentice-Hall)
[16] Nemaura T 2015 Modeling transportation of efavirenz: inference on possibility of mixed modes of transportation and kinetic solubility Front. Pharmacol 6 121
[17] Zakharov V E and Kuznetsov E A 1997 Hamiltonian formalism for nonlinear waves Physics ? Uspekhi, Russian Academy of Sciences 40 1087–116
[18] Wu X Y, Zhang B J, Liu X J, Li J W and Guo Y Q 2009 Quantum wave equation of non-conservative system Int. J. Theor. Phys. 48 2027
[19] Nemaura T 2016 Modelling the dynamical state of the projected Primary and Secondary Intra-Solution-Particle Movement System of Efavirenz in Vivo International Journal of Modern Nonlinear Theory and Application 5 235–47
[20] Hirsch M W, Smale S and Devaney R L 2012 Differential equations, Dynamical Systems, and an Introduction to Chaos (New York: Academic)
[21] Lynch S 2010 Dynamical Systems with Applications Using MAPLE. Birkhäuser
[22] Nemaura T 2016 The advection wave-in-secondary saturation movement equation and its application to concentration tension-driven saturation kinetic flow Journal of Applied Mathematics and Physics 4 2126–34
[23] Nemaura T 2016 The advection diffusion-in-secondary saturation movement equation and its application to concentration gradient-driven saturation kinetic flow Journal of Applied Mathematics and Physics 4 1998–2010
[24] Soetaert K and Petzoldt T 2010 Inverse Modelling, Sensitivity and Monte Carlo Analysis in R Using Package FME Journal of Statistical Software 33 1–28
[25] Soetaert K 2016 R Package FME: Inverse modelling, sensitivity, Monte CarloApplied to a dynamic simulation model (CRAN Vignette 2).[Available at https://cran.r-project.org/web/packages/FME/vignettes/NonIdyna.pdf.]
[26] Hamby D M 1994 A review of techniques for parameter sensitivity analysis of environmental models Environ Monitoring and Assessment 32 135–54
[27] Nguyen V N and Hernandez-Vargas E A 2017 Parameter estimation in mathematical models of viral infections using R Preprint (https://doi.org/10.1101/130674)
[28] Thomas I H 1927 The calculation of atomic fields Proc. Camb. Phil. Soc. 23 542
[29] Dung Ba V and Thien Van D 2014 The equation of backward diffusion and negative diffusivity Journal of Physics: Conf. Series 537 (Da Nang, Vietnam, 29 July to 1 August 2013) (Institute of Physics) https://doi.org/10.1088/1742-6596/537/1/012011
[30] Carey D 2014 Efavirenz 400 mg daily remains non–inferior to 600 mg: 96 week data from the double-blind, placebo-controlled ENCORE1 study Journal of the International AIDS Society 17 19523