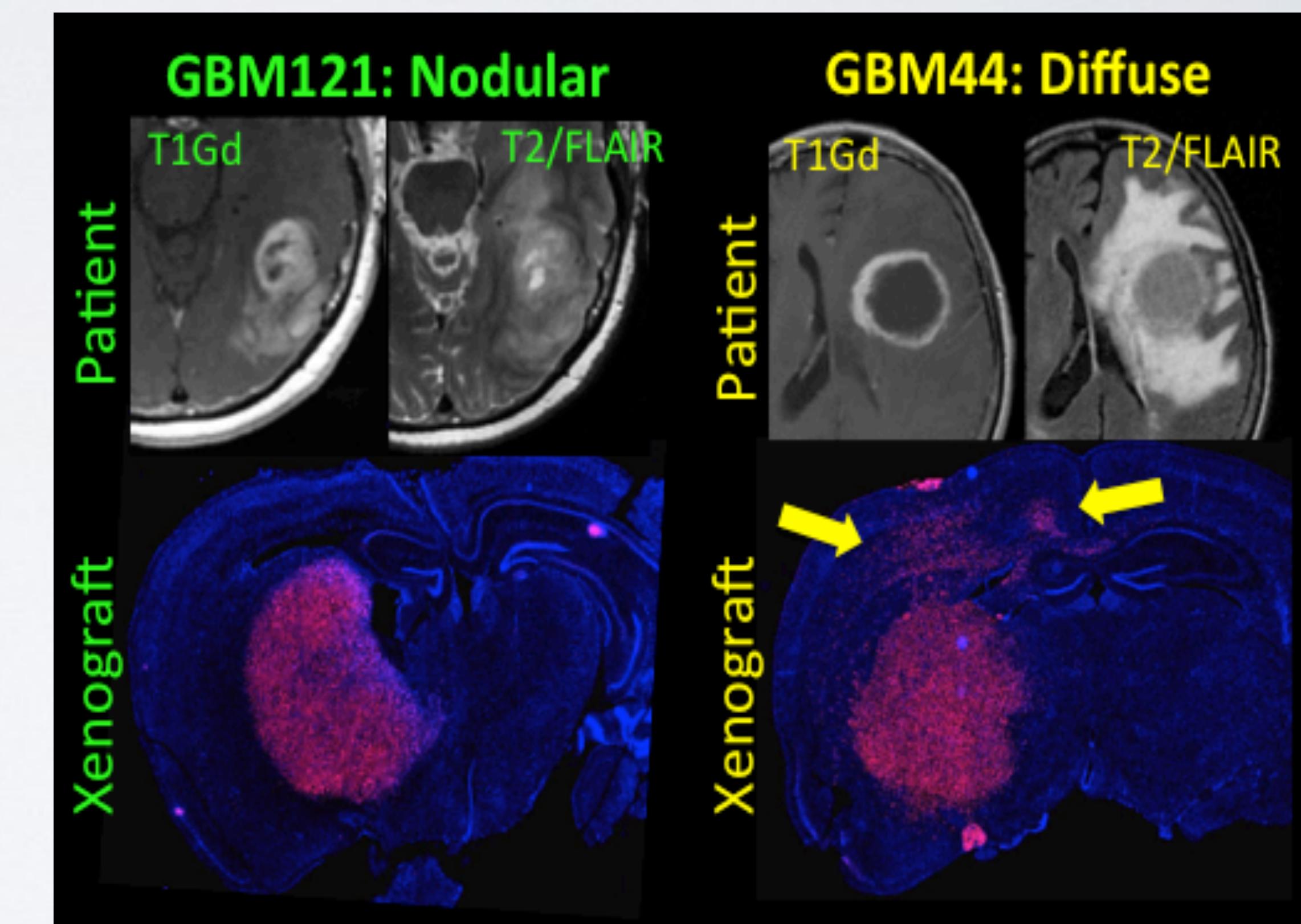
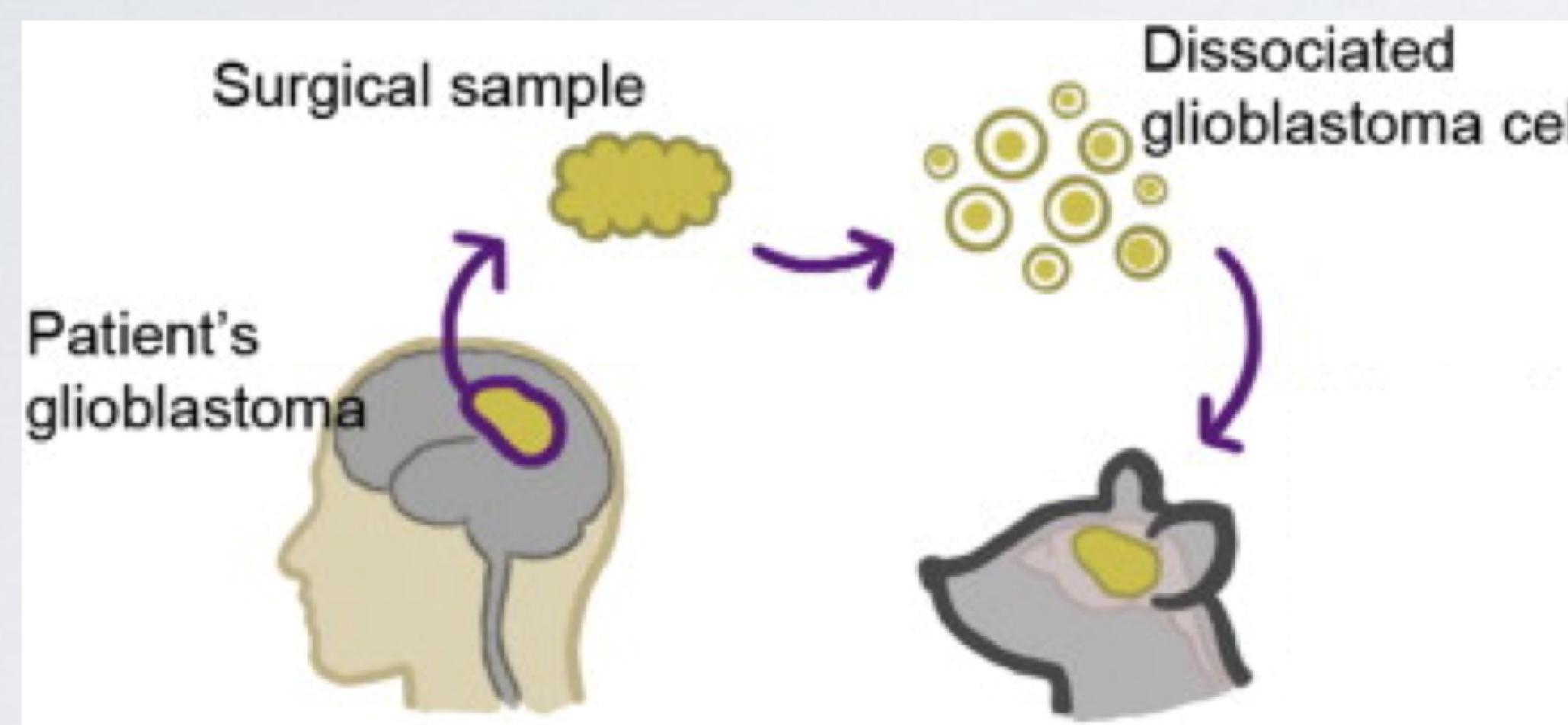


PATIENT DERIVED XENOGRAFTS

PRECLINICAL MODELS CAPTURE DIVERSITY ACROSS PATIENTS



BIOLUMINESCENCE IMAGING (BLI)

QUANTIFY PATIENT-DERIVED CELLS

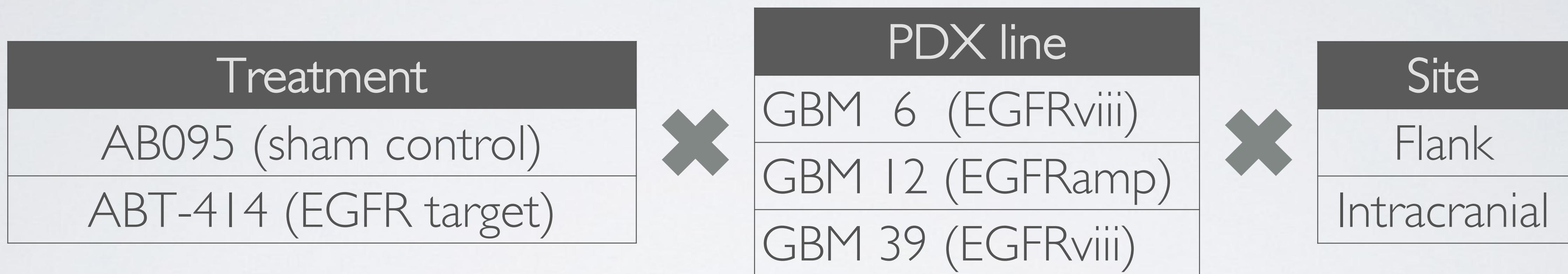
FIX SLIDE



BLI flux (p/s) is linearly correlated with total cell number.

EXPERIMENTAL DESIGN

EGFRmut TUMORS TREATED WITH CONTROL & ABT-414

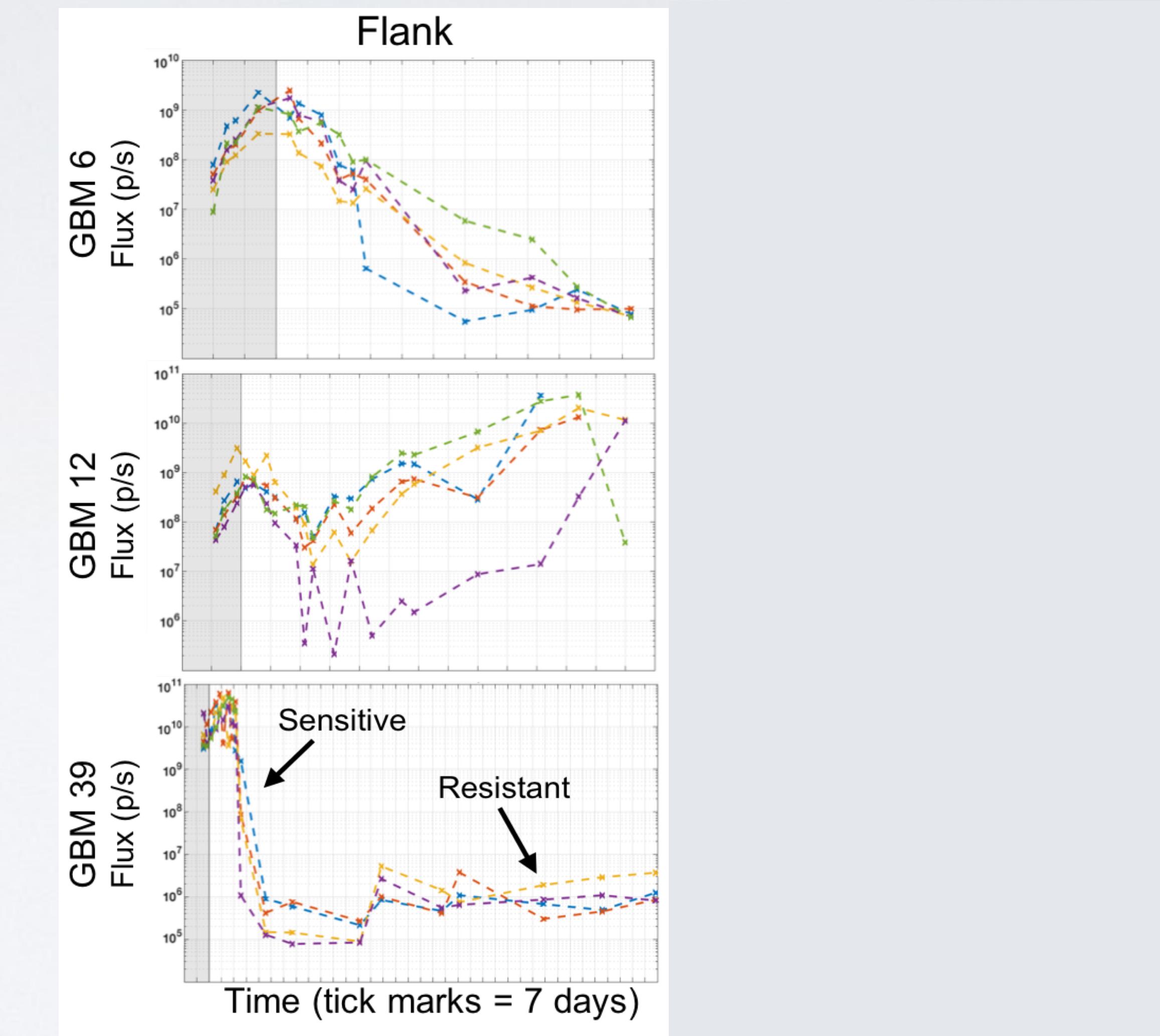
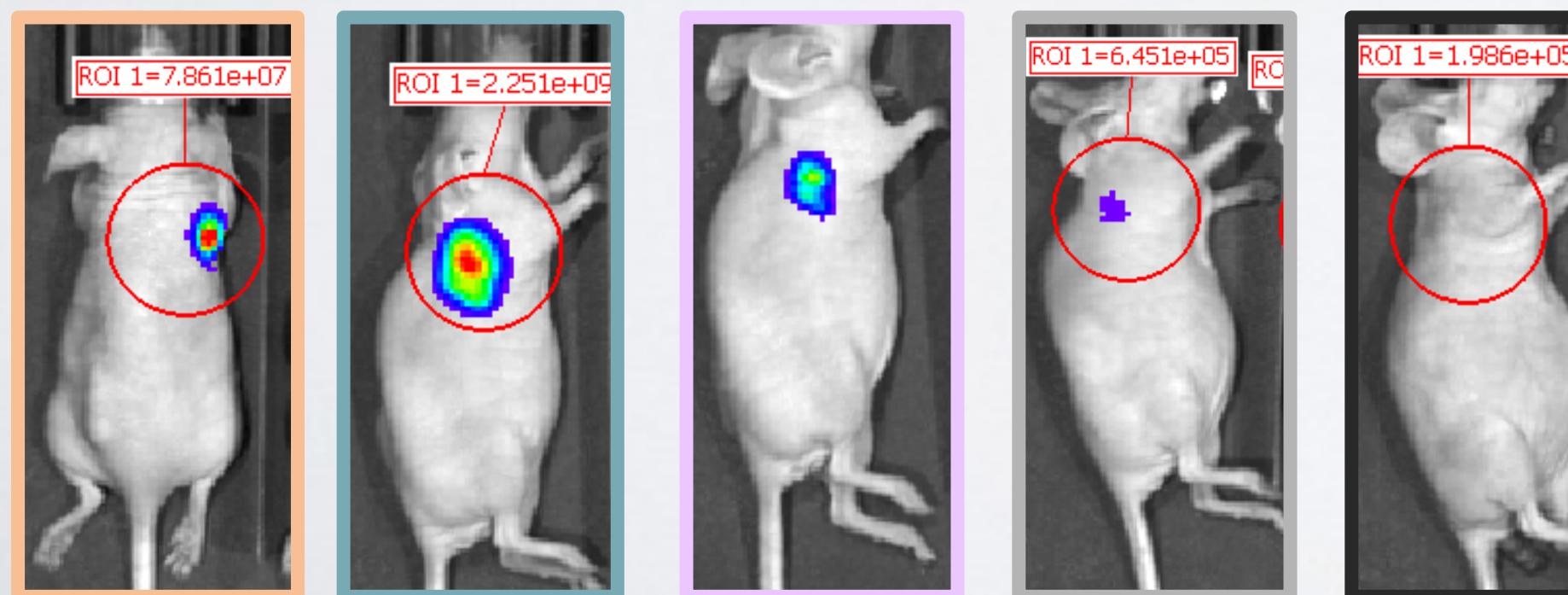
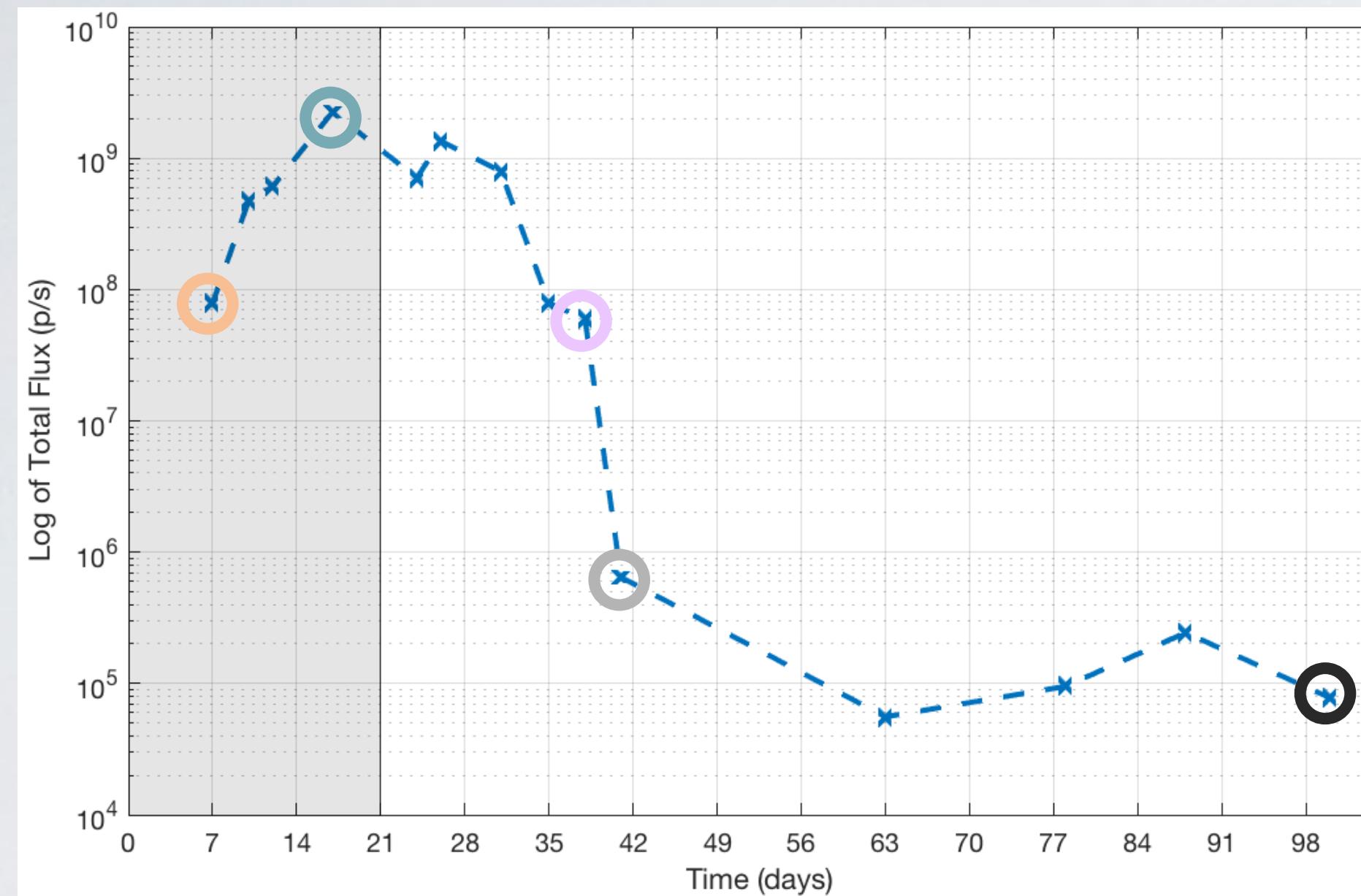


Treatment pulsed every 7 days after tumors established

Image with BLI over the course of treatment

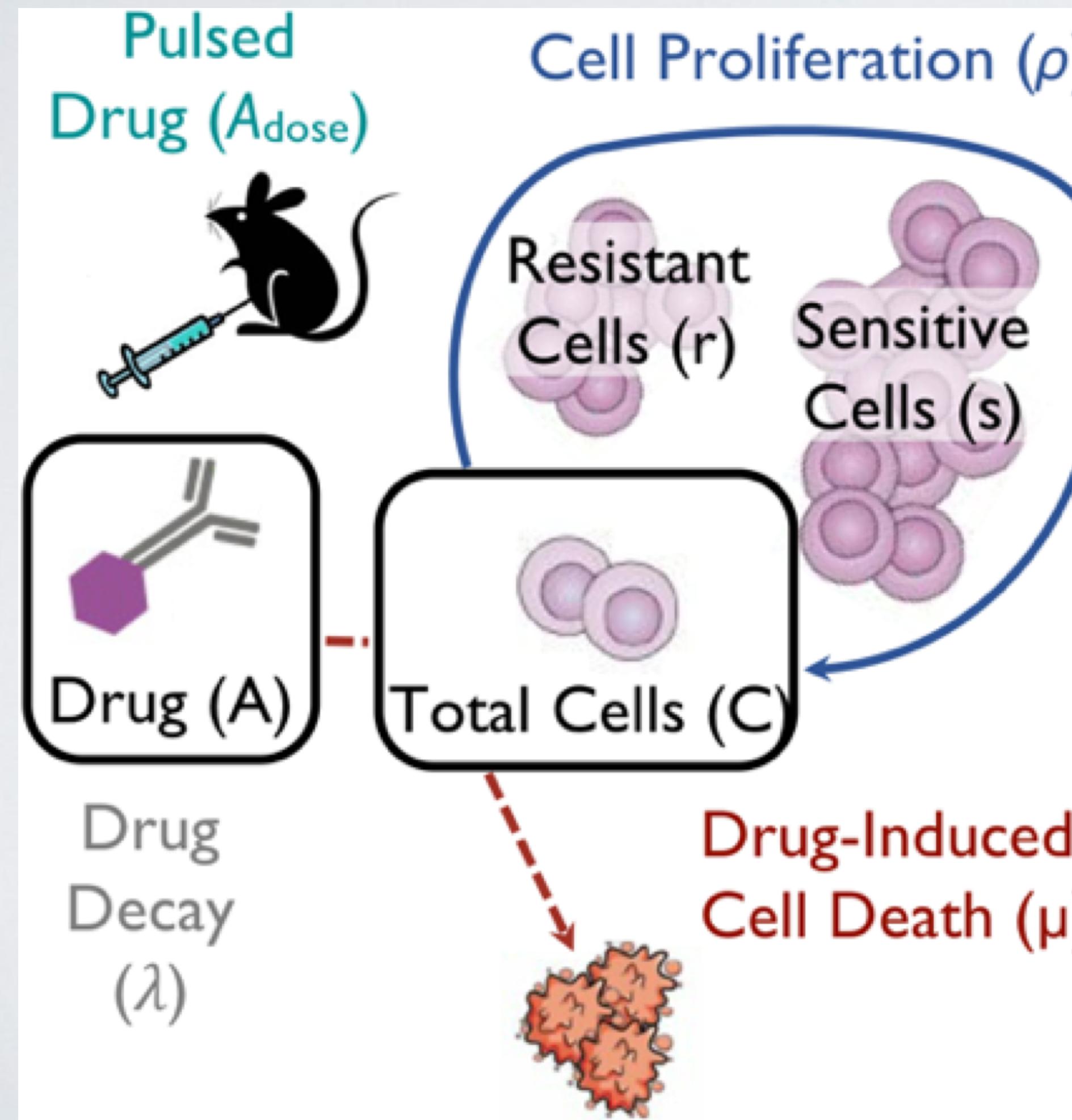
FLANK VS INTRACRANIAL TUMORS

DIFFERENT ABT-414 OUTCOMES DUE TO RESISTANCE OR DISTRIBUTION?



MODELING RESPONSE TO ABT-414

THREE ORDINARY DIFFERENTIAL EQUATIONS



Sensitive and Resistant Cells:

Proliferation

$$s_t =$$

$$\rho s$$

–

Agent-Induced Apoptosis

$$\mu_s \gamma A_s$$

$$r_t =$$

$$\rho r$$

–

$$\mu_r \gamma A_r$$

Agent Kill rate

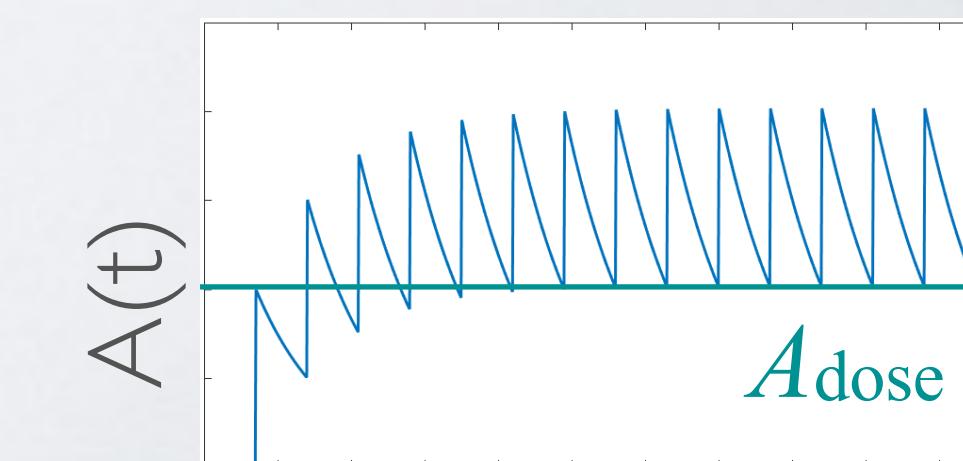
Exposure to Agent (BBB breakdown)

Agent:

$$A_t = A_{dose} \delta(t - \hat{t}) - \lambda A$$

$$A_{dose} = 0.1$$

$$\lambda = \ln(2)/7$$



PARAMETER ESTIMATES

FIT MODEL TO DATA USING LEAST SQUARES REGRESSION

Sensitive and Resistant Cells:

$$s_t = \rho_s - \mu_s \gamma A_s$$

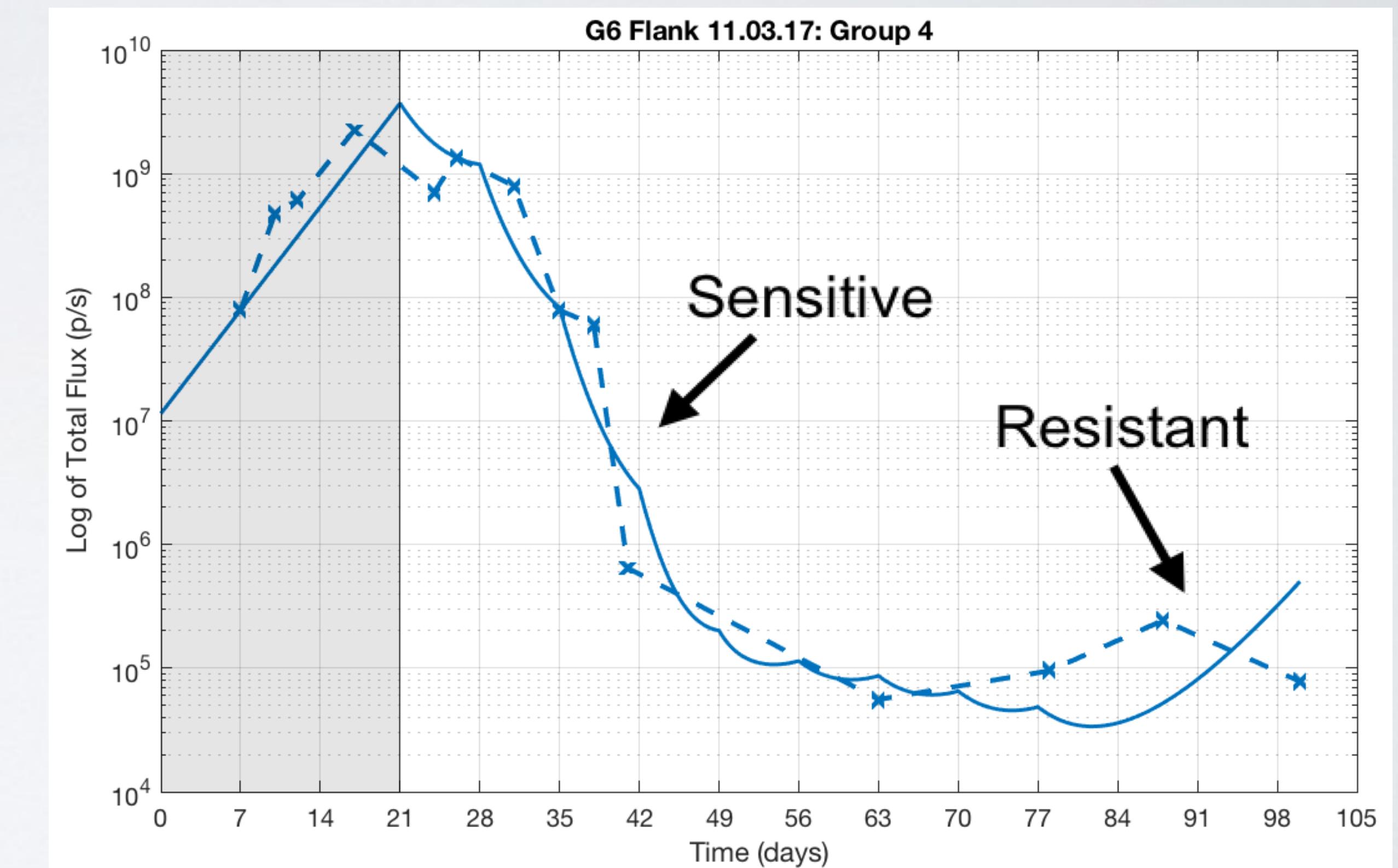
$$r_t = \rho_r - \mu_r \gamma A_r$$

Agent-Induced Apoptosis

Agent Kill rate Exposure to Agent (BBB breakdown)

Agent:

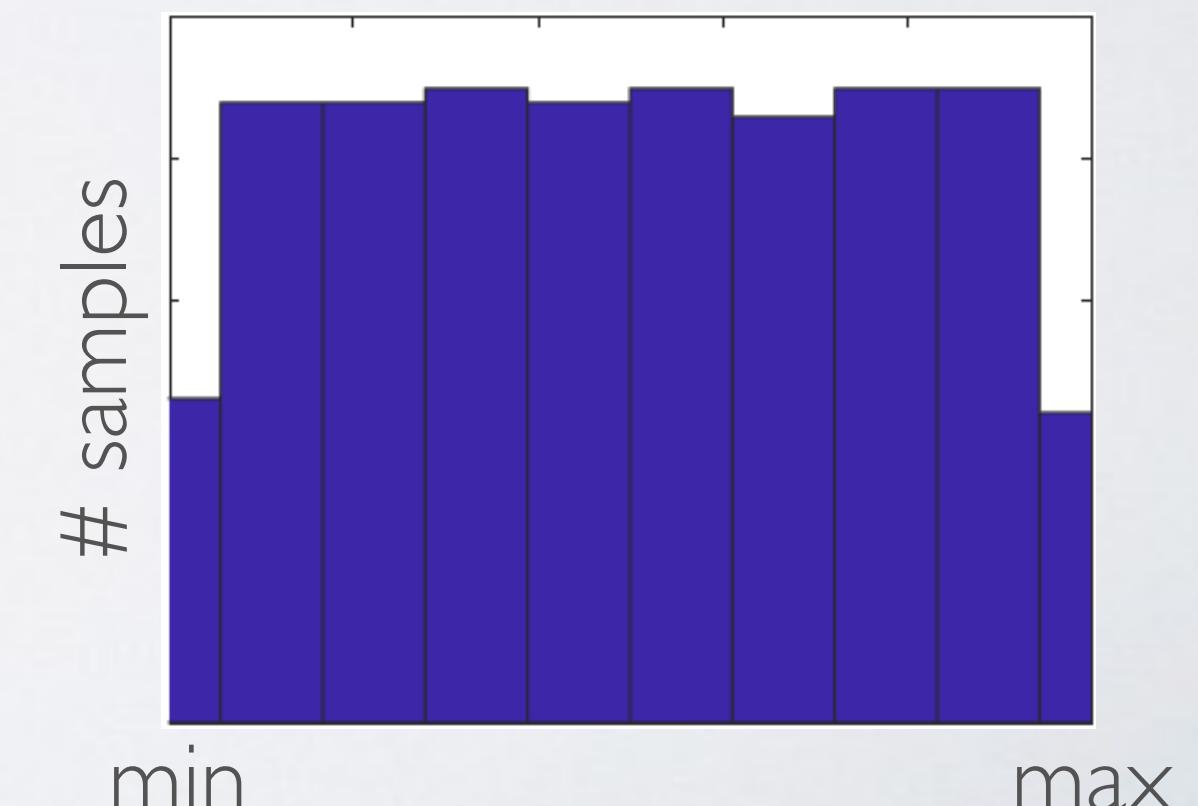
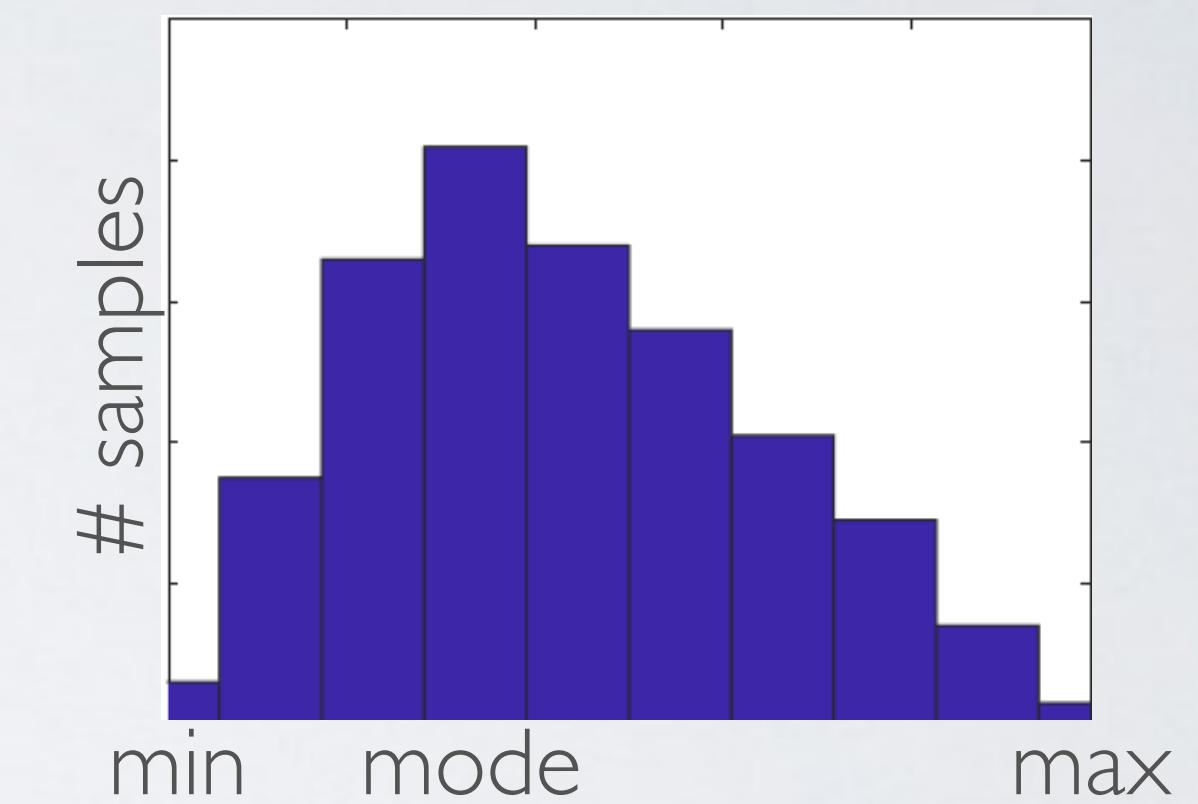
$$A_t = A_{dose} \delta(t - \hat{t}) - \lambda A$$



VARIANCE BASED SAMPLING

MODEL SENSITIVITY ANALYSIS

- Many parameters have natural distributions or can be approximated from observations:
 - Normally distributed observations with mean and variance (may not be able to assume with sparse observations)
 - low and high values vs most frequently observed (triangle distribution with min, max, and mode)
- Model constraints can also help define distributions
 - e.g., unitless scaling parameters $\in [0, 1]$ sampled uniformly



VARIANCE BASED SAMPLING

ONE-AT-A-TIME APPROACH

Parameter A							
Parameter B							
	X	X	X	X	X	X	X

Vary one parameter and fix the others

- Allows for seeing how one parameter affects the model
- Doesn't allow for interaction between multiple varied parameters
- Computationally inexpensive:
 M parameters, N samples
 $\Rightarrow N$ simulations

VARIANCE BASED SAMPLING

FULL FACTORIAL APPROACH

		Parameter A							
		X	X	X	X	X	X	X	X
Parameter B	X	X	X	X	X	X	X	X	X
	X	X	X	X	X	X	X	X	X
	X	X	X	X	X	X	X	X	X
	X	X	X	X	X	X	X	X	X
	X	X	X	X	X	X	X	X	X
	X	X	X	X	X	X	X	X	X
	X	X	X	X	X	X	X	X	X
	X	X	X	X	X	X	X	X	X

Vary all the parameters against each other

- Allows for seeing the interaction of multiple varied parameters values in the model
- Computationally expensive:

M parameters, N samples
 $\Rightarrow M^N$ simulations

VARIANCE BASED SAMPLING

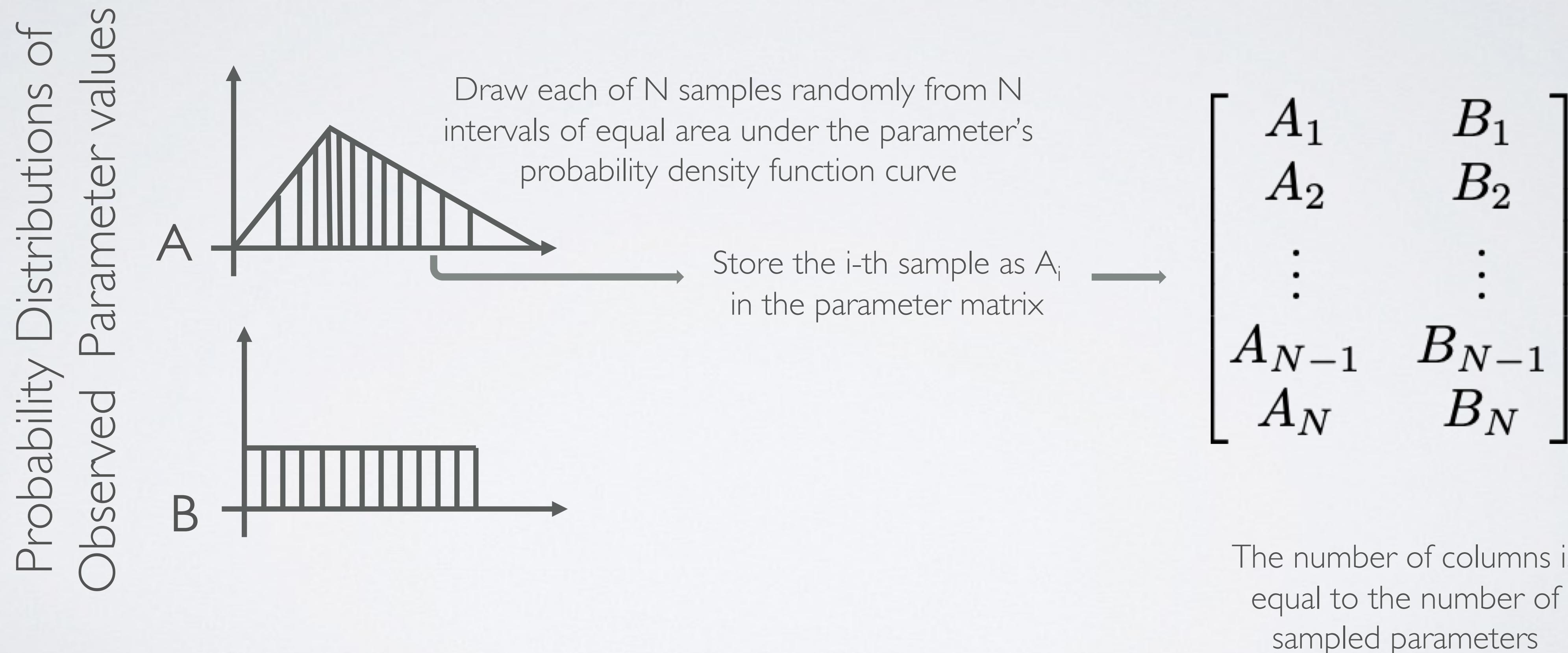
LATIN HYPERCUBE SAMPLING (LHS) APPROACH

Parameter A						
Parameter B						X
	X					
		X				
			X			
				X		
					X	
	X					

- Strategically vary all the parameters
- Allows for seeing the interaction of multiple varied parameters values in the model
 - Computationally in expensive:
 - M parameters, N samples
 - => N simulations

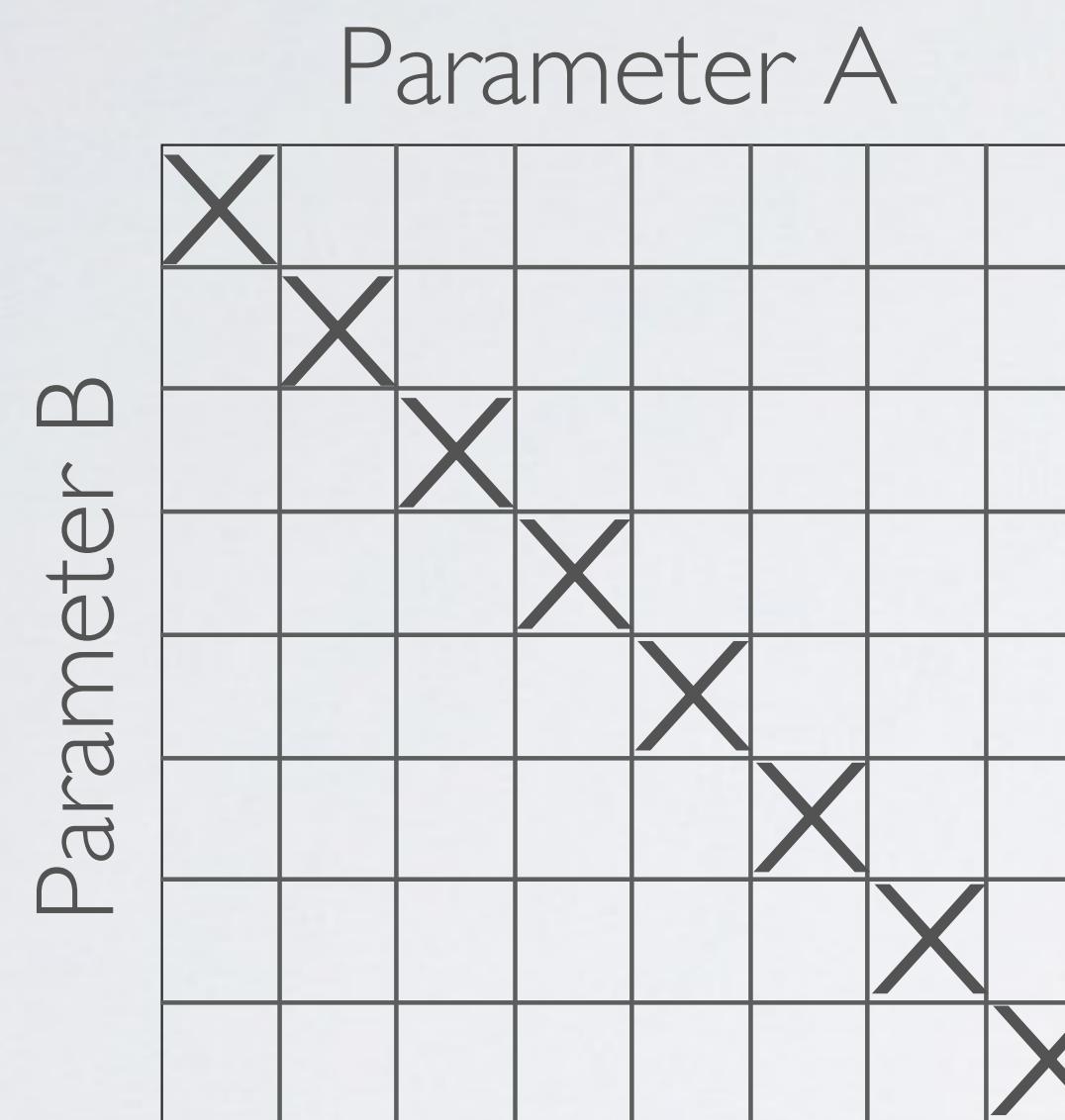
LATIN HYPERCUBE SAMPLING

STEP I: DRAW EQUIPROBABLE SAMPLES



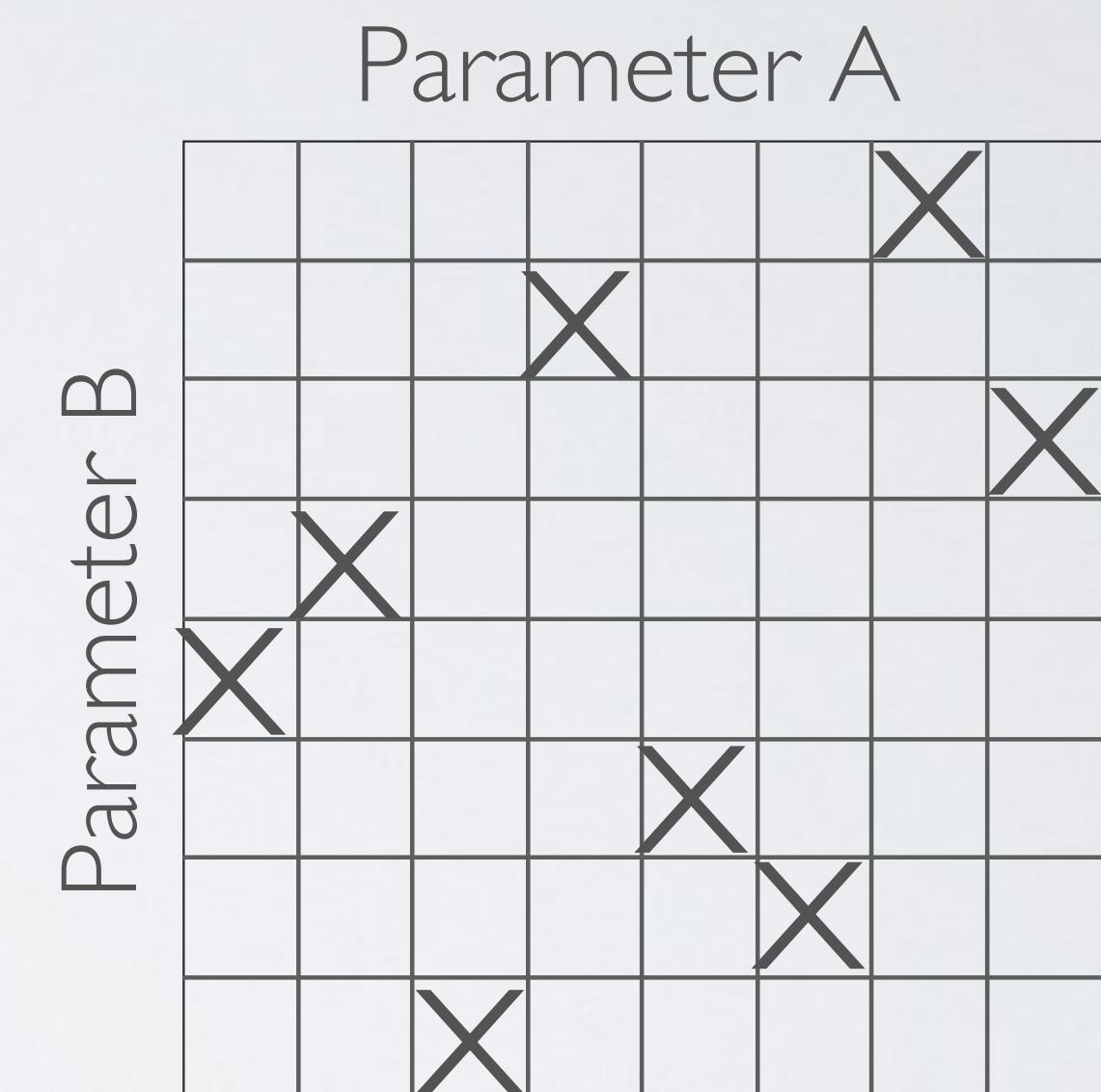
LATIN HYPERCUBE SAMPLING

STEP 2: RANDOMLY PAIR SAMPLES FOR MONTE CARLO SIMULATIONS



Randomly permute the entries in each column

$$\begin{bmatrix} A_1 & B_1 \\ A_2 & B_2 \\ \vdots & \vdots \\ A_{N-1} & B_{N-1} \\ A_N & B_N \end{bmatrix} \rightarrow \begin{bmatrix} A_6 & B_{N-1} \\ A_4 & B_2 \\ \vdots & \vdots \\ A_1 & B_5 \\ A_N & B_3 \end{bmatrix}$$



Each row j of sample values in the matrix is passed to the model for the j -th Monte Carlo simulation

LHS & PARTIAL RANK CORRELATION

STEP 3: COMPARE SAMPLES WITH OUTPUT FROM THE SIMULATIONS

Add output of interest to matrix with corresponding parameter values

Replace each matrix entry with it's ordinal rank among the column elements

Use the entries $r_{i,j}$ of the rank matrix to compute Pearson correlation coefficients

$$\begin{bmatrix} A_6 & B_{N-1} & x_1 \\ A_4 & B_2 & x_2 \\ \vdots & \vdots & \vdots \\ A_1 & B_5 & x_{N-1} \\ A_N & B_3 & x_N \end{bmatrix} \rightarrow \begin{bmatrix} 6 & N-1 & 2 \\ 4 & 2 & N \\ \vdots & \vdots & \vdots \\ 1 & 5 & N-1 \\ N & 3 & 6 \end{bmatrix} \rightarrow$$

$$c_{i,j} = \frac{\sum_{n=1}^N (r_{n,i} - \mu)(r_{n,j})}{\sqrt{\sum_{n=1}^N (r_{n,i} - \mu)^2 \sum_{k=1}^N (r_{k,j} - \mu)^2}}, \quad i, j = 1, 2, \dots, M, M+1$$

So in our example, C is a 3×3 matrix

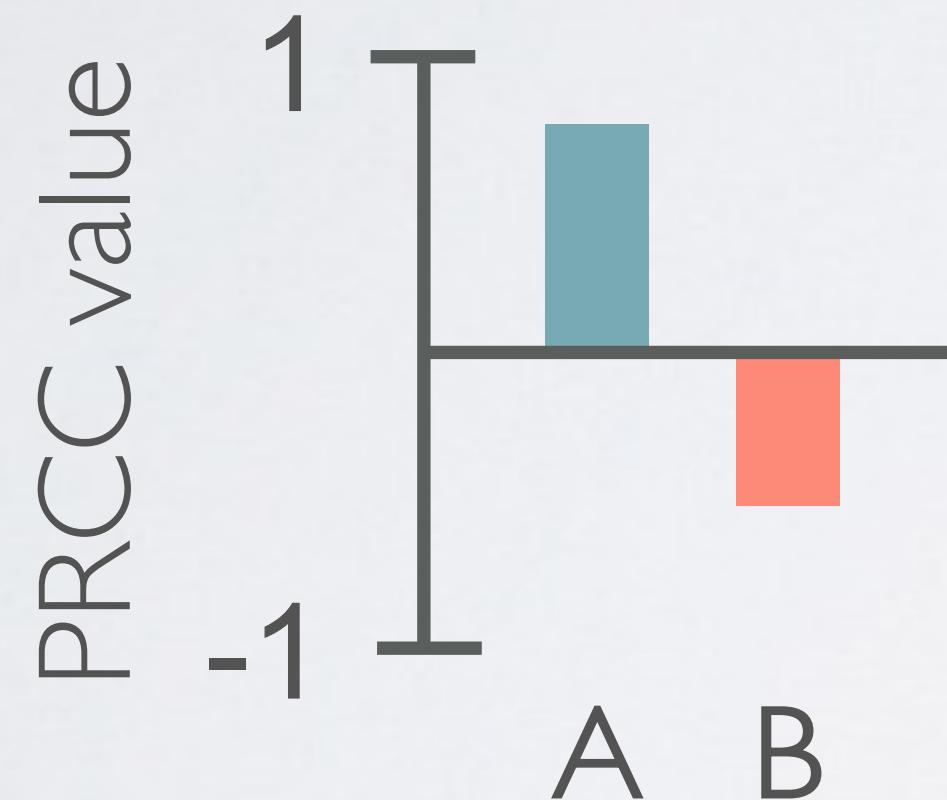
Invert C and use the entries to compute Partial Rank Correlation Coefficients

$$C^{-1} = Q = [q_{i,j}] \rightarrow \phi_i = \frac{-q_{i,M+1}}{\sqrt{q_{i,i}q_{M+1,M+1}}}$$

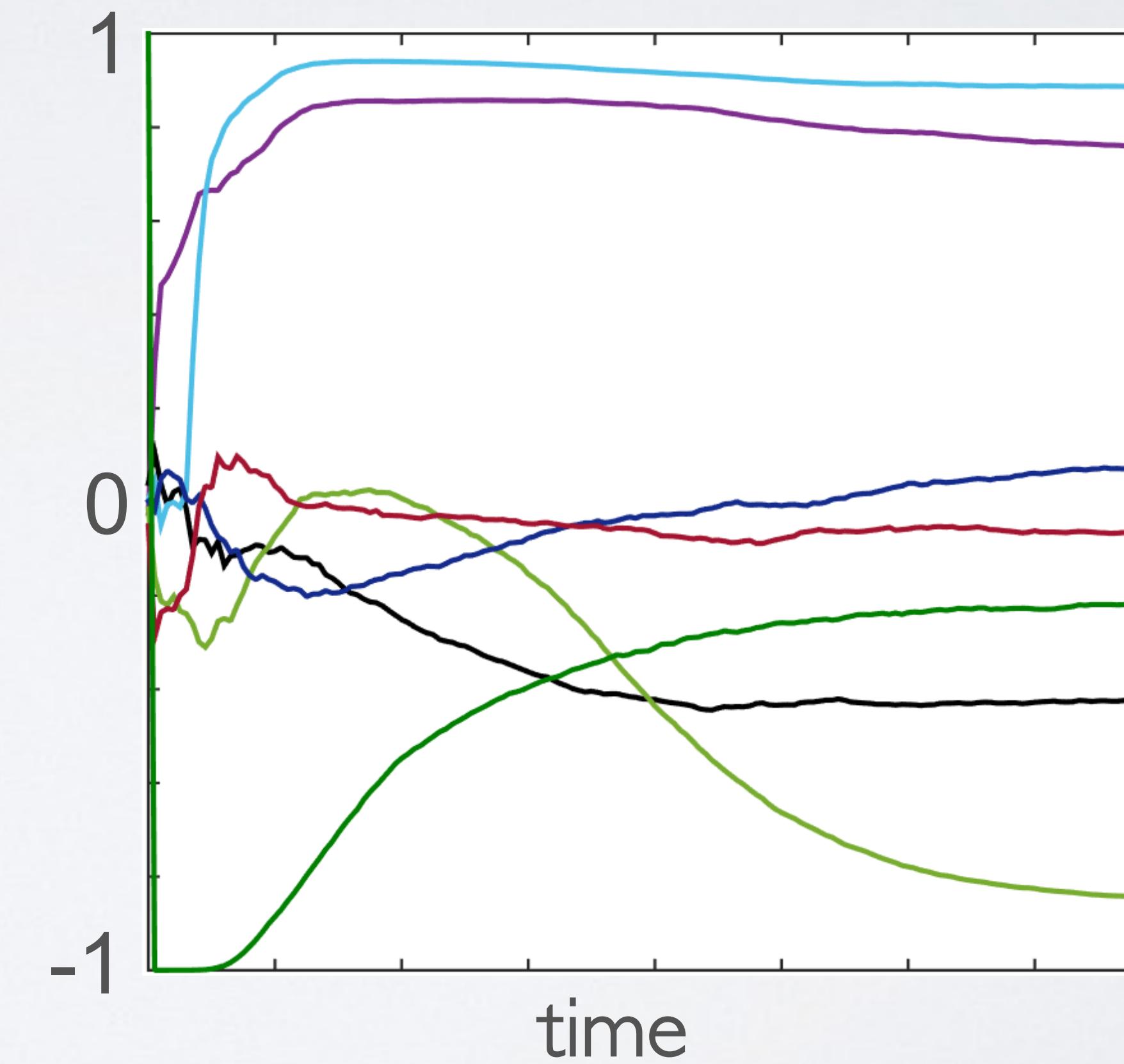
LHS & PARTIAL RANK CORRELATION

STEP 4: EXAMINE AND INTERPRET THE RESULTS!

One common visualization
is a waterfall plot

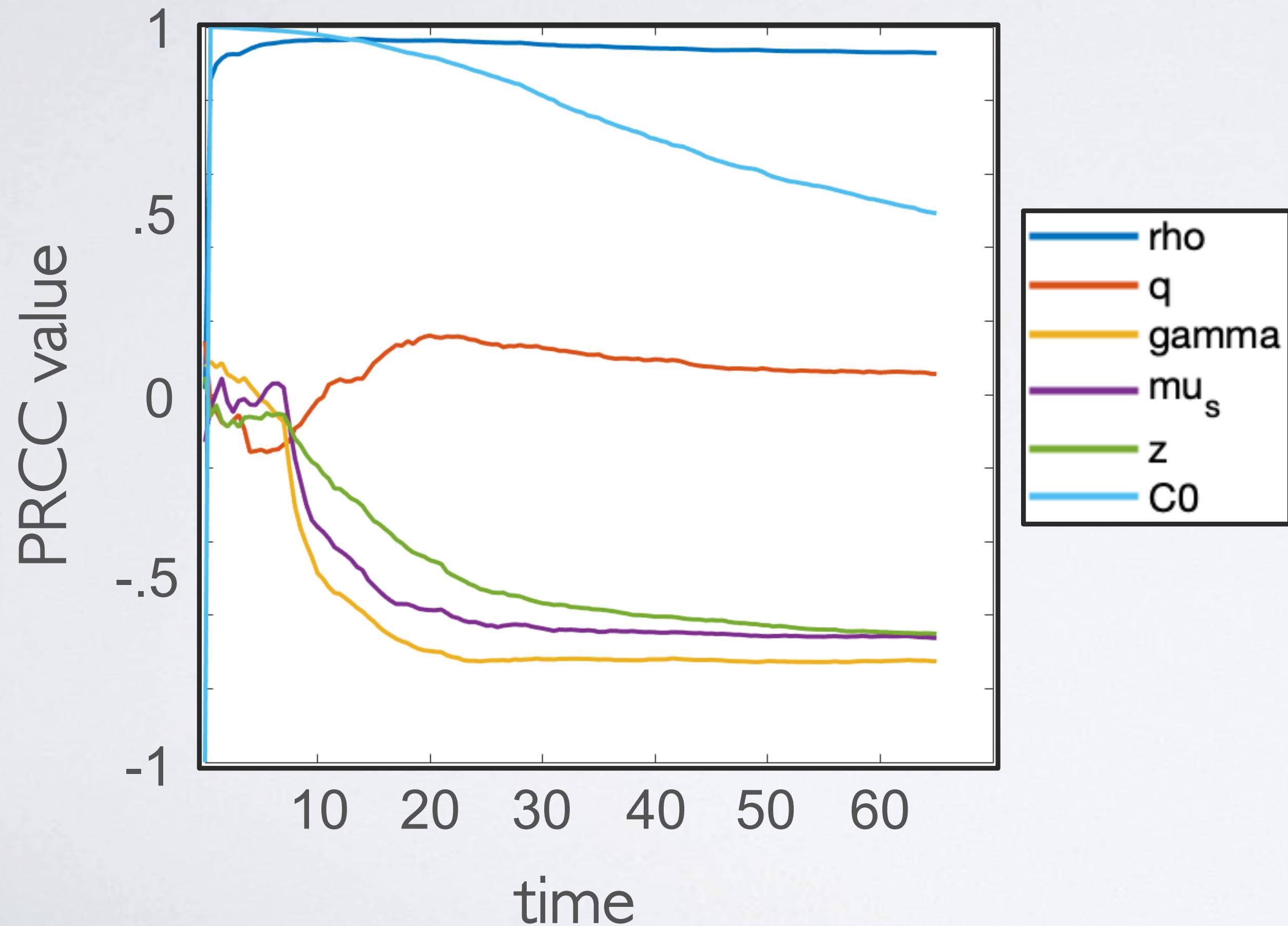


Can also examine how correlations with simulation results
change over time or space



LHS & PARTIAL RANK CORRELATION

RESULTS!



Model output compared:
total cells, $s + r$

- Growth rate ρ is most strongly positively correlated, followed by initial condition
- Percent tumor exposed to drug γ is most strongly negatively correlated, followed closely by drug kill rate parameters μ_s and z