Calculus for the Life Sciences

Lecture Notes – The Derivative of e^x and $\ln(x)$

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Outline

Introduction

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- 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) 1

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 availablity, which improves the patient's mood

Fluoxetine (Prozac)

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

Fluoxetine (Prozac)

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

Fluoxetine (Prozac)

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,
$$e^{1.5k} = 2 \quad \text{or} \quad k = \ln(2)/1.5 = 0.462$$

Fluoxetine (Prozac)

Model for Fluoxetine

A good model for blood plasma concentration of fluoxetine is

$$F(t) = 21\, e^{-0.462t}$$

Norfluoxetine Kinetic Model

Norfluoxetine Kinetic Model

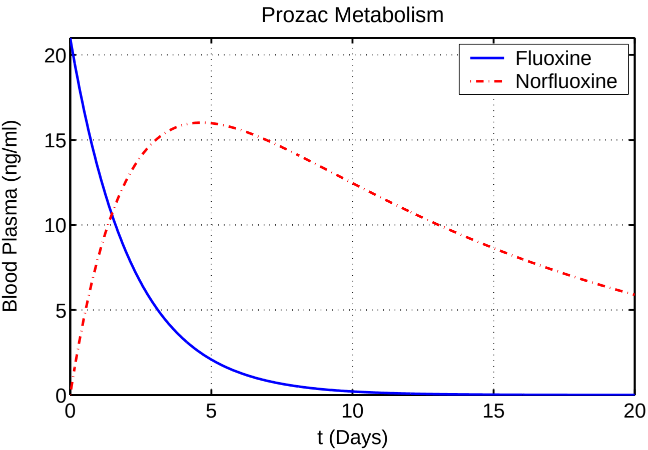
- Fluoxetine is metabolized in the liver and through a hepatic biotransformation becomes norfluoxetine (through a demethylation)
- Norfluoxetine continues to act as potent and specific serotonin reuptake inhibitor
- The half-life is taken to be 9 days for norfluoxetine
- A reasonable model using linear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

Fluoxetine (Prozac)

Graph of Fluoxetine and Norfluoxetine



Fluoxetine and Norfluoxetine Kinetic Models

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

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

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

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

$$\frac{d}{dx}(e^{kx}) = k\, e^{kx}$$

Example – Exponential Function

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

$$\begin{aligned} F'(2) &= -9.702\, e^{-0.462(2)} = -3.85 \text{ ng/ml/day} \\ F'(10) &= -9.702\, e^{-0.462(10)} = -0.0956 \text{ ng/ml/day} \end{aligned}$$

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

$$\begin{aligned} N'(t) &= 27.5(-0.077\,e^{-0.077t} + 0.462\,e^{-0.462t}) \\ &= 12.705\,e^{-0.462t} - 2.1175\,e^{-0.077t} \end{aligned}$$

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

$$\begin{aligned} N'(2) &= 12.705\,e^{-0.462(2)} - 2.1175\,e^{-0.077(2)} = 3.23 \text{ ng/ml/day} \\ N'(10) &= 12.705\,e^{-0.462(10)} - 2.1175\,e^{-0.077(10)} = -0.855 \text{ ng/ml/day} \end{aligned}$$

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

$$2.1175\, e^{-0.077t} = 12.705\, e^{-0.462t}$$

$$\begin{aligned} \frac{e^{-0.077t}}{e^{-0.462t}} &= \frac{12.705}{2.1175} \\ e^{0.385t} &= 6.0 \end{aligned}$$

The maximum occurs at

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

The maximum blood plasma concentration of norfluoxetine is

$$N(t_{max}) = 16.01 \text{ ng/ml}$$

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

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

$$\begin{aligned} \frac{e^{-0.077t}}{e^{-0.462t}} &= \frac{5.8697}{0.16305} \\ e^{0.385t} &= 36.0 \end{aligned}$$

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

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

with blood plasma concentration of norfluoxetine at

$$N(t_{poi}) = 12.91 \text{ ng/ml} \quad \text{and} \quad N'(t_{poi}) = -0.862 \text{ ng/ml/day}$$

Example – Polymer Drug Delivery System 1

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
  - Filteration 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 2

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 3

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

$$A_0 = \frac{C_0}{r}$$

Example – Polymer Drug Delivery System

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

Example – Polymer Drug Delivery System 5

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 6

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
- $$c'(5) = 2\, e^{-0.2(5)} - 0.1\, e^{-0.01(5)} = 0.64 \text{ mg/dl/day}$$
- $$c'(20) = 2\, e^{-0.2(20)} - 0.1\, e^{-0.01(20)} = -0.045 \text{ mg/dl/day}$$

Example – Polymer Drug Delivery System

Solution for Maximum for $c(t)$: Since the derivative is

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

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

Thus,

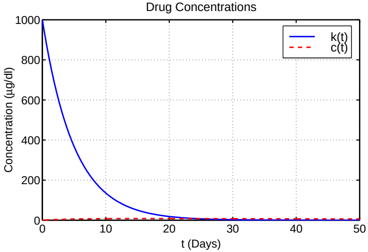
$$e^{-0.01t+0.2t} = e^{0.19t} = 20$$

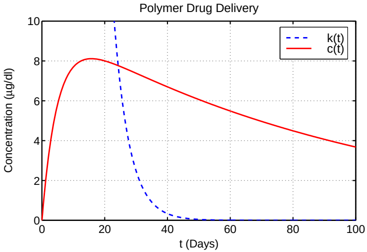
It follows that $t_{max} = \ln(20)/0.19 = 15.767$ days

The maximum occurs at $c(15.767) = 8.11\ \mu\text{g/dl}$

Example – Polymer Drug Delivery System

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 1

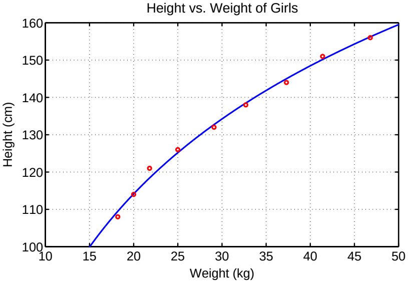
Height and Weight Relationship for Children:

age(years)	height(cm)	weight(kg)
5	108	18.2
6	114	20.0
7	121	21.8
8	126	25.0
9	132	29.1
10	138	32.7
11	144	37.3
12	151	41.4
13	156	46.8

Height and Weight Relationship for Children

Ehrenberg Model: Logarithmic relationship

$$H(w) = 49.5\,\ln(w) - 34.14$$



Want to find the find the **rate of change of height with respect to weight** for the average girl

Derivative of $\ln(x)$

Derivative of $\ln(x)$

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

$$\frac{d}{dx}\left(\ln(x)\right) = \frac{1}{x}$$

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

$$\frac{dH}{dw} = \frac{49.5}{w}\ \frac{\text{cm}}{\text{kg}}$$

- As the weight increases, the rate of change in height decreases
- At $w = 20$ kg

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

- At $w = 49.5$ kg

$$H'(49.5) = \frac{49.5}{49.5} = 1\ \text{cm/kg}$$

Example – Derivative of Logarithm

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 – Logarithm Function 1

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 2

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

Example – Logarithm Function

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)**

Example – Logarithm Function

Solution (cont): Graphing the Function

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