CMSE 201 PROJECT PROPOSAL

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Section 005

Original Ideas

- **Data: Evolution of the 3-Pointer in the NBA**
- I would use data from the NBA regular season games since the 2000s to understand how much more common 3-Pt shots have become in the NBA. I could also look to see if there a correlation between the pace (how many possessions per game) and the number of 3-pts attempted. I could create a scatter plot between number of possessions in a game and the number of 3-ptrs attempted per game. I could also create a scatter with the average seconds left on the shot clock when a 3ptr is attempted. I would need to become comfortable with pandas to be able to mine from a dataframe.
- **Model: PFAS in Ann Arbor**
- I could try looking over research reports, news articles, and a watershed map of Ann Arbor to try to create an computational model of PFAS spread through the Ann Arbor water shed and maybe see how many people in the greater A2 area would be affected by the PFAS in the next 5 years. This would require me to become quite comfortable with either ODEINT or ABM. Depending on the data I could find, I would then choose between the two.
- **Data: Spread of "Trump-ism"**
- An article in the New York Times talked about the effect that Trump's election has had on policies across the globe like Brexit in the UK and the election of Modi in India. After looking at election data and policy reform in various countries, I could categorize each policy or candidate on a liberal v conservative spectrum and isolationist v globalist spectrum and try to cross compare from one to another. I have no idea if I could even do this using Pandas.
- **Model: Drug Metabolism**
- I could research a well studied drug whose metabolism pathway has been clearly charted and try to model its plasma levels in patients using ODEINT. By looking at medical data, I could define the parameters to be the Kcat, Km, and [] of the enzymes involved in the pathway. If this drug were an opiod, I could try to see how a subtle shift in one parameter could cause the drug level to rise above the therapeutic window. I would need a lot of Biochem understanding and an even better understanding of ODEINT

Ask Dr. Hoogstraten to be pointed in the right direction. Use Kaggle as a database source.

DRUG METABOLISM

Motivations

- Why do you want to study this project? What question(s) do you want to answer?

I want to study the modeling of drug metabolism since its connected with the topics covered in one of my classes. Additionally, I want to focus on the drug metabolism of opioids specifically since opioid overdoses have become a pressing issues in recent years. I hope to get an understanding about why opioid overdoses are so common and if the overdoses are resulting from a tight therapeutic window and whether population variation over enzyme kcats and Km can force the drug dose to raise above the therapeutic window.

Model/Computing Method

- Briefly describe what model or computational method you plan to use for your project. [The class will cover more modeling material later; a rough sketch will do.]

I will try to model its plasma levels in patients using ODEINT. By looking at medical data, I could define the parameters to be the Kcat, Km, and [] of the enzymes involved in the pathway. If this drug were an opioid, I could try to see how a subtle shift in one parameter could cause the drug level to rise above the therapeutic window. I will have to create a compartmental model of the pathway first in order to define my differential equations.

Python Tools

- What tools do you expect to use for data manipulation and visualization (plots)?
  - matplotlib.pyplot
  - Seaborn for making my plots look nice
  - Numpy for making calculations using the data.
  - ODEINT from scipy.integrate

Main Opioid: Oxycodone

Focus: Use a pharmacokinetic model to model the blood plasma levels of oxycodone as it is cleared by one through the P450 pathway. I hope to also visualize the impact of common P450 inhibitors and activators on the levels of oxycodone.

Phases of the Project:

1. Research:
    1. Figure out which enzyme actually metabolizes oxycodone
    2. Get a list of Inhibitors and activators of the enzyme
    3. See if there are any alternative pathways for Oxycodone clearing
2. Coding
    1. Draw a simple compartmental model showing the interactions between inhibitors, activators, and substrate of the P450 pathway.
    2. Start off as a First-order reaction and then build up.

Time-permitting

- Coding
  - Try to encompass the minor drug-clearing pathways of oxycodone into the code.
  - Mess around by changing the dosage levels and the enzyme activity by changing the concentration of active enzyme

Final Outcome of the Project: An Interactive ODEINT model with interactive parameters that shows the change of the plasma levels of oxycodone and the necessary clearing time.

What I Have Done So Far: Research

- Metabolized by CYP34A
- Main parameter of interest is IC50 ~ Ki:
  - Equivalent to time of half-life
- Can use the Half-Life equation to find k
- Can use K to plot the concentration over time.

Summary of the Kinetics of Zero-Order, First-Order and Second-Order Reactions

Order	Rate Law	Concentration-Time Equation	Half-Life
0	rate = k	$[A] = [A]_0 - kt$	$t_{1/2} = \frac{[A]_0}{2k}$
1	rate = $k[A]$	$\ln[A] = \ln[A]_0 - kt$	$t_{1/2} = \frac{\ln 2}{k}$
2	rate = $k[A]^2$	$\frac{1}{[A]} = \frac{1}{[A]_0} + kt$	$t_{1/2} = \frac{1}{k[A]_0}$

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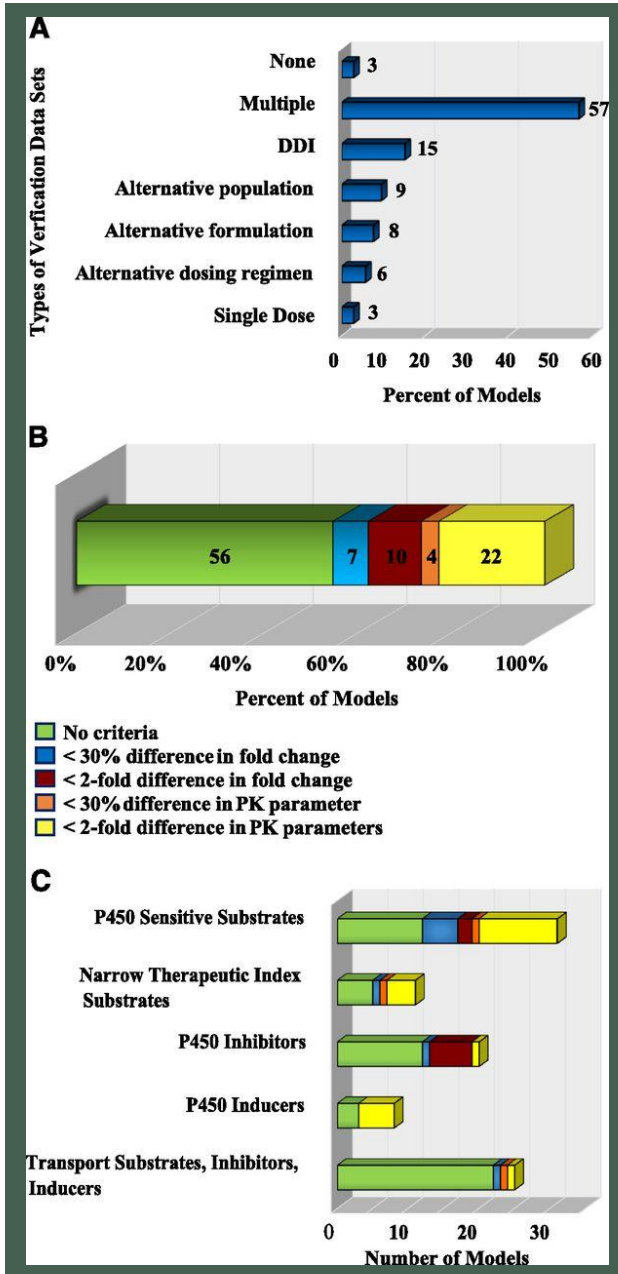
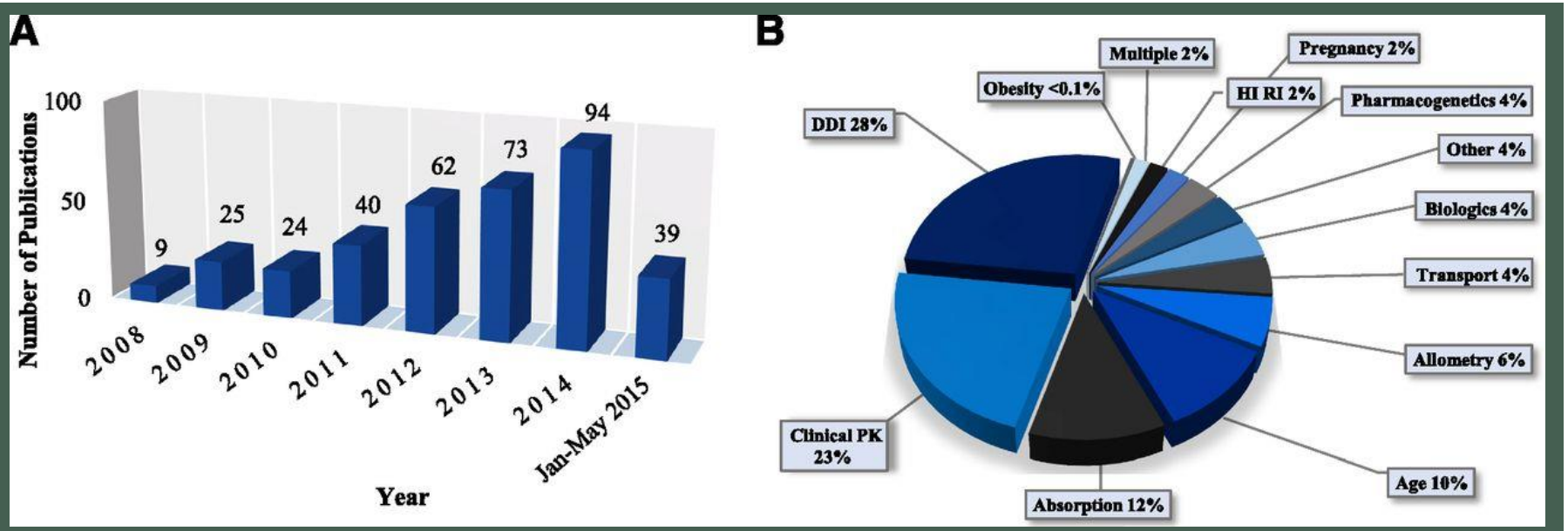
Research (Cont.)

- Used PubMed to find relevant papers to see whether or not people have modeled opioids before:

- Jennifer E. Sager, Jingjing Yu, Isabelle Ragueneau-Majlessi and Nina Isoherranen, Drug Metabolism and Disposition November 2015, 43 (11) 1823-1837; DOI: https://doi.org/10.1124/dmd.115.065920
- Rostami-Hodjegan, A. (2012), Physiologically Based Pharmacokinetics Joined With In Vitro–In Vivo Extrapolation of ADME: A Marriage Under the Arch of Systems Pharmacology. Clinical Pharmacology & Therapeutics, 92: 50-61. doi:10.1038/clpt.2012.65
- "Voricanizole drastically increases exposure to Oral oxycodone"
- "updated clinical pharmacokinetics and pharmacodynamics of oxycodone"
- https://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Roxane/Oxycodone%20HCl%20OS%205mg%20per%205mL%20Flavored/10009007%20Oxycodone%20HCl%20OS%205mgper5mL%20Flavored.pdf
  - A prescribing packet meant for doctors that details the IC50 values and shows some relevant sources.





Current Pharmacokinetic Modeling Research

Jennifer E. Sager, Jingjing Yu, Isabelle Ragueneau-Majlessi and Nina Isoherranen
Drug Metabolism and Disposition November 2015, 43 (11) 1823-1837; DOI: https://doi.org/10.1124/dmd.115.065920

Pitfalls

- Analysing and Understanding the the research
  - It's taking a lot more time to do the research than I anticipated and so I have not started coding yet.

- I hope to begin coding by 11/17
- Finish 1st order model by 11/23