Model-Based Optimisation Reveals Evolutionary Dynamics Conducive to New Therapeutic Strategy for Neuroblastoma

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INTRODUCTION

Neuroblastoma (NB) is the most common extra-cranial solid tumour in children accounting for 15 % of cancer-related deaths in children.

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

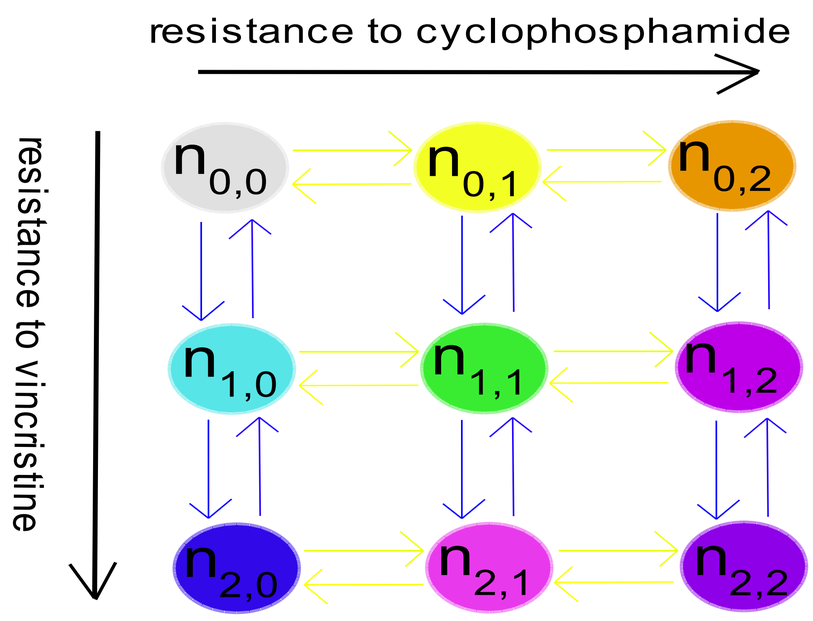
Questions: Can we improve COJEC? What is the optimal number of cycles? What are the optimal dosages in each cycle?

Solution: personalised protocols to optimally shrink the NB.

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: considering 2 drugs and calibration on published data.

METHODOLOGY



Population-based model: NB under vincristine and cyclophosphamide.
Drug resistance: genetic and plastic (drug acclimation).

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

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

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

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

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

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

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

Model calibration: reflects the behavior of NB cells under treatment observed in laboratory experiments on human, mice, and cell lines.

Model validation: analysing the model evolution in trivial and common situations; matching experiments on resistant clones related to drug acclimation and experiments involving multidrug resistance.

SIMULATIONS AND RESULTS

Real (COJEC) protocol: eight 2-week cycles with fixed dosages in each cycle; O dosage = 2 [ng/mL], C dosage = 2 [g/m^2].

Drug administration control problem with pre-chosen cycle number:

objective function: final population size

control variables: drug dosages

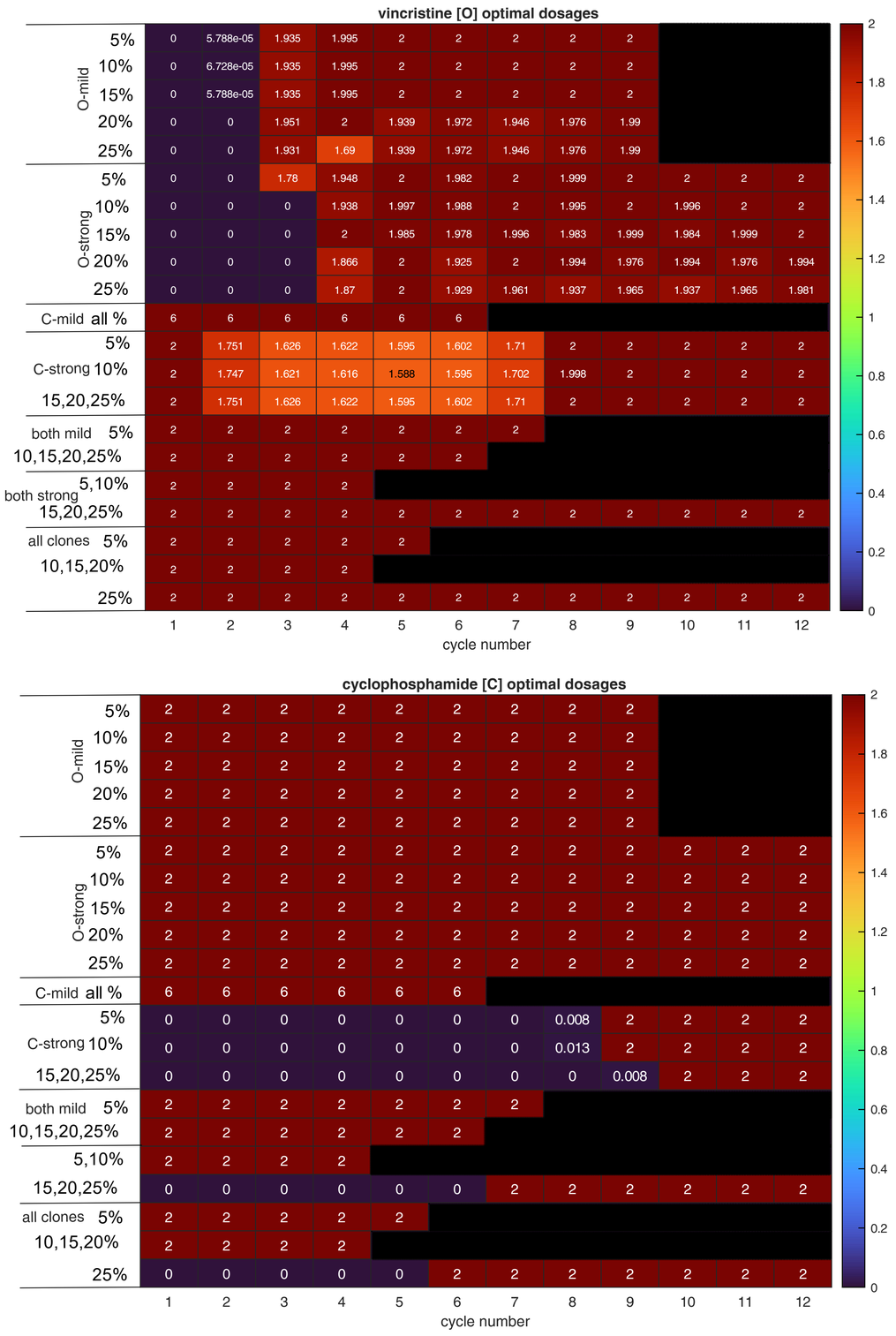
constraints: O dosage ≤ 2 [ng/mL] and C dosage ≤ 2 [g/m^2]

Optimisation algorithm: genetic algorithm + local search.

Virtual cohort: 3 year-old children (80 cm in height and 15 kg in weight); tumour population: N(0) = K/2; initial tumour compositions:

-**resistance levels**: 5, 10, 15, 20, and 25 % of tumour mass

-**resistance heterogeneity**: composed of only one type of resistant clone or different types (the other being sensitive)



CONCLUSIONS

-We developed a model reflecting the behavior of NB observed in laboratory without drugs, under vincristine, and cyclophosphamide.

-**Optimisation results**:

(a) COJEC protocol is only optimal when the tumour is initially sensitive.

(b) Otherwise, the oncologist would need to know the drug cytotoxicity, the tumour's clonal initial composition, and the fitness of each clone.

(c) 2 major strategies: delaying the application of one drug lengthening the cure, and using maximum dosages shortening the cure.

(d) With more drugs, it is hard to generalise ⟹ model-based protocols.

-Treat C resistant clones is more difficult.

-Subsequent evolutionary trap: enriched mutations and oncogenic pathways.

-Our model could absorb an evolutionary rulebook and patient-specific data ⟹ decision support system.

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