Mathematical model for BMP4 induced differentiation therapy in GBM

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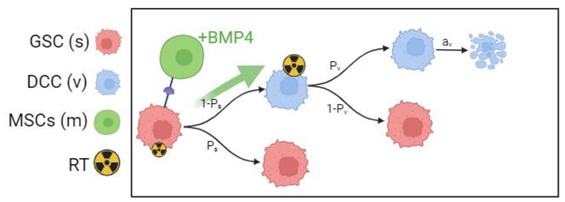
Glioblastoma, resistant stem cells and differentiation therapy

Glioblastoma (GBM) is the most aggressive and most common primary brain tumour in adults, with a poor median survival time of 15 months. GBMs are highly heterogeneous. Glioma stem cells (GSCs) are known to initiate and drive tumour growth. But GSCs are highly resistant to standard of care therapies (radio- and chemotherapy), compared to more differentiated cancer cells (DCCs). BMP4, a protein, has been shown to induce differentiation of GSCs, increasing radiosensitivity and decreasing proliferation rate. We develop a PDE model for this system that allows us to produce patient specific predications about tumour growth and therapy response.

Model assumptions and schematic

- GSCs are immortal, resistant to RT, and give rise to DCCs
- DCCs are sensitive to RT, undergo apoptosis, and dedifferentiate.
- BMP4 increases differentiation.



PDE model for GSC-driven growth and differentiation therapy

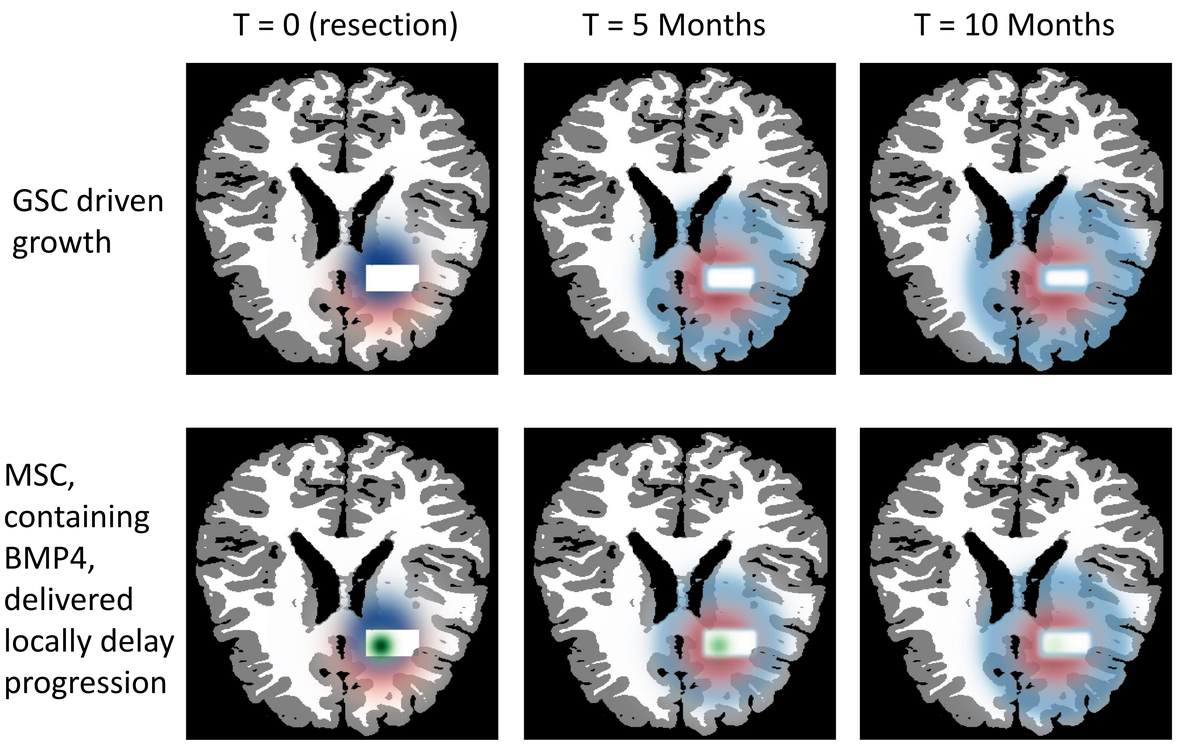
$$\underbrace{\frac{\partial s}{\partial t}}_{\text{GSCs}} = \underbrace{\nabla\cdot(D_s\nabla s)}_{\text{diffusion}} + \underbrace{(2P_s-1)K(N)m_s s}_{\text{self-renewal of } s} + \underbrace{2(1-P_v)m_v K(N)v}_{\text{dedifferentation}}$$

$$\underbrace{\frac{\partial v}{\partial t}}_{\text{DCCs}} = \underbrace{\nabla\cdot(D_v\nabla v)}_{\text{diffusion}} + \underbrace{2(1-P_s)K(N)m_s s}_{\text{differnetaiton of } s} + \underbrace{(2P_v-1)m_v K(N)v}_{\text{self-renewal of } v} - \underbrace{\frac{\lambda_v}{1+\xi}v}_{\text{apoptosis}}$$

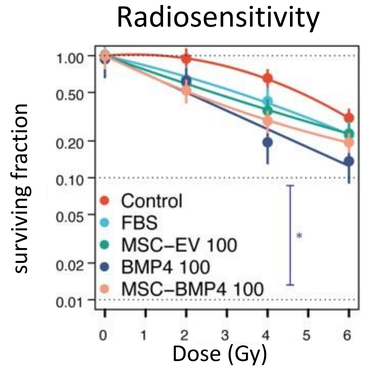
$$\underbrace{\frac{\partial m}{\partial t}}_{\text{MSCs}} = \underbrace{\nabla\cdot(D_m\nabla m)}_{\text{diffusion}} + \underbrace{\chi m\nabla N}_{\text{chemotaxis}} - \underbrace{\lambda_m m}_{\text{apoptosis}}$$

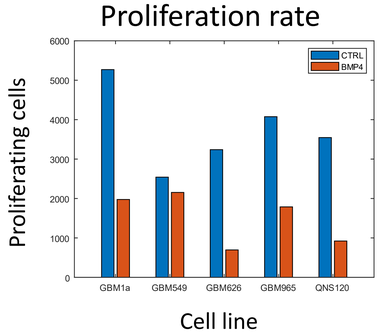
$$\underbrace{\frac{\partial B}{\partial t}}_{\text{BMP4}} = \underbrace{\nabla\cdot(D_B\nabla B)}_{\text{diffusion}} + \underbrace{Cm}_{\text{release}} - \underbrace{u_s Bs}_{\text{uptake}} - \underbrace{\lambda_B B}_{\text{decay}}$$

Model simulations



BMP4 increases radiosensitivity and decreases proliferation rate of GSCs





Future work: data integration and patient-specific therapy

- Compare model predictions to image localised biopsies.
- Optimise location of delivery of MSCs during resection.
- Patient specific optimised treatment plans informed via MRI and imaged localised biopsies.