A Pharmacokinetic Simulation-Based Module to Introduce Mass Balances and Chemical Engineering Design Concepts to Engineering Freshmen

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Introduction

Often the opportunities for freshmen engineering students to be exposed to chemical engineering are limited. Introduction to chemical engineering is typically a sophomore level course. Freshman general engineering courses come in a variety of forms from college orientation courses to lectures on basics of design and safety to project-based laboratory or design experiences. A recent survey of 50 chemical engineering undergraduate programs showed that 6% of those programs offered engineering laboratory experiences for freshmen through general engineering courses and 4% offered similar laboratory experiences through chemical engineering specific courses[1]. Several engineering educators have developed hands-on laboratory or design modules targeted for introducing freshmen to chemical and/or biomedical engineering topics and concepts using applications including sensors[1], evaporative cooling[2], water treatment[3], fuel cell cars[4], food and beverage science[5-9], drug delivery[10-12], and human physiology[13, 14]. Experiments, simulators, and lesson plans have also been developed for introducing pharmaceutical engineering to students in K-12 and in college beyond the freshman year[15-22]. The common thread through all of this previous work is that there is ample evidence that students consider hands-on experiences through experiments or simulations to be valuable.

Oklahoma State University, a large, public state university, has an annual three-week high school-to-college transitional program for incoming engineering freshmen. Successful completion of the program counts as the required general freshman engineering course. The program is targeted to students from underrepresented groups and to first-generation college students. Most of the students have not yet placed into Calculus I, so there is a strong math readiness component to the program. To enable exposure to engineering disciplines through active experiences, engineering departments are invited to contribute discipline-specific hands-on experimental or simulation-based design modules. The chemical, mechanical, industrial, and civil engineering departments at the university taught design modules in both 2015 and 2016. The students in the program attend daily sessions of engineering design and rotate between three of the disciplines during the three-week program allowing them to experience multiple engineering disciplines in a brief period. We have developed a simulation-based chemical engineering design module involving a set of interactive, hands-on computational activities that introduce engineering freshmen to the discipline of chemical engineering through a pharmacokinetics application. We taught the module over a five-hour period three times each in 2015 and 2016 during the high school-to-college transitional program. This paper describes our simulation-based module.

Many simulation tools have been developed to promote active learning of chemical engineering[22-25]. A study has shown that students can be engaged learners through the use simulations if the simulations are designed with learning as the primary goal and if they are easy to navigate and use[26]. We sought to build on these principles and best practices of previous simulation tools by designing a simulation that allows the users to manipulate intuitive variables and observe the dynamic impacts of pharmaceuticals on the human body. The learning objective

of the module is to introduce open-ended engineering design and problem solving through a pharmaceutical application of chemical engineering. Our goal for the module is to give students exposure to engineering design, basic concepts of chemical engineering mass balances, and motivation to pursue chemical engineering (either by persisting in the major or by switching into the major). It is of special interest to highlight a realistic biomedical application for chemical engineering design rather than the traditional refinery applications that are common in the energy industry-focused state where the university is located. The safety concerns and impracticalities for working with chemicals in a short-duration project and the authors' research interest in mathematical modeling led us to develop a simulation-based module. Pharmaceutical engineering is a topic that is approachable for freshmen students without formal training due to their prior experience of taking medicines. The module involves team work and emphasizes communication skills along with the altruistic problem of treating patients with high blood pressure. These components were intentionally chosen to foster interest and retention of the diverse student participants in the program, particularly women, following the recommendations in previous works focused on improving access to design projects for first-year engineering students to promote the retention of female students[27, 28]. The authors are all female chemical engineers and are enthusiastic about serving as role models for young engineers in the program and beyond.

Background

Two key terms in pharmaceutical engineering are pharmacokinetics and pharmacodynamics. Pharmacokinetics (PK) describes the movement of a drug into, through, and out of the body via absorption, distribution, metabolism, and excretion following its administration. Pharmacodynamics (PD) describes what the drug does to the body including the mechanism of drug action and the relationship between drug concentration and effect. PD, in combination with PK, helps explain the relationship between dose and response.

The application for the design module is the pharmaceutical regulation of blood pressure by controlling levels of the hormone angiotensin II (Ang II). Several pharmaceuticals known as angiotensin converting enzyme (ACE) inhibitors are on the market to block Ang II production. Ang II is a hormone that constricts blood vessels, which raises the blood pressure and increases the work required for the heart to pump blood. Blocking Ang II production with an ACE inhibitor can lower blood pressure. ACE inhibitors have also been proven to aid patients with heart failure, coronary artery disease, adult onset diabetes, "diabetic tendency" and high blood pressure, as well as mild kidney disease, particularly if there is protein in the urine.

A mathematical model for the chemical reaction kinetics involved in natural production of Ang II and the dynamic biological response to pharmaceuticals to lower blood pressure in a dose-dependent manner was formulated by the authors[29]. The PK/PD model quantifies the dynamic relationships between ACE inhibitor drug concentration and Ang II concentration[29]. The model was parameterized for two ACE inhibitor drugs benazepril and cilazapril and two cases of patient kidney function (KF): normal and impaired. To provide a simulation tool for our target audience of educators and students, we created an interactive graphical user interface (GUI) in MATLAB for manipulating the input parameters under various scenarios and viewing the dynamic model output on plots (Figure 1). We packaged the model code, GUI, and the parameter sets into a

MATLAB app that enables a single download for all the associated files for the model and the GUI. We have made app freely available online[30]. After download, the program opens with one click from the app panel in MATLAB. Even for students with little to no programming experience, this is very approachable. It only involves opening MATLAB and the app without requiring the user to view the code that runs the simulation. The MATLAB app was created to be interactive and intuitive for those with no background in chemical engineering, pharmacokinetic concepts, or mathematical modeling.

The simulation inputs are drug dose, frequency of usage, ACE inhibitor drug, patient kidney function, and treatment duration. The simulation produces plots of Ang II levels vs. time and the drug concentration in the body vs. time. On the plot of Ang II levels vs. time, a line for the target reduction percentage for a healthy person compared to a hypertensive patient is included so that the user may seek to keep levels below the target efficacy. Using these results, the user can determine the best dose size and frequency for the ACE inhibitor and kidney function selected, making an educated decision as to reasonable dosage regimes for the virtual patient.

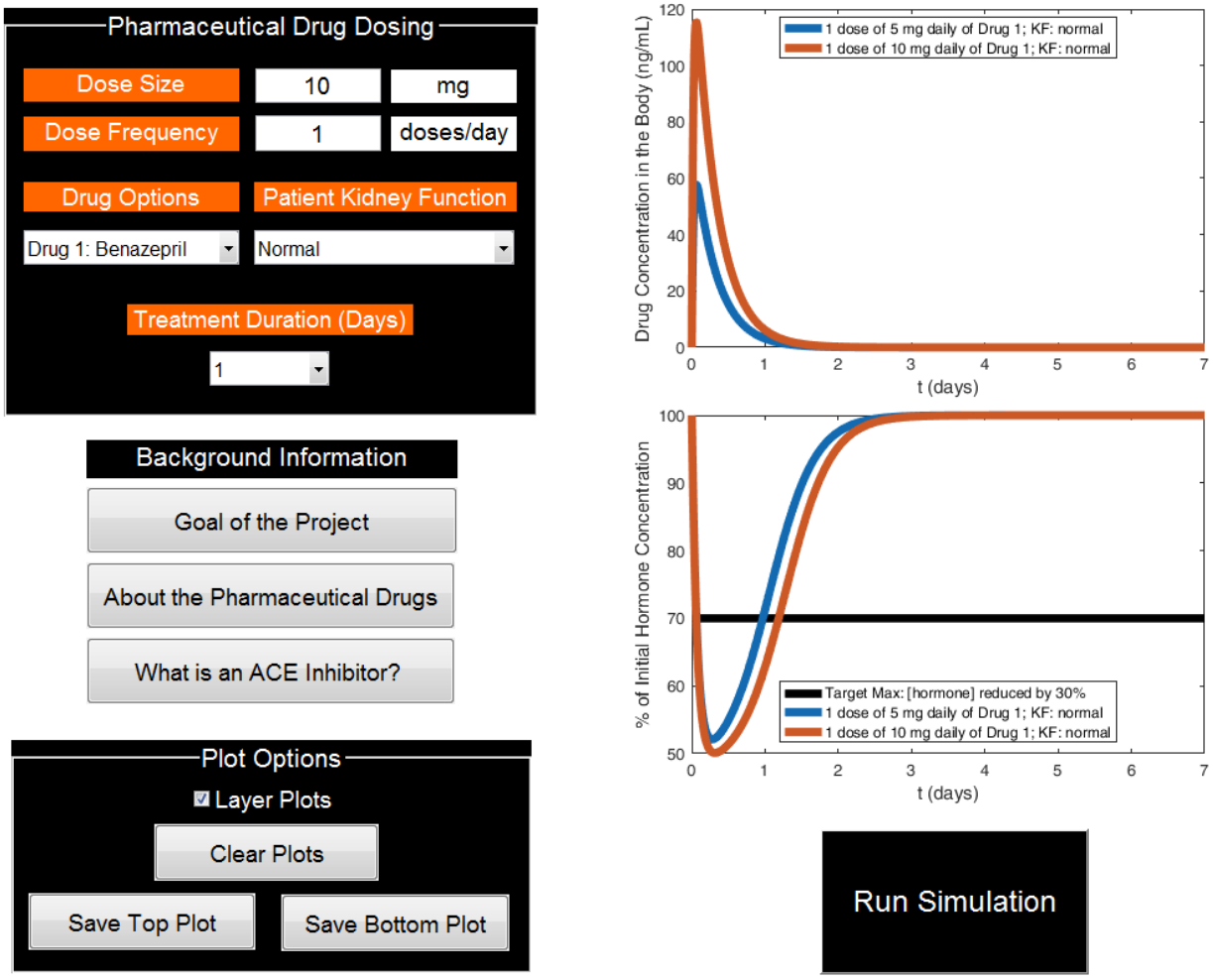

Figure 1: MATLAB graphical user interface for the pharmacokinetic/pharmacodynamics model of ACE inhibitor pharmaceuticals for normal and impaired kidney function.

Introductory Presentation

We start the module with introductions of the teaching team, which includes the senior author and undergraduate and graduate students from her research group. We then provide a high-level overview of chemical engineering for the students. We explain using Figure 2 that chemical engineers learn how to take raw materials in the forms of chemicals or energy; transport them; and transform them by mixing, adding or removing energy, reacting, or separating components in order to produce desired chemicals or energy forms. While we have had several chemical engineering students take the chemical engineering design module during the program, the majority of the students had declared other engineering majors. Even those declared as chemical engineering majors presumably have had little prior exposure to chemical engineering before college. Simple process flow diagrams for a petrochemical refinery and for blood pressure regulation in the human body are shown as examples of the boxes in Figure 2. Pharmaceutical dosage design is described as changing the raw materials when the physiological processes for transport and transformation may be disrupted in a patient in order to achieve the desired blood pressure product. After this introductory presentation, we move on to Activity 1.

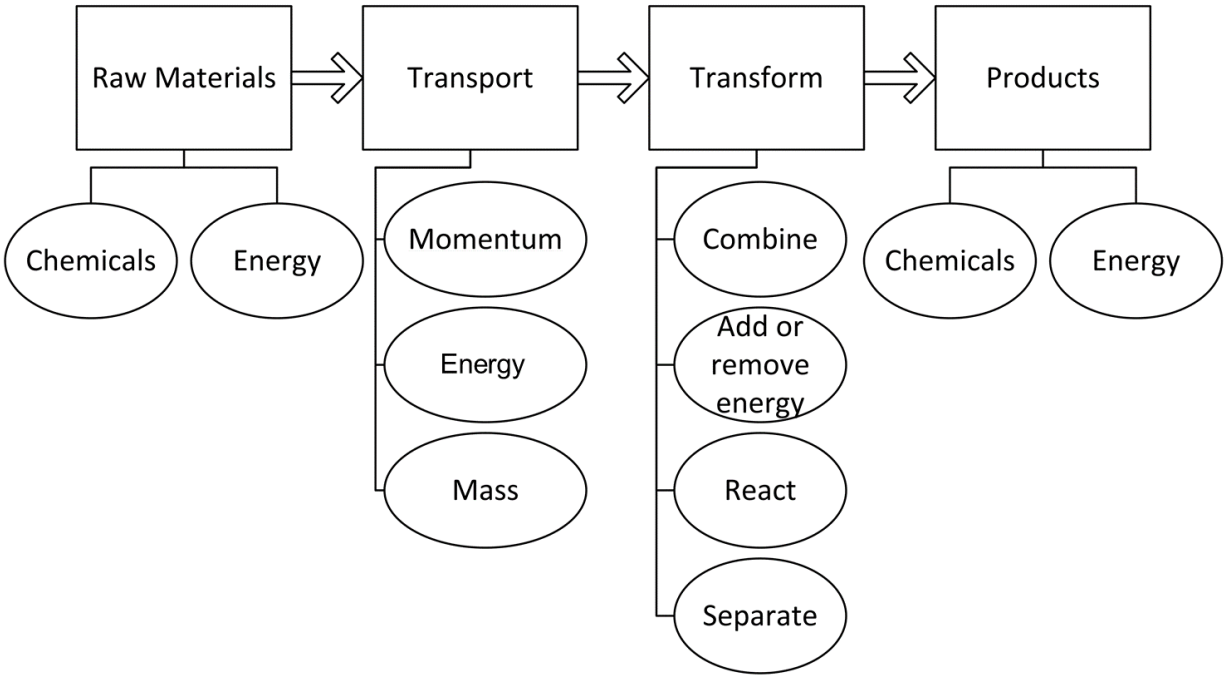

Figure 2: Flow chart of chemical engineering topics.

Activity 1: Student Development of a Dynamic Pharmacokinetic Model Using Mass Balances

In the first activity, the basic concept of mass balances is introduced as In – Out + Generation = Accumulation by drawing arrows into and out of a rectangle where mass accumulates in the illustration. Then we use Vensim PLE simulation software[31] to build simple dynamic models to describe the mass balances involved in tracking a pharmaceutical compound in the blood stream. We start by asking students inductive questions to describe inlets, outlets, generation terms, and locations where the drug might accumulate in the body. In Vensim arrows with a control valve

symbol and a source or sink cloud icon are used to represent the inlets, outlets, and generation terms. The volumes for accumulation are denoted by boxes. Students follow along with the instructor to draw the process flow diagram that is highlighted in the dashed box in Figure 3. The dynamic system represented in the figure is solved by ordinary differential equations in the background. A preconfigured PK model titled ''Pharma.mdl'' is available for free download from Shodor[32], a nonprofit that provides resources for computational science education. We use this preset model to accelerate student exploration with the model rather than focusing on entering the parameters and defining initial conditions. The "SyntheSim" option in Vensim is selected to activate slider bars on all model input variables. Students are asked to make predictions about the impacts of varying dosage amount, dosage per day, absorption rate constant, excretion rate constant, and drug half life on the plasma concentration of the medicine. The questions all relate back to the mass balances on the medicine in the digestive and plasma circulatory compartments.

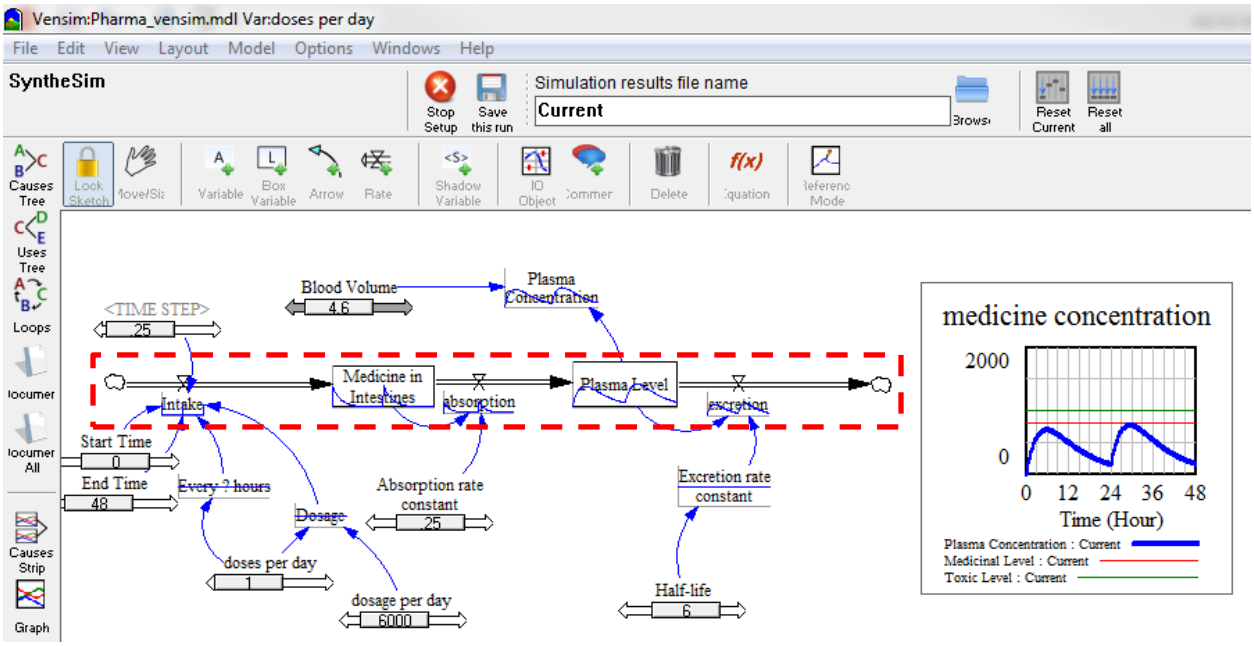

Figure 3: Vensim dynamic simulator displaying pharmaceutical PK model with slider bars enabled on all model input variables.

Activity 2: Design Project Using MATLAB Simulation App

The second activity extends the topics from the first activity into a chemical engineering design project that is engaging and approachable for students with little background knowledge in chemistry, mathematics, or engineering. In this activity, students engage in a design project using the interactive MATLAB simulation app for pharmaceutical regulation of blood pressure described in the Background section. First, the students watch a YouTube video on the Crash Course Kids channel about the engineering design process that emphasizes design as a trial and error cycle[33]. Students are assigned to work in teams of two or three to work through the steps of the engineering design process as defined by the TeachEngineering digital library[34]: researching a problem (high blood pressure), discussing potential solutions (ACE inhibitor pharmaceutical

drugs), and testing of possible designs (using the MATLAB app[30]). In Step 1 Ask: Identify the need & constraints, the students are introduced to the problem statement. The need: Design the best dose size and dosing frequency of pharmaceuticals (raw materials) that effectively reduce high blood pressure (the desired product). The constraints are student-defined pros/cons or "tradeoffs" for each design. Next, they are split into teams of two to three students and asked to do Step 2 Research the problem. They are pointed to a few websites on the background of hypertension, the symptoms of untreated hypertension, and ACE inhibitors for treating hypertension. For Step 3 Imagine possible solutions, students are asked to share findings from their readings to answer the following questions verbally during the class session:

- What are some possible solutions to treating hypertension with pharmaceuticals?
- What might an ACE inhibitor drug do?
- How would drug action change with amount or frequency of dose?
- How would the drug affect blood pressure?
- What are some factors and tradeoffs to consider when designing a drug dose?

In Step 4 Plan: Select a promising solution, students are assigned specific drug types and virtual patient kidney functions and asked how they could test possible drug dosing regimens. After brainstorming, the instructor introduces the ideas of pharmacokinetics, dynamic modeling using differential equations, and software tools for scientific computing. Then the students install the MATLAB app[30] on their lab computers.

The remaining three steps of the engineering design process comprise the bulk of the simulation-based design project. For Step 5 Create: Build a prototype, students specify the design case they have been assigned (Table 1) and chose trial input conditions. Next in Step 6 Test and evaluate prototype, the students run the simulation, analyze the plots critically to determine if the results are as expected and satisfactory. They are asked to list pros and cons for each prototype at this stage. Finally in Step 7 Improve: Redesign as needed, students chose another set of input conditions and retest until they have a design that best meets the design constraints they have imposed on themselves, such as convenient dosing frequency and achieving long period of therapeutic efficacy as indicated by lowering the blood pressure hormone (Ang II) below 70% of its original value.

Table 1: Design cases.

Case	Drug	Kidney Function
1	1	Normal
2	2	Normal
3	1	Impaired
4	2	Impaired

The MATLAB app allows students to interact with the pharmacokinetic simulation of the effects of two ACE inhibitors on Ang II levels by changing model parameters of dose size, frequency, drug compound, and patient cases. The simulation results for the drug concentration and

resulting Ang II levels are calculated upon a mouse click and are displayed in the app. Students can layer simulation results from previous trials to visualize the effects of changes in variables. Students brainstorm the relevant trade-offs for "optimizing" drug dosing. The problem is purposely open-ended to allow students the opportunity to design a dose schedule and to test it in a virtual patient. After they decide on a final design, the students are asked to use our template to create a one-slide presentation (Figure 4) to convey their results and learning outcomes to their peers. In the final class period, groups take turns giving 5 minute presentations will all group members participating. Each student provides written peer feedback in the form of pros and cons for the other teams. In the offerings of this simulation-based chemical engineering design module thus far, the students enjoyed seeing pharmaceutical applications of chemical engineering as well as the creative decision making aspect of the project.

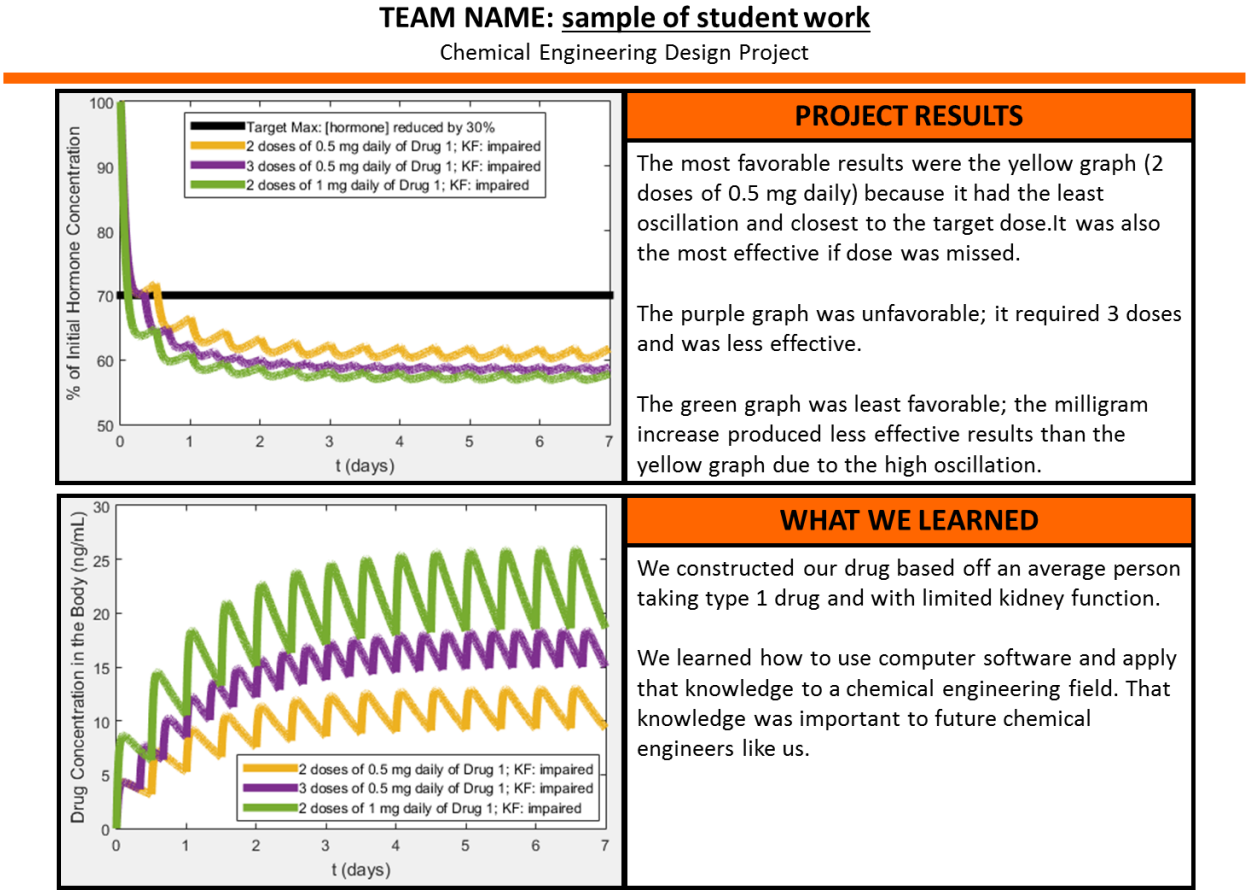

Figure 4: Sample presentation created by students to communicate their project results and key learning points.

Conclusions

The goal of the simulation-based design module is to introduce chemical engineering concepts in an interactive manner to students by having them design an optimal drug dosage and frequency of ACE inhibitors for different patient conditions. The two activites introduce students to the mass balances and the analysis of dynamic processes as well as basic concepts of differential equations and kinetic modeling. MATLAB applications are interactive simulations to perform

technical computing tasks. An app of this type has not been created previously for the same application and as an educational tool.

The Vensim and MATLAB simulation activities in this module are ways to work with the pharmaceutical side of chemical engineering by varying inputs and observing the results without actually having to do experiments. The simulations are portable and can be run on any computer with the software installed. The MATLAB simulation packaged with a graphical user interface in an app is student friendly, and minimal engineering or coding knowledge is necessary to operate and understand the application. The simulation is straightforward to run, so students spend the majority of their time running simulations and learning instead of trying to navigate the software. These qualities make it ideal for teaching high school or entry level college students.

The computational simulation-based module described here has also been utilized in other educational contexts including high school and middle school outreach events and a chemical reaction engineering course.

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