A Mathematical Model of the Effects of Antioxidants on Atherosclerotic Lesion Growth

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Abstract

Atherosclerosis is a form of cardiovascular disease characterized by an accumulation of cellular debris and inflammation in the innermost layer of the arterial wall. Statin drugs have been the primary method for treating atherosclerotic lesions, but recent research suggests that lifestyle changes, in particular consuming a diet rich in antioxidants, may be equally effective at preventing and potentially reversing the process of atherogenesis. In this paper, two mathematical models are developed to simulate the effects of antioxidants on lesion regression and the reaction-diffusion process of atherosclerosis at the biological level. The first model is a system of six ordinary differential equations, and the second is a one-dimensional spatial model composed of six partial differential equations. The ordinary differential equation model helps to define a healthy state through the computation of equilibrium values over a spatially uniform domain. Meanwhile, the partial differential equation system adopts the form of a discrete Taylor series approximation in order to model atherosclerosis under distinct parameters and boundary conditions. To avoid a numerical instability, a finite difference scheme is used to develop a diffusion coefficient for the model. Through the use of these equations, applied mathematicians can supply cardiologists with means for simulating and numerically analyzing various lesion regression scenarios.

1 Introduction

Heart disease is currently the leading cause of death in the United States. As of 2005, coronary heart disease (CHD) was responsible for approximately one of every five deaths in the U.S. [7]. Atherosclerosis is a specific type of heart disease, which can be described as an accumulation of modified lipoproteins and immune cells in the interior layer of the arterial wall. This agglomeration

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of cellular debris in the form of a lesion is primarily due to an inefficient immune system response and chronic inflammation [9]. Although plaque will augment in a variety of vessels carrying blood away from the heart, lesions have a tendency to form in larger arteries including the abdominal aorta, coronary arteries, and cerebral arteries [3]. Atherosclerosis is a precarious illness in that an accretion of plaque can serve as a precursor for more serious heart-related events including stroke or heart attack.

1.1   Lipoproteins and Artery Physiology

In order to model the behavior of atherosclerosis, it is first necessary to discern how lesions evolve at the molecular and biological level. This process can be understood best by examining the role of lipoproteins in the blood and the physiology of a human artery. Lipoproteins are micellar particles responsible for regulating cholesterol in the blood. There are four types of lipoproteins, namely very low-density lipoprotein, intermediate-density lipoprotein, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) [3]. For the purpose of this research endeavor, LDL, which is commonly perceived as the *bad* type of cholesterol, was of primary concern. In terms of physiology, a human artery is composed of three layers, namely the intima, media, and adventitia, which extend from the innermost layer lining the bloodstream to the exterior wall of the artery respectively. Atherosclerotic lesion growth develops within the intima, which accounts for less than ten percent of the entire arterial wall. The first biological event that triggers lesion growth within the intima is called *endothelial dysfunction*, which can be described as a change in permeability of the thin endothelial lining separating the intima from the arterial blood [10]. This event allows for enriched low-density lipoproteins to diffuse through the endothelium, which can be perceived as a *one-way gate*. Consequently, endothelial dysfunction is also characterized by an increase in adhesiveness, which consequently provides an ideal setting for lesion growth.

1.2   Inflammation and Foam Cell Development

It is also critical to understand the role that free radicals play in modifying low-density lipoprotein as well as the interaction between the human immune system and these foreign bodies. Interestingly, the low-density lipoprotein alone is not detrimental to the development of atherosclerosis. Instead, genetic alterations and the production of free radicals due to lifestyle behaviors and illnesses including cigarette smoking, diabetes, and hypertension

will stimulate endothelial dysfunction by chemically modifying LDL into a dangerous oxidized state [10]. The human immune system will attempt to destroy these foreign lipoproteins by sending macrophages to the site of LDL oxidation within the intima. Macrophages, which are a type of white blood cell that engorge foreign biological particles, are unable to destroy the oxidized LDL. Inflammation will form within the intima as the macrophages and oxidized low-density lipoproteins create a type of debris called *foam cells*. The immune system continues to send additional macrophages to attack the oxidized low-density lipoproteins, which consequently results in an accretion of foam cells and lesion growth.
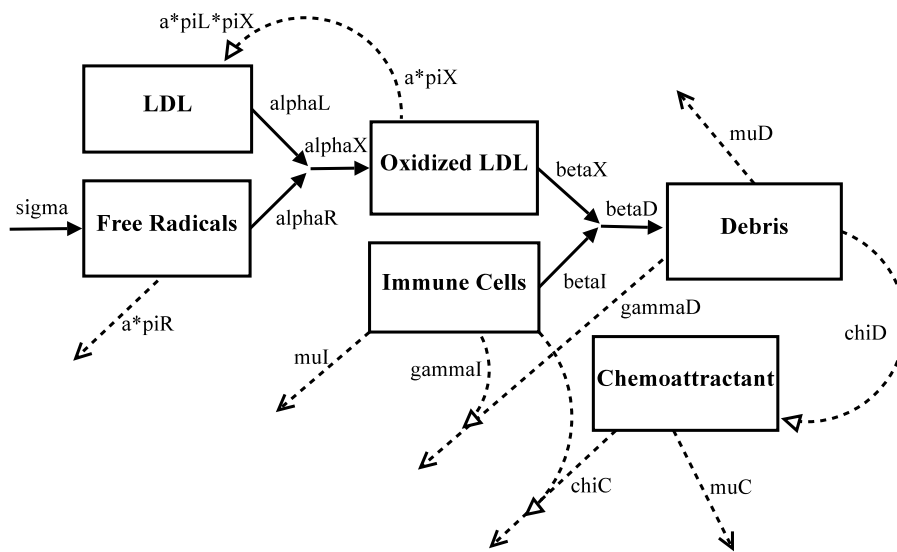

Figure 1: The biological process by which lesion growth occurs.

1.3   Antioxidants as a Treatment Method

The genesis of plaque formation in the intima can be attributed to a high free radical concentration triggering the modification of low-density lipoprotein into an oxidized form. Thus, it is necessary to block the behavior of free radicals in order to prevent atherosclerotic lesion growth. Although conventional medicine has provided numerous pharmaceutical treatment options specifically targeting low-density lipoprotein production, these drugs can produce adverse side effects involving the liver, kidneys, and skeletal muscle system including myalgia, myositis, muscular cramps, and weakness

[13]. Thus, the motivation to discover alternative treatment methods for atherosclerosis is currently very strong. Numerous studies, including one recently conducted in Korea, suggest that high intakes of antioxidants[1] appear to prevent atherosclerotic lesions from developing. In particular, large quantities of antioxidants will prevent a high free radical concentration from inciting LDL oxidation [11].

Thus, it is interesting to learn how effective an anti-inflammatory diet rich in antioxidants is at *reversing* lesion growth in an individual diagnosed with atherosclerosis. To this end, we develop two mathematical models, both of which simulate foam cell accumulation within the intima layer of the arterial wall. The first model is a system of six ordinary differential equations, while the second model is a one-dimensional spatial model comprised of six partial differential equations. Parameters were applied to these models and then altered to simulate various lesion growth and regression scenarios over both spatially uniform and finitely varied domains.

2   The Ordinary Differential Equation Model

The first step towards simulating plaque development in the intima was to develop a system of differential equations that would simulate key components in the biological growth process of an atherosclerotic lesion. This initial model is composed of six unique ordinary differential equations where t stands for time, and L, R, X, I, D, and C represent the concentrations of low-density lipoprotein, free radicals, oxidized low-density lipoprotein, immune cells, debris, and chemoattractant respectively. These individual formulae are based upon those given by Ibragimov, McNeal, Ritter, and Walton. They vary, however, in that both a function representing low-density lipoprotein concentration in the blood, $\psi_L(B - L)$, and a component modeling the quantity of chemoattractant triggering an immune system response $\psi_C C$, though discussed in [4], have been added to the equations L and I respectively. Within these additional components, ψ_L and ψ_C are reaction rate coefficients and B is the constant low-density lipoprotein concentration in the blood. Initially, we begin the modeling process of atherogenesis with the following ordinary differential equation model:

$$\frac{dL}{dt} = -\alpha_L LR + \pi_L \pi_X aX + \psi_L(B - L),$$

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[1] Antioxidant substances include beta-carotene, lutein, lycopene, selenium, vitamin A, vitamin C, and vitamin E. Although antioxidants are primarily found in fruits and vegetables, they are also found in nuts, grains, and some meats, poultry, and fish [8].

$$\begin{aligned}
\frac{dR}{dt} &= \sigma - \alpha_R LR - \pi_R a, \\
\frac{dX}{dt} &= \alpha_X LR - \beta_X XI - \pi_x aX, \\
\frac{dI}{dt} &= \beta_I XI + \gamma_I ID - \mu_I I + \psi_C C, \\
\frac{dD}{dt} &= \beta_D XI - \gamma_D ID - \mu_D D, \\
\frac{dC}{dt} &= \chi_D D - \chi_C CI - \mu_C C,
\end{aligned} \tag{1}$$

where a represents antioxidant intake levels, and σ is a constant representing lifestyle behaviors characteristic of cardiovascular disease, which ultimately dictates free radical concentration. Other parameters in (1) include α_L, α_R, and α_X, which are all coefficients representing the rate at which low-density lipoproteins progress to the oxidized state, and β_X, β_I, and β_D, which illustrate the rate at which oxidized low-density lipoproteins will evolve into foam cells with the assistance of the macrophages. The parameters μ_C, μ_D, μ_I, γ_D, γ_I, χ_C, and χ_D are death rates that prevent the development of debris through the chemoattractant stimulating the immune response of the macrophages. Furthermore, π_R, π_X, and π_L are coefficients for the rate at which antioxidants block the process of low-density lipoprotein oxidation.

2.1 Initial Conditions for Lesion Growth

It was necessary to assign values to the parameters in (1) that would yield lesion growth. One requirement is that there exists a small presence of low-density lipoprotein (L), free radicals (R), oxidized low-density lipoprotein (X), and chemoattractant (C) in order for foam cell formation to occur. Furthermore, the low-density lipoprotein blood concentration (B) must be equal to the initial value of low-density lipoprotein (L).

Component	B	L	R	X	I	D	C	t	Δt
Initial Value	1	1	1	1	0	0	1	0	0.01

Table 1: Initial conditions for lesion growth simulation.

Numerical estimates were assigned to the coefficients in (1) based upon a literary search [1]. To avoid the process of denominalization, these coefficient values were ranked along a zero to one time scale according to the rate at which each atherogenic process occurs. Also taken into consideration was the known concept that low-density lipoprotein oxidation occurs at a

quicker rate than foam cell formation and the necessary conditions that $\alpha_L + \alpha_R = \alpha_X$ and $\beta_X + \beta_I = \beta_D$ [5].

Parameter	Value	Parameter	Value
σ	1	a	1
ψ_L	0.01	ψ_C	0.01
α_L	0.25	α_R	0.25
α_X	0.5	β_X	0.25
β_I	0.25	β_D	0.5
π_L	0.5	π_R	0.25
π_X	0.5	μ_I	0.25
μ_D	0.25	μ_C	0.25
γ_I	0.25	γ_D	0.25
χ_D	0.5	χ_C	0.25

Table 2: Parameter Estimates for the ODE Model (1).

Notice the parameter values $\sigma = 1$ and $a = 1$ in Table 2, where σ represents detrimental lifestyle behavior that consequently bolsters free radical production, while a denotes the antioxidant intake quantity. Let $a = 1$ denote the antioxidant intake of an *average* American. This quantity is below the recommended daily antioxidant intake dosage, and thus is representative of an *unhealthy* parameter[2] [2].

2.2 Definition of a Healthy State

In order to analyze effectively both lesion growth and regression, it was necessary to define first a healthy state, which is mathematically characterized through equilibrium values. In particular, the system of ordinary differential equations (1) can be broken into two subsets, namely functions that dictate the oxidation process of low-density lipoprotein and equations that control immune and debris cell accumulation. Because foam cell formation is a consequence of the oxidative process of LDL, a healthy state can be numerically computed by setting to zero the equations $D(t)$, $I(t)$, and $C(t)$ in (1). Thus, a healthy state is medically perceived as one with an absence of debris (or more realistically, a low-presence of debris). Therefore, the original set of six equations in (1) reduces to a system of three, where equilibrium values can be computed for $L(t)$, $R(t)$, and $X(t)$:

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[2]In 2004, the average daily consumption of antioxidant-rich fruits and vegetables was 1.03 and 1.58 cups. These quantities are approximately 40 percent lower than the recommended intake values of 1.80 cups of fruit and 2.60 cups of vegetables per day.

$$0 = -\alpha_L LR + \pi_L \pi_X \, aX + \psi_L(B - L),$$
$$0 = \sigma - \alpha_R LR - \pi_R a,$$
$$0 = \alpha_X LR - \beta_X XI - \pi_x aX.$$

Setting these parameters equal to the initial conditions in (1) and coefficients in (2) yielded equilibrium values of $L(t) = 1$ and $R(t) = X(t) = 3$.

3 The Partial Differential Equation Model

The system of ordinary differential equations (1) only account for change with respect to time. Thus, it was necessary to incorporate a spatial component (x) into this model to account for individualistic growth over a discrete bounded space interval.

Figure 2: Cross-sectional view of a human artery showing the location of x over a space interval $[a, b]$.

Adding x into (1) yielded the following set of partial differential equations:

$$\frac{\partial L}{\partial t} = \frac{\partial^2 t}{\partial x^2} - \alpha_L LR + \pi_L \pi_X \, aX + \psi_L(B - L),$$
$$\frac{\partial R}{\partial t} = \frac{\partial^2 t}{\partial x^2} + \sigma - \alpha_R LR - \pi_R a,$$
$$\frac{\partial X}{\partial t} = \frac{\partial^2 t}{\partial x^2} + \alpha_X LR - \beta_X XI - \pi_x aX, \qquad (2)$$
$$\frac{\partial I}{\partial t} = \frac{\partial^2 t}{\partial x^2} + \beta_I XI + \gamma_I ID - \mu_I I + \psi_C C,$$
$$\frac{\partial D}{\partial t} = \frac{\partial^2 t}{\partial x^2} + \beta_D XI - \gamma_D ID - \mu_D D,$$
$$\frac{\partial C}{\partial t} = \frac{\partial^2 t}{\partial x^2} + \chi_D D - \chi_C CI - \mu_C C,$$

In order to analyze various lesion regression scenarios using the partial differential equation model (2), quantities were analyzed discretely with a

Taylor series approximation. In general, a first order Taylor series of a function of two variables is:

$$F(t + \delta t, x + \delta x) \approx F(t, x) + \frac{\partial F}{\partial t} \delta t + \frac{\partial F}{\partial x} \delta x.$$

Thus, an approximation over discrete intervals Δx and Δt is:

$$
\begin{aligned}
F(t + \Delta t, x) &\approx F(t, x) + \frac{\partial F}{\partial t} \Delta t, \\
&\approx F(t, x) + \frac{\frac{F(t, x + \Delta x) - F(t, x)}{\Delta x} - \frac{F(t, x) - F(t, x - \Delta x)}{\Delta x}}{\Delta x} \Delta t. \quad (3)
\end{aligned}
$$

3.1 Boundary Conditions

The next mathematical component that was included in the engineering of this model took into consideration conditions along the two boundary points a and b. The spatial domain of this model will be defined over the discrete space interval $[0, 10]$. Let the boundary upon which free transport of low-density lipoproteins exists due to an ambient blood concentration be denoted by $a = 0$. Recall that transport exists in only one direction as the endothelium serves as a *one-way gate*. Meanwhile, let $b = 10$ represent the boundary upon which forces press the intima against the media layer of the human artery. These boundary conditions in combination with the time derivative and spatial component provide a discrete approximation for the partial differential equation model [see appendix].

3.2 Application of a Finite Difference Scheme

To avoid a numerical instability as t grew large, a diffusion coefficient (τ) was incorporated into the discrete approximation the partial differential equation model (2) through the application of a finite difference scheme [12]:

$$\frac{F(t + \Delta t, x) - F(t, x)}{k} = b\frac{F(t, x + \Delta x) - 2F(t, x) + F(t, x - \Delta x)}{h^2},$$

or similarly,

$$F(t + \Delta t, x) = (1 - 2b\tau)F(t, x) + b\tau(F(t, x + \Delta x) + F(t, x - \Delta x)),$$

where $\tau = kh^{-2}$.

3.3 Additional Parameters

Since including both a spatial component and diffusion coefficient in the original model, it then became necessary to define two new parameters and to alter one previously set initial condition for Δt:

Variable	t	Δt	x	Δx	τ
Initial Value	0	0.0001	0	1	0.01

Table 3: New and additional initial conditions in the PDE model.

Note that it is a necessary condition for stability that $\Delta t < \Delta x$. This follows from the Courant-Friedrichs-Lewy Condition, which states that the magnitude of $a\lambda$ be at most one is the stability condition for finite difference schemes for hyperbolic systems in one space dimension. In other words, $|a\lambda| \leq 1$, where λ denotes time divided by space [12].

3.4 Lesion Regression over a Spatially Uniform Domain

The first step towards numerically analyzing outputs from the PDE model with spatially uniform initial conditions was to compute the maximum value of debris ($\max_{D(t)} : 0 \leq t \leq \infty$) over a time enduring interval. After applying the parameters from Table 2 and Table 3, the biological system will begin to naturally stabilize when $t > 10000$. The following limit values were calculated as $t \longrightarrow \infty$ at the spatial point $x = 5$: $L(t,5) = 0.9543$, $R(t,5) = 0.9609$, $X(t,5) = 0.4087$, $I(t,5) = 2.5283$, $D(t,5) = 0.5859$, and $C(t,5) = 0.3321$.

Over the interval $[0,\infty)$, debris reached a maximum value at the point $D(8208) = 0.6764$. If this quantity is medically perceived as *complete blockage*, parameters for lesion regression can be imposed prior to this point in time for which the biological system reaches a maximum value of debris accretion. Lesion growth circa seventy percent of complete blockage places an individual at an elevated risk of experiencing a cardiac event [6]. Thus, *healthy* parameters should be imposed when $D(t) < 0.4735$. Therefore, let these conditions be applied at the point $D(6500) = 0.4603$, where lesion growth reaches approximately 68 percent of its maximum value.

Thus, to simulate lesion regression[3] through time, a total of one million iterations were computed over the time interval $[0, 10000]$, where the values

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[3]This example is one particular application of the partial differential equation model for atherosclerotic lesion growth with spatially uniform initial conditions. Both the duration of time iterations after *healthy* parameter values are imposed, as well as the time at which these conditions are applied will influence the percentage of lesion regression.
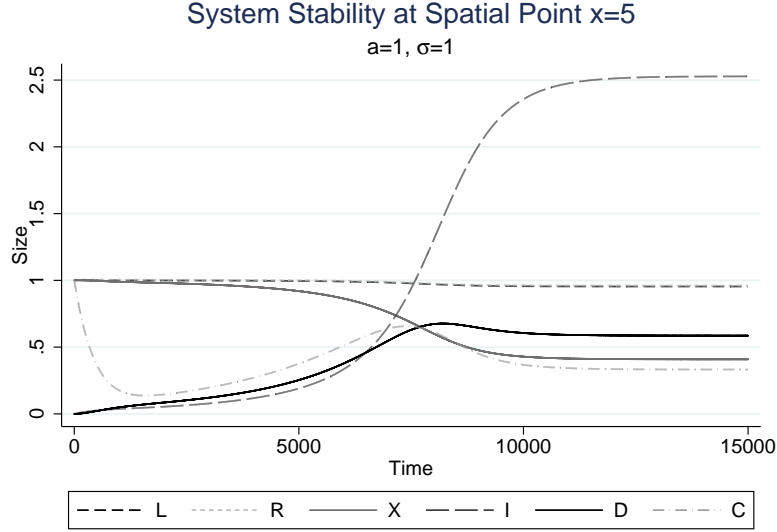
Figure 3: Evidence of stability when $t > 10000$.

in the time range $[0, 6500)$ were driven by *unhealthy* parameters, namely $a = 1$ and $\sigma = 1$, and the final iterations over the interval $[6500, 10000]$ were dictated by *healthy* parameters, where $1 < a$ and $0 \leq \sigma \leq 1$. The percent lesion regression was first calculated by taking the maximum size of the atherosclerotic lesion ($\max_{D(t)} : 0 \leq t \leq \infty$), which occurred at $t \geq 6500$ because there exists a small time lapse for which the biological system must adapt to the newly imposed parameters. The time duration of this transition phase decreases in length as a increases. The difference between $\max_{D(t)} : 0 \leq t \leq \infty$ and the size of the lesion at the points $D(8000)$ and $D(9500)$ was computed to determine the percent lesion regression exactly 1500 and 3000 time units after *healthy* parameters were first applied to the biological system.

3.5 Spatially Inconsistent Lesion Growth and Regression

Another topic worth investigating was lesion growth over a domain where debris was unevenly distributed. Let $I[3] = D[3] = 0.3$, $I[4] = D[4] = I[2] = D[2] = 0.2$, and $I[5] = D[5] = I[1] = D[1] = 0.1$. Meanwhile, let all other initial values for $I[x]$ and $D[x]$ equal zero. Under these initial conditions, plaque will augment within the artery until evenly distributed over the spatial domain. The lesion will then proceed to grow uniformly.
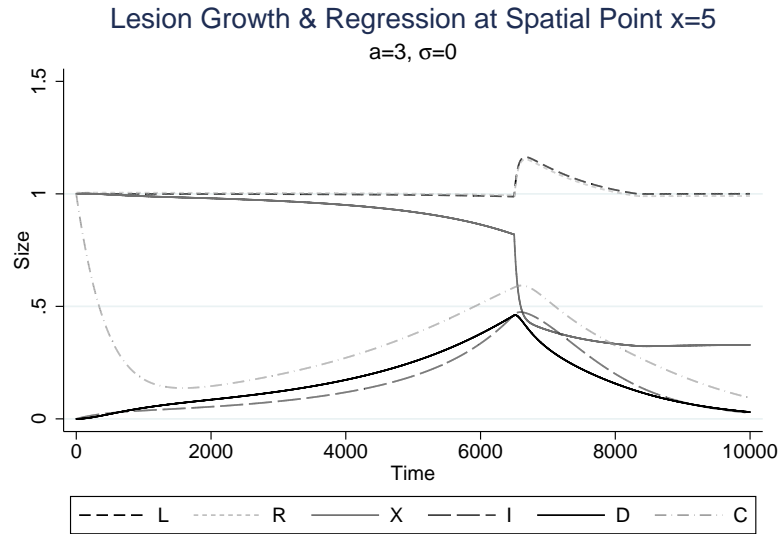
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Figure 4: Lesion growth and regression with spatially uniform initial conditions.

4   Analysis of Results and Conclusions

In this paper, a one-dimensional spatial model comprised of six partial differential equations was used to model the process of atherosclerotic lesion growth and regression in the human artery. After establishing for this model initial parameters for stimulating debris accretion, unique conditions along the boundary points $a = 0$ and $a = 10$, and a diffusion coefficient (τ) for numerical stability, it was possible to simulate the progression and regression of atherogenesis by simply altering values for a and σ. As evidenced in Table 4 and Table 5, significant lesion regression is most prominent when a increases and σ decreases. Though the model yields staggering results as a grows large, suggesting that with time it is possible to eliminate the presence of lesion debris almost entirely, a question worth proposing is what maximum quantity of antioxidants can the body absorb daily? Though it is difficult to numerically assess the body's maximum level of antioxidant absorbency, knowing such a number would place an upper bound on a allowing for a more realistic interpretation of the regression scenarios provided by this model.

In addition to showing the results of lesion regression over a spatially uniform domain, the PDE model also demonstrated the process by which

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a	$\sigma = 1$	$\sigma = 0.5$	$\sigma = 0$
1.69	29.53%	30.11%	30.69%
2	44.99%	45.41%	45.82%
3	65.65%	65.80%	65.94%
5	78.51%	78.59%	78.68%
8	86.05%	86.10%	86.15%
10	88.51%	88.55%	88.59%

Table 4: Lesion regression after 1500 time units.

a	$\sigma = 1$	$\sigma = 0.5$	$\sigma = 0$
1.69	43.64%	44.67%	45.68%
2	67.83%	68.37%	68.91%
3	89.52%	89.63%	89.74%
5	95.15%	95.18%	95.21%
8	97.56%	97.57%	97.58%
10	98.20%	98.21%	98.22%

Table 5: Lesion regression after 3000 time units.

lesion growth attempts to reach spatial uniformity over a domain with varied initial levels of debris. Ultimately, both the spatially varied and uniformly constant examples involving the PDE model revealed that increasing antioxidant consumption, regardless of changes in lifestyle behavior, will block the process of low-density lipoprotein oxidation, which consequently triggers lesion regression in patients diagnosed with athlerosclerosis.

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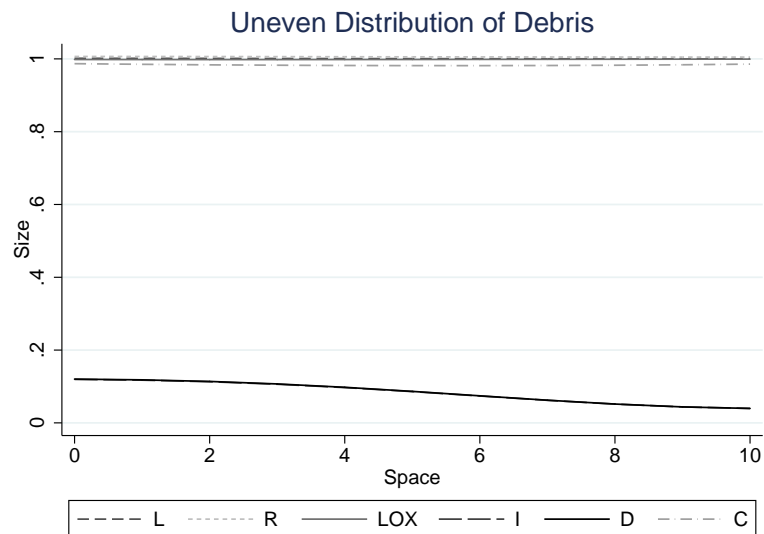
Figure 5: Evidence at $t = 10$ that initial quantities of unevenly dispersed debris cells over a spatial domain will reach spatial uniformity in time.

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Appendix

The following is a discrete approximation for the PDE model (2) with implemented boundary conditions over the space interval [0,10]:

$$L(t + \Delta t, x)$$
$$= L(t,x) + \begin{cases} \left(\frac{\frac{L(t,x+\Delta x)-L(t,x)}{\Delta x} - \psi_L(B-L)}{\Delta x} \right) \Delta t, & \text{if } x = 0, \\ \left(\frac{L(t,x+\Delta x)-2L(t,x)+L(t,x-\Delta x)}{\Delta x^2} \right) \Delta t, & \text{if } 0 < x < 10, \\ \left(0 - \frac{L(t,x)-L(t,x-\Delta x)}{\Delta x^2} \right) \Delta t, & \text{if } x = 10, \end{cases}$$
$$+ \left(-\alpha_L LR + \pi_L \pi_X a X + \psi_L(B-L) \right) \Delta t,$$

$$R(t + \Delta t, x)$$
$$= R(t,x) + \begin{cases} \left(\frac{R(t,x+\Delta x)-R(t,x)}{\Delta x^2} \right) \Delta t, & \text{if } x = 0, \\ \left(\frac{R(t,x+\Delta x)-2R(t,x)+R(t,x-\Delta x)}{\Delta x^2} \right) \Delta t, & \text{if } 0 < x < 10, \\ \left(0 - \frac{R(t,x)-R(t,x-\Delta x)}{\Delta x^2} \right) \Delta t, & \text{if } x = 10, \end{cases}$$
$$+ \left(\sigma - \alpha_R LR - \pi_R a \right) \Delta t,$$

$$X(t + \Delta t, x)$$
$$= X(t,x) + \begin{cases} \left(\frac{X(t,x+\Delta x)-X(t,x)}{\Delta x^2} \right) \Delta t, & \text{if } x = 0, \\ \left(\frac{X(t,x+\Delta x)-2X(t,x)+X(t,x-\Delta x)}{\Delta x^2} \right) \Delta t, & \text{if } 0 < x < 10, \\ \left(0 - \frac{L(t,x)-L(t,x-\Delta x)}{\Delta x^2} \right) \Delta t, & \text{if } x = 10, \end{cases}$$
$$+ \left(\alpha_X LR - \beta_X XI - \pi_x a X \right) \Delta t,$$

$$I(t + \Delta t, x)$$
$$= I(t,x) + \begin{cases} \left(\frac{I(t,x+\Delta x)-I(t,x)}{\Delta x^2} \right) \Delta t, & \text{if } x = 0, \\ \left(\frac{I(t,x+\Delta x)-2I(t,x)+I(t,x-\Delta x)}{\Delta x^2} \right) \Delta t, & \text{if } 0 < x < 10, \\ \left(0 - \frac{I(t,x)-I(t,x-\Delta x)}{\Delta x^2} \right) \Delta t, & \text{if } x = 10, \end{cases}$$
$$+ \left(\beta_I XI + \gamma_I ID - \mu_I I + \psi_C C \right) \Delta t,$$

$$
\begin{aligned}
D(t &+ \Delta t, x) \\
&= D(t,x) + \begin{cases} \left(\frac{D(t,x+\Delta x)-D(t,x)}{\Delta x^2}\right)\Delta t, & \text{if } x = 0, \\ \left(\frac{D(t,x+\Delta x)-2D(t,x)+D(t,x-\Delta x)}{\Delta x^2}\right)\Delta t, & \text{if } 0 < x < 10, \\ \left(0 - \frac{D(t,x)-D(t,x-\Delta x)}{\Delta x^2}\right)\Delta t, & \text{if } x = 10, \end{cases} \\
&\quad + (\beta_D XI - \gamma_D ID - \mu_D D)\,\Delta t,
\end{aligned}
$$

$$
\begin{aligned}
C(t &+ \Delta t, x) \\
&= C(t,x) + \begin{cases} \left(\frac{C(t,x+\Delta x)-C(t,x)}{\Delta x^2}\right)\Delta t, & \text{if } x = 0, \\ \left(\frac{C(t,x+\Delta x)-2C(t,x)+C(t,x-\Delta x)}{\Delta x^2}\right)\Delta t, & \text{if } 0 < x < 10, \\ \left(0 - \frac{C(t,x)-C(t,x-\Delta x)}{\Delta x^2}\right)\Delta t, & \text{if } x = 10, \end{cases} \\
&\quad + (\chi_D D - \chi_C CI - \mu_C C)\,\Delta t,
\end{aligned}
$$

Below is a discrete approximation for the partial differential equation model (2) after imposing a diffusion coefficient (τ) through the application of a finite difference scheme. This approximation was used to compute the lesion regression scenarios outlined in section (3.4):

$$
\begin{aligned}
L(t &+ \Delta t, x) \\
&= \begin{cases} (1-\tau+\psi\Delta x)L(t,x) + \tau(L(t,x+\Delta x) - \psi\Delta x B), & \text{if } x = 0, \\ (1-2\tau)L(t,x) + \tau(L(t,x+\Delta x) + L(t,x-\Delta x)), & \text{if } 0 < x < 10, \\ (1-\tau)L(t,x) + \tau L(t,x-\Delta x), & \text{if } x = 10, \end{cases} \\
&\quad + (-\alpha_L LR + \pi_L \pi_X aX + \psi_L(B-L))\,\Delta t,
\end{aligned}
$$

$$
\begin{aligned}
R(t &+ \Delta t, x) \\
&= \begin{cases} (1-\tau)R(t,x) + \tau R(t,x+\Delta x), & \text{if } x = 0, \\ (1-2\tau)R(t,x) + \tau(R(t,x+\Delta x) + R(t,x-\Delta x)), & \text{if } 0 < x < 10, \\ (1-\tau)R(t,x) + \tau R(t,x-\Delta x), & \text{if } x = 10, \end{cases} \\
&\quad + (\sigma - \alpha_R LR - \pi_R a)\,\Delta t,
\end{aligned}
$$

$$X(t + \Delta t, x)$$
$$= \begin{cases} (1 - \tau)X(t,x) + \tau R(t, x + \Delta x), & \text{if } x = 0, \\ (1 - 2\tau)X(t,x) + \tau(X(t, x + \Delta x) + X(t, x - \Delta x)), & \text{if } 0 < x < 10, \\ (1 - \tau)X(t,x) + \tau X(t, x - \Delta x), & \text{if } x = 10, \end{cases}$$
$$+ \left(\alpha_X LR - \beta_X XI - \pi_x aX \right) \Delta t,$$

$$I(t + \Delta t, x)$$
$$= \begin{cases} (1 - \tau)I(t,x) + \tau I(t, x + \Delta x), & \text{if } x = 0, \\ (1 - 2\tau)I(t,x) + \tau(I(t, x + \Delta x) + I(t, x - \Delta x)), & \text{if } 0 < x < 10, \\ (1 - \tau)I(t,x) + \tau I(t, x - \Delta x), & \text{if } x = 10, \end{cases}$$
$$+ \left(\beta_I XI + \gamma_I ID - \mu_I I + \psi_C C \right) \Delta t,$$

$$D(t + \Delta t, x)$$
$$= \begin{cases} (1 - \tau)D(t,x) + \tau D(t, x + \Delta x), & \text{if } x = 0, \\ (1 - 2\tau)D(t,x) + \tau(D(t, x + \Delta x) + D(t, x - \Delta x)), & \text{if } 0 < x < 10, \\ (1 - \tau)D(t,x) + \tau D(t, x - \Delta x), & \text{if } x = 10, \end{cases}$$
$$+ \left(\beta_D XI - \gamma_D ID - \mu_D D \right) \Delta t,$$

$$C(t + \Delta t, x)$$
$$= \begin{cases} (1 - \tau)C(t,x) + \tau C(t, x + \Delta x), & \text{if } x = 0, \\ (1 - 2\tau)C(t,x) + \tau(C(t, x + \Delta x) + C(t, x - \Delta x)), & \text{if } 0 < x < 10, \\ (1 - \tau)C(t,x) + \tau C(t, x - \Delta x), & \text{if } x = 10, \end{cases}$$
$$+ \left(\chi_D D - \chi_C CI - \mu_C C \right) \Delta t,$$