

# Incorporating HDL Interaction into an ODE Model of Atherosclerosis

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## Abstract

Atherosclerosis is a cardiovascular disease characterized by the build-up of fatty plaques in the intima of an arterial wall following inflammation of the lining of the artery, which slowly leads to occlusion of the arterial lumen and hardening of the artery walls. One third of Americans over the age of 35 die each year of atherosclerosis of the heart and half of men and women over the age of forty are reported to have some form of this illness. The medical community has long recognized that the concentration profile of low density lipoprotein (LDL), a.k.a "bad cholesterol" and high density lipoprotein (HDL), a.k.a "good cholesterol", in the blood plasma directly correlate to the risk of developing atherosclerosis. In this report, I go into the details of the physiology of atherosclerosis, propose a simple ODE model following some reasonable assumptions, and present equilibrium concentrations of LDL and other major atherosclerotic species.

## 1 Introduction

Atherosclerosis is a disease in which the human bodies normal metabolic processes can produce pathological effects over time. Atherosclerosis is characterized by erosion or damage of the artery wall which then leads to LDLs slipping underneath the lining of arterial walls. Once the LDL enters the wall, it is transformed by oxidative byproducts of the artery walls normal metabolic processes. The LDL thus becomes transformed into oxidated LDL which admits gradual, chronic, inflammatory immune response, eventually leading to a large plaque filled with fibrous fatty material surrounded by a hard cap. This plaque can succumb to the shear force of the heart pumping blood and rupture, resulting in the closing of the arterial lumen. Such an event is known by many names depending on which part of the body it happens in, a heart attack in the coronary arteries or a stroke in the vessel in the brain. Atherosclerosis is the leading cause of death in the United States and in the world [1]. It is for this reason that it is crucial to study and quantify this disease.

In this study, an extensive review of detailed biological information is presented in the following section to motivate the creation of an ODE model which aims to describe the progress of atherosclerosis. There are many ways of achieving this goal, but in this case, the topic of interest is in describing the behavior of HDL as a mitigator for atherosclerosis. Previous studies have shown that high LDL levels and low HDL levels in the blood plasma are the best indicators for risk of heart disease. This cholesterol profile causes atherosclerosis because while LDL functions to transport fatty materials throughout the body, HDL functions to collect excess cholesterol and return it to the liver to be excreted by the digestive system. The Methods and Results section presents the system of ODEs which model the concentrations of LDL, oxidized LDL, HDL, immune cells, foam cells, lipid debris, and oxidative species inside the intima. Exact equilibrium solutions were found computationally based on this system of equations; however, the solutions were complex and did not reveal any novel insights or quantifiable information relating to the behavior of the disease given the interaction of HDL. Some ideas for future directions are described in the discussion section of the paper.

## 2 Background

The human artery is composed of three main layers. Listed from from the outermost layer to the inner most, they are the *Tunica adventitia*, the *Tunica media*, and the *Tunica intima* [2]. The adventitia is an

elastic layer made of connective tissue that anchors the vessel to surrounding tissue [3]. The media is the thickest layer of the arterial wall and is primarily made smooth muscle cells, or SMCs, and elastic fibers in a transverse arrangement around the artery [3]. The media allows the artery to maintain its structure under the considerable pressure of blood flow. The intima is the innermost and thinnest layer of arterial wall and is composed of a thin layer of endothelial cells and the connective tissue that binds it to the media [3].

The thin design of the intima allows efficient transport of nutrients like cholesterol into the cells of bodily tissues. Normally, lipid laden LDL in the blood stream interact with endothelial surface proteins called *lipases* that receive cholesterol into the cell to be utilized for body and cell processes [4]. LDL then travels to the liver for processing and recycling [4] and are the last steps in a process known as *cholesterol metabolism* [4]. The reverse process, called *reverse cholesterol transport* or RCT, is when HDL in the bloodstream receives free, excess cholesterol from cells and tissues and transports them back to the liver for recycling or excretion [4]. Over time, the endothelial walls of arteries become damaged. Medical science is still unsure of exactly how or why this eventual erosion of the endothelial cells occur, but due to the fact that LDL delivers cholesterol to body tissues, it has been given the nickname, "bad cholesterol". HDL, which mitigates this process, has been named, "good cholesterol". What is clear, is that as the walls of the arteries become damaged, LDL is able to enter into the region where the media and intima meet and it then becomes oxidized by *free radicals* (unstable molecules that lack a full orbital of electrons) and other enzymes to form oxidized LDL or oxLDL [1]. Oxidative free radicals, along with other LDL modifying components are naturally found and produced inside the arterial walls and are conjectured to serve other useful physiological processes [5]; however, they are not designed to interact with LDL. The exact process by which LDL is modified into oxLDL is not yet fully understood, but it is considered by the medical community to be the onset of atherosclerosis and is known as the *oxidation hypothesis of atherosclerosis* [6].

Regardless of how oxLDL is formed biochemically, the inflammatory response that it admits is significant. When oxLDL interacts with the endothelial cells of the intima, it stimulates the cells to produce the proteins MCP-1 (Monocyte Chemotactic Protein 1) and mCSF (monocyte Colony Stimulating Factor) into the blood stream, resulting in the recruitment of *monocytes*, (a type of immune cell) into the intima [7]. Once inside the arterial wall, monocytes are differentiated into *macrophages* which are capable of scavenging oxldl due to specific cell surface receptors [7]. Once activated macrophages begin to take up oxldl, they are called *foam cells* because they become engorged with lipid overtime. If oxldl is the key molecule involved in atherosclerosis, then foam cells are the key cells in atherosclerosis. Foam cells produce a range of cytokines that create a positive feedback loop which facilitates and accelerates recruitment of monocytes into the intima [8]. Foam cells release free radical oxidative species which can increase the production of oxldl [9]. When foam cells accumulate and die off, they release free lipids, known as *debris*, into the intima. Foam cells also produce cytokines and growth factors which interact with SMCs in the tunica media and recruit them into the intima, where they proliferate and release collagen [10]. Collagen from SMCs form a fibrous matrix where foam cells and debris accumulate to form an *atherosclerotic plaque* [10]. The human body's only known defense against this process is RCT, which is mediated by HDL. HDL interacts with foam cells and debris to remove cholesterol from the intima and to transport it back to the liver [1].

### 3 Methods and Results

In this paper, I present a mathematical model that simulates the behavior of certain major chemical and biological species characterized in the previous section, namely, **LDL**, **HDL**, **oxldl**, **oxidative species**, **monocytes/macrophages**, **foam cells**, and, **debris**. The main focus of the study is to explore how individual species in an idealized atherosclerosis system change with respect to HDL concentration.

#### 3.1 Model Assumptions

For this model, we make the following assumptions:

- We assume that the species follow law of mass action, meaning that we are assuming that the rate of change the component concentrations are proportional to the product of the concentrations of their reactants and a proportionality constant, or rate constant.

Table 1: Variables of the model

| Variable | Description                               |
|----------|---|
| $L$      | LDL concentration                         |
| $I$      | Immune cell concentration                 |
| $F$      | Foam cell concentration                   |
| $D$      | Debris concentration                      |
| $L_{ox}$ | oxldl concentration                       |
| $M$      | Oxidative modifying species concentration |
| $H$      | HDL concentration                         |

- We assume that all concentrations and rate constants are always positive. The variables in this model represent the concentrations of the aforementioned biological and biochemical species and they are listed in Table 1.
- We assume that the oxidation hypothesis of atherosclerosis is true.
- We assume that we have a 'well stirred pot', meaning that every species has an equal chance of interacting with any species and we restrict the scope of the model to just the intima.

The last assumption mentioned means that we ignore the effects of diffusion or chemotaxis. Instead, to model the effects of chemotaxis, we assume that the concentration of a species rises in proportion to the concentration of the species that causes the chemotactic effect, e.g. if foam cells produce chemoattractant that causes monocytes to enter the intima without getting consumed itself, instead of a chemotaxis term, we can say that

$$\dot{I} = rF$$

where  $\dot{I}$  represents rate of change of the immune cell concentration,  $F$  represents the foam cell concentration,  $r$  is a rate constant. Instead of diffusion across the luminal endothelium, we can use an intrinsic growth term, e.g. if LDL travels across the endothelial layer at a certain rate and then can travel back across if unaffected, this is modeled by the equation

$$\dot{L} = lL$$

where  $\dot{L}$  is the rate of change in LDL concentration and  $l$  is an intrinsic production rate given by  $l = r_f - r_d$ , where  $r_f$  and  $r_d$  are constant formation and degradation rates respectively. Rate constants and their descriptions are listed in Table 2.

Table 2: Rate Constants

| Rate Constant | Description   |
|---------------|---|
| $l$           | Intrinsic production rate of $L$                                    |
| $r_4$         | Reaction rate of $L$ and $M$ reaction                               |
| $r_{19}$      | Rate of recruitment of $I$ by $L_{ox}$                              |
| $r_{20}$      | Rate of recruitment of $I$ by $F$                                   |
| $r_{18}$      | Reaction rate of $I$ and $L_{ox}$ reaction with respect to $I$      |
| $r_{10}$      | Reaction rate of $F$ and $H$ reaction                               |
| $r_6$         | Rate of foam cell degradation into debris                           |
| $r_{17}$      | Reaction rate of $D$ and $H$ reaction                               |
| $r_6$         | Reaction rate of $I$ and $L_{ox}$ reaction with respect to $L_{ox}$ |
| $m$           | Intrinsic production rate of $M$                                    |
| $r_{21}$      | Production rate of $M$ from $F$                                     |
| $h$           | Intrinsic production rate of $H$                                    |

### 3.2 Governing System of ODEs

The following system of ODEs is based on the variables listed in Table 1 and the rate constants listed in Table 2. Figure 1 illustrates the interactions between the different variables in a chemical reaction network.

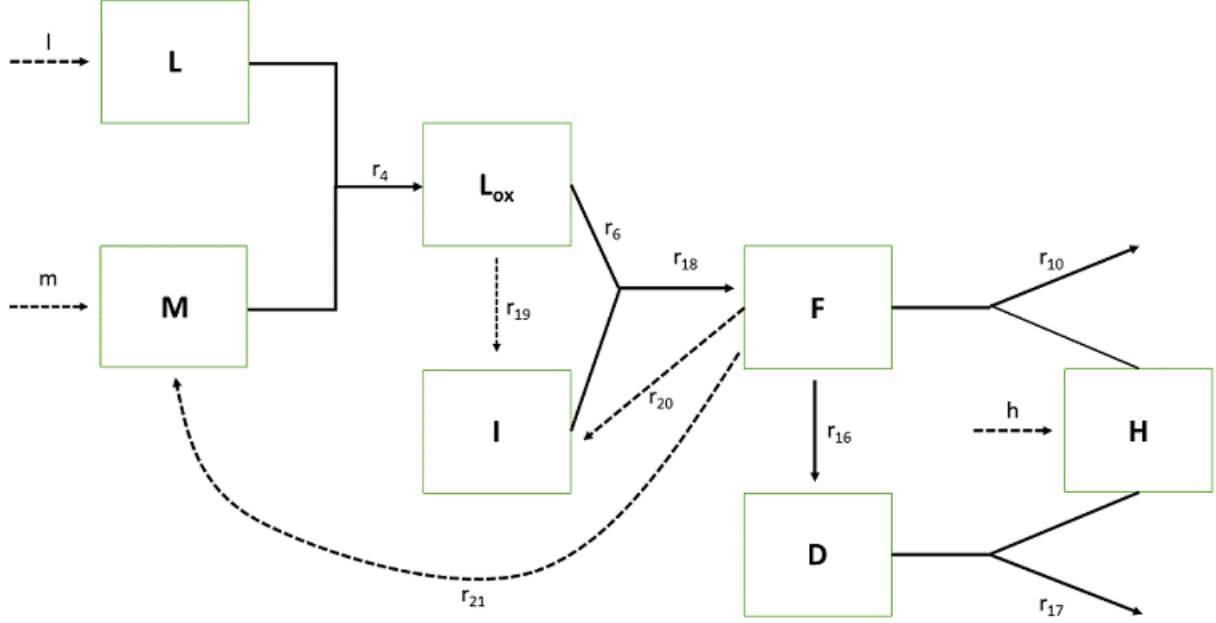


Figure 1: Chemical Reaction Network for Atherosclerosis

$$L^* = lL - r_4LM \quad (1)$$

$$I^* = r_{19} * L_{ox} + r_{20}F - r_{18}IL_{ox} \quad (2)$$

$$F^* = r_{18}IL_{ox} - r_{10}FH - r_{16}F \quad (3)$$

$$D^* = r_{16}F - r_{17}DH \quad (4)$$

$$L_{ox}^* = r_4LM - r_6IL_{ox} \quad (5)$$

$$M^* = mM + r_{21}F - r_4LM \quad (6)$$

$$H^* = H(h - r_{10}F - r_{17}D) \quad (7)$$

### 3.3 Steady State Analysis

The following are analytic solutions to the system of ODEs presented in the previous section.

$$L^* = \frac{0}{0} + \frac{\sqrt{h^2 r_4^2 r_6^2 r_{16}^2 - 2 h^2 r_4^2 r_6 r_{16} r_{18} r_{21}} + h^2 r_4^2 r_{18}^2 r_{21}^2 + 2 h l m r_4 r_6 r_{10} r_{16} r_{18} + 2 h l m r_4 r_{10} r_{18}^2 r_{21} + l^2 m^2 r_{10}^2 r_{18}^2}{2 l r_4 r_{10} r_{18}} + \frac{l m r_{10} r_{18} - h r_4 r_6 r_{16} + h r_4 r_{18} r_{21}}{2 l r_4 r_{10} r_{18}}$$

$$- \frac{\sqrt{h^2 r_4^2 r_6^2 r_{16}^2 - 2 h^2 r_4^2 r_6 r_{16} r_{18} r_{21}} + h^2 r_4^2 r_{18}^2 r_{21}^2 + 2 h l m r_4 r_6 r_{10} r_{16} r_{18} + 2 h l m r_4 r_{10} r_{18}^2 r_{21} + l^2 m^2 r_{10}^2 r_{18}^2}{2 l r_4 r_{10} r_{18}} - \frac{l m r_{10} r_{18} + h r_4 r_6 r_{16} - h r_4 r_{18} r_{21}}{2 l r_4 r_{10} r_{18}}$$

$$I^* = \frac{0}{0} - \frac{r_{19} r_{20} \left( \sqrt{h^2 r_4^2 r_6^2 r_{16}^2 - 2h^2 r_4^2 r_6 r_{16} r_{18} r_{21}} + h^2 r_4^2 r_{18}^2 r_{21}^2 + 2h l m r_4 r_6 r_{10} r_{16} r_{18} + 2h l m r_4 r_{10} r_{18}^2 r_{21} + l^2 m^2 r_{10}^2 r_{18}^2 \right)}{2(lm r_{10} r_{18}^2 r_{20} - h r_4 r_6 r_{18} r_{20}^2 - h r_4 r_{16} r_{18}^2 r_{21} + h r_4 r_{18}^2 r_{20} r_{21} + h r_4 r_6 r_{16} r_{18} r_{20})} + \frac{r_{19} r_{20} (r_{19} r_{20} l m r_{10} r_{18} - h r_4 r_6 r_{16} + h r_4 r_{18} r_{21})}{2(lm r_{10} r_{18}^2 r_{20} - h r_4 r_6 r_{18} r_{20}^2 - h r_4 r_{16} r_{18}^2 r_{21} + h r_4 r_{18}^2 r_{20} r_{21} + h r_4 r_6 r_{16} r_{18} r_{20})} + \frac{h r_4 r_{16} r_{19} (r_6 r_{20} - r_{18} r_{21})}{l m r_{10} r_{18}^2 r_{20} - h r_4 r_6 r_{18} r_{20}^2 - h r_4 r_{16} r_{18}^2 r_{21} + h r_4 r_{18}^2 r_{20} r_{21} + h r_4 r_6 r_{16} r_{18} r_{20}}$$

$$- \frac{r_{19} r_{20} \left( \sqrt{h^2 r_4^2 r_6^2 r_{16}^2 - 2h^2 r_4^2 r_6 r_{16} r_{18} r_{21}} + h^2 r_4^2 r_{18}^2 r_{21}^2 + 2h l m r_4 r_6 r_{10} r_{16} r_{18} + 2h l m r_4 r_{10} r_{18}^2 r_{21} + l^2 m^2 r_{10}^2 r_{18}^2 \right)}{2(lm r_{10} r_{18}^2 r_{20} - h r_4 r_6 r_{18} r_{20}^2 - h r_4 r_{16} r_{18}^2 r_{21} + h r_4 r_{18}^2 r_{20} r_{21} + h r_4 r_6 r_{16} r_{18} r_{20})} - \frac{r_{19} r_{20} (l m r_{10} r_{18} + h r_4 r_6 r_{16} - h r_4 r_{18} r_{21})}{2(lm r_{10} r_{18}^2 r_{20} - h r_4 r_6 r_{18} r_{20}^2 - h r_4 r_{16} r_{18}^2 r_{21} + h r_4 r_{18}^2 r_{20} r_{21} + h r_4 r_6 r_{16} r_{18} r_{20})}$$

$$F^* = \frac{0}{0} + \frac{\sqrt{h^2 r_4^2 r_6^2 r_{16}^2 - 2h^2 r_4^2 r_6 r_{16} r_{18} r_{21}} + h^2 r_4^2 r_{18}^2 r_{21}^2 + 2h l m r_4 r_6 r_{10} r_{16} r_{18} + 2h l m r_4 r_{10} r_{18}^2 r_{21} + l^2 m^2 r_{10}^2 r_{18}^2}{2 r_4 r_{10} r_{18} r_{21}} + \frac{l m}{r_4 r_{21}} - \frac{l m}{r_4 r_{21}} - \frac{\sqrt{h^2 r_4^2 r_6^2 r_{16}^2 - 2h^2 r_4^2 r_6 r_{16} r_{18} r_{21}} + h^2 r_4^2 r_{18}^2 r_{21}^2 + 2h l m r_4 r_6 r_{10} r_{16} r_{18} + 2h l m r_4 r_{10} r_{18}^2 r_{21} + l^2 m^2 r_{10}^2 r_{18}^2}{2 r_4 r_{10} r_{18} r_{21}} - \frac{l m r_{10} r_{18} + h r_4 r_6 r_{16} - h r_4 r_{18} r_{21}}{2 r_4 r_{10} r_{18} r_{21}}$$

$$D^* = \frac{0}{\frac{h}{r_{17}}} - \frac{l m r_{10} + h r_4 r_{21}}{r_4 r_{17} r_{21}} - \frac{\sqrt{h^2 r_4^2 r_6^2 r_{16}^2 - 2h^2 r_4^2 r_6 r_{16} r_{18} r_{21}} + h^2 r_4^2 r_{18}^2 r_{21}^2 + 2h l m r_4 r_6 r_{10} r_{16} r_{18} + 2h l m r_4 r_{10} r_{18}^2 r_{21} + l^2 m^2 r_{10}^2 r_{18}^2}{2 r_4 r_{17} r_{18} r_{21}} + \frac{l m r_{10} r_{18} - h r_4 r_6 r_{16} + h r_4 r_{18} r_{21}}{2 r_4 r_{17} r_{18} r_{21}}$$

$$+ \frac{l m r_{10} + h r_4 r_{21}}{r_4 r_{17} r_{21}} + \frac{\sqrt{h^2 r_4^2 r_6^2 r_{16}^2 - 2h^2 r_4^2 r_6 r_{16} r_{18} r_{21}} + h^2 r_4^2 r_{18}^2 r_{21}^2 + 2h l m r_4 r_6 r_{10} r_{16} r_{18} + 2h l m r_4 r_{10} r_{18}^2 r_{21} + l^2 m^2 r_{10}^2 r_{18}^2}{2 r_4 r_{17} r_{18} r_{21}} - \frac{l m r_{10} r_{18} + h r_4 r_6 r_{16} - h r_4 r_{18} r_{21}}{2 r_4 r_{17} r_{18} r_{21}}$$

$$L_{ox}^* = \frac{0}{0} - \frac{l m r_{20}}{r_4 r_{19} r_{21}} - \frac{(r_6 r_{20} - r_{18} r_{21}) \left( \sqrt{h^2 r_4^2 r_6^2 r_{16}^2 - 2h^2 r_4^2 r_6 r_{16} r_{18} r_{21}} + h^2 r_4^2 r_{18}^2 r_{21}^2 + 2h l m r_4 r_6 r_{10} r_{16} r_{18} + 2h l m r_4 r_{10} r_{18}^2 r_{21} + l^2 m^2 r_{10}^2 r_{18}^2 \right)}{2 r_4 r_6 r_{10} r_{18} r_{19} r_{21}} + \frac{(r_6 r_{20} - r_{18} r_{21}) (l m r_{10} r_{18} - h r_4 r_6 r_{16} + h r_4 r_{18} r_{21})}{2 r_4 r_6 r_{10} r_{18} r_{19} r_{21}}$$

$$+ \frac{l m r_{20}}{r_4 r_{19} r_{21}} + \frac{(r_6 r_{20} - r_{18} r_{21}) \left( \sqrt{h^2 r_4^2 r_6^2 r_{16}^2 - 2h^2 r_4^2 r_6 r_{16} r_{18} r_{21}} + h^2 r_4^2 r_{18}^2 r_{21}^2 + 2h l m r_4 r_6 r_{10} r_{16} r_{18} + 2h l m r_4 r_{10} r_{18}^2 r_{21} + l^2 m^2 r_{10}^2 r_{18}^2 \right)}{2 r_4 r_6 r_{10} r_{18} r_{19} r_{21}} + \frac{(r_6 r_{20} - r_{18} r_{21}) (l m r_{10} r_{18} - h r_4 r_6 r_{16} + h r_4 r_{18} r_{21})}{2 r_4 r_6 r_{10} r_{18} r_{19} r_{21}}$$

$$M^* = \frac{0}{\frac{l}{r_4}} - \frac{l}{r_4}$$

$$\begin{aligned}
& 0 \\
& 0 \\
H^* = & \frac{\sqrt{h^2 r_4^2 r_6^2 r_{16}^2 - 2 h^2 r_4^2 r_6 r_{16} r_{18} r_{21}} + h^2 r_4^2 r_{18}^2 r_{21}^2 + 2 h l m r_4 r_6 r_{10} r_{16} r_{18} + 2 h l m r_4 r_{10} r_{18}^2 r_{21} + l^2 m^2 r_{10}^2 r_{18}^2}{2 h r_4 r_6 r_{10}} \\
& + \frac{l m r_{10} r_{18} - h r_4 r_6 r_{16} + h r_4 r_{18} r_{21}}{2 h r_4 r_6 r_{10}} \\
& - \frac{\sqrt{h^2 r_4^2 r_6^2 r_{16}^2 - 2 h^2 r_4^2 r_6 r_{16} r_{18} r_{21}} + h^2 r_4^2 r_{18}^2 r_{21}^2 + 2 h l m r_4 r_6 r_{10} r_{16} r_{18} + 2 h l m r_4 r_{10} r_{18}^2 r_{21} + l^2 m^2 r_{10}^2 r_{18}^2}{2 h r_4 r_6 r_{10}} \\
& - \frac{l m r_{10} r_{18} + h r_4 r_6 r_{16} - h r_4 r_{18} r_{21}}{2 h r_4 r_6 r_{10}}
\end{aligned}$$

## 4 Discussion

While exact solutions to this system of equations were found computationally, they hold no intelligible significance other than that if those conditions are met, then the net plaque formation in the arteries is zero.

The difficulty in analyzing a system like lies in the assumptions that are made prior to and during model building. Truly, one of the best directions for the future is to reconsider the starting assumptions. Increasing the complexity of the model to support chemotaxis and diffusion will not only make the model more accurate, but also easier to analyze because the interactions won't be so muddy and idealized. No successful numerical simulations of this model were ever completed. Matlab was used for every attempt at creating plots of the system given initial conditions, but with the program run times stretching out to hours, the programs were all terminated before completion. Seeking ways to greatly reduce numerical simulation run times would definitely be a worthwhile direction to go in the future. Another assumption that can be assumed to be false can be the oxidation hypothesis. Without the assumption of the oxidation hypothesis, then systems can be created where non-immune components don't interact with immune components. One can then search for equilibrium solutions of the form  $(L, I, F, D, L_{ox}, M, H) = (L^*, 0, 0, 0, L_{ox}^*, M^*, H^*)$ . Such solutions are defined as *healthy-state equilibria* [11]. Such solutions are impossible for systems that assume oxidation hypothesis because as long as oxdl exists, then the concentration of immune cells in the intima will always change. Finally, one may seek to model other effects the HDL has been conjectured to have, namely, HDLs ability to absorb oxidative species and it's ability to get modified by them as well [1][10].

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