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Model of the development of atherosclerosis and its analytical, qualitative and numerical research

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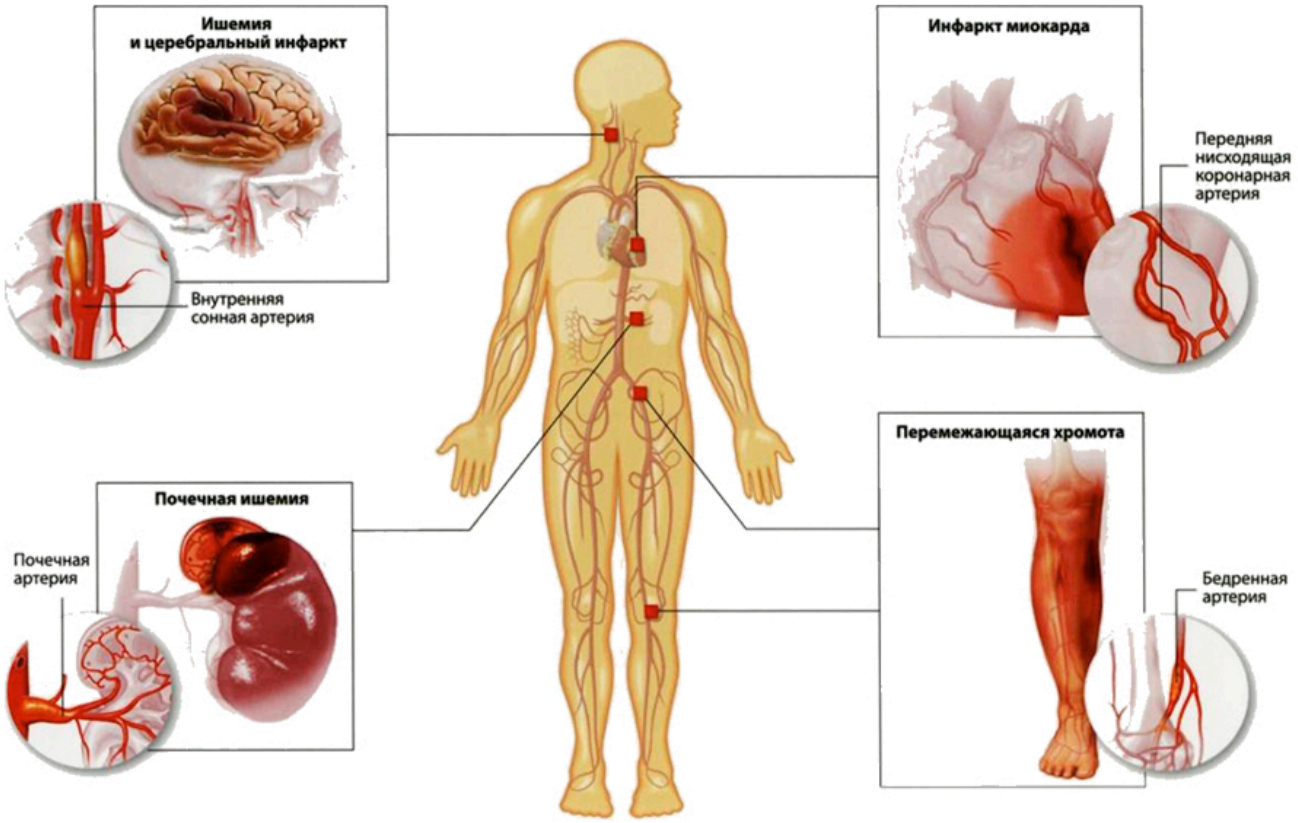
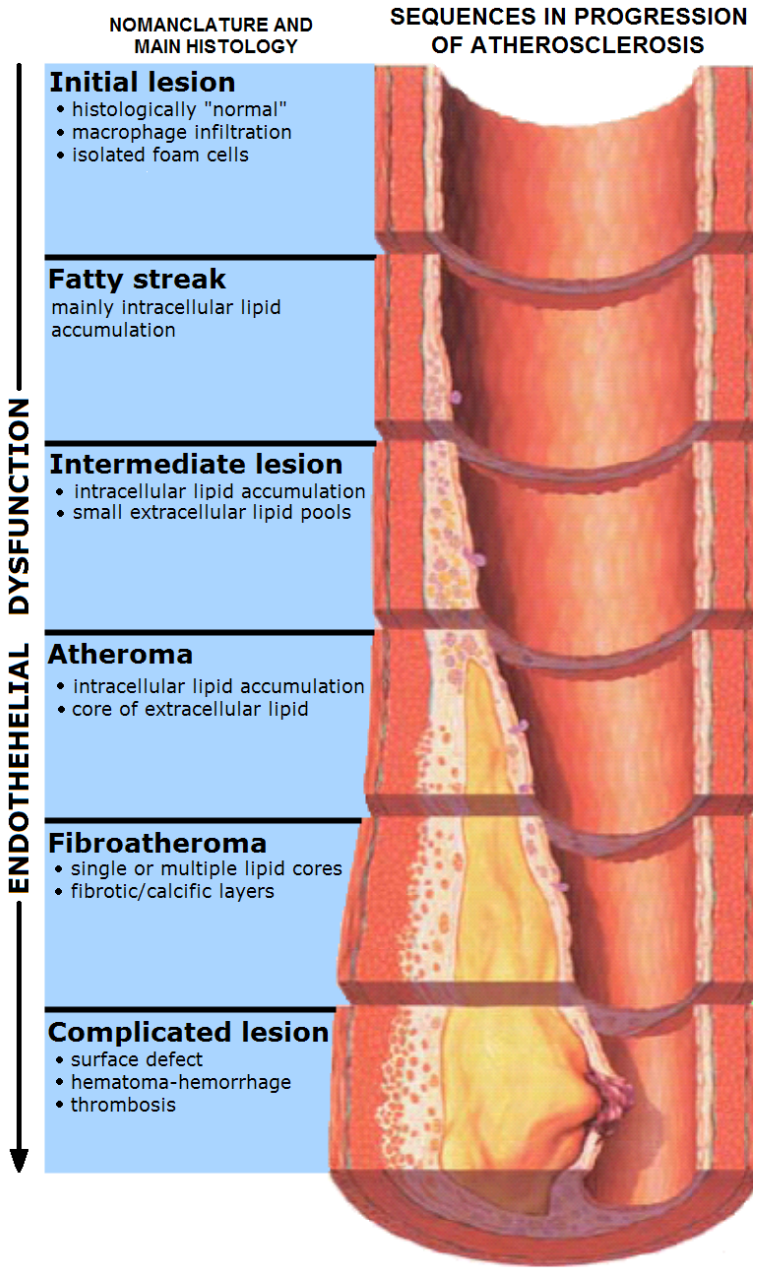
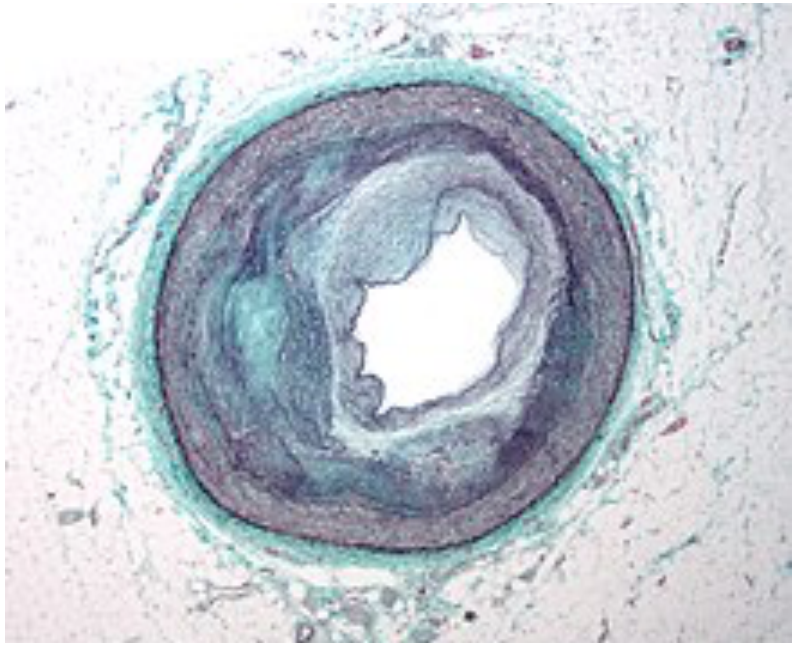
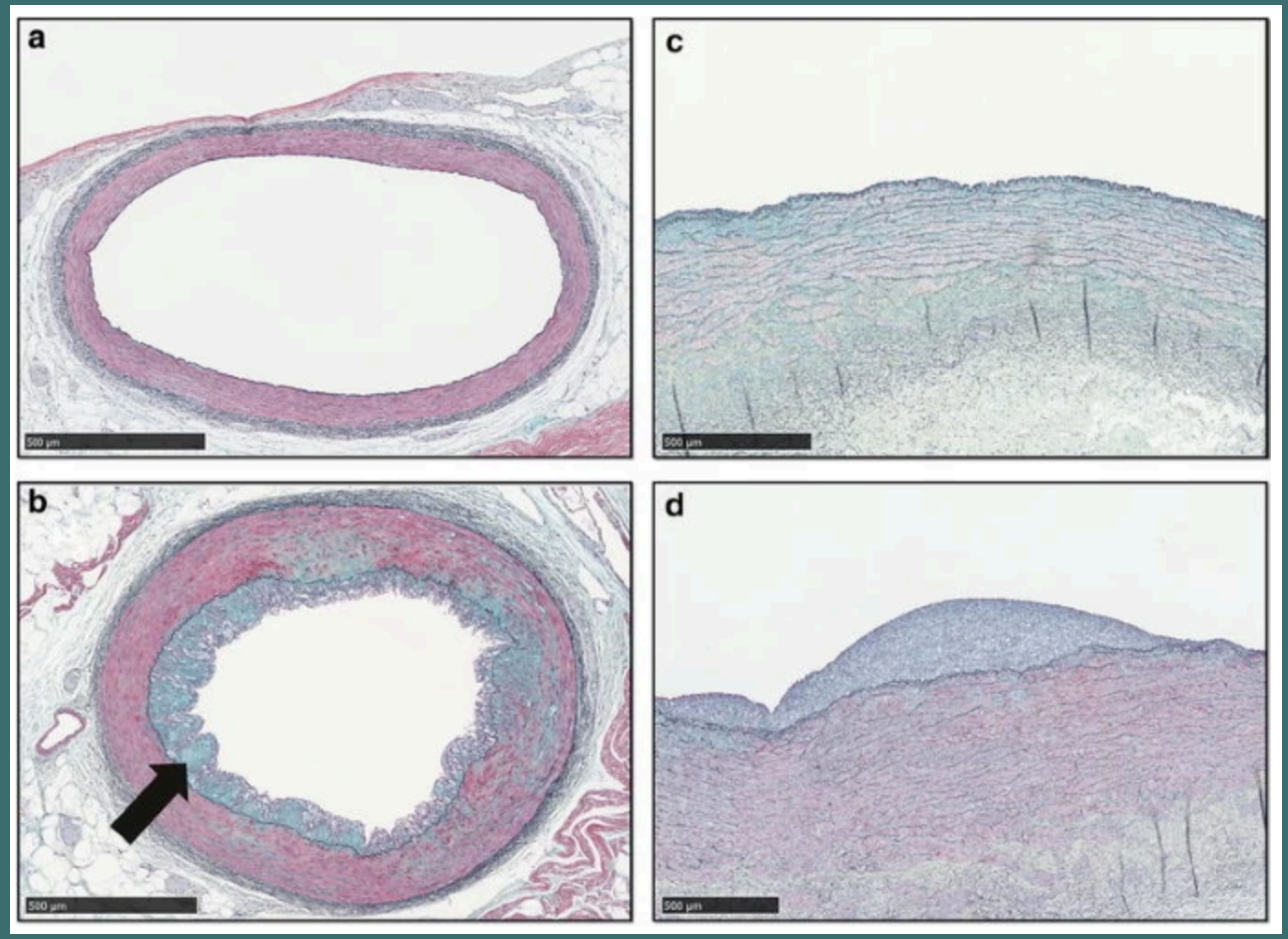
ATHEROSCLEROSIS





CHRONIC INFLAMMATION BLOOD VESSEL WALLS





THE MODEL OF CHRONIC INFLAMMATION

We consider the model of chronic inflammation in the blood vessel walls taking into account low density lipoproteins (LDL), high density lipoproteins (HDL), free radicals, various cell types (monocytes, macrophages, T-lymphocytes, foam cells), pro- and anti-inflammatory cytokines. Endothelial cells and smooth muscle cells are not considered explicitly in the model but their action is taken into account indirectly. Numerous cytokines participating in atherogenesis are not considered individually but grouped in pro-inflammatory and anti-inflammatory parts.

Bezyaev V., Sadekov N. and Volpert V. A model of chronic inflammation in atherosclerosis, ITM Web of Conferences 31 04002, 2020

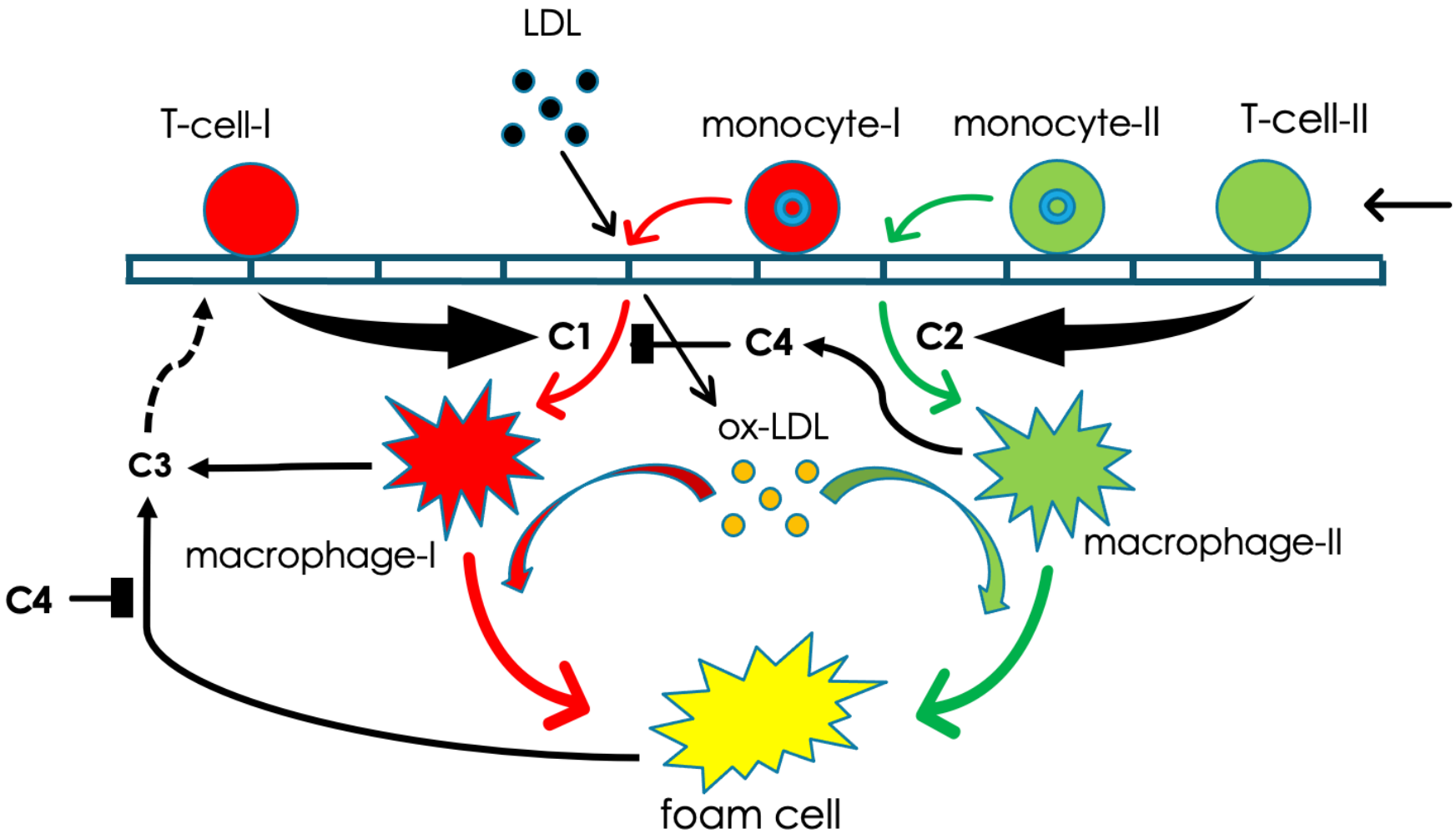
MODEL VARIABLES: CONCENTRATION AND DENSITY IN UNITS OF G/CM3

L	concentration of LDL	**T1**	density of proinflammatory 1-helpers cells
H	concentration of HDL	**T2**	density of anti-inflammatory 2-helper cells
Lox	concentration of ox-LDL	**C1**	concentration of 1-helpers of cytokines
r	concentration of free radicals	**C2**	concentration of 2-helpers of cytokines
A1	density of proinflammatory monocytes	**C3**	concentration of pro-inflammatory agents
A2	density of anti-inflammatory monocytes	**C4**	concentration of anti-inflammatory agents
M1	density of pro-inflammatory macrophages	**F**	density of foam cells
M2	density of anti-inflammatory macrophages		

THE PARAMETER USED OF THE MODEL

Parameter	Description	Value	Parameter	Description	Value
$\boldsymbol{\sigma_L}$	Rate of LDL penetration through the vessel wall	$1.0cm^{-1}$	$\boldsymbol{k_{L_{ox}}}$	Ox-LDL saturation for production of MCP-1	$0.5gcm^{-3}$
$\boldsymbol{L_0}$	Concentration of LDL in the blood	$7 * 10^{-4}\ g^{-1}cm^3day^{-1}$	$\boldsymbol{\lambda_{PA_1}}$	Rate of A_1 monocytes penetration though the vessel wall	$0.2cm^{-1}$
$\boldsymbol{k_L}$	Reaction rate of LDL and radical	$2.35 * 10^{-4}\ g^{-1}cm^3day^{-1}$	$\boldsymbol{A_1^0}$	Density of A_1 monocytes in blood	$5 * 10^{-5}\ gcm^{-3}$
$\boldsymbol{\sigma_H}$	Rate of HDL penetration through the vessel wall	$1.0cm^{-1}$	$\boldsymbol{r_0}$	Influx of radical into intima	$0.26gcm^{-3}day^{-1}$
$\boldsymbol{H_0}$	Concentration of HDL in the blood	$4 * 10^{-4}\ g^{-1}cm^3day^{-1}$	$\boldsymbol{d_{A_1}}$	Death rate of A_1 monocytes	$0.015day^{-1}$
$\boldsymbol{k_H}$	Reaction rate of HDL and radical	$5.29 * 10^{-6}\ g^{-1}cm^3day^{-1}$	$\boldsymbol{d_{T_1}}$	Death rate of T_1-cells	$0.33day^{-1}$
$\boldsymbol{\lambda_{L_{ox}M_1}}$	Rate of ox-LDL ingestion by M_1 macrophages	144.5	$\boldsymbol{d_F}$	Death rate of foam cells	$0.03day^{-1}$

SCHEMATIC NETWORK OF ATHEROSCLEROSIS



COMPLETE MODEL

- LDL

$$\frac{dL}{dt} = \sigma_L(L_0 - L) - k_L r L,$$

- HDL

$$\frac{dH}{dt} = \sigma_H(H_0 - H) - k_H r H,$$

- ox-LDL

$$\frac{dL_{ox}}{dt} = k_L r L - \lambda_{L_{ox}M_1}\frac{L_{ox}}{k_{L_{ox}}+L_{ox}}M_1 - \lambda_{L_{ox}M_2}\frac{L_{ox}}{k_{L_{ox}}+L_{ox}}M_2\,,$$

- free radical

$$\frac{dr}{dt} = r_0 + r_1 M_1 - r(k_L L + k_H H)\,,$$

- monocytes

$$\frac{dA_1}{dt} = \lambda_{PA_1}\frac{P}{k_{1P}+k_{2P}P}A_1^0 - \lambda_{C_1A_1}\frac{C_1}{k_{C_1}+C_1+k_4C_4}A_1 - d_{A_1}A_1\,,$$

$$\frac{dA_2}{dt} = \lambda_{PA_2}\frac{P}{k_{1P}+k_{2P}P}A_2^0 - \lambda_{C_2A_2}\frac{C_2}{k_{C_2}+C_2}A_2 - d_{A_2}A_2\,,$$

- macrophages

$$\frac{dM_1}{dt} = \lambda_{C_1A_1}\frac{C_1}{k_{C_1}+C_1+k_4C_4}A_1 - \lambda_{L_{ox}M_1}\frac{L_{ox}}{k_{L_{ox}}+L_{ox}}M_1 - d_{M_1}M_1\,,$$

$$\frac{dM_2}{dt} = \lambda_{C_2A_2}\frac{C_2}{k_{C_2}+C_2}A_2 - \lambda_{L_{ox}M_2}\frac{L_{ox}}{k_{L_{ox}}+L_{ox}}M_2 - d_{M_2}M_2\,,$$

- T-cells

$$\frac{dT_1}{dt} = \lambda_{PT_1}\frac{P}{k_{1P}+k_{2P}P}T_1^0 - d_{T_1}T_1\,,$$

$$\frac{dT_2}{dt} = \lambda_{PT_2}\frac{P}{k_{1P}+k_{2P}P}T_2^0 - d_{T_2}T_2\,,$$

- T-helper cytokines

$$\frac{dC_1}{dt} = \lambda_{C_1}T_1 - k_{C_1A_1}C_1A_1 - d_{C_1}C_1,$$

$$\frac{dC_2}{dt} = \lambda_{C_2}T_2 - k_{C_2A_2}C_2A_2 - d_{C_2}C_2,$$

- pro-inflammatory agents

$$\frac{dC_3}{dt} = \lambda_{C_4M_1}\frac{1}{k_{C_4}+C_4}M_1 - \lambda_{C_4F}\frac{1}{k_{C_4}+C_4}F - d_{C_3}C_3\,,$$

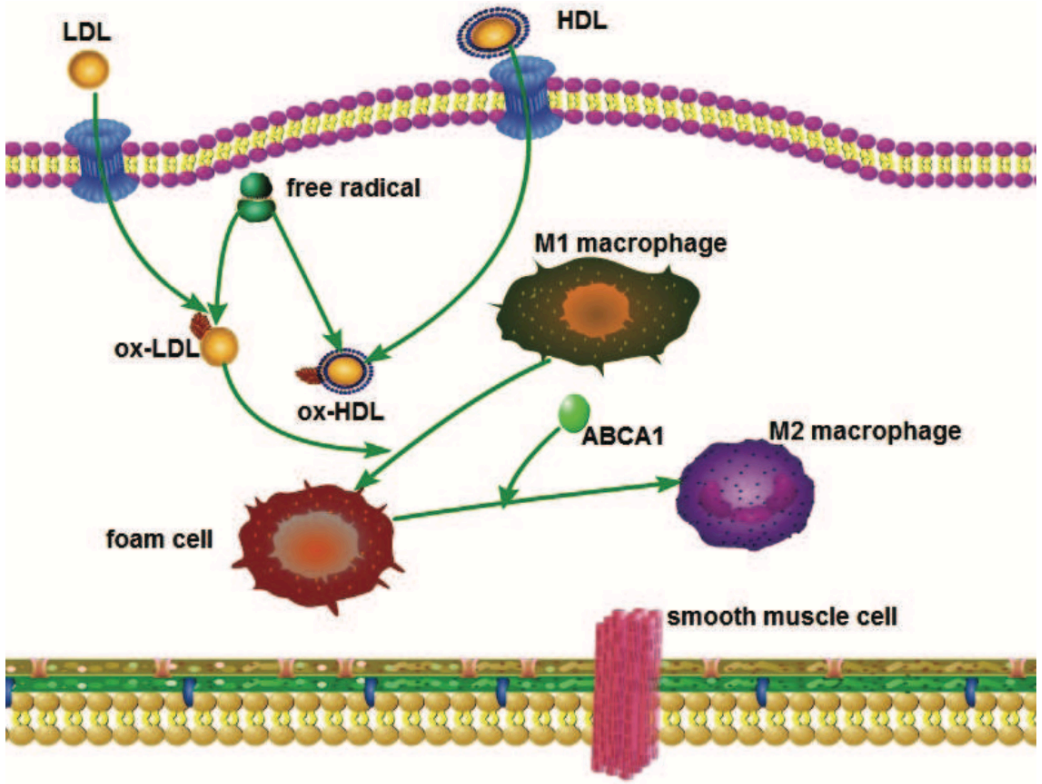
- anti-inflammatory agents

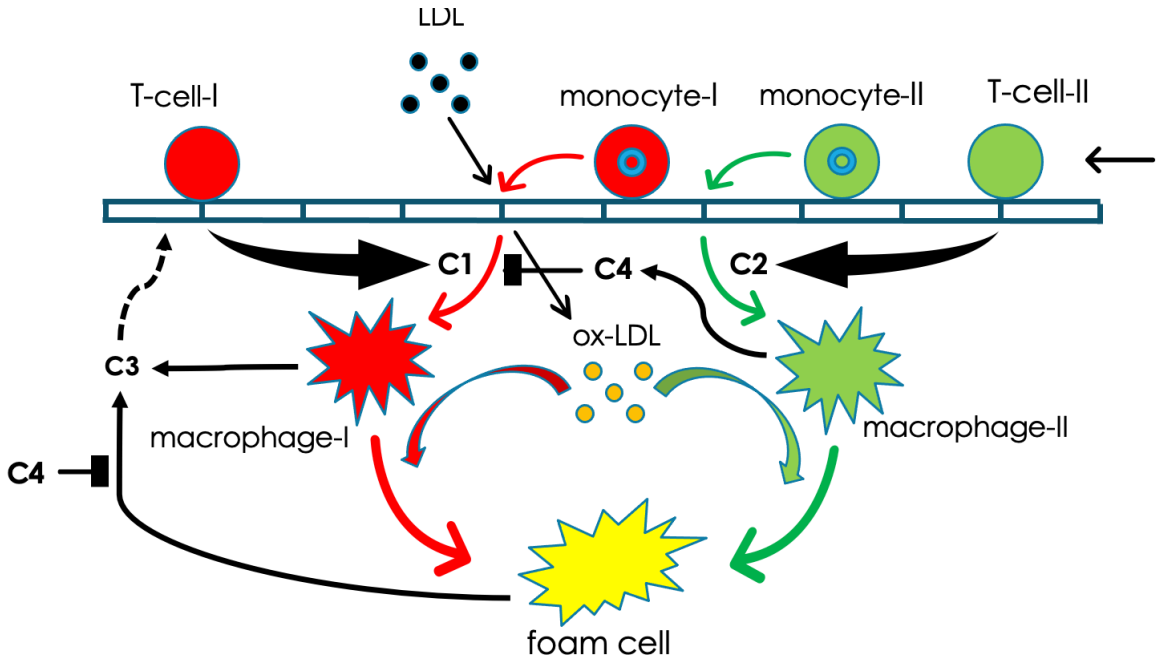
$$\frac{dC_4}{dt} = \lambda_{C_4}M_2 - d_{C_4}C_4,$$

- foam cells

$$\frac{dF}{dt} = \lambda_{L_{ox}M_1}\frac{L_{ox}}{k_{L_{ox}}+L_{ox}}M_1 - \lambda_{L_{ox}M_2}\frac{L_{ox}}{k_{L_{ox}}+L_{ox}}M_2 - d_F F.$$

COMPARISON OF MODELS





Friedman A., Hao W. A mathematical model of atherosclerosis with reverse cholesterol transport and associated risk factors, Bulletin of Mathematical Biology, 77, Issue 5, 2015, 758–781.

VARIABLE COMPARISON

L	LDL	Q	MMPs
H	HDL	Q_r	TIMP
L_{ox}	ox-LDL	S	SMCs
r	free radical	ρ	ECM
P	MCP-1	F	Foam cells
I_γ	IFN-γ	T	T cells
I_{12}	IL-12	M_1	pro-inflammatory macrophages
G	PDGF	M_2	anti-inflammatory macrophages

Friedman A., Hao W. A

L	LDL	**C1**	1-helpers of cytokines
H	HDL	**C2**	2-helpers of cytokines
Lox	ox-LDL	**C3**	pro-inflammatory agents
r	free radicals	**C4**	anti-inflammatory agents
A1	pro-inflammatory monocytes	**T1**	pro-inflammatory 1-helpers cells
A2	anti-inflammatory monocytes	**T2**	anti-inflammatory 2-helper cells
M1	pro-inflammatory macrophages	**F**	foam cells
M2	anti-inflammatory macrophages		

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REDUCTION 15 → 5

$$\frac{dL}{dt} = \sigma_L(L_0 - L) - k_L r L,$$

$$\frac{dH}{dt} = \sigma_H(H_0 - H) - k_H r H,$$

$$\frac{dL_{ox}}{dt} = k_L r L - \lambda_{L_{ox}M_1}\frac{L_{ox}}{k_{L_{ox}}+L_{ox}}M_1 - \lambda_{L_{ox}M_2}\frac{L_{ox}}{k_{L_{ox}}+L_{ox}}M_2\,,$$

$$\frac{dr}{dt} = r_0 + r_1 M_1 - r(k_L L + k_H H)\,,$$

$$\frac{dA_1}{dt} = \lambda_{PA_1}\frac{P}{k_{1P}+k_{2P}P}A_1^0 - \lambda_{C_1A_1}\frac{C_1}{k_{C_1}+C_1+k_4C_4}A_1 - d_{A_1}A_1\,,$$

$$\frac{dA_2}{dt} = \lambda_{PA_2}\frac{P}{k_{1P}+k_{2P}P}A_2^0 - \lambda_{C_2A_2}\frac{C_2}{k_{C_2}+C_2}A_2 - d_{A_2}A_2\,,$$

$$\frac{dM_1}{dt} = \lambda_{C_1A_1}\frac{C_1}{k_{C_1}+C_1+k_4C_4}A_1 - \lambda_{L_{ox}M_1}\frac{L_{ox}}{k_{L_{ox}}+L_{ox}}M_1 - d_{M_1}M_1\,,$$

$$\frac{dM_2}{dt} = \lambda_{C_2A_2}\frac{C_2}{k_{C_2}+C_2}A_2 - \lambda_{L_{ox}M_2}\frac{L_{ox}}{k_{L_{ox}}+L_{ox}}M_2 - d_{M_2}M_2,$$

$$\frac{dT_1}{dt} = \lambda_{PT_1}\frac{P}{k_{1P}+k_{2P}P}T_1^0 - d_{T_1}T_1\,,$$

$$\frac{dT_2}{dt} = \lambda_{PT_2}\frac{P}{k_{1P}+k_{2P}P}T_2^0 - d_{T_2}T_2\,,$$

$$\frac{dC_1}{dt} = \lambda_{C_1}T_1 - k_{C_1A_1}C_1A_1 - d_{C_1}C_1,$$

$$\frac{dC_2}{dt} = \lambda_{C_2}T_2 - k_{C_2A_2}C_2A_2 - d_{C_2}C_2,$$

$$\frac{dC_3}{dt} = \lambda_{C_4M_1}\frac{1}{k_{C_4}+C_4}M_1 - \lambda_{C_4F}\frac{1}{k_{C_4}+C_4}F - d_{C_3}C_3\,,$$

$$\frac{dC_4}{dt} = \lambda_{C_4}M_2 - d_{C_4}C_4,$$

$$\frac{dF}{dt} = \lambda_{L_{ox}M_1}\frac{L_{ox}}{k_{L_{ox}}+L_{ox}}M_1 - \lambda_{L_{ox}M_2}\frac{L_{ox}}{k_{L_{ox}}+L_{ox}}M_2 - d_F F.$$

Let us: $H = A_2 = M_2 = T_2 = C_2 = C_4 = 0,$

$$A_1 = A_1^0 = \text{const},\ C_1 >> 1.$$

Redesignation : $r = R_0,\ \lambda_1 = \lambda_{M_1L_{ox}},\ \lambda_2 = \lambda_{C_1A_1},$

$$\lambda_3 = \lambda_{C_4M_1},\ k_1 = k_{L_{ox}},\ k_2 = k_{C_1},\ k_3 = k_{C_4},$$

$$d_1 = d_{L_{ox}},\ d_2 = d_{M_1},\ d_3 = d_{C_3},\ d_4 = d_F$$

$$\frac{dL}{dt} = \sigma_L(L_0 - L) - k_L R_0 L\,,$$

$$\frac{dL_{ox}}{dt} = k_L R_0 L - \lambda_1\frac{L_{ox}}{k_1+L_{ox}}M_1 - d_1 L_{ox}\,,$$

$$\frac{dM_1}{dt} = \lambda_2\frac{C_3+L_{ox}}{k_2+C_3+L_{ox}} - \lambda_1\frac{L_{ox}}{k_1+L_{ox}}M_1 - d_2 M_1\,,$$

$$\frac{dC_3}{dt} = \lambda_3\frac{C_3}{k_3+C_3}M_1 - d_3 C_3,$$

$$\frac{dF}{dt} = \lambda_1\frac{L_{ox}}{k_1+L_{ox}}M_1 - d_4 F.$$

REDUCTION 5 → 2

Let us: $\lambda_1 = 0$.

Redesignation : $M_1 = M, C_3 = A, \alpha_1 = \lambda_2 L_{ox}, \beta_1 = \lambda_2, \tau_1 = k_1 + L_{ox}$,
$d_1 = \lambda_1, \alpha_2 = \lambda_3, \tau_2 = k_3, d_2 = \lambda_2$.

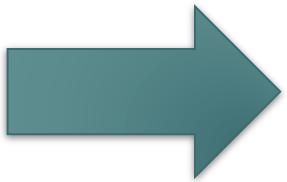
$$\frac{dL}{dt} = \sigma_L (L_0 - L) - k_L r L,$$

$$\frac{dL_{ox}}{dt} = k_L R_0 L - \lambda_1 \frac{L_{ox}}{k_1 + L_{ox}} M_1 - d_1 L_{ox} ,$$

$$\frac{dM_1}{dt} = \lambda_2 \frac{C_3 + L_{ox}}{k_2 + C_3 + L_{ox}} - \lambda_1 \frac{L_{ox}}{k_1 + L_{ox}} M_1 - d_2 M_1 ,$$

$$\frac{dC_3}{dt} = \lambda_3 \frac{C_3}{k_3 + C_3} M_1 - d_3 C_3,$$

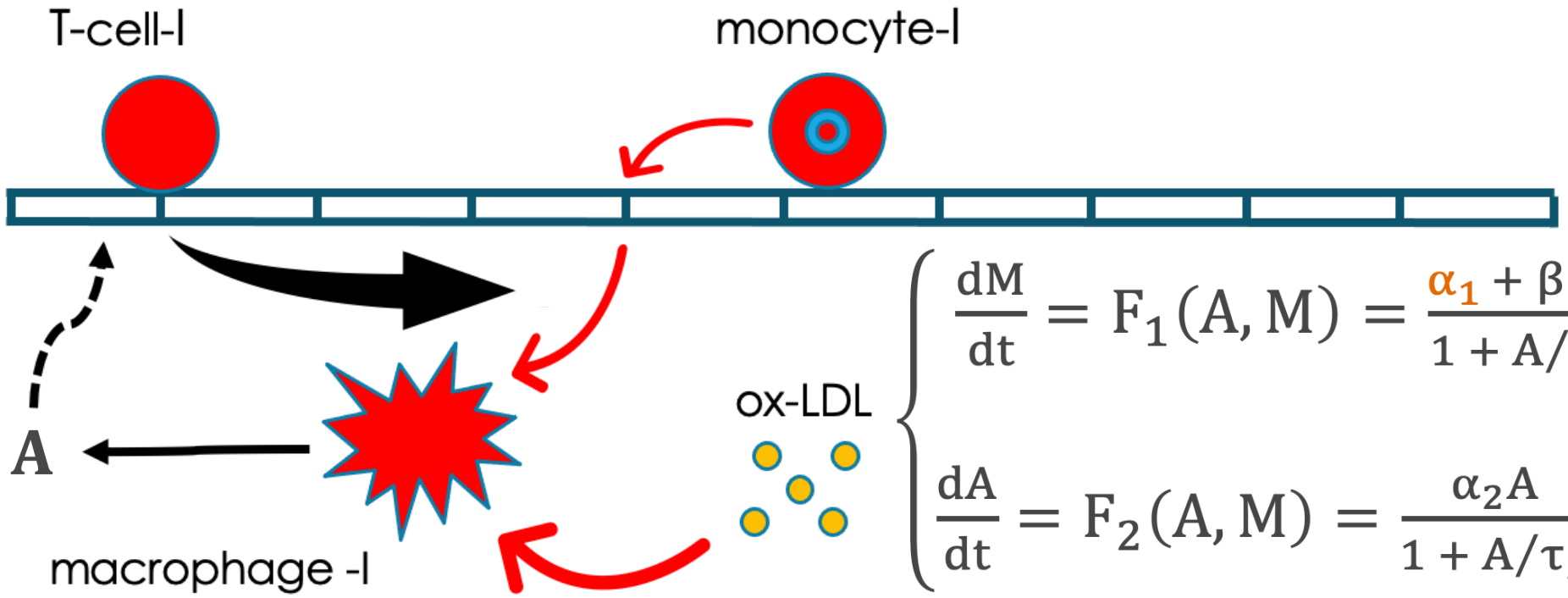
$$\frac{dF}{dt} = \lambda_1 \frac{L_{ox}}{k_1 + L_{ox}} M_1 - d_4 F.$$



$$\frac{dM}{dt} = \frac{\alpha_1 + \beta_1 A}{1 + A/\tau_1} - \lambda_1 M,$$

$$\frac{dA}{dt} = \frac{\alpha_2 A}{1 + A/\tau_2} M - \lambda_2 A.$$

SIMPLEST MODEL



$$\begin{cases} \frac{dM}{dt} = F_1(A, M) = \frac{\alpha_1 + \beta_1 A}{1 + A/\tau_1} - \lambda_1 M, \\ \frac{dA}{dt} = F_2(A, M) = \frac{\alpha_2 A}{1 + A/\tau_2} M - \lambda_2 A. \end{cases}$$

M– macrophages, A – pro-inflammatory agents

α_1 – Concentration of LDL in the blood

THREE PHYSIOLOGICAL CONDITIONS DEPENDING ON THE CHOLESTEROL LEVEL

Figure 1 α_1 small, disease free (the monostable case)

Figure 2 α_1 is intermediate, atherosclerosis can develop under certain conditions

Figure 3 α_1 large, atherosclerosis necessarily develops (bistable case)

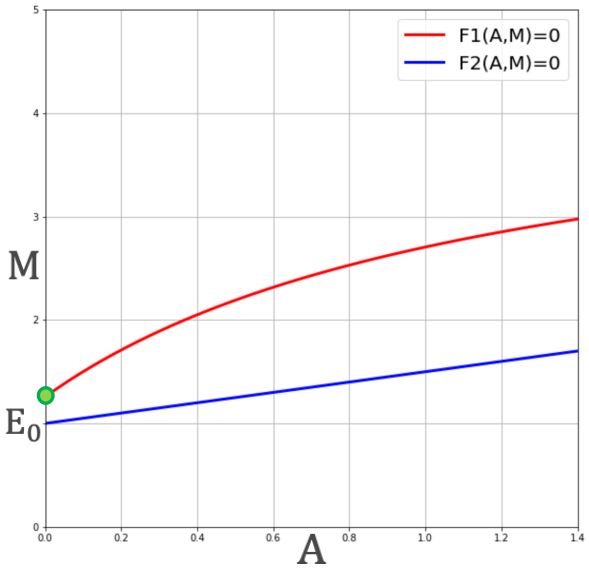


Figure 1

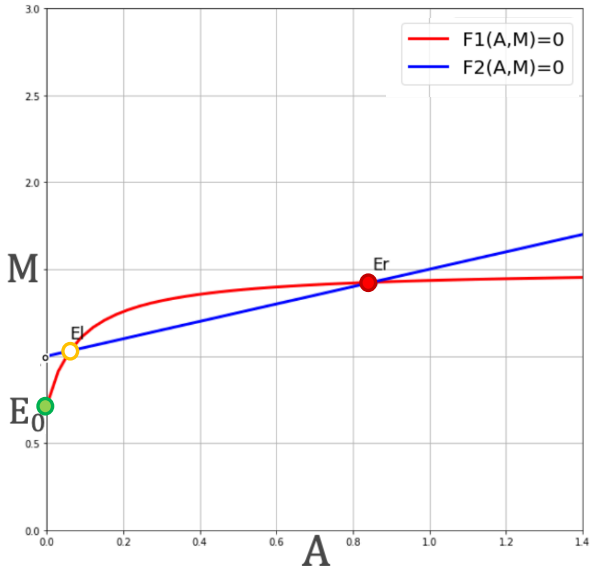


Figure 2

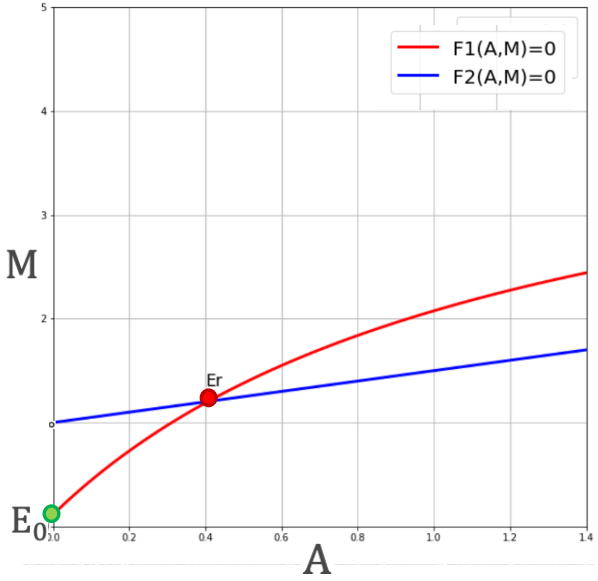
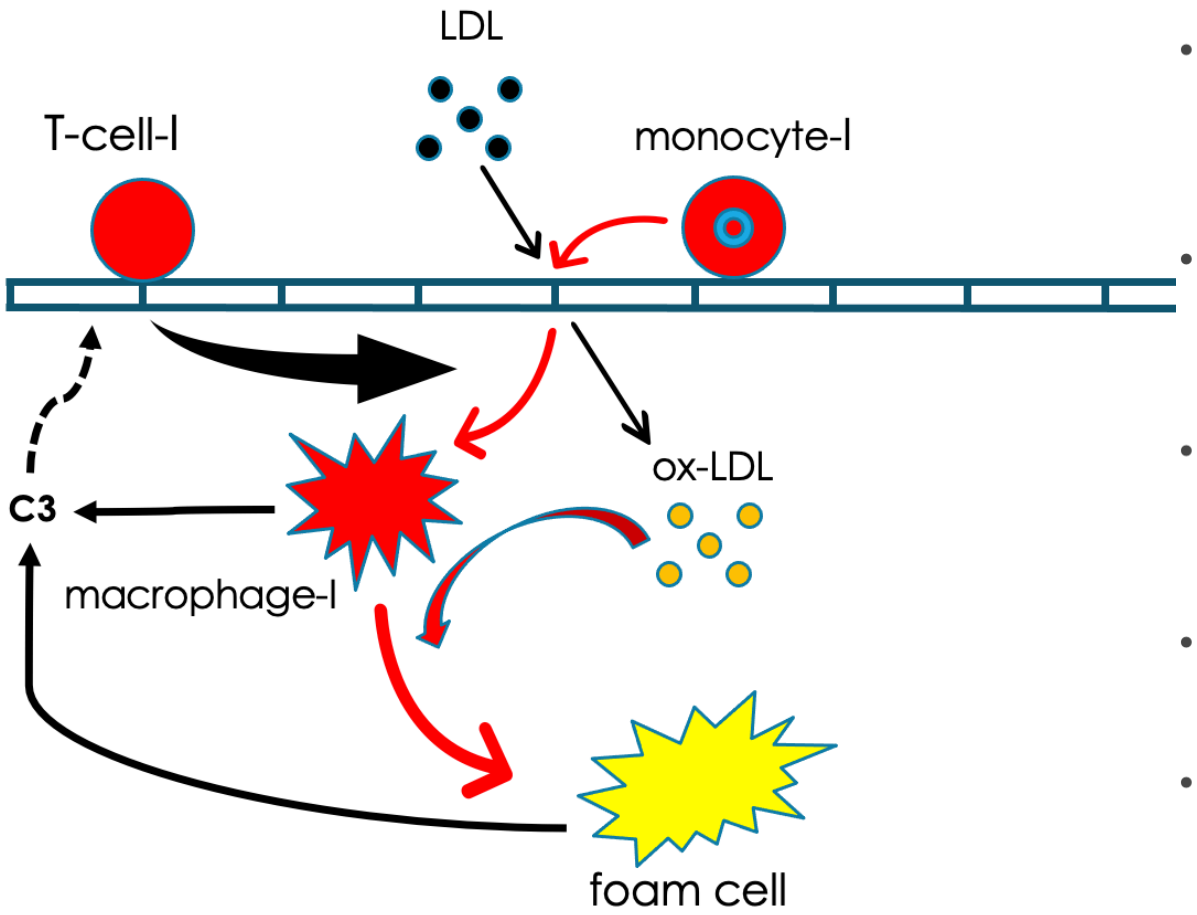


Figure 3

INFLAMMATORY RESPONSE MODEL



- **LDL**

$$\frac{dL}{dt} = \sigma_L(L_0 - L) - k_L R_0 L\,,$$

- **ox-LDL**

$$\frac{dL_{ox}}{dt} = k_L R_0 L - \lambda_1 \frac{L_{ox}}{k_1 + L_{ox}} M_1 - d_1 L_{ox}\,,$$

- **macrophages**

$$\frac{dM_1}{dt} = \lambda_2 \frac{C_3 + L_{ox}}{k_2 + C_3 + L_{ox}} - \lambda_1 \frac{L_{ox}}{k_1 + L_{ox}} M_1 - d_2 M_1\,,$$

- **pro-inflammatory agents**

$$\frac{dC_3}{dt} = \lambda_3 \frac{C_3}{k_3 + C_3} M_1 - d_3 C_3,$$

- **foam cells**

$$\frac{dF}{dt} = \lambda_1 \frac{L_{ox}}{k_1 + L_{ox}} M_1 - d_4 F.$$

THREE PHYSIOLOGICAL CONDITIONS DEPENDING ON THE CHOLESTEROL LEVEL

Figure 1 L_0 small, disease free.

Figure 2 L_0 is intermediate, atherosclerosis can develop under certain conditions (the monostable case).

Figure 3 L_0 large, atherosclerosis necessarily develops (bistable case).

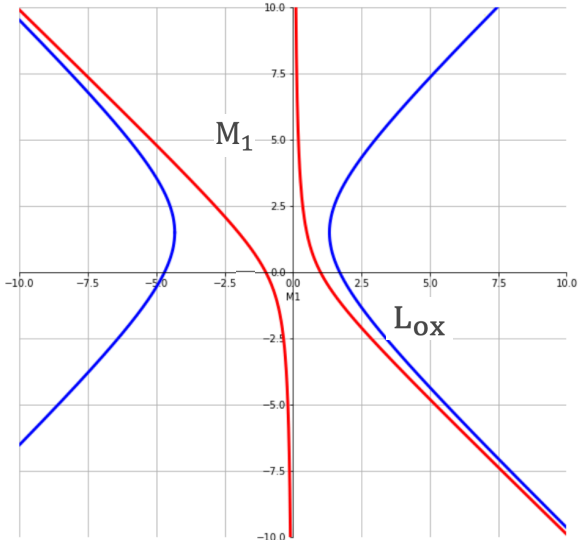


Figure 1

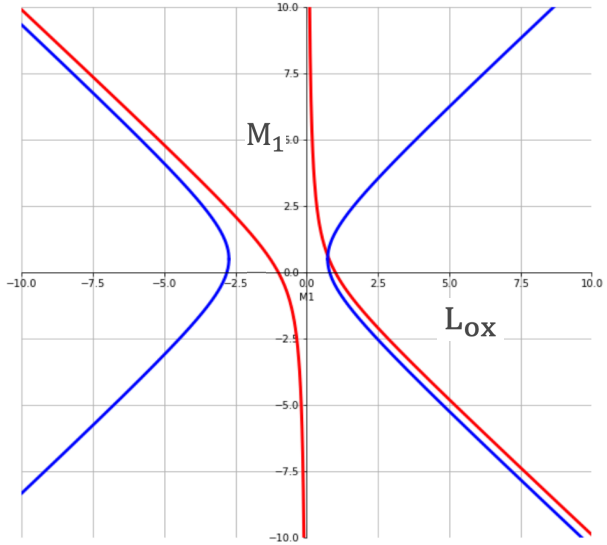


Figure 2

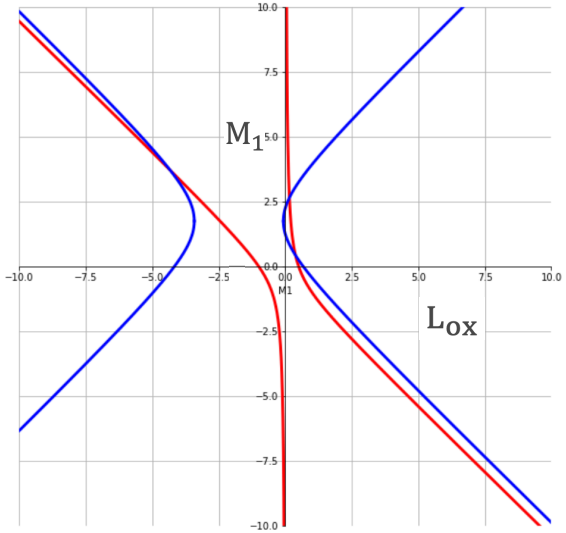


Figure 3

COMPLETE MODEL ANALYSIS PLAN

I would like to get the obtained results for a full-fledged model. We are trying to do this with the parameter continuation method. We will implement this method in programs such as:

- Python is a programming language.

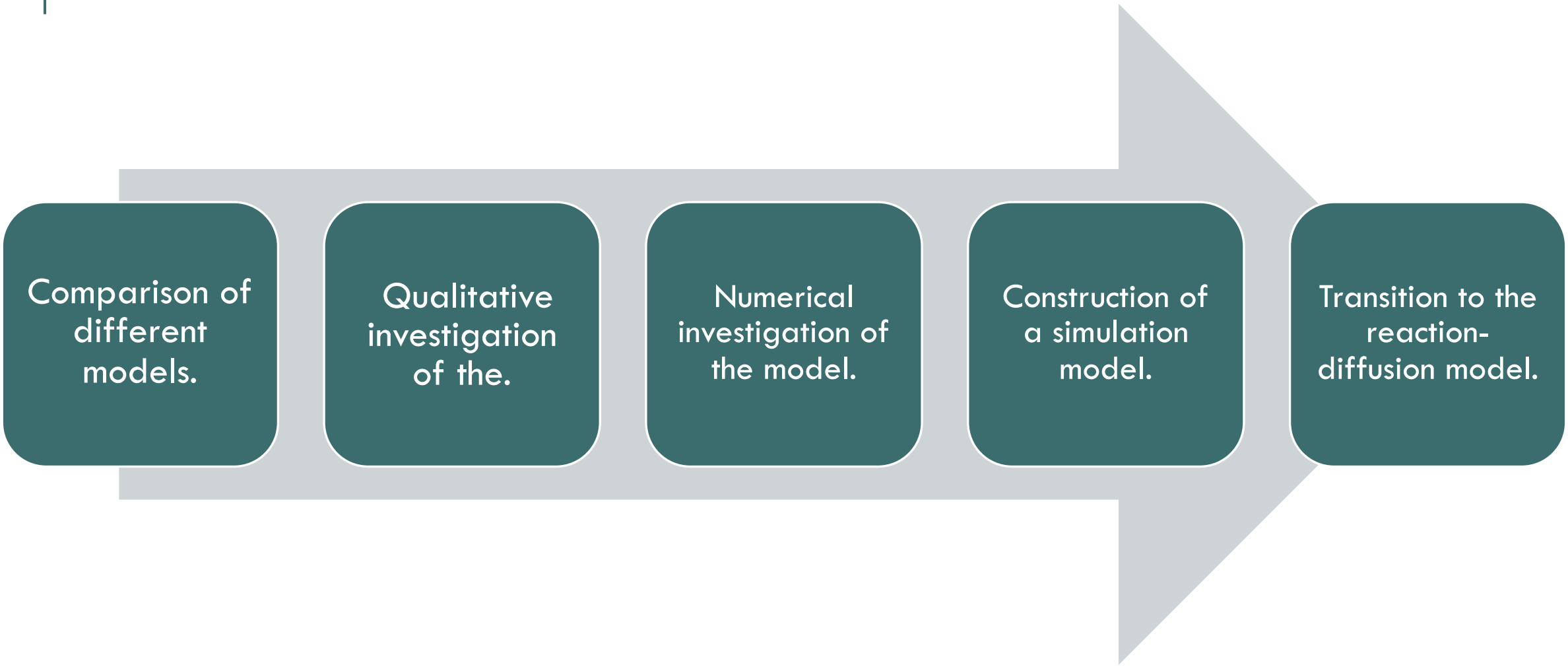
- XPPAUT is a tool for simulating, animating, and analyzing dynamical systems.

CONCLUSIONS

- We present a mathematical model of atherosclerosis development for the concentrations of cells and cytokines of innate immunity.
- The stationary points and their stability for reduced kinetic systems of two and five ODEs are investigated.
- Existence and stability of the equilibria of this model, depending on the level of cholesterol in blood and on other parameters, determine the development of atherosclerosis.
- The relationship of the obtained results is analyzed, and their biological interpretation is given.

CONCLUSIONS

PERSPECTIVES



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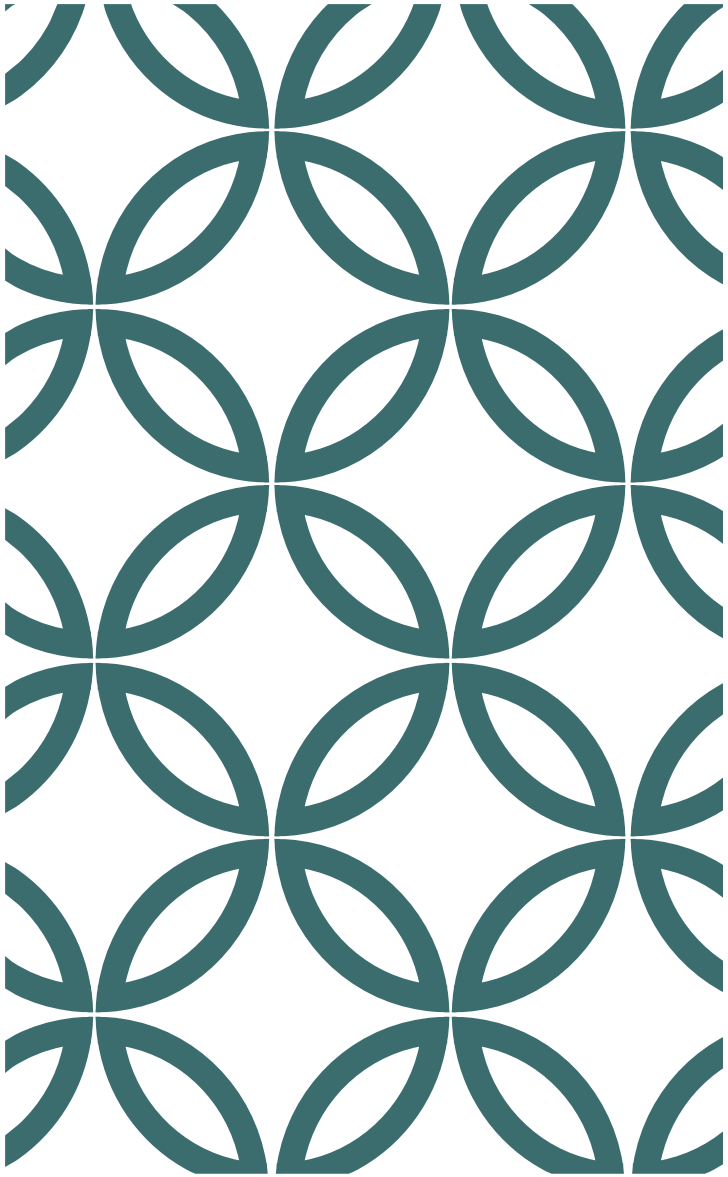
4. Friedman A., Hao W. A mathematical model of atherosclerosis with reverse cholesterol transport and associated risk factors, Bulletin of Mathematical Biology, 77, Issue 5, 2015, 758–781.



THANK YOU FOR ATTENTION