

Dynamic Response of Evolved Atherosclerotic Plaque Model and its Stability

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ABSTRACT

The present study is dealt with the formation of a mathematical model of atherosclerotic plaque evolved through the interactions among various cellular species in the biochemical process causing concern of health hazard for impairment of the cardiovascular system. Of many participating species several important species like LDLs, HDLs, radicals, oxidized LDLs, chemo-attractants, monocytes, macrophages, T-cells, smooth muscle cells (SMCs) and the necrotic core are selected to interact in the process. As the proposed model admits global stability, it can cater for larger range of parameter values towards acceptability for in silico studies on atherosclerotic plaque formation. The large system of differential equations (ODEs) emerging from the dynamics of all the cellular components forming plaque in the arterial lumen is reduced to smaller system for an in-depth study on the characteristics of the participating cellular species including their individual contributions to the association / dissociation of plaque. The quasi steady state approximation theory (QSSA) is induced for the purpose of reduction of the primal system into a smaller ones (Model A and Model B) by way of protecting contributions of those nonexistent species in terms of the concentrations of the participating species in the reduced system. The present model system experiences bifurcation with respect to a couple of parameters of significance. The applicability of the proposed plaque model is validated through a comparison of the present results with those of the existing experimental data.

Keywords: Atherosclerosis, Cholesterol efflux, Quasi Steady State Approximation (QSSA), Global Stability, Saddle Node Bifurcation.

2010 Mathematics Subject Classification: 34D23, 37G35, 34C23, 34K18

Journal of Economic Literature: C32, C62, C63

1 Introduction

Atherosclerosis is a chronic vascular disease causing hardening of the arteries. This is originated by inflammation in the intima, the inner lining of the arterial wall, where many cellular components like low density lipoproteins, monocytes and macrophages interact among themselves in the process to form complex fat-laden foam cells which are accumulated. This process of aggregation of such cells in the arterial lumen is in general termed as plaque formation (Libby, Ridker and Maseri, 2002). Atherosclerosis is the foremost agent for many diseases leading to the malfunction of the cardiovascular system. Cardiovascular diseases are usually

classified into two categories. One is in the presence of atherosclerosis, the ischaemic heart disease or coronary arterial disease, the cerebrovascular disease or lesions of blood vessels including hypertension and peripheral vascular diseases may emerge. Other cardiovascular diseases in the absence of atherosclerosis are the usual congenital heart disease, rheumatic heart disease, cardio-myopathies and cardiac arrhythmias (Organization, 2011).]. It has been reported that 31% death occurs due to cardiovascular diseases of which the ischaemic heart ailment and cerebro-vascular disease under atherosclerotic condition are the supreme cause of death worldwide setting very alarming statistical record.

Early stages of atherosclerosis are generally not symptomatic. In the pre-clinical stage, early atherosclerotic lesions of type I and type II get under way with a small bulge comprising lipid deposits in the arterial lumen (Kharbanda and MacAllister, 2005). In the wake of type III lesion development however requires longer spell of time nearly 14 – 15 years and it embodies extra-cellular lipid pool core with a fibrous cap concocted from collagen-rich matrix as evident from (Hansson and Libby, 2006) and (Kharbanda and MacAllister, 2005). It induces further towards advanced lacerations of type IV and type V comprising lipid core capped with a fibrous tissue. These highly developed plaques when experienced in the event of thrombosis or hemorrhage are referred to type VI lesions (Kharbanda and MacAllister, 2005).

According to the latest reports (Benjamin, 2017) it has been observed that outbreak of coronary heart disease is more common among patients of middle age group of forty plus. The prediction of WHO in its report (Parton, McGilligan, OKane, Baldrick and Watterson, 2015) seems to be alarming that the global population with sixty plus age group will be doubled to 22% in 2050 from its 11% in 2000. It underlines inordinate importance of coming up with expertise to enhance the therapeutic investigation on this disease.

This is a multiphase process involving several factors operating on different length scales, it is natural to approve mathematical modeling in order to understand the characteristics of complex dynamics emerging from the biochemical process for the appearance of the lesions. The evolution of atherosclerosis is contemplated here as a continuous process represented mathematically as a system of nonlinear ordinary differential equations. Both the transient and quasi-steady state responses of the participating cellular components involved in the proposed model are examined.

1.1 Pathogenesis of atherosclerosis

Atherosclerotic plaques are formed within the intima, the innermost layer of artery wall. Intima is separated from streaming blood by a thin permeable layer of endothelial cells, known as endothelium. The 'response to injury' theory by Ross and Glomset (Ross, Glomset and Harker, 1977) postulates that atherosclerosis formation gets underway with a lesion in the

arterial lumen which involves complex interactions among several cellular components like cholesterol, immune cells, smooth muscle cells (SMCs), together with the tissues of the artery wall and blood flow. Low density lipoproteins (LDLs), one of the five major lipoproteins of blood diffuse through the endothelium lesion and enter into the intima. LDLs are made up of lipid core, a surface protein and antioxidant (Cobbold, Sherratt and Maxwell, 2002). When LDLs are in the blood they don't get oxidised but once they enter into intima free radicals penetrate on the LDL particles and destroy their antioxidants. They form a new molecule, which is most commonly known as oxidised LDL (ox-LDL). When LDLs enter into the intima, HDLs also move into the intima and get oxidised by free radicals (McKay, McKee, Mottram, Mulholland, Wilson, Kennedy and Wadsworth, 2005). Unlike ox-LDL, oxidised HDL does not involve in the plaque formation, rather it obstructs the biochemical process (Barter, 2005). In the presence of ox-LDL, the ECs produce vascular cell adhesion molecule (VCAM1) (Libby et al., 2002) which attracts T-cells and monocytes into the intima. In addition to this ECs and SMCs secrete chemoattractant, in particular monocyte chemoattractant protein (MCP-1) in the intima. This triggers the inflammation process (McKay et al., 2005). Then the proliferation chemicals secreted from T-cells differentiate monocytes into macrophages. These macrophages have scavenger receptors. The macrophages ingest ox-LDL via scavenger receptors and turn into fat laden foam cells. These foam cells and several dead cells all together form the plaque. The oxidised HDL are not ingested by the macrophages while plaque formation. HDL secrete a protein namely, Apolipoprotein A-I which promotes the efflux of cholesterol from the accumulated plaque and HDL carries this cholesterol outside the intima (Linsel-Nitschke and Tall, 2005). This is the one of the major processes of cholesterol efflux. HDLs interact with all other species and strive to reduce the speed of plaque formation. SMCs are induced by chemoattractant and migrate into the intima. While in the intima SMCs secrete extra cellular matrix (Collagen) which forms a fibrous cap between the plaque and endothelium. When the plaque increases to such a level that the wall shear stress of endothelium layer crosses beyond a threshold value, plaque bulges into lumen and the fibrous cap ruptures. It disturbs the smooth blood flow in lumen and a thrombosis or haemorrhage occurs thereby ((Cobbold et al., 2002),(Hansson and Libby, 2006), (Libby et al., 2002),(McKay et al., 2005)).

1.2 Earlier models

Quite a good number of mathematical models in terms of both ordinary and partial differential equations (ODEs and PDEs) describing the evolution of atherosclerosis has been introduced in the recent past. Cobbold et al. (Cobbold et al., 2002) have demonstrated that HDL and vitamin-C are more favourable than the supplementation of vitamin E through their LDL oxidation model. An ODE model of the formation of atherosclerosis has been taken up by McKay et al. (McKay et al., 2005) which was modified subsequently into a PDE one depending on the objectives. All the stages in the making of atherosclerosis are described precisely without performing any quantitative analysis. Bulelzai et al. (Bulelzai and Dubbeldam, 2012) focused their attention on the effects of the wall shear stress and the radius of the arterial wall on the evolution of atherosclerosis in their ODE model. Ougrinovskaia et al. (Ougrinovskaia, Thompson

and Myerscough, 2010) has also considered an ODE model with three important components ox-LDL, macrophages and foam cells. They have set some values to the model parameters and successfully performed the phase plane analysis and the simulation as well. Utilising the set of parameter values they have shown that the macrophage proliferation instigates the lesion instability rather than the influx of LDL in intima. Subsequently, Cohen et al. (Cohen, Myerscough and Thompson, 2014) modified the model of Ougrinovskaia et al. (Ougrinovskaia et al., 2010) with the inclusion of HDL in the system. They have shown that HDL reduces the rate of plaque growth. An extensive list of all these previous models and their discussions are clearly pointed out in (Parton et al., 2015).

Recently, an ODE model for the development of disease has been conducted by Anlamlert et al. (Anlamlert, Lenbury and Bell, 2017) to study on proliferation rate of extra-cellular matrix (collagen). They investigated the stability and oscillatory behaviour of the system. On the other hand, a series of PDEs has been taken up by Hao et al. (Hao and Friedman, 2014) for model representation comprising several key cellular components forming atherosclerosis. They concentrated their study on the LDL-HDL ratio and estimated its effect on plaque formation. Another PDE model was also described by Chalmers et al. (Chalmers, Cohen, Bursill and Myerscough, 2015) who have identified the influences of two bifurcation parameters concerning the rate of LDL insertion into intima and blood monocyte count level together with their contribution to the evolution of atherosclerosis.

The proposed study is based on a mathematical ODE model of atherosclerotic plaque where many cellular species like LDL, HDL, radicals, oxidised LDL, chemoattractants, monocytes, macrophages, T-cells, smooth muscle cells and the necrotic core come into play. The quasi steady state approximation theory is inducted for reduction of the large system into smaller ones referred to Model A and Model B. Stability analysis of the models in this study is being done in a similar fashion provided in (Rahman and Chakravarty, 2013), (Ali and Chakravarty, 2015). The present model system experiences bifurcation with respect to a couple of parameters. An attempt has been made to validate the applicability of the proposed model.

The organisation of the article is: in Section 2 model is being formulated, in Section 3 the model is nondimensionalised and in Section 4 stability analysis of the rescaled model has been done. In Section 5 the model is reduced into 2 models, namely Model A including HDL and Model B without HDL. In Section 6 stability analysis is being performed for the reduced model. Next, in Section 7 numerical results of the theoretical findings are shown, in Section 8 the model is validated and finally in Section 9 the article is concluded with a concluding remark.

2 Formulation of the Model

Several important cellular species, namely LDLs, HDLs, free radicals, modified / oxidized LDLs, chemo-attractants, monocytes, macrophages, T-cells, smooth muscle cells, plaque (or, necrotic core) involved in atherosclerotic plaque formation are considered for the biochemical

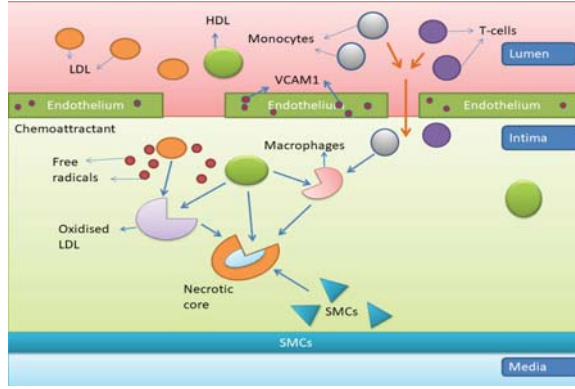


Figure 1: Schematic diagram of atherosclerotic plaque (necrotic core) formation and HDL involvement.

process as described in Figure 1. This process is modelled mathematically in terms of ten first order nonlinear ODEs. The model equations are defined below with proper explanation of all the terms involved therein.

$$\frac{d\tilde{L}}{dt} = \sigma_L - k_L \frac{\tilde{R}\tilde{L}}{\delta_R + \tilde{R}} - d_L\tilde{L}, \quad (2.1)$$

$$\frac{d\tilde{H}}{dt} = \sigma_H - k_H \frac{\tilde{H}\tilde{R}}{\delta_R + \tilde{R}} - \mu_H \frac{\tilde{H}\tilde{N}^2}{\delta_N^2 + \tilde{N}^2} - d_H\tilde{H}, \quad (2.2)$$

$$\frac{d\tilde{R}}{dt} = \sigma_R - (k_L\tilde{L} + k_H\tilde{H}) \frac{\tilde{R}}{\delta_R + \tilde{R}} - d_R\tilde{R}, \quad (2.3)$$

$$\frac{d\tilde{X}}{dt} = k_L \frac{\tilde{R}\tilde{L}}{\delta_R + \tilde{R}} - \frac{\rho_{im}\tilde{M}\tilde{X}^2}{\delta_X^2 + \tilde{X}^2} - q_X \frac{\tilde{X}\tilde{H}}{\delta_H + \tilde{H}} - d_X\tilde{X}, \quad (2.4)$$

$$\frac{d\tilde{C}}{dt} = \rho_C\tilde{X} - q_C \frac{\tilde{C}\tilde{H}}{\delta_H + \tilde{H}} - d_C\tilde{C}, \quad (2.5)$$

$$\frac{d\tilde{m}}{dt} = \rho_m\tilde{C} + \gamma \frac{\tilde{X}^2\tilde{m}}{\delta_X^2 + \tilde{X}^2} - \rho_M\tilde{m} - q_m \frac{\tilde{m}\tilde{H}}{\delta_H + \tilde{H}} - d_m\tilde{m}, \quad (2.6)$$

$$\frac{d\tilde{M}}{dt} = \rho_M\tilde{m} + \rho_{ef} \frac{\tilde{N}^2\tilde{H}}{\delta_N^2 + \tilde{N}^2} - \frac{\rho_{in}\tilde{M}\tilde{X}^2}{\delta_X^2 + \tilde{X}^2} - d_M\tilde{M}, \quad (2.7)$$

$$\frac{d\tilde{T}}{dt} = \rho_T\tilde{C} - q_T \frac{\tilde{T}\tilde{H}}{\delta_H + \tilde{H}} - d_T\tilde{T}, \quad (2.8)$$

$$\frac{d\tilde{S}}{dt} = \rho_S\tilde{C} - m_S\tilde{S} - q_S \frac{\tilde{S}\tilde{H}}{\delta_H + \tilde{H}} - d_S\tilde{S}, \quad (2.9)$$

$$\frac{d\tilde{N}}{dt} = \frac{\rho_{in}\tilde{M}\tilde{X}^2}{\delta_X^2 + \tilde{X}^2} + m_S\tilde{S} - \rho_{ef} \frac{\tilde{H}\tilde{N}^2}{\delta_N^2 + \tilde{N}^2} - d_N\tilde{N}, \quad (2.10)$$

Here $\tilde{L}$, $\tilde{H}$, $\tilde{R}$, $\tilde{X}$, $\tilde{C}$, $\tilde{m}$, $\tilde{M}$, $\tilde{T}$, $\tilde{S}$ and $\tilde{N}$ represent the respective time-dependent concentrations of LDLs, HDLs, free radicals, oxidized LDLs, chemo-attractants, monocytes, macrophages, T-cells, smooth muscle cells, plaques while the remaining parameters of the model have their nomenclatures listed in Table 2. In equation (2.1), the first term represents a constant source of LDL being supplied by the blood stream, the second term corresponds to reacting LDL with

free radicals resulting in reduction of LDL concentration and the third term denotes the death of LDL. Similarly in equation (2.2), first term represents constant source of HDL, second term is the loss of HDL due to interaction with radical, third term represents loss of HDL due to its involvement in efflux of cholesterol from plaque and the last term denotes death of HDL. Equation (2.3) governs the evolution of concentration of free radicals in which the first term relates to constant source of free radicals available from blood while the second term is its loss due to interaction with HDL and LDL and the third term denotes its natural death. HDL controls the biochemical process of plaque formation. HDLs presence affecting on oxidised LDL, chemoattractant, monocytes, T-cells, SMCs are described as $q_X \frac{\tilde{X}\tilde{H}}{\delta_H + \tilde{H}}$ in (2.4), $q_C \frac{\tilde{C}\tilde{H}}{\delta_H + \tilde{H}}$ in (2.5), $q_m \frac{\tilde{m}\tilde{H}}{\delta_H + \tilde{H}}$ in (2.6), $q_T \frac{\tilde{T}\tilde{H}}{\delta_H + \tilde{H}}$ in (2.8), $q_S \frac{\tilde{S}\tilde{H}}{\delta_H + \tilde{H}}$ in (2.9) respectively. The equation (2.4) corresponds to oxidized LDL concentration evolution expresses in terms of producing oxidized LDL due to reaction of LDL with free radicals and the loss incurred by macrophages ingestion specified by a response function $\frac{\rho_{in}\tilde{M}\tilde{X}^2}{\delta_X^2 + \tilde{X}^2}$ and interaction with HDL $q_X \frac{\tilde{X}\tilde{H}}{\delta_H + \tilde{H}}$ and the last term is the loss due to death. In equation (2.5), first term denotes the production (at a rate proportional to oxidized LDL), second term is loss due to interaction with HDL and the last term denotes death of chemoattractants. The evolved monocyte concentration in equation (2.6) has three terms on its right hand side of which the first term denotes its production due to presence of chemoattractant in the intima, second term $\gamma \frac{\tilde{X}^2\tilde{m}}{\delta_X^2 + \tilde{X}^2}$ relates to the interaction between monocytes and oxidized LDL resulting in the evolution of monocytes where γ is inversely proportional to wall shear stress, while the third denotes its reduction due to its differentiation into macrophages, fourth is its loss due to interaction with HDL and the rest is death of monocytes. In the equation (2.7), the first term appears from differentiation of monocytes into the form of macrophages, second term $\rho_{ef} \frac{\tilde{N}^2\tilde{H}}{\delta_N^2 + \tilde{N}^2}$ is a source term of macrophages due to efflux of cholesterol from plaque, third term $\frac{\rho_{in}\tilde{M}\tilde{X}^2}{\delta_X^2 + \tilde{X}^2}$ is the loss due to ingesting oxidized LDL and the last term represents the death of macrophages. In concentration rate of T-cells as in equation (2.8), the first term signifies its attraction by the chemo-attractants into the intima while the second term represents loss due to interaction with HDL and the third term is the loss by death. The terms of equation (2.9) comprise (i) induction of smooth muscle cells into the intima by chemo-attractants, (ii) loss of smooth muscle cells for production of collagen, (iii) loss due to interaction with HDL and (iv) death of smooth muscle cells. In equation (2.10) first term $\frac{\rho_{in}\tilde{M}\tilde{X}^2}{\delta_X^2 + \tilde{X}^2}$ represents elements of combined portion of foam cells and fibrous cap, together which is popularly known as plaque, second term is contribution of SMCs if formation of fibrous cap, third term is loss due to cholesterol efflux and the third term is the loss due to death. Contributing all other components' dead counterparts in foam cell formation is disregarded in order to reduce the complexity of the model analysis.

3 Rescaled model

To make the system dimensionless one may consider a rescaling in the time variable t by using the relation $\tau = rt$, in which r is dependent on the concerned time scale. Here t is first set in seconds and r is considered as $6 \times 10^{-7} \text{ sec}^{-1}$ (Chalmers et al., 2015), to make the equivalency as: $\tau = 1$ unit of non-dimensional time is equivalent to 19 days approximately. The

rescaled equations are:

$$\frac{dL}{d\tau} = b_{11} - b_{12} \frac{RL}{1+R} - b_{13}L, \quad (3.1)$$

$$\frac{dH}{d\tau} = b_{21} - b_{22} \frac{HR}{1+R} - b_{23} \frac{HN^2}{1+N^2} - b_{24}H, \quad (3.2)$$

$$\frac{dR}{d\tau} = b_{31} - (b'_{32}L + b''_{32}H) \frac{R}{1+R} - b_{33}R, \quad (3.3)$$

$$\frac{dX}{d\tau} = b_{12} \frac{RL}{1+R} - \frac{b_{42}MX^2}{1+X^2} - b_{43} \frac{XH}{1+H} - b_{44}X, \quad (3.4)$$

$$\frac{dC}{d\tau} = b_{51}X - b_{52} \frac{CH}{1+H} - b_{53}C, \quad (3.5)$$

$$\frac{dm}{d\tau} = b_{61}C + b_{62} \frac{X^2m}{1+X^2} - b_{63}m - b_{64} \frac{mH}{1+H} - b_{65}m, \quad (3.6)$$

$$\frac{dM}{d\tau} = b_{63}m + b_{72} \frac{N^2H}{1+N^2} - \frac{b_{42}MX^2}{1+X^2} - b_{74}M, \quad (3.7)$$

$$\frac{dT}{d\tau} = b_{81}C - b_{82} \frac{TH}{1+H} - b_{83}T, \quad (3.8)$$

$$\frac{dS}{d\tau} = b_{91}C - b_{92}S - b_{93} \frac{SH}{1+H} - b_{94}S, \quad (3.9)$$

$$\frac{dN}{d\tau} = \frac{b_{101}MX^2}{1+X^2} + b_{92}S - b_{102} \frac{HN^2}{1+N^2} - b_{103}N, \quad (3.10)$$

where,

$$\begin{aligned} L &= \tilde{L}/\delta_X, H = \tilde{H}/\delta_H, R = \tilde{R}/\delta_R, X = \tilde{X}/\delta_X, C = \tilde{C}/\delta_X, m = \tilde{m}/\delta_X, \\ M &= \tilde{M}/\delta_X, T = \tilde{T}/\delta_X, S = \tilde{S}/\delta_X, N = \tilde{N}/\delta_N, b_{11} = \sigma_L/\delta_X r, b_{12} = k_L/r, \\ b_{13} &= d_L/r, b_{21} = \sigma_H/\delta_H r, b_{22} = k_H/r, b_{23} = \mu_H/r, b_{24} = d_H/r, b_{31} = \sigma_R/\sigma_R r, \\ b'_{32} &= k_L\delta_X/r\delta_R, b''_{32} = k_H\delta_H/r\delta_R, b_{33} = d_R/r, b_{42} = \rho_{in}/r, b_{43} = q_X/r, \\ b_{44} &= d_X/r, b_{51} = \rho_C/r, b_{52} = q_C/r, b_{53} = d_C/r, b_{61} = \rho_m/r, b_{62} = \gamma/r, \\ b_{63} &= \rho_M/r, b_{64} = q_m/r, b_{65} = d_m/r, b_{72} = \rho_{ef}\delta_H/r\delta_X, b_{74} = d_M/r, \\ b_{81} &= \rho_T/r, b_{82} = q_T/r, b_{83} = d_T/r, b_{91} = \rho_S/r, b_{92} = m_S/r, b_{93} = q_S/r, \\ b_{94} &= d_S/r, b_{101} = \rho_{in}\delta_X/r\delta_N, b_{102} = \rho_{ef}\delta_H/r\delta_N, b_{103} = d_N/r. \end{aligned}$$

4 Stability Analysis

The following theorem shows that under certain suitable conditions, all the solutions of the system of equations (3.1) - (3.10) are non-negative. A set Γ in $\mathbb{R}_+^{10}$ may be ascertained such that all solutions starting in Γ remain bounded.

Theorem 4.1. *Let all the parameters of the system of equations (3.1) - (3.10) be positive and Γ be a region in $\mathbb{R}_+^{10}$ defined as,*

$\Gamma = \{(L, H, R, X, C, m, M, T, S, N) \in \mathbb{R}_+^{10} | 0 \leq L \leq \bar{L}, 0 \leq H \leq \bar{H}, 0 \leq R \leq \bar{R}, 0 \leq X \leq \bar{X}, 0 \leq C \leq \bar{C}, 0 \leq m \leq \bar{m}, 0 \leq M \leq \bar{M}, 0 \leq T \leq \bar{T}, 0 \leq S \leq \bar{S}, 0 \leq N \leq \bar{N}\}$. Then Γ is positive invariant and all the solutions starting from Γ are uniformly bounded, the parameters over bar are being the respective upper bounds.

Proof: First one may make an attempt to prove the positive invariant part.

Let $(L(0), H(0), R(0), X(0), C(0), m(0), M(0), T(0), S(0), N(0)) \in \Gamma$.

If possible, suppose $L(\tau)$ be non positive. Then there exists $\tau_0 > 0$ such that $L(\tau_0) = 0$ and $L(\tau) > 0$ for any τ satisfying $0 \leq \tau \leq \tau_0$. Then necessarily

$$\frac{dL}{d\tau}|_{\tau=\tau_0} \leq 0.$$

This is a contradiction, because

$$\frac{dL}{d\tau}|_{\tau=\tau_0} = b_{11} - b_{12} \frac{R(\tau_0)L(\tau_0)}{1 + R(\tau_0)} - b_{13}L(\tau_0) = b_{11} > 0.$$

Hence, $L(\tau)$ is positive $\forall \tau \geq 0$. In exactly similar way $H(\tau)$, $R(\tau)$, are positive $\forall \tau \geq 0$ can be shown, so these proofs are omitted here. Next, suppose $X(\tau)$ be non positive. Then there exists $\tau_0 > 0$ such that $X(\tau_0) = 0$ and $X(\tau) > 0$ for any τ satisfying $0 \leq \tau \leq \tau_0$. Then necessarily

$$\frac{dX}{d\tau}|_{\tau=\tau_0} \leq 0$$

This is a contradiction, because

$$\frac{dX}{d\tau}|_{\tau=\tau_0} = b_{12} \frac{R(\tau_0)L(\tau_0)}{1 + R(\tau_0)} - \frac{b_{42}M(\tau_0)X(\tau_0)^2}{1 + X(\tau_0)^2} - b_{43} \frac{X(\tau_0)H(\tau_0)}{1 + H(\tau_0)} - b_{44}X(\tau_0) = b_{12} \frac{R(\tau_0)L(\tau_0)}{1 + R(\tau_0)} > 0.$$

Hence, $X(\tau)$ is positive $\forall \tau \geq 0$. Similarly positivity of the remaining variables viz. $C(\tau)$, $m(\tau)$, $M(\tau)$, $T(\tau)$, $S(\tau)$ and $N(\tau)$ can be shown so those proofes are not being provided here. Next the part of boundedness may be shown as follows:

From equation (3.1), one may have

$$\begin{aligned} \frac{dL}{d\tau} &= b_{11} - b_{12} \frac{RL}{1 + R} - b_{13}L \\ \implies \frac{dL}{d\tau} + b_{13}L &\leq b_{11} \\ \implies L(\tau) &\leq \frac{b_{11}}{b_{13}} + \kappa_1 e^{(-b_{13}\tau)}, \end{aligned}$$

where κ_1 is a positive integrating constant. The term $\kappa_1 e^{(-b_{13}\tau)}$ vanishes as $t \rightarrow \infty$. So, $L(\tau) \leq \frac{b_{11}}{b_{13}}$ as, $t \rightarrow \infty$, i.e $L(\tau)$ remains bounded $\forall \tau \geq 0$. Similarly one can prove the boundedness of $H(\tau)$ and $R(\tau)$. Now to prove the boundedness part of $X(\tau)$, one may assume $W_1(\tau) = L(\tau) + X(\tau)$

Then,

$$\begin{aligned} \frac{dW_1}{d\tau} &= \frac{dL}{d\tau} + \frac{dX}{d\tau} \\ &= b_{11} - b_{12} \frac{RL}{1 + R} - b_{13}L + b_{12} \frac{RL}{1 + R} - \frac{b_{42}MX^2}{1 + X^2} - b_{43} \frac{XH}{1 + H} - b_{44}X \\ &\leq b_{11} - b_{13}L - b_{44}X \end{aligned}$$

Now from biological point of view, it is assumed here that b_{13} , death rate of LDL is greater than b_{44} death rate of oxidised LDL.

Consider,

$$\begin{aligned}
 \frac{dW_1}{d\tau} + b_{44}W &\leq b_{11} - b_{13}L - b_{44}X + b_{44}L + b_{44}X \\
 &= b_{11} - (b_{13} - b_{44})L \\
 &\leq b_{11} \\
 \implies W_1(\tau) &\leq \frac{b_{11}}{b_{44}} + \kappa_2 e^{(-b_{44}\tau)}
 \end{aligned}$$

Then from similar logical argument as above we can say that $W_1(\tau)$ is bounded and hence $X(\tau)$ is bounded. Next boundedness of $C(\tau)$, $m(\tau)$, $M(\tau)$, $T(\tau)$, $S(\tau)$ and $N(\tau)$ can be shown in similar fashion, as in (Anlamlert et al., 2017).

4.1 Equilibrium points

The above complex system (3.1) - (3.10) has only one equilibrium point namely, the interior one. Let us denote it by $\nu_e = (L_e, H_e, R_e, X_e, m_e, M_e, T_e, S_e, N_e)$, which is the non-zero ten-tuple solution of the following system;

$$b_{11} - b_{12} \frac{RL}{1+R} - b_{13}L = 0, \quad (4.1)$$

$$b_{21} - b_{22} \frac{HR}{1+R} - b_{23} \frac{HN^2}{1+N^2} - b_{24}H = 0, \quad (4.2)$$

$$b_{31} - (b'_{32}L + b''_{32}H) \frac{R}{1+R} - b_{33}R = 0, \quad (4.3)$$

$$b_{12} \frac{RL}{1+R} - \frac{b_{42}MX^2}{1+X^2} - b_{43} \frac{XH}{1+H} - b_{44}X = 0, \quad (4.4)$$

$$b_{51}X - b_{52} \frac{CH}{1+H} - b_{53}C = 0, \quad (4.5)$$

$$b_{61}C + b_{62} \frac{X^2m}{1+X^2} - b_{63}m - b_{64} \frac{mH}{1+H} - b_{65}m = 0, \quad (4.6)$$

$$b_{63}m + b_{72} \frac{N^2H}{1+N^2} - \frac{b_{42}MX^2}{1+X^2} - b_{74}M = 0, \quad (4.7)$$

$$b_{81}C - b_{82} \frac{TH}{1+H} - b_{83}T = 0, \quad (4.8)$$

$$b_{91}C - b_{92}S - b_{93} \frac{SH}{1+H} - b_{94}S = 0, \quad (4.9)$$

$$\frac{b_{101}MX^2}{1+X^2} + b_{92}S - b_{102} \frac{HN^2}{1+N^2} - b_{103}N = 0, \quad (4.10)$$

Theorem 4.2. *The system represented by (3.1) - (3.10) is locally asymptotically stable.*

Proof: To prove the system is locally stable, one needs to consider the corresponding linearised system. Let us suppose the Jacobian matrix corresponding to (3.1) - (3.10) is J . After evaluating this Jacobian matrix at the equilibrium positions of the system (3.1) - (3.10) one gets the characteristic polynomial at each of these equilibrium. As the calculation is quite complex, so here a general approach is provided to prove the stability of this system. Denote the jacobian matrix obtained at equilibrium point by V^* . Suppose the characteristic polynomial of V^* may be expressed as, $x^{10} + c_9x^9 + c_8x^8 + c_7x^7 + c_6x^6 + c_5x^5 + c_4x^4 + c_3x^3 + c_2x^2 + c_1x + c_0 = g(x)$, where $c_k = (-1)^{10-k} \sum_{|D|=10-k} V^*[D]$, i.e. c_k are the sum of all principal minors of order $(10-k)$

of the matrix V^* multiplied by $(-1)^{10-k}$. Here $\mathcal{D} \subseteq \{1, 2, \dots, 10\}$ and $V^*[\mathcal{D}]$ denotes the principal minors of V^* formed by the columns and rows with indices from $\mathcal{D}$. Let us denote, $1 = u_{101}$, $c_8 = u_{102}$, $c_6 = u_{103}$, $c_4 = u_{104}$, $c_2 = u_{105}$, $c_0 = u_{106}$, $c_9 = u_{91}$, $c_7 = u_{92}$, $c_5 = u_{93}$, $c_3 = u_{94}$, $c_1 = u_{95}$. Then Routh table of the polynomial $g(x)$ may be formed as in Table 1; where $u_{ij} = \frac{u_{(i+1)j}u_{(i+2)(j+1)} - u_{(i+1)(j+1)}u_{(i+2)j}}{u_{(i+1)j}}$, for $i = 0, 1, 2, \dots, 10$ and $j = 1, 2, \dots, 6$.

x^{10}	u_{101}	u_{102}	u_{103}	u_{104}	u_{105}	u_{106}
x^9	u_{91}	u_{92}	u_{93}	u_{94}	u_{95}	0
x^8	u_{81}	u_{82}	u_{83}	u_{84}	u_{85}	0
x^7	u_{71}	u_{72}	u_{73}	u_{74}	0	0
x^6	u_{61}	u_{62}	u_{63}	u_{64}	0	0
x^5	u_{51}	u_{52}	u_{53}	0	0	0
x^4	u_{41}	u_{42}	u_{43}	0	0	0
x^3	u_{31}	u_{32}	0	0	0	0
x^2	u_{21}	u_{22}	0	0	0	0
x	u_{11}	0	0	0	0	0
1	u_{01}	0	0	0	0	0

Table 1: Routh table of V^*

Routh-Hurwitz criterion states that a system is stable if and only if all terms in the first column are positive and if these conditions are not satisfied then there will be an unstable solution (Nise, Norman S, 2011).

Theorem 4.3. *The system (3.1)-(3.10) is globally asymptotically stable, if*

$$\min(V'_{ij}) \geq \max(V_{ij}), \text{ for } i=1,2,\dots,10 \text{ and } j=1,2,3.$$

where V'_{ij} , V_{ij} are defined in the proof section.

Proof: Consider ,

$$\begin{aligned}
 V &= (L - L_e - L_e \ln \frac{L}{L_e}) + (H - H_e - L_e \ln \frac{H}{H_e}) + (R - R_e - R_e \ln \frac{R}{R_e}) + (X - X_e - X_e \ln \frac{X}{X_e}) \\
 &\quad + (C - C_e - C_e \ln \frac{C}{C_e}) + (m - m_e - m_e \ln \frac{m}{m_e}) + (M - M_e - M_e \ln \frac{M}{M_e}) + (T - T_e - T_e \ln \frac{T}{T_e}) \\
 &\quad + (S - S_e - S_e \ln \frac{S}{S_e}) + (N - N_e - N_e \ln \frac{N}{N_e}) \\
 &= \sum_{i=1}^{10} V_i
 \end{aligned} \tag{4.11}$$

where $(L_e, H_e, R_e, X_e, m_e, M_e, T_e, S_e, N_e) = \nu_e$, say, is the interior equilibrium point of the system (3.1)-(3.10) and $V_i = (f_i - f_{ie} - f_{ie} \ln \frac{f_i}{f_{ie}})$ where $f_i = L, H, R, X, C, m, M, T, S, N$ for $i = 1, 2, \dots, 10$ respectively.

Now at ν_e the right hand sides of equations (3.1)-(3.10) is 0 and hence we obtain,

$$\begin{aligned}
 b_{11} - b_{12} \frac{R_e L_e}{1 + R_e} - b_{13} L_e &= 0 \\
 \implies b_{11} &= b_{12} \frac{R_e L_e}{1 + R_e} + b_{13} L_e, \\
 b_{21} - b_{22} \frac{H_e R_e}{1 + R_e} - b_{23} \frac{H_e N_e^2}{1 + N_e^2} - b_{24} H_e &= 0 \\
 \implies b_{21} &= b_{22} \frac{H_e R_e}{1 + R_e} + b_{23} \frac{H_e N_e^2}{1 + N_e^2} + b_{24} H_e, \\
 b_{31} - (b'_{32} L_e + b''_{32} H_e) \frac{R_e}{1 + R_e} - b_{33} R_e &= 0 \\
 \implies b_{31} &= (b'_{32} L_e + b''_{32} H_e) \frac{R_e}{1 + R_e} + b_{33} R_e, \\
 b_{12} \frac{R_e L_e}{1 + R_e} - \frac{b_{42} M_e X_e^2}{1 + X_e^2} - b_{43} \frac{X_e H_e}{1 + H_e} - b_{44} X_e &= 0 \\
 \implies b_{12} &= \frac{1 + R_e}{R_e L_e} \left[\frac{b_{42} M_e X_e^2}{1 + X_e^2} + b_{43} \frac{X_e H_e}{1 + H_e} + b_{44} X_e \right], \\
 b_{51} X_e - b_{52} \frac{C_e H_e}{1 + H_e} - b_{53} C_e &= 0 \\
 \implies b_{51} &= \frac{1}{X_e} \left[b_{52} \frac{C_e H_e}{1 + H_e} + b_{53} C_e \right], \\
 b_{61} C_e + b_{62} \frac{X_e^2 m_e}{1 + X_e^2} - b_{63} m_e - b_{64} \frac{m_e H_e}{1 + H_e} - b_{65} m_e &= 0 \\
 \implies b_{61} &= \frac{1}{C_e} \left[-b_{62} \frac{X_e^2 m_e}{1 + X_e^2} + b_{63} m_e + b_{64} \frac{m_e H_e}{1 + H_e} + b_{65} m_e \right], \\
 b_{63} m_e + b_{72} \frac{N_e^2 H_e}{1 + N_e^2} - \frac{b_{42} M_e X_e^2}{1 + X_e^2} - b_{74} M_e &= 0 \\
 \implies b_{63} &= \frac{1}{m_e} \left[-b_{72} \frac{N_e^2 H_e}{1 + N_e^2} + \frac{b_{42} M_e X_e^2}{1 + X_e^2} + b_{74} M_e \right], \\
 b_{81} C_e - b_{82} \frac{T_e H_e}{1 + H_e} - b_{83} T_e &= 0 \\
 \implies b_{81} &= \frac{1}{C_e} \left[b_{82} \frac{T_e H_e}{1 + H_e} + b_{83} T_e \right], \\
 b_{91} C_e - b_{92} S_e - b_{93} \frac{S_e H_e}{1 + H_e} - b_{94} S_e &= 0 \\
 \implies b_{91} &= \frac{1}{C_e} \left[b_{92} S_e + b_{93} \frac{S_e H_e}{1 + H_e} + b_{94} S_e \right], \\
 \frac{b_{101} M_e X_e^2}{1 + X_e^2} - b_{102} \frac{H_e N_e^2}{1 + N_e^2} - b_{103} N_e &= 0 \\
 \implies b_{101} &= \frac{1 + X_e^2}{M_e X_e^2} \left[b_{102} \frac{H_e N_e^2}{1 + N_e^2} + b_{103} N_e \right].
 \end{aligned}$$

Then using these above equations and performing a straight forward calculation one may get

$$\dot{V} = \sum_{i=1}^{10} \dot{V}_i = \sum_{i=1}^{10} \left(1 - \frac{f_{i_e}}{f_i} \right) \dot{f}_i \quad (4.12)$$

where,

$$\begin{aligned}
 \dot{V}_1 &\leq \underbrace{-b_{13}(L - L_e)^2}_{-V'_{11}} + \underbrace{b_{12}(R_e L_e L + L_e R L)}_{V_{11}}, \\
 \dot{V}_2 &\leq \underbrace{-b_{24}(H - H_e)^2}_{-V'_{21}} + \underbrace{b_{22}(H_e R_e H + H_e H R)}_{V_{21}} + \underbrace{b_{23}(H H_e N_e + H_e H N)}_{V_{22}}, \\
 \dot{V}_3 &\leq \underbrace{-b_{33}(R - R_e)^2}_{-V'_{31}} + \underbrace{b'_{32}(L_e R_e R + R_e L R)}_{V_{31}} + \underbrace{b''_{32}(H_e R_e R + R_e H R)}_{V_{32}}, \\
 \dot{V}_4 &\leq \underbrace{-b_{44} \frac{RL}{1+R} (X - X_e)^2}_{-V'_{41}} + \underbrace{b_{44} X (X R L + X_e R_e L_e)}_{V_{41}} + \underbrace{b_{42}(M_e X_e^2 R L X + R_e L_e X_e M X^2)}_{V_{42}} \\
 &\quad + \underbrace{b_{43}(X_e H_e X R L + X_e R_e L_e X H)}_{V_{43}}, \\
 \dot{V}_5 &\leq \underbrace{-b_{53} X (C - C_e)^2}_{-V'_{51}} + \underbrace{b_{52}(C_e H_e C X + C_e X_e C H)}_{V_{51}} + \underbrace{b_{53} C (C X + C_e X_e)}_{V_{52}}, \\
 \dot{V}_6 &\leq \underbrace{-(b_{63} + b_{65}) C (m - m_e)^2}_{-V'_{61}} + \underbrace{(b_{63} + b_{65}) m (C m + C_e m_e)}_{V_{61}} + \underbrace{b_{62}(C_e X^2 m^2 + X_e^2 m_e C m)}_{V_{62}} \\
 &\quad + \underbrace{b_{64}(m_e H_e C m + C_e m_e m H)}_{V_{63}}, \\
 \dot{V}_7 &\leq \underbrace{-b_{74} m (M - M_e)^2}_{-V'_{71}} + \underbrace{b_{72}(m_e M N^2 H + M_e N_e^2 H_e m)}_{V_{71}} + \underbrace{b_{42}(M_e X_e^2 m M + m_e M_e M X^2)}_{V_{72}} \\
 &\quad + \underbrace{b_{74} M (m M + m_e M_e)}_{V_{73}}, \\
 \dot{V}_8 &\leq \underbrace{-b_{83} C (T - T_e)^2}_{-V'_{81}} + \underbrace{b_{82}(T_e H_e C T + C_e T_e T H)}_{V_{81}} + \underbrace{b_{83} T (C T + C_e T_e)}_{V_{82}}, \\
 \dot{V}_9 &\leq \underbrace{-(b_{92} + b_{94}) C (S - S_e)^2}_{-V'_{91}} + \underbrace{(b_{92} + b_{94}) S (C S + C_e S_e)}_{V_{91}} + \underbrace{b_{93}(S_e H_e S C + C_e S_e H S)}_{V_{92}}, \\
 \dot{V}_{10} &\leq \underbrace{-b_{103} (N - N_e)^2 \frac{M X^2}{1 + X^2}}_{-V'_{101}} + \underbrace{b_{103}(M X^2 N^2 + M_e X_e^2 N_e N)}_{V_{101}} + \underbrace{b_{102}(H_e N_e^2 M X^2 N + M_e X_e^2 N_e H N^2)}_{V_{102}} \\
 &\quad + \underbrace{b_{92}(X_e^2 M S N + S_e N_e X^2 M)}_{V_{103}}.
 \end{aligned}$$

Hence, if,

$$\min(V'_{ij}) \geq \max(V_{ij}), \text{ for } i=1,2,\dots,10 \text{ and } j=1,2,3. \quad (4.13)$$

where V'_{ij} , V_{ij} are defined as above and remaining V'_{ij} , V_{ij} 's which are not provided here are assumed to be 0, for example $V_{12} = V_{13} = V_{23} = 0$ and so on, then we must have

$$\dot{V} \leq 0 \quad (4.14)$$

Also from equation (5.10) it is clear that $\dot{V} = 0$ at ν_e . Hence by Lyapunov-Lasalle's invariance principle (Hale, 1969) the proof follows.

5 Reduced model

The complexity of handling the large system compels one to reduce it to a smaller one in order to analyse it further. Fixing the parameters involved in this system (3.1)-(3.10) with numerical values provided in Table 2 one can consider the time-series plot of the entire system. In a similar fashion (Li and Xu, 2016) using Quasi Steady State Approximation (QSSA) theory one can reduce the system from a ten dimensional nonlinear ODE model into a four dimensional nonlinear ODE model involving LDLs, HDLs, monocytes and plaque as the dependent variable. Later on one can consider another submodel from this by switching off HDL entirely from this reduced model, in order to analyse the system in absence of HDL. As few of the parametric values are assumed due to nonavailability of sufficient clinical data, the dependent variables involved in the reduced model may alter if the numeric values of the parameters involved go through a significant change.

We rename the model involving HDL as one of the dependent variable as Model A and the submodel obtained from this by switching off HDL as Model B in our subsequent calculations and analyses. The steady state conditions are:

$$b_{31} - (b'_{32}L + b''_{32}H)\frac{R}{1+R} - b_{33}R = 0, \quad (5.1)$$

$$b_{12}\frac{RL}{1+R} - \frac{b_{42}MX^2}{1+X^2} - b_{43}\frac{XH}{1+H} - b_{44}X = 0, \quad (5.2)$$

$$b_{51}X - b_{52}\frac{CH}{1+H} - b_{53}C = 0, \quad (5.3)$$

$$b_{63}m + b_{72}\frac{N^2H}{1+N^2} - \frac{b_{42}MX^2}{1+X^2} - b_{74}M = 0, \quad (5.4)$$

$$b_{81}C - b_{82}\frac{TH}{1+H} - b_{83}T = 0, \quad (5.5)$$

$$b_{91}C - b_{92}S - b_{93}\frac{SH}{1+H} - b_{94}S = 0. \quad (5.6)$$

From (5.1) one may have,

$$R = \frac{-1}{2} \frac{\mu_1 - \sqrt{\mu_2}}{b_{33}}, \quad (5.7)$$

where,

$$\mu_1 = -b_{31} + b'_{32}L + b''_{32}H + b_{33}, \quad (5.8)$$

$$\begin{aligned} \mu_2 = & b_{31}^2 - 2b_{31}b'_{32}L - 2b_{31}b''_{32}H + 2b_{33}b_{31} + b_{32}'^2L^2 + 2b_{32}'Lb_{32}''H + 2b_{32}'Lb_{33} + b_{32}''^2H^2 \\ & + 2b_{32}''Hb_{33} + b_{33}^2. \end{aligned} \quad (5.9)$$

One can assume, death rate of macrophages $b_{74} = 0$ in steady state condition, as death rate of monocytes is already considered in the reduced model. Then from (5.4), one may obtain

$$\frac{MX^2}{1+X^2} = \frac{1}{b_{42}} \left(b_{63}m + b_{72}\frac{N^2H}{1+N^2} \right) = \mu_3(\text{say}). \quad (5.10)$$

From (5.2) and using (5.10) one may get,

$$X = \frac{b_{12}\frac{RL}{1+R} - b_{42}\mu_3}{b_{43}\frac{H}{1+H} + b_{44}}. \quad (5.11)$$

Again, from (5.10) one may get

$$M = \mu_3 \frac{1 + X^2}{X^2}. \quad (5.12)$$

Next from (5.3), one may obtain

$$C = \frac{b_{51}X}{b_{52}\frac{H}{1+H} + b_{53}}. \quad (5.13)$$

Next from (5.6), one may obtain

$$S = \frac{b_{91}C}{b_{92} + b_{93}\frac{H}{1+H} + b_{94}}. \quad (5.14)$$

Hence the reduced model is:

$$\frac{dL}{d\tau} = b_{11} - b_{12}\frac{RL}{1+R} - b_{13}L, \quad (5.15)$$

$$\frac{dH}{d\tau} = b_{21} - b_{22}\frac{HR}{1+R} - b_{23}\frac{HN^2}{1+N^2} - b_{24}H, \quad (5.16)$$

$$\frac{dm}{d\tau} = b_{61}C + b_{62}\frac{X^2m}{1+X^2} - b_{63}m - b_{64}\frac{mH}{1+H} - b_{65}m, \quad (5.17)$$

$$\frac{dN}{d\tau} = \frac{b_{101}MX^2}{1+X^2} + b_{92}S - b_{102}\frac{HN^2}{1+N^2} - b_{103}N. \quad (5.18)$$

where only L, H, m and N are dependent variables and all other variables from the original model system in steady states form, are assumed as described above. In subsequent calculations the system (5.15)-(5.18) is referred as Model A. Similar theoretical and numerical analysis have been carried out on Model B, consisting of equations (5.15),(5.17) and (5.18), in the absence of HDL.

6 Stability and Bifurcation Analysis of the Reduced Model

6.1 Positivity and boundedness

Positivity and boundedness of the dependent variables involved in (5.15) - (5.18) are similar to those corresponding to the original model represented by (3.1) - (3.10). Hence the cellular species involved in Model A and Model B are positive and bounded.

6.2 Equilibrium points

Similarly as the original system the reduced model system has also only the interior equilibrium point $E_0 = (L_0, H_0, m_0, N_0)$. One can obtain the equilibrium point by solving the following system:

$$b_{11} - b_{12}\frac{RL}{1+R} - b_{13}L = 0, \quad (6.1)$$

$$b_{21} - b_{22}\frac{HR}{1+R} - b_{23}\frac{HN^2}{1+N^2} - b_{24}H = 0, \quad (6.2)$$

$$b_{61}C + b_{62}\frac{X^2m}{1+X^2} - b_{63}m - b_{64}\frac{mH}{1+H} - b_{65}m = 0, \quad (6.3)$$

$$\frac{b_{101}MX^2}{1+X^2} + b_{92}S - b_{102}\frac{HN^2}{1+N^2} - b_{103}N = 0. \quad (6.4)$$

6.3 Global stability

Local and global stability of the dependent variables involved in (5.15) - (5.18) are similar to those corresponding to the original model represented by (3.1) - (3.10). Hence both the Model A and Model B are globally stable.

6.4 Bifurcation Analysis

Theorem 6.1. *The reduced system (5.15) - (5.18) exhibits a saddle node bifurcation around the equilibrium point E_0 at $b_{102} = b_{102}^{[sn]}$.*

Proof Let the Jacobian matrix corresponding to (5.15)-(5.18) at the equilibrium point E_0 be,

$$\Lambda = \begin{bmatrix} J_{11} & J_{12} & J_{13} & J_{14} \\ J_{21} & J_{22} & J_{23} & J_{24} \\ J_{31} & J_{32} & J_{33} & J_{34} \\ J_{41} & J_{42} & J_{43} & J_{44} \end{bmatrix} \quad (6.5)$$

where details of J_{ij} are not provided for the sake of brevity. The matrix Λ has a zero eigen-value iff $\det \Lambda = 0$. Solving $\det \Lambda = 0$ one gets, $b_{102} = b_{102}^{[sn]}$. The other eigen-values of Λ are evaluated at $b_{102} = b_{102}^{[sn]}$ and one of them must be negative in order to get a saddle-node bifurcation. Let ψ and $\tilde{\psi}$ be the eigen-vectors corresponding to the eigen-value 0 of the matrix Λ and its transpose Λ^T respectively.

The eigen-vectors are obtained as, $\psi = \begin{bmatrix} \theta_1 \\ \theta_2 \\ \theta_3 \\ \theta_4 \end{bmatrix}$ and $\tilde{\psi} = \begin{bmatrix} \delta_1 \\ \delta_2 \\ \delta_3 \\ \delta_4 \end{bmatrix}$, where θ_k for $k = 1, 2, 3, 4$ are the

roots of the sytem $\sum_{k=1}^4 J_{ik}\theta_k = 0$ for $i = 1, 2, 3, 4$ and δ_k for $k = 1, 2, 3, 4$ are the roots of the system $\sum_{k=1}^4 J_{ki}\delta_k = 0$ for $i = 1, 2, 3, 4$.

Denote RHS of (5.15) - (5.18) by H . Then we evaluate $H_{b_{102}}$. It is clear from the expres-

sions on RHS of (5.15) - (5.18), that $H_{b_{102}} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ \tilde{f} \end{bmatrix}$, where $\tilde{f}$ denotes the derivative of RHS

function in (5.18) w.r.t. b_{102} . So, $H_{b_{102}}(E_0, b_{102}^{[sn]}) = \begin{bmatrix} 0 \\ 0 \\ 0 \\ \tilde{f}^\dagger \end{bmatrix}$, where $\tilde{f}^\dagger$ denotes the value of

$\tilde{f}$ at $(E_0, b_{102}^{[sn]})$. So one may obtain then, $\tilde{\psi}^T H_{b_{102}}(E_0, b_{102}^{[sn]}) = \delta_4 \tilde{f}^\dagger \neq 0$. Also, we see that $\tilde{\psi}^T (D^2 H_{b_{102}}(E_0, b_{102}^{[sn]})(\psi, \psi)) \neq 0$, where D^2 operator is defined later, detailed explanation can be found in Perko, (Perko, 2008). Following **Sotomayor's theorem** given in Perko, (Perko, 2008) one may conclude that at $b_{102} = b_{102}^{[sn]}$, the system (5.15) - (5.18) goes through a saddle node bifurcation.

D^2 operator: Let $\dot{x} = F(x, \lambda)$, where $x = (x_1, x_2, x_3, x_4) \in \mathbb{R}^4$, λ is a parameter and $F =$

Parameters	Description	Numeric values*	Source
b_{11}	constant source of LDL	64	(Cobbold et al., 2002)
b_{12}	reaction rate of LDL and radicals	0.5×10^7	(Cobbold et al., 2002)
b_{13}	death rate of LDL	40	(Cobbold et al., 2002)
b_{21}	constant source of HDL	20	present study
b_{22}	reaction rate of HDL and radicals	6.7×10^5	(Cobbold et al., 2002)
b_{23}	cholesterol efflux rate	0.1	(Cohen et al., 2014)
b_{24}	death rate of HDL	0.1	present study
b_{31}	constant source of radicals	100	present study
b'_{32}	reaction rate of LDL and radicals	0.5×10^7	present study
b''_{32}	reaction rate of HDL and radicals	6.7×10^5	present study
b_{33}	death rate of radicals	2.3×10^6	(Cobbold et al., 2002)
b_{42}	ingestion rate of macrophages and ox-LDL	10^4	present study
b_{43}	interaction rate of oxidised LDL with HDL	0.1	present study
b_{44}	death rate of ox-LDL	10	present study
b_{51}	rate of production of chemoattractant	10	present study
b_{52}	interaction rate of chemoattractant with HDL	0.1	present study
b_{53}	death rate of chemoattractant	10	present study
b_{61}	production rate of monocytes	100	present study
b_{62}	monocyte insertion rate into intima inversely varying with WSS	1000	present study
b_{63}	differentiation rate of monocyte into macrophages	2	(Bulelzai and Dubbeldam, 2012)
b_{64}	interaction rate of monocytes with HDL	10	present study
b_{65}	death rate of monocytes	10	present study
b_{72}	macrophage production rate from effluxed cholesterol	0.009	(Cohen et al., 2014)
b_{74}	death rate of macrophages	0.1	(Chalmers et al., 2015)
b_{81}	rate of production of T-cells	0.1	present study
b_{82}	interaction rate of T-cells with HDL	0.1	present study
b_{83}	death rate of T-cell	7	(Hao and Friedman, 2014)
b_{91}	rate of production of SMCs	10	present study
b_{92}	migration rate of SMCs from media to intima	0.1	present study
b_{93}	interaction rate of SMCs with HDL	0.1	present study
b_{94}	death rate of SMCs	17	(Hao and Friedman, 2014)
b_{101}	production rate of plaque	10^4	present study
b_{102}	efflux rate of cholesterol	1	present study
b_{103}	death rate of foam cells	0.6	(Hao and Friedman, 2014)

Table 2: List of parameter values used in the model. *Numeric values are converted in the present scale.

(F_1, F_2, F_3, F_4) . So $\dot{x} = F(x, \lambda)$ is a 4 dimensional one parameter system. Let $U = (u_1, u_2, u_3, u_4)$ be a vector in $\mathbb{R}^4$, then

$$D^2 F(x, \lambda)(U, U) = \begin{bmatrix} \sum_{j_1, j_2=1}^4 \frac{\partial^2 F_1}{\partial x_{j_1} \partial x_{j_2}} u_{j_1} u_{j_2} \\ \sum_{j_1, j_2=1}^4 \frac{\partial^2 F_2}{\partial x_{j_1} \partial x_{j_2}} u_{j_1} u_{j_2} \\ \sum_{j_1, j_2=1}^4 \frac{\partial^2 F_3}{\partial x_{j_1} \partial x_{j_2}} u_{j_1} u_{j_2} \\ \sum_{j_1, j_2=1}^4 \frac{\partial^2 F_4}{\partial x_{j_1} \partial x_{j_2}} u_{j_1} u_{j_2} \end{bmatrix}.$$

Similarly, one can prove the system (5.15) - (5.18) has a saddle-node bifurcation at $b_{103} = b_{103}^{[sn]}$. Similar analysis can be developed for a three-dimensional system and one can prove that at $b_{62} = b_{62}^{[sn]}$ and $b_{103} = b_{103}^{[sn]}$ the Model B has a saddle-node bifurcation.

7 Numerical Simulation and Discussion of the Results

To establish the theoretical analysis it is natural to adopt numerical simulation method based on the parametric values provided in Table 2. The numerical values provided there are either collected from the sources provided and converted them in the present scale through a simple calculation or are assumed for the present study to serve the purpose. The proposed system is solved using Runge-Kutta 4th order method. Using the set of parametric values, only one non-negative equilibrium point for the system (3.1)-(3.10) is obtained as follows;

$\nu_0 = [L = 0.527163956259885, H = 1.80047807953131, R = 1.62811360373172 \times 10^{-05}, X = 0.134693652798373, C = 0.133833214820448, m = 21.9369264468098, M = 0.233220798536722, T = 0.00189450292254778, S = 0.0779718827275680, N = 66.2759573936474]$. It has been found that all eigenvalues of the Jacobian matrix of the system (3.1)-(3.10) with parametric values provided in Table 2 are either negative reals or complex conjugates with negative real parts. Hence, the system (3.1)-(3.10) is stable at ν_0 with the choice of the parametric values from Table 2.

The present time scale spanned over the stipulated ranges is chosen for the time series plots and all subsequent figures. As the nondimensional time $\tau = 400$ corresponds to 20 years actual time and an atherosclerotic plaque usually takes 14–15 years to grow fully and becomes active, so the present time scale is quite appropriate. Figure 2 (a) represents time-series plots for evolution of concentrations of all the species over a short period of time $\tau = 20$ (equivalent to 380 days), while those for $\tau = 400$ are presented in Figure 2 (b).

In Figures 3 (a) and (b) similar time-series plots are provided for evolution of concentration of species except monocytes and plaque for time-scale 20 and 400 respectively. It is clear from the Figures 2 and 3 that LDL, HDL, monocytes and plaques are the most important components to play the pivotal role in atherosclerosis formation. This motivates one to consider two models from the reduced one, one consisting of LDL, HDL, monocyte and plaque as dependent variables in Model A and other one consisting of LDL, monocytes and plaque as dependent variables in Model B.

The primal system (3.1)-(3.10) is globally stable and hence both the reduced models marked by Model A and Model B are globally stable. Since the primal system is quite large and specified by ten dimensional spaces, one may visualize its global stability numerically only by examining it through any two or three dimensional subspaces. The projections of three dimensional phase portraits in different frames are exhibited through Figures 4-6 involving the cellular species like LDL, HDL, oxidized LDL, monocytes, chemo-attractant, T- cells, SMCs and plaque while Figures 7-8 show their two dimensional counterparts implicating those cellular species responsible to the formation of atherosclerotic plaque. The common feature in all the panels is the convergence of all the trajectories of the proposed dynamical system towards the equilibrium position irrespective of the choice of the initial positions and the dimensions as well. All these portraits reflect closely the global stability of the system under consideration.

The proposed system experiences bifurcation with respect to some parameters of significance. One may record that in the presence of HDL in Model A, the parameters b_{102} signifying the ef-

flux rate of cholesterol from accumulated plaque in the intima and b_{103} indicating the death rate of plaque cells are of great consequence. On the other hand, the parameter b_{62} specifying the insertion rate of monocytes into the intima in Model B also appears to play an important role in the occurrence of bifurcation.

The bifurcation diagram displayed in Figure 9 corresponds to the behavior of plaque concentration as a function of b_{102} spanned over the range of values in $[0, 80]$ for Model A. Instability is found to occur in the range $0 \leq b_{102} \leq 40$ followed by a stable region for rest of the parameter values due to period halving phenomena of the system. This observation may be validated by the fact that in the event of reduction of efflux cholesterol rate from accumulated plaque in the intima from its certain threshold value, the speed of plaque formation continues to grow rapidly causing instability of the system.

Figure 10 represents the bifurcation diagram for the plaque concentration with respect to the parameter b_{103} of Model A over the range $0 \leq b_{103} \leq 50$ while keeping all other parameter values same as in Table 2. The instability region is located in the range $0 \leq b_{103} \leq 30$ followed by a complete stable region for rest of the parameter values due to the same period halving phenomena of the system. This behavior of the system may be explained from biological point of view that when expiration rate of plaque reduces from its threshold value, the accumulated plaque continues to swell out in the intima causing instability of the system.

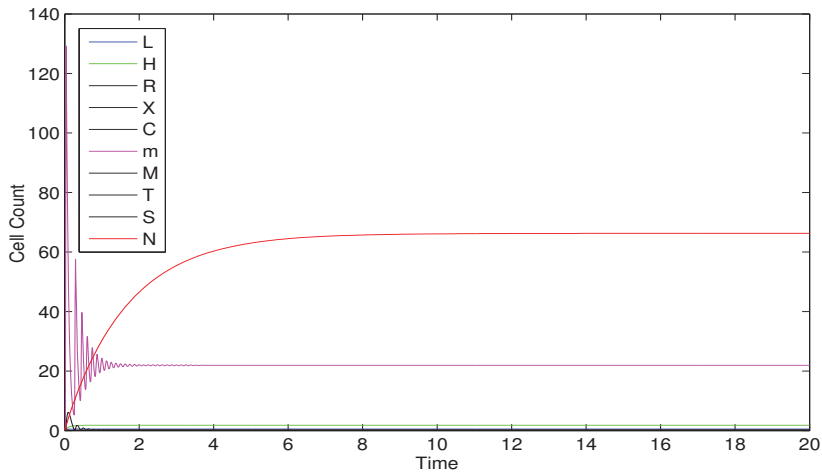
The onset of bifurcation experienced by Model B in the absence of HDL is also recorded for monocytes with respect to the parameter b_{62} over a stipulated range $0 \leq b_{62} \leq 100$ in Figure 11. The bifurcating region causing instability occurs in the range $0 \leq b_{62} \leq 30$ and beyond which the stability prevails for rest of the values of the parameter due to period halving characteristics of the system. As the parameter value b_{62} diminishes beyond a threshold value, more and more monocytes penetrate into the intima and the process of atherosclerotic plaque formation gets accelerated resulting in instability of the system. On the contrary, the enhancement of the parameter b_{62} brings the system into a stable situation which restricts the rate of plaque formation considerably.

The bifurcation diagram exhibited in Figure 12 corresponding to Model B designates the characteristics of plaque concentration with respect to plaque cell death rate parameter b_{103} in an analogous manner as described in Figure 10 for Model A. Studying such dynamical behavior of plaque concentration one may note that the expiration of plaque cells is a major concern in the evolution of atherosclerotic plaque.

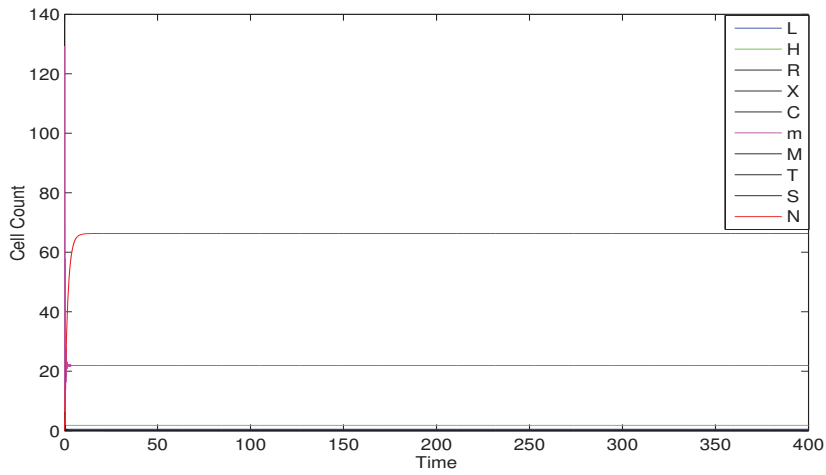
8 Model Validation

The validation of the proposed plaque models comprising major cellular species like LDL, monocytes, HDL and plaque in Model A and those without HDL in Model B can be performed

by means of three different approaches through the Figures 13-15. Firstly, a comparative study of the results of the evolution of the respective cellular components of both the models exhibited in Figure 13 reveals that both monocytes and plaque concentrations accumulate more in the event of the absence of HDL in Model B than in Model A. This behaviour does agree well with the pathogenesis in the formation of atherosclerotic plaque as far as HDL is concerned. Secondly, the results of Figure 14(a) demonstrate how the plaque concentration evolves with time for a fixed LDL source and varying HDL source in Model A while those of Figure 14(b) represent the time-variant concentration of monocytes subject to similar LDL-HDL input. One may record that increasing supply of HDL causes considerable reduction of both plaque and monocyte concentration and such observations are in concurrence again with the actual mechanisms of atherosclerosis. Finally, the proposed model is validated with the experimental data collected from (Hao and Friedman, 2014) through the portrayal of time-variant plaque concentration in Figure 15 subject to several pairs of input LDL-HDL in the system. It appears, as anticipated, that plaque concentration becomes higher and higher with lower supply of HDL and vice-versa and hence one of the remedial measures to get rid of abnormal growth of atherosclerotic plaque is to increase HDL level within its stipulated range.

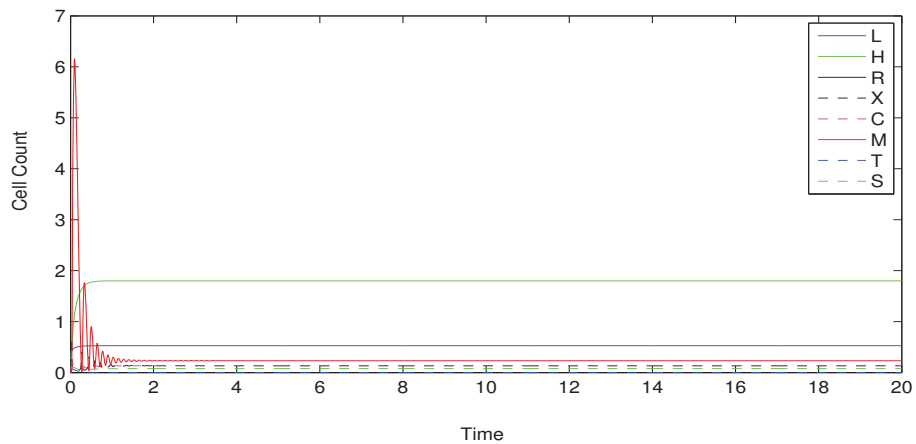


(a)

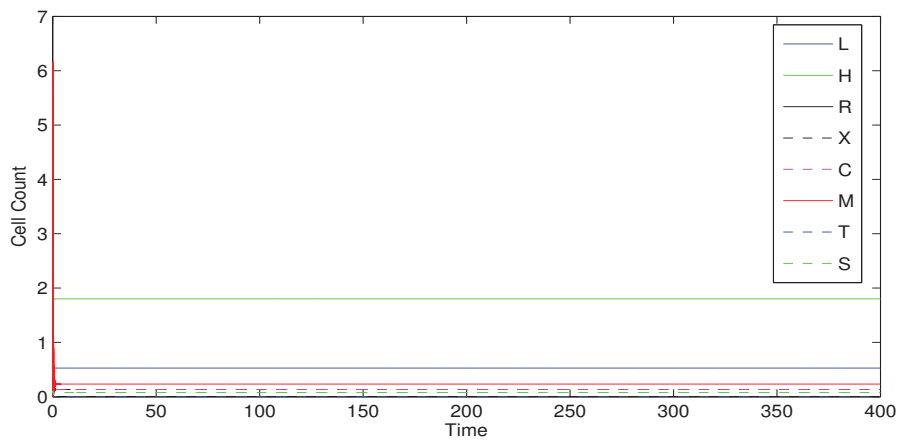


(b)

Figure 2: Time series representations of all cellular species corresponding to (a) smaller ($\tau = 20$) and (b) larger ($\tau = 400$) span of time.



(a)



(b)

Figure 3: Time series representations of those cellular species having smaller cell counts corresponding to (a) smaller ($\tau = 20$) and (b) larger ($\tau = 20$) span of time.

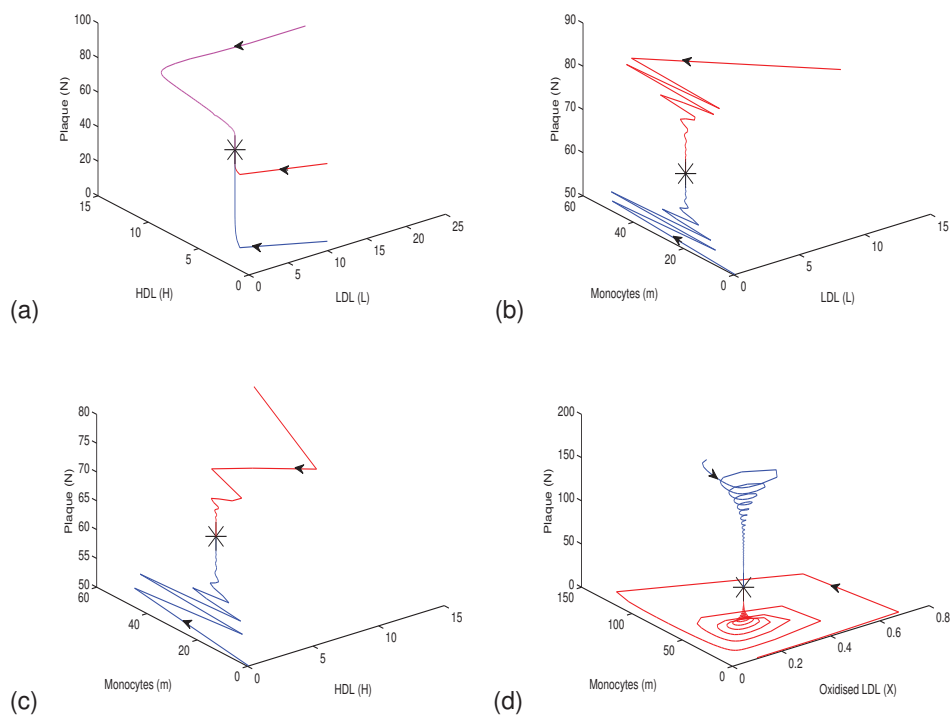


Figure 4: Several three dimensional phase portraits showing stability of equilibrium positions.

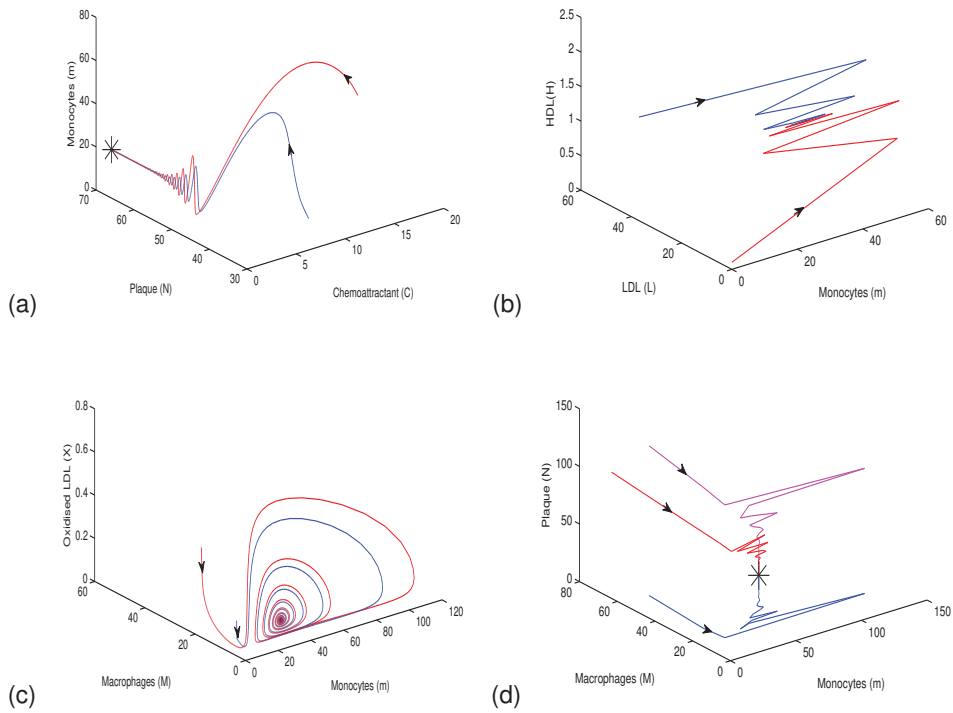


Figure 5: Three dimensional projections exhibiting stability of equilibrium positions.

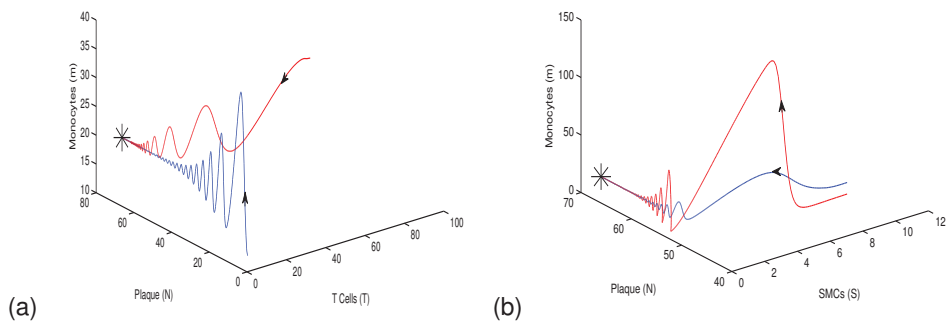


Figure 6: Three dimensional projections showing stability of subsystems.

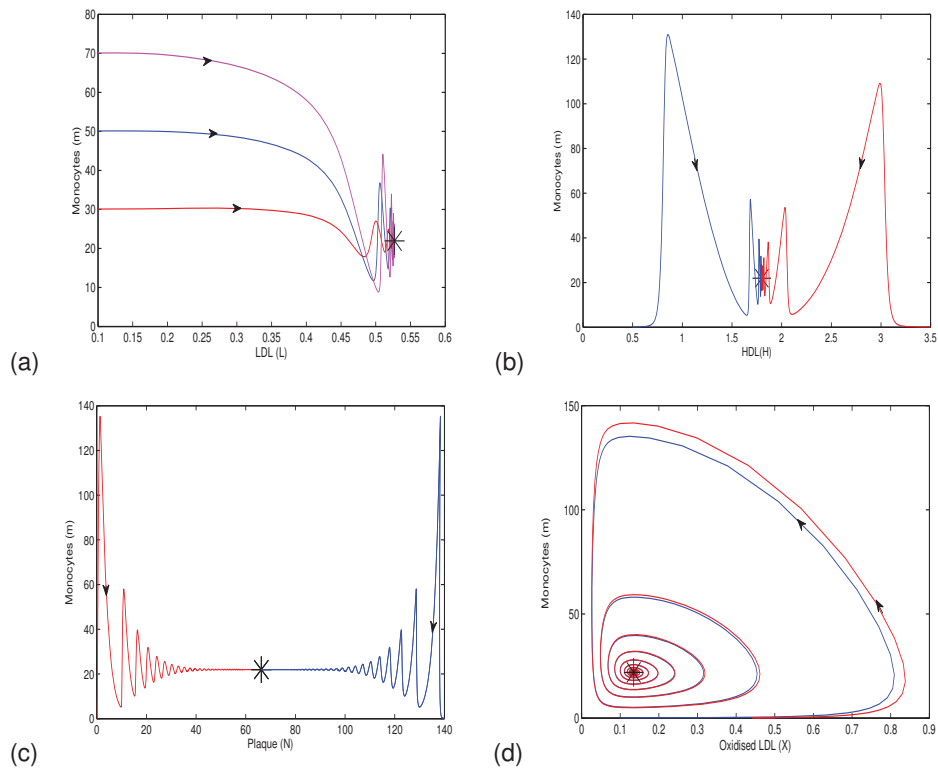


Figure 7: Two dimensional phase portraits involving key cellular components.

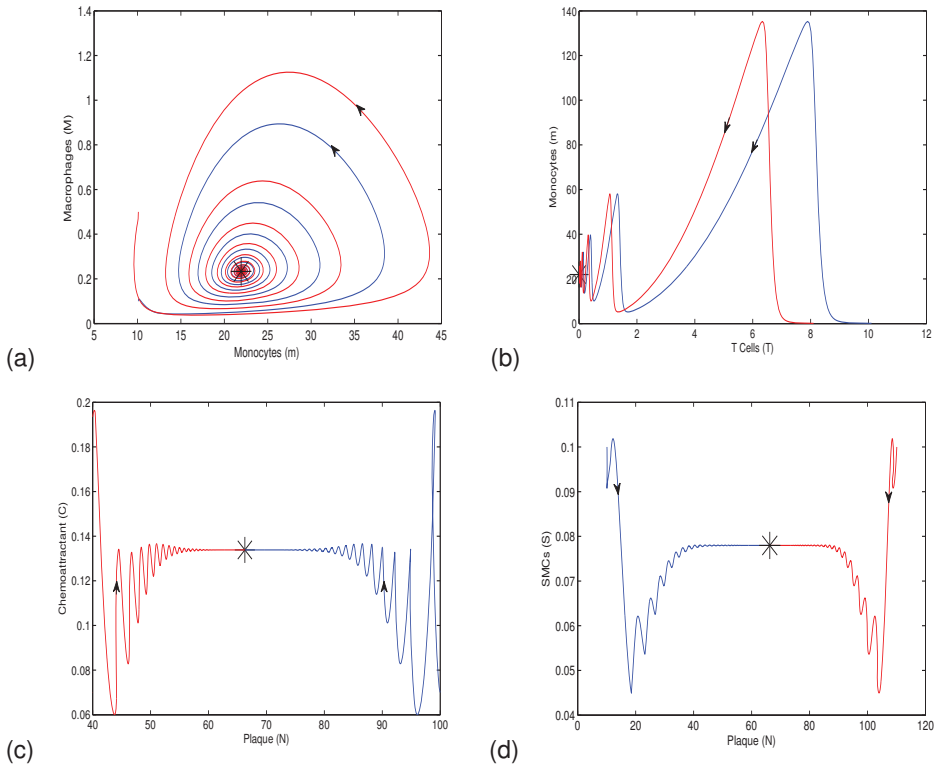


Figure 8: Two dimensional phase portraits of some selective cellular species.

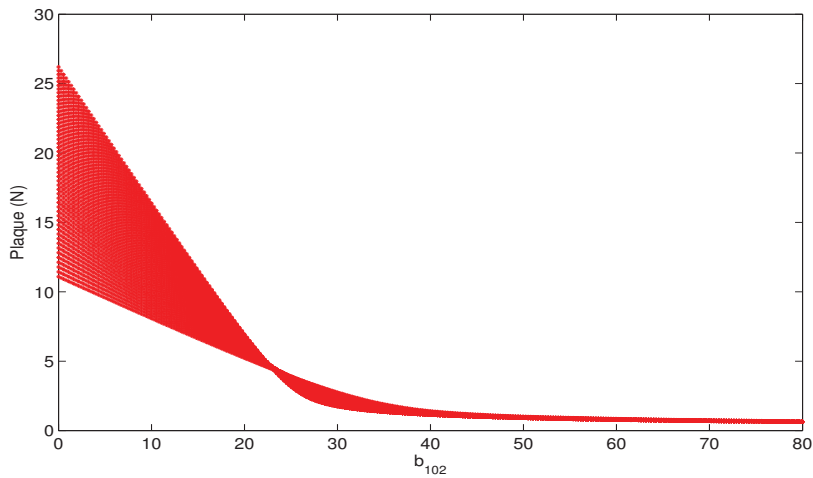


Figure 9: Saddle node bifurcation diagram of plaques' concentration with respect to b_{102} keeping all other parameter values of Table 2 same.

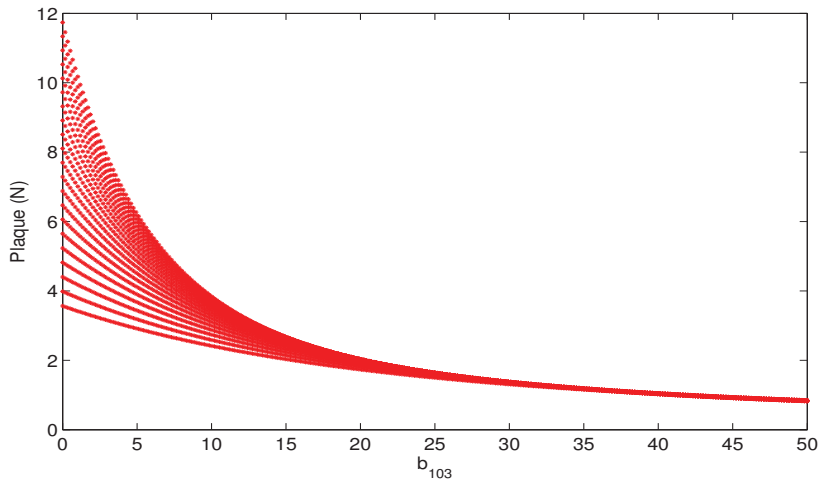


Figure 10: Saddle node bifurcation diagram of plaques' concentration with respect to b_{103} keeping all other parameter values of Table 2 same.

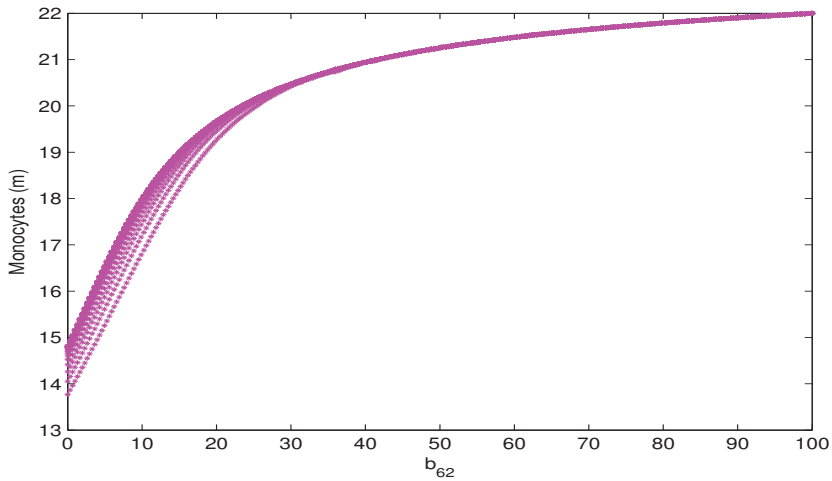


Figure 11: Saddle node bifurcation diagram of monocytes' concentration with respect to b_{62} keeping all other parameter values of Table 2 same, in absence of HDL.

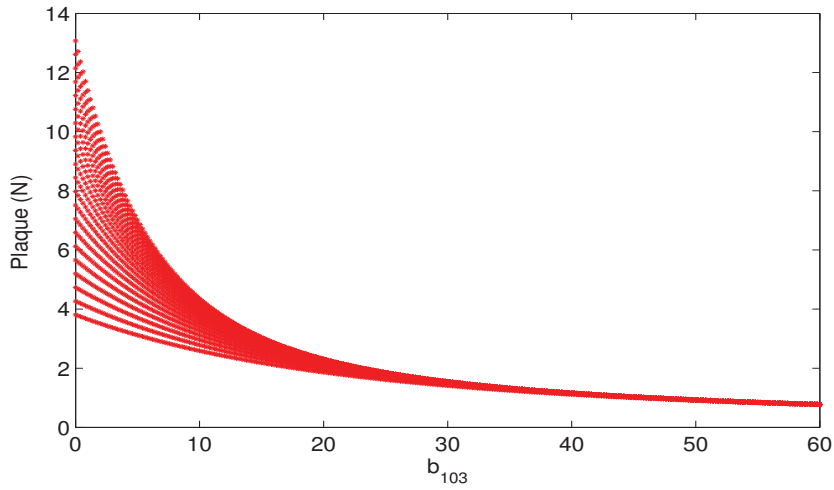


Figure 12: Saddle node bifurcation diagram of plaques' concentration with respect to b_{103} keeping all other parameter values of Table 2 same, in absence of HDL.

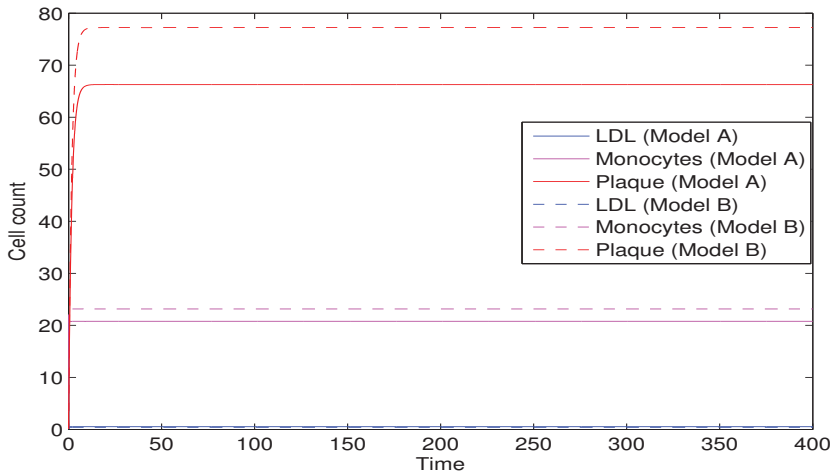
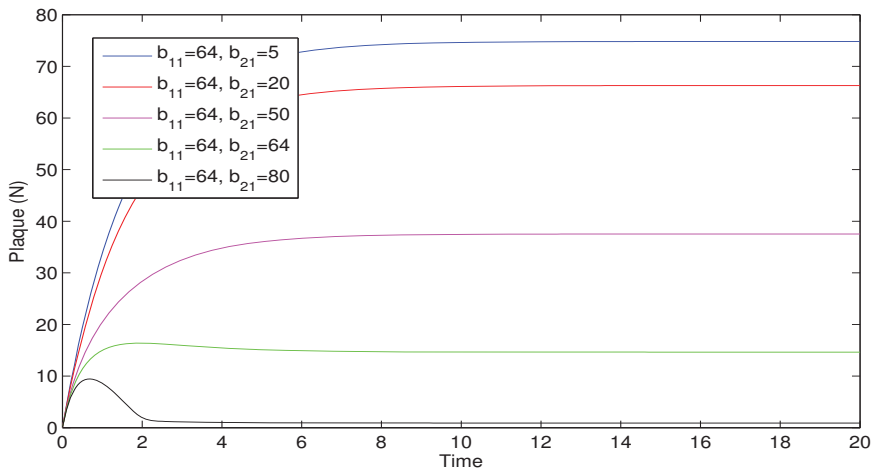
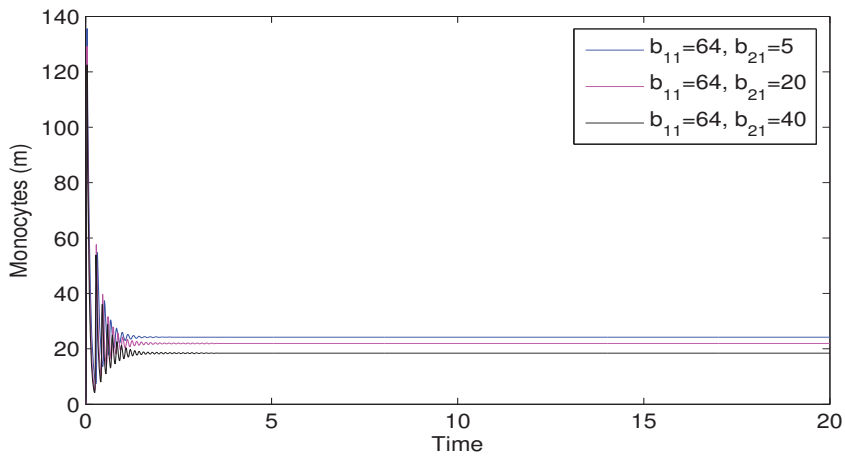


Figure 13: Time series plots of the constituents of two models A (in presence of HDL) and B (absence of HDL).



(a)



(b)

Figure 14: Time series plots of (a) Plaques (b) Monocytes for fixed LDL source and varying HDL source varying.

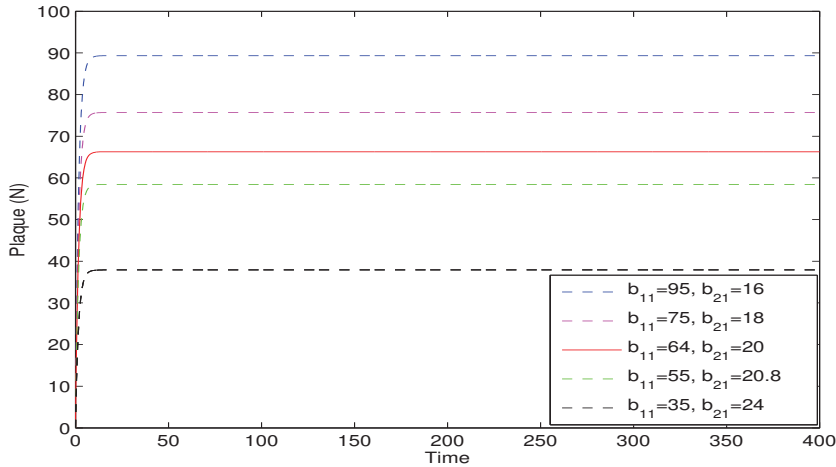


Figure 15: Comparison of the proposed results with experimental data .

9 Concluding Remarks

The proposed article deals with a mathematical model of evolution of atherosclerotic plaque comprising various cellular species like LDL, HDL, radicals, oxidized LDL, chemo-attractants, monocytes, macrophages, T-cells, SMCs and plaque cells participating in the biochemical process of evolution. The model represented by a large system of ordinary differential equations is shown to be globally stable analytically using Lyapunov's stability analysis. The quasi steady state approximation is used to reduce the large system into smaller ones for the purpose of undergoing an in-depth study over the situations. Two reduced models, namely Model A and Model B are examined for their dynamical characteristics in four and three dimensional sub-spaces respectively. The system experiences bifurcation with respect to some key model parameters. The important observations of the reduced models reveal that the expiration rate of plaque cells play significant role in atherosclerotic plaque formation. An effort is made to validate the applicability of the models undertaken through a comparative study of the results obtained and the experimental data from the existing literatures. The role of HDL is found to be very crucial in the biochemical process for the evolution of atherosclerotic plaque and care needs to be exercised for remedial measure.

Acknowledgements

The authors gratefully acknowledge the financial support by Special Assistance Programme (SAP-III) sponsored by the University Grants Commission (UGC), New Delhi, India [Grants No. F.510/3/DRS-III/2015(SAP-I)].

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