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Mathematical Model Of Thenfkβ Activating Interleukin-1β Through Caspase-1 Enzyme

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ABSTRACT:
The Caspase-1 enzyme is one of the crucial elements in activating the protein synthesis of interleukin-1β and leading its corresponding signaling transduction. On the contrary, intense signaling through IL-1β contributes to acting as an inflammatory mediator and further responsible to align various inflammatory-related diseases. We designed and developed an optimistic non-linear ordinary differential equation model of NFkβ activating IL-1β through the Caspase-1in the genetic regulatory path in macrophage cells. A representation of genetic transcription and translation of IL-1β is included in the mathematical compartment model, which is subsequently enabled by the Caspase-1 enzyme, which is a prime regulator of the transduction of IL-1β signals.In the case of body normal physiology, intense signal transduction due to IL-1β subsequently causes the regulation reduction of Caspase-1 activation through genetic control of NFKβ. The calculated parameter values from various literature held to understand the compartment model involve the rate of gene transcription and translation of IL-1β and its control effect through cellular Caspase-1transcribed enzyme level. The genetic process represented in the form of a compartment model of IL-1β signal transduction and its analysis spectacles that the positive state of the signal transduction capable of producing oscillatory convergence signal with consequent increase and decrease in parameter condition. We aimed to find how inflammatory mediator (IL-1β) is maintained within the immune cellular system and the harnessing benefit of our compartment model design and development are elaborated concerning other models of genetic control within the reviewed literature.
Keywords: Interleukin-1β, Caspase-1, NFkβ, Transcription, Translation, Oscillatory convergence.

1. INTRODUCTION

As an essential inflammatory mediator through immune cells, IL-1β is considered for the regulation of the signaling pathway of inflammation and consequently builds immune stability. However, intense signaling of inflammatory mediators IL-1β causes severe inflammation related to cellular stress and trauma, whereas an inadequate level of IL-1β causes immunocompromised cellular destruction [2]. Furthermore, Caspase-1 synthesis and NLRP1 activation is a prime modulator of IL-1β with the management of inflammation induces cellular stress and immune imbalance, thus at the cornerstone of managing inflammatory-related disorders [4]. It is therefore essential to strictly regulate the genetic

synthesis of intracellular IL-1β and to control its release [16]. The genetic modulation of IL-1β and various properties to regulate its signaling transduction to within body physiology results from a balance of various mechanisms includes thetranscription rate and translation of IL-1β followed by caspase 1 enzyme activation by its gene transcription and translation via NFkβ signaling pathway [5, 21]. Understanding the genetic mechanisms which regulate signal transduction and enzyme activation led by NFkß and Caspase-1 respectively for release of inflammatory mediator IL-1β, all these together helps to outline the pathology involved in causing various inflammatory-related cellular stress, trauma, and immune cause disorders [9].The genetic development and modulation of IL-1β depend on the synthesis rate of caspase 1 enzyme which helps to stimulate the genetic transcription and translation rate of IL-1β and also regulates its intracellular release in response to NFkß [15]. The macrophages prone to foreign material causing inflammatory disorders are responsible for the clearance through phagocytosis and intracellular components dissociation process representing IL-1β dissociation altogether causes IL-1β clearance and reducing its level in process of over activating the immune system [4, 24]. Thus, the rate-limiting step for signal transduction through IL-1β is the caspase- 1enzyme which is activated by NFkß [15]. The excessive genetic expression of IL-1β leading to intense inflammatory signal transduction can be modulated by its negative feedback mechanism that responds to regulate inflammatory mediating stress [13, 20]. This feedback mechanism exerts the major contribution of modulating the release of IL-1β by regulating the transcription and translation of caspase 1 enzyme protein[7] and NFkβ genetic protein, both these proteins together help leading immune signal transduction via the release of IL-1β [31]. In conversely, if it is a high level of intracellular IL-1β, thereforeprotein synthesis of NFkβ and Caspase-1 declines [29].The literature reportsadvising that CASP1 is possiblystimulated by NFkβ which further activates pro-IL-1β and consequently increases transcription and genetic expression of IL-1β mRNA [11, 25]. In particular, no compartment models were developed to date to represent a genetic sequence for the release of IL-1β. Such research lack provokes to develop the compartment model explaining the signal transduction pathway that triggers the release of IL-1β through various regulatory components and its modulation through genetic expression. The various inflammatory disorder results in the major contribution of pathology involving intense genetic expression and release of IL-1β [13]. The mathematical simulations of such compartment models will explicit interplay between genetic up and downregulation of CASP1 via NFkβ and genetic expression of inflammatory mediators IL-1β; the overall signaling pathway will enhance the understanding of the regulatory pathway of inflammatory stress via IL-1β. Among various inflammatory mediator, IL-1β is one of the most crucial signaling paths during inflammatory disorder induce stress, thus regulation of IL-1β helps to control and to eradicate inflammatory cellular stress and oxidation [12]. Genetic variation in NFkß and Caspase-1 enzyme has been associated with modulating IL-1β inducing signal transduction, Proposed gene expression induced by the Caspase-1 enzyme plays a crucial role in the control of the release of IL-1β inflammatory mediator [18, 29].

The compartment model has been designed to trace the signaling pathway leading to cause the release of IL-1β. It has been developed to investigate its rate of gene expression in the response of the Caspase-1 enzyme.

2. THE COMPARTMENT MODEL

Various interactions are characterizing cellular IL-1β release and its regulation by its genetic transcription factors [1]. As considering normal physiology,IL-1β inflammatory mediator stimulation is regulated by its genetic expression and rate of release, moreover, its rate of

expression is stimulated by the Caspase-1 enzyme, and quantitatively Caspase-1 is synthesized due to NFkß activation [15]. The literature review comments that in case of chronic inflammation excess amplification of the signal transduction causes excess release of IL-1β [20] and modulation of dynamic indicated in fig. 1 is difficult.

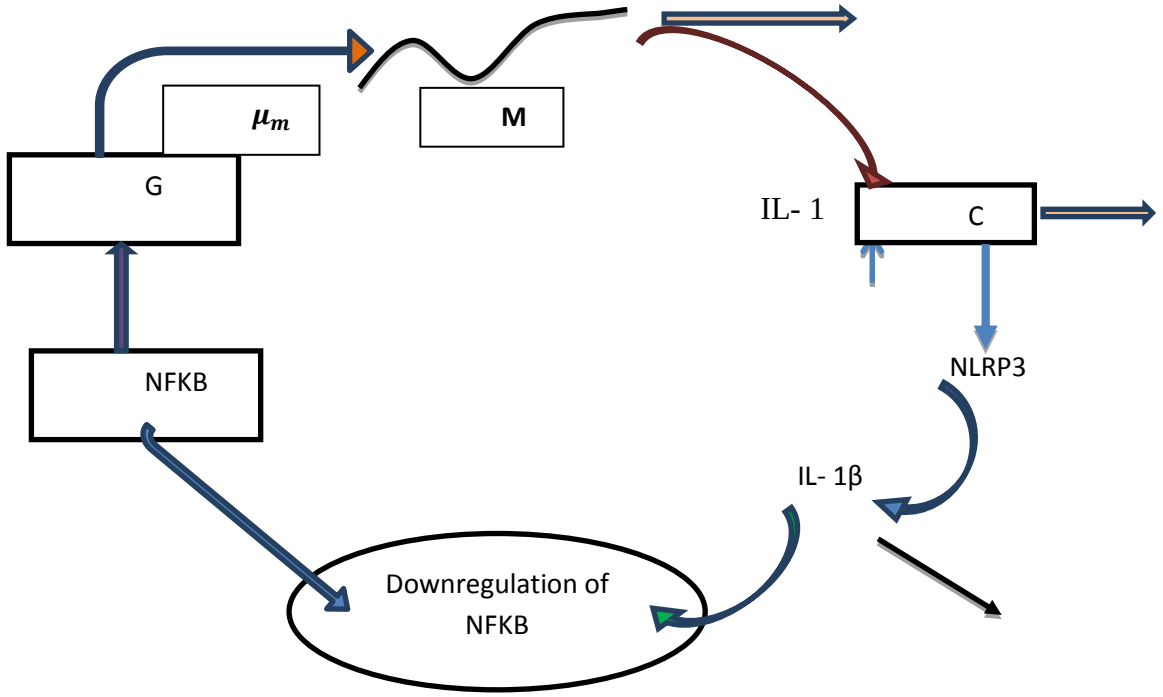

Figure:1. Compartment model representing Pharmacokinetics of IL-1β gene transcription

The IL-1β genetic regulation and its rate of release due to NFkβ. The Caspase-1 gene G is transcribed for the growth of Caspase-1 mRNA M at a rate of $\boldsymbol{\mu_m}$. This converts into the Caspase-1 enzyme C at a rate of $\boldsymbol{\mu_c}$. Caspase-1 then continues to catalyse the reaction at a rate of μ_I, producing the inflammatory mediator IL-1β. This process is mediated by the transcription factor NFkβ N, which serves as the pathway's transcription activator. Under conditions where the genetic expression of IL-1β I is excessive, NFkβ N is dysregulated and the target gene transcription decreases. At the $\boldsymbol{\delta_m}$, $\boldsymbol{\delta_c}$, and $\boldsymbol{\delta_I}$ concentrations, respectively, Caspase-1 mRNA, Caspase-1 enzyme, and IL-1β degrade.

T0 capture and design the longer-term dynamic of IL-1β expression and release due to the Caspase-1 enzyme catalyst, the complexity of inflammatory signal transduction was included here [11]. The additional necessity of the immune system should act naturally to regulate the expression and release through the NFkß signaling pathway of an inflammatory mediator such as IL-1β [31]. The simulation discussed in this paper focuses on the design and estimation of the NFkβ -IL-1β signaling pathway with an ordinary differential equation (ODEM) model. The objective of the work is to understand the modulation and release rate of IL-1β gene expression through its effect on NFkβ transcription downregulation and to what degree it affects the genetic expression of steady-state IL-1β within the cell nucleus.

3.MATHEMATICAL MODEL ANALYSIS

$$\frac{d\bar{g}}{dt} = \bar{k}_{-1}\bar{n}_b - \bar{k}_1\bar{n}^x\bar{g} \quad (1)$$

$$\frac{d\bar{n}}{dt} = x\bar{k}_{-1}\bar{n}_b - x\bar{k}_1\bar{n}^x\bar{g} - \bar{k}_2\bar{I}^y\bar{n} - \bar{k}_{-2}\overline{N} \quad (2)$$

$$\frac{d\bar{n}_b}{dt} = -\bar{k}_{-1}\bar{n}_b + \bar{k}_1\bar{n}^x\bar{g} \quad (3)$$

$$\frac{d\bar{m}}{dt} = \bar{\mu}_d\bar{n}_b - \bar{\delta}_m\bar{m} \quad (4)$$

$$\frac{d\bar{c}}{dt} = \bar{\mu}_c\bar{m} - \bar{\delta}_c\bar{c} \quad (5)$$

$$\frac{d\bar{I}}{dt} = \bar{\mu}_I\bar{I} + y\bar{k}_{-2}\overline{N} - \bar{\delta}_I\bar{I} - y\bar{k}_2\bar{I}^y\bar{n} \quad (6)$$

$$\frac{d\bar{N}}{dt} = \bar{k}_2\bar{I}^y\bar{n} - \bar{k}_{-2}\overline{N} \quad (7)$$

with initial conditions,

$$\bar{g}(0) = \bar{g}_0, \quad \bar{n}(0) = \bar{n}_0,$$
$$\bar{n}_b(0) = 0, \bar{m}(0) = \bar{m}_0, \bar{c}(0) = \bar{c}_0, \bar{I}(0) = \bar{I}_0, \bar{N}(0) = 0. \quad (8)$$

If we use the following notations in the above differential equations, the concentration denotes in square brackets as : $\bar{g} = [\bar{G}], \bar{n} = [\bar{n}], \bar{n}_b = [\bar{G}{:}\, x\bar{n}], \bar{m} = [\bar{M}], \bar{c} = [\bar{c}], \bar{I} = [\bar{I}], and\ \bar{N} = \left[[\bar{n}{:}\, y\bar{I}]\right]$.

In the first term of the equation (2), the coefficient x represents that x molecules ofthe unbound transcription factor are released by dissociation of a single dynamic DNA complex.In the second term of equation (2), The x coefficient reports that up to x binding sites of DNA are needed for the formation of one active DNA complex.

In a cell the number of genes is fixed, then from equations (1), and (2) we get

$$\frac{d\bar{g}}{dt} + \frac{d\bar{n}_b}{dt} = 0 \Longrightarrow \bar{g}(t) + \bar{n}_b(t) = \bar{g}_0 \quad (9)$$

Adopt that the equation (3) immediatelytouches equilibrium by using the initial conditions of (8). (an approximation of quasi-steady-state) such that

$$\frac{d\bar{n}_b}{dt} = 0 \quad (10)$$

From equations (9) and (10),

$$\bar{k}_1\bar{n}^x(\bar{g}_0 - \bar{n}_b) + \bar{k}_{-1}\bar{n}_b \approx 0 \Longrightarrow \bar{n}_b \approx \frac{\bar{g}_0\bar{n}^x}{\bar{k}_m{}^x + \bar{n}^x} \quad (11)$$

Where, $\bar{k}_m = \bar{k}_d{}^{1/x} = \left(\frac{\bar{k}_{-1}}{\bar{k}_1}\right)^{1/x}$ (12)

Here, the dissociation constant for a reaction between $\bar{n}$ and$\bar{G}$is $\bar{k}_d$.

And adding equations (2),(3), and (7), we get

$$\frac{d}{dt}(\bar{n} + \bar{n}_b + \bar{N}) = (1-x)\left(-\bar{k}_{-1}\bar{n}_b + \bar{k}_1\bar{n}^x\bar{g}\right)$$
$$= (1-x)\frac{d\bar{n}_b}{dt}(\because (3)) \quad (13)$$

Together with initial conditions (10), we get under the quasi-steady-state assumption of equation (10).

$$\frac{d}{dt}(\bar{n} + \bar{n}_b + \bar{N}) \backsimeq 0 \quad (14)$$

$$(\bar{n} + \bar{n}_b + \bar{N}) \backsimeq \bar{n}_0(\because (\bar{n}(0) = \bar{n}_0)) \quad (15)$$

We can also see that $\bar{n}_b \backsimeq \bar{n}_b(0) \backsimeq 0$,under approximation (10) which is anexact statement when weadopt that the concentration of binding sites on one specific gene for a specific transcription factor is extremely limited relative to the free transcriptfactor concentration existing withina cell. i.e., $\bar{n}_b << \bar{n}$. Equation (15) becomes

$$(\bar{n} + \bar{N}) \backsimeq \bar{n}_0 \quad (16)$$

At last, we adopt the binding responseamong $\bar{n}$ and $\bar{I}$is quicklybalanced in such a way that

$$\bar{k}_2 \bar{I}^y \bar{n} - \bar{k}_{-2}(\bar{n}_0 - \bar{n}) \backsimeq 0 \quad (17)$$

$$\bar{n} = \frac{\bar{n}_0}{1 + \left(\frac{\bar{I}}{\bar{k}_I}\right)^y} \quad (18)$$

we define, $\bar{k}_I = \left(\bar{k}_n\right)^{1/y} = \left(\frac{\bar{k}_{-2}}{\bar{k}_2}\right)^{1/y}$(19)

where$\bar{k}_n$denotes the dissociation constant for the responseamong$\bar{n}$ and $\bar{I}$.

From equations (11), (16), and (18) exclude equations (1), (2), (3), and (7) from the given equations (1) to (7), the simplified system is then obtained as,

$$\frac{d\bar{m}}{dt} = \frac{\bar{\mu}_m}{1 + \left(\frac{\bar{k}_m\left(1+\left(\frac{\bar{I}}{\bar{k}_I}\right)^y\right)}{\bar{n}_0}\right)^x} - \bar{\delta}_m \bar{m} = \bar{f}(\bar{m}, \bar{c}, \bar{I}) \quad (20)$$

$$\frac{d\bar{c}}{dt} = \bar{\mu}_c \bar{m} - \bar{\delta}_c \bar{c} = \bar{g}(\bar{m}, \bar{c}, \bar{I}) \quad (21)$$

$$\frac{d\bar{I}}{dt} = \bar{\mu}_I \bar{c} - \bar{\delta}_I \bar{I} = \bar{j}(\bar{m}, \bar{c}, \bar{I}) \quad (\mathbf{22})$$

withinitial conditions: $\bar{m}(0) = \bar{m}_0, \bar{c}(0) = \bar{c}_0, \bar{I}(0) = \bar{I}_0$ (**23**)

Here, $\bar{\mu}_m = \bar{\mu}_d \bar{g}_0$, where $\bar{\mu}_m$denotes the maximal rate of transcription.

*Non-dimensionalization***:** Non-dimensionalization is the full study of the model equations (20) to (22). The time is measured as

$$T = \bar{\mu}_c t \quad (24)$$

where T represents the non-dimensional time.

Then above non-dimensionalization becomes

$$\frac{dm}{dT} = \frac{\mu_m}{1 + \left(k_m\left(1 + \left(\frac{I}{k_I}\right)^y\right)\right)^x} - \delta_m m = f(m, c, I) \quad (25)$$

$$\frac{dc}{dT} = m - \delta_c c = g(m, c, I) \quad (26)$$

$$\frac{dI}{dT} = \mu_I c - \delta_I I = j(m, c, I) \quad (27)$$

With initial conditions:

$$m_0 = 3.95 \times 10^{-8}; c_0 = 1.60 \times 10^{-5}; \ and \ I_0 = 2.90 \times 10^{-2} \quad (28)$$

Where the non-dimensional parameter values are given by

$$\mu_m = \frac{\bar{\mu}_m}{\bar{\mu}_c \bar{n}_0}, \mu_I = \frac{\bar{\mu}_I}{\bar{\mu}_c}, k_m = \frac{\bar{k}_m}{\bar{n}_0}, k_I = \frac{\bar{k}_I}{\bar{n}_0}, \delta_I = \frac{\bar{\delta}_I}{\bar{\mu}_c}, \delta_c = \frac{\bar{\delta}_c}{\bar{\mu}_c}, \delta_m = \frac{\bar{\delta}_m}{\bar{\mu}_c} \quad (29)$$

Study of Models:

We analyze the behavior and stability of steady-states of equations (25)-(27).

Analysis of Fixed Point

The solution of equations (25)-(27) provides the steady states of equations (25)-(27)

$$0 = \frac{\mu_m}{1 + \left(k_m\left(1 + \left(\frac{I_{ss}}{k_I}\right)^y\right)\right)^x} - \delta_m m_{ss} \quad (30)$$

$$0 = m_{ss} - \delta_c c_{ss} \quad (31)$$

$$0 = \mu_I c_{ss} - \delta_I I_{ss} \quad (32)$$

where m_{ss}, c_{ss}, and I_{ss} are the steady-state values of m, c, and I. From the equations (31), and (32)it is fine to implement the equation (30) as

$$\alpha I_{ss}\left(1 + \left(k_m\left(1 + \left(\frac{I_{ss}}{k_I}\right)^y\right)\right)^x\right) - \mu_m = 0. \quad (33)$$

where $\alpha = \frac{\delta_m \delta_c \delta_I}{\mu_I}$(34)

the solution of the steady-state of the polynomial degree (xy+1) of the equation give as,

$$\frac{\xi}{\varrho^x} I_{ss}^{yx+1} + \frac{x\xi}{\varrho^{(x-1)}} I_{ss}^{y(x-1)+1} + \ldots\ldots\ldots\ldots\ldots + \frac{x\xi}{\varrho} I_{ss}^{y+1} + (\alpha + \beta) I_{ss} - \mu_m \quad (35)$$

where $\xi = \alpha k_m^x$, and $\varrho = k_I^x$.Since every parameter is positive, the effects of Descarte's Law of signs can be applied. As there is only one significant shift in the coefficient equation series (35).

Stability from Fixed Point:

By evaluating the characteristic values of the linearized Jacobian matrix **J**of the ODE's (25)-(27), we consider the stability froma fixed point. As follows, the Jacobian is:

Wecontemplate stability from a fixed point by measuring the characteristic values of the linearized Jacobian matrix J of the ODE's (25)-(27). The Jacobian is as follows,

$$J = \begin{bmatrix} f_m & f_c & f_I \\ g_m & g_c & g_I \\ j_m & j_c & j_I \end{bmatrix} = \begin{bmatrix} -\delta_m & 0 & -\phi \\ 1 & -\delta_c & 0 \\ 0 & \mu_I & \delta_I \end{bmatrix} \quad (36)$$

where $\phi = \frac{xy\, k_m^x\, c_{ss}^{y-1}\left(1+\left(\frac{c_{ss}}{k_I}\right)^y\right)^{x-1}}{k_I^y\left(1+k_m^x\left(1+\left(\frac{c_{ss}}{k_I}\right)^y\right)^x\right)^2}$ (37)

Since all parameter values are positive, we find $\phi > 0$, and $c_{ss} > 0$ are positive for physiologically relevant parameter ranges.

Hence, the characteristic equation of **J** is $|J - \lambda I| = 0$.(38)

Where λ*'s* are the characteristic values are to be measured, and **I**is the unit matrix of the same order as the matrix **J.**

Then equation (38) becomes,

$$\lambda^3 + (\delta_m + \delta_c + \delta_I)\lambda^2 + (\delta_m\delta_c + \delta_m\delta_I + \delta_c\delta_I)\lambda + (\delta_m\delta_c\delta_I + \mu_I\phi) = 0. \quad (39)$$

According to Descartes's Law of signs, there can be no strictly positive real characteristic values. The fixed point is stable if and only if the real parts are negative. Routh Hurwitz stability requirements are added to equation (39).

$$\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0 = 0. \quad (40)$$

are satisfied if and only if $a_i > 0$ $(i = 0,1,2), and\ a_1a_2 - a_0 > 0.$

$$(\delta_m + \delta_c + \delta_I) > 0. \quad (41)$$

$$(\delta_m\delta_c + \delta_m\delta_I + \delta_c\delta_I) > 0. \quad (42)$$

$(\delta_m\delta_c\delta_I + \mu_I\phi) > 0.$ (43)

$(\delta_m + \delta_c + \delta_I)(\delta_m\delta_c + \delta_m\delta_I + \delta_c\delta_I) - (\delta_m\delta_c\delta_I + \mu_I\phi) = \rho(\delta_m, \delta_c, \delta_I) > 0.$ (44)

Since all parameter values are real and positive, the equations (41)-(43) above are therefore preserved.

Case 1: $\rho(\delta_m, \delta_c, \delta_I) > 0$. All the real parts of the characteristic values are negative in this situation, and the study condition is also stable. This consistent equilibrium is possible in two ways: (i) Case 1a, which indicates that all the characteristic values are real and negative. The effect is a stable node with monotonically steady concentrations of mRNA, protein, and cholesterol. (ii) Case 1b: Where one characteristic value is real and the two negative characteristic values are complex and the negative real component is related to the negative. In this scenario, the fixed point is a stable spiral, which reflects oscillatory constant state convergence in the concentrations of mRNA, protein, and cholesterol.

Case2: $\rho(\delta_m, \delta_c, \delta_I) = 0$. By substituting this value of $(\delta_m\delta_c\delta_I + \mu_I\phi)$ into equation (39) now, we have the characteristic equation as,

$\lambda^3 + \xi_1\lambda^2 + \xi_2\lambda + \xi_1\xi_2 = 0.$(45)

which implies, $(\lambda + \xi_1)(\lambda^2 + \xi_2) = 0.$

where $\xi_2 = (\delta_m\delta_c + \delta_m\delta_I + \delta_c\delta_I)$, and $\xi_1 = (\delta_m + \delta_c + \delta_I)$.

Hence, theconjugate roots $\lambda_i(i = 1,2)$ on the imaginary axis, and one negative real eigenvalue λ_3 given by

$\lambda_j = \pm i\sqrt{(\delta_m\delta_c + \delta_m\delta_I + \delta_c\delta_I)}$, j=1,2 (46)

$\lambda_3 = -(\delta_m + \delta_c + \delta_I)$ (47)

One negative and two pure characteristic values that are imaginary. The presence on the imaginary axis of two conjugate characteristic values means that the equilibrium of stability cannot be determined directly.

Case 3: $\rho(\delta_m, \delta_c, \delta_I) < 0$.In such cases, there is one real and positive characteristic value, and two complex characteristic values combine with a positive real value. In this case, the equilibrium is unstable which will increase and unbound the concentration of the final product. That is why we neglect it. This instance is biologically impractical.

Fixed point stability- other than μ_I :

Under a variation of system parameters, the characteristic values of the equation (45) can be transferred between each instance. A pair of complex conjugate characteristic values, for instance,

At the critical value of $\mu_I$indicated by $\mu_I^*$the point where the characteristic values cross the imaginary axis happens. A specific closed periodic orbit will bifurcate from equilibrium locally at this point as it alters stability. As a limit cycle, the isolated, closed trajectory is noted and causes oscillatory nature. This phenomenon is referred to as the Hopf bifurcation (Guckenheimer, and Holmes, 1983), and the concentrations of m, c, and I can oscillate are determined by presence.

The significance of the Hopf bifurcation:

The bifurcation occurs at the equilibrium point (m_{ss}, c_{ss}, I_{ss})according to the Hopf bifurcation theorem (Guckenheimer, and Holmes,1983), for the critical value μ_I=μ_I^*,such that the below two conditions are met:

1.The matrix J has two complex characteristic values$\lambda_k = \chi(\mu_I) \pm i\nu(\mu_I)$, k=2,3. In some neighborhood of μ_I^*, and for μ_I= μ_I^*, the two characteristic valuesi.e., $\chi(\mu_I^*)$ = 0, and $\nu(\mu_I^*) \neq 0$. For the Hopf bifurcation, the above non-hyperbolicity condition is necessary.

2. The relation termed by $\frac{d\chi(\mu_I)}{d\mu_I}\Big|_{\mu_I=\mu_I^*} \neq 0$, holds μ_I^*in some neighborhoods. For the Hopf bifurcation, this is a sufficient condition and is also known as the transverse or Hopf bifurcation crossing condition. It ensures that at a non-zero speed, the characteristic values cross the imaginary axis and hence ensures that the crossing on the imaginary axis of the complex conjugate pair is not tangent to the imaginary axis. If this is not the case, we can follow the phase in which, for instance, the eigenvalues travel up to the imaginary axis and then reverse without crossing. It has already been shown that the first condition holds the critical value μ_I^*provided by the solution.

$$\mu_I^* = \frac{(\delta_m + \delta_c + \delta_I)(\delta_m\delta_c + \delta_m\delta_I + \delta_c\delta_I) - (\delta_m\delta_c\delta_I)}{\phi}.$$

Where $\phi$is described by equation (37), along with the equation specifying the equilibrium value for $\mu_I^*$of I_{ss}:

$$\frac{(I_{ss})^{yx+1}}{\left(k_I^y\right)^x} + x\frac{(I_{ss})^{y(x-1)+1}}{\left(k_I^y\right)^{x-1}} + \cdots\cdots\cdots + x\frac{(I_{ss})^{y+1}}{\left(k_I^y\right)} + \left(\frac{1}{k_m^x} + 1\right)I_{ss} - \left(\frac{\mu_m}{k_m^x\delta_m\delta_c\delta_I}\right)\mu_I^* = 0.$$

we know from the findings of Case II that the characteristic polynomial equation (39) has two purely imaginary roots $\pm i\nu(\mu_I^*)$, at this value of μ_I^* , given in equations (46), and (47), where

$$\nu(\mu_I^*) = \sqrt{(\delta_m\delta_c + \delta_m\delta_I + \delta_c\delta_I)} \neq 0. \quad (48)$$

we use the implicit function theorem to prove that the condition holds. For each $\mu_I \epsilon \mathbb{R}$, and the system concerns. Equations (25)-(27), interpret, $\Omega(\mu_I, \lambda) = p(\lambda)$.The function of two variables $\mu_I, and\ \lambda$, also $p(\lambda)$ denotes the characteristic polynomial of the equations (25)-(27) described by the equation (39).The roots of the characteristic polynomial are the complex conjugates $\lambda(\mu_I) = \chi(\mu_I) \pm i\nu(\mu_I)$. Therefore, we have characteristic values for this $\Omega\big(\mu_I, \lambda(\mu_I)\big) = 0$.(49)

This is an implicit function of two variables, respectively, μ_I, and λ respectively. The implicit function theorem shows us that $\mu_I$can be defined asthe λ function near $\big(\mu_I^*, \lambda(\mu_I^*)\big)$, and that the λ function provides the derivative of this function as

$$\frac{d\lambda}{d\mu_I}(\mu_I^*)\Big|_{\mu_I=\mu_I^*} = -\left(\frac{\frac{\partial\Omega}{\partial\mu_I}}{\frac{\partial\Omega}{\partial\lambda}}\right)_{\mu_I=\mu_I^*} \quad (50)$$

Providing $\frac{\partial\Omega}{\partial\lambda} \neq 0$.

we start by measuring the function $\Omega\big(\mu_I, \lambda(\mu_I)\big)$derivative concerning λ, and calculating this at the critical point μ_I^*.Then

$$\frac{d\Omega}{d\mu_I}(\mu_I, \lambda)\Big|_{(\mu_I,\lambda)=\left(\mu_I^*,\ \pm i\nu(\mu_I^*)\right)} = 3\lambda^2 + 2(\delta_m + \delta_c + \delta_I)\lambda + (\delta_m\delta_c + \delta_m\delta_I + \delta_c\delta_I)|_{(\mu_I,\lambda)=\left(\mu_I^*,\ \pm i\nu(\mu_I^*)\right)}$$

$$= 3\left(\pm i\nu(\mu_I^*)\right)^2 + 2(\delta_m + \delta_c + \delta_I) \pm i\nu(\mu_I^*) + (\delta_m\delta_c + \delta_m\delta_I + \delta_c\delta_I).$$

Simplifying, along with all the fact that$\nu^2(\mu_I^*) = (\delta_m\delta_c + \delta_m\delta_I + \delta_c\delta_I)$

From equation (42), we obtain

$$\frac{\partial\Omega}{\partial\lambda} = -2\nu^2(\mu_I^*) \pm 2i(\delta_m + \delta_c + \delta_I)\nu(\mu_I^*) \neq 0. \quad (51)$$

Furthermore, from the characteristic polynomial equation (39), we have

$$\frac{d\Omega}{d\mu_I}(\mu_I,\lambda)\Big|_{(\mu_I,\lambda)=\left(\mu_I^*,\ \pm i\nu(\mu_I^*)\right)} = \phi \qquad (52)$$

where we have $\phi \geq 0$.Though, in the case of$\phi = 0$, the matrix**J** becomes

$$J = \begin{bmatrix} -\delta_m & 0 & 0 \\ 1 & -\delta_c & 0 \\ 0 & \mu_I & \delta_I \end{bmatrix}.$$

This is lower triangular, and therefore has three real negative characteristic values given by the leading diagonal elements, specifically δ_m, δ_c, and δ_I. This violates the condition 1 requirement that there are two complex eigenvalues of the matrix **J.** TheHopf bifurcation case, we can therefore infer that $\phi \neq 0$, and we just need to be related to the strict inequality $\phi > 0$. Equations (51), and (52) along with equation (50) yield

$$\frac{d\lambda}{d\mu_I}(\mu_I^*) = \frac{1}{2\nu(\mu_I^*)}\left(\frac{\phi}{-\nu(\mu_I^*) \pm i(\delta_m+\delta_c+\delta_I)}\right)$$

Upon streamlining the denominator of this complex fraction, we'll get it,

$$\frac{d\lambda}{d\mu_I} = \frac{1}{2\nu(\mu_I^*)}\left(\frac{-\nu(\mu_I^*)\phi}{\nu^2(\mu_I^*)+(\delta_m+\delta_c+\delta_I)^2}\right) + \frac{i}{2\nu(\mu_I^*)}\left(\frac{\mp\phi(\delta_m+\delta_c+\delta_I)}{\nu^2(\mu_I^*)+(\delta_m+\delta_c+\delta_I)^2}\right)$$

and since $\phi > 0$.

$$\frac{\mathrm{d}\chi}{\mathrm{d}\mu_\mathrm{I}}(\mu_\mathrm{I})\Big|_{\mu_\mathrm{I}=\mu_\mathrm{I}^*} = \mathrm{Re}\left(\frac{\mathrm{d}\lambda}{\mathrm{d}\mu_\mathrm{I}}(\mu_\mathrm{I}^*)\right) = \frac{1}{2}\left(\frac{-\phi}{\nu^2(\mu_I^*)+(\delta_m+\delta_c+\delta_I)^2}\right) < 0.$$

It satisfies the second condition of the Hopf bifurcation theorem.Thus, the presence of the Hopf bifurcation at the critical value $\mu_\mathrm{I} = \mu_\mathrm{I}^*$has been shown.

Stability of Hopf bifurcation:

limit cycle that branches from the fixed point in a Hopf bifurcation can also be stable or unstable, just as the steady-states.

The limit cycle is absorbed by a stable spiral equilibrium at a subcritical bifurcation. The equilibrium switches stability at this stage and becomes unstable. mRNA, protein, and cholesterol concentrations exhibit stable oscillations here.Supercritical Hopf bifurcation can result in behavior similar to the physiological process of homeostasis. The stability of the Hopf bifurcation needs to be determined.

By applying the ODE15s solver in MATLAB software, numerical solutions to equations (25)-(27) were obtained. Using the MATLAB software, numerical continuation toolbox Matcont (Dhooge et al., 2003), the characteristics of system bifurcations, and limit cycles were explored.

A system of ODEs is considered as the basic concept of this toolbox

$$\frac{d\mathbb{x}}{dt} = f(\mathbb{x},\mu) \qquad \mathbb{x} \in \mathbb{R}^n, \mu \in \mathbb{R}^1 \qquad (53)$$

with $(\mathbb{x}_0,\mu_0)$ as the equilibrium point. A solution curve $\sigma\ of\ f(\mathbb{x}_0,\mu_0) = 0$. With $\sigma(0) = (\mathbb{x}_0,\mu_0)$ is needed for the concept of numerical continuation. Defines how the point of equilibrium varies. Using a predictor-corrector algorithm, the curve σ is traced, Using an efficient test function that changes the sign at the bifurcation point, bifurcations along with bifurcations are described.Matcont calculates the stability of the limitation period by determining the first Lyapunov coefficient or Lyapunov characteristic exponent.Specifically,

(i) $I_1(0) < 0$, then a stable periodic orbit is enticed by the system and

(ii) $I_1(0) > 0$, then an unstable periodic orbit is enticed by the system.

The propensity of a system to control its internal environment by retaining a stable state is homeostasis. To promote a constant stage, all homeostatic mechanisms leverage feedback

inhibition. The equilibrium is never perfectly preserved in a system controlled by feedback inhibition.

Table1: Model parameter values summary

Parameter	**Description**	**Non-dimensional value**
$\bar{\mu}_m$	Caspase-1 transcription rate	5.52×10^{5}
$\bar{\mu}_c$	Caspase-1 synthesis rate	5.28×10^{-3}
$\bar{\mu}_I$	IL-1β gene expression rate	5.195×10^{-4}
$\bar{\delta}_m$	Caspase-1 mRNA degradation rate	12.83×10^{-4}
$\bar{\delta}_c$	The caspase-1 enzyme degradation rate	4.53×10^{-5}
$\bar{\delta}_I$	IL-1β release rate	1.20×10^{-4}
$\bar{k}_m$	Caspase-1 gene dissociation rate	6.503×10^{17}
$\bar{k}_I$	IL-1β gene dissociation rate	843.08×10^{9}
x	Molecules of NFkβ binding to gene	4
y	Molecules of IL-1β down-regulate NFkβ	2

Table2:Values of Non-dimensional Parameters

Parameter	**Description**	**Non-dimensional value**
$\bar{\mu}_m$	Caspase-1 transcription rate	5.29×10^{-9}
$\bar{\mu}_I$	IL-1β gene expression rate	9.84×10^{-2}
$\bar{\delta}_m$	Caspase-1 mRNA degradation rate	2.42×10^{-1}
$\bar{\delta}_c$	The caspase-1 enzyme degradation rate	8.58×10^{-3}
$\bar{\delta}_I$	IL-1β release rate	2.27×10^{-2}
$\bar{k}_m$	Caspase-1 gene dissociation rate	32.4
$\bar{k}_I$	IL-1β gene dissociation rate	42.00×10^{-6}

Appendix A: Deriving and calculating parameters

A.1. Determination of parameters for synthesis

The calculation of genetic expression and release rates is hardly quantitative in terms of mass per unit time, but the constant rates are also estimated about the modulation procedure. Therefore, we define the best biological mechanisms and recorded values from the literature review to find the real meaning for these parameters.

A.2. Rate of Caspase-1mRNA transcription-

The macrophages are large white blood cells found in body tissue an essential component of the immune system and we assume only monocytes. The IL-1β signaling path is essentially traced in monocytes, thus these cells contain only one nucleus and one set of chromosomes with a normal amount of DNA expressions [1]. The white blood cells contain two or multiple nuclei that are ignored during parameter estimation to reduce complexity during the estimation of IL-1β signal regulation [20].

We determined the transcription rate constant for nucleotides per unit of time in a mammalian genome. In general, 14,000 base pairs can be transcribed by the cell in 50 minutes, taking into account the overall transcription time, including the 30-minute delay. The Caspase-1 enzyme gene has a length of 1185 bases [10]. One Caspase-1 mRNA molecule from one gene can be transcribed at a rate of twelve bases per second [3]. Therefore, one molecule of enzyme m

RNA, which corresponds to 5.526×10^{-4}molecules of the Caspase1 mRNA s-1per gene takes approximately 1898.75 seconds.

Considering an average cell volume to be $10^{-9}\, ml$, thus the nearby rate of Caspase-1 transcription will be calculated as

$$\bar{\mu}_m = \frac{5.52 \times 10^{-4}\, molecules\, s^{-1}}{1 \times 10^{-9}\, ml} \qquad A.2.1$$

A.3. Rate of Caspase-1 protein translation

Literature-based values were taken for calculations to estimate the rate constant of the Caspase-1 protein translation. To measure its translation rate, the amino acid sequence of the Caspase-1 enzyme is taken into consideration here. The translation rate reported by Bhattacharya et al. six amino acids/sec are suggested for mammalian cells, and 1 amino acid consists of three base pair nucleotides[3]. The Caspase-1 mRNA transcript here consists of 383 amino acid sequences [10], according to conditions. Thus, one ribosome will transcribe one Caspase-1 enzyme protein molecule from one Caspase-1 mRNA, taking into account the translation rate constant of 6 amino acids/sec and 3 bases of amino acids, henceforth presenting more calculations

$$\frac{383\, amino\, acid}{18\, amino\, acid\, s^{-1}} = 21.28\, sec.$$

Here literature report also suggests the delay in translation rate constant is considered to be about 60 minutes [3], this is added to the initial calculated translation rate constant. The result estimates each ribosome consuming about 3621.28sec. to synthesis one molecule of Caspase-1 enzyme protein from Caspase-1 mRNA transcripts. Then one ribosome equivalents to

$$\frac{1\, molecule}{3621.28\, sec.} = 2.76 \times 10^{-4}\, molecules\, s^{-1}.$$

Thus, 2.76×10^{-4}molecules of Caspase-1 enzyme protein are translated and synthesized per second and a ribosome can attach at every 20th nucleotide position [11], thus 19.15 ribosomes can bind per mRNA molecule of Caspase-1. Hence, per Caspase-1 enzyme protein molecule:

$$\bar{\mu}_c = 2.76 \times 10^{-4}\, molecules\, s^{-1} ribosome^{-1} \times 19.13 ribosomes$$

$$= 5.28 \times 10^{-3} molecules\, s^{-1} \qquad A.3.1$$

i.e., there are molecules of Caspase-1 enzyme protein being produced per second.

A.4. Rate of transcription of IL-1β

The rate of IL-1β transcription is calculated with similar conditions as applied for the transcription rate of Caspase-1 enzyme i.e. transcribing 12 bp/sec [3]. Here, IL-1β exhibit 1498 long base pair and 269 amino acid sequence [23]. The initiation of transcription considers 30 minutes delay and the type cell that expresses IL-1β is a haploid macrophage cell or monocytes, thus containing only one pair of chromosomes expressing the IL-1β gene[20].

Transcription =1498 base pairs,

Translation =269residues

Protein=269 amino acids

30 min. delay =1800 sec.

Then $\frac{1498bp}{12} = 124.84$, and in 30 minutes 1924.84.

$$\frac{1}{1924.84} = 5.195 \times 10^{-4}$$

$$\therefore \bar{\mu}_I = 5.195 \times 10^{-4} \qquad A.4.1$$

A.5. Estimation of degradation rates

The model parameters δ_m and $\delta_c$estimate the Caspase-1 mRNA and Caspase-1 enzyme molecule degradation rates. The derivation of these values is calculated using molecule half-

life's are as seen from the exponential dissociation or decay model of the molecules [8, 19]. The rate constant of deprivationof the variable is given by the dissociation constant δ,

$$\therefore \bar{\delta}_m = \frac{ln(2)}{t_{1/2}} \qquad A.5.1$$

The model parameter$\bar{\delta}_I$estimate the effective release or dissociation rate of IL-1β from monocyte based upon its half-life. As per the literature report, the dissociation constant is calculated considering the half-life of Capase1 mRNA, Caspase-1 protein, and IL-1β protein [24, 30].

The caspase-1 base is 1185 base pairs, 383 amino acids

Capase1 mRNA, $t_{1/2} = 9\ min.$

$$\bar{\delta}_m = \frac{ln(2)}{540\ sec.}$$

$$\therefore \bar{\delta}_m = 12.83 \times 10^{-4} \qquad A.5.2$$

Caspase-1 protein $t_{1/2} = 4.25\ hr\ = 15300\ sec.$

$$\therefore \bar{\delta}_c = \frac{ln(2)}{t_{1/2}}$$

$$\bar{\delta}_c = \frac{ln(2)}{15300} = 4.53 \times 10^{-5} \qquad A.5.3$$

IL-1β protein $t_{1/2} = 1.6hr\ = 5760\ sec.$

$$\therefore \bar{\delta}_I = \frac{ln(2)}{t_{1/2}}$$

$$\bar{\delta}_I = \frac{ln(2)}{5760} = 1.20 \times 10^{-4} \qquad A.5.4$$

A.6. Estimation of binding affinity parameters

The parameter defining the downregulation of NFkβ due to the intense release of inflammatory mediators IL-1β from monocytes [14]. As an increase in IL-1β causes downregulation of NFkβ to regulate inflammatory signaling transduction to avoid inflammation induces cellular stress and holds immune regulation [31].

A 108 nmol binding affinity is equal to

$$\frac{108 \times 10^{-9} \times moles/ml \times N_A}{1000}$$

$$= 108 \times 10^{-12} \times 6.022 \times 10^{23} (\because\ N_A = 6.022 \times 10^{23}) \qquad A.6.1$$

$$\bar{k}_m = 6.503 \times 10^{17}$$

Dissociation rate =1.4 nmol

$$\bar{k}_I = \frac{1.4 \times 10^{-9} \times moles/ml \times N_A}{1000}$$

$$= 1.4 \times 10^{-12} \times 6.022 \times 10^{23}\ =\ 843.08 \times 10^9 \qquad A.6.2$$

Dissociation rate =1.4 nmol

$$\bar{k}_I = \frac{1.4 \times 10^{-9} \times moles/ml \times N_A}{1000}$$

$$= 1.4 \times 10^{-12} \times 6.022 \times 10^{23}\ =\ 843.08 \times 10^9 \qquad A.6.3$$

A.7. Binding coefficients- x and y

As per the structural conformation of Caspase-1 enzyme, it consists of two heterodimers which suggest that it has four binding sites on the Caspase-1 gene are existing to synthesis IL-1β, and thus x value equals to 4, since, one Caspase-1 molecule is made up of two heterodimers i.e., two molecules of Caspase-1 can modulate to down-regulate NFkβ transcription in response to the high amount of IL-1β and thus y=2 [11].

A.8. The concentration of overall transcription factor

Generally, the overall transcription factor indicates low gene expression and consequently its present's low quantitative amount within the cell.

Avogadro's number ($N_A = 6.022 \times 10^{23}$)

$$\bar{n}_0 = \frac{0.11 \times 10^{-9} mol \times 6.022 \times 10^{23} molecules\ mol^{-1}}{3.3 \times 10^{-3} ml}$$

$$= 2.007 \times 10^{16}\ molecules\ ml^{-1}$$

A.8.1

4. RESULT: MATHEMATICAL SIMULATION

The numerical solution was calculated using parametric values mentioned in Table 1; and to the resulting equation 25, 26, and 27 the mathematical simulation was done using MATLAB (R2020a). While stimulation, the ODE15s solver was applied to estimate the pharmacokinetic path of IL-1β and its system behavior depending upon body condition. The parameter value of $\overline{\mu}_I$ range between $2.695 \times 10^{-2} s^{-1}$ and $7.695 \times 10^{-2} s^{-1}$ (calculated limit values). Here, $\overline{\mu}_I$ limit variation calculated to estimate the varied pharmacokinetic behavior of IL-1β as considered in Case I and II.Case-Ia depicted in Figure 2 explains initial monotonic non-oscillating convergence to a prolonged steady-state form. As $\overline{\mu}_I$ of IL-1β increases continuously over time twice than the case-Ithe steady-state graph shifts to oscillating convergence movement considered as Case-Ib and shown in figure 3, but still, $\overline{\mu}_c$ remains in the steady-state which explains that transcription of mRNA and translation of IL-1β is partially proportional irrespective of transcription of Caspase-1 enzyme. The amplitude of mRNA transcription rate oscillation is intense which leads to cause slight oscillatory movement of IL-1β translation rate, whereas the translation rate of Caspase-1 remains steady.

The period of oscillation in case-I a for $\bar{\mu}_I$ approximately last for 4.16 hrs and for $\bar{\mu}_m$ it prolongs to oscillate till 9.72 hrs. Simultaneously considering the condition of case-I b, graphical representation reveals the oscillatory period for $\bar{\mu}_I$ and $\overline{\mu}_m$ prolong for approximately 5.55 hrs and 13.88 hrs respectively.

Case II represents a further increase in $\overline{\mu}_I$ four times than the case I were the oscillatory movement of transcription rate $\bar{\mu}_m$ distinctly increases as illustrated in figure 4. Here, the oscillatory movement of $\bar{\mu}_m$ and $\overline{\mu}_I$ am visibly distinct and show a direct proportion among them. As the increase in the mRNA gene transcription rate, there is a simultaneous increase in the translation of IL-1β. Again here, there is no oscillatory movement of the translation rate of Caspase-1 and thus remains in steady form.

From case I b and II, the graph illustration clearly explains the increase in IL-1β transcription is enhanced due to the availability of transcribed Caspase-1 enzyme within the nucleus, rather than any activity outside the nucleus i.e. in cytoplasm remains unaltered e.g. No change in the rate of protein translation of Caspase-1 enzyme, and mRNA Caspase-1 transcription rate increases to increase the synthesis of IL-1β in the nucleus.

We also considered the degradation rates or dissociation rates ($\bar{\delta}_m$, $\bar{\delta}_I$, $\bar{\delta}_c$) and binding affinities ($\bar{k}_m$, $\bar{k}_I$) along with the synthesis rate of IL-1β and Caspase-1 mRNA. Such a phenomenon helps to calculate total IL-1β present in the body concerning time. In figure 5, the parallel slight oscillatory movement is seen among $\bar{\delta}_m$ and, $\overline{\delta}_c$, and simultaneously $\bar{\delta}_I$ oscillation is intensified based upon the molecule affinity throughout the pharmacokinetic path. The degradation of translated and transcribed Caspase-1 enzyme increases which enhance the intense degradation of IL-1β which can be visibly noted by varying amplitudes of $\bar{\delta}_m$, $\bar{\delta}_I$ and, $\overline{\delta}_c$ in figure 5. Such a system behavior phenomenon helps to understand the action of the inflammatory mediator i.e. IL-1β and protects the body from inflammatory disorder. As $\bar{\delta}_m$ and, $\overline{\delta}_c$ reaches its peak amplitude the resulting IL-1β degradation rate $\bar{\delta}_I$ fall

below steady-state, and when $\bar{\delta}_m$ and, $\bar{\delta}_c$ completely stops oscillating than the steady-state of IL-1β degradation

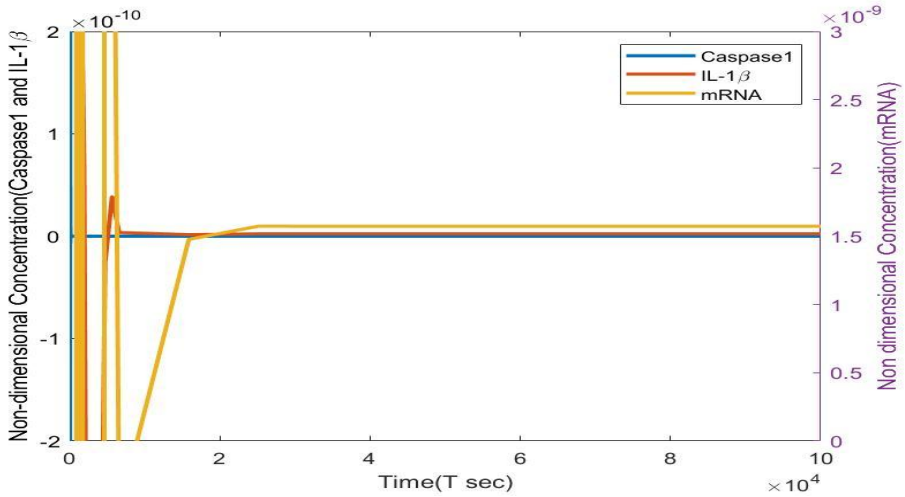

Figure 2: Each parameter is from Table 2 other than non-dimensional $\mu_I = 0.0954$.Nondimensional initial conditions are $m_0 = 3.95 \times 10^{-8}$,$c_0 = 1.60 \times 10^{-5}$,and $I_0 = 2.90 \times 10^{-2}$.

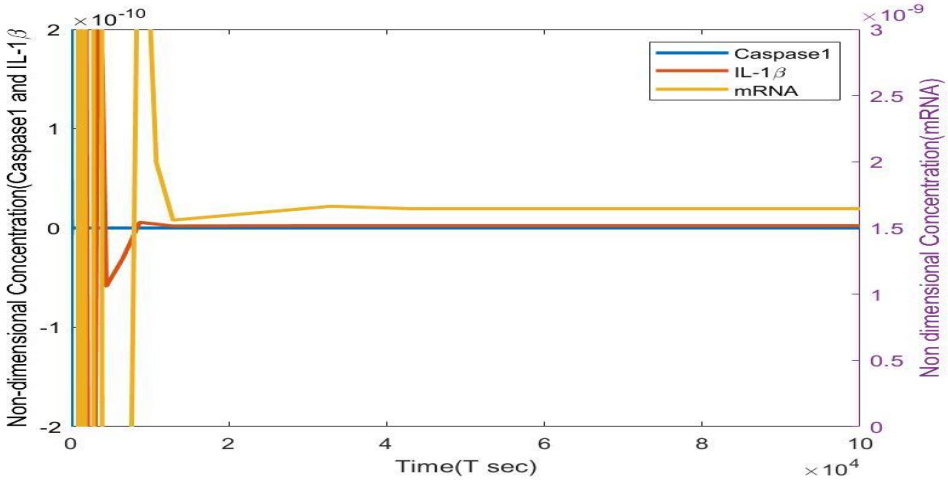

Figure 3: Each parameter is from Table 2 other than non-dimensional $\mu_I = 0.1908$. (since 2*μ_I)And nondimensional initial conditions are the same as in Figure 2.

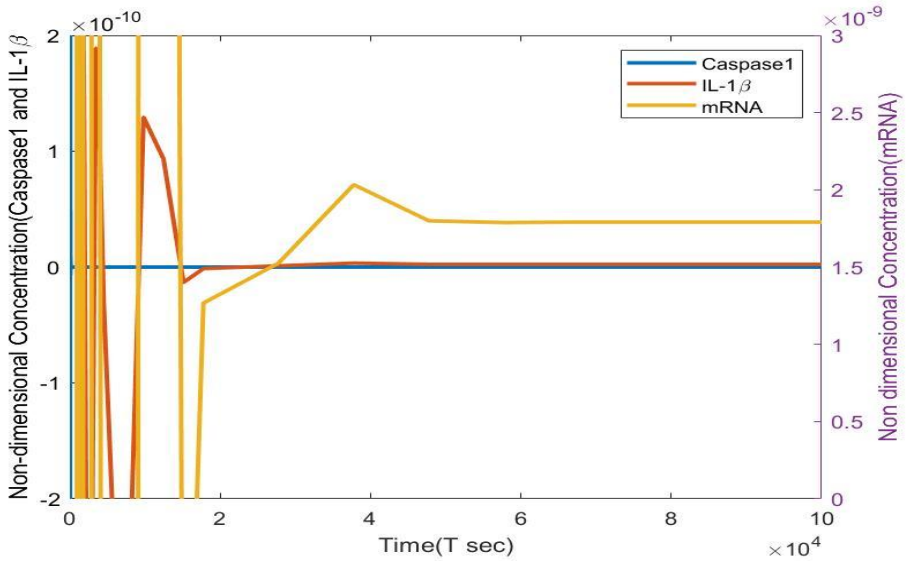

Figure 4: Each parameter is from Table 2 other than non-dimensional $\mu_I = 0.3816$ (since $4*\mu_I$)And nondimensional initial conditions are the same as in Figure 2.

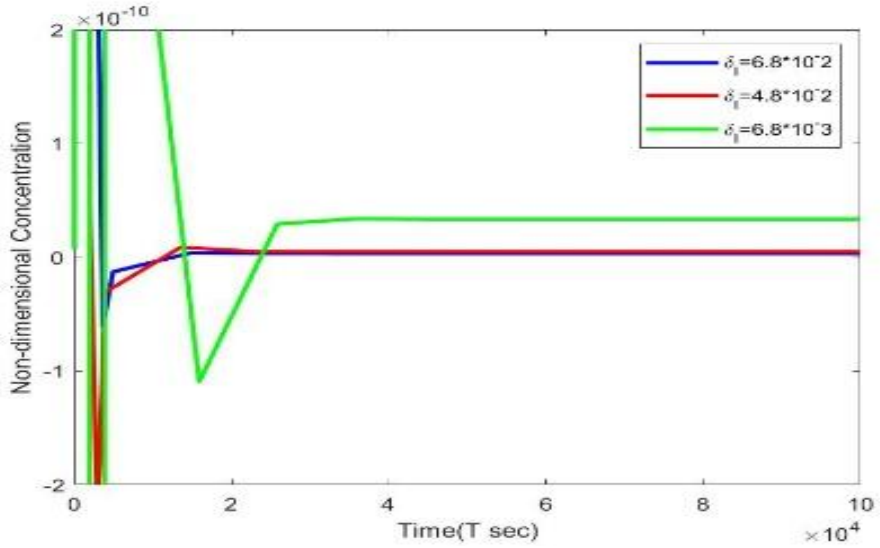

Figure 5: Each parameter is from Table 2 other than non-dimensional δ_I 's are successively different from nondimensional values asdesignated

5 DISCUSSION:

We have outlined the pharmacokinetic compartment model representing the synthesis and regulation of IL-β through the NFkβ signaling path and mathematical simulation done using ODE15s solver in MATLAB software. The simulation predicts the period of oscillatory convergence of transcription and degradation rate of IL-1β based upon parameter conditions. This helps to understand the pharmacology of inflammatory mediators IL-1β and its regulatory enzyme Caspase-1, further elaborating its subsequent regulation in case of an inflammatory disorder. Here the development of the compartment model makes ease to understand the dynamic mechanism of IL-1β, which explains that the transcription rate of IL-1β depends on the transcriptions rate of the Caspase-1 enzyme and synthesis of Caspase-1 enzyme is enhanced by NFkβ protein [17]. So indirectly NFkβ and IL-1β are interdependent which can effectively regulate inflammatory-related disorder.

According to Boucher et al. proinflammatory signaling transmission can be modulated through a negative feedback mechanism, thus the Caspase-1 enzyme through the signal feedback loop enables to timely suppression or elevate transcription of IL-1β depending on the physiology of the immune system [4]. This mechanism held us to design an outline of IL-1β pharmacokinetics and by mathematical simulation, the correlation between the transcription rate of IL-1β and Caspase-1 enzyme is well understood. The idea of developing and estimating such a kinetic compartment model procured from the research related to cholesterol synthesis and its regulation through negative feedback mechanism via SERB protein and HMGR reductase enzyme, and the research conducted by Bhattacharya et al [3]. Moreover, the research laid by scientists Wagner and Stolovitzkyexplains that the negative feedback mechanism is modulated based upon the amount of specific molecule in the body and according to its levels of mRNA gene expression can be reduced or increased via transcription, translation, and degradation rate [29]. The parameter values are effectively calculated based upon proven experimental data and known protein structure and gene expression of the Caspase-1 enzyme, and IL-1β.

6. CONCLUSION:

A compartment model of IL-1β gene expression, whereby mathematical simulation using MATLAB software depicted the correlation between the transcription rate of IL-1β and caspase 1 enzyme, consequently their degradation rate during the phase of increase IL-1β gene expression in macrophages. The graphical representation is shown oscillatory convergence depending upon the varying rate of transcription of IL-1β and dependently changes in oscillation of caspase 1 enzyme transcription rate. Altogether, we could conclude that IL-1β gene expression exhibit a negative feedback loop where we designed a compartment model and simulated results expressing IL-1β synthesis and degradation rate. Such results will enable us to understand the regulatory inflammation path via IL-1β and its modulatory impact in case of the underlying phenomenon of inflammatory disorders or cellular stress.

REFERENCES:

[1]. Bensi, G., Raugei, G., Palla, E., Carinci, V., Buonamassa, D.T. and Melli, M., 1987. Human interleukin-1 beta gene. *Gene*, *52*(1), pp.95-101.

[2]. Bent, R., Moll, L., Grabbe, S., and Bros, M., 2018. Interleukin-1 beta—a friend or foe in malignancies?. *International journal of molecular sciences*, *19*(8), p.2155.

[3]. Bhattacharya, B.S., Swaby, P.K., Minihane, A.M., Jackson, K.G., and Tindall, M.J., 2014. A mathematical model of the sterol regulatory element-binding protein 2 cholesterol biosynthesis pathway. *Journal of theoretical biology*, *349*, pp.150-162.

[4]. Boucher, D., Monteleone, M., Coll, R.C., Chen, K.W., Ross, C.M., Teo, J.L., Gomez, G.A., Holley, C.L., Bierschenk, D., Stacey, K.J. and Yap, A.S., 2018. Caspase-1 self-cleavage is an intrinsic mechanism to terminate inflammasome activity. *Journal of Experimental Medicine*, *215*(3), pp.827-840.

[5]. Brough, D., and Rothwell, N.J., 2007. Caspase-1-dependent processing of pro-interleukin-1β is cytosolic and precedes cell death. *Journal of cell science*, *120*(5), pp.772-781.

[6]. Bry, K., Lappalainen, U., and Hallman, M., 1993. Interleukin-1 binding and prostaglandin E2 synthesis by amnion cells in culture: regulation by tumor necrosis factor-α, transforming growth factor-β, and interleukin-1 receptor antagonist. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*, *1181*(1), pp.31-36.

[7]. Chang, H.Y. and Yang, X., 2000. Proteases for cell suicide: functions and regulation of caspases. *Microbiology and molecular biology reviews*, *64*(4), pp.821-846.

[8]. Chen, C.Y.A., Ezzeddine, N., and Shyu, A.B., 2008. Messenger RNA half- life measurements in mammalian cells. *Methods in enzymology*, *448*, pp.335-357.

[9]. Christgen, S., Place, D.E., and Kanneganti, T.D., 2020. Toward targeting inflammasomes: insights into their regulation and activation. *Cell Research*, pp.1-13.

[10]. Dang, W.T., Xu, D., Xie, W.G., and Zhou, J.G., 2015. Expression of Caspase-1 gene transcript variant mRNA in peripheral blood mononuclear cells of patients with primary gout in different TCM syndromes. *Evidence-Based Complementary and Alternative Medicine*, *2015*.

[11]. Datta, D., Scheer, J.M., Romanowski, M.J., and Wells, J.A., 2008. An allosteric circuit in caspase-1. *Journal of molecular biology*, *381*(5), pp.1157-1167.

[12]. Di Paolo, N.C. and Shayakhmetov, D.M., 2016. Interleukin 1α and the inflammatory process. *Nature immunology*, *17*(8), pp.906-913.

[13]. Dinarello, C.A., 2011. Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. *Blood, The Journal of the American Society of Hematology*, *117*(14), pp.3720-3732.

[14]. Hadadi, E., Zhang, B., Baidžajevas, K., Yusof, N., Puan, K.J., Ong, S.M., Yeap, W.H., Rotzschke, O., Kiss-Toth, E., Wilson, H. and Wong, S.C., 2016. Differential IL-1β secretion by monocyte subsets is regulated by Hsp27 through modulating mRNA stability. *Scientific Reports*, *6*, p.39035.

[15]. Lamkanfi, M., Declercq, W., Vanden Berghe, T., and Vandenabeele, P., 2006. Caspases leave the beaten track: caspase-mediated activation of NF-κB. *The Journal of cell biology*, *173*(2), pp.165-171.

[16]. Lee, D.J., Du, F., Chen, S.W., Nakasaki, M., Rana, I., Shih, V.F., Hoffmann, A. and Jamora, C., 2015. Regulation and Function of the Caspase-1 in an Inflammatory Microenvironment. *Journal of Investigative Dermatology*, *135*(8), pp.2012-2020.

[17]. Li, C., Zhang, F., Kurths, J., and Zeng, F., 2013. Equivalent system for a multiple-rational-order fractional differential system. *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences*, *371*(1990), p.20120156.

[18]. Lu, A., Li, Y., Schmidt, F.I., Yin, Q., Chen, S., Fu, T.M., Tong, A.B., Ploegh, H.L., Mao, Y. and Wu, H., 2016. Molecular basis of caspase-1 polymerization and its inhibition by a new capping mechanism. *Nature structural & molecular biology*, *23*(5), pp.416-425.

[19]. Lugowski, A., Nicholson, B., and Rissland, O.S., 2018. Determining mRNA half-lives on a transcriptome-wide scale. *Methods*, *137*, pp.90-98.

[20]. Madej, M.P., Töpfer, E., Boraschi, D., and Italiani, P., 2017. Different regulation of interleukin-1 production and activity in monocytes and macrophages: innate memory as an endogenous mechanism of IL-1 inhibition. *Frontiers in pharmacology*, *8*, p.335.

[21]. Mussbacher, M., Salzmann, M., Brostjan, C., Hoesel, B., Schoergenhofer, C., Datler, H., Hohensinner, P., Basílio, J., Petzelbauer, P., Assinger, A. and Schmid, J.A., 2019. Cell type-specific roles of NF-κB linking inflammation and thrombosis. *Frontiers in immunology*, *10*, p.85.

[22]. Pichardo-Almarza, C., and Diaz-Zuccarini, V., 2016. From PK/PD to QSP: understanding the dynamic effect of cholesterol-lowering drugs on atherosclerosis progression and stratified medicine. *Current pharmaceutical design*, *22*(46), pp.6903-6910.

[23]. Plüss, C., Werner, E.R., Blau, N., Wachter, H. and Pfeilschifter, J., 1996. Interleukin 1β and cAMP trigger the expression of GTP cyclohydrolase I in rat renal mesangial cells. *Biochemical Journal*, *318*(2), pp.665-671.

[24]. Reimers, J., Wogensen, L.D., Welinder, B., Hejnaes, K.R., Poulsen, S.S., Nilsson, P., and Nerup, J., 1991. The pharmacokinetics, distribution, and degradation of human recombinant interleukin 1β in normal rats. *Scandinavian journal of immunology*, *34*(5), pp.597-617.

[25]. Shalini, S., Dorstyn, L., Dawar, S., and Kumar, S., 2015. Old, new and emerging functions of caspases. *Cell Death & Differentiation*, *22*(4), pp.526-539.

[26]. Togi, S., Hatano, Y., Muromoto, R., Kawanishi, E., Ikeda, O., Hirashima, K., Kon, S., Kitai, Y., Yasui, T., Oritani, K. and Matsuda, T., 2016. caspase-dependent cleavage regulates protein levels of Epstein–Barr virus- derived latent membrane protein 1. *Feb Letters*, *590*(6), pp.808-818.

[27]. Vervoordeldonk, M.J., van Rossum, G.S., Sanchez, R.M., Neys, F.W., and Van den Bosch, H., 1997. The half-life of interleukin-1β-induced group II phospholipase A2 in rat mesangial cells. *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research*, *1355*(3), pp.315-322.

[28]. Wagner, J., and Stolovitzky, G., 2008. Stability and time-delay modeling of negative feedback loops. *Proceedings of the IEEE*, *96*(8), pp.1398-1410.
[29]. Walsh, J.G., Logue, S.E., Lüthi, A.U., and Martin, S.J., 2011. Caspase-1 promiscuity is counterbalanced by the rapid inactivation of the processed enzyme. *Journal of Biological Chemistry*, *286*(37), pp.32513-32524.
[30]. Wan, F., and Lenardo, M.J., 2009. Specification of DNA binding activity of NF-κB proteins. *Cold Spring Harbor perspectives in biology*, *1*(4), p.a000067.
[31]. Zhang, Q., Lenardo, M.J., and Baltimore, D., 2017. 30 years of NF-κB: a blossoming of relevance to human pathobiology. *Cell*, *168*(1-2), pp.37-57.