Original article

An algorithm for the automated generation of rate equations to simulate chemical reactions.

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Abstract
We have developed an approach to automatically generate models for chemical reactions in the form of rate equations from the stoichiometric equations of the reaction using MATLAB. These rate equations are then combined with kinetic parameters to simulate the reaction using the MATLAB ode15s solver, hence reducing the quantity of reactions that must be performed in the laboratory. This approach enables time and money to be saved in the chemical development process in industries such as the pharmaceutical industry, where there are high costs of chemical intermediates, as well as promoting sustainability. The developed approach is highly versatile since it is suitable for both stiff and non-stiff differential equations and can be applied to complex multistep reaction mechanisms, thus increasing its utility in industry and academia.

Keywords
Computational chemistry, Kinetic modeling, Rate equations, Reaction rate, Simulating chemical reactions, MATLAB, Ordinary differential equations, Reaction optimization, In silico, Elementary steps

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Introduction:

Reaction optimization involves finding the combination of reaction conditions that optimally produce the desired output and is crucial to utilizing resources in a maximally efficient way (1-2). It is essential to synthetic chemistry and plays a significant role in both industry and academia in selecting the most favorable experimental conditions and reactors (1, 3, 4).

In the laboratory, varying a single factor at a time while keeping others constant - commonly referred to as one factor at a time (OFAT) optimization - often misses the optimal conditions. This is typically employed as a rudimentary optimization technique, because it is generally not possible to run reactions with all permutations of reaction condition combinations, due to time constraints as well as the fact that experiments are expensive and require financial justification (1, 3, 4). The time and material constraints are particularly due to chemical reactants such as intermediates in the pharmaceutical industry. Chemical intermediates are used as building blocks in a wide variety of reactions and are thus highly demanded and expensive in terms of monetary value in addition to the chemist's time. This is especially prevalent in the pharmaceutical industry, where intermediates are crucial in drug production. Furthermore, the chemical industry is highly energy intensive and accounts for more than three percent of global greenhouse gas emissions. Experimental work also commonly involves hazardous materials and conditions, which can lead to chemical accidents resulting in casualties and financial losses (5, 6). To reduce the amount of time and money spent, in addition to decrease environmental impact and increase safety, reactions can be simulated and thereby optimized when optimal reaction conditions are determined.

Optimizing reactions using experimental simulation enables more efficient synthesis of pharmaceuticals by guiding scientists in which experiments to execute based on which ones best provide the desired output *in silico*. This leads to an overall reduction in time, money, and materials spent on unnecessary work in the laboratory (3). One method of simulating reactions is using design of experiments (DoE) software. DoE is used to identify the factors that most considerably influence the result of a reaction by predicting its outcome using various reaction conditions, followed by fitting a statistical model in the form of an equation for the dependent variable that considers the different impact of various independent variables. This helps with the planning of independent, dependent, and control variables to enable the experiment to take place under statistically optimal conditions, thus amplifying yield and purity by revealing which reaction conditions generate them (7). The approach to simulating reactions used in this work is kinetic modelling. This approach uses a set of rate equations for the concentration of each chemical species present to produce a model based on physicochemical information. More specifically, the rate equations form a system of ordinary differential equations (ODEs) consisting of the reaction rate expressions for each reaction in the mechanism, which are subtracted or added based on whether the species is a reactant or product in the given reaction, respectively. The rate equations can then be integrated to determine the concentration of each species at any time

over the course of the reaction (8). Kinetic models are mechanistic as opposed to statistical as they are based on the proposed reaction mechanism. Mechanistic models provide chemical insight and understanding that DoE does not by illustrating a quantitative relationship between the output of the experiment and significant design factors (9). This means they can be used to gain a deeper understanding of chemical reactions as well as to reveal the most suitable combination of reaction conditions by varying them (7, 9).

In this work, we have established a computational kinetic methodology for simulating reactions using ODEs on MATLAB to save time, money, and energy in addition to enhancing safety in both industrial and academic applications. This methodology is open-source, and provides simulation capabilities to chemical researchers working to optimize reactions (10).

Methods

Kinetic modelling and ODEs

Kinetic models permit scientists to understand and simulate reactions to determine how to optimize experimental factors *in silico* by quantitatively describing the progress of reactions in terms of mathematical models, specifically rate equations which predict the reaction rate given conditions such as temperature and concentration (9, 11). They assume the law of mass action, whereby the rate of an elementary reaction is directly proportional to the product of the concentrations of the reactants raised to the power of their stoichiometric coefficients (9). Kinetic models are mechanistic models, meaning they are derived from scientific understanding of the chemical process, specifically the reaction mechanism.

Chemical reaction mechanisms can consist of one or multiple steps. An elementary step is a direct conversion of one or more reactants into one or more products. These steps are typically unimolecular or bimolecular since the probability of three or more reactants colliding with the proper orientation and energy to react is extremely low. A multistep reaction occurs when not all bonds between the reactants are broken and formed simultaneously, but instead intermediates appear in the process of the transformation of the reactants to the products.

The reaction mechanism of a multistep reaction consists of a sequence of elementary steps demonstrating how the starting materials react to produce the final products (11). As per the law of mass action, each reaction has a rate expression including its reactants. The various steps of the mechanism contribute to the rate at which each species is consumed or produced. This means that steps consuming a species contribute a negative rate expression to the differential equation for its change in concentration since it is being depleted, while steps that produce a species contribute a positive rate expression since it is being created and its change in concentration is thus positive.

The concentration of a given species depends on the time elapsed since the beginning of the reaction. This means the rate equations are only dependent on one independent variable, making them ODEs. When solved, the rate equations reveal the species' concentrations at any time during the reaction, thereby

depicting the effect of starting inputs on the output. The following rudimentary example can be used to illustrate these concepts. It is a second order reaction, as the examples simulated below are as well, even though the developed approach is applicable regardless of the order of the reaction. For the elementary step

$$2A \xrightarrow{k1} B$$

the rate of change of the concentration of the reactant *A* can be described mathematically through the ODE, which can be solved analytically,

$$\frac{d[A]}{dt} = -k_1[A]^2,$$

$$\int_{A_0}^{A_t} \frac{1}{[A]^2} d[A] = -k_1 \int_0^t dt$$

$$\frac{1}{[A_t]} - \frac{1}{[A_0]} = k_1 t$$

$$\frac{1}{[A_t]} = k_1 t + \frac{1}{[A_0]}$$

$$[A_t] = \frac{1}{k_1 t + \frac{1}{[A_0]}}$$

$$[A_t] = \frac{[A_0]}{[A_0] k_1 t + 1}$$

$$[A_t] = \frac{1}{k_1 t} + [A_0]$$

Similarly, the rate of change of the concentration of the product *B* can be described mathematically using the ODE, which can also be solved analytically,

$$\frac{d[B]}{dt} = k_1[A]^2,$$

$$\int_{B_0}^{B_t} \frac{1}{[A]^2} d[A] = k_1 \int_0^t dt$$

$$\frac{-1}{[B_t]} + \frac{1}{[B_0]} = k_1 t$$

$$\frac{1}{[B_t]} = -k_1 t + \frac{1}{[B_0]}$$

$$[B_t] = \frac{1}{-k_1 t + \frac{1}{[B_0]}}$$

$$[B_t] = \frac{[B_0]}{-[B_0] k_1 t + 1}$$

$$[B_t] = \frac{-1}{k_1 t} + [B_0]$$

Nevertheless, in real world reactions, determining the concentration of each species is more demanding due to reasons including side product formation and mass-loss balance. Furthermore, the ODEs for reactions with more components and steps require more complex mathematics to be solved, which is why a numerical approach using MATLAB or other languages as opposed to an analytical approach is used (9). The specific MATLAB ODE solver used in this project is ode15s, which is designed to solve stiff equations. The assumption to use a solver for stiff equations increases the applicability of the developed methodology, as we do not know whether the automatically generated ODEs are going to be stiff or non-stiff, meaning that solving both needs to be possible (12).

Although this numerical approach to reaction optimization through kinetic modelling is frequently implemented in process laboratories in industry and academia, it is rarely employed by chemists due to the deeper understanding it requires of the

underpinning programming and mathematics (9). The versatility of kinetic models means they can be used for simple as well as highly complex processes involving numerous species; however, writing a rate equation for each species in a highly complex process, as those that commonly occur in pharmaceuticals and fine chemicals, can be very time consuming and challenging (11). This work addresses the concerns of kinetic modeling regarding limited time and knowledge of programming and mathematics by automatically generating and evaluating ODEs for the concentrations of the species participating in the reaction.

Automated ODE generation

Figure 1 provides an overview of the specific computational kinetic methodology developed.

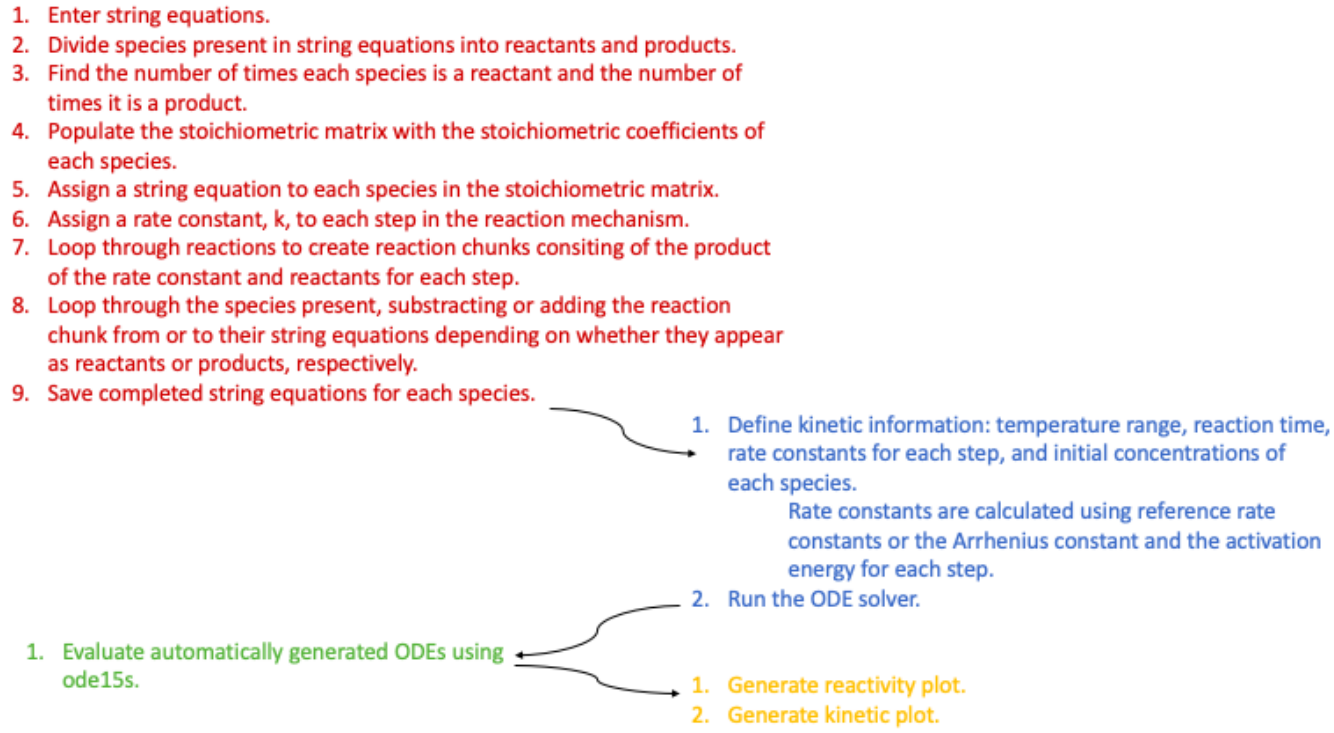
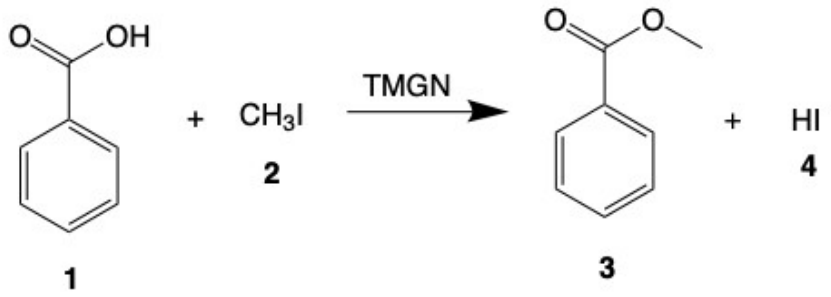


Figure 1: Pseudocode showing the methodology of the developed approach.

This methodology was then used to simulate several examples of varying degrees of complexity to illustrate its applicability to different reactions. To simulate the reactions, data from literature including the chemical equation, starting conditions, and kinetic parameters were inputted into MATLAB version 9.13.0, and following the generation of each species' rate equation, an ODE solver was used to model the change in the concentration of the species in the reaction over the given time range. The initial concentration ratios of reactants are chosen based on the stoichiometry of the overall reactions to ensure all the reactants are consumed to minimize left over reactants and thereby cost.

Results

The first example simulated is of benzoic acid alkylation. It is a simple reaction, as the mechanism only consists of one reaction. Namely, benzoic acid, species A, (**1**) reacts with iodomethane, species B, (**2**) in the presence of the base to form methyl benzoate product, species C, (**3**) and hydroiodic acid, species D, (**4**), as is presented in Scheme 1. The rate constant for the reaction was 0.57 M^{-1} s^{-1} (13).



Scheme 1: A reaction showing the formation of methyl benzoate from benzoic acid and iodomethane.

This reaction is significant because methyl benzoate is used as a solvent and as a pesticide, in perfume and in flavorings, and to produce other chemicals (14). The developed approach depicts the progression of the reaction through the concentrations of the participating species over time at the temperature 308.15 K, as shown in Figure 2.

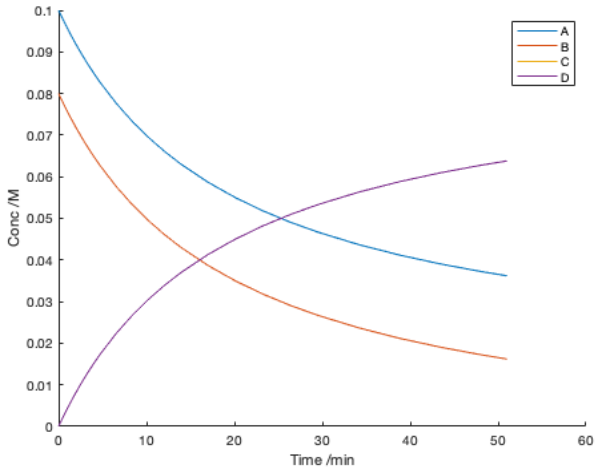


Figure 2: Kinetic plot illustrating the progression of the production of methyl benzoate from benzoic acid and iodomethane with initial concentrations of 0 M, 0.1 M, and 0.08 M, respectively.

In Figure 2, the initial concentrations of species A, B, C and D correspond to 0.1 M benzoic acid, 0.08 M iodomethane, 0 M methyl benzoate, and 0 M hydroiodic acid, respectively. The reaction was simulated at 308.15 K over a time interval of 60 minutes. The reaction was repeated at the same temperature and time with 0.1 M benzoic acid, 0.11 M iodomethane, 0 M methyl

benzoate, 0 M hydroiodic acid in Figure 3, illustrating the effects of higher initial concentration of the starting materials.

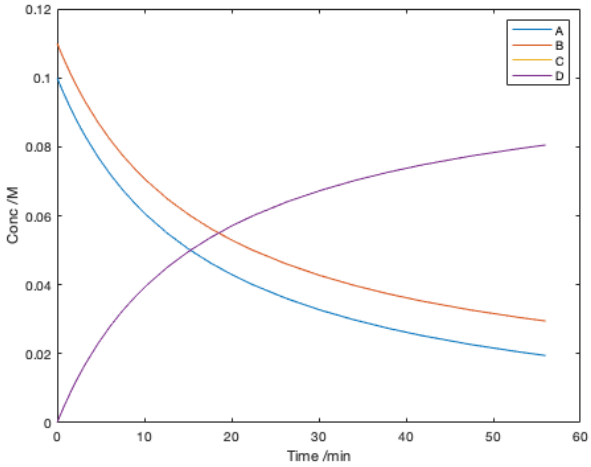


Figure 3: Kinetic plot illustrating the progression of the production of methyl benzoate from benzoic acid and iodomethane with initial concentrations of 0 M, 0.1 M, and 0.11 M, respectively.

The formation of methyl benzoate from benzoic acid and iodomethane was again simulated at the same temperature for the same time with higher initial concentrations of starting materials using 0.1 M benzoic acid, 0.15 M iodomethane, 0 M methyl benzoate, and 0 M hydroiodic acid in Figure 4.

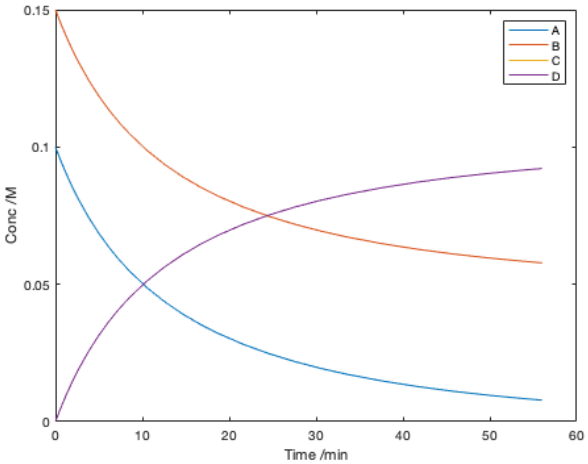


Figure 4: Kinetic plot illustrating the progression of the production of methyl benzoate from benzoic acid and iodomethane with initial concentrations of 0 M, 0.1 M, and 0.15 M, respectively.

Our approach further demonstrated the effect of allowing the reaction at the same temperature with initial starting conditions of 0.1 M benzoic acid, 0.08 M iodomethane, 0 M methyl benzoate, and 0 M hydroiodic acid to run for longer, 150 minutes, in Figure 5.

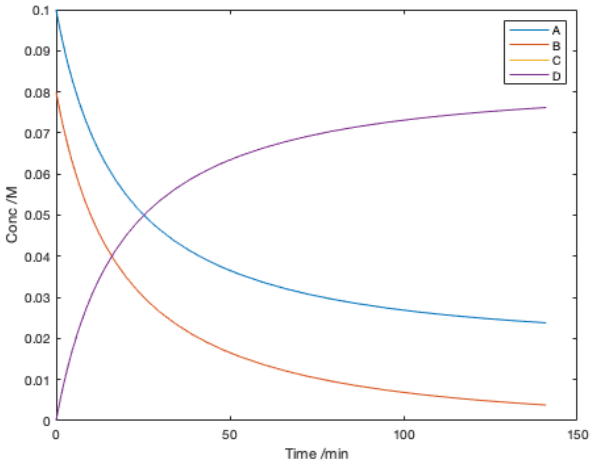
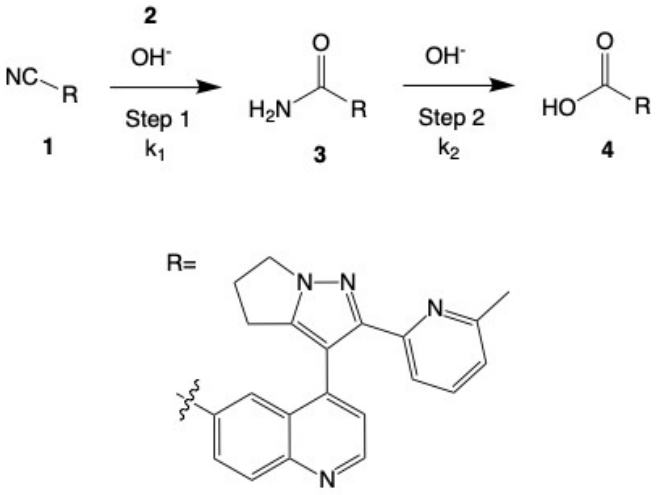


Figure 5: Kinetic plot illustrating the progression of the production of methyl benzoate from benzoic acid and iodomethane with initial concentrations of 0 M, 0.1 M, and 0.0.8 M, respectively, over a longer time interval of 150 minutes.

This example demonstrated that it was possible to apply the developed approach to simulate a simple system consisting of one reaction by inputting the chemical equation and kinetic parameters into the program.

The next example simulated is a slightly more complicated and thus more realistic one – the hydrolysis of a nitrile, species A, (**1**) by hydroxide, species B, (**2**) to form an amide, species C, (**3**), which is then further hydrolysed to form a carboxylic acid, species D, (**4**) and ammonia, as is illustrated in Scheme 2. The rate constants k_1 and k_2 were 0.00927 M^{-1} s^{-1} and 0.0000363 M^{-1} s^{-1}, respectively (15). Chiral nitriles play a significant role in the pharmaceutical industry because they can be converted into important amides and carboxylic acids through carbon chain extensions (16).



Scheme 2: The reaction of a nitrile and hydroxide forming the corresponding amide, which can then further react with hydroxide to form the carboxylic acid.

This reaction was simulated using the developed methodology with initial concentrations of 0.8 M, 1.8 M, 0 M, and 0 M for species A, B, C, and D, respectively, at a temperature of 348.15 K over a period of 300 minutes in Figure 6.

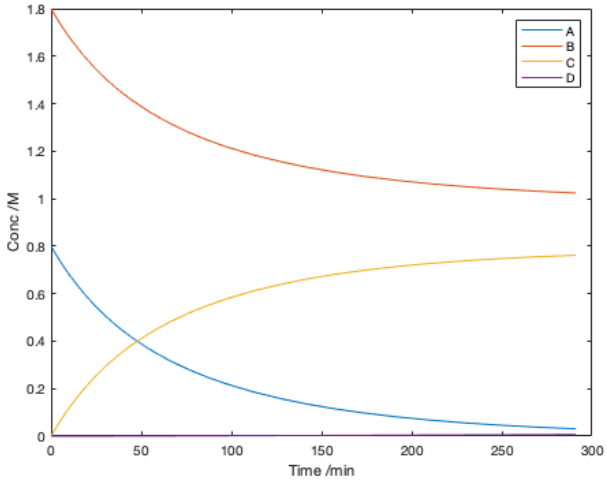
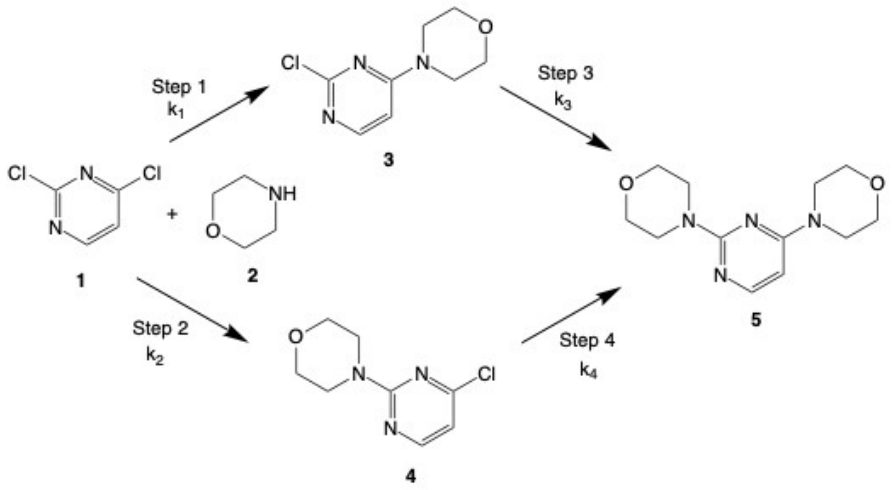


Figure 6: Kinetic plot illustrating the hydrolysis of a nitrile by hydroxide into an amide and then further into a carboxylic acid.

This instance illustrated that it was possible to use the created approach to identify the correct rate equation and simulate a multistep reaction mechanism.

The third reaction simulated features a mechanism of several steps and six different species. 2,4-dichloropyrimidine, species A, (**1**) reacts with morpholine, species B, (**2**) to form a 4-substituted product, species C, (**3**) or a 2-substituted product, species D, (**4**). These products then undergo another reaction with morpholine to yield a bis-substituted product, species E, (**5**). Each of these reactions produce hydrochloric acid as a byproduct, which is neutralized by excess base, as presented in Scheme 3. The rate constants k_1, k_2, k_3, and k_4 were 0.32945 M^{-1} s^{-1}, 0.07686 M^{-1} s^{-1}, 0.00018 M^{-1} s^{-1}, and 0.00037 M^{-1} s^{-1}, respectively (17).

Simulating this reaction is of high utility because it is often challenging to separate the intermediate isomers, rendering them of little use in the synthesis of other chemicals. This means that the simulation helps prevent unnecessary production of waste (19). Our approach enabled the simulation of the concentrations of the participating species over time, as shown in Figure 7. The initial concentrations of species A, B, C, D, and E were 1 M, 2.2 M, 0 M, 0 M, and 0 M, respectively. The reaction was simulated at 308.15 K over 400 minutes.



Scheme 3: The reaction of 2,4-dichloropyrimidine with morpholine forming the 4- substituted product and the 2-substituted product, followed by the reaction of the 4- substituted product with morpholine and the 2-substituted product with morpholine forming the bis-substituted product.

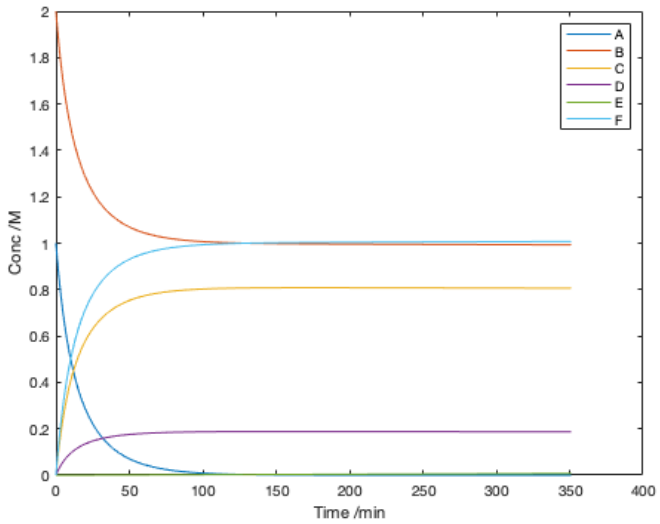
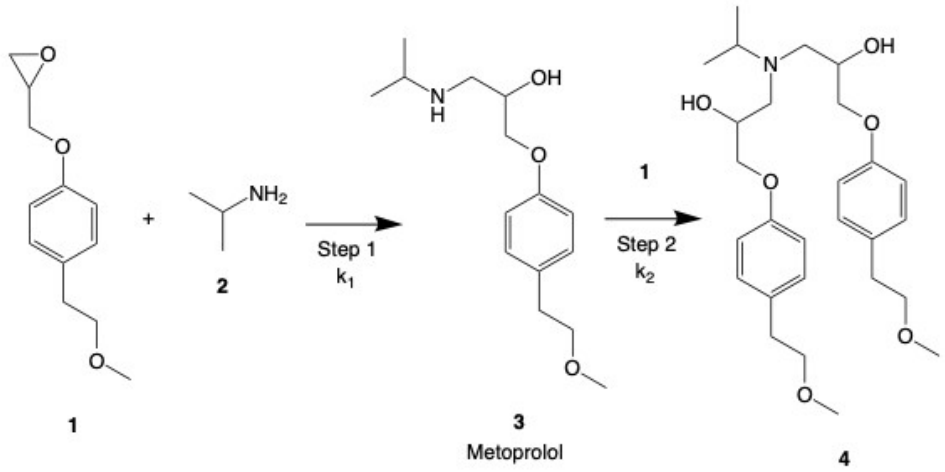


Figure 7: Kinetic plot showing the reaction of 2,4-dichloropyrimidine with morpholine forming the 4-substituted product and the 2-substituted product, followed by the reaction of the 4- substituted product with morpholine and the 2-substituted product with morpholine forming the bis-substituted product.

This third simulation demonstrated that the program was capable of identifying the correct rate equations for a more complex system and use them to model it, illustrating why simulation, in general, is such a useful tool.

A further example is one that was mentioned in the introduction and is of considerable value in the pharmaceutical industry – the production of metoprolol, a beta-blocker drug. As is presented in Scheme 4, the mechanism consists of two steps; first, an epoxide starting material, species A, (**1**) reacts with isopropylamine, species B, (**2**) to form metoprolol, species C, (**3**), after which metoprolol further reacts to form a bis-substituted impurity, species D, (**4**). The rate

constants k_1 and k_2 were 0.004762 M^{-1} sec^{-1} and 0.000318 M^{-1} sec^{-1}, respectively (8).



Scheme 4: The formation of metoprolol from an epoxide starting material and isopropylamine, followed by its overreaction to form the bis-substituted product.

The importance of this reaction in the pharmaceutical industry emerges from the fact that metoprolol is used extensively in the treatment of cardiovascular disorders including hypertension, angina, arrhythmias, myocardial infarction, and congestive heart failure (18).

The approach we have developed depicts the formation of Metoprolol through the concentrations of the participating species over time, as shown in Figure 8.

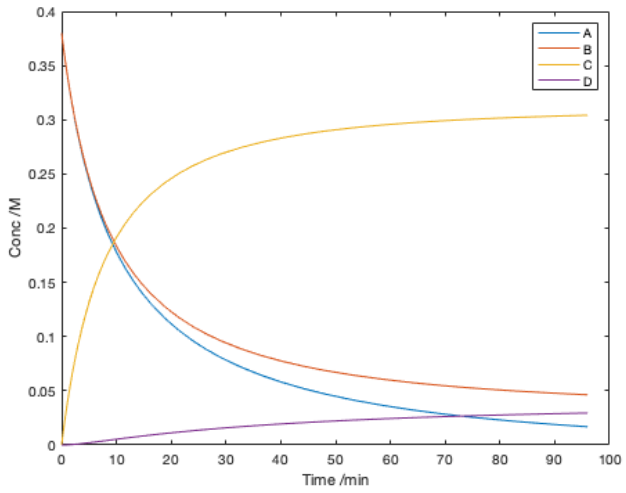


Figure 8: Kinetic plot illustrating the progression of the formation of metoprolol from an epoxide starting material and isopropylamine, followed by its overreaction to form the bis-substituted product at the temperature range 443.15 K.

The initial concentrations of species A, B, C, and D in Figure 8 were 0.38 M, 0.38 M, 0 M, and 0 M, respectively. This simulation occurred at the temperature 443.15 K.

Nevertheless, the developed methodology additionally enabled simulation of the same reaction at lower and higher temperature ranges. Figure 9 illustrates how a lower temperature, 338.15 K, affects the production of metoprolol. Similarly, Figure 10 presents the effect of a higher temperature, 528.15 K, on the production of metoprolol.

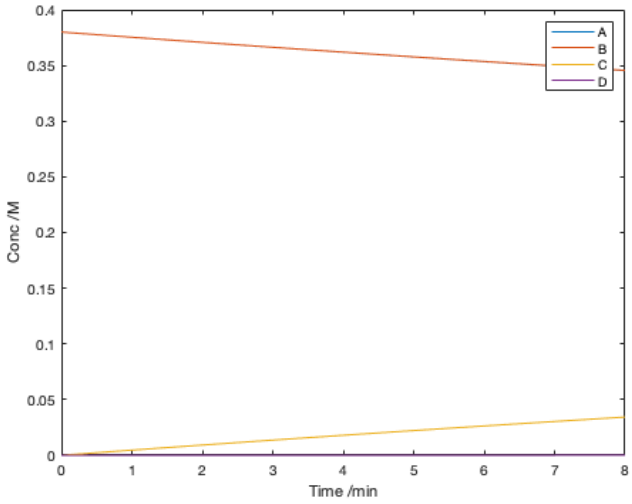


Figure 9: Kinetic plot illustrating the progression of the formation of metoprolol from an epoxide starting material and isopropylamine, followed by its overreaction to form the bis-substituted product at range 338.15 K.

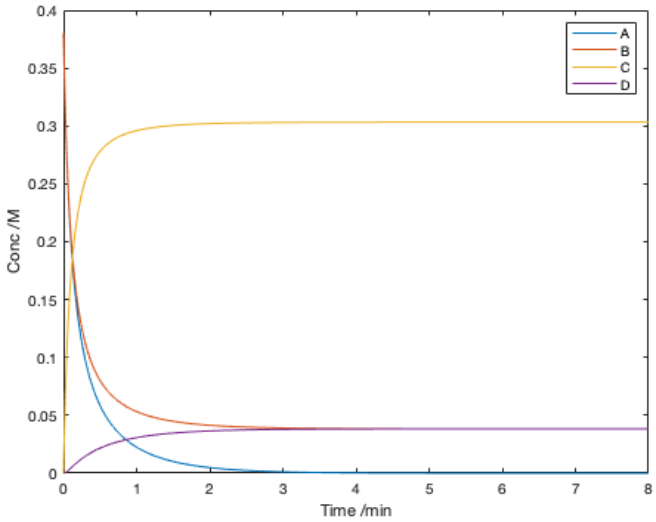


Figure 10: Kinetic plot illustrating the progression of the formation of metoprolol from an epoxide starting material and isopropylamine, followed by its overreaction to form the bis-substituted product at 528.15 K.

The above example demonstrated that the presented program can also be used to simulate highly relevant reactions in industry such as those used in the production of pharmaceuticals.

The final example presented in this paper is one that depicts the true power of this approach and to test it to its limits – namely, the ten component, ten step reaction mechanism of kerosene with oxygen in liquid rocket engines. This reaction was consequential in the study of hydrogen peroxide as a coolant in liquid rocket engines as a more environmentally friendly alternative to hydrazine propellants (20). The approach that the developed computational kinetic methodology took to modeling it is displayed in Figure 11.

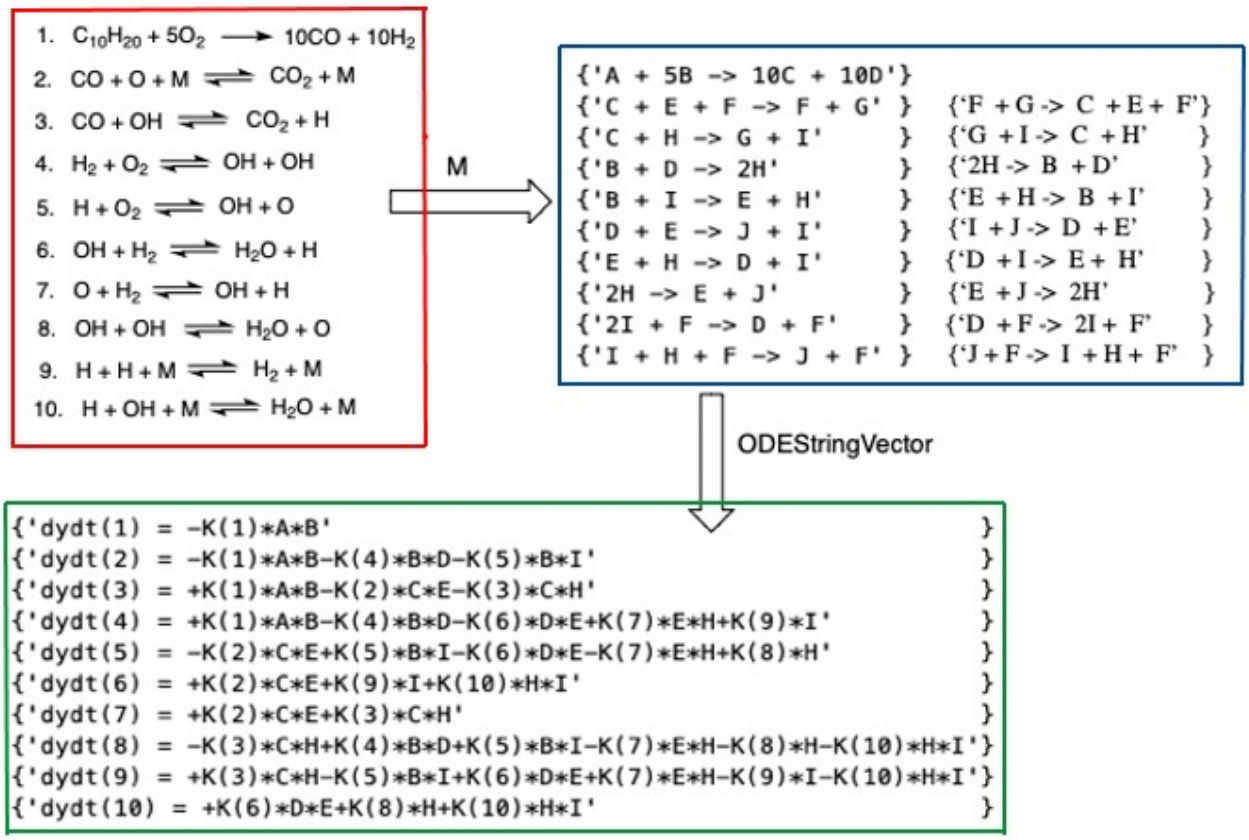


Figure 11: Diagram demonstrating how the approach developed in this project automatically generates rate equations for the species in a chemical reaction.

The equations in the top left corner of Figure 11 were entered as strings into the created program, after which the methodology displayed by the pseudocode in Figure 1 proceeded. Namely, the developed approach saved the string equations in the array M, from which the species present as reactants and products as well as the number of times they occured were evaluated. The steps of the reaction mechanism were then looped through, the rate constants and reactants were added to the rate expression for each reaction, and then finally these rate expressions were added to the rate equation for each species present in the reaction, which were saved in the array ODEStringVector. If kinetic parameters such as the concentrations of starting materials, time range of the reaction, and rate constants for each step in the system were known, then it could be fully simulated

as the previous reactions were. This example illustrates that the developed approach is even applicable to highly complex reaction systems, making it very versatile.

One can instantiate how much money this computational approach will save using the pharmaceutical reaction producing metoprolol presented above. Metoprolol can be synthesized by reacting 4-(2-methoxyethyl)phenol with epichlorohydride (21). Running one experiment using 10ml of epichlorohydrin would require 1.5g of 4-(2-methoxyethyl)phenol, which would cost 1.35 € for the epichlorohydrin and 2.39 € for the 4-(2-methoxyethyl)phenol, as well as the chemists' time and lab resources to run the reaction repeatedly (22). Furthermore, industry requires production on a much larger scale and thus encompasses much greater costs and time. Simulating the reaction, on the other hand, would not cost anything and only takes a fraction of the time.

Conclusion

We show that an automated computational approach to generating the rate equations for a reaction is possible in MATLAB. This open-source approach has been used to successfully generate ODEs for the concentrations of species in a reaction mechanism, regardless of its complexity, and then use them to simulate the reaction with various starting conditions (10). This enables a considerable reduction in both time, resource and monetary costs, in addition to increasing safety and decreasing environmental impact. The next steps would include extending this methodology to automate the concentrations of starting materials and rate constants, as well as to optimize the reaction rate.

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