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An Open-Source, Cross-Platform Resource for Nonlinear Least-Squares Curve Fitting

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Supporting Information

ABSTRACT: The quantitative evaluation of experimental data and their graphical presentation are integral to teaching and research in chemistry and the life sciences. Data are commonly fitted to physical models, which in all but the simplest cases are expressed as nonlinear mathematical functions. To facilitate data evaluation in both teaching and research contexts, the Fit-o-mat program, implemented in Python, offers versatile nonlinear least-squares curve fitting through a graphical user interface. Fit-o-mat supports near-arbitrary fitting functions, including numerical and discontinuous ones, produces vectorized graphics, runs on different operating systems, and is free of charge, thus promoting the adoption of the program by students and instructors in the classroom and beyond. An embedded tutorial mode facilitates integration of Fit-o-mat into teaching curricula at the undergraduate and graduate levels.

KEYWORDS: *Biochemistry, Computer-Based Learning, Graduate Education/Research, Kinetics, Quantitative Analysis, Upper-Division Undergraduate*

INTRODUCTION

The quantitative analysis of data and their graphical presentation are essential across many disciplines, including chemistry and the life sciences. In the classroom, as in the laboratory, experimental observables, called dependent variables y, are routinely evaluated as functions of one or several independent variables, denoted as x. Analysis according to functional relationships, denoted $y = f(x, a_1, a_2, \cdots)$, serves to verify (or invalidate) physical models underpinning the experimental data and to determine characteristic parameters $(a_1, a_2, \cdots)$ describing the system under study. For instance, the temperature dependence of rate constants k in chemistry and biochemistry can often be modeled according to the Arrhenius equation:[1,2]

$$k(T) = A\mathrm{e}^{-E_a/RT} \tag{1}$$

where A is the pre-exponential factor, E_a is the activation energy, R is the gas constant, and T is the absolute temperature. (Accordingly, in this example $k(T)$ and T are the dependent and independent variables, respectively.) To determine the parameters A and E_a, the rate constant of a reaction of interest is hence recorded at several temperatures.

For subsequent analysis, functional relationships are often transformed to linear equations. For example, in the Arrhenius formalism, the natural logarithm of $k(T)$ is linearly correlated with the reciprocal of the temperature T:

$$\ln k(T) = \ln A - E_a/RT \tag{2}$$

Although this transformation holds the obvious attraction of affording straightforward data evaluation by graphical means or via conventional spreadsheet software, students should be dissuaded from employing it.[3] As one reason, numerical software for the evaluation according to the original nonlinear equation exists (see below). More importantly, the transformation affects the distribution of errors (or uncertainties) σ_i for the individual data points i and hence can yield quite different fit parameter values.

To reiterate, transformation is best avoided, and parameter values should be determined by nonlinear curve fitting of the original data. In this procedure, the agreement between experimental data y_i and the (original, nonlinear) functional relationship $f(x_i)$ is usually evaluated as χ^2, which refers to the sum over i of the squared deviations between y_i and $f(x_i)$:

$$\chi^2 = \sum_i \{[y_i - f(x_i)]/\sigma_i\}^2 \tag{3}$$

In an iterative manner, parameter values are varied in such a way that the target function χ^2 is minimized, and the process is hence called nonlinear least-squares (NLLS) curve fitting. It should be noted that in eq 3, the errors σ_i serve as weighting factors for the individual data points i. Starting from an initial parameter set, an optimum set of parameters $(a_1, a_2, \cdots)$ is determined, commonly by using the Levenberg−Marquardt algorithm.[4,5] In addition to Arrhenius-type problems, students, instructors, and researchers encounter nonlinear relations in many areas of chemistry and biochemistry, such as (but not limited to) enzyme kinetics,[6−8] protein folding,[9] and cyclic voltammetry.[10]

Regular spreadsheet programs that are familiar and available to most students (e.g., Microsoft Excel) possess only rudimentary support for NLLS curve fitting, although efforts exist to expand such capabilities via additional modules.[11] Versatile NLLS fitting is offered by a series of powerful commercial software packages (e.g., Microcal Origin, Kaleida-

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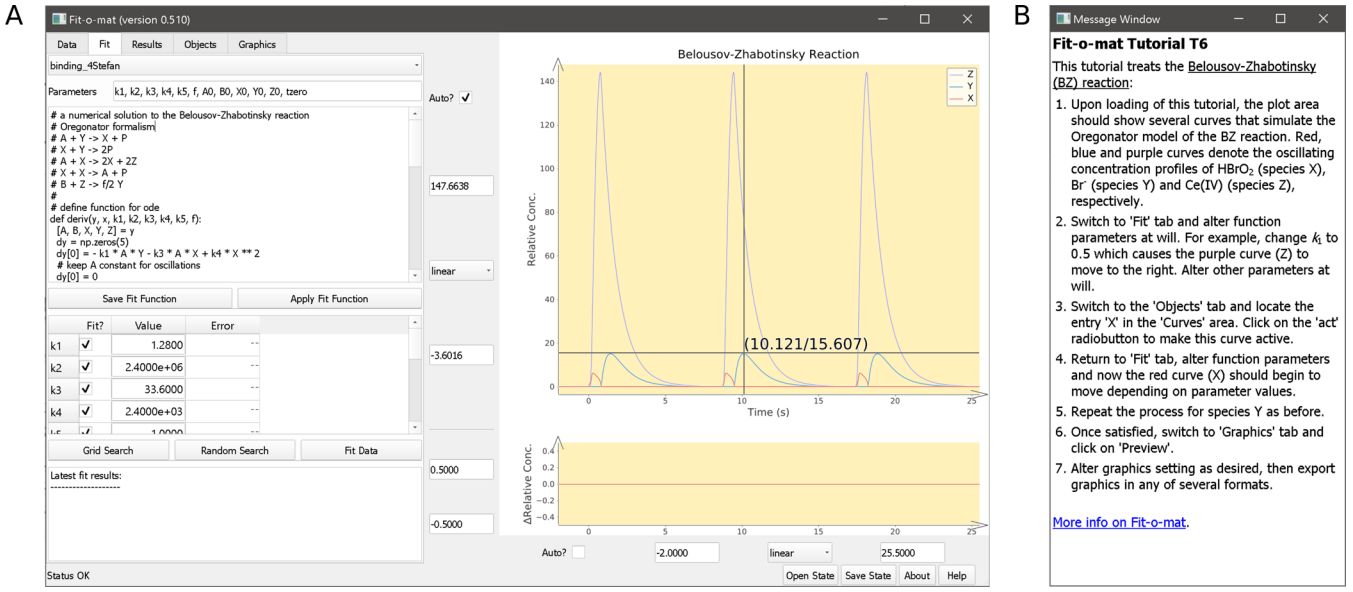

Figure 1. Fit-o-mat program. (A) Graphical user interface. (B) Integrated message window employed for tutorial sessions.

graph, GraphPad Prism, and MATLAB). Although these programs are exquisitely suited to fully meet most data-fitting needs, their adoption and continuing use by chemistry students is often hampered. Specifically, certain programs are not available for all of the most common operating systems, commercial software can incur significant expense, and numerical fitting functions (as opposed to analytical ones) are not implemented in all programs.

Advanced students and instructors overcome these limitations by resorting to computer programming, which provides a highly flexible and often cost-free option for NLLS analysis. Traditionally, pertinent programs have been implemented in languages like C or FORTRAN (see, e.g., refs 12 and 13) and compiled into bytecode. Because of advances in computing power, interpreted programming languages now provide a viable alternative platform for NLLS curve fitting. In particular, the language Python benefits from wide distribution, easily accessible syntax, and a broad base of high-level function libraries for numerical mathematics[14,15] and data plotting.[16] Consequently, Python has found ample application in academic curricula.[17]

Notwithstanding these benefits, mastering a programming language may represent a considerable barrier for many students. Against this backdrop, the Fit-o-mat software (Figure 1) was implemented in Python 3 as a versatile program for NLLS curve fitting of scientific data. Fit-o-mat provides an accessible graphical user interface yet retains full support for fitting of near-arbitrary user functions written in Python. Fit-o-mat is open-source and runs on Windows, Linux, and OS X platforms, thus facilitating classroom use and adoption by students.

THE FIT-O-MAT PROGRAM

Fit-o-mat features a graphical interface based on the *PyQt5*[18] framework and thereby provides a convenient front end for numerical procedures for NLLS analysis implemented in the Python libraries *NumPy*[14] and *SciPy*,[15] and for data plotting implemented in *matplotlib*.[16] Version 0.510 of the program source code is available free of charge from http://www.moeglich.uni-bayreuth.de/en/fit-o-mat or from http://github.com/TheAngulion/fit-o-mat; an accompanying manual covers program requirements, installation, and use. The program and tutorial files are also included in the Supporting Information. Fit-o-mat offers the following key features, certain of which are treated in more detail in the next section:

- cross-platform, Python 3-based architecture
- released under the GNU General Public License (version 3.0 or later)
- free of charge, free to distribute
- data import from text and Microsoft Excel files
- options for data reduction and transformation
- rigorous propagation of data errors
- NLLS fitting to arbitrary, user-defined Python functions, including discontinuous and numerical functions
- publication-quality graphics in various vectorized and bitmapped output formats
- style sheets for preparing consistent figures
- program session files to promote ready data exchange
- tutorial mode to facilitate deployment in the classroom (see Figure 1B)

USE CASES IN THE CLASSROOM AND LABORATORY

Over the course of several months, Fit-o-mat has been applied in both teaching and research settings and has thereby proven to be a versatile and dependable resource for quantitative data evaluation and presentation. Among other use cases, the program has found deployment in a course on Synthetic Biology at the M.Sc. level, both in the laboratory and for homework assignments. Moreover, members of my research group routinely evaluate their experimental data and prepare figures for publication with the software. The versatility and utility of Fit-o-mat are demonstrated below by way of four examples representative of undergraduate and graduate curricula in chemistry and the life sciences. At the same time, these tutorials are well-suited to familiarize students with the principal concepts of data reduction, data transformation, error propagation, and NLLS analysis. Tutorial files T1−T6

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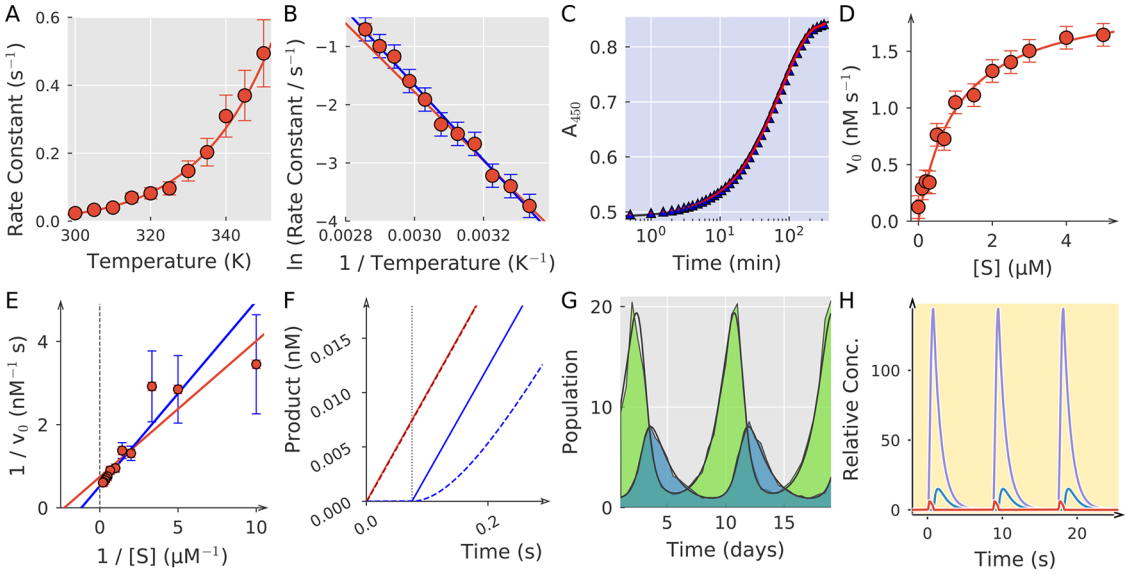

Figure 2. Gallery of exemplary figures prepared using Fit-o-mat (details are provided in the text). (A) Arrhenius fit of the temperature dependence of the rate constant k. (B) Fit of linearized data from (A) without (red curve) or with error propagation (blue curve). (C) Dark-recovery kinetics of the YF1 photoreceptor at 22 °C following saturating exposure to blue light as monitored by absorption at 450 nm. The original data points (red dots) were logarithmically reduced (blue triangles). (D) Evaluation of enzyme kinetics according to the Michaelis–Menten mechanism, where v_0 and $[S]$ denote the initial reaction velocity and substrate concentration, respectively. (E) Fit of linearized data from (D) without (red curve) or with error propagation (blue curve). (F) Comparison of initial reaction velocities v_0 calculated according to the Michaelis–Menten equation (eq 7, solid lines) or by numerical integration of the species rate equations implied by Scheme 1 (dashed lines). Good agreement is obtained in the quasi-stationary regime where $k_2 < k_{-1}$ (red), but significant deviations result for $k_2 > k_{-1}$ (blue). For clarity, in the latter scenario, the curves are slightly offset along the x axis, as indicated by the dotted line. (G) Prey–predator dynamics evaluated with the Lotka–Volterra model, with the prey and predator populations shown in green and cyan, respectively, and the global curve fit in black. (H) Numerical simulation of the Belousov–Zhabotinsky reaction using the Oregonator mechanism. Red, blue, and purple curves denote the oscillating concentration profiles of $HBrO_2$, Br^-, and Ce(IV), respectively.[22,23]

included with the Fit-o-mat program recapitulate in detail the examples discussed below (see the Supporting Information).

Use Case 1: Temperature Dependence of Reaction Rate Constants According to the Arrhenius Equation

As mentioned in the Introduction, the evaluation of the temperature dependence of rate constants k yields mechanistic insight into chemical reactions, notably by determining the energy barrier separating reactands and reaction products. The analysis is usually performed according to the Arrhenius equation (eq 1) or to the more elaborate transition-state formalisms by Eyring[19] and Kramers[20] if interpretation of the pre-exponential factor in thermodynamic terms is desired. NLLS fitting of the data contained in tutorial T1 to eq 1 yields parameter values of $A = (4.59 \pm 2.91) \times 10^7$ s^{-1} and $E_a = (53.5 \pm 1.7)$ kJ mol^{-1}, where the parameter errors represent confidence intervals of one standard deviation (Figure 2A). It should be noted that the parameter errors are assessed a posteriori on the basis of estimates of the variances σ_i^2 for the individual data points i.[21]

If instead the natural logarithm of k is evaluated as a function of T^{-1} according to the linear relationship shown in eq 2, a rather different parameter set results: $A = (8.03 \pm 6.69) \times 10^6$ s^{-1} and $E_a = (49.0 \pm 2.1)$ kJ mol^{-1} (Figure 2B). As remarked above, the data transformation of k affects the error distribution of the individual data points and hence their relative weights in the NLLS fit procedure (see eq 3). To remedy this problem, either data transformation should be avoided or data errors should be rigorously propagated.[5] If the dependent variable y is transformed to a new variable z that is a function of x and y, then the uncertainties σ_z of the transformed variable are given by eq 4:

$$\sigma_z^2 = [\sigma_x(\partial z/\partial x)]^2 + [\sigma_y(\partial z/\partial y)]^2 \quad (4)$$

The uncertainties σ_x of the independent variable x are commonly assumed to be negligible and are hence set to zero. Then eq 4 simplifies to

$$\sigma_z^2 = [\sigma_y(\partial z/\partial y)]^2 \quad (5)$$

When k and T are transformed, propagating the data errors according eq 4 and repeating the fit to eq 2 affords the parameter values $A = (4.47 \pm 2.66) \times 10^7$ s^{-1} and $E_a = (53.4 \pm 1.6)$ kJ mol^{-1}, which are closely similar to those obtained from the fit for the nontransformed data.

Aided by the accompanying tutorial T1, both undergraduate and graduate students in my laboratory have applied Fit-o-mat to similar problems. The students thereby familiarized themselves with fundamental concepts of NLLS fitting, the relevance of data errors, and the importance of propagating errors when transforming data. More generally, this example directly pertains to many scenarios that students in chemistry and the life sciences will encounter.

Use Case 2: Recovery Kinetics of Sensory Photoreceptor Proteins

Sensory photoreceptor proteins mediate diverse organismal adaptations to incident light.[24,25] At the molecular level, a chromophore cofactor absorbs light of a specific color and enters a series of reversible photochemical reactions called a photocycle. These reactions usually entail distinct changes in the absorption properties of the chromophore, and hence,

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spectroscopic measurements are well-suited to monitor progression through the photocycle. In particular, an advanced class in our M.Sc. Biochemistry program deals with photoreceptors of the flavin-nucleotide-binding light−oxygen−voltage (LOV) family.[26] Monitoring the recovery to the resting state of the receptor over time following exposure to blue light[27] allows inferences about the molecular environment of the chromophore to be drawn.[28−30] The so-called recovery kinetics of the absorption signal A can usually be described by a sum of n exponential functions according to eq 6:

$$A(t) = A_0 + \sum_i^n A_i \exp(-k_i t) \tag{6}$$

where the parameters A_i and k_i denote the amplitudes and rate constants, respectively, associated with the individual exponential functions. Knowledge of the recovery kinetics is practically relevant for the deployment of sensory photoreceptors as light-gated actuators in optogenetics for the accurate control of cellular physiology and parameters.[31] The accompanying tutorial T2 includes experimental data on the recovery reaction of the engineered photoreceptor YF1 at 22 °C,[32] which were acquired during class. The increase in absorption at 450 nm over time can be reasonably fitted by a single-exponential function (i.e., $n = 1$ in eq 6) and yields a rate constant of $k_1 = (1.37 \pm 0.002) \times 10^{-2}$ min^{-1} (Figure 2C). As is evident from Figure 2C, data were recorded on a linear time scale well into the regime where absorption has reached a constant plateau value. Fit-o-mat allows reduction of the experimental data to a desired number of logarithmically spaced data points while propagating data errors according to eq 4. A fit of the resultant data yields an almost identical value for k_1, thus demonstrating that the reduction did not incur any significant loss of information.

Use Case 3: Enzyme Kinetics

A hallmark of enzyme-catalyzed reactions is that their initial velocity v_0 does not scale linearly with concentration of reactants (or substrates) but hyperbolically approaches a limiting maximum value v_{max}. In their seminal work,[6,7] Michaelis and Menten accounted for this observation by proposing that the substrate, S, and enzyme, E, first form an enzyme−substrate complex, ES, before catalysis and formation of the product, P, and its release ensue (Scheme 1).

Scheme 1. Enzymatic Reaction Sequence According to Michaelis and Menten[6,7]

$$\mathrm{E + S} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{ES} \xrightarrow{k_2} \mathrm{EP} \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \mathrm{E + P}$$

Essentially the same formalism is still used to date to correlate initial reaction velocities v_0 of enzymatic reactions with the substrate concentration [S]:

$$v_0 = v_{max}[\mathrm{S}]/([\mathrm{S}] + K_M) \tag{7}$$

in which

$$v_{max} = k_2[\mathrm{E}_0] \tag{8}$$

where $[\mathrm{E}_0]$ is the total enzyme concentration. It should be noted that eq 8 reflects the fact that at high substrate concentrations almost all of the enzyme is in complex with substrate, and hence, $[\mathrm{ES}] \approx [\mathrm{E}_0]$. Under the assumption that the concentration of ES is quasi-stationary over time,[33] K_M is given by

$$K_M = (k_{-1} + k_2)/k_1 \tag{9}$$

Tutorial T3 contains enzyme kinetics data that, when evaluated according to eq 7, yield the Michaelis−Menten parameters $v_{max} = (2.00 \pm 0.01)$ nM s^{-1} and $K_M = (1.02 \pm 0.14)$ μM. Data from enzyme kinetics are frequently transformed to a linearized form following the Lineweaver−Burk formalism:[8]

$$\frac{1}{v_0} = \frac{1}{v_{max}} + \frac{K_M}{v_{max}} \cdot \frac{1}{[S]} \tag{10}$$

Whereas this transformation certainly holds merit for qualitative considerations, especially when appraising the effect of enzymatic inhibitors,[34] its use for quantitative data evaluation should be avoided (also see ref 3). This is readily demonstrated for the sample data upon transformation of v_0 and $[S]$ to their reciprocal values v_0^{-1} and $[S]^{-1}$. When the transformed data are fitted to eq 10, distinctly different parameter values result: $v_{max} = (1.35 \pm 0.29)$ nM s^{-1} and $K_M = (0.44 \pm 0.14)$ μM. Closer inspection reveals that upon transformation the data point with the originally largest relative uncertainty gained considerable weight in the fitting procedure, thus corrupting the results. As remarked above, this situation can be remedied by consequently propagating the data errors through all of the reduction and transformation steps. As is apparent from eq 4, the individual data errors in v_0 are thus scaled by the inverse square of v_0, and their relative weights in the NLLS fit are drastically altered. A fit of the data with propagated errors yields fit values of $v_{max} = (1.91 \pm 0.08)$ nM s^{-1} and $K_M = (0.85 \pm 0.11)$ μM, in better agreement with those for the nonlinearized data.

Students should be aware that the Michaelis−Menten equation yields an accurate estimate of the initial reaction velocity v_0 only if the assumption of quasi-stationarity of ES holds (Figure 2F). This can easily be recapitulated with Fit-o-mat by casting the Michaelis−Menten reaction scheme as a set of ordinary differential equations (ODEs). The Python library *SciPy* comprises efficient algorithms for the numerical solution of such ODE systems and can be imported into Fit-o-mat fit functions. Doing so reveals that for scenarios where the rate constant k_2 for the reaction of ES to EP (and onward to product) is large relative to the rate constant k_{-1} for the dissociation of the ES complex, significant deviations in the initial reaction time course result[35] (Figure 2F and tutorial T4).

Assigned as homework, tutorial T3 introduces students to the implications of the data transformation that is widely, albeit often uncritically, used in steady-state enzyme kinetics. Tutorial T4 provides students with the means to explore hands-on the assumptions underlying the Michaelis−Menten formalism.

Use Case 4: Oscillating Reactions

The final example regards oscillating reactions, which hold immediate fascination for students and teachers alike and are popular study subjects. Oscillatory phenomena generally take place far from equilibrium and constantly dissipate energy. Oscillations occur in nature and can be deliberately constructed in both biological[36] and chemical systems.[37,38] In a classical example, Lotka[39] and Volterra[40] modeled the

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interdependent temporal population dynamics of prey x and predator y according to the ODEs shown in eqs 11 and 12:

$$dx/dt = \alpha x - \beta xy \quad (11)$$

$$dy/dt = \delta xy - \gamma y \quad (12)$$

In the Lotka−Volterra model, prey procreates at a rate αx and dies off at a rate βxy that depends on the predator population. On the other hand, the predator procreates at a rate δxy that depends on the availability of prey and dies off at a prey-independent rate γy. Starting from a set of initial conditions (populations x_0 and y_0 for the prey and predator, respectively, at $t = 0$), the system of ODEs can be numerically integrated with *SciPy* to obtain the solutions $x(t)$ and $y(t)$ (see tutorial T5). A global NLLS fit of the simulated prey and predator populations to the numerical solution of eqs 11 and 12 faithfully recovers the parameters x_0, y_0, α, β, γ, and δ used to generate them (Figure 2G).

Oscillatory reactions are not confined to the realm of biology but also occur in chemistry, as best exemplified by the well-known Belousov−Zhabotinsky[37,38] (BZ) reaction. Mixed at appropriate ratios, aqueous solutions of cerium sulfate, potassium bromate, and malonic and citric acid display spontaneous and sustained oscillations that can be visually followed as cerium cycles between its yellow +IV and colorless +III oxidation states. As reviewed elsewhere,[37,38] the sequence of chemical reactions underpinning the BZ reaction is complex but can be simplified to the Oregonator model,[22,23] which comprises five second-order chemical reactions. These reactions give rise to a set of ODEs, which again can be numerically solved in time using *SciPy* functions (see tutorial T6). The implementation as a user function in Fit-o-mat enables students and teachers to readily simulate and recapitulate the BZ reaction for different parameter sets (Figure 2H). More generally, tutorials T5 and T6 demonstrate how numerical functions can be implemented in Fit-o-mat.

CONCLUSIONS

As the above case studies demonstrate, Fit-o-mat represents a versatile yet accessible platform for NLLS fitting and graphical presentation of diverse data in chemistry and the life sciences. A graphical user interface endows students, instructors, and researchers with ready access to well-honed Python libraries for numerical analysis and plotting. Application in classroom and laboratory settings has shown that students rapidly learn how to employ the program, even with limited prior instruction. The software thus facilitates the teaching of general concepts of data evaluation, NLLS fitting, and graphical presentation. Of particular benefit, the program conveys the significance of data reduction and error propagation, which, judging by experience in the classroom, represent aspects that are widely underappreciated by students. As Fit-o-mat runs on different operating systems and is free of charge, students are encouraged to install Fit-o-mat on their own computers and take it away from class. They are hence equipped with a tool to quantitatively analyze data according to various functional models, including functions of their own device, and potentially transcending the classroom. As a case in point, experience in my research group has shown that Fit-o-mat enables the evaluation of data acquired in the laboratory and the preparation of figures for scientific publications. Finally, Fit-o-mat compellingly illustrates the versatility of Python and may thus pique student interest in becoming familiar with this programming language.[17]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.8b00649.

ZIP archive containing the Fit-o-mat program, supporting files, documentation, and tutorials (ZIP)

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Notes

The author declares no competing financial interest.

The ZIP archive can also be downloaded free of charge from http://www.moeglich.uni-bayreuth.de/en/fit-o-mat or http://github.com/TheAngulion/fit-o-mat. An executable version for Windows is available from http://www.moeglich.uni-bayreuth.de/en/fit-o-mat.

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