Identifiability in ODE Models of Solid Tumor Chemotherapy

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June 11, 2015

Outline

- Overview
- Identifiability in an ODE model of tumor treatment with Taxol
- Identifiability in an ODE model tumor treatment with Oxaliplatin

Parameter Identifiability

Can model parameters be identified uniquely from the given data?

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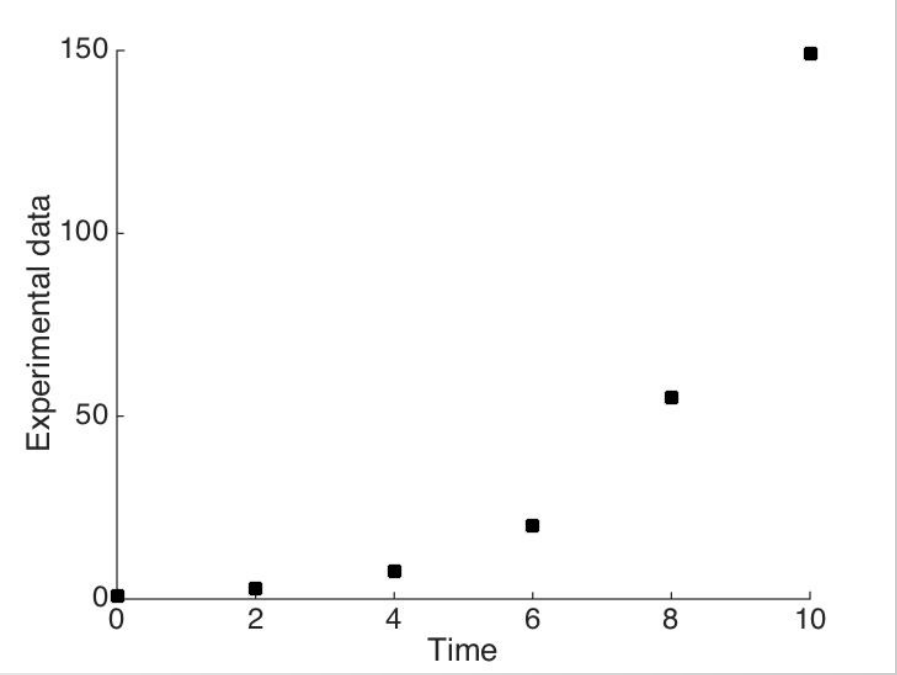

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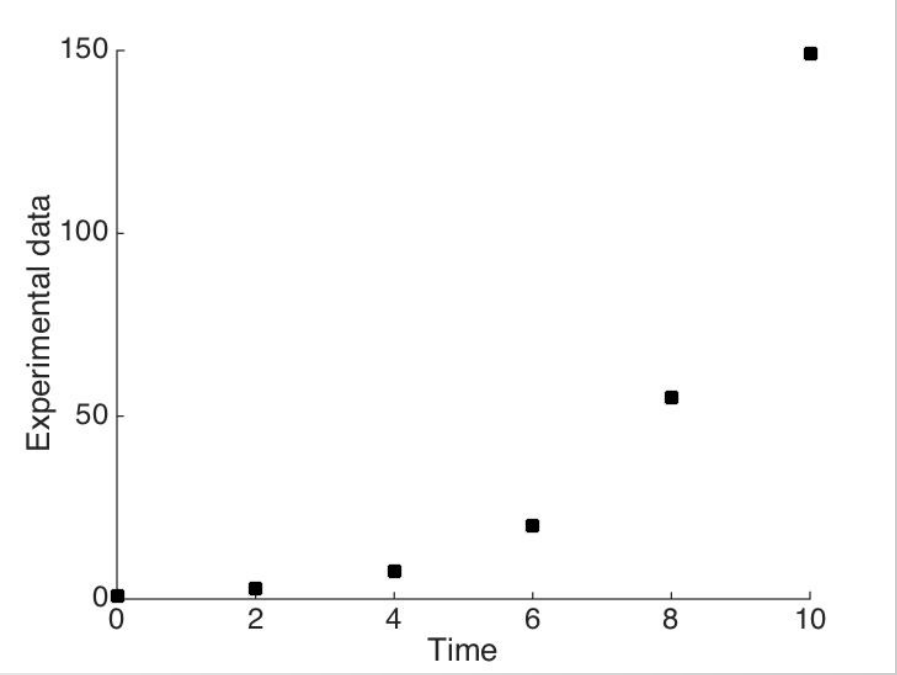
$$y(t) \quad = \quad e^{(a+b)\,t}$$



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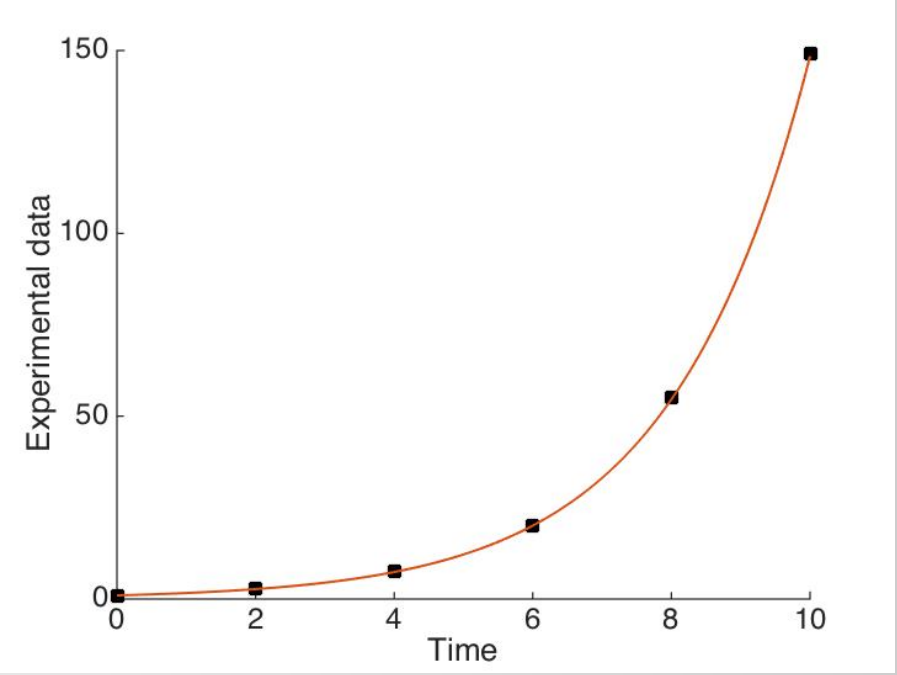
$$
\begin{aligned}
y(t) &= e^{(a+b)\,t} \\
a+b &= 0.5
\end{aligned}
$$



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2 types of identifiability:

Structural – Consider perfect, noise-free data. Can model parameters be uniquely identified?

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State variable time derivative

$$\dot{\vec{x}}(t, \vec{p}) = \vec{f}(\vec{x}, \vec{u}(t), t\,;\, \vec{p}), \qquad \vec{p} \geq 0$$

$\vec{p}$: Parameter vector

Output vector

$$\vec{y}(t, \vec{p}) = \vec{g}(\vec{x}\,;\, \vec{p})$$

Initial conditions

$$\vec{x}_0 = \vec{x}(0\,;\, \vec{p})$$

Input vector (e.g. drug dosage)

$$\vec{u}(t)$$

Parameter Identifiability

2 types of identifiability:

Structural – Consider perfect, noise-free data. Can model parameters be uniquely identified?

Eliminate the state variable to obtain input-output map:

$$\vec{y} = \vec{\phi}(\vec{p}, \vec{u})$$

Does the equation $\vec{\phi}(\vec{p}, \vec{u}) = \vec{\phi}(\vec{p^*}, \vec{u}) \Rightarrow \vec{p} = \vec{p^*}$?

Parameter Identifiability

2 types of identifiability:

Structural – Consider perfect, noise-free data. Can model parameters be uniquely identified?

Practical – Assuming identifiable combinations of parameters have been determined, how does imperfect data affect the uniqueness of our estimates?

Treating Solid Tumors

- Standard treatment – combination of anti-mitotic taxanes (e.g. Taxol, Paclitaxel) and Pt-based drugs (e.g. Oxaliplatin, Carboplatin) administered periodically

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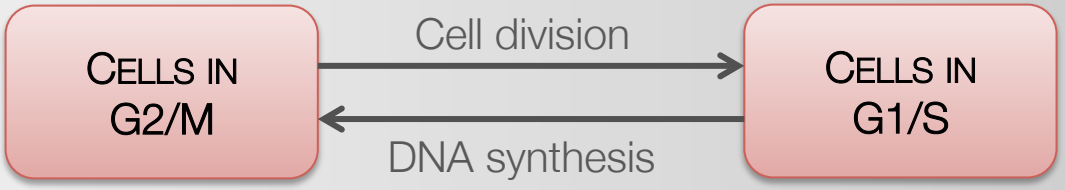
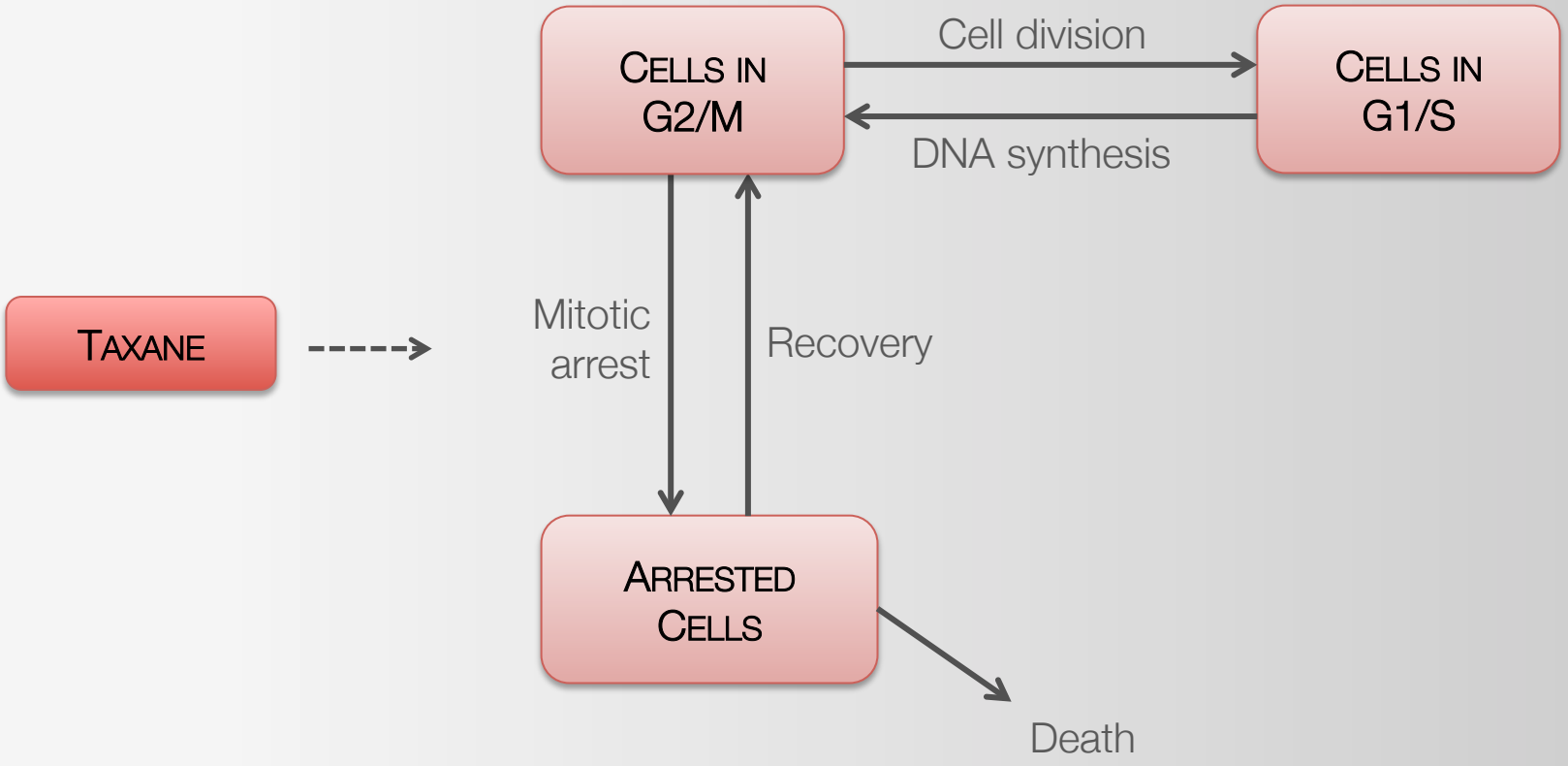
- Standard treatment – combination of anti-mitotic taxanes (e.g. Taxol, Paclitaxel) and Pt-based drugs (e.g. Oxaliplatin, Carboplatin) administered periodically
- Taxols target tubulin during cell division, leading to mitotic arrest and subsequent death – cell cycle specific
- Pt-drugs induce DNA damage, leading to cell cycle arrest and subsequent death – cell cycle non-specific

Compartmental Models of Tumor Chemotherapy

Treatment with Taxol



Treatment with Taxol



Model Equations

Dividing Cells

$$\frac{dP}{dt} = -\lambda P \frac{vol_{free}^{\theta}}{V_0^{\theta} + vol_{free}^{\theta}} + \alpha_{RP} R - \alpha_0 \frac{drug^n}{k_a^n + drug^n} P + \frac{\rho_0}{k_r^m + drug^m} A$$

Space-limited growth

G1/S to G2/M transition

Paclitaxel-induced mitotic arrest

Recovery from mitotic arrest

Resting Cells

$$\frac{dR}{dt} = 2\lambda P \frac{vol_{free}^{\theta}}{V_0^{\theta} + vol_{free}^{\theta}} - \alpha_{RP} R$$

Proliferation

G1/S to G2/M transition

Arrested Cells

$$\frac{dA}{dt} = \alpha_0 \frac{drug^n}{k_a^n + drug^n} P - \delta_0 \frac{drug^l}{k_d^l + drug^l} A - \frac{\rho_0}{k_r^m + drug^m} A$$

Paclitaxel-induced mitotic arrest

Death in mitotic arrest

Recovery from mitotic arrest

$$vol_{free} = K - P - R - A$$

What about Parameter Identifiability?

- 4 (control) + 6 (treatment) unknown parameters + 3 exponents

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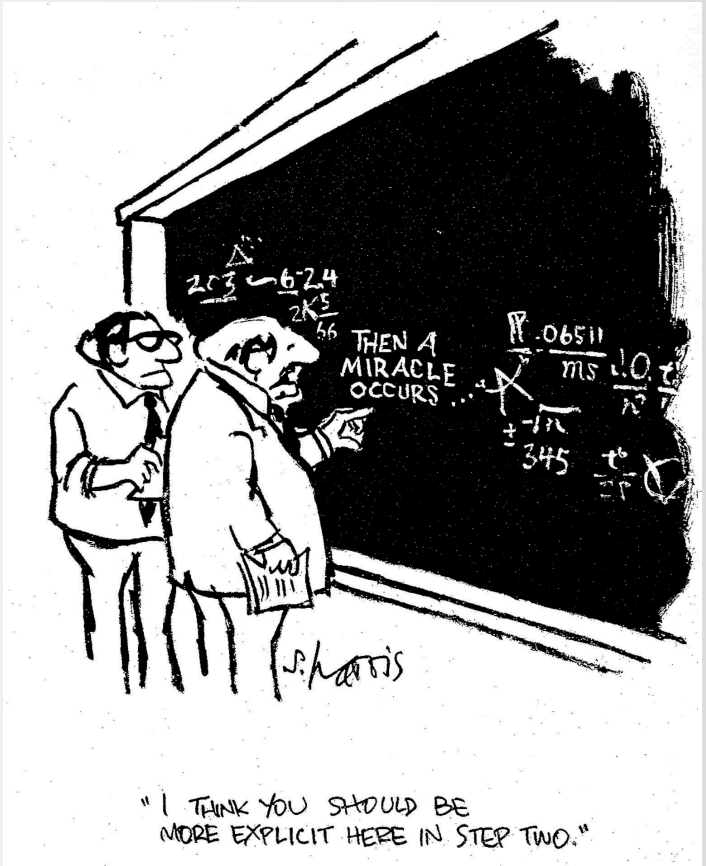

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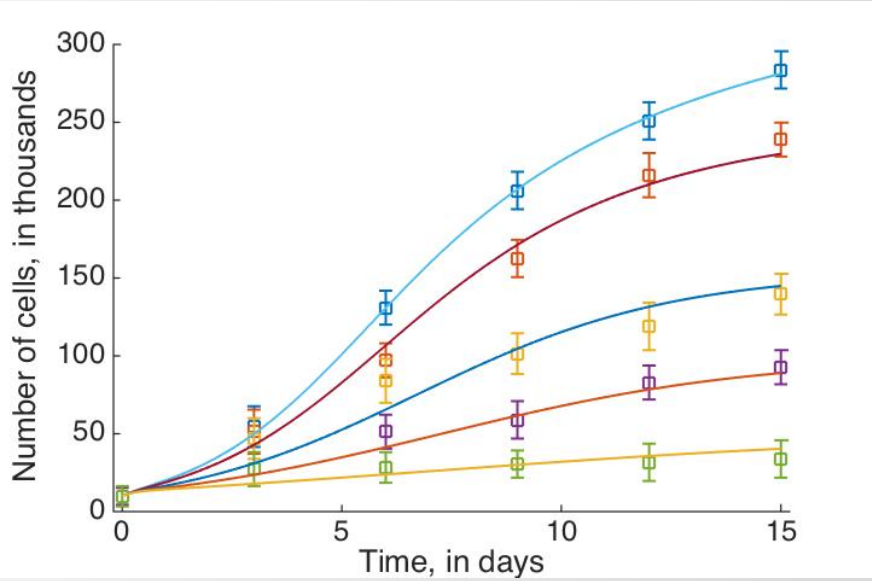


Data: Terzis et al. (1997)
British Journal of Cancer 75: 1744

Practical Identifiability

- One approach is to use the Fisher Information Matrix (FIM)
- However, it does not tell us which parameters are involved in an identifiable combination
- Moreover, FIM evaluated at single point in parameter space, making it difficult to determine functional forms of combinations

Practical Identifiability

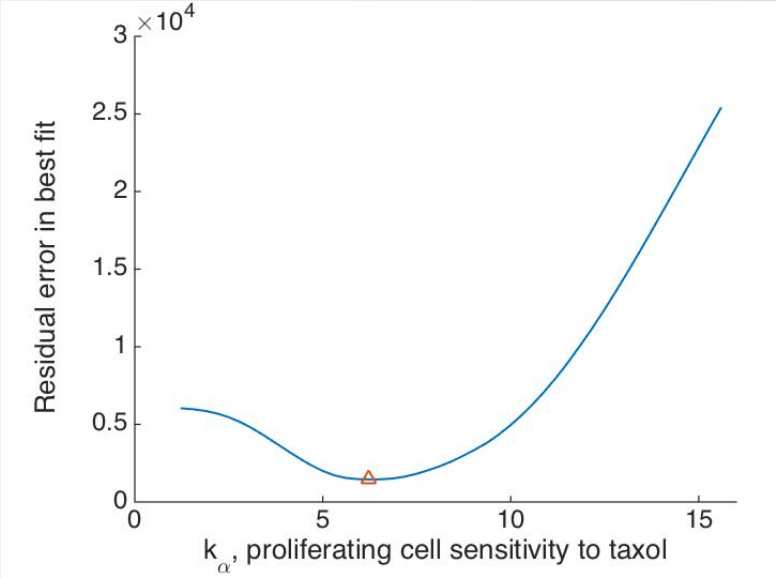
- One approach is to use the Fisher Information Matrix (FIM)
- However, it does not tell us which parameters are involved in an identifiable combination
- Moreover, FIM evaluated at single point in parameter space, making it difficult to determine functional forms of combinations
- What about our model?
- Rank (FIM) = 6, i.e. all parameters should be identifiable
- Scaled Eigenvalues (FIM) = 5e–6, 1.2e–4, 4.4e–4, 8.4e–3, 0.016, 1

Practical Identifiability

- Profile Likelihood Estimates – vary one parameter at a time, and fit the rest. Plot the error in fits.
- A unique minimum implies practical identifiability
- Completely flat line implies practical *un*identifiability

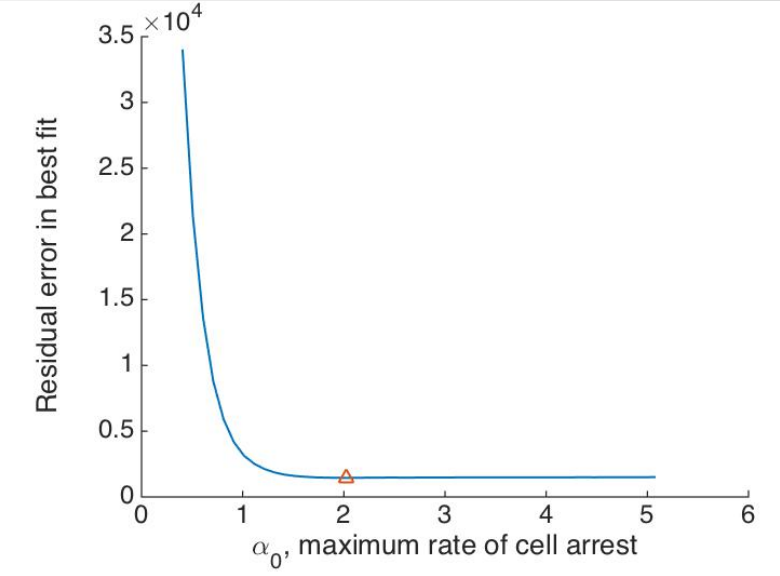
Practical Identifiability of k_α

- Vary k_α between fixed limits, and fit the rest. Record error in fits.
- A unique minimum implies practical identifiability



Practical Identifiability of α_0

- Vary α_0 between fixed limits, and fit the rest. Record error in fits.
- Practically unidentifiable from the right



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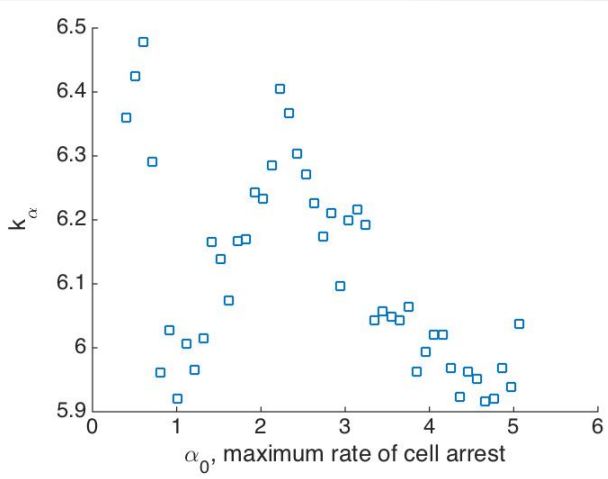

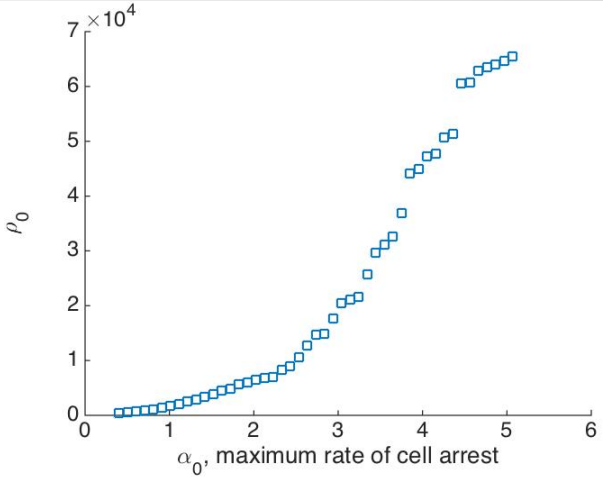

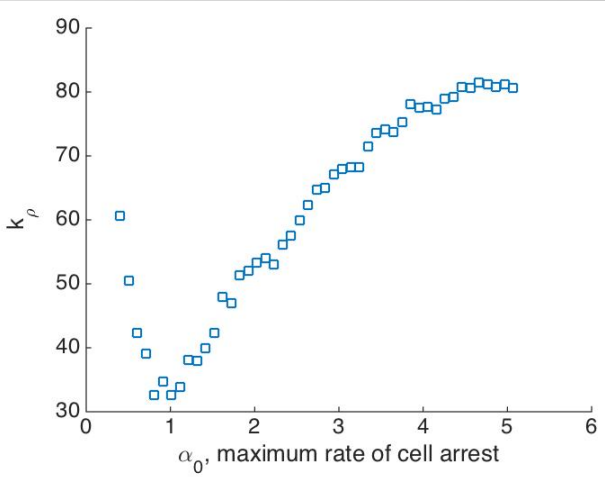

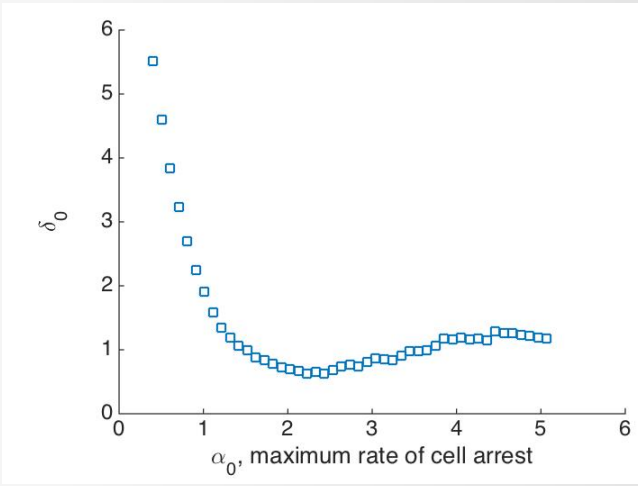

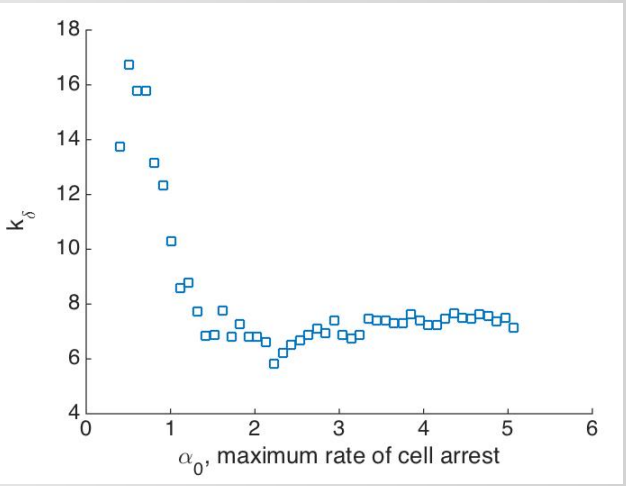

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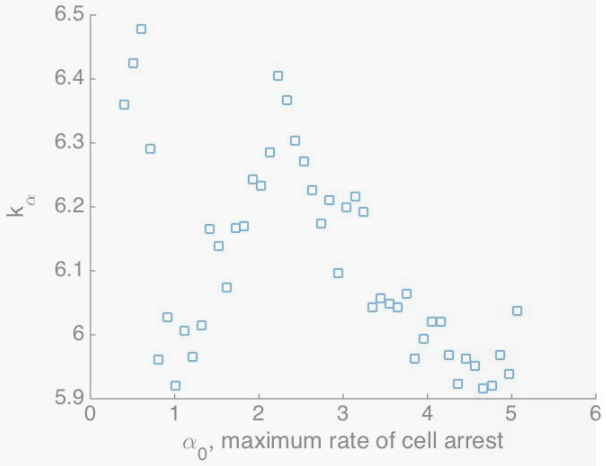
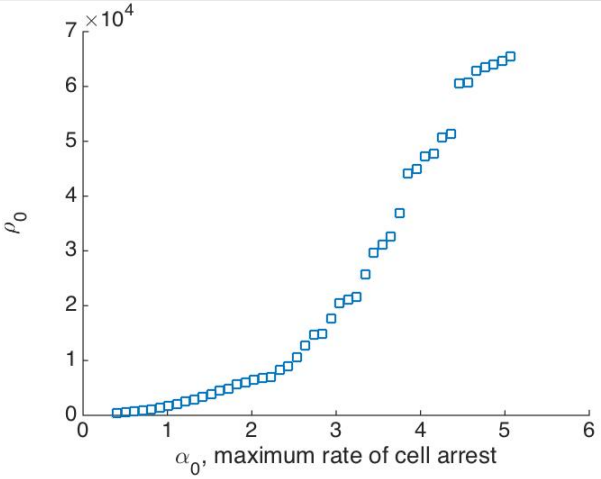
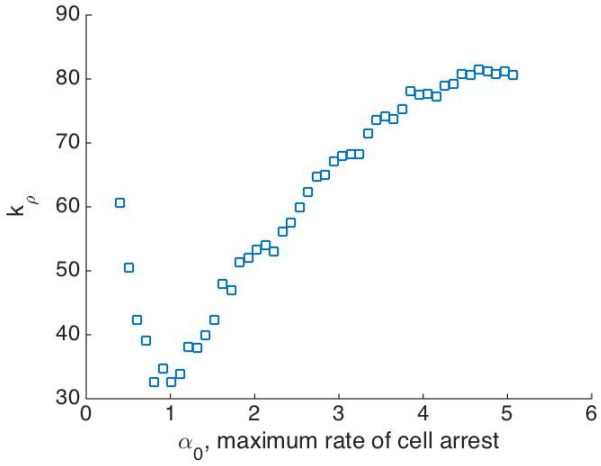
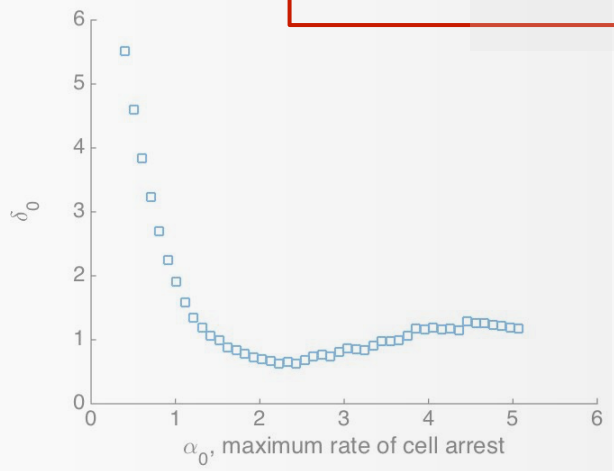
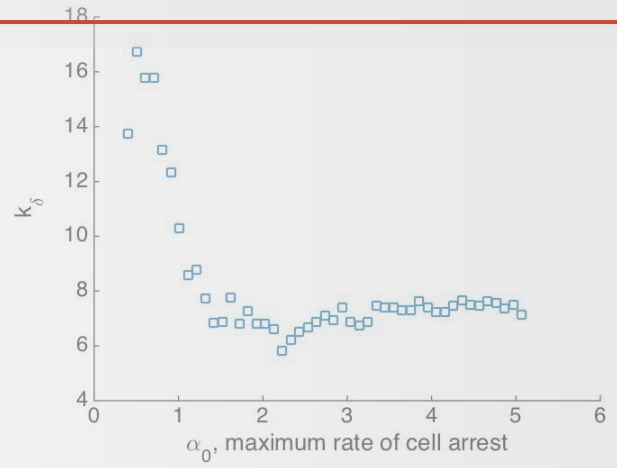






$\alpha_0,\ \rho_0,\ k_r$ form a practically identifiable combination





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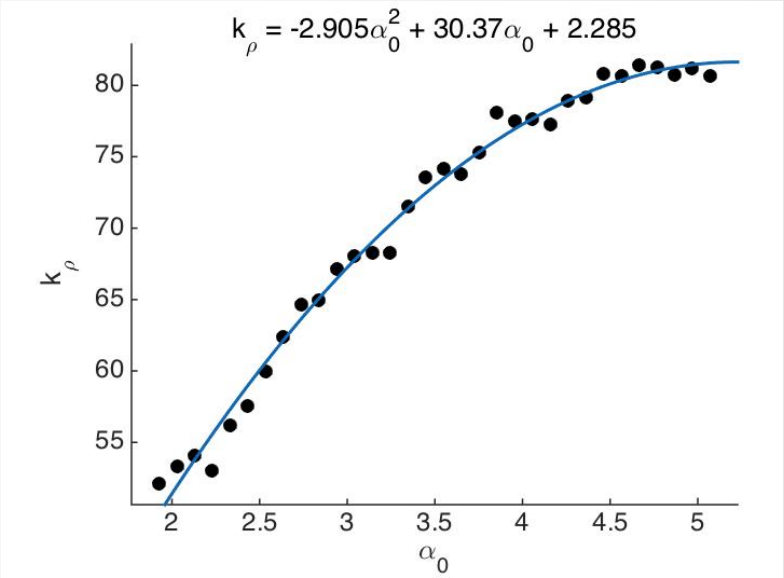
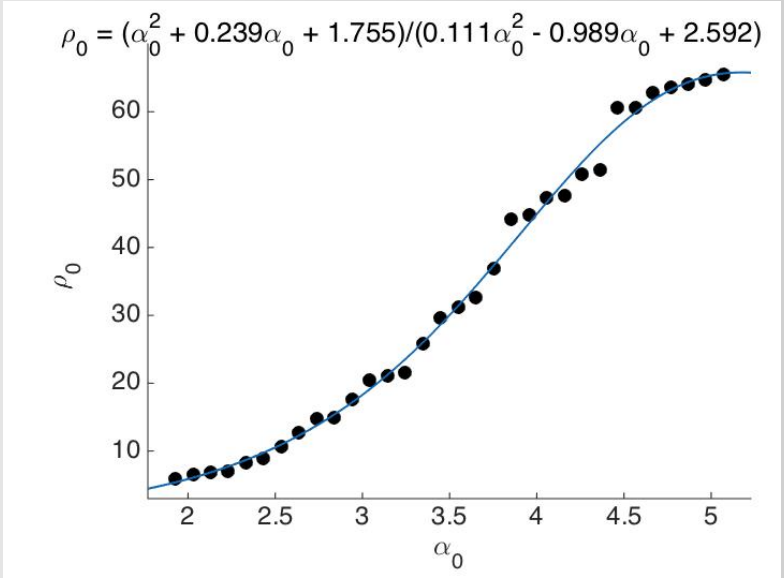
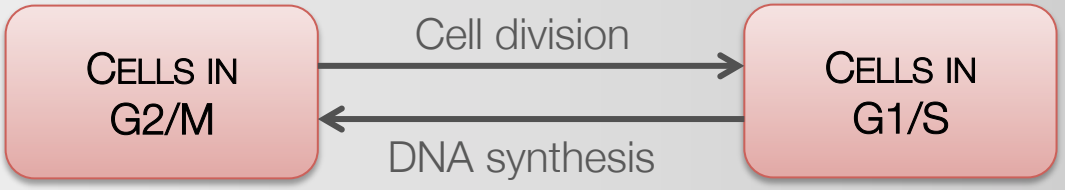




Summary I

- Data is seldom perfect, and the profile likelihood method provides a convenient numerical tool for parameter identifiabiity analysis
- It also provides functional forms of identifiable combinations, providing further insight into the model

Treatment with Oxaliplatin



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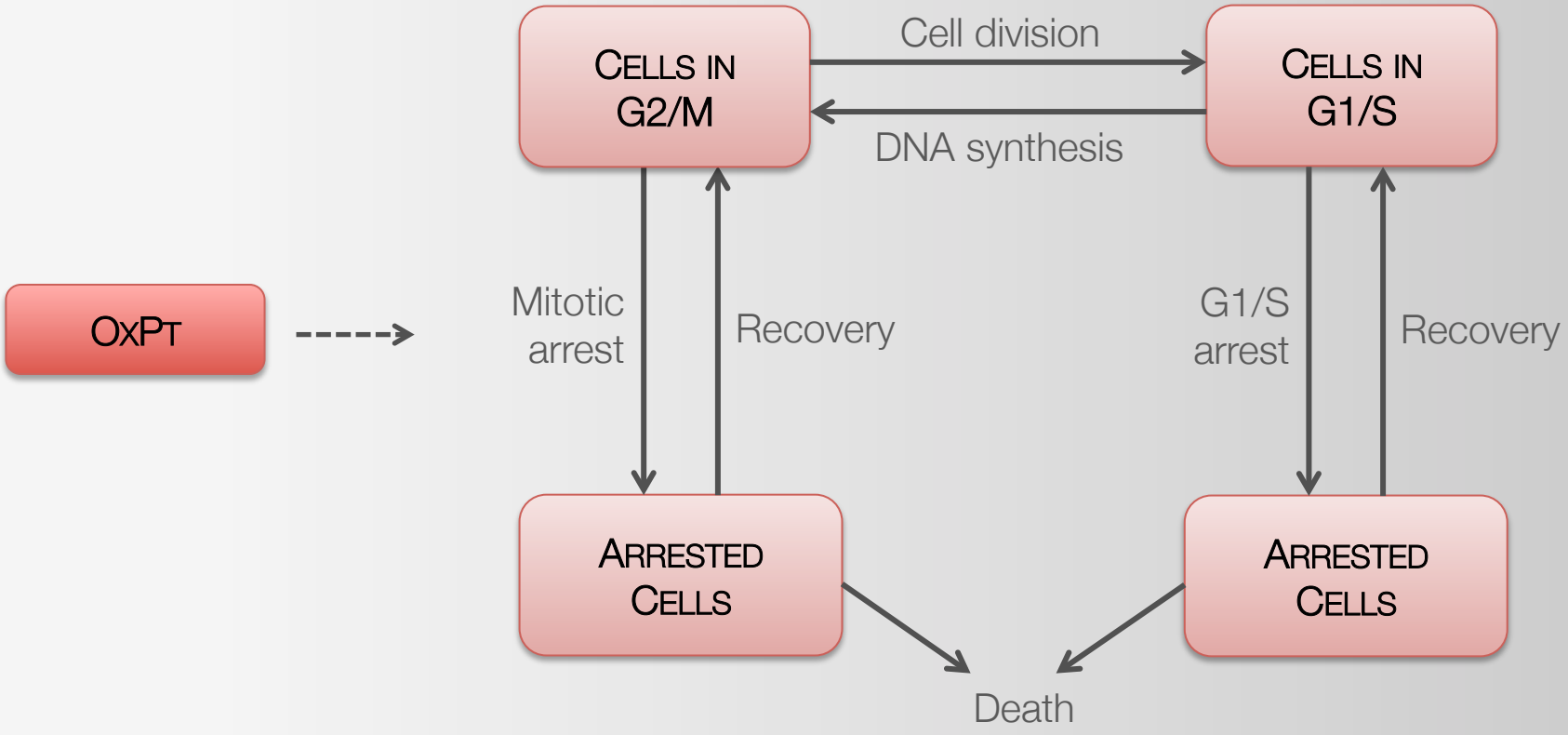

Model Equations

Dividing Cells

$$\frac{dP}{dt} = -\lambda P\left[1-\left(\frac{T}{K}\right)^{\theta}\right] + \alpha_{RP}R - \sigma_1\,\alpha_0\,\frac{drug^n}{k_a^n + drug^n}P + \frac{\rho_0}{k_r^m + drug^m}A_P$$

Space-limited growth | G1/S to G2/M transition | OxPt-induced mitotic arrest | Recovery from mitotic arrest

Resting Cells

$$\frac{dR}{dt} = 2\lambda P\left[1-\left(\frac{T}{K}\right)^{\theta}\right] + \alpha_{RP}R - \alpha_0\,\frac{drug^n}{k_a^n + drug^n}R + \frac{\rho_0}{k_r^m + drug^m}A_R$$

Proliferation | G1/S to G2/M transition | OxPt-induced G1/S arrest | Recovery from G1/S arrest

Arrested Cells

$$\frac{dA_P}{dt} = \sigma_1\,\alpha_0\,\frac{drug^n}{k_a^n + drug^n}P - \sigma_2\,\delta_0\,drug\,A_P - \frac{\rho_0}{k_r^m + drug^m}A_P$$

OxPt-induced mitotic arrest | Death in mitotic arrest | Recovery from mitotic arrest

Arrested Cells

$$\frac{dA_R}{dt} = \alpha_0\,\frac{drug^n}{k_a^n + drug^n}P - \delta_0\,drug\,A_R - \frac{\rho_0}{k_r^m + drug^m}A_R$$

OxPt-induced G1/S arrest | Death in G1/S arrest | Recovery from G1/S arrest

$$T = P + R + A_P + A_R$$

Parameter Identifiability?

- 4 control parameters + 7 treatment parameters - 6 unknown and 1 known + 2 exponents
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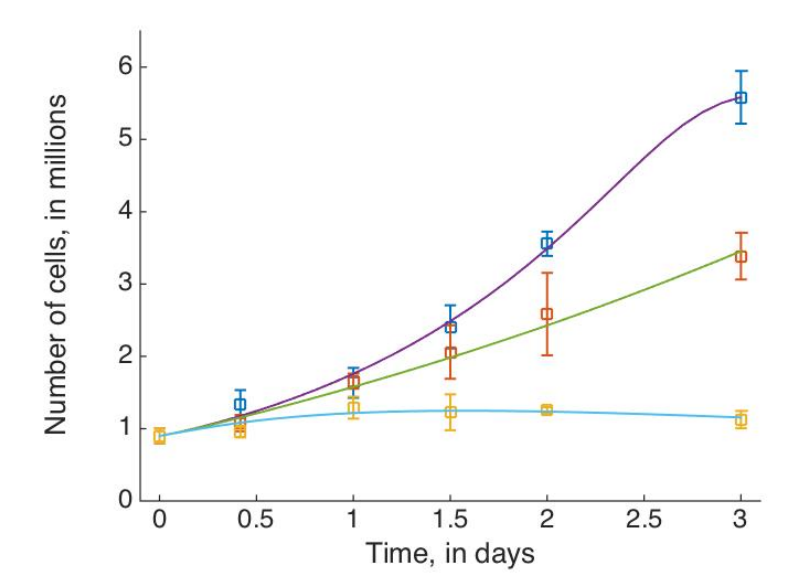
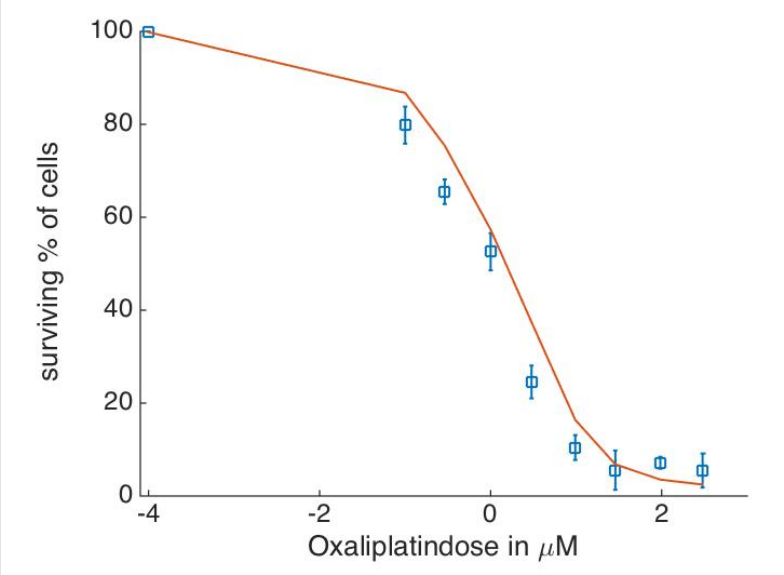
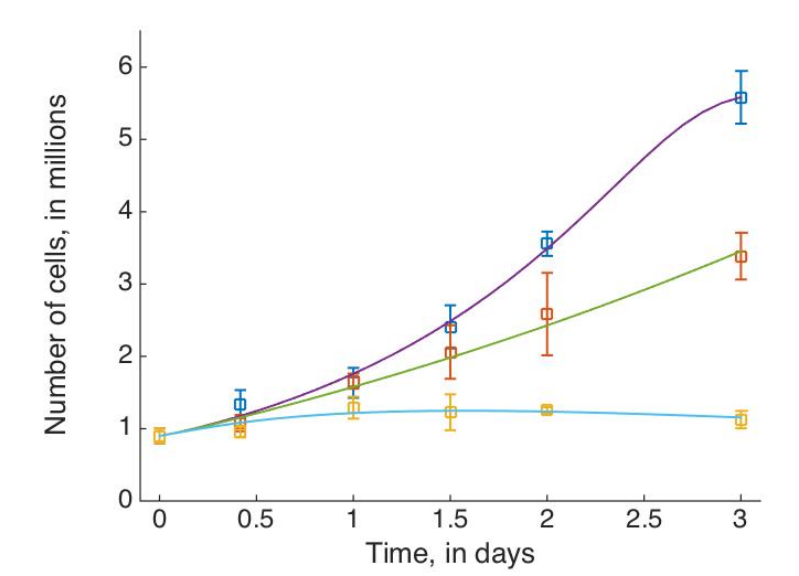


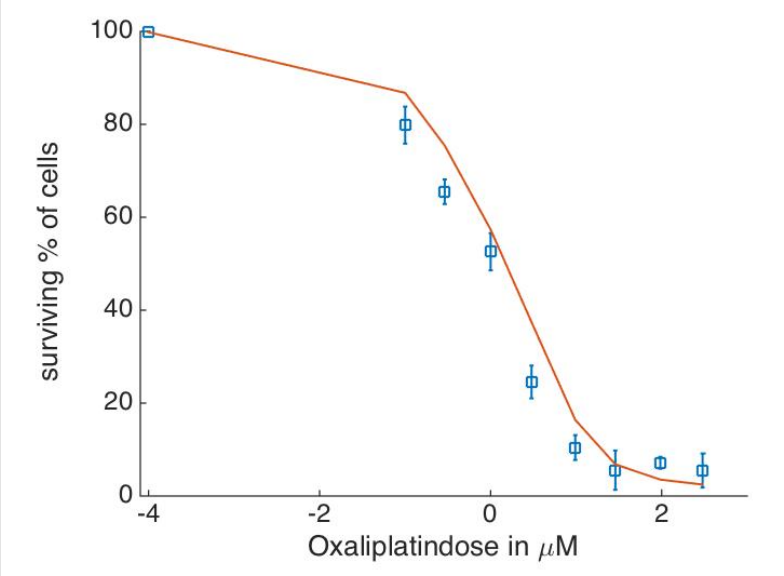


Data: Jang et al. (2002)
Cancer Res Treat 34: 372

Parameter Identifiability?

- FIM has full rank
- Scaled Eigenvalues are 8e–7, 3.6e–6, 1.8e–5, 9e–5, 0.02 and 1
- We only expect 1-2 identifiable combinations





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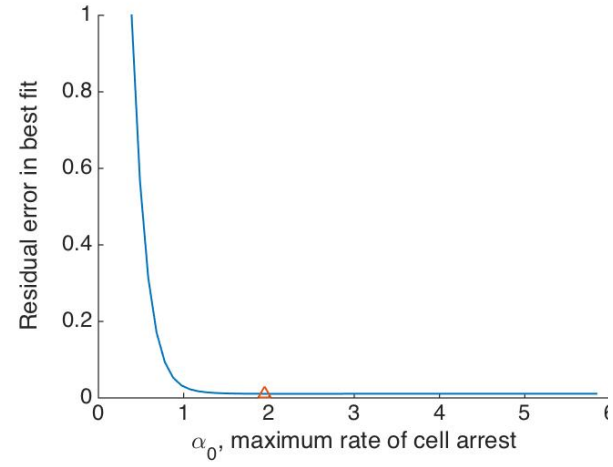
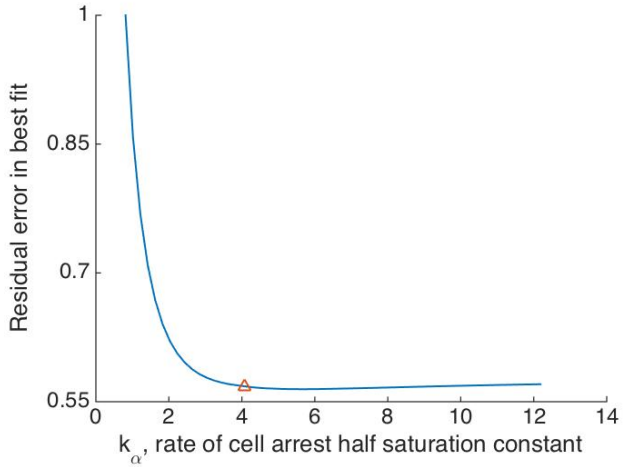
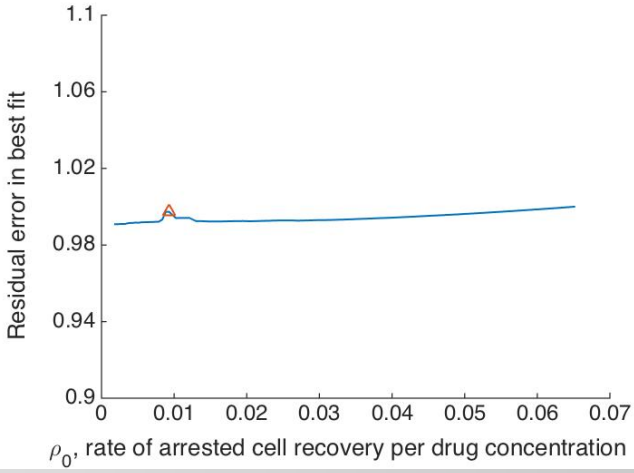
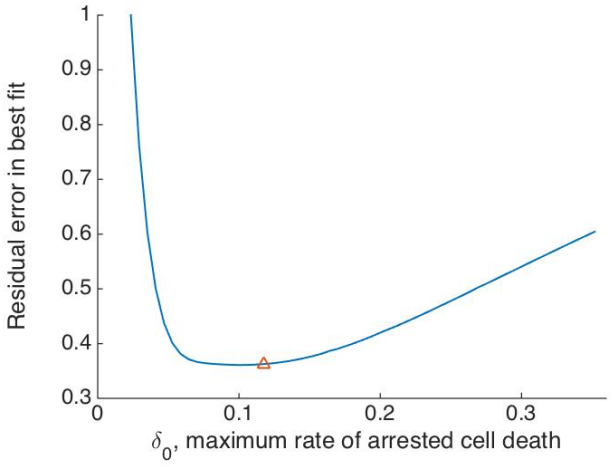
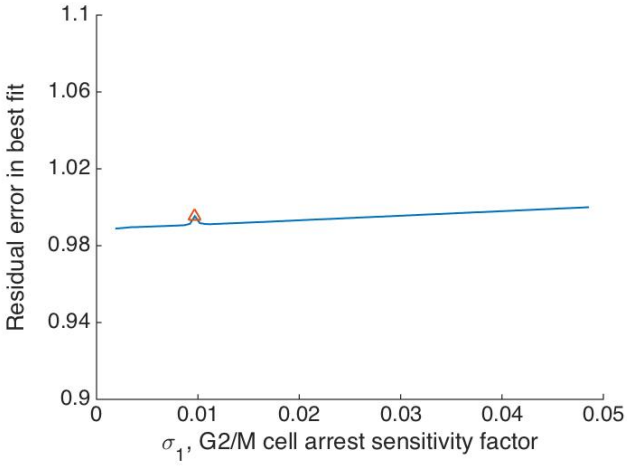
It's Pretty Ugly

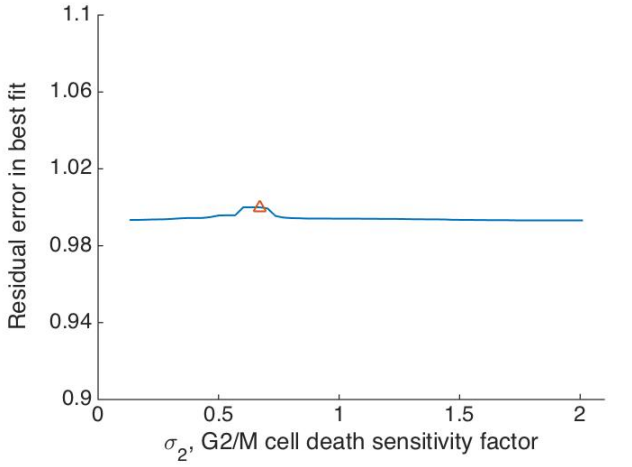






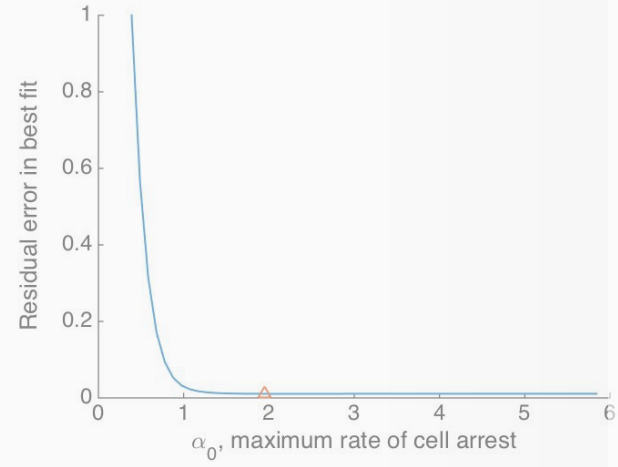


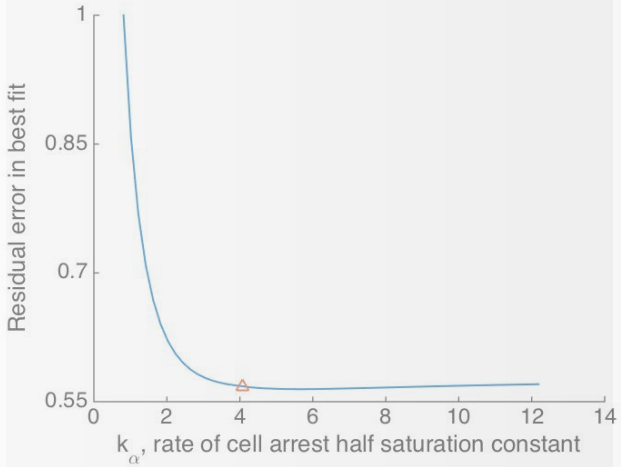


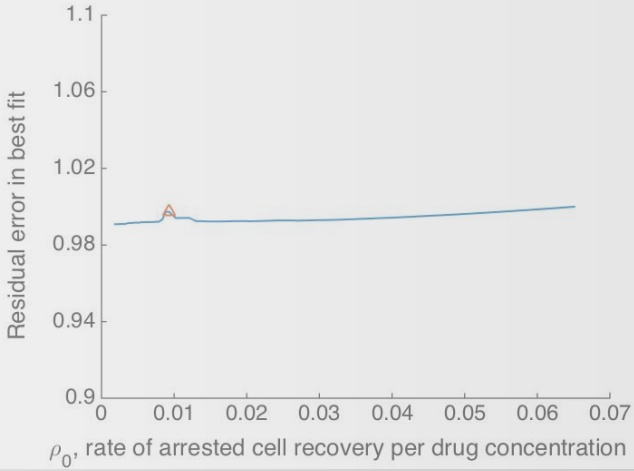


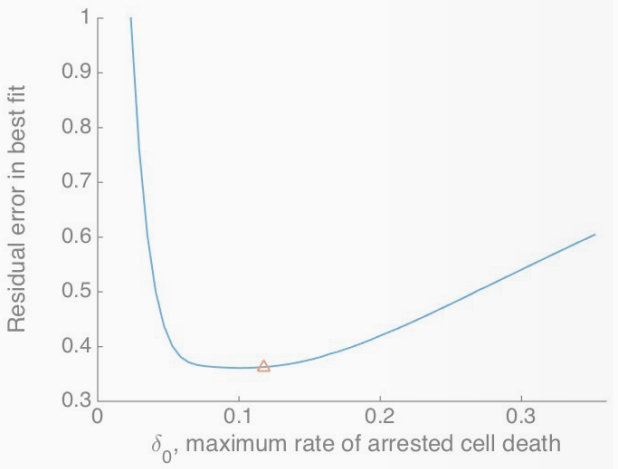
It's Pretty Ugly

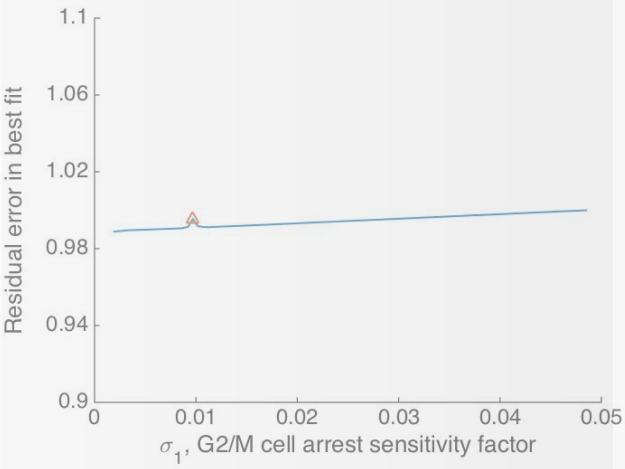
Leads to biologically incorrect hypotheses – the rate of arrested cell recovery is very low and rate of arrest in G2/M stage ~ 0

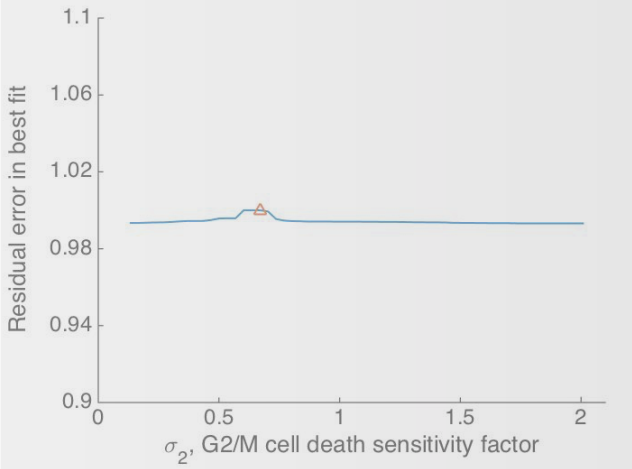




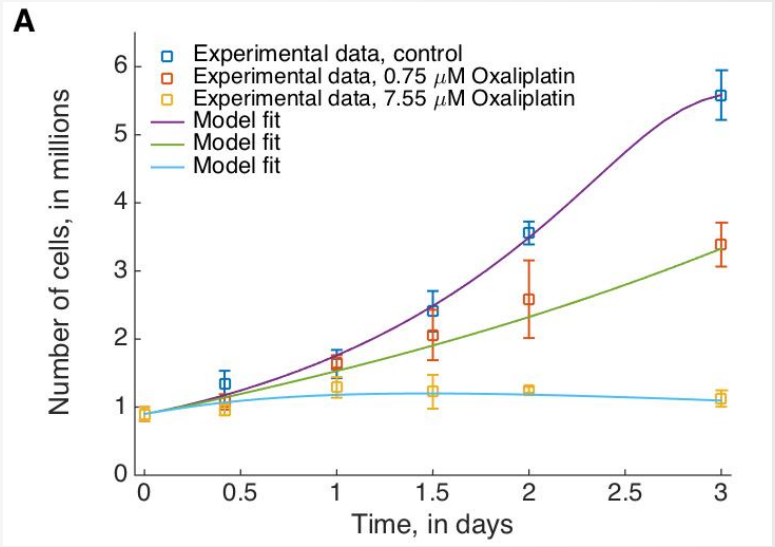


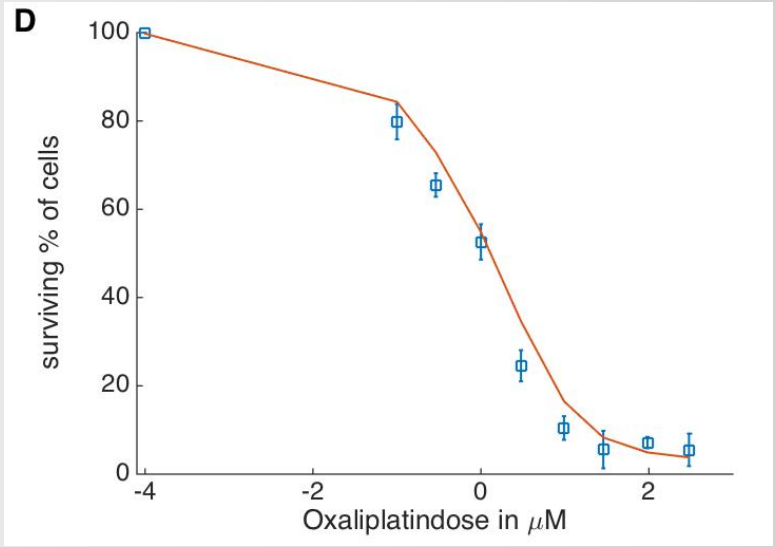


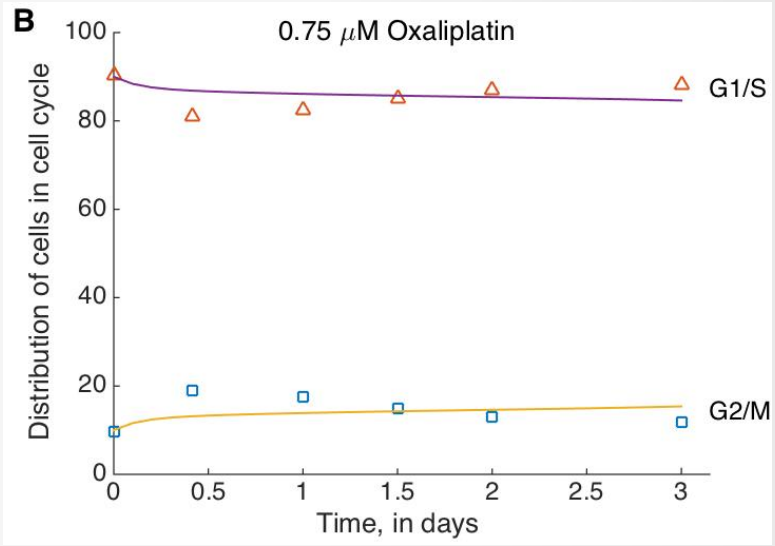


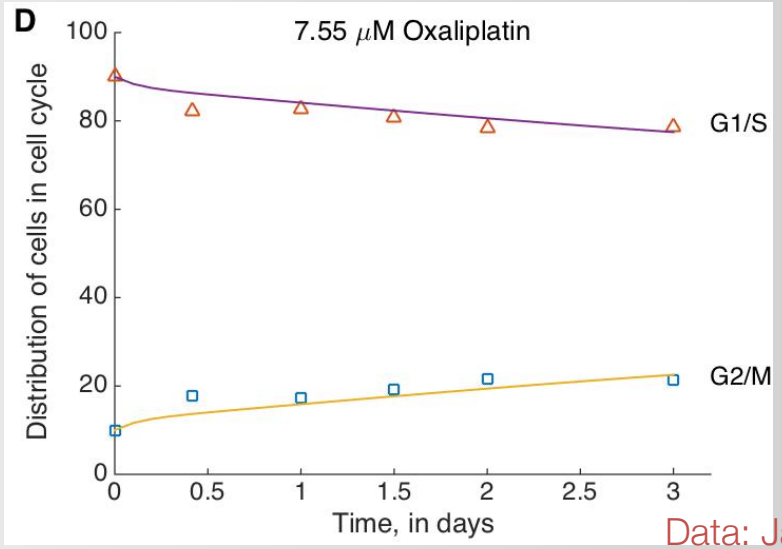


Luckily there's More Data









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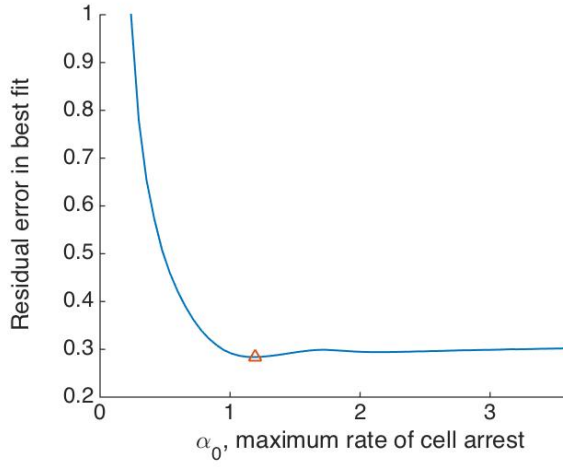
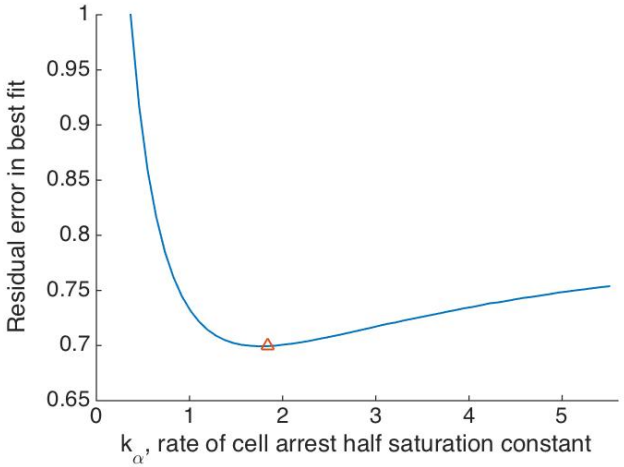
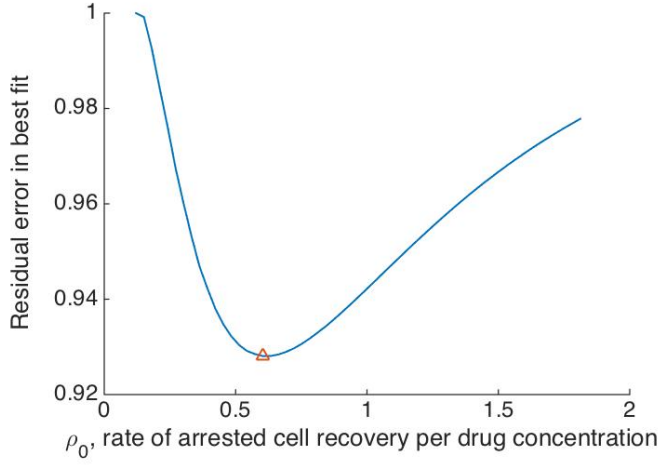
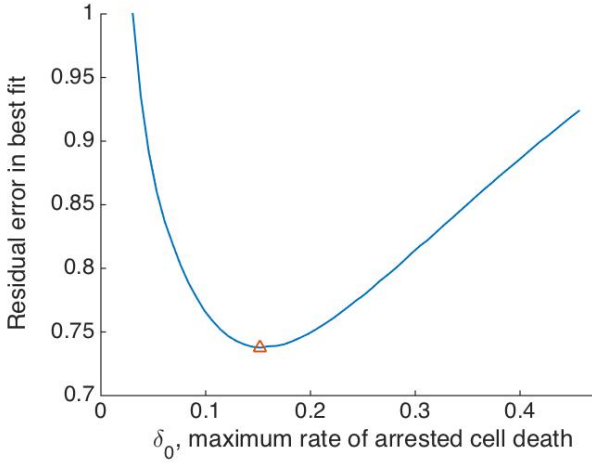
Cancer Res Treat 34: 372

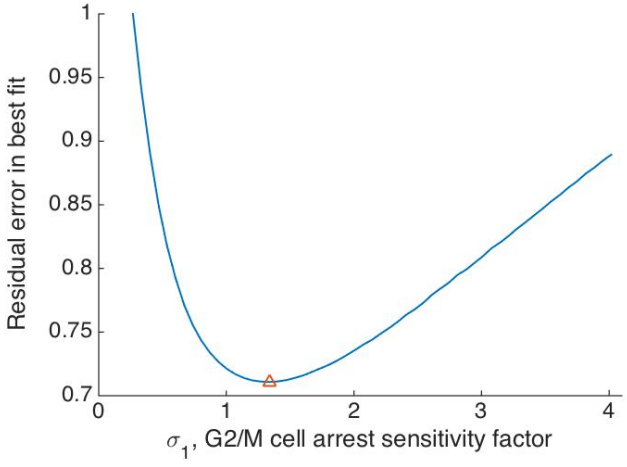
What about Profile Likelihoods now?

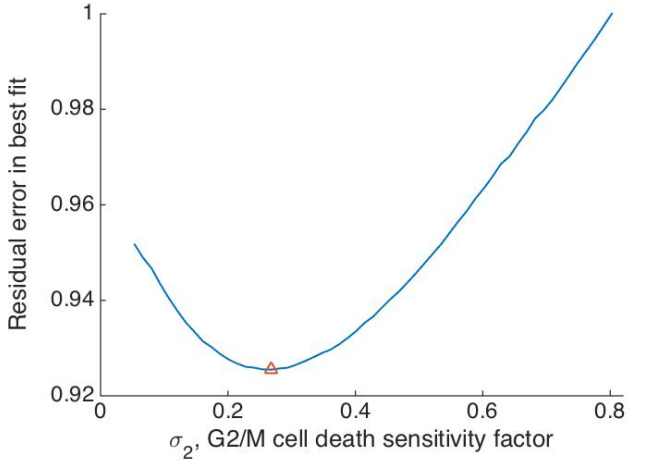












Summary II
(or, more data is good)

- Adding information about cell cycle distribution means all 6 parameters identifiable, as compared to 0 or 1 without this data
- Further, model fits now predict that G2/M cells are1.3 fold more susceptible to cell arrest as compared to G1/S
- However, arrested G1/S cells are 5 times more likely to die as compared to arrested G2/M cells!
- There is independent experimental evidence for this – provides an added degree of model validation
- Even though additional data only provides total numbers of cells in G1/S and G2/M, identifiability of the model implies we can deduce (with confidence) their numbers in all 4 compartments

Thank you!

Acknowledgements

- MBI ECA & NSF grant DMS 0931642
- Simons Foundation

Collaborator

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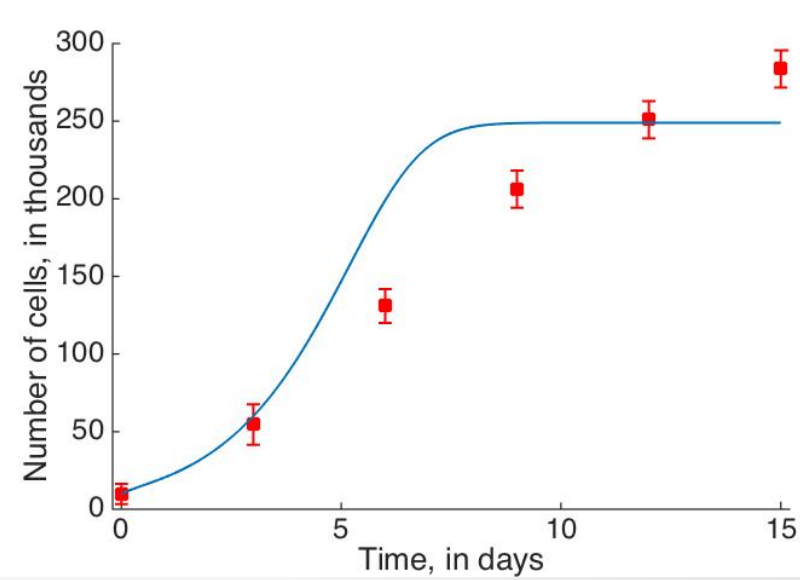
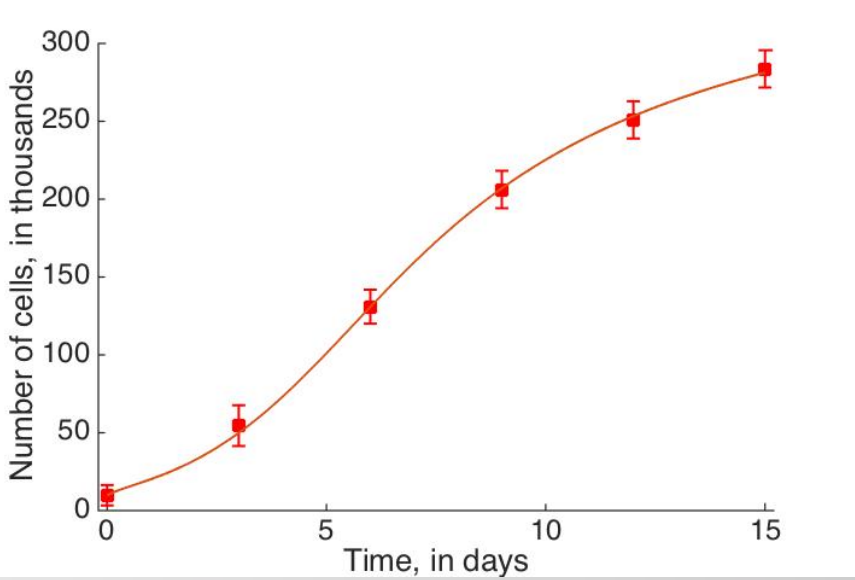
Why not Logistic Growth?

Logistic Growth



Our Model



Data: Terzis et al. (1997)
British Journal of Cancer 75: 1744