Mathematical Modeling in Cancer Therapy

- Speakers
  I. Clemens Grassberger: *Modeling interactions of biological agents & chemotherapy with radiation*
  II. Gilmer Valdes: *The Additive Tree*
  III. Guillaume Cazoulat: *Modeling Tissue Biomechanics for Image-Guided Cancer Therapy*

Modeling Interactions of Biological Agents & Chemotherapy with Radiation

Clemens Grassberger

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AAPM 2018 – Nashville

Outline

- Introduction / Motivation
- Modeling chemotherapy combined with radiation
  - Overview
  - TCP based modeling – population data
  - Dynamic Models of Clonogenic Growth
- Modeling targeted agents combined with radiation
  - Growth Modeling
  - Resistance Modeling
- Conclusion & Discussion

Introduction

- Optimization plays a large role in radiotherapy: delivery, fractionation, target dose, OAR tradeoffs
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Introduction

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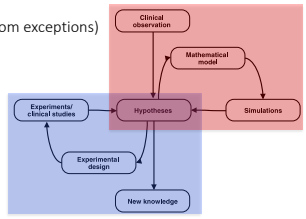
- Aim: introduce *clinically applicable* chemo-radiation modeling approaches & extensions necessary for modeling targeted agents



[1] Gallasch et al. 2013, Journal of Clinical Bioinformatics 2:23

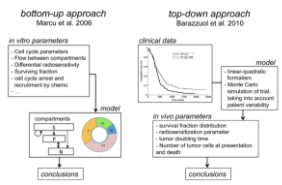
Prevalence of Concurrent Therapy → potential for Targeted Agents + RT

- Patients treated with combined chemo-radiation

Site	Incidence US 2015 number in '000 (% of total)	Percentage treated with chemotherapy and radiation	Targetable mutations
Breast	234 (14.1)	25%	HER2, mTor, CDK4/6
Lung	221 (13.3)	29%	EGFR, ALK, ROS, VEGF(R2), MET, PD-1
Colon	93(5.6)	40%**	VEGF(R2), EGFR, KIT/RAF
Bladder	74(4.5)	30%**	Possibly EGFR, FGFR3, mTOR, PIK3CA, RAS,
Non-HL	72(4.3)	12%	CD20/30, PI3K
Uterine corpus	55(3.3)	12%**	VEGF
Head and Neck	46(2.8)	30%*	EGFR, PI3K, Notch
Rectal	40(2.4)	12%	VEGF(R2), EGFR, KIT/RAF
Total	**835 (50.4)**	**26%**	

Modeling Therapy

- Two typical methods to develop a mathematic model



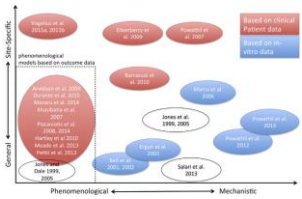
Grassberger & Paganetti, PMB 2016

Which approach is advisable depends on the research question and available data at hand, but generally it is assumed that:

- top-down approaches yield parameters that are closer to the in vivo situation,
- bottom-up models allow for more extrapolation outside of current clinical experience.

Types of Modeling Approaches

- Two "axes" on which models can be distinguished:
  - General <-> Site-Specific
  - Phenomenological <-> Mechanistic
- Models parameterized using
  - in vitro data
  - clinical patient data



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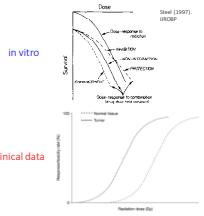
→ phenomenological models based on outcome data



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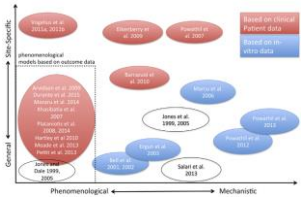

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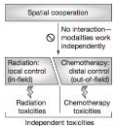
Modeling interaction of chemotherapy & radiation

- Two basic ways of thinking about cooperation
  - Spatial cooperation



Seiwert et al. (2007), Nat Clin Prac Onc

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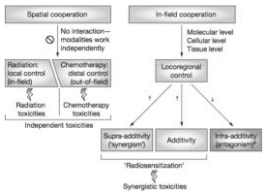

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Modeling interaction of chemotherapy & radiation

- Two basic ways of thinking about cooperation
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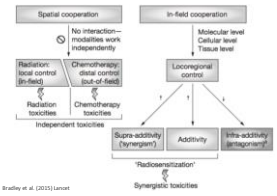
- Simplest way to "model" effect:
  Hazard Ratio

	60 Gy (n=232)*	74 Gy (n=207)	Cetuximab (n=222)*	No cetuximab (n=208)
Overall survival				
Dead	127	140	140	139
1 year	80·6% (73·9–86·7)	69·8% (62·3–76·6)	76·2% (70·2–81·1)	71·1% (64·1–76·6)
2 year	57·6% (50·0–64·5)	44·6% (37·1–51·7)	52·3% (45·6–58·5)	50·1% (43·1–56·6)
Median (months)	28·7 (24·1–34·5)	20·3 (17·7–25·0)	25·0 (20·7–30·5)	24·0 (19·5–31·6)
HR	1·38 (1·09–1·76)		1·07 (0·84–1·36)	-
p value (log-rank, one-sided)	0·004	-	0·29	-

Bradley et al. (2015) Lancet



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Modeling interaction of chemotherapy & radiation

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- Simplest way to "model" effect:
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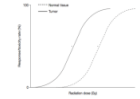
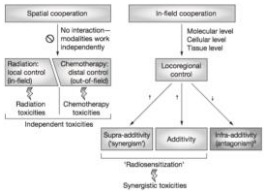
- Tumor Control Probability (TCP)





Seiwert et al. (2007). Nat Clin Prac Onc

Modeling interaction of chemotherapy & radiation

- Two basic ways to model chemotherapy combined with radiation
- Independent action

Chemo-only survival Radiation-only survival

$$OS = CS + RS(1 - CS)$$

chemo equals a dose of X GyE

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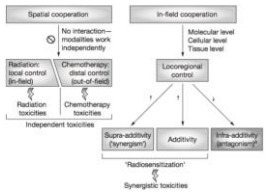
- Radiosensitization: TCP = f(BED)

$$BED = f_c D \left(1 + \frac{f_c * d}{\alpha/\beta}\right) - \frac{\ln 2}{\alpha} \cdot \frac{T}{T_d}$$

Radiosensitization factor: f_c

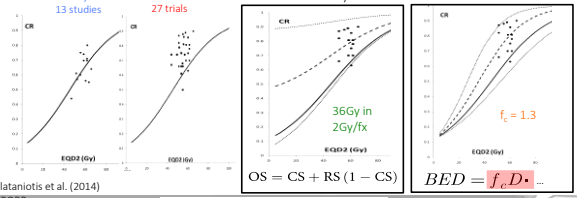


Seiwert et al. (2007). Nat Clin Prac Onc

Application – muscle-invasive bladder cancer

- modeling all published results of RT and chemo-RT in muscle-invasive bladder cancer
  - Used linear-quadratic model to fit radiation only

RT only: 13 studies Chemo-RT: 27 trials additive effect only Radiosensitization



Plataniotis et al. (2014) IJROBP

Overview over Clinical Studies

- Additive Effects:
  - Head and Neck: 7-12 Gy
  - Anal Cancer: 4-8 Gy
  - Cervical Cancer: 0.5-8 Gy
- radiosensitization factors: 1.2-1.35 in pancreas & bladder

Table 3. Quantified chemotherapy contributions either as chemo-equivalent radiation dose or as radiosensitization factor.

Source	Site	Effect type	Effect of chemotherapy
Plataniotis and Dale (2008)	Cervix	Independent action	Equivalent to 0.4–8 Gy in 2 Gy fractions, depending on tumor radiosensitivity
Kasibhatla *et al* (2007) and Fowler (2008)	Head and neck	Independent action	Equivalent to 8.8 Gy_{10} or 7.6 Gy in 2 Gy fractions
Monuru *et al* (2014)	Pancreas	Sensitization only	Radiosensitization factor 1.18–1.35
Plataniotis and Dale (2014)	Bladder	Independent action *or* sensitization	Equivalent to 36.3 Gy in 2 Gy fractions *or* radiosensitization factor of 1.3
Durante *et al* (2015)	Pancreas	Independent action	Equivalent to 94 $Gy_{2.35}$
Hartley *et al* (2010)	Head and neck	Independent action	Equivalent to 9.3 Gy_{10} for tumor and 6.4 Gy_{10} for mucosa
Pettit *et al* (2013)	Head and neck	Independent action	Equivalent to 3–12.7 Gy_{10}, depending on chemotherapy regimen
Pettit *et al* (2013)	Anal	Independent action	Equivalent to 4.1 Gy_{10} for 5-FU and 9.1 Gy_{10} for MMC/5-FU

Grassberger & Paganetti, PMB 2016

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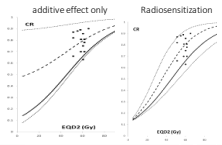

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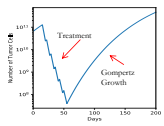
- Main Challenge: low "dimensionality" of clinical outcome data makes fitting of complex models difficult
- One solution: use the whole survival curve, or even patient-level data to inform models
- dynamic models of clonogenic growth

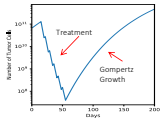


Dynamic Models of Clonogenic Growth

- formulations usually based on ordinary differential equations
  - Tumor growth: Gompertz
  - Radiation cell kill: Linear-Quadratic: $SF = e^{-(aD+bD^2)}$
  - Chemo cell kill: Log cell kill: $SF = e^{-(aD(t))}$

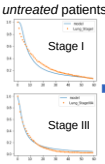
$$\frac{dN}{dt} = rN(t)\log\left(\frac{K}{N(t)}\right) - b_c C(t)N(t) - \left(aD + bD^2\right)N(t)$$

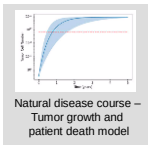
Growth → Gompertz; Chemotherapy → LOG cell kill; Radiation → Linear Quadratic



Modeling Multi-Modality Therapy for NSCLC

Survival of *untreated* patients





Natural disease course – Tumor growth and patient death model

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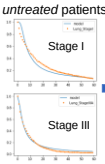
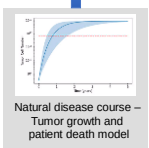
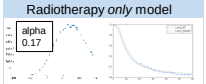




Natural disease course – Tumor growth and patient death model

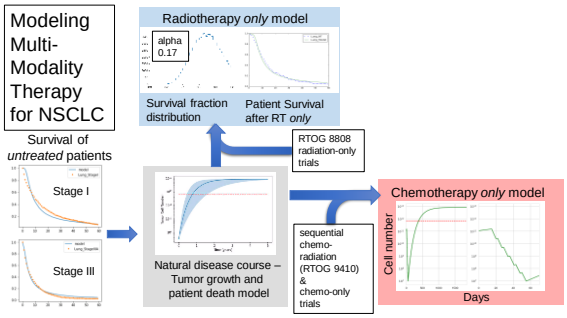
Radiotherapy *only* model

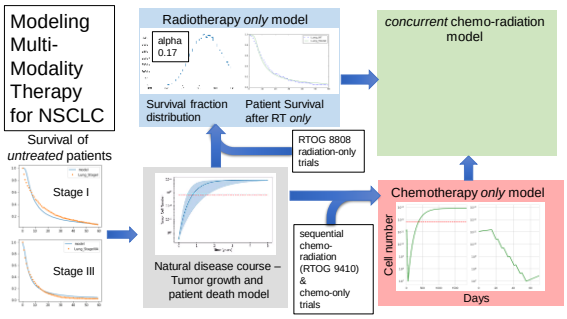


Survival fraction distribution

Patient Survival after RT *only*

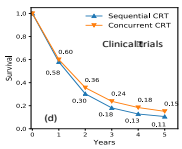
RTOG 8808 radiation-only trials





Concurrent vs Sequential CRT

- Idea: to combine radiation-only & chemo-only models → derive in-vivo radiosensitization factor



Auperin et al. JCO 2010

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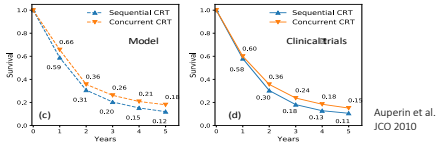

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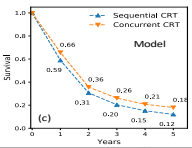
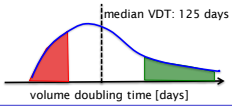
→ stratify the patients by growth rate results in variable difference between sequential and concurrent CRT





survival benefit concurrent vs sequential at 5 years	
top quartile	14.1%
bottom quartile	0.9%

Concurrent vs Sequential CRT

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→ stratify the patients by growth rate results in variable difference between sequential and concurrent CRT

- provides a framework for the optimization of combined chemo-radiation scheduling and sequencing, and can include other modalities, such as targeted agents

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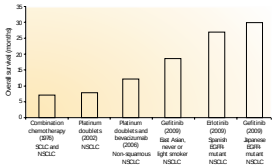
Targeted Therapy

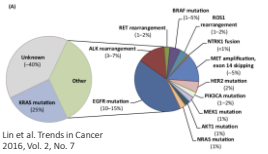
- Very successful in Non-Small Cell Lung Cancer (NSLC)



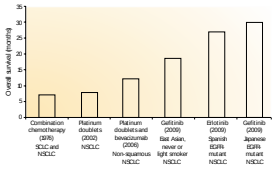
Pao et al. Nature Reviews 2010

Targeted Therapy

- Very successful in Non-Small Cell Lung Cancer (NSLC)
- Main oncogenic driver mutations for which FDA-approved inhibitors exist: EGFR & ROS/ALK



Lin et al. Trends in Cancer 2016, Vol. 2, No. 7



Pao et al. Nature Reviews 2010

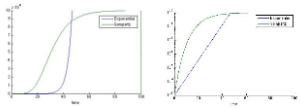
- better toxicity profiles

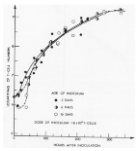
→ different mode of administration to chemo; not IV in cycles, but daily oral uptake

Targeted Agent Effect Models

- Similar to chemo, but need something additional → resistant sub-populations
- Modeling more sensitive to exact growth models
  - exponential growth is bad approximation over long time periods
  - more realistic growth models exhibit decreasing growth rate with increasing tumor size
  - most popular: Gompertz, Logistic

$$\frac{dV(t)}{dt} = r(t)V(t) \qquad \frac{dr(t)}{dt} = -\gamma \times r(t) \qquad \textit{Gompertz}$$

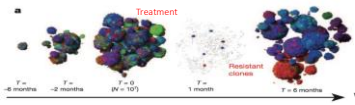




Laird 1964

Targeted Agent Effect Models

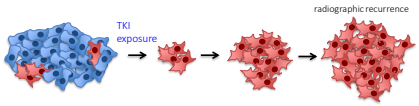
- Similar to chemo, but need something additional → resistant sub-populations
- Modeling more sensitive to exact growth models
- Resistance development
  - Develops in vast majority of cases
  - Mathematical formulation based on work in bacteriology (Luria & Delbrueck)
  - Used stochastic processes with a differentiation hierarchy to represent sensitive & resistant cells



Waclaw et al. Nature 2015

Modeling Resistance

- Pre-Existing Resistance



TKI-sensitive population N_S

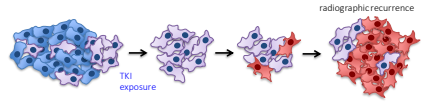
$$\frac{dN_S(t)}{dt} \simeq \begin{cases} l_S \times N_S(t) \log \frac{K(t)}{N_S(t)} & \text{growth in absence of drug} \\ -b \times l_S \times N_S(t) \log \frac{K(t)}{N_S(t)} & \text{cell loss in presence of drug} \end{cases}$$

TKI-resistant population N_R

$$\frac{dN_R(t)}{dt} = l_R \times N_R(t) \log \frac{K(t)}{N_R(t)}$$ growth independent of presence of drug

Modeling Resistance

- Pre-Existing Resistance
- Acquired Resistance (Persister-Evolution)

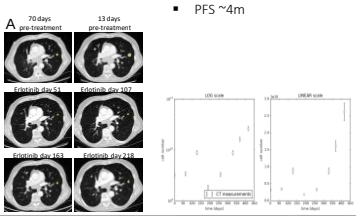


persister population N_P: $\frac{dN_P(t)}{dt} = -t(P \to R) \cdot N_P(t)$ — transition to resistant cells

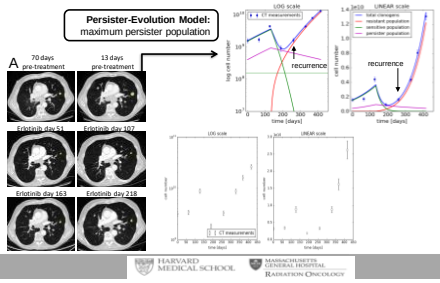
TKI-resistant population N_R: $\frac{dN_R(t)}{dt} = \begin{cases} l_R \times N_R(t) \log \frac{K(t)}{N_R(t)} \\ +t(P \to R) \cdot N_P(t) \end{cases}$ — growth independent of presence of drug; transition from persister cells

Modeling Resistance – Tumor Growth Trajectories

- stage IV NSCLC patient
- treated with erlotinib (EGFR-TKI)
- PFS ~4m

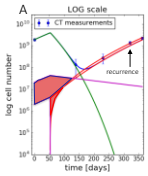


Modeling Resistance – Tumor Growth Trajectories

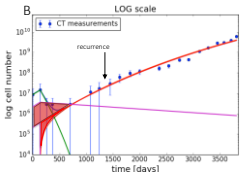


Modeling Resistance – Tumor Growth Trajectories

Patient 2: 8.7m PFS



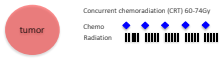
Patient 3: 36.3m PFS



- We can estimate the number of persister/resistant cells during therapy
- Why are we doing this?

Rationale for Modeling

- Targeted agents currently only used in a stage IV setting
- Targetable mutations also exist in stage III disease



Rationale for Modeling

- Targeted agents currently only used in a stage IV setting
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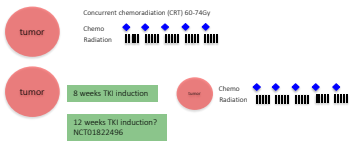
→ NCT01553942 – the ASCENT trial



Rationale for Modeling

- Targeted agents currently only used in a stage IV setting
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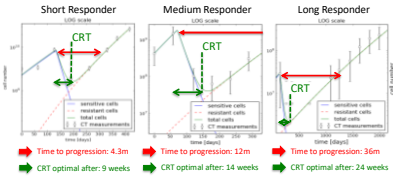
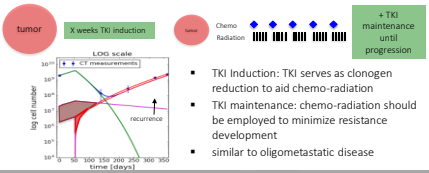
- Application: to find optimal induction lengths for stage III patients (patient-specific?)



Rationale for Modeling

- Targeted agents currently only used in a stage IV setting
- Targetable mutations also exist in stage III disease
- Application: to find optimal induction lengths for stage III patients (patient-specific?)
- Maintenance therapy



- TKI Induction: TKI serves as clonogen reduction to aid chemo-radiation
- TKI maintenance: chemo-radiation should be employed to minimize resistance development
- similar to oligometastatic disease

Take aways – chemo-radiation modeling

- 2 main ways to see chemo-radiation when analyzing clinical data: spatial vs. in-field cooperation
  additive action vs. radiosensitization
  - usually you go into data-analysis with a pre-existing assumption
  - Not the case for in-vitro / preclinical models (interaction via cell-cycle dynamics, inhibition of repair pathways, …)
  - standard biostatistical outcome analysis always a good idea
- Difference chemotherapy/RT modeling
  - RT: modeled continuously, linear-quadratic model
  - chemotherapy: modeled binary, no dose-dependence

Take aways – targeted agent modeling

- Combining RT with targeted agents requires new approaches & extended models
  - Growth – realistic growth models due to longer time frames
  - Resistance – emergence of completely resistant sub-populations
- shifting aims – is the purpose of the RT regimen either to
  - maximize cell kill OR
  - minimize resistance development (to EGFR/ALK/ROS inhibitor)
- Essential for their inclusion in stage III, raises interesting question/trade-off:
  - is RT there to support the agent or the other way round?
- the extent of molecular sub-typing will inhibit clinical trials for every indication & combination

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