Calculus for the Life Sciences I

Lecture Notes – Quotient Rule

Joseph M. Mahaffy,
⟨mahaffy@math.sdsu.edu⟩

Department of Mathematics and Statistics
Dynamical Systems Group
Computational Sciences Research Center
San Diego State University
San Diego, CA 92182-7720

http://www-rohan.sdsu.edu/~jmahaffy

Spring 2013

Outline

Hemoglobin Affinity for O_2 1

Hemoglobin Affinity for O_2

- **Hemoglobin** is the most important molecule in erythrocytes (red blood cells)
- It has evolved to carry O_2 from the lungs and remove CO_2 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 O_2

Hemoglobin Affinity for O_2 2

Hemoglobin Affinity for O_2

- Oxygen is required by all of our cells
- Hemoglobin uses **cooperative binding** to effectively load and unload O_2 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 O_2 3

Hemoglobin Affinity for O_2 – Cooperative Binding

- The protein has more of an **on/off function**
- The steepness in the dissociation curve is needed for effective O_2 exchange
  - A small partial pressure difference in the concentration of O_2 results in easy unloading of O_2 at the tissues
  - 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 4

Hemoglobin Affinity for O_2 – Cooperative Binding

- Oxygen affinity is expressed by a dissociation function that measures the percent of hemoglobin in the blood saturated with O_2 as a function of the partial pressure of O_2
- The fraction of hemoglobin saturated with O_2 satisfies the function

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

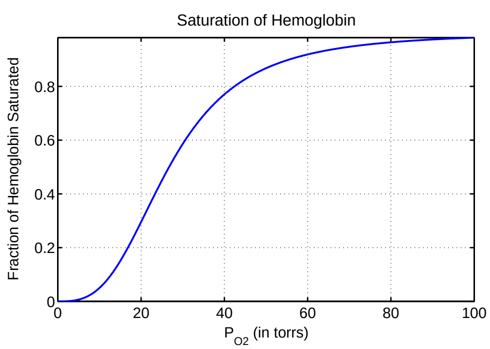
  - y is the fraction of hemoglobin saturated with O_2
  - P is the partial pressure of O_2 measured in torrs
  - The Hill coefficient n represents the number of molecules binding to the protein, typically measured between 2.7-3.2
  - K is the binding equilibrium constant

Hemoglobin Affinity for O_2 5

Hemoglobin Affinity for O_2: 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 6

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 1

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 2

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 3

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 4

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 5

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

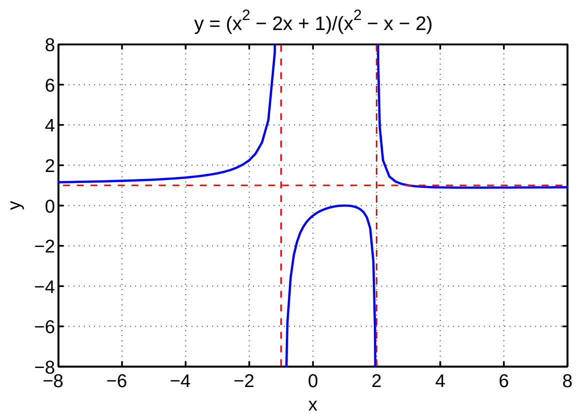
$$(x-1)(x-5) = 0$$

- 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 6

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

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



Example – Differentiation

Example: Differentiate the function

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

Skip Example

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

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

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 2

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 3

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 4

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 5

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

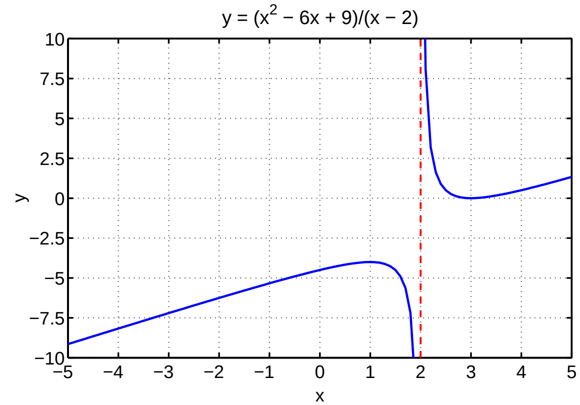
$$(x-1)(x-3) = 0$$

- 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 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

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

Compute the derivative using the quotient rule

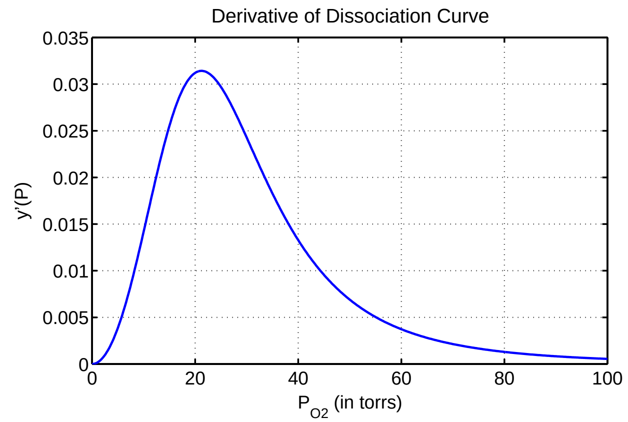
$$y'(P) = \frac{3P^2(19,100 + P^3) - P^3(3P^2)}{(19,100 + P^3)^2}$$

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

Dissociation Curve for Hemoglobin 2

Derivative of Dissociation Curve for Hemoglobin:

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



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

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

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 4

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

Mitotic Model 1

Mitotic Model: Multicellular organisms

Skip Example

- First cells grow exponentially (Malthusian growth)
- Cell growth regulated to develop particular patterns and shapes
- Cells differentiate into organs with specific functions
- Adult organisms maintain a constant number of cells

Mitotic Model 2

Mitosis

- **Mitosis** is the process of cellular division
- 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 3

Chalones

- The **regulation of mitosis**
- One controversial biochemical theory (late 1960s) was that cells communicated with neighboring cells by tissue-specific inhibitors known as **chalones**
- Chalones are released by cells and diffuse in the environment
- With sufficient quantities of chalones, cells are inhibited from undergoing mitosis

Mitotic Model 4

Mathematical Model for Mitosis

- Theory assumes that chalones bind specifically to certain proteins involved in mitosis
- The chalones inactivate the mitotic proteins, leaving the cell in a quiescent state
- The inhibition process of effector molecules binding to a protein is often modeled using a **Hill function**
- Let P_n represent a cell density at a particular time n

$$P_{n+1} = f(P_n) = \frac{2P_n}{1 + (bP_n)^c}$$

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

Mitotic Model 5

Mathematical Model for Mitosis

- The **discrete dynamical model** is

$$P_{n+1} = f(P_n) = \frac{2P_n}{1 + (bP_n)^c}$$

- The function $f(P_n)$ is known as an **updating function**
- When the cell density P_n is very low, then the denominator of the model is insignificant

$$P_{n+1} = 2P_n$$

- For low density the population doubles in each time period

Example – Mitotic Model 1

Example – Model for Mitosis

- Consider the **discrete mitotic model**

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

- 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 $P_{n+1} = P_n = P_e$

From the model

$$\begin{aligned} P_e &= \frac{2P_e}{1+10^{-8}P_e^4} \\ P_e(1+10^{-8}P_e^4) &= 2P_e \\ P_e(10^{-8}P_e^4 - 1) &= 0 \end{aligned}$$

- 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 3

Solution (cont): Graphing the Mitotic Updating Function

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

- 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

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

With the quotient rule

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

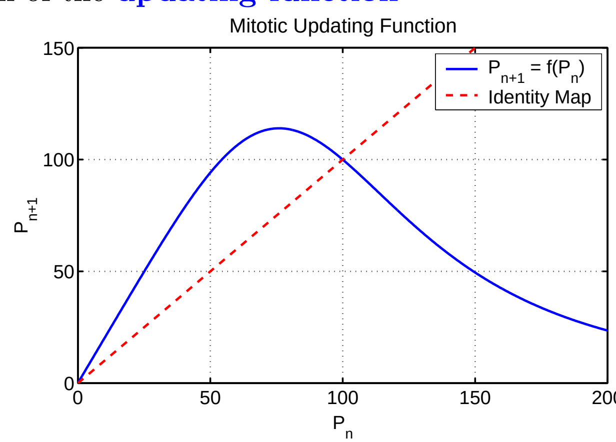
Setting this derivative equal to zero

$$\begin{aligned} 1-3\times 10^{-8}P^4 &= 0 \\ P^4 = \frac{10^8}{3} \quad &\text{or} \quad P = 75.98 \end{aligned}$$

Example – Mitotic Model 5

Solution (cont): Extrema for the Updating Function
From above there is a **maximum** at $(75.98, 113.98)$

The graph of the **updating function**



Example – Mitotic Model 6

Solution (cont): Graph of the Mitotic Updating Function

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

- The greatest production of cells occurs at a cell density of 75.98, producing 113.98 cells in the next generation
- At a cell density of $P_n = 100$, the production equals the number dying - the model is at **equilibrium** (Note: $f'(100) = -1$)
- 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

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 2

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 3

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

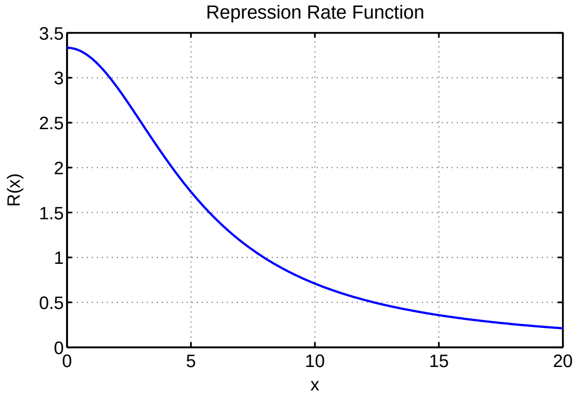
$$R'(x) = \frac{(27 + x^2) \cdot 0 - 90(2x)}{(27 + x^2)^2} = -\frac{180x}{(27 + x^2)^2}$$

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

Genetic Control – Repression

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

Derivative of Genetic Repression Rate function Graph of

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