Optimizing ovarian cancer treatment with Maths:

Carboplatin + Anti-Bcl-2/xL combo therapy

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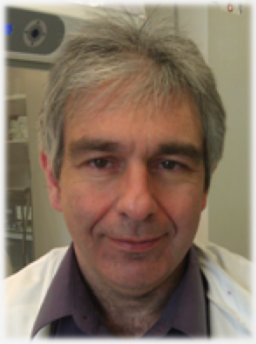
Oxford Centre for Collaborative Applied Mathematics
INSTITUTE FOR SCIENCE AND TECHNOLOGY IN MEDICINE

Collaborators



- Helen Byrne
  OCCAM, Mathematical Institute
  University of Oxford, UK

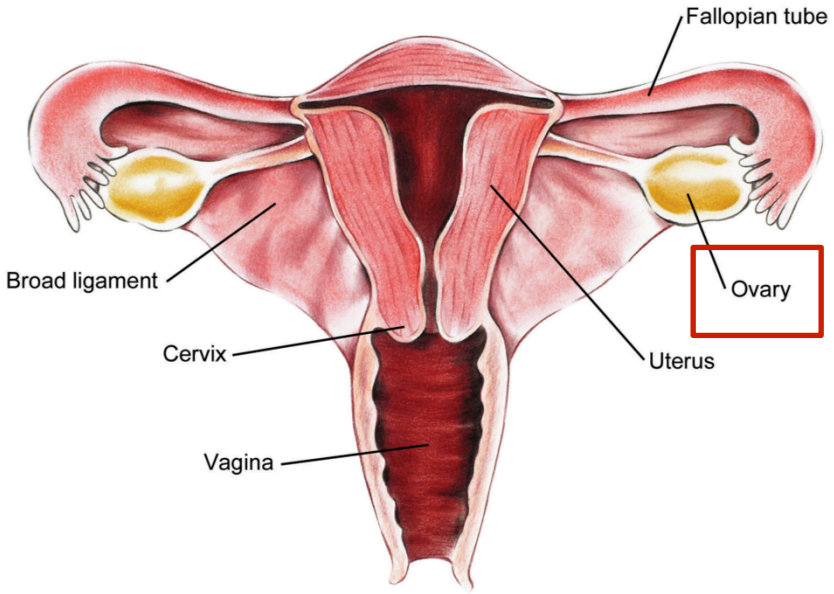
- Michael Meyer-Hermann
  Systems Immunology
  HZI, Germany

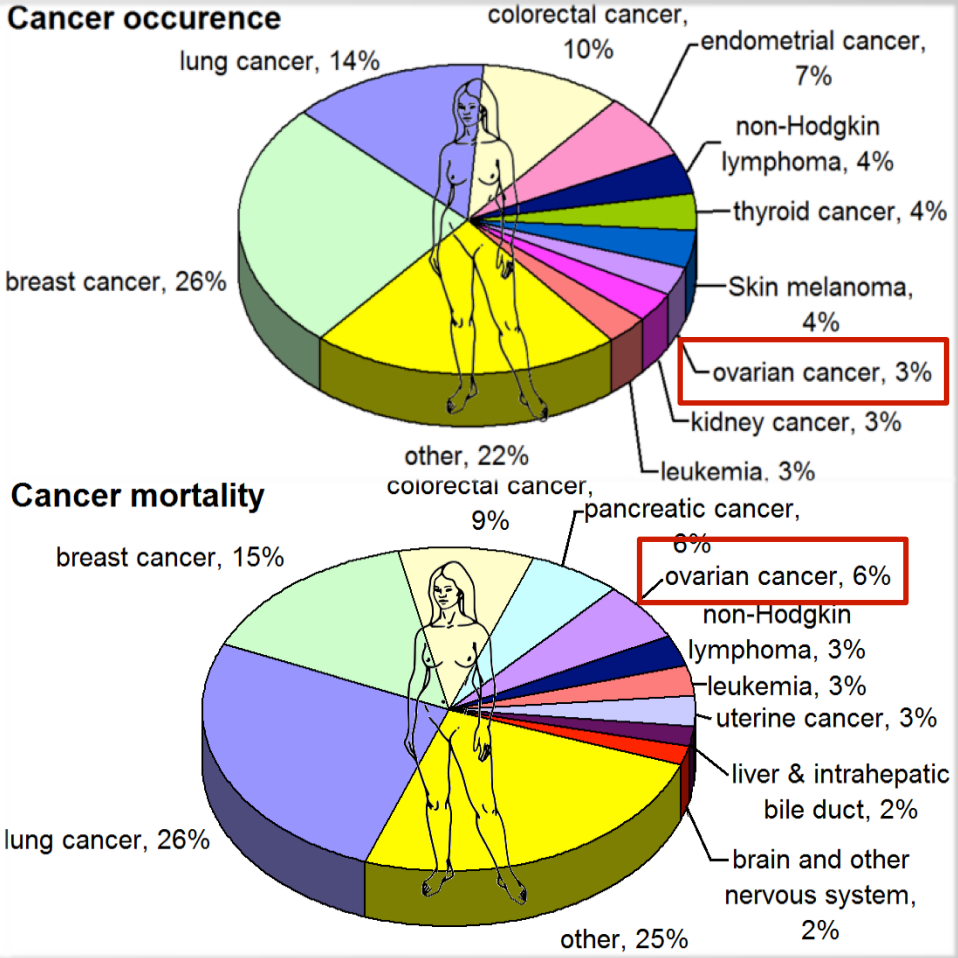
- Alan Richardson
  ISTM
  Keele University, UK

Outline

- Overview
- *In vitro* proof-of-concept model
- Simulating tumor xenograft experiments
- Clinical applications
- Where are we headed?

Ovarian Cancer





Figures/Data: www.metrohealth.org

Jemal A et al. (2008) *CA Cancer J Clin* 58:71-96

Treating Ovarian Cancer

- Standard treatment – combination of Pt-based drugs (e.g. Carboplatin) + anti-mitotic drugs (e.g. Paclitaxel)
- Pt-drugs induce DNA damage, leading to cell cycle arrest and subsequent death
- However, recurrent disease often associated with resistance

Mechanisms of Resistance

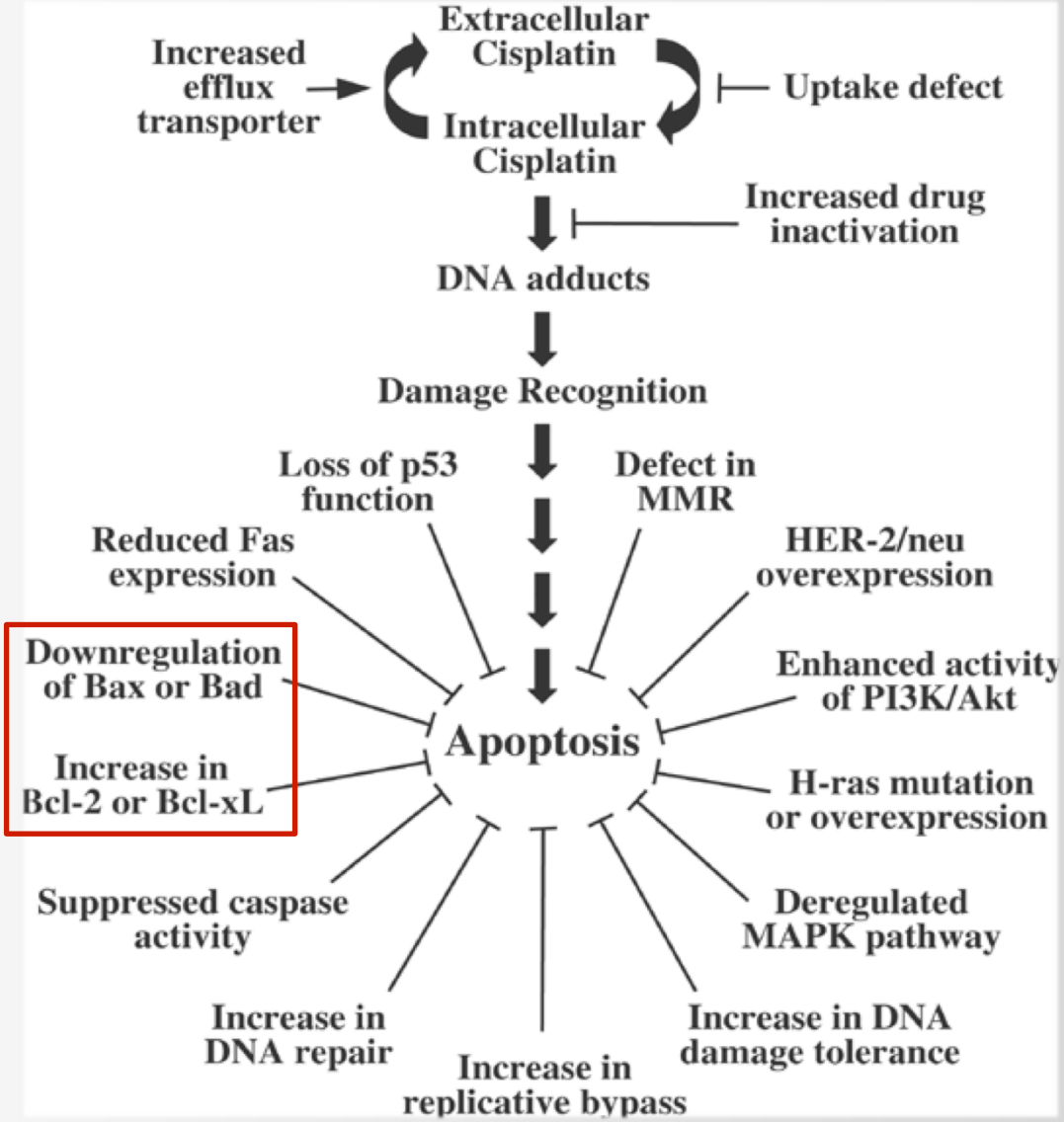
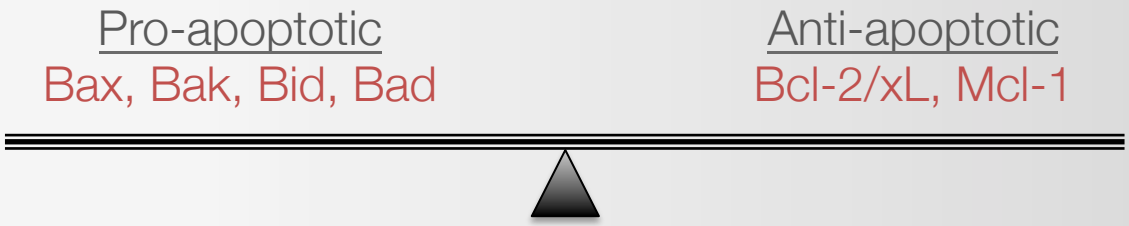


Figure: Siddik ZH (2003)
Oncogene 22:7265-7279

Targeting the Bcl-family

- Novel treatments in development include targeting Bcl-family proteins that regulate cell death (apoptosis)



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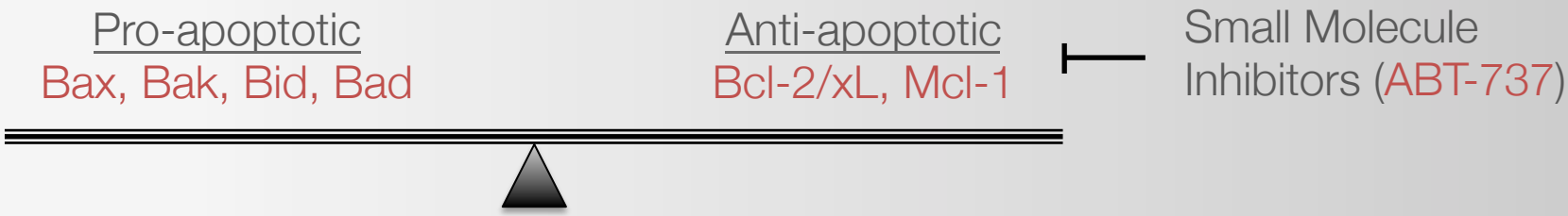

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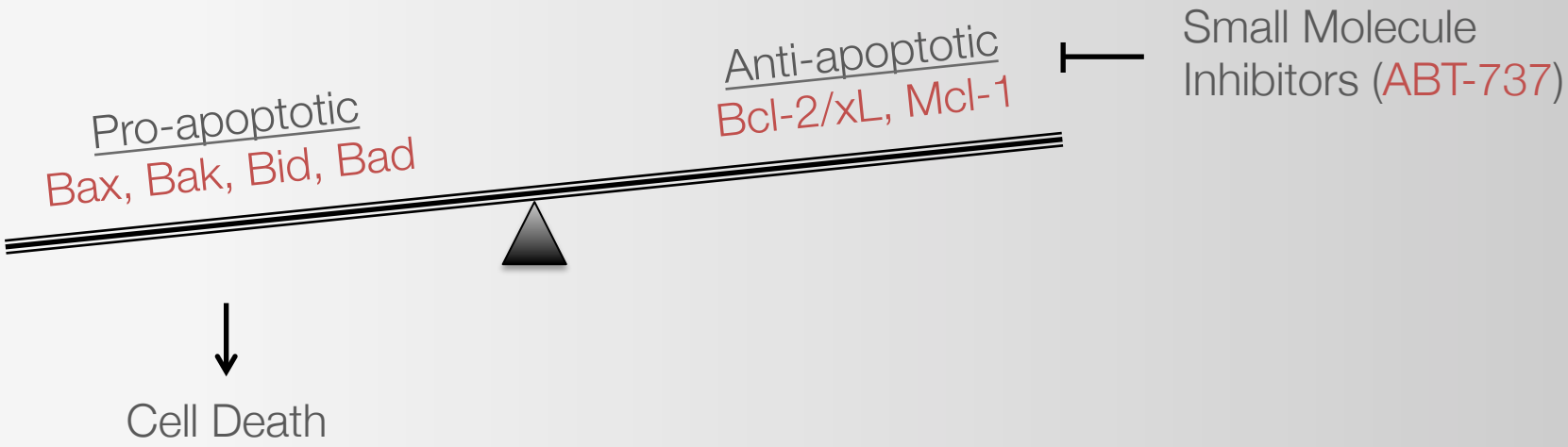
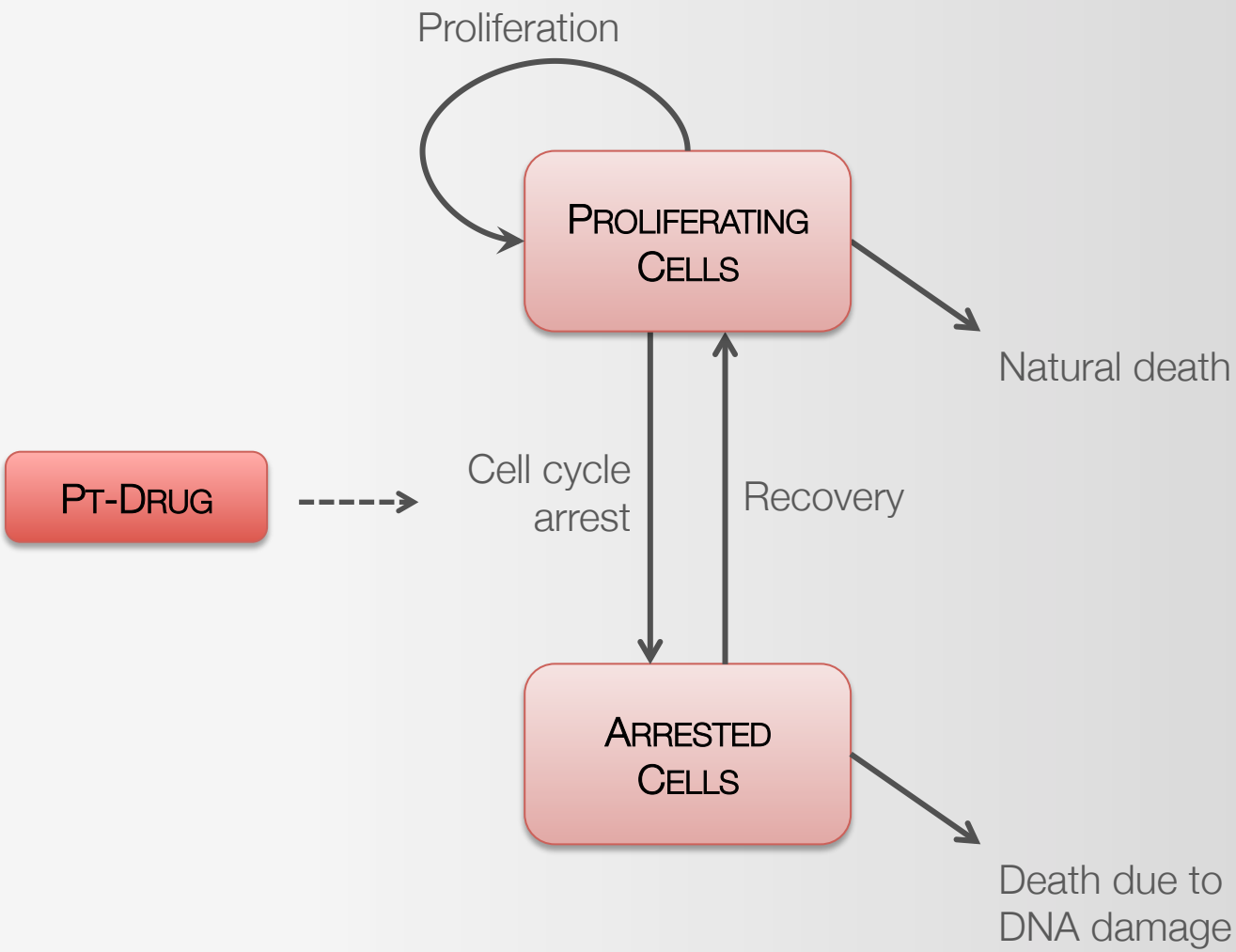


Model Schematic



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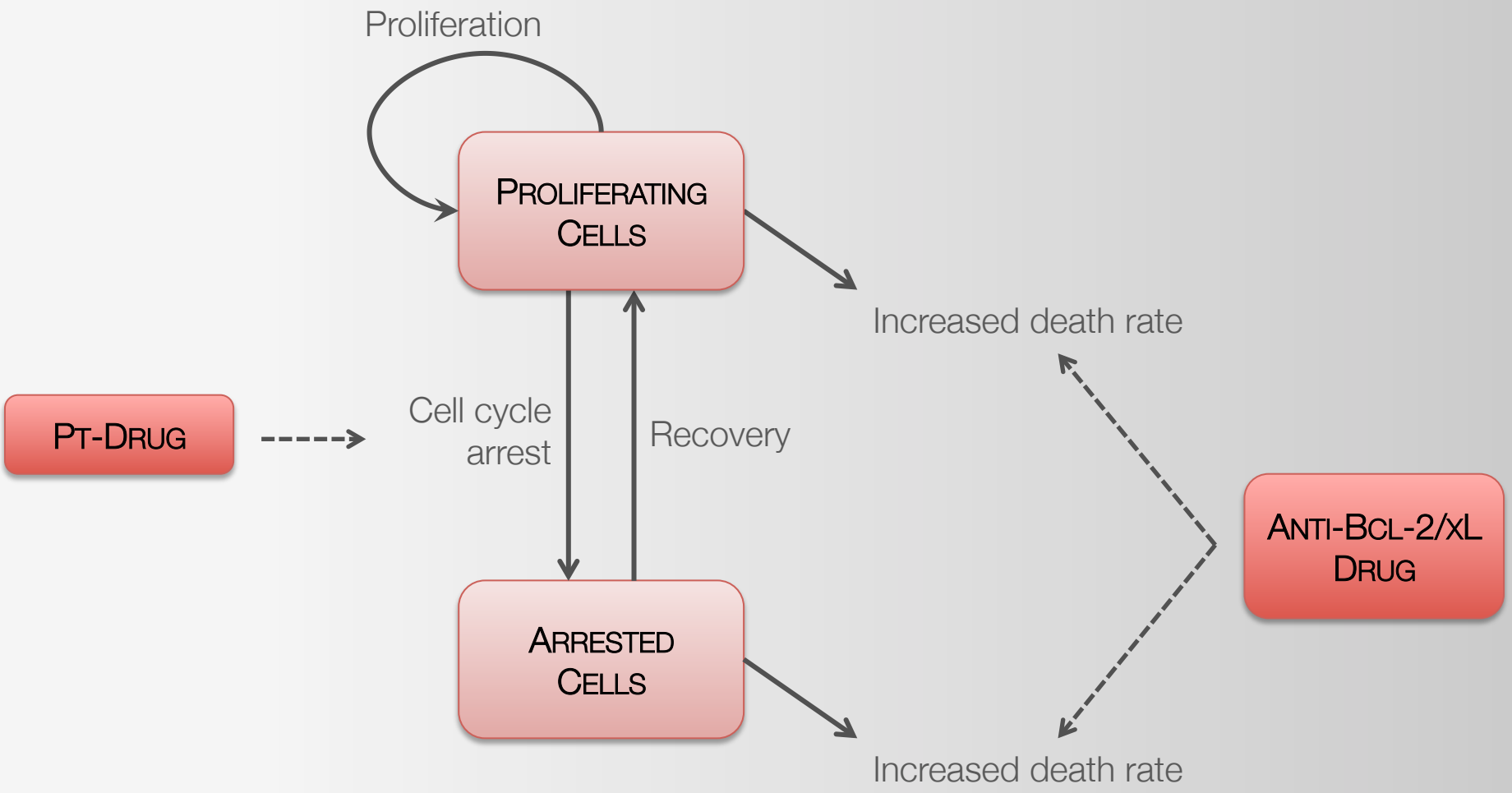
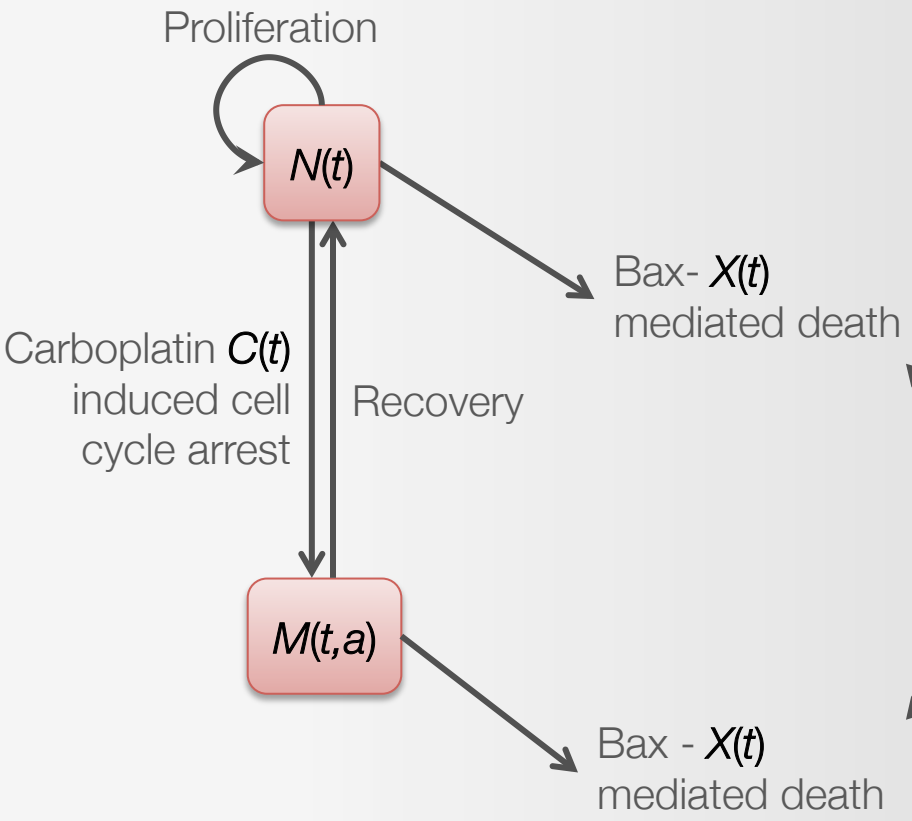


Model Variables



Intracellular Reaction

$$A(t) + B(t) \rightleftharpoons P(t),$$

ABT-737 Bcl-xL ABT-737-Bcl-xL Complex

$$X(t) + B(t) \rightleftharpoons Q(t)$$

Bax Bcl-xL Bax-Bcl-xL Complex

- t is time
- a is time cells have spent in the arrested compartment

Mathematical Model

Arrested Cells

$$\frac{\partial M}{\partial t} + \frac{\partial M}{\partial a} = -\underbrace{f(t-a)\,M(t,a)}_{\text{Drug-dependent death}}, \quad \text{where } M(t,0) = \alpha(t)\,N(t)$$

Proliferating Cells

$$\frac{dN}{dt} = \underbrace{N\left[1 - \left(N + \int_0^t M(t,a)da\right)\right]}_{\text{Logistic growth}} - \underbrace{\alpha(t)\,N}_{\substack{\text{Carboplatin-induced} \\ \text{cell arrest}}} - \underbrace{\beta(t)\,N}_{\substack{\text{ABT-737-induced} \\ \text{cell death}}} + \underbrace{M(t, a = a_r)}_{\substack{\text{Recovery from} \\ \text{arrested state}}}$$

- Here, $\alpha(t)$ and $f(t)$ are non-negative periodic functions, with period – say τ – corresponding to the period of therapy administration for the *in vivo* case.

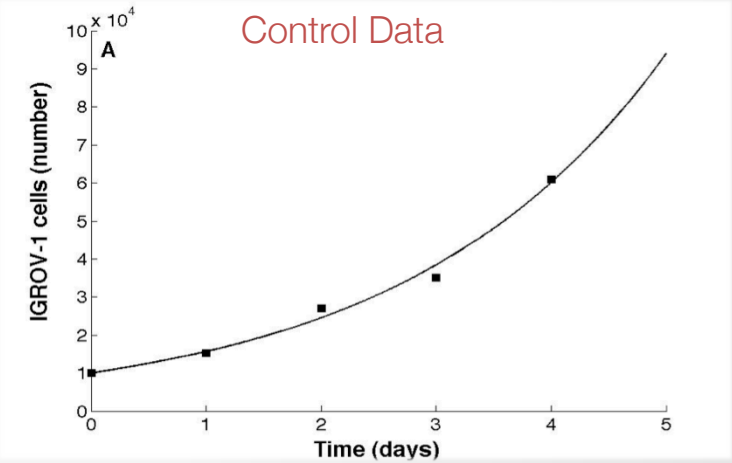
Molecular basis of synergy between carboplatin and ABT-737

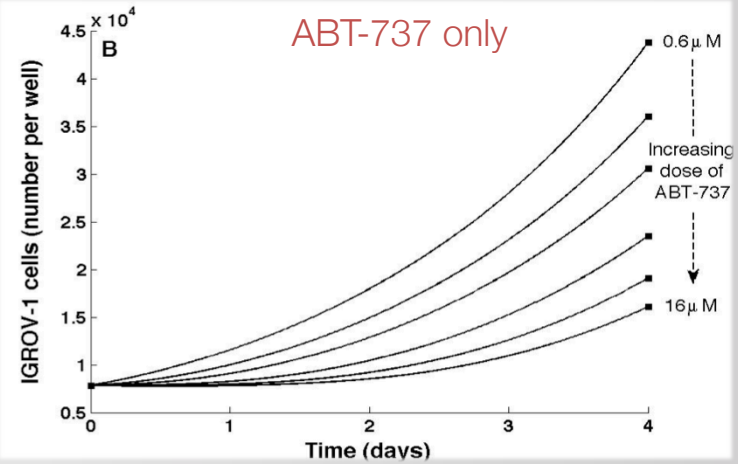
Witham J, Valenti MR, Richardson A et al. (2007)
Clinical Cancer Research 13(23):7191-7198

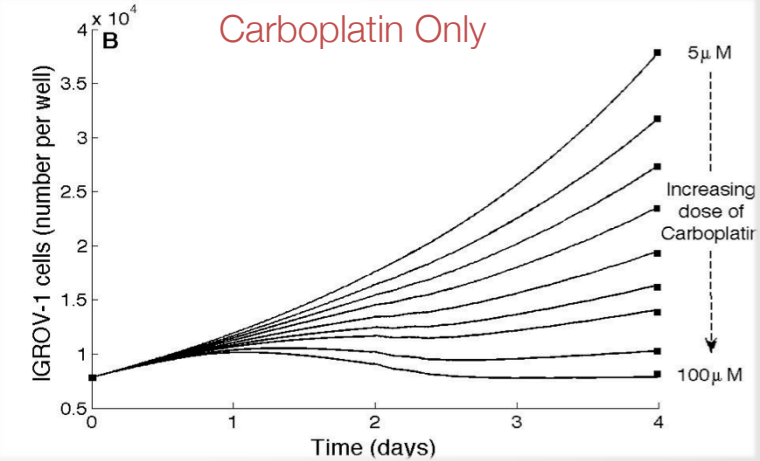
Modeling Objectives

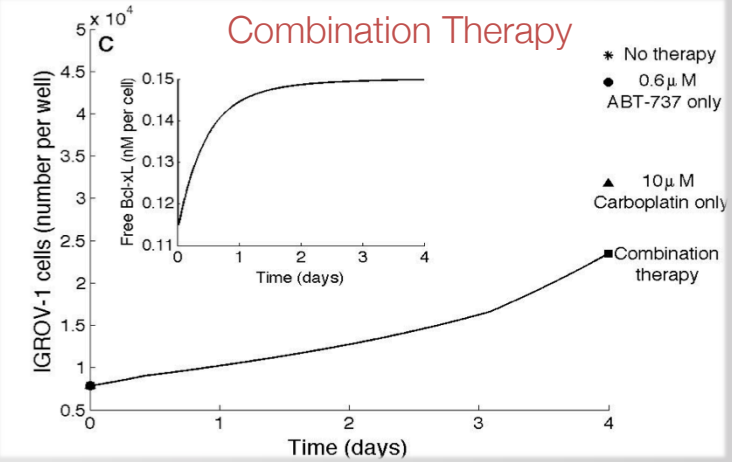
- Elucidate molecular basis of drug (carboplatin + ABT-737) action
- Predict optimal dosing and scheduling and treatment response
- Maximize synergy between the 2 drugs

In Vitro Fits



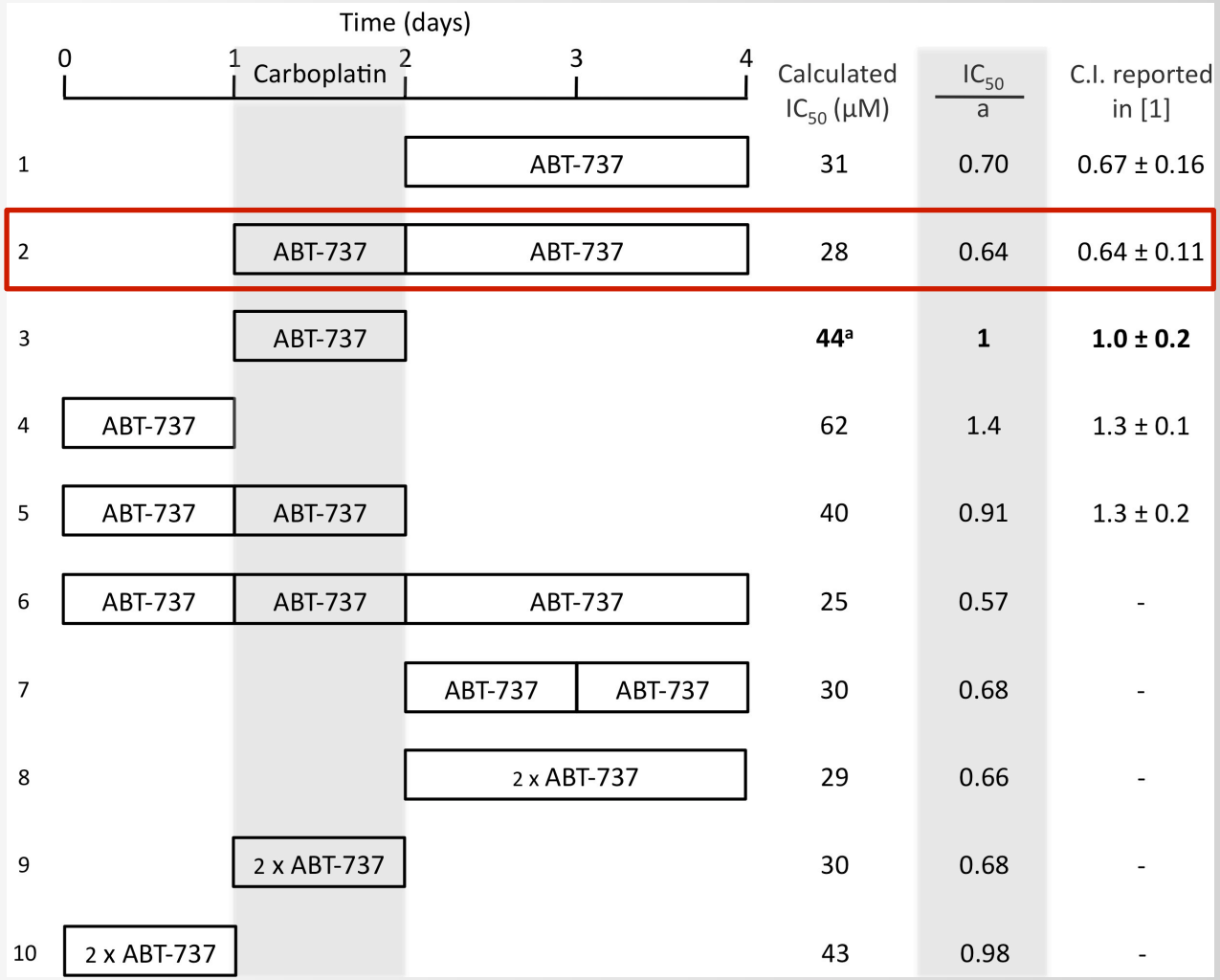






H V Jain and M Meyer-Hermann (2011)
Cancer Research 71(3):705-715

Optimal Scheduling



	Calculated IC_{50} (μM)	$\frac{IC_{50}}{a}$	C.I. reported in [1]
1	31	0.70	0.67 ± 0.16
2	28	0.64	0.64 ± 0.11
3	**44[a]**	**1**	**1.0 ± 0.2**
4	62	1.4	1.3 ± 0.1
5	40	0.91	1.3 ± 0.2
6	25	0.57	-
7	30	0.68	-
8	29	0.66	-
9	30	0.68	-
10	43	0.98	-

H V Jain and M Meyer-Hermann (2011)
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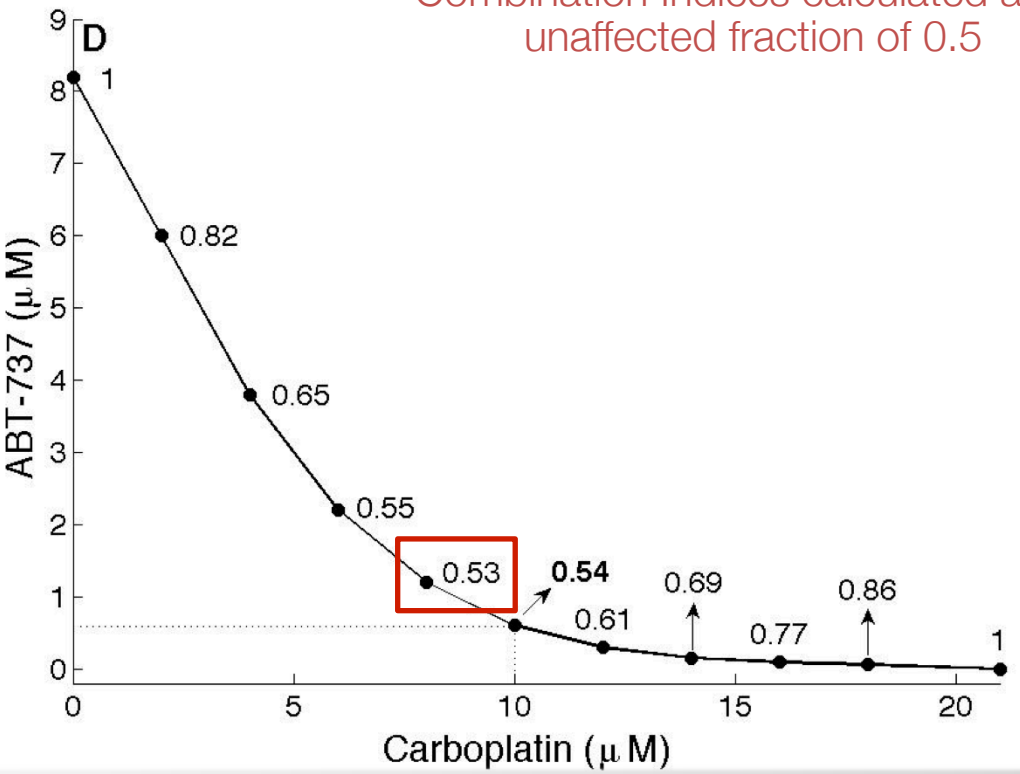
Optimal Dosing

Combination Indices calculated at an unaffected fraction of 0.5



$$C.I. = \frac{Dose\ Drug\ 1}{IC_{50}^{drug\ 1}} + \frac{Dose\ Drug\ 2}{IC_{50}^{drug\ 2}}$$

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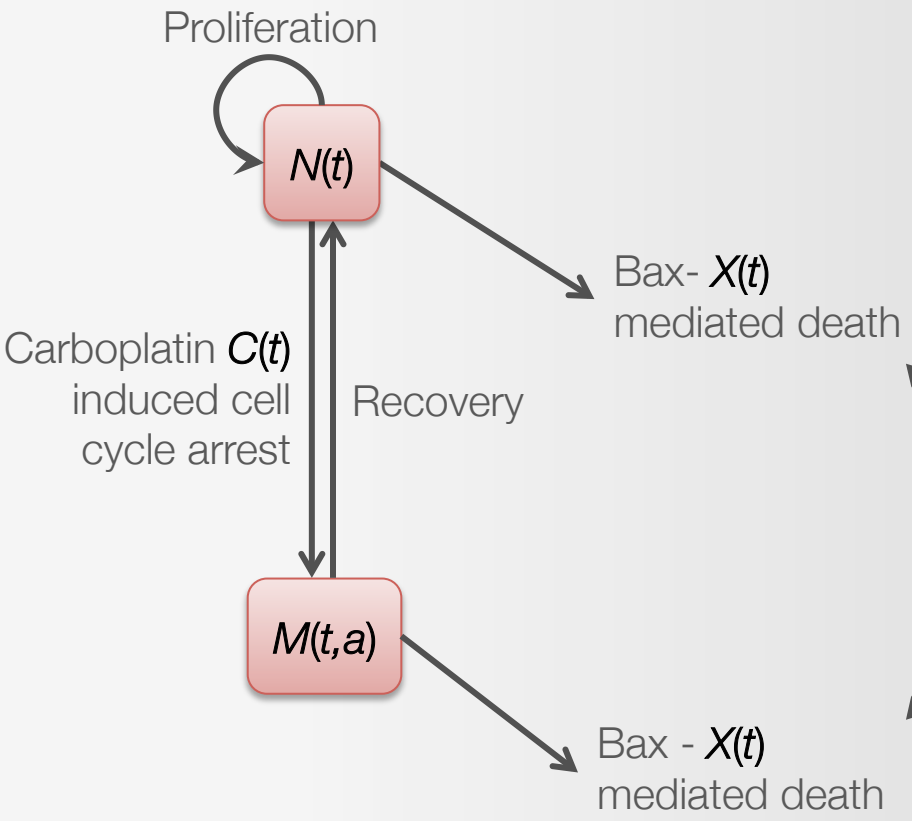
Summary of *In Vitro* Modeling

- Our approach novel because an age-structured model used for the first time to describe the effect of Pt-based chemotherapy
- Potential application in early stage drug discovery/development
  - The model validates and explains the hypothesis that carboplatin sensitizes cancer cells to anti-Bcl-2/xL therapy
  - Validated model used to predict optimal dosing and scheduling

In Vivo Tumor Xenograft Experiments

Model Variables



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- t is time
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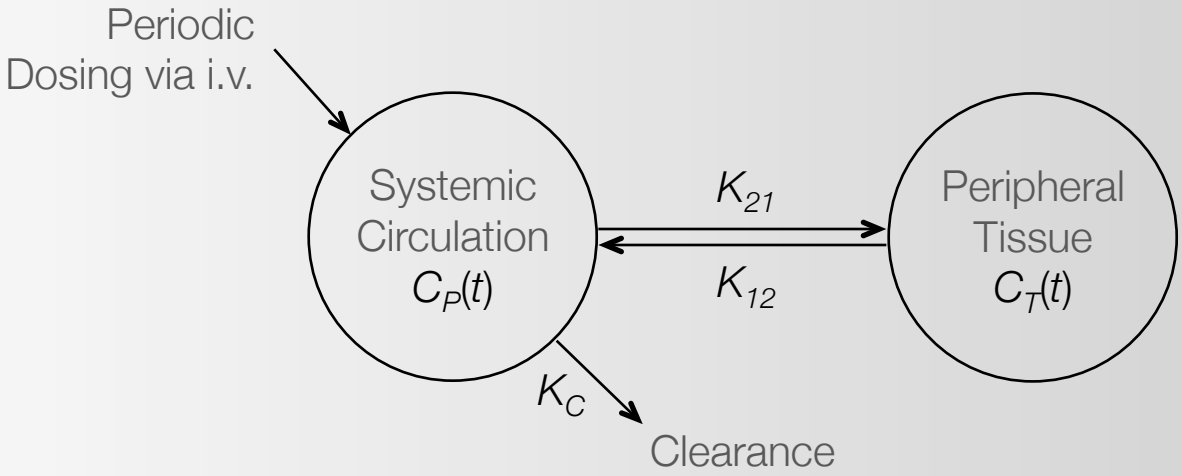
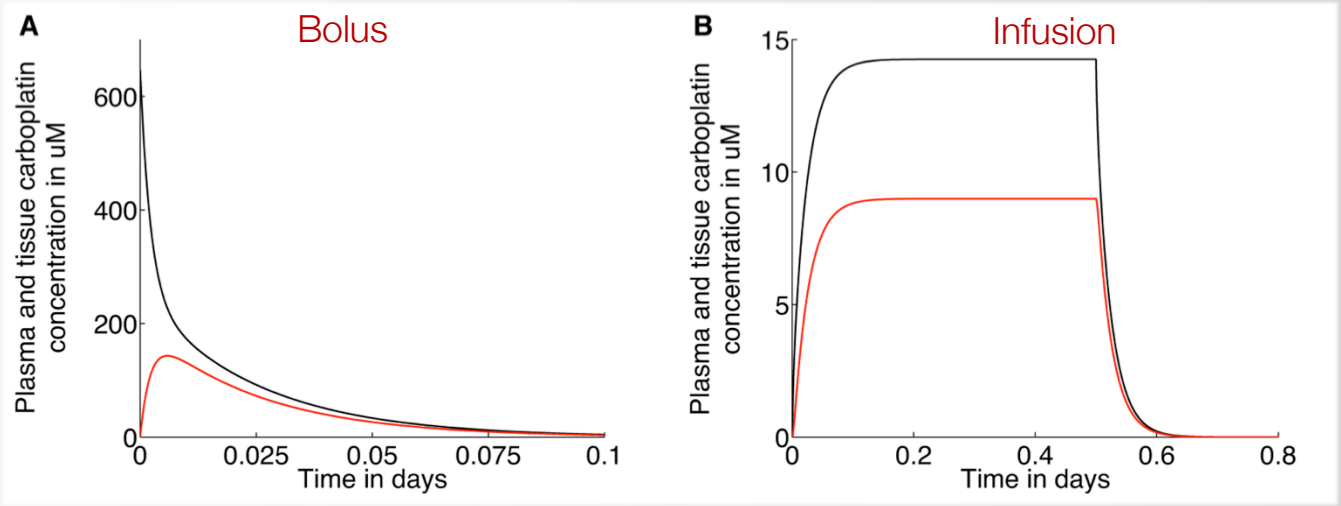
Carboplatin Pharmacokinetics





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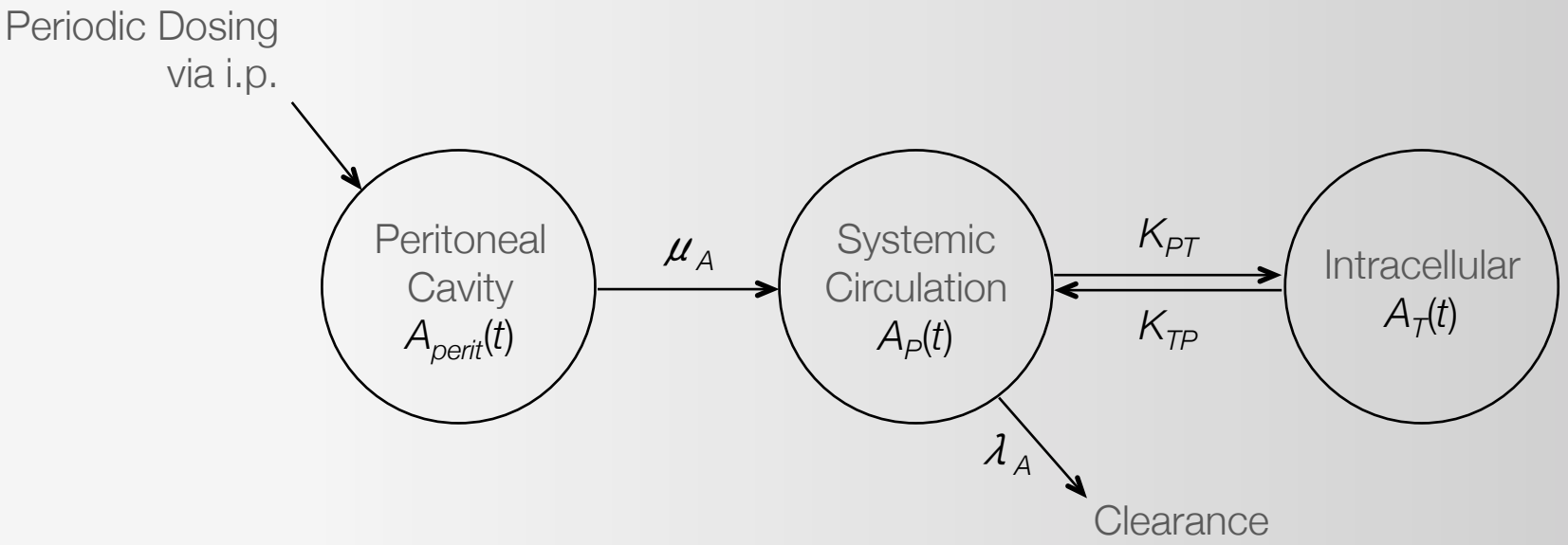

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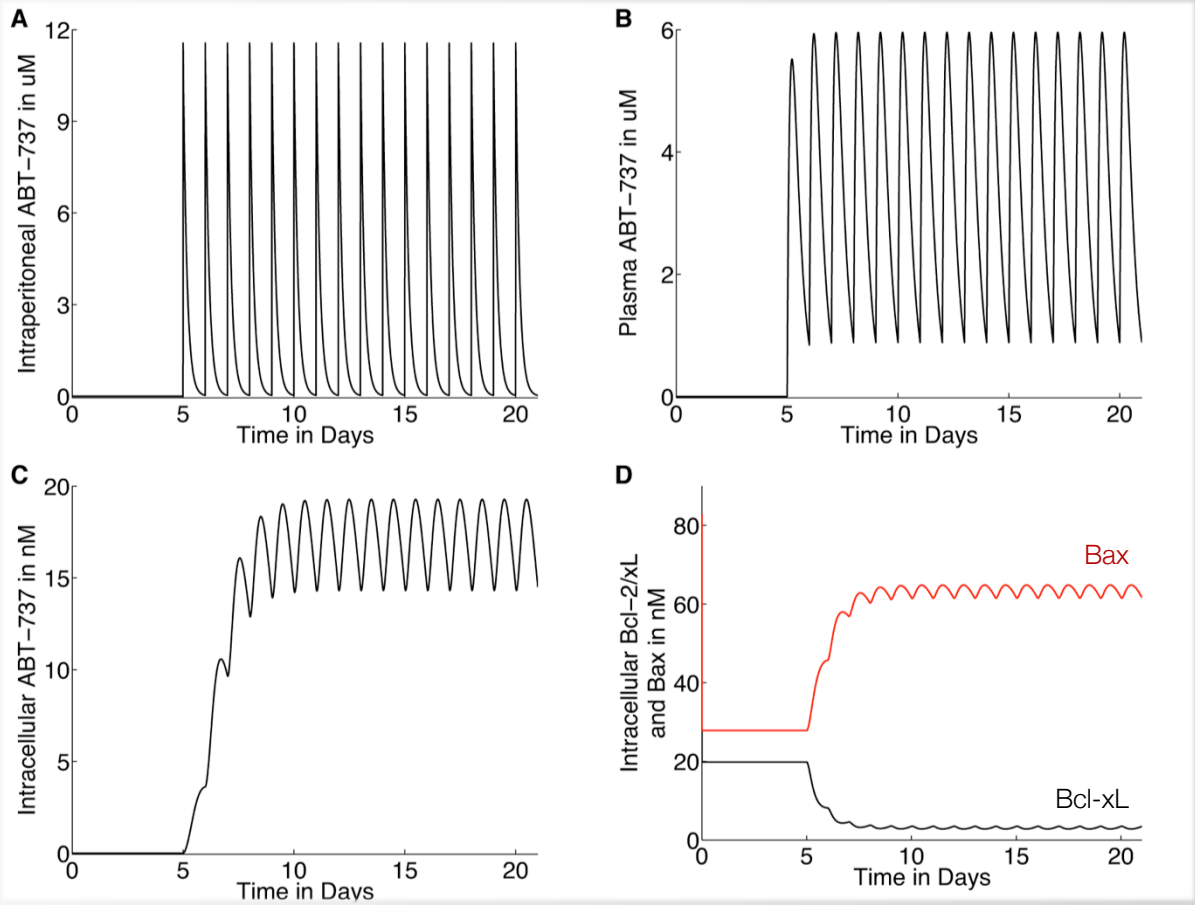


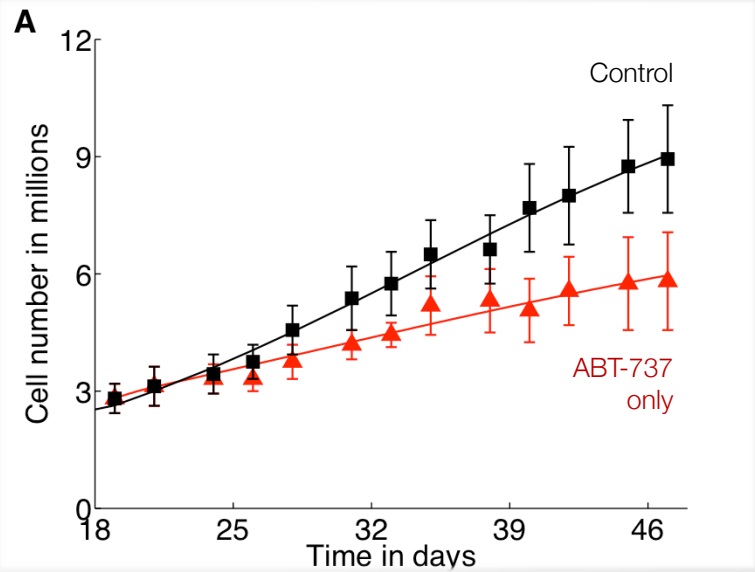
Full Model

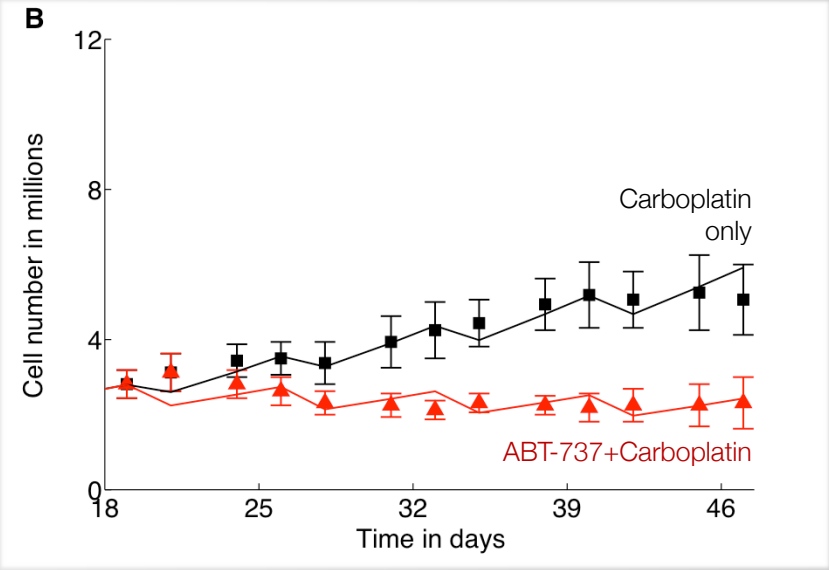
- 5 Algebraic equations, 2 ODEs, 1 DDE and 1 PDE
- 2 key parameters of interest

Rate of arrested cell death $= (\rho_0 + \boldsymbol{\rho_1}\, X(t))\; C(t-a)\, H(a - a_{char})$

Carboplatin Infusion time $= \boldsymbol{T_i}$

Model Validation





Data: Witham et al. (2007)
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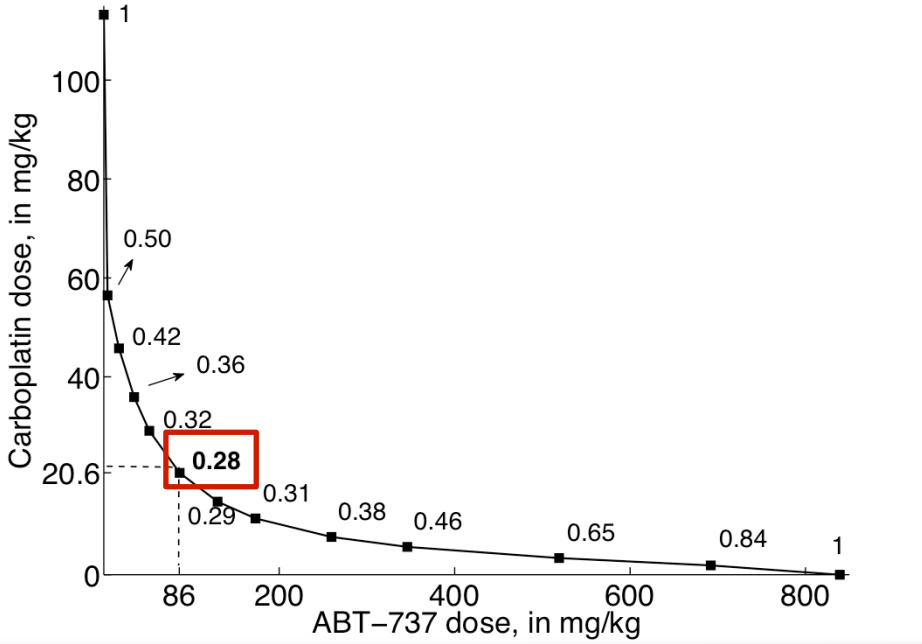
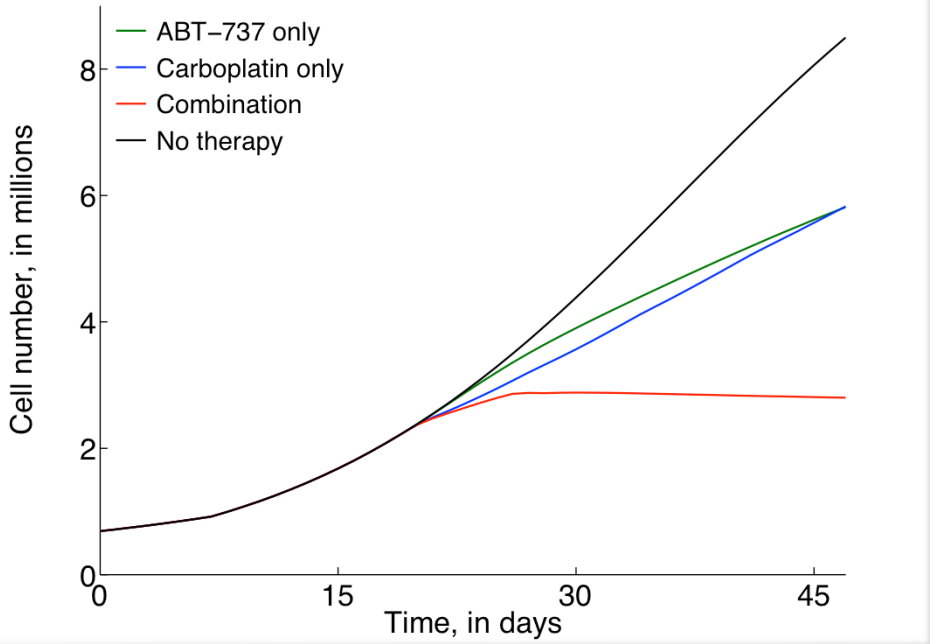
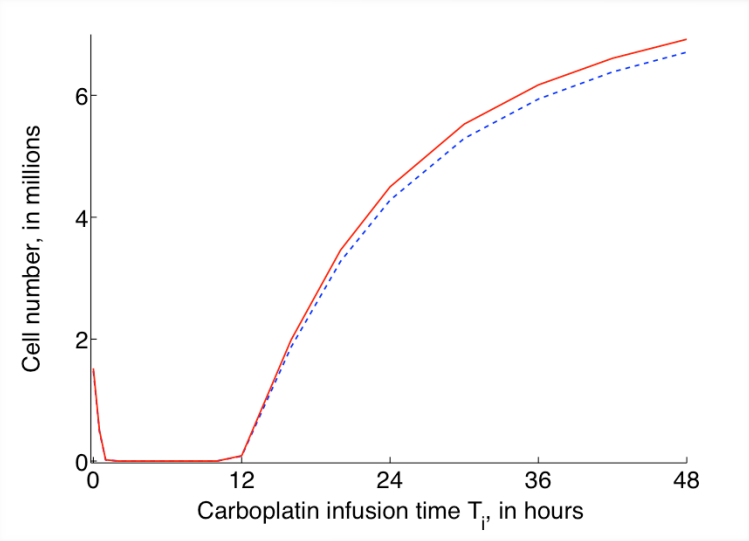
Optimal Dosing

Combination Indices calculated at an unaffected fraction of 1/3





Optimal Scheduling



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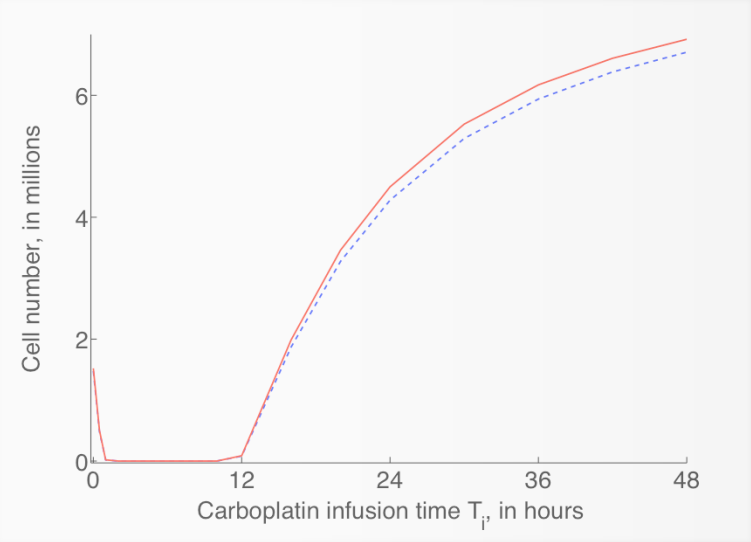

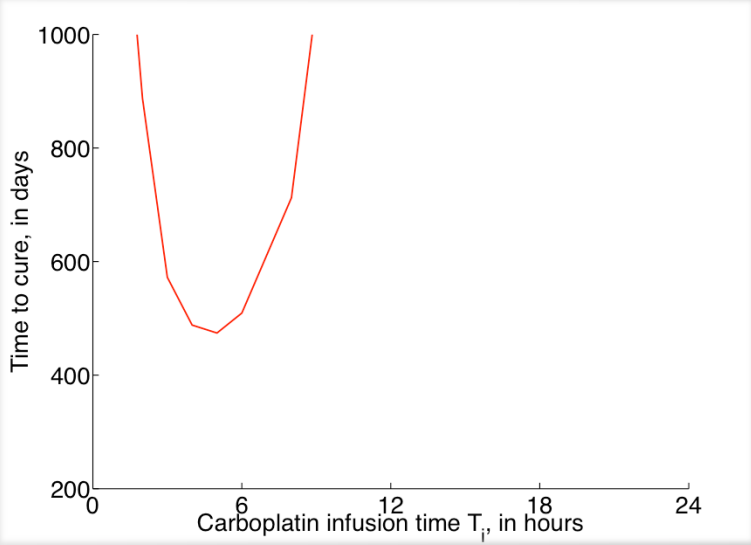

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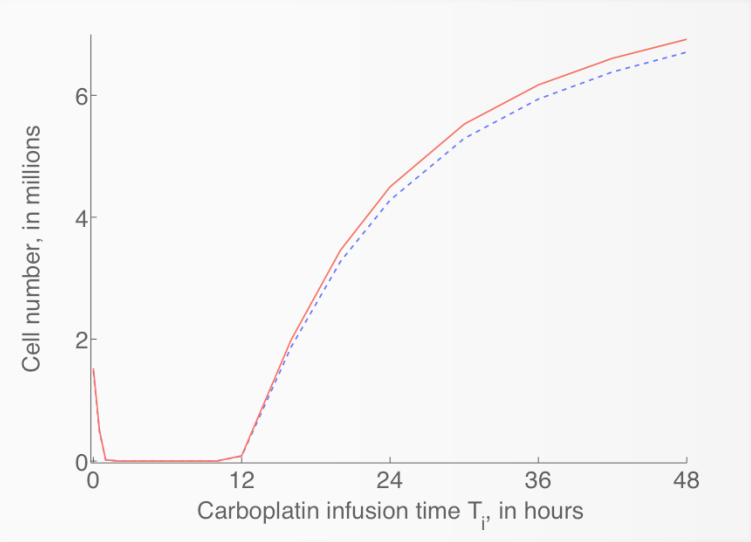
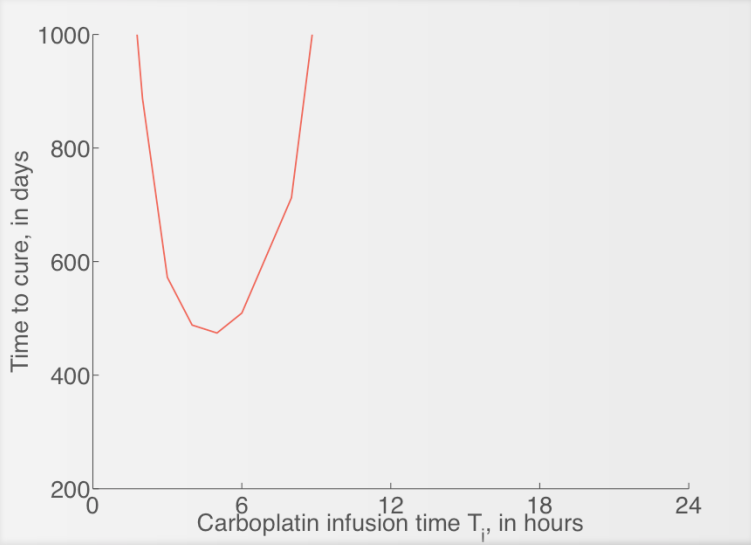
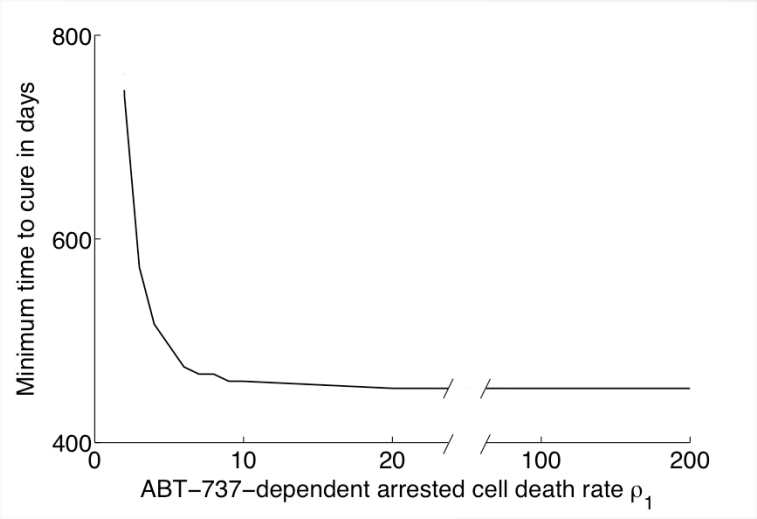
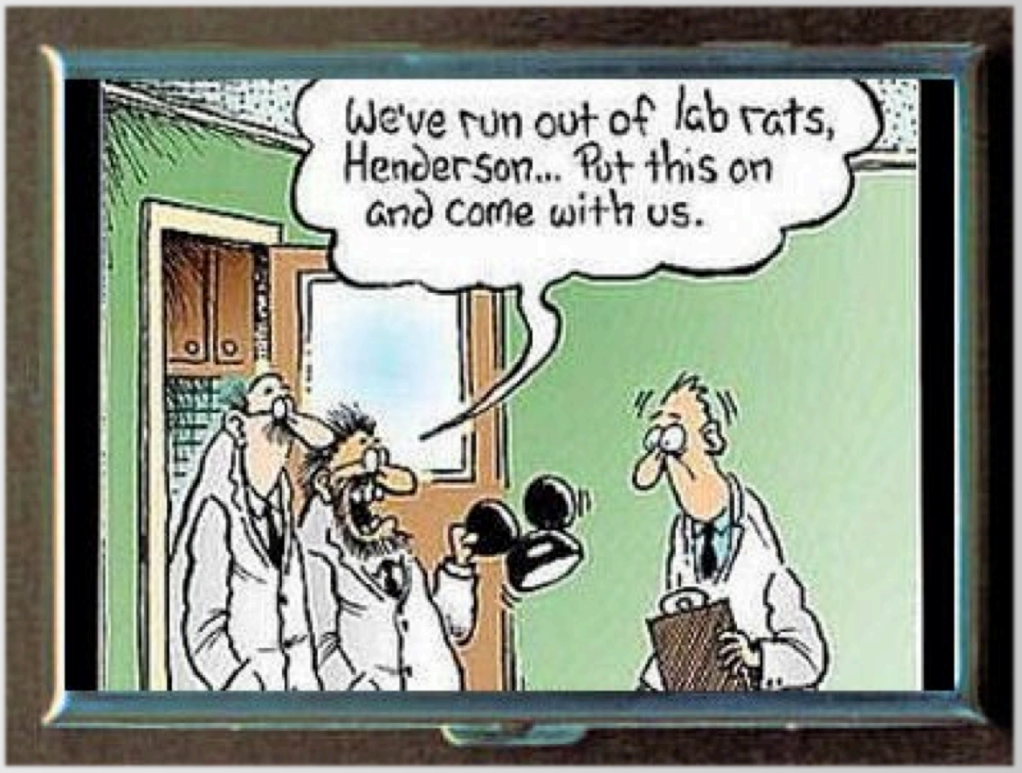






Summary of *In Vivo* Modeling

- Our model can help identify those parameters that have a crucial bearing on the predicted outcome of such novel therapeutic strategies
- It can be used to investigate non-obvious treatment strategies
- Potential to reduce 'bench to bedside' time, as it can predict optimal dose combinations and relative schedules
- Save lab animals



A Clinical Application: Modeling the Emergence of Carboplatin Resistance

2 Pathways to Resistance

- Active Pathway: Mutations arise due to DNA-mismatch repair

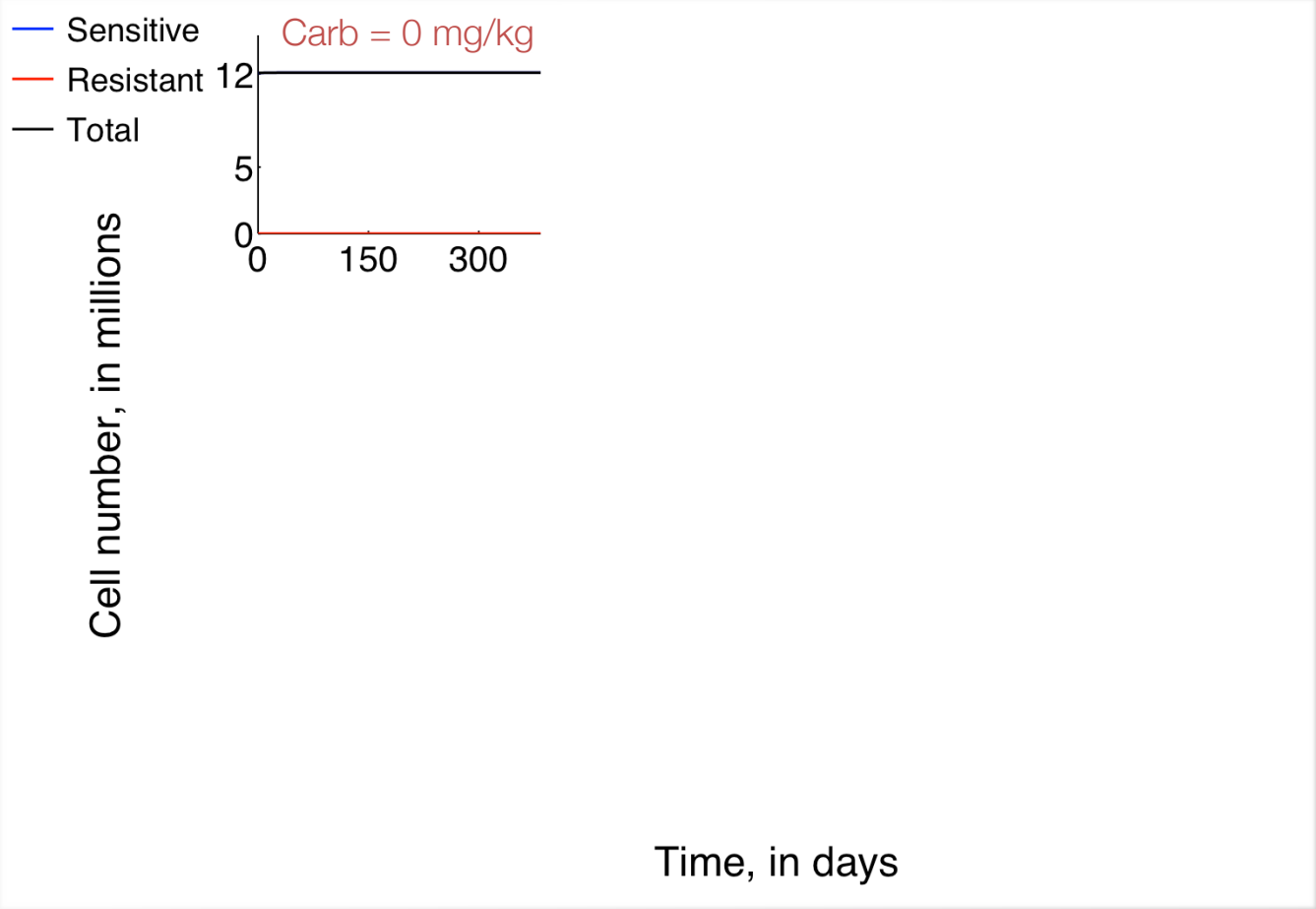
Sensitive Cells

$$\frac{dN}{dt} = f(N, M, R)\, N - \alpha(t)\, N + \mathbf{(1-p)}\, M(t, a = a_r)$$

Resistant Cells

$$\frac{dR}{dt} = f(N, M, R)\, R + \mathbf{p}\, M(t, a = a_r)$$

In Vivo Predictions - Active



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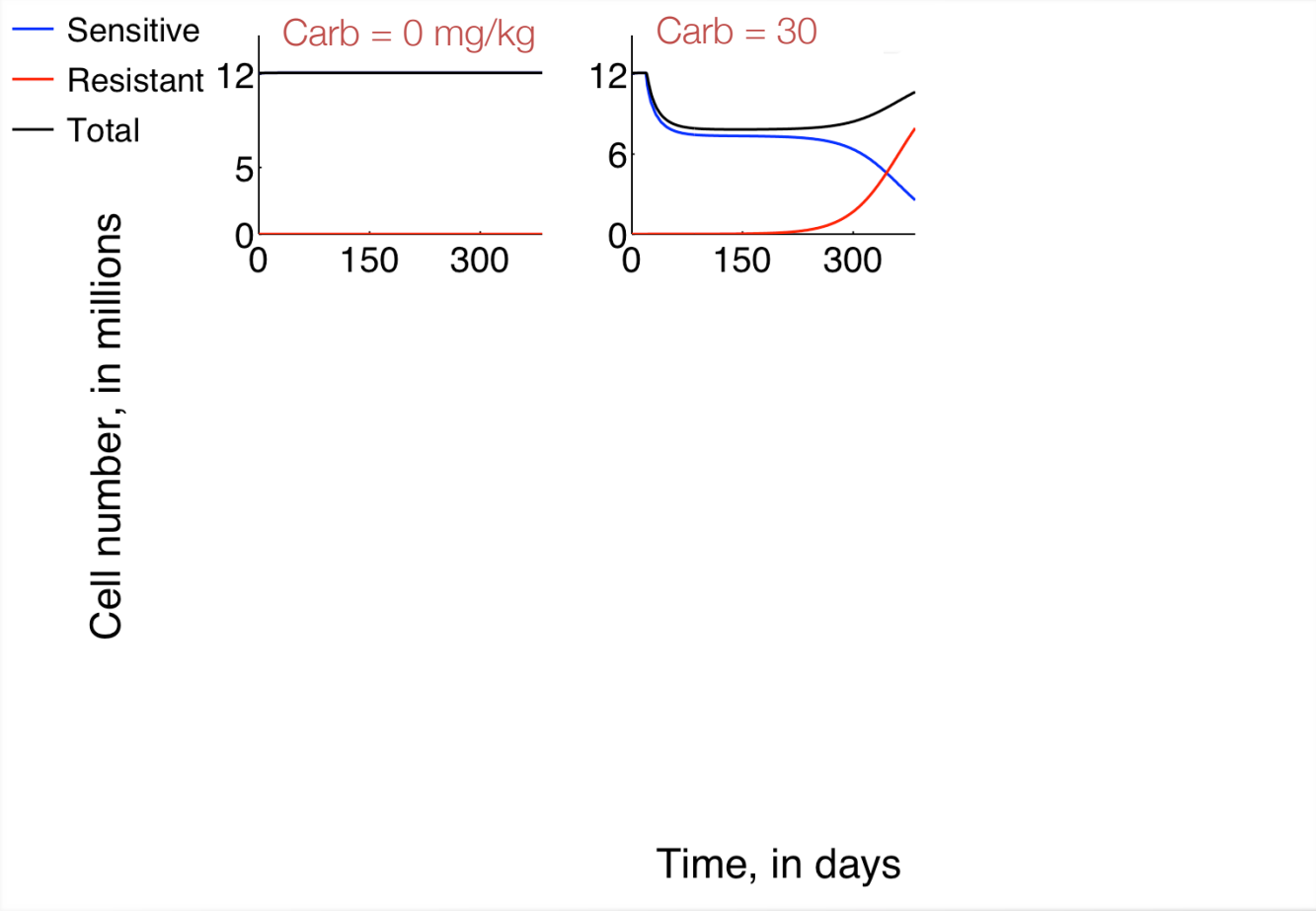

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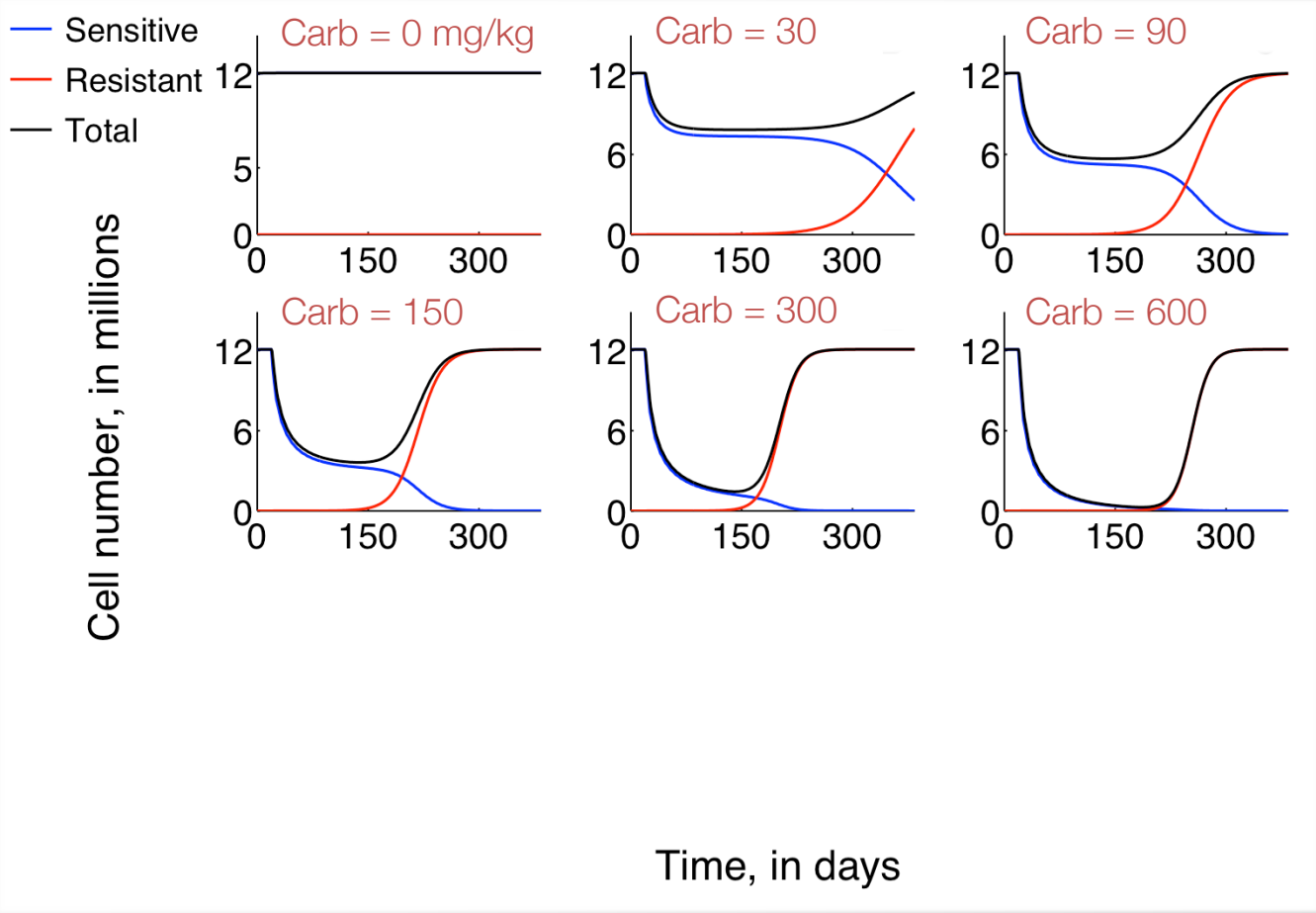

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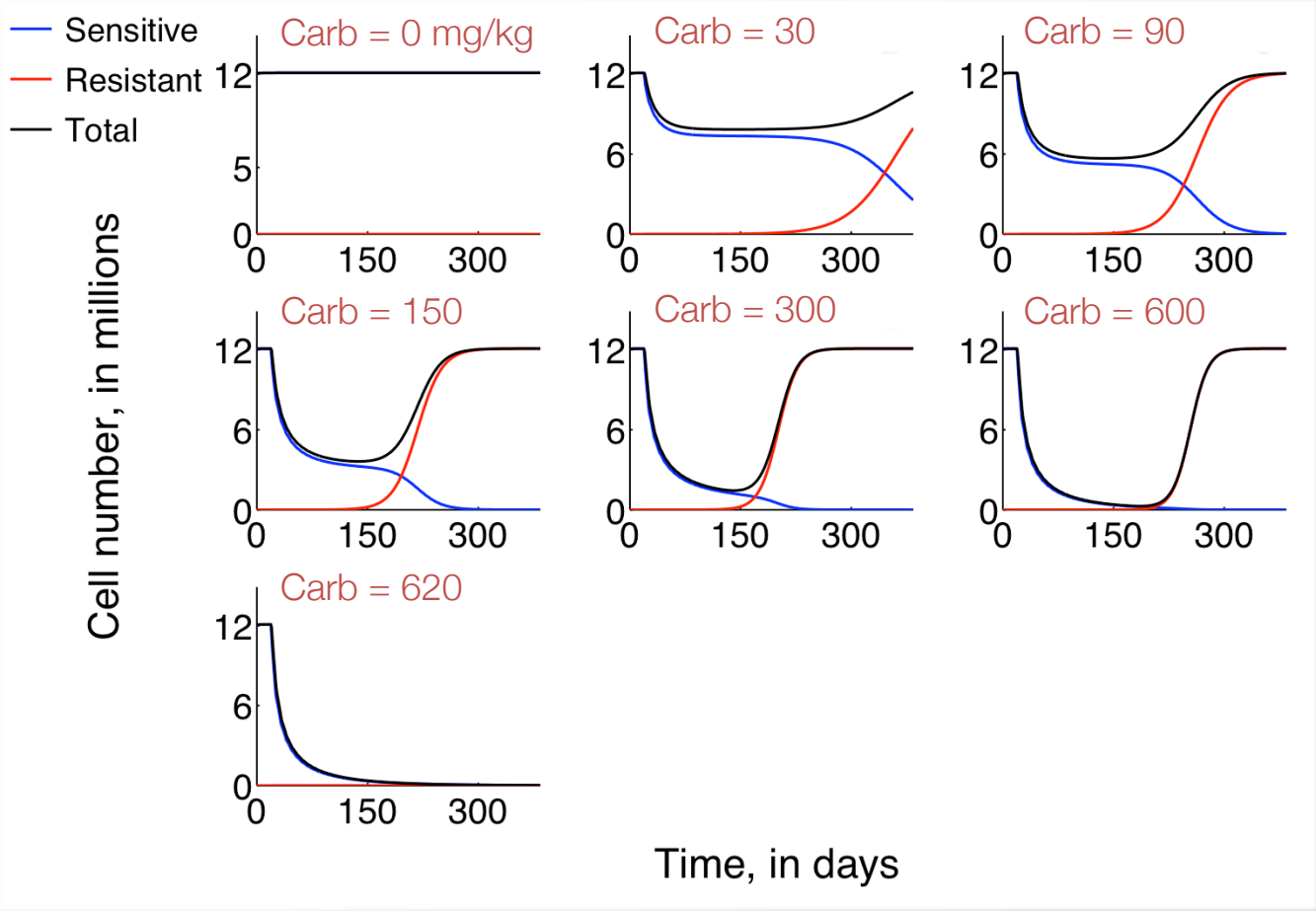

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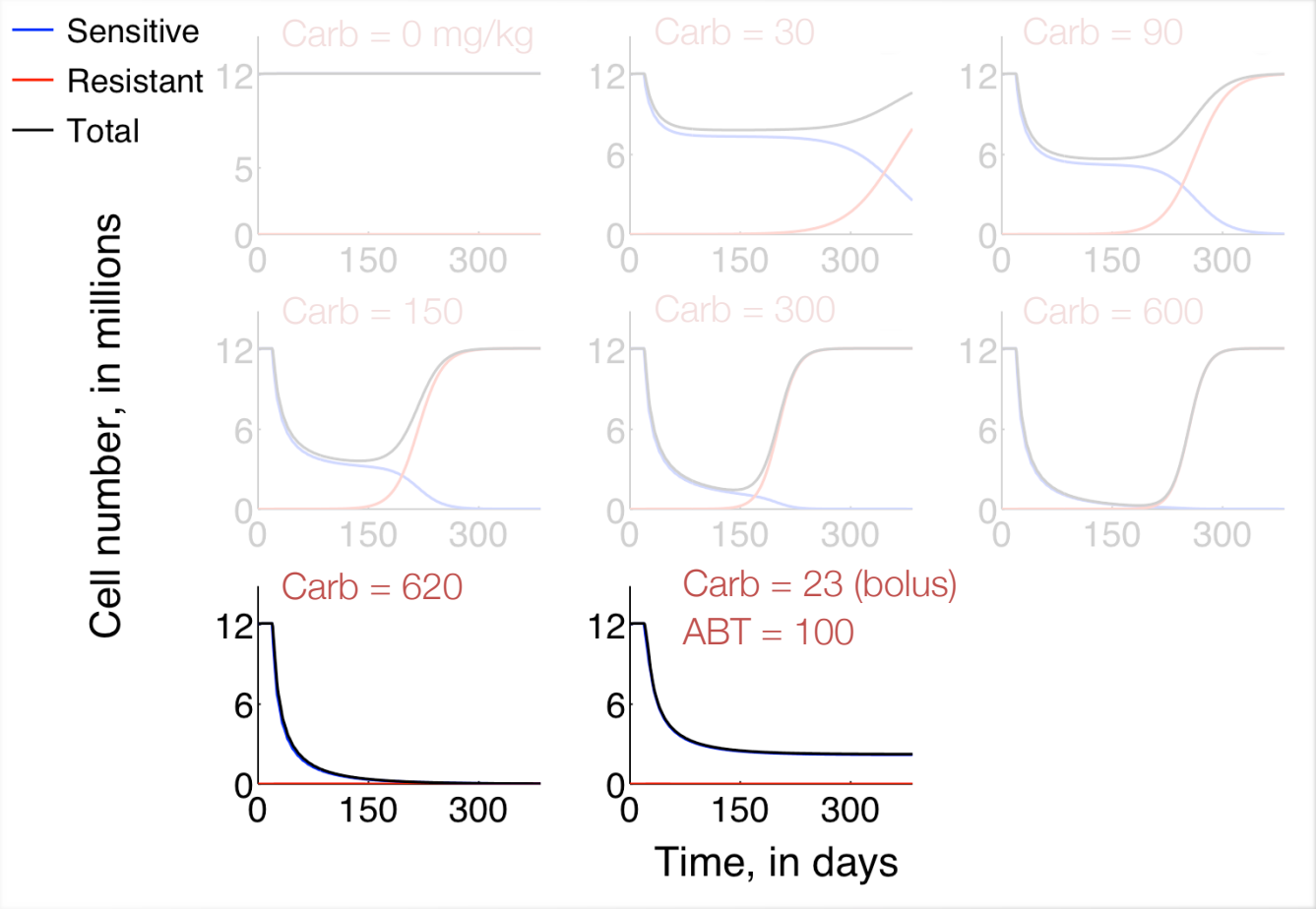

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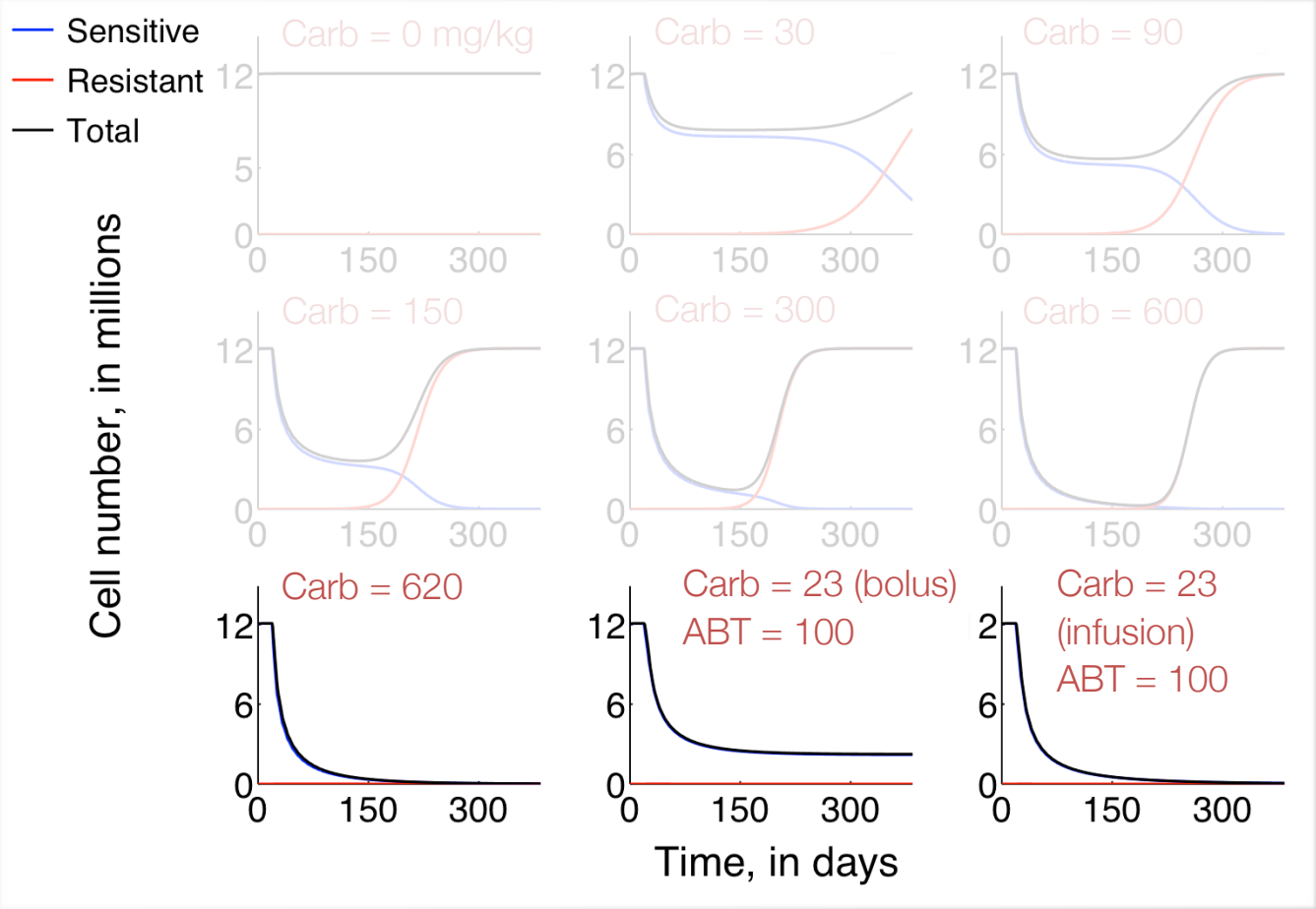


2 Pathways to Resistance

- Passive Pathway: Mutations arise spontaneously during proliferation

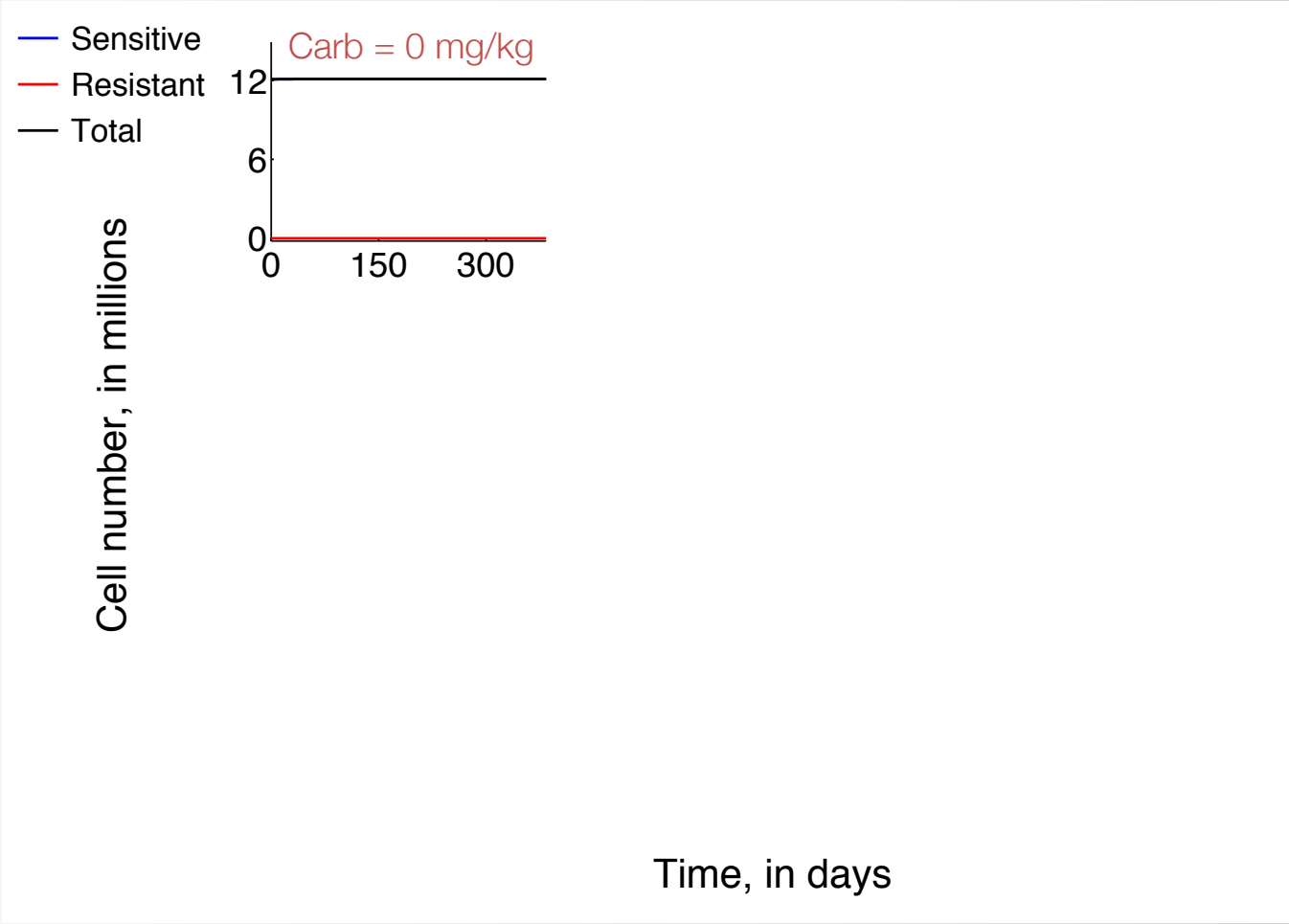
Sensitive Cells

$$\frac{dN}{dt} = f(N,M,R)\,N - \alpha(t)\,N + M(t, a = a_r) - \boldsymbol{p}\, f(N,M,R)\,N + \boldsymbol{p}\, f(N,M,R)\,R$$

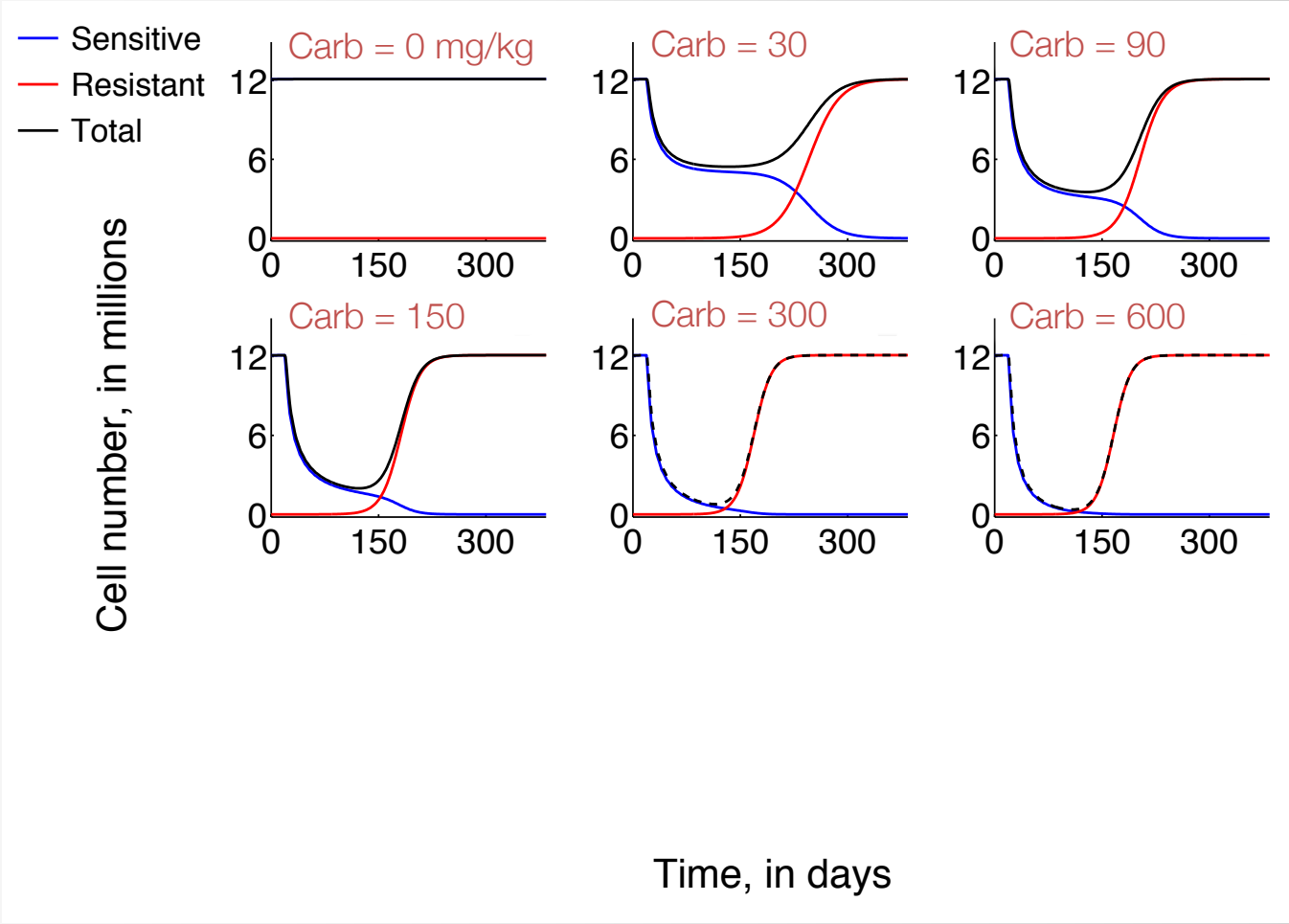
Resistant Cells

$$\frac{dR}{dt} = f(N,M,R)\,R + \boldsymbol{p}\, f(N,M,R)\,N - \boldsymbol{p}\, f(N,M,R)\,R$$

In Vivo Predictions - Passive



In Vivo Predictions - Passive



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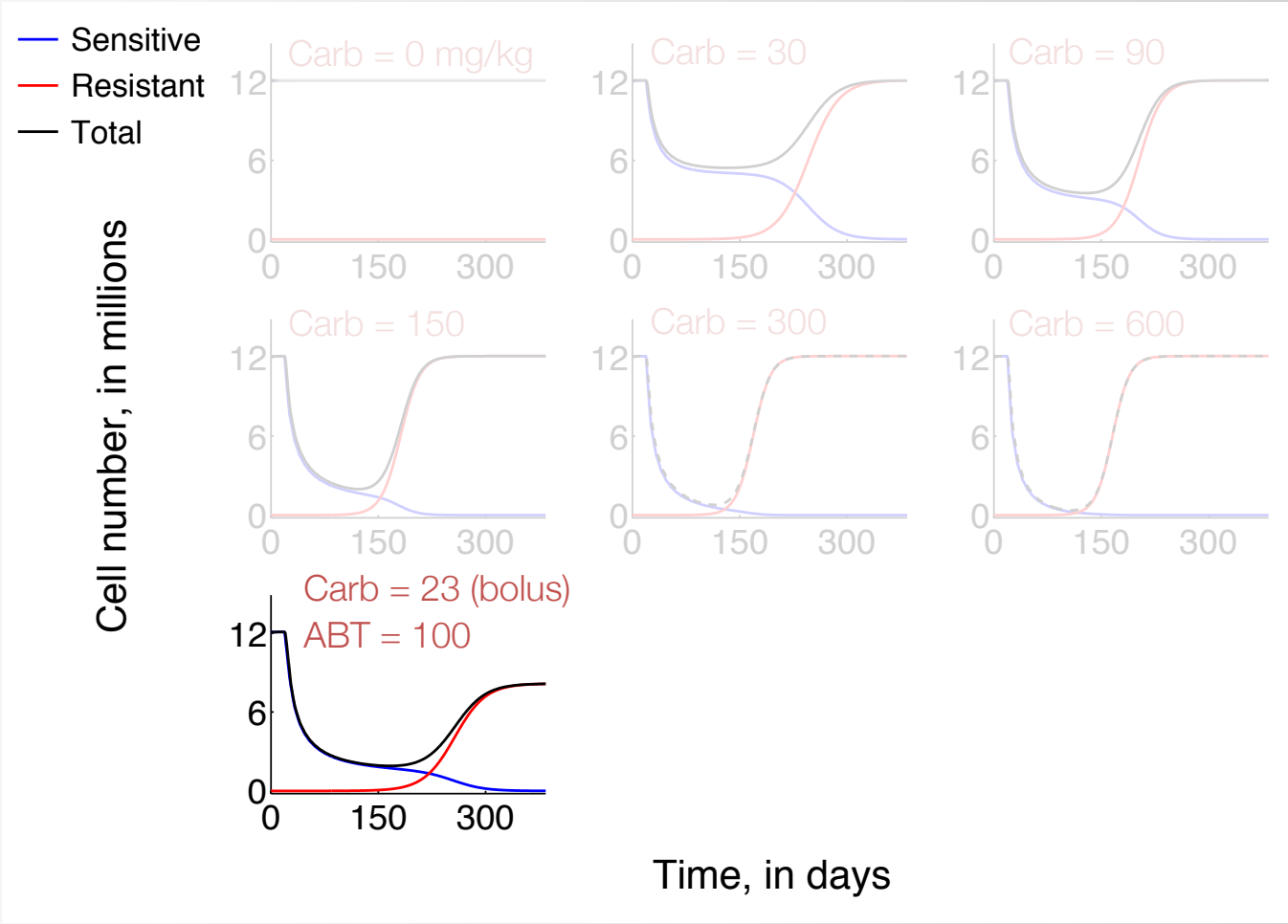

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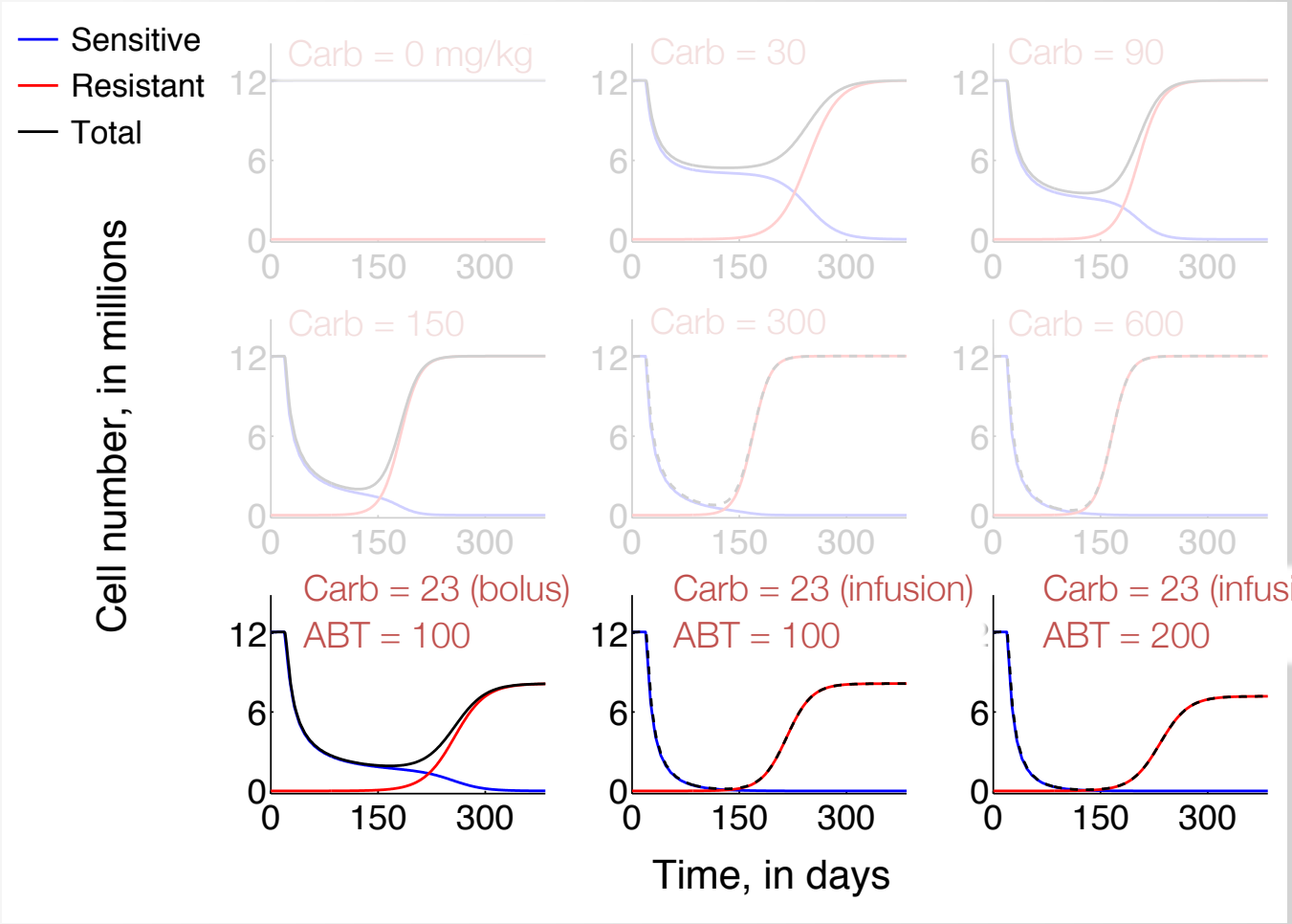
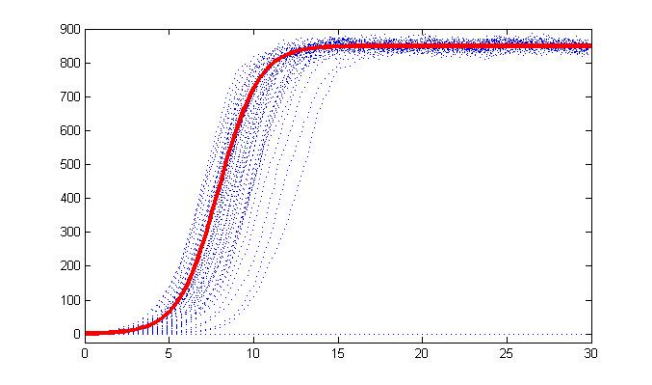


Summary of Clinical Application

- Highlights the need for combination therapy, to avoid resistance emergence
- Can be used to guide clinical oncologist in making treatment decisions, especially when calibrated versus ex vivo assays
- Can aid in drug discovery as it can distinguish between a number of types of mutation leading to carboplatin resistance

Future Directions

- A stochastic framework, to allow for the incorporation of a large number of cell phenotypes



- Distributed delays to model the recovery of arrested cells
- Include paclitaxel, and investigate combination therapy with all 3 drugs

Thank you!

Acknowledgements

- Prof. Avner Friedman
- Dr. Marisa Eisenberg
- MBI & NSF grant DMS 0931642