Developing A Multi Scale Cellular Automata Simulation Model Of A Vascularised Brain Tumour Environment To Predict Angiogenic Potential Of Brain Endothelial Cells.

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Abstract

Angiogenesis, the growth and formation of capillaries form pre-existing vessels, is involved in various disease pathologies including brain cancers which require new blood vessels for their growth and survival. Several aspects of angiogenesis have been uncovered, based on which novel agents have been developed to counteract tumour-induced angiogenesis. Within this project, a tool is developed to predict angiogenic potential in brain endothelial cells in a vascular tumour environment, based on a simulation of cell-to-cell Delta-NOTCH signalling in response to VEGF leading to cell migration and hereby vascular development using CompuCell3D.

Aims & Objectives

(1) Create a simulated vascularised brain tumour environment including VEGF secretion, Delta-Notch signalling in response to VEGF secretion and endothelial tip cell formation.
(2) Simulate and track endothelial cell tip formation and migration
(3) Employing implementing experimental data in form of converted, previously obtained images of endothelial cells.

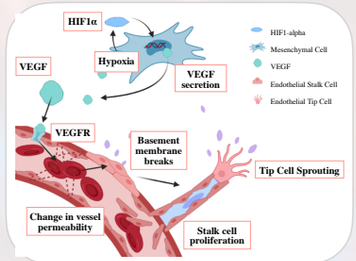
Conclusions

This study demonstrates the potential of combining experimental data with computational simulations to better understand angiogenesis and predict angiogenic potential. The model can be taken further towards personalised medicine, whereby patient cells could be linked to experimental data via cell banks, and used to predict likely treatment responses and outcomes. Other parameters, such as time frame, dosage and tumour progression, can be implicated in the simulation to investigate treatment strategies and aid in drug efficiency and clinical trials.

Project Background

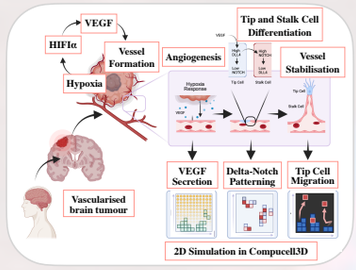
Angiogenesis

⇢ Hypoxia-inducible factor 1 (HIF1) up-regulation in hypoxic cells, VEGF transcription factors activated
⇢ VEGF secretion, bind on VEGFR on capillary surface
⇢ Change in vessel permeability
⇢ Endothelial tip cell to breaks down basement membrane, release metallo-proteinases (MMPs) to degrade surrounding extracellular matrix components
⇢ Stalk cells proliferate



Simulating Tumour Angiogenesis

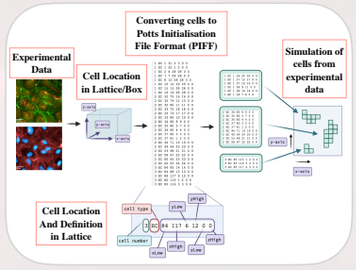
Brain Tumours rely blood supply to grow. VEGF mediated vessel growth and antigenic potential is measured through endothelial stalk- and tip cell formation, through Delta-Notch (DN) signalling in response to VEGF. Molecular processes are translated into a multi scale cellular automata simulation model in Compucell3D through VEGF secretion, DN patterning and endothelial tip cell migration.



Methods

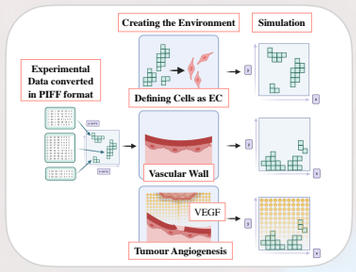
Experimental Data Conversion And Implementation

Images of experimental data obtained in our lab, Human umbilical vein endothelial cells (HUVEC) are cultured, imaged and converted into Potts Initialisation File Format (PIFF). Cells are located in the simulation lattice over multiple squares, and defined in code. The code is implemented in the simulation and angiogenic processes can be simulated in with real data.



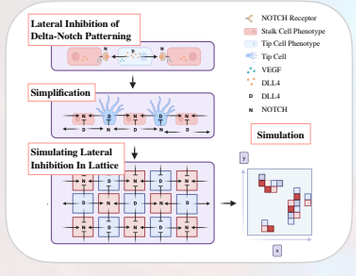
Creating A Vascularised Tumour Environment In CompuCell3D

Converted experimental data is implemented in the simulation, cells from the file defined as endothelial cells (EC) and simulation boundaries are adjusted according to the image. A vascular wall of EC can be created through enhanced cell size and adhesion. Hypoxia induced tumour angiogenesis is simulated through VEGF diffusion.



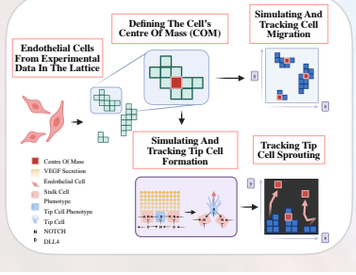
Delta-Notch Patterning In Response To VEGF

Lateral Inhibition: Cells with high VEGFR3 expression (tip cell phenotype): high VEGF take-up, high DLL4 (Delta) uptake and receptor (Notch) expression; cause Notch signalling pathway activation and Delta inhibition in neighbouring cells, adapting the stalk cell phenotype.
Simulation: DN signalling and lateral inhibition is translated onto experimental data in the simulation lattice.

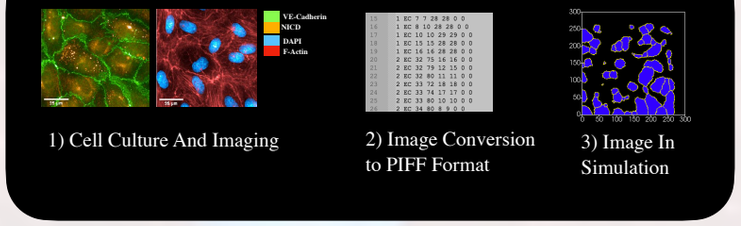


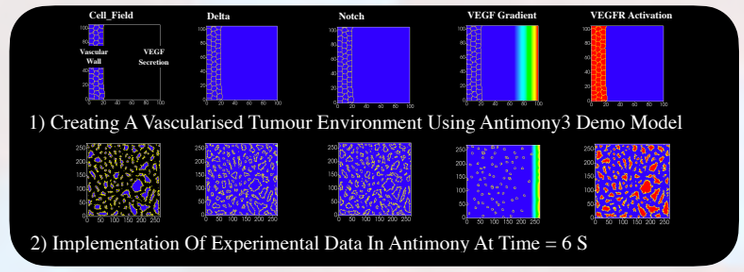
Tracking Tip Cell Formation, Sprouting And Migration

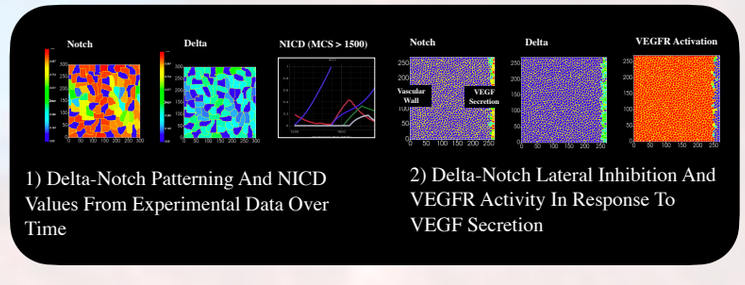
Endothelial cell migration through tip cell formation and sprouting is indicative of angiogenic potential and vessel stabilisation. This can be simulated by tracking cells by their centre of mass (COM), showing the sprouting cell as the red tip. The Delta-Notch-VEGF signalling loop is implemented onto the experimental data, resulting tip cell formation and sprouting tracked by their COM.

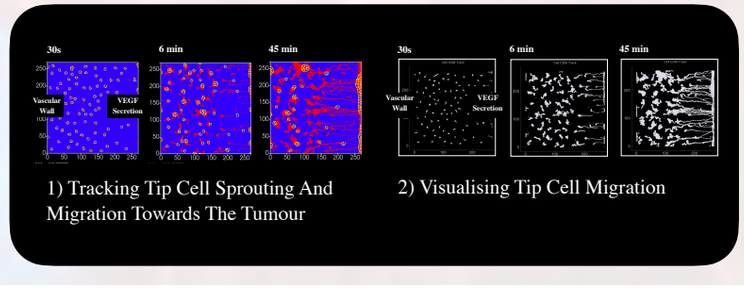


Results









Discussion

Relevance

We enhance the accuracy of studying biological processes occurring in tumour angiogenesis by combining experimental data and computational modelling based on theory, which we can replicate using induced pluripotent stem cells (iPSC) in-vitro and confirm. This can further be used in anti-angiogenic treatment optimisation, development and the study of other disease pathologies.

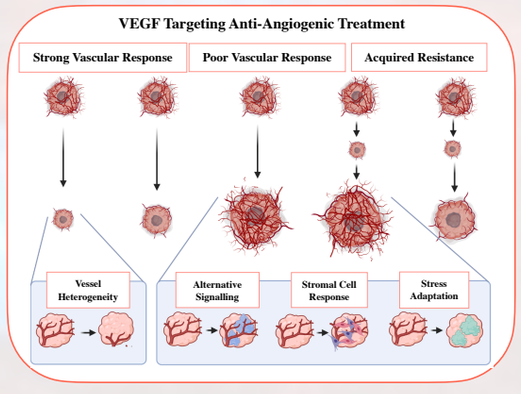
Limitations

1. Cellular automata modelling can't incorporate off-lattice biomechanics and interactions.
2. Models are restricted through fixed, programmed conditions e.g. developmental stage, temperature or number of cells.
3. Models cannot adapt to stress and morph its molecular makeup to survive as seen in nature.
4. Evolutionary learning requires further advances in computational modelling, possibly through machine learning and AI.

Translational Potential

Application And Relevance In Cancer Research

Today, a cure for brain cancers e.g. Glioblastoma multiform (GBM) is still extremely rare. GBM are often treated surgically, followed by radiotherapy and chemotherapy. The study of anti-angiogenic agents is key to developing treatment where new anti-angiogenic agents can be investigated through tissue specific simulation models as this and implicate various environmental and metastatic factors:



1 VEGF- Targeted Therapy Resistance: Simulating alternative angiogenesis pathways, stress adaptation and stromal cells.

2 Treatment Optimisation: Simulating dosage, time points and combination with other anti-angiogenic drugs and chemotherapeutic agents.

3 Treatment Development: Simulating Other Angiogenic Inhibitors to aid in clinical trials and predicted likely treatment responses.

Future Directions

1. Personalised Medicine:

Patient cells can be linked to experimental data via cell banks, and used to simulate and predict likely anti-angiogenic treatment responsiveness and outcomes.

2. Modelling Vessel Density:

High microvessel density indicates metastatic risk and can facilitates cancer cell migration into blood circulation. Implementing vessel density as a parameter in this model will aid in studying tumour recurrence and cancer spread.

3. Retinal Vascular Disease:

Here, leakage of retinal vessels causes vision loss and is often treated through VEGF inhibition. The disease specific hypoxia induced VEGF secretion is similar to the model in this study, and can be modified to simulate angiogenic potential in RVD to study underlying disease mechanisms and VEGF-induced treatment efficacy.

4. Modelling With Biopsy Specimen:

The quantification of angiogenesis in a tumour biopsy specimen can be used to predict metastasis and recurrence risks. Using biopsy data within our simulation model can be used to simulate metastasis and recurrence; and gain a deeper understanding of underlying mechanisms.