

The logic of containing tumours

Rob Noble
[@robjohnnoble](https://twitter.com/robjohnnoble)



An experimental system

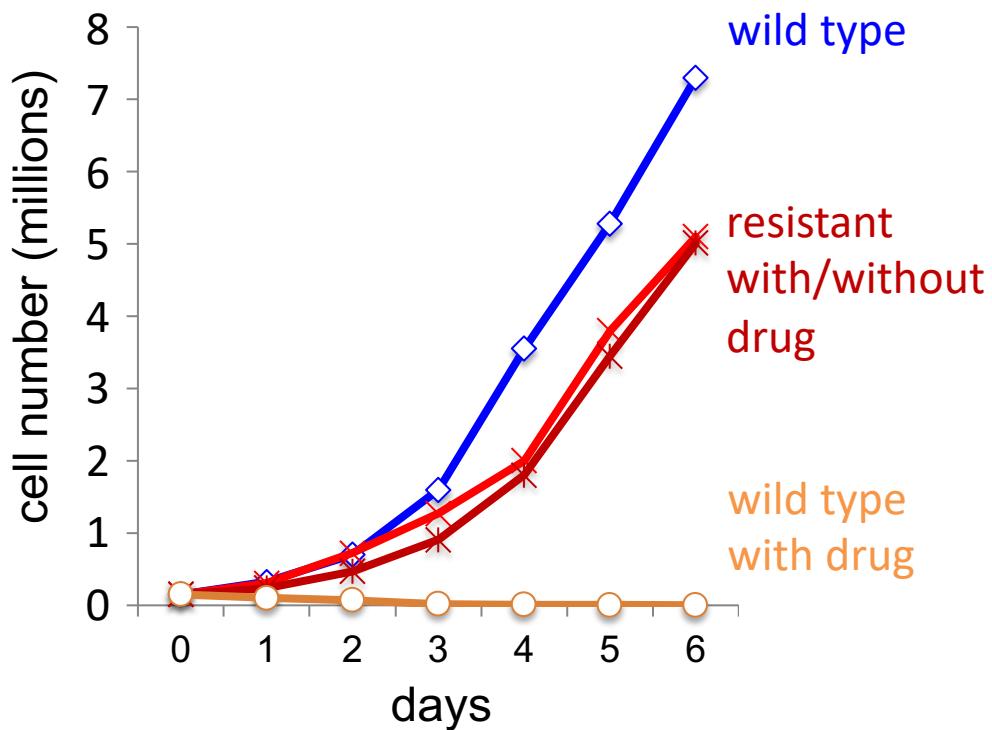
- HCT116 human colorectal tumour cells
- Generated lines irreversibly resistant to Cdk2 inhibitor NU6102
- Mixed sensitive and resistant cells in tumour spheroids

Fisher lab
(IGMM)

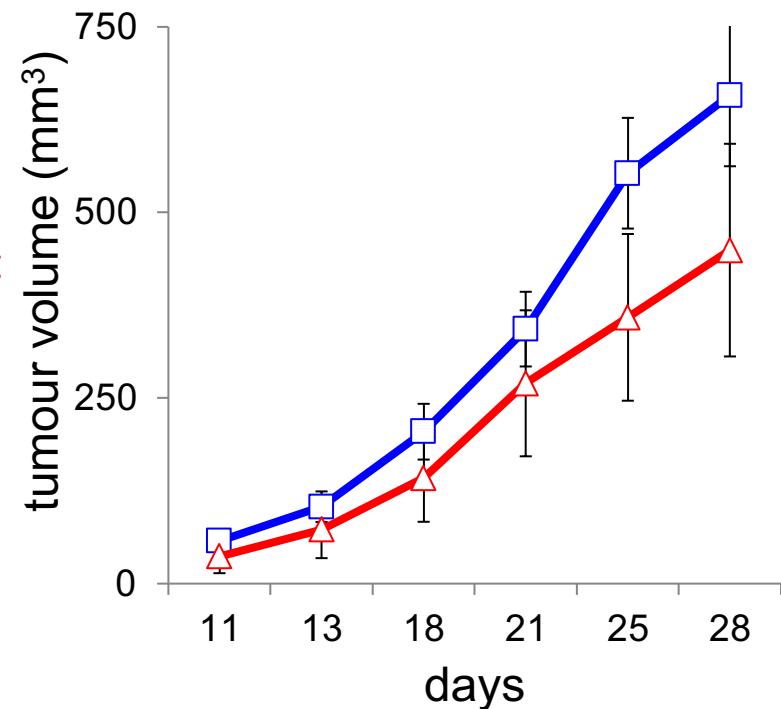


Fitness cost of resistance

In monolayer culture

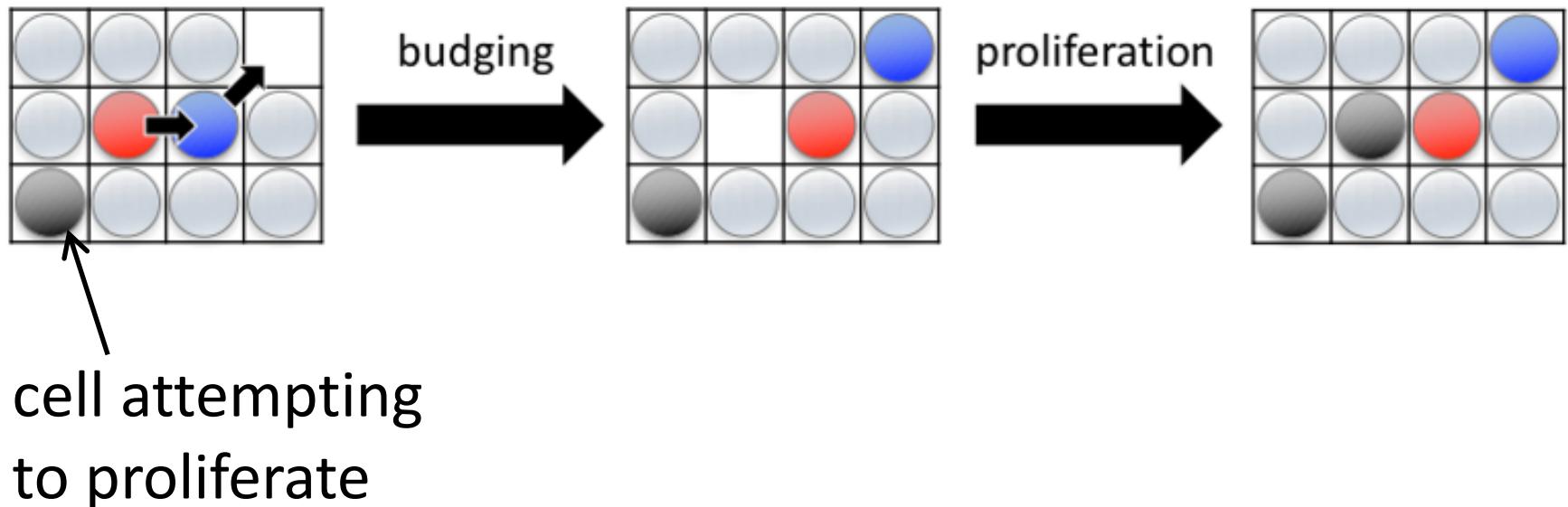


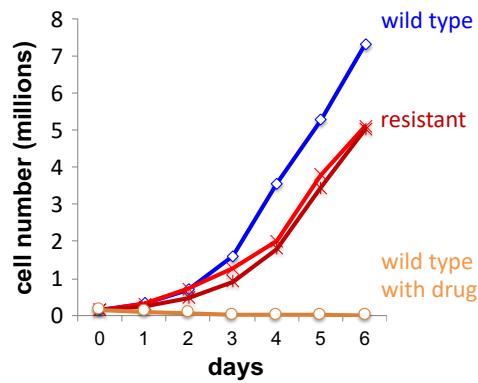
In nude mice



Not frequency-dependent

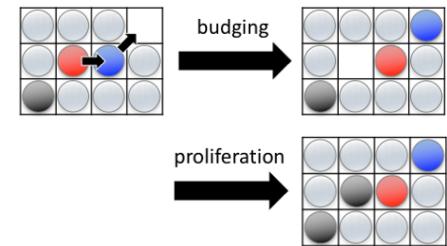
Contact inhibition and competition for space



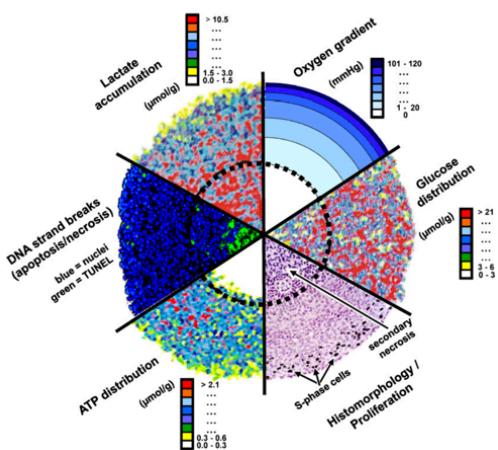


cost of resistance

distance from periphery



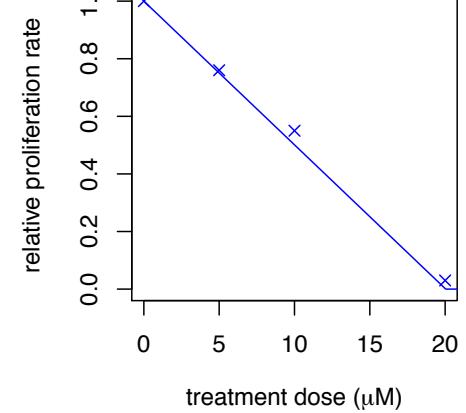
cell proliferation



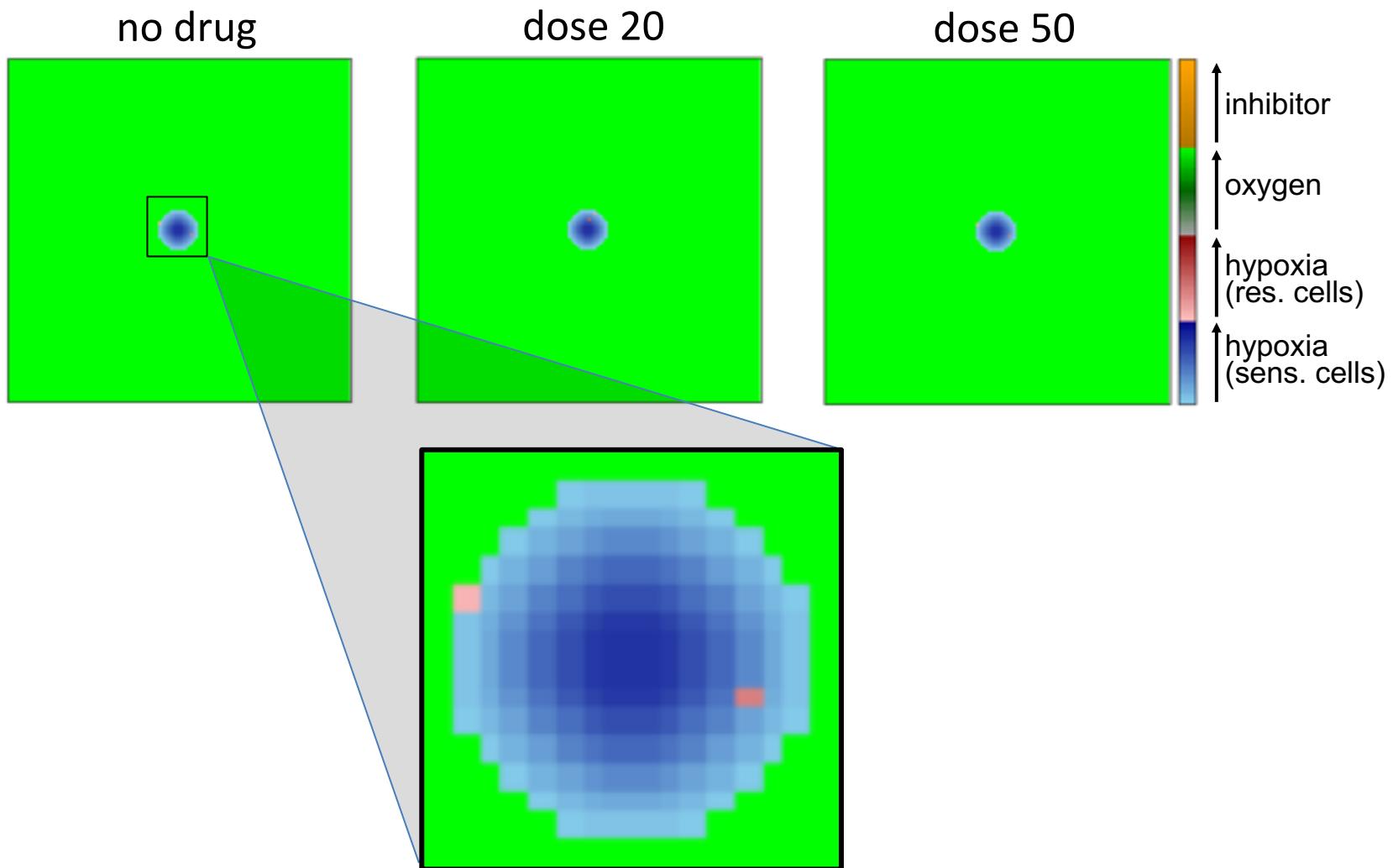
hypoxia

drug

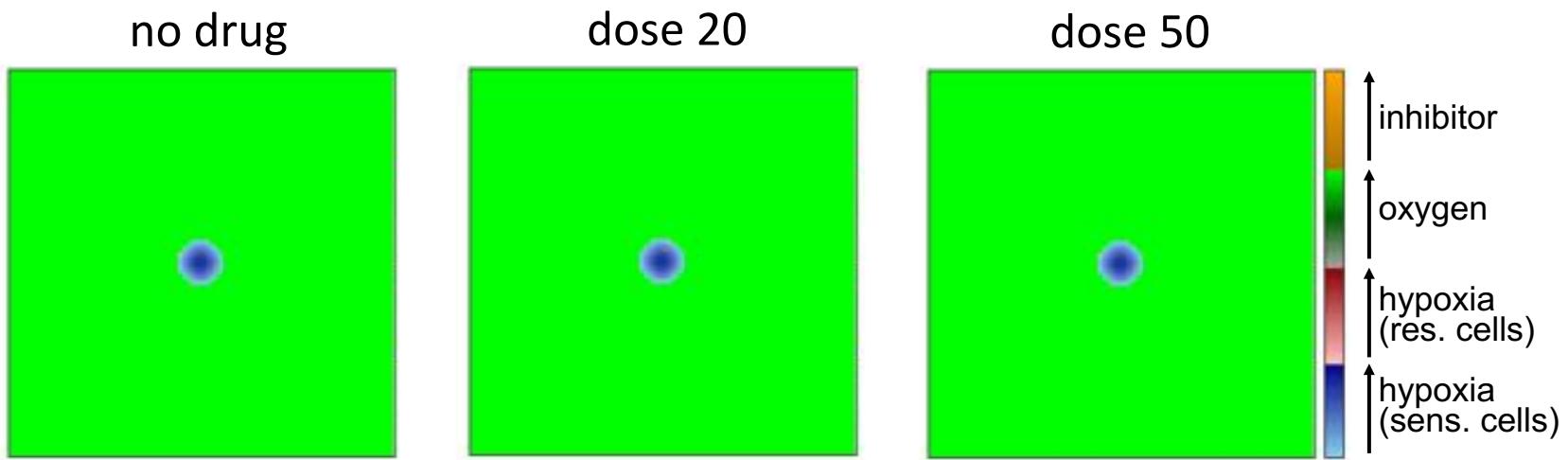
cell death



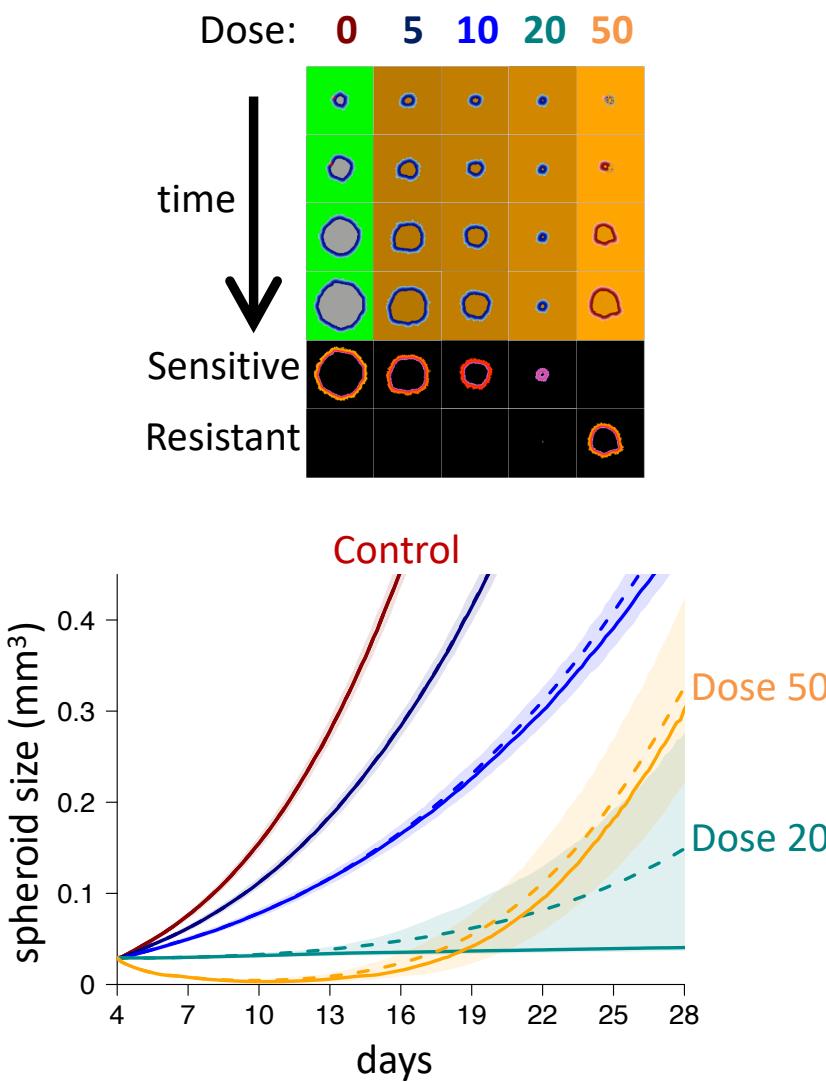
Computational model of a tumour spheroid



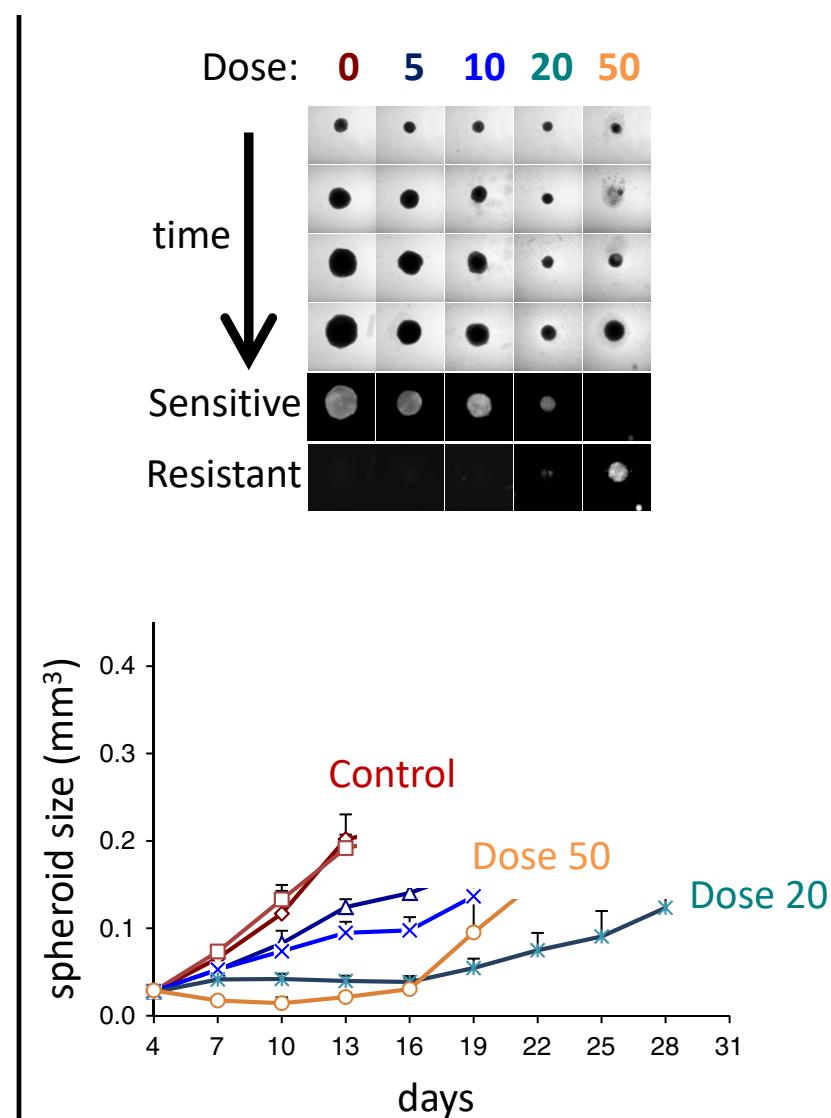
Computational model of a tumour spheroid



Computational model

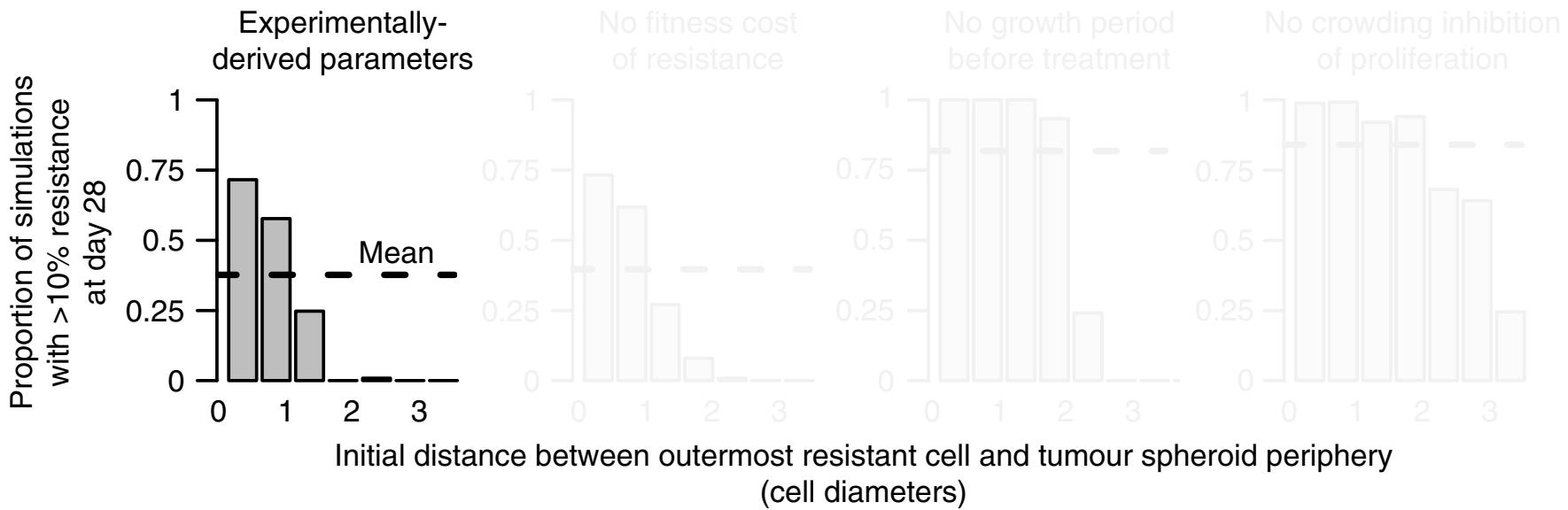


Actual tumour spheroids

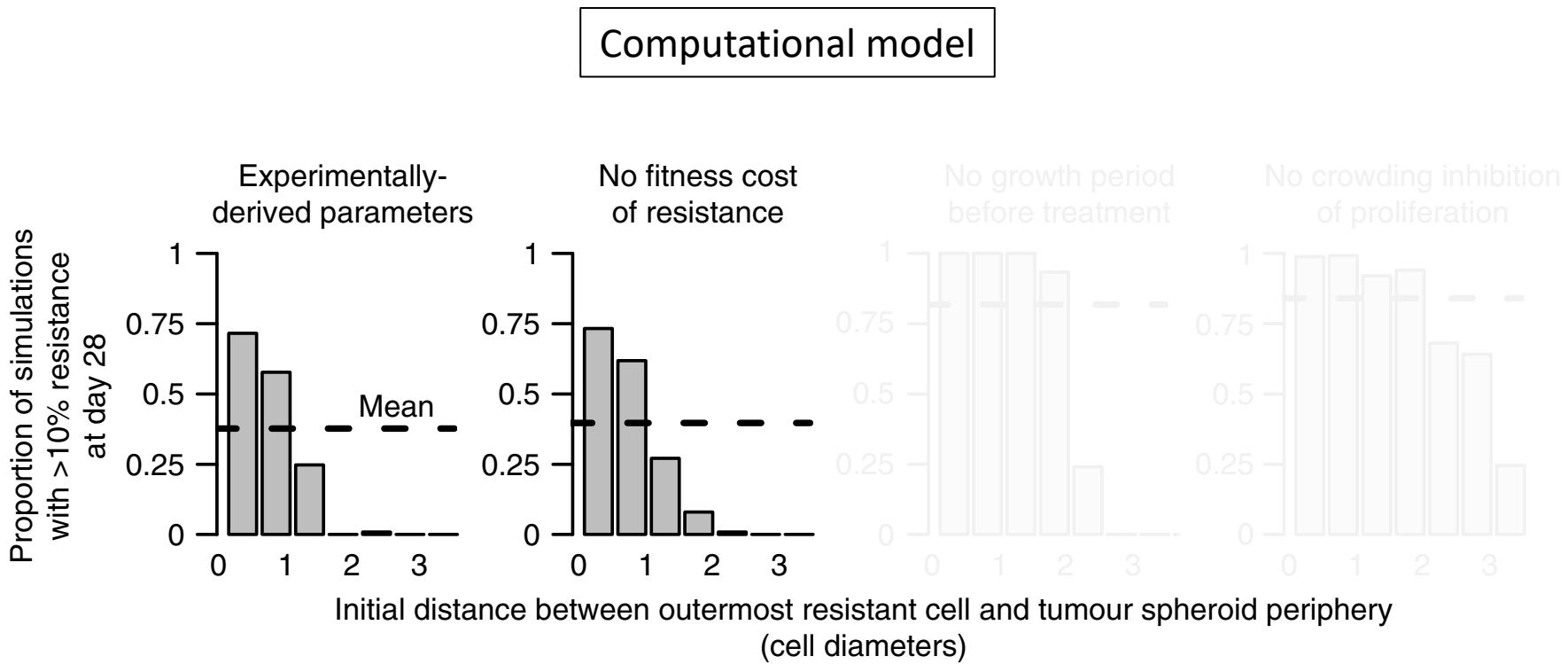


Is a cost of resistance really necessary?

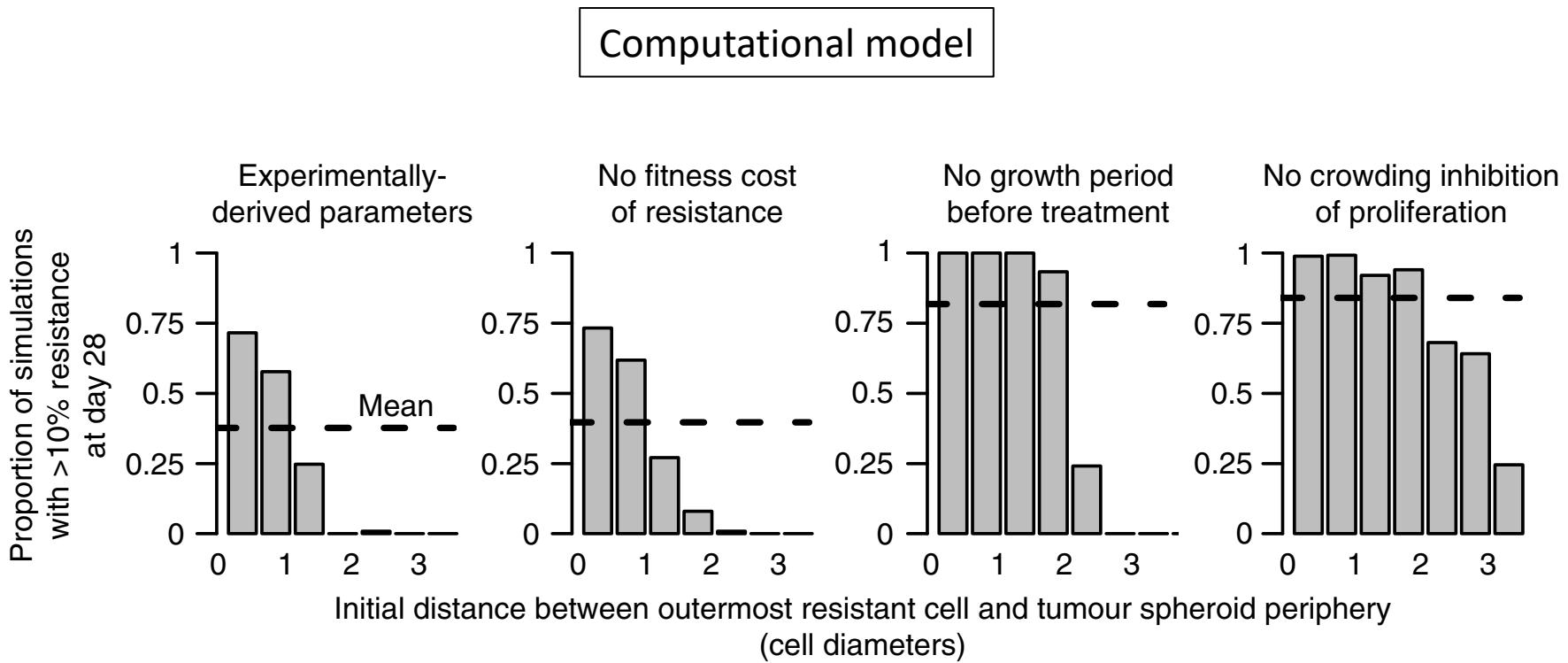
Computational model



Is a cost of resistance really necessary?



Is a cost of resistance really necessary?



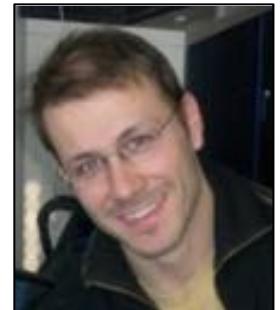
A general model

	growth rate	drug dose
sensitive cells:	$\dot{S}(t) = S(t)g_s(S(t), R(t), C(t))$	
resistant cells:	$\dot{R}(t) = R(t)g_r(S(t), R(t))$	

Assume

- g_s is non-increasing in C
 - g_r is non-increasing in S
 - g_r is independent of C
 - neglect mutations

Yannick Viossat
(Ceremade, Université
Paris-Dauphine)



Outcomes

Time to progression

tumour exceeds its initial size, N_0

Time to treatment failure

tumour exceeds a maximum tolerable size, N_{tol}

Survival time

tumour reaches lethal size, N_{crit}

Optimality of containment

We formally prove these results hold very generally for prolonging survival:

- optimal strategy maintains tumor burden as high as possible while sensitive cells remain – *ideal containment*
- worst option is to maximize kill rate – *maximum tolerated dose*

Mathematical intuition

For a small time step dt :

$$R(t + dt) = R(t) + dR$$

where

$$dR \approx \dot{R}(t)dt = g_r(R(t), S(t))dt$$

So time for R to grow from R_1 to $R_1 + dR$ is

$$dt \approx dR/g_r(R_1, S_1)$$

where S_1 is size of S when $R = R_1$

Mathematical intuition

If we contain the tumour at initial size N_0 then

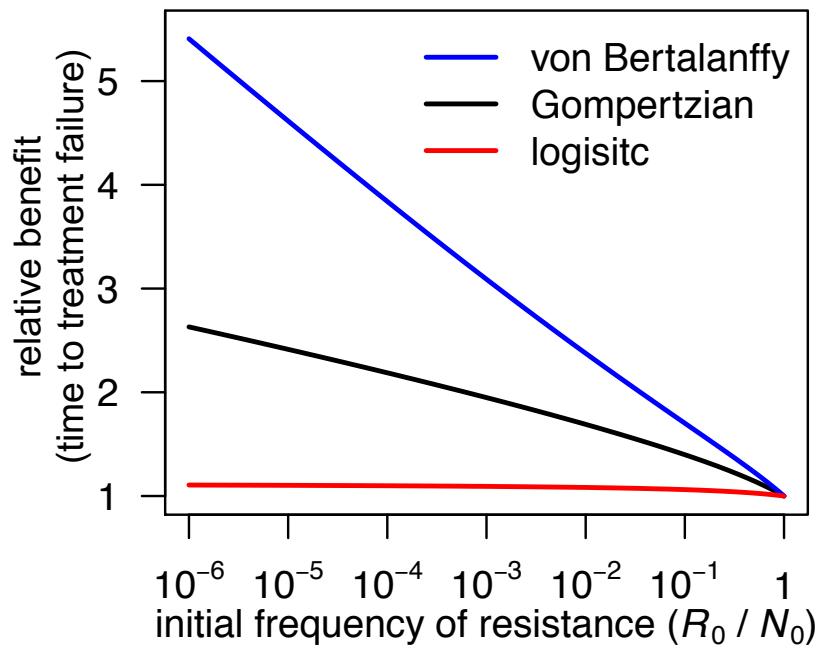
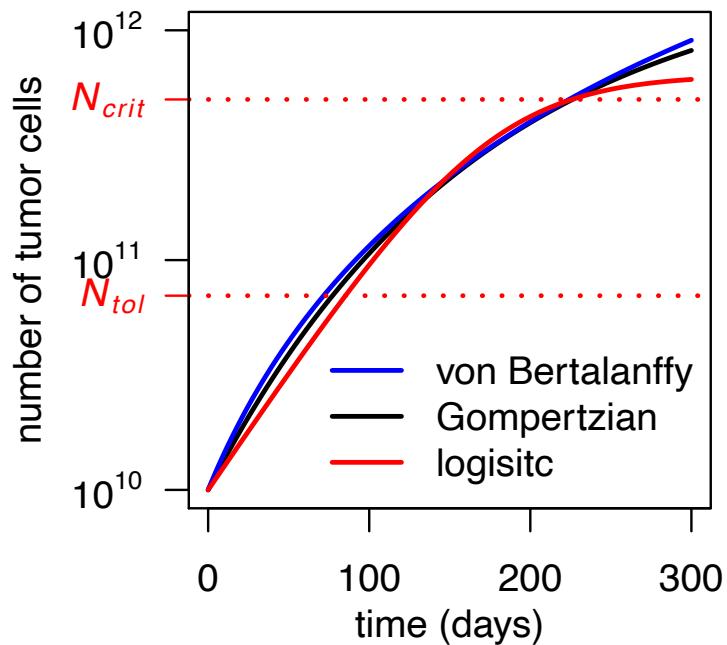
$$S_1 = N_0 - R_1$$

Under any other treatment, before progression
we have $S_1 + R_1 \leq N_0$ and so $S_1 \leq N_0 - R_1$

By assumption, larger S_1 implies smaller g_r ,
which in turn implies smaller dt (as $dt \propto 1/g_r$)

Hence containment minimizes growth of $R(t)$
and, since progression occurs when $R(t) = N_0$,
containment maximises time to progression

Clinical gains strongly depend on competition intensity



von Bertalanffy: $g(N) = \rho(N^{-1/3} - K^{-1/3})$

Gompertzian: $g(N) = \rho \ln(K/N)$

logistic: $g(N) = \rho(1 - N/K)$

A Gompertzian model

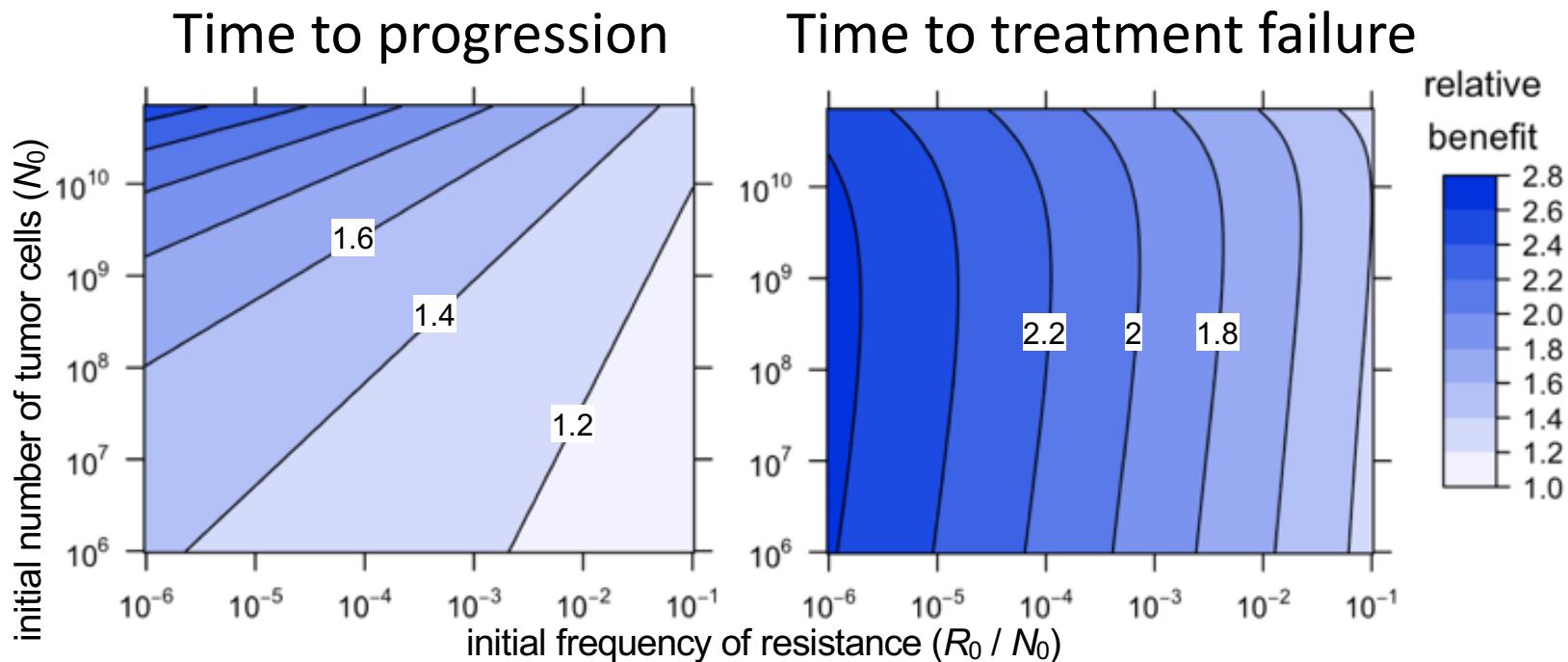
carrying capacity drug dose

sensitive cells: $\dot{S}(t) = \rho \ln(K/N(t)) (1 - \lambda C(t)) S(t),$

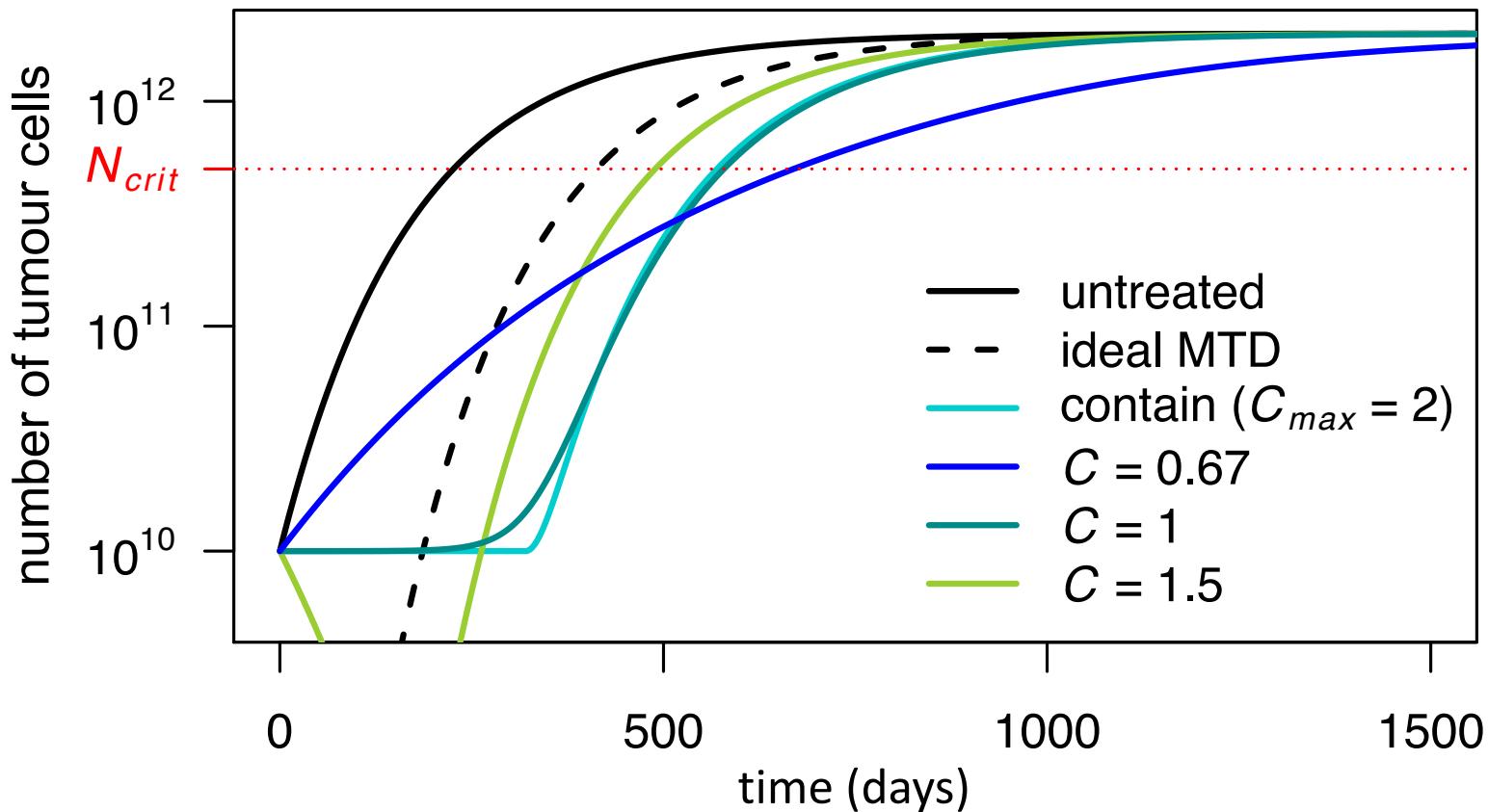
resistant cells: $\dot{R}(t) = \rho \ln(K/N(t)) R(t),$

Adapted from Monro & Gaffney (2009)

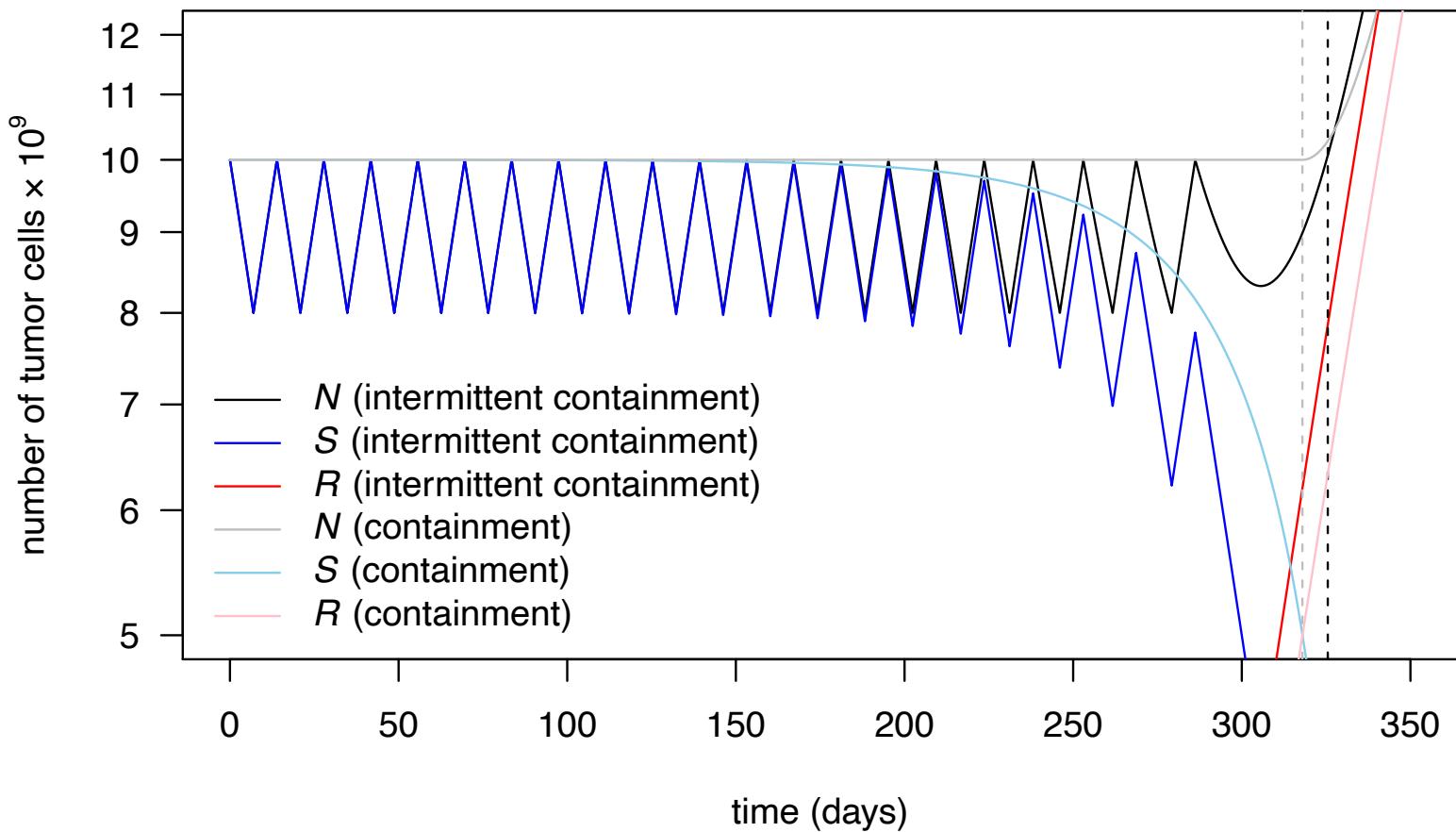
Predicted clinical benefits (Gompertzian model)



Practical treatment strategies can be close to optimal



Practical treatment strategies can be close to optimal



What about fitness costs of resistance?

“the theory behind adaptive therapy focuses on the phenotypic costs of the molecular mechanism(s) of resistance”

Enriquez-Navas, P. M., Wojtkowiak, J. W. & Gatenby, R. A. Application of Evolutionary Principles to Cancer Therapy (2015) *Cancer Research*

Gatenby, R. & Brown, J. The Evolution and Ecology of Resistance in Cancer Therapy (2018) *Cold Spring Harbor Perspectives in Medicine*

Fitness costs of resistance are unnecessary

sensitive cells: $\dot{S}(t) = S(t)g_s(S(t), R(t), C(t))$

resistant cells: $\dot{R}(t) = R(t)g_r(S(t), R(t))$

Assume

- g_s is non-increasing in C
- g_r is non-increasing in S
- g_r is independent of C
- neglect mutations

Modelling fitness costs of resistance

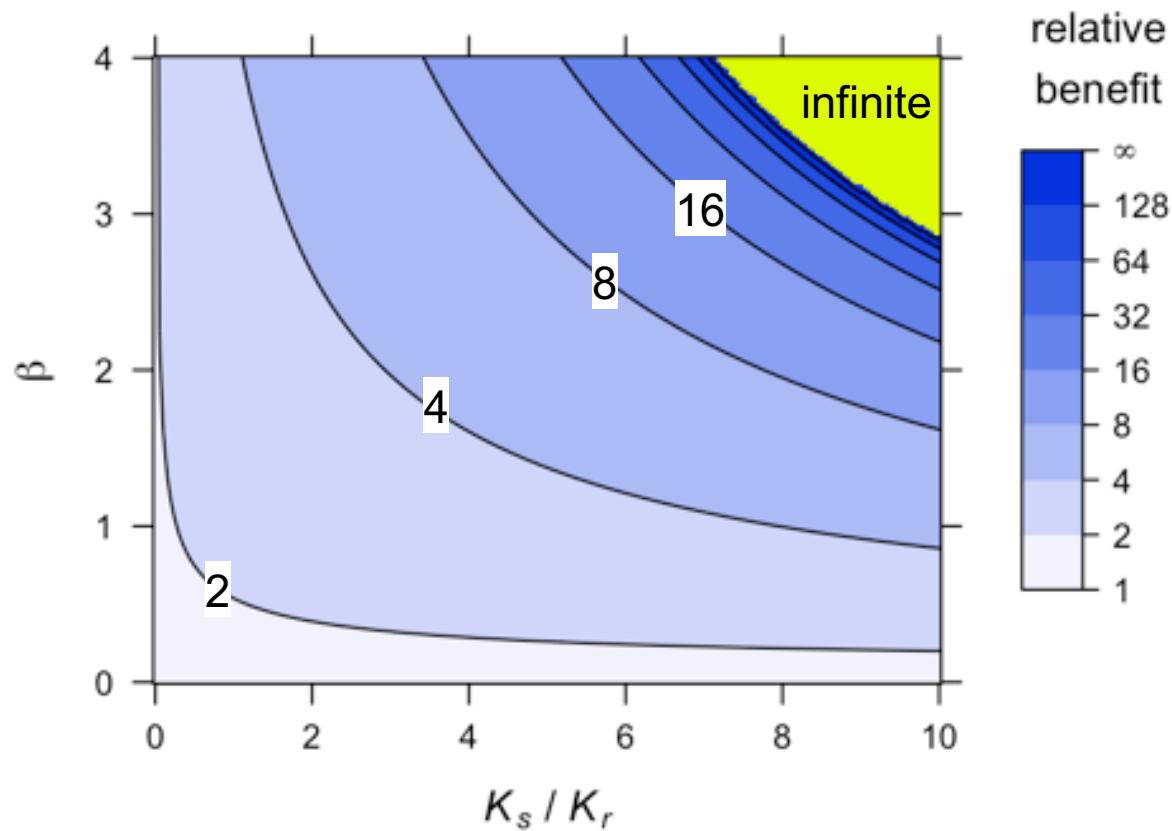
sensitive cells: $\dot{S}(t) = \rho_s \ln \left(\frac{K_s}{S(t) + \alpha R(t)} \right) (1 - \lambda C(t)) S(t),$

resistant cells: $\dot{R}(t) = \rho_r \ln \left(\frac{K_r}{R(t) + \beta S(t)} \right) R(t).$

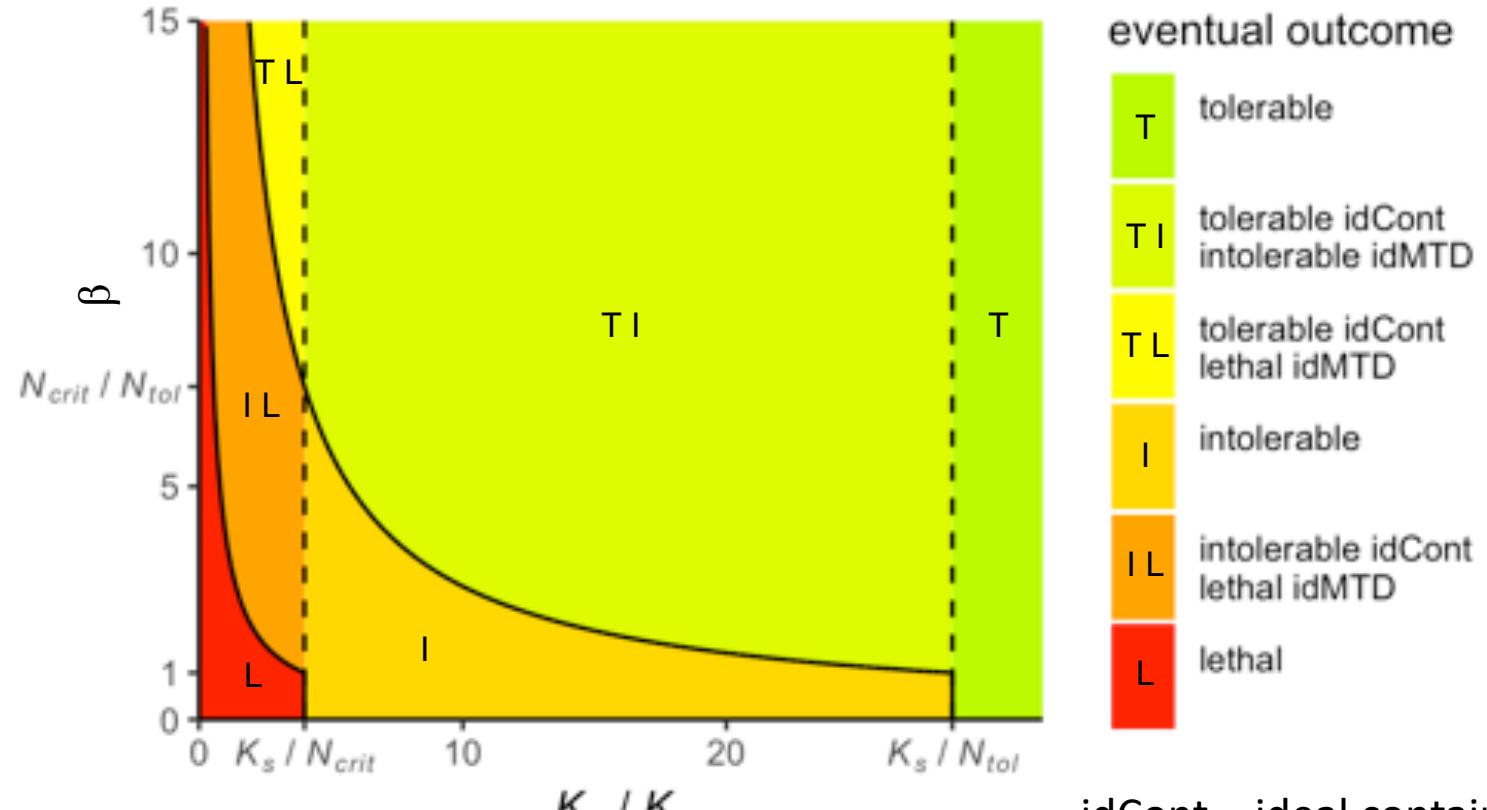
Resistance cost may correspond to:

- generally slower growth (low ρ_r)
- general inability to compete with other cells (low K_r)
- specific inability to compete with sensitive cells (high β)

Fitness costs of resistance are helpful (but not essential)

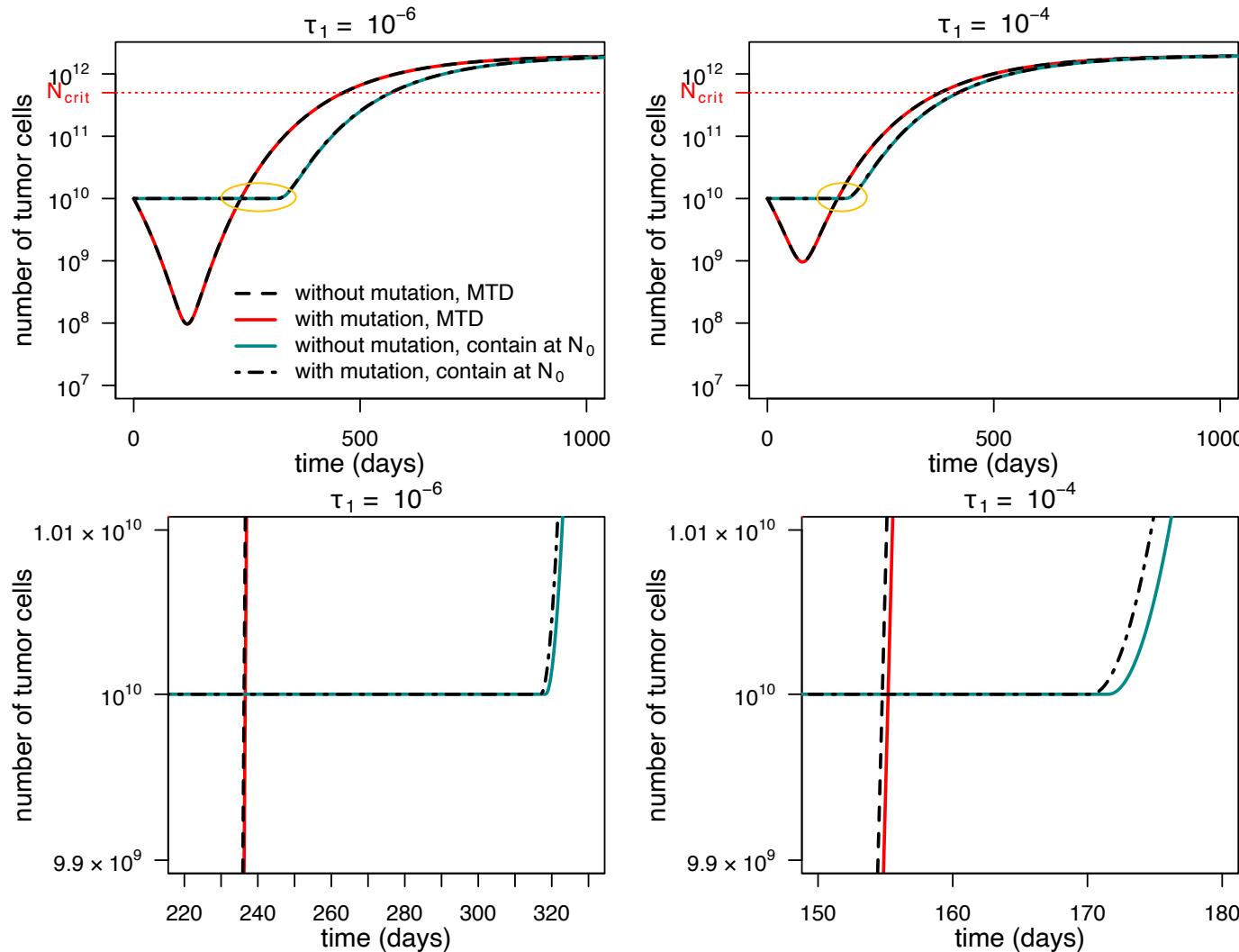


Fitness costs of resistance are helpful (but not essential)



idCont = ideal containment
idMTD = ideal MTD

Ongoing mutations (independent of drug dose) have negligible impact



Conclusions

Containment strategies generally improve on MTD

This is true even if resistance has no cellular fitness cost

Predicted clinical gains crucially depend on the intensity of competition between sensitive and resistant cells

Practical treatment strategies can be close to optimal

Support for further experimental and clinical trials

Thank you



Yannick Viossat
(Ceremade, Université
Paris-Dauphine)

Michael Hochberg
(ISEM; Sante Fe
Institute)



**Arizona Cancer
Evolution Center**

Bacevic & Noble *et al.* (2017) *Nature Comms*
Viossat & Noble (in press)

Daniel Fisher
Liliana Krasinska
Katarina Bacevic
Ahmed Soffar
and colleagues
(IGMM)



@robjohnnoble
robjohnnoble.github.io