Phenotypic Plasticity in Neuroblastoma: Implications for Evolutionary and Targeted Therapy

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Introduction

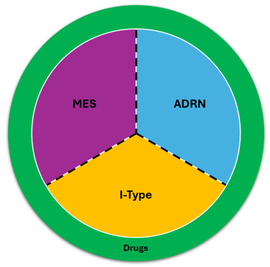
Neuroblastoma (NB) is a paediatric cancer, affecting children under the age of 5 years old, accounting for 15% of all paediatric cancer deaths [1,3].

Problem: NB contains 3 cell types: noradrenergic-like cells (ADRN), mesenchymal-like cells (MES) and an intermediate cell type (I-type). These cells show resistance to different treatments, and are able to interconvert into one another to escaping treatmen[2,4].

Research Aim: To understand and exploit the interconversion dynamics in the context of NB treatment with targeted therapies.

Model Structure

Population structure in Neuroblastoma



System of ODEs for each cell population and drug

N = ADRN , I = I-type, S = MES , D = Drug, T = Total population

$$T = (N + I + S) \quad (1)$$

$$\frac{dN}{dt} = k_1^N N\left(\frac{1-T}{K}\right) - k_2^N N D(t) + k_3^{S,N} S + k_3^{I,N} I - k_3^{N,S} N - k_3^{N,I} N \quad (2)$$

$$\frac{dS}{dt} = k_1^S S\left(\frac{1-T}{K}\right) - k_2^S S D(t) + k_3^{N,S} N + k_3^{I,S} I - k_3^{S,N} S - k_3^{S,I} S \quad (3)$$

$$\frac{dI}{dt} = k_1^I I\left(\frac{1-T}{K}\right) - k_2^I I D(t) + k_3^{N,I} N + k_3^{S,I} S - k_3^{I,N} I - k_3^{I,S} I \quad (4)$$

$$\frac{dD}{dT} = kw - kdD \quad (5)$$

k1 = growth rate. k2 = drug dependant death rate. k3 = Interconversion between the cell types

Simulation Configuration

Natural Tumour Growth → Treatment → Relapse

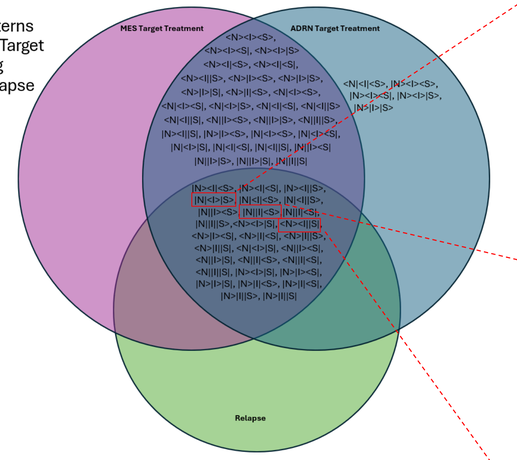
Parameter	Value
Initial Cell populations	0. 000001
N Growth Rate	0.75
I Growth Rate	0.5
S Growth Rate	0.25
Death Rate Target Cell	1
Death Rate None Target Cell	{0, 0.5}
Drug Concentrations	{0.1, 0.5, 0.9}
Interconversion Rates	{0, 0.5}

64 Interconversion Patterns (<> Open Path, | Closed Path)

Example: <N>|I>|S|

Results

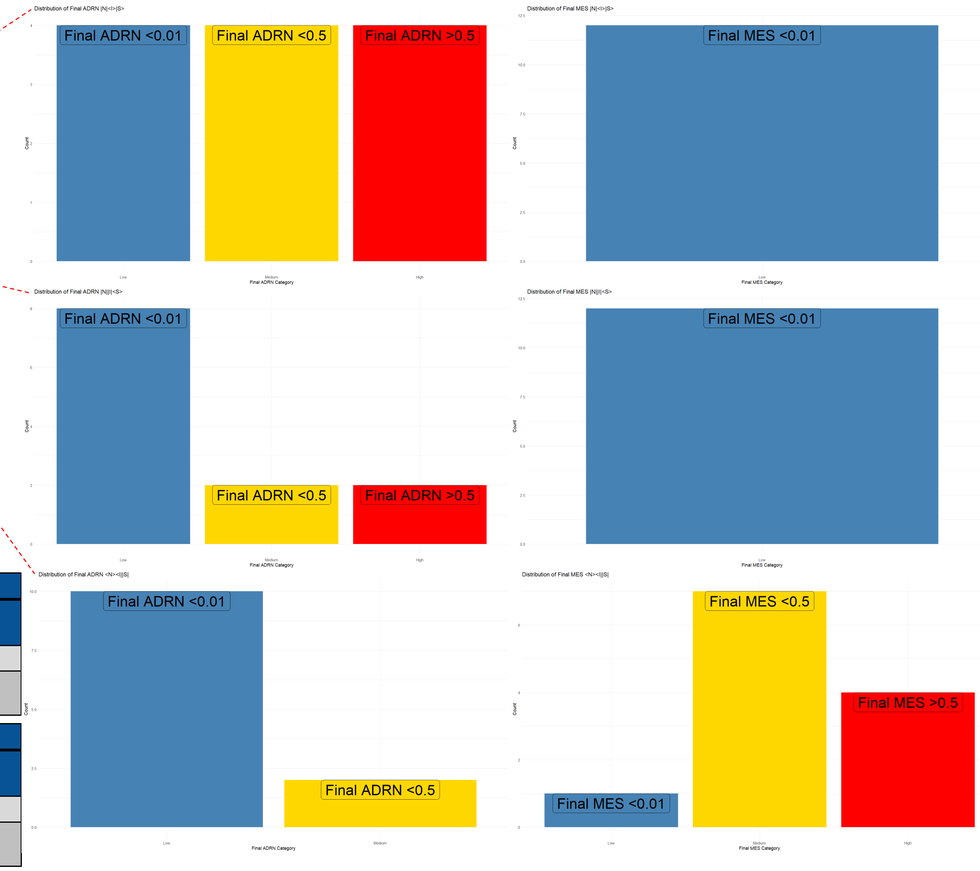
Distribution of Patterns That Reduce Final Target Populations During Treatment and Relapse



Stability Analysis

ADRN Target

MES Target



|N|<I>|S>

Origin	All Zero	N Dominant	I Dominant	S Dominant	Others	Total runs
Stable	0	52	0	0	0	52
Unstable	116	156	0	0	0	272

|N||I|<S>

Origin	All Zero	N Dominant	I Dominant	S Dominant	Others	Total runs
Stable	0	0	0	0	0	0
Unstable	27	31	0	265	0	324

<N><I||S|

Origin	All Zero	N Dominant	I Dominant	S Dominant	Others	Total runs
Stable	0	0	0	0	0	0
Unstable	60	0	240	24	0	324

Conclusions

- The model used to simulate the effect of phenotypic plasticity on targeted therapies.
- Certain interconversion patterns enhanced the drug's ability to reduce the number of target cells and sustain lower target cell levels during the relapse phase.
- The distribution of target cells in the final population varies between interconversion pattern, with some patterns leading to consistently low levels and others having a mix of low, medium and high levels.
- The stability of the model differed across different interconversion patterns, with some patterns showing no stable states and others having a mix of stable and unstable states.
- If we can induce specific interconversion patterns, we can make inhibitors of ADRN and MES cells more effective.

Acknowledgements

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References

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