Extending an alginate drug delivery experiment to teach computational modeling and engineering analysis to 1st year biomedical engineering students

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Abstract

Engaging biomedical engineering (BME) students in the first year has been an important part of The University of Texas at Austin's strategy to improve student motivation, retention, and self-efficacy. First year engineering curricula across the country have increasingly included an introduction to engineering or design course in addition to core math and science courses. At UT Austin, a first-year design course and drug-delivery design class module has been previously described[1]. This course has since been expanded from 1 credit hour to 3 credit hours and the drug-delivery design module has been enhanced to include computational design and analysis using 2 different tools (Microsoft Excel and MATLAB). Previously, students analyzed their experimental data using simple curve fitting to determine the diffusivity constant. This paper describes the instruction of a Fick's law-based computational simulation implemented in both Excel and MATLAB in order to match students' experimental data. Students were able to use their simulation to solve for the diffusion coefficient and to estimate the amount of drug (a dye was used as a surrogate for a drug) lost in the drug delivery device loading process. In addition, students learned how to use both Excel and MATLAB for engineering analysis so that they will be prepared for future engineering courses. General Excel and MATLAB competencies were tested using low-stakes in-class quizzes and students' attitudes were measured from end-of-semester course and instructor surveys. Students showed functional Excel and MATLAB knowledge and responded positively on course and instructor surveys.

1. Introduction

In the biomedical engineering (BME) department at the University of Texas at Austin, a first-year "Introduction to Biomedical Engineering" course has been an important component of the strategy to help students envision what a BME education and career would entail. Initially, this course was offered as a one-credit hour seminar format, however, the class was expanded to include a design component in order to engage students in formal engineering training early in their curriculum. This trend has occurred in many engineering programs across the United States[2]. The class (now called BME 303L) was increased to 2 credit hours in 2014 and to 3 credit hours in 2016 to allow for more time to teach engineering design and analysis topics. The first design/lab module for BME 303L is an alginate bead drug delivery which has been previously described[1]. This module has been expanded to include computational design and analysis in the lecture portion of the course because of the increase in credit hours and, correspondingly, classroom time.

One of the major learning objectives of BME 303L is to introduce students to some of the tools that they will need for engineering design and analysis. Use of Microsoft Excel is a ubiquitous and essential skill for nearly all industrial engineers[3]. To help learn some of the basics of Excel, students constructed a Fickian diffusion model in an Excel spreadsheet. The model was then related to their laboratory portion of the course to better understand how the parameters in the diffusion experiment affected the results. Another tool that students are required to use in future engineering courses in the UT BME curriculum is MATLAB. The same Fickian model was revisited using MATLAB to introduce students to computer programming. Student's learning of these tools was assessed using 5 different assignments: an Excel spreadsheet model, a MATLAB diffusion model, a written report from the diffusion experiment, and quizzes for both Excel and MATLAB which covered topics that were completely unrelated to drug delivery and diffusion.

2. Methods: Drug-Delivery Module

The goal of an engineered drug-delivery device is to deliver a drug to the body in an effective concentration over an extended period of time (Figure 1). Students explored the design of a drug-delivery device by encapsulating allura red dye (a proxy for a drug or small molecule) in spherical alginate beads and analyzed the results to calculate the diffusion coefficient, D, between the allura red and the alginate.

2.1 Laboratory-based activities

The laboratory portion of the exercise remains largely unchanged from previously reported.

Week 1: 3mM of allura red dye was dissolved with 2% w/v of alginate in water, using mild heat. The solution was loaded into syringes fitted with 14g, 19g, and 30g blunt-tipped needles. Droplets of the allura red/alginate solution were dispensed into a solution of 2 M CaCl2, where the droplets quickly crosslinked into spherical beads. The three sizes of needles allowed the creation of 3 difference size alginate beads. Beads were stored in a conical tube with a small amount of water to keep them hydrated.
Week 2: Students measured the size of alginate beads using a stereomicroscope and ImageJ for image analysis. The average radius of the beads was used as an input to the diffusion model.
Week 3: Students prepared to measure the amount of dye diffusing from the alginate beads by developing a standard curve of allura red concentration in water. The absorbance at 500 nm wavelength was measured at various dilutions of allura red using a UV/Vis spectrophotometer. In order to develop the standard curve between concentration and measured absorbance, Microsoft Excel was used to make a least squares linear fit.
Week 4: Diffusion of allura red from beads into pure water was measured over 90 minutes. The alginate beads were placed into 10 ml of water in a beaker with a stirbar and the water was sampled at 1,2,3,5,7,10,15,20,30,60, and 90 minutes from the start of the experiment. The concentration in the samples was determined using absorbance spectrophotometry with the previously determined calibration curve.

2.2 Lecture-based activities

During the lecture portion of the course, students were taught the basics of diffusion, including Fick's 1st law. After the diffusion lessons, 5 lecture periods were devoted to creating a model of the allura red diffusion experiment in an Excel spreadsheet (Figure 2A). The Ritger-Peppas approximation[4] (equation 1) was also implemented as a second model for the purpose of demonstrating that there is more than one way to analyze experimental data.

$$\frac{M_t}{M_\infty} = kt^n \qquad (1)$$

Excel model development was guided by the instructor walking students through techniques in Excel and challenging students to implement each step. A "think, pair, share" teaching model was used at each stage of model development. Later in the semester, MATLAB was taught in a similar method to create Fickian and Ritger-Peppas models of the alginate bead diffusion experiment. The Excel-based model served as a template for the tasks and equations needed in the MATLAB models.

2.3 Assessment

Five assignments were used to evaluate student learning. In order to demonstrate working models, students submitted their Excel spreadsheet and MATLAB code, which were worth 5% of the semester grade each. If the students were participating in the in-class exercises, they could expect fairly high grades for these assignments. The output were plots of the concentration of dye in the water and dye left in the beads (with dummy input data) to demonstrate that the Fick's law model was working correctly (Figure 2B). The Ritger-Peppas equation was also plotted (Figure 2C).

The third assignment was the drug-delivery device report, worth 10% of the semester grade. In the report, students fit the Fickian model to their experimental data using their experiment parameters (average radius of beads and number of beads). The diffusivity constant (D) and initial concentration (C_0) of allura red dye trapped in the beads were parameters that could be estimated to best fit the model to the experimental data. Likewise the Ritger-Peppas equation was fit to the model by solving for best fit k and n values. As part of their report, students compared the values of D, C_0, k, and n between bead sizes and discussed the ways that the drug delivery platform could be designed to achieve a target release profile.

Finally, students learning of Excel and MATLAB was assessed using quizzing with unrelated analysis problems to solve in Excel and MATLAB, respectively. The purpose of the quizzes was to test students' ability to apply these tools to new situations. Each quiz was worth 3% of the semester grade. All grades are presented as mean ± standard deviation.

3. Results and Discussion

3.1 Development of Excel and MATLAB models of drug delivery device.

Coming into BME 303L, students have very limited understanding of how to use Microsoft Excel for engineering design and analysis. They also have very little experience computer programming with no knowledge of MATLAB. The goal of adding the Excel and MATLAB analysis portions to the drug delivery experiment was to introduce engineering tools early in students' progression through the BME program.

3.2 Fitting models to experimental data

Students were able to use the Excel model that they developed to fit their experimental diffusion data. Students used parameters from the experiment as inputs to the Excel model including average bead size, number of beads used, and volume of water into which beads were placed. The remaining two inputs to the model, initial concentration of allura red in the beads (C_0) and the diffusivity constant (D) were unknowns, but could be solved by best fitting the model to experimental data (Figure 3A). Although the beads were synthesized with an initial concentration of 3 mM allura red dye, students found that in order to fit the "steady-state" portion of the model (past 60 minutes), the initial concentration had to be set less than 3 mM. This demonstrated that dye was lost in the manufacturing and storage processes before the experiment. The diffusivity constant was also fit to the curve as best possible resulting with a D in the range of ~$1x10^{-6}$ to $1x10^{-5}$ cm^2/sec, which agrees well with published reports of the diffusion coefficient for small molecules in alginate[5].

The Ritger-Peppas equation was used as an alternate model to fit the allura red dye diffusion from alginate beads

(Figure 3B). This equation is much simpler to implement in Excel and MATLAB than the Fick's law-based diffusion model and it fit the experimental data better that the Fick's law model for the 1st 10-15 minutes of data. As in the Fickian model, students "solved" for input parameters (in this case k and n) by best fitting the equation to their experimental data. The n value for the Ritger-Peppas equation for spherical shapes should be ~0.43 in its original formulation. However, some students found that values as low as 0.2 had to be used for n to best fit the equation to their data.

The MATLAB implementation of both the Fickian and Ritger-Peppas model followed the Excel implementation. Therefore when students fit the same experimental data in MATLAB, the same constants (C_0, D, k, and n) from the Excel model were used to fit data using the MATLAB model. The use of both Excel and MATLAB allowed students to validate their MATLAB code against the Excel spreadsheet.

3.3 Use of models to make conclusions about design of drug-delivery device

The purpose of using two different models was to demonstrate to students that often a single model of a system is not sufficient to adequately describe the behavior of the system. As part of their analysis, students analyzed how the parameters they calculated (C_0, D, k, and n) were impacted by how they executed the experiments and, conversely, how they could control these parameters to release the drug at a desired and designed rate.

In all cases, students observed that the initial concentration in the beads was less than the 3 mM that they initially synthesized in the beads. One of the important points of emphasis for this module was that the only way to accurately estimate how much dye was lost from the beads prior to the 'implantation' of the drug-delivery device was to implement the Fick's law model. Students were challenged to think of the loss in drug as an engineering design problem: what are some ways that a drug-delivery engineering company could modify the process to lose less drug and therefore save money?

Students were also asked to evaluate how the D could be altered in their device to better control the release of the drug. Students correctly concluded that bead size should not affect D (despite what their experimental results might have shown), but that the diffusion could be controlled by changing the alginate density or crosslinking or by modifying the drug to alter its diffusion rate.

Finally students found through their experiments and through research that the Ritger-Peppas parameters, k and n, could be affected by bead shape and size, as well as the properties of the alginate and the drug (as in the Fickian models).

3.2 Assessment of student learning

The graded results of the 5 assignments related to the diffusion experiment and Excel and MATLAB training are shown in Figure 4.

One learning outcome of the course is the ability to analyze data and draw conclusions. This outcome was assessed through a report describing the entire drug-delivery module (labeled controlled-release report in Figure 4). While students could not successfully complete this report without working Excel models, the drug-delivery report primarily measured students' writing and ability to make engineering conclusions and suggestions based on the data and their analysis. Student grades for the drug-delivery device report were 93.8 ± 10.2%, indicating that the students were successful at analyzing this data and presenting their results.

In order to assess the learning outcomes of applying Excel and MATLAB for engineering analysis, students had to submit complete Excel spreadsheet and MATLAB code as 'homework' assignments. The student scored 94.0 ± 6.2% on the Excel spreadsheet and 89.2 ± 8.9% on their MATLAB code. In-class quizzes (unrelated to diffusion modeling) were used to assess students' ability to use Excel and MATLAB to analyze data generically. In general, Excel quizzes tended toward financial problems and MATLAB quizzes were physics-based questions.

While quiz scores were lower for both the Excel (76.3 ± 7.2%) and MATLAB quizzes (62.5 ± 6.9%) than the other assignments, the activities that most students were able to do in a 50 minute quiz setting represent strong achievement. The results of both the model grades and the quiz grades show that students achieved more competency in Excel than MATLAB. This result was not unexpected due to the increase in complexity in going from a spreadsheet model to a computer-programming environment.

Based on the quiz results, students have shown some positive learning of Excel and MATLAB. However, there is still room for improving the way Excel and MATLAB are being taught in BME 303L. No initial assessment of Excel and MATLAB skills was done prior to the diffusion experiment, but students reported very low experience and skills using these tools. In the future, pre-testing can be used to gauge Excel and MATLAB competency in BME 303L at the start of the semester and to better quantify improvement in these areas. Furthermore, because of the in-class "think, pair, share" nature of the teaching how to model diffusion, students who are truly lost in the modeling process can remain lost while still submitting seemingly correct diffusion models for homework grades. In-class, these students can simply wait for other students who are more engaged to think for them and provide the answers and algorithms. Adding small outside-of-class homework assignments to encourage every student to be accountable for their own learning may help in this area.

4. Summary

Using computational tools to analyze data will continue to be an important outcome for engineering education. First year students are learning Excel and MATLAB in the context of a relevant biomedical engineering problem and are analyzing data that they collected using these tools. This paper demonstrates the initial steps taken to expand upon a

successful laboratory experiment and pair it with computational modeling to achieve learning Excel and MATLAB tools.

Acknowledgement

All results presented were collected from student work submitted in BME 303L from Fall 2016-Fall 2017.

References

[1] S. R. Marek, W. Liechty, and J. W. Tunnell, "Controlled drug delivery from alginate spheres in design-based learning course," in *American Society for Engineering Education*, 2012, no. 2012, p. 25.345.1-13.

[2] J. E. Froyd, P. C. Wankat, and K. A. Smith, "Five major shifts in 100 years of engineering education," in *Proceedings of the IEEE*, 2012, vol. 100, pp. 1344–1360.

[3] K. A. Woodbury, R. P. Taylor, J. Huguent, T. Dent, J. Chappell, and K. Mahan, "Vertical integration of Excel in the thermal mechanical engineering curriculum," in *Proceedings of the IMECE2008*, 2008, pp. 1–9.

[4] P. L. Ritger and N. A. Peppas, "A simple equation for description of solute release I. Fickian and non-fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs," *J. Control. Release*, vol. 5, no. 1, pp. 23–36, 1987.

[5] J. Oyaas, I. Storrø, H. Svendsen, and D. W. Levine, "The effective diffusion coefficient and the distribution constant for small molecules in calcium-alginate gel beads.," *Biotechnol. Bioeng.*, vol. 47, no. 4, pp. 492–500, Aug. 1995.

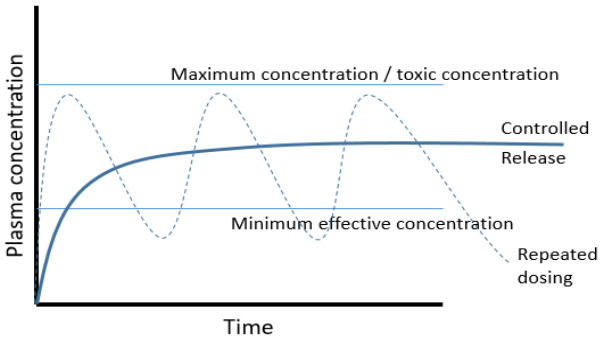

Figure 1 – A controlled release drug delivery device can deliver a drug to an effective therapeutic concentration over a long period of time, compared to repeated dosing, such as oral medication

A

dt	C0	r bead	N beads	V beads	V H2O	SA beads		Dij	k	0.3
(sec)	(mM)	(cm)		(ml)	(ml)	(cm^2)		(cm^2/sec)	n	0.43
60	1	0.1585	100	1.667925	10	31.56955		1.00E-05		
time	Beads			Water			dC/dr	J	Diffused	R-P Eqn
(sec)	C (mM)	C (mol/ml)	(moles)	C (mM)	C (mol/ml)	(moles)	(mol/ml/cm)	(mol/cm^2 sec)	(moles)	(Mt/Minf)
0	1.0000	1.000E-06	1.668E-06	0.0000	0.000E+00	0.000E+00	-6.309E-06	6.309E-11	1.195E-07	0.0000
60	0.9284	9.284E-07	1.548E-06	0.0120	1.195E-08	1.195E-07	-5.782E-06	5.782E-11	1.095E-07	0.3000
120	0.8627	8.627E-07	1.439E-06	0.0229	2.290E-08	2.290E-07	-5.298E-06	5.298E-11	1.004E-07	0.4042
180	0.8025	8.025E-07	1.339E-06	0.0329	3.294E-08	3.294E-07	-4.855E-06	4.855E-11	9.197E-08	0.4812
240	0.7474	7.474E-07	1.247E-06	0.0421	4.214E-08	4.214E-07	-4.449E-06	4.449E-11	8.428E-08	0.5445

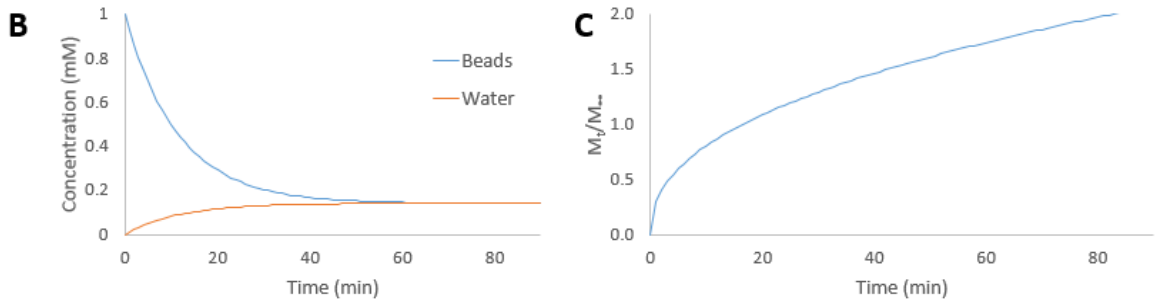

Figure 2 – (A) Fick's Law model and Ritger-Peppas equation implemented in an Excel spreadsheet. Constants are stored in the top 3 rows with the model implemented as a function of time. (B) The model demonstrated that the concentration of allura red in the alginate beads and diffused into pure water equilibrate over time. (C) The Ritger-Peppas model plotted from Excel spreadsheet.

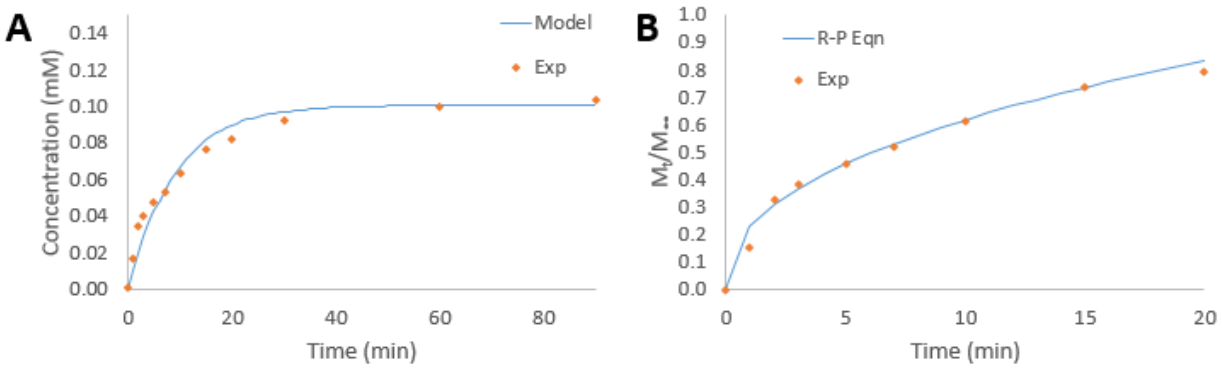

Figure 3 – (A) Excel Fick's law model fit to match experimental data. The initial concentration of allura red in alginate beads was adjusted to match the conditions after 60 minutes and the diffusion constant was adjusted to match the initial 20 minutes of data. (B) Ritger-Pepppas equation, with k and n values adjust to match the experimental data for the 1st 20 minutes of diffusion better than the Fick's law model

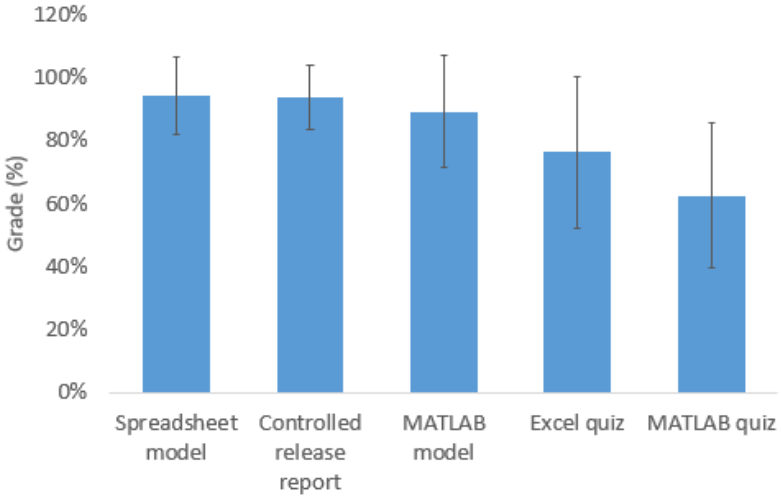

Figure 4 – Student grades for the 5 assignments demonstrate learning of both Excel and MATLAB