Outline

1. Riemann sums.
2. Trapezoid & midpoint rules.
3. Over and under estimates.

Handout 4: The Oral Bioavailability of a Drug

The specific learning goals of this handout are for you to:

- Use a calculator to approximate the area under curves.
- Use areas under curves to calculate the absolute oral bioavailability of a pharmaceutical drug.
- Learn about some of the factors that can influence the dose of a drug that a physician prescribes to a patient.

Lifestyle drug market booming[1]

Lifestyle drugs – medicines that treat conditions associated with lifestyle such as weight-loss tablets, anti-smoking agents, impotence therapies and hair restorers – are now a major research and development area for the pharmaceutical industry. In fact, companies have invested over $20 billion in research into such drugs since the 1990's. The reason is clear: the market lifestyle for drugs is forecast to rise to over $29 billion by 2007 from its current $20 billion.

The market is driven predominantly by Western countries, where an image conscious, aging society is prepared to pay high prices for compounds that promise to slow the aging process, improve mental agility, reduce weight gain and rejuvenate sexual function.

Perhaps the first lifestyle drugs were Viagra for erectile dysfunction (ED) and ant anti-depressant Prozac, whereas newer products include the anti-wrinkle agent Botox. Although the sector is far from saturated, competition is already tight. For example, in the area of ED, new products include Abbot's Uprima (apomorphine), which was launched in Europe in May 2001, and Lilly ICOS's Cialis (talalafil. Both are considered to offer advantages over current therapies, such as faster onset of action and duration of efficacy and will undoubtedly cannibalize Viagra's share of the ED market – worth an estimated $2 billion in 2001.

When you take a drug orally, not all of the drug enters your system. The percentage of the drug that enters your system is called the *bioavailability*[2] of the drug. In this problem you will use information from clinical trials to calculate the *bioavailability* of the well-known lifestyle drug Viagra (sildenafil citrate). The methods that you will use are identical to the methods that medical researchers use to calculate *bioavailability.*

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[1] This story is excerpted from: Atkinson, T. 2002. Lifestyle drug market booming. *Nature Medicine*, 8(9): 909.

[2] To be 100% medically accurate, this is the *absolute oral bioavailability.*

Figure 1: The lifestyle drug Viagra (sildenafil citrate).

During clinical trials, researchers create *plasma concentration curves* for the drug they are studying.

To create such a curve, the researchers administer a set quantity of the drug (usually 100mg) to a patient. The researchers administer the drug orally (e.g. as a tablet or capsule) or intravenously (e.g. by injection).

The researchers then take blood samples from the patient during the 12 hours following administration of the drug, and measure the concentration of the drug in the patient's blood.

The *plasma concentration curve* is a graph with time (in hours) as the independent variable (x) and the concentration of the drug as the dependent variable (y). The units of drug concentration are usually ng/ml.

(a) The plasma concentration curve for **orally administered** Viagra is quite well approximated by the equation:

$$y = 425 \cdot e^{-1 \cdot \left(\frac{x}{4.5}\right)^2} + 25.$$

Use this equation to approximate the area under the plasma concentration curve between $x = 0$ and $x = 12$ using left-hand Riemann sums with 10, 50 and 100 rectangles. Record your results in a table like Table 1. Roughly, what is the area under the plasma concentration curve between x=0 and x=12?

Number of rectangles	Area under plasma concentration curve
10	2249.38
50	2045.59
100	2020.11

Table 1.

(b) Now approximate the area under the plasma concentration curve between $x = 0$ and $x = 12$ using 100 rectangles and a right-hand Riemann sum.

1969.15

Trapezoid = 1994.63.

(c) The plasma concentration curve for **intravenously administered** Viagra is quite well approximated by the equation:

$$y = 3300 \cdot e^{-1 \cdot \left(\frac{x}{1.5}\right)^2} + 25.$$

Use this equation to approximate the area under the intravenous plasma concentration curve between x=0 and x=12 using left-hand and right-hand Riemann sums with 100 rectangles. Record your results in the table given below.

Type of sum used	Area under plasma concentration curve
Left-hand Riemann Sum	4884.82
Right-hand Riemann Sum	4488.82

Trapezoid = 4686.82

(d) The area under the plasma concentration curve for an orally administered drug is usually represented by the symbols AUC_{ORAL}. The area under the plasma concentration curve for an intravenously administered drug is usually represented by the symbols AUC_{IV}. The medical definition of bioavailability[3] is:

$$\text{Bioavailability } (\%) = \frac{AUC_{ORAL}}{AUC_{IV}} \times \frac{100}{1}.$$

According to Pfizer, Inc. the bioavailability of sildenafil citrate delivered by Viagra® tablets is "...about 40%."[4] Is this claim medically accurate?

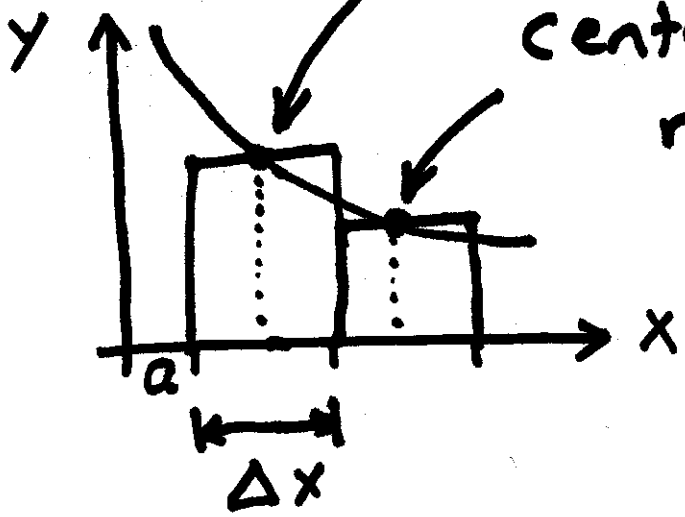
$$\% = \frac{1994.63}{4686.82} \times \frac{100}{1} = 42.56\%$$

(e) The most commonly used area approximation method used in pharmacy is the trapezoid rule. If you use the trapezoid rule to calculate the bioavailability, what result do you get?

[3] More specifically, this is the definition of *absolute oral bioavailability*.
[4] Source: Physicians' Desk Reference (2001 Edition), p. 2535.

2. Trapezoid and Midpoint Rules

- Area under a curve can be approximated by:

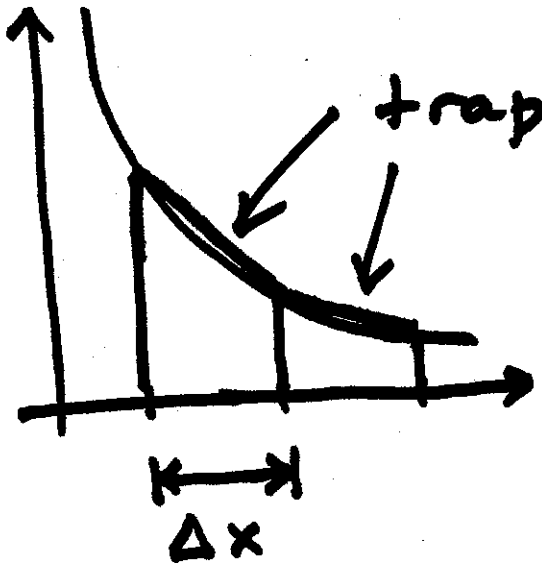


Height of f(x) at center of each rectangle is used to give a midpoint sum.

Evaluating on a calculator:

sum(seq(Y1(A+0.5W+K*W)*W,
K, 0, N-1))

- Area can also be approximated using <u>trapezoids</u>.

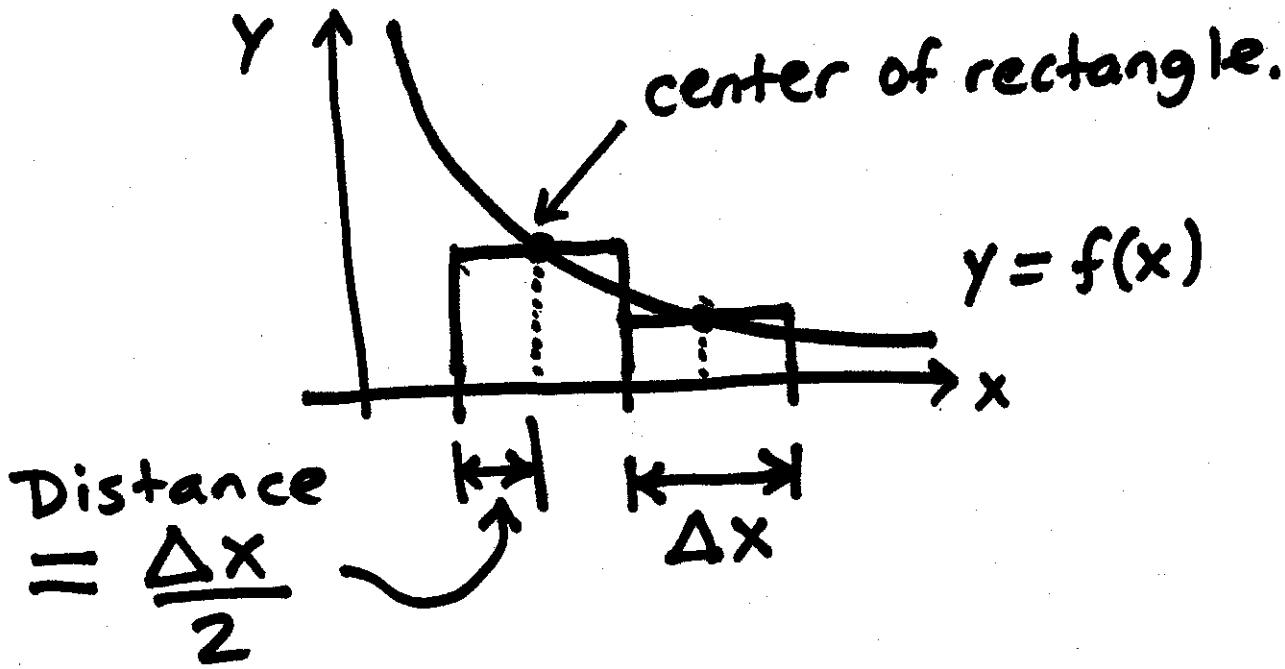


$$\text{Trapezoid Rule} = \frac{\text{Left Riemann Sum} + \text{Right Riemann Sum}}{2}$$

2. Trapezoid and Midpoint Rules

(a) Midpoint

- Use rectangles to approximate area.
- Height is value of $f(x)$ at center of rectangle.



To evaluate on a calculator:

$$\text{sum}(\text{seq}(Y1(A + 0.5*W + K*W)*W, K, 0, N-1))$$

add an additional $0.5 * W$

(b) Trapezoid Rule

Trapezoid Rule =

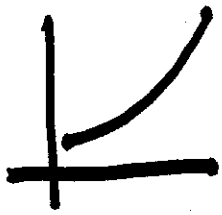
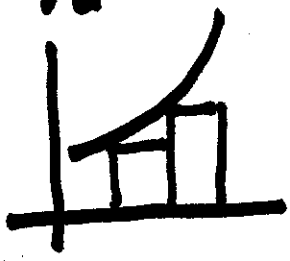
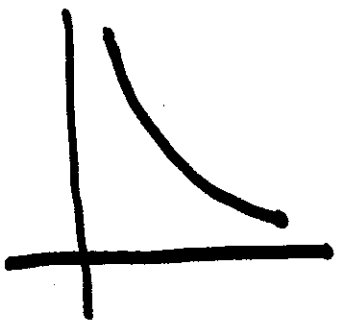
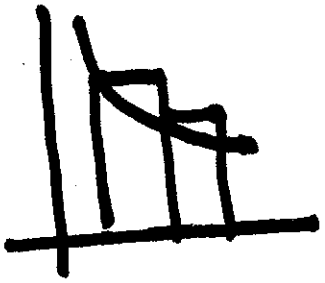
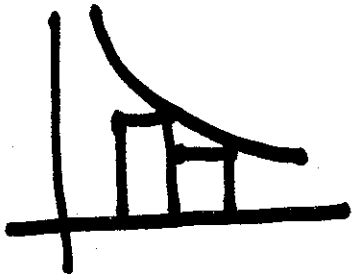
$$\frac{\text{LH Riemann Sum} + \text{RH Riemann Sum}}{2}$$

3. Under and Over Estimates of $\int_a^b f(x)dx$

- Midpoint and trapezoid estimates are closer to the actual value of $\int_a^b f(x)dx$ than Riemann Sums.

(a) Riemann Sums

- which is above $\int_a^b f(x)dx$ depends on increasing/decreasing properties of $f(x)$ on the interval (a,b).

$f(x)$	Left Riemann Sum	Right Riemann Sum
Increasing on (a,b) 	Underestimate of $\int_a^b f(x)\,dx$ 	Overestimate of $\int_a^b f(x)\,dx$ 
Decreasing on (a,b) 	Overestimate of $\int_a^b f(x)\,dx$ 	Underestimate of $\int_a^b f(x)\,dx$ 

(b) Trapezoid and Midpoint

- Over and under estimates depend on the concavity of $f(x)$ on (a,b).