The First Multi-Cellular Model of Neuroblastoma

K. Y. Wertheim, R. Chisholm, P. Richmond, D. Walker

University of Sheffield, Sheffield, South Yorkshire S10 2TN
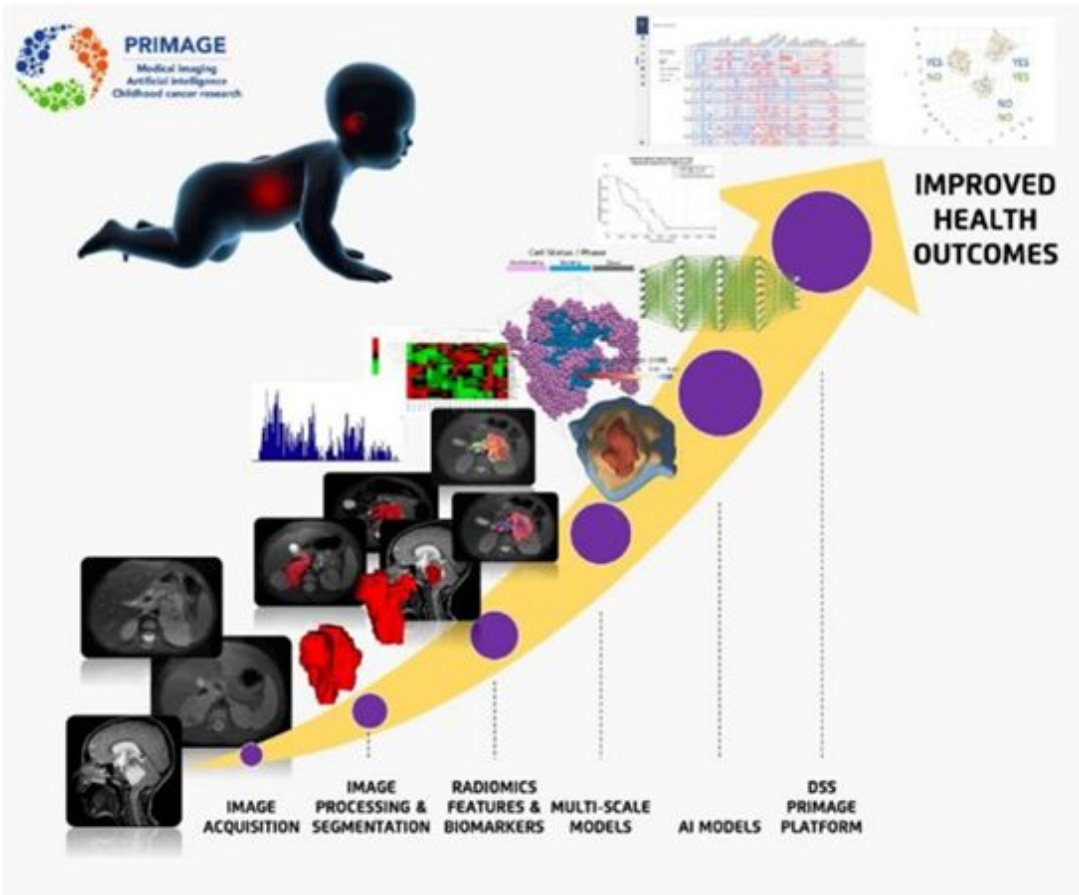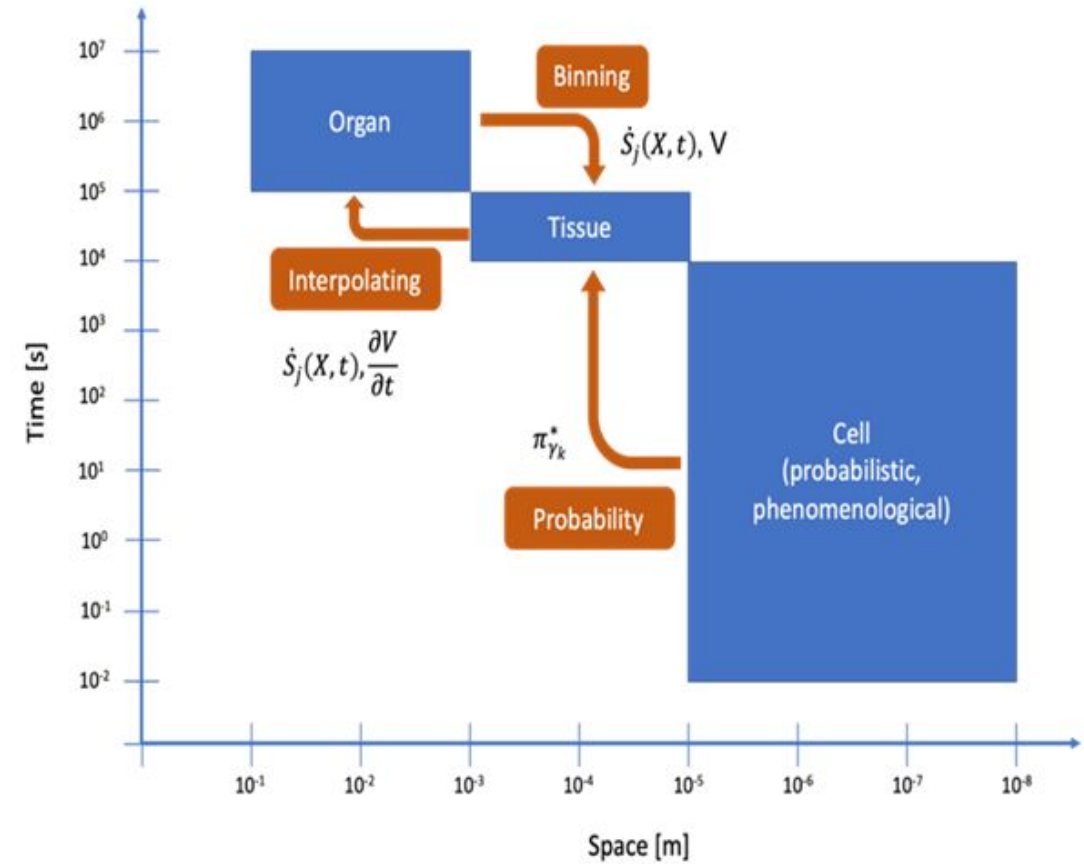
k.wertheim@sheffield.ac.uk

PRIMAGE

Medical imaging
Artificial intelligence
Childhood cancer research

Horizon 2020
European Union Funding
for Research & Innovation

(Martí-Bonmatí *et al*. 2020) (de Melo Quintela *et al*. 2021)

Decision support system for the clinical management of malignant solid tumours.

1. Image acquisition, processing, and segmentation.
2. Integrate radiomic features with other biomarkers, such as mutations and histology.
3. **Multiscale models: organ/tumour, <u>tissue</u>, and intracellular.**
4. Machine learning techniques extract insights from simulation results.
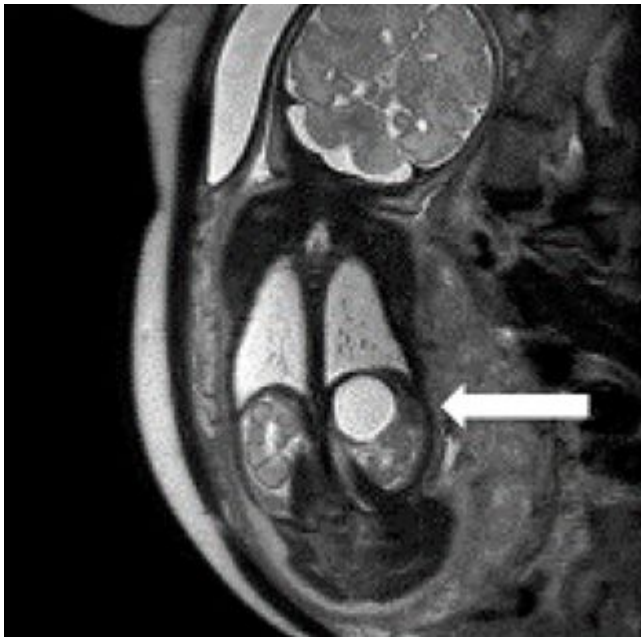
(Louis and Shohet 2015)

Context: neuroblastoma.
- Most common extracranial solid tumour of childhood.
- 15 % of cancer-related deaths in children.
- Primary tumour site, usually adrenal medulla.
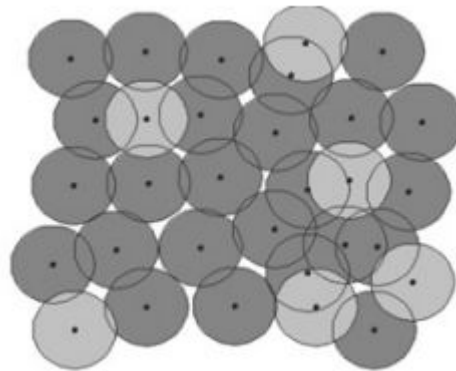- < 50 % survival rate in high-risk cases.
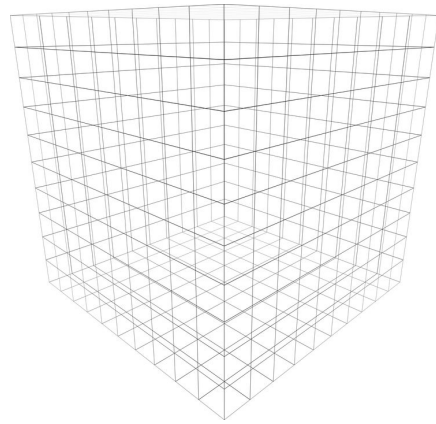
Part 1: continuous automaton.
- Voxelate the tumour microenvironment.
- Spatial distributions of cells and matrix.
- Oxygen, nutrients, and chemotherapeutic drugs (uniform).
- Inflammation (uniform).

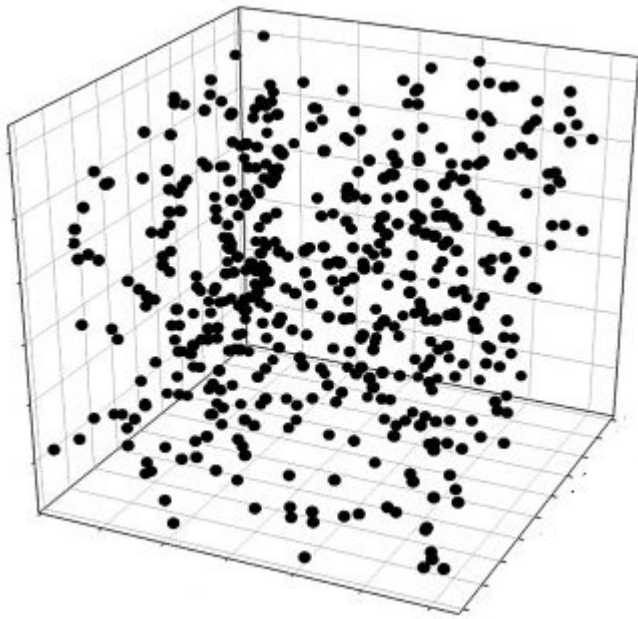(Pathmanathan *et al.* 2009)
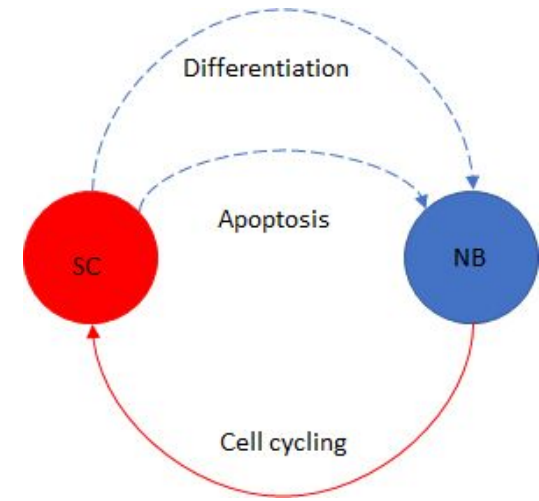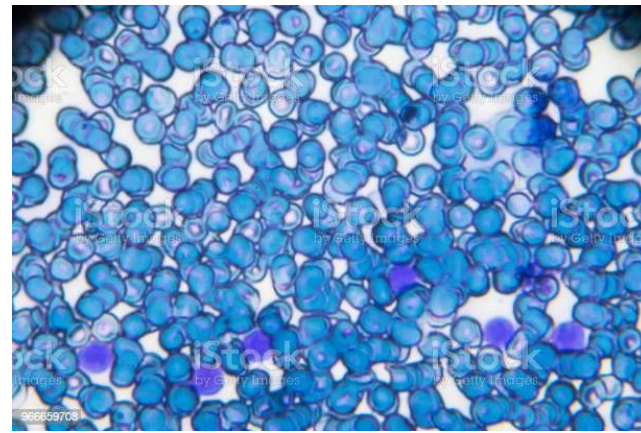
Part 2: discrete agents.
- Neuroblasts and Schwann cells.
- Mutations and gene expression levels.
- DNA status (short telomeres, unreplicated, and generic damage).
- Cell cycling (proliferation and division).
- Cell death (apoptosis and necrosis).

Part 3: centre-based mechanical model.
- Cell migration resolves cell-cell overlap.
- Boundary conditions and matrix abundance.

(Ackermann *et al.* 2018)

	Three-stage fit	95% CI	Direct fit	95% CI
Maximum oxygen consumption rate, q_{max} (mmHg · s^{-1})	17.5	15.3–25.1	16.3	15.3–17.9
P_{O_2} for 50% drop in consumption, $P_{50,q}$ (mmHg)	2.7	0.0–12.5	1.6	1.2–2.1
Maximum misonidazole binding rate, $k_{b,0}$ ($\times 10^{-4}$ s^{-1})	4.5	3.9–4.9	4.4	2.5–5.3
P_{O_2} for 50% drop in binding, $P_{50,b}$ (mmHg)	1.4	0.3–2.6	1.4	1.1–2.5
P_{O_2} for 50% necrosis, $P_{50,n}$ (mmHg)	1.2	0.1–4.9	1.0	0.4–1.2

(Warren and Partridge 2016)
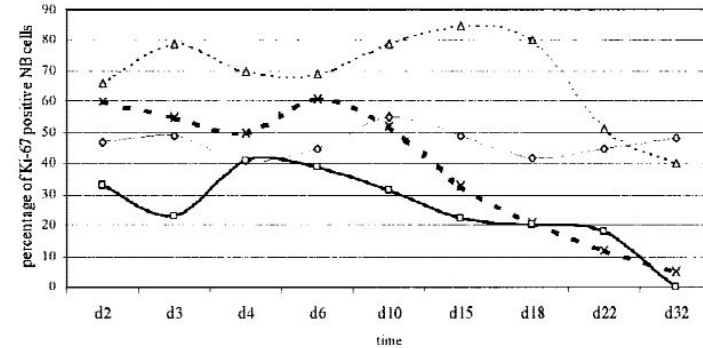
High-Performance computing.
- Millions of cells in > 4 months.
- 50 *runs* per configuration.
- 3000 parametric combinations tested in around 20 studies.
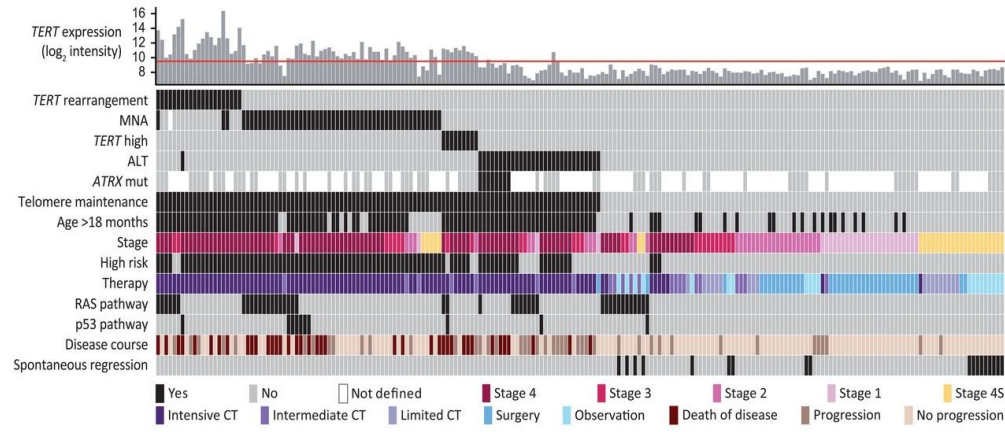- Simulations on GPUs enabled by FLAMEGPU.

Latin hypercube sampling.
- 20 fitting parameters.
- 3000 parametric combinations.
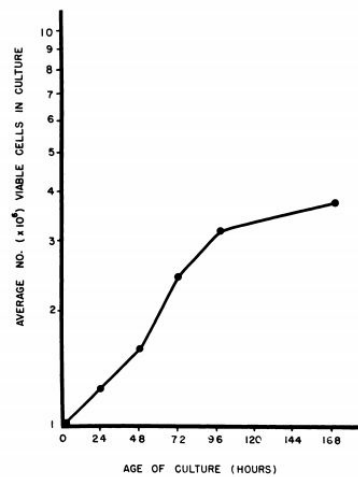
Data aggregated from different sources.
- Clinical outcomes associated with different mutations.
- Cell death triggered by hypoxia.
- Growth kinetics.
- Clinical outcomes and cell behaviours associated with different histologies.

(Tumilowicz *et al.* 1970)

(Ambros *et al.* 2001)

FLAME GPU
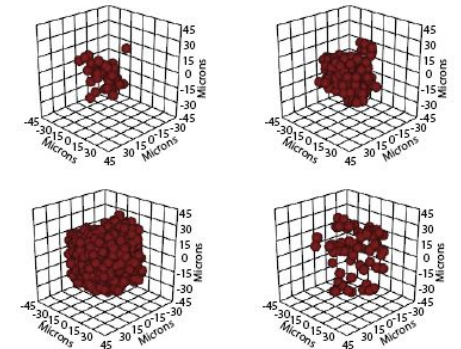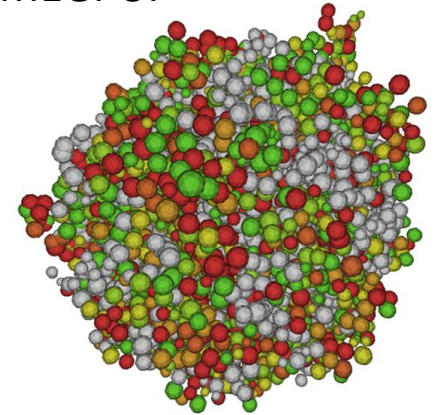
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