Opportunities for integration of imaging-based tumor growth and response models into multi-modal clinical trials

Robert Jeraj
Departments of Medical Physics, Human Oncology, Radiology and Biomedical Engineering
University of Wisconsin Carbone Cancer Center
rjeraj@wisc.edu
Why modeling?

Modeling bridges the gap between biology and outcomes.
Problem of dose painting

Anatomical imaging
Population-based
Uniform dose

Molecular imaging
Patient-specific
Non-uniform dose
Why modeling?

- Biological data
- Computational tumor modeling
- Observed therapeutic response

Experiments

Clinical trials

TOP-DOWN

BOTTOM-UP
How much dose?

Recurrence at Time Point

No Recurrence at Time Point

Dose 1
Dose 2
Dose 3

Uptake

Empirical fit
Upper 95 % C.I.
Lower 95 % C.I.
Response to different doses

- Measured response in FDG at 3 months is significantly different between two dose levels in patient population ($p = 0.02$)

Bowen et al 2012, Radiother Oncol, 105(1), 41
Empirical prescription function

\[
D_0(FDG_{pre}) \approx D_0(FDG_{pre}) + \frac{dD}{d(FDG_{pre})} \left( \frac{d(FDG_{post})}{d(FDG_{pre})} \right) \left( FDG_{post} - \langle FDG_{post} \rangle \right) - \langle FDG_{post} \rangle
\]

\[
D(FDG_{pre}) \approx 50 \text{Gy} + \frac{8 \text{Gy}}{\langle FDG_{post} \rangle_{42 \text{Gy}} - \langle FDG_{post} \rangle_{50 \text{Gy}}} \cdot (\beta_{42 \text{Gy}} - \beta_{50 \text{Gy}}) (FDG_{pre} - \langle FDG_{pre} \rangle)
\]

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( &lt;FDG_{post} &gt;_{42 \text{Gy}} )</td>
<td>Mean 3 month post Tx FDG in response to 42 Gy</td>
<td>2.22 SUV</td>
</tr>
<tr>
<td>( &lt;FDG_{post} &gt;_{50 \text{Gy}} )</td>
<td>Mean 3 month post Tx FDG in response to 50 Gy</td>
<td>1.18 SUV</td>
</tr>
<tr>
<td>( \beta_{42 \text{Gy}} )</td>
<td>( FDG_{pre} ) regression coefficient in response to 42 Gy</td>
<td>0.84</td>
</tr>
<tr>
<td>( \beta_{50 \text{Gy}} )</td>
<td>( FDG_{pre} ) regression coefficient in response to 50 Gy</td>
<td>0.15</td>
</tr>
</tbody>
</table>
“Top-down” derived dose prescription

$FDG_{\text{pre}}$

$D(FDG_{\text{pre}})$
Why modeling?

**TOP-DOWN**

- Biological data
- Computational tumor modeling
- Observed therapeutic response

**BOTTOM-UP**

- Experiments
- Clinical trials
Computational tumor modeling

MACROSCOPIC MODELS
+ model tumor propagation and boundary phenomena
+ can utilize clinical imaging
  – limited biology (if at all)

HYBRID MULTISCALE MODELS

MICROSCOPIC MODELS
+ cells modeled separately
+ can refer to microscopy
  – very simplistic/idealized
  – tumor size limit 1-2 mm³
Hybrid multiscale model

**Therapy**
Administration of radiation, monitor levels of e.g. VEGF-A, bevacizumab and other chemotherapeutic agents

*(Simulate effects of different therapies over time)*

**General (globally valid)**
input parameters

**Patient-specific**
input from clinical imaging

- CT
- PET<sub>1</sub>
- PET<sub>2</sub>

- Initial anatomy
- Proliferation
- Hypoxia

**Cell-line-specific**
input from preclinical tumor models

**Cellular layer**
Assuming 10<sup>6</sup> cells/mm<sup>3</sup>, simulate cellular growth and death within ROI (or voxels) based upon biological principles, imaging data, and preclinical tumor models

**Tissue layer**

- simCT
- simPET
- simPET

- Anatomy
- Proliferation
- Hypoxia

**ROI-based application**
(average values)

- avg. & peak pO2
- avg. & peak SUV(FLT)
- avg. & peak SUV(CuATSM)
- avg. & peak PR
- SUV<sub>total</sub> etc.

**Voxel-based application**
(ROI is spatially resolved)

- pO2 [i,j,k]
- SUV(FLT) [i,j,k]
- SUV(CuATSM) [i,j,k]
- PR [i,j,k]
- Voxels of ROI interact

*Feedback*

Titz and Jeraj 2008, Phys Med Biol, 53: 4471
Tumor simulation workflow

- Pre- and mid-treatment PET data
- Creation of $a_{FLT}$ map
- Development of dose painting plans
- Simulation of end-of-treatment FLT

Titz and Jeraj 2008, Phys Med Biol, 53: 4471
### Benchmarking the model

<table>
<thead>
<tr>
<th></th>
<th>Hypoxia pre-XRT</th>
<th>Proliferation pre-XRT</th>
<th>Proliferation early response</th>
<th>Proliferation SIMULATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>sag</td>
<td>![Image]</td>
<td>![Image]</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
<tr>
<td>ax</td>
<td>![Image]</td>
<td>![Image]</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
<tr>
<td>cor</td>
<td>![Image]</td>
<td>![Image]</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
</tbody>
</table>

Titz and Jeraj 2008, Phys Med Biol, 53: 4471
Tuning of the free parameters

**Constant cell cycle time**

\[ R^2 = 0.7920 \]
\[ P = <0.0001 \]

**Proliferation-dependent cell cycle time**

\[ R^2 = 0.9360 \]
\[ P = <0.0001 \]

---

Titz and Jeraj 2012, Phys Med Biol, 57: 6079
Adding vasculature

Initial vasculature map → Angiogenesis → Update Vasculature map

Cu-ATSM (Hypoxia) → $pO_2$ (Oxygen) → TAF → Update pO$_2$ map

Time $t_0$ → SUV

FLT (Proliferation) → Update proliferation tumor volume
Simulated vasculature based on hypoxia

Adhikarla et al 2012, Phys Med Biol, 57: 6103
Simulating IHC

Input hypoxia on top of vessels and proliferating cells

Simulated hypoxia & proliferating cells overlaid on vessels

Adhikarla et al 2012, Phys Med Biol, 57: 6103
Adding therapeutic module…

VEGFR TKI

Dose response relationships

SU plasma concentration

Initial vasculature map

Angiogenesis

Update Vasculature map

Initial vasculature map

Angiogenesis

Update pO$_2$ map

Update pO$_2$ map

Update proliferation tumor volume

Cu-ATSM (Hypoxia)

pO$_2$ (Oxygen)

TAF

Update proliferation tumor volume

pO$_2$ (Oxygen)

SUV plasma concentration

Time $t_0$

Time $t$
Response to VEGFR TKI

**Vessels**

**Day 0**

- **Control**
- **SU 10 mg/kg/day**
- **SU 40 mg/kg/day**

**pO₂ mmHg**

- 30
- 0

**Day 6**

**Day 14**
How to apply this to dose painting?

Extracting “radiosensitivity” ($\alpha_{\text{eff}}$)

Imaging-based input
- FDG_pre PET
- FLT_pre PET
- CuATSM_pre PET
- FLT_mid PET

simulate FLT_mid PET scan

compare, calculate RSS

can RSS be minimized?
- yes
- no

1. stat analysis of $\alpha_{\text{eff}}$ data
2. correlation with PET tracers
Extracting “radiosensitivity” $\alpha_{eff}$ values
Optimization based on $\alpha_{\text{eff}}$ values

\[ D_i = D_{\text{Rx}} \left[ \frac{D_{\text{base}}}{D_{\text{Rx}}} + \left( \frac{D_{\text{redistributed}}}{D_{\text{Rx}}} \right) \cdot \frac{\tilde{\alpha}_{\text{FLT}}}{\alpha_{\text{FLT},i}} \cdot \kappa \right] \]

- 5%, 10%, 25%, 50% and 100% redistributed $D_{\text{RX}}$
- $D_{i,max} = 200\% D_{\text{RX}}$ and integral dose constant

Harmon et al 2013, Phys Med Biol (in submission)
Simulation results - proliferation

Dose Plan | simFLT after 5 fx | simFLT after 10 fx | SF_{FLT} after 10 fx
--- | --- | --- | ---
Uniform Dose | ![Image](image1.png) | ![Image](image2.png) | ![Image](image3.png)
25% D_{Rx} redistributed | ![Image](image4.png) | ![Image](image5.png) | ![Image](image6.png)
50% D_{Rx} redistributed | ![Image](image7.png) | ![Image](image8.png) | ![Image](image9.png)
100% D_{Rx} redistributed | ![Image](image10.png) | ![Image](image11.png) | ![Image](image12.png)
How much dose to redistribute?

High gains suggest good candidacy.

Low gains suggest poor candidacy.
Why differences?

\[ \alpha_{FLT} \text{ (Gy}^{-1}\text{)} \]

\[ \alpha_{FLT} \text{ (Gy}^{-1}\text{)} \]

\[ \alpha_{FLT} \text{ (Gy}^{-1}\text{)} \]
Why optimum?

\[ \approx 56\% \ D_{Rx} \]

10% Radioresistant subvolume 10% Radiosensitive subvolume

10% Radioresistant subvolume 10% Radiosensitive subvolume
Conclusion

- Modeling **bridges the gap** between biology and clinical outcomes

- **“Top down” approach:**
  - Heuristically determine dose response parameters based on clinical response data

- **“Bottom up” approach:**
  - Developing the models based on basic biological principles
  - Fitting the models to observed phenotypes (e.g., “radiosensitivity”)

- **Hybrid approach:**
  - Where do the worlds meet?
Thanks to:

- **Image-guided therapy group**
  - Vikram Adhikarla
  - Tyler Bradshaw
  - Enrique Cuna
  - Ngoneh Jallow
  - Matt La Fontaine
  - Stephanie Harmon
  - Surendra Prajapati
  - Urban Simoncic
  - Peter Scully
  - Damijan Valentinuzzi
  - Natalie Weisse
  - Stephen Yip
  - Former students…

- **Funding**
  - NIH, PCF, UWCCC, Pfizer, AstraZeneca, Amgen, EntreMed

- **Medical Oncology/Hematology**
  - Glenn Liu
  - George Wilding
  - Mark Juckett
  - Brad Kahl
  - Anne Traynor

- **Human Oncology**
  - Søren Bentzen
  - Bert van der Kogel
  - Paul Harari
  - Mark Ritter

- **Radiology**
  - Scott Perlman
  - Chris Jaskowiak

- **Veterinary School**
  - Lisa Forrest
  - David Vail

- **Medical Physics**
  - Rock Mackie
  - Jerry Nickles
  - Onofre DeJesus

- **Phase I and GU Office**