Cancer and Tumor Growth: Mathematical Role

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

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

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
  \[ \lim_{N \to 0} G(N) = 0 \]

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

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

\[ G(N) = N(0.4126 - 0.0439 \ln(N)) \]

- 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

\[ \ln(N_e) = \frac{b}{a} \]

\[ N_e = e^{\frac{b}{a}} \]

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.

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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**

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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:

\[
\frac{d}{dx} (f(x)g(x)) = f(x) \frac{dg(x)}{dx} + \frac{df(x)}{dx} g(x)
\]

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.
**Example** – Product Rule

**Example:** Consider the function

\[ g(x) = (x^2 + 4) \ln(x) \]

Find the derivative of \( g(x) \)

**Solution:** From the product rule

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

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

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**Example – Graphing**

**Example:** Consider the function

\[ f(x) = (2 - x)e^x \]

**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
  \[ (1 - x)e^x = 0 \]

- 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 \((1, e^1)\)
Maximum Growth for the Gompertz Tumor Growth Model:

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

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

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

$$N_{\text{max}} = e^{(9.399-1)} = 4.441 \times 10^6$$

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

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

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 Oscillator Model

\[ h(t) = A e^{-at} \sin(bt) \]

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

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 \( \frac{\pi}{b} \)

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 \( \beta \)-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 (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

\[ G(t) = G_0 + A e^{-\alpha t} \cos(\omega (t - \delta)) \]

- **5 parameters** fit to GTT blood data
  - Use parameters \( \alpha \) and \( \omega \) to detect diabetes

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

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<th>t (hr)</th>
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<th>B</th>
<th>t (hr)</th>
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</table>

Model for **Normal Patient** with best parameters

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

Model for **Diabetic Patient** with best parameters

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

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

\[ G_1'(t) = 171.5 \left(-1.81 e^{-0.99t} \sin(1.81(t - 0.901)) - 0.99 e^{-0.99t} \cos(1.81(t - 0.901))\right) \]
\[ = -171.5 e^{-0.99t}(1.81 \sin(1.81(t - 0.901)) + 0.99 \cos(1.81(t - 0.901))) \]

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 \textbf{maximum} and \textbf{minimum} satisfy
\[ \tan(1.81(t - 0.901)) = -\frac{0.99}{1.81} = -0.547 \]
Inverting this expression gives
\[ 1.81(t - 0.901) = \arctan(-0.547) = -0.501, \]
\[ t_{\text{max}} = 0.901 - \frac{0.501}{1.81} = 0.624 \]

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

The \textbf{maximum} and \textbf{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
\[ 1.03(t - 1.52) = \arctan(-0.612) = -0.549, \text{ or } t_{\text{max}} = 0.987 \]

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

Since the maximum occurs at \( t_{\text{max}} = 0.624 \text{ hr} \), the \textbf{minimum} occurs half a period \( (T_1 = 3.471 \text{ hr}) \) later, so
\[ t_{\text{min}} = 0.624 + 1.736 = 2.360 \text{ hr}, \]
with \( G_1(t_{\text{min}}) = 64.7 \text{ ng/dl} \)

\textbf{Note:} This shows that a \textbf{normal person} gets a \textbf{sugar low} about 2-3 hours after ingesting a large amount of sugar.

Model for \textbf{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 (\textbf{product rule})
\[
G_2'(t) = 263.2 \left( -1.03e^{-0.63t} \sin(1.03(t - 1.52)) - 0.63e^{-0.63t} \cos(1.03(t - 1.52)) \right) \\
= -263.2e^{-0.63t} \left( 0.63 \sin(1.03(t - 1.52)) + 0.63 \cos(1.03(t - 1.52)) \right)
\]

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

The \textbf{minimum} occurs half a period \( (\frac{T_2}{2} = 3.050 \text{ hr}) \) later, so
\[ t_{\text{min}} = 0.987 + 3.050 = 4.037 \text{ hr}, \]
with \( G_2(t_{\text{min}}) = 77.6 \text{ ng/dl} \)

The \textbf{Ackerman Test} examines the \textbf{natural frequency}, \( \omega_0 \), and period, \( T_0 \), of the models, where
\[ \omega_0^2 = \alpha^2 + \omega^2 \quad \text{and} \quad T_0 = \frac{2\pi}{\omega_0} \]

Our models give the \textbf{normal subject}
\[ \omega_0 = 2.067 \quad \text{and} \quad T_0 = 3.04 \text{ hr} \]
and the \textbf{diabetic subject}
\[ \omega_0 = 1.210 \quad \text{and} \quad T_0 = 5.19 \text{ hr} \]

\textbf{Note:} \( T_0 > 4 \) suggests diabetes
Example – Ricker Function: Consider the Ricker function

\[ R(x) = 5xe^{-0.1x} \]

The function is used in modeling populations.

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

Solution: For the Ricker function

\[ R(x) = 5xe^{-0.1x} \]

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

By the product rule, the derivative is

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

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

\[ 1 - 0.1x = 0 \quad \text{or} \quad x = 10 \]

There is a maximum at

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

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

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

The second derivative of the Ricker function is

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

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

\[ (20, 100e^{-2}) \quad \text{or} \quad (20, 13.5) \]
Example: Consider the function
\[ f(x) = x \ln(x) \]

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

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
  \[ x = 1 \]

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 \((e^{-1}, -e^{-1})\)