Calculus for the Life Sciences I

Lecture Notes – Quotient Rule

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Outline

Hemoglobin Affinity for O_2 1

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- **Hemoglobin** is the most important molecule in erythrocytes (red blood cells)

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- It has evolved to carry O_2 from the lungs and remove CO_2 from the tissues

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- 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 O_2

Hemoglobin Affinity for O_2 2

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  - 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 O_2

Hemoglobin Affinity for O_2 – Cooperative Binding

- The protein has more of an **on/off function**

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Hemoglobin Affinity for O_2 3

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  - In the lungs, the O_2 readily loads onto the hemoglobin molecules
  - A different dissociation curve allows the removal of CO_2
- The dissociation curve for hemoglobin is highly sensitive to pH, temperature, and other factors

Hemoglobin Affinity for O_2

Hemoglobin Affinity for O_2 – Cooperative Binding

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  - K is the binding equilibrium constant

Hemoglobin Affinity for O_2

Hemoglobin Affinity for O_2: Fraction of hemoglobin

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Hemoglobin Affinity for O_2: Fraction of hemoglobin

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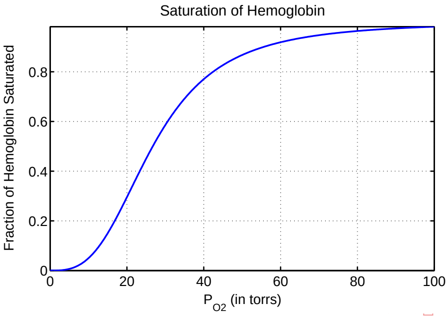
Experimental measurements show that the values of $n = 3$ and $K = 19,100$



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- 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

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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

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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 1

Example: Consider the function

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

Skip Example

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

Example – Quotient Function 2

Solution: The function

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    - Set the numerator equal to zero

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  - The x-intercept is $x = 1$

Example – Quotient Function 3

Solution (cont): The function

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Example – Quotient Function 4

Solution (cont): Extrema

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Example – Quotient Function

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The **derivative** uses the **quotient rule**:

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Example – Quotient Function 5

Solution (cont): Critical Points

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Example – Quotient Function

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

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- Set the numerator equal to zero or

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

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- Evaluating the function $f(x)$ at these critical points

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    - Local maximum at $(1, 0)$

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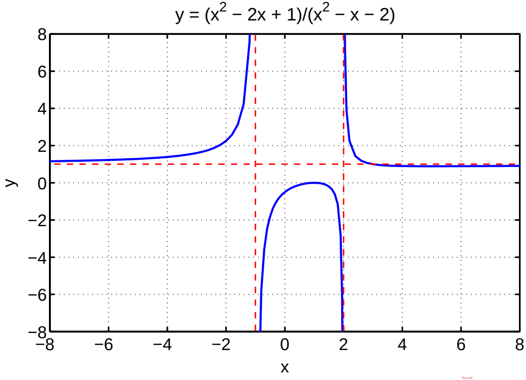
- Evaluating the function $f(x)$ at these critical points
  - Local maximum at $(1, 0)$
  - Local minimum at $(5, \frac{8}{9})$

Example – Quotient Function

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

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



Example – Differentiation

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Solution: Apply the quotient rule to $f(x)$

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

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

Example – Rational Function 1

Example: Consider the function

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

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

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  - The x-intercept is $x = 3$

Example – Rational Function 3

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Asymptotes:

Example – Rational Function 3

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- **Horizontal asymptotes**
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  - There are **no horizontal asymptotes**

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Example – Rational Function

Solution (cont): Critical Points

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Example – Rational Function 5

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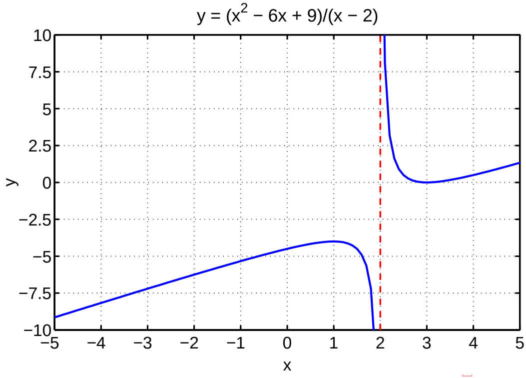
  - Local minimum at $(3, 0)$

Example – Rational Function 6

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

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



Dissociation Curve for Hemoglobin 1

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

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

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Dissociation Curve for Hemoglobin 2

Derivative of Dissociation Curve for Hemoglobin:

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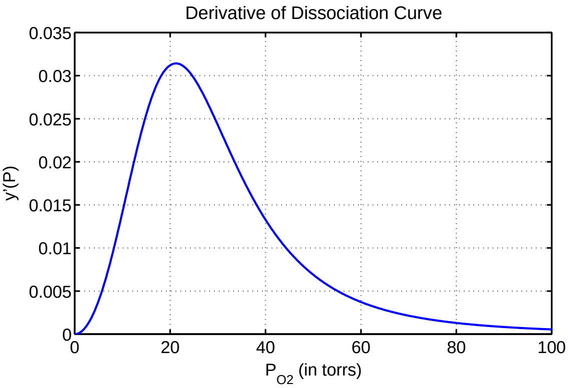

Dissociation Curve for Hemoglobin 3

Maximum of the Derivative: The maximum derivative occurs at about $P_{O2} = 21$ torrs, where the **second derivative** is zero

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

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The second derivative is

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

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With some algebra or Maple

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

Dissociation Curve for Hemoglobin 4

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- 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

Mitotic Model 1

Mitotic Model: Multicellular organisms

Skip Example

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- First cells grow exponentially (Malthusian growth)

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- Cells differentiate into organs with specific functions
- Adult organisms maintain a constant number of cells

Mitotic Model 2

Mitosis

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- Cancer is the breakdown of control in cellular division
- How does a cell recognize when it should divide?
  - Cells must recognize their neighboring environment of other cells
  - For example, a skin cell obviously needs to undergo mitosis when either wear or damage of the skin requires replacement cells

Mitotic Model

Chalones

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Mitotic Model 3

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- Chalones are released by cells and diffuse in the environment
- With sufficient quantities of chalones, cells are inhibited from undergoing mitosis

Mathematical Model for Mitosis

Mitotic Model 4

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- b and c are parameters that fit the data based on chalone kinetics

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- When the cell density P_n is very low, then the denominator of the model is insignificant

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- For low density the population doubles in each time period

Example – Mitotic Model 1

Example – Model for Mitosis

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Example – Model for Mitosis

- Consider the **discrete mitotic model**

$$P_{n+1} = f(P_n) = \frac{2P_n}{1 + (0.01P_n)^4} = \frac{2P_n}{1 + 10^{-8}P_n^4}$$

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- Determine what the cell density is at equilibrium
- Graph the updating function $f(P_n)$
- Give some biological interpretations

Example – Mitotic Model 2

Solution: Equilibria of the Mitotic Model are found by letting $P_{n+1} = P_n = P_e$

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- The equilibria are $P_e = 0$ or $P_e = 100$
  - First equilibrium is the trivial equilibrium (no cells exist)
  - The second equilibrium is the preferred density of cells in a particular tissue

Example – Mitotic Model

Solution (cont): **Graphing the Mitotic Updating Function**

$$f(P_n) = \frac{2P_n}{1 + 10^{-8} P_n^4}$$

Example – Mitotic Model 3

Solution (cont): Graphing the Mitotic Updating Function

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Example – Mitotic Model 3

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Example – Mitotic Model 3

Solution (cont): **Graphing the Mitotic Updating Function**

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- The only intercept is $(0, 0)$, the origin
- The denominator is always positive, so no vertical asymptotes
- Since the power of P_n in the denominator is 4, which exceeds the power of P_n in the numerator, there is a horizontal asymptote at $y = 0$

Example – Mitotic Model 4

Solution (cont): Extrema for the Updating Function

$$f(P) = \frac{2P}{1 + 10^{-8}P^4}$$

Example – Mitotic Model

Solution (cont): Extrema for the Updating Function

$$f(P) = \frac{2P}{1 + 10^{-8}P^4}$$

With the quotient rule

$$f'(P) = 2\frac{(1 + 10^{-8}P^4) - P \cdot 4 \times 10^{-8}P^3}{(1 + 10^{-8}P^4)^2}$$

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Example – Mitotic Model 4

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Setting this derivative equal to zero

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Setting this derivative equal to zero

$$1 - 3 \times 10^{-8}P^4 = 0$$

$$P^4 = \frac{10^8}{3} \qquad \text{or} \qquad P = 75.98$$

Example – Mitotic Model 5

Solution (cont): Extrema for the Updating Function

From above there is a **maximum** at $(75.98, 113.98)$

Example – Mitotic Model 5

Solution (cont): Extrema for the Updating Function

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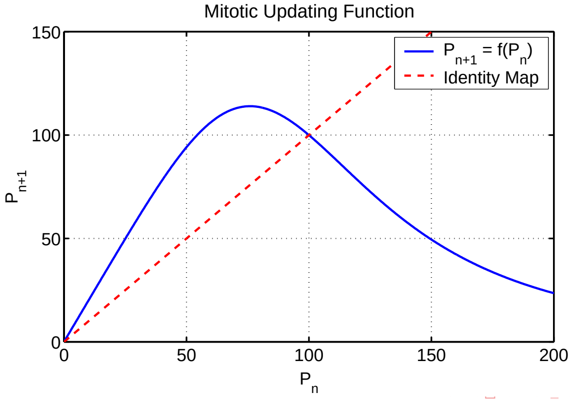
The graph of the **updating function**



Example – Mitotic Model

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- The greatest production of cells occurs at a cell density of 75.98, producing 113.98 cells in the next generation

Example – Mitotic Model

Solution (cont): **Graph of the Mitotic Updating Function**

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- At a cell density of $P_n = 100$, the production equals the number dying - the model is at **equilibrium** (Note: $f'(100) = -1$)

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- At high density, this model predicts a toxic effect from crowding
- This gives a major die-off so that the next time period has a very low density
- This model is very simplistic, but it does demonstrate some of the important concepts behind **biochemical inhibition**

Genetic Control – Repression 1

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- The biochemical kinetics of repression of a substance x satisfies a rate function

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

Genetic Control – Repression 2

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- 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

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Genetic Control – Repression 3

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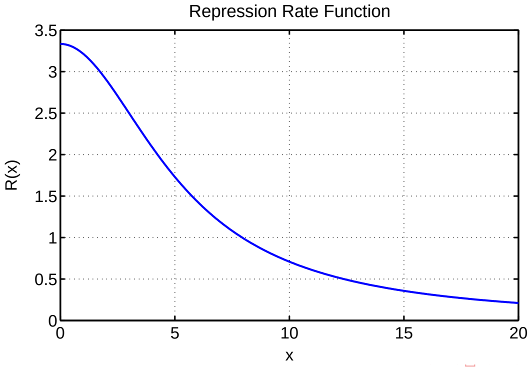
- For $x > 0$, the derivative of the rate function is negative (**decreasing**)
- There is clearly a maximum at $x = 0$

Genetic Control – Repression 4

Solution (cont): **Genetic Repression** Graph of

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



Genetic Control – Repression

Derivative of Genetic Repression Rate function

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

Genetic Control – Repression 5

Derivative of Genetic Repression Rate function

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- The second derivative is

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

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

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Genetic Control – Repression 6

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- There is a **horizontal asymptote**, $R'(x) = 0$

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