Math, magnets, and mice!
(but actually rats)

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What is biomedical engineering?

- Biomechanics: Heart valves, knee replacements, prosthetics
- Biomaterials: Drugs, coatings/materials for implants, anything that goes in or on the body
- Instrumentation: basically everything else….  
  - Imaging, pacemakers, ECG machines, anything with computers, neuro-stimulators, cochlear implants
How did I get to the field of computational oncology?
Medical Imaging

X-ray
1895

Ultrasound
1950-60s

CT (Computed Tomography)
The math ~1917
The method 1963

Magnetic Resonance Imaging
1973
Magnetic Resonance Imaging

Large magnet

1 T (Tesla) = 10,000 Gauss

Fridge magnet ~ 100 Gauss. The Earth ~ .5 Gauss

3T Human (Clinical) Scanner

7T Small Animal (Pre-clinical) Scanner
Role of medical imaging in cancer

**Screening:** Mammogram in breast cancer, dental x-rays (for cavities)

**Diagnosis:** Contrast-enhanced brain scan

**Treatment planning:** Biopsy placement, surgery, radiation therapy

Predict how a patient will respond to therapy, change therapy if standard of care is not good enough.

**Assessing Response:** Is the tumor shrinking?

Predict if a patient will respond before end of therapy.
Measuring/quantifying tumors

What are some ways we can describe the tumor in this image?
What if we want to make a prediction?

Let’s assume it grows at a constant rate per day!

Volume Day 10 = 54.4 mm$^3$
Volume Day 12 = 68.5 mm$^3$

Difference: 14.1 mm$^3$
(7.05 mm$^3$/day)

Predicted at Day 14 = 82.6 mm$^3$
Measured at Day 14 = 114.4 mm$^3$

$$\text{Percent error} = 100\% \left( \frac{\text{Model} - \text{Measured}}{\text{Measured}} \right)$$

Percent error = 27.8 % error
Okay how can we characterize this growth?

What is a model?

\[ \text{Volume}(t_2) = \text{Volume}(t_1) + X(t_2 - t_1) \]

What is the change in volume over time?

\[ \text{Volume}(t_2) - \text{Volume}(t_1) = X(t_2 - t_1) \]

Change in volume

\[ \frac{\Delta V}{\Delta t} = \frac{\text{Volume}(t_2) - \text{Volume}(t_1)}{(t_2 - t_1)} = X \]

Growth Rate

(Volume Increase per day)

Model Predicted Measure

Volume Day 10 = 54.4 mm$^3$
Volume Day 12 = 68.5 mm$^3$
Difference: 14.1 mm$^3$

\[ X = (7.05 \text{ mm}^3/\text{day}) \]
Let’s update our model with the new measurement

**Generic equation to find volume at any time point**

\[
Volume(t_i) = Volume(t_1) + (t - t_1) \cdot X
\]

What X works best to describe volume at both \( t_2 \) and \( t_3 \)?

<table>
<thead>
<tr>
<th></th>
<th>( X = 7.05 )</th>
<th>( X = 14 )</th>
<th>( X = 21 )</th>
<th>( X = 13 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Error at ( t_1 )</td>
<td>0</td>
<td>-13.88</td>
<td>-27.87</td>
<td>-11.87</td>
</tr>
<tr>
<td>Error at ( t_2 )</td>
<td>31.86</td>
<td>4.06</td>
<td>-23.94</td>
<td>8.06</td>
</tr>
<tr>
<td>Total Squared Error</td>
<td>1015</td>
<td>209.02</td>
<td>1350</td>
<td>206</td>
</tr>
</tbody>
</table>

19% error
Okay how can we characterize this growth?

Constant growth didn’t work well…what else can we try?

\[
Volume(t_i) = Volume(t_1) + Volume(t_{i-1}) \cdot X \cdot (t_i - t_1)
\]

Future Volume \quad Initial Volume \quad Previous Volume

If \( X = \frac{1}{2} \) the tumor would double in volume in two days

\[
Volume(t_2) = Volume(t_1) + Volume(t_1) \cdot \left( \frac{1}{2} \right) \cdot (2)
\]

\[
Volume(t_2) = 2 \cdot Volume(t_1)
\]

What is the change in volume over time?

\[
\frac{\Delta V}{\Delta t} = \frac{Volume(t_i) - Volume(t_1)}{(t_i - t_1)} = Volume(t_{i-1}) \cdot X
\]

Change in volume \quad \Delta V

change in time \quad \Delta t
Let’s update our model with the new measurement

Generic equation to find volume at any time point

\[ Volume(t_i) = Volume(t_{i-1}) + Volume(t_{i-1}) \cdot X \cdot (t_i - t_{i-1}) \]

What \( X \) works best to describe volume at both \( t_2 \) and \( t_3 \)?

<table>
<thead>
<tr>
<th>( X )</th>
<th>( X = 1 )</th>
<th>( X = .5 )</th>
<th>( X = .25 )</th>
<th>( X = .125 )</th>
<th>( X = .18 )</th>
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<tr>
<td>Error at ( t_1 )</td>
<td>-333</td>
<td>-79.3</td>
<td>-21.15</td>
<td>-1.32</td>
<td>-9.266</td>
</tr>
<tr>
<td>Error at ( t_2 )</td>
<td>-2854.5</td>
<td>-287.35</td>
<td>-33.37</td>
<td>24.8</td>
<td>3.218</td>
</tr>
<tr>
<td>Total Squared Error</td>
<td>8,259,300</td>
<td>88,858</td>
<td>1561</td>
<td>616.2</td>
<td>96.214</td>
</tr>
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</table>

11% error
Let’s update our model with the new measurement.
Which model works the best?

What can you tell us about how the model fits the curve?

\[
\frac{\Delta V}{\Delta t} = \frac{Volume(t_2) - Volume(t_1)}{(t_2 - t_1)} = Volume(t_1) \cdot X \cdot \left(1 - \frac{Volume(t_1)}{Volume_{max}}\right)
\]

Growth rate changes with volume
Which model works the best?

Short Term predictions

Long Term predictions
What does this plot remind you of?

What can we use this prediction for?
Volume is one thing….

What else can we model?
Modeling Immune system response

Modeling tumor genetic instability

Modeling tumor metabolism

Modeling Angiogenesis

Anderson et al

Perez-Garcia et al

Enderling et al

Cai et al
What can we measure non-invasively? How do these measures change with cancer?

• Tumor size and shape

• Tumor cellularity

• Blood vessels, blood flow

• Oxygenation, or hypoxia

• Glucose usage
Let’s add cellularity to the model!

Diffusion-Weighted MRI
• An imaging measurement sensitive to how freely water moves in tissue
• How is that related to cells?
Let’s add cellularity to the model!

**Diffusion-Weighted MRI**

\[ S(b) = S_0 \exp(-b \cdot ADC) \]

\[ ADC = 0.72 \, \mu m^2/ms \]
Modeling changes in cellularity over time

Change in volume

\[
\frac{\Delta V}{\Delta t} = \frac{Volume(t_2) - Volume(t_1)}{t_2 - t_1} = Volume(t_1) \cdot X \cdot \left( 1 - \frac{Volume(t_1)}{Volume_{\text{max}}} \right)
\]

Growth rate changes with volume

Replace Volume with \(N_T\)
\(N_T\) = the number of tumor cells

Change in cell number

\[
\frac{\Delta N_T}{\Delta t} = \frac{N_T(t_2) - N_T(t_1)}{t_2 - t_1} = N_T(t_1) \cdot X \cdot \left( 1 - \frac{N_T(t_1)}{N_T_{\text{max}}} \right)
\]

Growth rate changes with cell number

Add the location of each imaging point \((x,y)\)

\[
\frac{\Delta N_T(x,y)}{\Delta t} = \frac{N_T(x,y,t_2) - N_T(x,y,t_1)}{t_2 - t_1} = N_T(x,y,t_1) \cdot X \cdot \left( 1 - \frac{N_T(x,y,t_1)}{N_T_{\text{max}}} \right)
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Growth rate changes with cell number
Modeling changes in cellularity over time

\[
\frac{\Delta N_T(x,y)}{\Delta t} = \frac{N_T(x,y,t_2) - N_T(x,y,t_1)}{(t_2 - t_1)} = N_T(x,y,t_1) \cdot X \cdot \left(1 - \frac{N_T(x,y,t_1)}{N_T^{\text{max}}}ight)
\]

Change in cell number

\[
\frac{\Delta N_T(x,y)}{\Delta t}
\]

Change in time

\[
\Delta t
\]

Growth rate changes with cell number

\[
Growth\ rate\ changes\ with\ cell\ number
\]

BUT! Cells don’t stay put over time

\[
\frac{\Delta N_T(x,y)}{\Delta t} = N_T(x,y,t_2) - N_T(x,y,t_1) = (\text{Entering} - \text{Leaving} + \text{Staying}) + N_T(x,y,t_1) \cdot X \cdot \left(1 - \frac{N_T(x,y,t_1)}{N_T^{\text{max}}}ight)
\]

Amount of cells moving around

\[
\text{Growth rate changes with cell number}
\]

We model cell movement using a diffusion term

\[
\frac{\Delta N_T(x,y)}{\Delta t} = D \left( \nabla^2 N_T(x,y,t) \right) + N_T(x,y,t_1) \cdot k \cdot \left(1 - \frac{N_T(x,y,t_1)}{N_T^{\text{max}}}ight)
\]

Change in cell number

\[
\frac{\Delta N_T(x,y)}{\Delta t}
\]

Change in time

\[
\Delta t
\]

Amount of cells moving around

\[
\nabla^2
\]

Diffusion

\[
Growth\ rate\ changes\ with\ cell\ number
\]

Proliferation

\[
Proliferation
\]
How do we individualize this?

Generic equation to find volume at any time point

\[
\text{Volume}(t_i) = \frac{\text{Volume}(t_i) + \text{Volume}(t_{i-1}) \cdot X \cdot (t_i - t_{i-1})}{\text{Future Volume} + \text{Initial Volume} + \text{Previous Volume}}
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What \( X \) works best to describe volume at both \( t_2 \) and \( t_3 \)?

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\[
\frac{\Delta N_T(x, y)}{\Delta t} = D \left( \nabla^2 N_T(x, y, t) \right) + N_T(x, y, t_1) \cdot k \left( 1 - \frac{N_T(x, y, t_1)}{N_T{}^{max}} \right)
\]

Change in cell number

Amount of cells moving around

Growth rate changes with cell number

Instead of finding \( X \), we are now going to find \( K, D, \) and \( N_T{}^{max} \).
The model doesn’t have any death terms…what can we add?
Let's add vasculature

Change in cell number
\[ \frac{\Delta N_T(x,y)}{\Delta t} = N_T(x,y,t_2) - N_T(x,y,t_1) \]
\[ \frac{\Delta t}{(t_2 - t_1)} = \left( \text{Entering} - \text{Leaving} + \text{Staying} \right) + N_T(x,y,t_1) \cdot X \cdot \left( 1 - \frac{N_T(x,y,t_1)}{N_T^{\text{max}}} \right) \]

Amount of cells moving around

Growth rate changes with cell number

How can we change this model to add vasculature?
What do blood vessels do?

We could connect it to the proliferation rate!

\[ X(x,y,t) = \begin{cases} \frac{X > 0}{\text{growing}}, \text{High } N_V \\ \frac{X \leq 0}{\text{Dieing}}, \text{Low } N_V \end{cases} \]
Measuring tumor vasculature

Dynamic Contrast Enhanced MRI (DCE-MRI)
\[
\frac{\Delta C_{\text{Tissue}}}{\Delta t} = K_{\text{Trans}} C_{\text{Blood}} - \frac{K_{\text{Trans}}}{v_e} C_{\text{Tissue}}
\]

- Amount entering the tissue
- Amount leaving the tissue
Modeling vasculature changes

Change in cell number

\[
\frac{\Delta N_T(x,y)}{\Delta t} = \frac{N_T(x,y,t_2) - N_T(x,y,t_1)}{(t_2 - t_1)} = (\text{Entering} - \text{Leaving} + \text{Staying}) + N_T(x,y,t_1) \cdot X(x,y,t) \cdot \left(1 - \frac{N_T(x,y,t_1)}{N_{T,\text{max}}} \right)
\]

Amount of cells moving around

Growth rate changes with cell number

We can use a very similar model to describe how the vasculature grows, dies, and moves over time.

Change in blood vessels

\[
\frac{\Delta N_V(x,y)}{\Delta t} = \frac{N_V(x,y,t_2) - N_V(x,y,t_1)}{(t_2 - t_1)} = (\text{Entering} - \text{Leaving} + \text{Staying}) + N_V(x,y,t_1) \cdot X_V(x,y,t) \cdot \left(1 - \frac{N_V(x,y,t_1)}{N_{V,\text{max}}} \right)
\]

Amount of cells moving around

Vasculature Growth or Death Rate

We now have 2 equations we need to at each time point.
Modeling vasculature changes

Measured tumor cells

Predicted tumor cells
Modeling vasculature changes
What else can we add?

What is missing in this model that nearly every patient gets?

Treatment!

- Chemotherapy
- Radiation Therapy
- Surgery
- Immunotherapy
What are we trying to use this data for?

When and what type of drugs should the patient receive?

When and how much radiation should the patient receive?

Will this person respond to the treatment?

Tumors are unique, they grow uniquely, the respond uniquely.
Crowd-sourcing cancer therapy innovations!
Want to learn more about computational oncology?

Mission

The past decade has witnessed a dramatic increase in our knowledge of cancer on multiple scales leading to a host of potential drug targets and subsequent clinical trials. Yet the outcome for many cancers has not improved. A fundamental reason for this sobering reality is that we do not have a validated theoretical framework to understand tumor initiation and development or how the individual patient may respond to particular therapeutic regimens; that is, there is no accepted mathematical description that enables us to generate testable, patient-specific hypotheses.

Currently, providing optimal therapies for a specific tumor phenotype, particularly with combinations of therapies, is extraordinarily difficult, as the number of potentially important adjustable parameters, such as the order and dosages of therapy, is too large to span in clinical trials and patient response is heterogeneous. Clinical trials too frequently lead to inconclusive and confusing results such that approximately half are never even published.

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