IMPERIAL

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Conceptual Building Blocks for Novel Evolutionary and Targeted Therapies for Neuroblastoma

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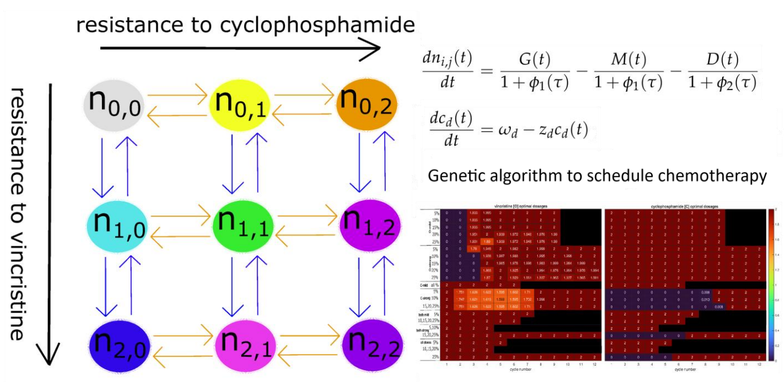
Neuroblastoma:

- Most common extracranial solid tumour in childhood [1].
- High-risk cases, five-year survival rate 50%, *MYCN* amplification [1].
- p53 is rarely mutated at diagnosis [2].
- Cancer cells interconvert between NOR-like (N) and MES-like (S) phenotypes [3].

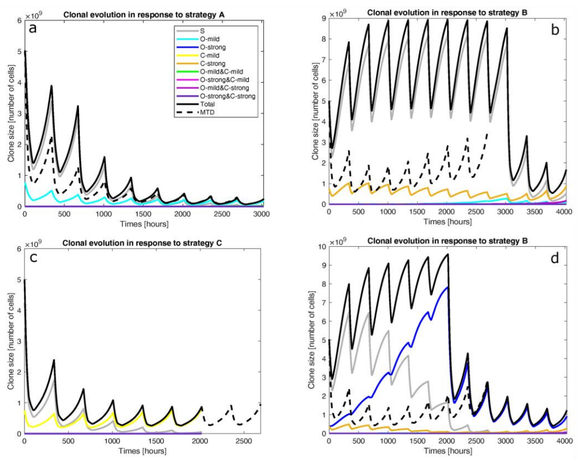
Can phenotypic plasticity be exploited to enhance evolutionary therapy?



$$\frac{dn_{i,j}(t)}{dt} = \frac{G(t)}{1+\phi_1(\tau)} - \frac{M(t)}{1+\phi_1(\tau)} - \frac{D(t)}{1+\phi_2(\tau)}$$

$$\frac{dc_d(t)}{dt} = \omega_d - z_d c_d(t)$$

Genetic algorithm to schedule chemotherapy



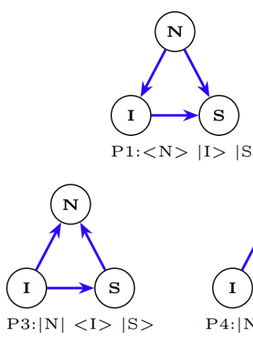
- Cyclophosphamide resistance. Mild: use both drugs. Strong: prolong adaptive therapy [4].

$$\frac{dN}{dt} = k_1^N N(\frac{1-P}{K}) - k_2^N ND + k_3^{(S,N)} S + k_3^{(I,N)} I - k_3^{(N,S)} N - k_3^{(N,I)} N$$

$$\frac{dS}{dt} = k_1^S S(\frac{1-P}{K}) - k_2^S SD + k_3^{(N,S)} N + k_3^{(I,S)} I - k_3^{(S,N)} S - k_3^{(S,I)} S$$

$$\frac{dI}{dt} = k_1^I I(\frac{1-P}{K}) - k_2^I ID + k_3^{(S,I)} S + k_3^{(N,I)} N - k_3^{(I,S)} I - k_3^{(I,N)} I$$

$$P = N + S + I$$



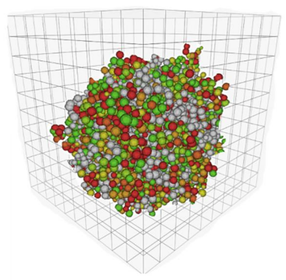
Plus S inhibitors

Plus N inhibitors

- Five out of 64 interconversion patterns have therapeutic potential.
- Target NOR-like or MES-like cells without letting intermediate (I) cells build up [5].

How do cellular phenomena arise from non-linear intracellular dynamics?

GPU-accelerated multicellular model



Mechanical model of cell-cell repulsion

Overlap

$$\delta_{1,2} = R_1 + R_2 - \|\boldsymbol{r}_1 - \boldsymbol{r}_2\|$$

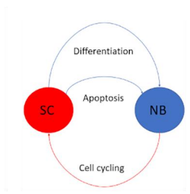
Repulsive force

$$F_{1,2} = k_1 \delta_{1,2}$$

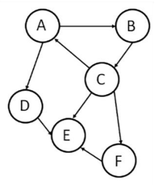
Equation of motion

$$F^x = \mu(1+M)\frac{dx}{dt}$$

Intercellular interactions

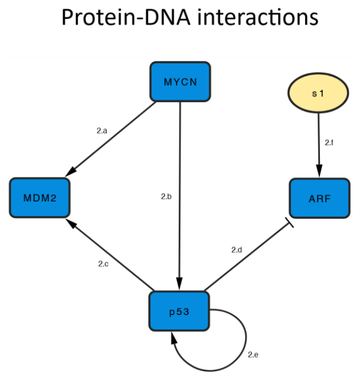


Probabilistic conditional statements about an intracellular network of 20 gene products

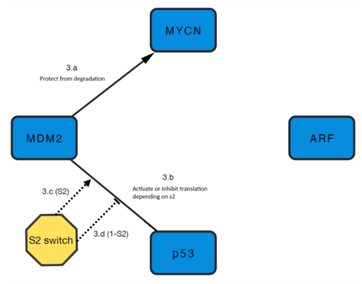


- Inhibiting p53 could unexpectedly result in regression [6]. DNA damage repair.

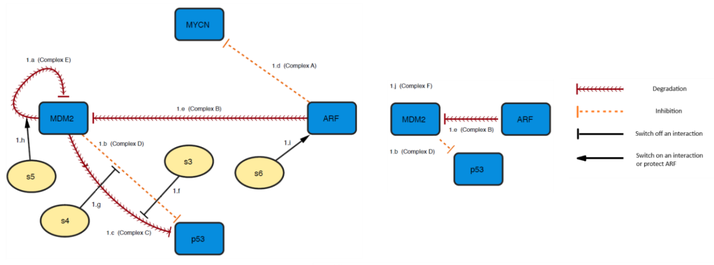
Protein-DNA interactions



Protein-mRNA interactions

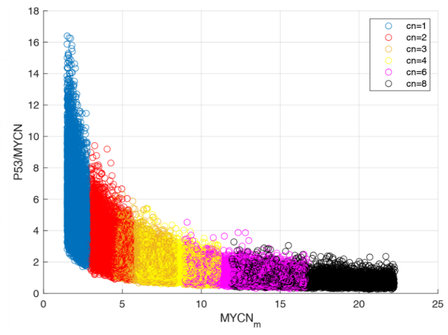


Protein-protein interactions



$$\frac{dm_i(t)}{dt} = k_i - \delta_{m_i} m_i(t)$$

$$\frac{dp_i(t)}{dt} = l_i m_i(t) - \delta_{p_i} p_i(t)$$



- Clinical outcome has a non-linear relationship with *MYCN* expression [7].
- p53/MYCN is a better prognostic metric.

Next: Learn representations of hybrid multi-omic datasets, predict model parameters, and design evolutionary targeted therapies *in silico*.

References: [1] Matthay, K., Maris, J., Schleiermacher, G. *et al.* Neuroblastoma. *Nat Rev Dis Primers* **2**, 16078 (2016). https://doi.org/10.1038/nrdp.2016.78, [2] Almeida, Joana, et al. "Deciphering the role of p53 and TAp73 in neuroblastoma: from pathogenesis to treatment." *Cancers* 14.24 (2022): 6212, [3] Durbin, Adam D., and Rogier Versteeg. "Cell state plasticity in neuroblastoma." *EJC paediatric oncology* 4 (2024): 100184, [4] Italia, Matteo, et al. "Mathematical model of clonal evolution proposes a personalised multi-modal therapy for high-risk neuroblastoma." *Cancers* 15.7 (2023): 1986, [5] Walton, Jeanette D., et al. "Characteristics of stem cells from human neuroblastoma cell lines and in tumors." *Neoplasia* 6.6 (2004): 838-845, [6] Wertheim, Kenneth Y., et al. "Multicellular model of neuroblastoma proposes unconventional therapy based on multiple roles of p53." *PLOS Computational Biology* 20.12 (2024): e1012648, [7] Tang, Xao X., et al. "The MYCN enigma: significance of MYCN expression in neuroblastoma." *Cancer research* 66.5 (2006): 2826-2833.