Model-Based Optimisation Reveals Evolutionary Dynamics Conducive to Effective Therapy for Neuroblastoma

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Contents

Introduction

Neuroblastoma (NB) is the most common extra-cranial solid cancer in children.

High-risk NB usually relapse and survival is rare$\Rightarrow$ poor prognosis!

Problem: one-size-fits-all chemotherapy, e.g., COJEC protocol: cisplatin [C], vincristine [O], carboplatin [J], etoposide [E], and cyclophosphamide [C].

Introduction

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Problem: one-size-fits-all chemotherapy, e.g., COJEC protocol: cisplatin [C], vincristine [O], carboplatin [J], etoposide [E], and cyclophosphamide [C].

Solution:
personalised protocols to optimally shrink the NB overcoming drug resistance.

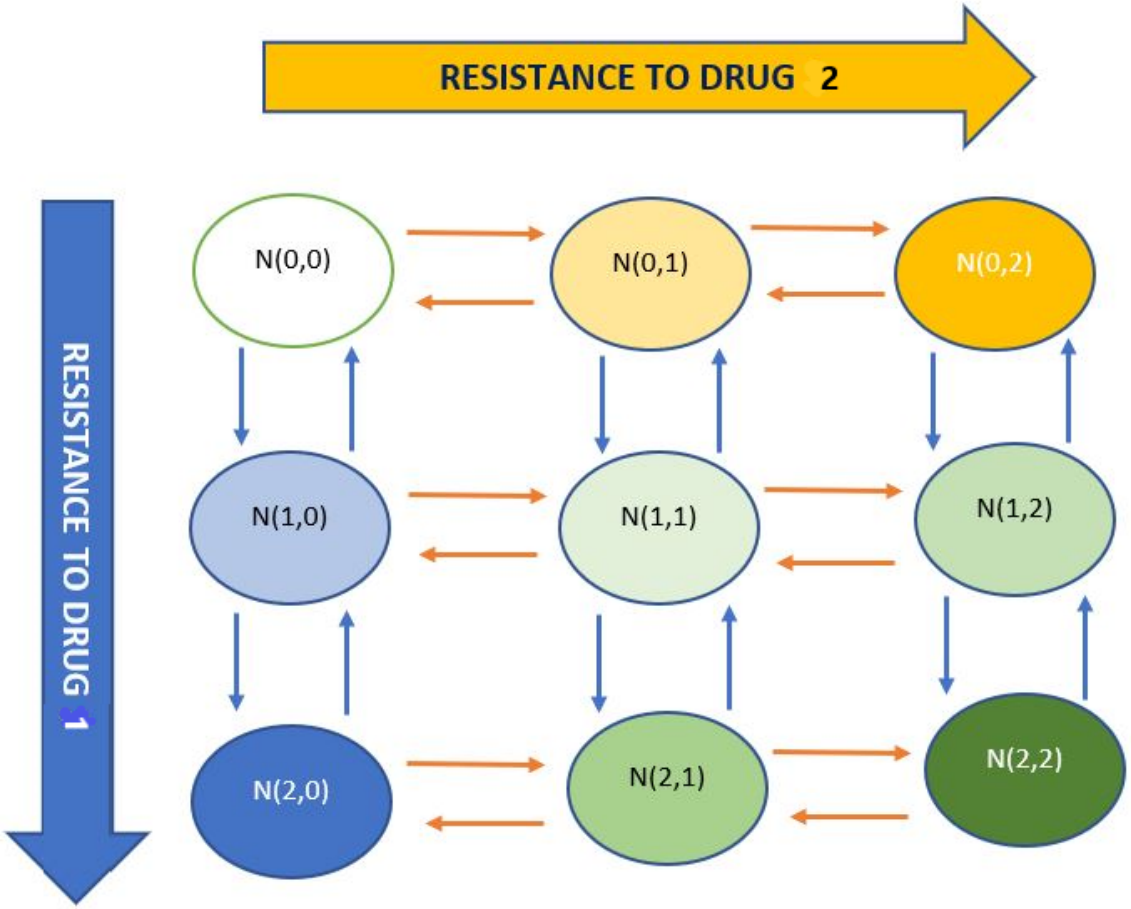
1. develop calibrated evolutionary models
2. understand patient's tumor state
3. solve drug administration control problem
4. treat patient with the optimal protocol
5. subsequent evolutionary trap: exploit targetable mutations (e.g., ALK) and oncogenic pathways (e.g., RAS-MAPK)

Simplifications: consider 2 drugs and calibrate the model on published data.

Graphical representation

Population-based model: NB under vincristine (VCR) and cyclophosphamide (CPM).

Drug resistance: genetic and plastic.



Mathematical model

A system of ODEs, one for each sub-population + one for each drug:

$$\frac{dn_{i,j}(t)}{dt} = \frac{G(t)}{1+\alpha_r\phi(\tau)} - \frac{M(t)}{1+\alpha_r\phi(\tau)} - \frac{D(t)}{1+\alpha_m\phi(\tau)}, \quad i,j = 0,1,2 \tag{1}$$

$G(t) = \left(1 - \frac{\sum_{k,l} n_{k,l}(t)}{K}\right)\left(r_{i,j}n_{i,j}(t)\right)$ is the logistic **growth rate**

$M(t) = \mu\left(1 - \frac{\sum_{k,l} n_{k,l}(t)}{K}\right)\left(\gamma_{i,j}r_{i,j}n_{i,j}(t) - \sum_{p,q} r_{p,q}n_{p,q}(t)\right)$ is the result of **mutation** events

$D(t) = \sum_d m_d^{i,j}(c_d(t))n_{i,j}(t)$ is the rate of **drug-induced death**

$\phi(\tau) = \frac{\tau}{\tau_{max}}$ represents the **plastic response** development

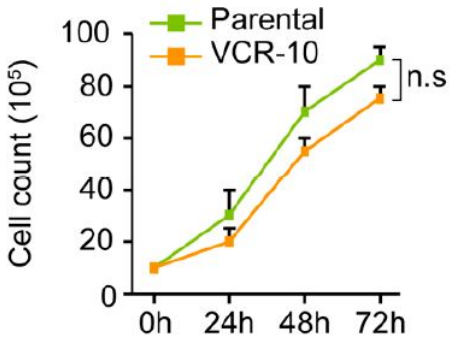
$$\frac{dc_d(t)}{dt} = \omega_d(t) - z_d c_d(t), \quad d = 1,2 \tag{2}$$

$\omega_d(t)$ are the **drug dosages**, i.e., the control variables.

Model calibration

Goal: reflect the **biological behavior** of NB cells under treatment with VCR and CPM observed in **laboratory experiments** on human, mice, and cell lines:

1. data from low-density drug-free experiments $\Rightarrow$ growth rates



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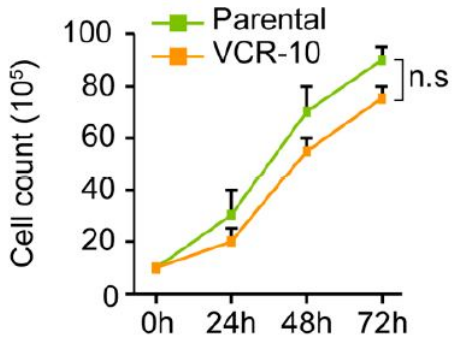
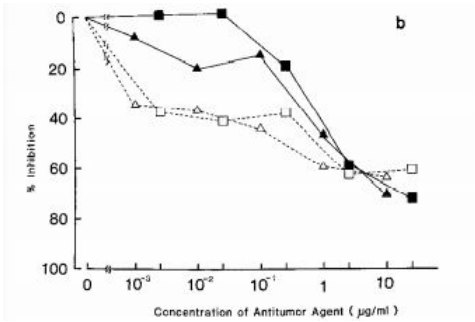
2. data of inhibited NB with different resistance levels and drug concentrations
   $\Rightarrow$ drug-induced mortality rates





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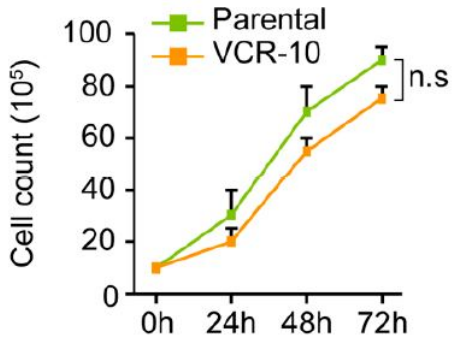
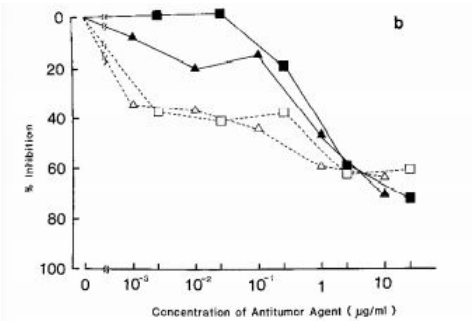
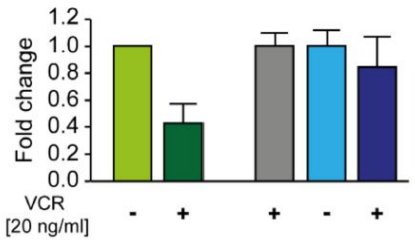


2. data of inhibited NB with different resistance levels and drug concentrations ⇒ drug-induced mortality rates

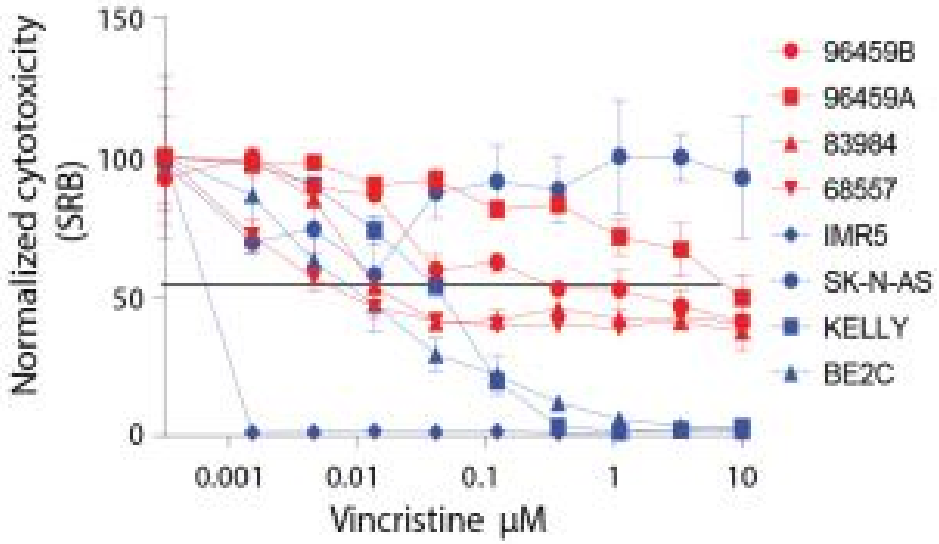


3. data where mortality has been re-tested after some weeks from the last treatment ⇒ plastic response



Model validation

1. Analyzing the model evolution in common and naive situations.
2. Matching experiments on VCR resistant clones related to VCR drug acclimation.
3. Matching experiments involving multidrug resistance:
   CPM resistant clone treated with VCR at different concentrations.



Control problem: drug administration optimization

Real (COJEC) protocol: fixed eight 2-week cycles, VCR dosage $= 2[\frac{ng}{mL}]$, CPM dosage $= 2[\frac{g}{m^2}]$

Problem: can we improve COJEC?
(a) What is the optimal number of cycles? (b) What are the optimal dosages in each cycle?

Solution: drug administration control problems with pre-chosen number of cycles:

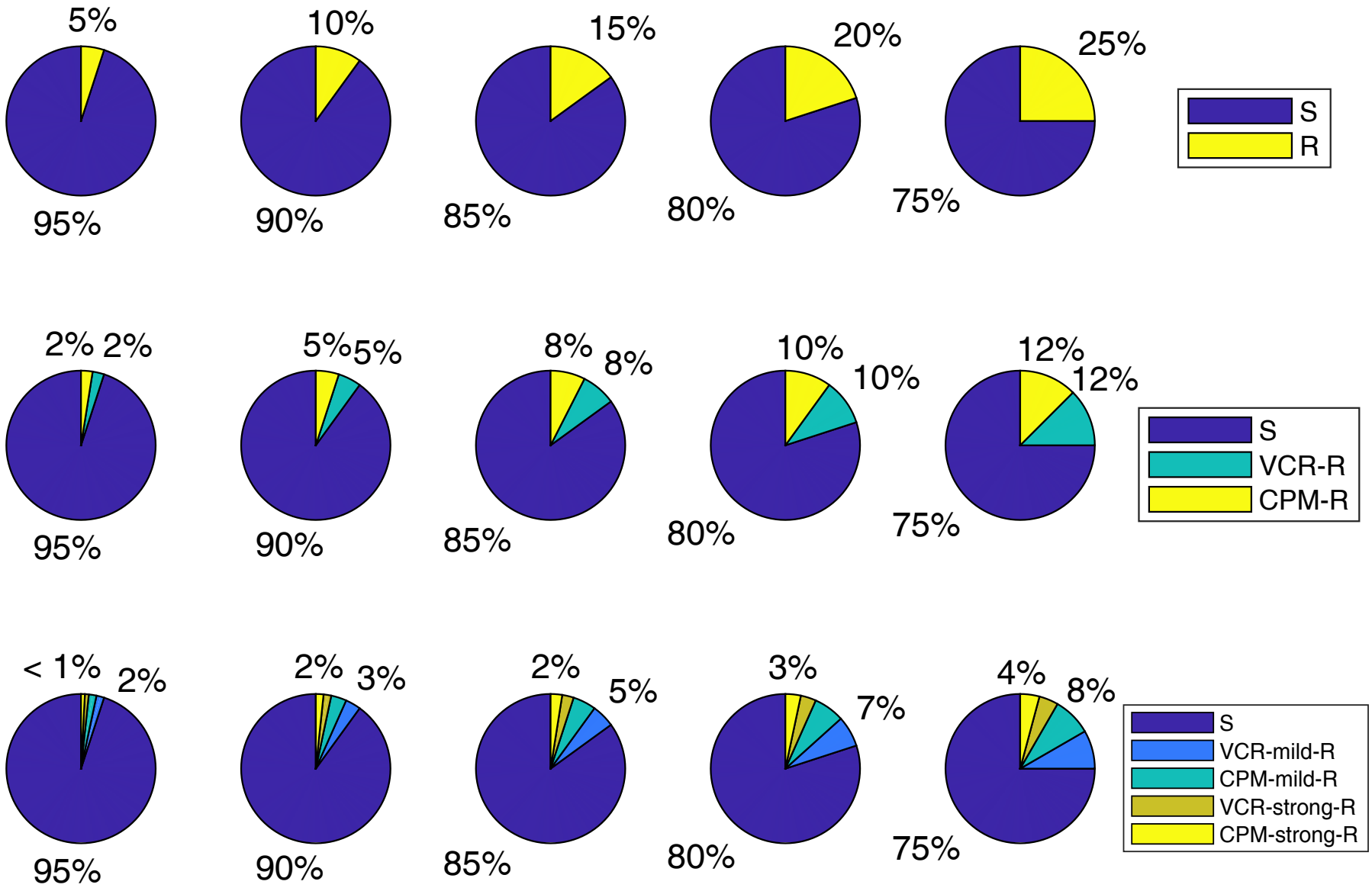
- objective function: final population size
- control variables: drug dosages
- constraints:
  VCR dosage $\leq 2[\frac{ng}{mL}]$, CPM dosage $\leq 2[\frac{g}{m^2}]$ (maximum tolerated doses (MTD))

Optimal treatment research: local research (fmincon MatLab function) starting from the optimal solution proposed by a global research (genetic algorithm).

Child data: 3 year-old, 80 cm in height and 15 kg in weight.

Initial tumor population: $N(0) = \sum_{i,j} n_{i,j}(0) = K/2$

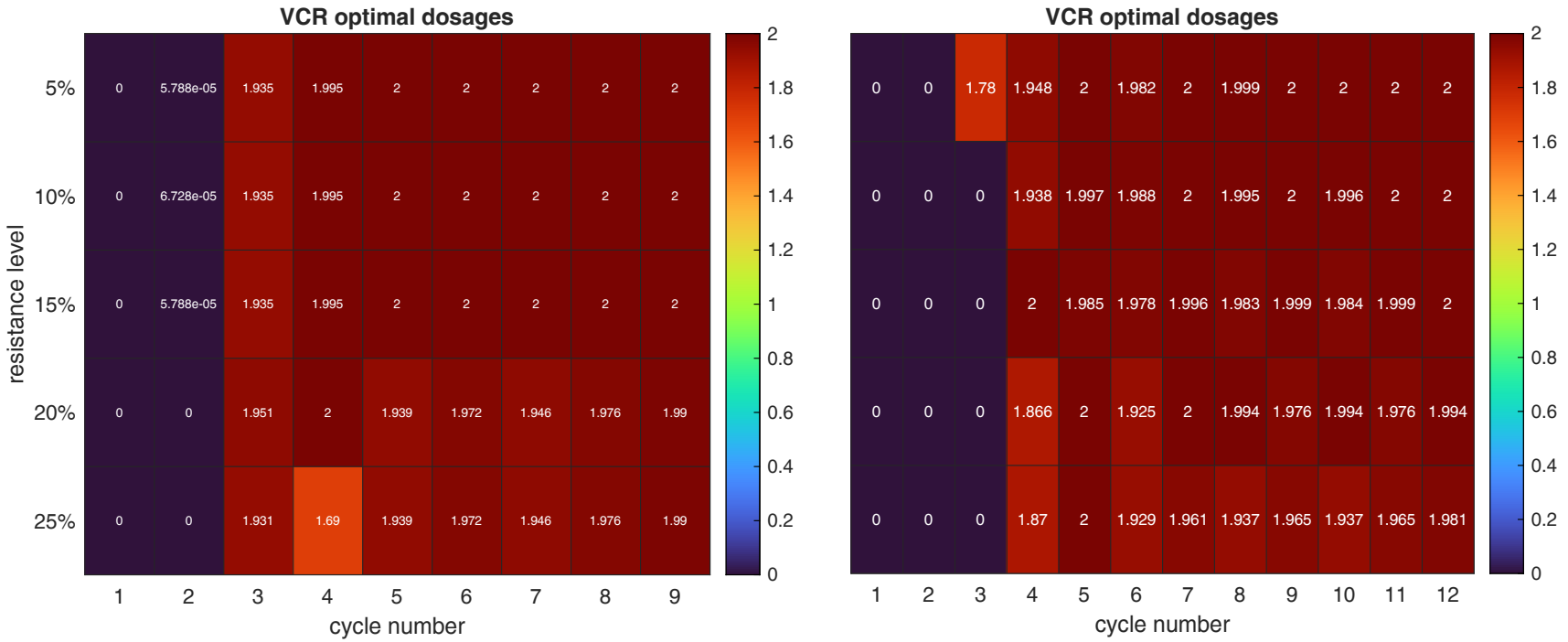
Initial cancer compositions



Optimal protocols with VCR resistant clones

What should the oncologist do when the cancer is resistant to VCR?

Mild- and strong-resistant clones on the left and right, respectively



CPM dosages $= 2[\frac{g}{m^2}]$.

Optimal protocols with CPM resistant clones

What should the oncologist do when the cancer is resistant to CPM?

CPM mild-resistant clone: 6 cycles with both VCR and CPM always at MTD.

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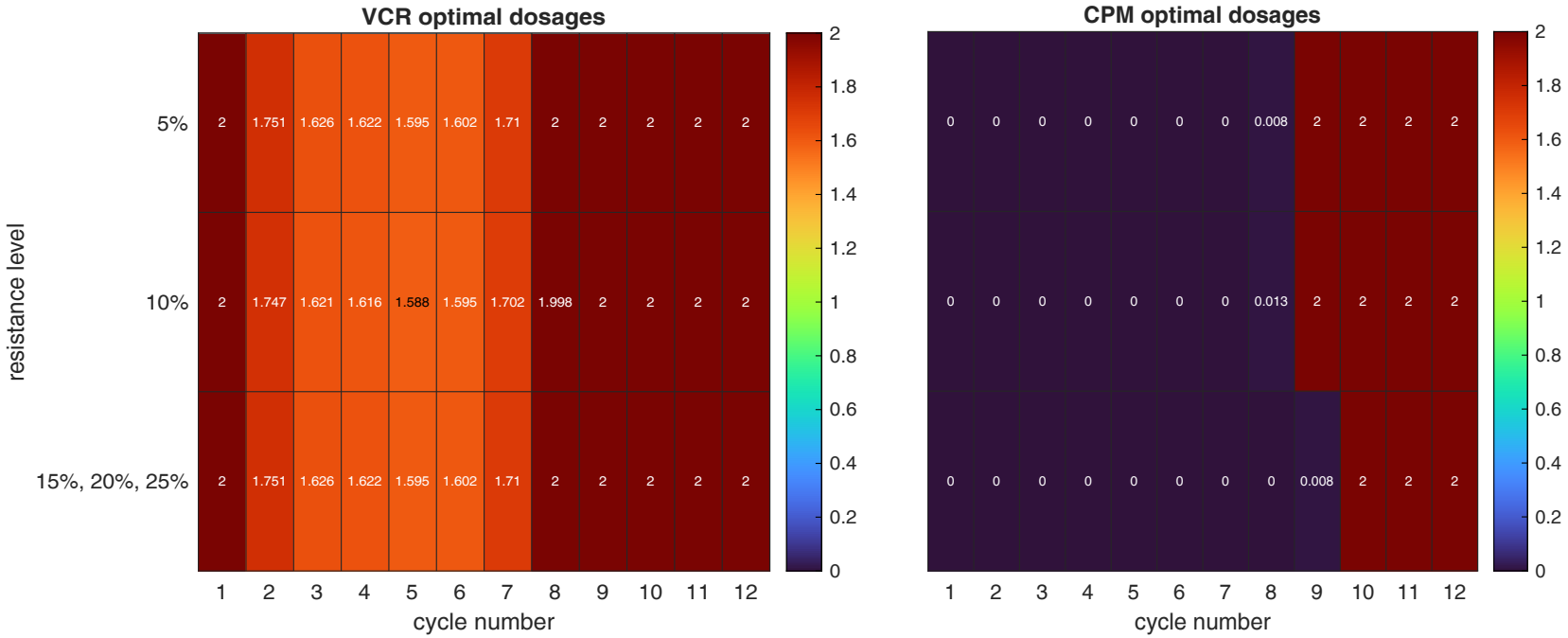
CPM strong-resistant clone:



Opt. protocols with both VCR and CPM resistance

What should the oncologist do when the cancer is resistant to VCR and CPM?

- **mild-resistant clones**: administering both VCR and CPM at MTD for 6 cycles except for 5% of initial resistance with MTD for 7 cycles.
- **strong-resistant clones**: administering both VCR and CPM at MTD for 4 cycles in cases of 5% and 10% of initial resistance. With 15%, 20%, and 25%, 12 cycles with VCR at MTD and with CPM administered only in the last 6 cycles at MTD (null for the first 6 cycles).
- **mild- and strong-resistant clones**: administering always both VCR and CPM at MTD for 5 cycles in case of 5% of initial resistance and for 4 cycles in the other cases up to 20%. With 25%, 12 cycles with VCR always at MTD and with CPM administered only in the last 7 cycles at MTD (null for the first 5 cycles).

$\Rightarrow$ same logic as the cases with only the CPM resistant clones.

Sizes and gains with respect to the standard protocol

res. (%)	VCR mild Cells ($\cdot 10^8$)	gain (%)	VCR strong Cells ($\cdot 10^8$)	gain (%)	CPM mild Cells ($\cdot 10^8$)	gain (%)	CPM strong Cells ($\cdot 10^8$)	gain (%)
5	1.1699	16.09	0.534240	50.48	4.208527	8.40	9.927225	61.40
10	1.7957	21.18	1.107225	51.35	6.704239	10.10	13.99521	55.89
15	2.3842	21.40	1.107225	51.35	8.700067	8.58	16.66951	51.57
20	2.9086	21.07	1.357534	51.00	10.33132	6.65	19.19666	46.59
25	3.4220	19.46	1.597761	50.25	11.68843	4.79	21.59912	41.49

res. (%)	both mild Cells ($\cdot 10^8$)	gain (%)	both strong Cells ($\cdot 10^8$)	gain (%)	all Cells ($\cdot 10^8$)	gain (%)
5	3.043112	1.31	7.668535	58.60	5.424849	45.06
10	4.920316	4.3	11.376	55.02	8.138322	47.17
15	6.404044	4.82	12.273	57.42	10.04542	46.31
20	7.724313	4.01	12.526	59.58	11.82512	43.90
25	8.809467	2.98	12.684	60.92	12.122	46.95

Conclusions

- We have developed and validated a calibrated PB model reflecting the behavior of NB under VCR and CPM observed in laboratory experiments

- Optimization results:
  (a) MTD protocol is optimal when the cancer is sensitive to the drugs the protocol contains.

  (b) Otherwise, an oncologist would need to know the cytotoxicity of each drug, the cancer's clonal composition, and the fitness of each clone to find the optimal protocol.

  (c) Here, the two major strategies are delayed application of one drug lengthening the number of cycles and using MTD dosages shortening the number of cycles.

  (d) With three or more drugs, it is impossible to generalise, hence the importance of model-based protocols.

- Treat CPM resistant clones is more difficult than VCR resistant clones

- The oncologist would customise the subsequent evolutionary trap according to the enriched mutations and the selected oncogenic pathways by drugs.

- Our model can absorb an evolutionary rulebook and patient-specific data (e.g., real-time liquid and biopsies, chemoresistant gene signature) to form a decision support system.