ICE - Area Under a Curve

Figure 1: OxyContin (R) tablets.

"Hillbilly Heroin" is one of the many nick-names[1] that have been given to the prescription medicine OxyContin®[2] (see Figure 1[3]). Other nick-names[4] include far more sinister appellations such as "Killers" and "OxyCoffins." The active ingredient in OxyContin® is the chemical oxycodone (a close cousin of heroin, see Figure 2[5]. According to the DEA[6] oxycodone abuse has been a problem in the United States since the early 1960's. One of the best known oxycodone-based prescription medications is Percodan, which was even mentioned during several episodes of the hit TV show "The Simpsons."[7]

In 1970, Congress passed the Controlled Substances Act. A provision of this act gave oxycodone-based medications Schedule II status. According to the DEA publication "Drugs of Abuse[8]" a Schedule II controlled substance is one that meets the following definition:

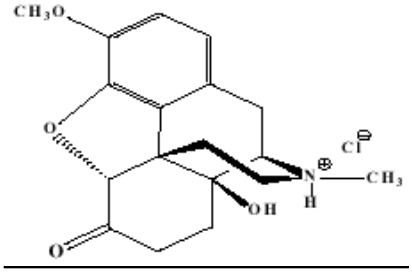

Figure 2: Chemical structure of oxycodone.

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[1] Source: CNN. "States work to control OxyContin abuse." July 20, 2001.

[2] OxyContin® is a registered trade mark of Purdue Pharma, L.P. Any reference to OxyContin® in this document that does not include the ® symbol reflects an omission of this symbol in the original document quoted.

[3] Image source: http://www.npr.org/

[4] Source: http://www.oxyabusekills.com

[5] Image source: http://www.purduepharma.com

[6] Source: http://www.deadivision.usdoj.gov/drugs_concern/oxycodone/summary.htm

[7] Herschel Krustofski (a.k.a. "Krusty the Klown") is a Percodan addict. This is mentioned in episodes 9F07 (in which Homer buys a pickup truck with a plow and goes into business as "Mr. Plow") and 2F32 (in which Bart accidentally ingests a "free jagged metal Krusty-O" in his Krusty-O's breakfast cereal and has to be hospitalized). An actual person who struggled with Percodan addiction for many years is comedian Jerry Lewis. This coincidence (and others, such as telethons for sick children) have led serious students of "The Simpsons" to suggest that the character of Herschel Krustofski may be based on Jerry Lewis.

[8] Source: Drug Enforcement Agency, U.S. Department of Justice.

- The drug or other substance has a high potential for abuse.
- The drug or other substance has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions.
- Abuse of the drug or other substance may lead to severe psychological or physical dependence.

Figure 3: DEA Administrator Asa Hutchinson.

Examples of other Schedule II controlled substances include morphine, PCP, cocaine, methadone and methamphetamine. Despite this status, oxycodone abuse has continued and has recently gained a great deal of media attention due to deaths related to abuse of the prescription medicine OxyContin® and the implication of Purdue Pharma L.P. (the manufacturers of OxyContin®) by DEA Administrator Asa Hutchinson (see Figure 3[9])[10].

Federal officials have described OxyContin® as "the most widely abused prescription drug ... in the last twenty years." The statement below is taken from the Drug Enforcement Administration's web site[11] and gives some idea of the seriousness with which the DEA view the issue of OxyContin® abuse.

> "Information received from the Drug Abuse Warning Network (DAWN) indicates that instances of emergency department episodes and medical examiners reports involving oxycodone, the active ingredient in OxyContin®, have increased significantly since 1996. Reports from 20 metropolitan areas within the continental U.S. report that oxycodone-related deaths and emergency department episodes have increased 400 percent and 100 percent respectively.
>
> Most deaths reported in the media and attributed to OxyContin® have generally occurred in areas outside the DAWN system, such as Maine, West Virginia, and rural Kentucky. DEA has been actively collecting and evaluating data from medical examiners in these areas to more clearly ascertain the extent of abuse problems.
>
> Drug treatment programs have also provided evidence regarding in increase in OxyContin® abuse. Programs in West Virginia, Pennsylvania, Kentucky and Virginia, the states that have been most severely affected by this trend, report that 50 to 90 percent of newly admitted patients identified OxyContin® as their primary drug of abuse."

Sometimes lost in the media coverage of OxyContin® and oxycodone abuse is the fact that these substances have legitimate medical uses. OxyContin® for example, was developed to relieve chronic pain. In this ICE, you will replicate some of the results obtained by FDA and Purdue Pharma researchers during the clinical trials of OxyContin®.

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[9] Image source: http://www.usdoj.gov/dea/

[10] On December 11, 2001, Administrator Hutchinson testified before Congress implicating Purdue Pharma L.P. in the "escalating abuse and diversion of the drug." The full text of Administrator Hutchinson's testimony can be found at: http://www.usdoj/dea/pubs/testimony.htm

[11] Source: http://www.deadivision.usdoj.gov/drugs_ceoncern/oxycodone/oxycontin_faq.htm

As shown in Figure 1, OxyContin® is a tablet that is intended to be taken orally. Oral dosage is one of the least effective ways of delivering a drug to a patient, compared to intravenous injection of the drug. The reduction of the effectiveness of a drug when administered orally can be due to many reasons. Two of the most important are:

- The drug molecule may be disrupted or destroyed by the action of salivary enzymes, stomach acid and digestive enzymes.

- The drug molecule may react with other molecules present in the stomach (for example from food or beverages that the patient has ingested) and form insoluble or dangerous compounds.

When pharmaceutical companies perform clinical trials on new drugs that are intended for oral administration, the companies must determine the *bioavailability* ***of the drug. This quantity is defined by the equation:***

$$Bioavailability = \frac{AUC_{ORAL}}{AUC_{INTRAVENOUS}} \times 100\%.$$

where AUC_{ORAL} ***is the area under the oxycodone plasma concentration curve (between 0 and 12 hours) for a patient who was dosed with oxycodone orally and*** $AUC_{INTRAVENOUS}$ ***is the area under the oxycodone plasma concentration curve (between 0 and 12 hours) for a patient who was given an equivalent dose of oxycodone through intravenous injection.***

- ***Figure 4[12] (below) shows the oxycodone plasma concentration curve for a patient who received a 20mg dose of OxyContin® administered orally. Use rectangles with a base width of 1 hour to approximate*** AUC_{ORAL}***.***

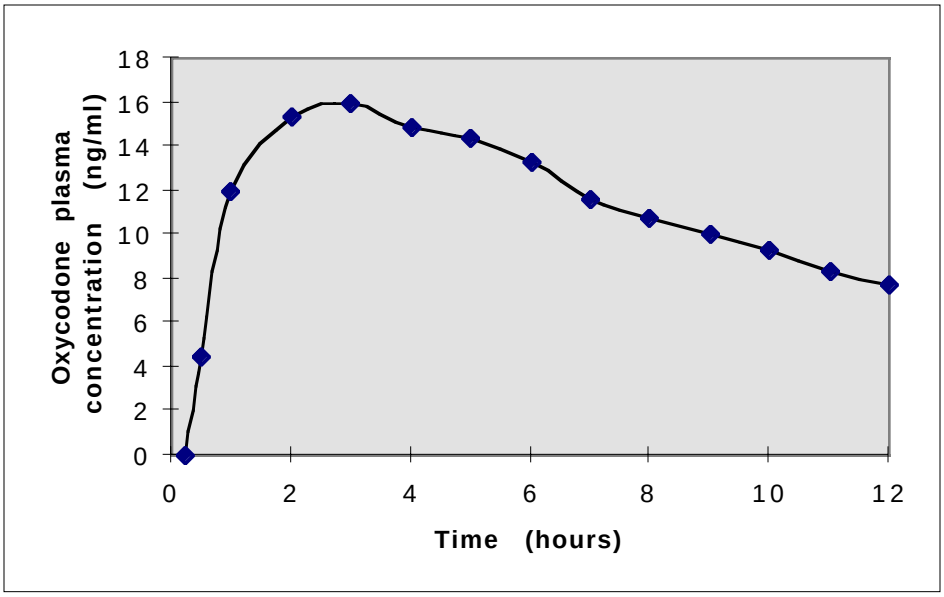


Figure 4: Oxycodone plasma concentration for patient who received oral dose of oxycodone.

[12] Source: http://www.purduepharma.com/PI/Prescription/Oxycontin.pdf

- ***Sketch the rectangles that you have used on Figure 4. Based on this, do you think that the number that you have calculated for AUC_{ORAL} is an over- or an under-estimate? How could you improve the accuracy of this estimate?***

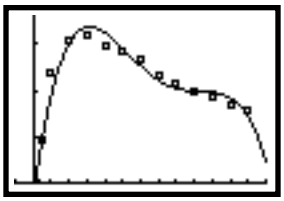


Figure 5: Oxycodone plasma concentration data and quartic polynomial.

- ***Table 1[13] gives some of the actual data collected by clinical researchers during trials of OxyContin®. Enter this data into you graphing calculator and find the equation of the quartic polynomial that best fits the data. (Figure 5 shows the data points and the quartic polynomial confirming that this function will do a very good job of representing the patterns in the oxycodone plasma concentration data between zero and twelve hours.) Write your equation here.***

Time since oxycodone administered (hours)	Oxycodone plasma concentration (ng/ml)	Time since oxycodone administered (hours)	Oxycodone plasma concentration (ng/ml)
0.24	0	6	13.34
0.5	4.53	7	11.55
1	11.97	8	10.75
2	15.40	9	10.00
3	15.96	10	9.31
4	14.86	11	8.35
5	14.33	12	7.77

Table 1: Oxycodone plasma concentrations obtained during clinical trials of OxyContin®.

Figure 6 shows a procedure that you could use to find the approximate area under the curve

$$y = f(x) = x\cdot(x-1)\cdot(x-2)$$

between $x = 0$ ***and*** $x = 1$ ***using 20 rectangles.***

[13] Source: http://www.purduepharma.com/PI/Prescription/Oxycontin.pdf

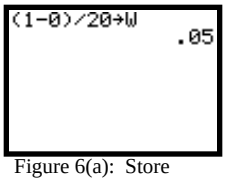


Figure 6(a): Store the width of the rectangles in W.

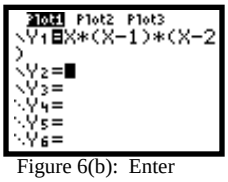


Figure 6(b): Enter the equation of the function into Y1.

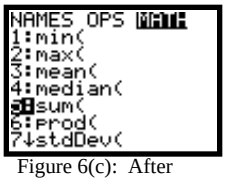


Figure 6(c): After returning to the main screen, use the LIST menu to obtain the sum(command.

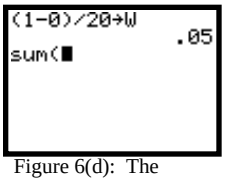


Figure 6(d): The main screen of your calculator should now look something like this.

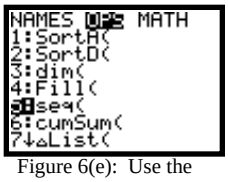


Figure 6(e): Use the list menu to obtain the seq(command.

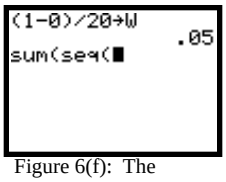


Figure 6(f): The main screen of your calculator should now look something like this.

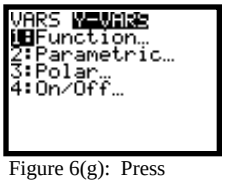


Figure 6(g): Press the VARS button and select the Y-VARS menu. Press ENTER to select the "Function" option.

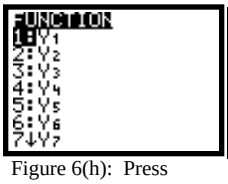


Figure 6(h): Press ENTER to choose Y1.

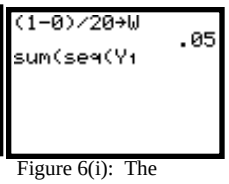


Figure 6(i): The main screen of your calculator should now look something like this.

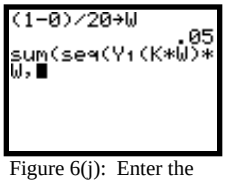


Figure 6(j): Enter the appropriate symbols into your calculator so that the calculator will sum:

$f(k*\Delta x)*\Delta x$

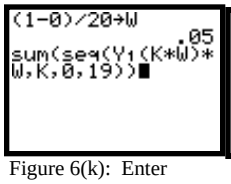


Figure 6(k): Enter the appropriate limits of summation (here they are 0 and 19) for the number of rectangles added.

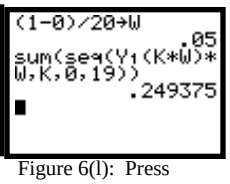


Figure 6(l): Press ENTER and the calculator will work out the total area of all of the rectangles.

- ***Use the quartic polynomial that you found and as many rectangles as you think you need for an accurate result to calculate*** AUC_{ORAL}***.***

- ***During clinical trials,*** $AUC_{INTRAVENOUS}$ ***was measured with a very similar method to the one that you have just used to find*** AUC_{ORAL}***. The figure obtained was:***

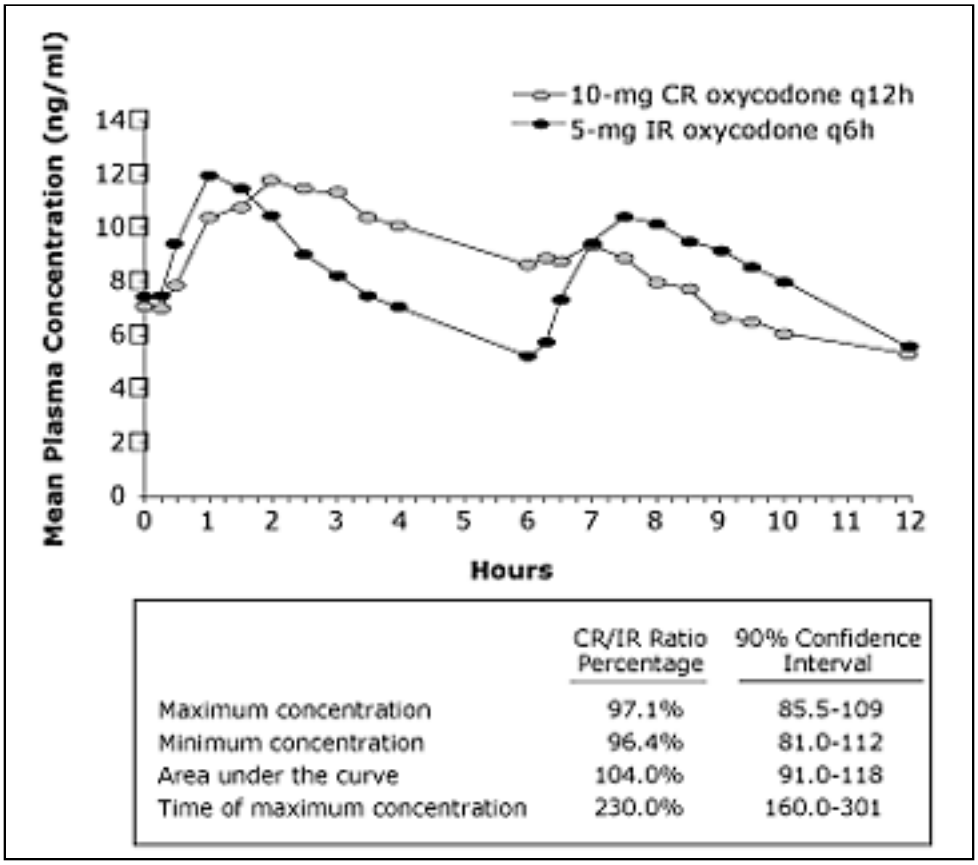
$$AUC_{INTRAVENOUS} = 187.74 \frac{ng \cdot hour}{ml}.$$

Calculate the *bioavailability* ***of oxycodone when it is delivered in oral form via an OxyContin® tablet.***

Epilogue:

Areas under curves (AUC's) are widely used in pharmacological investigations to compare the efficiencies of different drug delivery methods. The example shown in Figure 7[14] is taken from the paper:

- R. B. Pratt (1996) "Using controlled-release oxycodone for the management of chronic cancer and non-cancer pain." *American Pain Society Bulletin*, **6**(4).



	CR/IR Ratio Percentage	90% Confidence Interval
Maximum concentration	97.1%	85.5-109
Minimum concentration	96.4%	81.0-112
Area under the curve	104.0%	91.0-118
Time of maximum concentration	230.0%	160.0-301

Figure 7: Plasma concentration curves and experimental results from a trial comparing a continuous release (CR) method of delivering oxycodone and an immediate release (IR) method.

This diagram shows the use of areas under curves (AUC's) to compare the efficacy of a steady release form of oxycodone (OxyContin®) compared to regular dosage with an immediate release (e.g. injection) form of oxycodone. To compare the two methods, the ratio of the two AUC's has been found and converted to a percentage, much like your calculation of bioavailabilty.

[14] Image source: http://www.ampainsoc.org/pub/bulletin/jul96/innovate.htm