CHEMICAL ENGINEERING TRANSACTIONS
VOL. 71, 2018
A publication of AIDIC
The Italian Association of Chemical Engineering
Online at www.aidic.it/cet
Guest Editors: Xiantang Zhang, Songrong Qian, Jianmin Xu

ISBN 978-88-95608-68-6; **ISSN** 2283-9216
DOI: 10.3303/CET1871148

Application of Differential Equations in Enzyme Kinetics

Caihong Fan [a], Ping Li [a], Yingzhen Xue [b]

[a] Key Laboratory for Soil Modification and Comprehensive Utilization of Mineral Soil of Inner Mongolia Autonomous Region, Jining Normal University, Inner Mongolia 012000, China
[b] Xi'an International University, Shaanxi 710077, China
caihongfan2933@163.com

This paper discusses the application of simplified differential transformation method in the solution of nonlinear differential equations and the application of characteristic set method in the analysis of enzyme dynamic system. It can be found through the solution of the Burgers equation and other evolution equations that RDTM is a more accurate and efficient method than ADM, VIM, and DTM. When seeking the approximate solution of an equation through RDTM, there is no restriction required, such as disturbance technique, linearization or discretization. Under the assumption that the initial concentration of the enzyme is much larger than that of the matrix, the nonlinear equation sets of the reaction system are transformed into linear equation set and then the dsolve command of the computer algebra software MAPLE is used for the solution, obtaining the time-varying functional relationship between concentration of matrix s, the product P and composite c and the rationality of this method is illustrated by an example drawing.

1. Introduction

Since the end of the 19th century, many scholars have studied the enzymic catalytic reaction and want to use mathematical knowledge to explain the reaction process. Some scholars believe that compound can be formed in the catalytic reaction and the reaction can be expressed by expressions. In the research of enzyme kinetics, some researchers have applied the steady state concept to explain the characteristics of enzyme kinetics. The nonlinear fireworks equation has wide application value in engineering, physics and other fields, and can express parameter relation through analytical solutions. For example, in the study of mechanics, physics or biology, nonlinear equations can be used to solve problems. In the study of enzyme kinetics, the nonlinear problem can be solved by differential transformation method and the related characteristics of enzyme dynamics can be expressed by differential equations.
Based on this, this paper mainly studies the application of the solution and characteristic set method of enzyme kinetics and nonlinear evolution equations in the analysis of unstable enzyme kinetic system and analyzes the application effect of the differential method.

2. Literature review

Since the end of the 19th century, many scholars have studied enzymic catalytic reactions, and they want to expound the reaction process with mathematical knowledge. Link et al. believed that the enzymic catalytic reaction can generate compounds, and the reaction process can be expressed with expressions (Link et al., 2014). In the study of enzyme kinetics, some researchers have applied the concept of steady state to explain the characteristics of enzyme kinetics.
Kinetic models are essential for quantitatively understanding and predicting how functional behavior arises from changes in the dynamic concentration of cell components. In the past 100 years, deterministic rate equations have been successfully used to infer the enzymatic reaction mechanism and estimate the rate constants of the reaction kinetics experiments conducted in vitro. In recent years, sophisticated experimental techniques have been developed that begin to allow the measurement of enzymatic and other biopolymer mediated reactions within a single cell at the single-molecule level (Grima et al., 2014). Vogt used the homotopic perturbation method to extend the approximate analytic solution of the nonlinear reaction equation

Please cite this article as: Fan C., Li P., Xue Y., 2018, Application of differential equations in enzyme kinetics, Chemical Engineering Transactions, 71, 883-888 DOI:10.3303/CET1871148

describing enzyme kinetics, in which the solution obtained by the parameter combination in previous work was invalid. In addition, by constructing new homotopy, approximate analytical expressions of substrate, substrate - enzyme compound and product concentration were found. These first-order approximation solutions provide more accurate results than the second-order approximate value obtained in previous work (Vogt, 2013). Double substrate enzyme kinetics plays a leading role in product quantification and optimization in different chemical and biochemical fields. The mathematical method of controlling these reactions at different stages through appropriate parameters added new content to this interdisciplinary research field. Roy and Ghosh developed a two-matrix mathematical model of the enzymatic kinetic reaction system with control measures to observe the effects of these measures on the concentration changes of substrates, enzymes, compounds and final products (Roy and Ghosh, 2013). Abbreviated expression of enzyme kinetic expression, such as the Michaelis-Menten (M-M) equation, is based on the premise that the enzyme concentration is lower compared to the substrate and product. The idealization of the condition is violated when the solute is consumed to form a series of products during the conversion process (Bassingthwaighte and Chinn, 2013). The Michaelis-Menten equation is usually used to estimate the kinetic parameters V and KM. Schnell provided a critical review of the validity criteria for the steady-state hypothesis after a brief overview of the Michaelis-Menten equation for single-enzyme and single-substrate reactions. The application of the steady-state hypothesis implicitly assumes that there is an initial transient, during which the substrate concentration remains approximately constant, equal to the initial substrate concentration, and at the same time the concentration of enzyme - substrate compound increases. This implicit assumption is called the reactant static hypothesis. Schnell provided evidence that the reactant static hypothesis is different from the steady state hypothesis and independent of the steady state hypothesis. Contrary to the widely held view that the Michaelis-Menten equation can always be applied under the steady-state hypothesis, the reactant stabilization hypothesis is indeed a necessary condition to estimate the validity of the dynamic parameters of the Michaelis-Menten equation. Therefore, the application of the Michaelis-Menten equation only leads to an accurate estimation of the kinetic parameters when it is used under experimental conditions satisfying the reagent static assumptions. The validity criteria for the reagent static assumption don't require the limiting condition of selecting substrate concentrations well above the enzyme concentration in the initial rate experiment (Schnell, 2014). Alarcon proposed two methods: in the random model of enzymatic catalysis regulation, the quasi-stationary approximation was performed based on the asymptotic property of WKB of the chemical principal equation or the corresponding partial differential equation of the generation function (Alarcón, 2014). Covalent inhibition is a reoccurring example of kinase drug design, but the role of inhibitor binding affinity and chemical reactivity in overall efficacy is unclear. To characterize potential molecular processes and determine appropriate kinetic constants at the micro level, Schwartz et al. developed special experimental designs and advanced numerical integrals of differential equations. These methods, parameters and insights provided a reasonable framework for evaluating and designing effective covalent inhibitors (Schwartz et al., 2014). Wang et al. established the monolignol biosynthesis pathway of predictive kinetic metabolism - flux model of 21 enzymes and 24 metabolites with the secondary differentiated xylem of western balsam poplar (Wang et al., 2014). Weaver et al. developed a conventional differential equation model for the heterologous mevalonate pathway in escherichia coli with kinetic parameters screened from the literature and enzyme concentration derived from selective reaction monitoring mass spectra (srm-ms) (Weaver et al., 2015).

To sum up, there are various calculation models of enzyme kinetics, but none of them can be widely accepted and widely used. And the nonlinear evolution equation has wide application value in engineering, physics and other fields, and can express parameter relations through analytical solutions. For example, in the study of mechanics, physics or biology, nonlinear equations can be used to solve problems. In terms of enzyme kinetics research, the nonlinear problem can be solved with differential transformation method, and the characteristics of enzyme kinetics can be expressed with differential equation. Based on this, the application of the solution of enzyme kinetics and nonlinear evolution equations, and characteristic methods in the analysis of unstable enzyme dynamic systems are discussed, and the application effect of differential methods is also analyzed.

3. Method

3.1 Enzyme Kinetics

Enzymes are the basis of life activities. Enzymes are involved in almost all chemical reactions in organisms and the metabolic system is a complex system of many anabolic and catabolic reactions under the catalysis of enzymes. The development and growth of organisms are inseparable from the catalytic action of enzymes. The relationship between enzymes and life is so close that the origin of life is closely related to enzymes and the origin of life is a most important issue in modern biological research. Therefore, the in-depth study of enzymes is of great biological significance. The enzyme is a biocatalyst, which is a substance that can

accelerate the chemical reaction. Each chemical reaction involves three aspects: direction, extent and speed, of which the direction and extent are determined by the intrinsic properties of the reaction while the speed of the chemical reaction is not only related to the internal factors, but affected by external conditions. In a chemical reaction, the catalyst is an external substance that accelerates the reaction. However, it cannot change the direction and extent of the reaction and itself will not change at the end of the entire chemical reaction.

The main discussion in enzyme kinetics is the speed of the catalytic reaction. By analyzing the influence of various conditions on the reaction speed, the changing process of various substances in the reaction is explained. Enzyme kinetics play an extremely important role in biology, chemistry and especially in enzymology. For example, the mechanism of the enzymatic reaction can be judged by referring to the influence of some factors on the speed of the enzymatic reaction. For another example, to accurately determine the enzyme activity unit (since most enzyme preparations are not pure enzymes, and the enzyme is biologically active, so it will gradually lose its activity during storage; also, the molecular weight of some enzymes is unknown; considering these factors, the weight or molar concentration method is not used in the accurate expression of enzyme amount, but the enzyme activity unit. The enzyme activity unit, referred to as the enzyme unit, refers to the amount of conversion from the substrate or the amount of new substance produced under specific conditions. That is to say, the amount of enzyme is measured by its catalytic ability, so it is necessary to explore the optimal condition and the role of various factors in the reaction.

3.2 Solution of Nonlinear Evolution Equations

When the RDTM is used to solve nonlinear evolution equations, it has small quantity of and simple computation. It can be seen from Table 1 that RDTM is more accurate and efficient than other methods.

Table 1: Absolute error of 5 items of DTM and RDTM when c= port =1

x	t	ADM	VIM	DTM	RDTM
	0.06	0.05987378635	0.05987378626	0.05987378634	1.796843937E-11
0.1	0.1	0.0997089993	0.0997089995	0.0997089991	2.56E-10
	0.8	0.7584451973	0.7584451965	0.7584451976	9.5653E-6
	0.06	0.0613753250	0.0613753252	0.0613753250	1.2437015E-11
0.5	0.1	0.0988444913	0.0988444900	0.0988444911	1.09900641E-9
	0.8	0.7227917001	0.7227917005	0.7227917003	2.41296538E-4
	0.06	0.0765880976	0.0765880983	0.0765880986	1.0014064E-10
0.9	0.1	0.1087949671	0.1087949656	0.1087949660	8.358282E-10
	0.8	0.6496835430	0.6496835435	0.6496835450	2.71475306E-4

Table 2 shows the absolute errors when using the ADM, VIM, DTM and RDTM methods. It can be seen that RDTM is a more accurate and efficient method than the other methods. In fact, the quantity of computation is smaller and it is easier to us RDTM to transform the equation into a single-parameter recursive equation and solve this nonlinear evolution equation than other methods.

Table 2: Absolute error when using ADM, VIM, DTM and RDTM at α=1

x	t	ADM	VIM	DTM	RDTM
	0.01	0.008803235	0.008803231	0.008803245	1.434147934E-9
0.1	0.02	0.016678387	0.01 6678563	0.01 6678577	7.285421E-10
	0.03	0.023529025	0.02352903l	0.023529052	1.125179E-6
	0.01	0.008733634	0.008733636	0.008733649	1.55624E-9
0.5	0.02	0.016761753	0.016761763	0.016761773	6.77725E-11
	0.03	0.026998267	0.026998266	0.026998273	4.354038E-10
	0.01	0.038472762	0.038472758	0.03 8472760	0.000000
0.9	0.02	0.066834273	0.066834286	0.066834281	1.4916725E-9
	0.03	0.099889920	0.099889915	0.099889920	7.74011E-11

3.3 Application of Characteristic Set Method in the Analysis of Unstable Enzyme Dynamic System

The computer algebra technology is used to solve the very complex algebraic expressions encountered in the analysis of enzyme system. The computer algebra system is a powerful mathematical software that can replace traditional manual calculation. In addition, computer algebra systems can implement more powerful symbolic calculation function, drawing the image of two- or three-dimensional functions and writing specific

programs. When facing complex calculation results, in order to reduce the workload, the approximate number such as rounding off is usually adopted in manual calculations. Therefore, the calculated results are not accurate while symbolic calculation just overcomes this deficiency. Nowadays, computer algebra system has been widely used and recognized by many scientists, engineers and mathematicians. More and more computer algebra software has also emerged, such as MAPLE, MACSYMA, REDUCE, SCRATPAD and so on. Although the internal system structure of these software varies widely, they have identical attributes. The enzymatic kinetics reaction in the simplest case is considered in this paper, which is the enzymatic kinetics reaction of a single matrix and a single product.

4. Result Analysis

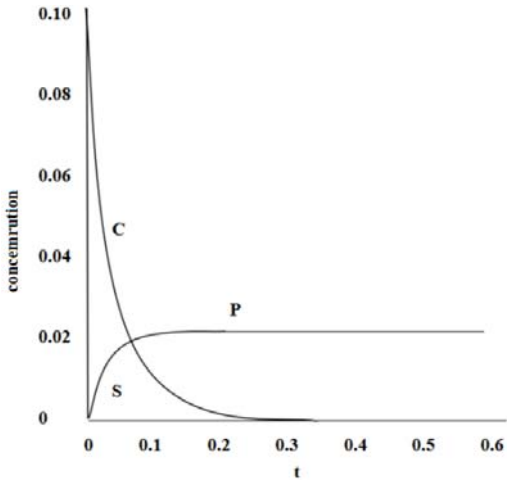

Figure 1: changing process of the concentration

Figure 1 shows the whole changing process of the concentration of the matrix S, the product P and the complex C starting from t=0. It can be intuitively seen that the concentration of complex C decreases with time to 0; the concentration of product P increases with time until remaining consistent at a certain constant; and the concentration of matrix S decreases significantly to 0. In fact, this situation is not consistent with the reality, because at the very beginning of the reaction, the composite C is unlikely to be the most, but should be 0. Also, the description of the matrix S is not obvious. Therefore, the time is further divided and the following graphs are drawn. A series of graphs in time have accurately described the relationship between several substances over time.

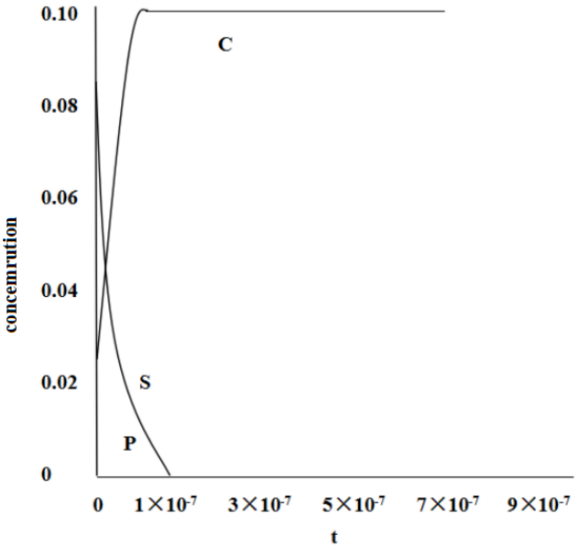

Figure 2: the concentration of three substances

Figure 2 shows the concentration of three substances over time in 0-9×10-7(s) and it can be seen that the concentration of matrix s decreases rapidly from the initial value of 0.1 to 0, and then remains unchanged; the concentration of compound c rapidly increases from the initial value of 0 to 0.1 and then remains unchanged; and for the product p, there is almost no change in the concentration at this stage, the concentration value of which is close to zero.

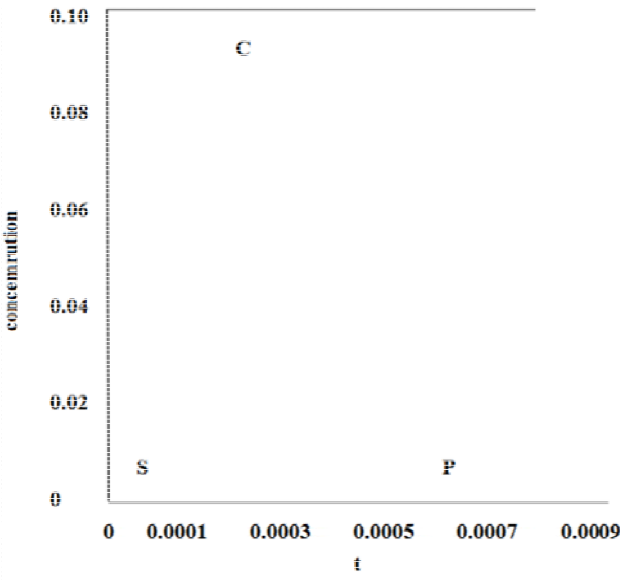

Figure 3: the time period of 9×10-7-9×10-4(s)

Figure 3 shows the time period of 9×10-7-9×10-4(s) and it can be seen that there is no significant change of the concentration of the matrix S and the product P during this time period, the concentration value of which is almost 0; The concentration of compound c decreases slightly with time.

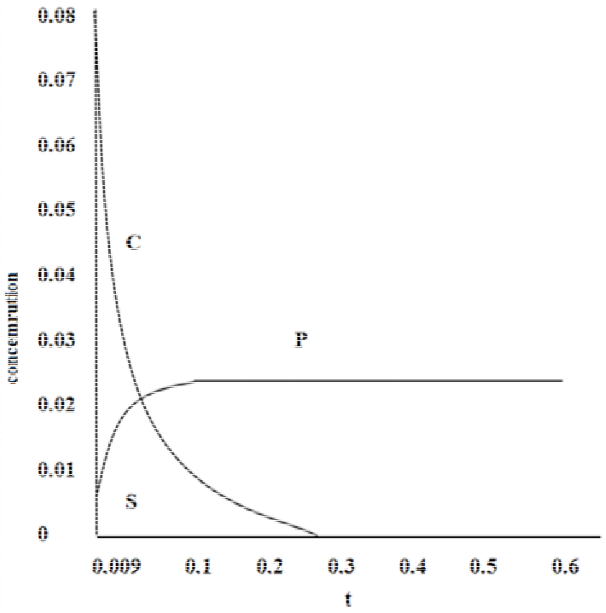

Figure 4: the time period after9×10-3(s)

Figure 4 shows the time period after9×10-3(s) and the Figure is basically consistent with Figure 1, reflecting the concentration of the three substances over time in the later stage of the reaction. It is obvious that the

relationship between the concentration of three substances described in these Figures is consistent with the reality, which demonstrates the rationality of the method used in this paper.

5. Conclusion

Complex algebraic expressions are often encountered in the analysis of enzyme kinetics system, even in simple enzyme kinetics system. If the traditional calculation method is used to perform the inferential calculation, it will take too much time and effort. Computer algebra is a powerful technique that helps us deal with such complex expressions.

The theory of computer algebra technology and enzyme dynamics system can be used to obtain the analytical solution of ordinary differential equation system, which describes the characteristics of the simplest enzyme dynamic system. The nonlinear enzyme dynamic system is transformed into a linear system under the condition that the initial concentration of the enzyme is much larger than the substrate concentration, and the Maple software is used for the solution.

Acknowledgments

This work was partially supported by the National Natural Science Foundation of Inner Mongolia Autonomous Region (No. 2017MS0117 and No. 2017MS0213). Supported by shaanxi education science "13th five-year plan" project (No.SGH18H544).Supported by Xi 'an International university seven party education research institute bidding project in 2018 (No.18qfy110), Supported by shaanxi province higher education society 2017 higher education scientific research project (No.XGH17208).

Reference

Alarcón T., 2014, Stochastic quasi-steady state approximations for asymptotic solutions of the chemical master equation, Journal of Chemical Physics, 140(18), 05B609_1, DOI: 10.1063/1.4874653

Bassingthwaighte J.B., Chinn T.M, 2013, Reexamining michaelis-menten enzyme kinetics for xanthine oxidase, American Journal of Physiology Advances in Physiology Education, 37(1), 37-48, DOI: 10.1152/advan.00107.2012

Grima R., Walter N.G., Schnell S., 2014, Single‐molecule enzymology à la Michaelis–Menten, The FEBS journal, 281(2), 518-530, DOI: 10.1111/febs.12663

Link H., Christodoulou D., Sauer U., 2014, Advancing metabolic models with kinetic information, Current opinion in biotechnology, 29, 8-14, DOI: 10.1016/j.copbio.2014.01.015

Olaiju O.A., Hoe Y.S., Ogunbode E.B., Fabi J.K., Egba E.I., 2018Achieving a Sustainable Environment using Numerical Method for the Solution of Advection Equation in Fluid Dynamics, Chemical Engineering Transactions, 63, 631-636, DOI: 10.3303/CET1863106

Roy P.K., Ghosh M.K., 2013, Modeling of a control induced system for product formation in enzyme kinetics, Journal of Mathematical Chemistry, 51(10), 2704-2717. DOI: 10.1007/s10910-013-0232-x

Schnell S., 2014, Validity of the Michaelis–Menten equation–steady‐state or reactant stationary assumption: that is the question, The FEBS journal, 281(2), 464-472, DOI: 10.1111/febs.12564

Schwartz P.A., Kuzmic P., Solowiej J., 2014, Covalent EGFR inhibitor analysis reveals importance of reversible interactions to potency and mechanisms of drug resistance, Proceedings of the National Academy of Sciences, 111(1), 173-178, DOI: 10.1073/pnas.1313733111

Vogt D., 2013, On approximate analytical solutions of differential equations in enzyme kinetics using homotopy perturbation method, Journal of Mathematical Chemistry, 51(3), 826-842, DOI: 10.1007/s10910-012-0121-8

Wang J.P., Naik P.P., Chen H.C., 2014, Complete proteomic-based enzyme reaction and inhibition kinetics reveal how monolignol biosynthetic enzyme families affect metabolic flux and lignin in Populus trichocarpa, The Plant Cell, tpc-113, DOI: 10.1105/tpc.113.120881

Weaver L.J., Sousa M.M., Wang G., 2015, A kinetic‐based approach to understanding heterologous mevalonate pathway function in E. coli, Biotechnology and bioengineering, 112(1), 111-119, DOI: 10.1002/bit.25323