Investigating environmental effects on chronic myelomonocytic leukemia (CMML) recurrence

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INTRODUCTION: CMML

Chronic myelomonocytic leukemia (CMML) is a leukemia that occurs due to an accumulation of mutations over time, resulting in the dysregulation of normal monocytic growth and the accumulation of immature monocytes, which are subsequently pushed out into circulation, resulting in splenomegaly roughly 50% of the time (3). CMML is a remarkably deadly form of leukemia, with a median age of diagnosis at approximately 65 years and survival rate at 38 and 24 months respectively for Type-1 or Type-2 (1, 2), with a 30% chance of progressing onto acute myeloid leukemia (4).

RUXOLITINIB AND RESISTANCE

While there is no cure for CMML, treatments have been approved to relieve pain within patients. One such treatment is Ruxolitinib, a JAK-STAT pathway inhibitor, the effects of which are simulated in this presentation. Ruxolitinib interferes with the proliferation of cells by preventing the dimerization of JAK2 proteins (5), decreasing the proliferation of malformed monocytes and relieving the symptoms of CMML. However, presumably as cells develop resistance, the classical U-shaped model of resistance completes. This model focuses on one of two hypotheses proposed by Kaznatcheev et al.

LAMARCKIAN SELECTION

Lamarckian selection suggests that the microenvironment in which the leukemia develops has an epigenetic selective effect on the leukemia itself. One hypothesis suggests that uneven oxygenation of the bone marrow microenvironment resulted in hypoxic regions in which Ruxolitinib has less efficacy in a nonlinear fashion (9). Another suggests that the mechanism proposed by Koppikar et al (8) is non-genetically heritable due to environmental pressures i.e. that induced hypoxia results in more heteodimeric JAK family pairs to bypass inhibition. The model used in this technical report focuses on Lamarckian selection, exploring the interplay between bone marrow conditions and Ruxolitinib dosage regime.

INITIAL CONDITIONS

Initial condition	Value	Units	Citation
Starting Radius	5	Cell widths	(10)
Side_Len	100	Pixels	(10)
xDim/yDim	1000	Pixels	(10)
STARTING_POP	4400	Cells	(13)(12)

ACKNOWLEDGEMENTS

Special thank you to Rafael Bravos for the use of his framework, Heiko Enderling and the entire Integrated Mathematical Oncology department at Moffitt Cancer Research Center, the Dartmouth Guarini Institute, and the Dartmouth Mathematics Department for this opportunity to study abroad on the Mathematical Oncology DSP in Tampa, FL.

MODEL & METHODOLOGY

Starting with a simple model of proliferating cells (green), blood vessels (red) were added as a secondary cell type as sources for oxygen and Ruxolitinib diffusion, differentiated from the motile cancer cells in color, size, and inability to move. Diffusion functions were added to simulate the movement of oxygen and Ruxolitinib from the vessels to the surrounding bone marrow cells. A boundary was imposed onto the diffusion gradients and the simulation visualization, simulating the assumed shape of the bone marrow cross section. Contact inhibition was also introduced to simulate cells' true interaction. Division probability was modified via contact inhibition and the local oxygen diffusion concentration using a heavy-side function. The blood vessels were given an arbitrary radial distribution using the Gaussian function from the framework to approximate the real distribution in bone marrow.

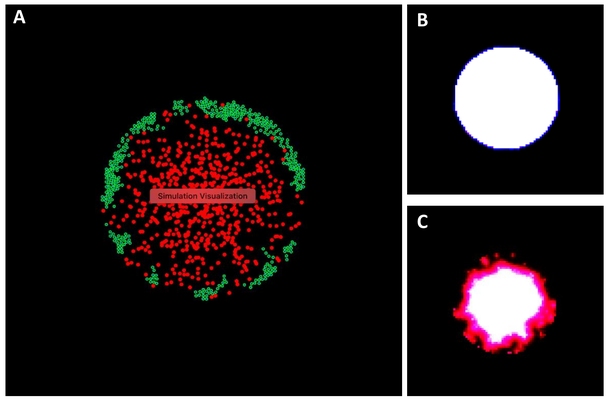

Figure 1: (A) 2D cross section of bone containing CMML cells (green) and blood vessels (red). (B) Oxygen diffusion map. (C) Ruxolitinib diffusion map.

LITERATURE SEARCH: PARAMETERS

Parameter name	Parameter Value	Parameter units	Citation
DIVISION_PROB	0.002	Cells/cell cycle	(11) (13)
DEATH_PROB	0.0002	Cells/cell cycle	*
CELL_RAD	{0.4, 0.5}	Unitless ratio	(12)
productionRate	10.42	Mols/day	(15)(16)
rxRate	4.896	Mols/day	(5)
DIV_BIAS	1e2	Unitless ratio	Arbitrary
INHIB_WEIGHT	1	Unitless ratio	Arbitrary
Diffusion {Ox, Rx}	{1.56e-11, 0.25}	Mols/day	(12)(5)
Decay {Ox, Rx}	{0.56e-11, 0.01}	Mols/day	(14)(5)
Threshold {Ox, Rx}	{5.28e-13, 0.1044}	Mols/day	(12)(5)
alpha	0.3	unitless	Arbitrary

VARIATION OF PARAMETERS

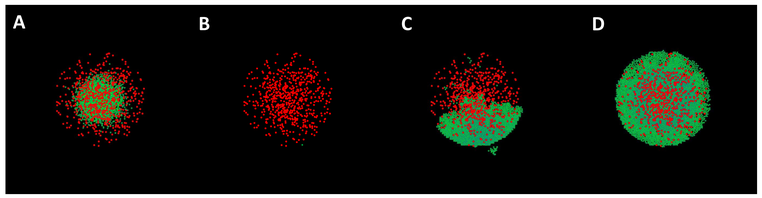

Figure 2: Snapshots of a single run done using literature values. A: t = 0, B: application of Rx t = 20, C: t = 2050, D: t = 4990.

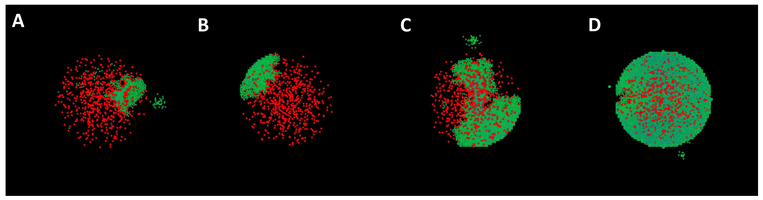

Figure 3. Sampled at t = 4990, these runs were done with rxRate manipulated. A) 50% literature value, B) 10%, C) 1%, D) 0.1%.

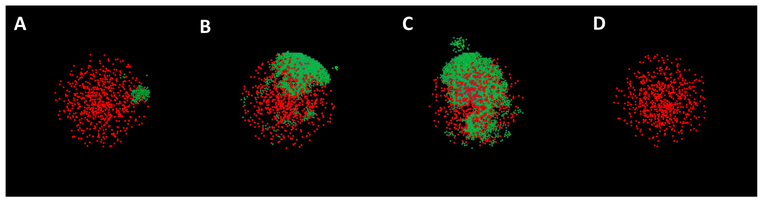

Figure 4. Multiple trials using literature values demonstrate the heterogeneity in cancer population regrowth in a Gaussian distribution of blood vessels sampled at t = 4990. In twenty trials, 8 of them resembled 4D.

DISCUSSION AND FUTURE WORK

- Cancer cells are unable to reproliferate so long as there is Ruxolitinib in the area and hypoxia is high. Once treatment ends, however, CMML is able to grow back.
- The model qualitatively matches that of the literature concerning environmental selection within the bone marrow.
- Unsurprisingly, the less overall drug applied, the faster the cancer is able to repopulate.
- Reproliferative heterogeneity suggests that distribution plays a large inhibitory role in Ruxolitinib's ability to alleviate symptoms.
- It would be interesting to utilize patient blood vessel maps to generate hypoxia maps in order to see if they impact the survival rates of cancer cells.

CITATIONS

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