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

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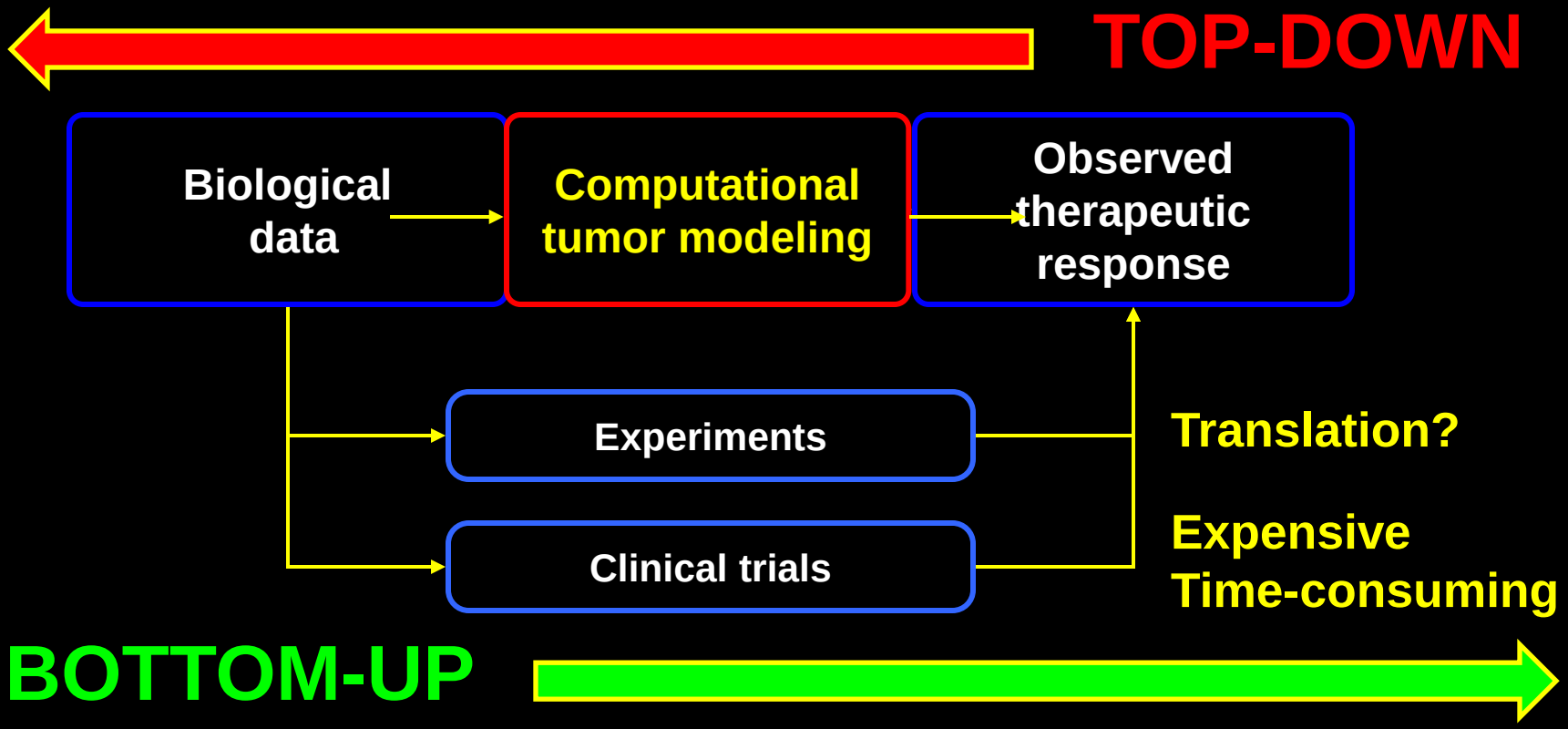
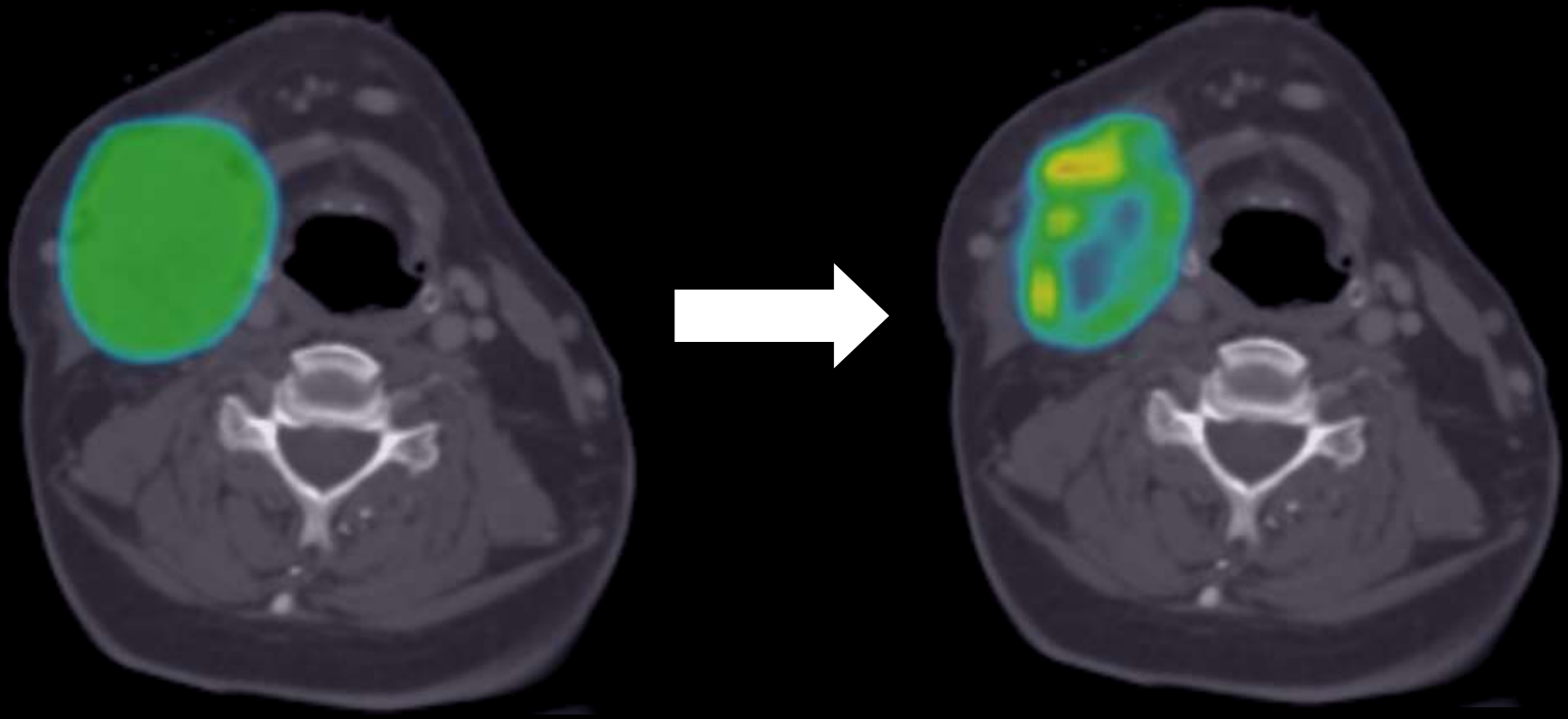
Why modeling?



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

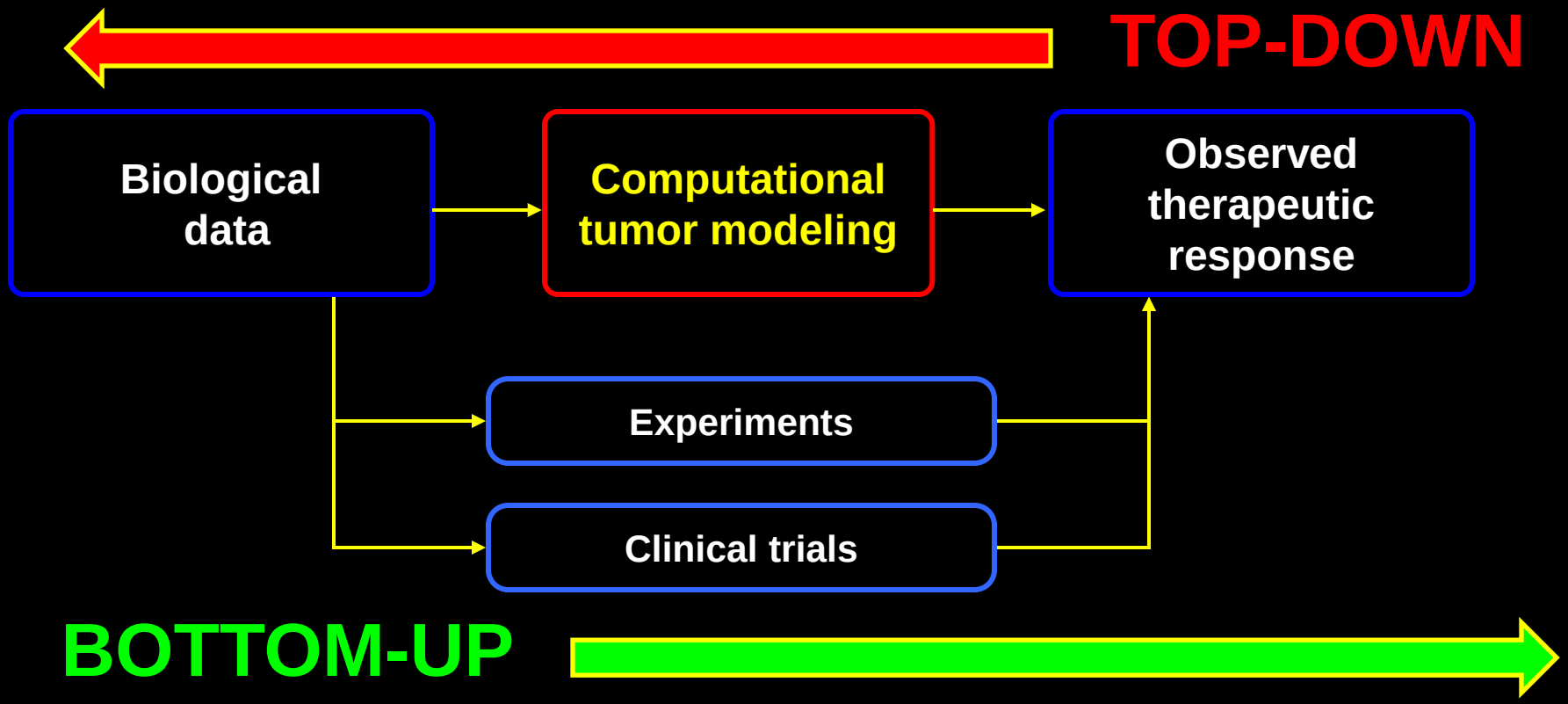
Problem of dose painting



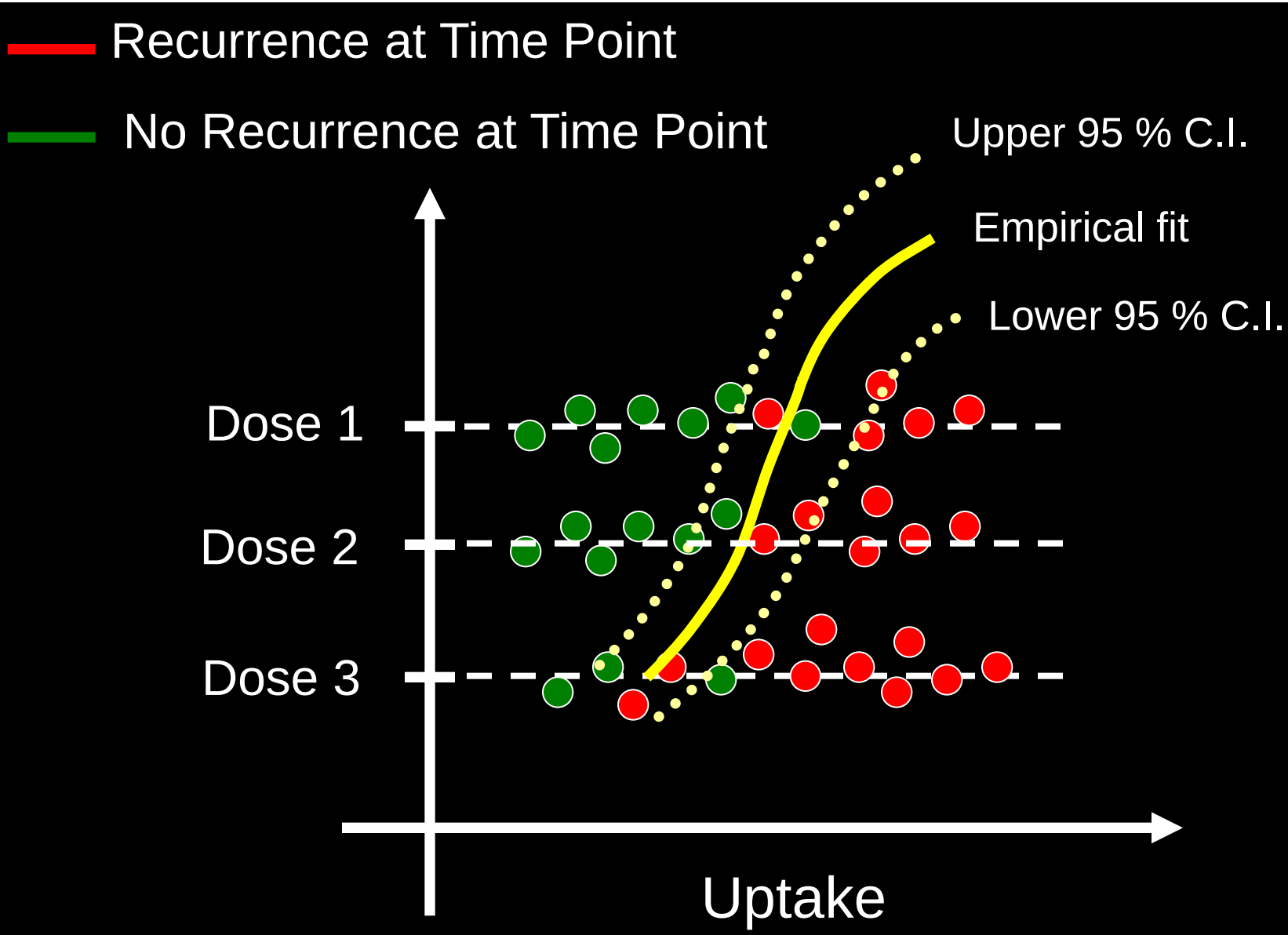
Anatomical imaging
Population-based
Uniform dose

Molecular imaging
Patient-specific
Non-uniform dose

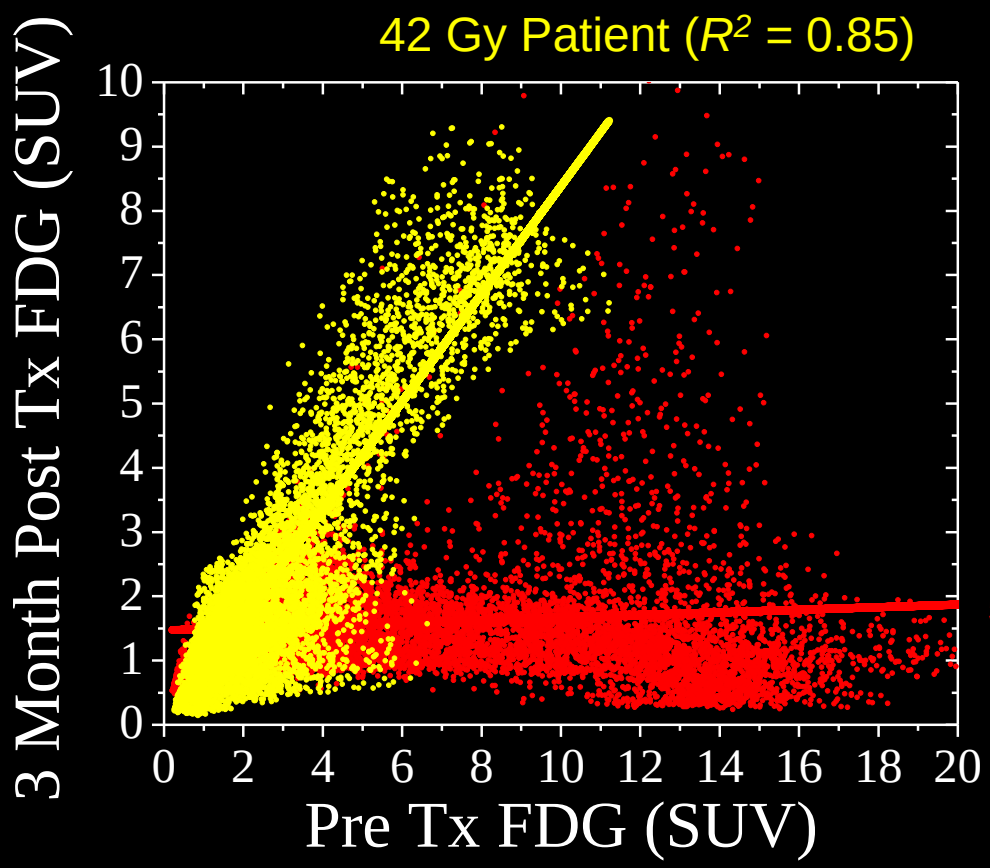
Why modeling?



How much dose?



Response to different doses



Observed Response to 50 Gy

Predicted Response to 50 Gy

Observed Response to 42 Gy

Predicted Response to 42 Gy

50 Gy Patient (R^2 = 0.38)

- 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

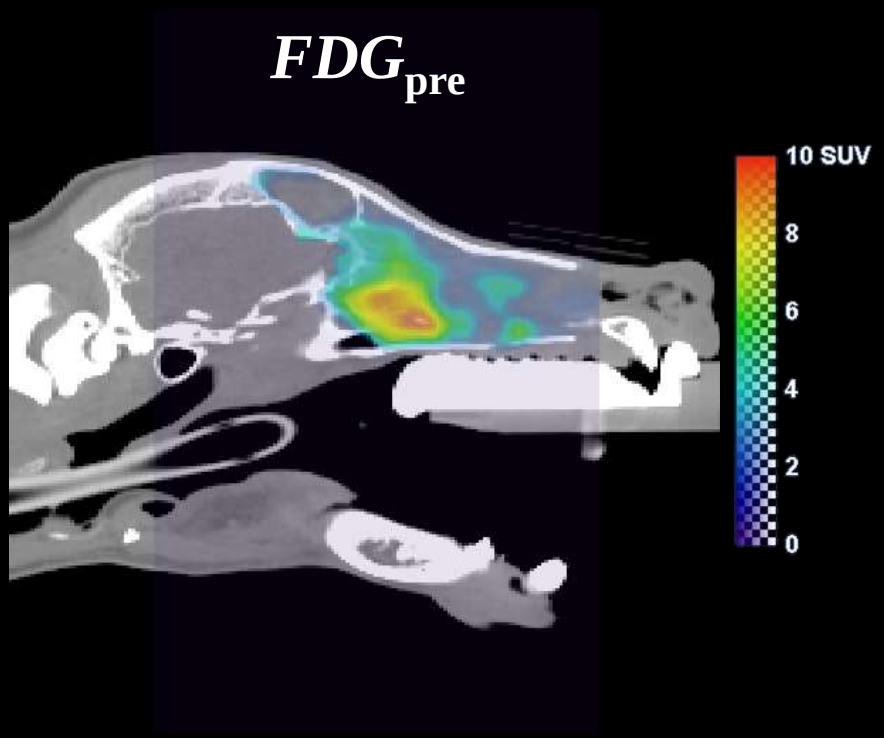
Empirical prescription function

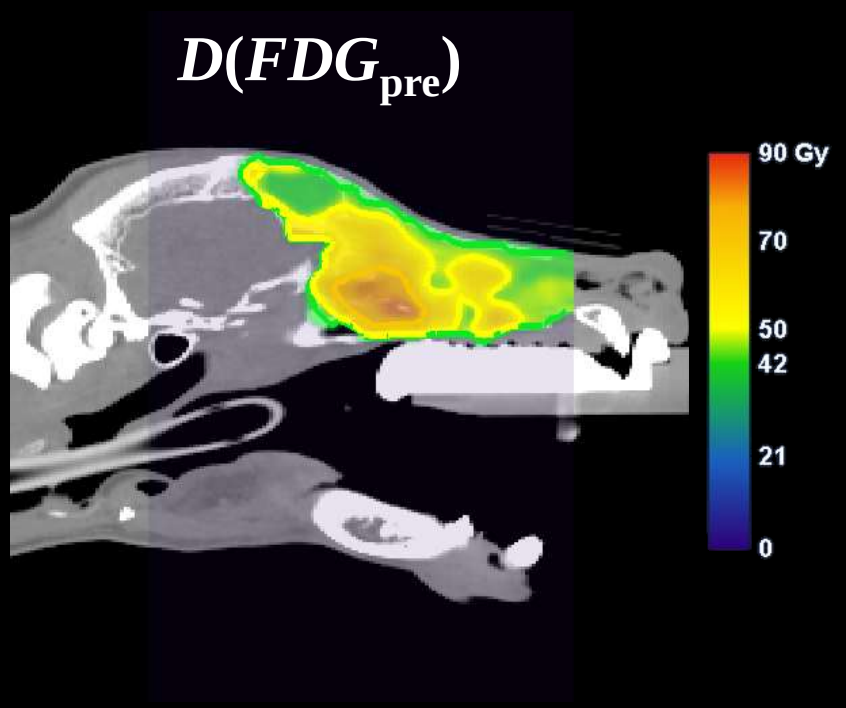
$$D\left(FDG_{pre}\right) \approx D\left(\left\langle FDG_{pre}\right\rangle\right) + \frac{dD}{d\left(FDG_{post}\right)} \cdot \frac{d\left(FDG_{post}\right)}{d\left(FDG_{pre}\right)} \left(FDG_{pre} - \left\langle FDG_{pre}\right\rangle\right)$$

$$D\left(FDG_{pre}\right) \approx 50Gy + \frac{8Gy}{\left\langle FDG_{post}\right\rangle_{42Gy} - \left\langle FDG_{post}\right\rangle_{50Gy}} \cdot \left(\beta_{42Gy} - \beta_{50Gy}\right)\left(FDG_{pre} - \left\langle FDG_{pre}\right\rangle\right)$$

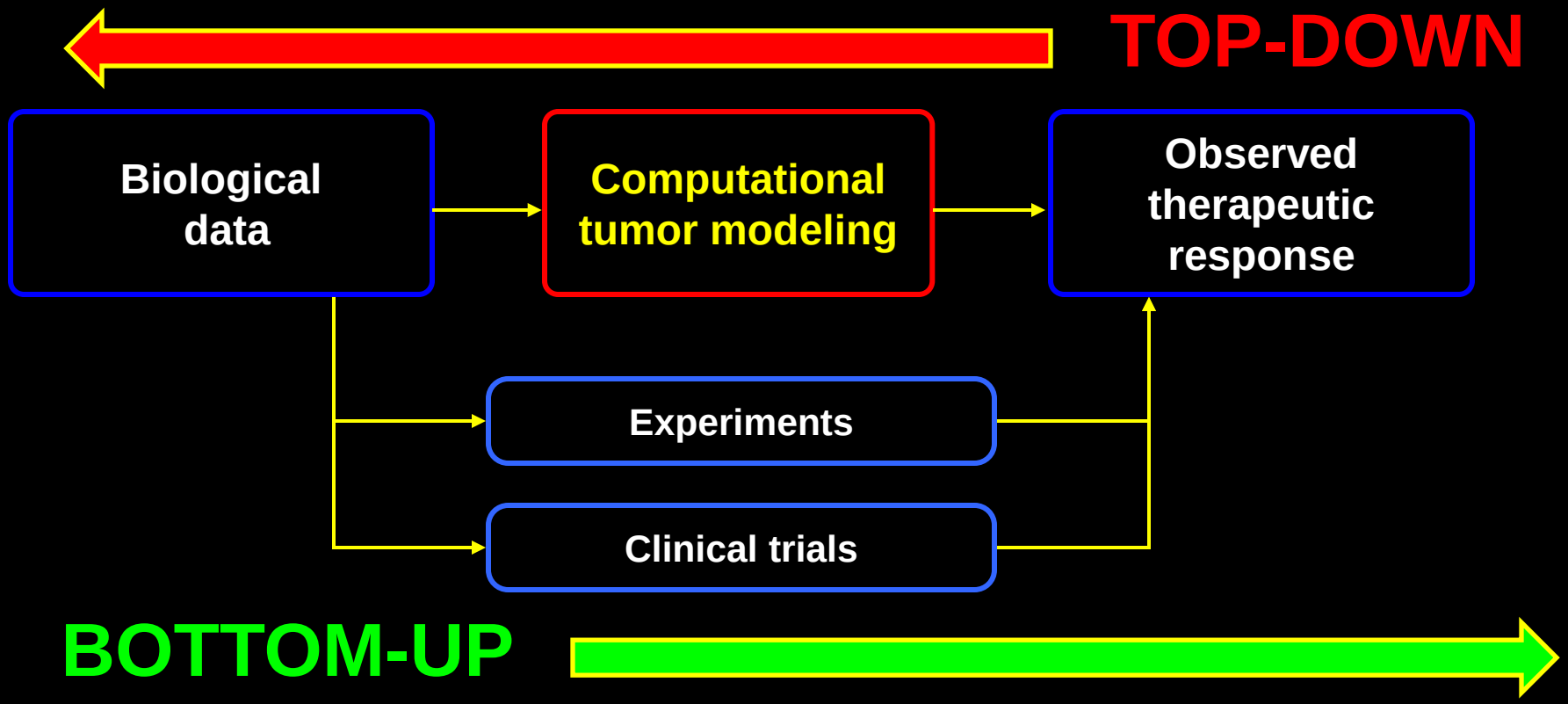
Symbol	Parameter	Value
$<FDG_{post}>_{42Gy}$	Mean 3 month post Tx FDG in response to 42 Gy	2.22 SUV
$<FDG_{post}>_{50Gy}$	Mean 3 month post Tx FDG in response to 50 Gy	1.18 SUV
β_{42Gy}	FDG_{pre} regression coefficient in response to 42 Gy	0.84
β_{50Gy}	FDG_{pre} regression coefficient in response to 50 Gy	0.15

“Top-down” derived dose prescription





Why modeling?



Computational tumor modeling

MACROSCOPIC MODELS

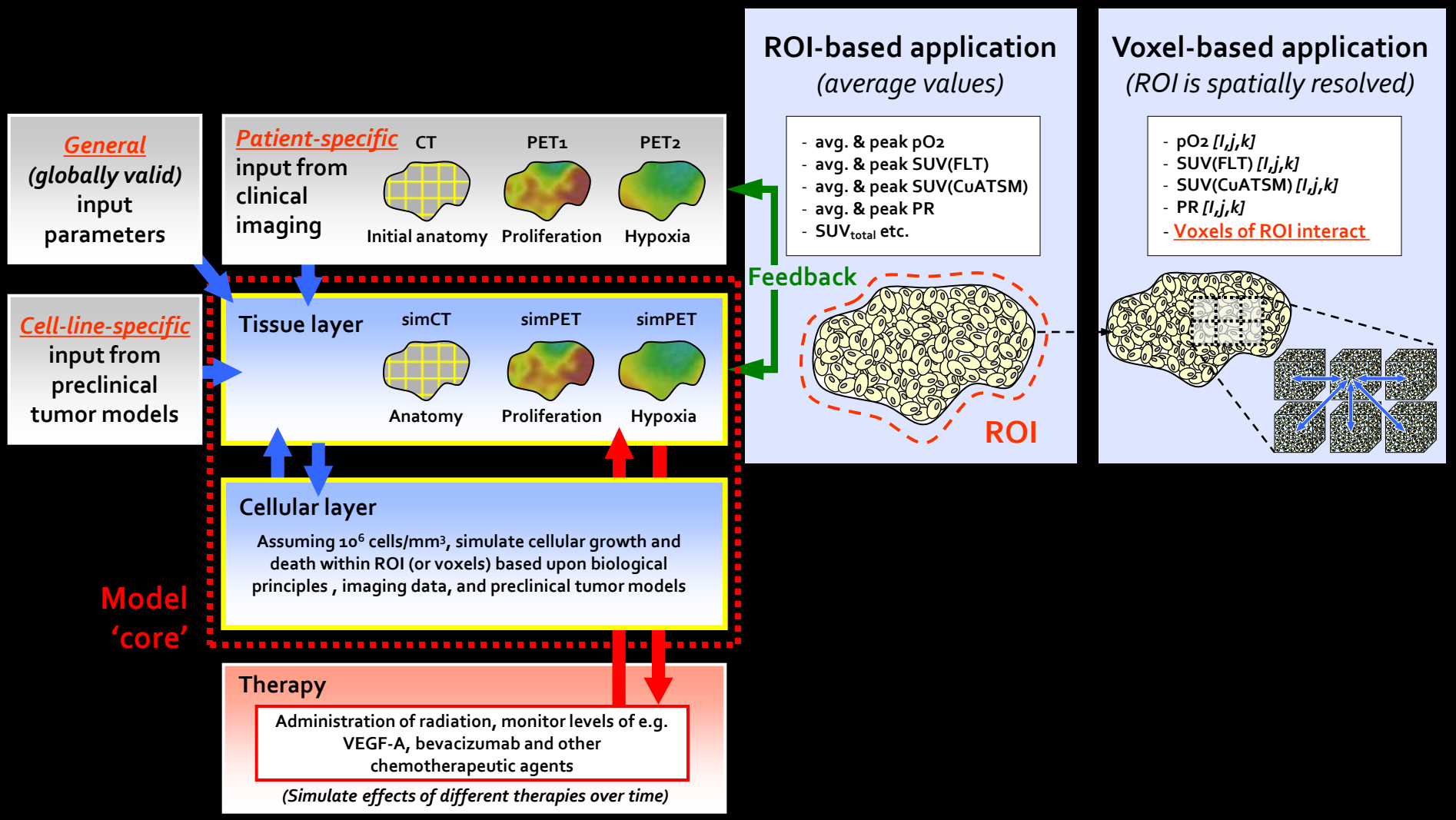
+ model tumor propagation and boundary phenomena
+ can utilize clinical imaging
– limited biology (if at all)

HYBRID MULTISCALE MODELS

MICROSCOPIC MODELS

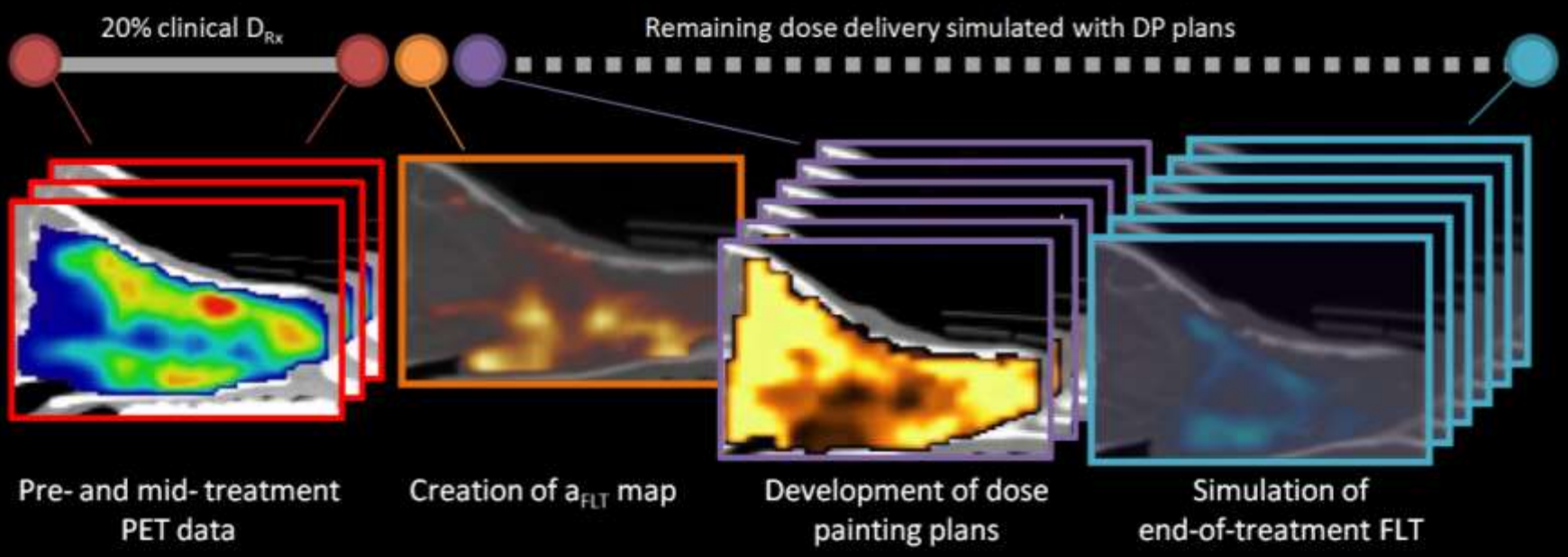
+ cells modeled separately
+ can refer to microscopy
– very simplistic/idealized
– tumor size limit 1-2 mm^3

Hybrid multiscale model



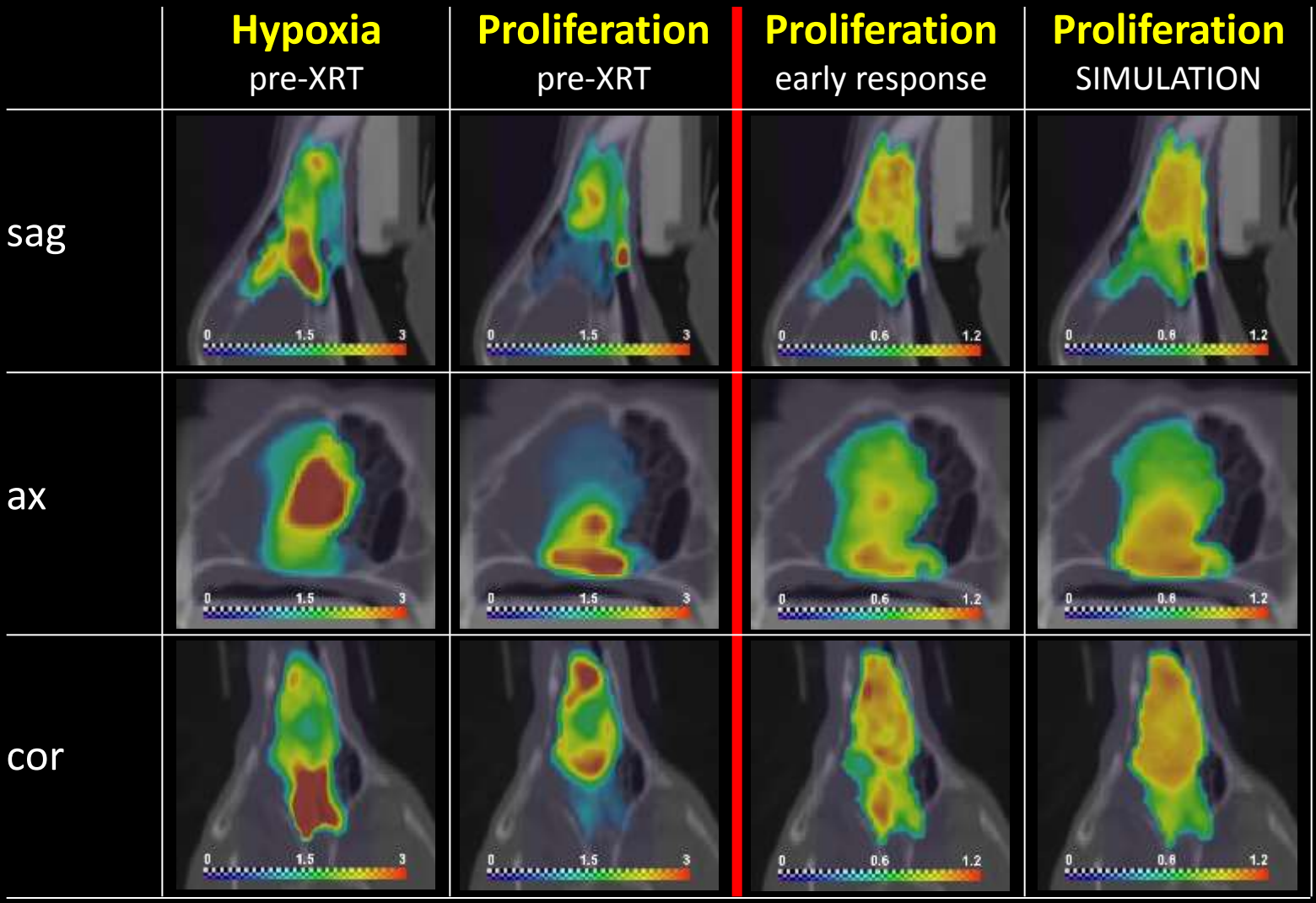
Titz and Jeraj 2008, Phys Med Biol, 53: 4471

Tumor simulation workflow



Titz and Jeraj 2008, Phys Med Biol, 53: 4471

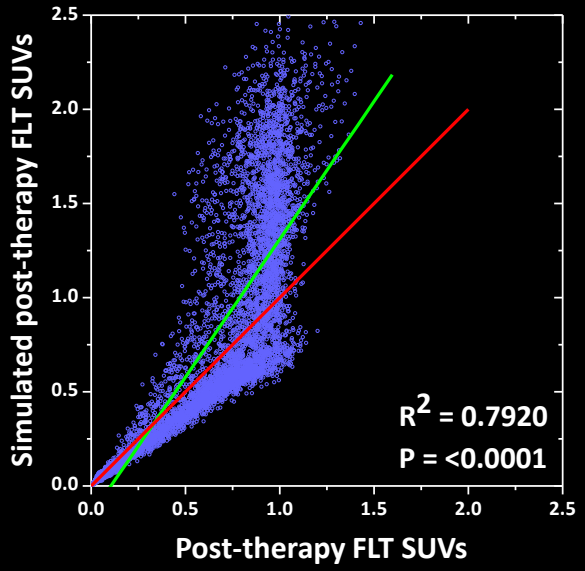
Benchmarking the model



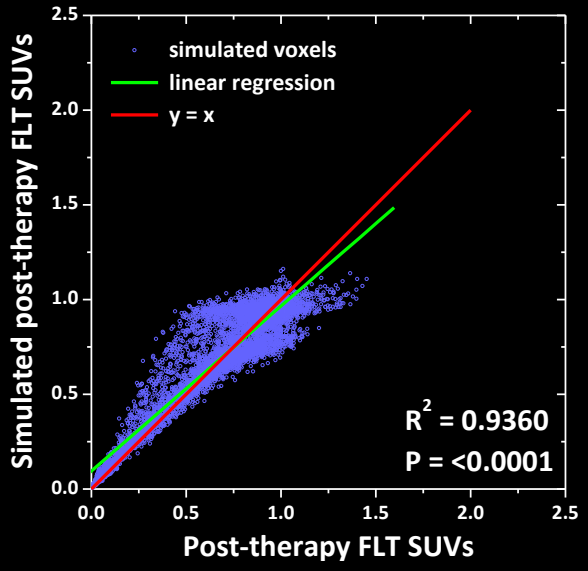
Titz and Jeraj 2008, Phys Med Biol, 53: 4471

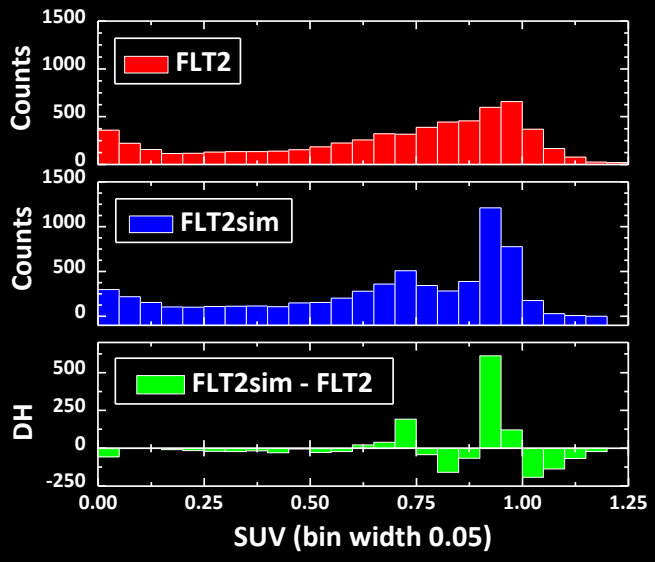
Tuning of the free parameters

Constant cell cycle time



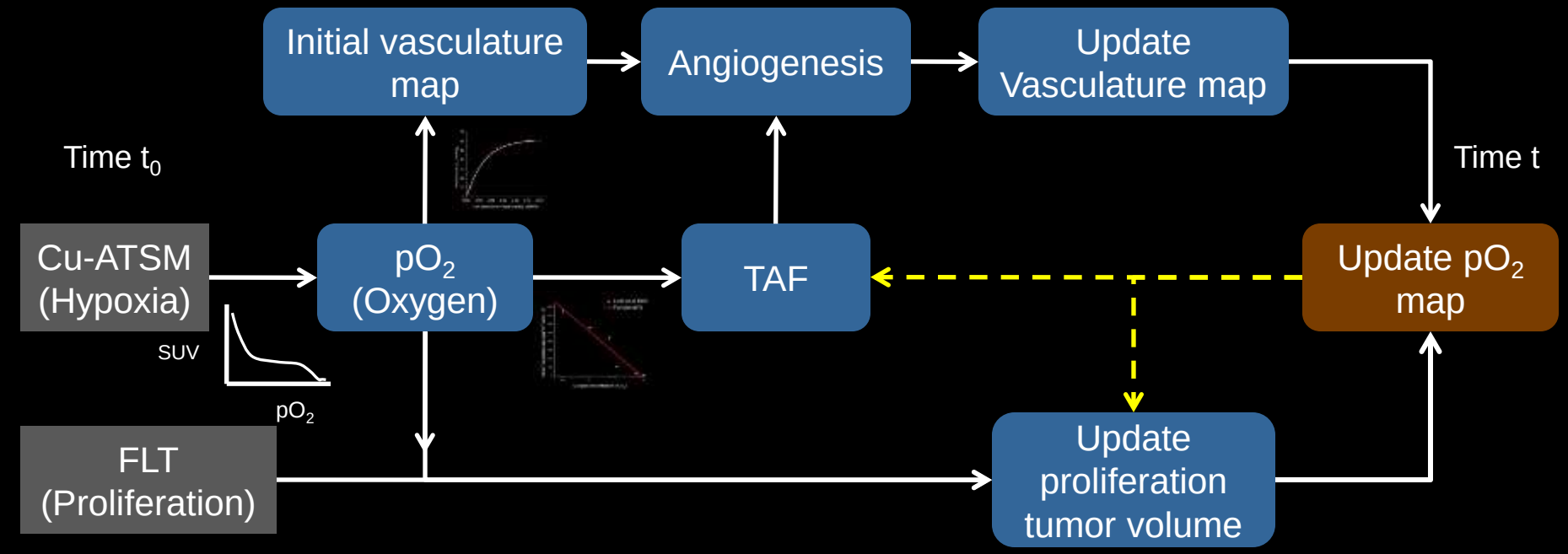
Proliferation-dependent cell cycle time



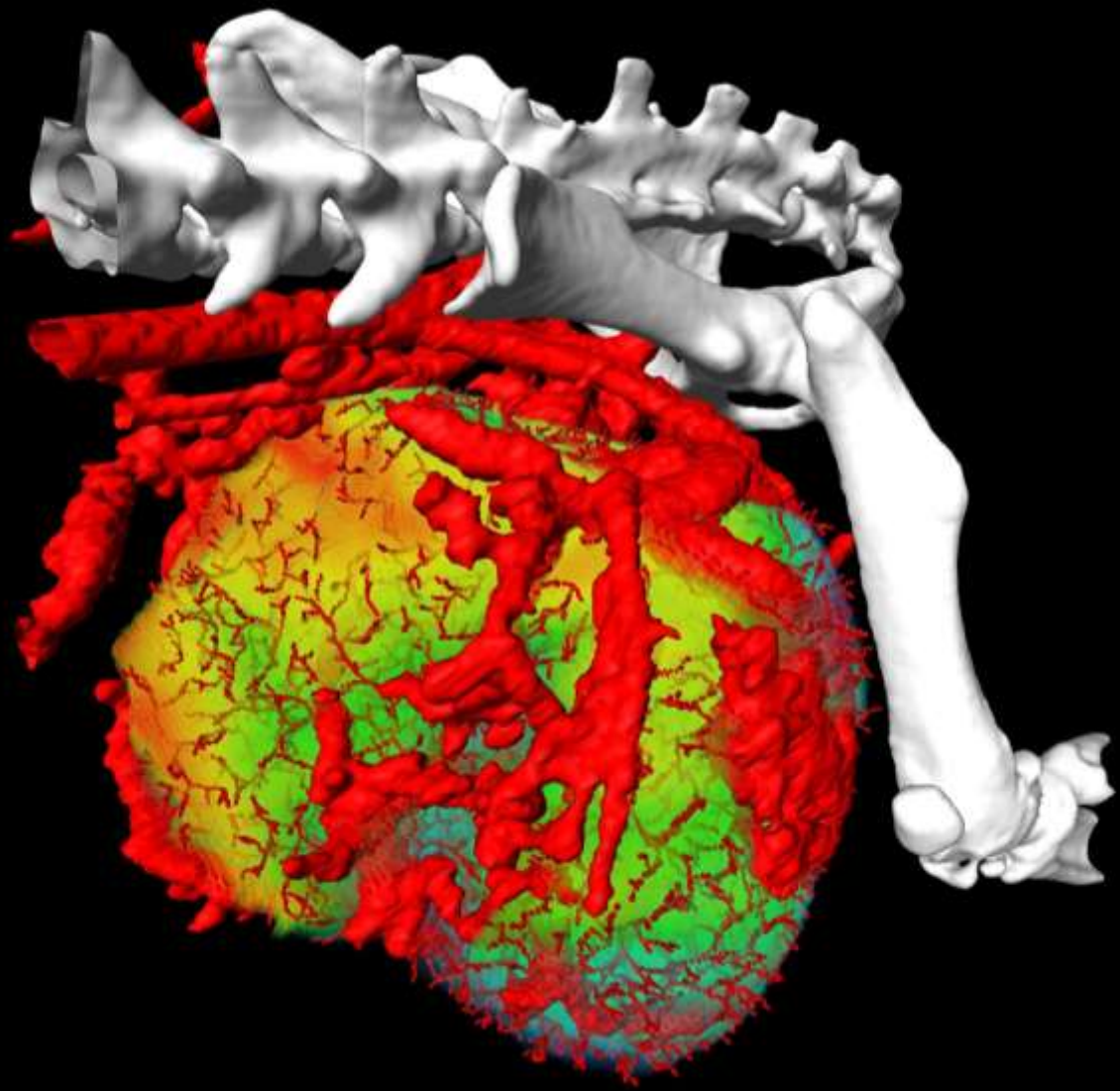


Titz and Jeraj 2012, Phys Med Biol, 57: 6079

Adding vasculature



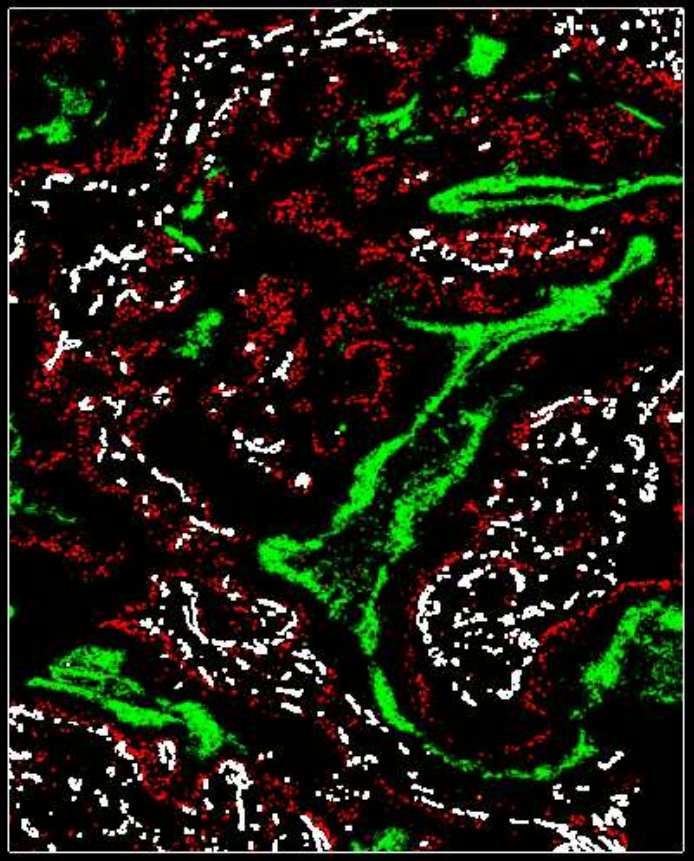
Simulated vasculature based on hypoxia



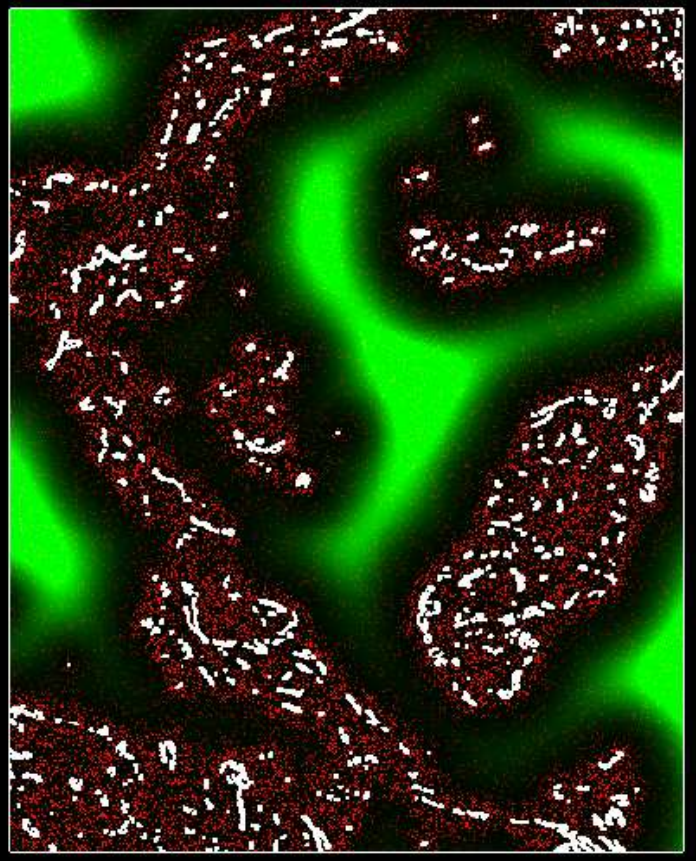
Adhikarla et al 2012, Phys Med Biol, 57: 6103

Simulating IHC

Vessels Proliferating cells Hypoxic cells



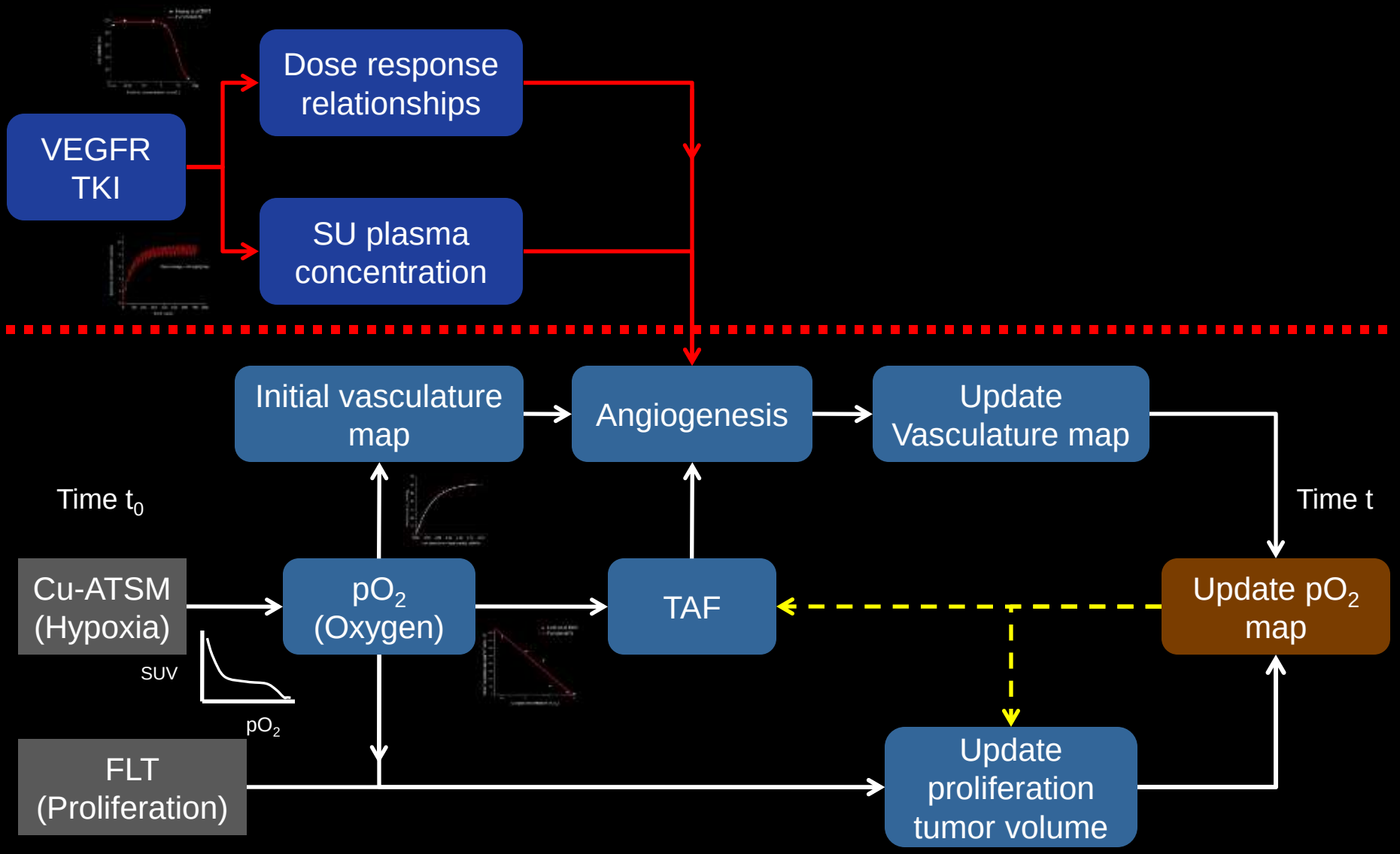
Input hypoxia on top of vessels and proliferating cells



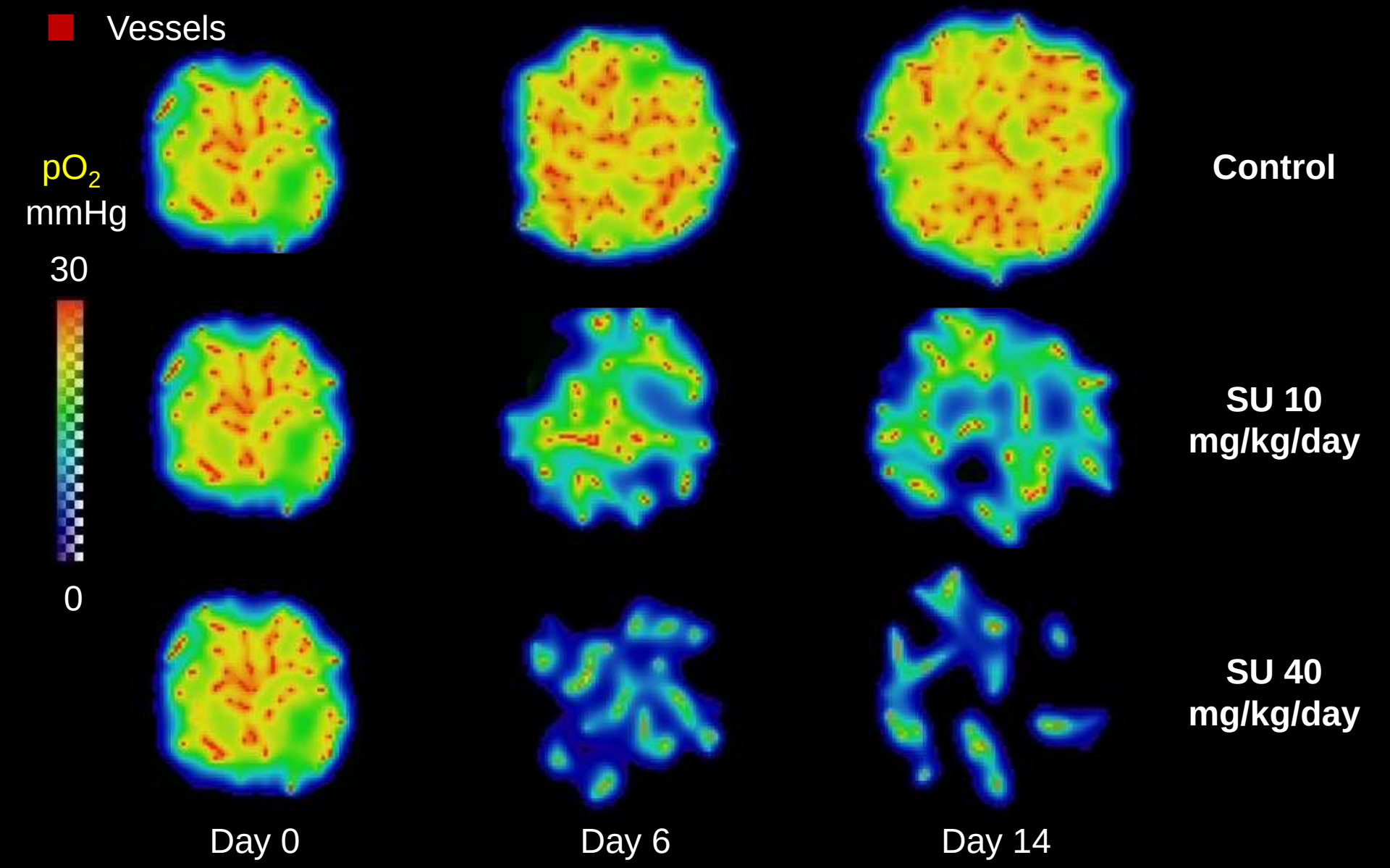
Simulated hypoxia & proliferating cells overlaid on vessels

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

Adding therapeutic module…

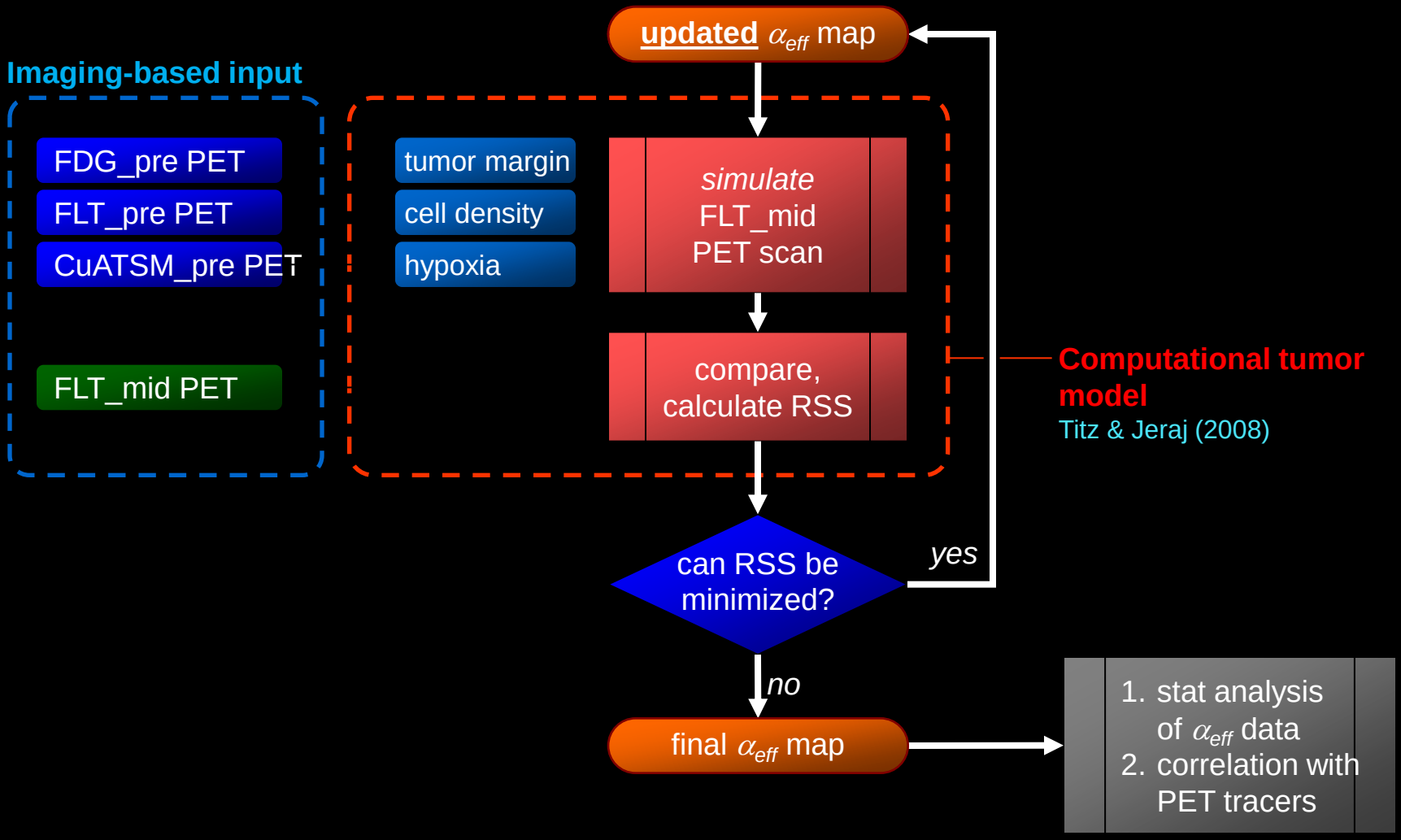


Response to VEGFR TKI

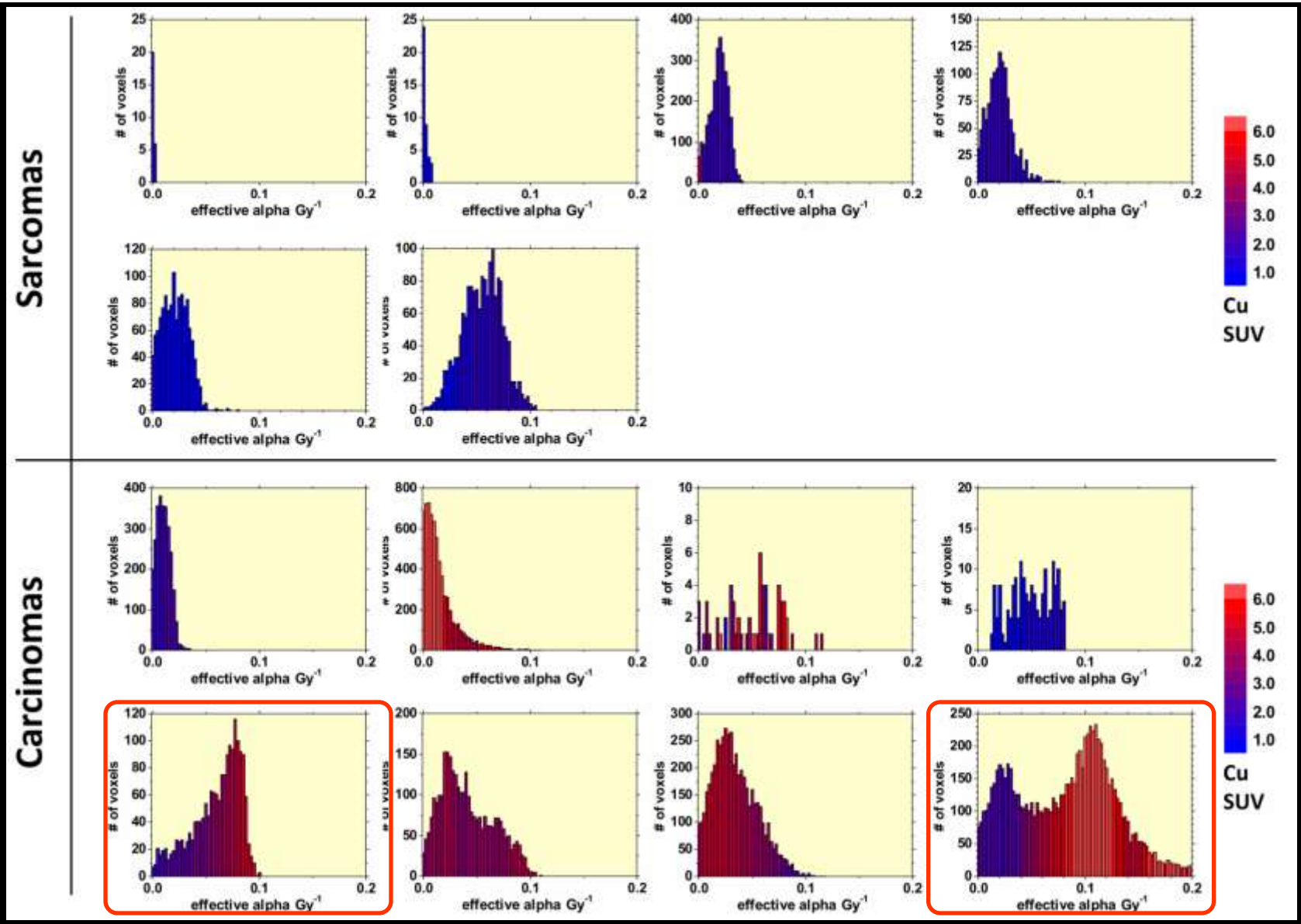


How to apply this to dose painting?

Extracting "radiosensitivity" (α_{eff})



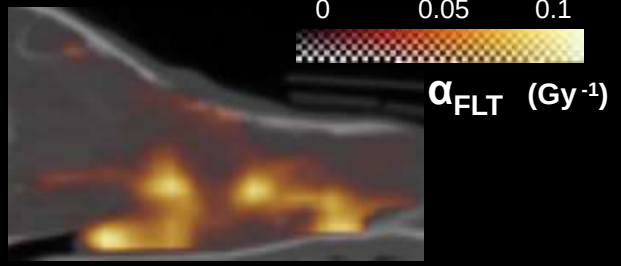
Extracting "radiosensitivity" α_{eff} values



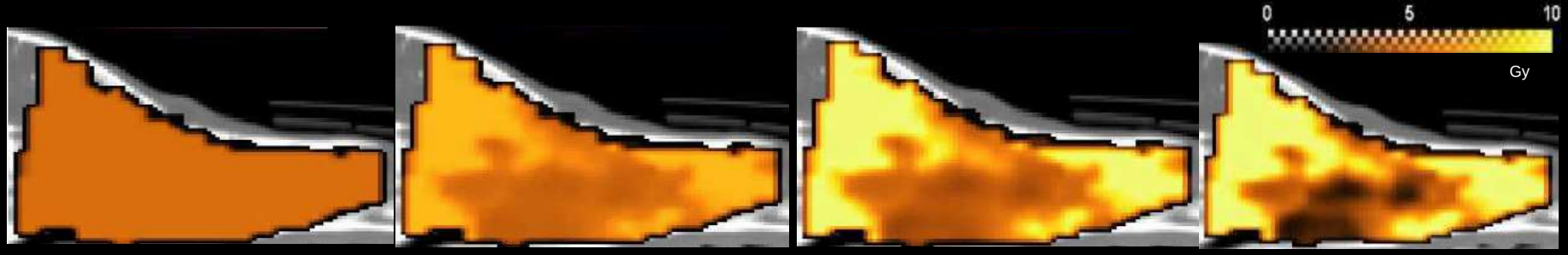
Optimization based on α_{eff} values

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

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

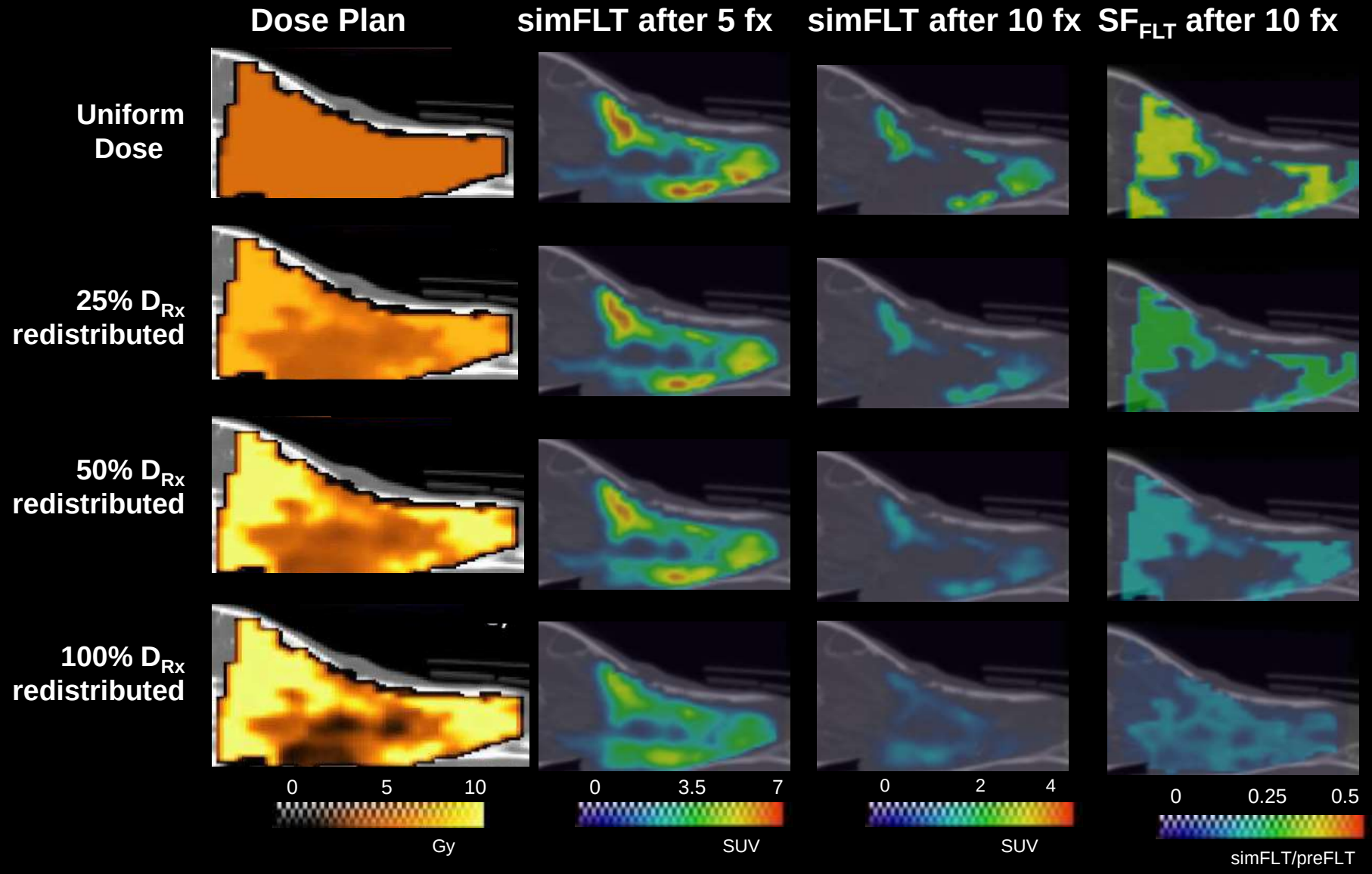


Uniform Dose | **25% D_{Rx} redistributed** | **50% D_{Rx} redistributed** | **100% D_{Rx} redistributed**

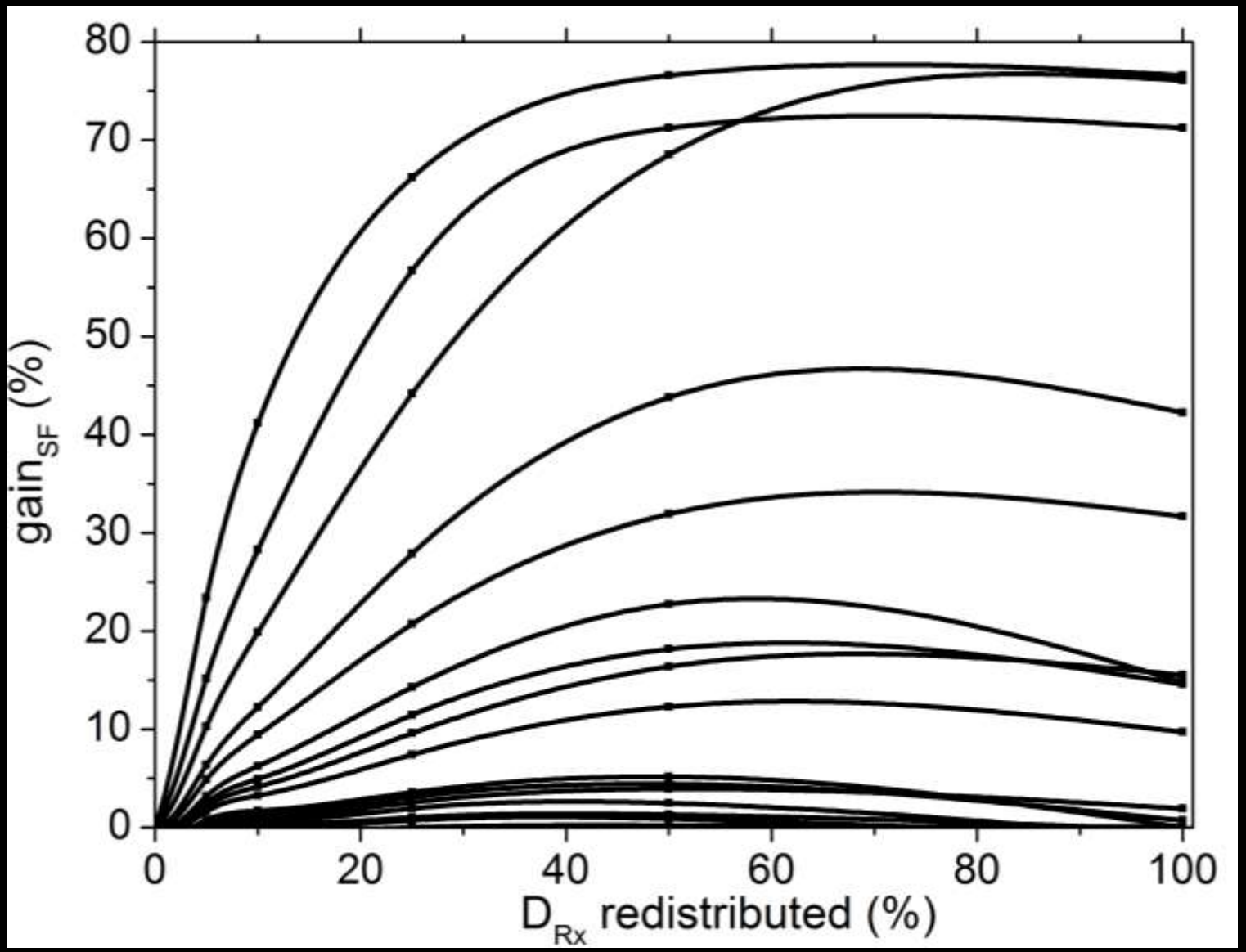


Harmon et al 2013, Phys Med Biol (in submition)

Simulation results - proliferation



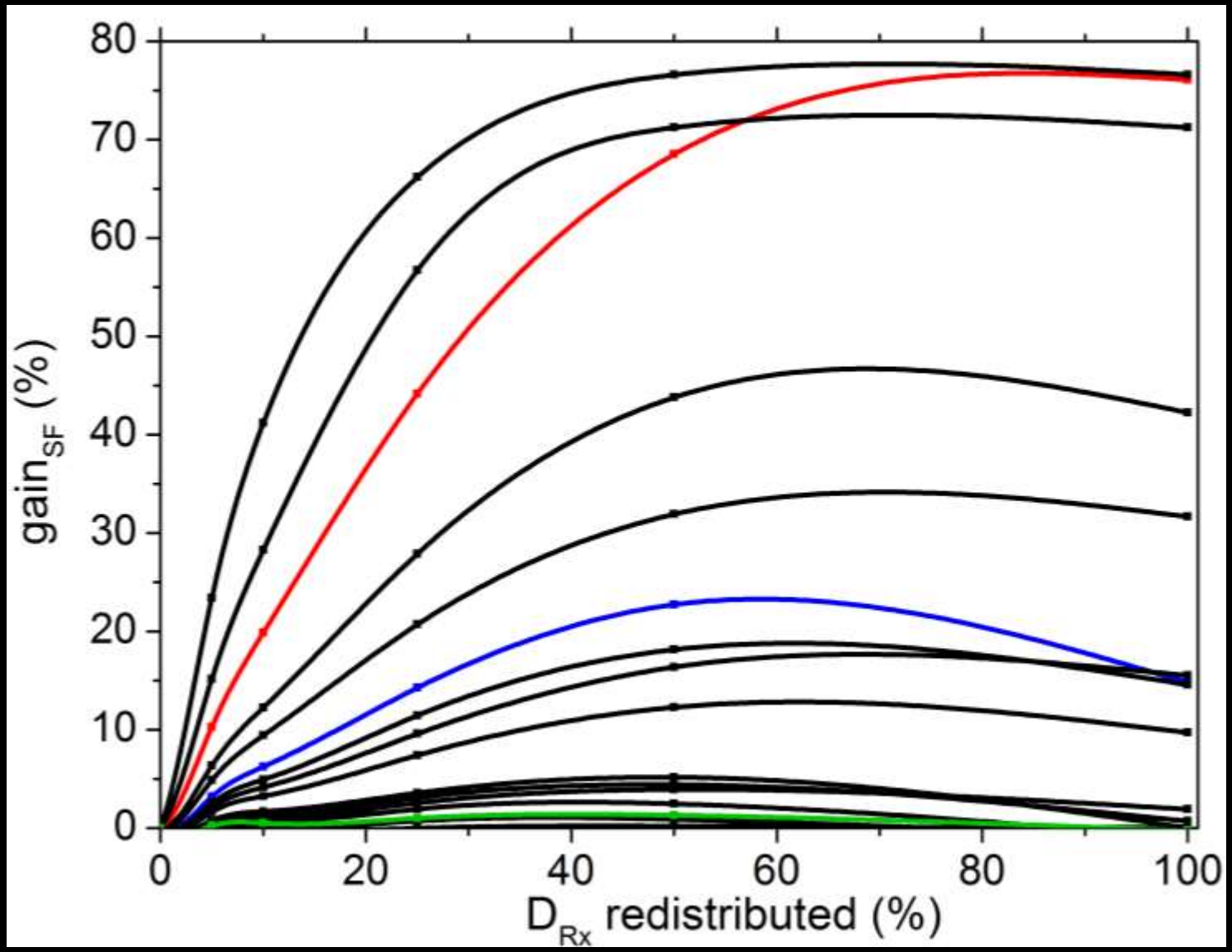
How much dose to redistribute?

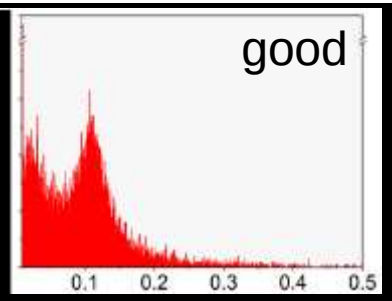


High gains suggest good candidacy

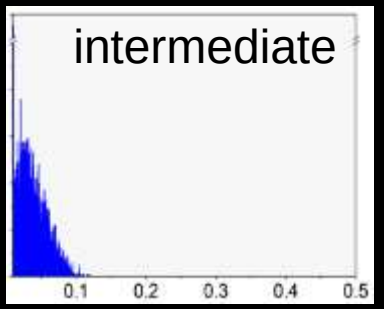
Low gains suggest poor candidacy

Why differences?

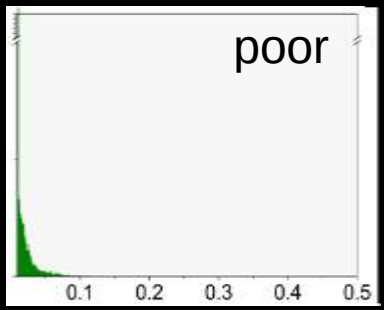




α_{FLT} (Gy^{-1})

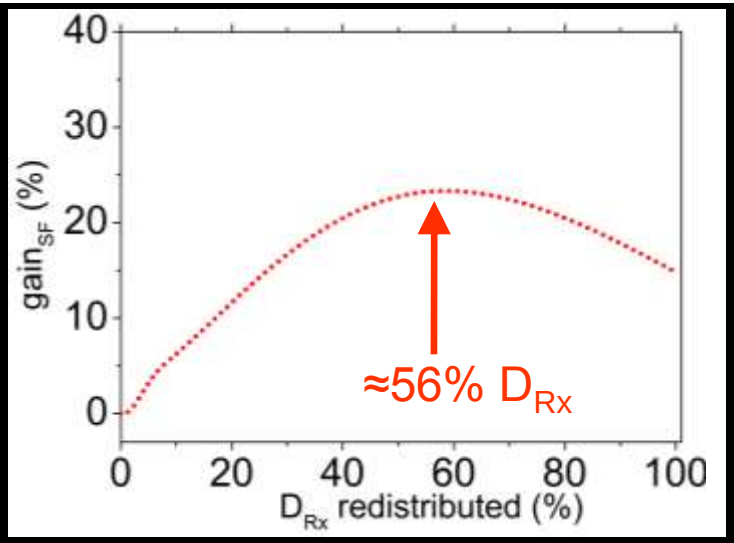


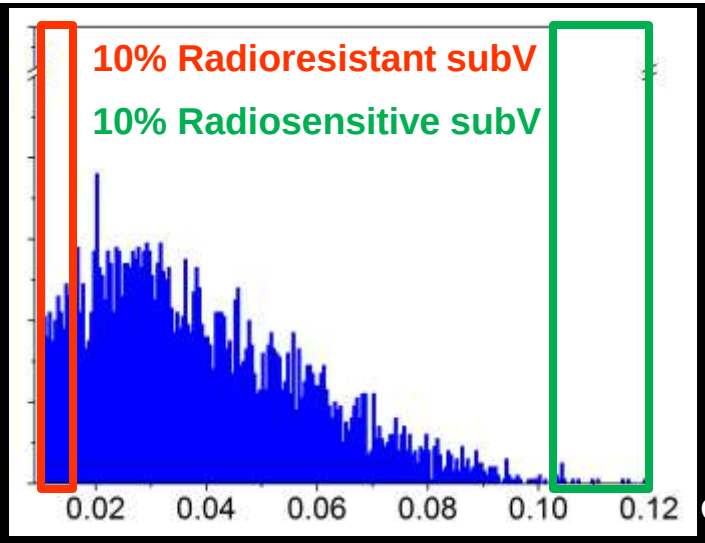
α_{FLT} (Gy^{-1})



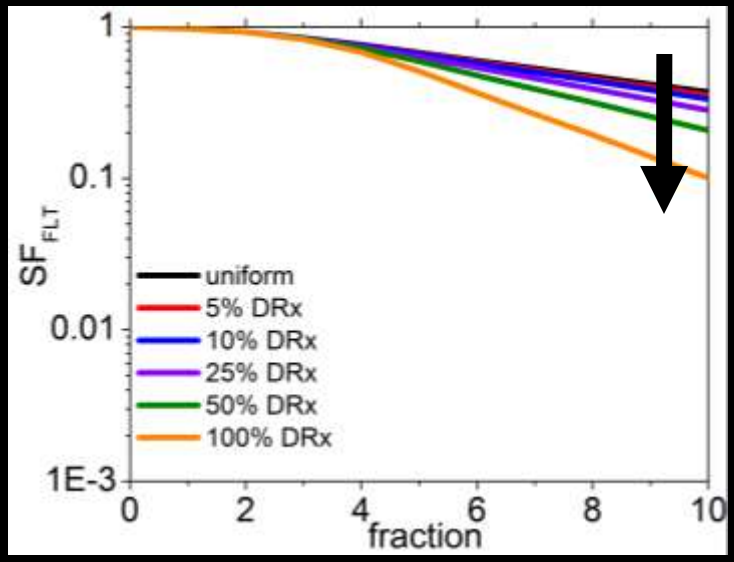
α_{FLT} (Gy^{-1})

Why optimum?

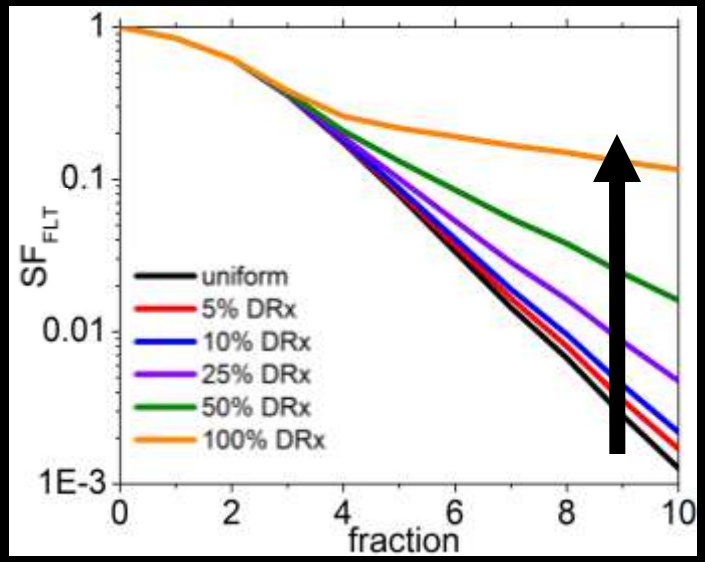




10% Radioresistant subvolume



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**