APPLIED PHYSICS AND BIOSTATISTICS

MODULE MATH6 — Integrals and the Area Under the Curve (AUC)

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MODULE MATH6 — INTEGRALS

Integrals Add Up a Rate into a Total

An integral is the area under a curve — and area means an accumulated total.

Integrating a concentration over time gives the AUC: the total drug exposure.

Integrating a rate gives an amount: dose delivered, volume filtered, substance produced.

The fundamental theorem links integration and differentiation as inverse operations.

Wherever a derivative gave a rate, an integral gives back the accumulated quantity.

The concept of the integral is linked to the solution of two classes of problems:
Indefinite Integral:

- Calculation of the analytic expression of a function from the derivative of the function itself

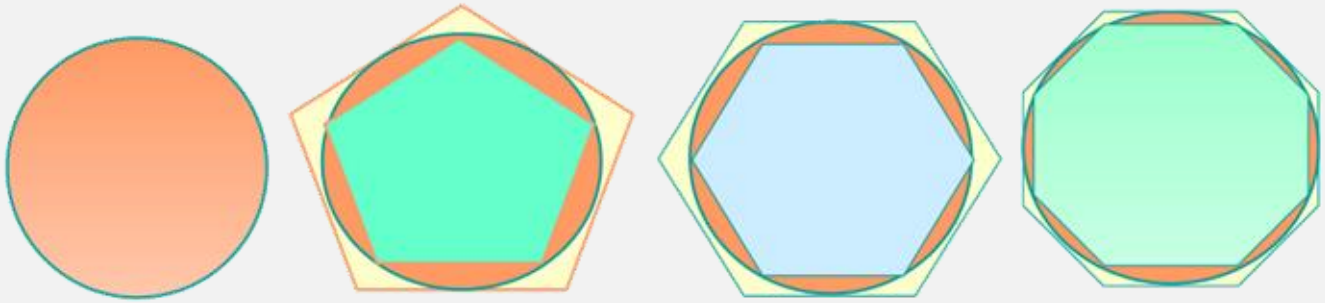
- Definite Integral:
  - calculation of the areas of figures bounded by curves
  - calculation of volumes
  - calculation of the work done by a force
  - …..

Example: area of the circle.

Archimede di Siracusa (287 a.C. – 212 a.C.): method of exhaustion for the area of the circle/area subtended by a branch of a parabola

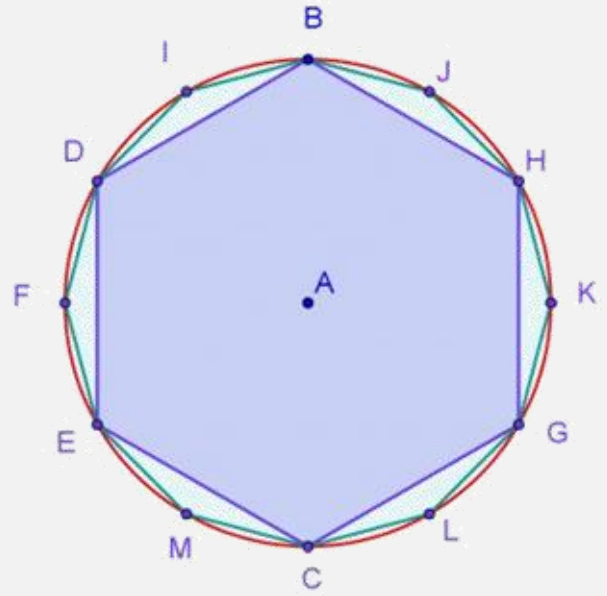
It is possible to calculate the area through successive approximations by means of regular polygons inscribed in the circle and regular polygons circumscribed about the circle.

It is shown that the area of the circle is equal to the common limit, when the number of sides tends to ∞, to which the sequences formed by the areas of the polygons inscribed in and circumscribed about the circle tend.



area circle = 28.27

area hexagon = 23.38



area dodecagon = 27

Integral Calculus: Area Under the Graph of a Function

The problem of integration for real functions of a real variable →this problem is historically linked to the problem of measure (computing the area of figures with 'curvilinear' boundaries).

We will relate the problem of integration to the problem of the antiderivative, namely:

Given a function $f : I \to \mathbb{R}$, determine (all) functions $F : I \to \mathbb{R}$ such that

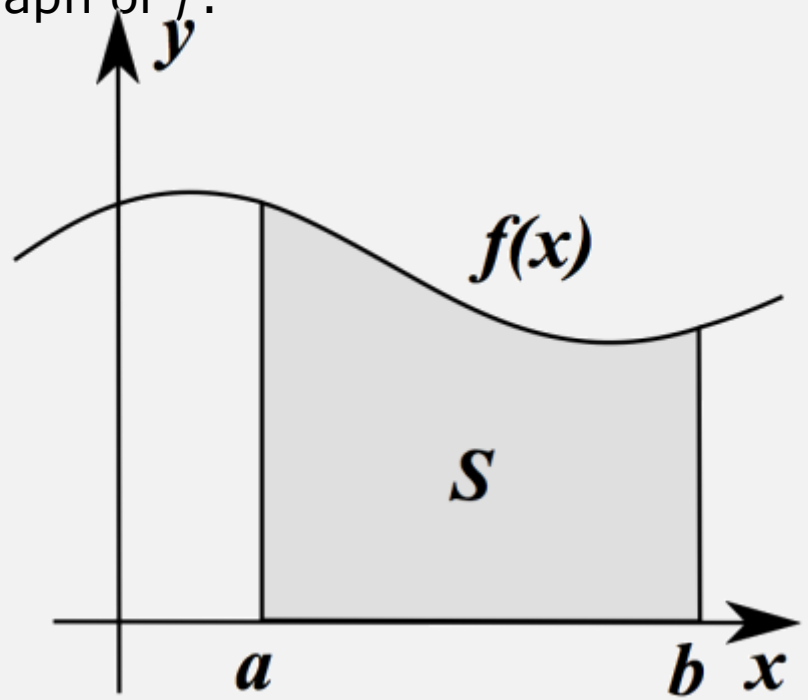
$$F'(x) = f(x) \quad \forall x \in I$$

F is called an antiderivative of F'

Motivations: Computing an Area

Let $f : a, b \to \mathbb{R}$ continuous and positive.
Compute the area A of the planar region (called the subgraph of f) contained between the graph of f and the x-axis.

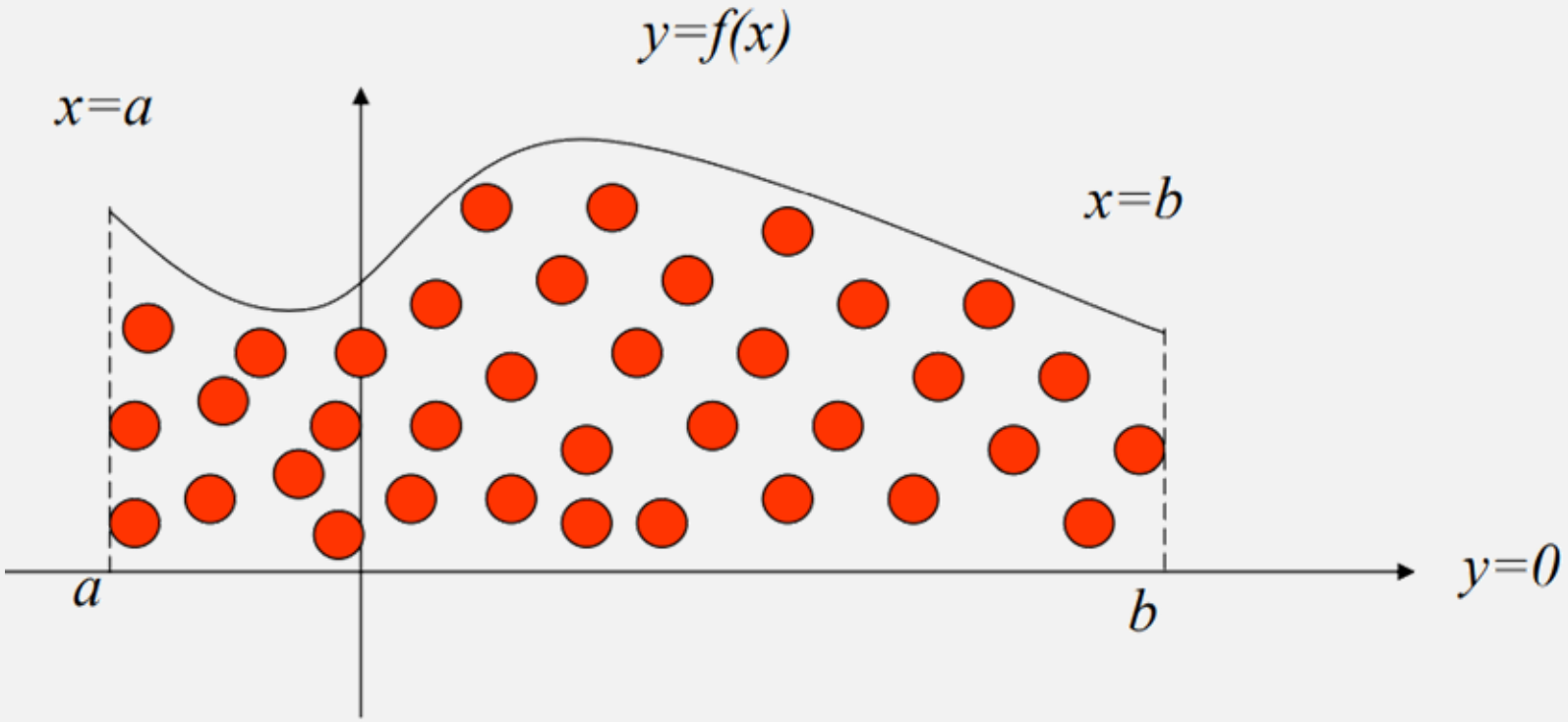
This problem makes sense, because we assume $f \geq 0$.
Otherwise it would make no sense to speak of the subgraph of f.



The Concept of the Integral: Calculation of Areas

Area of the rectangle relative to a function

Given a function f continuous on the interval $[a, b]$, we wish to compute the area of the plane region comprised between the x-axis, the two vertical lines with equation $x = a$ and $x = b$ and the graph of f. Such a plane region is called the rectangle relative to the function f.



Definite Integral of a Function: Definition

Given a function f continuous on the interval $[a, b]$, the definite integral of the function $f(x)$ in the interval $[a, b]$ is the measure of the area of the rectangular prism R associated with the function f and is denoted by the symbol:

$$\int_a^b f(x)dx = Area\ R$$

The problem is to determine the area of a region of the plane R which lies, in an orthogonal Cartesian coordinate system, above the x-axis and below the graph of a continuous and non-negative function $f(x)$ as the variable x varies over an interval $[a, b]$ closed and bounded.

Example – AUC: Total Drug Exposure

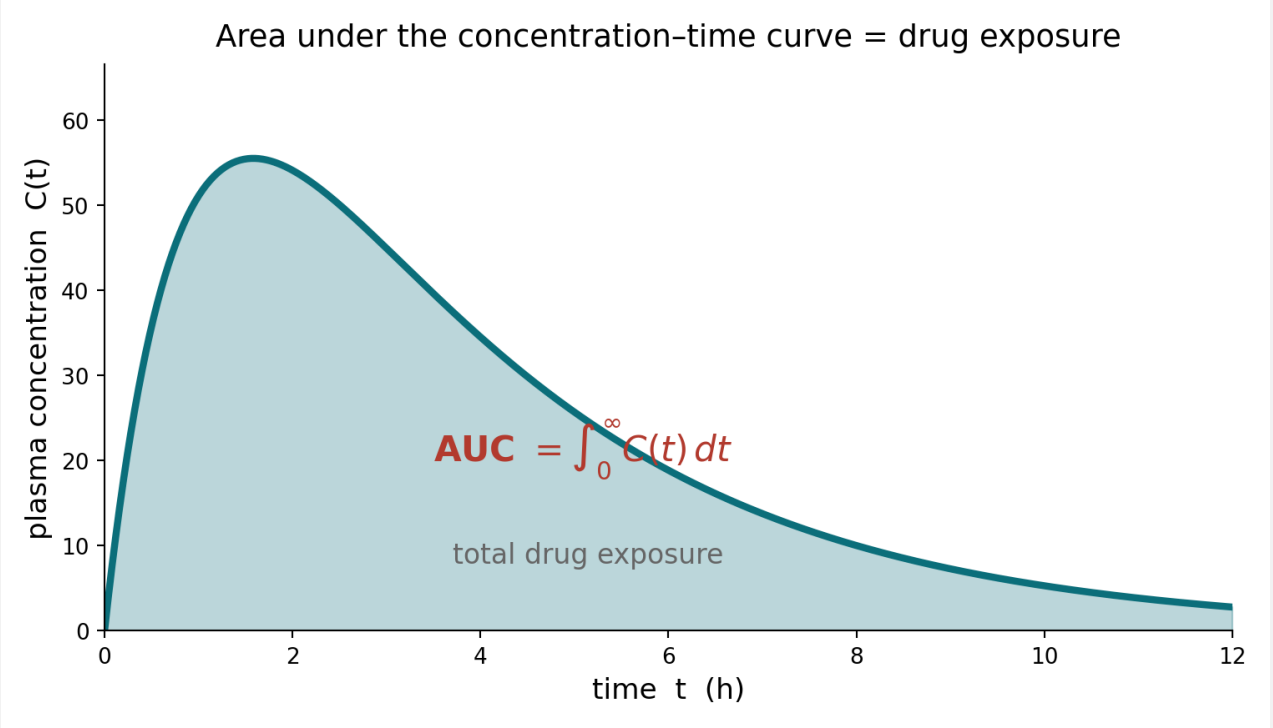
After a dose, plasma concentration rises and falls; the total exposure is the area under that curve.

$$AUC = \int_0^{\infty} \mathrm{C(t)}\,\mathrm{dt}$$

AUC measures how much drug the body actually 'sees' — central to dosing and bioequivalence.

In practice it is estimated from blood samples by the trapezoidal rule.

Two formulations with the same AUC deliver the same total exposure.



Starting from the minima m_i in each of the partial intervals, it is possible to build n rectangles whose base is always equal to the width h of each partial interval, and whose height is equal to m_i

It is hence possible to compute the area of each of these rectangles.
For example, the area of the first is:

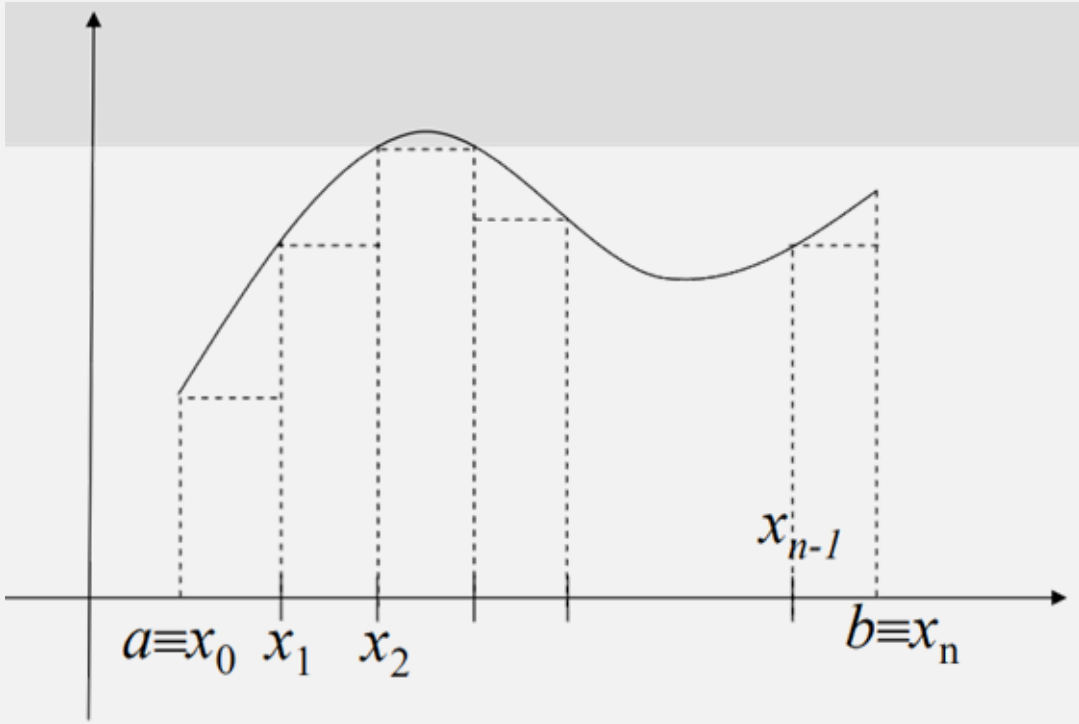
$$m_1(x_1 - x_0) = m_1 \frac{b-a}{n} = m_1 h$$

Similarly, the area of the second is:

$$m_2(x_2 - x_1) = m_2 \frac{b-a}{n} = m_2 h$$

And the area of the n-th is:

$$m_n(x_n - x_{n-1}) = m_n \frac{b-a}{n} = m_n h$$



Hence, the sum of the area of the n rectangles whose height is m_i is:

$$s_n = m_1 h + m_2 h + \cdots + m_n h$$

Starting from the maxima Mi in each of the partial intervals, one can construct n rectangles whose base is always equal to the width h of each partial interval, and whose height is equal to Mi

It is then possible to calculate the area of each of these rectangles.
For example, the area of the first is:

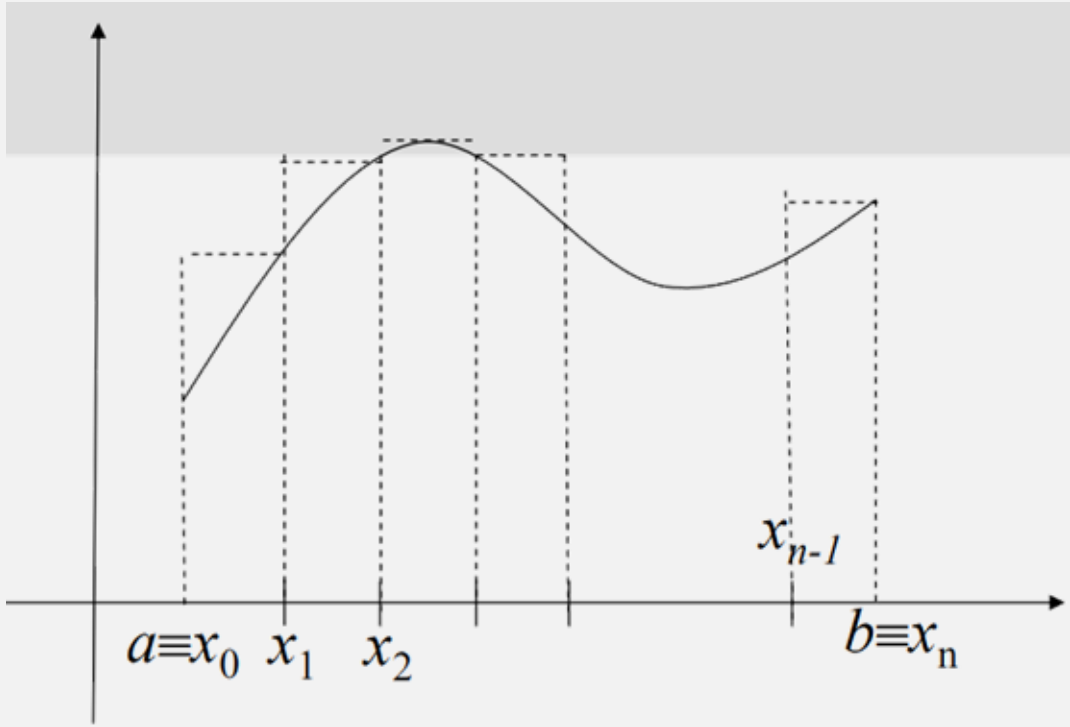
$$M1h$$

Analogously, the area of the second is:

$$M2h$$

And that of the n-th is:

$$Mn\mathrm{h}$$



Thus the sum of the areas of the n rectangles of height Mi is:

$$Sn = M1y + M2h + \cdots + Mn\mathrm{h}$$

Ultimately, by definition one has:

$$\int_a^b f(x)dx = \lim_{n\to+\infty} s_n = \lim_{n\to+\infty} S_n = Area\ R$$

Under the stated assumptions, the definite integral is a number greater than zero.

Properties of Definite Integrals

Let $f, g : [a, b] \to \mathbb{R}$ integrable. Then, $\forall \lambda \in \mathbb{R}$ the functions

$$f + g, \quad \lambda f, \quad |f| \text{ are integrable}$$

$$\forall [c, d] \subset [a, b], \quad f_{[c,d]} \text{ is integrable}$$

Moreover, the following properties hold:

- Linearity $\forall \alpha \in \mathbb{R}$

$$\int_a^b \big(\alpha f(x)\big) dx = \alpha \int_a^b f(x) dx$$

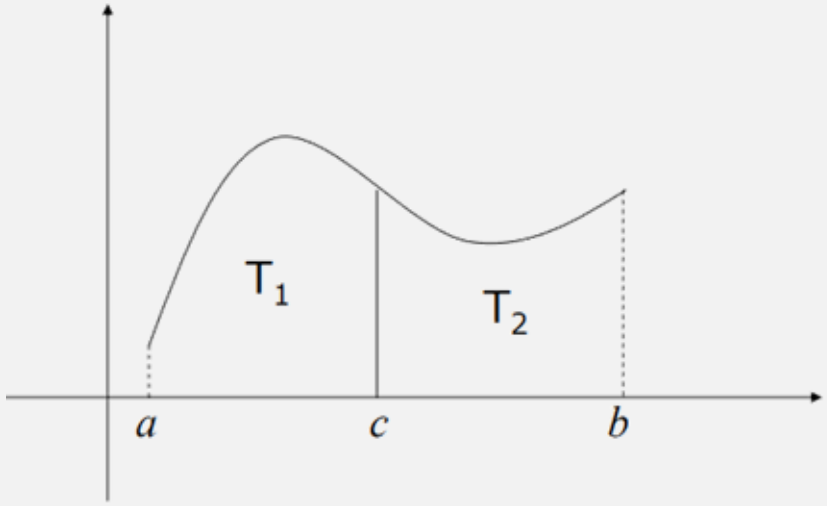
$$\Longrightarrow \int_a^b -f(x) dx = -\int_a^b f(x) dx$$

- Additive property: $\forall c \in (a,b) : a < c < b$

$$\int_a^b f(x)dx = \int_a^c f(x)dx + \int_c^b f(x)dx$$

Clear geometric meaning with positive functions:

$$Area\ R = Area\ T_1 + Area\ T_2$$



First Fundamental Theorem of Integral Calculus

Let $f(x)$ be a continuous and positive function on $[a, b]$.
Fixed x in $[a, b]$, we define:

$$\frac{d}{dx}\int_a^x f(t)dt = f(x)$$

In other words, the integral provides us with a way to construct a function with a prescribed derivative. In other words, the function

$$F(x) = \int_a^x f(t)dt$$

is a solution of the equation

$$\frac{dF}{dx} = f$$

Practical example:
In the interval $[0, x]$, the integral of the function $2t$ is x^2:

$$F(x) = \int_0^x 2t\, dt = x^2$$

The integrand function $f(x)$ is $f(x) = 2x$

The integral function $F(x)$ is $F(x) = x^2$

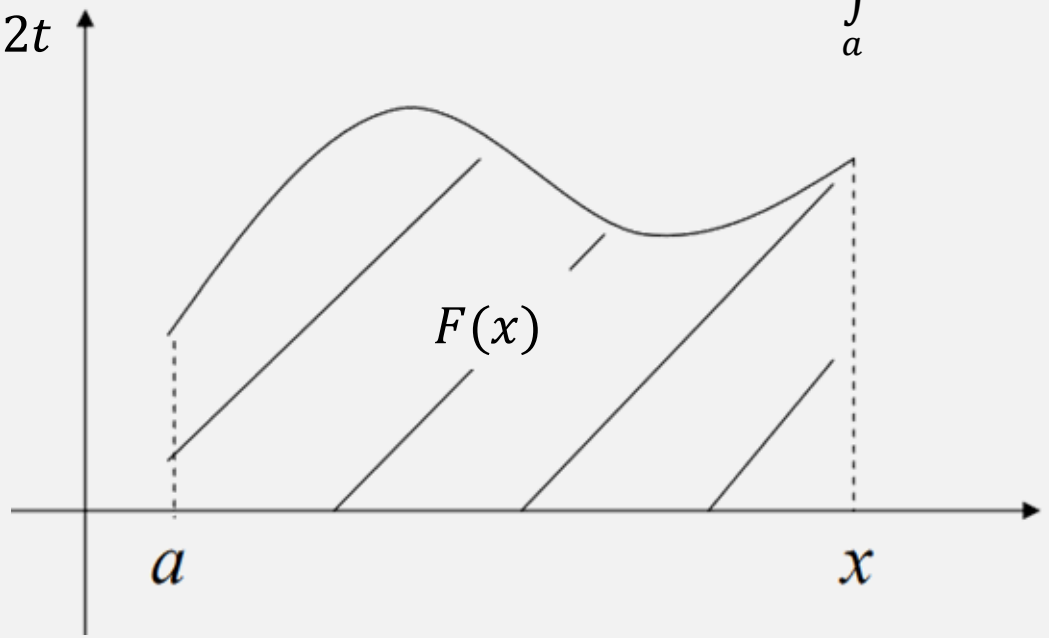
The derivative of the integral function is

$$F'(x) = \frac{d}{dx} x^2 = 2x$$

Hence, the derivative of the integral function $F'(x)$ is equal to the integrand function $f(t)$ calculated for $t = x$:

$$F'(x) = f(x)$$

$$F(x) = \int_a^x f(t)dt$$



Second Fundamental Theorem of Integral Calculus

The Second Fundamental Theorem of Integral Calculus provides a first method to calculate some forms of integrals. Let us start from the definition:

$$\int_a^b f(t)dt = F(b) - F(a)$$

From the formula $\frac{d}{dx}x^{n+1} = (n+1)x^n$ we deduce that $\frac{d}{dx}\left(\frac{1}{n+1}x^{n+1}\right) = x^n$.

Hence:

$$\int_a^b x^n dx = \frac{1}{n+1}x^{n+1}|_a^b = \frac{b^{n+1} - a^{n+1}}{n+1}$$

In this way, we can calculate the integral of whatever polynomial:

$$\int_1^2 (6x^2 + 2x - 3)dx = 6\int_1^2 x^2 dx + 2\int_1^2 x dx - 3\int_1^2 dx =$$

$$= 6\frac{1}{3}x^3|_1^2 + 2\frac{1}{2}x^2|_1^2 - 3(2-1) = 14$$

Example – From a Rate to a Total Amount

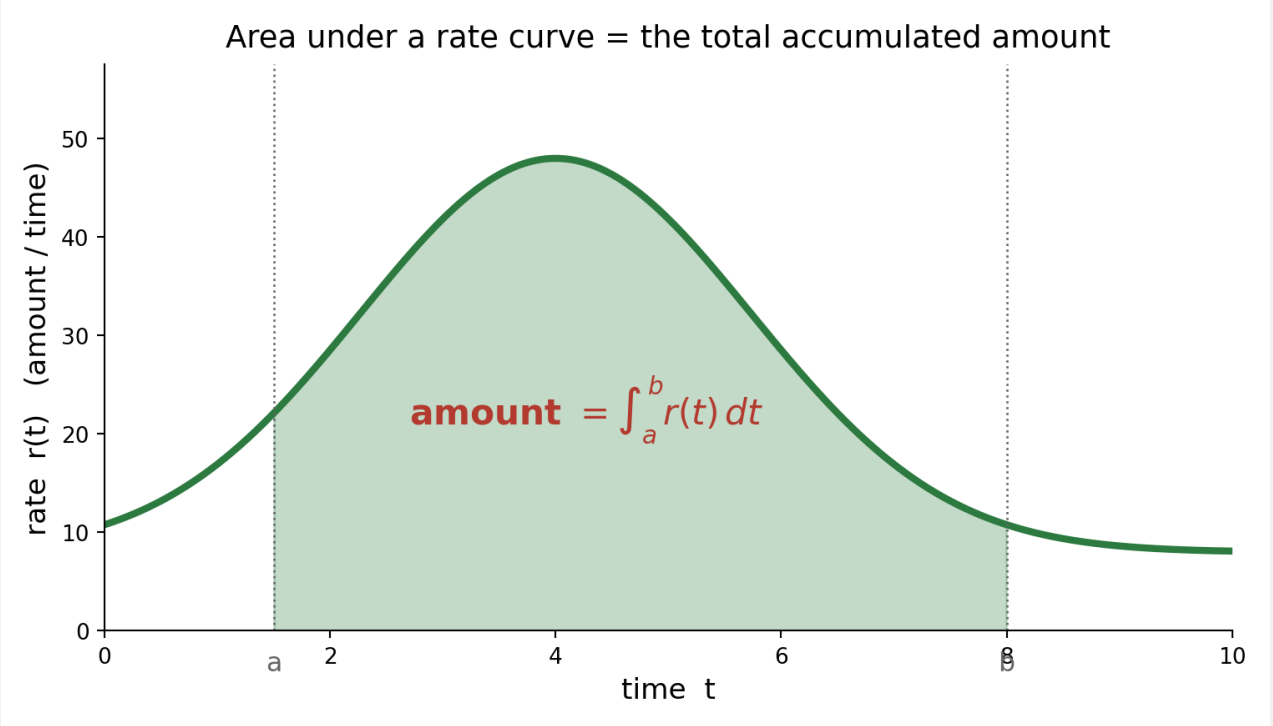
If you know the rate at which something happens, integrating it gives the total amount.

$$quantity = \int_a^b r(t)\,dt$$

Drug infused = ∫ infusion-rate dt; urine volume = ∫ flow dt; O_2 consumed = ∫ VO_2 dt.

This is the fundamental theorem: the integral of a rate is the net accumulated change.

Integration reverses differentiation — it rebuilds the total from its rate.



Indefinite Integral – Antiderivative Function

If f is the derivative of the function F, it is said that F is an indefinite integral (or an antiderivative) of f and it is written:

$$\int f(t)dt = F(t) + c$$

The reason for this notation is that two indefinite integrals of f differ by an additive constant (since they have the same derivative): therefore, as the constant $c \in \mathbb{R}$ varies, the right-hand side of the equation describes all possible indefinite integrals (or all antiderivatives) of f.
Moreover:

$$\int f(t)dt = F(t) + c \Leftrightarrow \int_a^b f(t)dt = F(t)|_a^b$$

In the definition provided, the limits of integration do not appear: the formula is valid on every interval $[a, b]$ where f is the derivative of F.

Antiderivative Function

A function $F(x)$ defined and differentiable on $[a,b]$, is called antiderivative of $f(x)$, defined and continuous on $[a,b]$, if it holds that:

$$F'(x) = f(x), \qquad \forall x \in [a,b]$$

Observation.
If $F(x)$ is an antiderivative of the function $f(x)$ (hence $F'(x) = f(x)$), then $F(x) + c$ is still an antiderivative of $f(x), \forall c \in \mathbb{R}$ and vice versa (in fact: $(F(x) + c)' = f(x), \forall c \in \mathbb{R}$)



if $F(x)$ is an antiderivative of f, all the antiderivatives of f are obtained by adding a constant to F

Characterization of the Antiderivatives of a Function

If $F(x)$ and $G(x)$ are two antiderivatives of the same function f on an interval



Then $F(x)$ and $G(x)$ differ by a constant, that is:

$$F(x) = G(x) + c, \qquad \forall c \in \mathbb{R}$$

Theorem: by adding a constant to an antiderivative, one still obtains an antiderivative

On this basis, it follows that if a function f admits an antiderivative, then it has infinitely many

Example. Compute the antiderivative of the following functions.

$f(x) = x$

$F(x) = \frac{x^2}{2}$, in fact $F'(x) = \frac{1}{2}2x = x = f(x)$

Moreover, also $F(x) = \frac{x^2}{2} + 1$ is an antiderivative of the function $f(x) = x$

Given the theorem on the sum of a constant and an antiderivative function, we can write:

$$F(x) = \frac{x^2}{2} + c$$

$f(x) = e^x$

$F(x) = e^x + c \rightarrow$ in fact $F'(x) = e^x = f(x)$

$f(x) = \frac{1}{x}$

$F(x) = \ln x + c \rightarrow$ in fact $F'(x) = \frac{1}{x} = f(x)$

$$F(x) = G(x) + c, \qquad \forall c \in \mathbb{R}$$

Theorem: by adding a constant to an antiderivative, one still obtains an antiderivative
On this basis, it follows that if a function f admits an antiderivative, then it has infinitely many

The set of functions $Gx + c, \forall c \in \mathbb{R}$ represents exactly all the functions whose derivative is $f(x)$ and is called the indefinite integral of f, which is denoted by the following symbol:

$$\int f(x)\, dx$$

By definition:

$$\int f(x)\, dx = F(x) + c \Leftrightarrow F'(x) = f(x)$$

$$\int f(x)\,dx = F(x) + c \;\Leftrightarrow F'(x) = f(x)$$

The indefinite integrals have properties that derive from the fact that the integral is a linear operator, meaning $D[c_1 \cdot f_1(x) + c_2 \cdot f_2(x)] = c_1 \cdot f_1'(x) + c_2 \cdot f_2'(x)$.

This is reflected on the following properties of indefinite integrals:

- The integral of the product between a constant and a function is equal to the product between the constant and the integral of the function. A multiplicative constant $k \in \mathbb{R}$ can hence be brought inside or outside the integral sign:

$$\int k \cdot f(x)dx = k \cdot \int f(x)dx$$

- The integral of the sum of two or more functions is equal to the sum of the integral calculated on each function:

$$\int [f_1(x) + f_2(x)]dx = \int f_1(x)dx + \int f_2(x)dx$$

- Combining the two properties, the indefinite integral results to be a linear operator → the integral of a linear combination of functions is equal to the linear combination of their integrals: for each k_1 and k_2 being real constants and for each function f_1 and f_2 it holds:

$$\int [k_1 \cdot f_1(x) + k_2 \cdot f_2(x)]dx = k_1 \int f_1(x)dx + k_2 \int f_2(x)dx$$

Example: compute the integral of a polynomial

$$f(x) = 10x^4 + 4x^3 + 5x^2 + 3$$

$$\int f(x)dx = \int [10x^4 + 4x^3 + 5x^2 + 3]dx = 10\int x^4 dx + 4\int x^3 dx + 5\int x^2 dx + 3\int dx$$

$$10\int x^4 dx = 10 \cdot \left[\frac{x^5}{5} + c_1\right] = 2x^5 + c_1$$

$$4\int x^3 dx = 4 \cdot \left[\frac{x^4}{4} + c_2\right] = x^4 + c_2$$

$$5\int x^2 dx = 5 \cdot \left[\frac{x^3}{3} + c_3\right] = \frac{5}{3}x^3 + c_3$$

$$3\int dx = 3\int x^0 dx = 3 \cdot \left[\frac{x^1}{1} + c_4\right] = 3x + c_4$$

By adding the terms (and indicating by a generic c all the constants):

$$\int f(x)dx = \int [10x^4 + 4x^3 + 5x^2 + 3]dx = 2x^5 + x^4 + \frac{5}{3}x^3 + 3x + c$$

The indefinite integral of a function $f(x)$ consists of all its antiderivatives, that is, all those functions whose derivatives yield precisely f.

Summary table of the most common antiderivatives:

1. Antiderivatives of functions: constant, power, root
2. Antiderivatives of trigonometric functions
3. Antiderivatives of exponential and logarithmic functions

Function $f(x)$	**Indefinite integral $\int f(x)dx$**
k (constant function)	$\int dx = \int k dx = kx + c$
x	$\int x dx = \frac{1}{2}x^2 + c$
x^α, with $\alpha \in \mathbb{R}, \alpha \neq -1$	$\int x^\alpha dx = \frac{1}{\alpha+1}x^{\alpha+1} + c$
$\frac{1}{x} = x^{-1}$	$\int \frac{1}{x} dx = \ln\lvert x\rvert + c$

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Funzione $\boldsymbol{f(x)}$	Integrale indefinito $\int \boldsymbol{f(x)dx}$
$\sin x$	$\int \sin x\, dx = -\cos x + c$
$\cos x$	$\int \cos x\, dx = \sin x + c$
$\frac{1}{\cos^2 x}$	$\int \frac{1}{\cos^2 x} dx = \tan x + c$
$\frac{1}{\sin^2 x}$	$\int \frac{1}{\sin^2 x} = \cot x + c$
$\tan x$	$\int \tan x\, dx = -\ln\lvert\cos x\rvert + c$
$\cot x$	$\int \cot x\, dx = -\ln\lvert\sin x\rvert + c$

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Function $f(x)$	**Indefinite integral $\int f(x)dx$**
e^x	$\int e^x dx = e^x + c$
a^x, with $a \in \mathbb{R}, a \neq 1$	$\int a^x dx = \frac{1}{\ln a} a^x + c = a^x \log_a e + c$