Model-Based Optimisation Reveals Evolutionary Dynamics Conducive to New Therapeutic Strategy for Neuroblastoma Matteo Italia¹, Kenneth Y. Wertheim², Sabine Taschner-Mandl³, Dawn Walker², and Fabio Dercole¹ ¹Politecnico di Milano, ²University of Sheffield, and ³St. Anna Children's Cancer Research Institute

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

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/m²].

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/m²]

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

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

resistance to cyclophosphamide





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

					vincrist		optimal c	iosages				
5%	0	5.788e-05	1.935	1.995	2	2	2	2	2			
<u></u> 10%	0	6.728e-05	1.935	1.995	2	2	2	2	2			
	0	5.788e-05	1.935	1.995	2	2	2	2	2			
20%	0	0	1.951	2	1.939	1.972	1.946	1.976	1.99			
25%	0	0	1.931	1.69	1.939	1.972	1.946	1.976	1.99			
5%	0	0	1.78	1.948	2	1.982	2	1.999	2	2	2	2
_{ರಾ} 10%	0	0	0	1.938	1.997	1.988	2	1.995	2	1.996	2	2
15%	0	0	0	2	1.985	1.978	1.996	1.983	1.999	1.984	1.999	2
് 20%	0	0	0	1.866	2	1.925	2	1.994	1.976	1.994	1.976	1.994
25%	0	0	0	1.87	2	1.929	1.961	1.937	1.965	1.937	1.965	1.981
C-mild all %	6	6	6	6	6	6						
5%	2	1.751	1.626	1.622	1.595	1.602	1.71	2	2	2	2	2
C-strong 10%	2	1.747	1.621	1.616	1.588	1.595	1.702	1.998	2	2	2	2
15,20,25%	2	1.751	1.626	1.622	1.595	1.602	1.71	2	2	2	2	2
both mild 5%	2	2	2	2	2	2	2					
,15,20,25%	2	2	2	2	2	2						
5,10%	2	2	2	2								
15,20,25%	2	2	2	2	2	2	2	2	2	2	2	2
all clones 5%	2	2	2	2	2							
10,15,20%	2	2	2	2								
25%	2	2	2	2	2	2	2	2	2	2	2	2
	1	2	3	4	5	6	7	8	9	10	11	12

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^Ē 15%	2	2	2	2	2	2	2	2	2				
20%	2	2	2	2	2	2	2	2	2				
25%	2	2	2	2	2	2	2	2	2				
5%	2	2	2	2	2	2	2	2	2	2	2	2	
_{ರ್} 10%	2	2	2	2	2	2	2	2	2	2	2	2	
15%	2	2	2	2	2	2	2	2	2	2	2	2	
ల్ 20%	2	2	2	2	2	2	2	2	2	2	2	2	-
25%	2	2	2	2	2	2	2	2	2	2	2	2	
C-mild all %	6	6	6	6	6	6							-
5%	0	0	0	0	0	0	0	0.008	2	2	2	2	
C-strong 10%	0	0	0	0	0	0	0	0.013	2	2	2	2	-
15,20,25%	0	0	0	0	0	0	0	0	0.008	2	2	2	
both mild 5%	2	2	2	2	2	2	2						-
0,15,20,25%	2	2	2	2	2	2							
5,10%	2	2	2	2									-
15,20,25%	0	0	0	0	0	0	2	2	2	2	2	2	
all clones 5%	2	2	2	2	2								
10,15,20%	2	2	2	2									
25%	0	0	0	0	0	2	2	2	2	2	2	2	
	1	2	3	4	5	6	7	8	9	10	11	12	

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:

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

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

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

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

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

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

 $\omega_d(t)$ 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.

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





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St. Anno Kinderkrebs Forschung St. Anna Kinderkrebstorschung CHILDREN'S CANCER RESEARCH INSTITUTE 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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