Calculus for the Life Sciences

Lecture Notes – Product Rule

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

Tumor Growth) 1

Cancer and Tumor Growth: Mathematical Role

- Image Processing
- Calculating therapeutic doses
- Epidemiology of cancer in a population
- Growth of tumors

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Tumor Growth 2

Tumor Growth

- Tumors grow based on the nutrient supply available
- **Tumor angiogenesis** is the proliferation of blood vessels that penetrate into the tumor to supply nutrients and oxygen and to remove waste products
- The center of the tumor largely consists of dead cells, called the **necrotic center** of the tumor
- The tumor grows outward in roughly a spherical shell shape

Gompertz Growth Model 1

Gompertz Growth Model

- Laird (1964) showed that tumor growth satisfies Gompertz growth equations:

$$G(N) = N(b - a\ln(N))$$

- N is the number of tumor cells
- a and b are constants matched to the data
- This function is not defined for $N = 0$
  - However, can be shown that

$$\lim_{N\to 0} G(N) = 0$$

Gompertz Growth Model 2

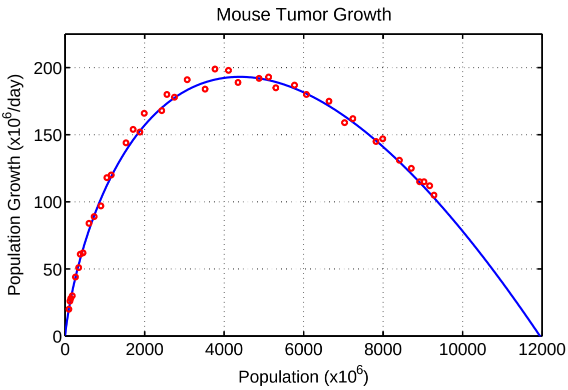
Tumor Growth: Simpson-Herren and Lloyd (1970) studied the growth of tumors

- They studied the C3H Mouse Mammary tumor
- Tritiated thymidine was used to measure the cell cycles
- This gave the growth rate for these tumors

Gompertz Growth Model

Mouse Tumor Growth and Gompertz Model: The best fit to the Gompertz Model is

$$G(N) = N(0.4126 - 0.0439 \ln(N))$$



Gompertz Growth Model

Tumor Growth and Gompertz Model:

- The growth of the tumor stops at equilibrium
- The tumor is at its maximum size supportable with the available nutrient supply
- We also want to know when the tumor is growing most rapidly
  - This occurs when the derivative is zero
  - Most cancer therapies attack growing cells
  - Treatment has its maximum effect when maximum growth is occurring

Equilibrium for Gompertz Model

Equilibrium for Gompertz Model: The equilibrium satisfies:

$$G(N) = N(b - a\ \ln(N)) = 0$$

Since $N > 0$, this occurs when $b - a\ \ln(N_e) = 0$ or

$$\begin{aligned} \ln(N_e) &= \frac{b}{a} \\ N_e &= e^{b/a} \end{aligned}$$

This is the unique equilibrium of the **Gompertz Model** or its **carrying capacity**

For the mouse tumor data above

$$N_e = e^{0.4126/0.0439} = e^{9.399} = 12,072,$$

which matches the P-intercept on the graph

Maximum Growth from Gompertz Model

Maximum Growth from Gompertz Model: The Gompertz Model is

$$G(N) = N(b - a\ln(N))$$

- The graph shows the maximum growth occurs near where the population of tumor cells is about 4,000 ($\times 10^6$)
- Our techniques of Calculus can find the maximum – set the derivative equal to zero
- Finding the derivative of $G(N)$ requires **product rule for differentiation**

Product Rule

Product Rule: Let $f(x)$ and $g(x)$ be differentiable functions. The product rule for finding the derivative of the product of these two functions is given by:

$$\frac{d}{dx}\left(f(x)g(x)\right) = f(x)\frac{dg(x)}{dx} + \frac{df(x)}{dx}g(x)$$

In words, this says that the **derivative of the product of two functions** is the **first function times the derivative of the second function plus the second function times the derivative of the first function**

Product Rule - Example

Product Rule Example: By the **Power rule** we know that if $f(x) = x^5$, then

$$f'(x) = 5x^4$$

Let $f_1(x) = x^2$ and $f_2(x) = x^3$, then $f(x) = f_1(x)f_2(x)$

From the **product rule**

$$\begin{aligned} f'(x) &= f_1(x)f_2'(x) + f_1'(x)f_2(x) \\ &= x^2(3x^2) + (2x)x^3 \; = \; 5x^4 \end{aligned}$$

Example – Product Rule

Example: Consider the function

$$g(x) = (x^2 + 4)\ln(x)$$

Find the derivative of $g(x)$

Skip Example

Solution: From the **product rule**

$$g'(x) = (x^2 + 4)\frac{1}{x} + (\ln(x))(2x)$$

$$g'(x) = x + \frac{4}{x} + 2x\ \ln(x)$$

Example – Graphing 1

Example: Consider the function

$$f(x) = (2 - x)e^{x}$$

Skip Example

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

Example – Graphing 2

Solution: For $f(x) = (2-x)e^x$

- Since $f(0) = 2$, the y-intercept is $(0, 2)$
- Since the exponential function is never zero, the x-intercept is $(2, 0)$
- It can be shown

$$\lim_{x \to -\infty} f(x) = 0$$

  - An exponential function dominates any polynomial function
  - $f(x)$ goes to 0, so there is a **horizontal asymptote** to the left at $y = 0$

Example – Graphing

Solution (cont): For $f(x) = (2-x)e^x$ by the product rule the derivative is

$$f'(x) = (2-x)e^x + (-1)e^x = (1-x)e^x$$

- The **critical point** satisfies

$$(1-x_c)e^{x_c} = 0$$

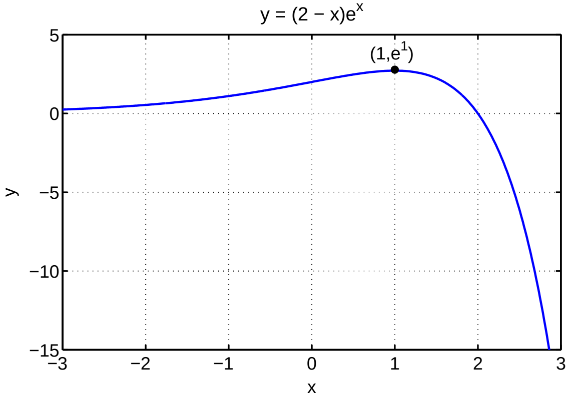
- The critical value is $x_c = 1$
- The function value at the critical point is

$$f(1) = e^1 \approx 2.718$$

- There is a **maximum** on the graph at $(1, e^1)$

Example – Graphing 4

Solution (cont): The graph of $f(x) = (2 - x)e^x$ is



Maximum Growth for the Gompertz Tumor Growth Model 1

Maximum Growth for the Gompertz Tumor Growth Model:
Apply the Product Rule to the Gompertz Growth function

$$G(N) = N(b - a\ \ln(N))$$

The **derivative** is

$$\begin{aligned}\frac{dG}{dN} &= N\left(-\frac{a}{N}\right) + (b - a\ \ln(N)) \\ \frac{dG}{dN} &= (b - a) - a\ \ln(N)\end{aligned}$$

Maximum Growth for the Gompertz Tumor Growth Model 2

Maximum Growth for the Gompertz Tumor Growth Model:

The maximum occurs when $G'(N) = 0$ or

$$a\ \ln(N_{max}) = b - a \quad \text{and} \quad N_{max} = e^{(b/a-1)}$$

Applied to the Gompertz model for the mouse mammary tumor, then the maximum occurs at the population

$$N_{max} = e^{(9.399-1)} = 4,441(\times 10^6)$$

Substituted into the Gompertz growth function, the maximum growth of mouse mammary tumor cells is

$$G(N_{max}) = 4441(0.4126 - 0.0439\ \ln(4441)) = 195.0(\times 10^6/\text{day})$$

Damped Oscillators 1

Damped Oscillators

- Classical physical examples
  - Spring-mass system, electronic circuit, simple pendulum
- Many biological phenomena behave like damped oscillators
  - Muscle fibers, hair cells in the ear, flagella, bone structures, etc.
- General model for a damped oscillator:

$$h(t) = A\, e^{-at} \sin(bt)$$

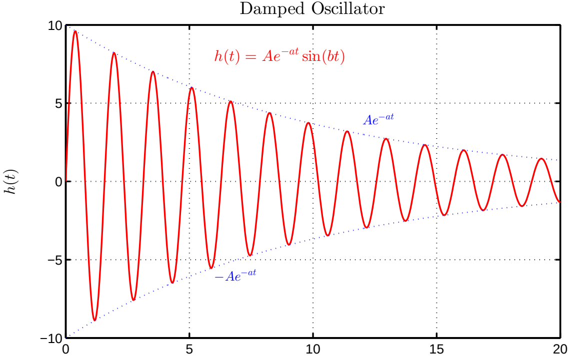
- Use Calculus techniques to study this example

Damped Oscillators

Damped Oscillator Model

$$h(t) = A\,e^{-at}\sin(bt)$$

From the properties of the sine function, the damped oscillator passes through zero whenever $t = \frac{n\pi}{b}, \quad n = 0, 1, ...$



Damped Oscillators

Damped Oscillator Model

$$h(t) = A\,e^{-at}\sin(bt)$$

To find the **Relative Maxima** and **Minima**, differentiate $h(t)$

$$\begin{aligned} h'(t) &= A\left(e^{-at}(b\cos(bt)) + (-ae^{-at})\sin(bt)\right) \\ &= A\,e^{-at}(b\cos(bt) - a\sin(bt)) \end{aligned}$$

The **Relative Extrema** satisfy

$$\begin{aligned} h'(t) &= 0 \\ b\cos(bt) &= a\sin(bt) \\ \tan(bt) &= \frac{b}{a} \end{aligned}$$

$h(t) = A\,e^{-at}\sin(bt)$ 4

There are **Relative Extrema** whenever

$$\tan(bt) = \frac{b}{a} \quad \text{or} \quad t = \frac{1}{b}\arctan\left(\frac{b}{a}\right)$$

- This has infinitely many solutions
- For solutions with $t \geq 0$
  - The function begins with $h(0) = 0$ and initially increases
  - The function first goes to an **Absolute Maximum** at the first **Critical Point**
  - The function next passes through a **zero**
  - The function next goes to an **Absolute Minimum** at the second **Critical Point**
  - All **Relative Extrema** are separated by $\frac{\pi}{b}$

Glucose Tolerance Test 1

Diabetes (diabetes mellitus) is a disease characterized by excessive glucose in the blood

- There are **3 forms**
  - **Type 1** or **juvenile diabetes** is an autoimmune disorder, where the β-cells in the pancreas are destroyed, so insulin cannot be produced
  - **Type 2** or **adult onset diabetes** is where cells become insulin resistant, often caused by excessive weight and poor exercise
  - **Gestational diabetes** happens in some pregnant women
- This study concentrates on **Type 1** diabetes
- Affects 4-20 per 100,000 with peak occurrence around 14 years of age
- Causes serious health conditions, especially heart disease and nerve damage

Glucose Tolerance Test

Glucose Tolerance Test (GTT) and Ackerman Model

- **GTT**
  - Patient fasts for 12 hours
  - Patient drinks 1.75 mg of glucose/kg of body weight
  - Glucose levels in blood is monitored for 4-6 hours
- **Ackerman Model**
  - Compartmental model for glucose and insulin in the body
  - Model tracks glucose in the blood
  - Model given by equation

$$G(t) = G_0 + Ae^{-\alpha t}\cos(\omega(t-\delta))$$

  - **5 parameters** fit to GTT blood data
  - Use parameters α and ω to detect diabetes

Glucose Tolerance Test

Data for a **Normal Subject A** and **Diabetic Subject B**

t (hr)	**A**	**B**	t (hr)	**A**	**B**
0	70	100	2	75	175
0.5	150	185	2.5	65	105
0.75	165	210	3	75	100
1	145	220	4	80	85
1.5	90	195	6	75	90

Model for **Normal Patient** with best parameters

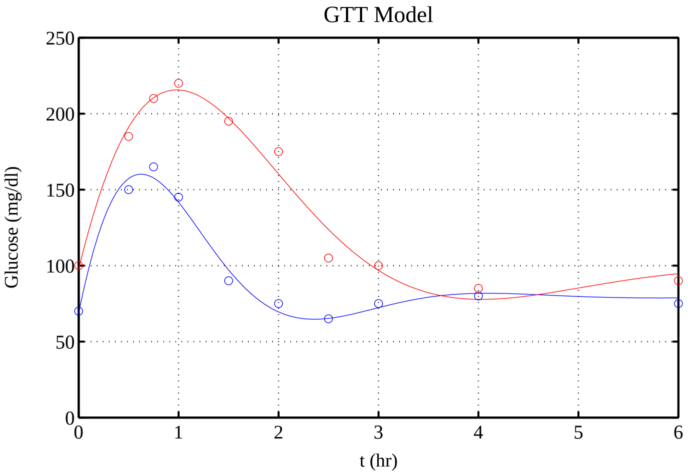
$$G_1(t) = 79.2 + 171.5e^{-0.99t}\cos(1.81(t - 0.901))$$

Model for **Diabetic Patient** with best parameters

$$G_2(t) = 95.2 + 263.2e^{-0.63t}\cos(1.03(t - 1.52))$$

Glucose Tolerance Test

Graph of data and models



Glucose Tolerance Test

Model for **Normal Patient** with best parameters is

$$G_1(t) = 79.2 + 171.5e^{-0.99t}\cos(1.81(t - 0.901))$$

The graph shows a **maximum** and **minimum**, which we find here

First note that the period of the cosine function is $T_1 = \frac{2\pi}{1.81} = 3.471$

The product rule gives

$$\begin{aligned} G_1'(t) &= 171.5\left(-1.81e^{-0.99t}\sin(1.81(t-0.901)) - 0.99e^{-0.99t}\cos(1.81(t-0.901))\right) \\ &= -171.5e^{-0.99t}\left(1.81\sin(1.81(t-0.901)) + 0.99\cos(1.81(t-0.901))\right) \end{aligned}$$

The **maximum** and **minimum** satisfy $G_1'(t) = 0$, which is equivalent to

$$1.81\sin(1.81(t - 0.901)) + 0.99\cos(1.81(t - 0.901)) = 0$$

Glucose Tolerance Test

Since

$$1.81\sin(1.81(t-0.901)) + 0.99\cos(1.81(t-0.901)) = 0,$$

the **maximum** and **minimum** satisfy

$$\tan(1.81(t-0.901)) = -\frac{0.99}{1.81} = -0.547$$

Inverting this expression gives

$$\begin{aligned} 1.81(t-0.901) &= \arctan(-0.547) = -0.501, \\ t_{max} &= 0.901 - \frac{0.501}{1.81} = 0.624 \end{aligned}$$

It follows that the maximum occurs at $t_{max} = 0.624$ hr, with $G_1(t_{max}) = 160.3$ ng/dl

Glucose Tolerance Test

Since the maximum occurs at $t_{max} = 0.624$ hr, the **minimum** occurs half a period ($T_1 = 3.471$ hr) later, so

$$t_{min} = 0.624 + 1.736 = 2.360 \text{ hr},$$

with $G_1(t_{min}) = 64.7$ ng/dl

Note: This shows that a **normal person** gets a **sugar low** about 2-3 hours after ingesting a large amount of sugar

Model for **Diabetic Patient** with best parameters is

$$G_2(t) = 95.2 + 263.2e^{-0.63t}\cos(1.03(t-1.52)),$$

which has a derivative (**product rule**)

$$\begin{aligned} G_2'(t) &= 263.2\left(-1.03e^{-0.63t}\sin(1.03(t-1.52)) - 0.63e^{-0.63t}\cos(1.03(t-1.52))\right) \\ &= -263.2e^{-0.63t}\left(1.03\sin(1.03(t-1.52)) + 0.63\cos(1.03(t-1.52))\right) \end{aligned}$$

Glucose Tolerance Test

The **maximum** and **minimum** satisfy

$$1.03\sin(1.03(t-1.52)) + 0.63\cos(1.03(t-1.52)) = 0,$$

or

$$\tan(1.03(t-1.52)) = -\frac{0.63}{1.03} = -0.612$$

Inverting the tangent gives

$$1.03(t-1.52) = \arctan(-0.612) = -0.549, \quad \text{or} \quad t_{max} = 0.987$$

It follows that the maximum occurs at $t_{max} = 0.987$ hr, with $G_2(t_{max}) = 215.8$ ng/dl

Glucose Tolerance Test

The cosine function of the model has a period $T_2 = \frac{2\pi}{1.03} = 6.100$ hr

The **minimum** occurs half a period ($\frac{T_2}{2} = 3.050$ hr) later, so

$$t_{min} = 0.987 + 3.050 = 4.037 \text{ hr},$$

with $G_2(t_{min}) = 77.6$ ng/dl

The **Ackerman Test** examines the **natural frequency**, ω_0, and period, T_0, of the models, where

$$\omega_0^2 = \alpha^2 + \omega^2 \qquad \text{and} \qquad T_0 = \frac{2\pi}{\omega_0}$$

Our models give the **normal subject**

$$\omega_0 = 2.067 \qquad \text{and} \qquad T_0 = 3.04 \text{ hr}$$

and the **diabetic subject**

$$\omega_0 = 1.210 \qquad \text{and} \qquad T_0 = 5.19 \text{ hr}$$

Note: $T_0 > 4$ suggests diabetes

Ricker Function

Example – Ricker Function: Consider the Ricker function

$$R(x) = 5x\,e^{-0.1x}$$

The function is used in modeling populations.

- Find intercepts
- Find all extrema
- Find points of inflection
- Sketch the graph

Ricker Function 2

Solution: For the Ricker function

$$R(x) = 5x\, e^{-0.1x}$$

The only intercept is the origin, **(0, 0)**

By the **product rule**, the derivative is

$$\frac{dR}{dx} = 5x(-0.1\, e^{-0.1x}) + 5\, e^{-0.1x} = 5\, e^{-0.1x}(1 - 0.1\, x)$$

Since the exponential is never zero, the only **critical point** satisfies

$$1 - 0.1\, x = 0 \quad \text{or} \quad x = 10$$

There is a maximum at

$$(10, 50\, e^{-1}) \quad \text{or} \quad (10, 18.4)$$

Ricker Function 3

Solution (cont): The derivative of the Ricker function is

$$\frac{dR}{dx} = 5\,e^{-0.1x}(1 - 0.1\,x)$$

The second derivative of the Ricker function is

$$\frac{d^2R}{dx^2} = 5\,e^{-0.1x}(-0.1) + 5(-0.1)e^{-0.1x}(1 - 0.1x) = 0.5\,e^{-0.1x}(0.1\,x - 2)$$

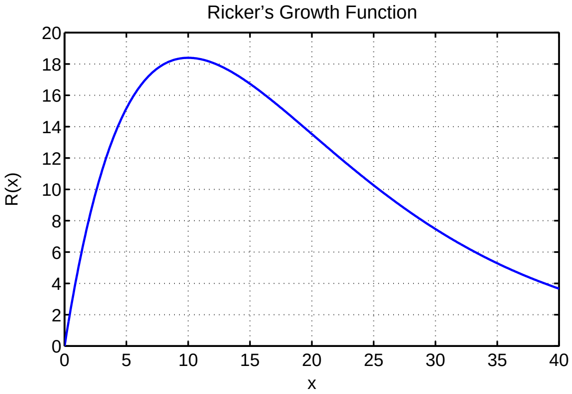
- The point of inflection is found by solving $R''(x) = 0$
- The point of inflection occurs at $x = 20$

$$(20, 100\,e^{-2}) \quad \text{or} \quad (20, 13.5)$$

Ricker Function

Solution (cont): Graph of the Ricker function

$$R(x) = 5x\, e^{0.1x}$$



Example – Graphing 1

Example: Consider the function

$$f(x) = x \ln(x)$$

Skip Example

- Determine the domain of the function
- Find any intercepts
- Find critical points and extrema
- Sketch the graph of $f(x)$ for $0 < x \leq 2$

Example – Graphing 2

Solution: For $f(x) = x\ \ln(x)$

- The domain of the function is $x > 0$
- There is no y-intercept
- It can be shown
$$\lim_{x \to 0^+} f(x) = 0$$
- The x-intercept is found by solving $f(x) = 0$, which gives $x = 1$

Example – Graphing 3

Solution (cont): For $f(x) = x\ln(x)$ by the product rule the derivative is

$$f'(x) = x\left(\frac{1}{x}\right) + \ln(x) = 1 + \ln(x)$$

- The **critical point** satisfies

$$1 + \ln(x_c) = 0$$

- Thus, the critical value of x_c satisfies

$$\ln(x_c) = -1 \quad \text{or} \quad x_c = e^{-1} \approx 0.3679$$

- The function value at the critical point is

$$f(e^{-1}) = -e^{-1} \approx -0.3679$$

- There is a **minimum** on the graph at $(e^{-1}, -e^{-1})$

Example – Graphing

Solution (cont): The graph of $f(x) = x\ \ln(x)$ is