An Educational MATLAB App for Pharmacokinetic/Pharmacodynamic Modeling of ACE Inhibition

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Acknowledgments

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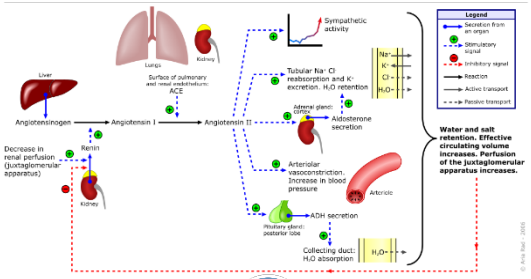
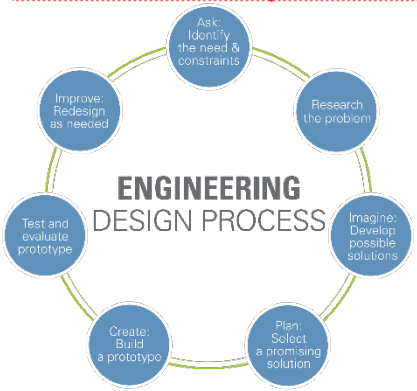
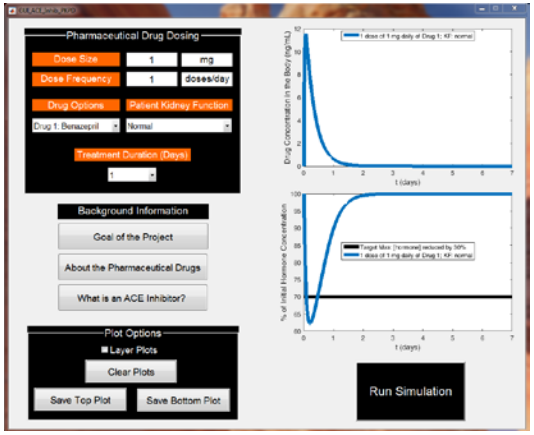
Our goal was to introduce chemical engineering & engineering design

- We developed
  - An interactive, hands-on design project to be completed with a MATLAB computer simulation packaged as an app
  - A module of exercises supporting the design project
- Target audience
  - Incoming freshmen participants in the CEAT Summer Bridge residential summer camp
  - Freshmen in Intro to Engineering course
  - Potentially for upper division CHE courses or outreach for HS students
- Topic motivation
  - Students have experience with pharmaceuticals
  - Our lab has research interests in the hormone Angiotensin II & its effects on diabetic kidneys

This talk focuses on three aspects of the educational PKPD MATLAB app







PKPD modeling and the biomedical/pharmaceutical application

Module of activities used to teach freshmen before the design project

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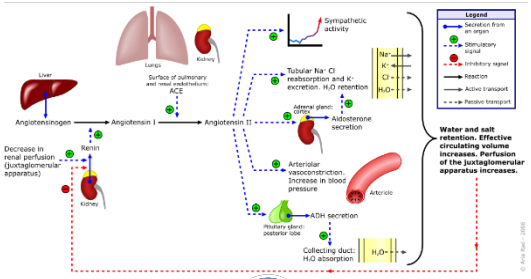

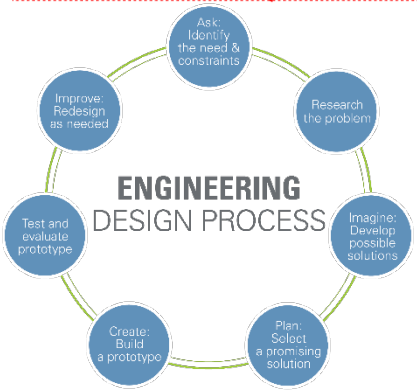

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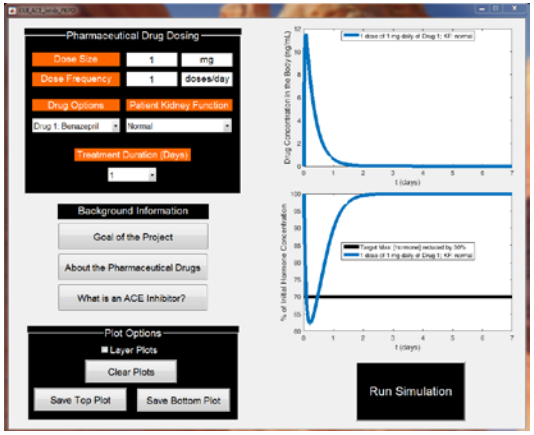
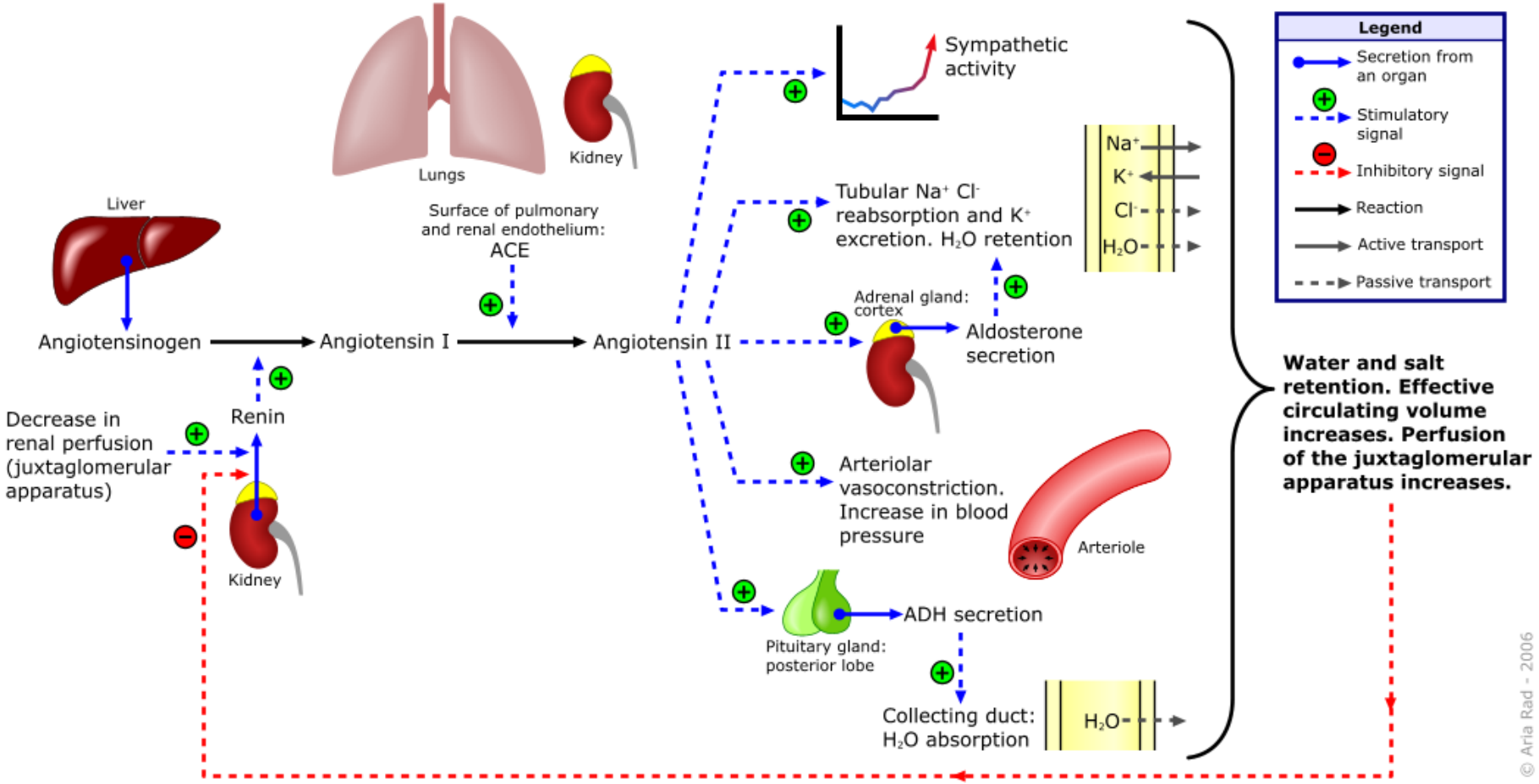


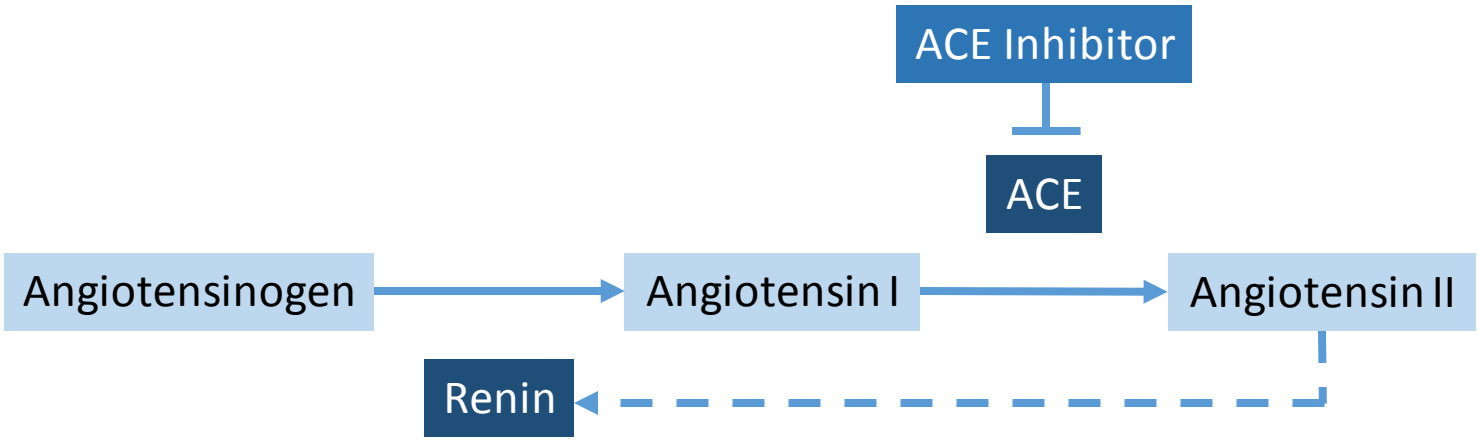
Design project

Renin Angiotensin System (RAS) regulates blood pressure & fluid balance through hormones



ACE inhibitors treat dysregulation of the RAS

- Angiotensin-converting-enzyme (ACE) is a key enzyme in the production of Angiotensin II in the RAS
- ACE inhibitors are pharmaceutical drugs used for the treatment of hypertension to lower blood pressure
- Many ACE inhibitors are on the market



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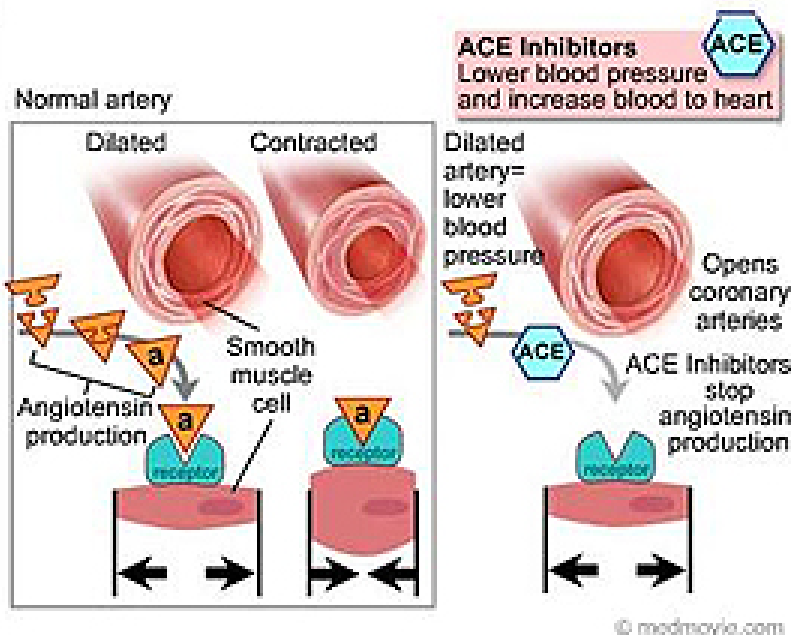
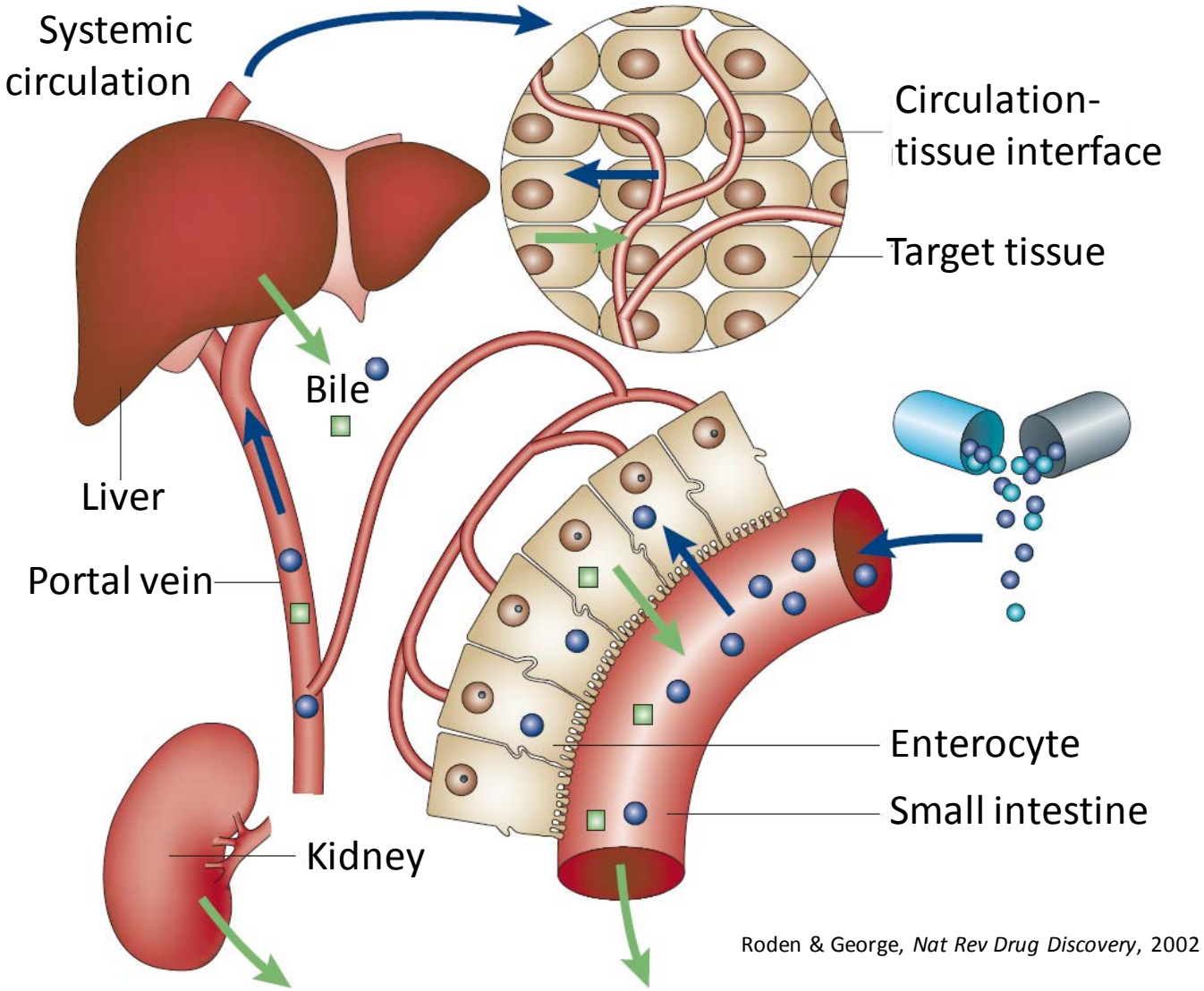


Pharmacokinetics (PK) describes the body's effect on a drug



Roden & George, *Nat Rev Drug Discovery*, 2002

Movement of drug into, through, & out of the body

Pharmacokinetic (PK) model for the drug concentration for multiple doses

$$C = \frac{Dk_a}{\frac{V}{F}(k_a - k_e)}\left[\frac{[1-\exp(-nk_e\tau)](\exp(-k_e t))}{1-\exp(-k_e\tau)} - \frac{[1-\exp(-nk_a\tau)](\exp(-k_a t))}{1-\exp(-k_a\tau)}\right]$$

$$k_e = \frac{\ln(2)}{t_{1/2}}$$

$$\frac{V}{F} = \frac{D}{AUCk_e}$$

$$t_{max} = \frac{ln(\frac{k_a}{k_e})}{(k_a - k_e)}$$

C = drug concentration
k_a = absorption rate constant
k_e = elimination rate constant
t = time
τ = dosage interval
$t_{1/2}$ = half time
D = dose size
F = fraction absorbed
V = volume
AUC = area under curve

Pharmacodynamics (PD) describes the effect of a drug on the body

Mechanisms of drug action & the relationship between drug concentration & effect

$$\boldsymbol{Inhibition = I_{max} C/(C_{50} + C)}$$

$$\frac{\boldsymbol{I}}{\boldsymbol{K_I}} = \frac{\boldsymbol{Inhibition}\left(\frac{[\boldsymbol{AngI}]_0}{\boldsymbol{K_m}} + \boldsymbol{1}\right)}{\boldsymbol{1 - Inhibition}}$$

I_{max} = max inhibition
C_{50} = concentration at 50% of max effect
$\frac{I}{K_I}$ = competitive inhibition term
K_m = Michaelis constant

Pharmacodynamic (PD) model of ACE inhibitor effects on RAS

Differential equations used to track variable hormone and enzyme concentrations of AngI, AngII, and Renin

$$\frac{d[AngI]}{dt} = r_1 - r_2 - r_5 \qquad \frac{d[AngII]}{dt} = r_2 - r_3 \qquad \frac{d[Renin]}{dt} = -r_4 + r_6 - r_7$$

Baseline constants found by setting differential equations equal to zero and substituting in rate equations

$$B_{AngI} = \frac{V_{max,AngI}[AngI]_0}{K_{m,AngI} + [AngI]_0} + K_{degAngI}[AngI]_0$$

$$B_{AngII} = \frac{V_{max,AngI}[AngI]_0}{K_{m,AngI} + [AngI]_0}$$

$$B_{Renin} = K_{degRenin}[Renin]_0$$

Harrell, McPeak, & Ford Versypt, In Prep, 2016

Pharmacodynamic (PD) model of ACE inhibitor effects on RAS

Consumption AGT: $r_1 = B_{AngI} + K_{Renin}([Renin] - [Renin]_0)$

Consumption AngI: $r_2 = \frac{V_{max,AngI}[AngI]}{[AngI]+K_{m,AngI}(1+\frac{I}{K_I})}$

Conversion AngII -> downstream products:

$r_3 = B_{AngII} + K_{AngII}([AngII] - [AngII]_0)$

Negative feedback of AngII on Renin production:

$r_4 = -K_{fb}([AngII] - [AngII]_0)(1 - \frac{[AngII] - [AngII]_0}{f_c})$

Degradation of AngI: $r_5 = \frac{ln(2)}{t_{\frac{1}{2},AngI}}[AngI]$

Baseline Renin production: $r_6 = B_{Renin}$

Degradation of Renin: $r_7 = \frac{ln(2)}{t_{\frac{1}{2},Renin}}[Renin]$

Harrell, McPeak, & Ford Versypt, In Prep, 2016

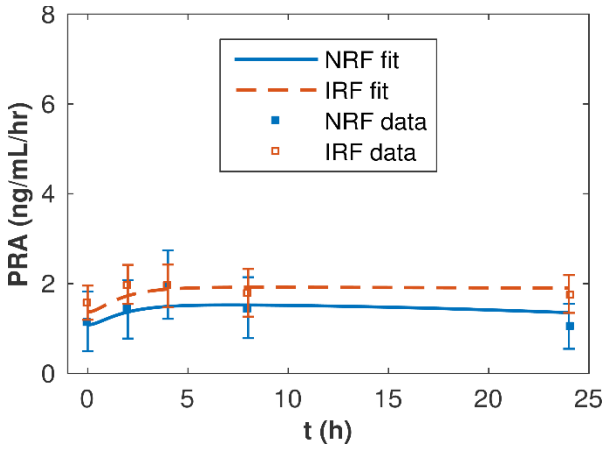
Model was parameterized with data for 2 drugs for patients with normal & impaired renal function

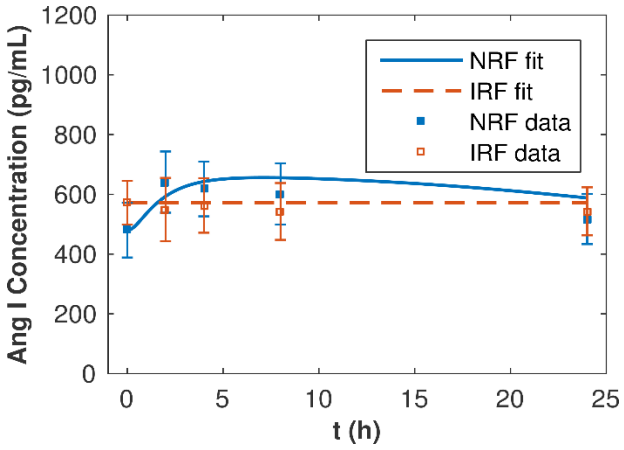
Model parameters

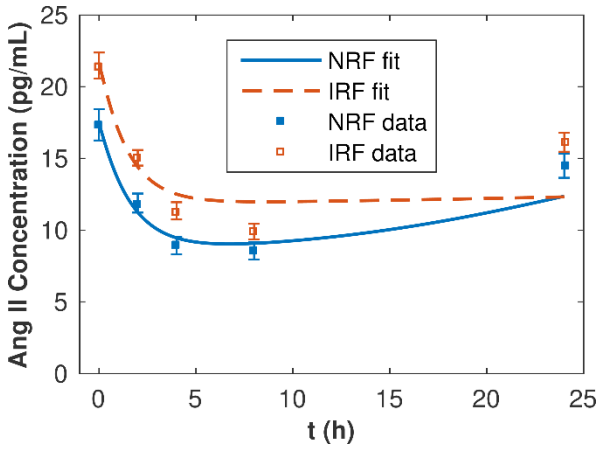
Parameter	Benazapril		Cilazapril	
	NRF	IRF	NRF	IRF
$K_{m,AngI}$	2.10e+4	1.96e+3	1.03e+4	2.42e+4
$V_{max,AngI}$	3.04e+2	3.00e+1	1.01e+5	4.59e+3
K_{Renin}	5.83e+4	1.32e-4	4.93e+3	4.02e+3
K_{fb}	6.76e-2	7.36e-2	3.41e-1	1.55e-1
f_c	1.73e+1	4.59e+3	2.62e+2	1.72e+2
$K_{degAngII}$	6.13e-1	7.00e-1	1.42e+1	1.17

Harrell, McPeak, & Ford Versypt, In Prep, 2016

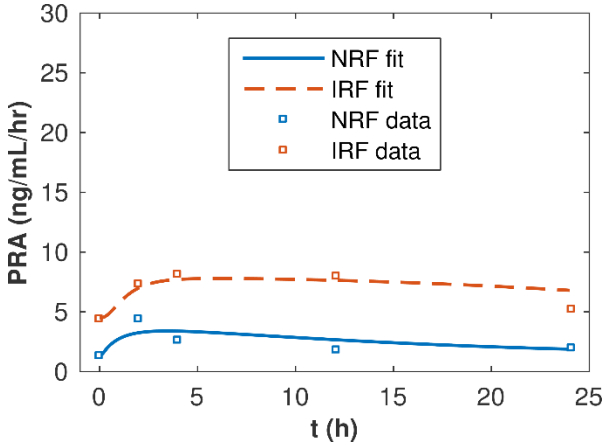
Simulation & data comparisons

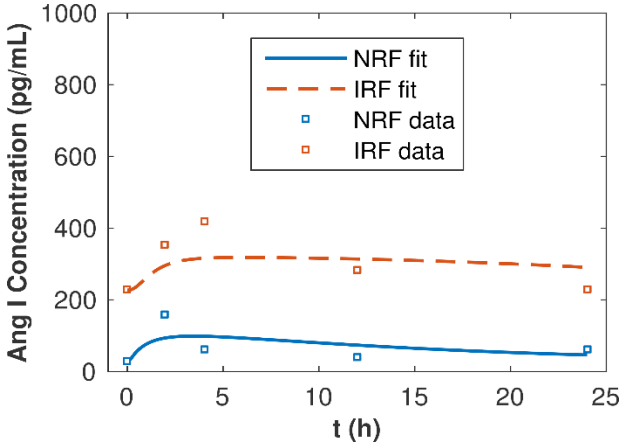


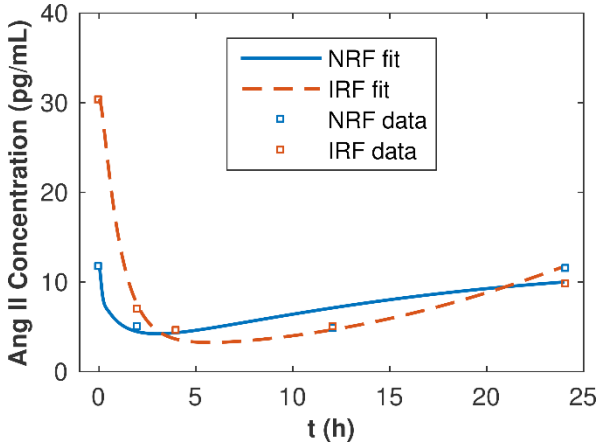




Benazepril







Cilazapril

Harrell, McPeak, & Ford Versypt, In Prep, 2016

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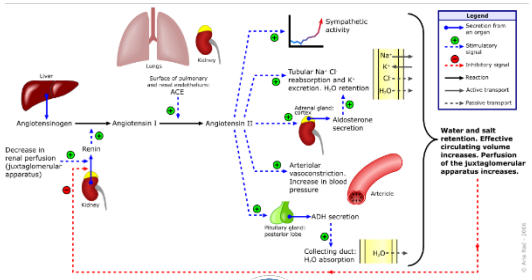
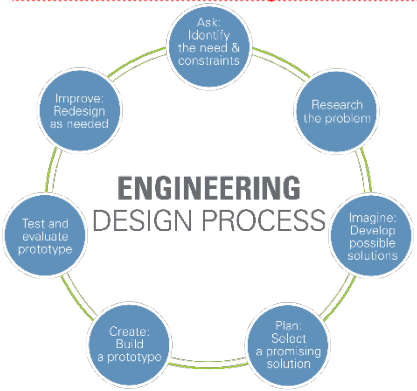
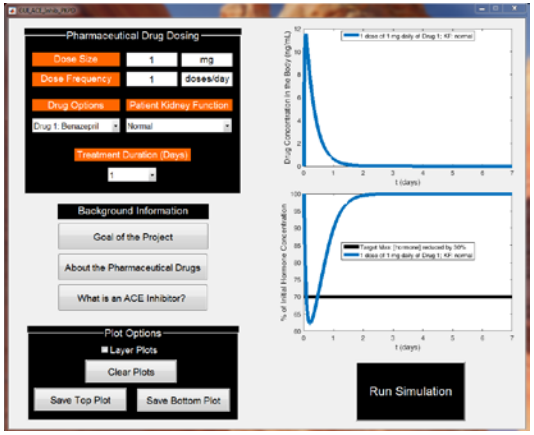






PKPD modeling and the biomedical/pharmaceutical application

Module of activities used to teach freshmen before the design project

Design project

Design module has been used in two years of the Summer Bridge Program at OSU

- 3 week summer camp for incoming freshmen
- Underrepresented groups, low- to mid-range ACT scores, first generation, all CEAT majors
- Three days of two-hour classes for CHE design
- Repeated three times
- Simulation-based

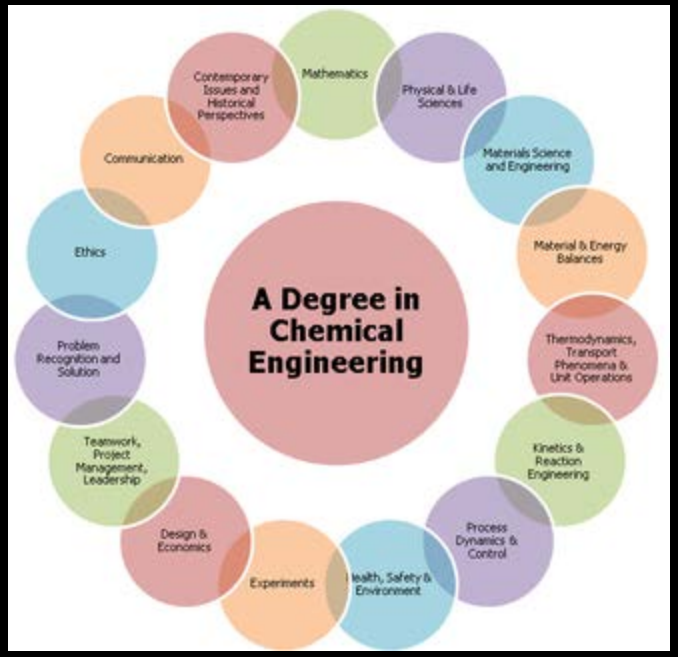
Engineer Your Future
College of Engineering, Architecture & Technology
Summer Bridge Program
Campus Orientation. Academic Preparation. Community Involvement.
Oklahoma State University

Topics/Student Activities

- Intro to CHE presentation
- Dynamics and computational thinking
- Engineering design process
- Design project using MATLAB app to design "best" drug dosing schedule
- Team presentations of a single slide of results

Chemical engineering aka “ChemE” or CHE

Not simply chemistry + mechanical engineering



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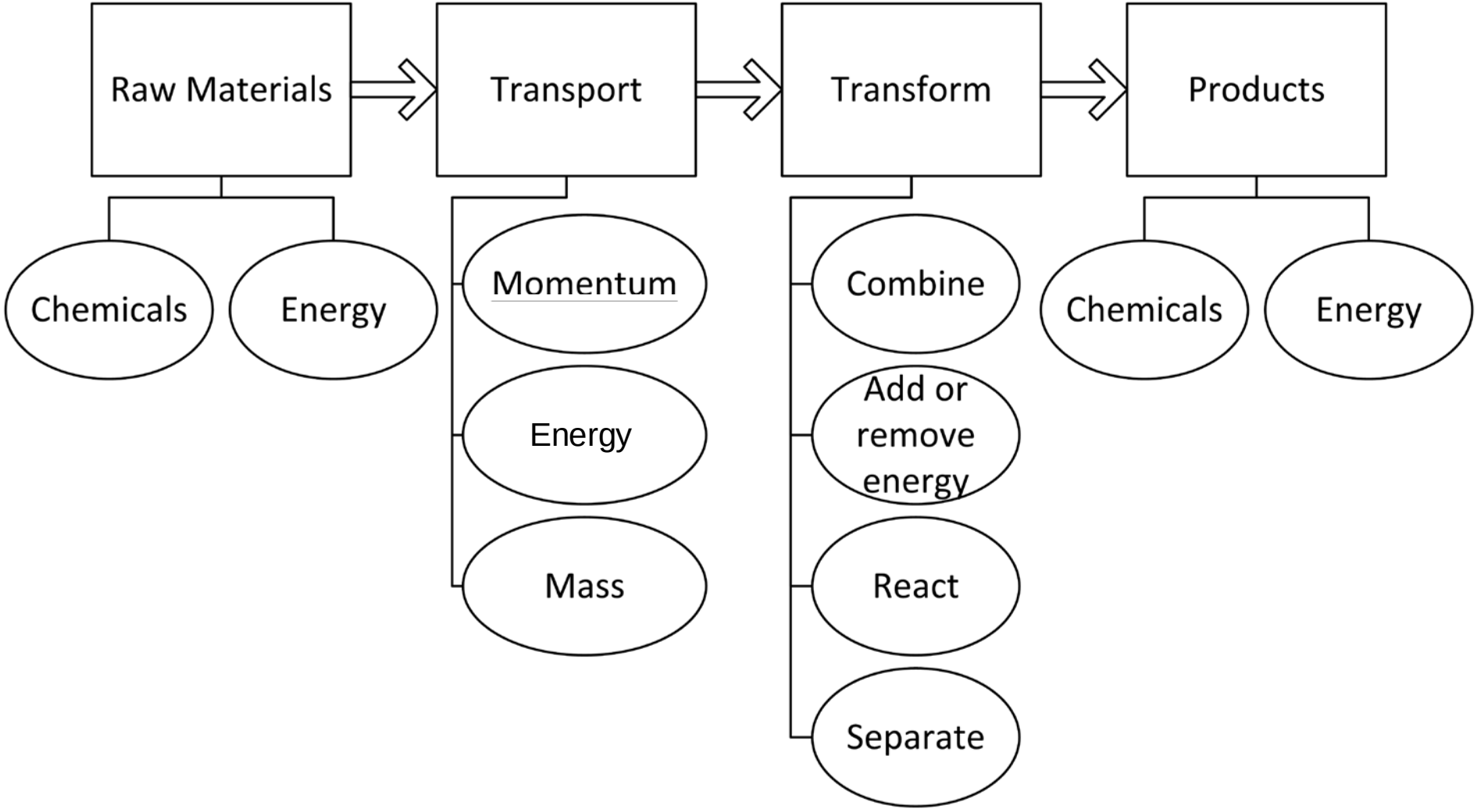
What is chemical engineering?



Classical chemical engineering example: petrochemical refinery

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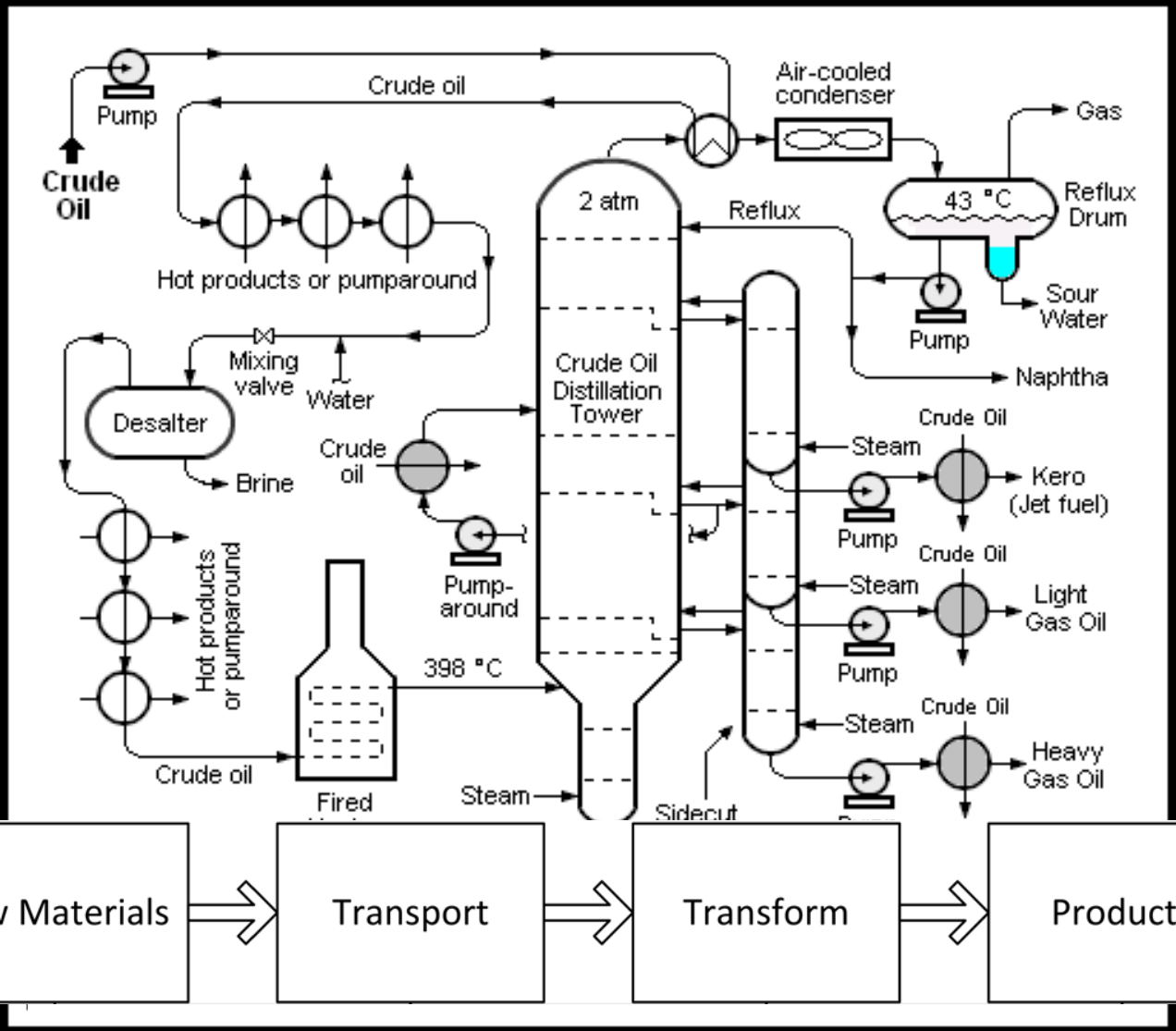
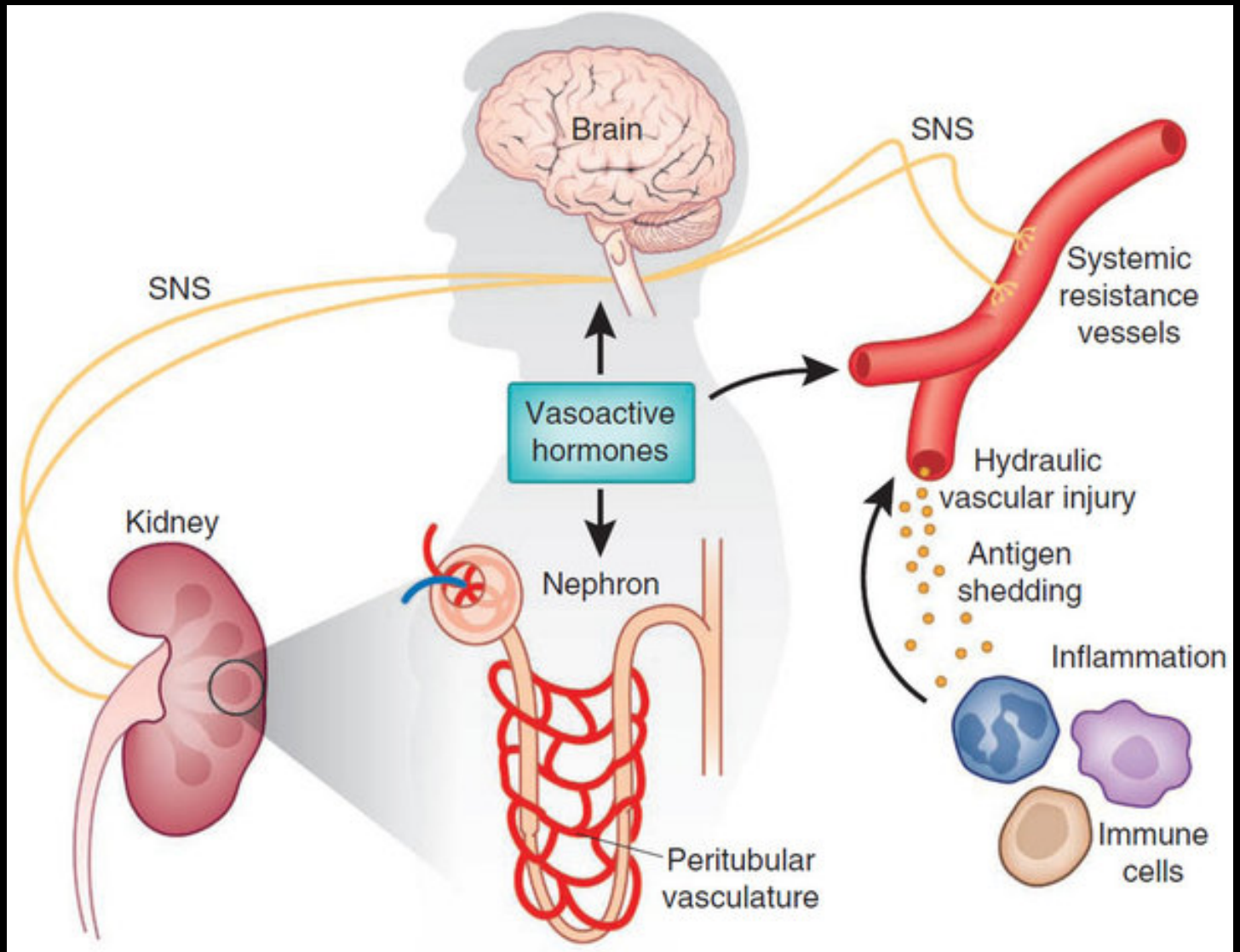


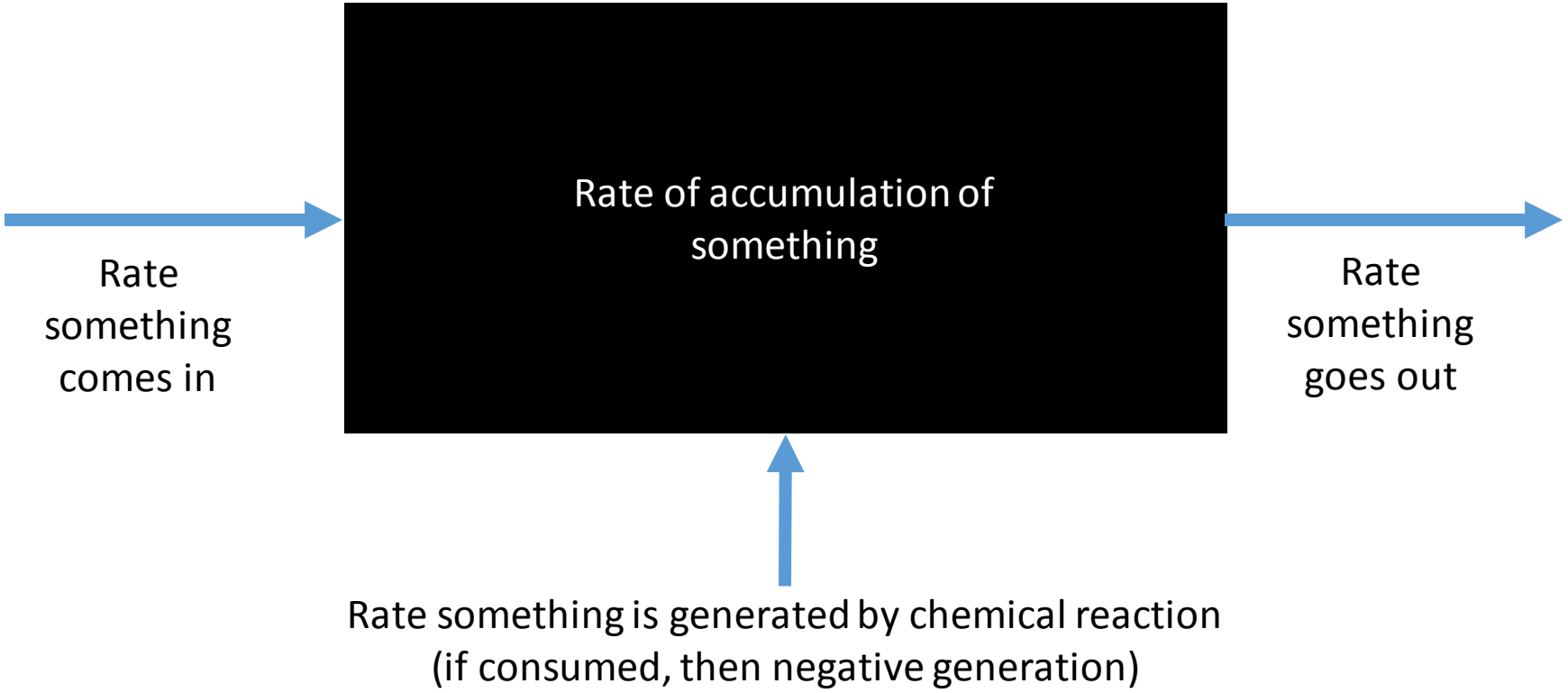
Raw Materials ⇒ Transport ⇒ Transform ⇒ Products

Biomedical chemical engineering example: blood pressure regulation in human body

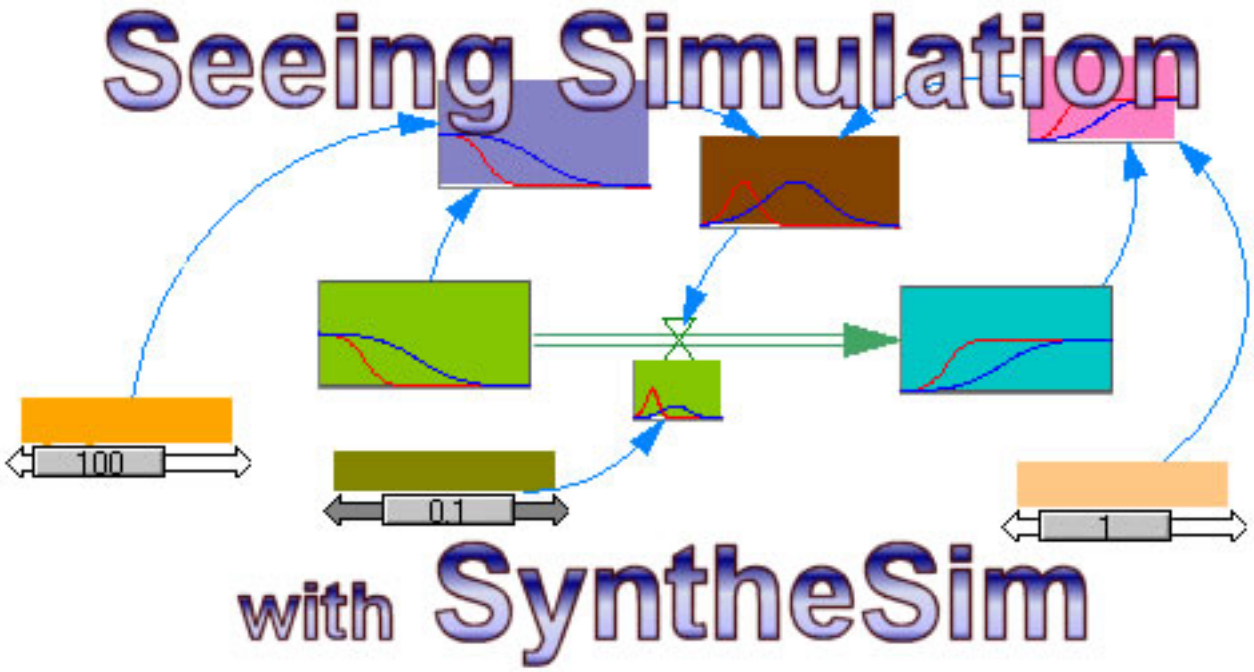


We introduced the mass balance as a central idea of chemical engineering

How do we know how much of something is in some container as time goes on?



We used VenSim dynamic simulator to build a simple PK model with mass balance concepts



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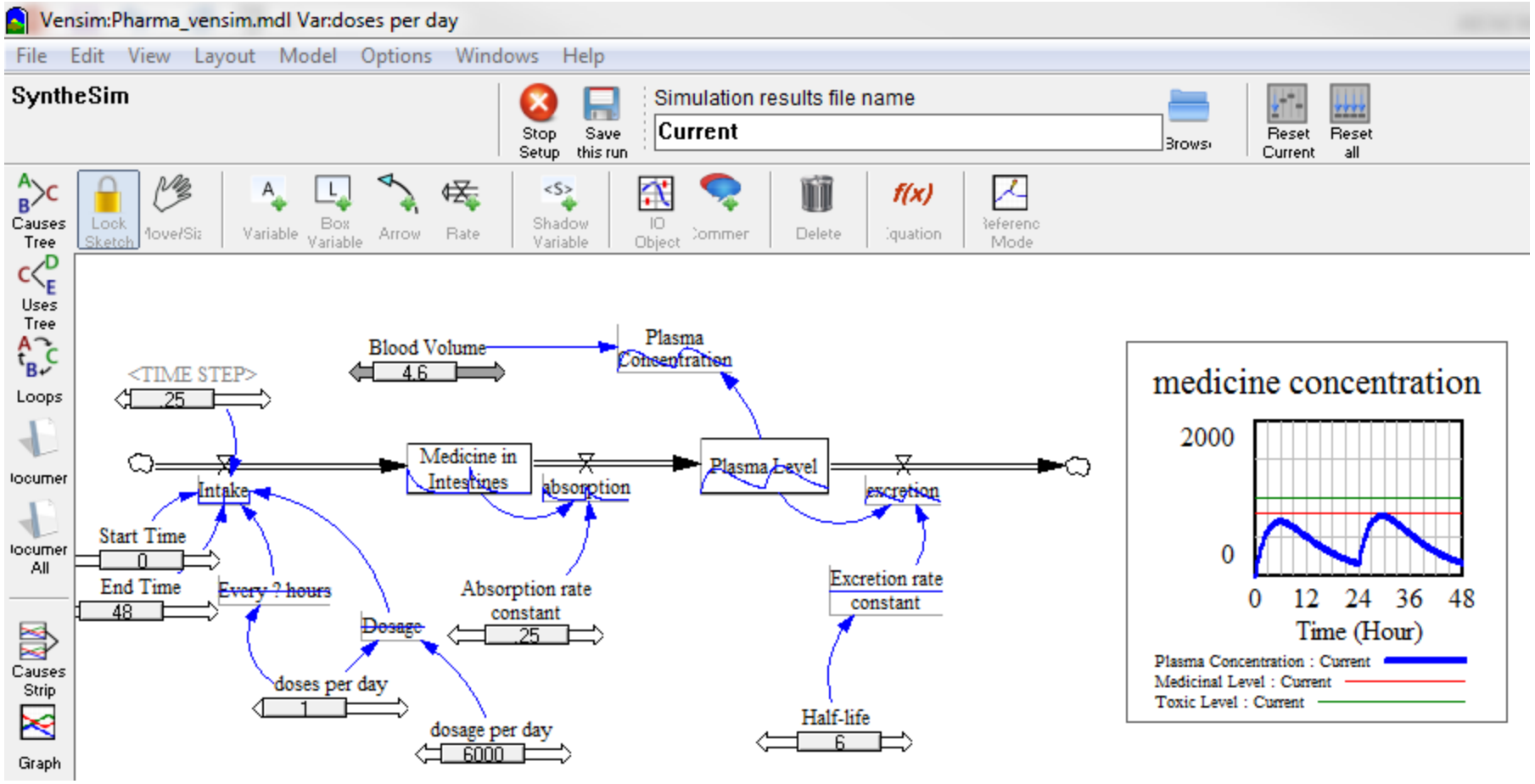
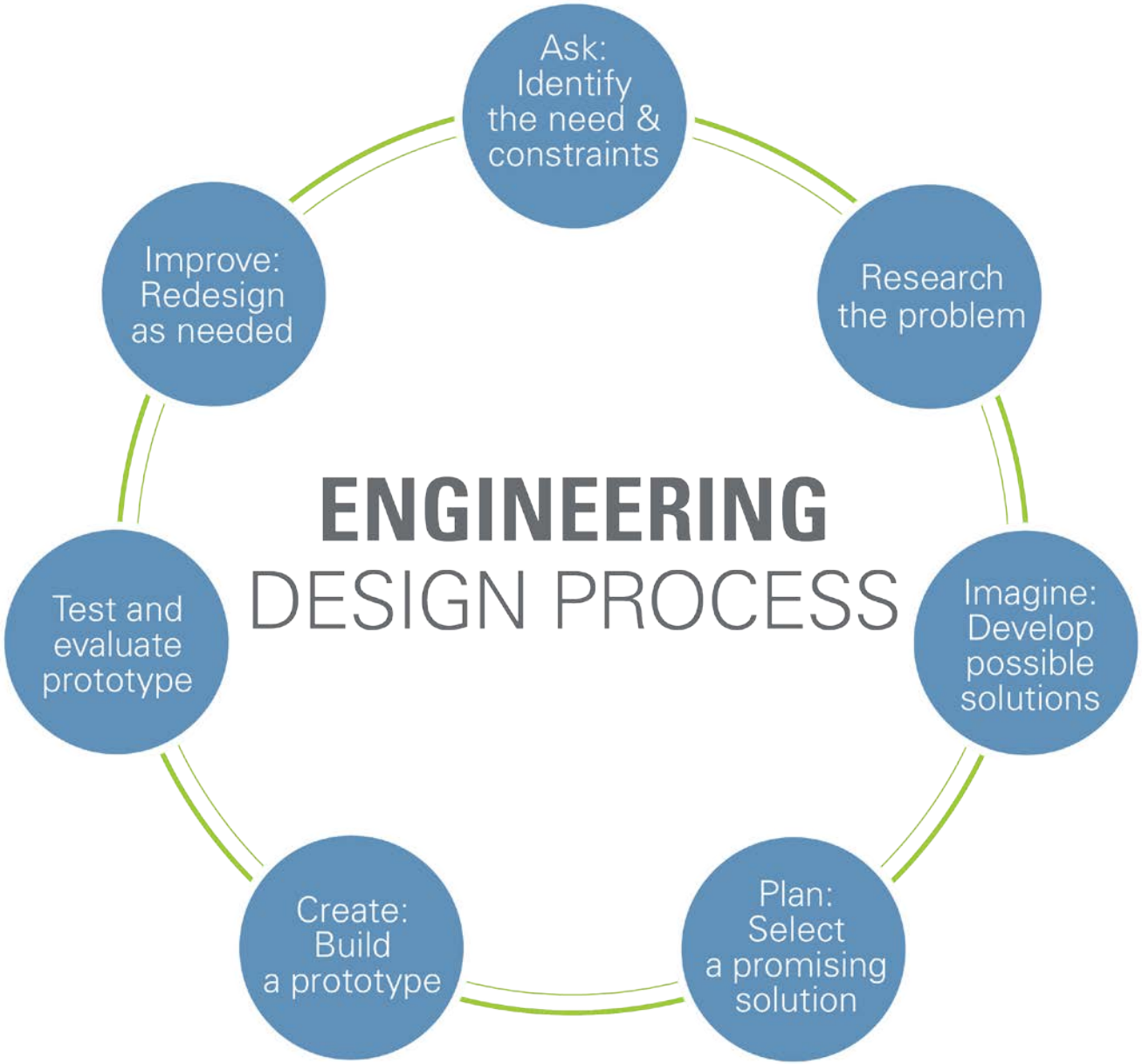


We worked the engineering design process applied to treating high blood pressure



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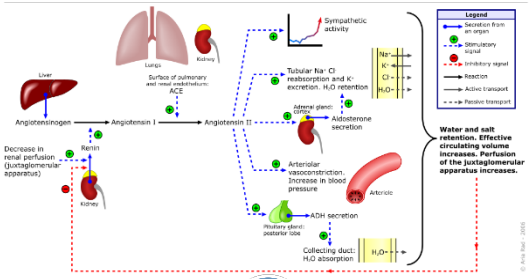
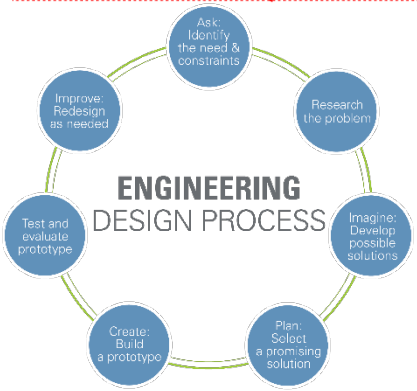
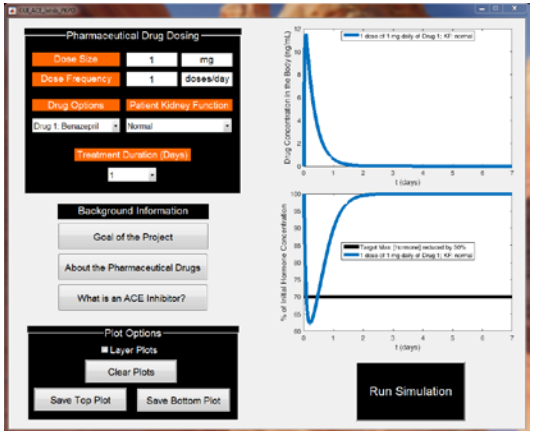






PKPD modeling and the biomedical/pharmaceutical application

Module of activities used to teach freshmen before the design project

Design project

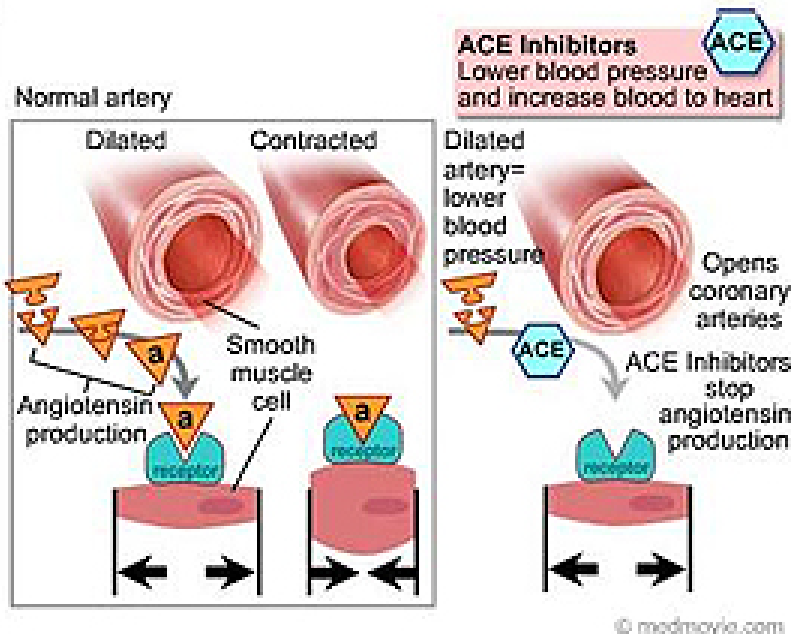
Summer Bride CHE design project: treat high blood pressure with ACE inhibitors

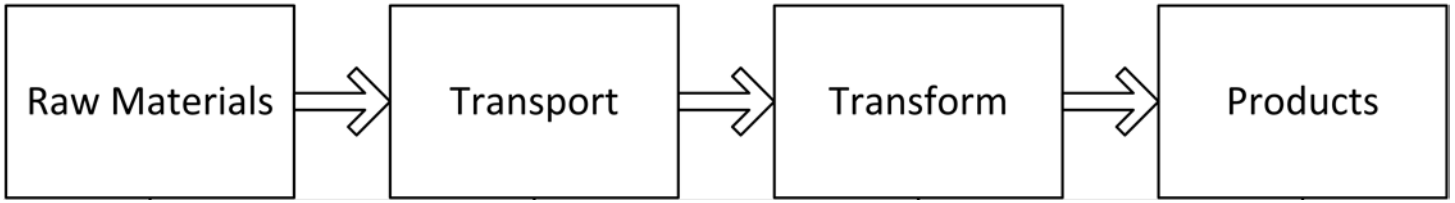
The need

Design the best dose of pharmaceuticals (raw materials) that effectively reduces high blood pressure (the desired product)

Constraints

Pros/cons or “tradeoffs” for each design



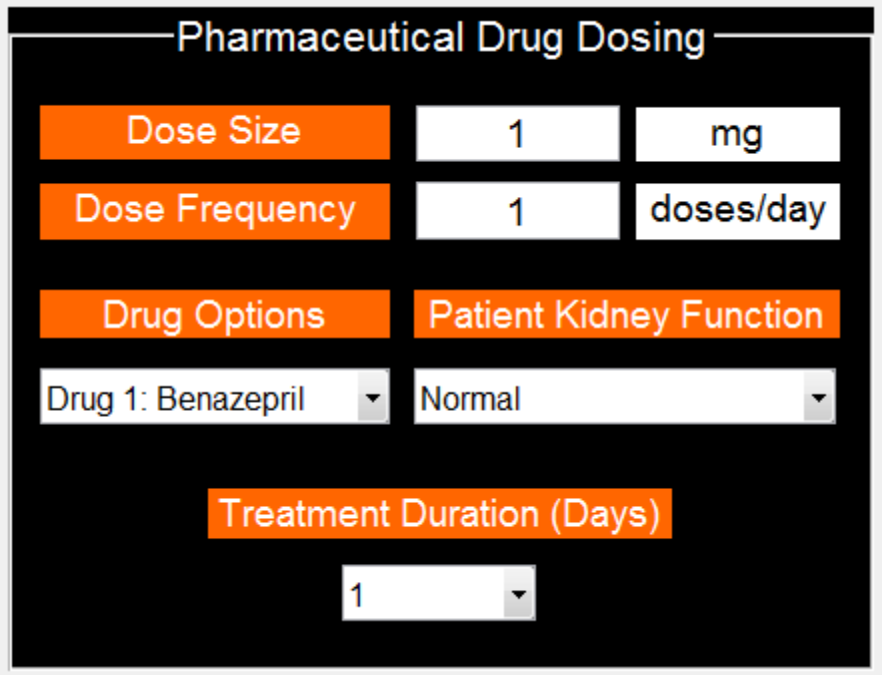


MATLAB GUI/app for running the PKPD model

MATLAB GUI/app for running the PKPD model

Input variables

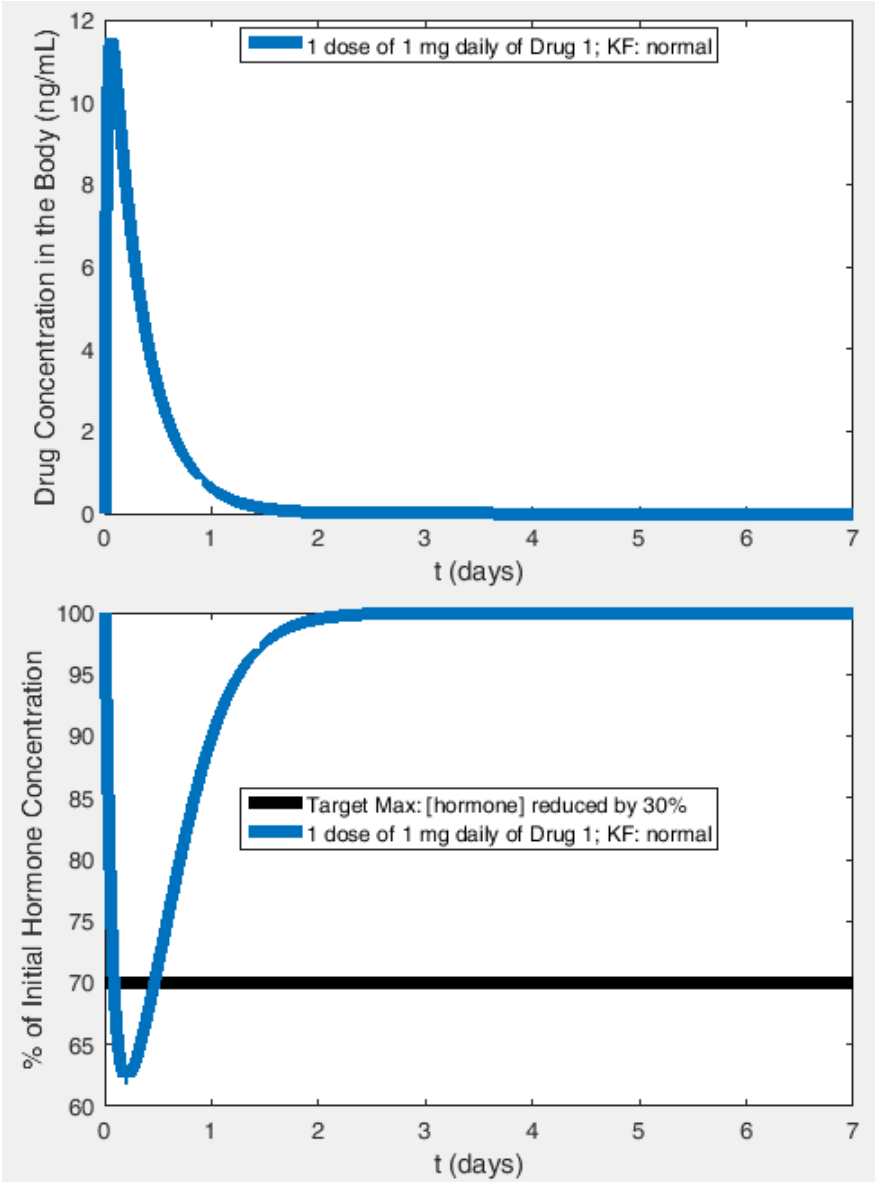
- Dose size
- Frequency of dosage
- Patient kidney function
- Drug type
- Treatment duration



MATLAB GUI/app for running the PKPD model

Output from simulation

- Drug concentration vs. time
- Angiotensin II concentration vs. time



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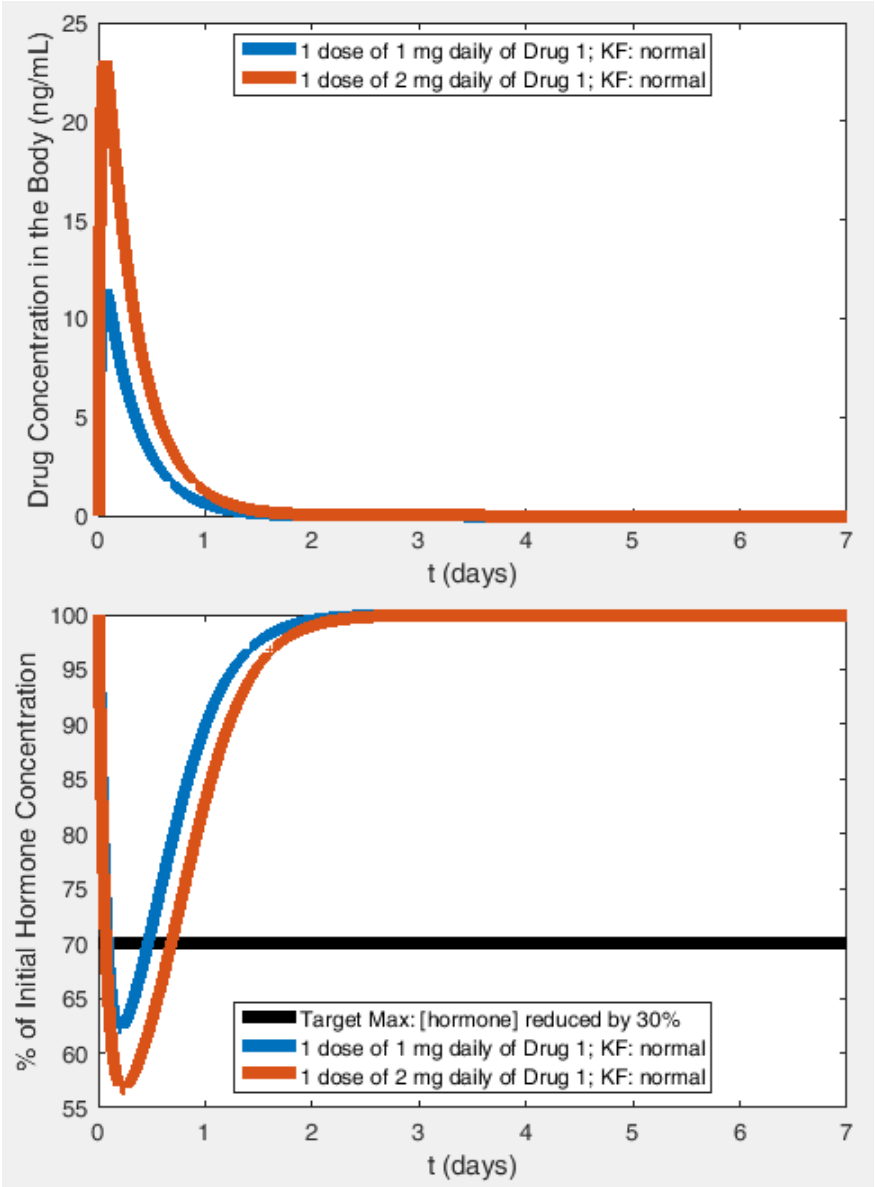


Instructions for design project with the MATLAB PK/PD app: design the best drug dose

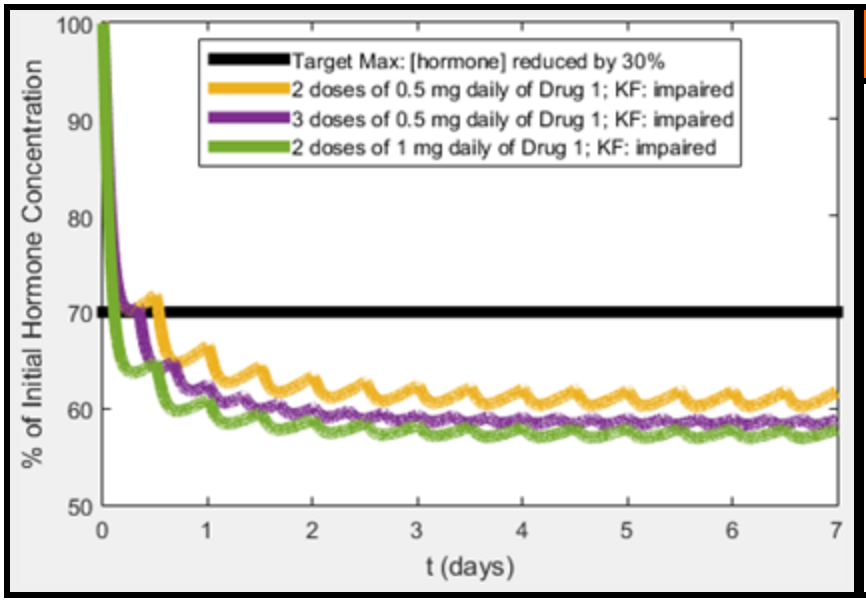
- **Create the prototype simulation conditions**
  Specify the case assigned to you using the drop down menus. Chose an input condition.

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

- **Test & evaluate the conditions**
  Click run simulation. Analyze the plots to determine if the results are expected and satisfactory. What are the pros and cons of the design?
- **Improve & redesign**
  Choose another set of input conditions and retest until you have a design that best meets your constraints.
- **Share your results**
  When you have a design you like, click save top plot or save bottom plot and then rename.

TEAM NAME: sample of student work

Chemical Engineering Design Project

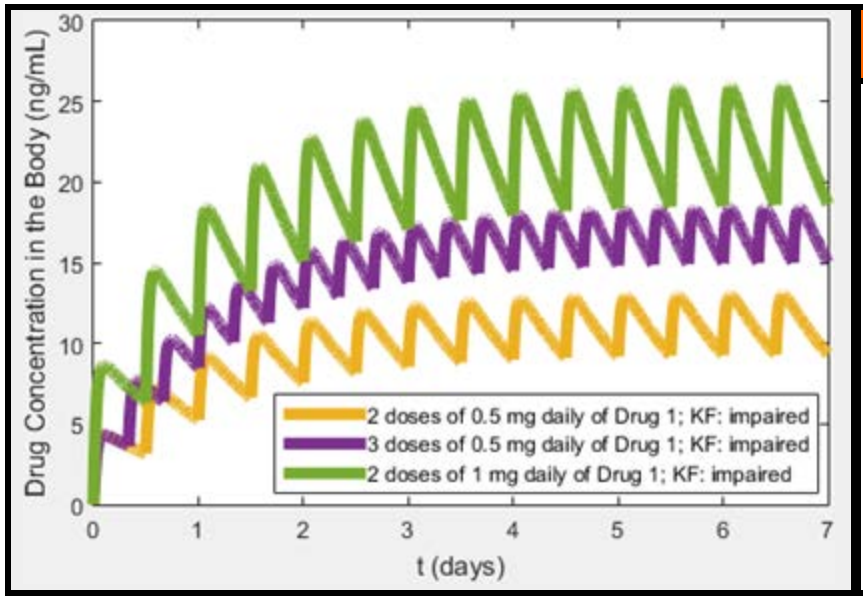


PROJECT RESULTS

The most favorable results were the yellow graph (2 doses of 0.5 mg daily) because it had the least oscillation and closest to the target dose.It was also the most effective if dose was missed.

The purple graph was unfavorable; it required 3 doses and was less effective.

The green graph was least favorable; the milligram increase produced less effective results than the yellow graph due to the high oscillation.



WHAT WE LEARNED

We constructed our drug based off an average person taking type 1 drug and with limited kidney function.

We learned how to use computer software and apply that knowledge to a chemical engineering field. That knowledge was important to future chemical engineers like us.

Student learning outcomes

- Learned about fundamental chemical engineering concepts
- Practiced open-ended engineering design
- Solved a realistic chemical engineering problem
- Constructed & gave a brief scientific presentation & peer feedback

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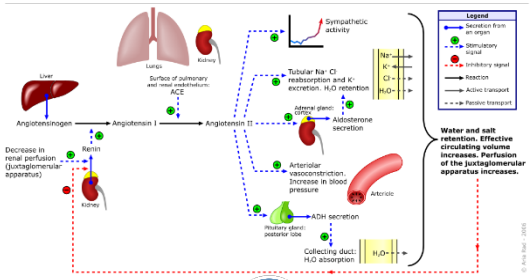

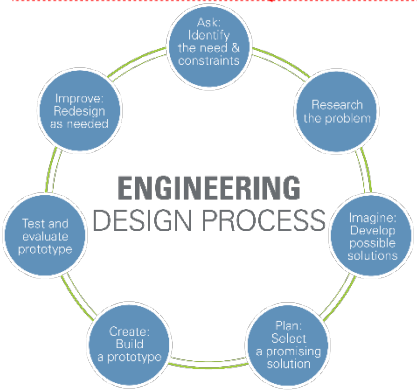

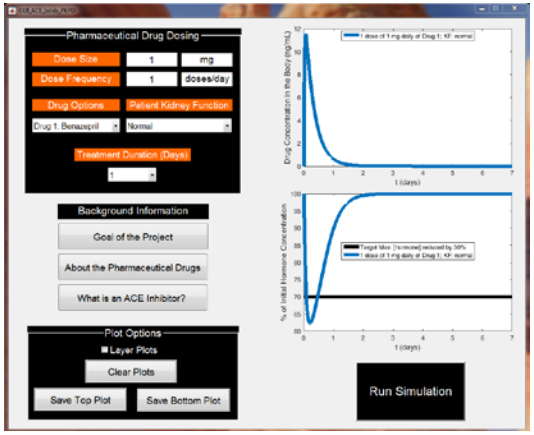

PKPD modeling and the biomedical/pharmaceutical application

Module of activities used to teach freshmen before the design project

Design project

Questions?