Lecture 22: **Surging up and down**

Learning objectives

✓ Analyse the trend in data representing drug concentrations in the blood

Scientific examples

✓ Pharmacokinetics

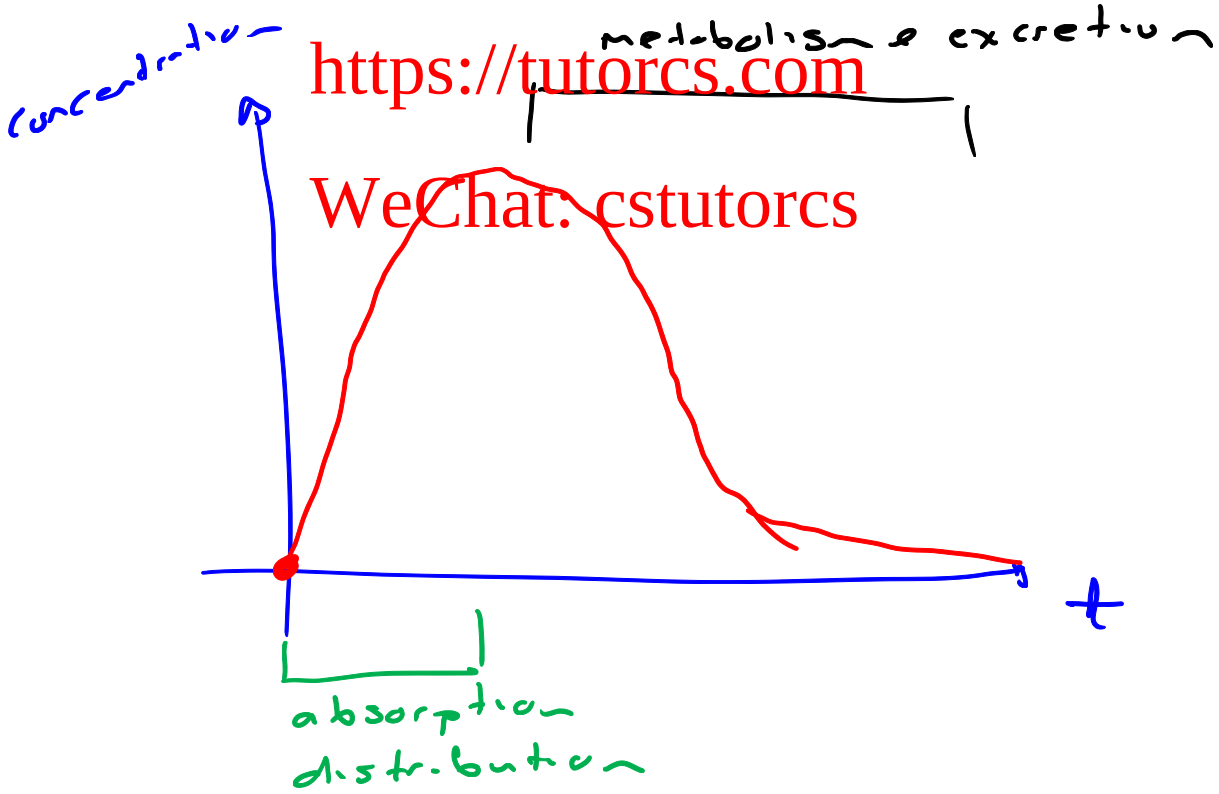
Maths skills

✓ Understand the form of surge functions and their graphs

8.3 Drugs in the blood and surge functions

Question 8.3.1

Suppose a patient consumes a drug. Sketch a graph of concentration of the drug in their blood over time. What are the key features of the graph and what are their physical meaning for the patient?



Some drug-related terminology

Broadly speaking, a *drug* is any externally derived chemical substance introduced into an organism that affects the function of that organism. Drugs may enhance physical or mental well-being, and include both medicinal and so-called recreational drugs.

Pharmacology studies the properties of drugs and their effects on living organisms.

Pharmacokinetics studies what happens to drugs inside the body, particularly the extent and rates of **absorption**, **distribution**, **metabolism** and **excretion**.

Drug concentrations

After the administration of a drug, key determinants of its impact on the body are the drug **concentration** in the bloodstream, which is commonly measured as mass per volume (such as mg/L), and the **time** over which that concentration occurs. Concentrations can be measured at various times after drug administration and plotted on a *drug concentration curve*.

- Mathematics and functions are particularly important when modelling the *change* in drug concentrations over time, as they help to predict the *impact* of the drug and the *timing* of subsequent interventions.

Case Study 16: Zoloft and depression

- Depression is one of the most common mental health problems.
- Unlike many health problems, depression (and other mental illnesses) can occur more frequently in young adults than in older adults; see Figure 8.7.

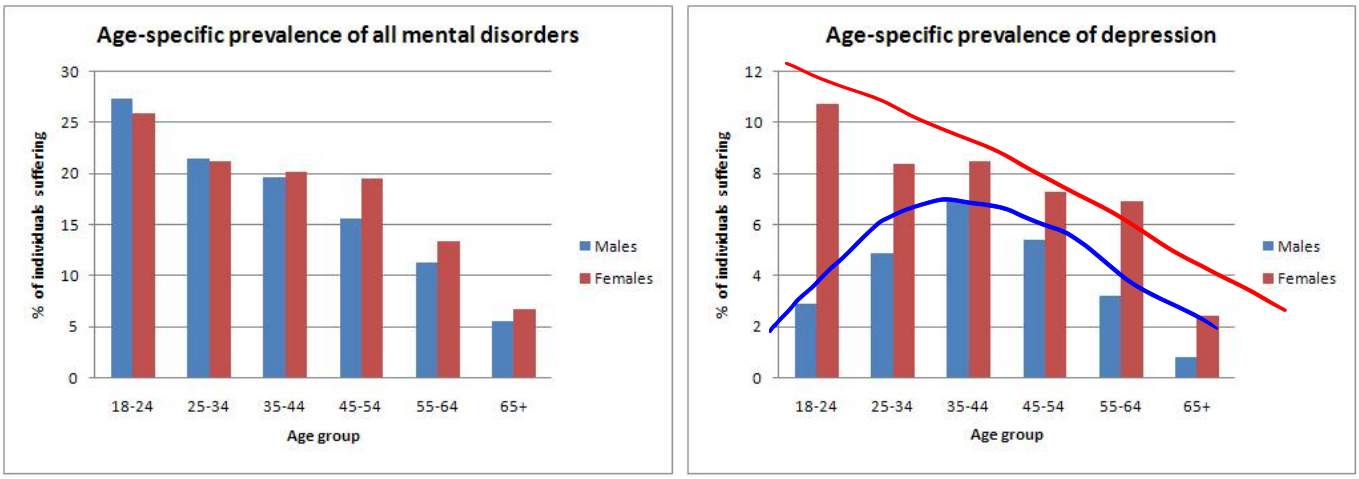


Figure 8.7: Age-specific prevalence of mental disorders and depression in Australian adults. (Source: National Survey of Mental Health and Wellbeing, 2007, Australian Bureau of Statistics.)

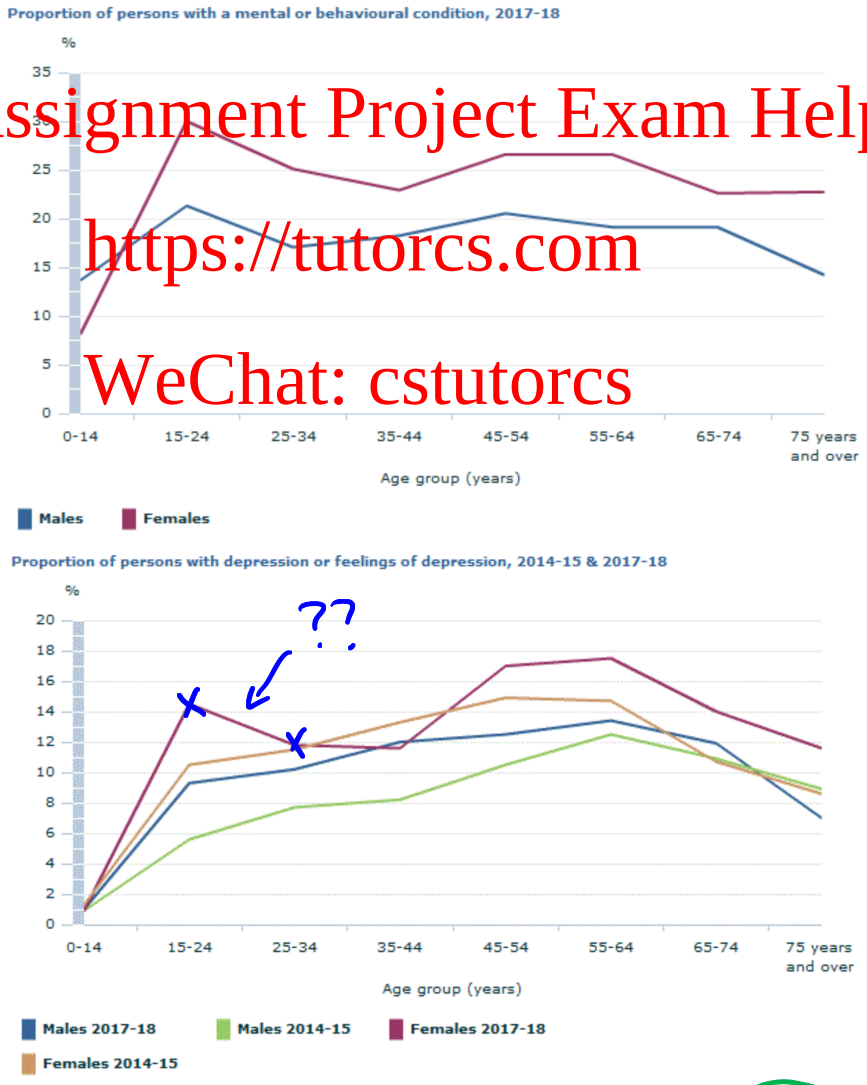


Figure 8.8: Age-specific prevalence of mental disorders and depression in Australian. (Source: National Survey of Mental Health and Wellbeing, 2018, Australian Bureau of Statistics.)

Question 8.3.2

Discuss the meaning and ramifications of the data represented in Figure 8.7 and Figure 8.8. Which figures are better for the communication of science? Why?

- more prevalent at younger ages (2007 data - decrease with age for all disorders)
- 2007 data - males peak 35-44 age group - "mid-life crisis"
- column graph - no "interpolation"

- There are multiple treatments available for depression, including a variety of therapy-based treatments and pharmacological interventions.
- *Zoloft* (and a number of generically branded equivalents) is the brand name of the drug *sertraline hydrochloride*, which is an antidepressant of the SSRI class (Selective Serotonin Reuptake Inhibitor).
- The Consumer Medicine Information fact sheet explains that SSRIs "... are thought to work by blocking the uptake of a chemical called serotonin into nerve cells in the brain. Serotonin and other chemicals called amines are involved in controlling mood".
- Zoloft is the most commonly prescribed antidepressant in Australia, and one of the most prescribed drugs overall on the Australian Pharmaceutical Benefits Scheme.
- Zoloft is taken orally as a pill. The usual dosage ranges from 25 mg per day to 200 mg per day.
- Zoloft has a number of comparatively mild side effects (including insomnia, loss of appetite, and some sexual impairment), and is generally believed to be both effective and well tolerated.

Question 8.3.3

Drug concentration curves (for sertraline or other drugs) allow pharmacologists to observe, measure and analyse factors including each of the following:

(a) the peak drug concentration C_{max};

(b) the time t_{max} at which C_{max} occurs;

(c) the *half-life* $t_{1/2}$ of the drug, which is the time taken for the concentration to fall to half of its previous value;

(d) the times at which the maximum rates of drug absorption/removal occur;

(e) the "total exposure" of the body to the drug.

Figure 8.9 shows the average blood sertraline concentrations for 11 young women involved in a study [48] (with straight lines interpolating data points). Participants received daily oral doses of sertraline over 30 days (to achieve 'steady state' concentrations), then a final dose was administered and blood concentrations monitored. Mark on the graph the values (or possible values) of each of (a) to (e) described above.

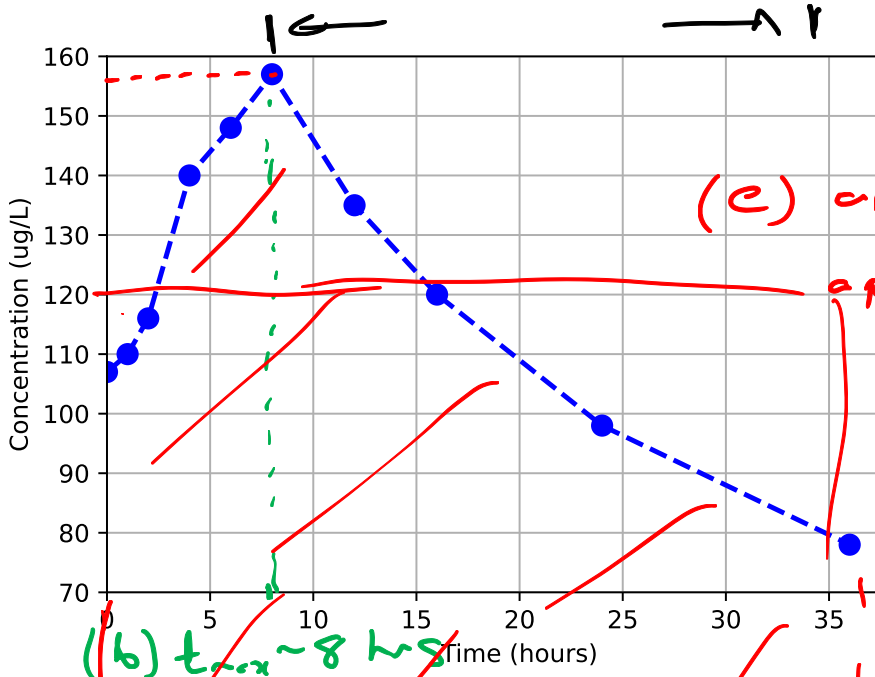


Figure 8.9: Blood sertraline concentrations in young women.

- Compare the information on Zoloft in the following example with some of the features/observations in Example 8.3.3. Also note the use of mathematical rates of change in the example.

***Example** 8.3.4*

(The following is taken from the sertraline fact sheet at *www.pbs.gov.au*.)

"**Pharmacokinetics:** In humans, following oral once-daily dosing over the range of 50 to 200 mg for 14 days, mean peak plasma concentrations (C_{max}) of sertraline occurred between 4.5 to 8.4 hours post dosing. The average terminal elimination half-life of plasma sertraline is about 26 hours. Based on this pharmacokinetic parameter, steady-state sertraline plasma levels should be achieved after approximately one week of once-daily dosing. Linear dose-proportional pharmacokinetics were demonstrated in a single dose study in which the C_{max} and area under the plasma concentration time curve (AUC) of sertraline were proportional to dose over a range of 50 to 200 mg.

Dosage: Adults (18 years and older) The usual therapeutic dose for depression is 50 mg/day. . . patients not responding to a 50 mg/day dose may benefit from dose increases up to a maximum of 200 mg/day. Given the 24 hour elimination half-life of sertraline, dose changes should not occur at intervals of less than 1 week. The onset of therapeutic effect may be seen within 7 days . . . .

Use in Children and Adolescents aged less than 18 years: Sertraline should not be used in children and adolescents below the age of 18 years for the treatment of major depressive disorder. The efficacy and safety of sertraline has not been satisfactorily established for the treatment of major depressive disorder in this age group.

Overdosage: On the evidence available, sertraline has a wide margin of safety in overdose. Overdoses of sertraline alone of up to 13.5 g have been reported. Deaths have been reported involving overdoses of sertraline, primarily in combination with other drugs . . . ."

- The general shape of the blood sertraline concentration curve shown in Figure 8.9 is typical of many drug concentration curves. The corresponding functions are sometimes called *surge* functions.

Surge functions

In a **surge** function, the value initially rises rapidly before falling off exponentially over time. A general equation for a surge function is

$$f(t) = at^p e^{-bt}$$

where the values of a, p and b depend on the phenomenon $(0 < p < 1)$. Figure 8.10 shows the general shape of a surge function.

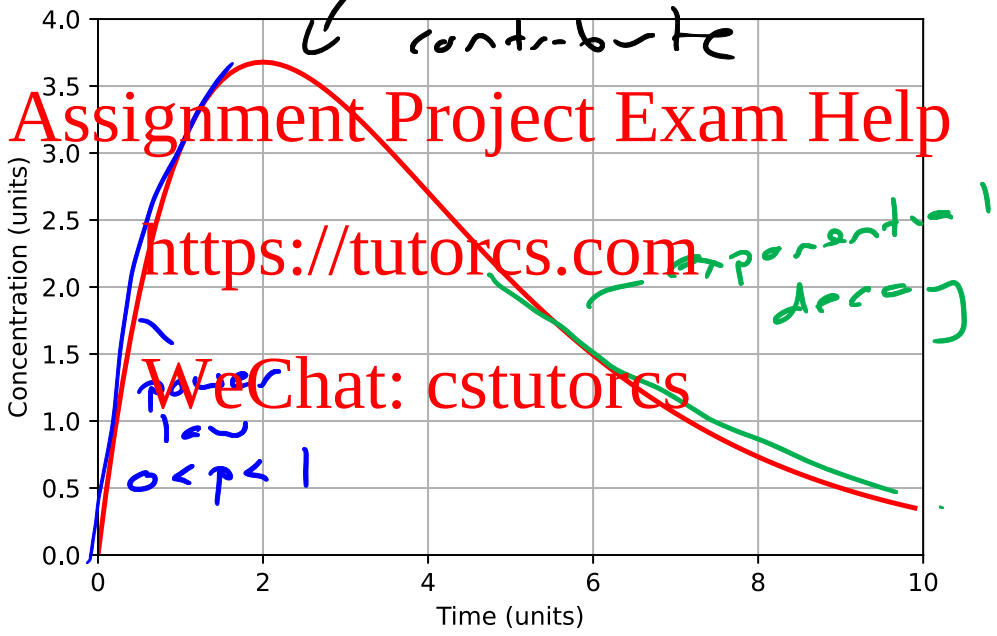


Figure 8.10: General shape of a surge function.

A surge function, as defined above, will reach a maximum when $t = \frac{p}{b}$.

Question 8.3.5

(a) Explain mathematically why functions of the form $f(t) = at^p e^{-bt}$ have a 'surge function shape'.

At early times ($t \approx 0$), $e^{-bt} \approx e^0 = 1$, power term dominates

At large times $e^{-bt} = \frac{1}{e^{bt}}$, exponential dominates

(b) Soon we will study some examples of surge functions, including blood concentrations of:

- paracetamol: $C_1(t) = 1.4t^{0.6}e^{-0.5t}$ µg/mL.
- a long-lasting contraceptive: $C_2(t) = 0.87t^{0.15}e^{-0.0008t}$ ng/mL.

Without drawing them, briefly discuss how the graphs of C_1 and C_2 would appear, including their similarities and differences. Time is measured in hours for both. Ignore the differences in concentration units.

- contraceptive has slower decay (b is smaller)
- paracetamol has a faster rise (p is larger)
- time to maximum
  t_{max} (paracetamol) $= \frac{0.6}{0.5} \sim 1$ hour
  t_{max} (cont.) $= \frac{0.15}{0.0008} \gg 1$ hour (190 hrs)

End of Case Study 16: Zoloft and depression.