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 \( \alpha \) and two \( \beta \) 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 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

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

Experimental measurements show that the values of \( n = 3 \) and \( K = 19, 100 \)

\[
\begin{array}{|c|c|c|c|c|c|}
\hline
P_O₂ (in torrs) & 0 & 20 & 40 & 60 & 80 & 100 \\
\hline
\text{Fraction of Hemoglobin Satuated} & 0 & 0.2 & 0.4 & 0.6 & 0.8 & 1.0 \\
\hline
\end{array}
\]

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
- Where the dissociation curve is steepest, the O₂ binds and unbinds to hemoglobin over the narrowest changes in partial pressure of O₂
- This allows the most efficient exchange of O₂ 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

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

- \( y \) 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
**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.

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**Example – Quotient Function 1**

Consider the function
\[
f(x) = \frac{x^2 - 2x + 1}{x^2 - x - 2}
\]

**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 \( x = 1 \)
- Find any intercepts
- Find any asymptotes
- Find critical points and extrema
- Sketch the graph of \( f(x) \)

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**Example – Quotient Function 2**

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 \( x = -1 \) and \( x = 2 \)
- 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:

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

\[ = \frac{x^2 - 6x + 5}{(x^2 - x - 2)^2} \]

\[ = \frac{(x-1)(x-5)}{(x^2 - x - 2)^2} \]

The critical points are found by setting the derivative equal to zero.

1. Set the numerator equal to zero:
   \[ (x-1)(x-5) = 0 \]
   \[ x = 1, 5 \]

2. 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): 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:
  \[ (x-1)(x-5) = 0 \]
  \[ x = 1, 5 \]

- 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 \( f(x) \)

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

Consider the function:

\[ y(x) = \tan(x) = \frac{\sin(x)}{\cos(x)} \]

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

\[ \frac{dy}{dx} = \frac{\cos(x)\cos(x) - \sin(x)(-\sin(x))}{\cos^2(x)} \]

\[ = \frac{\cos^2(x) + \sin^2(x)}{\cos^2(x)} \]

\[ = \frac{1}{\cos^2(x)} = \sec^2(x) \]
Example – Rational Function

Example: Consider the function
\[ f(x) = \frac{x^2 - 6x + 9}{x - 2} \]

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 \( x = 3 \)

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

Solution (cont): Extrema

The derivative uses the quotient rule:
\[
 f'(x) = \frac{(x - 2)(2x - 6) - (x^2 - 6x + 9) \cdot 1}{(x - 2)^2} \\
 = \frac{x^2 - 4x + 3}{(x - 2)^2} \\
 = \frac{(x - 1)(x - 3)}{(x - 2)^2}
\]
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 \((3, 0)\)
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

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

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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

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

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?
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 \( x = 0 \)

Derivative of Genetic Repression Rate function

\[ R'(x) = -\frac{180x}{(27 + x^2)^2} \]

- The second derivative is

\[ R''(x) = -180 \left( \frac{27 + 54x^2 + x^4}{(27 + x^2)^2} - x(108x + 4x^3) \right) \]

\[ = \frac{540(x^2 - 9)}{(27 + x^2)^3} \]

- This second derivative is zero when \( x = 3 \)
- \( x = -3 \) is outside the domain

\[ R'(x) \] 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, \( R'(x) = 0 \)
**Derivative of Genetic Repression Rate function**

Graph of

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