MATH 3MB3 Final Project
Drugs in the Body

Group 22

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Background and Motivation

Painkillers are a very useful tool in medicine used to combat pain caused by a variety of ailments and injuries. Almost every adult will have had some sort of pain medication administered to them and while medications, dosages, and reactions vary from person to person, everyone can benefit from them. We take them for a variety of reasons, from combating inflammation to dealing with chronic conditions to being able to continue on with our daily lives while healing from an injury. Our project is about the mathematical process of how drugs are metabolised within the body. We focus specifically on how painkillers move through the body and how long they last. Drug metabolism refers to the process in which the body digests and transforms the drug, and then excretes it. This process can take a couple hours to several days depending on the chemical compound, it's strength, quantity, as well as the method of administration. Below we can see a table that shows how long different drugs may last in different bodily fluids,

Type of Painkiller	Urine	Blood	Saliva
Codeine	24 - 48 hrs	24 hrs	24 - 96 hours
Hydrocodone	48 - 96 hours	24 hours	12 - 36 hours
Morphine	48 - 72 hours	12 hours	96 hours
Fentanyl	24 hours	12 hours	reliable

As we can see above, different drugs have various time periods as to how long they last in our system. We want to model different dosages and explore different time frames to find out how long the drugs are in the body. This would be important to those competing in competitions and need to pass a drug test, to those that may be taking several types of drugs and want to avoid negative interactions between them or overdosing, as well as for those that want to know how long they must wait until they can drive or operate machinery if the medication causes one to be drowsy. It's important to note that there are different strength levels of painkillers and they serve different purposes. Long-acting pain killers are used for people who suffer from chronic pain, these kinds of painkillers include Oxycontin and Methadone. Short-Acting pain killers would be used for a short term injury or recovery, these kinds would include Codeine and Morphine[10]. Lastly, rapid-onset pain killers include Intranasal Fentanyl and Sublingual Fentanyl and these would be used for immediate strong pain relief. Each drug has a different processing rate since their chemical makeup is different. [7]

Painkillers and drugs can come in different compounds, we will be focusing on ones administered intravenously and ones that can be taken through a dissolving drug. Common painkillers like Aspirin and ibuprofen can be taken in a dissolving pill and takes 15 to 30 mins to begin working and usually lasts between 4 to 6 hours. Painkillers that can be taken intravenously include morphine and codeine which begin working immediately and last between 3-4 hours. In our list of resources, we have included links that included recommended dosing. For example, Advil Extra strength is a 400mg pill that is recommended to be taken every 6 - 8 hrs and ASPIRIN regular strength is a 325mg pill that is recommended to be taken every 4-6 hours, note that a dosage of 1 or 2 pills can be taken. Other dosages are included in the sources below and dosing rates will be included in the base model construction section.

Research Question

As what we mentioned above, there are a plenty amount of different types of painkillers in the world. In our model, we want to focus on one specific drug Ibuprofen, which is one of the most used painkiller by general population and we want to discover how long does it take for Ibuprofen to leave the body based on dosage, type of drug, and if it was administered intravenously or through a dissolving pill?

Model construction and analysis

Based on our research question, we came up with 3 different derivations for our base model. Each one of these derivations corresponds to a sub-section that corresponds to our main research question.

Model 1: Different dosing for Ibuprofen

In this first section we are looking at the intravenous model. We are focusing on ibuprofen, a common painkiller known as Advil that is used as an everyday painkiller. In our first model, suppose the total drug amount is M, the total dosing time that is needed for this drug to be properly dosed is k. Before this specific time k, the dosing rate of the drug should be M/k, in which we denote as d. The general processing rate for the entire human body denoted as p and A represents the current dose. Therefore, we are able to construct a piece-wise functions that models the flow of drugs in versus out, which gives up the total amount of drugs at time t, this id denoted by $\frac{dA}{dt}$.

$$\frac{dA}{dt} = \begin{cases} D(t) - pA & 0 \leq t \leq k \\ -pA & t > k. \end{cases}$$

When the drugs are administered intravenously with one dose:

$$D(t) = \begin{cases} d & \text{if } 0 \leq t \leq k \\ 0 & \text{if } t > k \end{cases}$$

Therefore, the amount of drugs in the body can be represented by the following equation:

$$\frac{dA}{dt} = \begin{cases} d - pA & 0 \leq t \leq k \\ -pA & t > k \end{cases}$$

We can tell that the kids dose will exit the body the fastest, followed by adults and then the serious patients. Therefore, the time in which it takes for the drugs to leave the body is directly correlated to the dose here. This is not surprising since our model has the same processing rate, and the larger the dose, the longer it will take to leave.

The following are some explanation for the parameters used in our model.
A= Current dose amount in the human body. (Starting at 0 mg)
p = the processing/clearance rate for dosed drugs in a human body.(we picked 0.05(/h))
d = constant dosing rate for Ibuprofen(Advil) intravenously. (25mg/h,50mg/h,100mg/h) [5] [6]

k = Total time taken for the amount to be dosed properly. (8h)
t = Current time within the entire processing state.(h)

Based on our research, age is the most important reason that the dosing amount of painkillers are used differently for different people. Hence, in our first model, we isolated the ages for the patients and let them take different doses based on the given clustering. There are 3 different kinds of patients that we are focusing on, kids, adults, and serious patients (patients with extreme pain).
Based on our research, kids cannot take regular adult dosing amounts because the toxins within the drugs are able to stay in the body, which might lead to stomach problems, confusion, and possible kidney problems. However, kids are still a huge part of users of painkillers because of fever, aches and minor injuries. Hence, we are assigning kids with half the dosing amount which is 200mg/injection for our graphs.[11] [12] For normal adults, the amount is given normally which is 400mg, based on our research, the upper limit for a human adult to take is 1200mg/day, therefore we left some space for those who can't get treated with only 400mg injections. We call these people the serious group since they have severe pain. The serious group will have a double injection amount which is 800mg and the graph shows how the amount of ibuprofen is changing in the body within a 3 day period. The only values that we did not find a strong support is the numerical value of the processing rate. Our group believe that the human body need a relatively slow rate to generate all the drugs taken. This is due to the metabolism of drug process requires enzymes being produced, and too much amount of extra enzymes produced might lead to a bad injury for organs. That is the situation we do not want to see. Thus, our group picked processing rate as 0.05, which is 1/20 of the total amount so that human can sufficiently absorb the drug while not interrupting other functionalities for a human's daily life.

Our model is a continuous time model. This is because the general drugging process in the real world is based on continuous time, especially with our topic of painkillers. Painkillers obtain a constant dosing rate for a certain amount of time until all the amounts are being dosed. Other model choices such as discrete model is not valid for our topic. This is because that the drug process will be continuous through the time when it is in the human body. There are no breaks for the processing of drugs hence continuous model fits our purpose better.

The very first assumption that we've made for this model is that people are having the same processing rate for all ages. This is different from the real world since different people based on age, weight, gender, etc., would cause their metabolism speed to change which in return could possibly cause different processing rate p for them. However, in our model, to make the model simple, we choose not to talk about the effect of metabolism and assume that everyone is in the same condition. At the same time, there are no extra parameters concluded for metabolism speed as well.

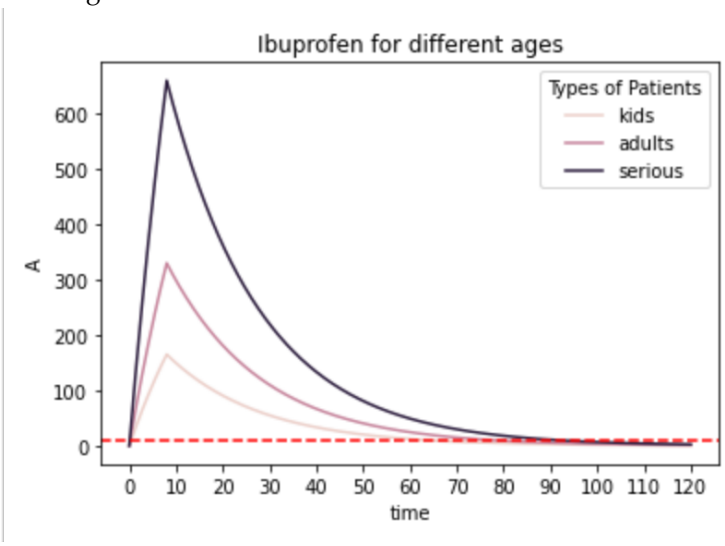
Regarding our second assumption, the injection only contains one type of medicine. In real life scenarios, it is possible that a patient needs different types of drugs for the treatment of reducing pain, but in our model we assume that taking ibuprofen is enough to manage there pain. Taking multiple drugs might change the processing function of human body which will complicate our model, hence we choose to focus on studying the total amount of drugs in the body at time t with only taking ibuprofen.

Another very important assumption is that the drugs are carried by blood with a constant speed. This assumption doesn't really affect the graph at first but it ensures the exponential processing and dosing simulation can happened for our model. Without a constant blood absorbing speed, the dosing rate and processing rate can be affected by a small amount which we also will talk in our stochastic element.

There are also some other assumptions around the health condition of the patients that could be mentioned in the report. However, since these topics could be concluded in the effect of processing rate, our group decides not to bring it up in the report. For those who interested in the topics, some basic assumptions that we've made includes: diet habits, health conditions, allergy conditions can be furthermore developed as well.

0.1 Model 1: Analysis

The graph below shows how Ibuprofen is reacting in human body with different amount of dosages.



As we can see, the three curves in the graph express as 3 different types of patients and they all share a constant dosing time of 8 hours, the only different is that the dosing rate for each type of patient are different. The red dotted line stands for the proposed 0 amount for dosage. This is because that our model is an exponential model, which means that the dosage should be theoretically out of human body. In the next few sections, we will be focusing on finding the equilibrium, stability and some other numerical values for this model derivation.

- Equilibrium:
  The general equilibrium happens when

$$0 = \begin{cases} D(t) - pA & 0 \leq t \leq k \\ -pA & t > k. \end{cases}$$

  The equilibrium for the model stands for that the amount of drugs will not change in human body anymore. For the equilibrium at the first part, where the dosing rate

parameter is still positive, reaching equilibrium means that the amount of drugs stay at a constant amount with perfect gaining at losing. For the equilibrium during the dropping process, it means that the drugs will properly get out of the human body, which is what we desire to find for our main research question.

When the time of the process is before time k, we want to show that 0= D(t)-pA, since in out model, p is a constant as 0.05 and the D(t) is constant for kids, adults, and serious injury as well. We can find the corresponding equilibrium A value at 500, 1000 and 2000. However, these values will never be reached in our experiment. This is because that our desired injection amount will never reach these values, hence our equilibrium will not reach at all for the first part.

When the time is greater than k, which means that the dosing process has been ended for the drugs. If we use the original equilibrium equation, we will end up having 0 = -pA, which will return a A = 0 as equilibrium. However, this would not make sense since our model will not hit 0 as an exponential model. The better way to do this is to find out where each curve has been intersected with the red dotted line, which is our ideal amount of drugs which stands for drug clearance. Whenever, the drug amount in the body is less than the red line, the amount will not be able to impact a human anymore. In the graph, we can tell that kids amount reaches the line at around 62 hour, the adults amount reaches the line at around 75 hour and the serious injury curve reaches the red line at around 90 hours. Therefore, we are able to conclude that, the more dosing that we have given to the human, the longer the drugs stay in his body.

- Highest drug amount point:
  The highest drug amount is always sitting at 8 hours. That is because of our piece-wise function ends dosing at the 8th hour. This makes sense because our processing rate p is positive and after the 8hour the change of amount is always negative.

- Stability:
  Similar to what we've got for equilibrium, we need to work the stability for different time intervals. Before the specific time k, in order to find the stability we should take the derivative of the first part where f'(A) = -p . When -p ¡0, we know that the function is stable and when -p ¿ 0, the function is unstable. In our specific model, our choice of p value is always positive, which lead to a constant negative value for -p. Therefore, the stability for the first half of the model is stable. For the second half of the model, the derivative is also -p, and since we have the same p value for the entire model, this model is also stable.

- Analytic solution: $\frac{dA}{dt} = d - pA$
  $\frac{1}{d-pA}dA = dt$
  $\frac{-1}{up}du = dt$
  $\frac{1}{u}du = -pdt$
  $u(A) = u(0)e^{-pt}$
  $d - pA(t) = (d - pA(0))e^{-pt}$
  $A(t) = \frac{(d-pA(0))e^{-pt}-d}{-p}$

As we have mentioned in the equilibrium analysis, the kids will reach this amount within 3 days however the adult and serious patient will not reach, this means that the pills should

normally lasts for more than 3 days which is good enough as a general period for pain relief. We can easily conclude that Ibuprofen should be some kind of good painkillers for human. However, our group is wondering whether there are better types of drugs that suit general population better.

0.2 Model 2: Different types of drugs

From the final question from last part, our group pulls out 2 other different types of painkillers to compare with the result we've got for Ibuprofen. We choose Aspirin and Morphine as the two drugs used to compare with Ibuprofen, this is because these two types of drugs are also very popular among the choices of painkillers. For this part of the derivation, we have the exactly same base model and the following are some explanation for the parameters used in our model.

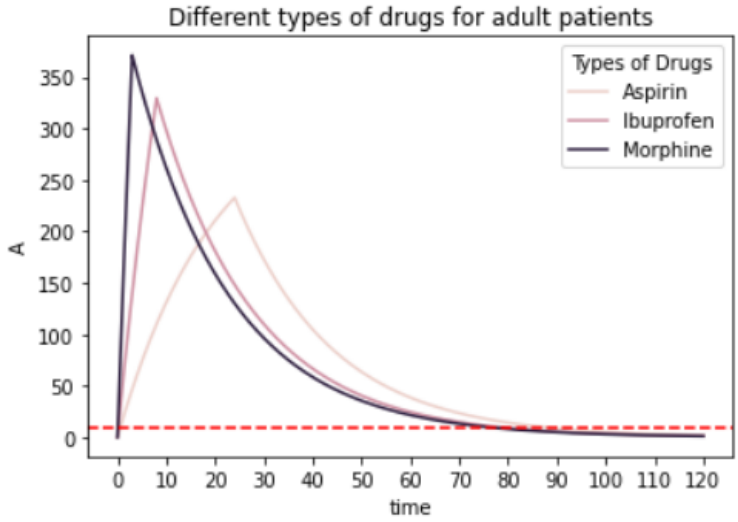
A= Current dose amount in the human body. (Starting at 0 mg, total dosing amount 400mg for all types)
p = the processing/clearance rate for dosed drugs in a human body.(we picked 0.05(/h) for all types of drugs)
d = constant dosing rate for Ibuprofen(Advil) intravenously. (400/k mg/h)
k = Total time taken for the amount to be dosed properly. (8h for ibuprofen, 3h for morphine, 24h for aspirin)
t = Current time within the entire processing state.(h)

In order to compare the time effect of different drugs, our group decides to control the total dosing amount for different types of drugs. For different drugs, the amount of time for them to be properly dosed are different, therefore we changed the variable k mentioned in the previous model when we are computing different data for different drugs. However, in order to show the differences in speed, we made the injection amount the same for each kind of drug. The number we picked is 400mg, which is the acceptable adult usage for all drugs. Based on our research, Morphine has the quickest dosing time and Aspirin has the longest dosing time. This is also one of the reasons why people might like Ibuprofen more compared to other drugs since it is more neutral compared to the rapid drugs such as Morphine, at the same time it is in a reasonable period for patients to get the treatment.

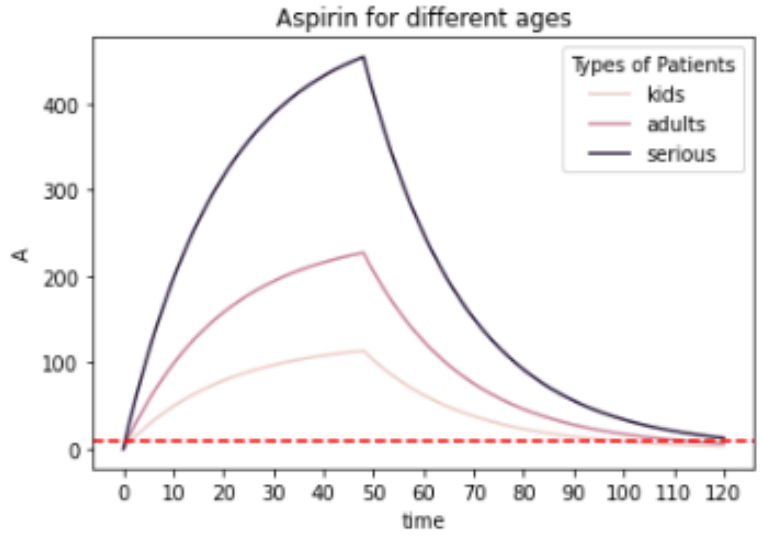
For this specific model, most assumptions that are made are the same as the previous model, however, we need to emphasis the importance of not mixing up drugs again. Based on research, taking too much amount of Aspirin or Ibuprofen can cause stomach bleeding, which would emphasizes the negative effect of overdosing The risk of stomach bleeding from these drugs continues to increase if you: are older than 60 years. Other assumptions are the same as what is mentioned in the previous derivation.

0.3 Model 2: Analysis

In this simulation we are comparing three different types of drugs, Aspirin, ibuprofen and morphine, for adult patients.



Since the mathematical model is pretty much the same as what we have in the very first derivation, we are not gonna redo most mathematical part for this simulation. Looking at morphine curve in the graph, we can see that it peaks the fastest at about 5 hours with over 350mg, next is ibuprofen at about 10 hours with 325mg and aspirin peaks last at about 25 hours with 225mg. Also notice that morphine makes it's way out of the body the fastest, followed by ibuprofen and then aspirin. If an athlete or someone who needed pain relief but also needed to compete or work, based on this graph morphine would be the best option since the total amount peaked the fastest and also decreased the fastest. For an adult with more severe pain, Aspirin would not be a good choice since it not only took the longest to get to its maximum amount but its maximum amount is also less then the other two options. Also as the amount set is also 10mg, which from research represents the general amount used for one kg in this graph. The graph shows the effect of those three painkillers are enough to last for 5 days as well. In order to better emphasizes why most people would choose Ibuprofen, we have also prepared the graph of Aspirin to compare with what we have gotten in the first model.



As we can very easily discover, the time it takes for aspirin to stay in human body is generally longer than the same dosing amount with Ibuprofen, however, the amount of drugs within the bloodstream is significantly less than what we have with Ibuprofen. This means that the effect of Aspirin might not help relief the pain as good as Ibuprofen do, which could possibly be the reason that more people and leaning towards using Ibuprofen over Aspirin.
Therefore, we have shown that Ibuprofen is clearly better than the other types of drugs for multiple reasons. However, not everyone is able to take an injection treatment right now, especially with the current situation where covid are spread all out, people are having less chance to take a injection shot than it used to be. Pills, another very popular types of drugging process are being considered by our group. In our next session, we want to discover which method would help the patients better.

0.4 Model 3: Different methods of dosing Ibuprofen

The third model compares the differences between taking a painkiller pill and a intravenous injection. As different types of pills and gels are made by different companies, pills are becoming more acceptable as a household necessity for everyone. We want to model the total amount of drugs a human can process with different methods of administration, the first being a dissolving pill and the second being the intravenous model. The intravenous model is the same from our first and second models. If the drugs are administered through a dissolving pill, we change our dosing model to the following:

$$D(t) = d_{max} e^{\frac{-t}{k}}$$

Therefore, the amount of drugs in the body can be represented by the following equation:

$$\frac{dA}{dt} = d_{max} e^{\frac{-t}{k}} - pA$$

The following are some explanation for the parameters used in our model.
A= Current dose amount in the human body. (Starting at 0 mg)
p = the processing/clearance rate for dosed drugs in a human body.(we picked 0.05(/h))
d = constant dosing rate for Ibuprofen(Advil) intravenously. (50mg/h)
d_{max} = constant dosing rate for Ibuprofen(Advil) pills. (50mg/h)
k = constant value parameter where affects the dosing rate of pilling method. (4h).
t = Current time within the entire processing state.(h)

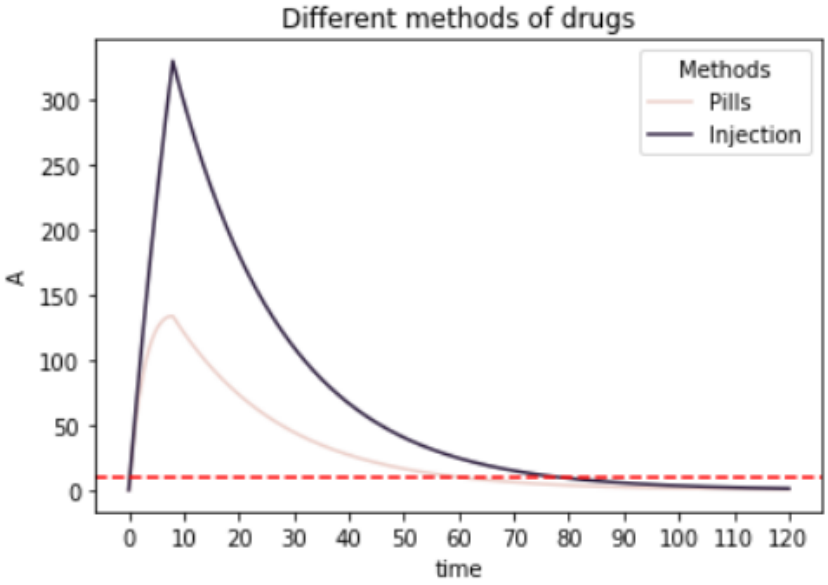
For this specific derivation, we used 2 different models, since we have introduced the intravenous injection model before, we are not gonna mention it here again. For the dissolving pill model, with similar reasoning, the dissolving pill model should be a continuous time model, since the processing of drug in human body is always continuous, there is no gap between processing each mg of drugs. There is a new parameter added in this model, the small k. This parameter stands for the time where pills starts to run out of effect. We picked 4 for this value, since based on research the pills of ibuprofen would last its effects for 3-4 hour, which means that the dosing amount should be dropping significantly after 4 hours but still dosing until around 8 hours. After 4 hours time period, the function will become $e^{-}j$ where j¿1 which makes the value of

There are some different assumptions that we've made for this model, the first assumption that we made for this comparison is that the dosing rate for injection is the same as the max dosing rate of pills. This is because we want to show the pros and cons for using pills. In real life, pills are usually made with very little amount since the rapid dosing given to body would causes negative effects. However, in order to show the differences we made the pills having a significant amount in order to make the comparison more obvious.

Other assumptions are almost the same as what we have before. One thing to notice is that in the extension part, we will be focusing on constructing models about how metabolism will affect our original model and how taking different types of drugs at the same time, would affect the human body. In the next part, we'll have some graphs for all the derivation that we've had above and we can talk about what does these model tells us about our research question.

0.5 Model 3: Analysis

In this simulation we are comparing the two methods, pills versus intravenous (injection). Similarly as the previous models, we will work on equilibrium, stability and other mathematical parameters first.



The intravenous model was the one used in the first simulation. For the pills, we used the following model:

$$\frac{dA}{dt} = d_{\max} e^{\frac{-t}{k}} - pA$$

- The equilibrium point exists at $0 = d_{\max} e^{\frac{-t}{k}} - pA$

$$d_{\max} e^{-\frac{t}{k}} - pA = 0$$
$$d_{\max} e^{-\frac{t}{k}} = pA$$
$$A = \frac{d_{\max} e^{-\frac{t}{k}}}{p}$$

This equilibrium stands for the amount where there will not be a change of value for drug amount in the body. However, for our exponential model, theoretically there should not be such an equilibrium because $d_{\max} e^{-\frac{t}{k}}$ will not reach 0 at all, so the change for drugs should not reach 0 at all. Therefore, we can only find the proposed equilibrium at where it reaches the desired red line as we've mentioned before. In the graph, pills will reach the clearance amount at around 55 hours while the injection will reach at around 75 hours.

- We find that the analytic solution is:

$$\begin{aligned}
\frac{dA}{dt} &= d_{\max} e^{\frac{t}{k}} - pA \\
\frac{dA}{dt} + pA &= d_{\max} e^{\frac{t}{k}} \\
e^{pt}\frac{dA}{dt} + e^{pt} pA &= e^{pt} d_{\max} e^{\frac{t}{k}} \\
(e^{pt}A)' &= e^{pt} d_{\max} e^{\frac{t}{k}} \\
e^{pt}A &= d_{\max} \int e^{t(p+\frac{1}{k})} dt \\
A &= \frac{d_{\max}}{e^{pt}} \int e^{t(p+\frac{1}{k})} dt
\end{aligned}$$

- Note that the stability of the dissolving pill model is the same at the intravenous model, therefore f'(A) = -p and since p is always positive in our definition, our dissolving pill model is always stable. This indicates that the model is always stable while considering the pilling method and it makes sense since the whole process will end up with very little amount of drugs left in our body.

In the above graph, we are comparing the time and the amount of drug for the two drug administration methods. Note that the red dotted line represents "0"mg in the body. The pill model is exponential and never truly reaches 0, therefore it has been set to 10mg which we will use consider 0mg in the body. For the dissolving pill, we can see that the amount of mg in the body peaks at about 5hrs for just below 250mg. We can see that it peaks faster then the injection but the injections provides higher amounts of the drug. The injections reaches its maximum at about 10 hours for an amount around 350mg in the body. We can also see that the pill goes to zero faster then the injection. At hour 65, the body has 0mg of the dissolving pill and it's not until 10 hours later that the injection has reached 0mg.

We can see that there are pros and cons of each method, the pill peaking sooner and having a shorter time in the body compared to the injection, but the injections provides more drug which may be beneficial for people that suffer with more pain. For someone competing or wanting to work/study and not feel the effects of the painkiller, the pill may be the better option as it leaves the body sooner, but for someone with chronic pain or severe pain the injection may be preferable.

Extension model:

As we've mentioned in the first derivation of the base model session, we have set up some assumptions that the metabolism does not take count as a parameter that affect the whole process of drugging. At the same time, we negate the possibility for a patient to accidentally mix the two types of drugs together and take it. However, this is very different from what is happening in the real world, in the following two sections, we are going to separately talk about how these two cases separately.

Extension 1: The logistic model for the processing rate.

The general idea for this specific extension is very similar to what we have in the base model, however there is a new parameter q stands for the negative effects that human

metabolism will bring to the processing of the drug. Therefore, the model becomes the following:

$$\frac{dA}{dt} = \begin{cases} d - (pA - qA^2) & 0 \leq t \leq k \\ -(pA - qA^2) & t > k \end{cases}$$

Consider the model with two doses: the model becomes the following:

$$\frac{dA}{dt} = \begin{cases} d - (pA - qA^2) & 0 \leq t \leq k/2 \\ -(pA - qA^2) & t > k \end{cases}$$

Parameters with units:
A = Current dose amount in the human body. (mg)
p = the processing rate for dosed drugs in a human body. (mg/h)
d = constant dosing rate for the specific type of drugs. (mg/h)
k = The total amount of time that it requires for the specific amount of drugs to be dosed. (h)
t = Current time tick within the entire processing state.(h)
q = the negated processing rate because of metabolism (mg/h)

As we mentioned before, metabolism wasn't an issue for our base model, however in our first extension, we want to consider the influences of the drug process that are bring by the metabolism. There are many factors that affect metabolism, including age, diet, gender, smoking, alcohol consumption and disease, etc. These factors may enhance drug clearance, leading to failure of drug treatment, or inhibit drug elimination, leading to adverse reactions. Such as Cirrhosis can reduce drug metabolism and clearance by 30 percent to 50 percent, men have higher CYP1A2 and CYP2E1 activity than women, so the Morphine clearance in men is higher than in women. Also non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used drugs for the treatment of acute and chronic pain, and their anti-inflammatory, analgesic, and antipyretic effects are achieved by inhibiting cyclooxygenase (COX). Inhibiting CYP1A2 activity will decrease the metabolism rate of ibuprofen and aspirin. So we make the assumptions that those factors will not influence the metabolism speed and discuss how the model if we consider a constant metabolism rate q in mg/h.[13]

The first assumption that we've made for this model is that people are having the same processing rate and metabolism speed for all ages. This is different from the real world since medicine clearance is reduced by around 50 percent in 60-70-year-old people than in 30-year-old adults. And the clearance rate of caffeine in premature infants is about $1/9$ that of adults in the real world. So different people based on age, weight, gender, etc., would case their metabolism speed to change which in return could possibly cause different processing rate p for them. However, we consider that the people of all ages are having the same processing rate and metabolism speed to prevent the model become complex.

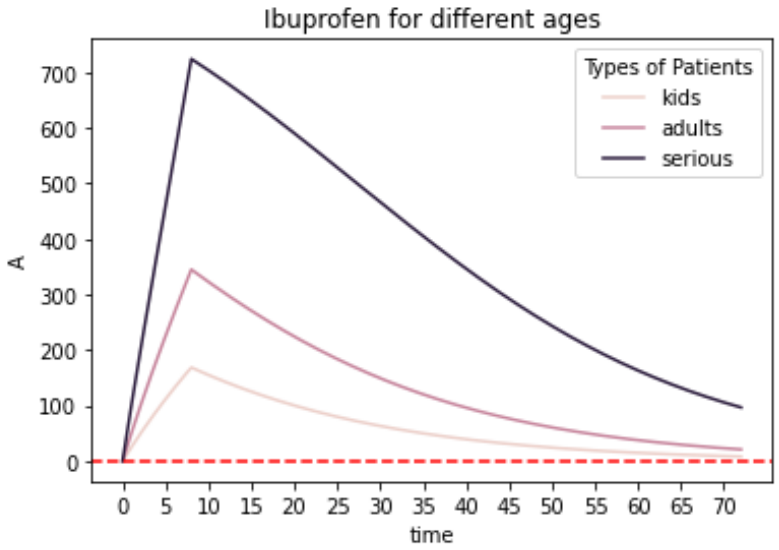
Same as the second assumption in base model one, the injection only contains one type of medicine. In real life scenarios, it is possible that a patient needs different types of drugs for the treatment of reducing pain, but in our model we assume that taking ibuprofen is enough to manage there pain. Taking multiple drugs might change the processing function of human body which will complicate our model, hence we choose to focus on studying the total amount of drugs in the body at time t with only taking ibuprofen.

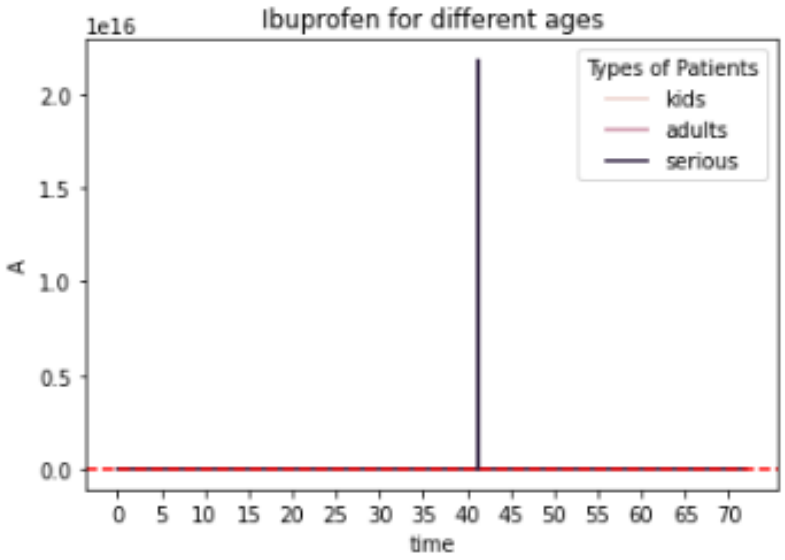
The third assumption is that the diet will not cause the metabolic rate to change. In real world the metabolic rate is partial dependent on the enzyme in our body, Enzymatic will increase metabolism speed and the enzymatic inhibition will decrease the metabolism speed. For example, taking grapefruit, soybean, mint, chamomile, dandelion and pomegranate that inhibit CYP1A2 activity which will decrease the metabolism rate of Morphine. [1,2] Taking caffeinated beverages, green tea, black tea, Brussels sprouts, cabbage and cauliflower induce CYP1A2 activity which will increase the metabolism rate of Morphine. [3,4] The third assumption is different from the real world since the diet will influenced the metabolism speed. However, we assume that this will not cause our model to change here.

Another very important assumption is that the drugs are carried by blood with a constant speed. This assumption doesn't really affect the graph at first but it ensures the exponential processing and dosing simulation can happened for our model. Without a constant blood absorbing speed, the dosing rate and processing rate can be affected by a small amount which we also will talk in our stochastic element.

The other assumptions that we have are very similar with what we have in the base model except for the part of ignoring the metabolism in human body. Compared to the original base model, this model is more similar to what is happening in the real world where people cannot fully process painkillers because of metabolism. It takes longer for people to fully observe the drug. Even though this model is still pretty far from what is happening in reality, by comparing the current model and the base model, we can start to see what role metabolism acts in the human body.

Analysis For the first model extension: First, we would have two graphs for this model as below.





The only difference between these two graphs are the choice of the q parameter, which stands for the metabolism affect rate for processing. The first graph has q at 0.00005 and the second graph has it at 0.00008. It is really surprising that such a small change of value would change the graph by this much, however it is very reasonable as well. In the second graph, since the q value is too much, this causes the dA/dt function to have a very small change all the time, all the dosing amount are getting processed once it is dosed. Such rapid rate of metabolism causes the drug loses very quickly, therefore the therapeutic concentration of the drug in the blood and tissues may not be reached.

When values are reasonably high, the curve is more flatten compare to the original curve, this is because the increase of metabolism factor actually slows down the processing action, which makes the drug stay longer in the human body, which could lead to a increase in the efficiency. These situations might happen with a great regular diet and regular timetable of a person. Because of that, we should try to stay a healthy life in order to make the drugs more efficient.

There is another situation where the metabolism rate is really small or even negative, in that case the processing rate is too rapid which gives a similar situation than the over metabolism rate scenario.

The equilibrium of the model happens when $pA = d + qA \cdot A$, this happens when the dosing amount and processing amount are the same, resulting in an over metabolism. The model is stable if $qA < p$ and is unstable when $qA > p$, which also indicates that a big q value is not acceptable.

From the above analysis and what we can see from the comparison between these two given graphs, we can tell that our Ibuprofen process is extremely sensitive to the metabolism parameter. This indicates that

Extension 2:

For the second extension, we want to discover how does Ibuprofen with other sources

of medication.Our general setup includes three cases. The first one is how will people with high blood pressure(who needs to take treatment like pills) react with painkillers. When they are taking pills that treat high blood pressure, will that negates the effect of painkiller or not. We came up with this idea because one of our group members grandparents have blood pressure issues, so we want to see if there are extra precautions when they take painkillers.

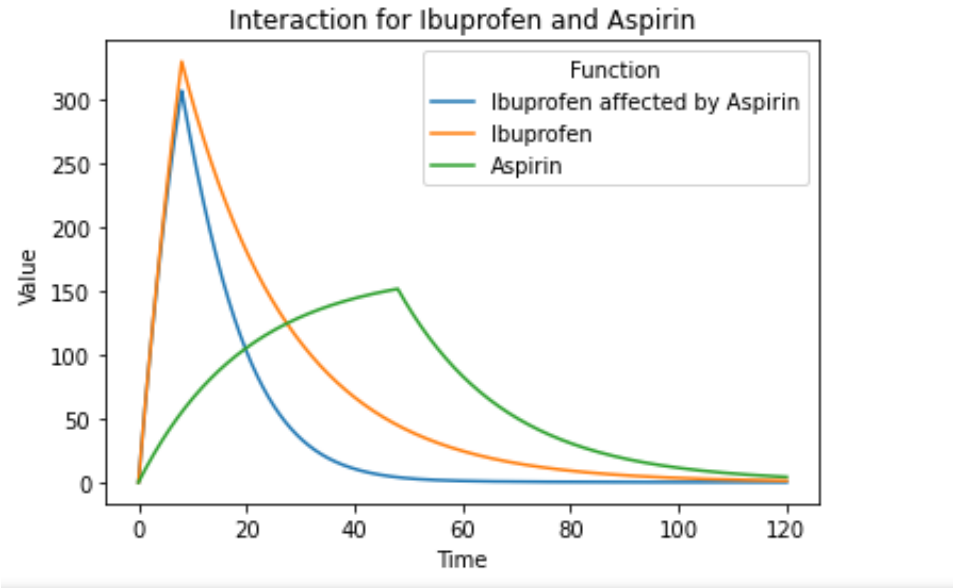
The second case, will people who take allergy treatments react negatively when the treatment is combined with painkillers. We came up with this idea since a lot of our friends have allergies to common things like peanuts, alcohol, eggs, etc. Some of them are taking pills to help against these allergies, hence we wonder if they accidentally were to get hurt after taking the allergy treatment, will they be able to get the same treatment as someone without allergies.

The third case, can we take two different types of painkillers? We came up with this thought because there are a tremendous amount of different painkillers in the market. For newbies, it is hard for them to tell which one to pick. Some of them might take multiple brands of painkillers at the same time and we want to see if there's a negative effect.

In our extension, we want to focus on the third case where two painkillers interact with each other because we think that is the most common case in real life. The extra parameters are still q, however the q here stands for the interaction factor that how Aspirin will affect Ibuprofen. In our model construction, we didn't add the qAB parameter to the dB/dt model which relates to Aspirin, this is because we want to simplify the model and focuses on the effects on Ibuprofen. Therefore, the total model should be looking like below:

$$\frac{dA}{dt} = \begin{cases} d - pA + q * A * B & 0 \leq t \leq k \\ -(pA - q * A * B) & t > k \end{cases}$$

$$\frac{dB}{dt} = \begin{cases} f - pB & 0 \leq t \leq j \\ -(pB) & t > j \end{cases}$$



Parameters with units:
A= Current dose amount of Drug A in the human body. (mg)
p = the processing rate for dosed drugs in a human body. (mg/h)
d = constant dosing rate for Ibuprofen. (mg/h)
k = The total amount of time that it requires for the specific amount of drug A to be dosed. (h)
t = Current time tick within the entire processing state.(h)
q = the negated processing rate because of metabolism ($0.00005/mgh$)
B = Current dose amount of Drug B in the human body. (mg)
f = Constant dosing rate for Aspirin.

In this specific model, we first tried to add the logistic parameter for both Ibuprofen model and Aspirin model, however, we discover it is hard to get a very reasonable graph when both parameters exist. Hence our group decides to work on the model where only Ibuprofen are getting affected with the injection of aspirin at the same time. The parameter actually stands for p/j in reality where p is the processing rate in the human body and j is a parameter shows how much metabolism effect does the dosing bring. Based on our test, we pick a value of j as 1000, which leads to q = 0.00005. This is because we think that the interaction rate should be considered by per 1000 mg, and the graph looks nice with this guess.

Aspirin and Ibuprofen are both very popular painkillers in the real world, for people who lack medical knowledge, there could be some chances that they mix these two types drugs together. However, based on our research, taking aspirin and Ibuprofen at the same time will can cause stomach aches and more seriously injury's like stomach bleeding. We want to show the reader that mixing these drugs together can cause a negative effect therefore convincing them to not take these painkillers together.

The very first assumption that we've made is that the effect of the metabolism is concluded in the parameter q. This is because stomach bleeding will change the metabolism of the human body hence it will become an inevitable element to consider. However, it is not our main focus so it should be mentioned less.

The second assumption is that the amount of aspirin dosed is not affected by the common factor qAB, this is not usual since the interaction of effects between pills should affect both types. Since we would like to focus mainly on how Ibuprofen is affected, the effects on Aspirin is simplified, which should not happen in real life.

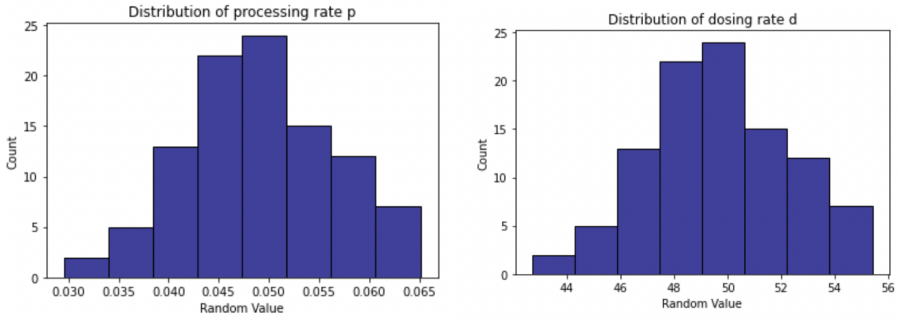
The third assumption is that we are using the adult usage for the comparison instead of all ages. In general cases, overdose for kids or seniors will result in a even more dangerous situation. However, since there would most likely be guardians for these groups of people, we are limiting our research to how adults are getting hurt when they accidentally take two painkillers at a same time.

Proposed Stochastic Element

Our research is primarily focused on the total time that Ibuprofen takes to exit the body. Since the dosages of Ibuprofen can be changed for different scenarios and processing rates vary for each person, we are interested in exploring stochasticity in the processing/clearance rate p and the dosing rate d. In the real world, the processing rate parameter

has much variability as bodies will naturally metabolize at a different rate due to several differences such as age, weight, gender, medical conditions etc. Our processing rate does not include how these physical differences might affect how a body metabolizes a drug at a different rate then another. These are important rates to explore since there could be a defective set of pills or intravenous injection that may have a few more or less mg then intended.

We want to randomize this parameter to see if the amount of drugs in the body will differ a lot between different processing rates. Our research showed that, since children on average have a faster metabolism they have the ability to metabolize drugs faster, though it is important to remember that children have lower drug dosages then adults. [12] [13] In the background section we have some estimates of how long some painkillers will last in certain bodily fluids, naturally these will differ based on a person but they provide some idea as to how long it will take to clear. We want to use the technique of random parameters drawn from a normal distribution, this randomizes the processing/clearance rate p by drawing a sample value from a normal distribution using a mean value and standard deviation for p. Using a similar process we are going to do the same with the dosing rate d. We want to randomize the dosing rates to see if the dosages will greatly affect the total time a particular drug spends in the body. Also, it's important to look at the varying dosage amounts since different drugs/pain killers will have different doses depending on there chemical compound and doses will vary in strength due to the purpose of the drug and a patients pain. For a petite person 50mg/hr may be administered and for a significantly taller adult 55mg/hr may be administered. We are curious if these changes in dosages will affect the time it takes to metabolize in the body. Below we have two graphs to chart the normal distribution of the processing rate p and dosing rate d, the processing rate was set to a mean of 0.05 with a standard deviation of 0.007 and the dosing rate was set to a mean of 50 with a standard deviation of 2.5. The standard deviations were educated guesses based on trial and error. For the processing rate p, with a standard deviation of 0.007 we can see that on the low end we get $p = 0.03$mg/hr and on the high end we get $p = 0.065$ mg/hr. For the dosing rate d, with a standard deviation of 2.5 we can see that on the low end we get $d = 44$mg/hr and on the high end we get $d = 56$ mg/hr.

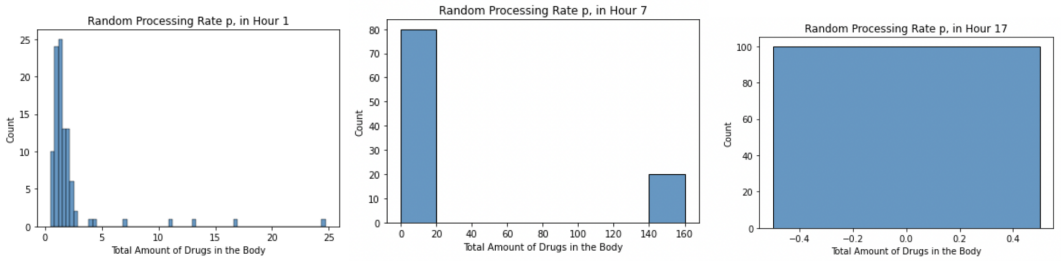


The graphs above give us an idea as to how our values will be chosen for our stochastic analysis. We are going to investigate what happens when the processing rate is pulled from a normal distribution, and when the processing rate and the dosing rate is pulled from a normal distribution. We will do this for both the intravenous administration and the dissolving pill, in total making 4 cases. Since we are looking into how long drugs are

in the body for, we have graphed all four situations at three different time points for 100 cases.

Case 1: Intravenous with varying processing rate

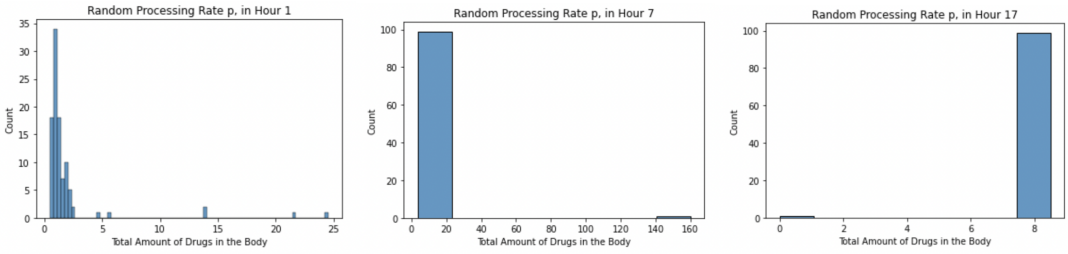
Parameter p have been drawn from a normal distribution with mean set to 0.05 with a standard deviation of 0.007 (note both were educated guesses) with a dosing rate of 50mg/hr.



We can see that at hour 1 the majority of people had between 0 - 5mg in the body, with only 5 out of 100 cases surpassing this amount, based on the intravenous model this may mean those that had a larger amount of drugs in the body had a slower processing rate then those that had 0 - 5mg in the body. At hour 7 we can see that the total amounts have increased about 80 cases had less then 20mg in the body and 20 cases had around 120mg in the body. By hour 17, we can see that all 100 cases had around 0.0mg in the body. The little variance in the amount of drugs in the body at hour 17 shows us that the different processing rates do not have a large effect on total time in the body or how long it takes for them to pass through the body, the different processing rates have the largest effect in the first several hours.

Case 2: Dissolving pill with varying processing rate

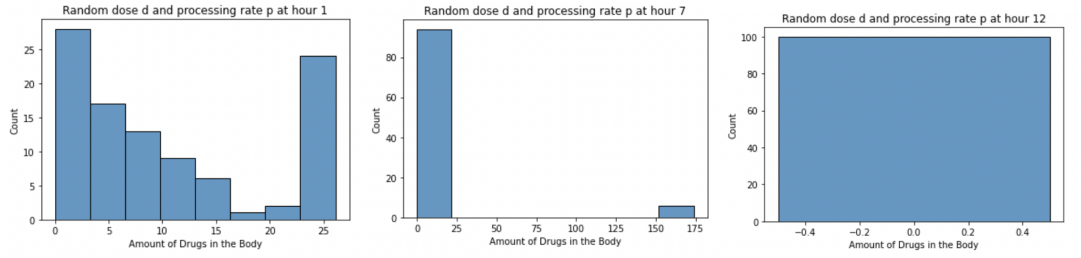
Parameter p have been drawn from a normal distribution with the mean set to 0.05 with a standard deviation of 0.007 (note both were educated guesses) with a max dosing rate of 50mg/hr.



We can see that at hour 1 the majority of people had between 0 - 2.5mg in the body, with only several people surpassing this amount. Based on the dissolving pill model this may mean those that had significantly more drugs in the body had a slower processing rate then those that had 0 - 2.5mg in the body. At hour 7, almost all 100 cases have around 20mg or less in the body with only 1 case at 150mg. By hour 17, the amount of drugs in the body hit a minimum of 8mg (the amount never truly hits zero). For the except of the single case, we can see that the varying processing rates have little effect after several hours as the amount of drugs increase and then decrease together. The variation of processing rates has the most effect on the amount of drugs in the first couple of hours, but has little affect

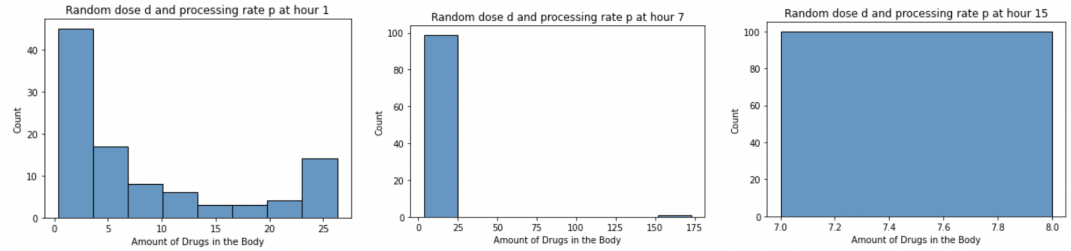
on the total time for the drugs to leave the body.

Case 3: Intravenous with varying processing rate and dosage
Parameter d has been drawn from a normal distribution with the mean set to 50 with a standard deviation of 2.5 and parameter p have been drawn from a normal distribution with mean set to 0.05 with a standard deviation of 0.007.



In hour 1, we can see a large distribution of amount of drugs in the body, at one end we have more then 45 cases with 5mg or less and at the other end we have around 25 cases with about 25mg in the body. In hour 7, we can see that almost all cases have less than 25mg in the body with just a couple at between 150-175mg. By hour 12, all the 100 cases have hit 0.0mg in the body. The lack of variation shows us that the varying processing and dosing rates have little to no affect on the individual 100 cases as they all go to zero by hour 12.

Case 4: Dissolving pill with varying processing and dosage
Parameter d has been drawn from a normal distribution with the mean set to 50 with a standard deviation of 2.5 and parameter p have been drawn from a normal distribution with mean set to 0.05 with a standard deviation of 0.007.



In hour 1, we can see a large distribution of amount of drugs in the body, though the largest amount is around 5mg or less. In hour 7, we can see that almost all cases have less than 25mg in the body with just a couple at between 150-175mg and by hour 15 all the 100 cases a minimum of 7.5mg in the body. The lack of variation shows us that the varying rates have little to no affect on the individual cases.

We can see that there are some differences between the cases with just varying processing rates compared to the cases with varying processing and dosing rates. For the intravenous model we can see that there is a lot more variation in total amount of drugs in hour 1 in Case 3 compared to Case 1, as well as it takes 17 hours for the total amount of drugs to be 0 in Case 1 and it only takes 12 hours in Case 3. Similarly, in the dissolving pill model, we can see that the total time for the amount of drugs to be minimized in the

body is also smaller when there are varying dosing and processing rates, in Case 2 we have that it takes 17 hours and in Case 4 it only takes 15. Overall, we can see that the varying processing rates and dosing rates have the most effect on total amount of drugs in hour 1 and do not have much of an affect after several hours, and that individual cases tend to move together as seen in Case 1, 3 and 4 by the end.

Exploring these stochastic elements helps us to get an idea as to how long drugs will be in the body for, overall small changes will only effect the total time spent by 2 - 4 hours. From looking at the different distributions and the different cases we can see that slightly different doses or processing rates will not result in big differences in the real world and will not cause harm if someone was to be administered a few more mg/hr then intended or if someone was to ingest a defective ibuprofen pill where it had 53mg instead of 50mg, it wouldn't have any long term affects. Also, in a case where a person may be in the hospital receiving an intravenous pain treatment which caused drowsiness, if they were administered 45mg/hr instead of 50mg/hr, it would roughly still take the amount of time that the full 50mg/hr dose takes to leave the body, they still wouldn't be able to drive or go back to work several hours earlier just because they received a couple less mg/hr. Also, different processing rates that people might have does not have an affect on total time that drugs will spend in the body. Specifically, when the dose was the same for the intravenous method and there were 100 different processing rates, the time spent in the body was all the same, this tells us that in the real world the individual differences that bodies have and that affect their metabolism will not affect total time spent in the body.

Summary

In conclusion, the research project for our project mainly focused on how long would the typical painkiller Ibuprofen, stay in the human body in order to help the patients relief the pain sufficiently. In our analysis, we find out that the effect for children patient with half dosing releases after 60 hours, whether the adult patient with normal dosing can hold the effect for more than 70 hours and the patient with serious injury will have the painkiller treatment effect for more than 80 hours. This indicates that Ibuprofen can stay in human body for 3 days with a regular dosing amount. At the same time, we also shown that Aspirin and Morphine can also keep the effect for 3 days, however for Morphine, human body would produce extra enzymes since the dosing is too rapid. For Aspirin, the amount of drugs is less compare to Ibuprofen, hence we can conclude that Ibuprofen are better comparing to the chosen 2 types of drugs. At the same time, in our last derivation, we have shown that the injection method is significantly better than pill method, since painkiller pills can only stay in human body for around 50 hours.

In the stochastic element part, we explored stochasticity in the processing rate and the dosing rate. We chose to do this because in the real world people have different processing rates due to age, gender, health conditions etc., and we wanted to simulate what would happen when this value is taken from a normal distribution as well as the dosing rates will not always be the same as people will need different quantities for different levels of pain. From our simulations we saw how there was extremely little variations between the total length of time that ibuprofen was in the body. For 3 of the 4 cases we saw the 100 different cases often went to zero at the same time, therefore showing that differences in processing rates will not cause large deviations in how long it takes for the drugs to leave the body.

From the base model construction, our group mainly focused on two assumptions: how metabolism will affect the treatment process and how taking two different types of drugs will affect the treatment process. Both of these topics are being expanded in the model extensions.

In our extension 1, we understand how important it is to have a reasonable metabolism factor. A large or small metabolism factor will either change or hurt the model itself and make it less reliable. Therefore we can tell the audience that when choosing painkillers, we need to care about those factors which may influence the metabolism of the drug. As we mentioned in the extension part, age, gender, disease, diet, medicine are all potential factors that can change the metabolism rate in human body. We know that the drugs in the human body are mostly catalytic by the enzyme, so all of the factors can make a difference of the enzyme which in return could possibly change the metabolism speed.

In the second extension model, we mainly focused on how the taking both Aspirin and Ibuprofen will hurt a human body. As we mentioned in the previous session, taking two such drugs will causing a negative effect because of the extra enzymes used. At the same time, since the cons include things like stomach bleeding is hard to tell without getting a proper body check, we need to take these scenarios more seriously and think about taking different pills more carefully. This would also tell us the necessity of knowing some fundamental medical knowledge and listen to the doctor's note instead of taking random drugs on your own.

However, there could still be some improvement for our models provided. In the future, if anyone wants to keep developing this topic, they should be working on adding the effect for Aspirin in the extension model 2. With that extra addressing, the comparison between taking Aspirin and Ibuprofen will be more reliable and we can further develop the

relationship between taking these two drugs together. At the same time, the health condition could be developed more by future researcher as well. For example, checking how Ibuprofen will react in patient with high blood pressure will also be an interesting topic whereas a lot of high blood pressure patient are afraid to take painkillers without a doctor note in real life.

Also, some limitations of our work include that the processing rate does not account for age, weight, sex, health conditions, stress levels, exercise levels etc. Potential future advances of this model would be creating a function for the processing rate which could take in parameters such as age and weight to give a more accurate processing rate. Also, we used this model to explore how long painkillers were in the body for, but it could also be used for other intravenous medications like insulin shots and oral pills such as oral acne medications or birth control.

Code :

Base model 1:

[1]:
```
import numpy as np
from scipy.integrate import odeint
import matplotlib.pyplot as plt
import seaborn as sns
import pandas as pd
import math

def dosing_injection(A,t,k,d,p):
    if t <= k:
        return d-p*A
    dx = -p*A
    return dx

# Injections for Ibuprofen
# Assumptions made: all amount will be dosed in 8 hours
A = 0 #Starting amount
k = 8 #total time of dosing
d = 50 #regular dosing amount
p = 0.05 #processing rate
t = np.arange(0, 120, 0.01) ## goes from 0 to 20 by increments of 0.01
d1_rep = np.repeat(d, len(t))
x1 = odeint(dosing_injection,A,t,args=(k,d,p,))

#half dosing (kids/senior purposes)
d = 25
d2_rep = np.repeat(d, len(t))
x2 = odeint(dosing_injection,A,t,args=(k,d,p,))

#double dosing (serious situation purposes)
d = 100
d3_rep = np.repeat(d, len(t))
x3 = odeint(dosing_injection,A,t,args=(k,d,p,))

results = np.zeros((len(x1)*3, 3))

results[:, 0] = np.transpose(np.concatenate((t, t, t)))
results[:, 1] = np.transpose(np.concatenate((x1, x2, x3)))
results[:, 2] = np.transpose(np.concatenate((d1_rep, d2_rep, d3_rep)))

df = pd.DataFrame({
    'time': results[:,0],
    'A': results[:,1],
    'd': results[:,2]
})

print(df)
sns.lineplot(data=df, x='time', y='A', hue='d').set(title='Ibuprofen for different ages')
plt.legend(title='Types of Patients', loc='upper right', labels=['kids', 'adults','serious'])
plt.axhline(y=10, color='r', linestyle='dashed')
plt.xticks(np.arange(0, 121, step=10))
plt.show()
```

Base model 2:

```
]: #comparison for different types of drugs
   #Assumptions made: all taking 400mg for one injection
   A = 0 #starting amount for all types of drugs
   k = 8 #dosing time for Ibuprofen
   d = 50 #ibuprofen
   p = 0.05 #processing rate (educated guess)
   t = np.arange(0, 120, 0.01) ## goes from 0 to 20 by increments of 0.01
   d1_rep = np.repeat(d, len(t))
   x1 = odeint(dosing_injection,A,t,args=(k,d,p,))

   #Aspirin
   k = 24 #dosing time for Aspirin
   d = 400/24 #dosing rate for Aspirin
   d2_rep = np.repeat(d, len(t))
   x2 = odeint(dosing_injection,A,t,args=(k,d,p,))

   #Morphine
   k = 3 #dosing time for Morphine
   d = 400/3 #dosing rate for Morphine
   d3_rep = np.repeat(d, len(t))
   x3 = odeint(dosing_injection,A,t,args=(k,d,p,))


   results = np.zeros((len(x1)*3, 3))

   results[:, 0] = np.transpose(np.concatenate((t, t, t)))
   results[:, 1] = np.transpose(np.concatenate((x1, x2, x3)))
   results[:, 2] = np.transpose(np.concatenate((d1_rep, d2_rep, d3_rep)))

   df = pd.DataFrame({
       'time': results[:,0],
       'A': results[:,1],
       'd': results[:,2]
   })

   print(df)
   sns.lineplot(data=df, x='time', y='A', hue='d').set(title='Different types of drugs for adult patients')
   plt.legend(title='Types of Drugs', loc='upper right', labels=['Aspirin','Ibuprofen', 'Morphine'])
   plt.axhline(y=10, color='r', linestyle='dashed')
   plt.xticks(np.arange(0, 121, step=10))
   plt.show()
```

Base model 3:

In [4]:
```
#comparison for Ibuprofen but different methods
#Assumptions made: all taking 400mg
def dosing_pills(A,t,K,d,p):
    return d*(math.exp(-t/K))-p*A


#injection
A = 0 #starting amount
k = 8 #dosing time for injection
K = 4 #expiring time of dosage for pills
d = 50 #ibuprofen
p = 0.05 #processing rate (educated guess)
t = np.arange(0, 120, 0.01) ## goes from 0 to 20 by increments of 0.01
d1_rep = np.repeat(d, len(t))
x1 = odeint(dosing_injection,A,t,args=(k,d,p,))

#Pills
d2_rep = np.repeat(1, len(t))
x2 = odeint(dosing_pills,A,t,args=(K,d,p,))


results = np.zeros((len(x1)*2, 3))

results[:, 0] = np.transpose(np.concatenate((t, t)))
results[:, 1] = np.transpose(np.concatenate((x1, x2)))
results[:, 2] = np.transpose(np.concatenate((d1_rep, d2_rep)))

df = pd.DataFrame({
    'time': results[:,0],
    'A': results[:,1],
    'd': results[:,2]
})

print(df)
sns.lineplot(data=df, x='time', y='A',hue='d').set(title='Different methods of drugs')
plt.legend(title='Methods', loc='upper right', labels=['Pills','Injection'])
plt.axhline(y=10, color='r', linestyle='dashed')
plt.xticks(np.arange(0, 121, step=10))
plt.show()
```

```
         time          A     d
0        0.00   0.000000  50.0
```

Extension 1:

In [5]:
```
#extension 1
def dosing_injection_met_(A,t,k,d,p,q):
    if t <= k:
        return d-p*A+q*(A**2)
    dx = -p*A + q*(A**2)
    return dx

# Injections for Ibuprofen
# Assumptions made: all amount will be dosed in 8 hours
A = 0 #starting amount
k = 8 #dosing time
d = 50 #regular dosing
p = 0.05 #processing rate
q = 0.00005 #p/1000 for metabolism rate
t = np.arange(0, 72, 0.01) ## goes from 0 to 20 by increments of 0.01
d1_rep = np.repeat(d, len(t))
x1 = odeint(dosing_injection_met,A,t,args=(k,d,p,q,))

#half dosing (kids/senior purposes)
d = 25
d2_rep = np.repeat(d, len(t))
x2 = odeint(dosing_injection_met,A,t,args=(k,d,p,q,))

#double dosing (serious situation purposes)
d = 100
d3_rep = np.repeat(d, len(t))
x3 = odeint(dosing_injection_met,A,t,args=(k,d,p,q,))

results = np.zeros((len(x1)*3, 3))

results[:, 0] = np.transpose(np.concatenate((t, t, t)))
results[:, 1] = np.transpose(np.concatenate((x1, x2, x3)))
results[:, 2] = np.transpose(np.concatenate((d1_rep, d2_rep, d3_rep)))

df = pd.DataFrame({
    'time': results[:,0],
    'A': results[:,1],
    'd': results[:,2]
})

print(df)
sns.lineplot(data=df, x='time', y='A', hue='d').set(title='Ibuprofen for different ages')
plt.legend(title='Types of Patients', loc='upper right', labels=['kids', 'adults','serious'])
plt.axhline(y=10, color='r', linestyle='dashed')
plt.xticks(np.arange(0, 72, step=5))
plt.show()
```

Extension 2:

```
5]: # extension 2
def model(state, t, k, p, d, q, k2, f):
    A, B =state
    if t <= k:
        dAdt = d-p*A -q*A*B

    else:
        dAdt = -p*A-q*A*B
    if t <= k2:
        dBdt = f-p*B
    else:
        dBdt = -p*B
    return [dAdt, dBdt]

A = 0 #starting amount for Ibuprofen
B = 0 #starting amount for Aspirin
t = np.arange(0, 120, 0.01)
k = 8 #dosing time
p = 0.05 #processing rate of human body
d = 50 # dosing rate
q = 0.0005 #interchage rate for Aspirin to Ibuprofen
k2 = 48 # aspirin dosing time
f = 400/48 #aspirin dosing rate
r = 0.00002 #

init_cond = [A, B]
params = (k, p, d, q, k2, f)


result = odeint(model, init_cond, t,args=params)
result1=odeint(dosing_injection,A,t,args=(k, d, p,))

df_x = pd.DataFrame({
    'time': t,
    'A': result[:, 0]
})
print(df_x)

df_y = pd.DataFrame({
    'time': t,
    'B': result[:, 1]
})
print(df_y)
df_z = pd.DataFrame({
    'time': t,
    'A': result1[:, 0]
})
sns.lineplot(data=df_x, x='time', y='A', label='Ibuprofen affected by Aspirin')
sns.lineplot(data=df_z, x='time', y='A', label='Ibuprofen')
sns.lineplot(data=df_y, x='time', y='B', label='Aspirin')
plt.xlabel('Time')
plt.ylabel('Value')
plt.legend(title='Function')
plt.title('Interaction for Ibuprofen and Aspirin');
```

Supportive graph aspirin model:

```
#asprin
A = 0
k = 48
d = 600/48 #regular dosing
p = 0.05 #processing rate
t = np.arange(0, 5*24, 0.01) ## goes from 0 to 20 by increments of 0.01
d1_rep = np.repeat(d, len(t))
x1 = odeint(dosing_injection,A,t,args=(k,d,p,))

#half dosing (kids/senior purposes)
d = 300/48
d2_rep = np.repeat(d, len(t))
x2 = odeint(dosing_injection,A,t,args=(k,d,p,))

#double dosing (serious situation purposes)
d = 1200/48
d3_rep = np.repeat(d, len(t))
x3 = odeint(dosing_injection,A,t,args=(k,d,p,))

results = np.zeros((len(x1)*3, 3))

results[:, 0] = np.transpose(np.concatenate((t, t, t)))
results[:, 1] = np.transpose(np.concatenate((x1, x2, x3)))
results[:, 2] = np.transpose(np.concatenate((d1_rep, d2_rep, d3_rep)))

df = pd.DataFrame({
    'time': results[:,0],
    'A': results[:,1],
    'd': results[:,2]
})

print(df)
sns.lineplot(data=df, x='time', y='A', hue='d').set(title='Aspirin for different ages')
plt.legend(title='Types of Patients', loc='upper right', labels=['kids', 'adults','serious'])
plt.axhline(y=10, color='r', linestyle='dashed')
plt.xticks(np.arange(0, 121, step=10))
plt.show()
```

Stochastic element:

```
def dosing_injection(A,t,k,d, mean, sd):
    p = rd.normal(mean, sd)
    if t <= k:
        dx = d - p*A
    else:
        dx = -p*A
    return dx
```

```
#CASE 1
A = 0
t = np.arange(0,20,0.5)
k = 8
d = 50
mean = 0.05
sd = 0.008

sets = 100

results = np.zeros((len(t), sets))
times = np.arange(sets)

for i in times:
    rd.seed(i)
    results[:, i] = odeint(dosing_injection,A,t,args=(k,d,mean,sd,)).flatten()

df_rnd_d = pd.DataFrame(results)
```

```
rnd_r_one= df_rnd_d.iloc[1]
sns.histplot(x=rnd_r_one)
plt.xlabel("Total Amount of Drugs in the Body")
plt.title("Random Processing Rate p, in Hour 1");

rnd_r_seven= df_rnd_d.iloc[7]
sns.histplot(x = rnd_r_seven)
plt.xlabel("Total Amount of Drugs in the Body")
plt.title("Random Processing Rate p, in Hour 7");

rnd_r_seventeen = df_rnd_d.iloc[17]
sns.histplot(x=rnd_r_seventeen)
plt.xlabel("Total Amount of Drugs in the Body")
plt.title("Random Processing Rate p, in Hour 17");
```

```
def dosing_pills(A,t,k,d,mean, sd):
    p = rd.normal(mean, sd)
    if t <= k:
        return d*(math.exp(t/k))-p*A
    dx = -p*A
    return dx
```

```
#CASE 2
A = 0
k = 8
d = 50
t = np.arange(0,20,0.5) ## goes from 0 to 20 by increments of 0.01
mean = 0.05
sd = 0.007

sets = 100

results = np.zeros((len(t), sets))
times = np.arange(sets)

for i in times:
    rd.seed(i)
    results[:, i] = np.transpose(odeint(dosing_pills,A,t,args=(k,d,mean,sd,)))
diss_pill = pd.DataFrame(results)
```

```
rnd_r_one = diss_pill.iloc[1]
sns.histplot(x=rnd_r_one)
plt.xlabel("Total Amount of Drugs in the Body")
plt.title("Random Processing Rate p, in Hour 1");

rnd_r_seven = diss_pill.iloc[7]
sns.histplot(x=rnd_r_seven)
plt.xlabel("Total Amount of Drugs in the Body")
plt.title("Random Processing Rate p, in Hour 7");

rnd_r_twelve = diss_pill.iloc[12]

sns.histplot(x=rnd_r_twelve)
plt.xlabel("Total Amount of Drugs in the Body")
plt.title("Random Processing Rate p, in Hour 17");
```

```
def dosing_injection(A,t,k, mean1, sd1, mean2, sd2):
    p = rd.normal(mean1, sd1)
    if t <= k:
        d = rd.normal(mean2, sd2)
        dx = d - p*A
    else:
        dx = -p*A
    return dx
```

```
#CASE 3
A = 0
t = np.arange(0,20,0.5)
k = 8
mean2 = 50
sd2 = 2.5
mean1 = 0.05
sd1 = 0.007

sets = 100

results = np.zeros((len(t), sets))
times = np.arange(sets)

for i in times:
    #rd.seed(i)
    results[:, i] = odeint(dosing_injection,A,t,args=(k, mean1, sd1, mean2, sd2))
    .flatten()

df_rnd_d = pd.DataFrame(results)
```

```
rnd_r_one = df_rnd_d.iloc[1]
sns.histplot(x=rnd_r_one)
plt.xlabel("Amount of Drugs in the Body")
plt.title("Random dose d and processing rate p at hour 1");

rnd_r_seven = df_rnd_d.iloc[7]
sns.histplot(x=rnd_r_seven)
plt.xlabel("Amount of Drugs in the Body")
plt.title("Random dose d and processing rate p at hour 7");

rnd_r_twelve = df_rnd_d.iloc[12]
sns.histplot(x=rnd_r_twelve)
plt.xlabel("Amount of Drugs in the Body")
plt.title("Random dose d and processing rate p at hour 12");
```

```
def dosing_pills(A,t,k,mean1, sd1, mean2, sd2):
    p = rd.normal(mean1, sd1)
    if t <= k:
        d = rd.normal(mean2, sd2)
        return d*(math.exp(t/k))-p*A
    dx = -p*A
    return dx
```

```
#CASE 4
A = 0
k = 8
t = np.arange(0,20,0.5) ## goes from 0 to 20 by increments of 0.01
mean2 = 50
sd2 = 2.5
mean1 = 0.05
sd1 = 0.007

sets = 100
results = np.zeros((len(t), sets))
times = np.arange(sets)

for i in times:
    rd.seed(i)
    results[:, i] = np.transpose(odeint(dosing_pills,A,t,args=(k,mean1,sd1, mean2, sd2)
diss_pill = pd.DataFrame(results)
```

```
rnd_r_one = diss_pill.iloc[1]
sns.histplot(x=rnd_r_one)
plt.xlabel("Amount of Drugs in the Body")
plt.title("Random dose d and processing rate p at hour 1");

rnd_r_seven = diss_pill.iloc[7]
sns.histplot(x=rnd_r_seven)
plt.xlabel("Amount of Drugs in the Body")
plt.title("Random dose d and processing rate p at hour 7");

rnd_r_fifteen = diss_pill.iloc[15]
sns.histplot(x=rnd_r_fifteen)
plt.xlabel("Amount of Drugs in the Body")
plt.title("Random dose d and processing rate p at hour 15");
```

Individual Contributions

Alexa:

- Completed stochastic element and with the help of Yiren's base model codes was able to create stochastic code for the graphs.
- Completed stochastic element and with the help of Yiren's base model codes was able to create stochastic code for the graphs.
- Added modifications to the background and motivations.
- Help with base model analysis and summary. Wrote the simulation analysis and gave ideas for mathematical simulation
- Revised and compiled P4 document.

Mingqing:

- Gave ideas of research questions.
- Did assumptions for the base model.
- Completed the motivation, assumption, real world parts for extension 1 and motivation for extension 2.
- Helped with simulation and real world connection parts for analysis.
- Did parts of summary and answer the discussion questions in the discussion part. Gave ideas of limitation and direction.

Yiren:

- Constructed base model using python related lab codes.
- Completed the base model construction parameters, assumptions and model constructions, explained how the context is interested and builds up connection from real world to our case.
- Helped finish math analysis of the base model and connected real world scenarios to each of the model.
- Completed extension model parameters and constructions, helped with assumptions , completed extension model analysis.
- Helped with stochastic element codes. Give ideas on how the discussion part should be and having discussion questions prepared.

Ravel:

- Background and motivation
- helped with base model assumptions doses and time information for different drugs, edited final document.
- organized citations for background information
- helped analyzed problems in code

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