

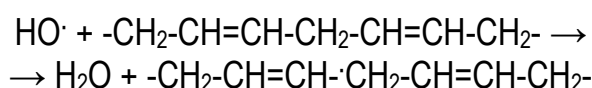
АНАЛИЗ И МОДЕЛИРОВАНИЕ НЕЛИНЕЙНЫХ ДИНАМИЧЕСКИХ ПРОЦЕССОВ

УДК 004

ALGORITHMIC SIMULATION IN STUDYING THE KINETICS OF LIPID PEROXIDATION**Anatole D. Ruslanov, Anton V. Bashylau***State University of New York, Fredonia, New York, USA*

The biochemical model we use is a set of chain reactions of lipid peroxidation, thus being a complex system of chemical interactions that includes the following stages:

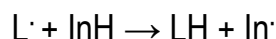
1. *Chain initiation.* During the interaction of a strong oxidizer with an unsaturated fatty acid, specifically with the $-\text{CH}_2$ -group in the α -position relative to the double bond, a hydrogen atom detaches from the bond, forming a free radical (mostly alkyl radicals) of a fatty acid ($\text{L}\cdot$). The free radicals such as hydroxyl radical $\text{HO}\cdot$ are the most frequent reagents capable of the separation of the hydrogen atom:



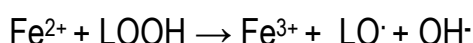
2. *Chain prolongation.* In an environment that contains oxygen, the oxygen molecule rapidly bonds to one of the carbon atoms with unpaired electrons, usually to the outermost carbon atom. Thus, the lipid peroxide radical ($\text{LO}_2\cdot$) is formed. The radical $\text{LO}_2\cdot$ readily takes the hydrogen atom from a neighboring unsaturated fatty acid forming a new lipid alkyl radical and, thereby, forming a chain reaction.

3. *Chain breaking.* The development of free-radical chain reactions is stopped by the reactions of chain breaking. This happens due to the disappearance of free radicals $\text{L}\cdot$ and $\text{LO}_2\cdot$, which directly contribute to the oxidation chain. In lipid-containing systems, the length of these chains can be tens or hundreds of links.

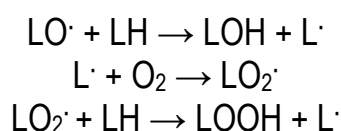
For the cells, the development of the oxidation chains is an undesirable phenomenon both because it leads to useless burning of valuable cell components and because some products of lipid peroxidation are toxic. In this regard, cells have a whole system of protection against peroxidation, in particular the antioxidants, which impede the oxidation chain reaction by breakage of chains:



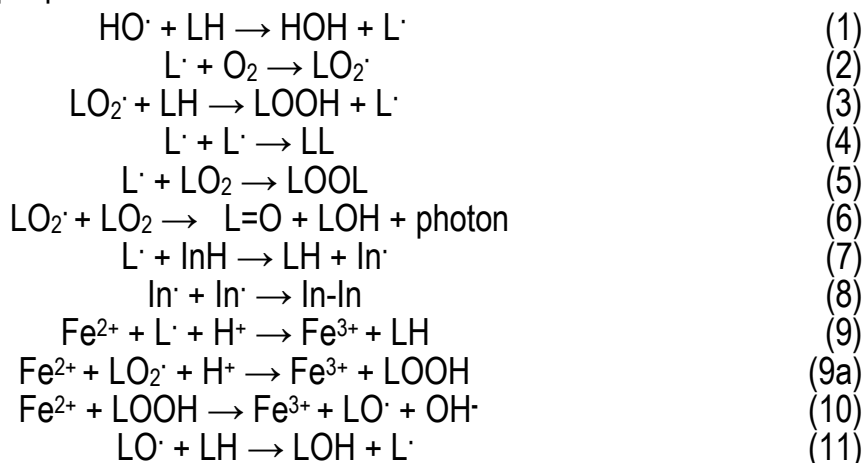
4. *Chain branching.* In most cases, Fe^{2+} cations have prooxidant properties, i.e., they do not suppress but rather reinforce the process of lipid peroxidation. This is because iron cations react with the peroxidation products—lipid hydroperoxides:



As a result, a new free lipid alkoxy radical $\text{LO}\cdot$ appears, which initiates the formation of a new oxidation chain:



The combination of chemical kinetics equations of the chain oxidation of lipids in the system iron (II)-ascorbate-dependent lipid peroxidation is as follows:



The system of differential equations that describes the process of lipid peroxidation is complex and the speed constants of most of these reactions are unknown. The system of chemical and, therefore, differential equations can be significantly simplified if we assume the following:

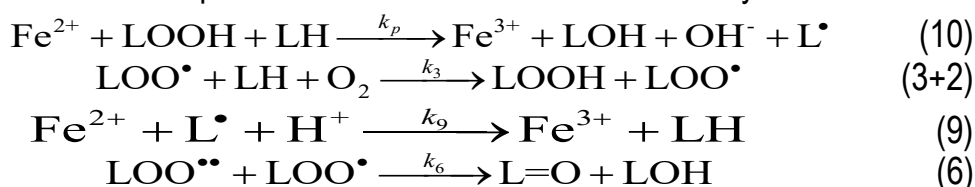
1: The speed of several consecutive reactions is equal to the speed of the slowest one. This allows replacing the sequential reaction with one generalized reaction, taking the speed constant of this reaction to be equal to the speed constant of the slowest of the successive reactions. In our case, the reactions 2 and 3 are sequential reactions. For our purposes, it is not important to consider which of the reactions should be considered the slowest. In an environment that contains oxygen, the rate of reaction 3 is many times lower than the speed of reaction 2, so the equation for the continuation of the chain reaction can be written as follows:



The rate constant of this reaction will be equal to the rate constant of reaction 3, which we denote as k_3 .

2: Among the several parallel reactions, the fastest one of the greatest importance. This permits us to simplify the above system of the eleven events. In the presence of molecular oxygen, the concentrations of radicals $\text{LO}\cdot$ and $\text{L}\cdot$ are much less than that of the radicals $\text{LOO}\cdot$; therefore reactions 4 and 5 can be neglected, leaving only the radical interaction reaction—the reaction 6. In the presence of ions Fe^{2+} in the environment and at low concentrations of other antioxidants, the reaction 7 can also be often ignored, leaving only the reaction 9. In addition, we shall not yet take into account the reaction 9a.

In the absence of other sources of free radicals, the formation of new radicals occurs only in the reaction 10 (the chain branching reaction). Let k_p denote the rate constant for this reaction. The reaction 1 can be neglected, if the source of the radical $\text{HO}\cdot$ does not exit. After all these simplifications, we obtain a system of chemical equations for LPO that contains a total of only four reactions:



The reactions 9 and 10 appear as trimolecular or as third order reactions. In the water environment, however, the concentration of H^+ is constant, and this value can be included in the constant for speed of k_9 . Therefore, we shall consider the reaction 9 as a bimolecular reaction with the second order rate constant k_9 . In addition, the concentration of oxidation substrate for LH within the membrane is sufficiently large and changes little over time; thus, the reaction 10 can also be assumed bimolecular (second order).

After this introduction, we write the kinetic differential equations that describe the speed for the particular lipid peroxidation chain reactions described above as follows:

$$v_3 - k_3[\text{LH}][\text{LOO}\cdot] \quad (11)$$

$$v_6 - k_6[\text{LOO}\cdot]^2 \quad (12)$$

$$v_9 - k_9[\text{Fe}^{3+}][\text{LOO}\cdot] \quad (13)$$

$$v_p - k_p[\text{Fe}^{2+}][\text{LOOH}] \quad (14)$$

The differential equations that describe the changes in the concentrations of the major participants in the above reactions, while taking into account the equations described above, can be written as follows:

$$\frac{d[\text{LOOH}]}{dt} = v_3 - v_p \quad (15)$$

$$\frac{d[\text{LOO}\cdot]}{dt} = v_p - v_6 - v_9 \quad (16)$$

$$\frac{d[\text{Fe}^{2+}]}{dt} = -v_9 - v_p \quad (17)$$

This final system of third order equations cannot be solved analytically, even after the simplifications made above. However, if the velocity constants and the initial concentrations of the reaction reagents are known, the changes in time for the concentrations of all participants in the reactions can be computed numerically using these equations, i.e., modeled algorithmically in a computational environment.

The easiest method for such modeling is of Euler and Cauchy, in which infinitesimal increments are replaced by sufficiently small increments and thus the integration is replaced by summation. The algorithm for computation is as follows:

1. The system of differential equations is reduced to its algebraic form, using infinitely small increments for the reagent concentrations and for time:

$$\Delta[\text{LOOH}] = (v_3 - v_p)\Delta t \quad (18)$$

$$\Delta[\text{LOO}\cdot] = (v_p - v_6 - v_9)\Delta t \quad (19)$$

$$\Delta[\text{Fe}^{2+}] = (-v_9 - v_p)\Delta t \quad (20)$$

2. The initial values for $[\text{LOOH}]$, $[\text{LOO}\cdot]$, and $[\text{Fe}^{2+}]$ are substituted into the right side of the equations. Specifying an infinitely small value for t , we compute the values $D_1[\text{LOOH}]$, $D_1[\text{LOO}\cdot]$, and $D_1[\text{Fe}^{2+}]$.

3. We find the values for the time $t_1 = 0 + t$:

$$[\text{LOOH}]_1 = [\text{LOOH}]_0 + D_1[\text{LOOH}] \quad (21)$$

$$[\text{LOO}\cdot]_1 = [\text{LOO}\cdot]_0 + D_1[\text{LOO}\cdot] \quad (22)$$

$$[\text{Fe}^{2+}]_1 = [\text{Fe}^{2+}]_0 + D_1[\text{Fe}^{2+}] \quad (23)$$

4. Based on the new values of the current concentrations of $[\text{LOOH}]$, $[\text{LOO}\cdot]$ и $[\text{Fe}^{2+}]$, we compute the new values for concentrations increments $D_2[\text{LOOH}]$, $D_2[\text{LOO}\cdot]$, and $D_2[\text{Fe}^{2+}]$.

5. We find values for the time $t_2 = t_1 + D_t$:

$$[\text{LOOH}]_2 = [\text{LOOH}]_1 + k_2[\text{LOOH}] \quad (24)$$

$$[\text{LOO}\cdot]_2 = [\text{LOO}\cdot]_1 + D_2[\text{LOO}\cdot] \quad (25)$$

$$[\text{Fe}^{2+}]_2 = [\text{Fe}^{2+}]_1 + D_2[\text{Fe}^{2+}] \quad (26)$$

6. Repeating the steps 4 and 5, we compute concentrations for the reagents in the lipid peroxidation reaction for any given time.

7. Finally, we compare the kinetic curves that are computed with the experimental data.

With some additional simplification of the system it is possible to reduce the system of differential equations to equations of the first order, which can be solved analytically. These simplifications, however, may deny the opportunity to construct a complete curve for the kinetics of the process, but may allow computation for small segments of the process, and more importantly may allow for better understanding of some features of these reactions.

The first simplification is based on the assumption that the speed of the particular reaction significantly exceeds the rate of the chain oxidation as a whole. The meaning of this assumption can be explained by analyzing the equation that describes the rate of change of the radical $\text{LOO}\cdot$ concentration:

$$\frac{d[\text{LOO}\cdot]}{dt} = k_p[\text{Fe}^{2+}][\text{LOOH}] - k_9[\text{Fe}^{2+}][\text{LOO}\cdot] \quad (27)$$

It follows from Equation 27 that the rate of appearance for the new radicals is determined by the difference in the velocities of the two particular reactions: the chain branching and the chain breaking. If we assume that the rate of the radical formation is significantly less than the speed of each of these particular reactions, then the right-hand side of the equation can be assumed to be equal to zero. Then

$$k_p[\text{Fe}^{2+}][\text{LOOH}] = k_9[\text{Fe}^{2+}][\text{LOO}\cdot] \quad (28)$$

The order of the system of equations is, thus, reduced by one unit. Such simplification, called the Bodenshteyn-Semionov stationary approximation, assumes long oxidation chains. It should be noted, however, that the main conclusion remains without the Bodenshteyn-Semionov approximation but requires a more complex mathematical computation.

Let us rewrite the expanded form of the equation using the Bodenshteyn-Semionov approximation:

$$k_p[\text{Fe}^{2+}][\text{LOOH}] = k_9[\text{Fe}^{2+}][\text{LOO}\cdot] \quad (29)$$

$$\frac{d[\text{LOOH}]}{dt} = k_3[\text{LH}][\text{LOO}\cdot] - k_p[\text{Fe}^{2+}][\text{LOOH}] \quad (30)$$

In addition to the concentrations of hydroperoxides and radicals, the equations include another variable, the concentration of Fe^{2+} . Therefore, in order to solve the system of equations, it is necessary to use very small time intervals in which the value of $[\text{Fe}^{2+}]$ does not change much and can be assumed to be constant with a known value in that segment of time. With this additional assumption, we can substitute the values $[\text{LOO}\cdot]$ from the first equation into the second and divide the variables:

$$\frac{d[\text{LOOH}]}{dt} = k_3[\text{LH}] \frac{k_p[\text{LOOH}]}{k_9} - k_p[\text{Fe}^{2+}][\text{LOOH}]$$

$$\frac{d[\text{LOOH}]}{dt} = \gamma[\text{LOOH}]$$

$$\frac{d[\text{LOOH}]}{[\text{LOOH}]} = \gamma dt$$

$$\text{where } \gamma = k_p \left(\frac{k_3[\text{LH}]}{k_9} - [\text{Fe}^{2+}] \right) \quad (31)$$

Integrating the last equations we get:

$$\int_{[\text{LOOH}]_0}^{[\text{LOOH}]} \frac{d[\text{LOOH}]}{[\text{LOOH}]} = \gamma \int_0^t dt$$

$$\ln \frac{[\text{LOOH}]}{[\text{LOOH}]_0} = \gamma t \quad (33)$$

The equations 31-33 imply that:

$$[\text{LOOH}] = [\text{LOOH}]_0 e^{\gamma t}$$

$$[\text{LOO}^\bullet] = [\text{LOO}^\bullet]_0 e^{\gamma t} \quad (34)$$

The last equation demonstrates that the hydroperoxide concentration in the system and the concentration of oxidation chains (which is equal to the concentration of the radicals that lead the chain) varies in time exponentially. Acceleration or deceleration of the reaction depends on the sign of the degree.

Existence of many antioxidant types with different mechanisms of action complicates determination of the antioxidant activity in biological systems. In this work, we used mathematical modeling for achieving algorithmic simulation to study the kinetics of iron (II)-ascorbate-dependent lipid peroxidation. We selected the minimum number of reactions, the combination of which allowed us to reproduce the phenomenology of the experiments. We then explored the mechanisms and characteristics of these active substances under various conditions, including theoretical predictions of their antioxidant behavior. Pursuing an understanding of antioxidant activity of medicinal substances of plant origin is important as many known diseases are associated with an oxidative stress, i.e., an impairment of antioxidant activity.

УДК 004

ПОДХОД К ЧИСЛЕННОМУ АНАЛИЗУ ЭЛЕМЕНТОВ РЭА

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В данной работе отражены два подхода к численному анализу теплового режима: метод начальных параметров и метод конечных элементов. Пользуясь методом абстрагирования, мы рассмотрим проводник, на который воздействует тепловое поле, и проведем аналогию с закрепленной балкой с воздействием сосредоточенных сил.

Расчет ведут для того, чтобы рассчитанные температурные характеристики теплового режима не превышали предельные допустимые нормы.

Метод начальных параметров

Необходимо определить прогиб проводника с 3 опорами (рис. 1) с приложенной сосредоточенной силой F и находящимися на расстоянии $-x$ и $+x$ силами $F/2$, эквивалентными тепловому воздействию на участке $[L_2-x, L_2+x]$.