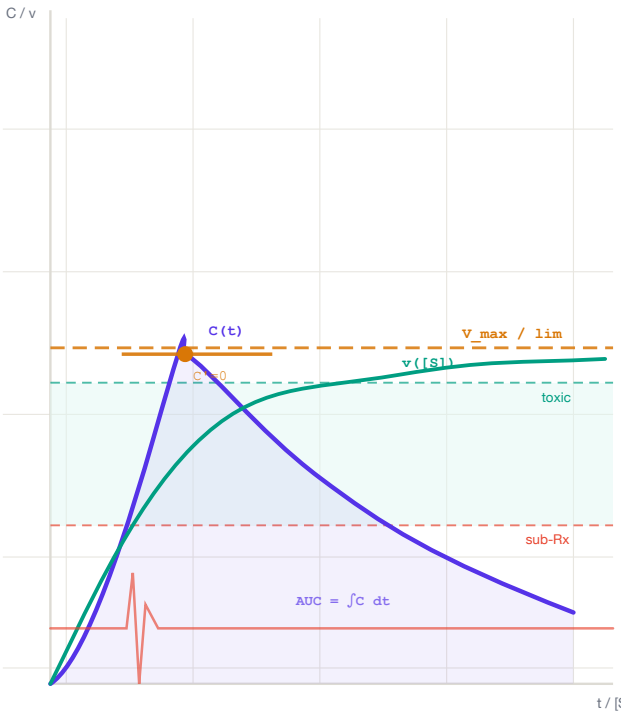
CALCULUS FOR PRE-MED STUDENTS

Limits, Derivatives & Integrals through the lens of medicine, pharmacology, and patient care.

01 · Limits | 02 · Derivatives | 03 · Integrals

REAL MEDICINE · REAL MATH · REAL INSIGHT



CH. 01

Limits

Why enzyme reaction rates can't increase forever. Michaelis-Menten kinetics and the biological boundaries of molecular machines.

CH. 02

Derivatives

How fast is a drug entering or leaving the bloodstream right now? The rate of change that drives dosing decisions and toxicity warnings.

CH. 03

Integrals

AUC — Area Under the Curve — is literally the FDA's standard measure of total drug exposure. Integrals are already built into medicine.

INTRODUCTION

Why Calculus?

Because the human body is not static. It changes, reacts, adapts — and measuring those changes is what calculus is for.

When a physician orders a drug at 500 mg every 8 hours, that interval isn't a guess. It's derived from a pharmacokinetic model that calculates how fast the drug enters the bloodstream, when it reaches peak concentration, and how quickly the kidneys and liver eliminate it. Every one of those calculations uses calculus.

From the action potentials that fire your neurons to the enzyme reactions that digest your food, the biological world runs on rates of change and accumulated quantities. Calculus is the language that describes them precisely.

Limits

What value does a biological process approach? Enzyme saturation, maximum heart rate, homeostatic set points — all are limits that physiology approaches but cannot exceed.

Derivatives

How fast is something changing *right now*? Drug absorption rate, tumor growth velocity, the slope of an action potential — these are all derivatives.

Integrals

How much has accumulated? Total drug exposure (AUC), cumulative radiation dose, total oxygen consumed during surgery — integrals already have FDA-approved names.

> *Every dosing interval, every IV drip rate, every half-life calculation that keeps a patient in the therapeutic window — calculus is the invisible engine running underneath all of it.*
>
> — CLINICAL PHARMACOKINETICS PERSPECTIVE

Where You'll See This in Medicine

- **Pharmacokinetics:** modeling drug absorption, distribution, metabolism, and elimination (ADME)
- **Physiology:** action potentials, enzyme kinetics, cardiac output, lung compliance curves
- **Epidemiology:** SIR disease models use derivatives to predict infection spread; R_0 is a limit concept
- **Medical imaging:** CT reconstruction uses the Radon transform — a family of integrals

CHAPTER ONE

1 Limits

Enzymes can only work so fast. What happens as substrate floods the cell?

Enzyme Saturation: Biology's Speed Limit

Every enzyme has a maximum reaction rate — V_{max}. As you add more substrate (reactant), the enzyme works faster and faster — but it can't work *infinitely* fast. At some point, every active site is occupied, and adding more substrate changes nothing. The reaction rate *approaches* V_{max} but never exceeds it.

This is described by the **Michaelis-Menten equation**, and its core behavior is a limit: as [S] → ∞, v → V_{max}.

MICHAELIS-MENTEN EQUATION

$$v = V_{max} \cdot [S] / (K_m + [S])$$

v = reaction velocity, [S] = substrate concentration, K_m = Michaelis constant (substrate at half V_{max}). As [S] → ∞, the K_m term becomes negligible, so v → V_{max}.

THE LIMIT

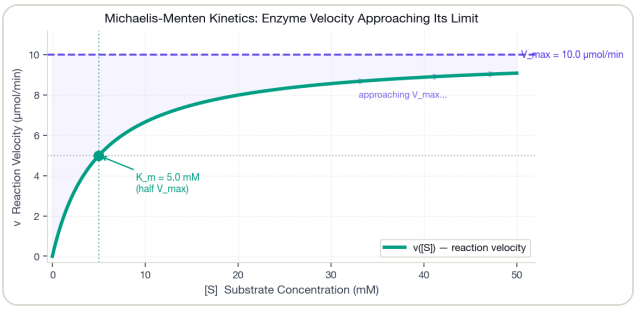
$$\lim_{[S]\to\infty} v([S]) = V_{max}$$

No matter how much substrate is present, the enzyme cannot exceed its maximum rate. V_{max} is a biological limit — a ceiling the system approaches asymptotically.

K_m and drug design: Competitive inhibitors (like many drugs) *increase* the apparent K_m — they shift the curve right, making it harder to reach V_{max}. This changes the limit's approach without changing the limit itself.

MORE LIMITS IN MEDICINE

- **Max heart rate:** $\lim_{effort\to max}$ HR = 220 − age (a biological limit approached under exertion)
- **Drug half-life:** concentration decays toward zero — C(t) → 0 as t → ∞, but never truly reaches it
- **Herd immunity:** as vaccination rate → threshold, epidemic probability → 0 (a public health limit)



Reaction velocity approaches V_{max} as substrate concentration increases — a hyperbolic curve with a horizontal asymptote. K_m marks the half-maximum point.

DEFINITION OF A LIMIT

$$\lim_{x\to a} f(x) = L$$

As x gets arbitrarily close to a, f(x) gets arbitrarily close to L. For enzyme kinetics: as [S] gets very large, v gets very close to V_{max} — without ever equaling it.

Zero-order kinetics: When [S] ≫ K_m, the enzyme is saturated and operates at constant V_{max}. This is why ethanol metabolism is zero-order — the enzyme is always fully occupied.

CHAPTER TWO

2 Derivatives

At exactly two hours after taking a pill, is the drug entering or leaving your bloodstream — and how fast?

The Rate That Drives Dosing

A one-compartment oral pharmacokinetic model describes drug concentration as a function of time: first a rapid rise as the drug absorbs from the gut, then a slower decline as the kidneys and liver eliminate it. The **derivative** C′(t) tells you the instantaneous rate of change at any moment.

When C′(t) > 0, the drug is being absorbed faster than it's eliminated — concentration is rising. When C′(t) < 0, elimination dominates. At the peak concentration, $C'(t_{max}) = \mathbf{0}$ — the derivative is zero at a maximum, a critical clinical moment.

PHARMACOKINETIC MODEL

$$C(t) = A \cdot (e^{-k_e t} - e^{-k_a t})$$

k_a = absorption rate, k_e = elimination rate, A = scaling factor. Its derivative: $C'(t) = A \cdot (-k_e e^{-k_e t} + k_a e^{-k_a t})$

TIME OF PEAK CONCENTRATION

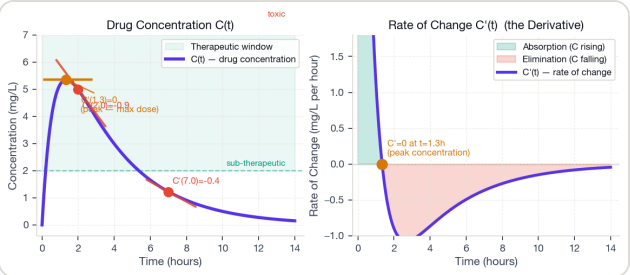
$$t_{max} = \ln(k_a/k_e) \,/\, (k_a - k_e)$$

Set C′(t) = 0 and solve — the peak occurs where the derivative equals zero. With k_a=1.5, k_e=0.3: $t_{max} \approx 1.3$ h, $C_{max} \approx 5.3$ mg/L.

DERIVATIVES THROUGHOUT MEDICINE

- **Absorption rate:** C′(t) > 0 — concentration rising during the absorption phase
- **Elimination rate:** C′(t) < 0 — concentration falling; drives redosing schedule
- **Action potential:** dV/dt is the rate of membrane voltage change — spikes when Na^+ channels open
- **Tumor growth:** dV/dt of tumor volume determines whether treatment is working

Half-life connection: For pure elimination $C(t) = C_0 \cdot e^{-k_e t}$, the derivative $C' = -k_e \cdot C_0 \cdot e^{-k_e t} = -k_e \cdot C(t)$. Half-life = $\ln(2)/k_e \approx 0.693/k_e$.



Left: C(t) with tangent lines and the therapeutic window (teal band). Right: C′(t) — positive during absorption (teal), negative during elimination (coral), zero at the peak.

THE DERIVATIVE DEFINITION

$$C'(t) = \lim_{h \to 0} [C(t+h) - C(t)] / h$$

The instantaneous rate of concentration change. A clinician reading "the drug level is falling at 0.4 mg/L/hour" is reading a derivative.

3

CHAPTER THREE

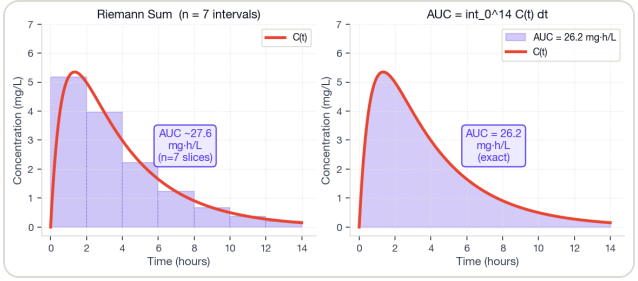
Integrals

AUC — Area Under the Curve — is already a standard FDA metric. You've been doing integrals in pharmacology without knowing it.

Total Drug Exposure

The FDA defines **AUC (Area Under the Concentration-Time Curve)** as the standard measure of total drug exposure in the body. It's used to determine bioavailability, set dosing equivalences between generic and brand-name drugs, and assess drug accumulation in renal failure patients.

AUC is literally a definite integral: $\int_0^\infty C(t)\,dt$. A drug with higher AUC delivers more total exposure per dose — regardless of how the peaks and troughs are shaped.



Left: the trapezoidal approximation used in clinical PK studies (n=7). Right: the exact AUC — the FDA-standard measure of total drug exposure.

AUC — AREA UNDER THE CURVE

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

For a one-compartment model: AUC = Dose × F / (V · k_e), where F = bioavailability, V = volume of distribution. In our example: AUC = 26.2 mg·h/L.

FUNDAMENTAL THEOREM OF CALCULUS

$$\int_a^b \mathbf{C'(t)\ dt = C(b) - C(a)}$$

The total change in concentration from time a to b equals the integral of its rate of change. Integrating the elimination rate gives you exactly how much drug was cleared.

TRAPEZOIDAL RULE (CLINICAL PRACTICE)

$$\mathbf{AUC \approx \Sigma\ [(C_i + C_{i+1})/2]\ \cdot \Delta t}$$

In practice, AUC is estimated from blood draws at discrete time points using the trapezoidal rule — a Riemann-sum approximation. This is calculated for every pharmacokinetic study.

INTEGRALS THROUGHOUT MEDICINE

- **Bioavailability:** F = AUC_{oral} / AUC_{IV} — ratio of two integrals compares drug routes
- **Radiation dose:** ∫(dose rate) dt — total absorbed radiation during a procedure
- **Cardiac output:** ∫(flow rate) dt over one cardiac cycle = stroke volume
- **CT imaging:** each slice is reconstructed from line integrals of X-ray attenuation (Radon transform)

Generic drug approval requires demonstrating AUC bioequivalence within 80–125% of the brand-name drug. The FDA is literally requiring that two integrals be approximately equal.

The FTC Connection:

$C(t) \xrightarrow{d/dt} C'(t) \xrightarrow{d/dt} C''(t)$

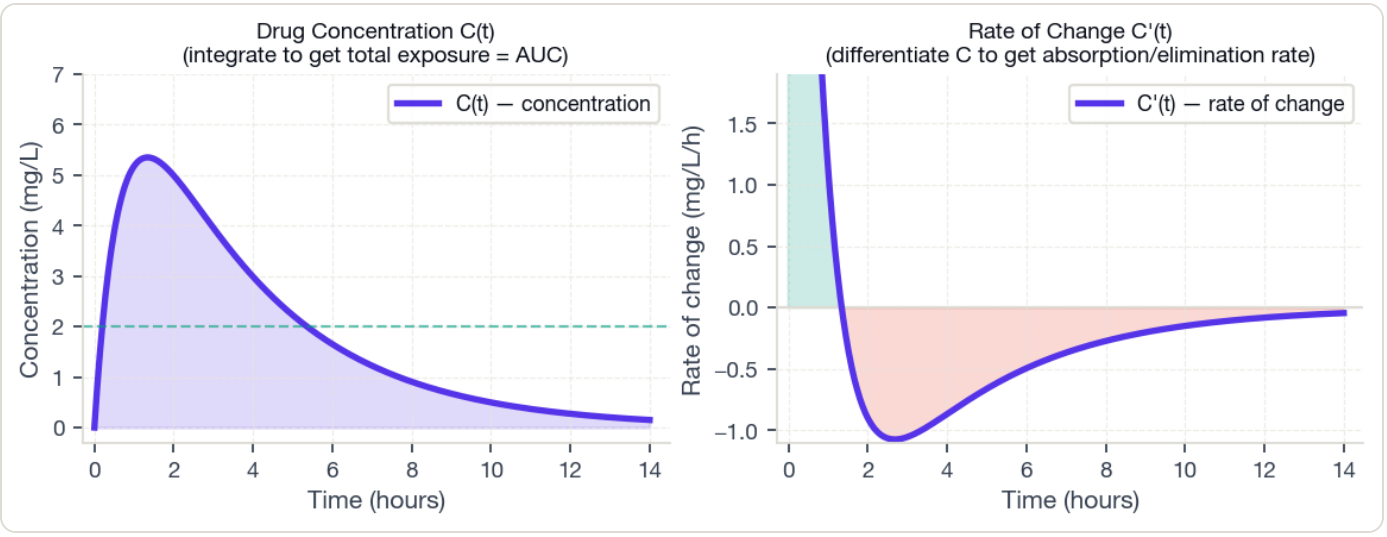
$C''(t) \xrightarrow{\int dt} C'(t) \xrightarrow{\int dt} C(t)$

Differentiation and integration are inverses. Knowing C(t) tells you everything about its rate of change and total exposure.

PUTTING IT TOGETHER

The Playbook

Quick reference and practice problems — all in a clinical context.



The same drug described two ways. Left: C(t) with AUC shaded and therapeutic window marked. Right: C′(t) showing absorption (teal) and elimination (coral) phases. They contain identical information.

CONCEPT	QUESTION IT ANSWERS	FORMULA	MEDICAL EXAMPLE
Limit	What value does a process approach?	$\lim_{[S]\to\infty} v = V_{max}$	Enzyme saturation — maximum reaction rate that cannot be exceeded
Derivative	How fast is concentration changing?	$C'(t) = \lim_{h\to 0} \Delta C/\Delta t$	Drug absorption/elimination rate; C′=0 at peak concentration
Integral	What is the total drug exposure?	$AUC = \int_0^\infty C(t)\,dt$	FDA bioavailability metric; required for generic drug approval

Practice Problems

Limits — Enzyme Saturation

An enzyme follows Michaelis-Menten kinetics with V_{max} = 12 μmol/min and K_m = 8 mM. (a) Find v at [S] = 8 mM. (b) Find v at [S] = 80 mM. (c) What is $\lim_{[S]\to\infty} v([S])$?

Hint: Use $v = V_{max}[S]/(K_m+[S])$. At $[S]=K_m$, $v = V_{max}/2$ by definition.

Derivatives — Drug Elimination Rate

A drug's concentration follows $C(t) = 80\cdot e^{-0.2t}$ mg/L (pure elimination model). (a) Find C′(t). (b) How fast is concentration falling at t = 5 h? (c) At what time is C = 40 mg/L (the half-life)?

Hint: $d/dt(e^{kt}) = k\cdot e^{kt}$. Half-life = $\ln(2)/k_e \approx 0.693/0.2$.

Integrals — AUC Calculation

After an IV bolus, $C(t) = 100\cdot e^{-0.25t}$ mg/L. Calculate the total AUC from t=0 to t=∞. If a generic drug achieves AUC = 370 mg·h/L, is it bioequivalent (within 80–125%)?

Hint: $\int_0^\infty e^{-kt}\,dt = 1/k$. So AUC = C_0/k_e.

All Three — Full Pharmacokinetic Analysis

Enzyme: $v([S]) = 15[S]/(3+[S])$. Drug: $C(t) = 8\cdot(e^{-0.3t} - e^{-1.2t})$. (a) What is $\lim_{[S]\to\infty} v$? (b) Find t_{max} by setting $C'(t)=0$. (c) Estimate $AUC_{0\to 6h}$ using a 3-rectangle Riemann sum ($\Delta t=2$h).

Hint for (b): $C'(t)=0 \to 1.2e^{-1.2t} = 0.3e^{-0.3t}$ → solve for t using natural log.