

Calculus for the Life Sciences

Lecture Notes – Quotient Rule

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Spring 2017

Outline

- 1 Hemoglobin
 - Background
 - Cooperative binding
 - Model for Hemoglobin Saturation
- 2 Quotient Rule
 - Examples
- 3 Dissociation Curve for Hemoglobin
- 4 Genetic Control – Repression

Hemoglobin Affinity for O₂

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Hemoglobin Affinity for O₂

- **Hemoglobin** is the most important molecule in erythrocytes (red blood cells)
- It has evolved to carry O₂ from the lungs and remove CO₂ from the tissues
- For humans, the hemoglobin molecule consists mainly of two α and two β polypeptide chains
- Each polypeptide chain contains a porphyrin ring with iron near the active binding site
- The four polypeptide chains fold into a quaternary structure that has evolved to very efficiently bind up to four molecules of O₂

Hemoglobin Affinity for O₂

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Hemoglobin Affinity for O₂

- Oxygen is required by all of our cells
- Hemoglobin uses **cooperative binding** to effectively load and unload O₂ molecules
 - Binding of one molecule facilitates the binding of one or more other molecules
 - Cooperative binding is often seen where a steep dissociation curve is needed
- It is a variant of the **Michaelis-Menten velocity** curve with a characteristic **S-shape**

Hemoglobin Affinity for O₂

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Hemoglobin Affinity for O₂ – Cooperative Binding

- The protein has more of an **on/off function**
- The steepness in the dissociation curve is needed for effective O₂ exchange
 - A small partial pressure difference in the concentration of O₂ results in easy unloading of O₂ at the tissues
 - In the lungs, the O₂ readily loads onto the hemoglobin molecules
 - A different dissociation curve allows the removal of CO₂
- The dissociation curve for hemoglobin is highly sensitive to pH, temperature, and other factors

Hemoglobin Affinity for O₂

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Hemoglobin Affinity for O₂ – Cooperative Binding

- Oxygen affinity is expressed by a dissociation function that measures the percent of hemoglobin in the blood saturated with O₂ as a function of the partial pressure of O₂
- The fraction of hemoglobin saturated with O₂ satisfies the function

$$y(P) = \frac{P^n}{K + P^n}$$

- y is the fraction of hemoglobin saturated with O₂
- P is the partial pressure of O₂ measured in torrs
- The Hill coefficient n represents the number of molecules binding to the protein, typically measured between 2.7-3.2
- K is the binding equilibrium constant

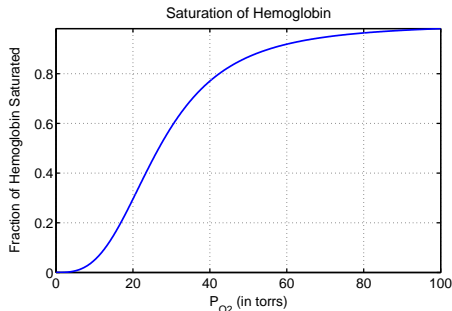
Hemoglobin Affinity for O₂

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Hemoglobin Affinity for O₂: Fraction of hemoglobin

$$y(P) = \frac{P^n}{K + P^n}$$

Experimental measurements show that the values of $n = 3$ and $K = 19,100$



Hemoglobin Affinity for O_2

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Hemoglobin Affinity for O_2 – Cooperative Binding

- Where the dissociation curve is steepest, the O_2 binds and unbinds to hemoglobin over the narrowest changes in partial pressure of O_2
- This allows the most efficient exchange of O_2 in the tissues
- The steepest part of the dissociation curve is where the derivative is at its maximum
- This is the **point of inflection**
- The curve is defined by a rational function, so we need a **quotient rule** to find its derivative

Quotient Rule

Quotient Rule: Let $f(x)$ and $g(x)$ be two differentiable functions

The **quotient rule** for finding the derivative of the quotient of these two functions is given by

$$\frac{d}{dx} \left(\frac{f(x)}{g(x)} \right) = \frac{g(x)f'(x) - f(x)g'(x)}{(g(x))^2}$$

where $f'(x)$ and $g'(x)$ are the derivatives of the respective functions

The **quotient rule** says that the **derivative of the quotient** is the **bottom times the derivative of the top minus the top times the derivative of the bottom** all over the **bottom squared**

Example – Quotient Function

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Example: Consider the function

$$f(x) = \frac{x^2 - 2x + 1}{x^2 - x - 2}$$

Skip Example

- Find any intercepts
- Find any asymptotes
- Find critical points and extrema
- Sketch the graph of $f(x)$

Example – Quotient Function

Solution: The function

$$f(x) = \frac{x^2 - 2x + 1}{x^2 - x - 2}$$

- The y -intercept is given by $y = f(0) = -\frac{1}{2}$
- The x -intercept solves $f(x) = 0$
 - Set the numerator equal to zero

$$x^2 - 2x + 1 = (x - 1)^2 = 0$$

- The x -intercept is $x = 1$

Example – Quotient Function

Solution (cont): The function

$$f(x) = \frac{x^2 - 2x + 1}{x^2 - x - 2} = \frac{(x - 1)^2}{(x + 1)(x - 2)}$$

- The **vertical asymptotes** are when the denominator is zero
 - The vertical asymptotes are

$$x = -1 \quad \text{and} \quad x = 2$$

- The **horizontal asymptote** examines $f(x)$ for large values of x
 - The largest exponents in the numerator are both 2
 - For large x , $f(x)$ behaves like $\frac{x^2}{x^2} = 1$
 - The horizontal asymptote is $y = 1$

Example – Quotient Function

Solution (cont): Extrema

$$f(x) = \frac{x^2 - 2x + 1}{x^2 - x - 2}$$

The derivative uses the **quotient rule**:

$$\begin{aligned} f'(x) &= \frac{(x^2 - x - 2)(2x - 2) - (x^2 - 2x + 1)(2x - 1)}{(x^2 - x - 2)^2} \\ &= \frac{x^2 - 6x + 5}{(x^2 - x - 2)^2} \\ &= \frac{(x - 1)(x - 5)}{(x^2 - x - 2)^2} \end{aligned}$$

Example – Quotient Function

Solution (cont): Critical Points

$$f'(x) = \frac{(x-1)(x-5)}{(x^2-x-2)^2}$$

- The **critical points** are found by setting the derivative equal to zero
- Set the numerator equal to zero or

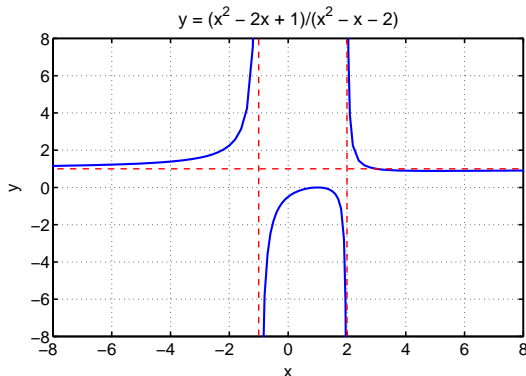
$$(x-1)(x-5) = 0$$

- The critical points are $x_c = 1$ and $x_c = 5$
- Evaluating the function $f(x)$ at these critical points
 - Local maximum at $(1, 0)$
 - Local minimum at $(5, \frac{8}{9})$

Example – Quotient Function

Solution (cont): Graph of $f(x)$

$$f(x) = \frac{x^2 - 2x + 1}{x^2 - x - 2}$$



Derivative of $\tan(x)$

Consider the function:

$$y(x) = \tan(x) = \frac{\sin(x)}{\cos(x)}.$$

Use the quotient rule to differentiate $y(x)$.

$$\begin{aligned} \frac{dy}{dx} &= \frac{\cos(x) \cos(x) - \sin(x)(-\sin(x))}{\cos^2(x)} \\ &= \frac{\cos^2(x) + \sin^2(x)}{\cos^2(x)} \\ &= \frac{1}{\cos^2(x)} = \sec^2(x) \end{aligned}$$

Example – Rational Function

1

Example: Consider the function

$$f(x) = \frac{x^2 - 6x + 9}{x - 2}$$

Skip Example

- Find any intercepts
- Find any asymptotes
- Find critical points and extrema
- Sketch the graph of $f(x)$

Example – Rational Function

Solution: The function

$$f(x) = \frac{x^2 - 6x + 9}{x - 2}$$

- The y -intercept is given by $y = f(0) = -\frac{9}{2}$
- The x -intercept solves $f(x) = 0$
 - Set the numerator equal to zero

$$x^2 - 6x + 9 = (x - 3)^2 = 0$$

- The x -intercept is $x = 3$

Example – Rational Function

Solution (cont): The function

$$f(x) = \frac{x^2 - 6x + 9}{x - 2}$$

Asymptotes:

- The **vertical asymptote** is when the denominator is zero
 - The vertical asymptote is

$$x = 2$$

- **Horizontal asymptotes**
 - The power of the numerator exceeds the power of the denominator
 - There are **no horizontal asymptotes**

Example – Rational Function

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Solution (cont): Extrema

$$f(x) = \frac{x^2 - 6x + 9}{x - 2}$$

The derivative uses the **quotient rule**:

$$\begin{aligned} f'(x) &= \frac{(x - 2)(2x - 6) - (x^2 - 6x + 9) \cdot 1}{(x - 2)^2} \\ &= \frac{x^2 - 4x + 3}{(x - 2)^2} \\ &= \frac{(x - 1)(x - 3)}{(x - 2)^2} \end{aligned}$$

Example – Rational Function

Solution (cont): Critical Points

$$f'(x) = \frac{(x-1)(x-3)}{(x-2)^2}$$

- The **critical points** are found by setting the derivative equal to zero
- Set the numerator equal to zero or

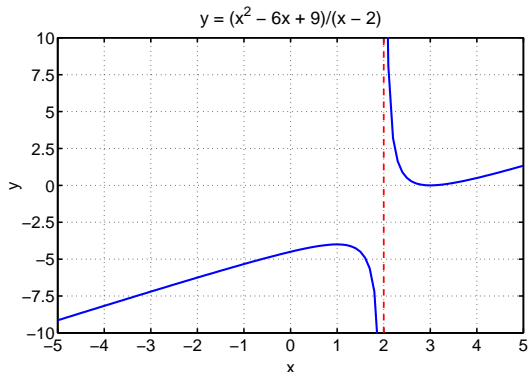
$$(x-1)(x-3) = 0$$

- The critical points are $x_c = 1$ and $x_c = 3$
- Evaluating the function $f(x)$ at these critical points
 - Local maximum at $(1, -4)$
 - Local minimum at $(3, 0)$

Example – Rational Function

Solution (cont): Graph of $f(x)$

$$f(x) = \frac{x^2 - 6x + 9}{x - 2}$$



Dissociation Curve for Hemoglobin

Dissociation Curve for Hemoglobin: The dissociation curve for O_2 with hemoglobin shown above uses the specific function

$$y(P) = \frac{P^3}{19,100 + P^3}$$

Compute the derivative using the quotient rule

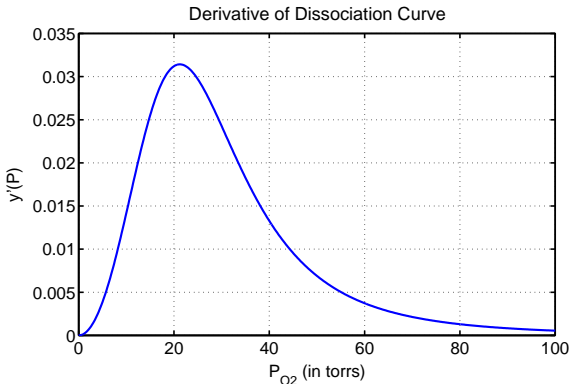
$$y'(P) = \frac{3P^2(19,100 + P^3) - P^3(3P^2)}{(19,100 + P^3)^2}$$

$$y'(P) = \frac{57,300P^2}{(19,100 + P^3)^2}$$

Dissociation Curve for Hemoglobin

Derivative of Dissociation Curve for Hemoglobin:

$$y'(P) = \frac{57,300P^2}{(19,100 + P^3)^2}$$



Dissociation Curve for Hemoglobin

Maximum of the Derivative: The maximum derivative occurs at about $P_{O_2} = 21$ torrs, where the **second derivative** is zero

$$y'(P) = \frac{57,300P^2}{19,100^2 + 38,200P^3 + P^6}$$

The second derivative is

$$y''(P) = \frac{114,600P(19,100^2 + 38,200P^3 + P^6) - 57,300P^2(114,600P^2 + 6P^5)}{(19,100^2 + 38,200P^3 + P^6)^2}$$

With some algebra or Maple

$$y''(P) = -\frac{229,200P(P^3 - 9,550)}{(19,100 + P^3)^3}$$

Dissociation Curve for Hemoglobin

Maximum of the Derivative: The **second derivative** is

$$y''(P) = -\frac{229,200P(P^3 - 9,550)}{(19,100 + P^3)^3}$$

- The second derivative is equal to zero when

$$P = 0 \quad \text{or} \quad P = 9550^{1/3} = 21.22$$

- The point of inflection occurs at $P_p = 21.22$
- $y(P_p) = 0.333$ or about 1/3 of the hemoglobin is saturated by O_2

Genetic Control – Repression

Genetic Control – Repression

- In 1960, Jacob and Monod won a Nobel prize for their theory of **induction** and **repression** in genetic control
- Many metabolic pathways in cells use **endproduct repression** of the gene or **negative feedback** to control important biochemical substances
- The biochemical kinetics of repression of a substance x satisfies a rate function

$$R(x) = \frac{a}{K + x^n}$$

Genetic Control – Repression

Example: Genetic Repression

- Consider the specific rate function

$$R(x) = \frac{90}{27 + x^2}$$

- Differentiate this rate function
- Find all intercepts, any asymptotes, and any extrema for the rate function and its derivative
- Sketch a graph of this rate function and its derivative
- When is the rate function decreasing most rapidly?

Genetic Control – Repression

Solution: Genetic Repression: Rate function

$$R(x) = \frac{90}{27 + x^2}$$

- The rate function has an R -intercept, $R(0) = \frac{90}{27} = \frac{10}{3}$
- There is a **horizontal asymptote** of $R = 0$
- **Quotient rule** gives

$$R'(x) = \frac{(27 + x^2) \cdot 0 - 90(2x)}{(27 + x^2)^2} = -\frac{180x}{(27 + x^2)^2}$$

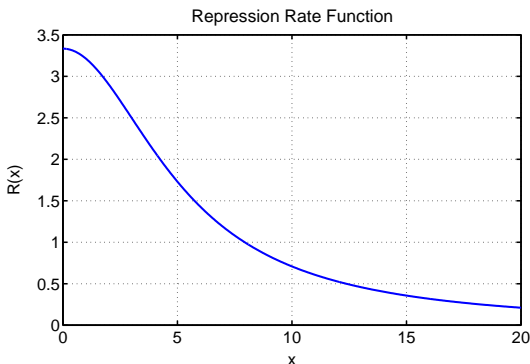
- For $x > 0$, the derivative of the rate function is negative (**decreasing**)
- There is clearly a maximum at $x = 0$

Genetic Control – Repression

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Solution (cont): Genetic Repression Graph of

$$R(x) = \frac{90}{27 + x^2}$$



Genetic Control – Repression

Derivative of Genetic Repression Rate function

$$R'(x) = -\frac{180x}{(27 + x^2)^2} = -\frac{180x}{(27^2 + 54x^2 + x^4)}$$

- The second derivative is

$$\begin{aligned} R''(x) &= -180 \frac{(27^2 + 54x^2 + x^4) - x(108x + 4x^3)}{(27^2 + 54x^2 + x^4)^2} \\ &= \frac{540(x^2 - 9)}{(27 + x^2)^3} \end{aligned}$$

- This second derivative is zero when $x = 3$
- $x = -3$ is outside the domain

Genetic Control – Repression

Derivative of Genetic Repression Rate function

$$R'(x) = -\frac{180x}{(27^2 + 54x^2 + x^4)}$$

- The derivative has an intercept at $(0, 0)$
- Since second derivative is

$$R''(x) = \frac{540(x^2 - 9)}{(27 + x^2)^3},$$

$R'(x)$ has a minimum at $(3, -\frac{5}{12})$

- The original **rate function** is decreasing most rapidly at $x = 3$ (**Point of Inflection**)
- There is a **horizontal asymptote**, $R'(x) = 0$

Genetic Control – Repression

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Derivative of Genetic Repression Rate function Graph of

$$R'(x) = -\frac{180x}{(27^2 + 54x^2 + x^4)}$$

