Stochastic individual based models with application to modelling of cancer therapy

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CIRM, 29.06.2018

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PROBABILISTIC STRUCTURES IN EVOLUTION
DFG SPP 1590

ImmunoSensation
the immune sensory system Bonn cluster of excellence

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- drift towards higher fitness (canonical equation)
- evolutionary branching (splitting of populations to reduce competition)

The standard model

Markov processes on space of positive measures.

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- Generator acting on functions $f : \mathcal{M}_p(\mathcal{X}) \to \mathbb{R}$ by

$$\begin{aligned} Lf(\nu) &= \int_{\mathcal{X}} [f(\nu + \delta_x) - f(\nu)] b(x)(1 - m(x))\nu(dx) \\ &+ \int_{\mathcal{X}} [f(\nu - \delta_x) - f(\nu)] \left[d(x) + \int_{\mathcal{X}} c(x,y)\nu(dy) \right] \nu(dx) \\ &+ \int_{\mathcal{X}} \int_{\mathcal{X}} [f(\nu + \delta_{x+y)}) - f(\nu)] m(x) M(x, dy)\nu(dx). \end{aligned}$$

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- $M(x, dy)$: probability distribution of the type of a mutant child of an individual of type x.

Application to modelling of cancer evolution and therapy

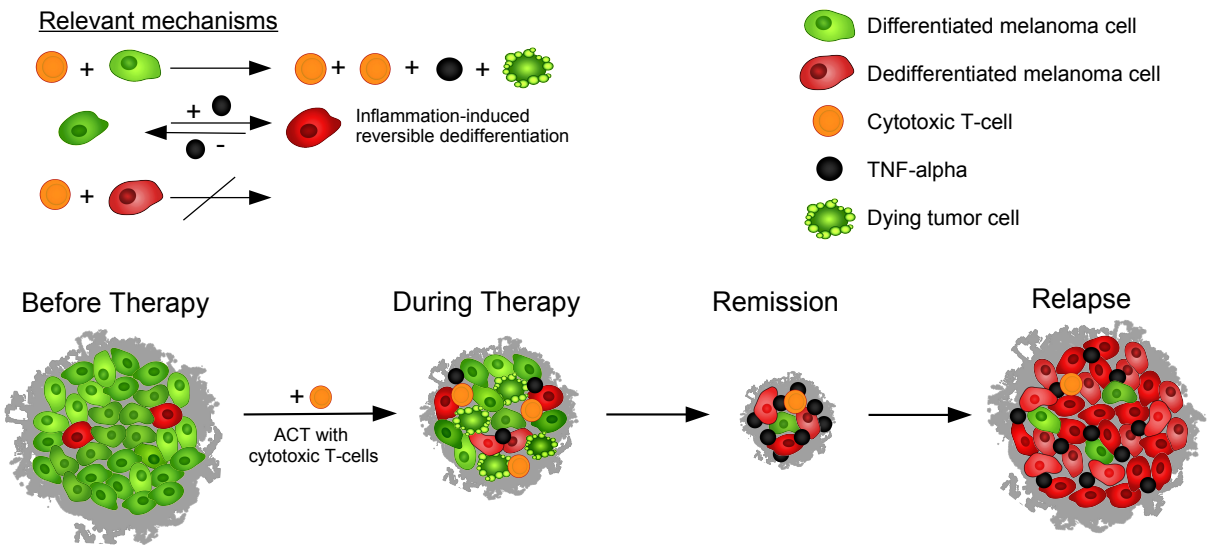
Can these models be applied to cancer and its treatment?

This would require: :

- Identification of the key mechanisms and players effecting the evolution of a tumour under treatment
- Quantitative identification of parameters
- Efficient numerical simulation of the model

Immunotherapy of melanoma

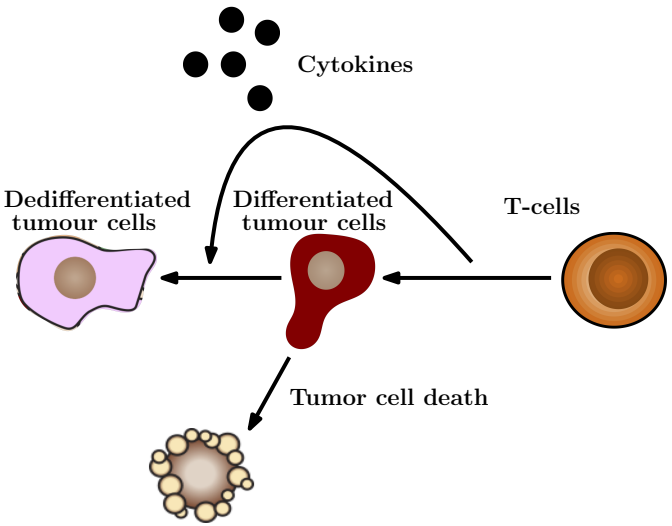
Over the last years, we have tried to do all this for specific immunotherapies of melanoma in a mice model that was implemented at Bonn University Hospital. Starting point were experiments by Landsberg et al. where the following scenario was observed:



A first model

New feature to be included in the model:

- genetically identical individuals can express different phenotypes
- phenotypes switch randomly within lifecycle ("bet hedging")
- switch rates can be changed by the presence of other "individuals" ("phenotypic plasticity")



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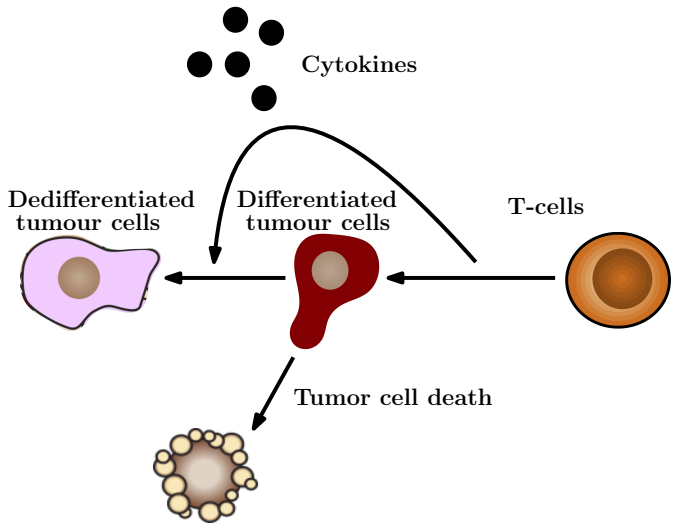
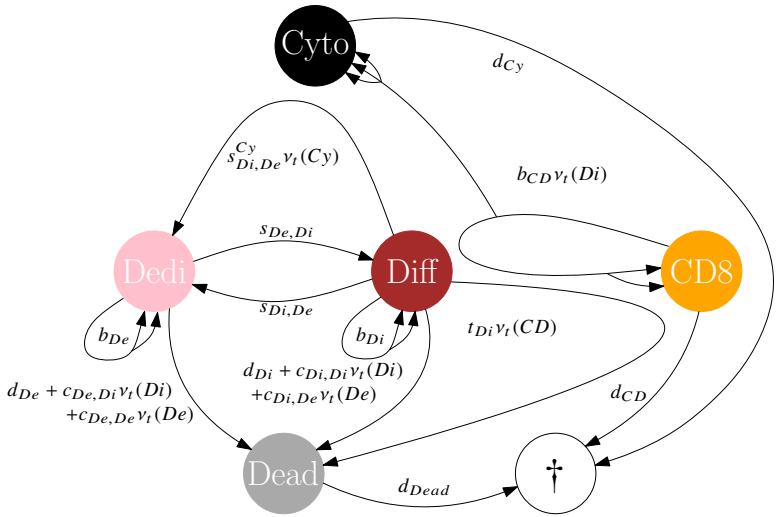
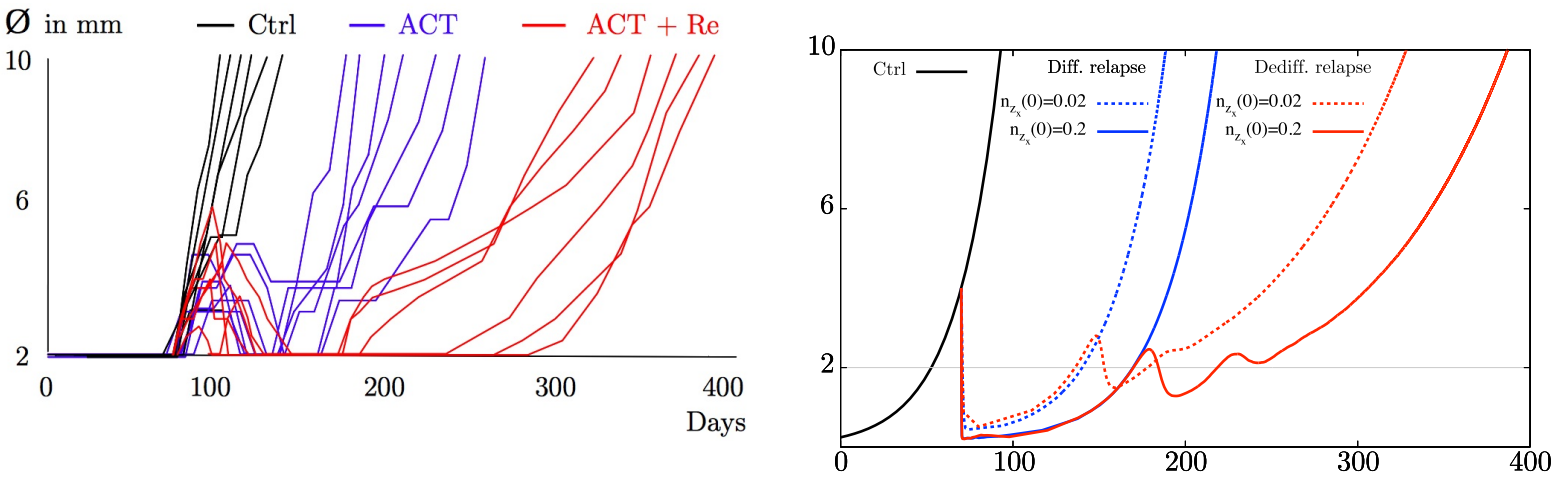




Comparison of experimental data

obtained by Landsberg et al. with simulations for biologically reasonable parameters



Left: Blue and red curves show therapy with and without reactivation of T-cells.
Right: Blue curves correspond to simulations where the T-cell population becomes extinct (can be seen as therapy without reactivation) and red curves to survival of T-cells (can be seen as therapy with reactivation).

Combination treatment

- Glodde studied evolution of melanomas under adoptive cell transfer therapy (ACT) combined with MET-inhibitor INC280
- Therapy protocol: HCmel12 melanoma cells are transplanted into the mouse and left to grow
  - after 16 days (tumour size 3-4mm diam) cytotoxic T-cells are injected
  - for the first five days (16-21) METi is injected twice daily

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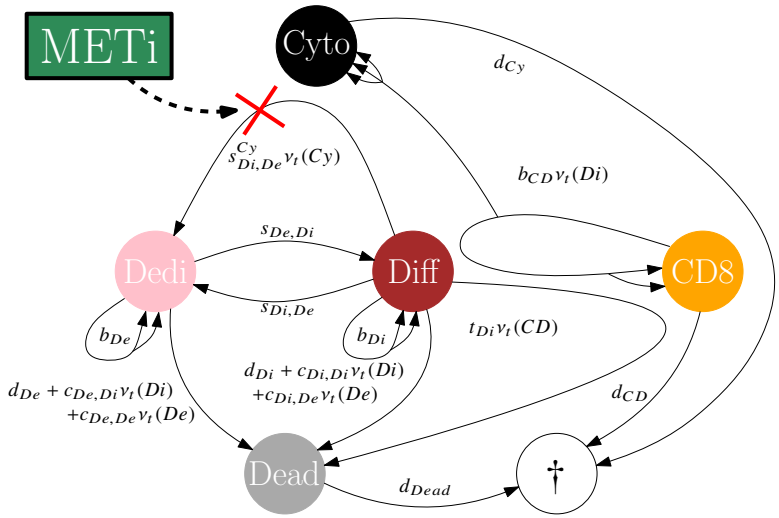
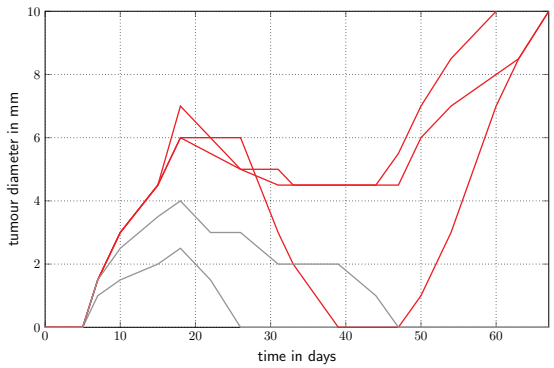
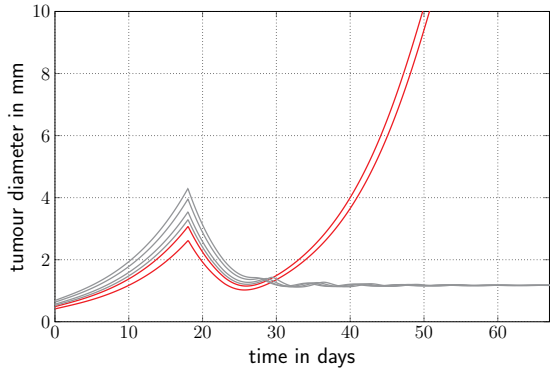


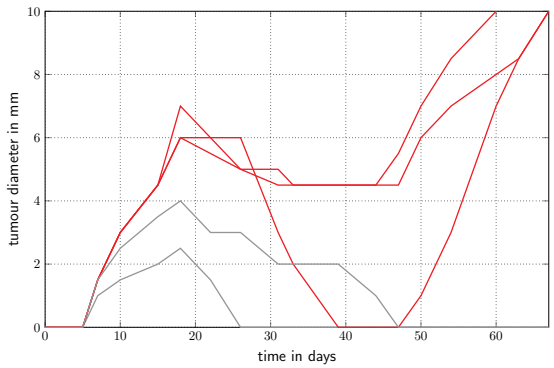
First try

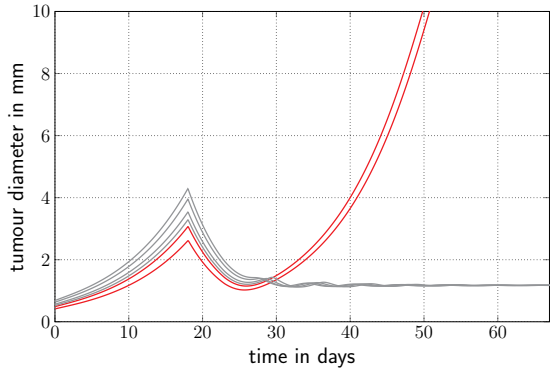




Problem: Therapy appears more effective for large tumours contrary to experiments!

First try





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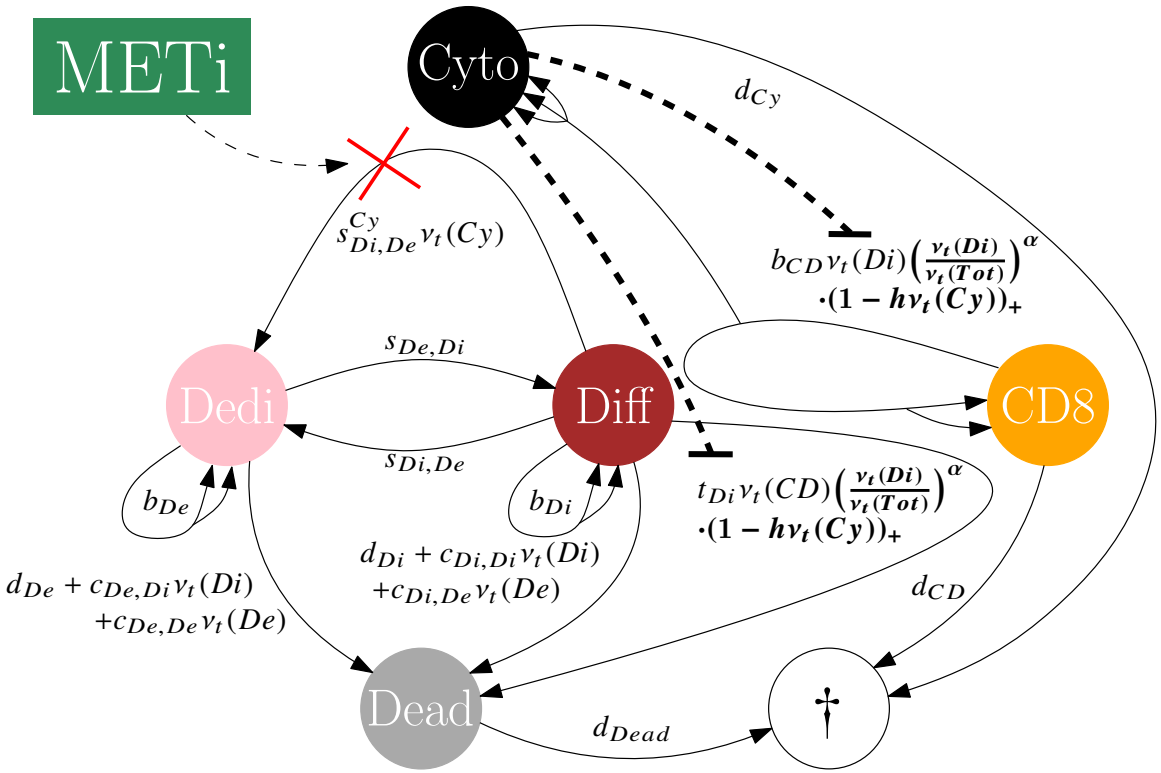
Solution:

- Include the effect of T-cell exhaustion to slow down immune response
- Include spatial structure of the tumour

Exhaustion and spatial structure



The full generator

$$
\begin{aligned}
&(\mathcal{L}\phi)(\nu_t)\\
&\quad = \left(\phi\left(\nu_t + \delta_{Di}\right) - \phi(\nu_t)\right)(1-m)b_{Di}\nu_t(Di)\\
&\qquad + \left(\phi\left(\nu_t - \delta_{Di} + \delta_{Dead}\right) - \phi(\nu_t)\right)\left(d_{Di} + c_{Di,Di}\nu_t(Di) + c_{Di,De}\nu_t(De) + c_{Di,KO}\nu_t(KO)\right)\nu_t(Di)\\
&\qquad + \left(\phi\left(\nu_t + \delta_{De} - \delta_{Di}\right) - \phi(\nu_t)\right)\left(s_{Di,De} + s^{Cy}_{Di,De}\nu_t(Cy)\right)\nu_t(Di)\\
&\qquad + \left(\phi\left(\nu_t + \delta_{De}\right) - \phi(\nu_t)\right)(1-m)b_{De}\nu_t(De)\\
&\qquad + \left(\phi\left(\nu_t - \delta_{De} + \delta_{Dead}\right) - \phi(\nu_t)\right)\left(d_{De} + c_{De,Di}\nu_t(Di) + c_{De,De}\nu_t(De) + c_{De,KO}\nu_t(KO)\right)\nu_t(De)\\
&\qquad + \left(\phi\left(\nu_t + \delta_{Di} - \delta_{De}\right) - \phi(\nu_t)\right)s_{De,Di}\nu_t(De)\\
&\qquad + \left(\phi\left(\nu_t + \delta_{KO}\right) - \phi(\nu_t)\right)\left(b_{KO}\nu_t(KO) + mb_{Di}\nu_t(Di) + mb_{De}\nu_t(De)\right)\\
&\qquad + \left(\phi\left(\nu_t - \delta_{KO} + \delta_{Dead}\right) - \phi(\nu_t)\right)\left(d_{KO} + c_{KO,Di}\nu_t(Di) + c_{KO,De}\nu_t(De) + c_{KO,KO}\nu_t(KO)\right)\nu_t(KO)\\
&\qquad + \left(\phi\left(\nu_t - \delta_{Dead}\right) - \phi(\nu_t)\right)d_{Dead}\nu_t(Dead)\\
&\qquad + \left(\phi\left(\nu_t + \delta_{CD} + 3\delta_{Cy}\right) - \phi(\nu_t)\right)b_{CD}\nu_t(Di)\nu_t(CD)(1-h\nu_t(Cy))_+\left(\frac{\nu_t(Di)}{\nu_t(Tot)}\right)^{\alpha}\\
&\qquad + \left(\phi\left(\nu_t - \delta_{Di} + \delta_{Dead}\right) - \phi(\nu_t)\right)t_{Di}\nu_t(Di)\nu_t(CD)(1-h\nu_t(Cy))_+\left(\frac{\nu_t(Di)}{\nu_t(Tot)}\right)^{\alpha}\\
&\qquad + \left(\phi\left(\nu_t - \delta_{CD}\right) - \phi(\nu_t)\right)d_{CD}\nu_t(CD)\\
&\qquad + \left(\phi\left(\nu_t - \delta_{Cy}\right) - \phi(\nu_t)\right)d_{Cy}\nu_t(Cy)
\end{aligned}
$$

Results including T-cell exhaustion, spatial structure

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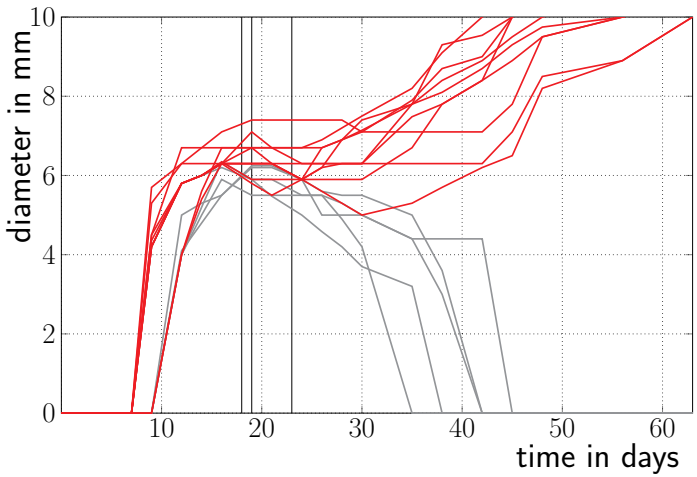

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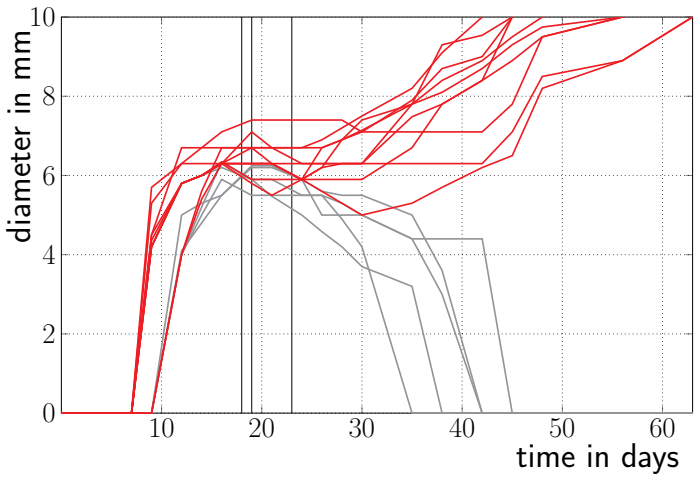
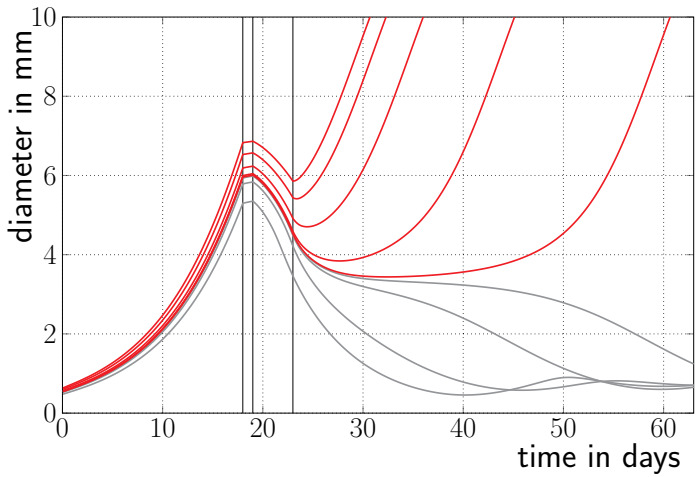
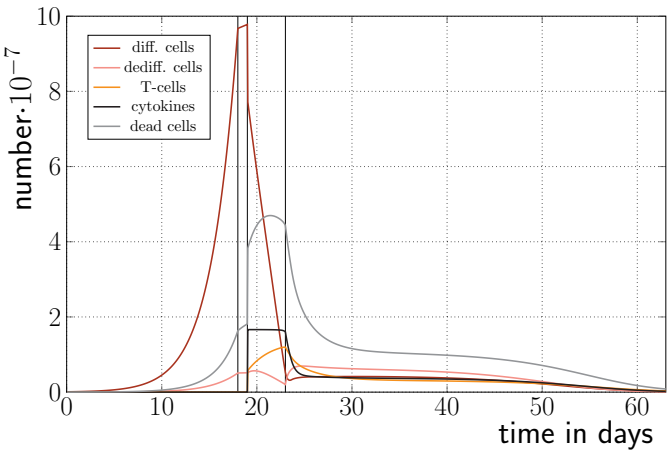
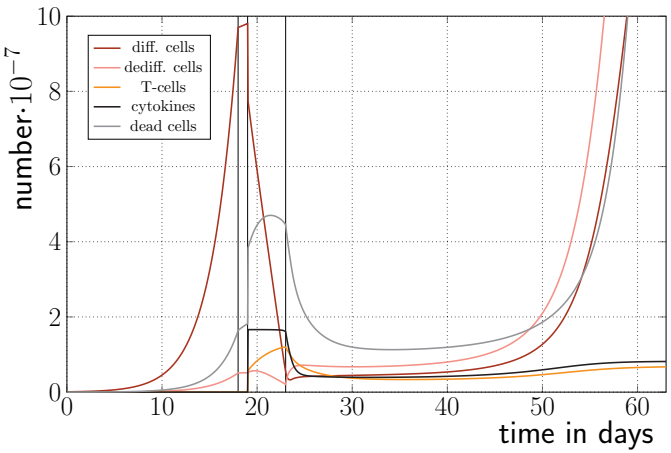




Late relapse

- Stochastic effects play a role even in large populations





KO mutants

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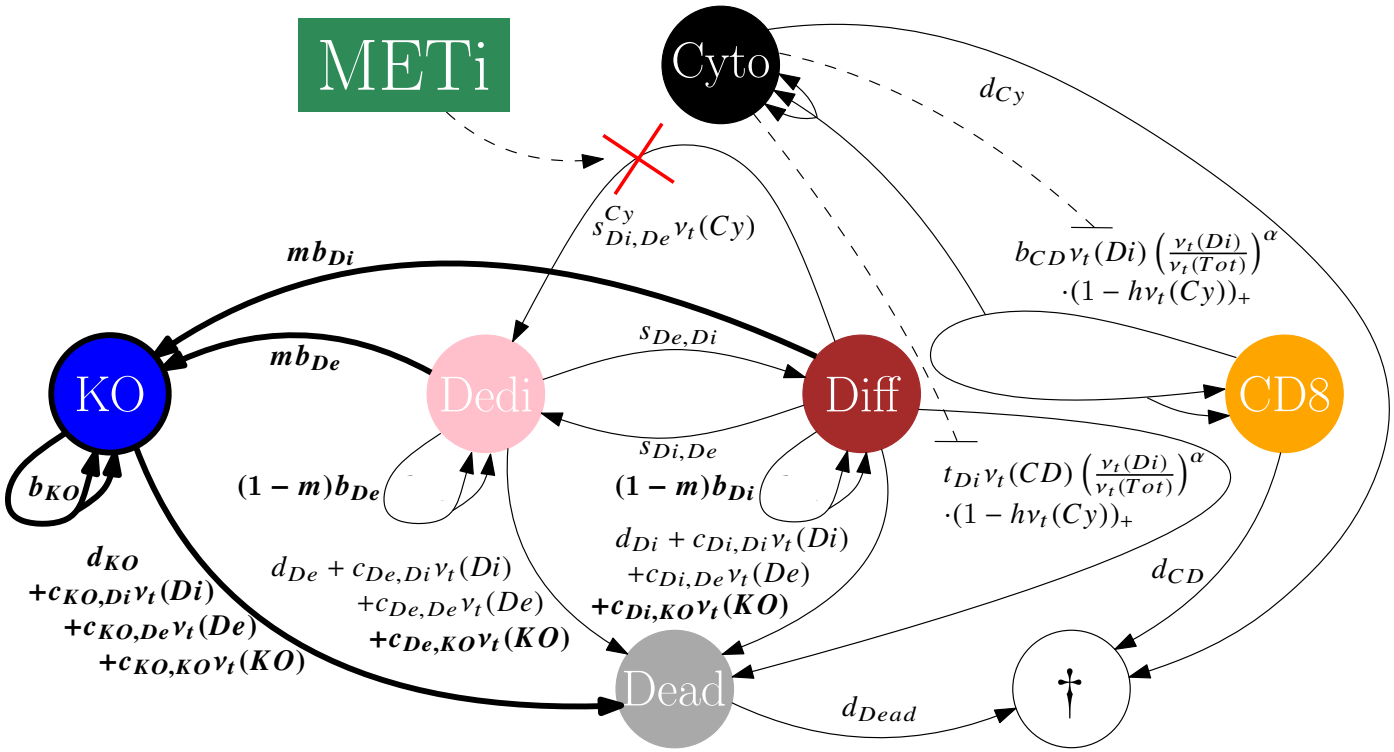

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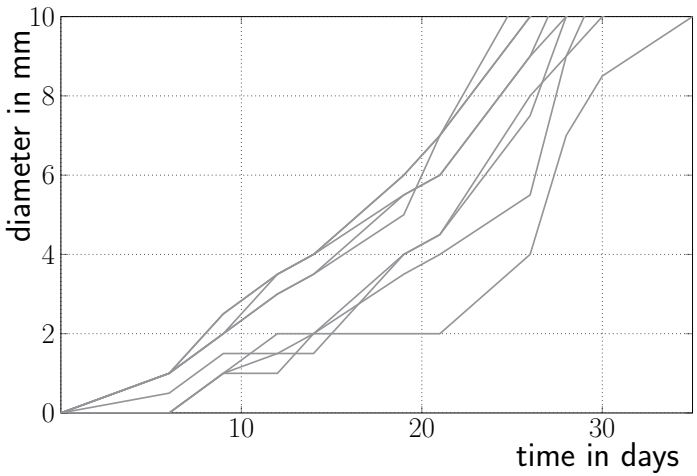
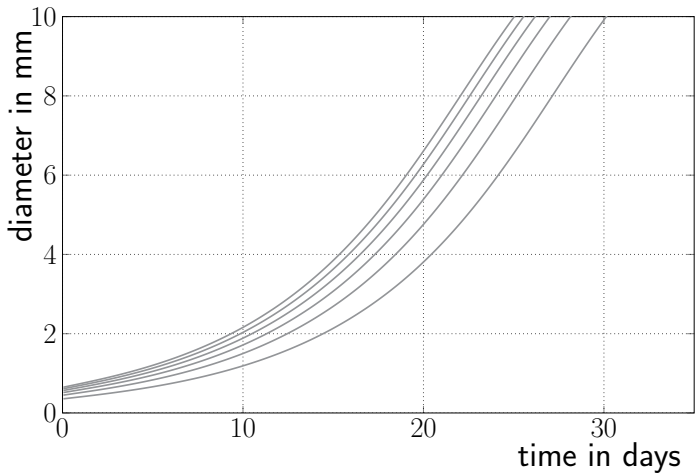

diameter in mm
time in days
0
2
4
6
8
10
10
20
30


diameter in mm
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0
2
4
6
8
10
0
10
20
30

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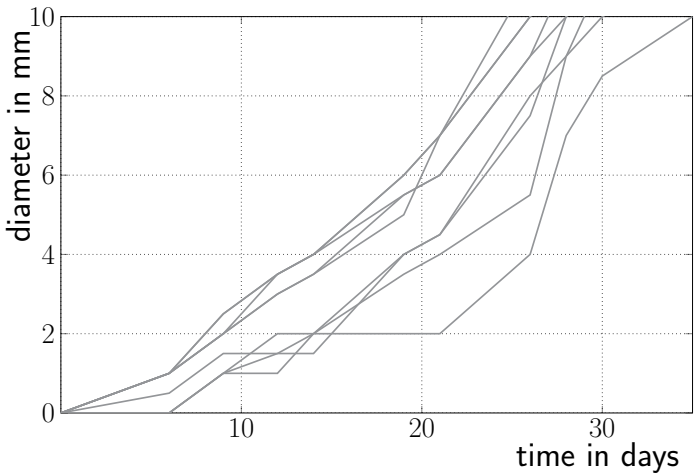

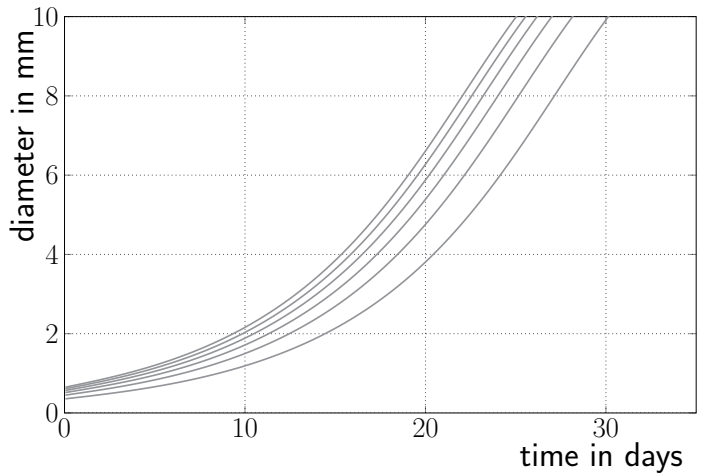

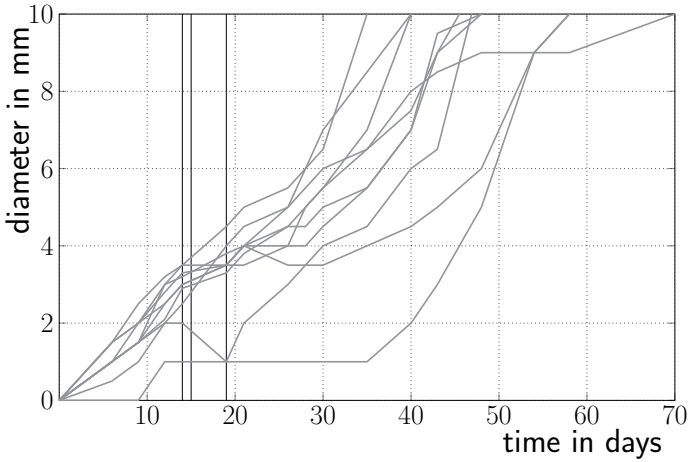

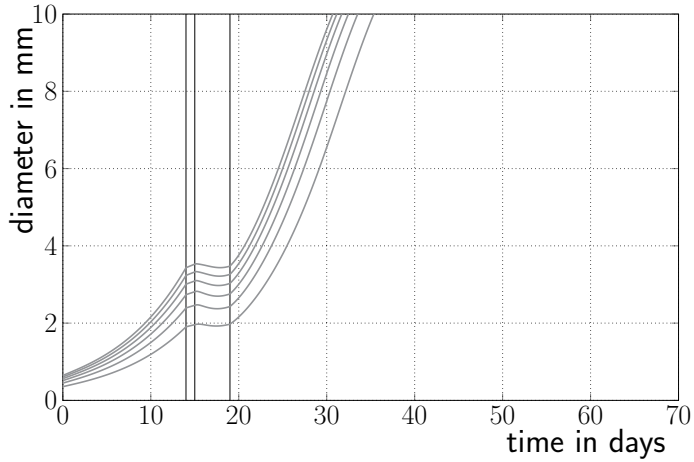

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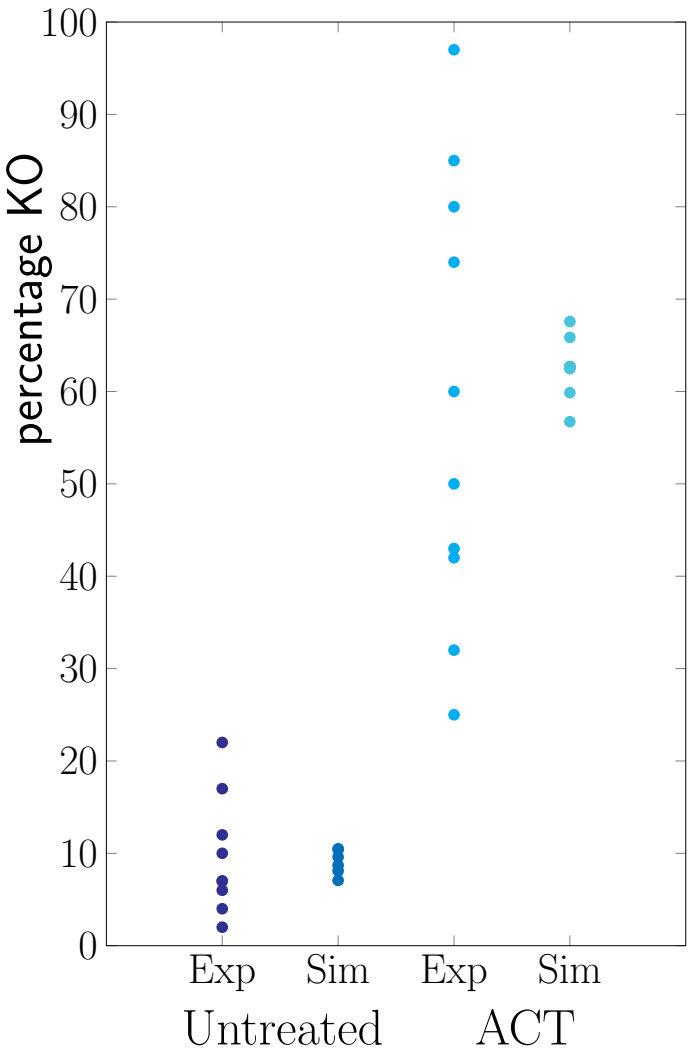
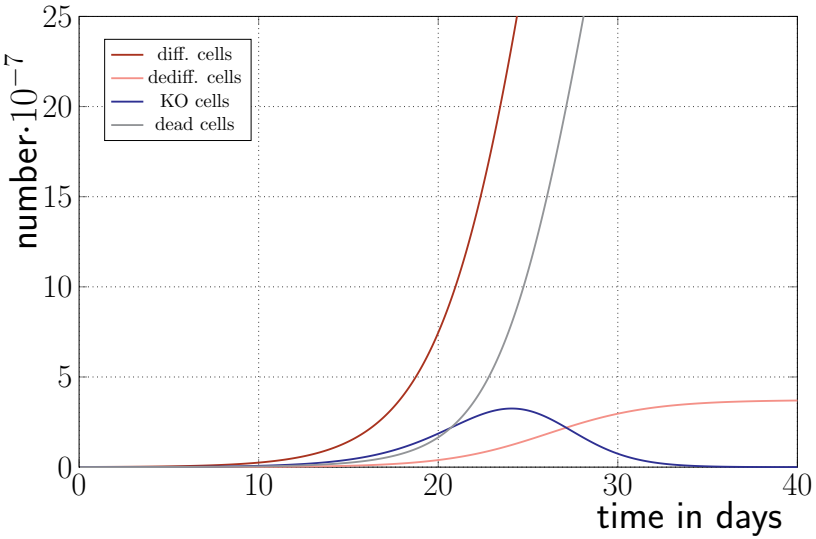
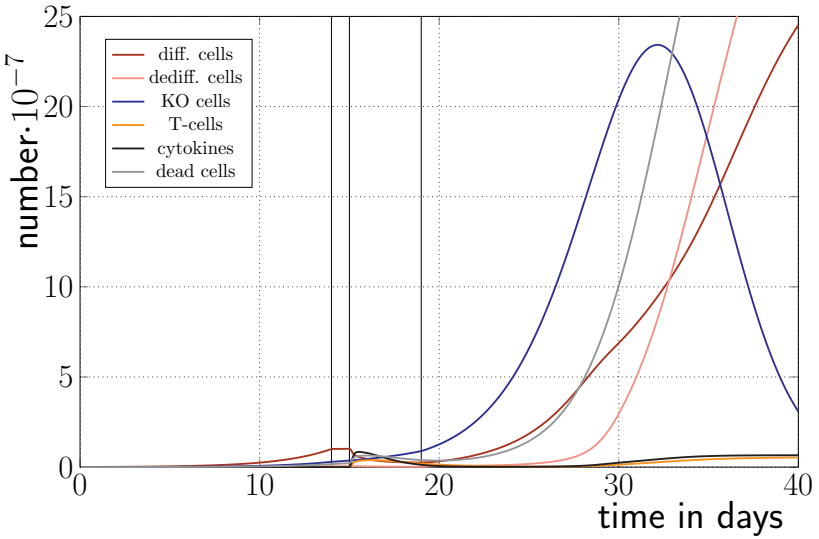

percentage KO
100
90
80
70
60
50
40
30
20
10
0
Exp
Sim
Exp
Sim
Untreated
ACT

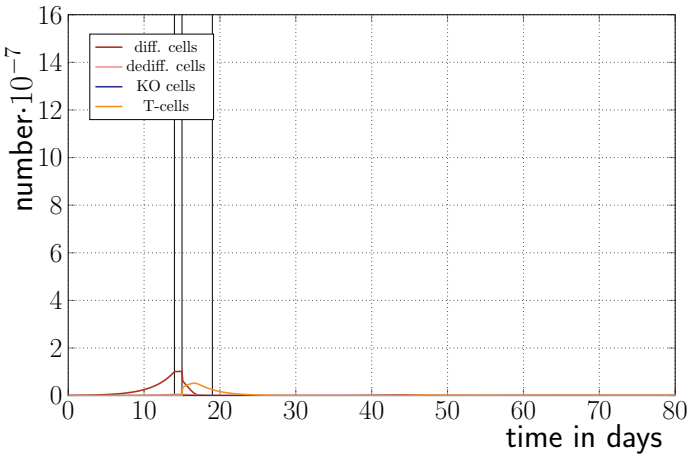
KO simulations

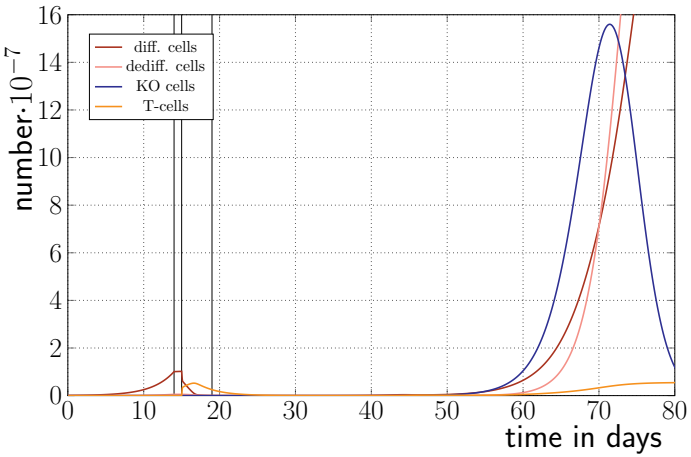




- Without treatment the knockout is suppressed by the wildtype
- Under therapy the knockout prevails
  - No competitive pressure when the wildtype is in remission

KO mutants, natural mutations





Conclusion

- Experimental data can be described by the probabilistic/deterministic model
- New key aspects have been identified: T-cell exhaustion, spatial structure
- Random fluctuations determine the success of therapy
- Phenotypic switch and genetic selection as mechanism to escape therapy

Thank you for your attention!


Baar M, Coquille L, Mayer H, Hölzel M, Rogava M, Tüting T and Bovier A.
A stochastic individual-based model for immunotherapy of cancer.
Scientific Reports 6, 24169 (2016)


Landsberg J, Kohlmeyer J, Renn M, Bald T, Rogava M, Cron M, Fatho M, Lennerz V, Wölfel T, Hölzel M and Tüting T.
Melanomas resist t-cell therapy through inflammation-induced reversible dedifferentiation. *Nature* 490:412–416 (2012)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Reactive neutrophil responses dependent on the receptor Tyrosine Kinase c-Met limit cancer immunotherapy.
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Plasticity of tumour and immune cells: a source of heterogeneity and a cause for therapy resistance? *Nat Rev Cancer* 13:365–376 (2013)

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