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To cite this article: Néstor Torres & Guido Santos (2017) A simple simulator to teach enzyme kinetics dynamics. Application in a problem-solving exercise, Higher Education Pedagogies, 2:1, 14-27, DOI: 10.1080/23752696.2017.1307693

To link to this article: https://doi.org/10.1080/23752696.2017.1307693

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Published online: 12 Apr 2017.

Article views: 5851

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A simple simulator to teach enzyme kinetics dynamics. Application in a problem-solving exercise

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ABSTRACT
Enzyme kinetics is an essential part of biochemistry programs, which have been gaining importance in recent years for their applications in biotechnology and biomedicine. The teaching and learning of these issues has been traditionally hampered by difficulties that stem mainly from the dynamic and mathematical nature of the topic and the introduction of some abstract concepts. In this paper, we propose a simple, home-made application developed in Excel or, alternatively, in Libre Office (SIMENKIN), which allows students to view and interact with the dynamics of enzymatic reactions. The contribution of this specific application stems from the simulation of substrate loss and the associated initial rate of the enzyme catalysed reaction over time, which is not always incorporated into these packages. We illustrate its use applying it in a practical problem-solving approach module, designed to facilitate the learning of the fundamental concepts of enzyme kinetics.

1. Introduction
The teaching of enzyme kinetics has been a central, unavoidable part of biochemistry courses for almost 40 years. In fact in the last decade, the topic of enzymology has become increasingly relevant in several active fields of research (Dick & Burns, 2011; Khosla, 2000; Murakami, Kikuchi, Hisaeda, & Hayashida, 1996). These range from the development of genetic techniques to produce artificially modified enzymes, where the precise determination of kinetic parameters is critical to quantifying small differences in activity between mutant forms, to the development of new drugs and pesticides, to name just a few.

This subject is based on the well-known Michaelis–Menten model that describes the dynamics of enzyme-catalysed reactions (Henri, 1903; Johnson, & Goody, 1913) and the subsequent development in the case of allosteric enzymes showing cooperativity (Koshland, Némethy, & Filmer, 1966; Monod, Wyman, & Changeux, 1965). Accordingly, great attention has been paid to the presentation of this subject in biochemistry texts (Cook & Cleland,
2007; Cornish-Bowden, 2004; see also the textbooks Berg, Tymoczko, & Stryer, 2012; Nelson & Cox, 2013) and many methods to teach it either in the classroom or in the laboratory have been proposed (Barbarić & Ries, 1988; Buckley, Blackwell, Dunn, & Hill, 1990; Hutchinson, Bretz, Mettee, & Smiley, 2005; Levashov & Ryabov, 1986; Rain-Guion & Chambon, 1982).

For an enzyme-catalysed reaction the simplest mechanism can be written as:

\[
E + S \xrightleftharpoons[k_{-1}]{k_1} ES \xrightarrow[k_2]{k_{-2}} E + P
\]

where \( k_1 \) and \( k_{-1} \) are rate constants for the forward and reverse reactions between substrate and enzyme, respectively, and \( k_2 \), the turnover number. The aim of the enzyme kinetics model obtained under steady-state conditions is to estimate the values of \( K_m \) and \( V_{\text{max}} \) by assigning sets of initial reaction rate and substrate concentration to the Michaelis–Menten equation:

\[
V_0 = \frac{V_{\text{max}} \cdot S}{K_m + S}
\]

In this equation, \( V_0 \) is the initial rate at substrate concentration \( S \), \( V_{\text{max}} \) is the maximum, limiting rate at saturating substrate concentration and \( K_m \) is the Michaelis constant.

The Michaelis–Menten model also allows mathematical representation of the mechanisms involved in reversible inhibition, where a chemical interacts with the enzyme through noncovalent association/dissociation reactions. Reversible inhibitors fall into two major categories: competitive and non-competitive, and the effect is represented by the inhibition constant \( K_i \) or \( K_i' \), respectively.

\[
V_0 = \frac{V_{\text{max}} \cdot S_0}{((1 + I/K_i) \cdot K_m + (1 + I/K_i') \cdot S_0)}
\]

Another type of enzyme kinetics is what is observed when the binding of one molecule of the substrate to the enzyme protein molecule makes it easier for additional substrate molecules to bind to the same protein molecule, a phenomenon known as cooperativity. In these cases, the rate vs. substrate concentration plots yield S-shaped curves rather than rectangular hyperbolas, indicating that the rate depends on \([S]^n\), where \( n > 1 \).

\[
V_0 = \frac{[S_0]^n}{(K + [S_0]^n)}
\]

In the above equation \( K \) is the dissociation constant of the process \( E + nS \xrightleftharpoons{K_m, V_{\text{max}}} ES_n \), and \( n \) is the Hill coefficient.

Anyone who has been confronted with teaching enzyme kinetics to undergraduate students knows what a daunting task lies ahead. Students must deal with kinetic constants such as \( K_m, V_{\text{max}} \) and turnover numbers based on rate constants (Anderson, Crossley, & Grayson, 1999; Ochs, 2000). The abstract nature of the underlying model and the ‘static’ presentation of the mathematical formulae (where time is not explicit) are natural difficulties in teaching this subject, which is further complicated by the somewhat enigmatic relationship between reaction rate and substrate concentration. This all together makes the subject difficult to comprehend and apply for many students.

There is one important aspect of the Michaelis–Menten kinetics model that very often goes unnoticed – the fact that \( V_0 \) in Equations (1)–(3) represents the rate of the reaction at the exact and unique value of \( S_0 \) that is at the very initial conditions. However, since the initial value of substrate in a typical enzymatic assay is not constant, the value of \( V_0 \) is always changing as well. Accordingly, the true meaning of \( S_0 \) and \( V_0 \) as initial substrate and reaction...
rate are very often misleading and students tend to consider these values as constant. In addition, Equations (1)–(3) do not allow a direct calculation of the change of the substrate concentration over time and how this change affects the rate of the equation. On the other hand, in spite of the fact that the integration of Equations (1)–(3) to determine the values of the rate and substrate concentration is essential to many applications in biotechnology and biomedicine, little attention has been paid to the development of strategies to practically teach these particular issues.

In this work we introduce a problem-solving module for the learning of the basic principles of enzyme kinetics. The module was designed to prepare students to relate the content of the enzyme kinetics lessons to a real world situation, and solving a given problem through activities and investigations based on the theories, concepts and principles that they have previously learned. This learning strategy helps to develop problem-solving skills through practice and students are trained to have thinking skills, being able to justify with proofs and find alternatives solutions (Browne & Keeley, 1990). Also, through this method, students are prompted actively to be involved in the search of the solution while teachers act as a facilitator in the construction of their knowledge (Woods, 1985).

In this trend towards the student to become active learners, the computer has played an important role (Downie & Alexander, 1989; McDermott, 1985; Rivers & Vockell, 1987) and there is ample evidence on the positive perception to the computer assisted learning practices (Apostolides, 1987; Whiting, 1986) by the students. Although based on models of the behaviour of biological entities, an attempt like the one presented here is intended as simulations. There are many assays that are hard for students to carry out, or concepts that are difficult for the teacher to illustrate practically. The value of the computer software here is that it can be used to overcome these restrictions so that some concepts that might be excluded, or are dealt unsatisfactorily can be explored by the students.

In this line, we have designed a simple, home-made spreadsheet application (developed in Excel or in LibreOffice) called SIMENKIN (that stands for Simulation of Enzyme Kinetics), which allows students to visualise and interact with the dynamics of enzymatic reactions. SIMENKIN allows the simulation of substrate loss and the associated initial rate of the enzyme catalysed reaction over time, a feature not always incorporated into these packages. To illustrate its use, we have prompted our students to use it in a practical problem-solving exercise, where application of the fundamental concepts of enzyme kinetics is required.

2. SIMENKIN: software for the practical application of enzyme kinetic concepts

Currently there are sound reasons for using inexpensive microcomputers as an educational resource in biochemistry. SIMENKIN is an open, free, simple and easy to operate tool that can be easily adapted to specific needs and run on any laptop. With SIMENKIN, any student can use a microcomputer as a personal tutor to learn to appreciate the qualitative and the quantitative relationships between substrate concentration and rate of enzyme-catalysed reactions. The main novelty of this programme is that it allows a monitoring of substrate loss over time under different biological conditions something that is not implemented in the usually available programs for enzyme kinetics simulation.

The most important and distinctive characteristics of SIMENKIN are that it allows the user to: (i) observe how initial rate \( V_0 \) changes with time as the initial concentration of
substrate \((S_0)\) is consumed. This is particularly relevant to help students understand the meaning of initial rate, a concept that very often is not truly demonstrated in the teaching of this topic. (ii) It also allows the user to visualize the substrate consumption over time as the reaction occurs. This is a feature not included in currently available programs for the teaching of enzyme kinetics. These two novel features allow students to explore and visualize the dynamics of substrate, product and reaction rate. (iii) The programme allows the user to modify the enzyme kinetic parameters and initial conditions of a given enzyme assay. This constitutes an additional advantage of SIMENKIN as the user can identify, in the different plots, the effects of \(S\), \(V_{\text{max}}\), \(K_m\), \(K_i\), \(K\) and the Hill exponent within the time course of an enzymatic assay and (iv) The spreadsheet shows the classical hyperbolic \(V_{\text{0}}\) vs. \(S_0\) plot and the double inverse Lineweaver–Burk plot Lineweaver and Burk (1934).

SIMENKIN can be easily implemented in Excel and/or LibreOffice and it can be provided to students as a .xlsx or .odt file. The programme has two differentiated modules and is presented in separate sheets. The spreadsheet file is freely available at https://figshare.com/articles/SIMENZKIN_biochemistry_seminar_xlsx/4264988 (see also Supplementary Materials).

The first one is a linear regression module that permits taking the slope and intercept of the Lineweaver–Burk plot for a given set of data. This module is designed to operationalise the kinetic characterisation of an enzyme. Students are confronted with the task of translating the raw experimental data of initial rate and substrate concentration into kinetic parameters. The linear regression module allows the input of initial velocity and substrate concentration data taken from an enzyme-catalysed assay. The plot slope and the intercepts at the two given axes provide information about the kinetic parameters of the enzyme, once the treated Lineweaver–Burk plot data are introduced (Figure 1). This module shows students how, in spite of some unavoidable experimental errors, \(K_m\) and \(V_{\text{max}}\) can be determined and how these parameters relate with the experimental conditions. Since they can give an almost instant output from the data input, they get a direct impression of the impact of the experimental measurements on the kinetic parameters.

Provided with the concrete values of \(K_m\) and \(V_{\text{max}}\) they are able to run the second module, the enzyme kinetics simulator. This module (Figure 2) is used to make simulations of enzyme-catalysed reactions once the kinetic parameters of the enzyme \((K_m\) and \(V_{\text{max}}\) but also \(K_i\) and the Hill exponent) and the experimental conditions, such as initial concentration of substrate and concentration of inhibitor, are introduced. This application module is provided with four panels (see Figure 2). In the first one (Panel 1), you can see how the concentration of substrate (initially, \(S_0\)) varies as it is consumed while the product concentration increases \((P)\). The initial rate \((V_0)\) changes can also be observed as the reaction progresses, thus visualising the effect of the decreasing initial substrate concentration on the initial reaction rate (Panel 2).

Panel 3 and 4 are complementary to the previous ones. Panel 3 shows the classical Michaelis–Menten plot \((V_0\) vs. \(S_0\)) and Panel 4, the corresponding Lineweaver–Burk plot. In all panels, up to two different times courses are shown, for the sake of comparison.

The programme shows the substrate concentration, product concentration and initial rate in the case of reactions catalysed by inhibited enzymes under different circumstances (competitive, non-competitive and uncompetitive inhibitors) and in cases of cooperativity. Since the programme allows the user to modify the data and to simulate the assay’s output
for different experimental settings, the student can recognise and observe, in the different plots, the effect of changing conditions on the time course of the reaction.

In settings like this, there is always the risk that students merely punch numbers into the spreadsheet without a real understanding of the equations that drive the outputs. In order to prevent this, the underlying equations (both for un-inhibited and inhibited conditions) are shown on the same sheet where the dynamics of the variables are represented. Thus, students can directly interpret and associate the observed result with the underlying equations and parameters.
Furthermore, in the first part of the practical session (Activity 1, see following section), students are presented with a short review of the fundamentals of the Michaelis–Menten enzyme kinetics model and equations. At this point, special emphasis is given to the fact that the parameters that characterise an enzyme are directly related to the Michaelis–Menten model, and therefore must be interpreted in this context.

3. A case study for the application deployment: design of an enzyme-based biomedical protocol

The main purpose of this exercise is to use SIMENKIN to help students understand and visualise some dynamic aspects of enzyme-catalysed reactions that are not directly evident from a study of the Michaelis–Menten model equation and to better perceive the influence of operating conditions on reaction rate. With this programme we can propose an enzyme kinetic exercise when evaluating the dynamics of the reactants and reaction products is central, thus allowing students to visualize and interact with the dynamics of the reaction in a self-directed problem-solving way.

For this purpose, students are prompted to recreate a real-life scenario, where their knowledge should be contextualised in a project-based learning environment. In particular, they should activate their understanding of $V_{\text{max}}$, $K_m$, $K_i$, $K$, $n$ (the Hill exponent) and $V_0$ to solve a practical question with the help of SIMENKIN.

In the project-based learning approach, students are asked to find solutions to nontrivial problems in an active manner through the presentation of a real problem; they should understand the context of the question and decide on the relevant information needed and choose the methodology to solve it (Blumenfeld et al., 1991). We have designed and implemented this practical classroom module as an efficient means to test the utility of SIMENKIN in helping students to use and handle experimental data of kinetic character, interpreting these results and applying them to real cases.

This training module can be taught in any course of biochemistry containing enzymology issues, regardless of the degree in question. It is intended to be given in groups of 20–25 students as a general introduction to biochemistry. Students must therefore have an existing background in general science and they should be familiar with the basics of mathematics, chemistry and biology. Each student had to carry out three types of activities. While working on the module, they should have free access to the bibliographical and information resources they require.

3.1. Activity 1: enzyme kinetics concepts review and presentation of the application

This activity begins with a short review of the fundamental concepts of enzyme kinetics. This part of the seminar follows a flipped classroom approach, since the main concepts have already been presented to the students. It should be noted that at this point the student has been taught the basics of enzyme kinetics and the Michaelis–Menten and Hill model, and they will therefore be familiar with the subject. Ideally, this module should be imparted before the students perform any laboratory practicals where they carry out kinetic characterisation of an enzyme and/or enzyme inhibition studies. However, it is also useful if it is done once these practical exercises have been performed.
The review will focus on the fact that the parameters that characterise an enzyme are directly related to the Michaelis–Menten and Hill model, and therefore it must be interpreted in this context. Attention is also drawn to the fact that despite its limitations, the concepts and values of the key parameters such as $V_{\text{max}}$ and $K_m$ are derived from the model application and they are of general utility.

The second part (40 min) is dedicated to present the SIMENKIN (see Figures 1 and 2) application to the students. Once the main features of SIMENKIN were presented, some time was devoted to practise using SIMENKIN. In addition, for the Spanish-speaking students, there is an interactive online presentation of SIMENKIN, available at http://www.genial.ly/57d53dea4b1ab31ac86d9060/guia-de-manejo-del-simenzkin that allows the students to become familiar with the concepts and tools required for the seminar of the activity. Students were asked to use the programme to respond to some questions related to the behaviour of enzymatic reactions. These questions were designed to specifically master the special features of SIMENKIN. A typical example is the following:

An enzyme with a $K_m$ of 0.5 mM and $V_{\text{max}}$ of 10 mM/min is in a medium with a 10 mM substrate concentration. How long will it take to transform 80% of the substrate to product? What would be the required value of $K_m$ of an enzyme with the same $V_{\text{max}}$ to take four times as long to perform the same transformation?

With this, we help the students to practically apply the concepts and tools that have been reviewed and presented and to help them to acquire the minimum necessary skills to use SIMENKIN. Once they have a basic command of the application, have explored its possibilities and are quite familiar with the programme, they are ready for the next activity, where they will focus on solving problems.

### 3.2. Activity 2: practical case resolution with SIMENKIN

In this activity, students are asked to design a protocol to solve a practical matter. For the sake of this paper, we will show the case of the clinical use of succinylcholine. Here, students face a problem that requires them applying their knowledge of enzyme kinetics. They can perform this part with the help of the available information. Once they have an understanding of the biological meaning of the gathered information and data, they can transform, interpret and punch them into the SIMENKIN spreadsheet in order to solve the question. This process is significantly different from other settings where students simply apply the equations or type numbers into programs without a true association with the real situation.

Succinylcholine is a fast-acting muscle relaxant used in bronchial and tracheal exploration carried out using a bronchoscope (Kupeli, Karnac, & Mehta, 2010). A few seconds after the administration of succinylcholine, patients experience muscle paralysis, thus allowing for a bronchoscope to be used. However, as plasma cholinesterase is present in the blood, succinylcholine is hydrolysed immediately after administration, so its action disappears after a few minutes. In fact, it is known that for the relaxing effects to last, it is essential that its concentration in blood is never lower than 2 mM. Moreover, it should be noted that a bronchoscopy procedure takes at least 3 min.

The problem to be solved is to determine the lowest possible amount of succinylcholine that would guarantee that a proper bronchoscopy can be performed. The students are informed of the results of an assessment of the activity of blood cholinesterase in a given patient (data of initial concentrations of succinylcholine vs. initial rates). They are then
asked to determine how much succinylcholine should be administered in individuals where one of two genetic abnormalities is present. In the first case, there is higher than normal cholinesterase activity in blood; while in the other, a mutation in the gene cholinesterase has been shown to affect the enzyme's affinity with succinylcholine in such a way that the enzyme has a higher $K_m$ than that of the unmutated enzyme.

During the development of this part the students worked individually. However, they were free to talk to each other and discuss the issues raised and the best approach to the solution. Although the questions were the same for all, since the numerical values were different for each student, the interaction among students was focused in establishing the method to solve the problem or the interpretation of the available information. At this phase the teacher assisted the students as a mere counsellor, avoiding responding directly to concrete questions, but instead helping to solve doubts or suggesting possible ways of solving them.

4. Assessment

Since the experimental data are not directly connected with the equations that have been presented to the students in the theory classes, they have to find the solution by using the application SIMENKIN. We also assessed how SIMENKIN was useful for the understanding of the basic concepts of enzyme kinetics, particularly the evolution over time of the substrate concentration and initial rate, through a survey.

The grading of this activity is based on the assessment of a brief report (3 pages, 12,000 characters) written by each student. The report should have three different sections: problem presentation, results and discussion. In the discussion, interpretation of the results obtained in the biological context of the problem must be included. In the rating of the report, aspects such as the quality of the writing, organisation in the description of the findings were considered. But, above all, it took into account the soundness of the approach to derive the solution, the implementation process and the discussion of the whole project. In order to evaluate the quality and soundness of the approach used to derive the solution, we looked at how the students were able to build on and process the available ‘raw’ information to generate the kinetic parameters of the enzyme; as well as the rationale followed to determine the minimum substrate concentration required for the operation to be successful in the different conditions considered (see Figures 1 and 2).

The nature of the proposed exercise requires a proper understanding not only of the basic principles of enzyme kinetics, but also of the dynamics of the enzyme assay. This is because the provided data are not directly connected with the equations; instead, the students have to find the connection between them by understanding the biological meaning and how they are related. It is through the examination of this rationale that this key aspect of the self-directed problem-solving was evaluated.

In the two years that this module has been taught, 178 students have been evaluated. Most of them have been able to successfully complete the exercise and the grades were overwhelmingly positive, with an evaluation score mostly around 8/10.

Figure 3 shows the grades obtained. As can be seen in both courses, the vast majority received scores above 5: 99% in first year and 89% in the second, with mean scores of 8.2 and 7.3, respectively.
As can be seen, there are differences in the results of the two cohorts. This is due to the penalisation applied to the scores of some of the reports (10). In the course 2015–2016, it was observed that some students were late in presenting their results/reports. Also, cases of plagiarism from reports of the previous year were detected. We consider that in spite of this anomaly, the overall results are still satisfactory.

In order to evaluate how this intervention contributed to the learning of the students we carried out an assessment exercise designed to measure the improvement in the understanding of key concepts of the topic, such as initial speed, its dependence on the substrate concentration or enzyme activity or they mastering of the handling of units and dimensions, among others. The exercise consisted in two tests of 10 questions (four options, one correct) directly related to the topics developed in the seminar. One was carried out just before the seminar and the other once the seminar was completed. 75 students performed both test. We found that 65% of them increase their marks in the test after the seminar. Also, we found that the average of the marks increased from 5.00 to 5.91 (see Figure 4). The paired \( t \)-test showed that the significance of this yielded a \( p \)-value of 0.0001136. This is a very low value that qualifies the rejection of the null hypothesis, thus supporting the better marks of the ex-post test.

The assessments from end-of-course evaluations (Figure 5) carried out in the second course are also relevant for the purpose of this communication. As it can be seen, the cohorts perceived the activity as valuable and interesting. Nevertheless, the responses to the question on the difficulties encountered during the implementation of the exercise provide some interesting observations.

In most of the dimensions evaluated, the students reported being mostly ‘satisfied’ (organisation, material supplied, content, coordination and educational yield) and only a minor proportion indicated that they were very satisfied. This indicates that, in spite of the fact that the majority finds the exercise satisfactory, there is still some room for improvement. We are committed to work in this direction by asking students how the activity might be

**Figure 3.** Scores obtained by two cohorts of students. In the first year (left panel) there were 90 students, while in the second, there were 88.
improved. From the answers already obtained, we have reached some conclusions. Some students’ comments alluded to the time required to complete the report and the time spent using the SIMENKIN application:

… should be given more time to explain … how to solve the kinds of problems that were addressed in the seminar …
… it is a good activity to prepare for the future, but the time available to solve the problem is insufficient, considering our experience in solving biochemical problems.

In this same vein, some aspects should be considered in order to optimise the design. These include consideration of the difficulty of the exercise and the lack of previous knowledge of the subject. As a consequence, the students do not believe that the activity will be easy or simple. In our view, this is mainly a consequence of them not being familiar with the problem-solving exercise approach, where they have full control while looking for the solution. In fact, for most if not all of them, this was their very first encounter with this type of challenge. Therefore, this kind of feedback is by no means surprising. It should be noted, however, that the exercise was strongly facilitated by the availability of the SIMENKIN programme to the extent that without it such an exercise it would have been impossible. Some student comments in this line are the following:

… it was of great help to discuss with others; that served to better understand and resolve the issue … (This type of exercise) helps understand the concepts as we are not just concerned with finding the correct answer …

What I liked most about this activity is the philosophy of independently searching for the solution. I think this is the purpose of university, to teach us to be independent thinkers and to learn to work with others to overcome problems.

Overall I am very pleased with this activity because it helps us to acquire some skills in problem-solving …

Finally, it should be noted that the problems posed here are difficult if not impossible for students to carry out and thus the training in the use of the related concepts. This is the case of the initial rate in an enzymatic reaction, or the evolution of the consumption of a substrate in a biochemical reaction. The computer software here is instrumental in the sense that it can be used to overcome these restrictions so that some concepts that are excluded, or are dealt unsatisfactorily in the lessons, can be actively explored by the student.

5. Discussion

An important point to be underlined is how teaching traditionally difficult topics such as those involved in enzyme kinetics (the underlying model and the mathematical model founded on parameters and concepts) can be facilitated by the use of the SIMENKIN application. Such an application is easy to build and adapt to different types of problems and real contexts within the realm of biochemistry. Through the use of this freely available software, students can ‘see’ the time course of the reactions, capture the operational meaning of the initial rate ($V_0$) and appreciate how it changes with time as the initial concentration of substrate ($S_0$) is consumed. This is a key feature that is however not implemented in most available programs for the teaching of enzyme kinetics.

One of the main challenges encountered in the teaching of enzyme kinetics is ensuring that students understand the qualitative and quantitative relationships between velocity and substrate concentration and how the same relate to the kinetic parameters. With the advent and availability of microcomputers, many programs designed to facilitate the teaching of enzyme kinetics through simulation (Clark, 2004; Dahmer, 1987; González-Cruz, Rodríguez-Sotres, & Rodríguez-Penagos, 2003; Williams, 1983) were quickly presented. When assayed, these approaches revealed that there are varied benefits in the use of these
strategies. However, there is still a lack of a comprehensive pedagogical approach that, based on the simulation of enzyme kinetics within the framework of learning strategies that rely on student autonomy, would aid in the learning about these specific topics.

We have presented an Excel/LibreOffice template to simulate enzyme kinetics (SIMENKIN) that allows students to view and interact with the dynamics of enzymatic reactions. This application is used within the framework of a practical problem-solving approach module, designed to facilitate the learning of some fundamental concepts of enzyme kinetics.

In this activity, using the application allows students to view and interact with the dynamics of enzymatic reactions. The learning gains of students are thus linked to the nature of the activity: students learn how to obtain information from various sources; they integrate that information with the thinking process; learning becomes cumulative and the stimulation of existing knowledge facilitates the linking of new knowledge; effective reasoning skills and the practice to question critically are developed. In this line, it should be noted that the proper implementation of such a problem-solving exercise should consider differences in students’ rate of learning with self-learning materials. This is an aspect currently being developed in our institution.

Although SIMENKIN (and the approach where it is used) is designed for a specific purpose (the teaching of enzyme kinetics) it can be relevant to other bioscience educators to teach many topics in many different areas. Since biology is essentially a mathematical science that ultimately must be described in mathematical terms (Torres & Santos, 2015), the simulation of systems dynamics can greatly benefit from the availability of a tool like SIMENKIN, where a simple model with analytical solutions can be easily implemented to allow students to observe and explore some critical behaviours that are inaccessible without the numerical integration of the model equations. The plethora of already available models, to name a few, range from the classic model of microbial growth (DiToro, 1980; Monod, 1942), to plant physiology (Steele, 1962) and the effect of temperature on chemical reaction rates or on enzyme activity using the Arrhenius equation (Prosser & Brown, 1961).

Finally, we must highlight that for a proper implementation of a problem-solving unit it should be made of the different learning rates amongst the students. Each student needs exposition of the theory to understand and apply it to the problem. In following iterations of the implementation of the educational unit we will apply the concept of the flipped classroom (Sams, Bergmann, et al., 2014). This is one of the multiple ways to compensate the heterogeneities of the students in a problem-solving seminar.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by MINECO [project number BIO2014-54411-C2-2-R]; DISEÑO MATEMÁTICO DE ESTRATEGIAS PARA LA INGENIERÍA METABÓLICA DE CEPAS DE E. COLI COMO PLATAFORMA PARA BIO-RUTAS SINTÉTICAS ROBUSTAS [project number BIO2014-54411-C2-2-R].
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