Dose and schedule -dependence of Antibody Dependent Cell-mediated Cytotoxicity (ADCC) capacity and efficiency

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on behalf of the ADCC in GlycoMabs working group

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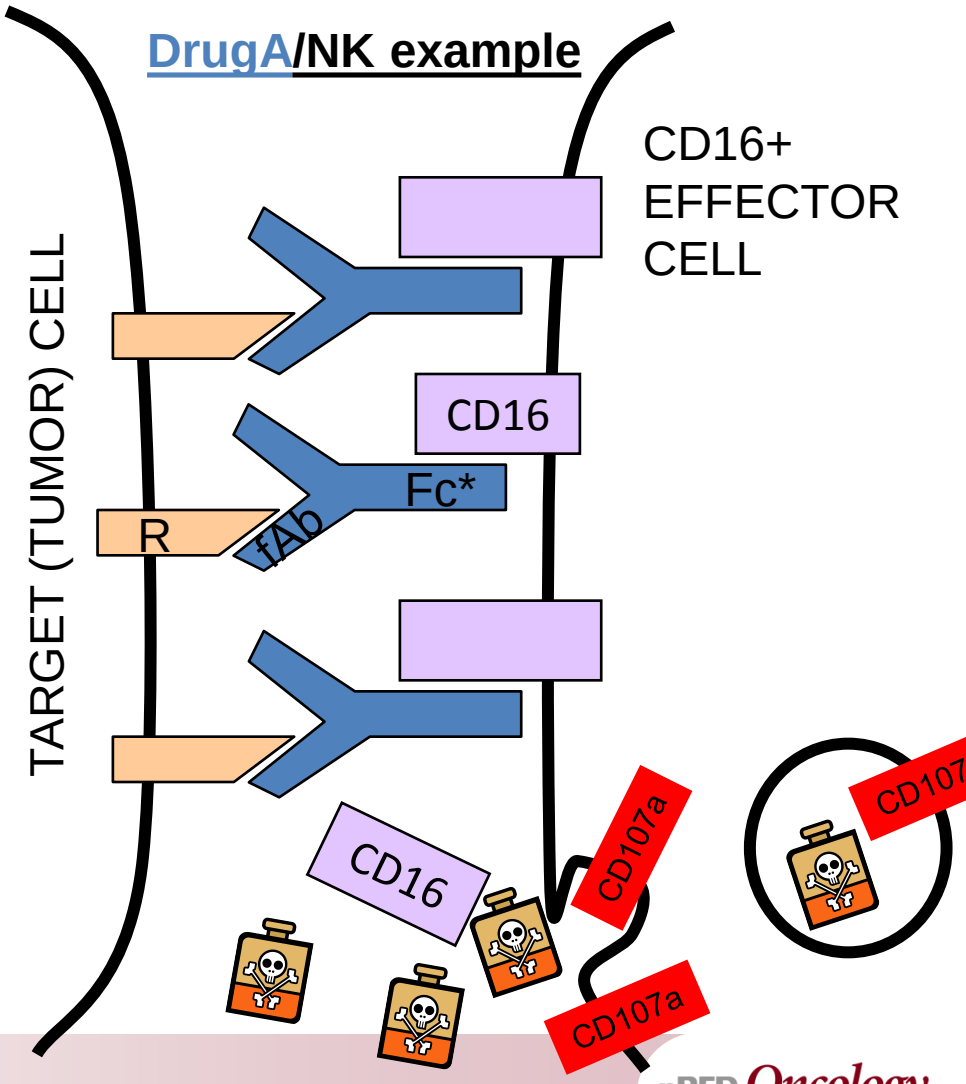
Acknowledgements & main collaborators

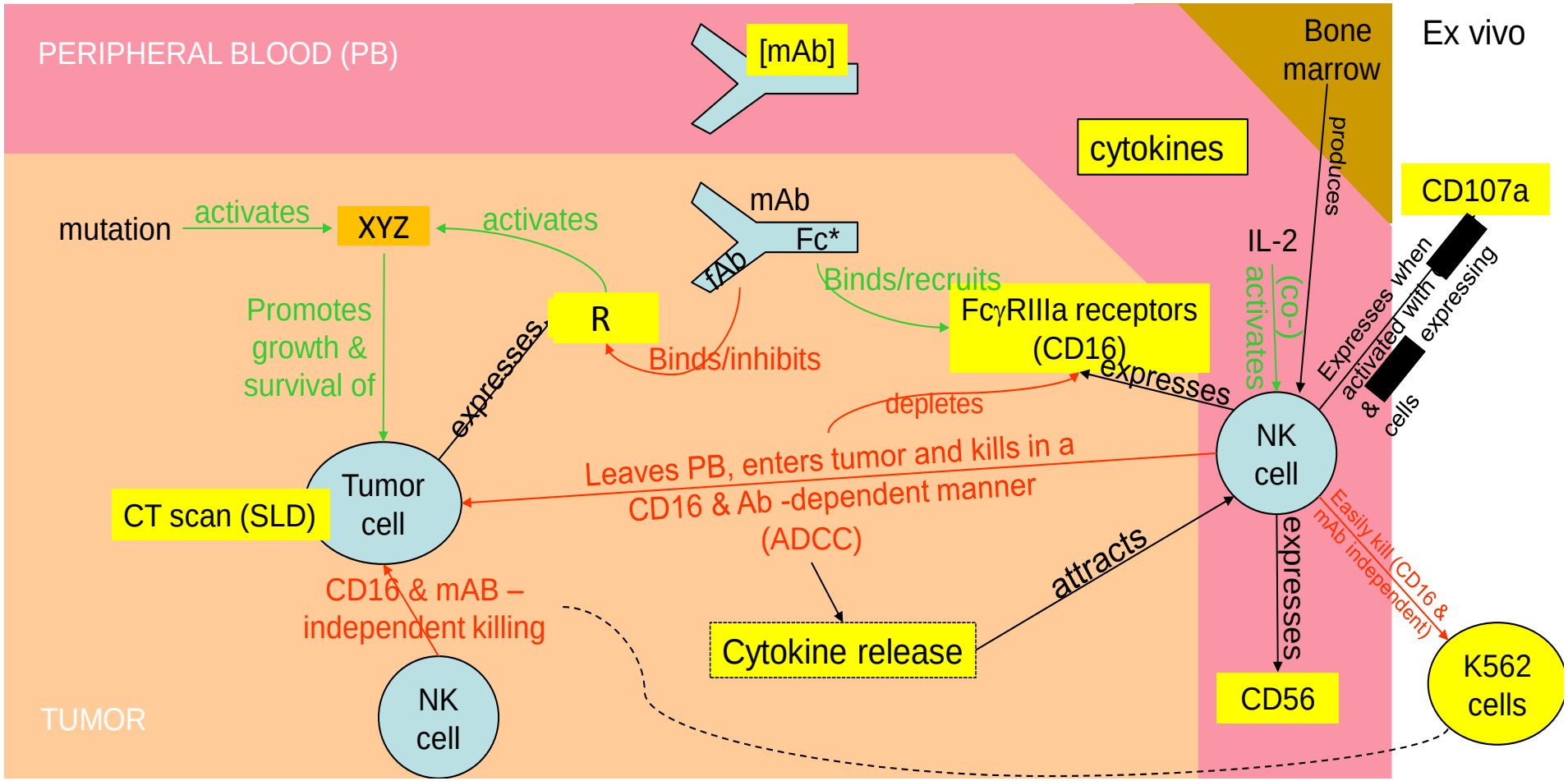
- **Sylvia Herter,** Roche Glycart cell biology
- **Marion Ott,** onc translational medicine
- **Marina Bacac,** Roche Glycart cell biology
- **Cheikh Diack,** clinical pharmacology
- **David Carlile,** clinical pharmacology
- **Eliezer Shochat,** clinical pharmacology
- **Alex Passioukov,** onc translational medicine

ADCC background/definitions

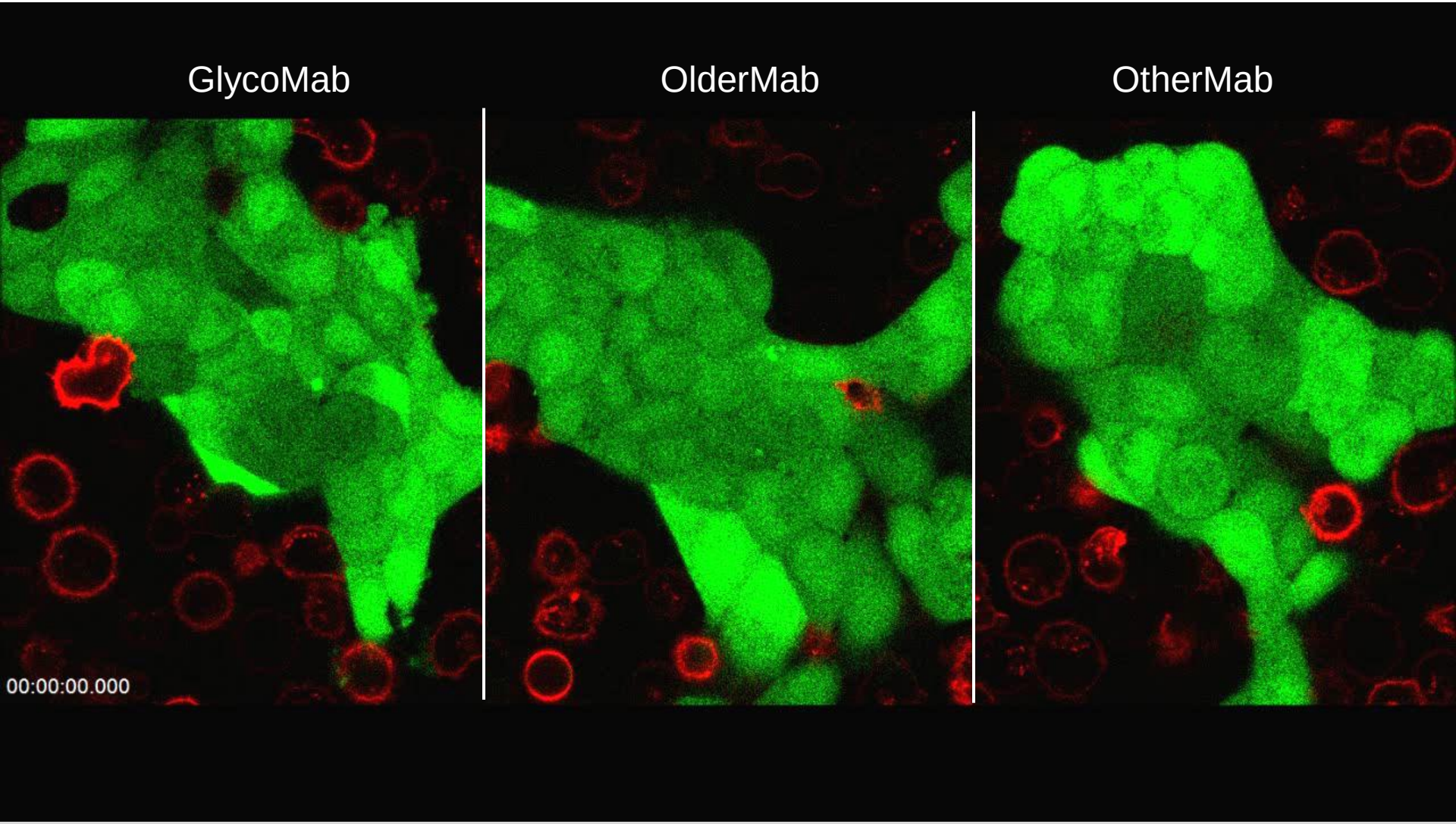
- ADCC = **A**ntibody **D**ependent **C**ell-mediated **C**ytotoxicity
- ADCC in cancer:
  1. mAb's variable region (fAb) binds to Receptor on tumor cell.
  2. A **N**atural **K**iller (NK) cell or **m**acro**ph**age (MΦ) binds to the mAb's Fc
  3. Release of cytotoxins and death of the target cell
- Many anti-signaling mAbs may also elicit ADCC
- Glycoengineering the Fc domain → ↑affinity to Fc receptors (FcγRIIIa = CD16) on NK & MΦ's



Graphical model of NK-mediated ADCC



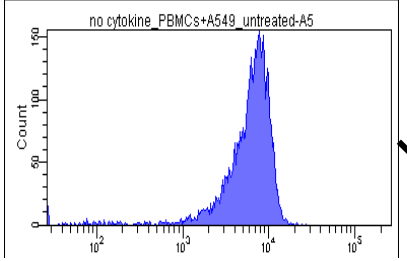
Comparison: ADCC induction by Glycomab vs other mAbs



Experimental Conditions:

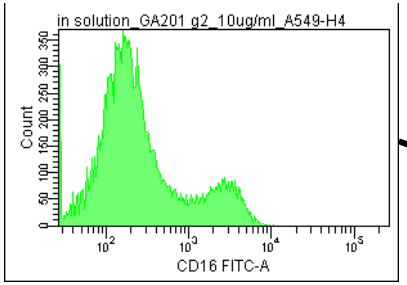
- T/E ratio = 1:2
- c [mAbs] = 200ng/ml
- YYY tumor cell labeled with green viability marker CMFDA (2µM for 30min prior to exp.)
- NK cells labbeled with red cell tracker PKH26 (2µM for 3 min)
- YYY cells grown on glass bottom culture dishes, then first add NK cells, wait a few min, then add antibody)
- Experiments performed by O. Mundigl, PLBDB

Kinetics of CD16 expression recovery after ADCC (From S. Herter & M. Bacac)

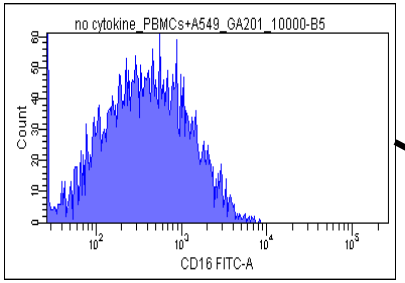


before ADCC T<0

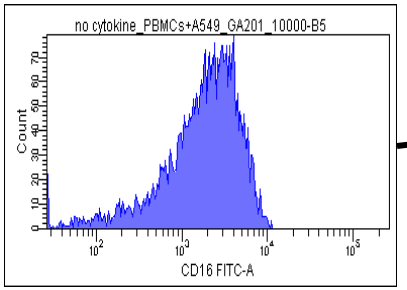
X axis = intensity ~ # of receptors/cell



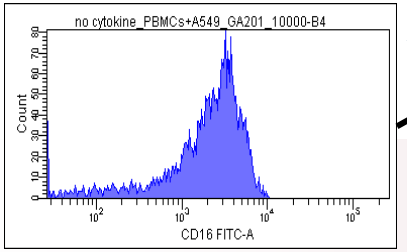
ADCC 3h



25 h



47 h



73 h

T<<0

T=0

T=3h

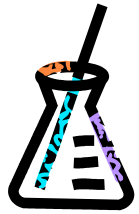
T=25h

T=47h

T=73h

Donor provides 2ml blood, PBMC's isolated

PBMC's put in medium with XXX (target) cells and DrugA



PBMC's washed (Drug A and XXX removed)

PBMC's "recover" from ADCC

Gating color code

GREEN = "P2" = $CD3^{-}/CD56^{dim}$ ('worker' NKs)

BLUE = "P3" = $CD3^{-}/CD56^{dim}/PI^{-}$ (still alive)

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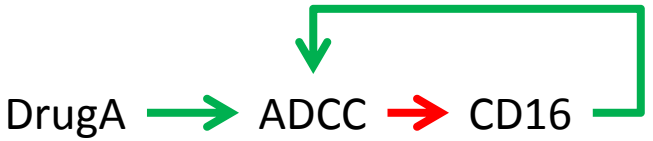
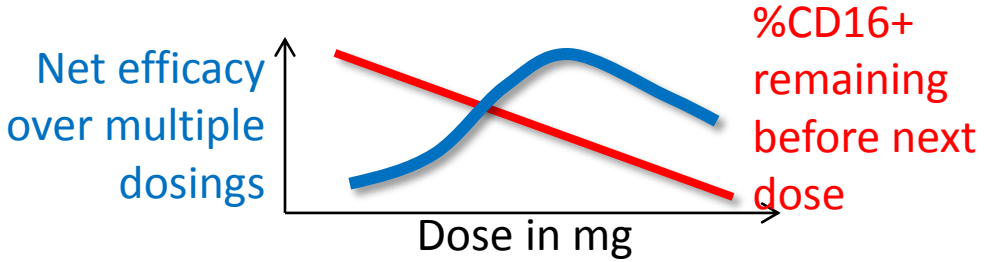
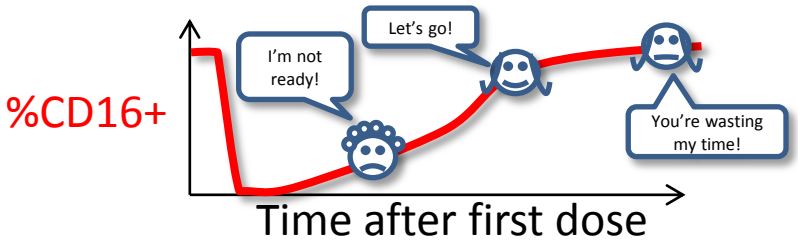
Motivating clinical questions

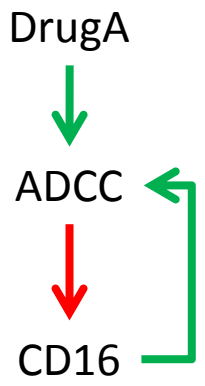
- Given that:
  - DrugA stimulates ADCC
  - ADCC transiently depletes CD16 on effector cells
  - CD16 is required for ADCC
- Can a lower DrugA dose actually give us better anti-tumor efficacy than a higher dose?
- Can a longer gap between DrugA doses give us better anti-tumor efficacy?
- Can we lower the dose from the recommended dose without losing efficacy?







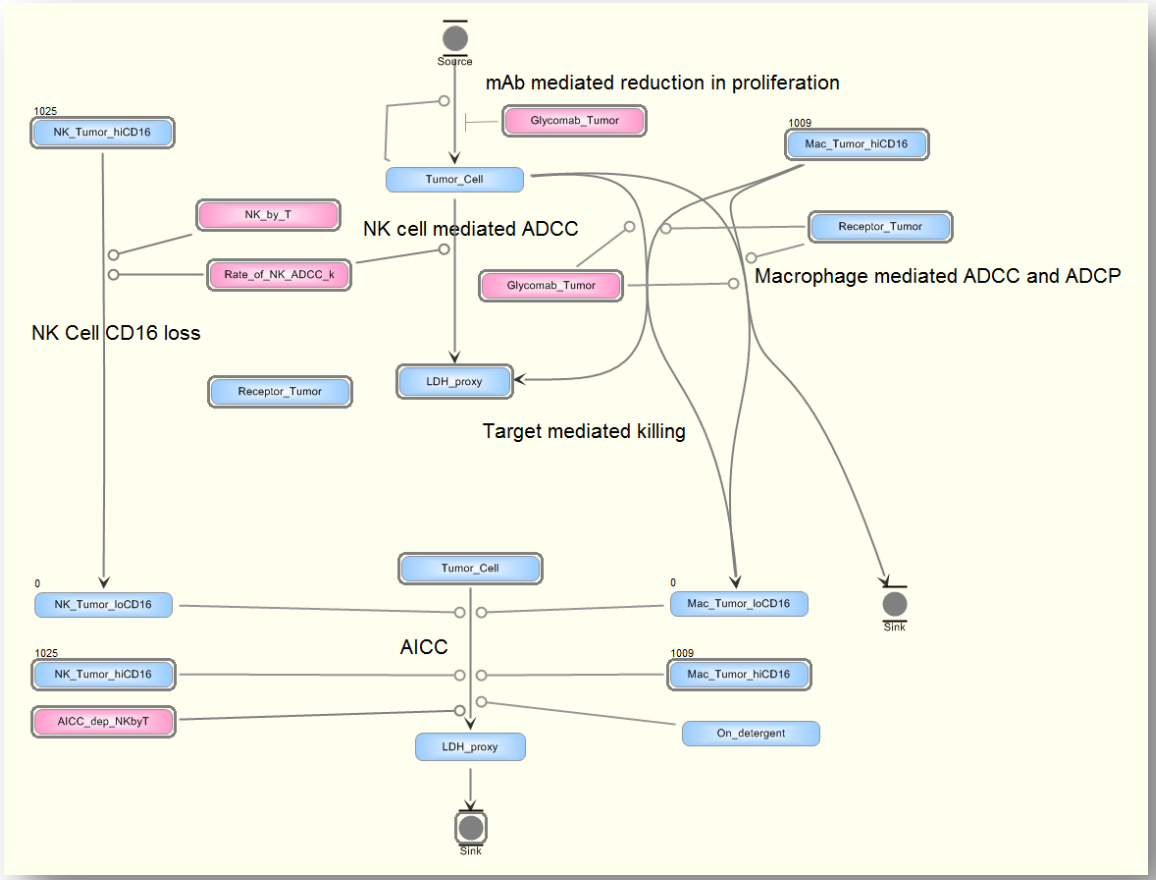
Related modeling questions

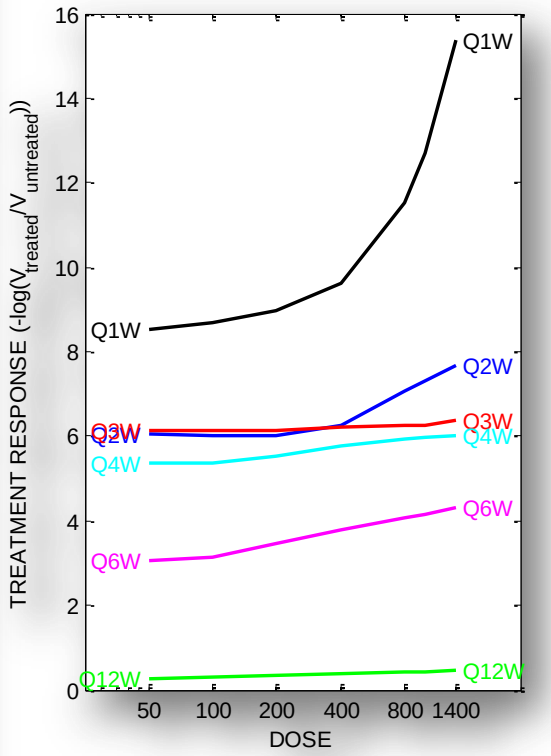


- Given a mathematical model based on:
  - In vitro concentration-dependent % ADCC killing data
  - In vitro %CD16+ depletion & recovery kinetic observations
  - In vitro "second ADCC" cell killing observations
  - Clinical DrugA population PK modeling
- Are there any physiologically reasonable parameter ranges for which the model predicts:
  - A bell-shaped dose-efficacy relationship?
  - Better efficacy from a longer dosing interval?
- If the model can be qualified for this purpose, is the predicted dose-response relationship flat in the dose range of interest?
- What are the major drivers of efficacy? Is dose one of them?

Let's ask the mechanistic model…

…developed in collaboration with Rosa Drug Development Partners





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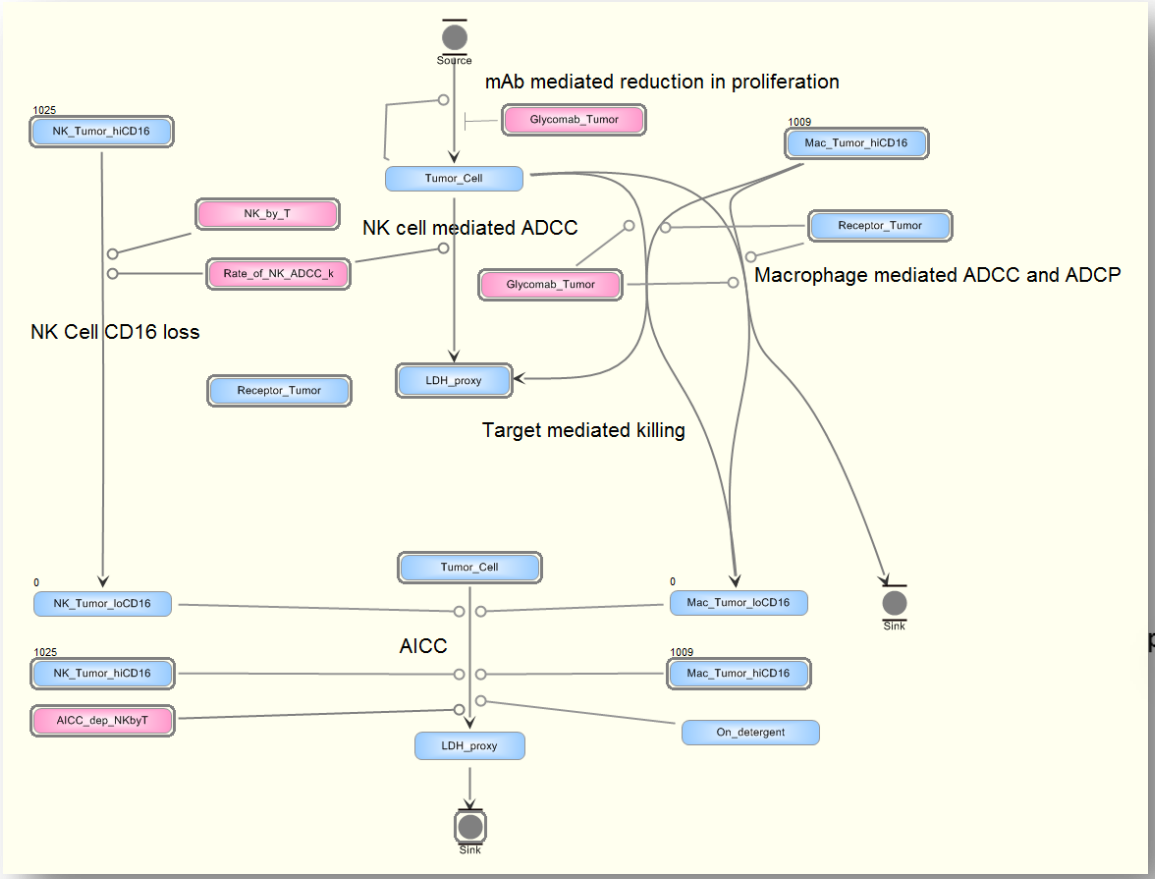
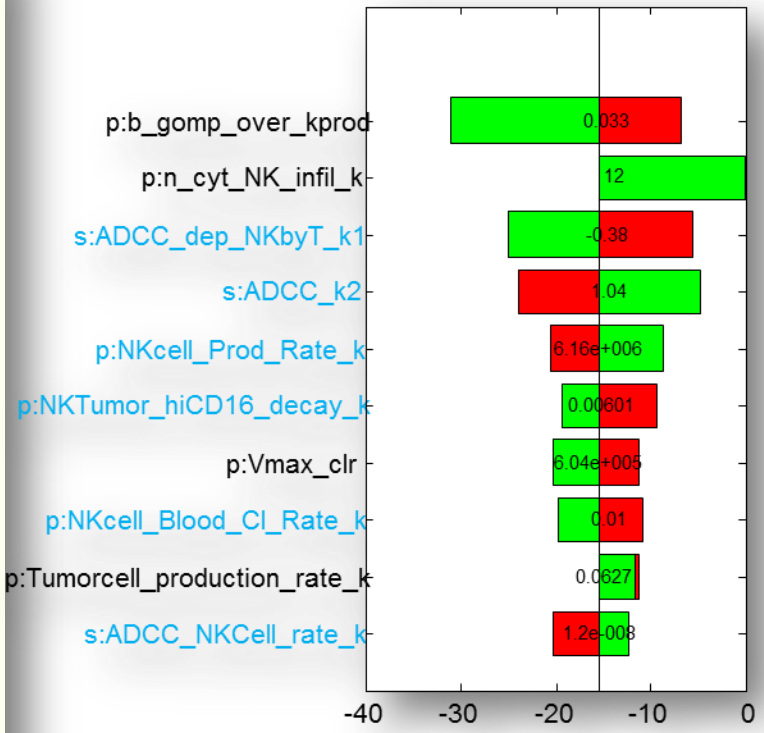
Sensitivity analysis points to key ADCC parameters and processes requiring further investigation





Predicted tumor volume change relative to untreated

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WorkFlow

1. Specify structural model & assumptions
2. Using data from in vitro assays with HV blood:
    1. Fit to ADCC & CD16 [DrugA]-response data
    2. Fit to ADCC & CD16 kinetic/recovery data (not yet done)
    3. Predict 2nd ADCC experiments, compare to data
3. Extrapolate to clinical scenario:
    1. Use popPK model & additional assumptions to predict $M(t)=[DrugA]_{tumor}$ over a range of doses & schedules
    2. Use M(t) to 'drive' in vitro ADCC model & predict %CD16+ and tumor kill kinetics over several cycles
4. Assess whether bell-shaped dose-efficacy is predicted or whether waiting longer between doses is predicted to increase efficacy

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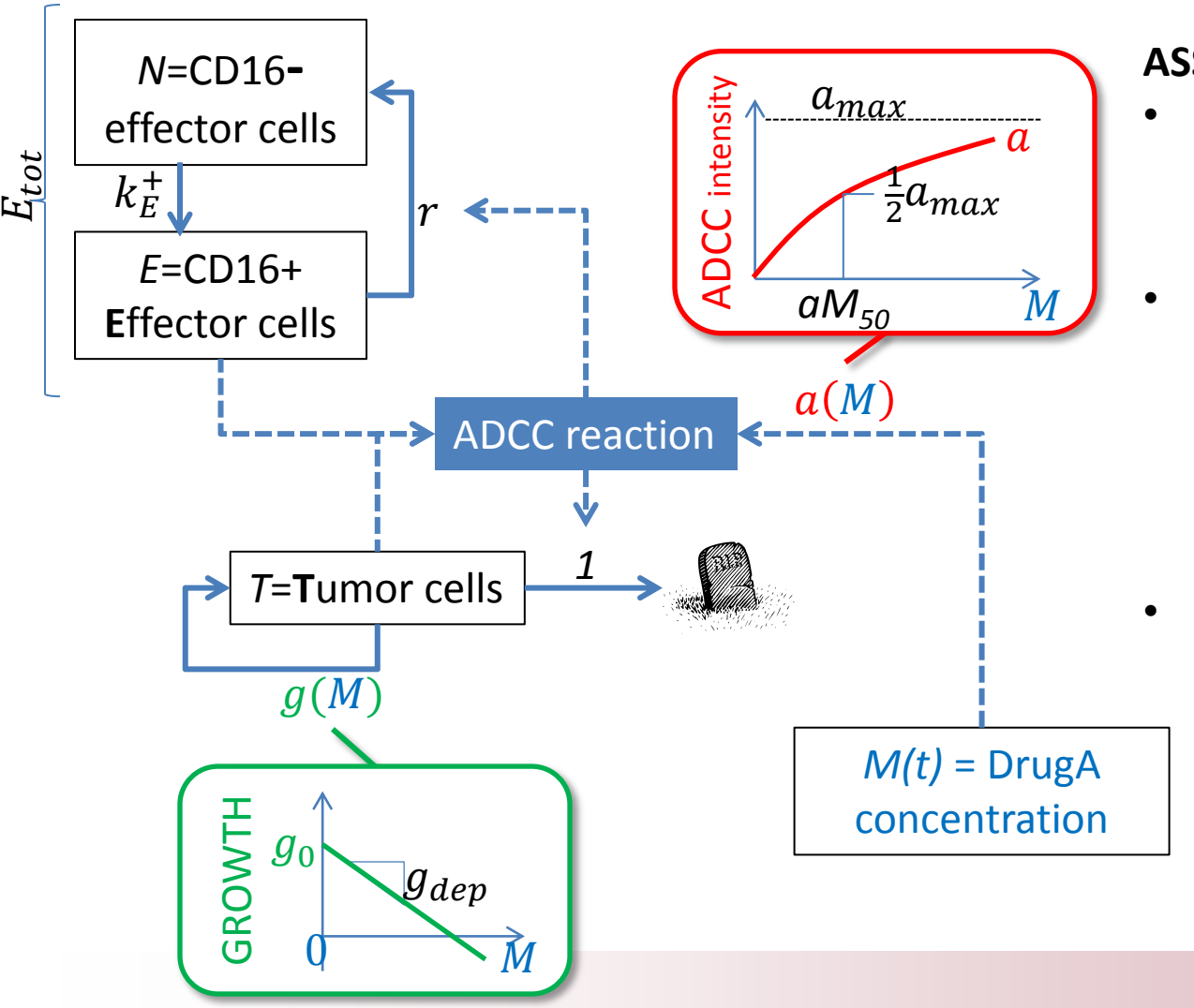
Simple cellular ADCC model: schematic



ASSUMPTIONS

- CD16+ effector cells (E) are produced/recover at a constant rate kE+. N+E = E_{tot} assumed constant.
- Absent ADCC, tumor cells (T) proliferate exponentially at a net rate g, which can be attenuated by Receptor inhibition as a function of [mAb]=M. AICC effects are implicit in g_0.
- In the presence of E and mAb, ADCC can occur at an [mAb]=M dependent rate $a(M(t))ET$. Each ADCC reaction results in loss of one tumor cell and *r* CD16+ effector cells.

Simple cellular ADCC model: equations pre-treatment

$$N = E_{tot} - E$$

First order conversion of CD16- to CD16+ cells

Rate of change of CD16+ **E**ffector cells

$$\frac{dE}{dt} = (E_{tot} - E)k_E^+$$

Rate of change of **T**umor cells

$$\frac{dT}{dt} = g_0 T$$

Exponential tumor growth

Simple cellular ADCC model: equations on DrugA treatment

First order conversion of CD16- to CD16+ cells

Loss of CD16+ cells (to CD16-) due to ADCC

Rate of change of CD16+ **E**ffector cells

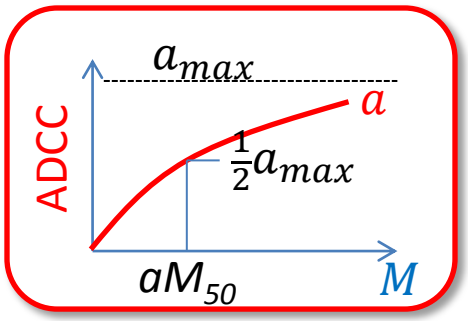
$$\frac{dE}{dt} = (E_{tot} - E)k_E^+ - ra(M(t))E^rT$$

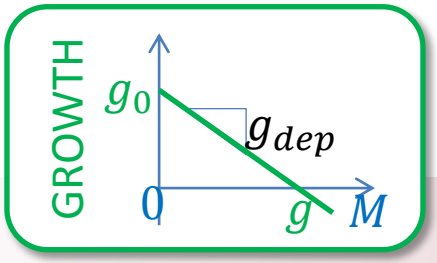
Rate of change of **T**umor cells

$$\frac{dT}{dt} = g(M(t))T - a(M(t))E^rT$$

Exponential tumor growth

Loss of tumor cells due to ADCC = "ADCC rate" or R_{ADCC}





M(t) = DrugA concentration

Simple cellular ADCC model: equations on DrugA treatment in XYZ^{mut}

First order conversion of CD16- to CD16+ cells

Loss of CD16+ cells (to CD16-) due to ADCC

Rate of change of CD16+ **E**ffector cells

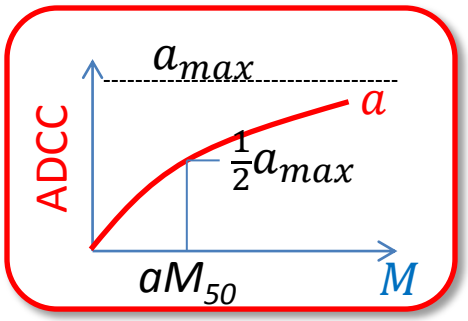
$$\frac{dE}{dt} = (E_{tot} - E)k_E^+ - ra(M(t))E^rT$$

Rate of change of **T**umor cells

$$\frac{dT}{dt} = g_0T - a(M(t))E^rT$$

Exponential tumor growth unaffected by [mAb] in XYZ mutant setting

Loss of tumor cells due to ADCC = "ADCC rate" or R_{ADCC}



M(t) = DrugA concentration

Variables & parameters

$$\frac{dE}{dt} = (E_{tot} - E)k_E^+ - ra\big(M(t)\big)E^rT$$

$$\frac{dT}{dt} = g(M(t))T - a\big(M(t)\big)E^rT$$

	alias	Description	Units
E	E	#/vol of CD16+ **E**ffector cells (state variable)	Cells (/vol)
T	T	#/vol of viable **T**umor (target) cells (state variable)	Cells (/vol)
$M(t)$	mab	**m**Ab concentration in tumor as function of time	ng/ml
E_{tot}	Etot	Total number of (CD16+ and CD16-) effector cells	Cells (/vol)
k_E^+	kEprod	Production/recovery rate of CD16+ Effector cells	1/day
r	r	**R**atio: # of CD16+ cells depleted per tumor cell killed	1
a_{max}	amax	**Max**imum **A**DCC intensity as $M \to \infty$	1/(cells x day)
am_{50}	am50	**m**Ab concentration giving **50**% of max **A**DCC intensity	ng/ml
g_0	g0	Intrinsic tumor **g**rowth rate (including AICC offset)	1/day

Summary of model assumptions

- **Closed system:** Effector cells are neither destroyed nor replaced
- **ADCC interaction:** ADCC occurs when r (r~1) CD16+ cells encounter a tumor cell in the presence of mAb and cytokines. A single ADCC reaction kills one tumor cell and converts r CD16+ cells to CD16-.
- **CD16 Recovery:**
  - CD16- cells can return to CD16+ (1^{st} order).
  - CD16-/+ gating equivalent to ADCC incompetence/competence

This system of ODE's exhibits bi-stable behavior depending on the ratio ϕ of tumor growth rate g_0 to ADCC intensity a and total effector cell number E_{tot}

Nondimensionalized ODEs (r=1):

$$\frac{de}{d\tau} = 1 - e - \gamma_1 eu$$

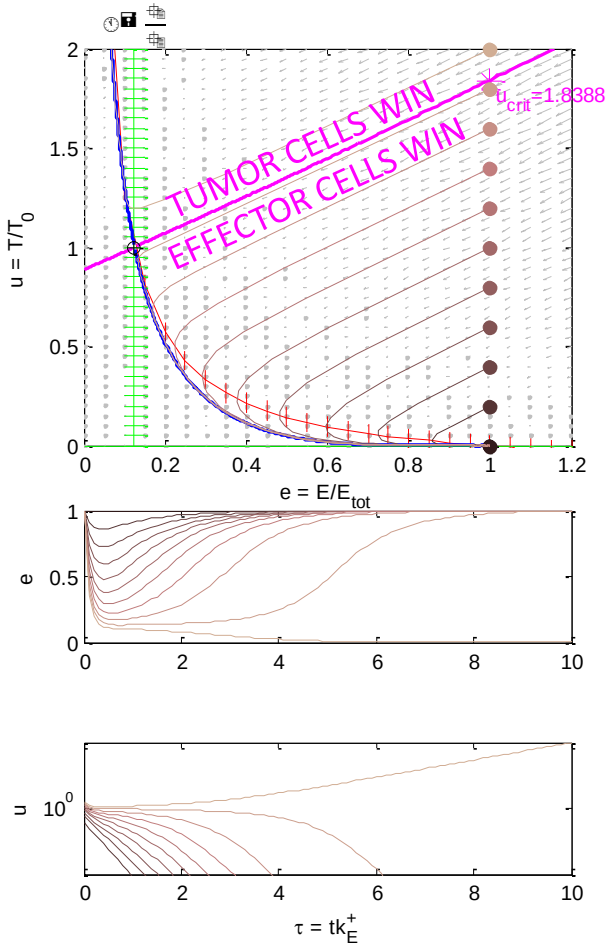
$$\frac{du}{d\tau} = \gamma_2 u - \gamma_3 eu$$

Where:

$$e = \frac{E}{E_{tot}}, u = \frac{T}{T_0}, \tau = k_E^+ t,$$

$$\gamma_1 = \frac{aT_0}{k_E^+}, \gamma_2 = \frac{g_0}{k_E^+}, \gamma_3 = \frac{aE_{tot}}{k_E^+}$$

System behavior is highly sensitive to $\phi \equiv \frac{\gamma_2}{\gamma_3} = \frac{g_0}{aE_{tot}}$



WorkFlow

1. Specify structural model & assumptions
2. Using data from in vitro assays with HV blood:
   1. Fit to ADCC & CD16 [DrugA]-response 4h ADCC data
   2. Fit to ADCC & CD16 kinetic/recovery data
   3. Predict 2nd ADCC experiments, compare to data
3. Extrapolate to clinical scenario:
   1. Use popPK model & additional assumptions to predict M(t)=[DrugA]$_{tumor}$ over a range of doses & schedules
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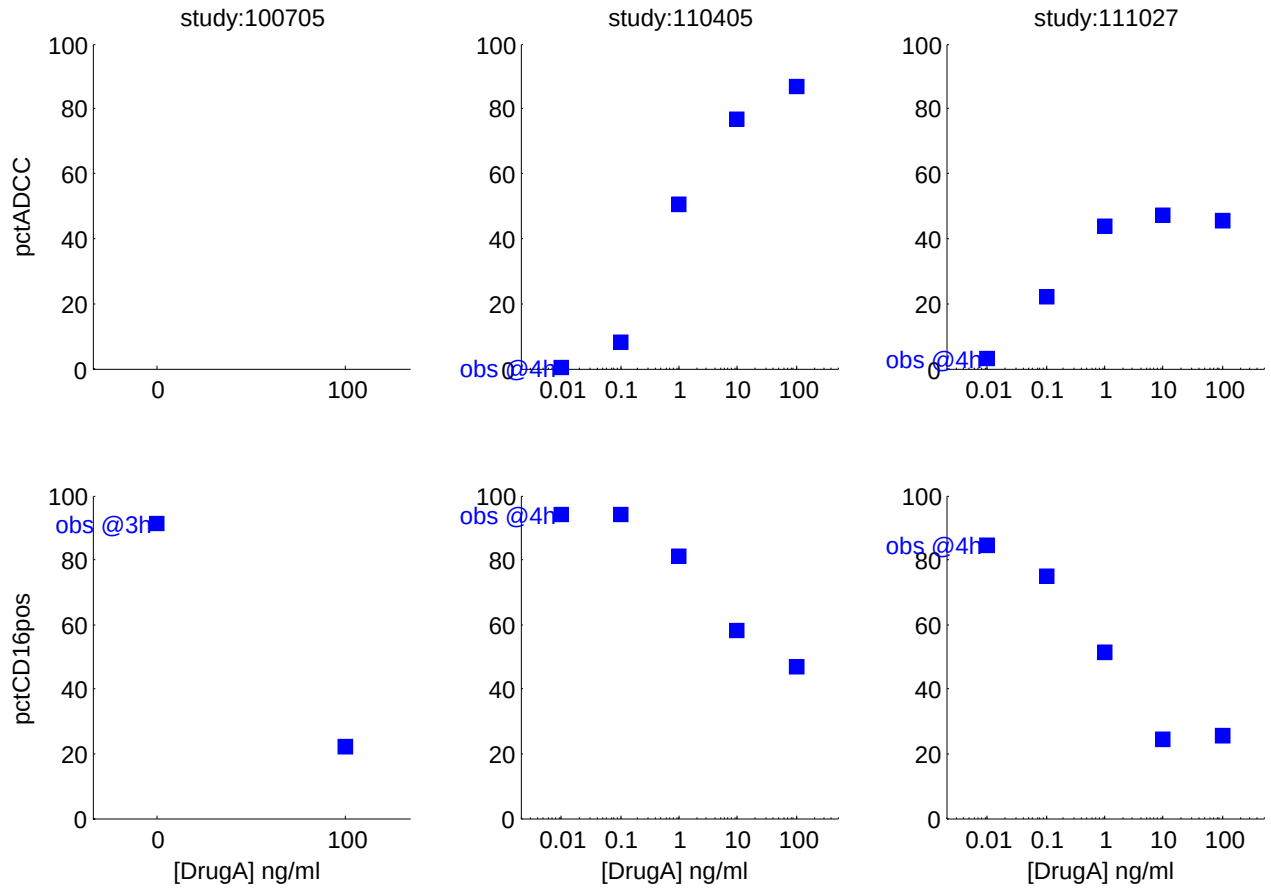
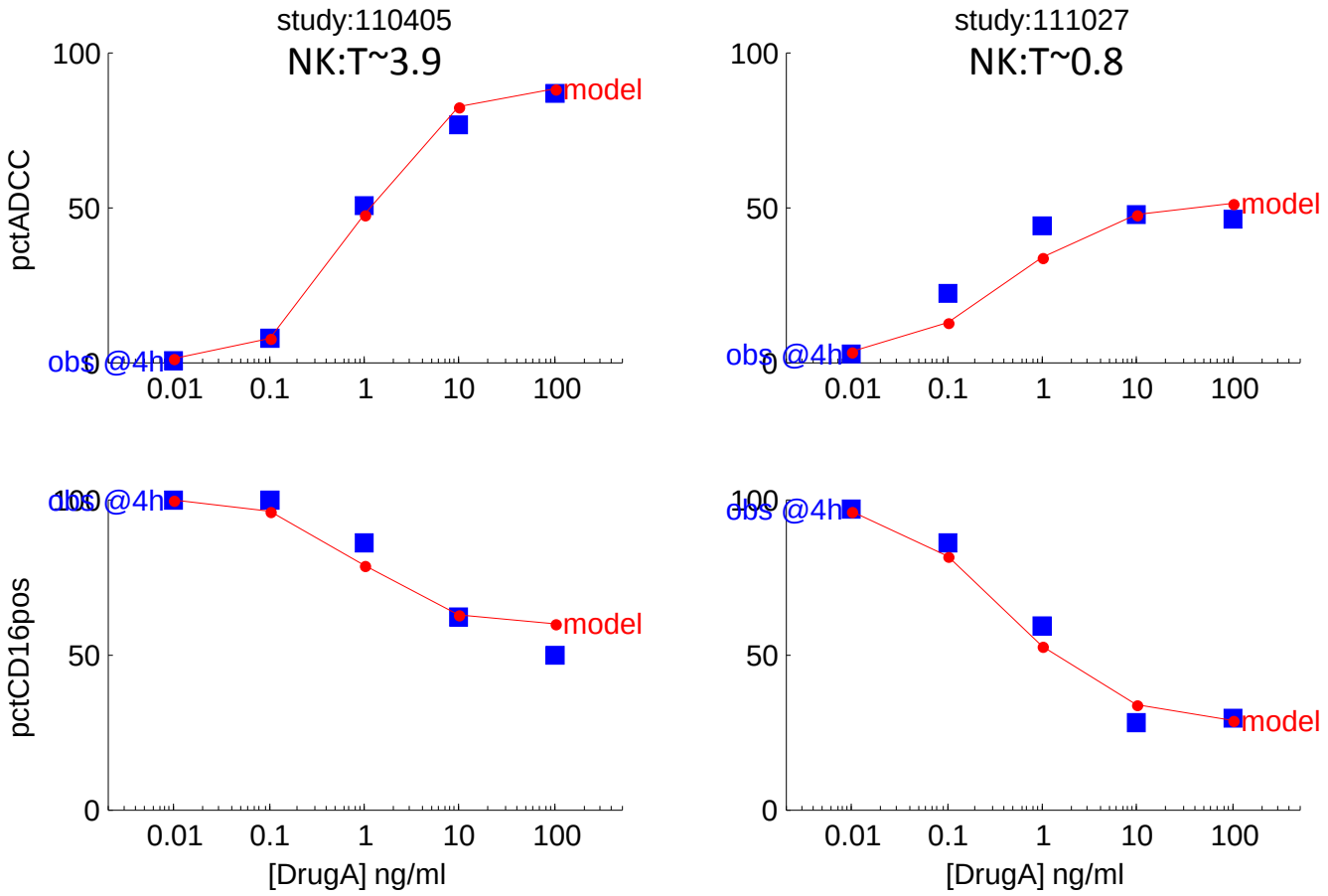
In vitro %ADCC %CD16+ assay probes [DrugA]-dependence of cell killing & CD16 depletion

- PBMCs from healthy volunteers incubated with (XYZ^{mut}) cells in presence of DrugA with NK:T ~ (2.5 & 1) for 4h.
- $\%ADCC \equiv 100 \frac{LDH_{exper} - LDH_{spont}}{LDH_{max} - LDH_{spont}}$
  - "experimental" is with given [DrugA] in presence of effector cells
  - "Spontaneous" is in presence of effector cells but no DrugA (~AICC)
  - "Maximal" is detergent treated
- $\%CD16^{+} \equiv \frac{E(4h)}{E_{tot}}$ gives fraction of (NK) cells that are CD16 positive (rel to gate).

After 3-4h of incubation, %ADCC increases while %CD16+ decreases with increasing [DrugA]



The model parameters can be adjusted to simultaneously reproduce the observed in vitro concentration-response of %ADCC and %CD16+



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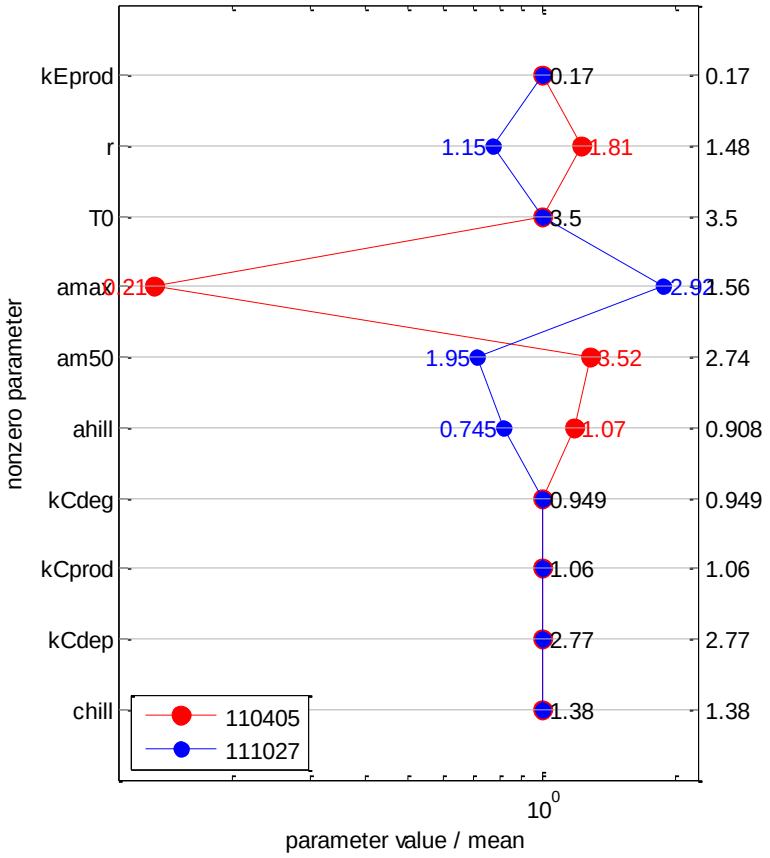
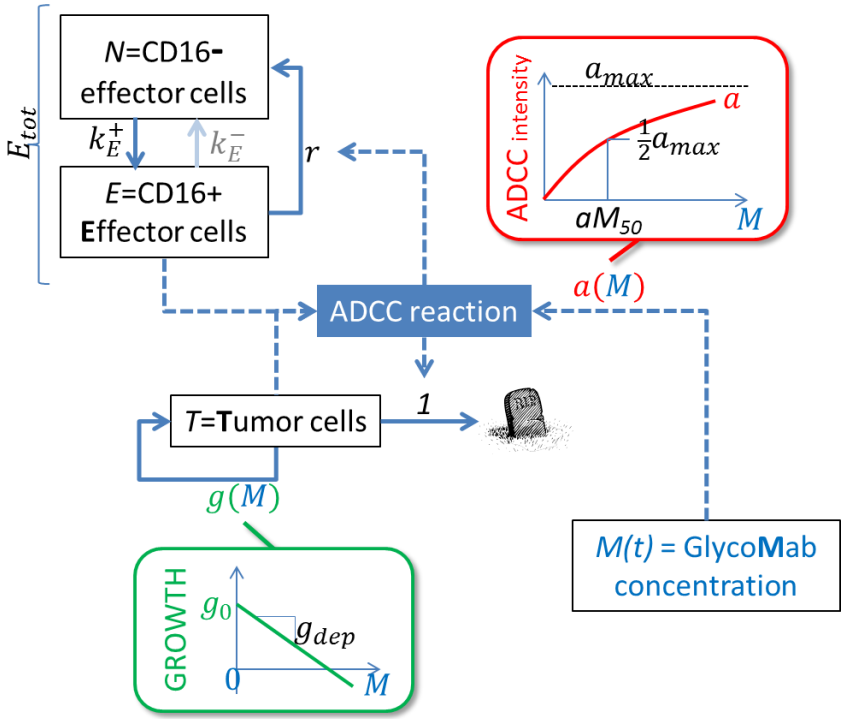
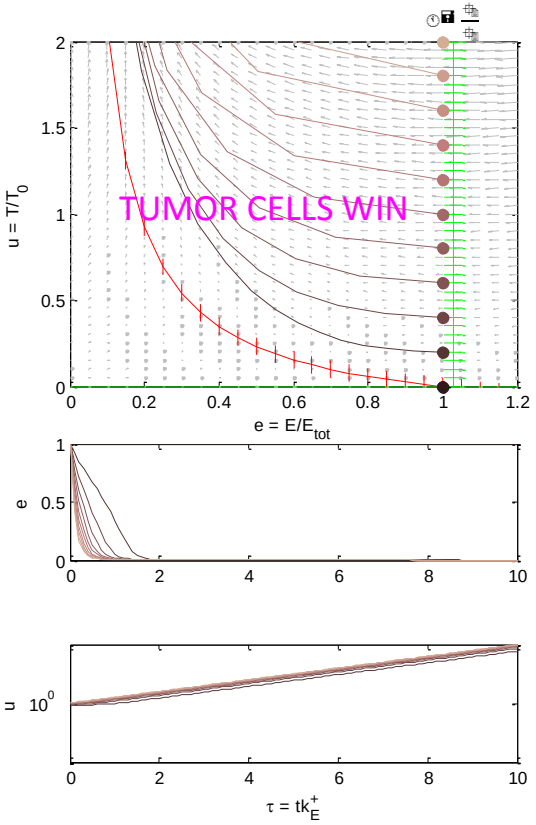
Parameter estimates (least squares followed by shrinking step)





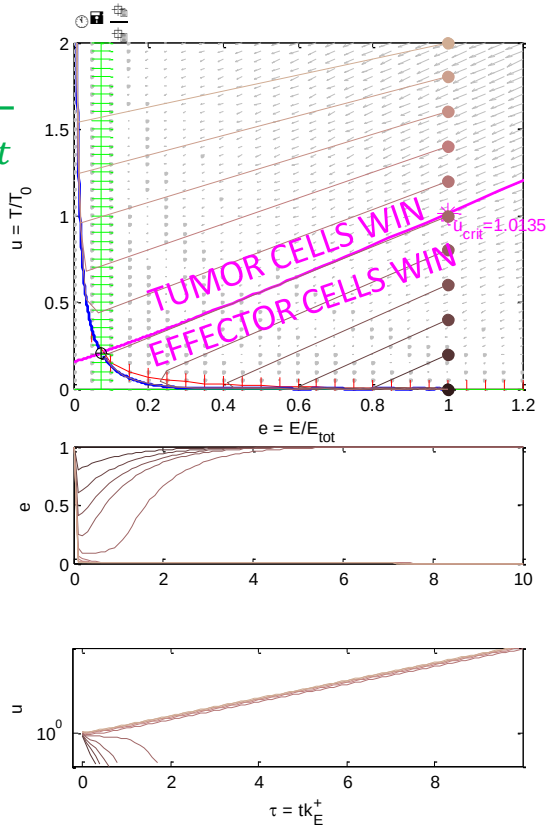
Stability analysis using parameter estimates from in vitro assays (at $a=a_{max}$, NK:T~1)

110405 (ϕ=1.03)

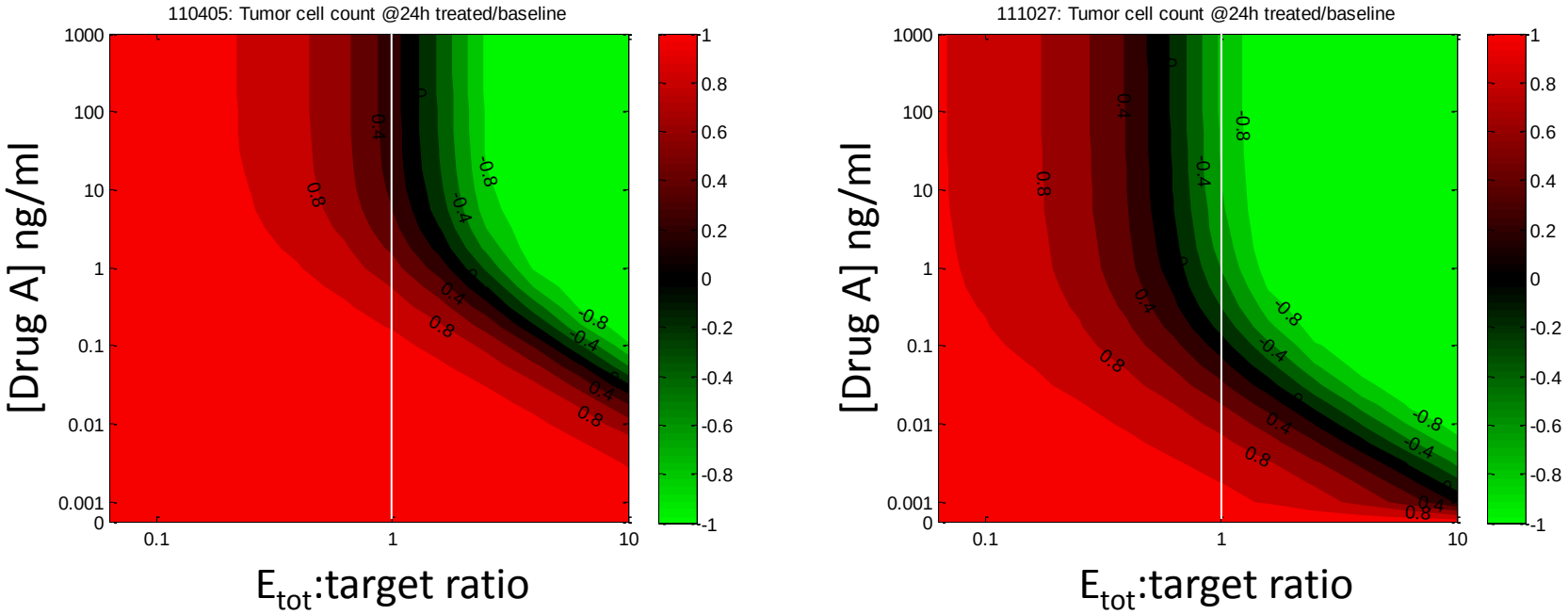


$$\phi \equiv \frac{\gamma_2}{\gamma_3} = \frac{g_0}{aE_{tot}}$$

111027 (ϕ=0.07)

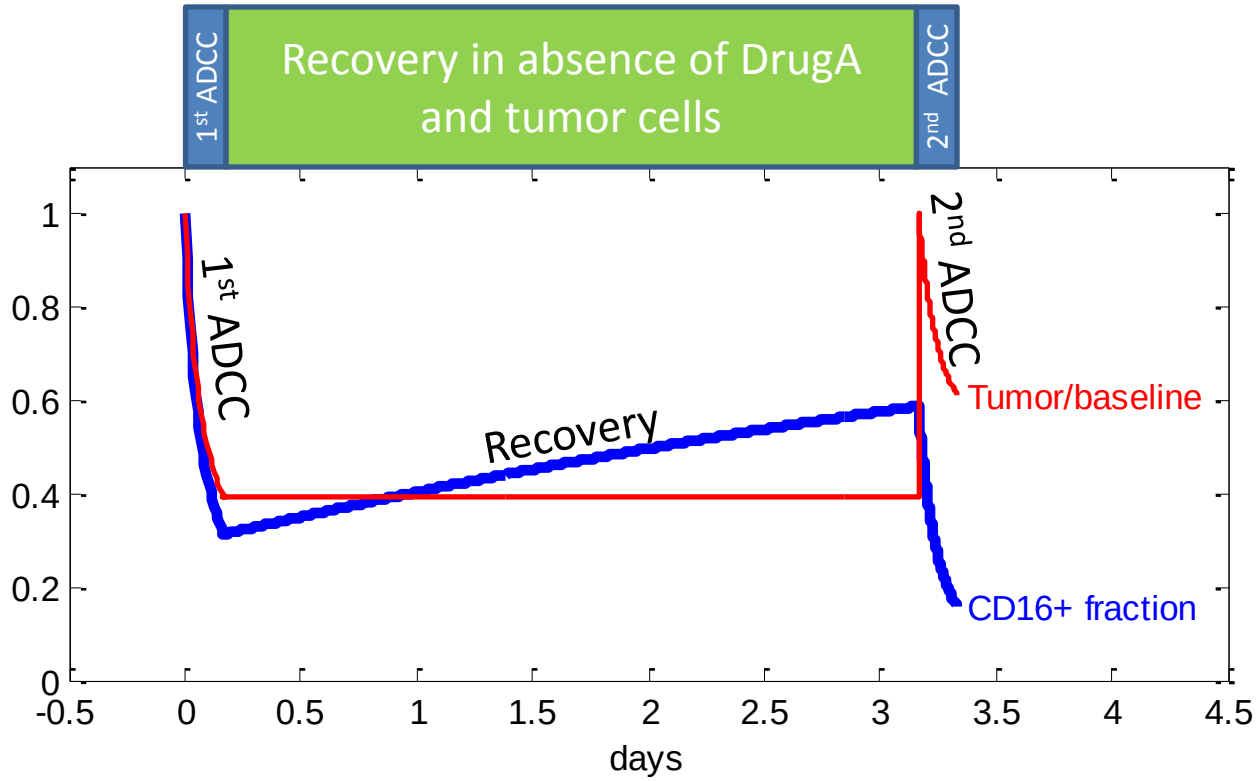


Simulated E:T & exposure dependence (24h incubation)



24h simulated incubation
22h doubling time assumed
No effect on growth, ADCC only

2nd ADCC experiments & simulations



Second ADCC simulations

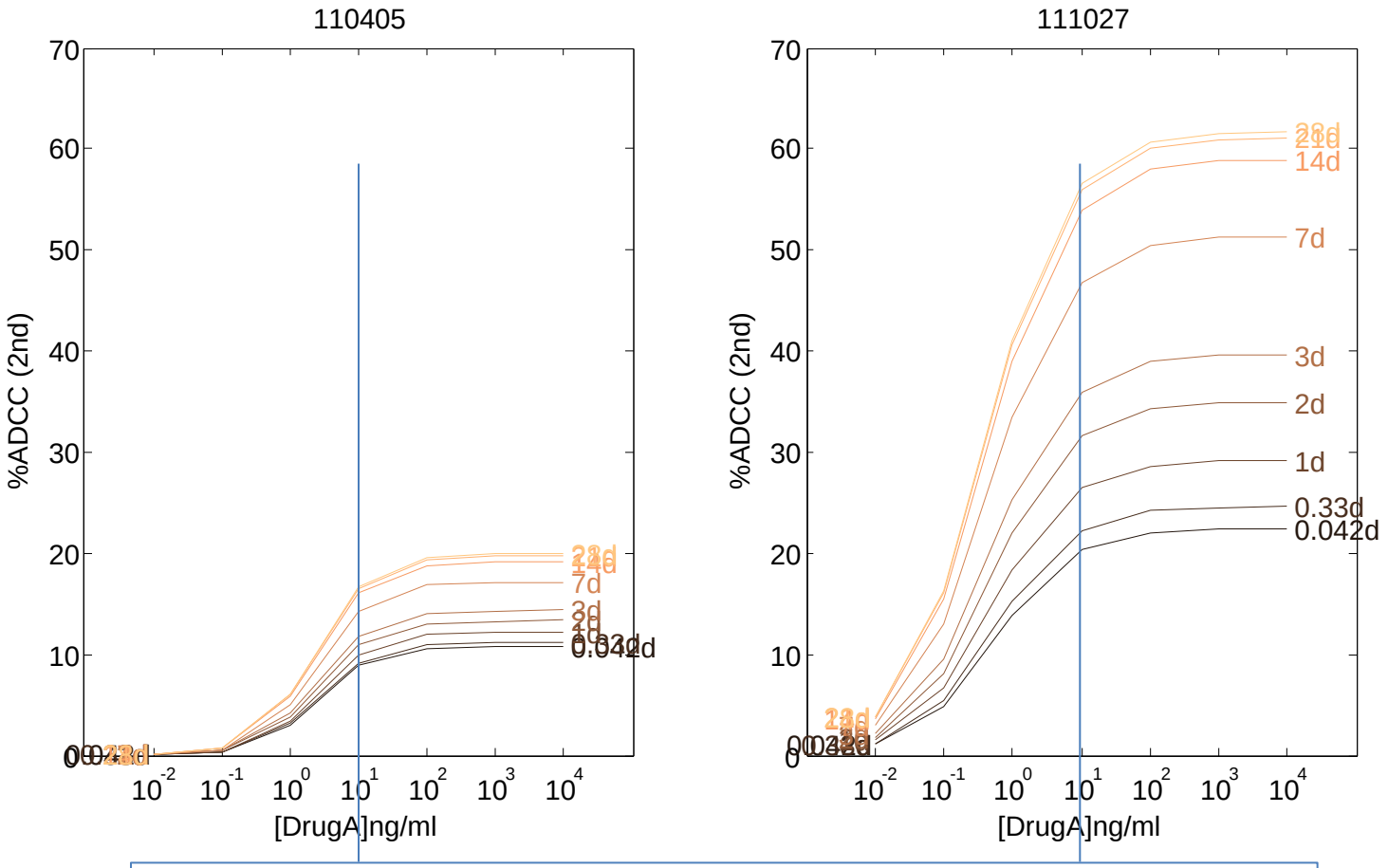
IN VITRO

- PBMCs isolated from subject 110711
- 1st ADCC conditions
  - NK:T ratio ~ 1
  - [DrugA] = 100ng/ml
  - 4 hours incubation
- Washout DrugA & tumor cells & allow PBMC recovery for 3 days
- PBMC's may become 'unhappy' in culture after 3 days
- 2nd ADCC conditions
  - NK:T ratio 1:1
  - [DrugA] = .1,1,10,100 ng/ml
  - 4 hours incubation

IN SILICO

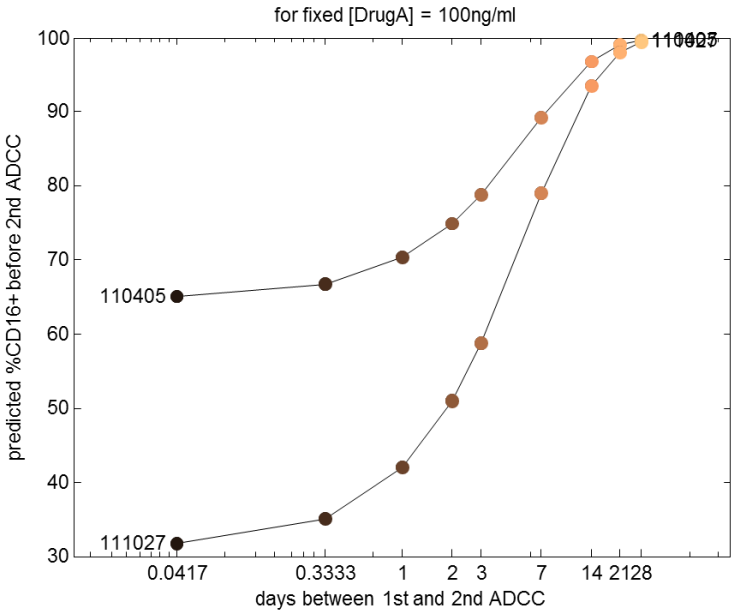
- Parameters as calibrated to subjects 110405 & 111027
- 1st ADCC conditions
  - NK:T ratio ~ 1
  - [DrugA] = 100ng/ml
  - 4 hours simulated time
- Set [DrugA]=0 after 4h and allow CD16 recovery for 1h, 8h, 1, 2, 4, 7, 14, 21, 28days
- Virtual cells are always happy…
- 2nd ADCC conditions
  - Etot held constant, tumor cells set back to original T0 value.
  - [DrugA] = .01,0.1,1,10,100,10^3,10^4
  - 4 hours simulated time

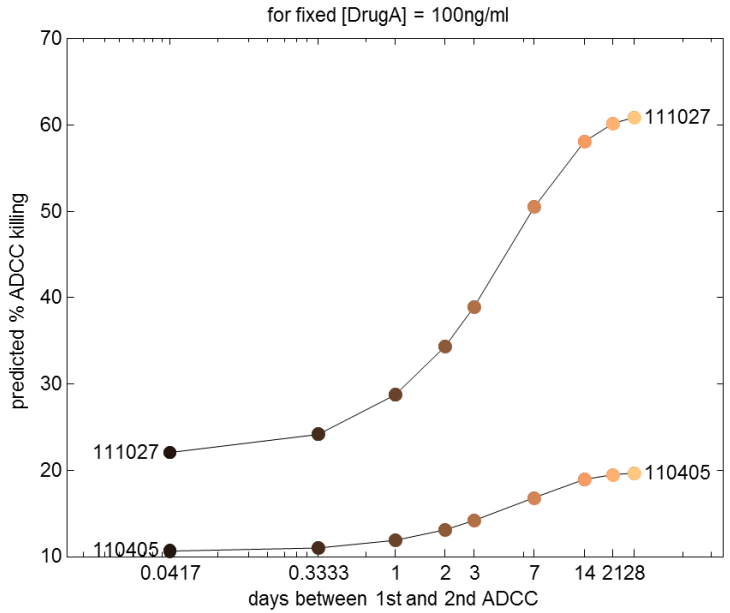
2nd ADCC simulations predict dependence on both concentration and recovery time.



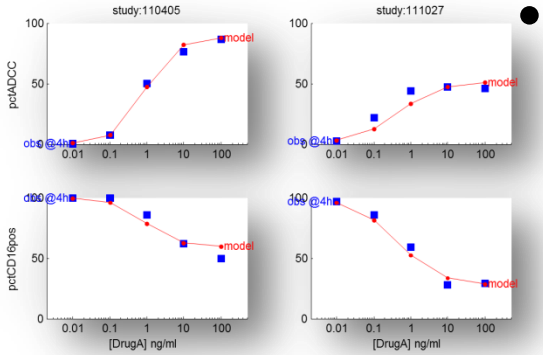
Next slide: look at 100ng/ml "slice" through the above graphs

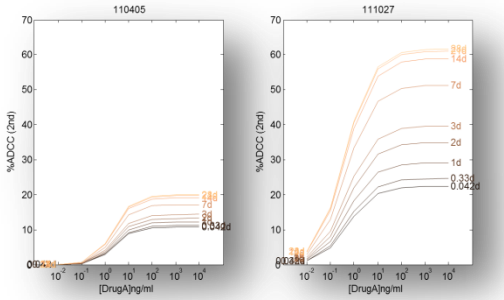
Model predicts that in vitro, ADCC is sensitive to recovery time up to ~14 days (but inter-individual variability is even more important)



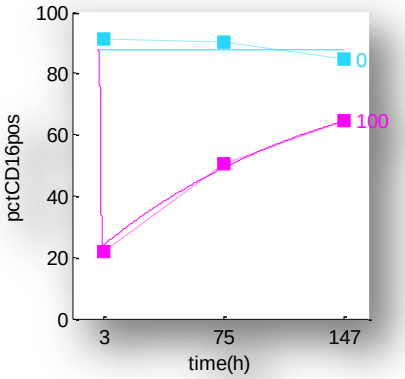


Conclusions of this section





- In vitro model can capture:
  - Mab-dependence of tumor cell killing and CD16+ depletion.
  - CD16+ recovery kinetics after ADCC
  - Qualitative 2nd ADCC dependence on recovery time and DrugA concentration



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WorkFlow

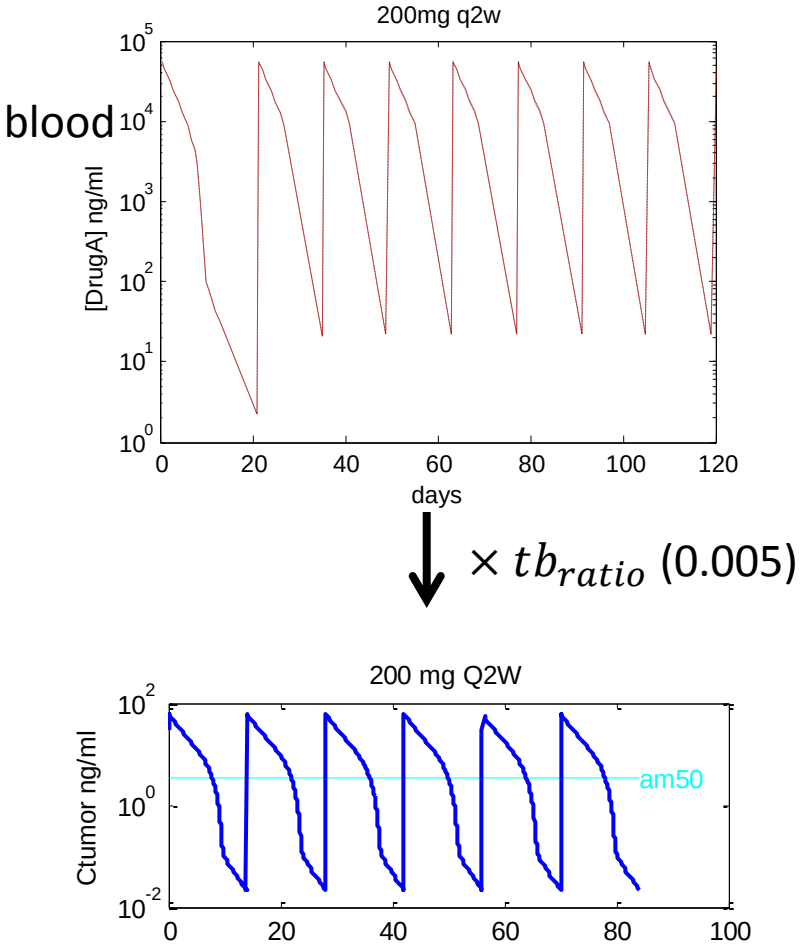
1. Specify structural model & assumptions
2. Using data from in vitro assays with HV blood:
   1. Fit to ADCC & CD16 [DrugA]-response 4h ADCC data
   2. Fit to ADCC & CD16 kinetic/recovery data (not yet done)
   3. Predict 2nd ADCC experiments, compare to data
3. Extrapolate to clinical scenario:
   1. Use popPK model & additional assumptions to predict $M(t)=[DrugA]_{tumor}$ over a range of doses & schedules
   2. Use M(t) to 'drive' in vitro ADCC model & predict %CD16+ and tumor kill kinetics over several cycles
4. Assess whether U-shaped dose-efficacy is predicted or whether waiting longer between doses is predicted to increase efficacy

Use popPK model & additional assumptions to predict M(t)=$[DrugA]_{tumor}$ over a range of doses & schedules

- For simplicity, we approximate M(t) = $[DrugA]_{tumor}$ by assuming

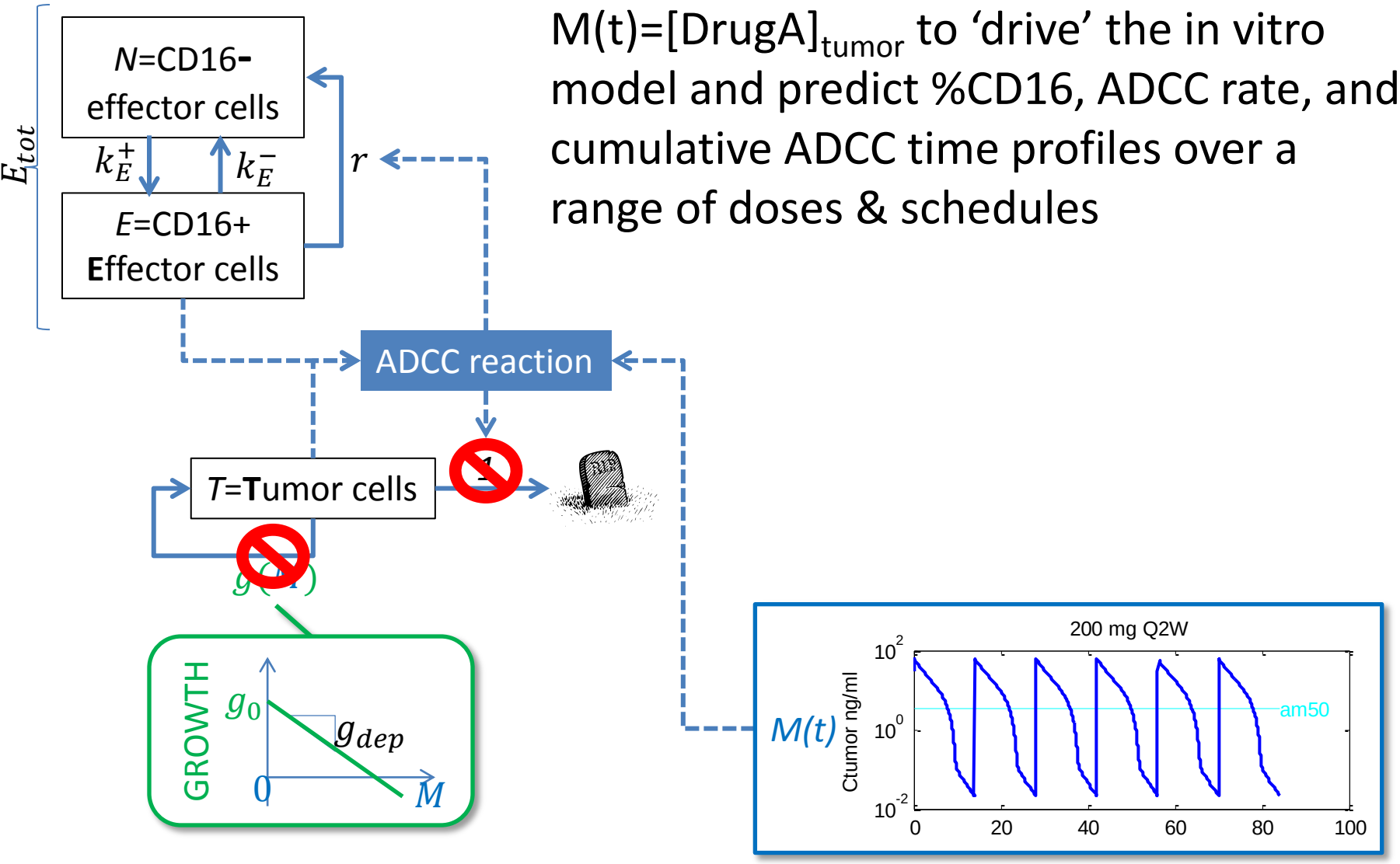
$$M(t) \approx tb_{ratio}[DrugA]_{blood}*$$

- Literature (Wittrup) suggests generic IgG1 tb_{ratio} (at vessel wall) to be ~0.006, so we use a range of 0.001 to 0.01



*[DrugA] time profile at a given location in the tumor interstitium is a complex function of blood concentration, vascular permeability, diffusivity, distance from nearest vessel, Receptor density & internalization, CD16 density, and other factors.

Next, clamp tumor size & use $M(t)=[DrugA]_{tumor}$ to 'drive' the in vitro model and predict %CD16, ADCC rate, and cumulative ADCC time profiles over a range of doses & schedules



WorkFlow

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4. Assess whether bell-shaped dose-efficacy is predicted or whether waiting longer between doses is predicted to increase efficacy ("inverse schedule dependence")

First some more definitions…

$$\frac{dE}{dt} = (E_{tot} - E)k_E^+ - rR_{ADCC}$$

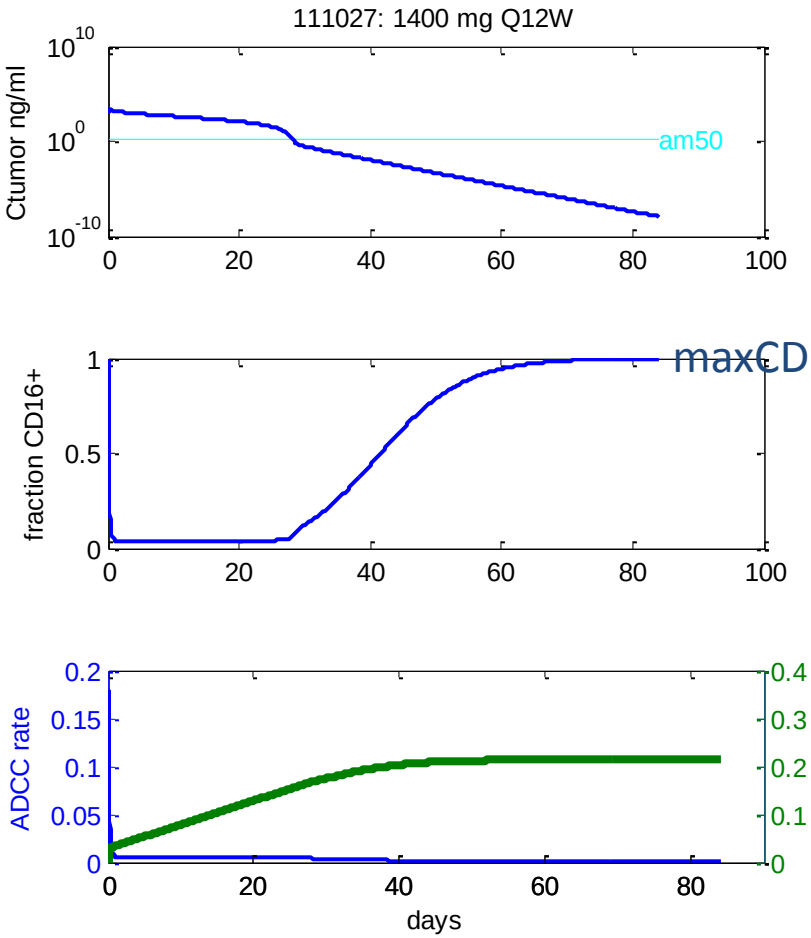
$$\frac{dT}{dt} = g_0 T - R_{ADCC}$$

$$R_{ADCC} \equiv E^r T \left(\frac{a_{max} M^{h_m}}{am_{50}^{h_m} + M^{h_m}} \right)$$

$$\text{"\%}CD16^+\text{"}(t) \equiv \frac{E(t)}{E_{tot}}$$

$$ADCC_{cum}(t) \equiv \int_0^t R_{ADCC}(\tau) d\tau$$

$$maxCD16 \equiv \max_{t>28d} E(t)/E_{tot}$$



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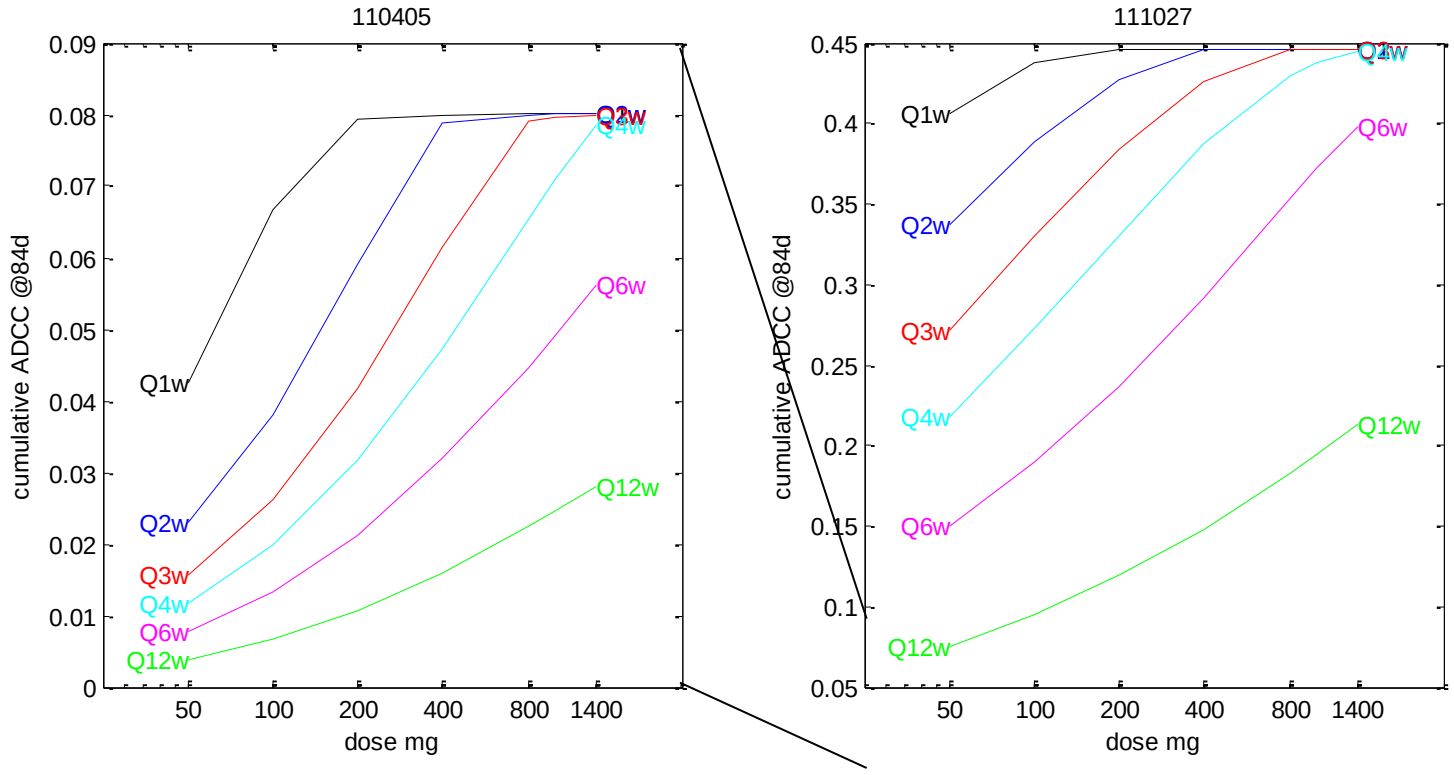
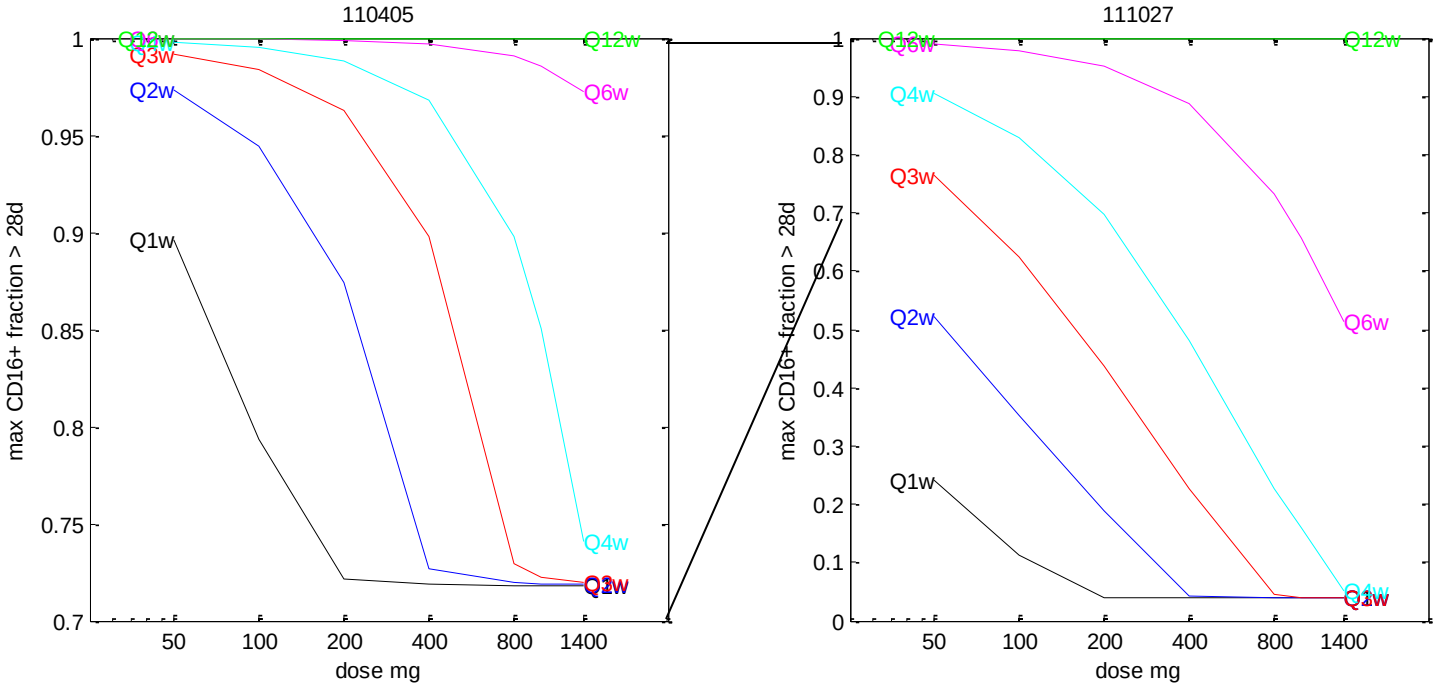
Simulations predict cumulative ADCC is neither bell-shaped in dose nor “reverse schedule-dependent”

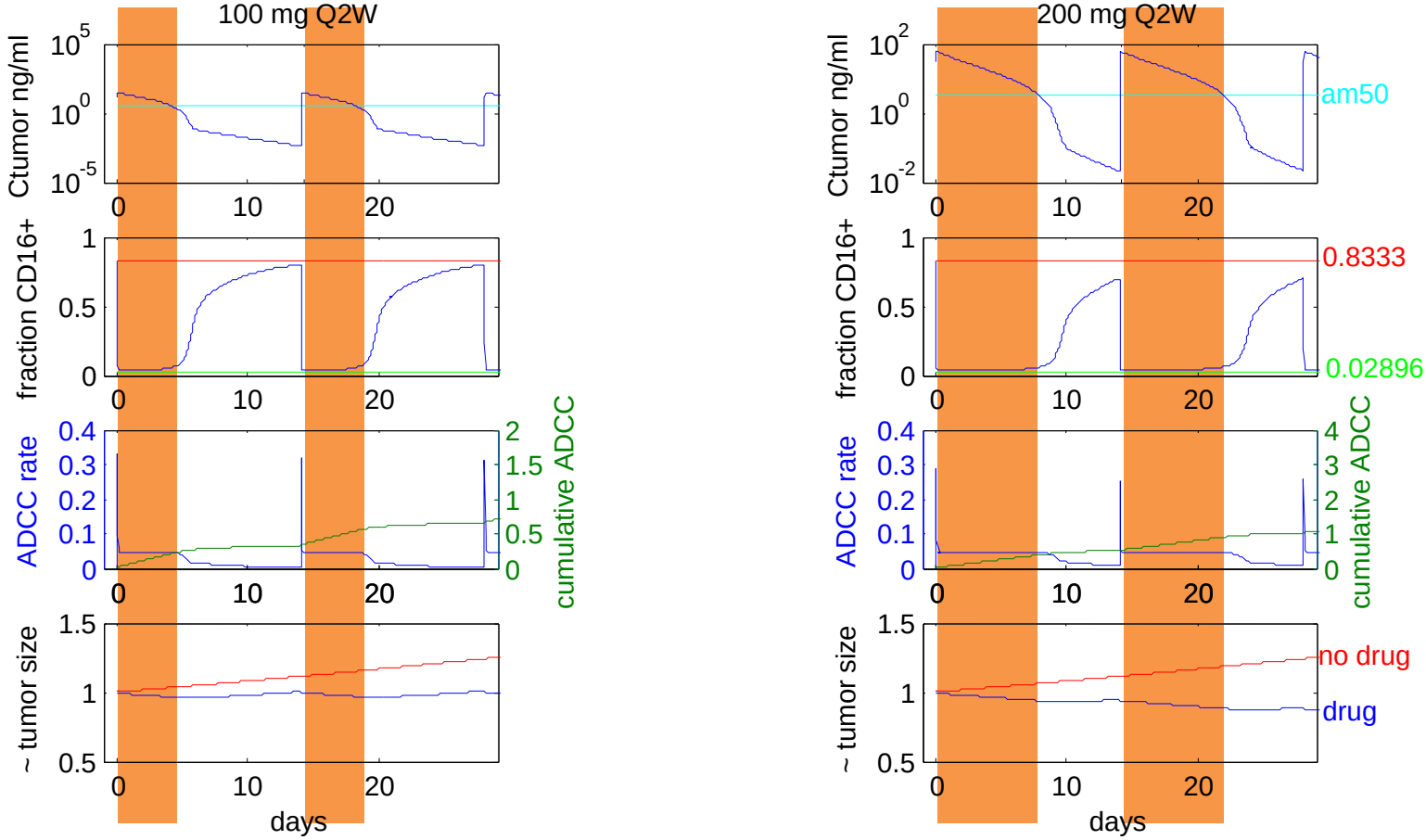


… even though %CD16+ acts the way we think it would…

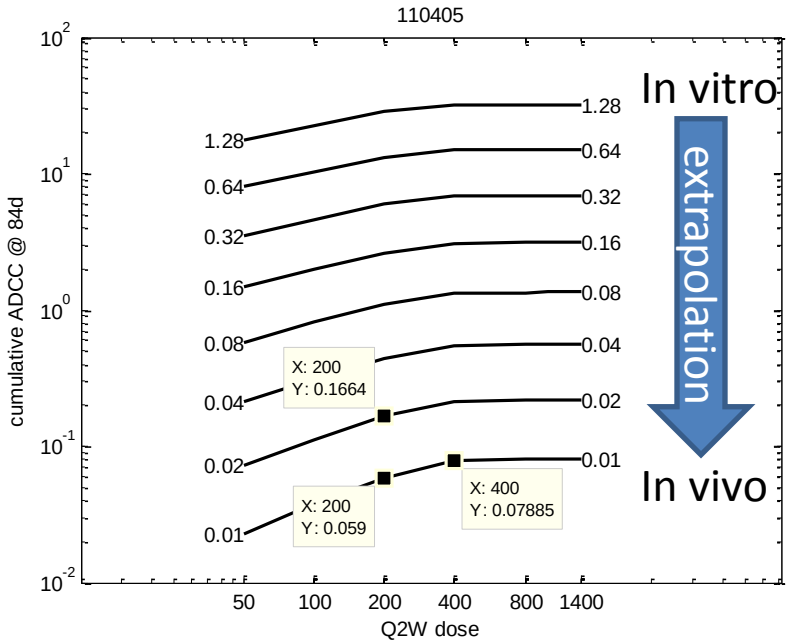


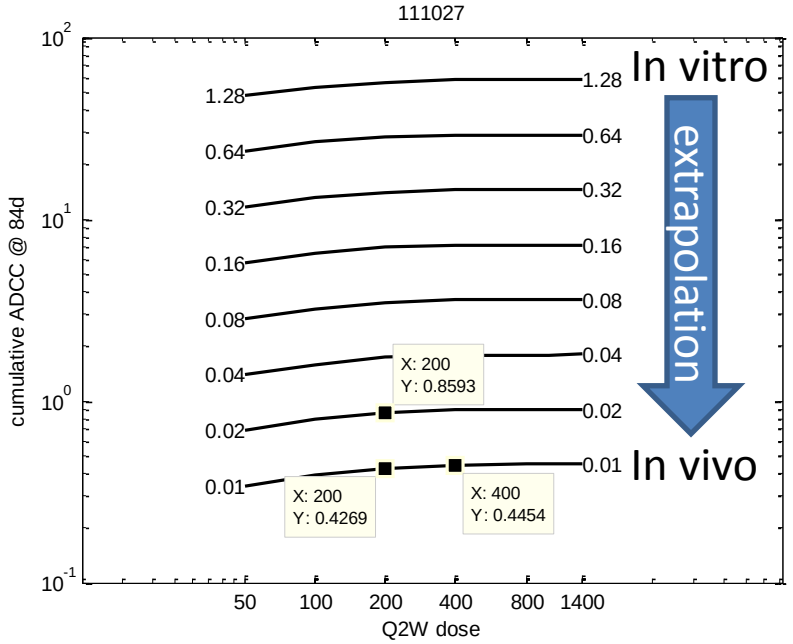
What's going on?

Model predicts that most ADCC occurs when [mAb]>am_{50} & %CD16+ is low



Additional prediction/insight: cumulative ADCC is much more sensitive to E_{tot}:T ratio than to dose





Doubling dose 200→400: ADCC 0.06→0.08 (+33%)
Doubling E:T 0.01→0.02: ADCC 0.06→0.17 (+200%)

Doubling dose 200→400: ADCC 0.43→0.45 (+4%)
Doubling E:T 0.01→0.02: ADCC 0.43→0.86 (+100%)

Conclusions

- In spite of interesting ADCC/CD16 dynamics, both the complex and simple multi-scale models predict
  - Strictly monotonic dose-efficacy relationship
  - No inverse schedule dependence at relevant doses
  - Higher sensitivity to Effector:Target ratio than to Drug A dose
- Complex models are useful for
  - Encompassing many potential mechanisms and their interactions
  - Sensitivity analysis pointing to sub-models of interest
- Simpler models are useful for
  - Deconstructing counterintuitive behavior (of bigger model) via phase plane & bifurcation analysis
  - Faster analyses and better defined parameter estimation
  - Explaining quickly to wide audiences

Technical appendix

And archive of paths not taken or to be taken

Nondimensionalize

$$\frac{dE}{dt} = E_{tot}k_E^+ - (k_E^+ + k_E^-)E - r a' E^r T$$

$$\frac{dT}{dt} = g' T - a' E^r T$$

- Scale time by CD16 turnover rate: $\tau = k_E^- t$
- Scale E by Etot so that e is the CD16+ ratio: $e = \frac{E}{E_{tot}}$.
- Scale T by initial tumor size: $u = \frac{T}{T_0}$.
- Let:
- $\gamma_1 = \frac{k_E^+}{k_E^-}$
- $\gamma_2 = \frac{T_0 r E_{tot}^{r-1} a'}{k_E^-}$
- $\gamma_3 = \frac{g'}{k_E^-}$
- $\gamma_4 = \frac{a' E_{tot}^r}{k_E^-}$

$$\frac{de}{d\tau} = \frac{k_E^+}{k_E^-} - \left(\frac{k_E^+}{k_E^-} + 1\right) e - \frac{T_0 r E_{tot}^{r-1} a'}{k_E^-} e^r u$$

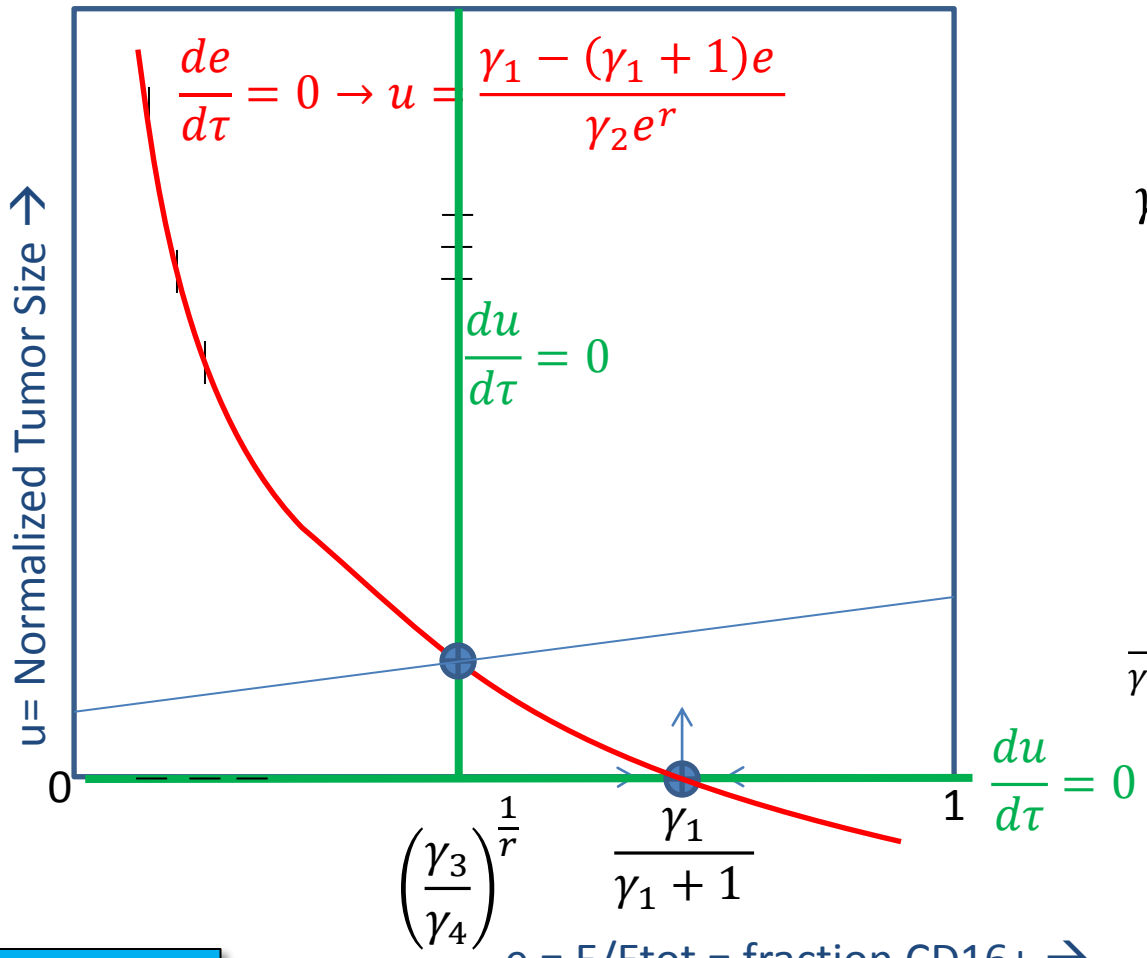
$$\frac{du}{d\tau} = \frac{g'}{k_E^-} u - \frac{a' E_{tot}^r}{k_E^-} e^r u$$

$$\frac{de}{d\tau} = \gamma_1 - (\gamma_1 + 1)e - \gamma_2 e^r u$$

$$\frac{du}{d\tau} = \gamma_3 u - \gamma_4 e^r u$$

Stability analysis
drug: g=g'>0, a'>0

$$\frac{de}{d\tau} = \gamma_1 - (\gamma_1 + 1)e - \gamma_2 e^r u$$
$$\frac{du}{d\tau} = \gamma_3 u - \gamma_4 e^r u$$



$$\gamma_1 = \frac{k_E^+}{k_E^-}$$
$$\gamma_2 = \frac{T_0 r E_{tot}^{r-1} a'}{k_E^-}$$
$$\gamma_3 = \frac{g'}{k_E^-}$$
$$\gamma_4 = \frac{a' E_{tot}^r}{k_E^-}$$

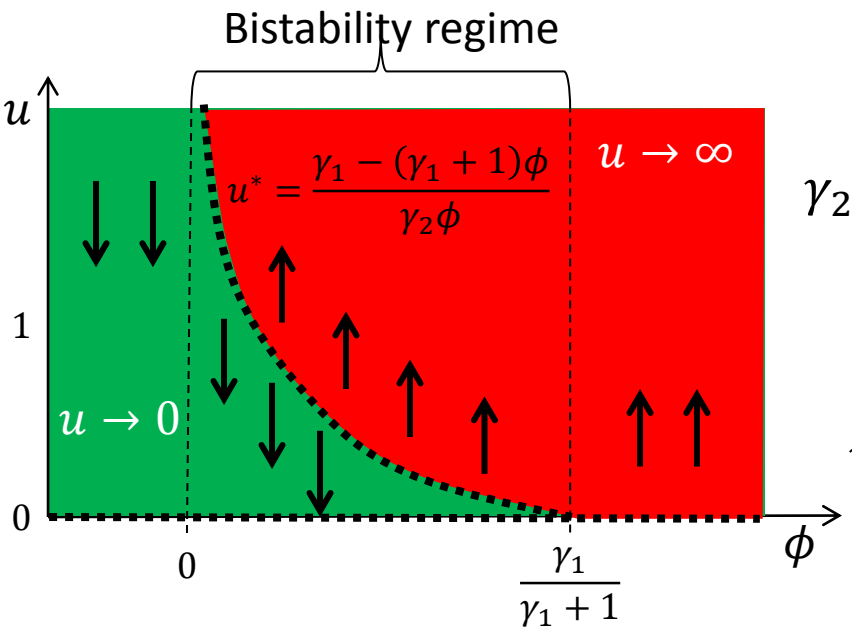
$$\frac{\gamma_1}{\gamma_1 + 1} = \frac{k_E^+}{k_E^+ + k_E^-}$$

$$\phi \equiv \left(\frac{\gamma_3}{\gamma_4}\right)^{\frac{1}{r}} = \left(\frac{g'}{a'}\right)^{\frac{1}{r}} \frac{1}{E_{tot}}$$

Bifurcation stuff

$$\frac{de}{d\tau} = \gamma_1 - (\gamma_1 + 1)e - \gamma_2 e^r u$$
$$\frac{du}{d\tau} = \gamma_3 u - \gamma_4 e^r u$$

- Key parameter $\phi \equiv \frac{\gamma_3}{\gamma_4} = \frac{g'}{a' E_{tot}}$
- Absent drug, $\phi > \frac{\gamma_1}{\gamma_1 + 1}$, otherwise tumor wouldn't grow.
- As we add more drug, ϕ gets smaller because g'gets smaller and a' gets bigger. When $\phi < \frac{\gamma_1}{\gamma_1 + 1}$, we get a saddle at ($\phi$,u*) and two regions. If u is small enough the tumor shrinks to zero, otherwise it grows without bound.
- If Receptor inhibition is strong enough to actually shrink the tumor, ie, g' <0, then we get down to $\phi < 0$, in which case the tumor shrinks no matter what.



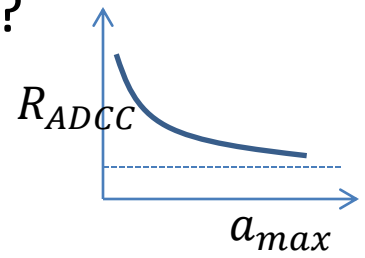
$$\gamma_1 = \frac{k_E^+}{k_E^-}$$
$$\gamma_2 = \frac{T_0 r E_{tot}^{r-1} a'}{k_E^-}$$
$$\gamma_3 = \frac{g'}{k_E^-}$$
$$\gamma_4 = \frac{a' E_{tot}^r}{k_E^-}$$

$$\phi \equiv \left(\frac{\gamma_3}{\gamma_4}\right)^{\frac{1}{r}} = \left(\frac{g'}{a'}\right)^{\frac{1}{r}} \frac{1}{E_{tot}}$$

$$\frac{\gamma_1}{\gamma_1 + 1} = \frac{k_E^+}{k_E^+ + k_E^-}$$

This model predicts that significant ADCC can occur even when %CD16+ is tiny!

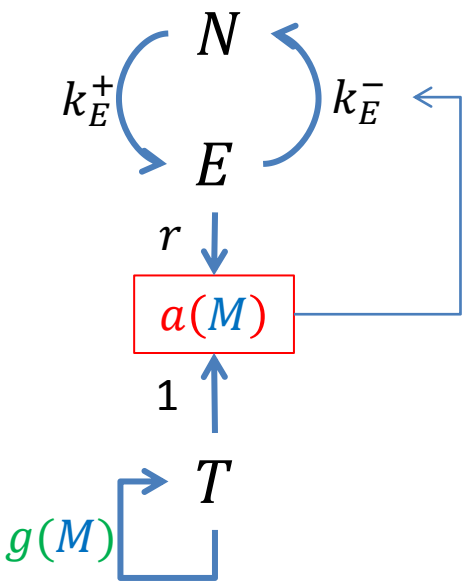
- 'Thought experiment': If we assume constant tumor T_0 and r = 1, what happens to the ADCC rate R_{ADCC} if we have sustained high concentrations of DrugA and a high a_{max} (max ADCC efficiency)?
  - No ADCC because %CD16+ gets knocked way down?
  - Some ADCC because we have DrugA on board?
  - Lots of ADCC because $a \sim a_{max}$, which is big?
- The answer, according to the model, is:



$$\%CD16^+ \to 0, \text{ but } R_{ADCC} \to E_{tot} k_E^+ > 0 \text{ as } a_{max} \to \infty$$

- In other words, *even if a_{max} is big enough to make $CD16^+ \sim 0$, the ADCC rate can still be nonzero!*

New model

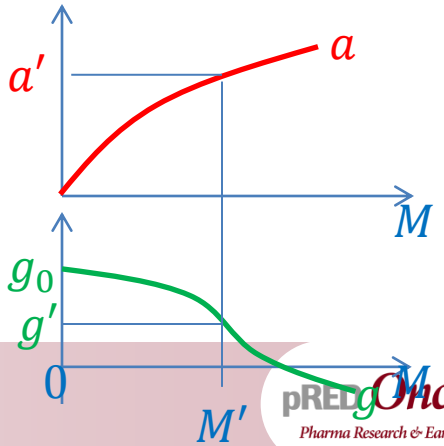


ASSUMPTIONS

- CD16+ effector cells (E) are produced/recover at a constant rate kE+ and 'decay' absent ADCC activity at a rate kE-. N is the number of CD16 Negative cells. N+E = E_{tot} assumed constant for now (in vitro).
- Absent ADCC/AICC, tumor cells (T) proliferate exponentially at a net rate g, which can be attenuated by Receptor inhibition as a function of [mAb]=M, ie g(M). AICC effects are implicit in g.
- In the presence of E and mAb, ADCC can occur at an [mAb]=M dependent rate $a(M(t))ET$. Each ADCC reaction results in loss of one tumor cell and *r* CD16+ effector cells.

Effector cells: $$\frac{dE}{dt} = (E_{tot} - E)k_E^+ - k_E^- E - ra(M(t))E^r T$$

Tumor cells: $$\frac{dT}{dt} = g(M(t))T - a(M(t))E^r T$$



The model

$$\frac{dE}{dt} = (E_{tot} - E)k_E^+ - k_E^- E - ra\big(M(t)\big)E^r T$$

$$\frac{dT}{dt} = g(M(t))T - a\big(M(t)\big)E^r T$$

	Description	Value
E	#/vol of CD16+ **E**ffector cells (state variable)	>0
T	#/vol of viable **T**umor (target) cells (state variable)	>0
E_{tot}	Total number of (CD16+ and CD16-) effector cells	>0
k_E^+	Production/recovery rate of CD16+ Effector cells	>0
k_E^-	Baseline 1st order degradation rate of CD16+ Effector cells	>0
r	**R**atio of how many CD16+ cells depleted per tumor cell killed	>0
$a(M)$	**A**DCC efficiency as function of mAb concentration	>0
$M(t)$	**m**Ab concentration as function of time	>=0
$g(M)$	Tumor **g**rowth rate as function of mAb concentration Baseline growth rate g_0 includes AICC effects	$-\infty < g < +\infty$ $g(0) = g_0 > 0$

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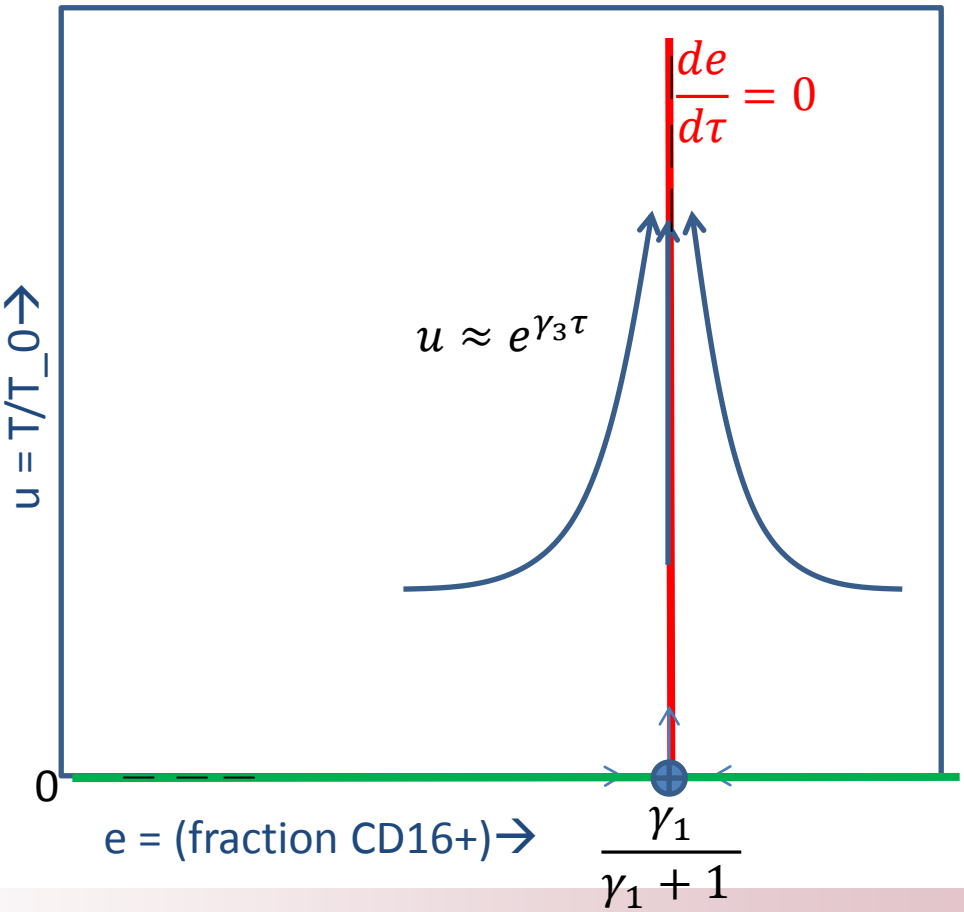
Stability analysis

No drug: $g=g_0$, $a'=0$

$$\frac{de}{d\tau} = \gamma_1 - (\gamma_1 + 1)e - \gamma_2 e^r u$$
$$\frac{du}{d\tau} = \gamma_3 u - \gamma_4 e^r u$$



$$\gamma_1 = \frac{k_E^+}{k_E^-}$$

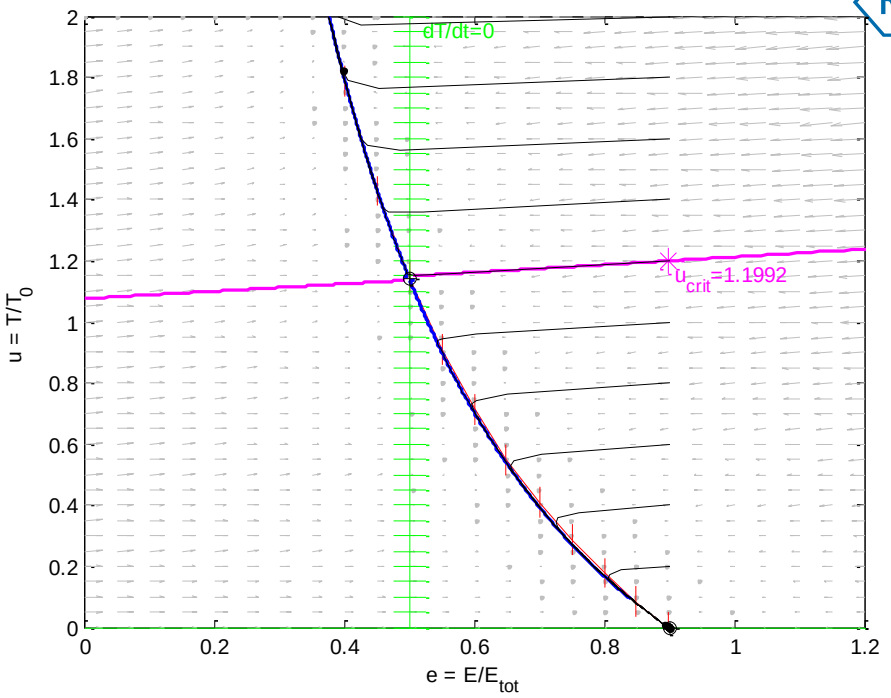
$$\gamma_2 = \frac{T_0 r E_{tot}^{r-1} a'}{k_E^-} = 0$$

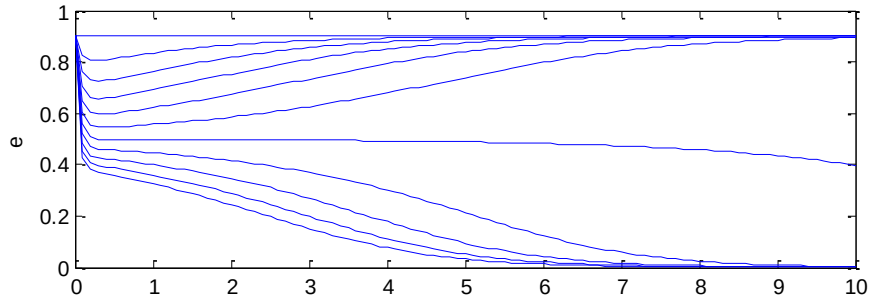
$$\gamma_3 = \frac{g'}{k_E^-} = \frac{g_0}{k_E^-}$$

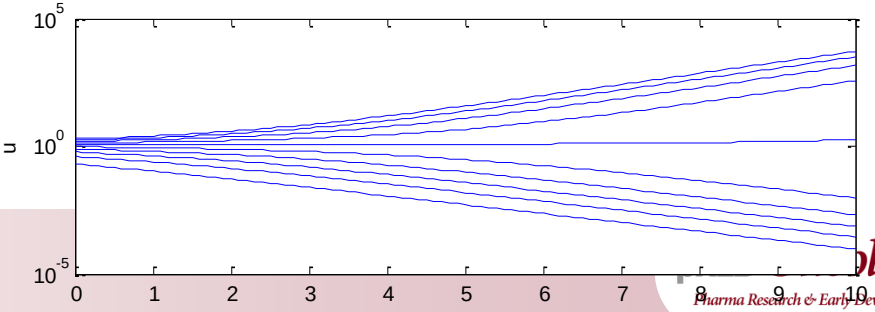
$$\gamma_4 = \frac{a' E_{tot}^r}{k_E^-} = 0$$

$$\frac{\gamma_1}{\gamma_1 + 1} = \frac{k_E^+}{k_E^+ + k_E^-}$$

Simple_cell_model.m







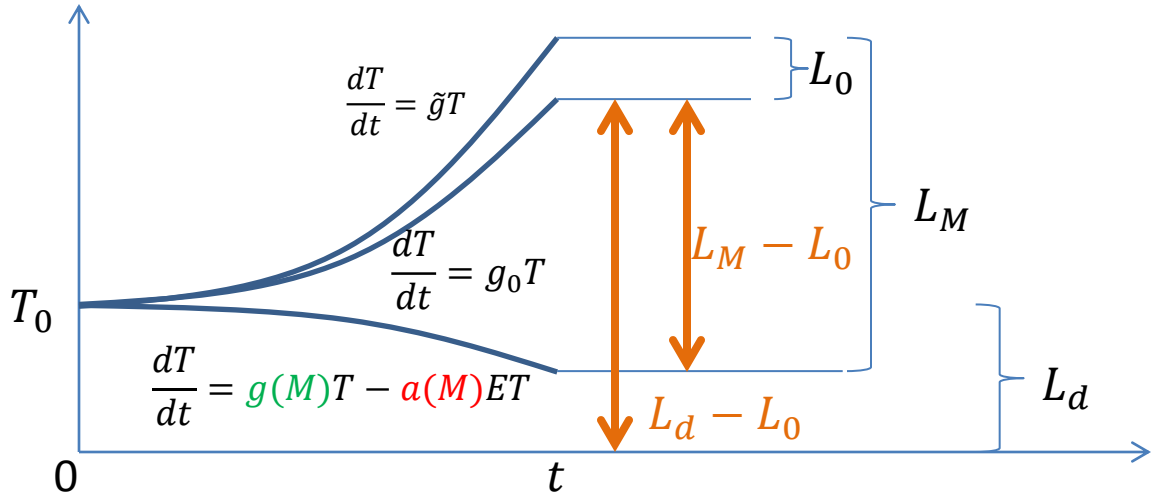
LDH data

$$\frac{dE}{dt} = E_{tot}k_E^+ - (k_E^+ + k_E^-)E - ra(M)E^rT$$
$$\frac{dT}{dt} = g(M)T - a(M)E^rT$$

- The %ADCC is calculated as: (experimental LDH release - spontaneous LDH release)/(maximal LDH release – spontaneous LDH release)x100. = 100 α (see equation →)
  - "experimental" is with given conc of DrugA in presence of effector cells
  - Spontaneous is in presence of effector cells but no DrugA
  - Maximal is detergent treated

$$\alpha(M) \equiv \frac{L_M - L_0}{L_d - L_0}$$

$$g_0 = \tilde{g} - \underbrace{k_i E_{tot}}_{AICC} = \tilde{g} - \tilde{k}_i$$



$$\alpha(t;m) = \frac{T_0e^{g_0t} - T(t;M)}{T_0e^{g_0t}} = 1 - \frac{T(t;M)}{T_0e^{g_0t}} = 1 - u(t;M)e^{-g_0t}$$