Calculus for the Life Sciences
Lecture Notes – The Derivative of $e^x$ and $\ln(x)$

Joseph M. Mahaffy,
⟨jmahaffy@mail.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

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Outline

1. Fluoxetine (Prozac)
   - Background
   - Drug Kinetics
   - Norfluoxetine Kinetics

2. Derivative of $e^x$
   - Derivative of Prozac Model
   - Polymer Drug Delivery System

3. Derivative of Natural Logarithm
   - Height and Weight Relationship for Children
   - Examples
Introduction

- Special functions often arise in biological problems
  - Biochemical Kinetics
  - Population dynamics
- Need the derivatives for $e^x$ and $\ln(x)$
- Find maxima, minima, and points of inflection
Fluoxetine (Prozac)

- **Fluoxetine** (trade name **Prozac**) is a selective serotonin reuptake inhibitor (SSRI)
- This drug is used to treat depression, obsessive compulsive disorder, and a number of other neurological disorders
- It works by preventing serotonin from being reabsorbed too rapidly from the synapses between nerve cells, prolonging its availability, which improves the patient’s mood
Fluoxetine (Prozac) - cont

- Fluoxetine is metabolized in the liver and transformed into a slightly less potent SSRI, norfluoxetine.
- Both compounds bind to plasma protein, then become concentrated in the brain (up to 50 times more concentrated).
- Fluoxetine and norfluoxetine are eliminated from the brain with characteristic half-lives of 1-4 days and 7-15 days, respectively.

Joseph M. Mahaffy, {jmahaffy@mail.sdsu.edu}
Drug Kinetics

- It is very important to understand the kinetics of the drug in the body
- Drugs metabolized into another active form make modeling more complex
- Models below examine first order kinetic models for the concentrations of fluoxetine \( F(t) \) and norfluoxetine \( N(t) \) in the blood
Half-Life of a Drug

- A subject taking a 40 mg oral dose of fluoxetine rapidly exhibits a blood stream concentration of 21 ng/ml.
- One study of healthy volunteers showed the half-life of fluoxetine was 1.5 days.
- When a drug is either filtered out by the kidneys or metabolized by some organ such as the liver proportional to its concentration, then the drug is said to exhibit first-order kinetics.
- The drug decays exponentially with a characteristic half-life.
Fluoxetine (Prozac)  

**Half-Life of a Drug - Calculation**

- Assume instantaneous uptake of the drug, then the initial blood concentration of fluoxetine is

\[ F(0) = 21 \text{ ng/ml} \]

- Fluoxetine is metabolized in both the brain and liver, so satisfies the kinetic equation

\[ F(t) = 21e^{-kt} \]

- With a half-life of 1.5 days, we have

\[ F(1.5) = 10.5 = 21e^{-1.5k} \]

- Solving this equation for \( k \),

\[ e^{1.5k} = 2 \quad \text{or} \quad k = \ln(2)/1.5 = 0.462 \]
Model for Fluoxetine

A good model for blood plasma concentration of fluoxetine is

\[ F(t) = 21 e^{-0.462t} \]
Norfluoxetine Kinetic Model

- Fluoxetine is metabolized in the liver and through a hepatic biotransformation becomes norfluoxetine (through a demethylation)
- Norfluoxetine continues to act as potent and specific serotonin reuptake inhibitor
- The half-life is taken to be 9 days for norfluoxetine
- A reasonable model using linear kinetics for the blood plasma concentration of norfluoxetine is

\[ N(t) = 27.5(e^{-0.077t} - e^{-0.462t}) \]

- Pharmokinetic models often are composed of the difference of two decaying exponentials
Graph of Fluoxetine and Norfluoxetine

Prozac Metabolism

Blood Plasma (ng/ml)

Fluoxetine
Norfluoxetine

Joseph M. Mahaffy, ⟨jmahaffy@mail.sdsu.edu⟩
Lecture Notes – The Derivative of $e^x$ and $\ln(x)$ — (11/38)
Fluoxetine and Norfluoxetine Kinetic Models

- Determine the rate of change of fluoxetine and norfluoxetine
- Find the time of maximum blood plasma concentration of norfluoxetine and what that concentration is
- To solve these problems, we need to learn the formula for the derivative of the exponential function
Derivative of $e^x$

- The exponential function $e^x$ is a special function
- It’s the only function (up to a scalar multiple) that is the derivative of itself

$$\frac{d}{dx}(e^x) = e^x$$
**Derivative of** $e^x$

\[
\frac{d}{dx}(e^x) = e^x
\]

One definition of the number $e$ is the number that makes

\[
\lim_{h \to 0} \frac{e^h - 1}{h} = 1
\]

From the definition of the derivative and using the properties of exponentials

\[
\frac{d}{dx}(e^x) = \lim_{h \to 0} \frac{e^{x+h} - e^x}{h} = e^x \lim_{h \to 0} \frac{e^h - 1}{h} = e^x
\]
Derivative of $e^x$

Geometrically, the function $e^x$ is a number raised to the power $x$, whose slope of the tangent line at $x = 0$ is 1.

**General rule for the derivative of $e^{kx}$**

The derivative of $e^{kx}$ is

$$\frac{d}{dx}(e^{kx}) = k \cdot e^{kx}$$
Example: Find the derivative of

\[ f(x) = 5 e^{-3x} \]

Solution: From our rule of differentiation and the formula above

\[ f'(x) = -15 e^{-3x} \]
Application of the Derivative to Prozac Model

Derivative of Prozac Model: Find the rate of change of the fluoxetine model

\[ F(t) = 21 e^{-0.462t} \]

Solution: The derivative is

\[ F'(t) = (-0.462)21 e^{-0.462t} = -9.702 e^{-0.462t} \]

The rate of change of blood plasma concentration of fluoxetine at times \( t = 2 \) and \( 10 \) is

\[ F'(2) = -9.702 e^{-0.462(2)} = -3.85 \text{ ng/ml/day} \]
\[ F'(10) = -9.702 e^{-0.462(10)} = -0.0956 \text{ ng/ml/day} \]
Application of the Derivative to Norfluoxetine Model

**Derivative of Norfluoxetine Model:** Find the rate of change of the norfluoxetine model

\[ N(t) = 27.5(e^{-0.077t} - e^{-0.462t}) \]

**Solution:** The derivative is

\[ N'(t) = 27.5(-0.077e^{-0.077t} + 0.462e^{-0.462t}) \]

\[ = 12.705e^{-0.462t} - 2.1175e^{-0.077t} \]

The rate of change of blood plasma concentration of norfluoxetine at times \( t = 2 \) and \( 10 \) is

\[ N'(2) = 12.705e^{-0.462(2)} - 2.1175e^{-0.077(2)} = 3.23 \text{ ng/ml/day} \]

\[ N'(10) = 12.705e^{-0.462(10)} - 2.1175e^{-0.077(10)} = -0.855 \text{ ng/ml/day} \]
Maximum Concentration of Norfluoxetine Model

**Maximum of Norfluoxetine Model:** The derivative is

\[ N'(t) = 12.705 e^{-0.462t} - 2.1175 e^{-0.077t} \]

The maximum occurs when the derivative is zero or

\[ 2.1175 e^{-0.077t} = 12.705 e^{-0.462t} \]

\[ \frac{e^{-0.077t}}{e^{-0.462t}} = \frac{12.705}{2.1175} \]
\[ e^{0.385t} = 6.0 \]

The maximum occurs at

\[ 0.385t = \ln(6) \quad \text{and} \quad t_{\text{max}} = 4.654 \text{ days} \]

The maximum blood plasma concentration of norfluoxetine is

\[ N(t_{\text{max}}) = 16.01 \text{ ng/ml} \]
Maximum Removal of Norfluoxetine

**Maximum Removal of Norfluoxetine:** The derivative is

\[ N'(t) = 12.705 e^{-0.462t} - 2.1175 e^{-0.077t} \]

The second derivative satisfies

\[ N''(t) = -5.8697 e^{-0.462t} + 0.16305 e^{-0.077t} \]

\[
\frac{e^{-0.077t}}{e^{-0.462t}} = \frac{5.8697}{0.16305} \\
\frac{e^{0.385t}}{e^{0.385t}} = 36.0
\]

The **point of inflection** with **maximum decrease** occurs at

\[ 0.385t = \ln(36) = 2 \ln(6) \quad \text{and} \quad t_{poi} = 9.308 \text{ days} \]

with blood plasma concentration of norfluoxetine at

\[ N(t_{poi}) = 12.91 \text{ ng/ml} \quad \text{and} \quad N'(t_{poi}) = -0.862 \text{ ng/ml/day} \]
Drug Delivery: Drugs are often administered by a pill or an injection

- The body receives a high dose rapidly
- The drug remaining in the blood disappears exponentially
  - Filtration by the kidneys
  - Metabolism of the drug
- Model for Injection of a Drug

\[ k(t) = A_0 e^{-qt} \]

- Concentration of the drug, \( k(t) \)
- Total dose, \( A_0 \)
- Rate of clearance, \( q \)
Example – Polymer Drug Delivery System

**Polymer Drug Delivery System:**

- Scientists invented polymers that are implanted to deliver a drug or hormone
  - Deliver the drug (or hormone) for a much longer period of time
  - Drug doses can be lower
- Several long term birth control devices
  - Devices deliver the hormones estrogen and progesterone
  - Delivery gives a more uniform level of the hormones over extended periods of time to prevent pregnancy
- New drug delivery devices
  - Diabetes sufferers could receive a more uniform level of insulin
  - Chemotherapeutic drugs to cancer patients could extend over a much longer period of time at lower doses to maximize their efficacy
**Example – Polymer Drug Delivery System**

**Model for a Polymer Drug Delivery Device:**
Mathematically, this is described by two decaying exponentials

\[ c(t) = C_0(e^{-rt} - e^{-qt}) \]

- \( c(t) \) is the concentration of the drug
- \( C_0 \) relates to the dose in the polymer delivery device
- \( r \) relates to the decay of the polymer, releasing the drug \((q > r)\)
- \( q \) is a kinetic constant depending on how the patient clears the drug
- The amounts of drug are the same when

\[ A_0 = \frac{C_0}{r} \]
Drug Delivery: This example examines the same amount of drug delivered by injection and a polymer delivery device

- Suppose the drug is injected

\[ k(t) = 1000 e^{-0.2t} \]

- \( k(t) \) is a concentration in mg/dl and the time \( t \) is in days

- The same amount of drug is delivered by a polymer drug delivery device satisfies

\[ c(t) = 10(e^{-0.01t} - e^{-0.2t}) \]

- \( c(t) \) is a concentration in mg/dl
**Drug Delivery:** Comparing the injected and polymer delivered drug systems

- Find the rate of change in concentration for both \(k(t)\) and \(c(t)\) at \(t = 5\) and 20
- Determine the maximum concentration of \(c(t)\) and when it occurs
- Graph each of these functions
Example – Polymer Drug Delivery System

**Solution:** Since \( k(t) = 1000 e^{-0.2t} \), the derivative is

\[
k'(t) = (-0.2)1000 e^{-0.2t} = -200 e^{-0.2t}
\]

- The rate of change of the drug concentrations at times \( t = 5 \) and 20 for the injected drug is
  - \( k'(5) = -200 e^{-0.2(5)} = -73.58 \text{ mg/dl/day} \)
  - \( k'(20) = -200 e^{-0.2(20)} = -3.66 \text{ mg/dl/day} \)
Example – Polymer Drug Delivery System

Solution (cont): Since \( c(t) = 10(e^{-0.01t} - e^{-0.2t}) \), the derivative is

\[
c'(t) = 10(-0.01 e^{-0.01t} - (-0.2)e^{-0.2t}) = 2 e^{-0.2t} - 0.1 e^{-0.01t}
\]

The rate of change of the drug concentrations at times \( t = 5 \) and \( 20 \) for the injected drug is

\[
c'(5) = 2 e^{-0.2(5)} - 0.1 e^{-0.01(5)} = 0.64 \text{ mg/dl/day}
\]

\[
c'(20) = 2 e^{-0.2(20)} - 0.1 e^{-0.01(20)} = -0.045 \text{ mg/dl/day}
\]
Solution for Maximum for $c(t)$: Since the derivative is

$$c'(t) = 2e^{-0.2t} - 0.1e^{-0.01t}$$

$$2e^{-0.2t} - 0.1e^{-0.01t} = 0 \text{ or } 0.1e^{-0.01t} = 2e^{-0.2t}$$

Thus,

$$e^{-0.01t + 0.2t} = e^{0.19t} = 20$$

It follows that $t_{max} = \ln(20)/0.19 = 15.767$ days

The maximum occurs at $c(15.767) = 8.11 \mu g/dl$
Graph: Drug Delivery

The polymer delivered drug over a longer period of time.

These graphs show the obvious advantages of the time released drug if it has serious side effects or toxicity.
Height and Weight Relationship for Children:

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<tr>
<th>age (years)</th>
<th>height (cm)</th>
<th>weight (kg)</th>
</tr>
</thead>
<tbody>
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<td>5</td>
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<td>18.2</td>
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<tr>
<td>6</td>
<td>114</td>
<td>20.0</td>
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<td>7</td>
<td>121</td>
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<tr>
<td>13</td>
<td>156</td>
<td>46.8</td>
</tr>
</tbody>
</table>
**Ehrenberg Model:** Logarithmic relationship

\[ H(w) = 49.5 \ln(w) - 34.14 \]

Want to find the rate of change of height with respect to weight for the average girl.
**Derivative of \( \ln(x) \)**

The derivative of the natural logarithm, \( \ln(x) \), is given by the formula

\[
\frac{d}{dx} \ln(x) = \frac{1}{x}
\]

This relationship is most easily demonstrated after learning the Fundamental Theorem of Calculus (later in the course), which centers about the integral.
Derivative of Ehrenberg Model

**Derivative of Ehrenberg Model:** The Ehrenberg model for the previous data

\[ H(w) = 49.5 \ln(w) - 34.14 \]

The derivative is given by

\[ \frac{dH}{dw} = \frac{49.5}{w} \text{ cm/kg} \]

- As the weight increases, the rate of change in height decreases
- At \( w = 20 \text{ kg} \)

\[ H'(20) = \frac{49.5}{20} = 2.475 \text{ cm/kg} \]

- At \( w = 49.5 \text{ kg} \)

\[ H'(49.5) = \frac{49.5}{49.5} = 1 \text{ cm/kg} \]
Example: Find the derivative of

\[ f(x) = \ln(x^2) \]

Solution: From our properties of logarithms and the formula above

\[ f(x) = \ln(x^2) = 2 \ln(x) \]

The derivative is given by

\[ f'(x) = \frac{2}{x} \]
Example: Consider the following function

\[ y = x - \ln(x) \]

- Find the first and second derivatives of this function
- Find any local extrema
- Graph the function
Example – Logarithm Function

Solution: The function \( y = x - \ln(x) \) has the derivative

\[
\frac{dy}{dx} = 1 - \frac{1}{x} = \frac{x - 1}{x}
\]

The second derivative is

\[
\frac{d^2y}{dx^2} = \frac{1}{x^2}
\]

Note that since \( y''(x) > 0 \), this function is concave upward.
Solution (cont): Graphing the Function

- This function is only defined for $x > 0$
- There is no $y$-intercept
- There is a vertical asymptote at $x = 0$

Extrema: Solve the derivative equal to zero

$$\frac{dy}{dx} = \frac{x - 1}{x} = 0$$

Thus, $x = 1$

There is an extremum at $(1,1)$
Solution (cont): Graphing the Function

- Since the second derivative is always positive
- The point (1, 1) is a minimum

\[ y = x - \ln(x) \]