Optimal Therapeutic Strategies for HER2+ Breast Cancer Treatment: A Mathematical Modeling Approach

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Outline

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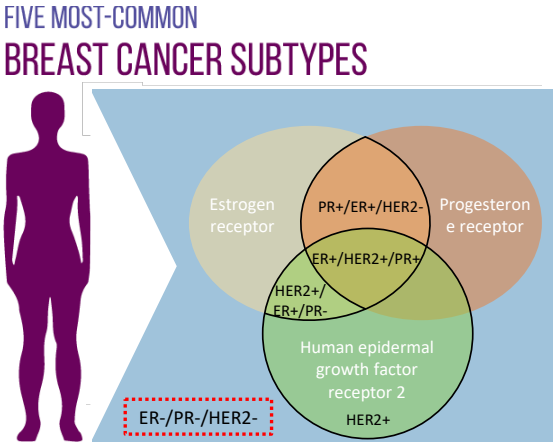
Clinical problem



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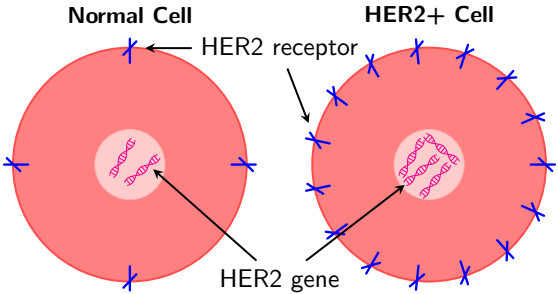
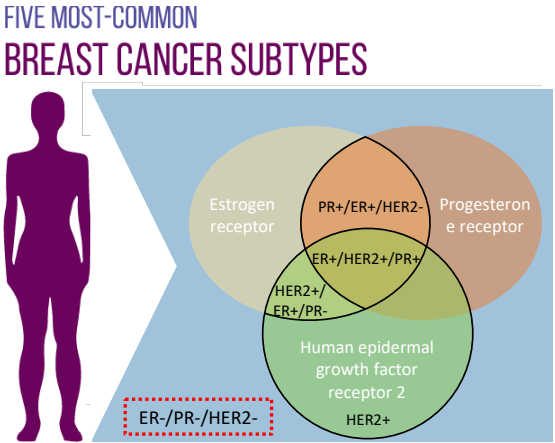


- **15-20%** breast cancers are HER2+.



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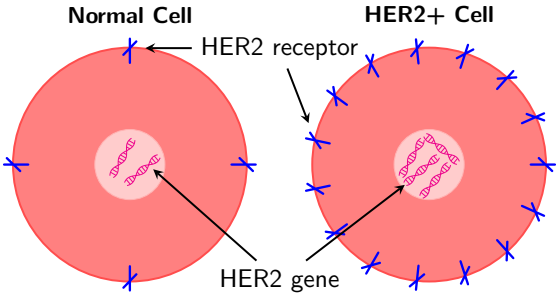

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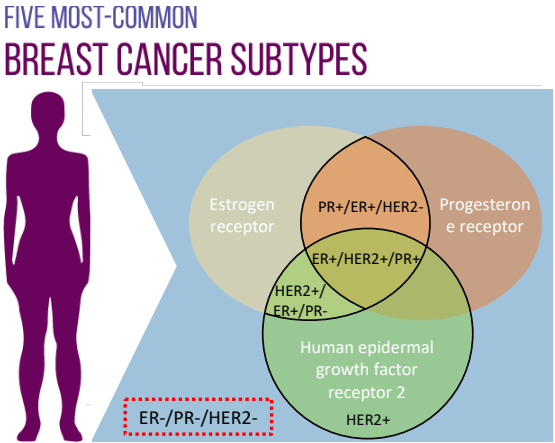
- Treatments that specifically target HER2 are **very effective**.



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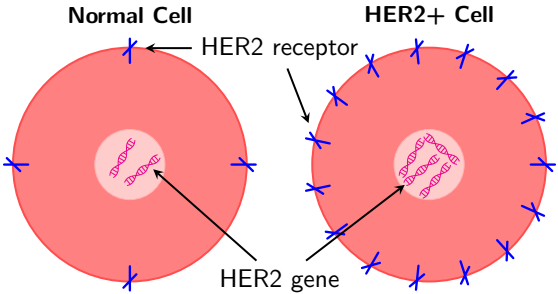

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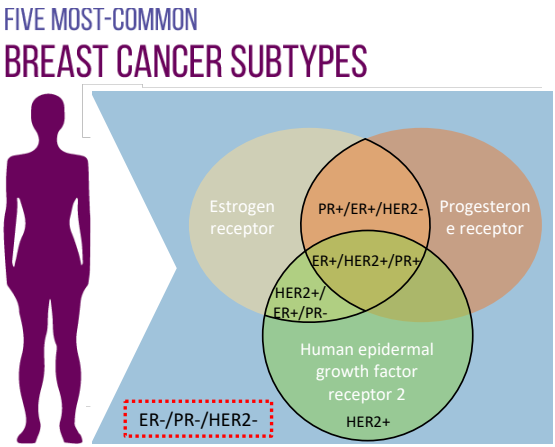

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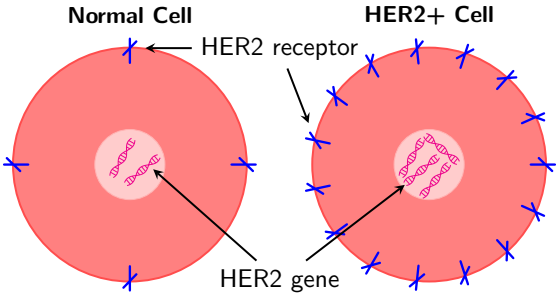

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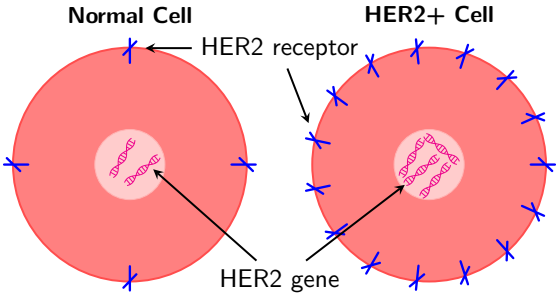

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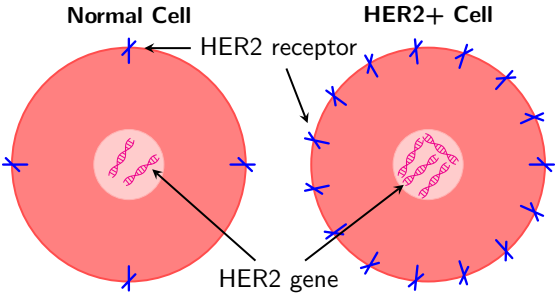

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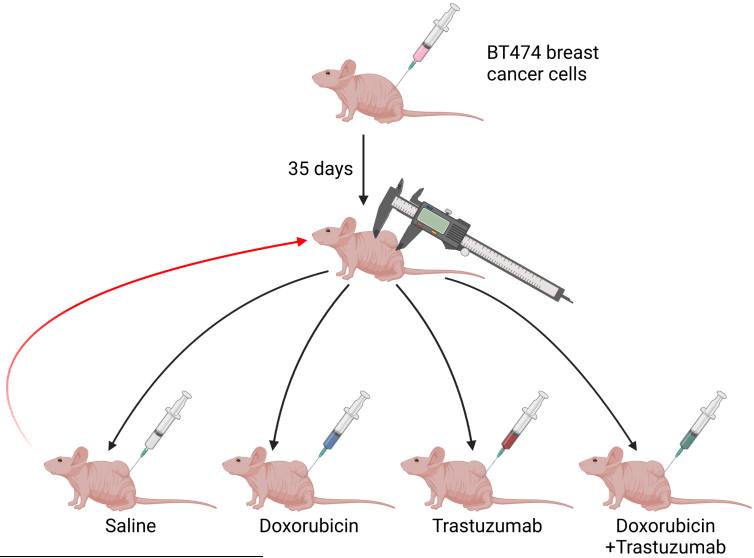
Open problem

Determine the therapeutic regimen that optimally combines these two treatments to yield **optimal tumor control**.

Murine model of HER2+ breast cancer



Sorace, et al., Breast cancer research and treatment (2016)

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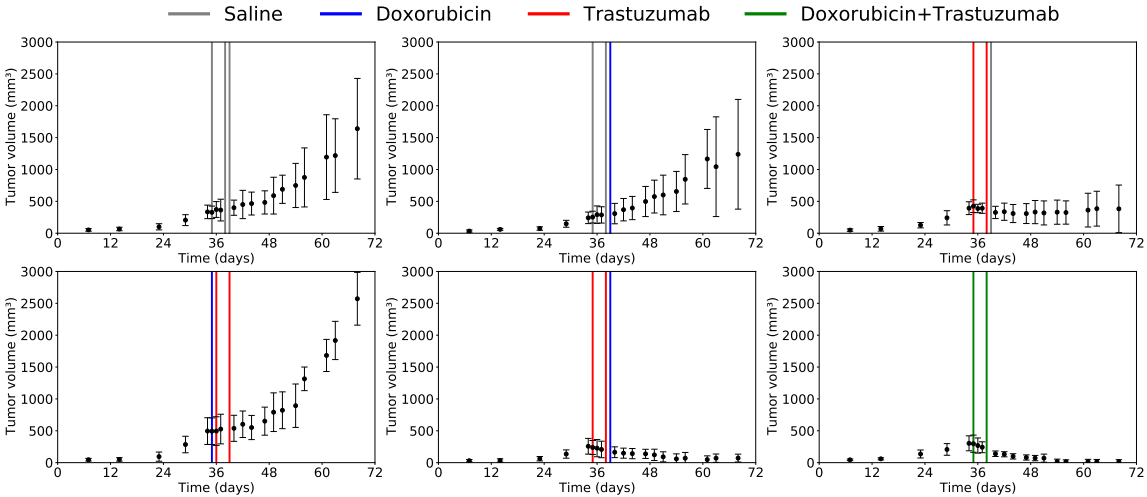

Conclusion: prior treatment with trastuzumab will increase the efficacy of doxorubicin.

Sorace, et al., Breast cancer research and treatment (2016)

Goals

Model development and calibration

Develop and calibrate mathematical models that capture the experimental tumor dynamics and the direct effects of doxorubicin and trastuzumab therapies.

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Treatment optimization

Use **optimal control theory** to find the **"best" treatment protocol**.

Outline

Initial approach

Treatment protocols

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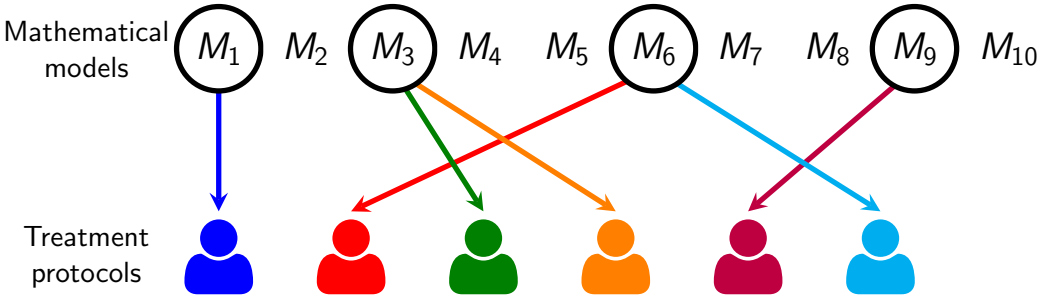
Mathematical models M_1 M_2 M_3 M_4 M_5 M_6 M_7 M_8 M_9 M_{10}

Treatment protocols

Initial approach



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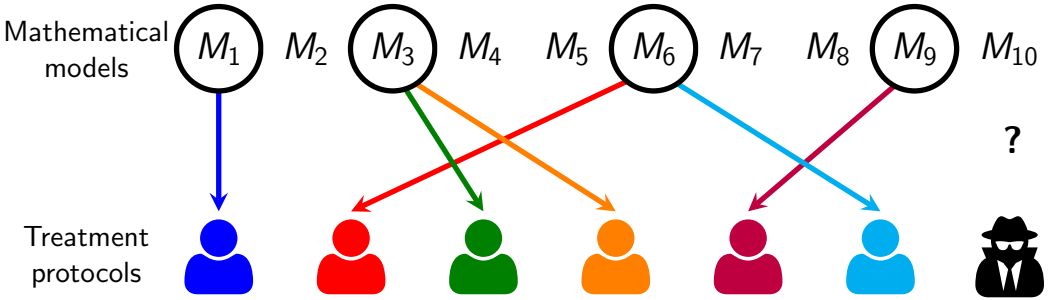

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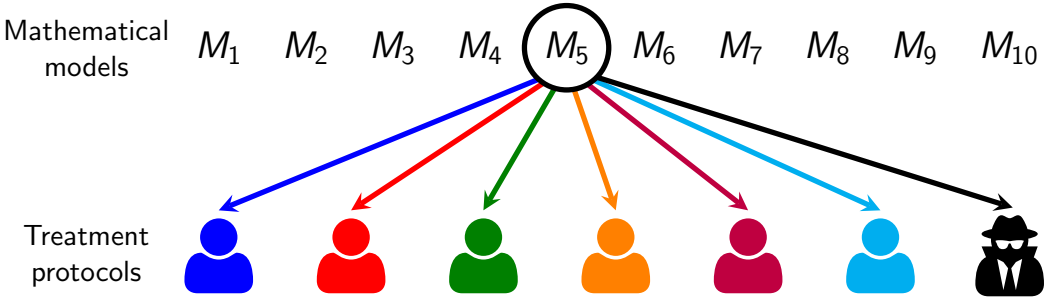
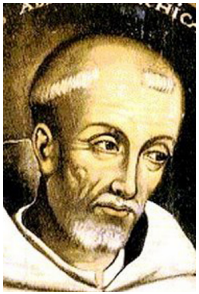


Occam's Razor

Occam's Razor

Non sunt multiplicanda entia sine necessitate

Entities should not be multiplied beyond necessity



When choosing among a set of models:

The simplest valid model is the best choice.

- simple $\Rightarrow$ number of parameters
- valid $\Rightarrow$ passes validation test

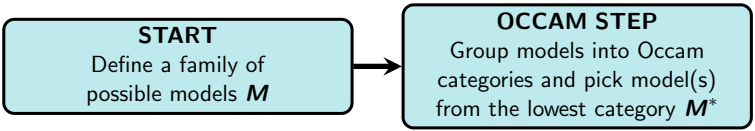
How do we choose a model that adheres to this principle?

The Occam-Plausibility Algorithm [1] + Optimal Control

START
Define a family of
possible models $\boldsymbol{M}$

[1] K. Farrell, J. T. Oden, D. Faghihi, Journal of computational physics (2015)

The Occam-Plausibility Algorithm [1] + Optimal Control



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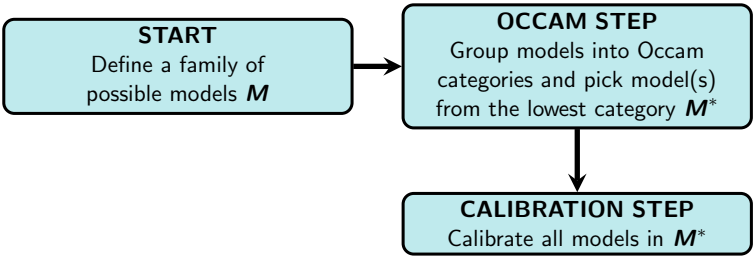

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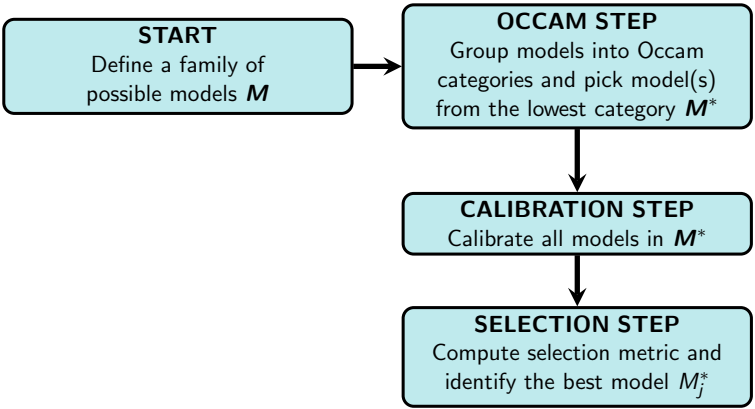

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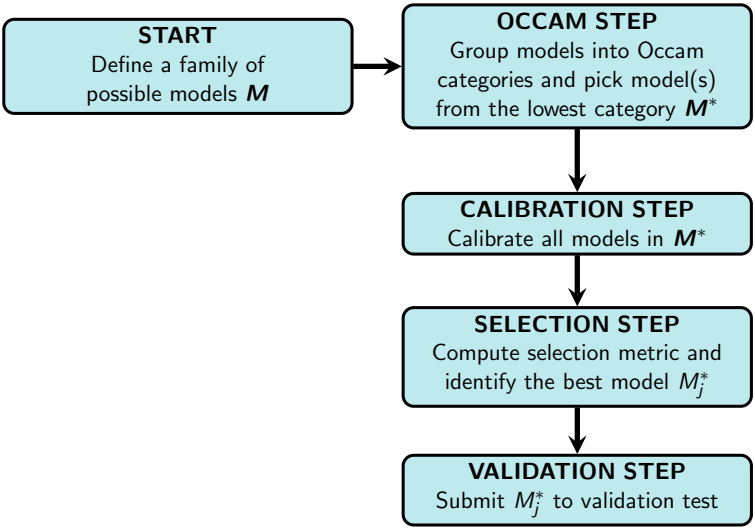

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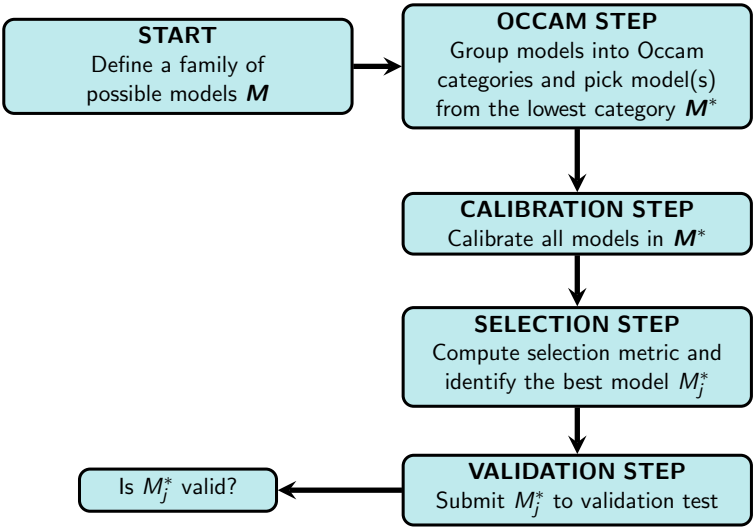

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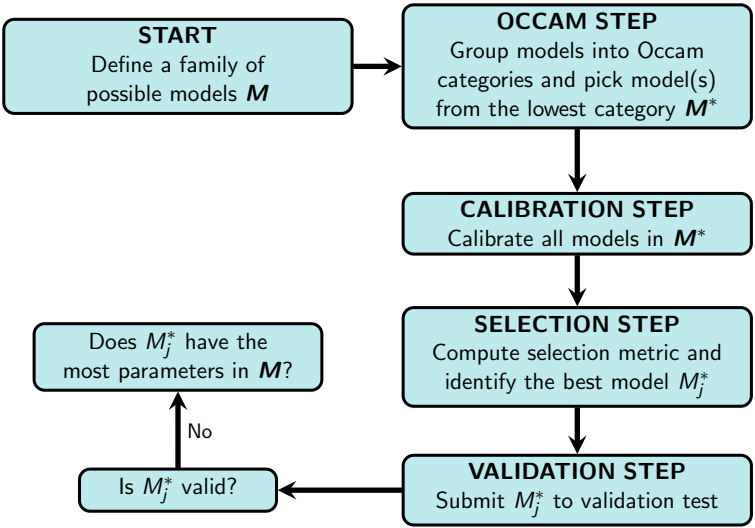

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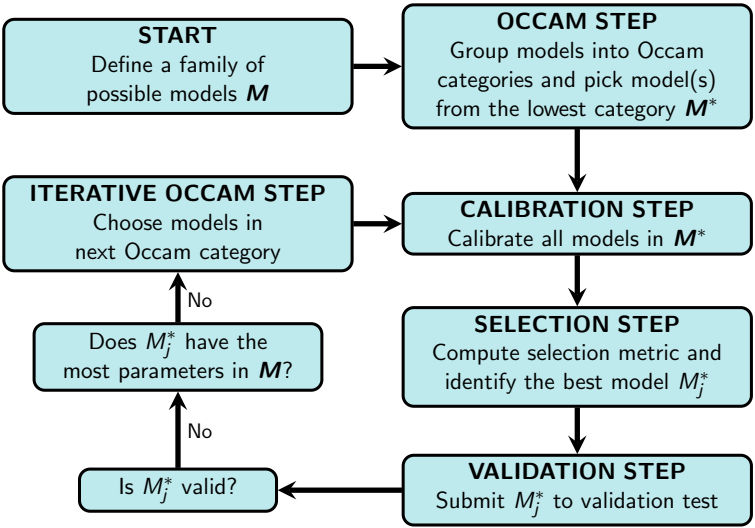

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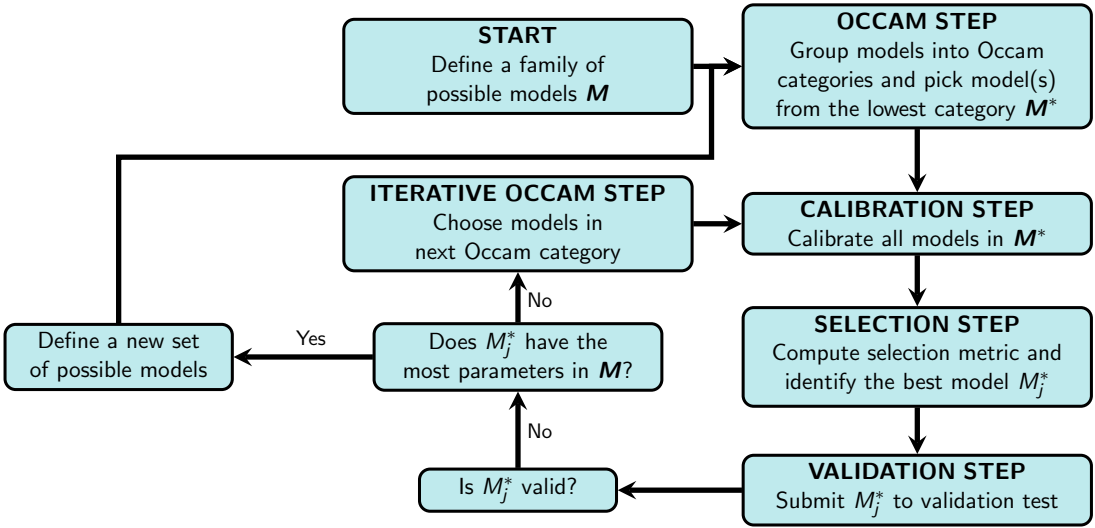

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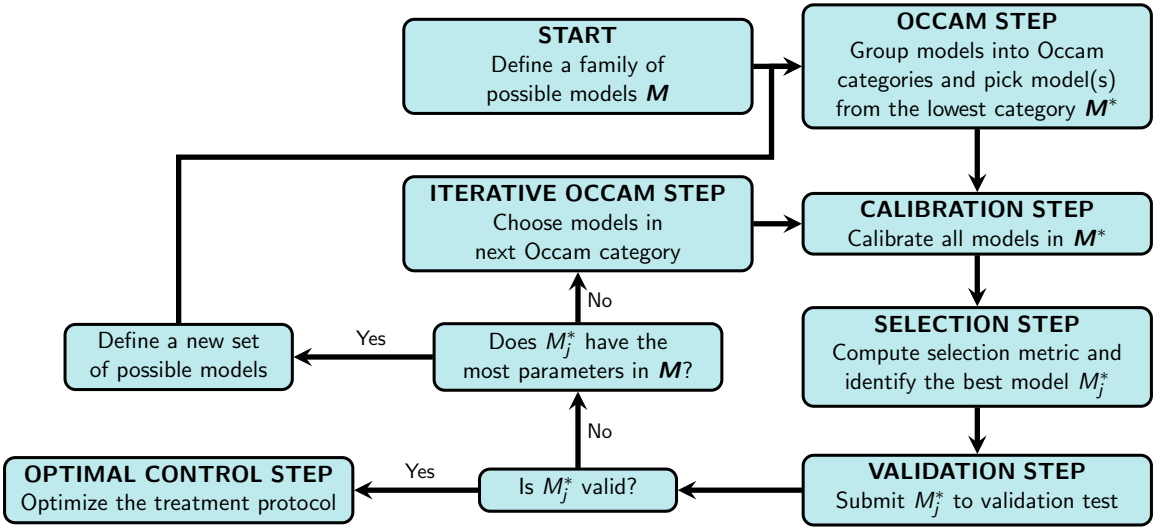

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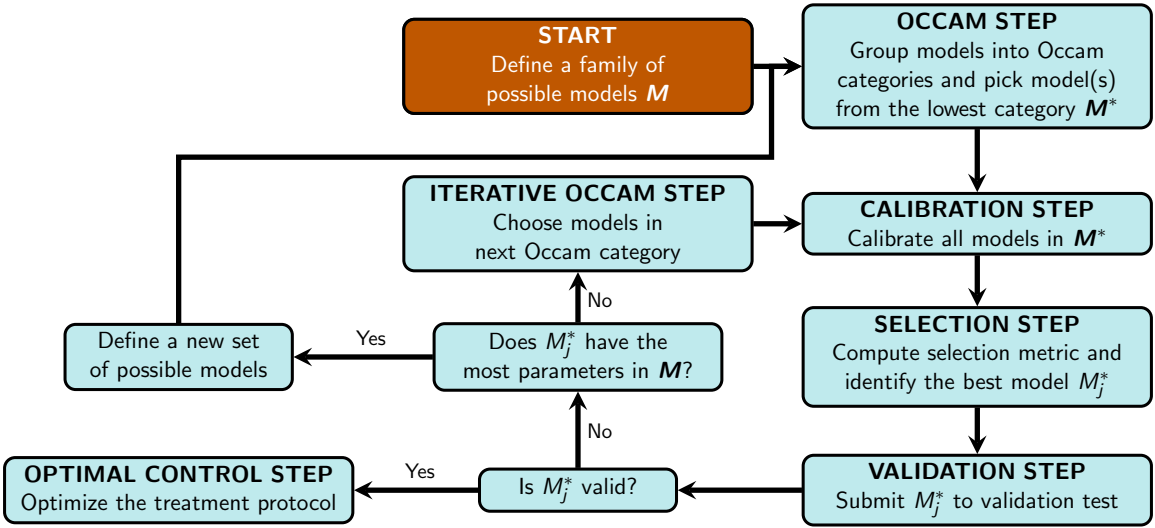

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Three-constituent model

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\dfrac{dV_t}{dt} = \left(\underbrace{r}_{\text{growth rate}} - \underbrace{\lambda_t B_t}_{\text{death by trastuzumab}} - \underbrace{\lambda_d B_d}_{\text{death by doxorubicin}} - \underbrace{\lambda_{td} B_d B_t}_{\text{death by drug combination}} \right) \mathcal{P}(V_t), \\
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V_t	tumor volume
B_d	doxorubicin availability
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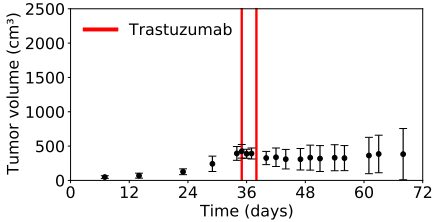

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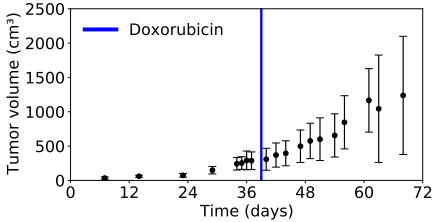

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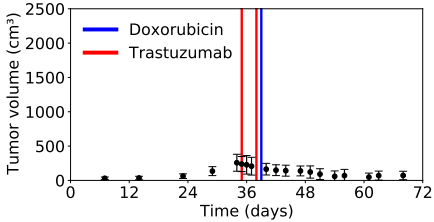

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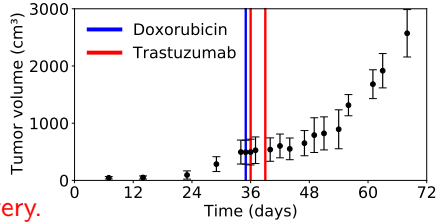
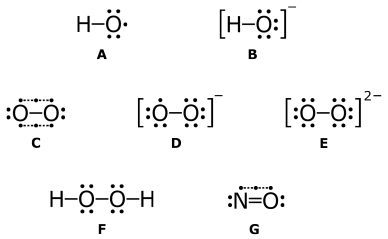


- Doxorubicin: decreases the total vascular density.
- Reduction in vascular density ⇒ reduces trastuzumab delivery.

Four-constituent model

Reactive oxygen species (ROS)

- The term reactive oxygen species (ROS) is usually used to signify **any oxygen-containing molecule capable** of initiating some kind of **deleterious reaction**.
- A build up of ROS in cells may cause damage to DNA, RNA, and proteins, and may cause **cell death**.
- **Trastuzumab[1] and doxorubicin[2] increases ROS production.**



[1] N. Mohan et al., Molecular cancer therapeutics (2016)
[2] S. Kim et al., Experimental & molecular medicine (2006)

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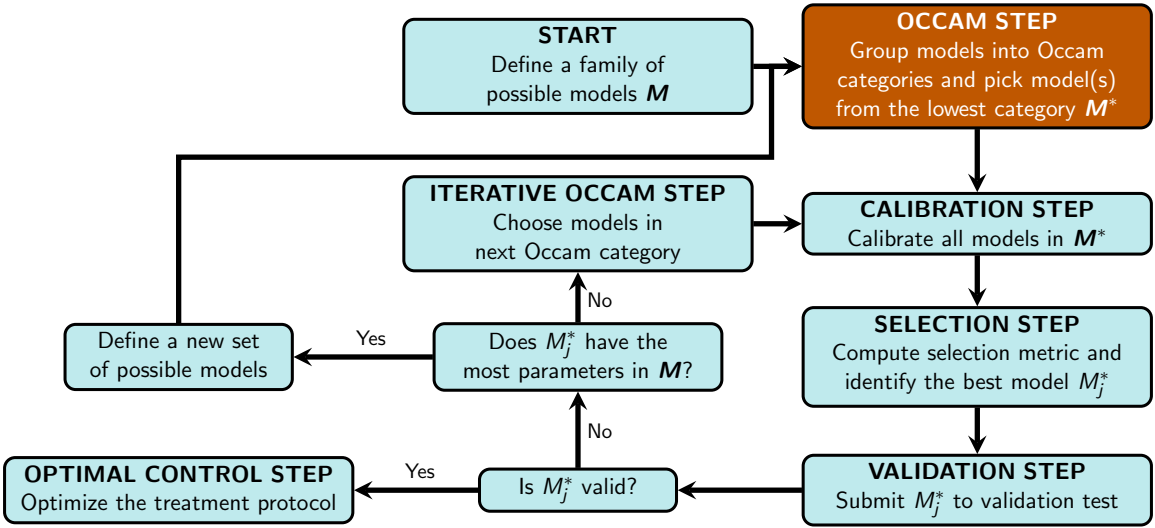
\dfrac{dR_o}{dt} = - \underbrace{\tau_o R_o}_{\text{ROS decay}} + \underbrace{\lambda_{od} B_d}_{\text{production by doxorubicin}} + \underbrace{\lambda_{ot} B_t}_{\text{production by trastuzumab}} + \underbrace{\lambda_{odt} B_d B_t}_{\text{production by drug interaction}},
\end{cases}
$$

V_t	tumor volume
B_d	doxorubicin availability
B_t	trastuzumab availability
R_o	Reactive oxygen species (ROS)

The Occam-Plausibility Algorithm [2] + Optimal Control



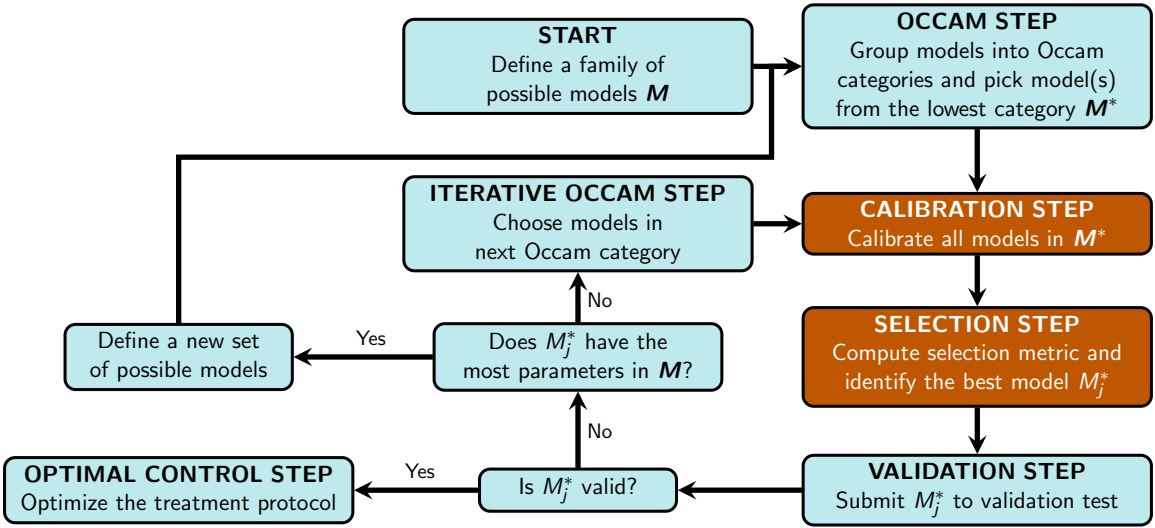
[2] K. Farrell, J. T. Oden, D. Faghihi, Journal of computational physics (2015)

Set of possible models

Table: Set of models developed to reproduce the tumor growth under doxorubicin and trastuzumab treatment. The variables V_t, B_d, and B_t, and the parameters r, τ_d, τ_t, and λ_{di} are present in every model.

Model	Variable ROS	Parameter										#P
		λ_t	λ_d	λ_{td}	K	λ_o	λ_{to}	τ_o	λ_{od}	λ_{ot}	λ_{odt}	
3CEM0		✓		✓								6
3CLM0		✓		✓	✓							7
3CEM		✓	✓	✓								7
3CLM		✓	✓	✓	✓							8
4CEM1	✓	✓					✓	✓	✓			8
4CEM2	✓	✓				✓		✓			✓	8
4CEM3	✓					✓		✓		✓	✓	8
4CLM1	✓	✓			✓		✓	✓	✓			9
4CLM2	✓	✓			✓	✓		✓			✓	9
4CLM3	✓				✓	✓		✓		✓	✓	9

The Occam-Plausibility Algorithm [3] + Optimal Control



[3] K. Farrell, J. T. Oden, D. Faghihi, Journal of computational physics (2015)

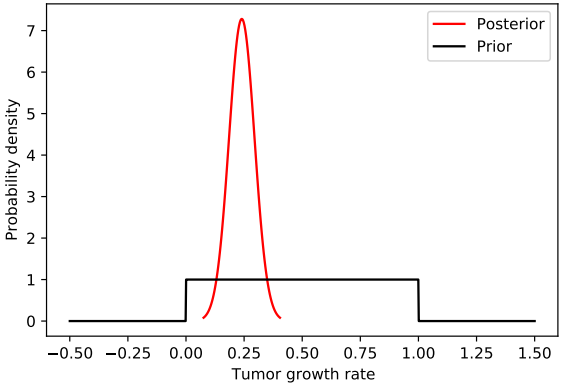
Model calibration and selection (Bayesian approach)

Bayes' Rule

$$\underbrace{\pi(\boldsymbol{\theta}|\boldsymbol{D})}_{\text{posterior}} = \frac{\overbrace{\pi(\boldsymbol{D}|\boldsymbol{\theta})}^{\text{likelihood}}\overbrace{\pi(\boldsymbol{\theta})}^{\text{prior}}}{\underbrace{\pi(\boldsymbol{D})}_{\text{evidence}}};$$

$\boldsymbol{D}$: data

$\boldsymbol{\theta}$: model parameters



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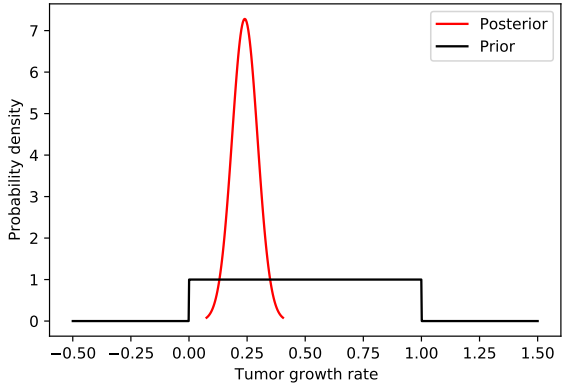

Model plausibility of model M_j (ρ_j)

$$\rho_j = \pi(M_j|\boldsymbol{D},\boldsymbol{M}) = \frac{\pi(\boldsymbol{D}|M_j,\boldsymbol{M})\pi(M_j|\boldsymbol{M})}{\pi(\boldsymbol{D}|\boldsymbol{M})};$$

Outline

Computational cost

Model calibration

- Python code: emcee[4] implementation of Goodman & Weare's Affine Invariant Markov chain Monte Carlo (MCMC) Ensemble sampler
- 8 parameters to calibrate
- MCMC chain length: 150,000

16 chains - 8 cores

- Serial calibration: $\sim$ 108 minutes
- Parallel calibration (number of chains / 2): $\sim$ 31 minutes
- $\sim$ 3.5 times faster than serial

80 chains - 40 cores

- Serial calibration: $\sim$ 549 minutes
- Parallel calibration (number of chains / 2): $\sim$ 41 minutes
- $\sim$ 13.4 times faster than serial

[4] Foreman-Mackey, et al., emcee: The MCMC Hammer (2013)

Outline

Model selection

Model	#P	Plausibility	Error (%)
3CEM0	6	n/a	28.51 ± 17.24

Model selection

Model	#P	Plausibility	Error (%)
3CEM0	6	n/a	28.51 ± 17.24
3CLM0	7	1.00	25.29 ± 15.37
3CEM	7	0.00	

Model selection

Model	#P	Plausibility	Error (%)
3CEM0	6	n/a	28.51 ± 17.24
3CLM0	7	1.00	25.29 ± 15.37
3CEM	7	0.00	
3CLM	8	1.00	29.06 ± 21.78
4CEM1	8	0.00	
4CEM2	8	0.00	
4CEM3	8	0.00	

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Model	#P	Plausibility	Error (%)
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4CEM2	8	0.00	
4CEM3	8	0.00	
4CLM1	9	0.86	29.03 ± 22.65
4CLM2	9	0.00	
4CLM3	9	0.14	

Model selection

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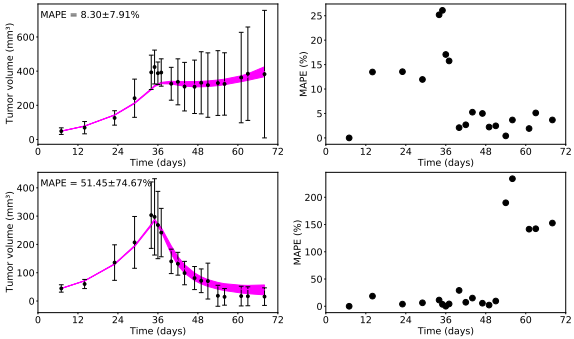

$$\begin{cases} \dfrac{dV_t}{dt} &= (r - \lambda_t B_t - \lambda_{td} B_d B_t)\, V_t \left(1 - \dfrac{V_t}{K}\right), \\ \dfrac{dB_d}{dt} &= -\tau_d B_d + u_d(t), \\ \dfrac{dB_t}{dt} &= -\tau_t B_t + u_t(t) \exp(-\lambda_{di} B_d), \end{cases}$$

- **Note**: the MAPE value is artificially inflated because, as the tumor volume decreases, **small errors in tumor volume generate high percent errors**.

Model selection

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3CEM0	6	n/a	28.51 ± 17.24
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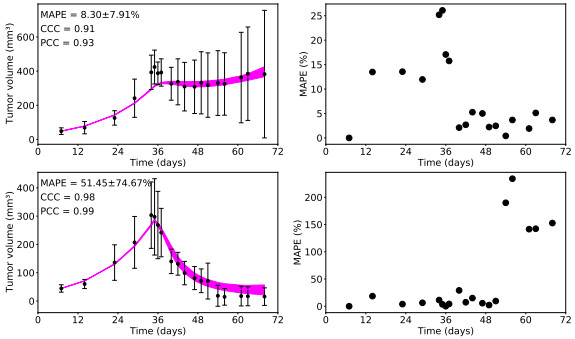

$$\begin{cases} \dfrac{dV_t}{dt} &= (r - \lambda_t B_t - \lambda_{td} B_d B_t)\, V_t \left(1 - \dfrac{V_t}{K}\right), \\ \dfrac{dB_d}{dt} &= -\tau_d B_d + u_d(t), \\ \dfrac{dB_t}{dt} &= -\tau_t B_t + u_t(t) \exp(-\lambda_{di} B_d), \end{cases}$$

- **Added other metrics**: Concordance Correlation Coefficient (CCC) and Pearson Correlation Coefficient (PCC).

Model selection

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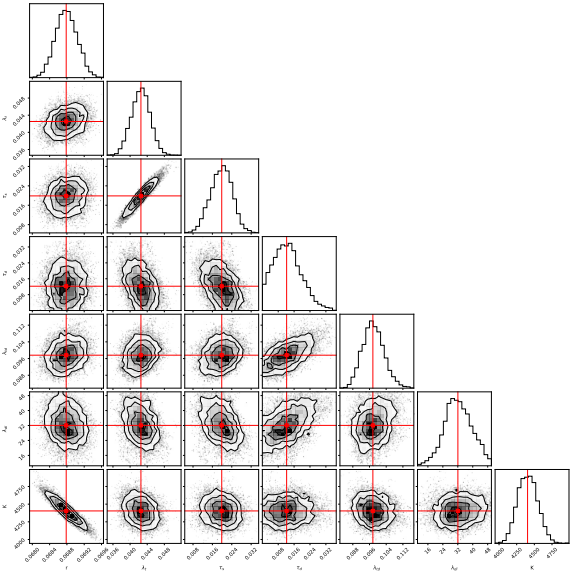
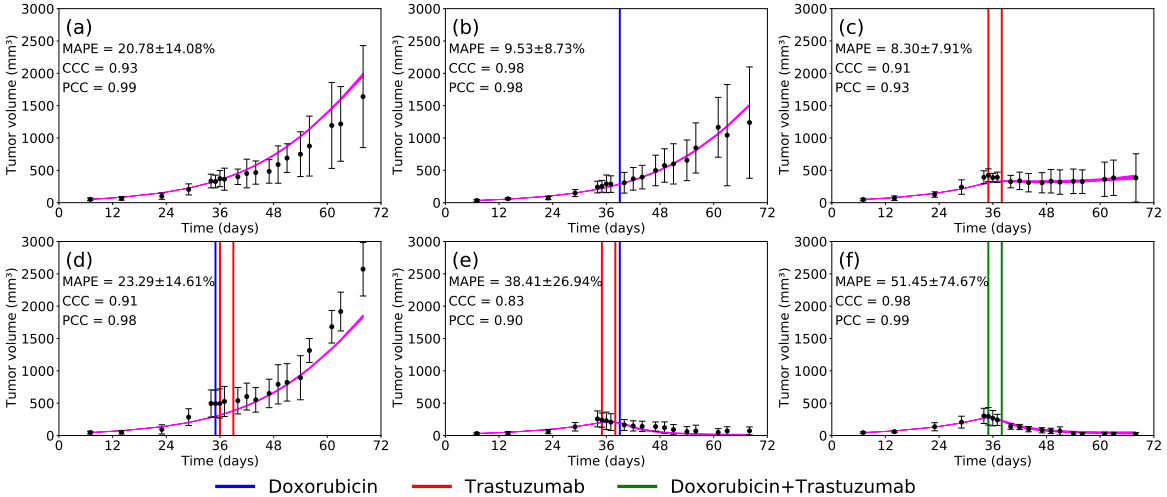
$$
\begin{cases}
\dfrac{dV_t}{dt} &= (r - \lambda_t B_t - \lambda_{td} B_d B_t)\, V_t \left(1 - \dfrac{V_t}{K}\right), \\
\dfrac{dB_d}{dt} &= -\tau_d B_d + u_d(t), \\
\dfrac{dB_t}{dt} &= -\tau_t B_t + u_t(t) \exp(-\lambda_{di} B_d),
\end{cases}
$$

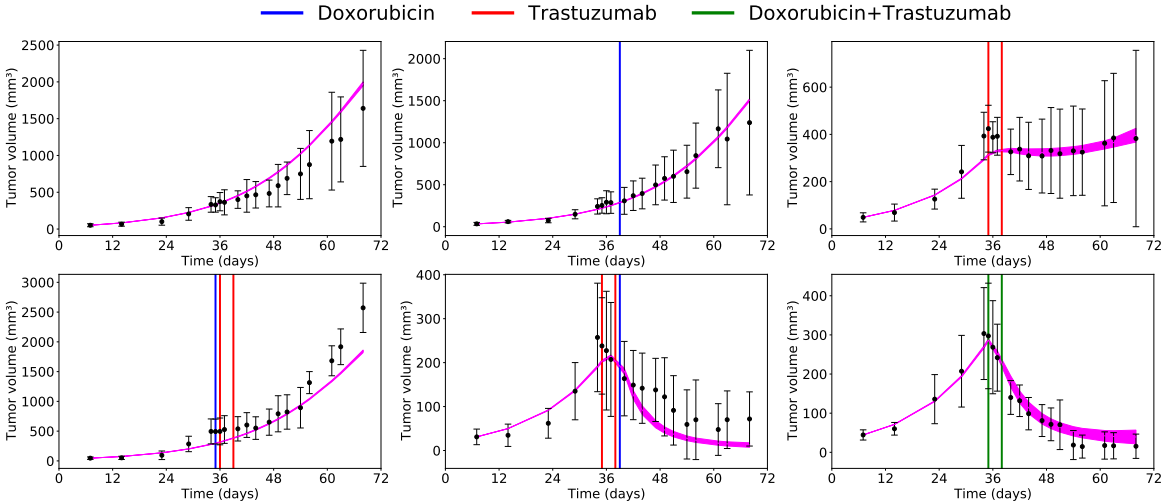


Tumor dynamics (model 3CLM0)



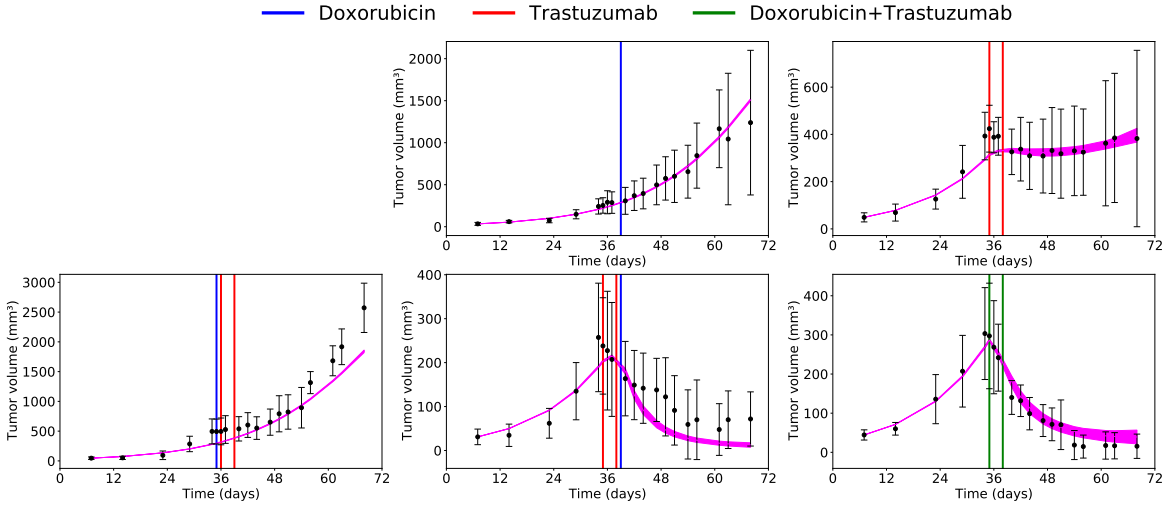
Outline

Cross-validation (model 3CLM0)



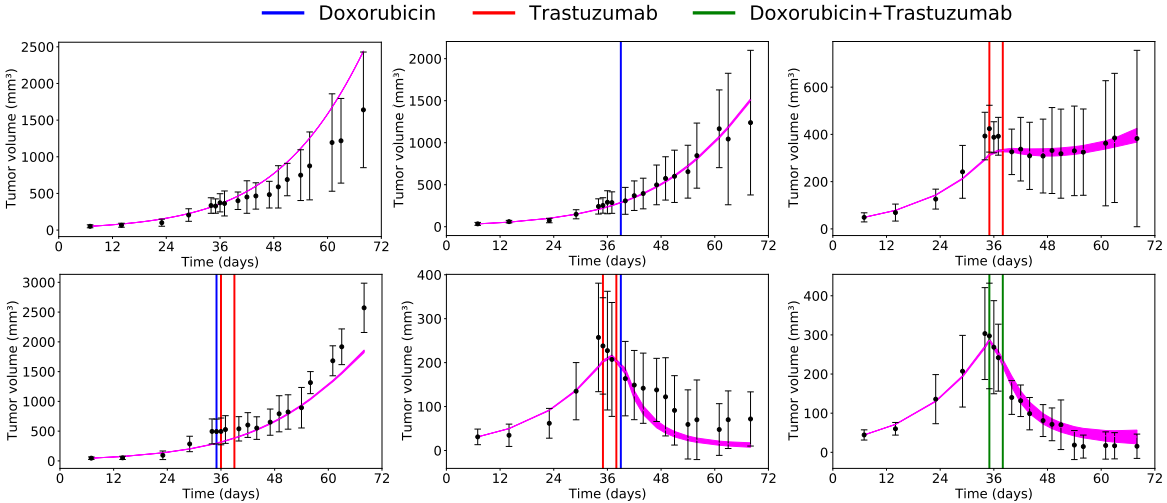
- **Model calibration**: calibrate the model using the six-scenarios.

Cross-validation (model 3CLM0)



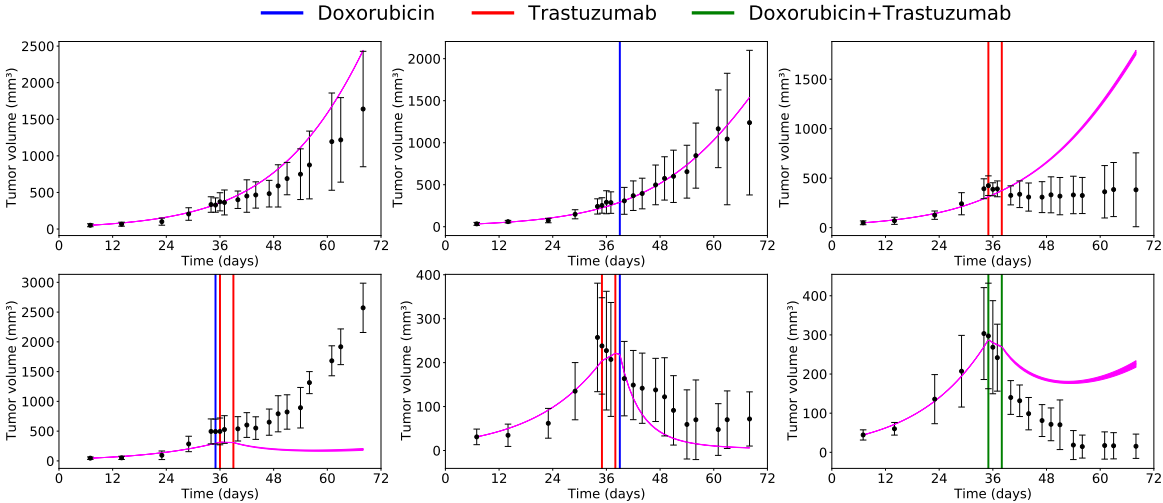
- **Cross-validation, step 1**: calibrate the model using the **five-scenarios**.

Cross-validation (model 3CLM0)



- **Cross-validation, step 2**: predict the tumor volume in the scenario left out.

Cross-validation (model 3CLM0)



- **Cross-validation**: repeat the steps to all possible combinations, and check which scenarios can we recover.

Outline

Optimal treatment protocol

Best experimental protocol

One dose of trastuzumab and doxorubicin at days 35 and 38.

Optimal treatment protocol

Best experimental protocol

One dose of trastuzumab and doxorubicin at days 35 and 38.

1) Minimize total tumor volume

Minimize the following objective function:

$$J = \int_{t_i}^{t_f} V_t^2 \, dt,$$

t_i and t_f are the first and last day that the treatment can be delivered, respectively.

Restrictions:

- same trastuzumab and doxorubicin total and daily doses as the experiments;
- treatment is allowed to start at day 35.

Optimal treatment protocol

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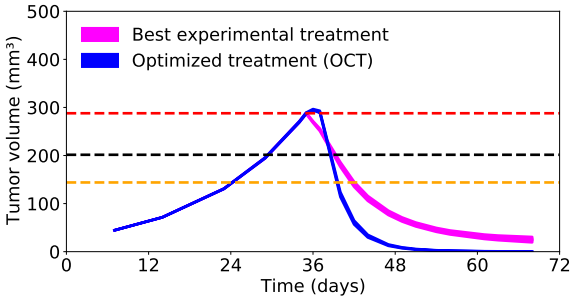

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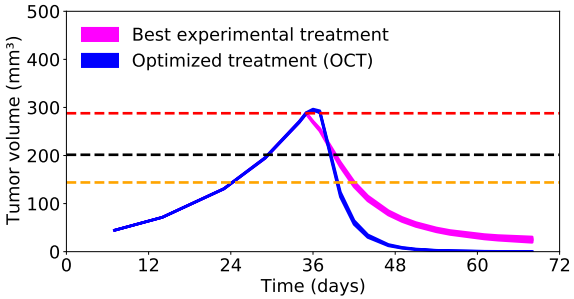

Optimal protocol

One dose of trastuzumab at days 35 and 36, and one dose of doxorubicin at days 37 and 38.

- 45.34% tumor burden reduction.
- 30% tumor reduction: 0.6 days earlier.
- 50% tumor reduction: 2.25 days earlier.
- Complete response: day 59

Cardiotoxicity

Treatment complications

- cardiotoxicity is a common complication of doxorubicin;
- can lead to heart failure and ultimately death;
- it is the second cause of mortality in breast cancer survivors;
- doxorubicin cardiotoxicity is cumulative, dose dependent, and irreversible;
- trastuzumab cardiotoxicity is reversible (in the majority of patients).

Optimal treatment protocol

Best experimental protocol

One dose of trastuzumab and doxorubicin at days 35 and 38.

Optimal treatment protocol

Best experimental protocol

One dose of trastuzumab and doxorubicin at days 35 and 38.

2) Minimize doxorubicin total dose

Minimize the following objective function:

$$J = \int_{t_i}^{t_f} u_d^2(t)\, dt.$$

Restrictions:

- same trastuzumab total and daily doses as the experiments;
- same total tumor volume as the best experimental treatment protocol;
- treatment is allowed to start at day 35.

Optimal treatment protocol

Best experimental protocol

One dose of trastuzumab and doxorubicin at days 35 and 38.

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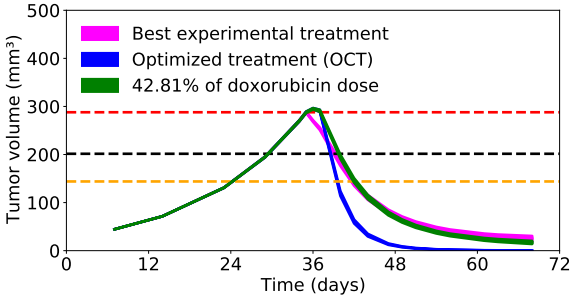

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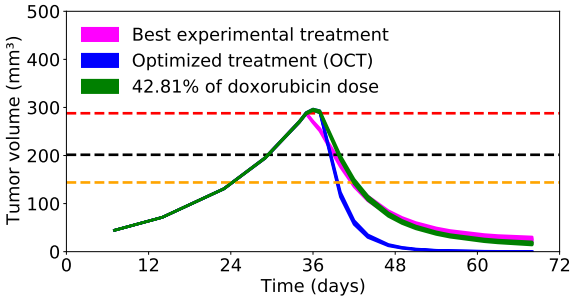


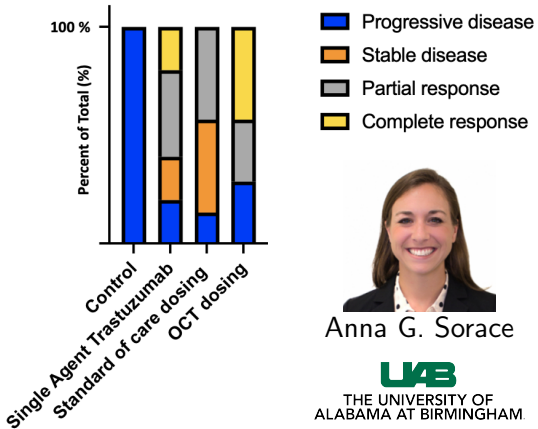
Optimal protocol

One dose of trastuzumab at days 35 and 36, and one dose of doxorubicin at days 37 and 38.

- 42.81% doxorubicin dose reduction.

Outline

Preliminary results (9-11 mice per treatment protocol)



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- We are currently performing the necessary experiments to confirm, or improve, the optimized treatment protocol.

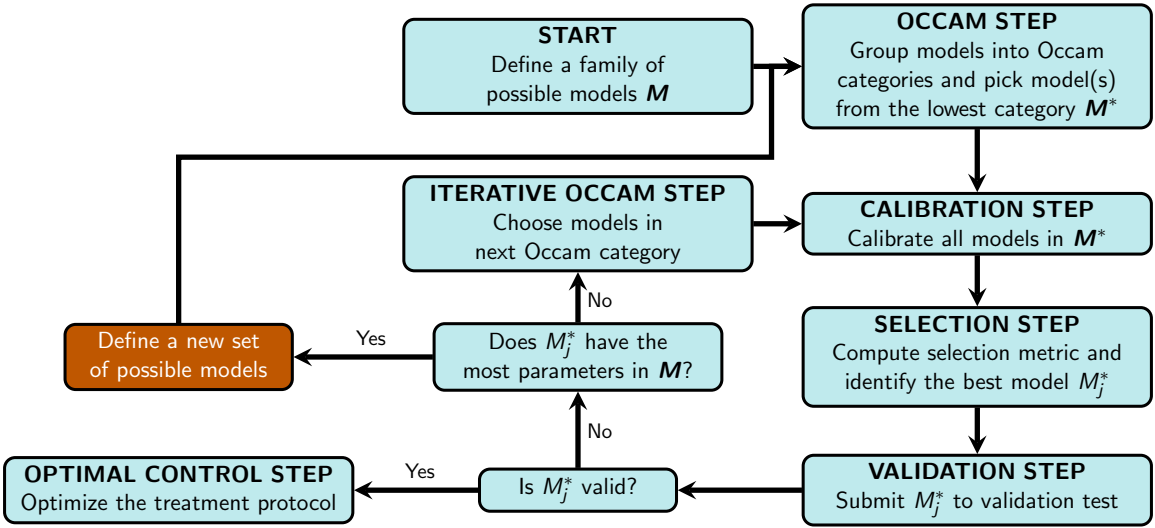
Preliminary conclusions

- OCT dosing outperformed standard-of-care dosing in more responsive tumors and tumors that had a complete response
- single-agent trastuzumab when dosed following OCT math modeling guidance, outperformed standard-of-care that had both HER2 targeted trastuzumab and chemotherapy.

Unpublished Data - Do not share

Outline

The Occam-Plausibility Algorithm [5] + Optimal Control



[5] K. Farrell, J. T. Oden, D. Faghihi, Journal of computational physics (2015)

First set of models (35 models with less than 10 parameters)

Model ID	Model
$C1M1$	$T' = rT - \delta_d S_d T - \delta_h S_h T$
$C2M1$	$T' = rT(1 - T/K) - \delta_d S_d T - \delta_h S_h T$
$C2M2$	$T' = (r - \delta_d S_d - \delta_h S_h) T(1 - T/K)$
$C2M3$	$T' = (r - \delta_d S_d) T(1 - T/K) - \delta_h S_h T$
$C2M4$	$T' = (r - \delta_h S_h) T(1 - T/K) - \delta_d S_d T$
$C2M5$	$T' = rT(1 - T/(K - \delta_d S_d - \delta_h S_h))$
$C2M6$	$T' = rT(1 - T/(K - \delta_d S_d)) - \delta_h S_h T$
$C2M7$	$T' = rT(1 - T/(K - \delta_h S_h)) - \delta_d S_d T$
$C2M8$	$T' = (r - \delta_h S_h) T(1 - T/(K - \delta_d S_d))$
$C2M9$	$T' = (r - \delta_d S_d) T(1 - T/(K - \delta_h S_h))$
$C3M1$	$T' = rT(1 - A/T) - \delta_d S_d T - \delta_h S_h T$
$C3M2$	$T' = (r - \delta_d S_d - \delta_h S_h) T(1 - A/T)$
$C3M3$	$T' = (r - \delta_d S_d) T(1 - A/T) - \delta_h S_h T$
$C3M4$	$T' = (r - \delta_h S_h) T(1 - A/T) - \delta_d S_d T$

First set of models (35 models with less than 10 parameters)

Model ID	Model
$C3M5$	$T' = rT(1-(A-\delta_d S_d-\delta_h S_h)/T)$
$C3M6$	$T' = rT(1-(A-\delta_d S_d)/T)-\delta_h S_h T$
$C3M7$	$T' = rT(1-(A-\delta_h S_h)/T)-\delta_d S_d T$
$C3M8$	$T' = (r-\delta_h S_h)T(1-(A-\delta_d S_d)/T)$
$C3M9$	$T' = (r-\delta_d S_d)T(1-(A-\delta_h S_h)/T)$
$C4M1$	$T' = rT(1-T/K)(1-A/T)-\delta_d S_d T-\delta_h S_h T$
$C4M2$	$T' = (r-\delta_d S_d-\delta_h S_h)T(1-T/K)(1-A/T)$
$C4M3$	$T' = (r-\delta_d S_d)T(1-T/K)(1-A/T)-\delta_h S_h T$
$C4M4$	$T' = (r-\delta_h S_h)T(1-T/K)(1-A/T)-\delta_d S_d T$
$C4M5$	$T' = rT(1-T/(K-\delta_d S_d-\delta_h S_h))(1-A/T)$
$C4M6$	$T' = rT(1-T/(K-\delta_d S_d))(1-A/T)-\delta_h S_h T$
$C4M7$	$T' = rT(1-T/(K-\delta_h S_h))(1-A/T)-\delta_d S_d T$
$C4M8$	$T' = (r-\delta_h S_h)T(1-T/(K-\delta_d S_d))(1-A/T)$
$C4M9$	$T' = (r-\delta_d S_d)T(1-T/(K-\delta_h S_h))(1-A/T)$

First set of models (35 models with less than 10 parameters)

Model ID	Model
$C4M10$	$T' = rT(1 - T/K)(1 - (A - \delta_d S_d - \delta_h S_h)/T)$
$C4M11$	$T' = rT(1 - T/K)(1 - (A - \delta_h S_h)/T) - \delta_d S_d T$
$C4M12$	$T' = rT(1 - T/K)(1 - (A - \delta_d S_d)/T) - \delta_h S_h T$
$C4M13$	$T' = (r - \delta_d S_d)T(1 - T/K)(1 - (A - \delta_h S_h)/T)$
$C4M14$	$T' = (r - \delta_h S_h)T(1 - T/K)(1 - (A - \delta_d S_d)/T)$
$C4M15$	$T' = rT(1 - T/(K - \delta_d S_d))(1 - (A - \delta_h S_h)/T)$
$C4M16$	$T' = rT(1 - T/(K - \delta_h S_h))(1 - (A - \delta_d S_d)/T)$

First set of models (35 models with less than 10 parameters)

Model ID	Model
$C4M10$	$T' = rT(1 - T/K)(1 - (A - \delta_d S_d - \delta_h S_h)/T)$
$C4M11$	$T' = rT(1 - T/K)(1 - (A - \delta_h S_h)/T) - \delta_d S_d T$
$C4M12$	$T' = rT(1 - T/K)(1 - (A - \delta_d S_d)/T) - \delta_h S_h T$
$C4M13$	$T' = (r - \delta_d S_d)T(1 - T/K)(1 - (A - \delta_h S_h)/T)$
$C4M14$	$T' = (r - \delta_h S_h)T(1 - T/K)(1 - (A - \delta_d S_d)/T)$
$C4M15$	$T' = rT(1 - T/(K - \delta_d S_d))(1 - (A - \delta_h S_h)/T)$
$C4M16$	$T' = rT(1 - T/(K - \delta_h S_h))(1 - (A - \delta_d S_d)/T)$

Calibrated every model

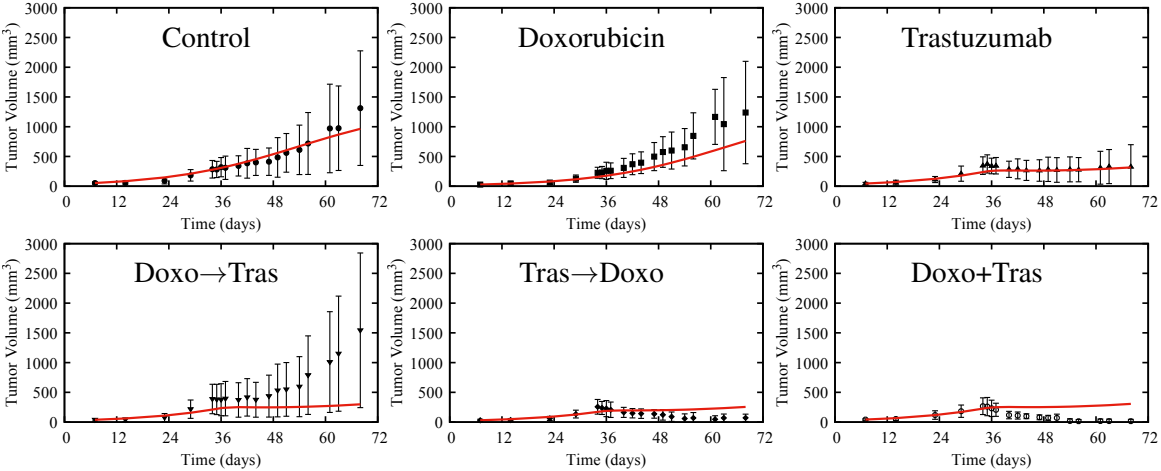
First set of models (35 models with less than 10 parameters)

Model ID	Model
C4M15	$T' = rT(1 - T/(K - \delta_d S_d))(1 - (A - \delta_h S_h)/T)$
C4M16	$T' = rT(1 - T/(K - \delta_h S_h))(1 - (A - \delta_d S_d)/T)$

Not a single one fitted every scenario. . .

Calibrated every model

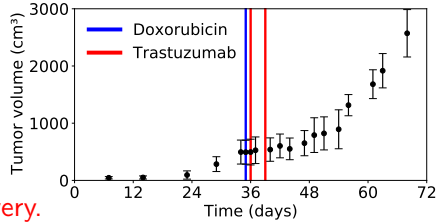
Best model from the first set



Three-constituent model

$$
\begin{cases}
\dfrac{dV_t}{dt} = \left(\underbrace{r}_{\text{growth rate}} - \underbrace{\lambda_t B_t}_{\text{death by trastuzumab}} - \underbrace{\lambda_d B_d}_{\text{death by doxorubicin}} - \underbrace{\lambda_{td} B_d B_t}_{\text{death by drug combination}} \right) \mathcal{P}(V_t), \\
\dfrac{dB_d}{dt} = - \underbrace{\tau_d B_d}_{\text{doxorubicin decay}} + \underbrace{u_d(t)}_{\text{doxorubicin delivery}}, \\
\dfrac{dB_t}{dt} = - \underbrace{\tau_t B_t}_{\text{trastuzumab decay}} + \underbrace{u_t(t) \exp(-\lambda_{di} B_d)}_{\text{trastuzumab delivery inhibition by doxorubicin}}, \\
\mathcal{P}(V_t) = \begin{cases} V_t, & \text{if exponential growth,} \\ V_t \left(1 - \dfrac{V_t}{K}\right), & \text{if logistic growth.} \end{cases}
\end{cases}
$$

V_t	tumor volume
B_d	doxorubicin availability
B_t	trastuzumab availability



- Doxorubicin: decreases the total vascular density.
- Reduction in vascular density ⇒ reduces trastuzumab delivery.

Outline

Summary

- Developed a family of models to capture the tumor dynamics and the direct effects of doxorubicin and trastuzumab therapies.
- Calibrated every model using data from a murine model of human HER2+ breast cancer.
- Optimized the treatment protocol with the "best" model.
- Best treatment protocol: deliver all trastuzumab prior to doxorubicin.
- This research may provide a framework suitable for application in future clinical trials of novel therapies.

Lima, E. A. B. F., Wyde, R. A. F., Sorace, A. G., and Yankeelov, T. E.. "Optimizing combination therapy in a murine model of HER2+ breast cancer." CMAME (2022): 115484.

Thank you!

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- National Institute of Health: R01CA240589, R01CA276540, and U24CA226110
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THE CENTER FOR COMPUTATIONAL ONCOLOGY

TACC TEXAS ADVANCED COMPUTING CENTER

TEXAS The University of Texas at Austin

UAB THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Model calibration, selection and validation (Bayesian approach)

Given events A and B:

$$P(A,B) = P(A|B)P(B);$$
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Converting to probability densities π, if A represents the parameter $\boldsymbol{\theta}$ of a model, and B the observational data $\boldsymbol{D}$:

$$\underbrace{\pi(\boldsymbol{\theta}|\boldsymbol{D})}_{\text{posterior}} = \frac{\overbrace{\pi(\boldsymbol{D}|\boldsymbol{\theta})}^{\text{likelihood}}\overbrace{\pi(\boldsymbol{\theta})}^{\text{prior}}}{\underbrace{\pi(\boldsymbol{D})}_{\text{evidence}}};$$

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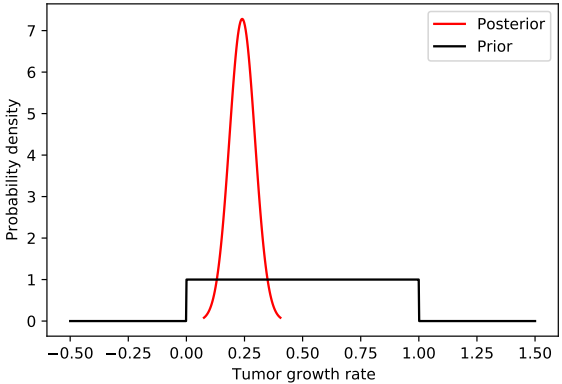

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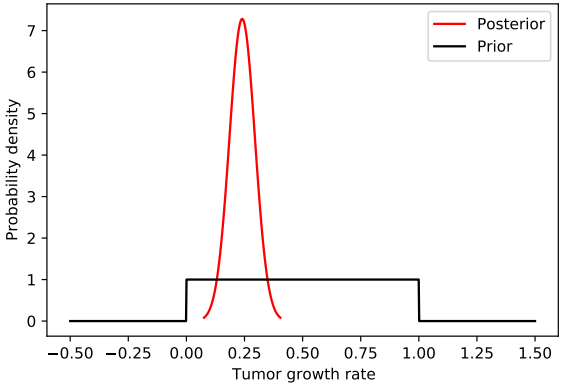

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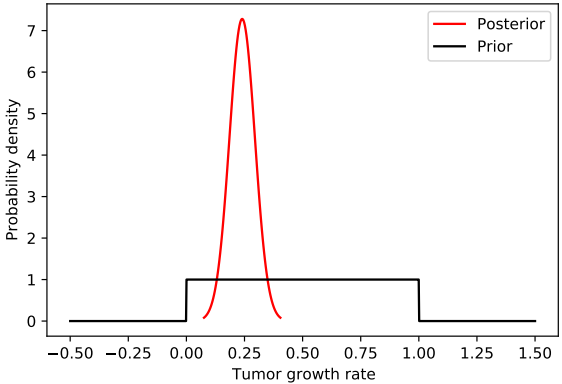

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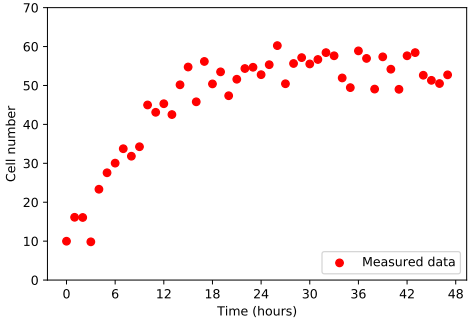

- $\boldsymbol{D}$: measured data;

Mathematical model

$$\frac{dN}{dt} = rN\left(1 - \frac{N}{K}\right),$$

- $\boldsymbol{\theta}$: vector of model parameters, $\boldsymbol{\theta} = (r, K)$;
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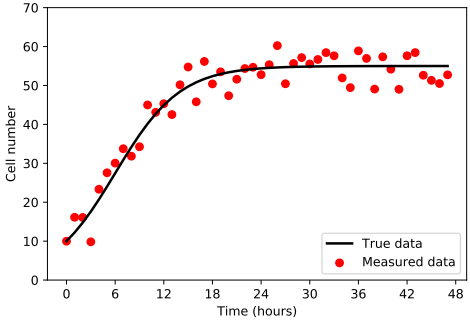

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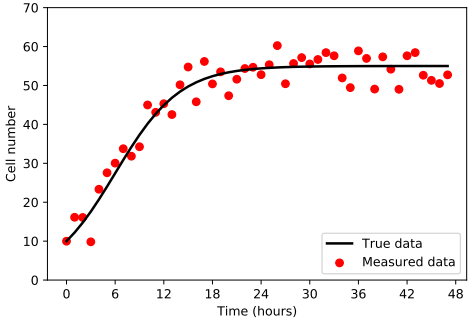

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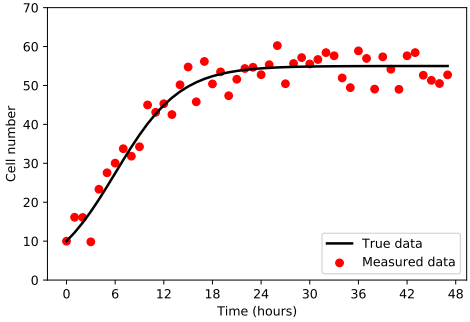

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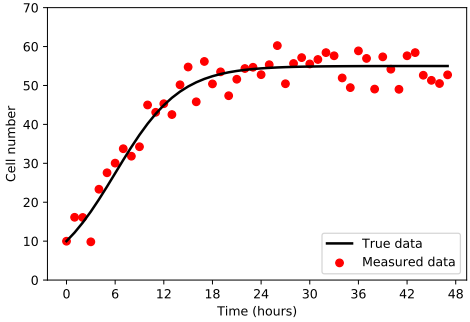

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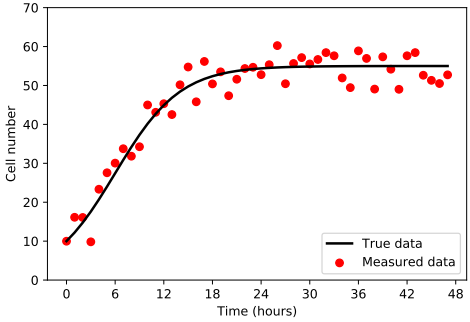

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Likelihood

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Assuming:

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$$\pi(\boldsymbol{D}|\boldsymbol{\theta}) = \prod_{i=1}^{N_t} \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{(D_i - Y_i(\boldsymbol{\theta}))^2}{2\sigma^2}},$$

- N_t: the number of data points.

Model selection

odel	#P	AICw/BICw	Error (%)
EM0	6	n/a	28.51 ± 17.24
LM0	7	1.00	25.29 ± 15.37
CEM	7	0.00	
CLM	8	1.00	29.06 ± 21.78
EM1	8	0.00	
EM2	8	0.00	
EM3	8	0.00	
LM1	9	0.44	29.03 ± 22.65
LM2	9	0.10	
LM3	9	0.46	

$$\frac{dV_t}{dt} = (r - \lambda_t B_t - \lambda_{td} B_d B_t)\, V_t \left(1 - \frac{V_t}{K}\right),$$
$$\frac{dB_d}{dt} = -\tau_d B_d + u_d(t),$$
$$\frac{dB_t}{dt} = -\tau_t B_t + u_t(t) \exp(-\lambda_{di} B_d),$$

AIC weight

Akaike information criterion

$$AIC = -2\log(like) + 2k$$

where k is the number of parameters

$$AICw_j = \frac{\exp\left\{-\frac{1}{2}\left(AIC_j - AIC_{min}\right)\right\}}{\sum_{r=1}^{m} \exp\left\{-\frac{1}{2}\left(AIC_r - AIC_{min}\right)\right\}}$$

BIC weight

Bayesian information criterion

$$BIC = -2\log(like) + k\log(n_d)$$

where k is the number of parameters, and n_d the number of data points.

$$BICw_j = \frac{\exp\left\{-\frac{1}{2}\left(BIC_j - BIC_{min}\right)\right\}}{\sum_{r=1}^{m} \exp\left\{-\frac{1}{2}\left(BIC_r - BIC_{min}\right)\right\}}$$