Lecture 28: Areas in action

Learning objectives

✓ Interpret different applications of areas under curves and ratios of these areas

Scientific examples

✓ Glycaemic Index

✓ Bioavailability of a drug

Maths skills

✓ Estimate areas under curves

✓ Interpret graphs

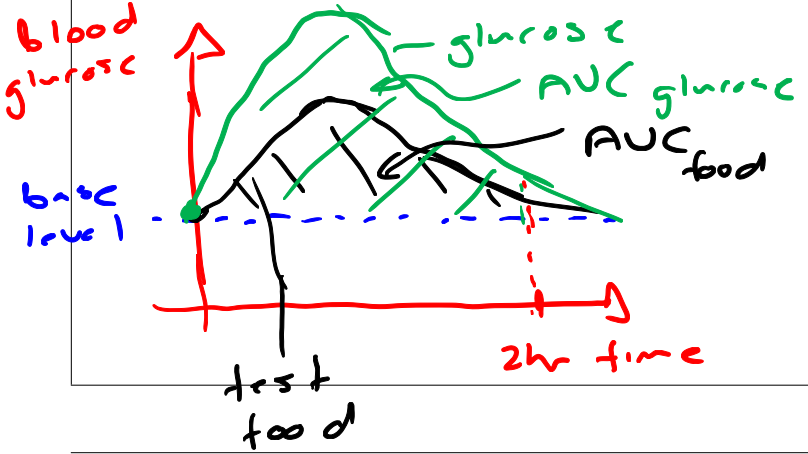
Case Study 23: Hi GI!

- The *Glycaemic Index* or GI of foods is often mentioned in marketing campaigns and in association with dietary health claims.
- GIs range between 0 and 100, and indicate the relative extent by which blood glucose levels rise after the consumption of a food. Hence, GI scores are only valid for foods containing carbohydrates.
- Researchers classify foods into the following GI categories.
  - *Low GI* – when GI is ≤ 55, digestion of carbohydrates is slow, with a slow rise and lower peak in blood sugar level. Examples of Low GI foods include cherries, skim milk, apples, chick peas, oranges and carrots.
  - *Medium GI* – when the GI is between 56 and 69, the digestion of carbohydrates occurs at a moderate rate. Examples of Medium GI foods include boiled potato, honey, ice cream and sultanas.
  - *High GI* – when the GI is 70 or higher, the digestion of carbohydrates is fast, leading to a rapid rise and high peak in blood sugar level. Examples of High GI foods include mashed potato, white bread, cornflakes, watermelon and steamed white rice.
- The many claimed health benefits of Low GI diets include weight loss and improved weight control, improved management of diabetes, reduced risk of cardiovascular disease and increased physical stamina.

- Criticisms of focusing on GIs as a dietary tool include:
  - GIs can vary greatly for a given food, depending on how ripe it is, and how it is processed, stored and cooked; moreover, the GI of a food may be less important than the *quantity* consumed;
  - Measured GIs may not be very exact or reliable; the GI of a given food is measured at different times of the day then the results can differ quite substantially.
- Researchers calculate the GI of a food in the following way:
  - Ten healthy people fast overnight. In the morning, each person consumes a controlled dose of the test food, with known total carbohydrate content (typically 50 g). Over a 2 hour period, researchers measure the increase in the blood glucose level above baseline for each participant, produce graphs, and calculate the AUCs for the test food using the trapezoid rule.
  - On a separate day, participants undergo the same procedure, but consume a glucose solution which contains the same amount of total carbohydrate. Researchers calculate the AUC for glucose (the reference food) for each individual.
  - The **definition** of the GI is: divide the AUC above base level of the test food by the AUC above base level for glucose, and multiply by 100%. An average of the individual GI scores represents the overall GI for the test food.

Question 10.2.2

Use a diagram to illustrate calculation of GI for a test food.



$$GI_{food} = \frac{AUC_{food}}{AUC_{glucose}} \times 100$$

Question 10.2.3

A study [57] recorded the following blood glucose levels when an individual consumed a controlled quantity of bread in one test, then lentils in another test. The increase in the AUCs above baseline glucose levels is 29mmol/L · min for lentils, and 66mmol/L · min for bread. Given that the GI of bread is around 70, find the GI of lentils.

Time (mins)	Glucose (mmol/L) Bread	Lentils
0	4.3	4.3
15	4.8	4.8
30	6.2	4.8
45	5.5	4.3
60	5.0	4.4
90	3.9	4.5
120	4.1	4.7

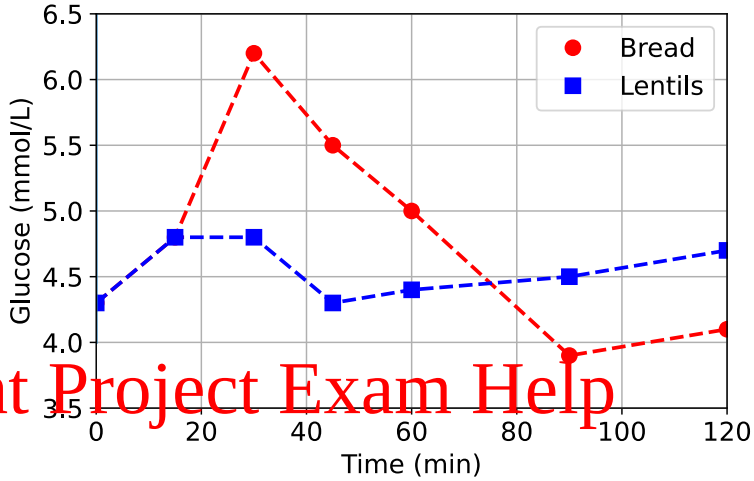


Figure 10.7: Mean blood glucose levels.

Given: $AUC_L = 29$ mmol/L · min

$AUC_B = 66$ mmol/L · min

$GI_B = 70$

$GI_L = ??$

$GI_B = \frac{AUC_B}{AUC_G} \times 100$

$GI_L = \frac{AUC_L}{AUC_G} \times 100$

Method (1)

$\frac{GI_B}{GI_L} = \frac{\frac{AUC_B}{AUC_G} \times 100}{\frac{AUC_L}{AUC_G} \times 100}$

$= \frac{AUC_B}{AUC_L}$

$GI_L = GI_B \times \frac{AUC_L}{AUC_B} = 70 \times \frac{29}{66} \simeq 31$

AUC_G = AUC glucose (unknown)

Method (2)

$AUC_G = \frac{AUC_B \times 100}{GI_B}$

$= \frac{66 \times 100}{70}$

$\simeq 94$ mmol/L · min

$GI_L = \frac{29}{94} \times 100$

$= 31$

End of Case Study 23: Hi GI!.

Case Study 24: Bioavailability of drugs

- Drugs can be administered via many routes, including:
  - orally, such as the contraceptive pill;
  - as a gas, such as nicotine from a cigarette;
  - through the skin, such as a nicotine patch;
  - nasally, such as "snorted" cocaine;
  - intravenously, such as chemotherapy drugs for treating cancer;
  - sublingually, such as nitroglycerin used to treat angina; and
  - rectally, such as a paracetamol suppository.
- Different routes of drug delivery are required depending on the drug type, duration and frequency of treatment, and the condition of the patient. Oral administration is common, but other routes may be more convenient for drugs that cause nausea or vomiting, or for patients who cannot swallow.
- After administration of a drug, it typically needs to pass through a number of stages before it enters general circulation and has a chance to act. This can have a substantial impact on the proportion of the dose available to achieve the desired pharmacological impact. For example, the following *first pass effects* reduce the availability of orally-administered drugs:
  - how readily and rapidly the drug dissolves in the digestive tract;
  - whether the drug is damaged by acidic stomach contents;
  - whether the drug is partially metabolised by bacteria in the gut;
  - how much of the drug is absorbed across the intestinal wall;
  - the digestive health of the individual (for example, vomiting or diarrhoea may cause mechanical expulsion of the drug); and
  - how much of the drug is metabolised in the liver prior to entering general circulation (because blood travels from the small intestine to the liver and then to the rest of the body).

- After administering a drug by a given route, its relative **bioavailability** F is the fraction of the dose that enters general circulation compared to a dose administered via a more direct route, usually *intravenously* (IV).

Definition of bioavailability

If $R(t)$ is the blood concentration of a drug after giving a dose by some route and $I(t)$ is the concentration after an IV dose of **the same size**, then the bioavailability F of the drug administered via this route is

$$F = \frac{\int_0^\infty R(t)\,dt}{\int_0^\infty I(t)\,dt}. \quad \simeq \quad \frac{AUC_R}{AUC_I}$$

Question 10.2.4

(a) Explain the meaning of the expression for F.

compares exposure to the drug administered by some route (eg oral) compared to IV ("gold standard")

$0 \leq F \leq 1$

(b) How is the method of calculating the bioavailability of a drug similar to the method of calculating the GI of a food? How is it different?

Similar
- use AUC
- compare to standard (glucose / IV)
- both are ratios

Different
- GI - 0 → 100
  F - 0 → 1
- GI - 2 hrs
  F - longer (until removed)
- GI - non-zero baseline
  F - baseline = 0

Question 10.2.5

In [44] and [32], on separate occasions, test subjects were each administered 1000 mg doses of paracetamol. In [44], doses were intravenous and in oral tablet form. In [32], an aqueous dose was administered as a rectal suppository. Figure 10.8 plots the blood concentrations of paracetamol obtained for these subjects over the following six hours.

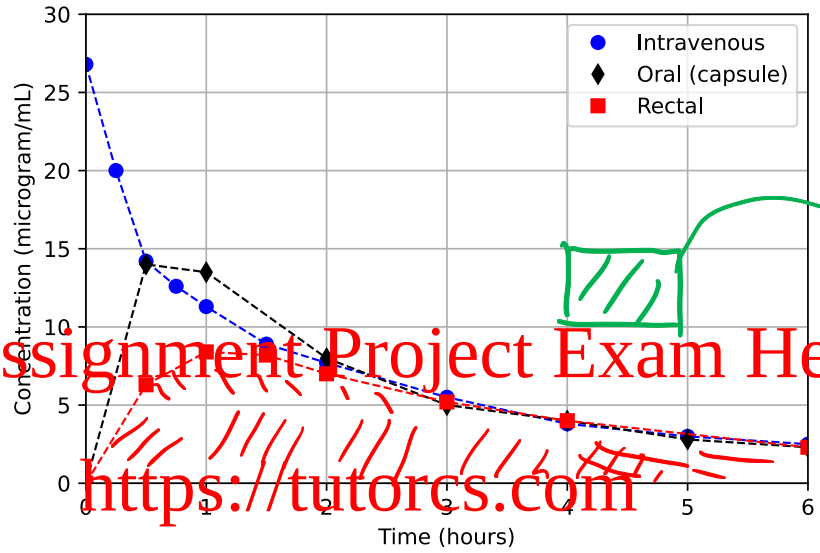


Figure 10.8: Blood concentration curves for paracetamol administered in various ways.

(a) Discuss the shapes of the three curves in Figure 10.8.

oral & rectal – surge

IV – exponential decay

(b) **Estimate** the bioavailabilities of the oral and rectal doses.

	Squares	Area (μg/mL × hr)	F
IV	8.5	42.5	1
Oral	7.5	37.5	$\frac{37.5}{42.5} = 0.88$
Rectal	6	30.0	$\frac{30}{42.5} = 0.71$

***Question** 10.2.5 (continued)*

(c) For the IV dose (see [44]), the blood paracetamol concentration in μg/mL at time t in hours after dosing is modelled using the equation

$$I(t) = 13.8e^{-2.55t} + 13e^{-0.28t}.$$

Figure 10.9 plots the measured values and $I(t)$. Using integration, the AUC for this curve is 51.84 μg hr/mL. In [44], the AUC for the oral tablet dose is around 44 μg hr/mL. Calculate the bioavailability of the oral tablet dose.

$$F_{oral} = \frac{AUC_{oral}}{AUC_{IV}}$$

$$= \frac{44}{51.84}$$

$$\simeq 0.85$$

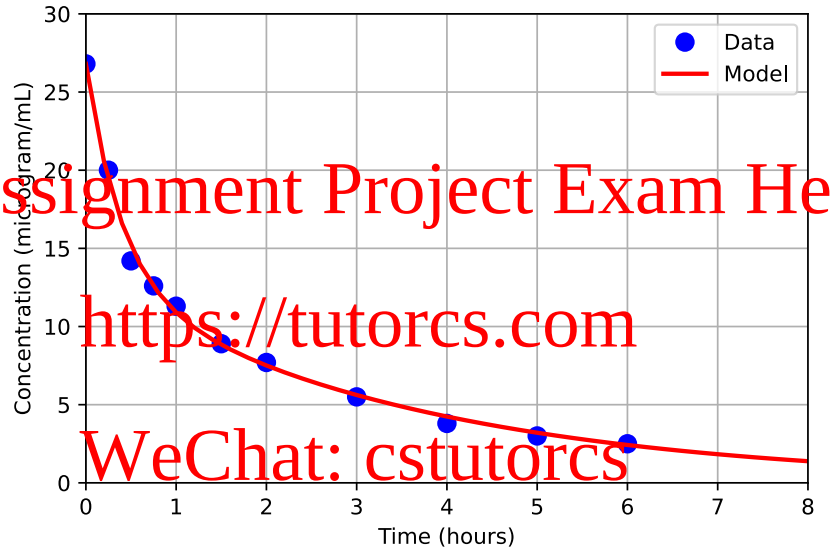


Figure 10.9: The graph of $I(t)$, following an intravenous dose of 1000 mg of paracetamol.

(d) In [32], the AUC given for the rectal dose is around 2290 μg/mL/min. Comment on the AUC units, then calculate the dose bioavailability.

another error - should be 2290 $\frac{mg}{mL}$ min

convert units

$AUC_{rectal} = 2290 \frac{mg}{mL} \times \cancel{min} \times \frac{1 hr}{60 \cancel{min}} = 38 \frac{mg}{mL} hr$

$F_{rectal} = \frac{38}{51.84} \simeq 0.74$

(e) Compare your answers to Parts (c) and (d) with those to Part (b).

	estimate	calculated	
oral	0.88	0.85	close!
rectal	0.71	0.74	

End of Case Study 24: Bioavailability of drugs.