Network Modeling and Simulation

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Mathematical modelling of cancer stem cell-targeted immunotherapy

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Cancer Cells: CSCs and nCSCs

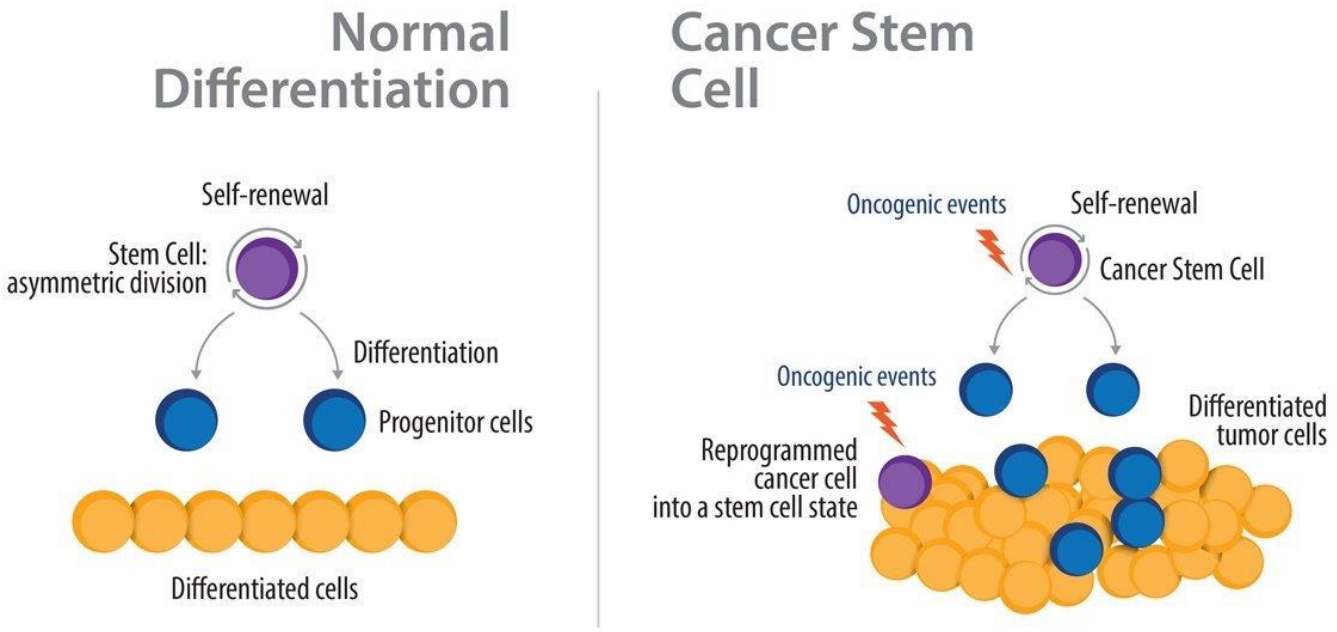
Cancer Stem Cells (CSCs) - ALDH high:

- Non-differentiated cells
- Most potential for self-renewal and differentiation
- Only constitute about 1-10% of the tumor size
- Contribute to faster tumor growth (high tumorigenicity)

Non-CSC (nCSCs) - ALDH low:

- Differentiated cells
- Include cancer cells with different features → Different degrees of differentiation

Introduction



Main Goal:

Modelling tumor growth and therapy response discriminating between CSCs and nCSCs

Populations Considered by the Model:

CSCs (S)

nCSCs (P)

Dendritic Cells (D_i)

Cytotoxic T-cells (T_i)

} Either CSC or nCSC specific

Chemotherapeutic agent (C)

Model

Assumptions:

- S could undergo symmetric division, asymmetric division or interconversion, P may revert to S
- Dendritic cells assume 2 different activated phenotypes Dp, Ds
- Dendritic cells activate cytotoxic T-cells giving rise to 2 phenotypes Ts, Tp
- All cells die by natural processes
- T-helper cells activity not considered

$$\frac{dS}{dt} = \alpha_S S + \rho_{PS} P - \rho_{SP} S - \beta_S S T_S - \delta_S S - \Gamma_S S C$$

$$\frac{dP}{dt} = \alpha_P P + \alpha_{SP} S + 2\rho_{SP} S - \rho_{PS} P - \beta_P P T_P - \delta_P P - \Gamma_P P C$$

$$\frac{dT_S}{dt} = \kappa_{TS} T_S^n \frac{D_S}{s_{TS} + D_S} - \delta_{TS} T_S$$

$$\frac{dT_P}{dt} = \kappa_{TP} T_P^n \frac{D_P}{s_{TP} + D_P} - \delta_{TP} T_P$$

$$\frac{dD_S}{dt} = \gamma_{DS} DS - \beta_{DS} D_S T_S - \delta_{DS} D_S$$

$$\frac{dD_P}{dt} = \gamma_{DP} DP - \beta_{DP} D_P T_P - \delta_{DP} D_P$$

$$\frac{dC}{dt} = - e_C C$$

Parameters

Parameter values were estimated exaclty only in the case they are not host specific or drug specific. In all the other cases boundaries were set

Parameter	Description	Units
α_i	reproduction rate of cell type i	day^{-1}
α_{ij}	production of cell type j through the asymmetrical division of cell type i	$\text{nCSC/CSC} \cdot \text{day}^{-1}$
ρ_{ij}	conversion rate of cell type j to type i	day^{-1}
β_i	death rate of cell type i due to CTCs	$\text{aCTC cells}^{-1} \cdot \text{day}^{-1}$
δ_i	death rate of cell type i due to natural processes	day^{-1}
T_i^n	population of naive CTCs specific to cell type i (constant)	mDCs
κ_i	saturated activation rate of CTCs due to activation by mDCs	$(\text{aCTCs/nCTCs}) \cdot \text{day}^{-1}$
s_i	mDC EC_{50} for CTC activation rate	mDCs
γ_i	maturation rate of DCs due to consumption of cancer cells	$(\text{mDCs/iDCs}) \cdot \text{day}^{-1} \cdot \text{cancer cell}^{-1}$
D	population of iDCs (constant)	iDCs
Γ_i	rate of killing of cell type i by the chemotherapeutic agent	$\text{day}^{-1} \cdot (\mu\text{g/mL})^{-1}$
e_C	elimination rate of the chemotherapeutic agent	day^{-1}

Host-specific parameter	Value
α_S	$0.14 - 0.76\ \text{day}^{-1}$
α_{SP}	$0.4 - 6\ \text{day}^{-1}$
α_P	$0 - 0.8\ \text{day}^{-1}$
ρ_{PS}	fit as needed to keep %CSCs within 1–10% (see A.3)
ρ_{SP}	$0 - 0.76\ \text{day}^{-1}$
δ_S	$0 - 0.25\ \text{day}^{-1}$
δ_P	$0 - 0.39\ \text{day}^{-1}$
δ_{DS}, δ_{DP}	$0.2 - 0.8\ \text{day}^{-1}$
Non-host-specific parameter	Value
β_S, β_P	$6.2 \times 10^{-8}\ \frac{1}{\text{aCTCs-day}}$
$\kappa_{TS}\, T_S^n$, $\kappa_{TP}\, T_P^n$	$4.5 \times 10^4\ \frac{(\text{aCTCs}/\mu\text{L})}{\text{day}}$
s_{TS}, s_{TP}	$2.5 \times 10^4\ \text{mDCs}/\mu\text{L}$
δ_{TS}, δ_{TP}	$0.02\ \text{day}^{-1}$
$\gamma_{DS} D$, $\gamma_{DP} D$	$0.0063\ \frac{\text{mDCs}/\mu\text{L}}{\text{day-cancer cell}/\mu\text{L}}$
β_{DS}, β_{DP}	$6.2 \times 10^{-8}\ \frac{1}{\text{aCTC cells}/\mu\text{L-day}}$
Drug-specific parameter	Value
Γ_S	$7.8 - 14 \times 10^{-4}\ \text{day}^{-1} \cdot (\mu\text{g/mL})^{-1}$
Γ_P	$5.2 - 7.0 \times 10^{-3}\ \text{day}^{-1} \cdot (\mu\text{g/mL})^{-1}$
e_C	$49 - 124\ \text{day}^{-1}$

Deterministic Simulations

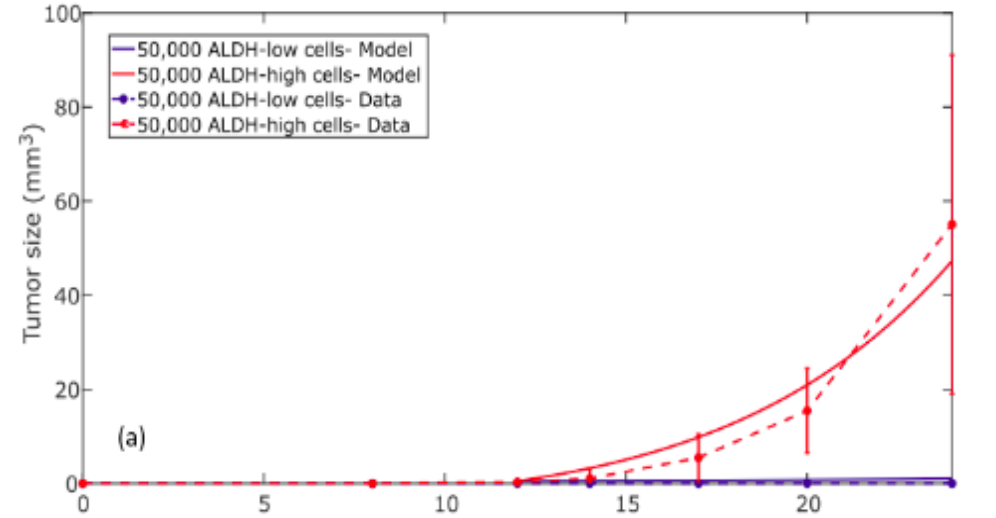
Runge Kutta45 employed for the simulatons

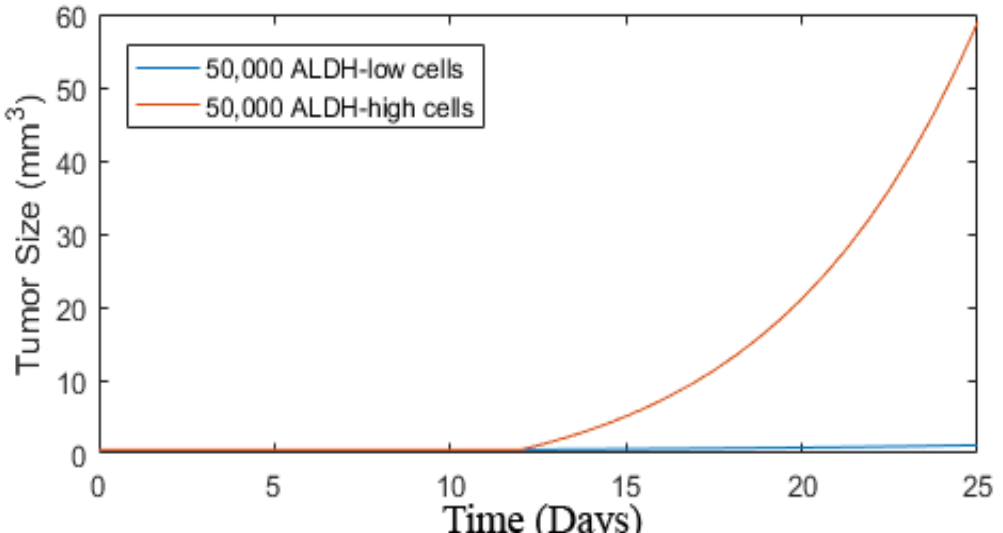
Settings:

2 Simulations representing inoculation of 50,000 CSCs and nCSCs respectively

12 days necessary for taking roots

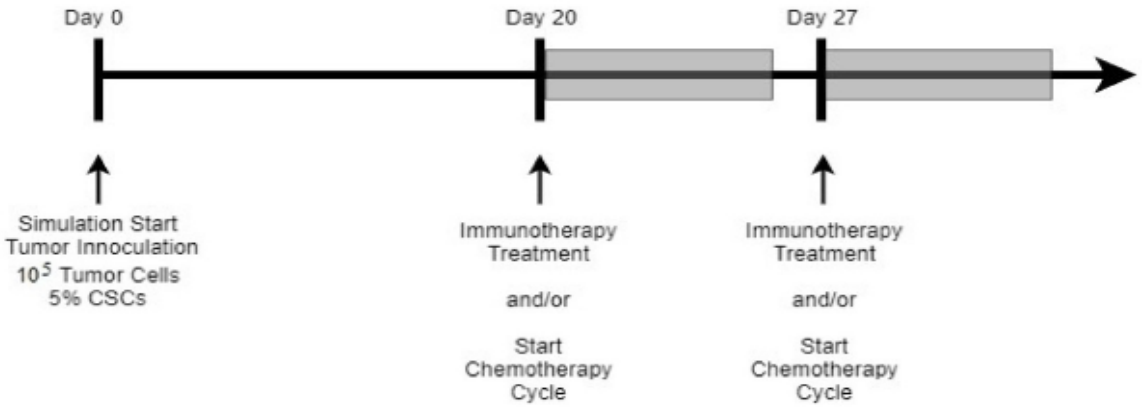
Numerical differences because of different algorithms

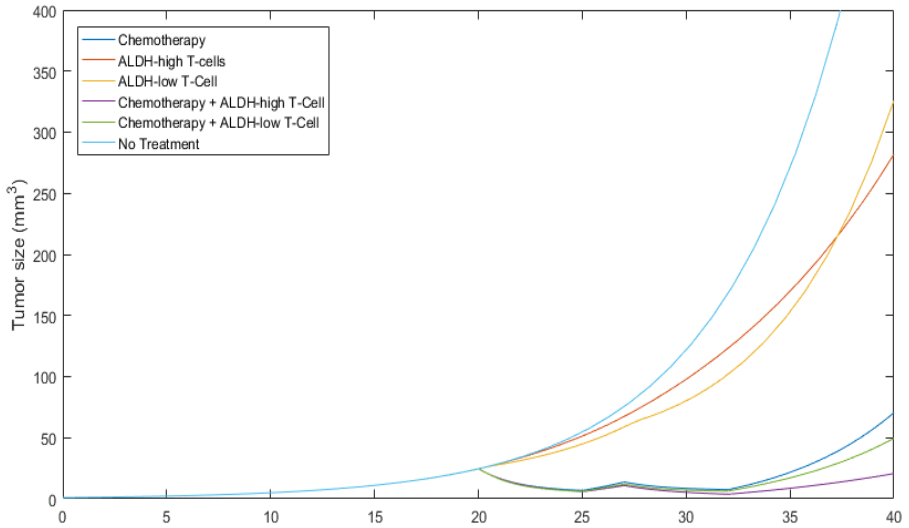


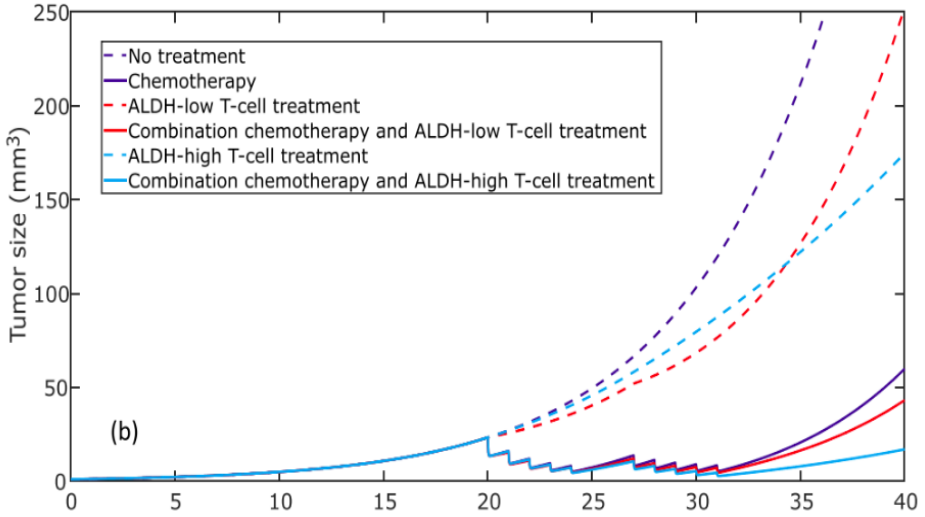


Deterministic Simulations

- Non treated
- Immunotherapy (CTCs , CTCp)
- Chemotherapy
- Immunotherapy + chemotherapy

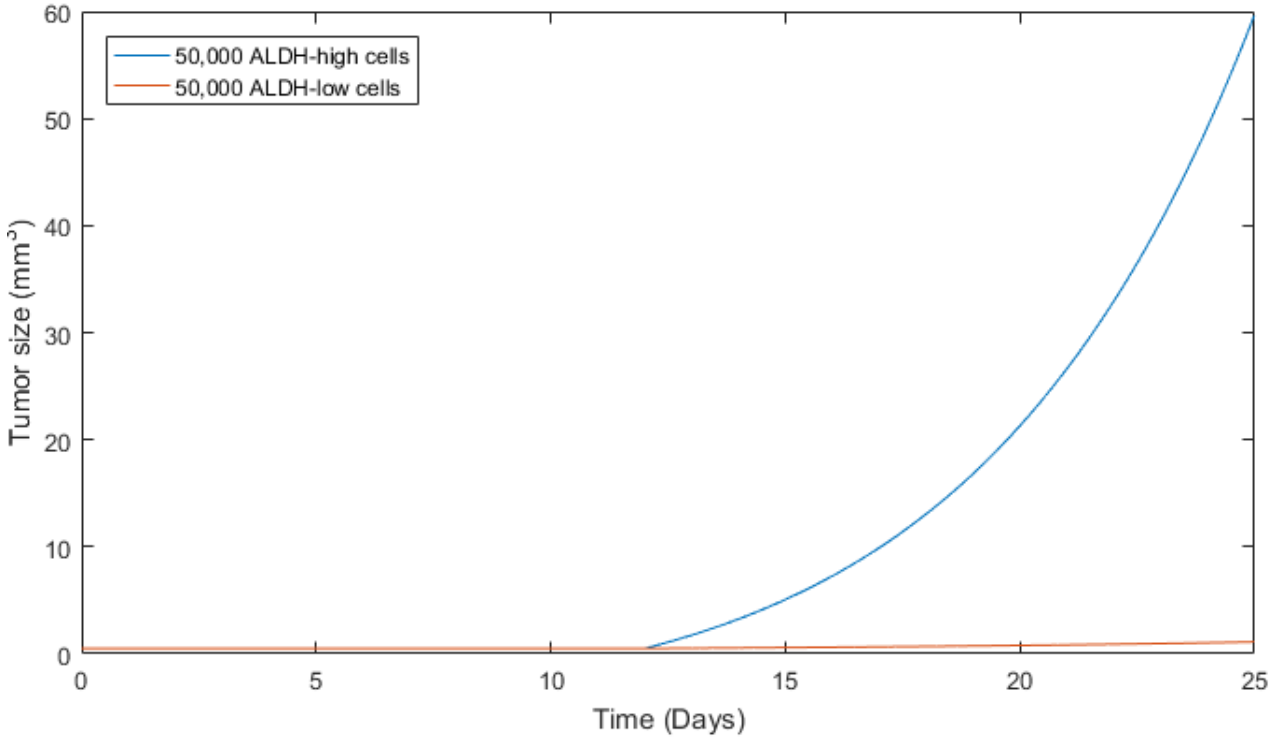






Stochastic Simulations

- ODEs translated into reactions to perform a stochastic simulation.
- Discretised direct method used in the simulation.



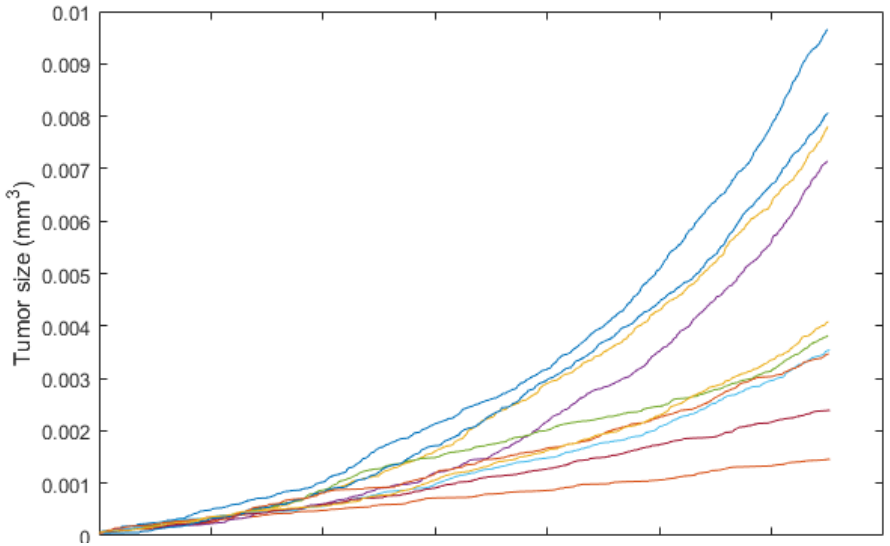
1. $\mathrm{S} \rightarrow 2\mathrm{S}$ $\quad c = r_S$
2. $\mathrm{P} \rightarrow \mathrm{S}$ $\quad c = \rho_{PS}$
3. $\mathrm{S} \rightarrow 2\mathrm{P}$ $\quad c = \rho_{SP}$
4. $\mathrm{P} \rightarrow 2\mathrm{P}$ $\quad c = r_P$
5. $\mathrm{S} \rightarrow \mathrm{S} + \mathrm{P}$ $\quad c = \alpha_{SP}$

Similar results to deterministic setting but faster computations:

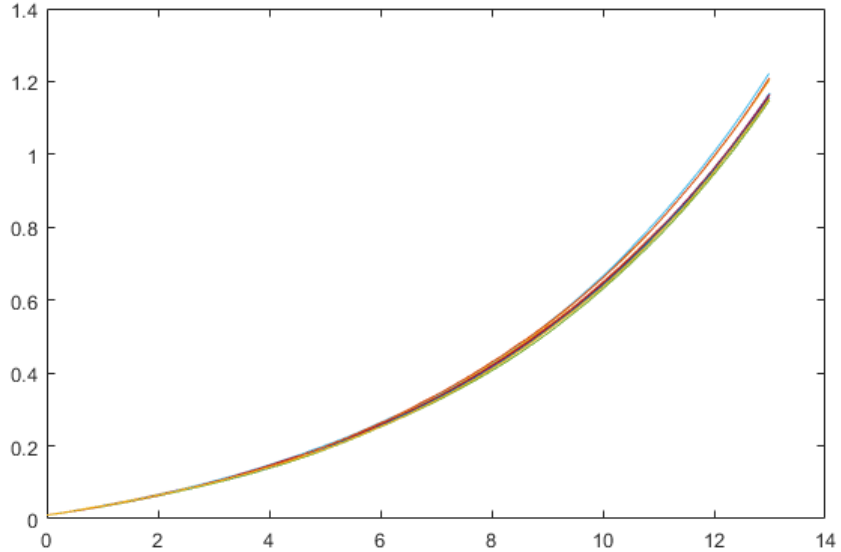
Deterministic ~ 0.08 s

Stochastic ~ 67 s

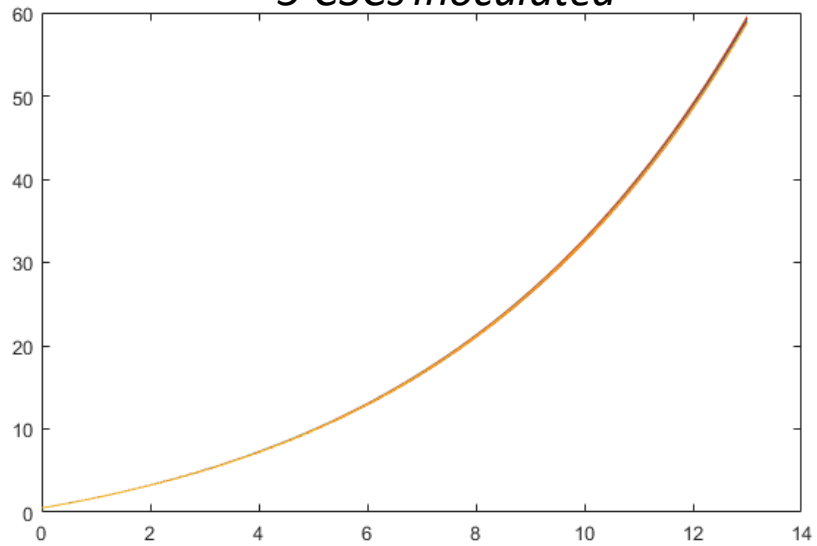
Stochastic Simulations



5 CSCs inoculated



1,000 CSCs inoculated



50,000 CSCs inoculated

Stochasticity only plays a significant role when considering low cell numbers

Paper Parameter estimation

- Boundaries set empirically from literature
- Should be estimated independently to avoid overfitting

Non specific parameters determined fitting experimental data or making averages from different article estimations

Host and drug specific parameters must be estimated every time for each case fitting experimental data

Host-specific parameter	Value
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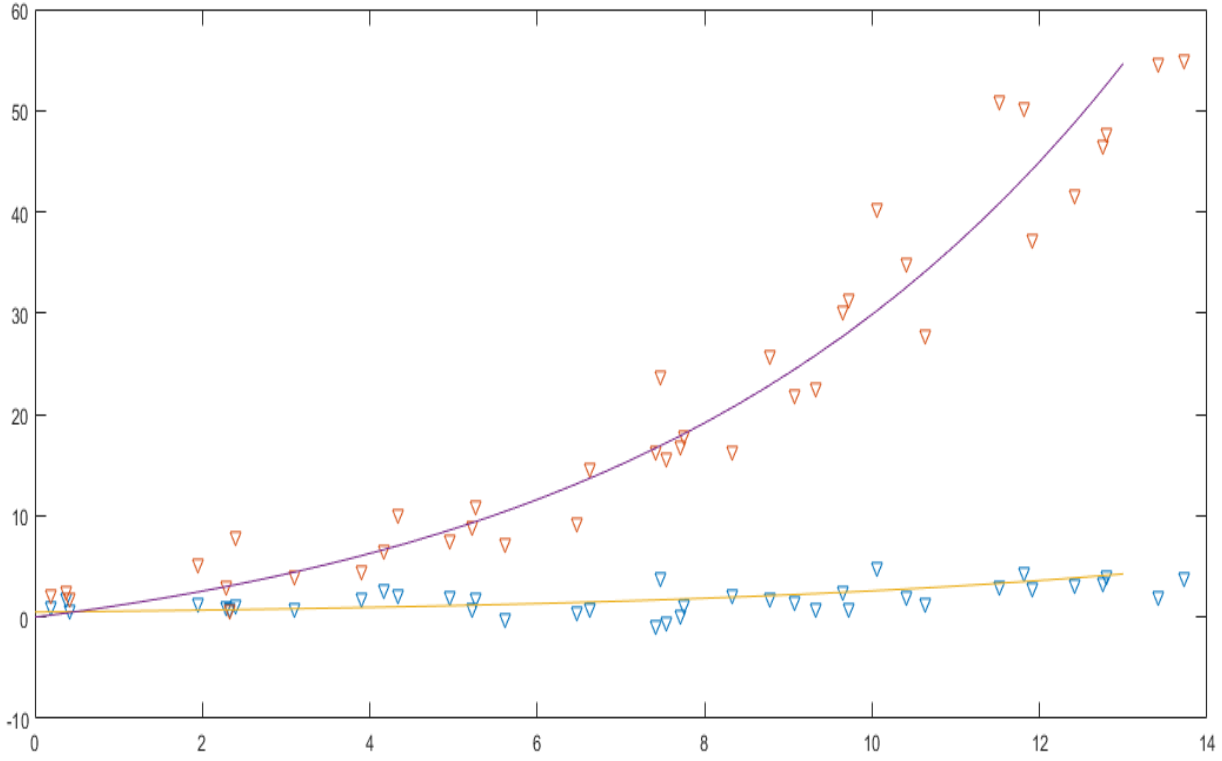
e_C	$49 - 124\ \text{day}^{-1}$

Our Parameter estimation

No experimental data available in our case!

Considered data generated by the model affected by an error following a standard normal

Multistart non linear least square method employed for finding parameters value in first simulation



Model par	$r_s = 0.3000$	$\rho_{ps} = 5.3 \times 10^{-4}$	$\rho_{sp} = 0.1500$	$r_p = 0.0500$	$\alpha_{sp} = 1.8000$
Our par	$r_s = 0.4747$	$\rho_{ps} = 10^{-4}$	$\rho_{sp} = 0.7600$	$r_p = 0.0279$	$\alpha_{sp} = 1.4930$

Conclusions

- The optimal treatment is combining the chemotherapy with CSC specific immunotherapy

  → Ensures high tumor size reduction and low CSC amounts (recurring tumors less likely)

- Assumptions of the deterministic model are not fully satisfied
- Stochasticity is negligible at high cell numbers

  → Stochastic approach is still necessary if we want to model early tumor phases

- Possible applications in the medical field to decide optimal treatment

Thank you for your attention