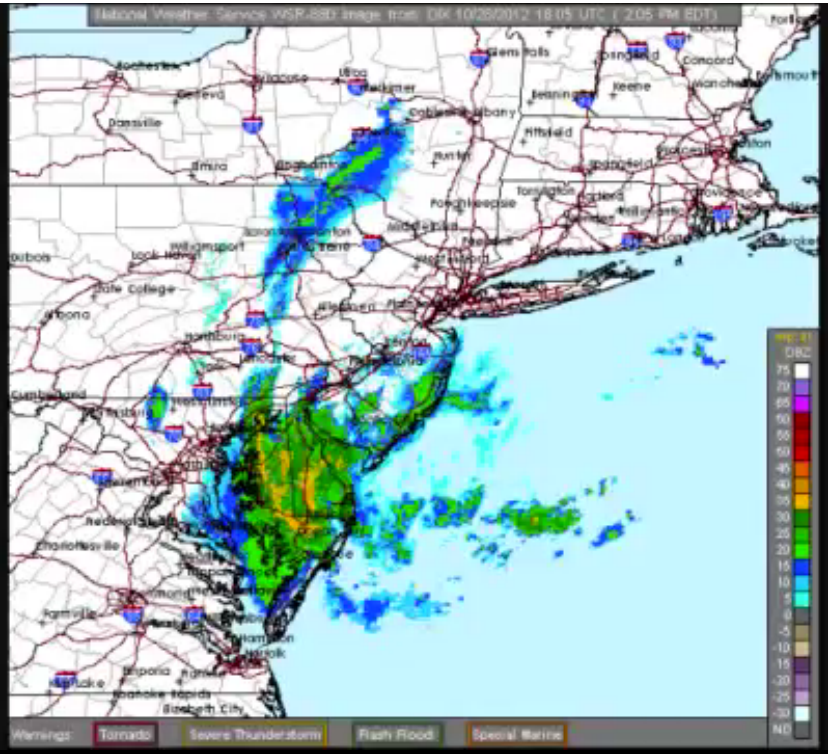


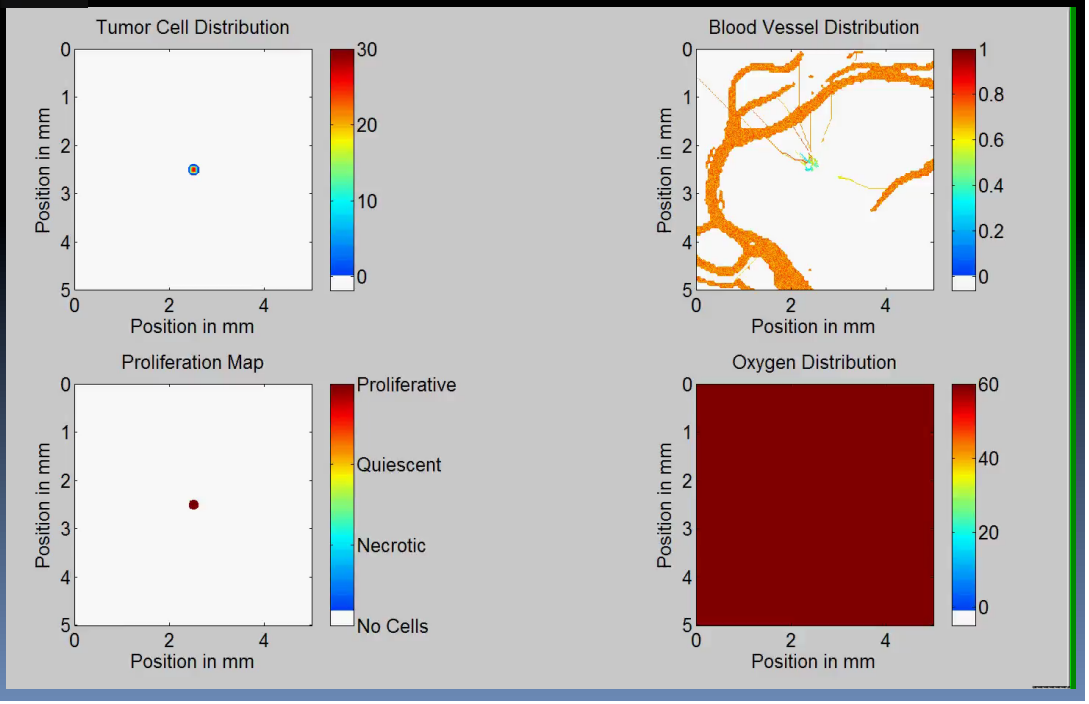
Building Tumor Forecasts from Noninvasive Imaging and Biophysical Models

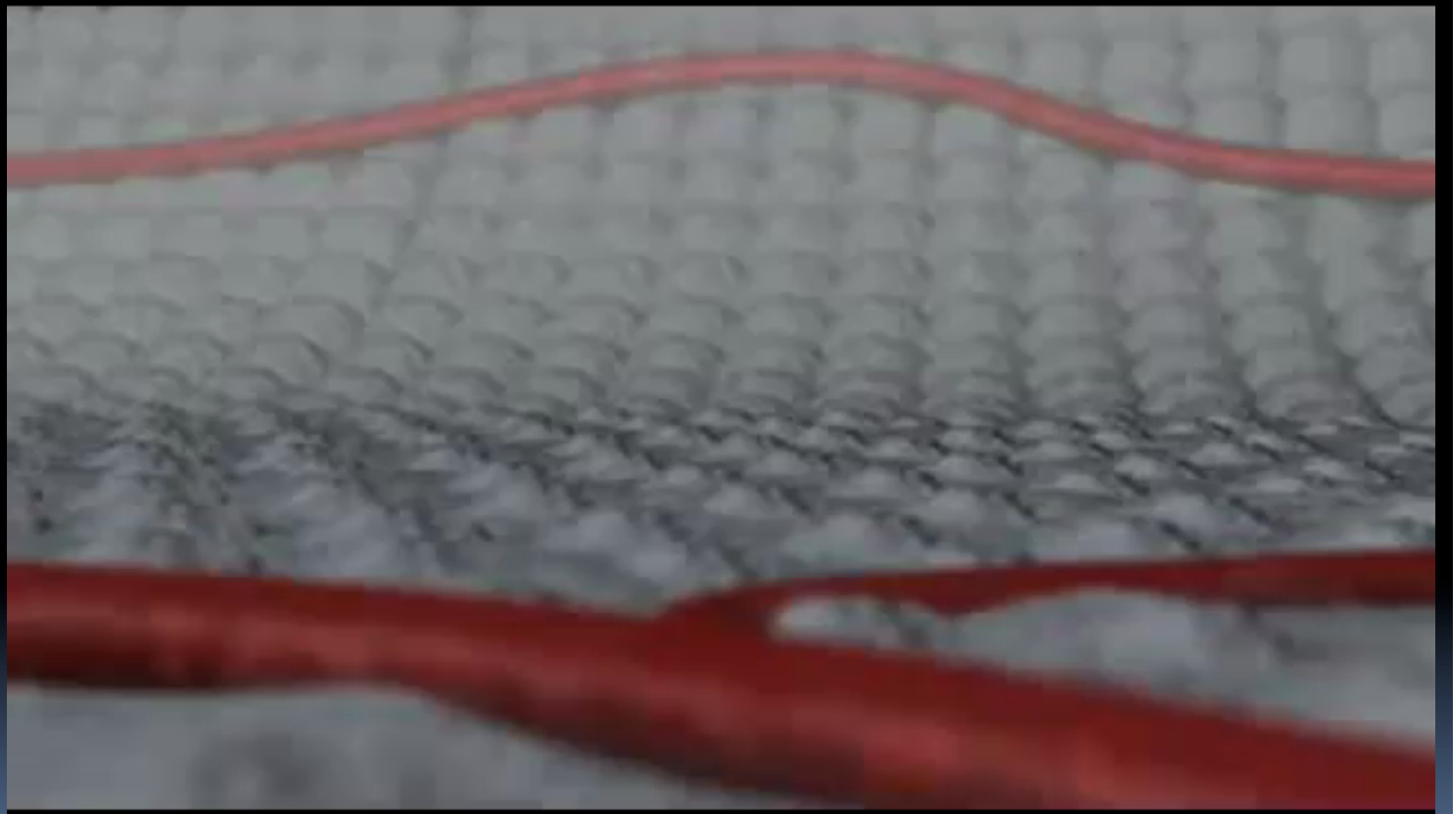
Tom Yankeelov

Departments of Radiology, Physics, Biomedical Engineering, Cancer Biology

Vanderbilt University

21 February 2013





www.youtube.com/watch?v=YYUoDdlBOQI

Motivation

[ECM] $$\frac{\partial c_f}{\partial t} = -\delta c_m c_f$$

[MDE] $$\frac{\partial c_m}{\partial t} = D_m \nabla^2 c_m + \mu_T T_{ij} + \mu_\varepsilon E_{ij} - \lambda c_m$$

[O_2] $$\frac{\partial c_o}{\partial t} = D_o \nabla^2 c_o + \beta c_f + \omega E_{ij} - \gamma_T T_{ij}$$

[EC] $$\frac{\partial e}{\partial t} = D_e \nabla^2 e - \nabla \bullet \left(\frac{\phi_c}{1 + \sigma c_v} e \nabla c_v + \phi h \nabla c_f \right)$$

[VEGF] $$\frac{\partial c_v}{\partial t} = D_v \nabla^2 c_v - \theta c_v + \chi T_{ij} - \varepsilon E_{ij} + \xi c_f$$

Motivation

[ECM] $$\frac{\partial c_f}{\partial t} = -\delta c_m c_f$$

[MDE] $$\frac{\partial c_m}{\partial t} = D_m \nabla^2 c_m + \mu_T T_{ij} + \mu_\varepsilon E_{ij} - \lambda c_m$$

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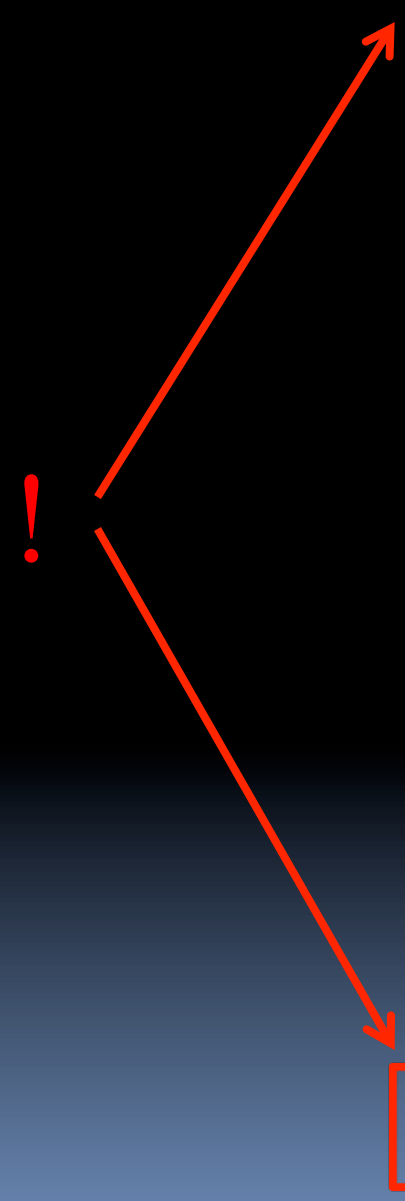
Motivation



Parameter No.	Parameter	Value (Units)
1	D_O	8×10^{-5} ($cm^2\ s^{-1}$)
2	K_T^O	1.25×10^{-1} ($cm\ s^{-1}$)
3	k_O	1.75×10^{-4} ($mM\ s^{-1}$)
4	O_v	0.07 (mM)
5	D_T	5.5×10^{-11} ($cm^2\ s^{-1}$)
6	k_T	6×10^{-5} (s^{-1})
7	K_T^T	6.5×10^{-5} ($cm\ s^{-1}$)
8	T_v	2.7×10^{-1} (nM)
9	g_1	1.57×10^{-3} ($nM\ s^{-1}$)
10	K_M^O	0.37 (mM)
11; 12; 13	$a_{O,Q;\ M;\ P}$	2 (4, 4)
14	μ_{max}	2.2×10^{-5} (s^{-1})
15	C_{mass}^{ave}	2 (arbitrary units)
16	C_{mass}^{max}	8 (arbitrary units)
17	h_n	0.0033 (nM)
18	s_n	200 (dimensionless)
19	P_{QM}	0.2
20	h_{QM}	90 (nM)
21	s_{QM}	0.14 (nM^{-1})
22	P_{QP}	0.1
23	h_{QP}	100 (nM)
24	s_{QP}	0.14 (nM^{-1})
25	P_{MM}	0.9
26	h_{MM}	90 (nM)
27	s_{MM}	0.14 (nM^{-1})
28	P_{MP}	0.05
29	h_{MP}	100 (nM)
30	s_{MP}	0.14 (nM^{-1})
31	vo_{min}	0.1
32	vo_{max}	0.5
33	ERK_{tot}	3×10^{2} (nM)
34	r_c	1×10^{-3} cm
35	r_v	5×10^{-3} cm

- **Drake equation** = an attempt to estimate the number, *N*, of extraterrestrial civilizations in Milky Way we might be able to contact

$$N = R \times f_p \times n_e \times f_l \times f_i \times f_c \times L$$

R = rate of star formation per year **~ 10**

f_p = fraction of those stars that have planets **~ 0.5**

n_e = average number of planets that can support life **No clue**

f_l = fraction of n_e that develop life **No clue**

f_i = fraction of $f_l \cdot n_e$ that develop intelligent life **No clue**

f_c = fraction of civilizations that release detectable signals **No clue**

L = length of time such civilizations release detectable signals into space **No clue**

→ $N \approx (10)(0.5)(\text{No clue})^5$

Thus, N is somewhere between "0" and "No clue".

Lessons from Meteorology

→ Contrast this with weather modeling: Earth's atmosphere is modeled as a fluid governed by the Navier-Stokes equations

→ Forecast models solve these equations on a 3D grid, using *observations* of the atmosphere to predict the evolution of wind, temperature and humidity

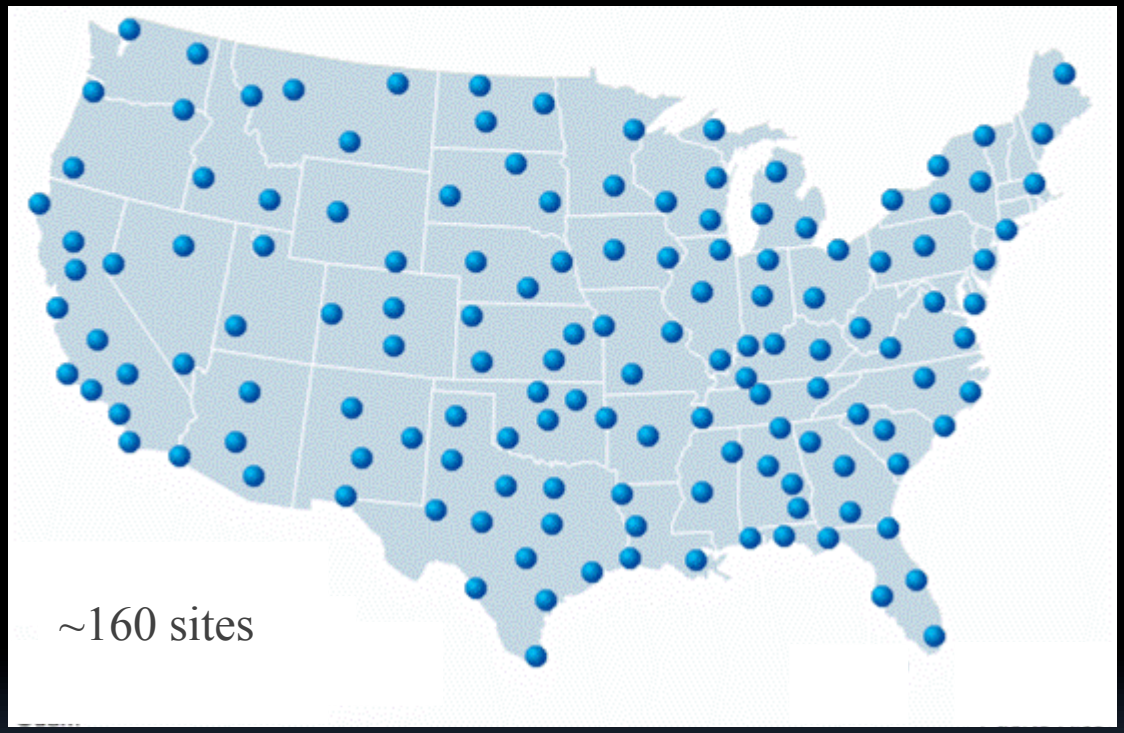
---

- In order to have meaningful weather predictions, you need:
  1) Rudimentary understanding of atmospheric dynamics
  2) Regular radiosonde measurements (...and then satellite data)
  3) Stable numerical methods
  4) Electronic computers

→ Better modeling and better data!

Lessons from Meteorology

National Climate Data Center NEXRAD (NEX generation RADar) Data Sites



~700 sites in Tennessee (NCDC sites + COOP sites) providing data for weather modeling

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→ *100 years ago, none of this existed*

Lynch. J Computational Physics 2008;227:3431-44.

Lessons from Meteorology

"A century ago, weather forecasting was a haphazard process, very imprecise and unreliable. Observations were sparse and irregular, especially for the upper air and over the oceans. The principals of theoretical physics played little or no role in practical forecasting: the forecaster used crude techniques of extrapolation, knowledge of local climatology and guesswork on intuition; forecasting was more an art than a science."

Lynch. J Computational Physics 2008;227:3431-44.

Lessons from Meteorology

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Lynch. J Computational Physics 2008;227:3431-44.

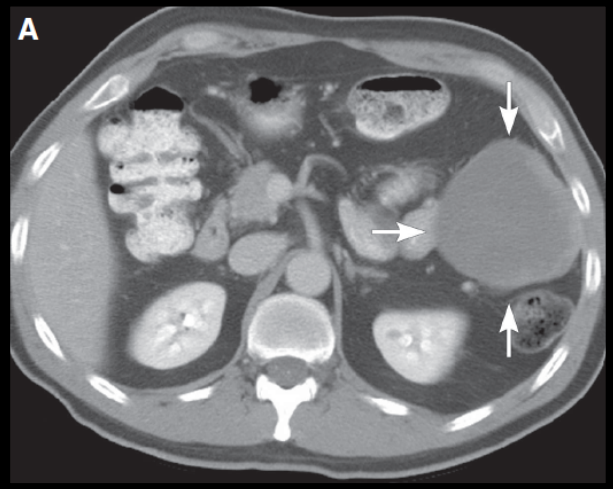
Lessons from Meteorology

"A century ago, predicting tumor response was a haphazard process, very imprecise and unreliable. Observations were sparse and irregular, especially for the GI and respiratory tract. The principals of theoretical physics played little or no role in predicting tumor response: the oncologist used crude techniques of extrapolation, knowledge of local anatomy and guesswork on intuition; predicting tumor response was more an art than a science."

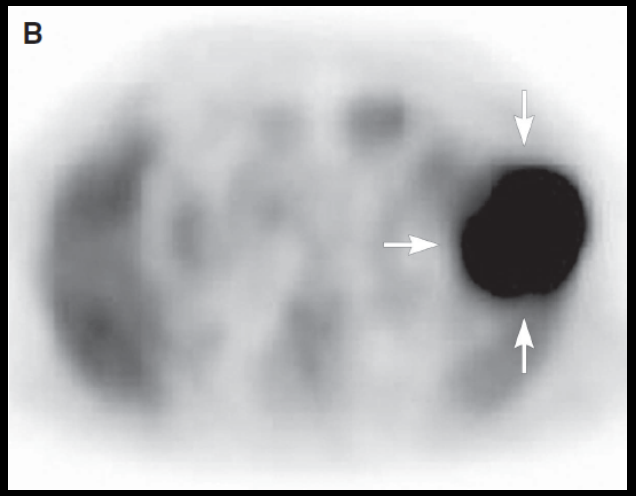
Jane Doe. J Theoretical Oncology 2111;1:1-11.

The clinical problem

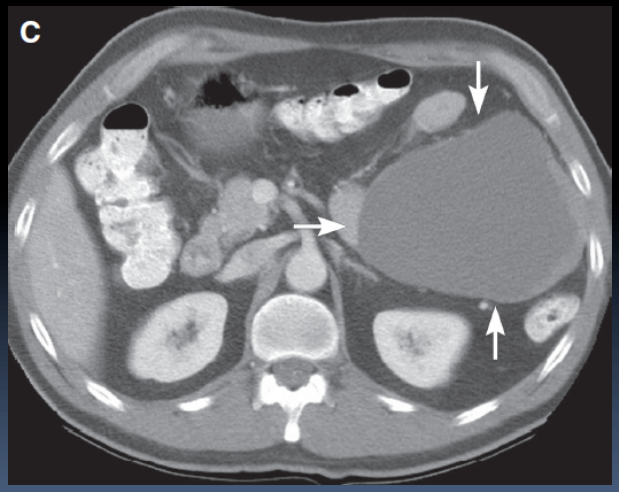
FDG-PET



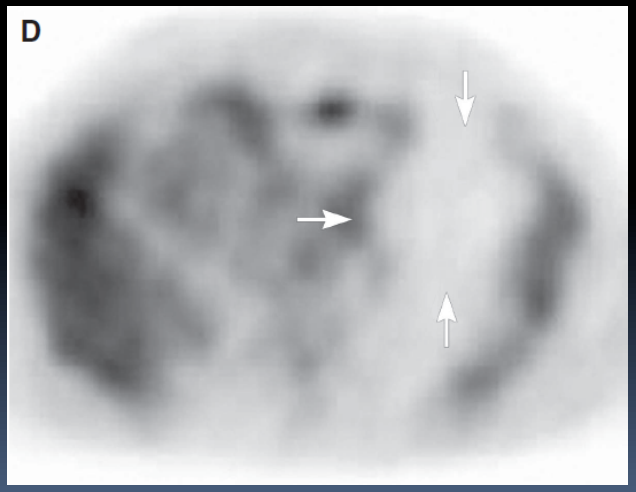
Pre-therapy



Pre-therapy



2 months post-therapy



2 months post-therapy

Choi et al. Am J Roentgenology 2004;183:1619-27.

Working hypothesis:

Readily-available, multi-scale imaging techniques can provide the data to initialize/constrain *predictive* models of tumor growth and treatment response for clinical application.

Next ~40 minutes of Your Life

1. What can imaging provide?
2. Imaging-Driven Models of Tumor Growth/Treatment Response

Next ~40 minutes of Your Life

1. What can imaging provide?
2. Imaging-Driven Models of Tumor Growth/Treatment Response

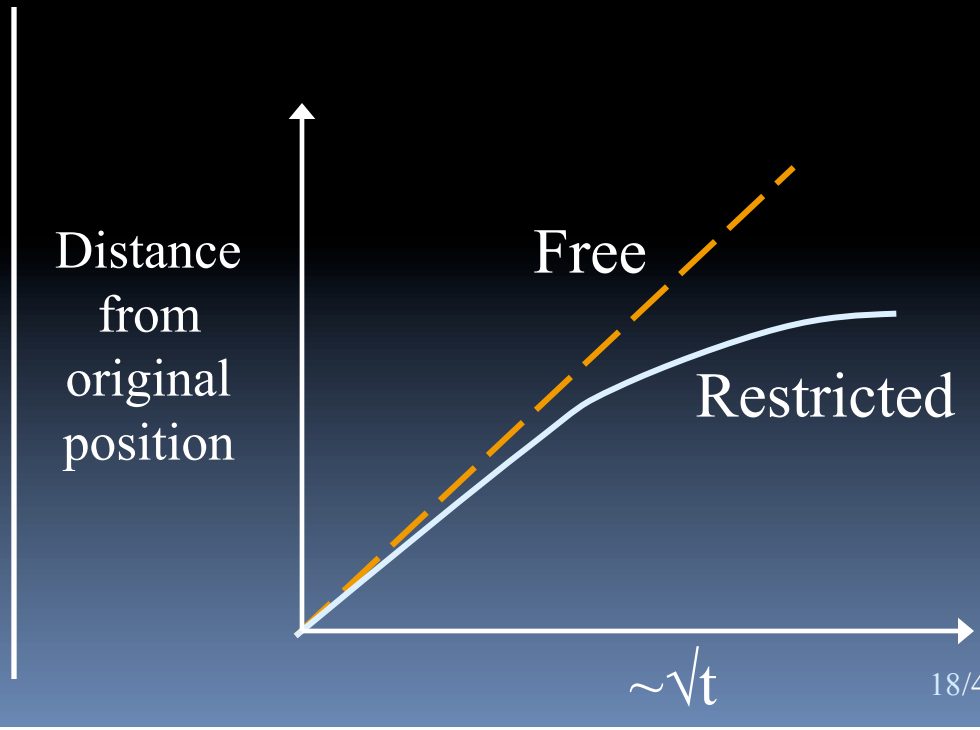
Magnetic resonance imaging (MRI)

Magnetic Resonance Imaging, 1/5

Diffusion weighted MRI

- Water molecules wander about randomly in tissue (Brownian Motion)
- In a free solution, after a time *t*, molecules travel (on average) a distance *L* from where they started
- But in tissue, compartment effects may hinder movement = restricted diffusion

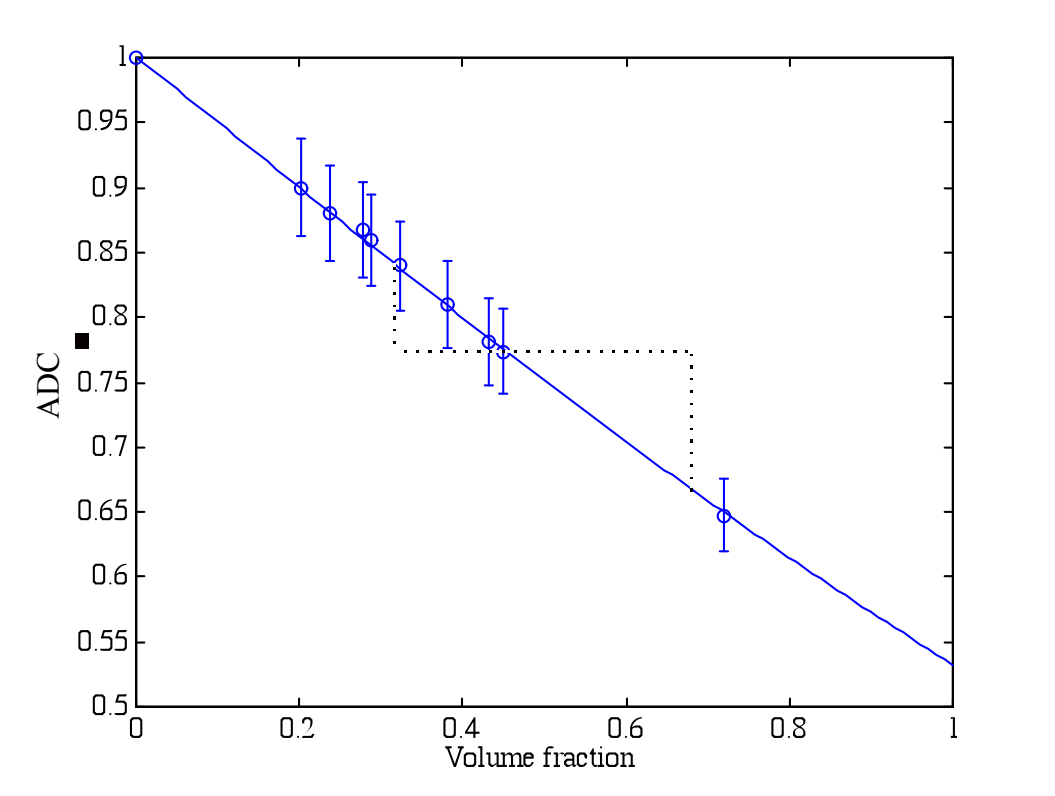
- Boundaries may reduce distance molecules travel when compared to free molecules
- Thus, the ***Apparent Diffusion Coefficient*** (ADC) is lowered

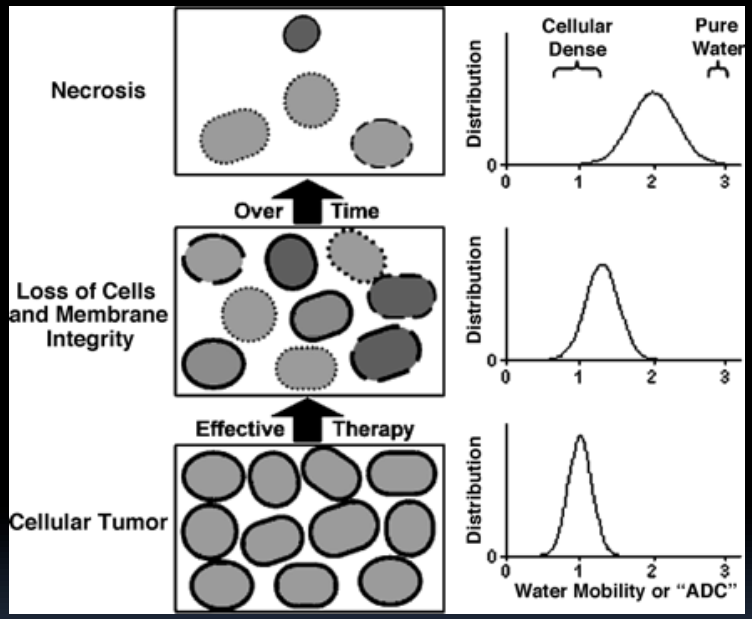


Magnetic Resonance Imaging, 2/5

Diffusion weighted MRI

- ADC depends on cell volume fraction





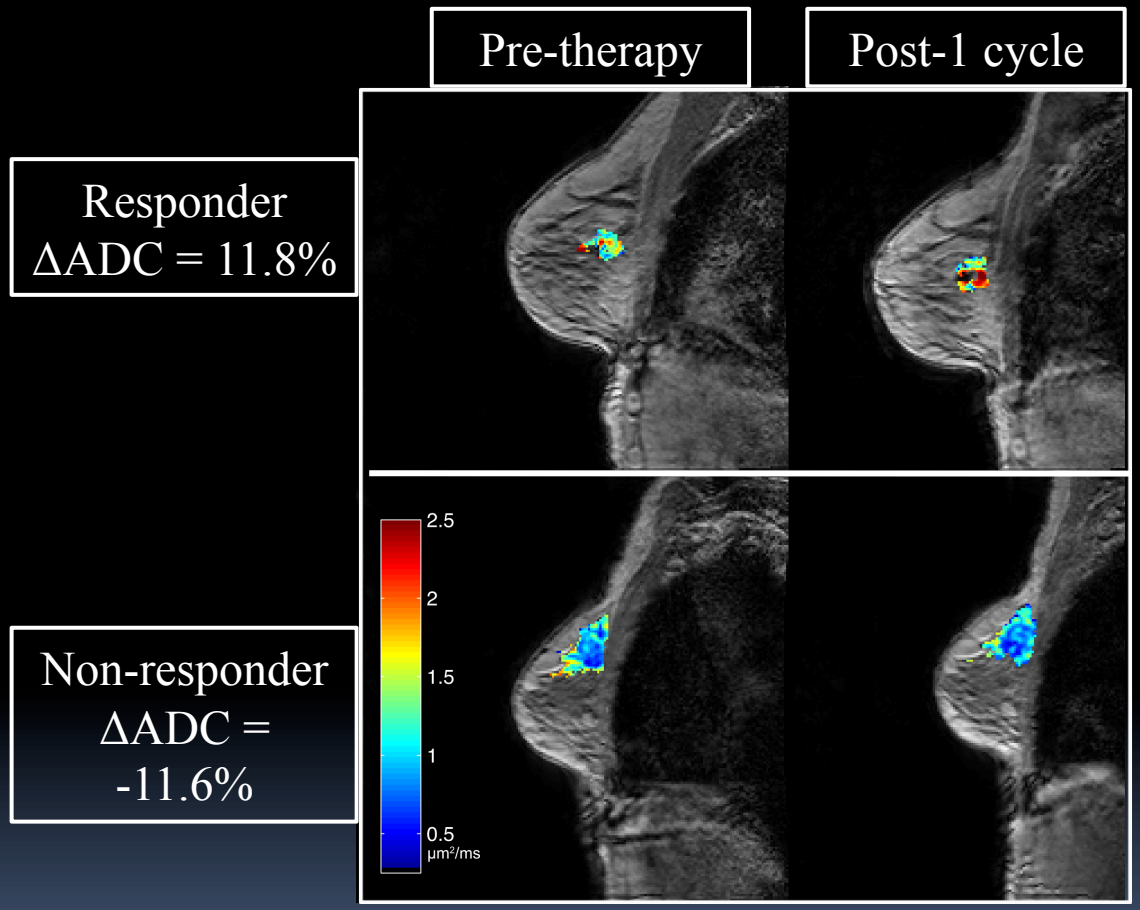
- Increasing cell density *(cellularity);* more cell membranes per unit distance to hinder diffusion → lower ADC
- Tumor cellularity may be monitored by DWI

Anderson et al. Magn Reson Imaging. 2000;18:689-95.

Hall et al. Clin Canc Res 2004;10:7852

Magnetic Resonance Imaging, 3/5

Diffusion weighted MRI, clinical example



ROC Analysis
Sensitivity = 0.64
Specificity = 0.93
AUC = 0.70

→ Sensitivity = true positive rate = TP/(TP+FN)

→ Specificity = true negative rate = TN/(FP + TN)

Magnetic Resonance Imaging, 4/5

Dynamic contrast enhanced MRI (DCE-MRI)

- Serial acquisition of images before, after an injection of contrast agent (CA)
- As CA perfuses into tissue, the T_1 and T_2 values of tissue water decrease
- Each voxel yields a signal intensity time course
- By fitting data to model, extract parameters that report tissue characteristics

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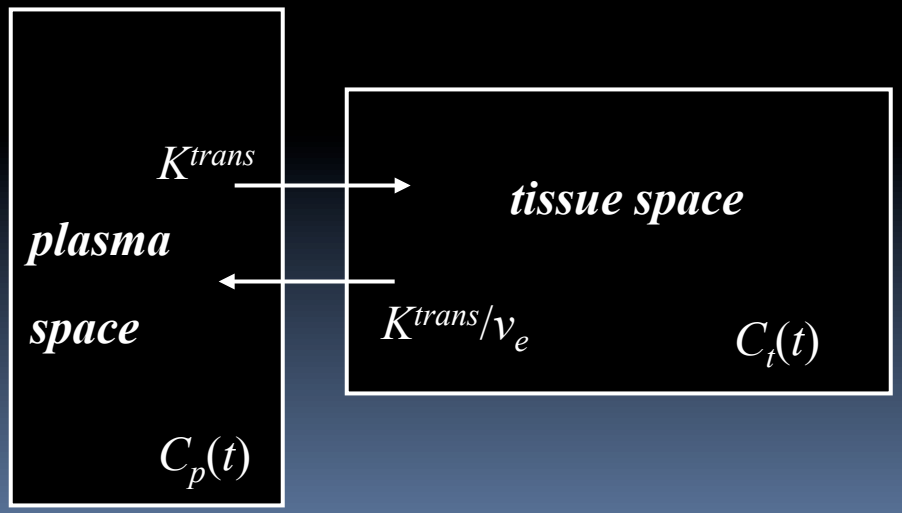


K^{trans} = transfer rate constant

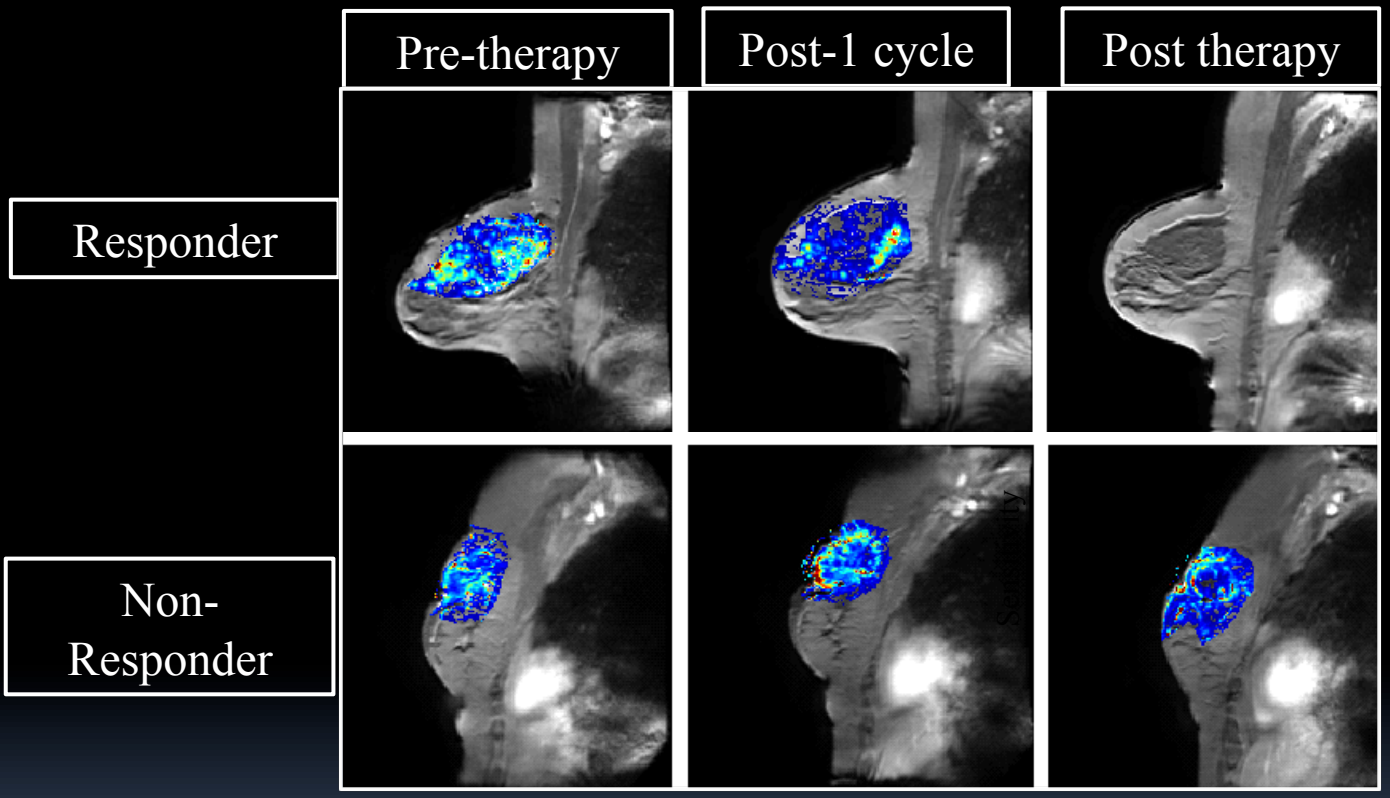
v_e = extravascular extracellular volume fraction

v_b = blood volume fraction

Tofts, et al. J Magn Reson Imaging 1999;10:223-232.

Magnetic Resonance Imaging, 5/5

DCE-MRI, Clinical Example



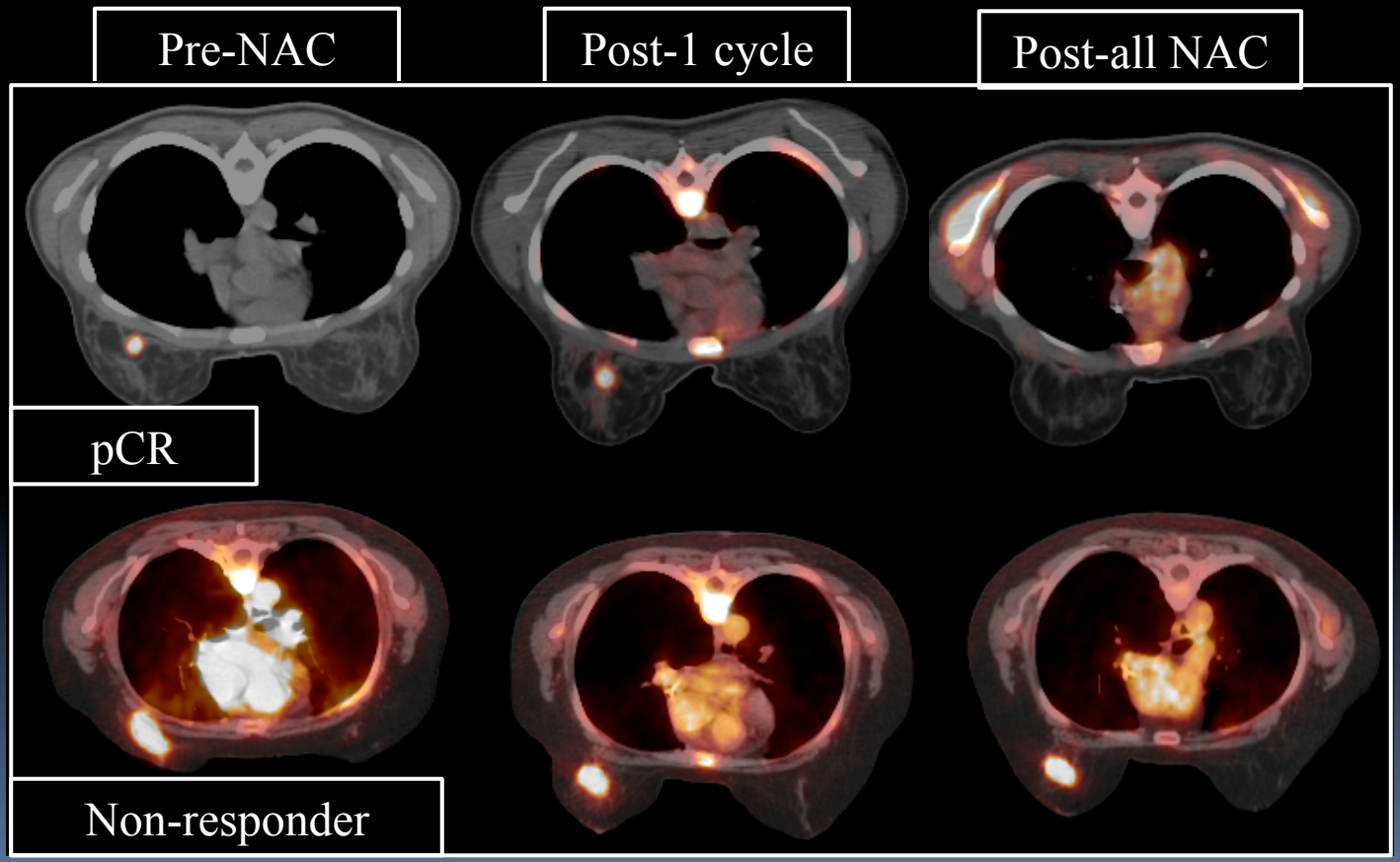
ROC Analysis
Sensitivity = 0.81
Specificity = 0.75
AUC = 0.80

When combining DW-MRI & DCE-MRI data:
Sensitivity = 0.88
Specificity = 0.82
AUC = 0.86

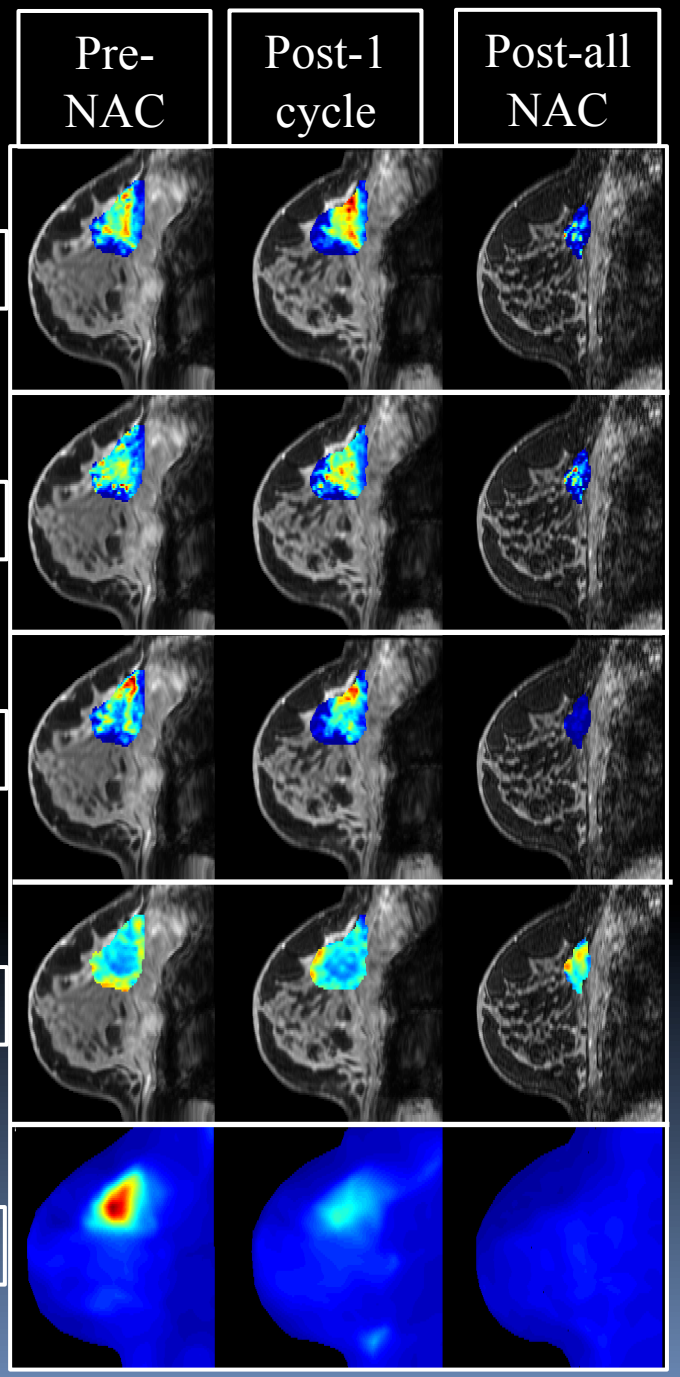
Lisa Li et al.

Positron emission tomography (PET)

Positron Emission Tomography, 1/1



PET-MRI of breast cancer



blood perfusion and permeability

extravascular extracellular volume fraction

plasma volume fraction

cellularity

FDG-PET (glucose metabolism)

Xia Li, Nkiruka Atuegwu, Lori Arlinghaus

Quantitative Imaging of Cancer

Imaging Summary

- Dramatic increases in quality of data available from non-invasive imaging

  → Moving *from* qualitative anatomical data *to* quantitative functional data
- Quantitatively assess tumor status at physiological, cellular, & molecular levels

---

- We talked about:

  MRI—anatomy, blood vessels, blood flow, cellularity

  PET—metabolism, proliferation
- Other imaging measurements we did not talk about:

  → cell membrane turnover, pH, pO_2 (MRI)

  → Receptor expression, apoptosis (PET & SPECT)

Next ~20 minutes of Your Life

1. What can imaging provide?
2. Imaging-Driven Models of Tumor Growth/Treatment Response

Imaging + modeling: a first attempt

- Let the tumor cells proliferate up to a certain "carrying capacity" = θ

$$\frac{dN(t)}{dt} = kN(t)\left(1 - \frac{N(t)}{\theta}\right)$$

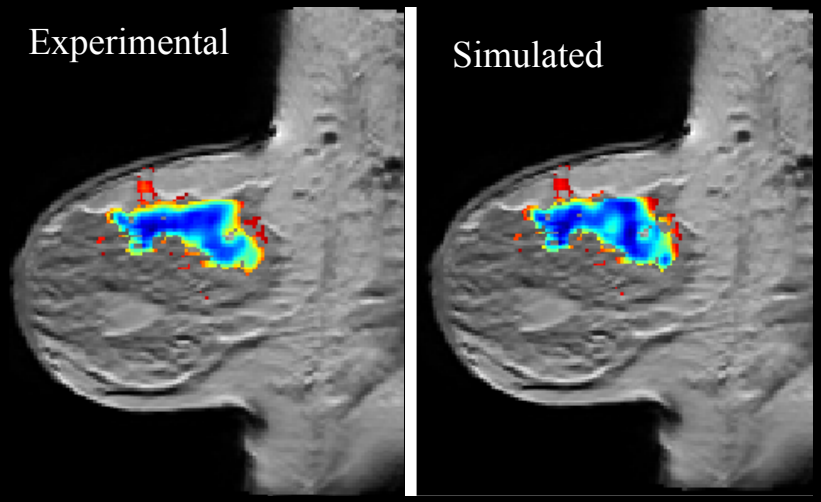
- Solution is given by:

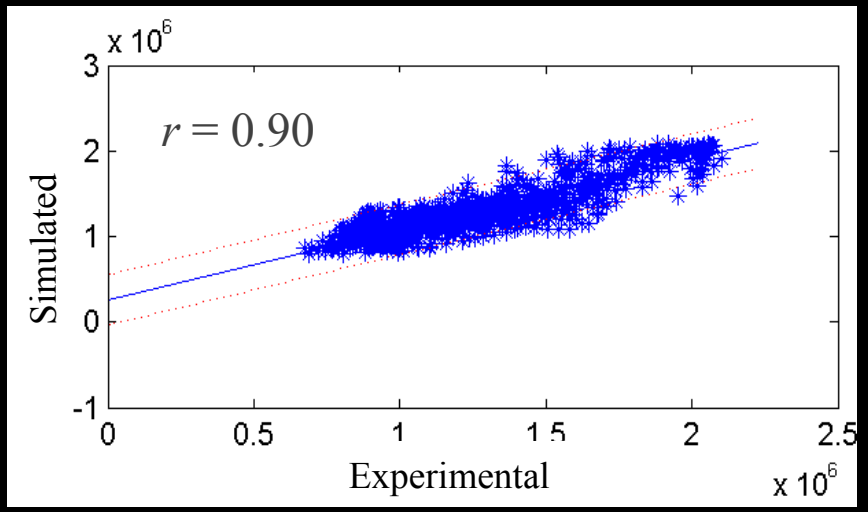
$$N(t) = \frac{\theta N_0}{N_0 + (\theta - N_0)\,\mathrm{e}^{-kt}}$$

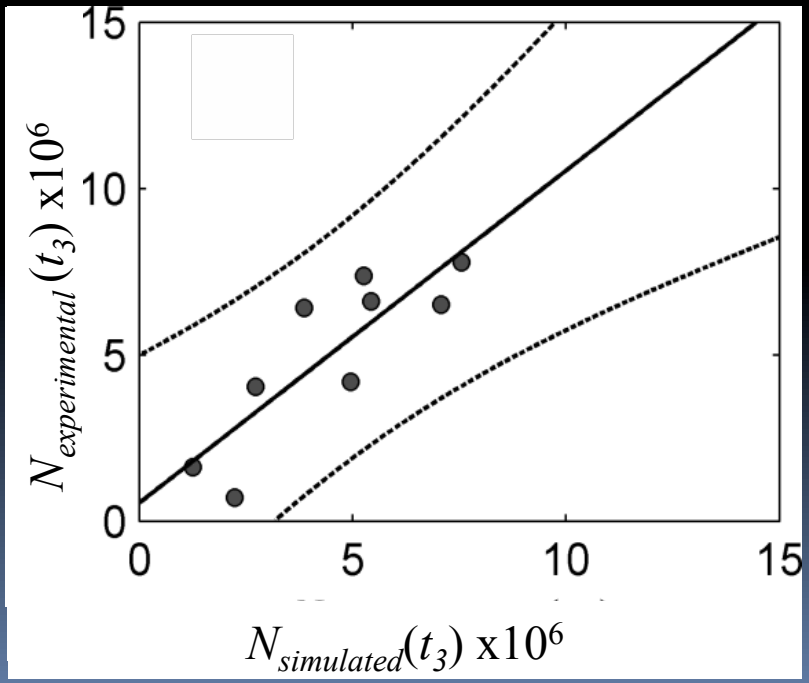
- <u>Basic Idea:</u>

1) Measure ADC data before and after the first cycle of therapy
2) Use that data & above equation to "fit" for proliferation, k
3) Use k with $N(r, t = t_2)$ to project $N(r, t = t_{end})$

Imaging + modeling: a first attempt







Some summary stats (n = 27):

- PCC = 0.83 (p = 0.004), CCC = 0.81
- *k* separates responders from non-responders after 1 cycle of therapy (p = 0.021)
  - → sensitivity = 0.82
  - → specificity = 0.73
  - → AUC = 0.76

Imaging + modeling: a second attempt

Reaction-diffusion $$\frac{\partial N}{\partial t} = \nabla \cdot \left(D \nabla N \right) + kN\left(1 - \frac{N}{\theta} \right)$$

Mechanical coupling $$D = D_0 e^{-\gamma \sigma_{vm}}$$

Mechanical equilibrium $$\nabla \cdot \sigma + \lambda \nabla N = 0$$

N = cell number
D = cell diffusion coefficient
k = growth rate
θ = carrying capacity
γ, λ = coupling coefficients
σ_{vm} = Von Mises stress

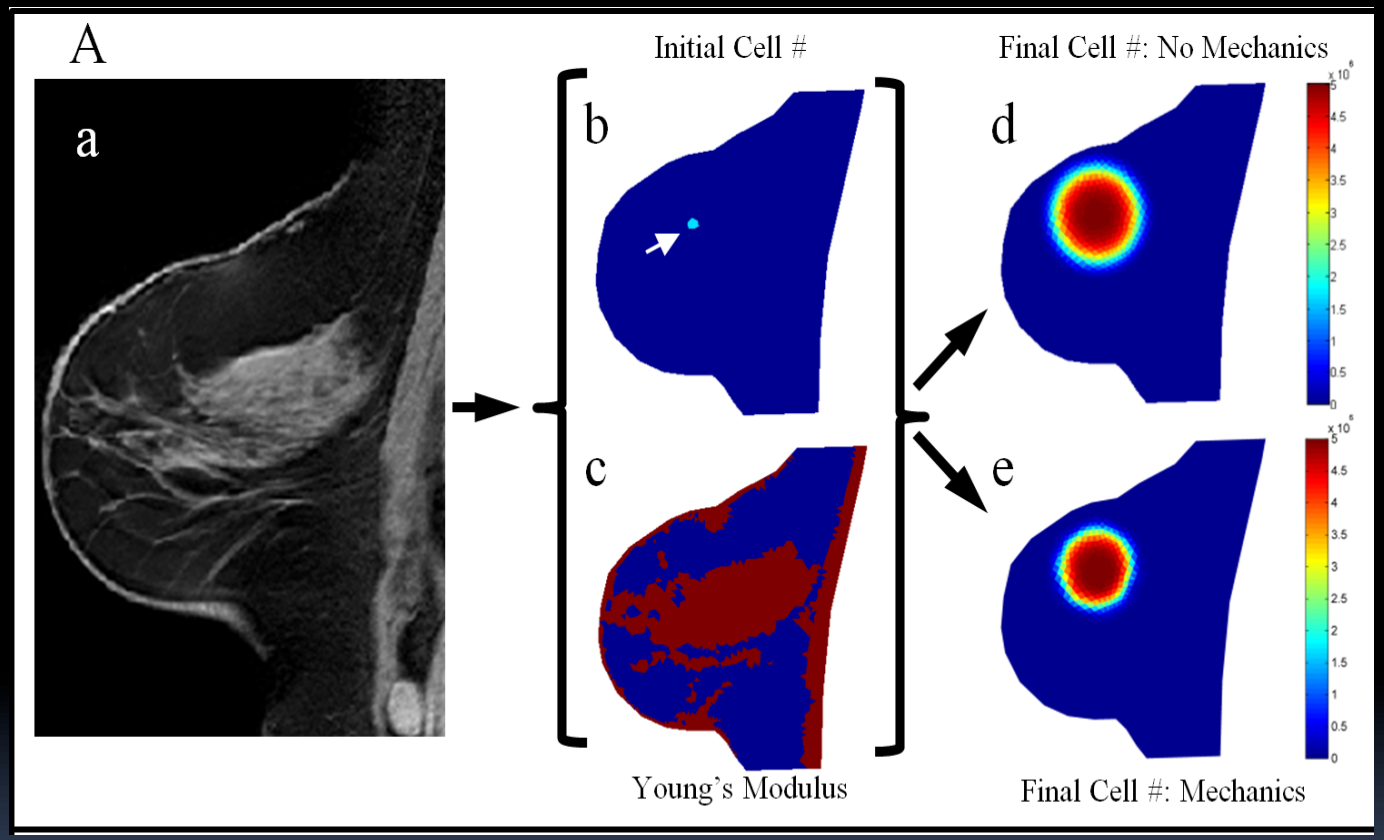
Top equation - rate of change of tumor cell number as sum of cell diffusion, logistic growth

Middle equation - cell diffusion term, D, is linked to surrounding tissue stiffness, where σ_{vm} is the von Mises stress, D_0 is the diffusion in absence of stress

Bottom equation - describes mechanical equilibrium; governs how the stress tensor, σ, is subject to an expansive force determined by changes in tumor cell number

Jared Weis, Mike Miga et al

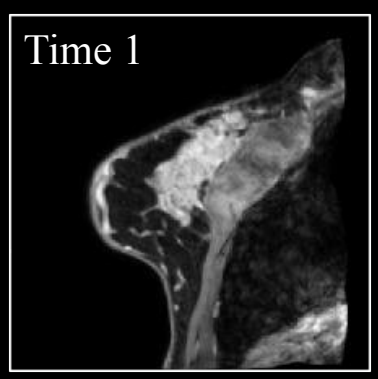
Imaging + modeling: a second attempt

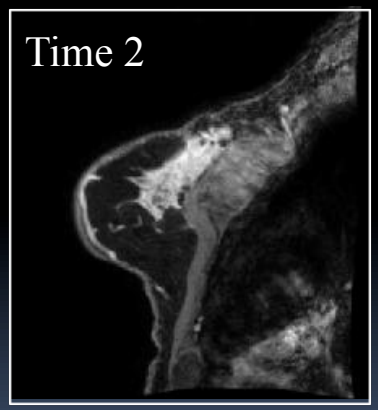


In silico tumor growth with and without mechanical coupling to surrounding tissue

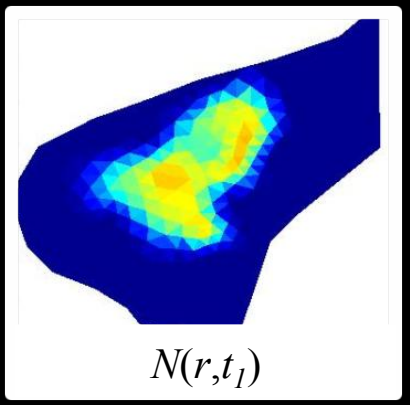
Jared Weis, Mike Miga et al

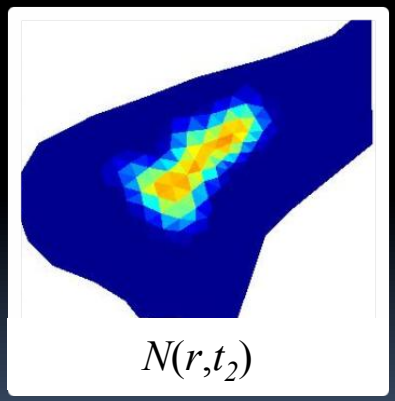
Imaging + modeling: a second attempt





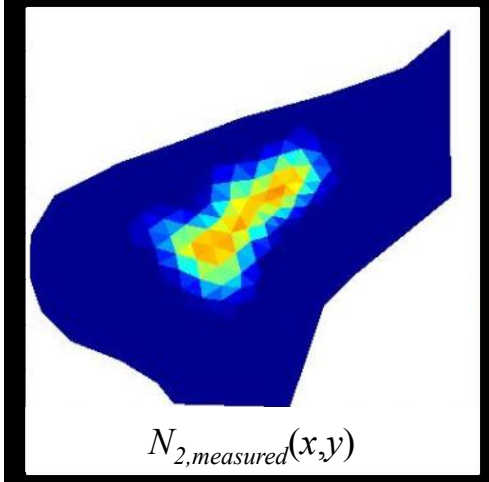
ADC data
(MRI)



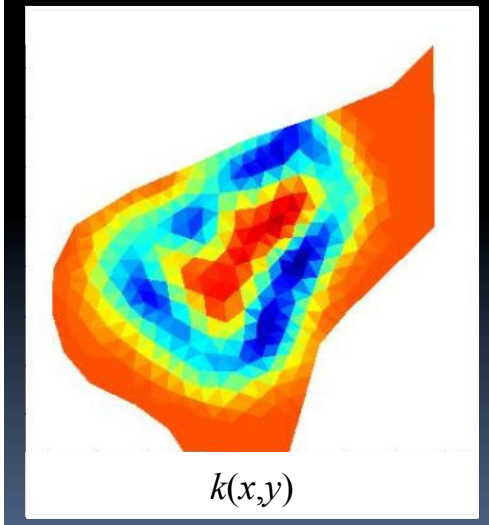


Run model from time 1 to time 2 to estimate D and $k(x,y)$

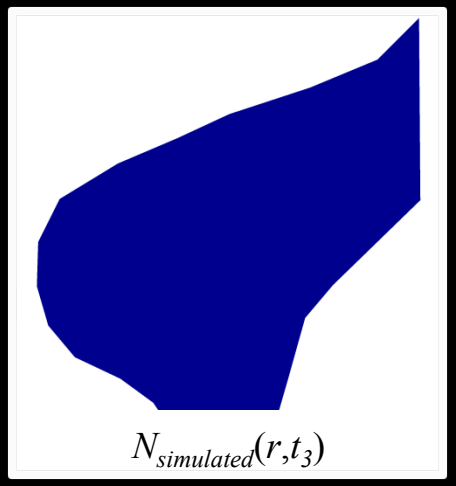
Imaging + modeling: a second attempt



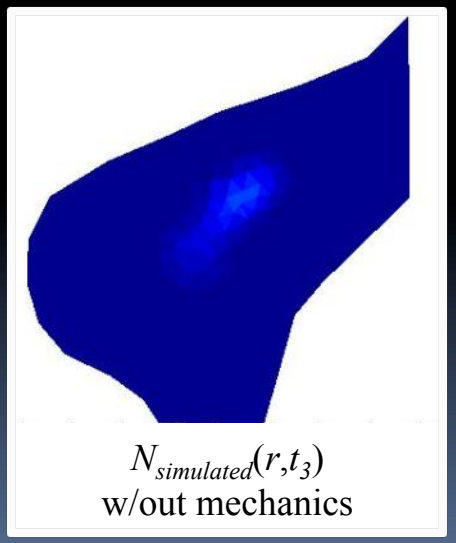
$N_{2,measured}(x,y)$



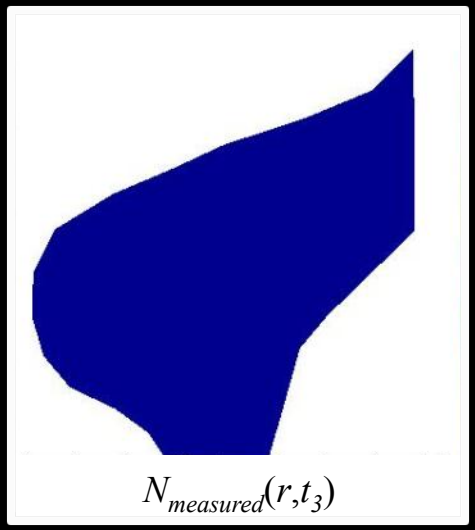
$k(x,y)$



$N_{simulated}(r,t_3)$



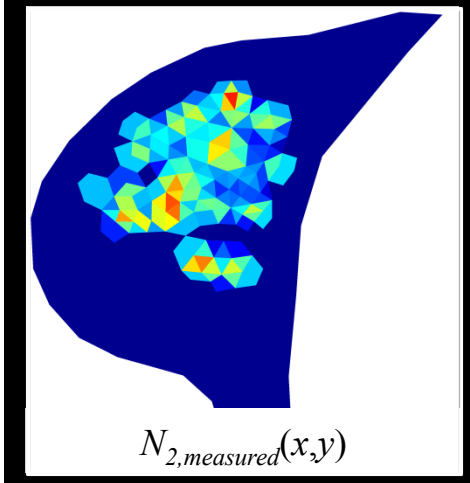
$N_{simulated}(r,t_3)$
w/out mechanics



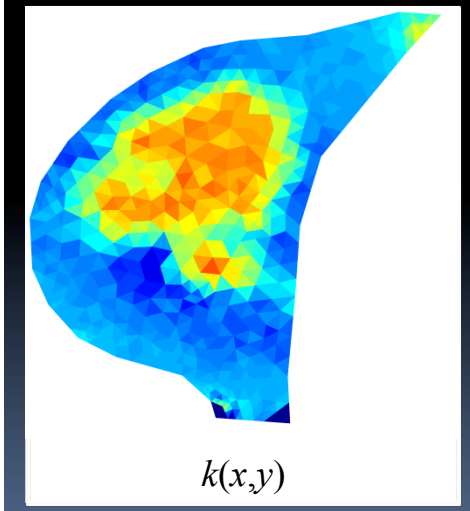
$N_{measured}(r,t_3)$

→ The model w/mechanical coupling correctly predicts response, while the model w/out mechanical coupling predicts a non-zero residual tumor burden

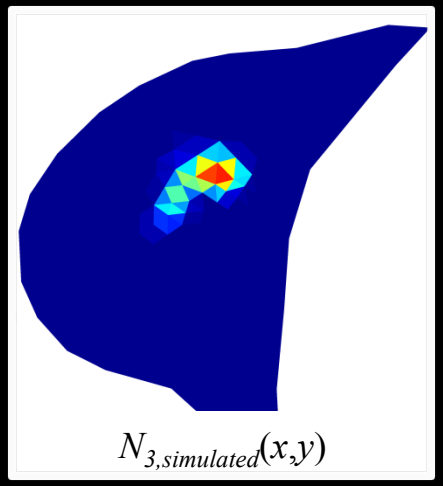
Imaging + modeling: a second attempt



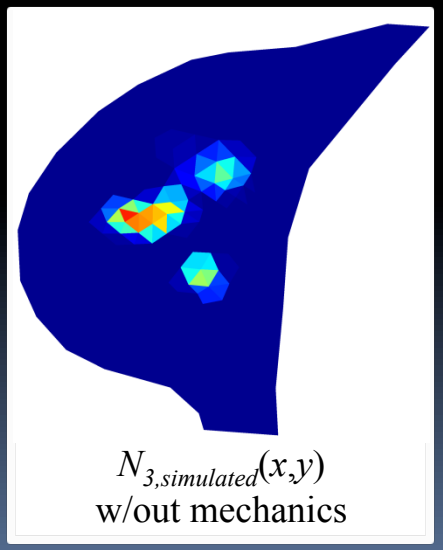
$N_{2,measured}(x,y)$



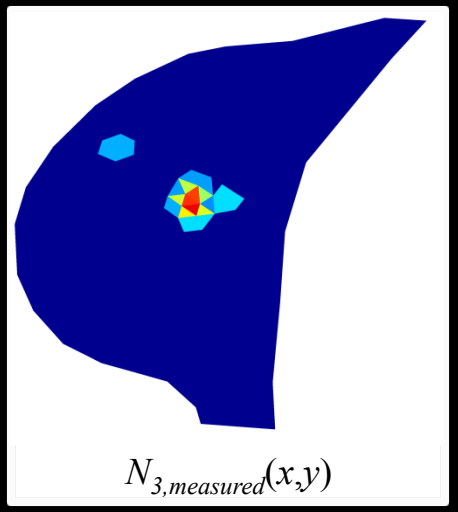
$k(x,y)$



$N_{3,simulated}(x,y)$



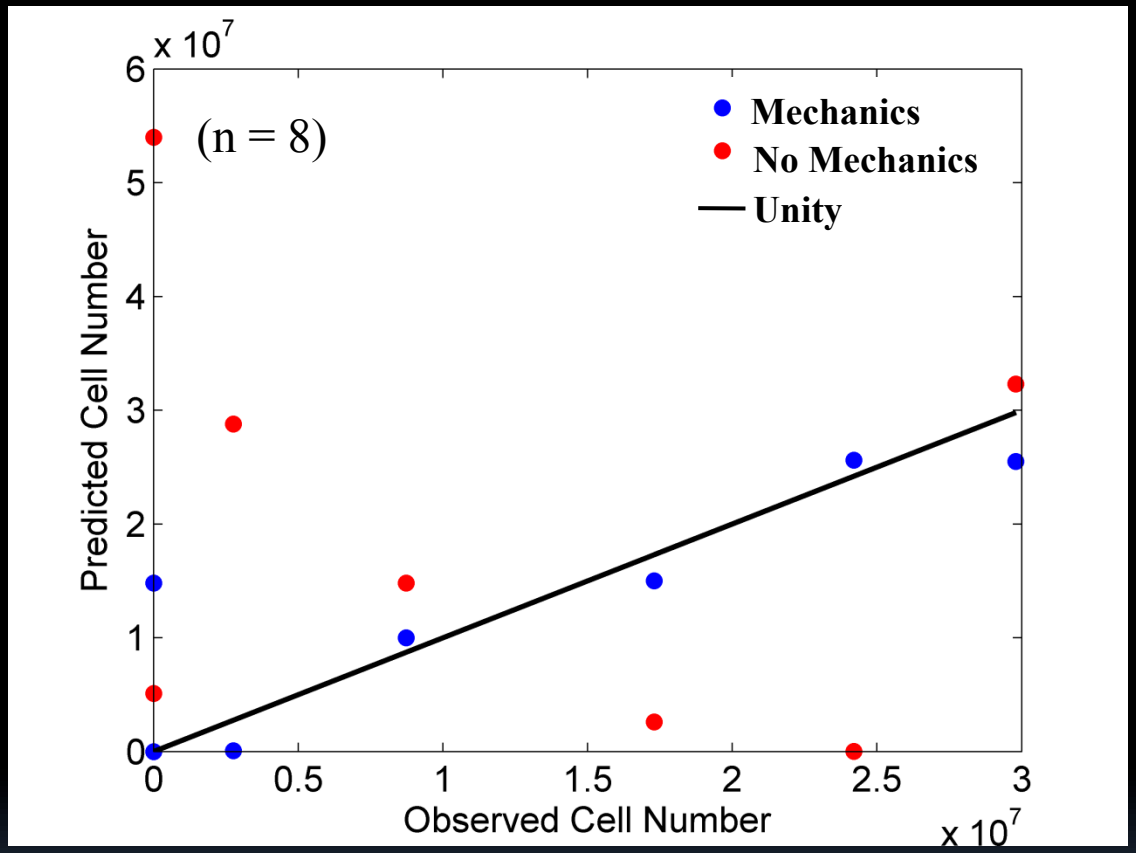
$N_{3,simulated}(x,y)$
w/out mechanics



$N_{3,measured}(x,y)$

→ While both models correctly predict residual tumor burden, the model w/mechanical coupling captures the spatial distribution more accurately

Imaging + modeling: a second attempt



- Comparing observed and predicted tumor cell number:

→ W/mechanics PCC/CCC = 0.85/0.84

→ W/out mechanics PCC/CCC = -0.29/-0.23

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Imaging + modeling: a third attempt

- Going forward, need to make greater use of available data

$$\boxed{\text{Rate of chance of \# of tumor cells}} = \frac{\partial N_{TC}(r,t)}{\partial t} = \underbrace{k(r)N_{TC}(r,t)\left(1-\frac{N_{TC}(r,t)}{\theta}\right)}_{\text{Proliferation of tumor cells}} + \underbrace{D_{TC}\nabla^2 N_{TC}(r,t)}_{\text{Random dispersal of tumor cells (diffusion)}}$$

→ ADC values from DW-MRI to assign $N_{TC}(r,t)$ and extract $k(r)$

→ Everything on the right hand side is known

Imaging + modeling: a third attempt

- Going forward, need to make greater use of available data

Rate of chance of # of tumor cells

$$= \frac{\partial N_{TC}(r,t)}{\partial t} = \underbrace{k(r)N_{TC}(r,t)\left(1 - \frac{N_{TC}(r,t)}{\theta}\right)}_{\text{Proliferation of tumor cells}} + \underbrace{D_{TC}\nabla^2 N_{TC}(r,t)}_{\text{Random dispersal of tumor cells (diffusion)}}$$

Rate of change of # of endothelial cells

$$= \frac{\partial N_{EC}(r,t)}{\partial t} = \underbrace{D_{EC}\nabla^2 N_{EC}(r,t)}_{\text{Diffusion of EC}} - \underbrace{\nabla\bullet(\chi N_{EC}(r,t)\nabla c)}_{\text{Chemotaxis of EC}}$$

Assume chemotaxis is in direction of areas of proliferating cells of higher density; can also estimate this from DW-MRI data

Imaging + modeling: a third attempt

- Going forward, need to make greater use of available data

Rate of chance of # of tumor cells

$$= \frac{\partial N_{TC}(r,t)}{\partial t} = \underbrace{k(r)N_{TC}(r,t)\left(1-\frac{N_{TC}(r,t)}{\theta}\right)}_{\text{Proliferation of tumor cells}} + \underbrace{D_{TC}\nabla^2 N_{TC}(r,t)}_{\text{Random dispersal of tumor cells (diffusion)}}$$

Rate of change of # of endothelial cells

$$= \frac{\partial N_{EC}(r,t)}{\partial t} = \underbrace{D_{EC}\nabla^2 N_{EC}(r,t)}_{\text{Diffusion of EC}} - \underbrace{\nabla\bullet(\chi N_{EC}(r,t)\nabla c)}_{\text{Chemotaxis of EC}}$$

Rate of change of O_2

$$= \frac{\partial C_{o_2}(r,t)}{\partial t} = \underbrace{D_{o_2}\nabla^2 C_{o_2}(r,t)}_{\text{Diffusion of } O_2} - \underbrace{\gamma_{o_2} T_{o_2}(r,t)}_{O_2 \text{ use by TC}} + \underbrace{F_{o_2}(r,t)}_{\text{Delivery of } O_2}$$

O_2 use by TC → ADC & PET data

Delivery of O_2 → Perfusion data from DCE-MRI

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Imaging + modeling: a third attempt

- Going forward, need to make greater use of available data

Rate of chance of # of tumor cells

$$= \frac{\partial N_{TC}(r,t)}{\partial t} = \underbrace{k(r)N_{TC}(r,t)\left(1-\frac{N_{TC}(r,t)}{\theta}\right)}_{\text{Proliferation of tumor cells}} + \underbrace{D_{TC}\nabla^2 N_{TC}(r,t)}_{\text{Random dispersal of tumor cells (diffusion)}}$$

Rate of change of # of endothelial cells

$$= \frac{\partial N_{EC}(r,t)}{\partial t} = \underbrace{D_{EC}\nabla^2 N_{EC}(r,t)}_{\text{Diffusion of EC}} - \underbrace{\nabla\bullet(\chi N_{EC}(r,t)\nabla c)}_{\text{Chemotaxis of EC}}$$

Rate of change of O_2

$$= \frac{\partial C_{O_2}(r,t)}{\partial t} = \underbrace{D_{O_2}\nabla^2 C_{O_2}(r,t)}_{\text{Diffusion of } O_2} - \underbrace{\gamma_{O_2} T_{O_2}(r,t)}_{O_2 \text{ use by EC}} + \underbrace{F_{O_2}(r,t)}_{\text{Delivery of } O_2}$$

Rate of change of glucose

$$= \frac{\partial C_G(r,t)}{\partial t} = \underbrace{D_G\nabla^2 C_G(r,t)}_{\text{Diffusion of glucose}} - \underbrace{\gamma_G T_G(r,t)}_{\text{glucose use by EC}} + \underbrace{F_G(r,t)}_{\text{Delivery of glucose}}$$

ADC & FDG data

Perfusion data from DCE-MRI

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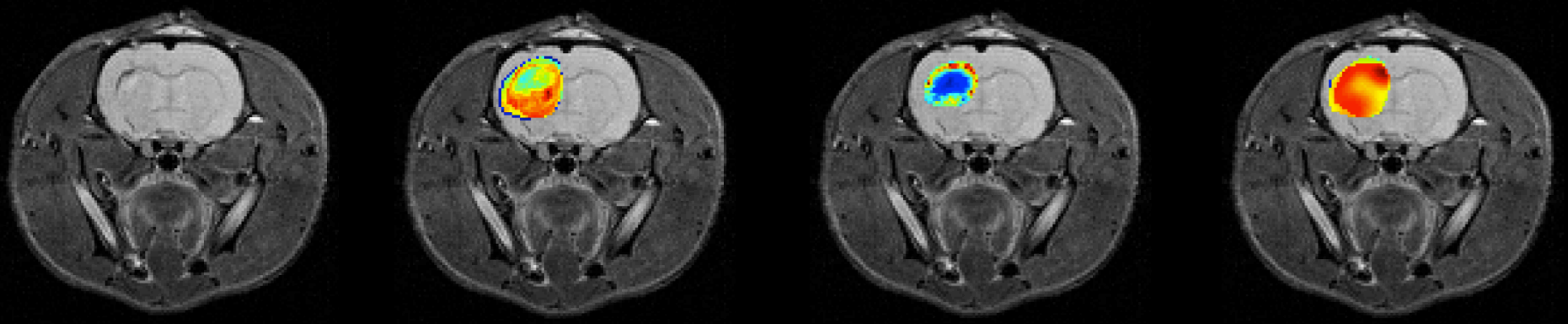
Imaging + modeling: a third attempt

Experimental system – rat brain tumor



Anatomical (Registration)

DW-MRI Cell Number

DCE-MRI K^{trans}, v_e, and v_p

^{18}F-FDG PET

MRI on days 9, 10, 11, 13, 15, and 17

PET on days 9, 15, and 17

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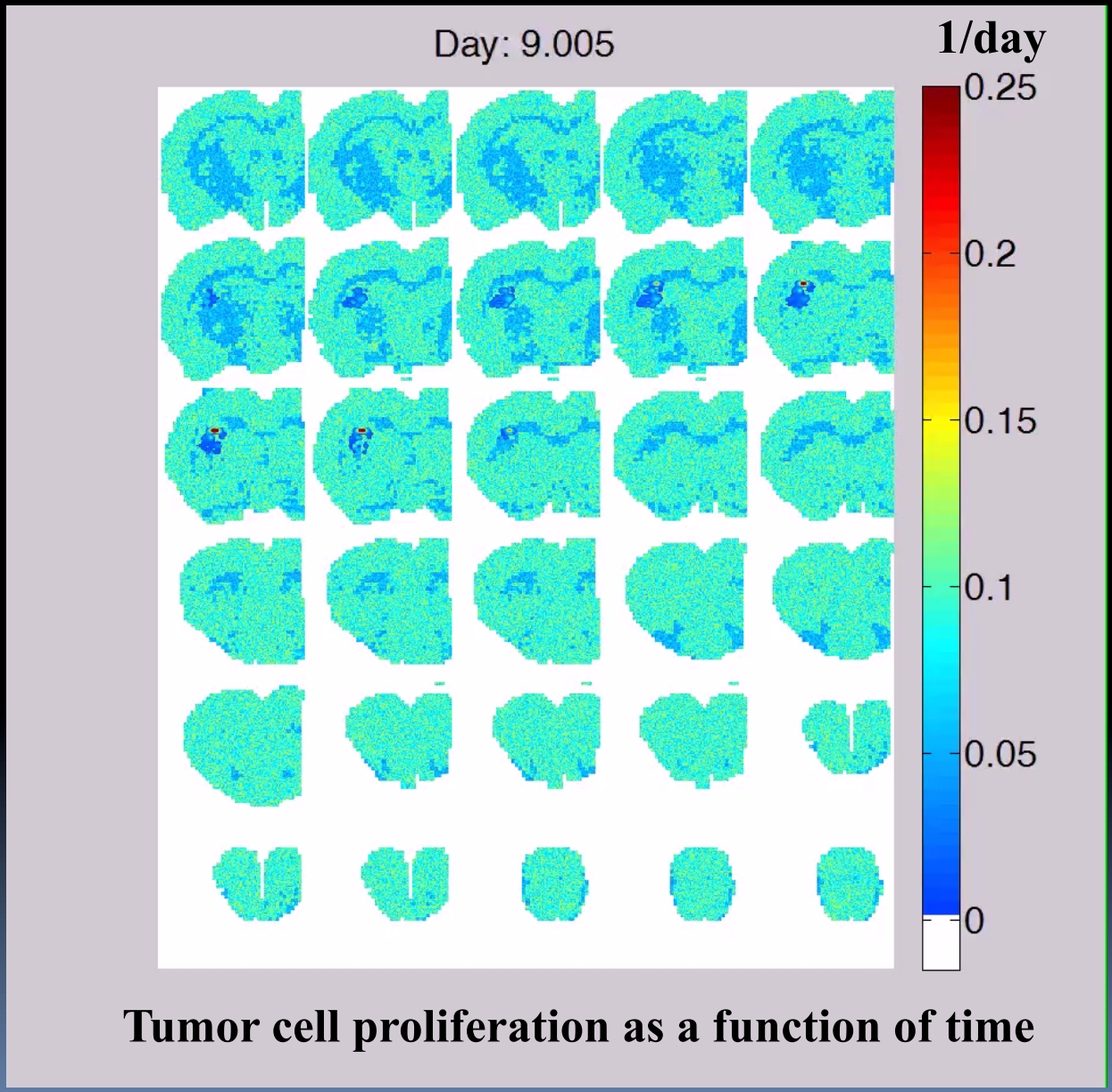

Tumor cell proliferation as a function of time

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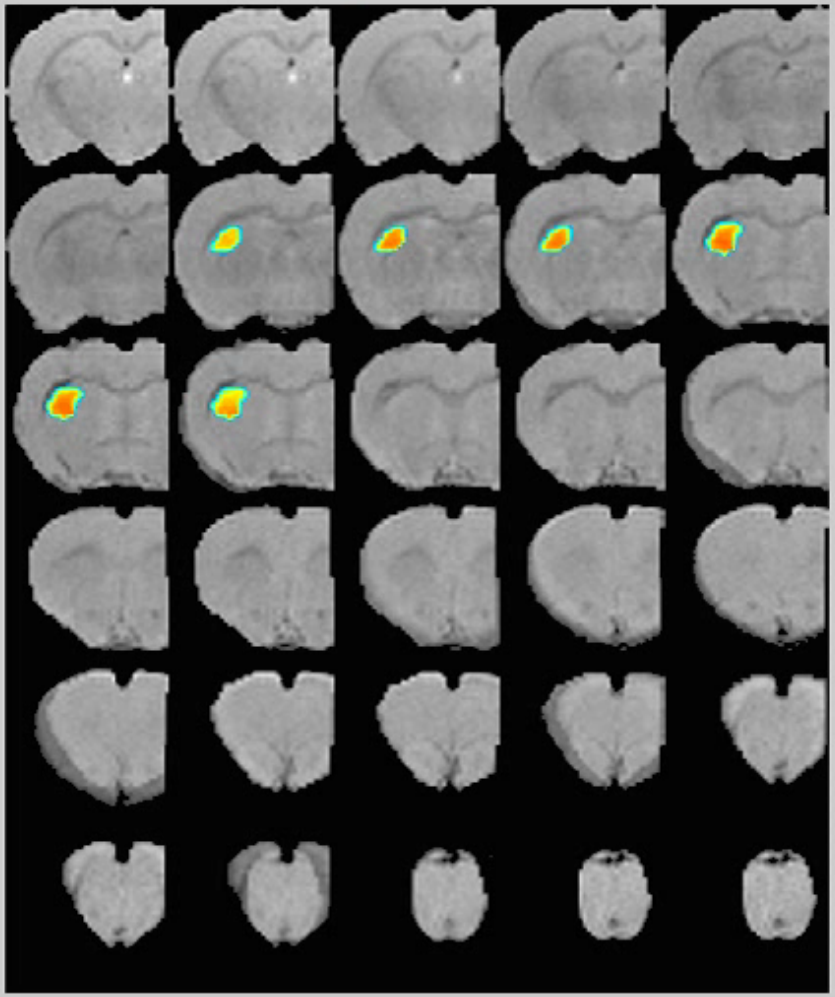

Tumor cell number as a function of time

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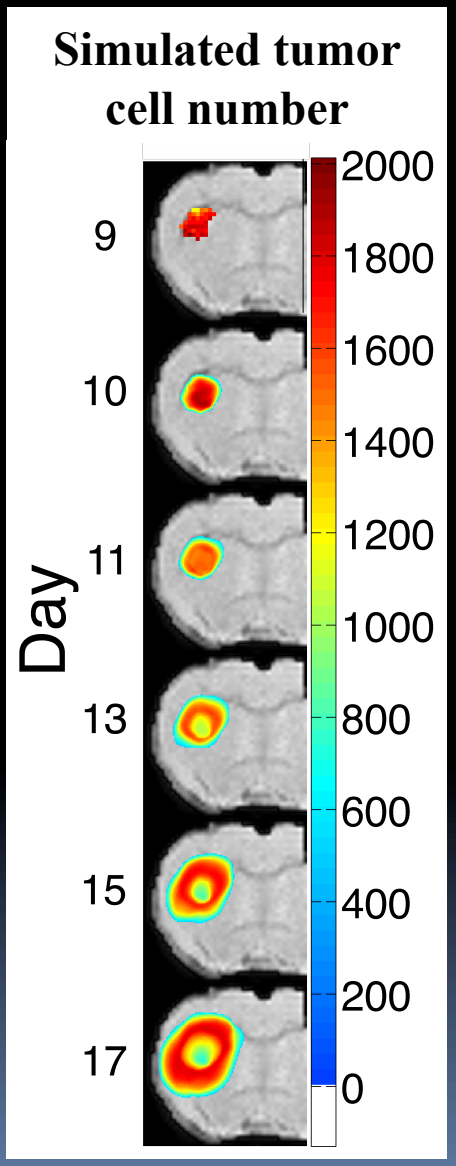
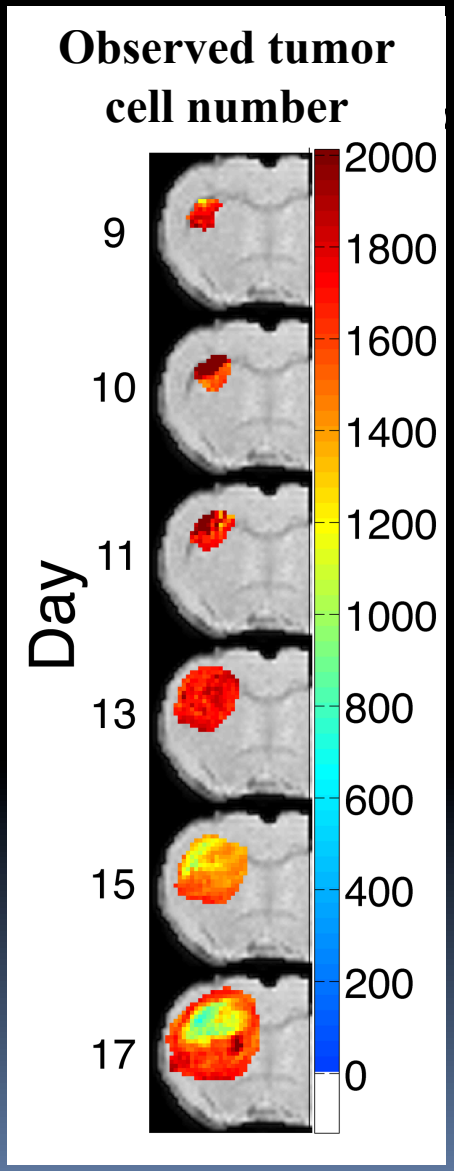
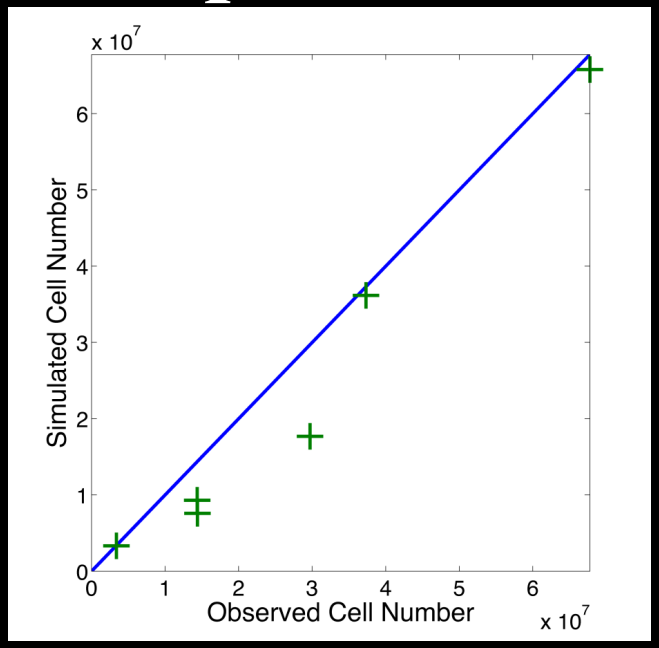
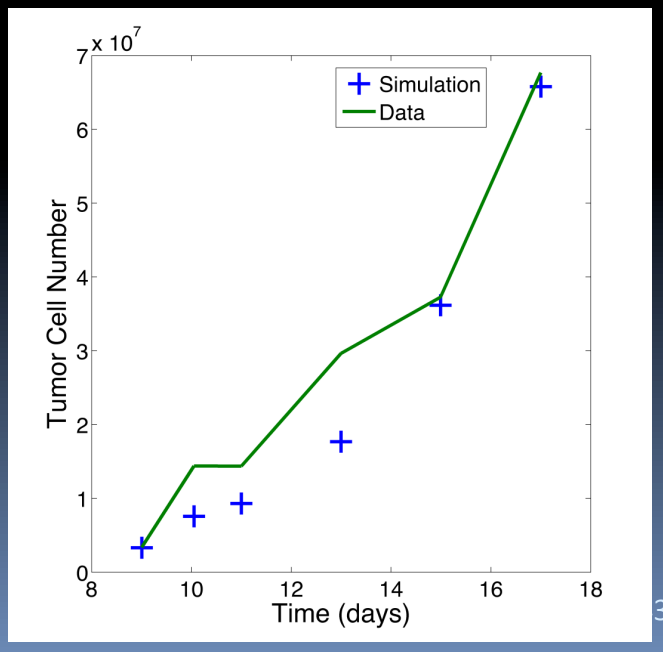
Imaging + modeling: a third attempt









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Summary and Future directions

• Having a model, driven by patient specific data would enable personalized, *in silico* therapy modeling → theoretical/predictive oncology

• Could "give" the patient therapy *in silico*, then see how they "respond"

→ Could systematically adjust therapies, order of combination therapy, dosing scheduling, etc.

→ Could enable (more) rational clinical trials design/execution

→ Eminently testable in pre-clinical setting… and is translatable

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→ *Since the quantitative imaging data can be acquired in 3D, at multiple time points and noninvasively, it is the only game in town*

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