Mathematical modelling of differentiation therapy for glioma stem cells

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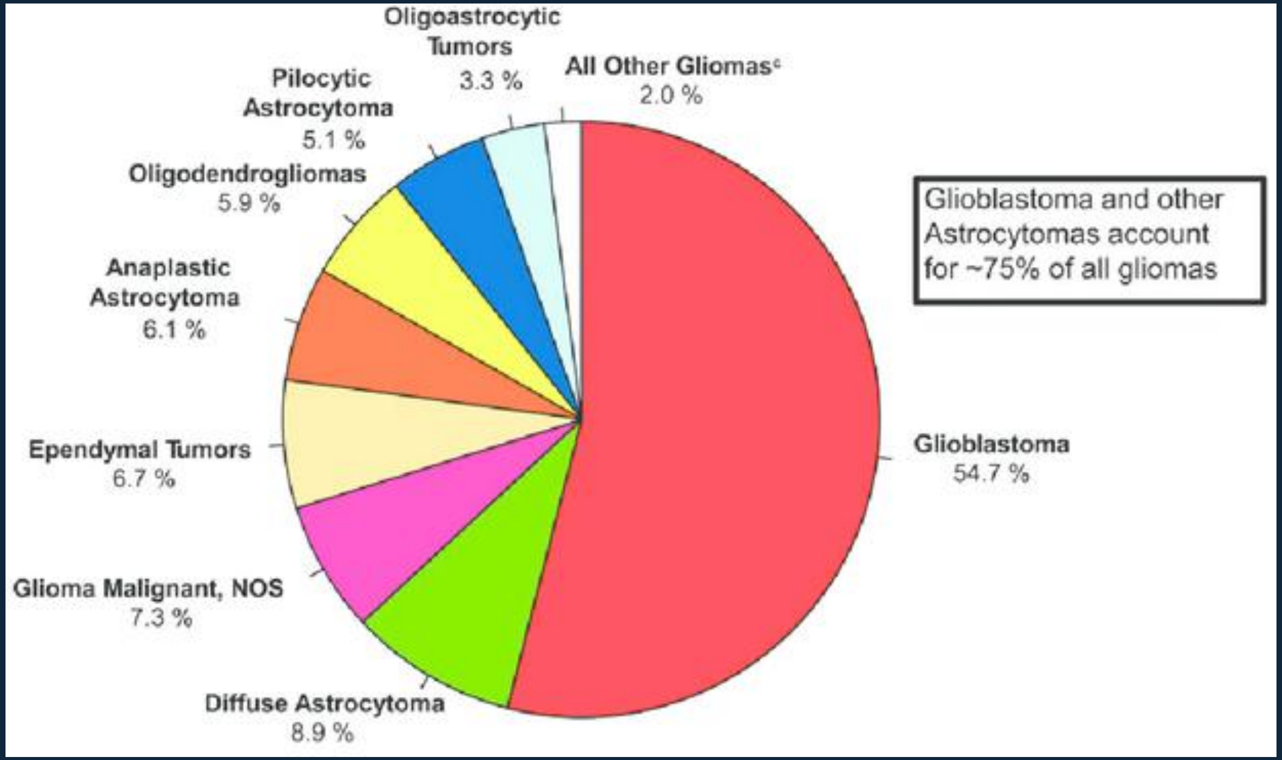
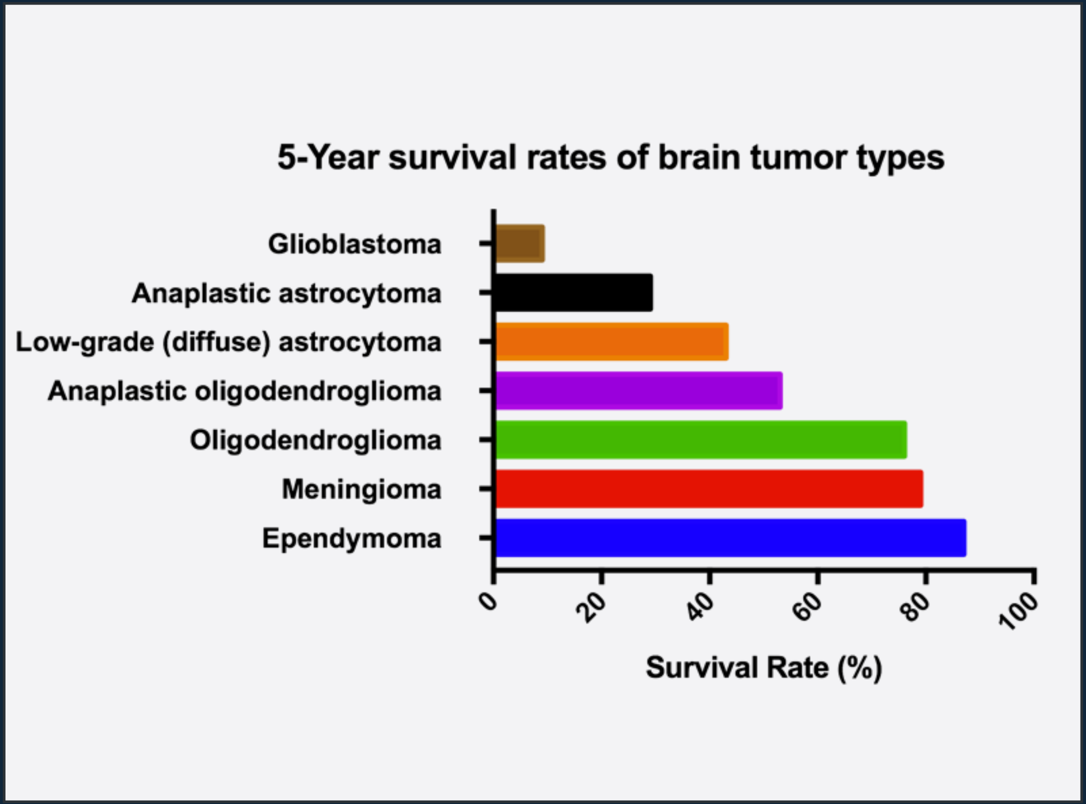
Glioblastoma (GBM)

GBM is the most common primary malignant brain tumour



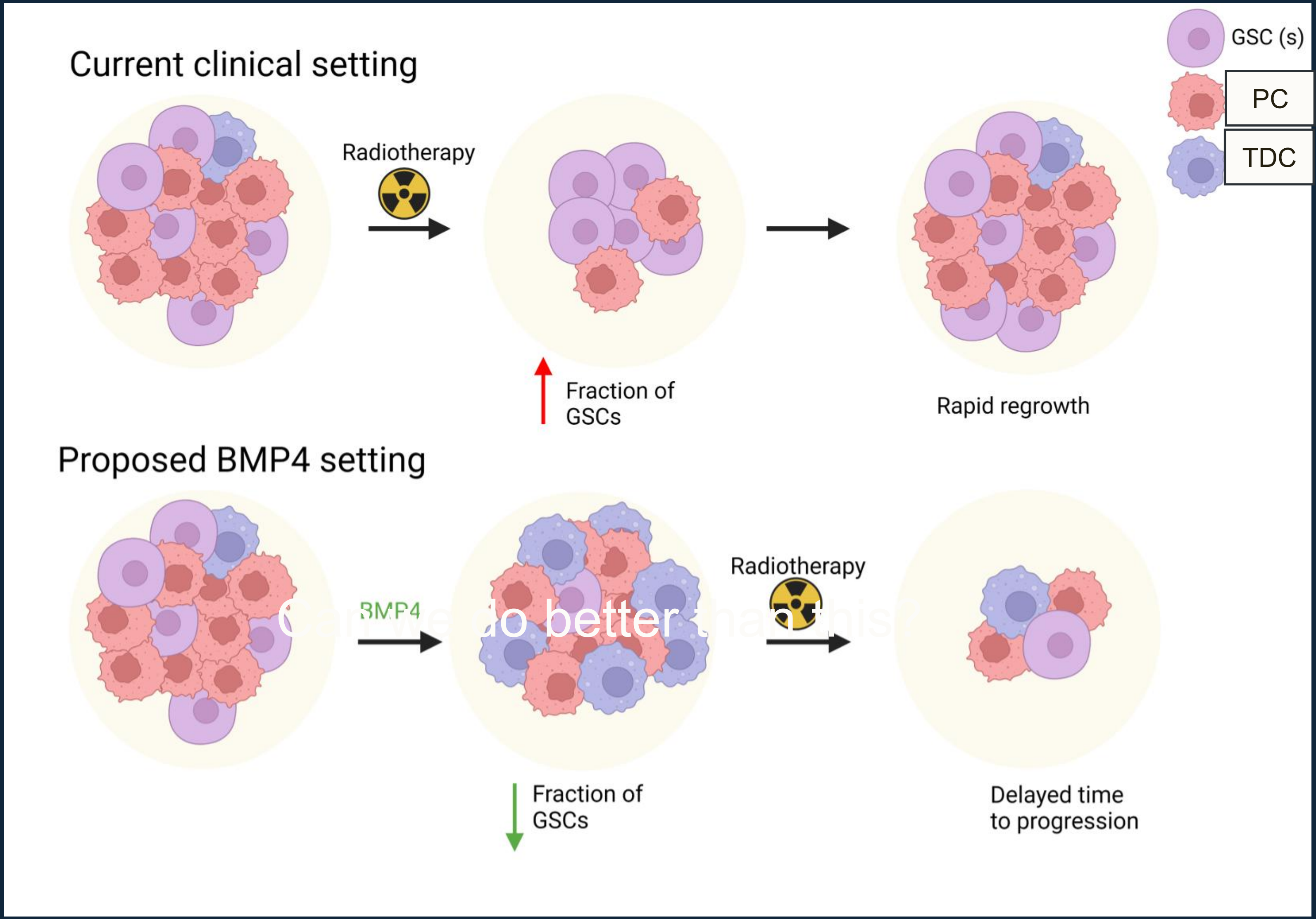
10.1093/neuonc/nou223

GBM has 5-year survival rate of only 5%



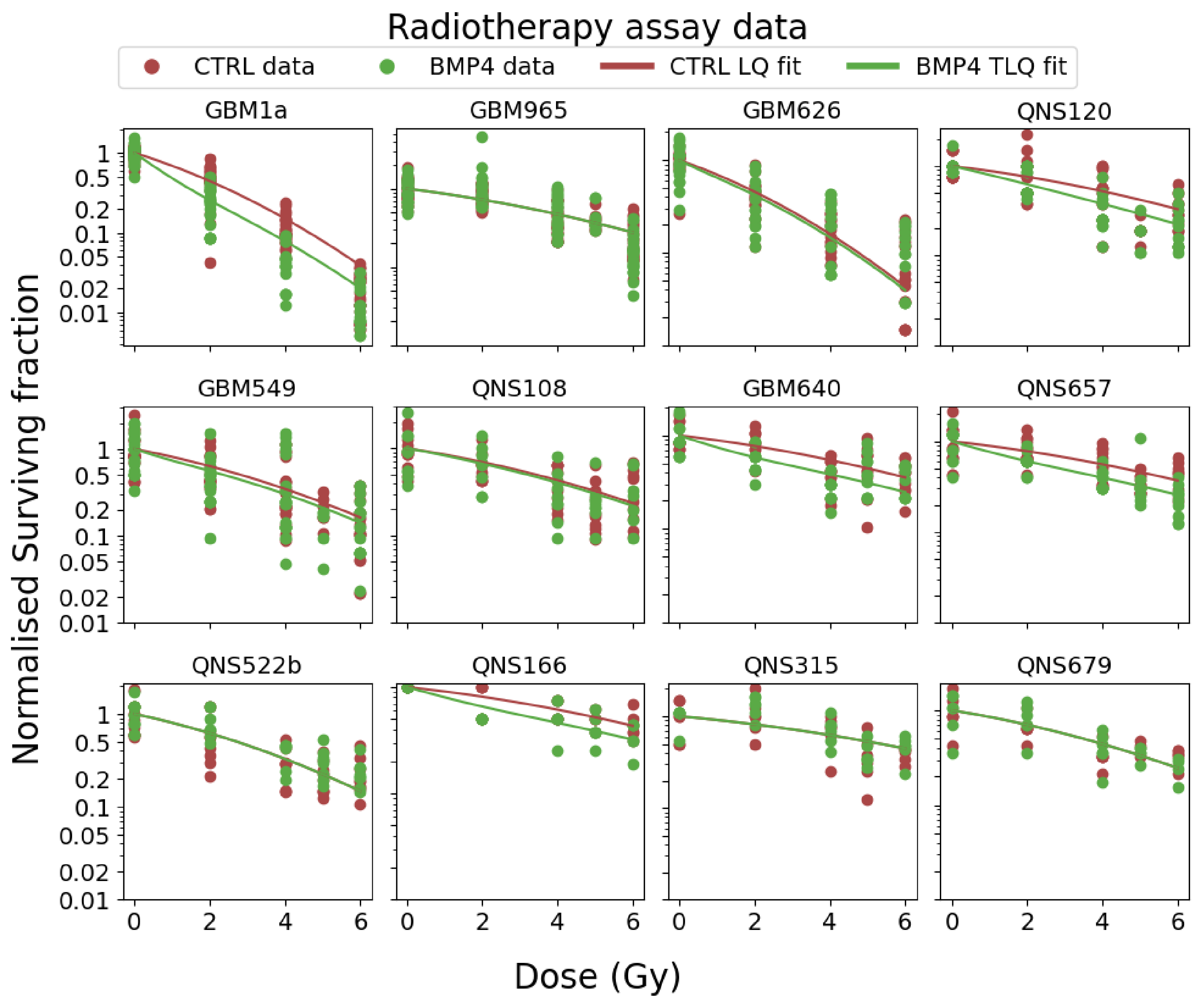
Glioblastoma — Laboratory for Precision Cancer Medicine (lpcm.be)

Heterogeneity limits treatment effectiveness

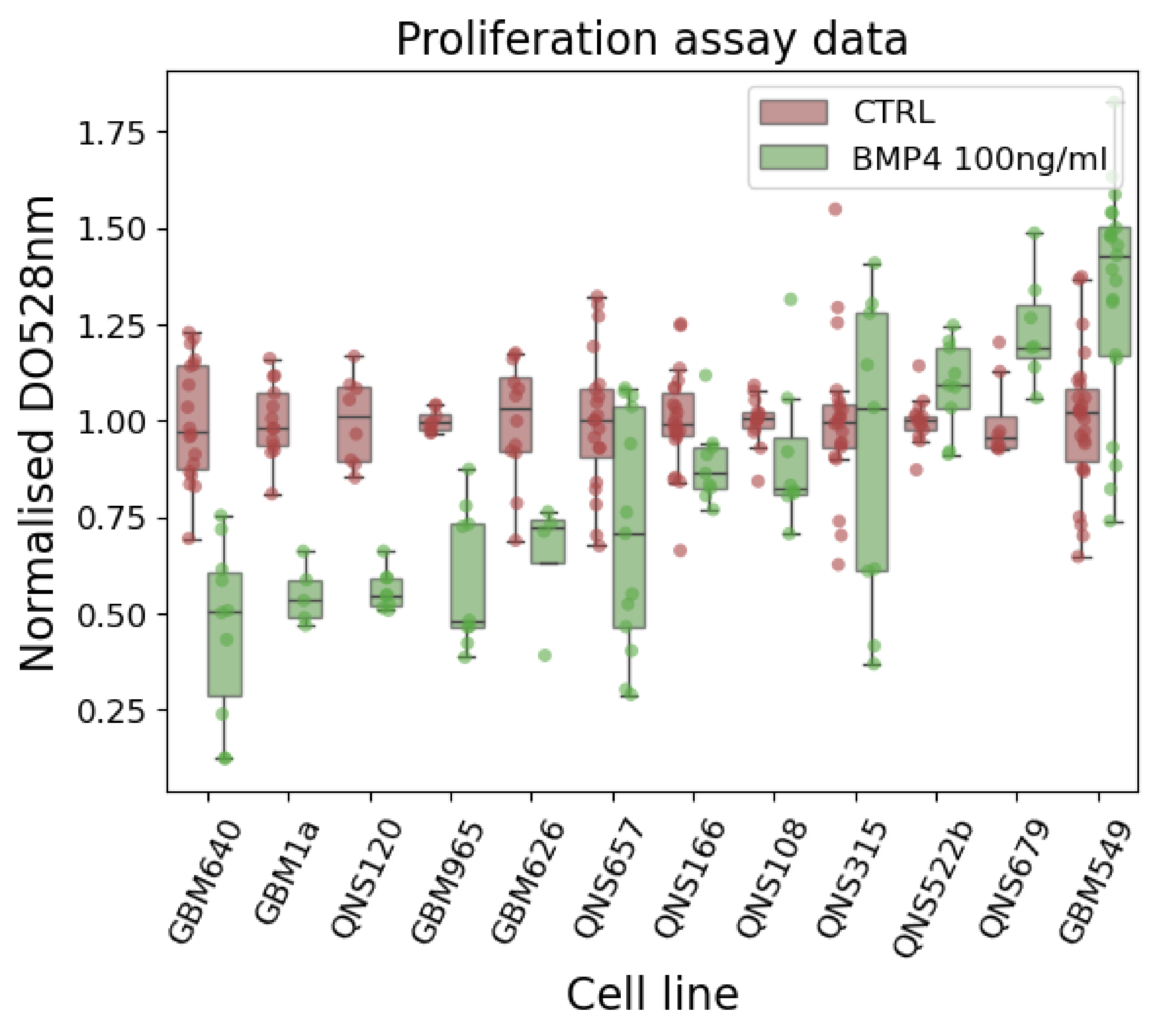


Can we do better than this?

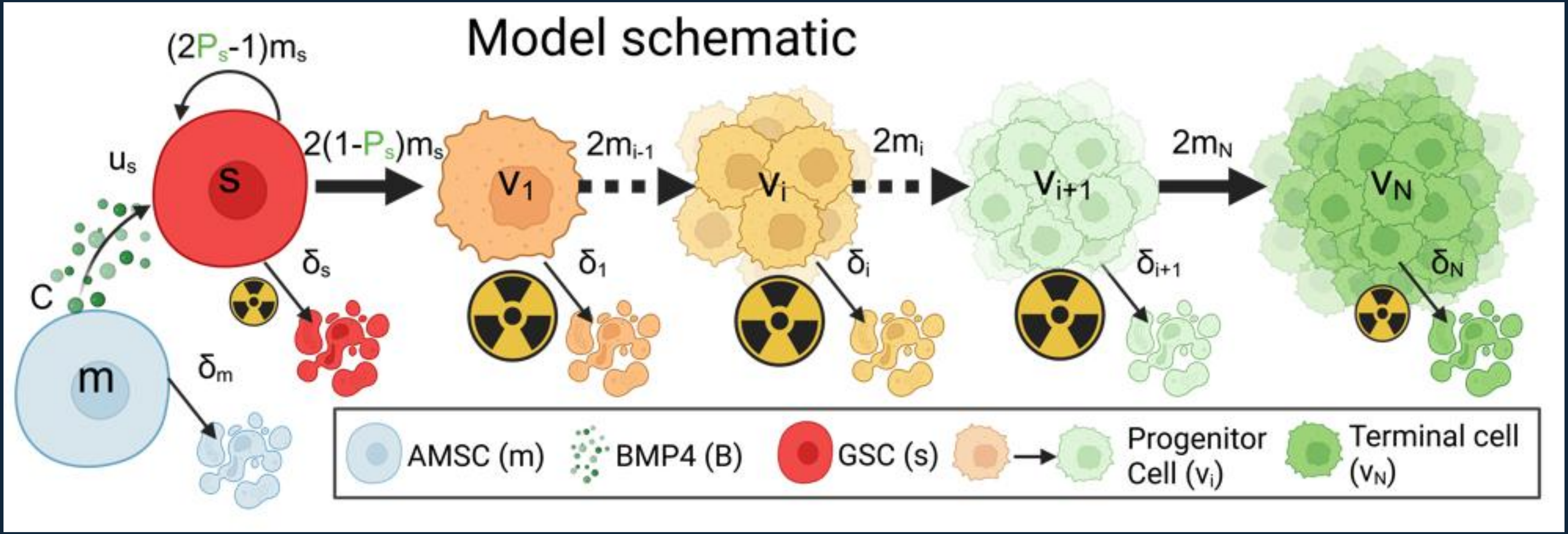
The Data – RT assay



The Data – Proliferation assay



The Model - Schematic



The Model - Equations

$$\underbrace{\frac{ds}{dt}}_{\substack{ROC\\GSCs}} = \underbrace{(2P_s - 1)m_s s\left(1 - \frac{N}{k}\right)}_{Self\ renewal\ of\ GSCs} - \underbrace{\delta_s s}_{Apoptosis}$$

$$\underbrace{\frac{dv_1}{dt}}_{\substack{ROC\\PCs}} = \underbrace{2(1 - P_s)m_s s\left(1 - \frac{N}{k}\right)}_{Differentatition\ of\ GSCs} - \underbrace{m_1 v_1\left(1 - \frac{N}{k}\right)}_{Proliferation\ of\ PCs} - \underbrace{\delta_1 v_1}_{Apoptosis}$$

$$\underbrace{\frac{dv_i}{dt}}_{\substack{ROC\\PCs}} = \underbrace{2m_{i-1}v_{i-1}\left(1 - \frac{N}{k}\right)}_{Proliferation\ of\ PCs} - \underbrace{m_i v_i\left(1 - \frac{N}{k}\right)}_{Differentation\ of\ PCs} - \underbrace{\delta_i v_i}_{Apoptosis}$$

$$\underbrace{\frac{dv_n}{dt}}_{\substack{ROC\\TCs}} = \underbrace{m_{n-1}v_{n-1}\left(1 - \frac{N}{k}\right)}_{Differentation\ of\ PCs} - \underbrace{\delta_n v_n}_{Apoptosis}$$

The Model - Reduced

$$\underbrace{\frac{ds}{dt}}_{\substack{ROC\\GSCs}} = \underbrace{(2P_s - 1)m_s s\left(1 - \frac{N}{k}\right)}_{Self\ renewal\ of\ GSCs} - \underbrace{\delta_s s}_{Apoptosis}$$

$$\underbrace{\frac{dV}{dt}}_{\substack{ROC\\PCs}} = \underbrace{2(1 - P_s)m_s s\left(1 - \frac{N}{k}\right)}_{Differentatition\ of\ GSCs} + \underbrace{S_{pro}V\left(1 - \frac{N}{k}\right)}_{Proliferation\ of\ PCs} - \underbrace{S_{death}V}_{Apoptosis}$$

Where

$$S_{pro} = \frac{\sum_{i=1}^{m-1} m_i \prod_{j=2}^{i} \alpha_j}{1 + \sum_{i=2}^{m} \prod_{j=2}^{i} \alpha_j}$$

$$S_{death} = \frac{\sum_{i=1}^{m-1} \delta_i \prod_{j=2}^{i} \alpha_j}{1 + \sum_{i=2}^{m} \prod_{j=2}^{i} \alpha_j}$$

$$\alpha_j = \frac{2m_{i-1}\left(1 - {}^{N}/_{k}\right)}{\delta_i + m_i\left(1 - {}^{N}/_{k}\right)}$$

Hillen, Enderling and Hahnfeldt (2012)

$$\dot{U}(t) = (2p - 1)m_U k(P(t))U(t)$$

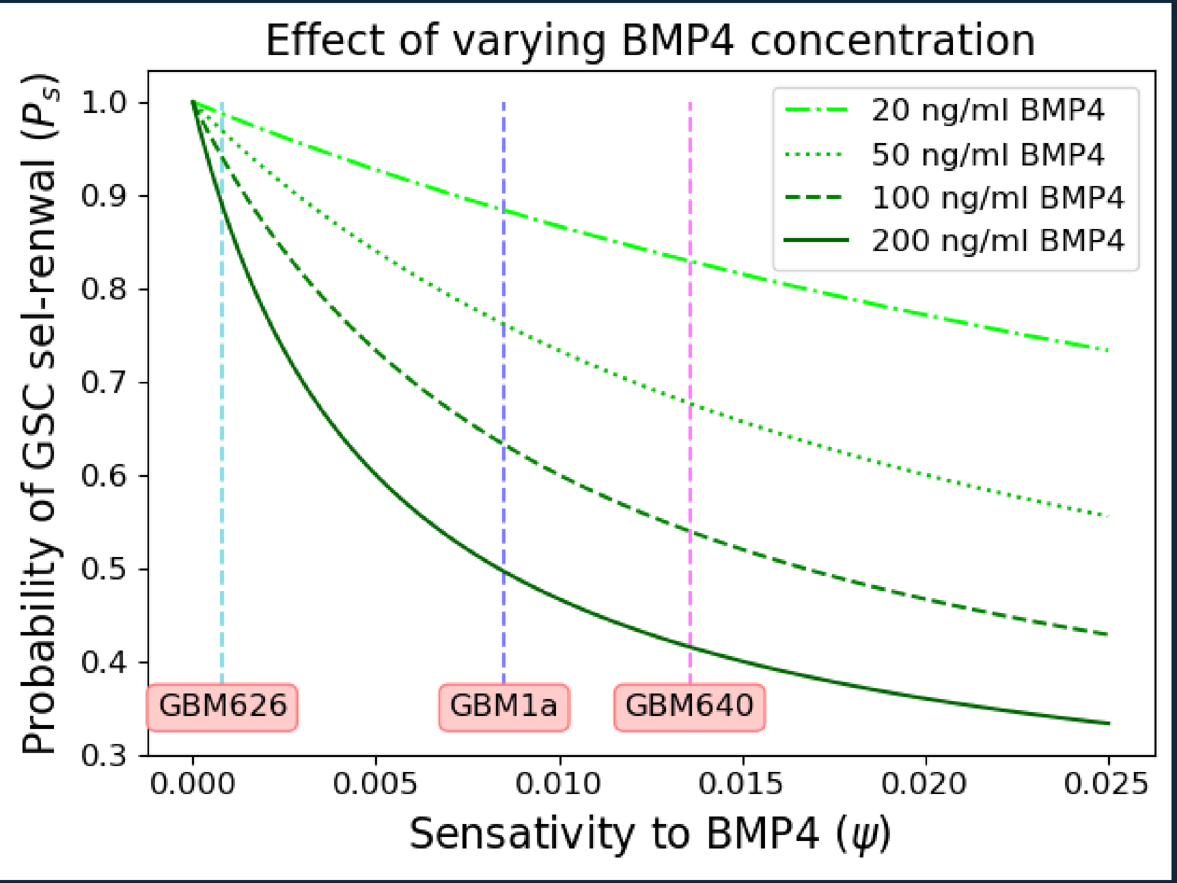
$$\dot{V}(t) = 2(1 - p)m_U k(P(t))U(t) + m_V k(P(t))V(t) - a_V V(t)$$

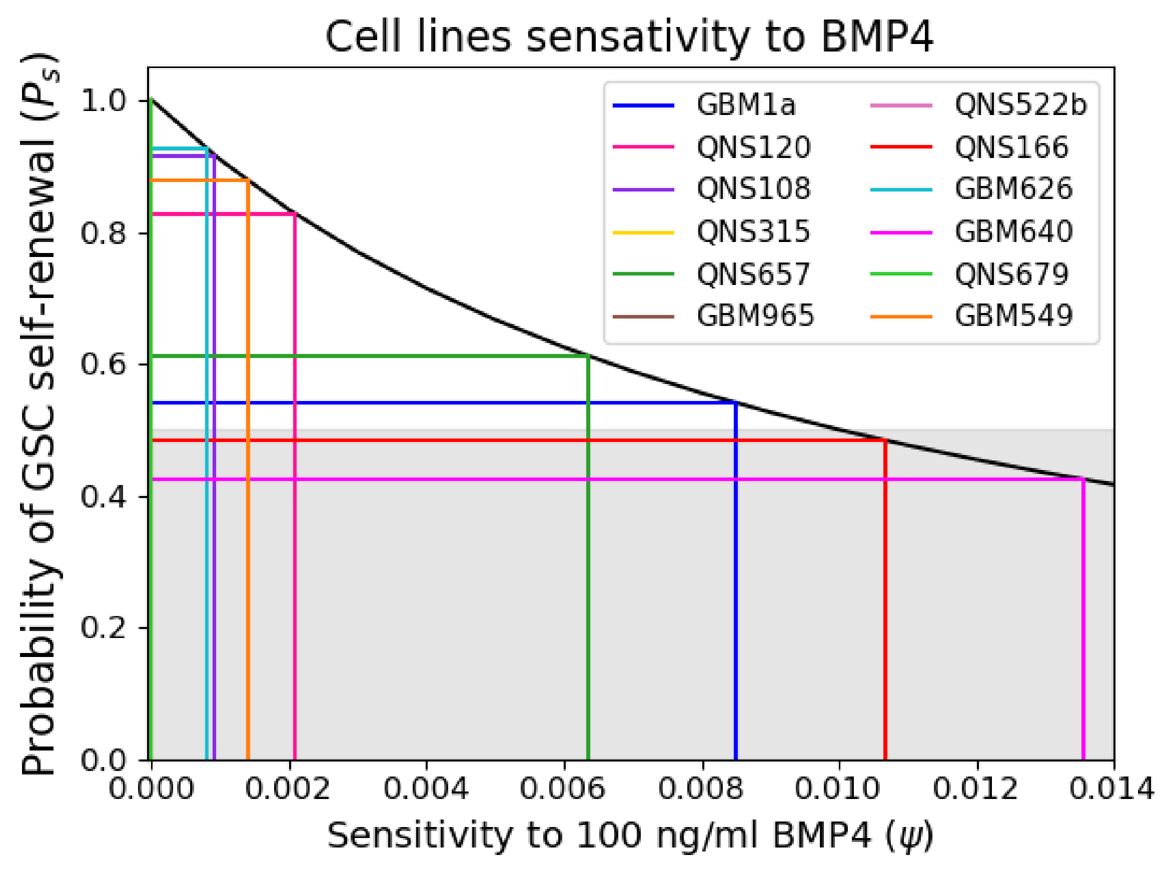
10.1007/s11538-012-9798-x 10.3389/fonc.2013.00052

Probability of GSC self-renewal as a function of differentiation promoter

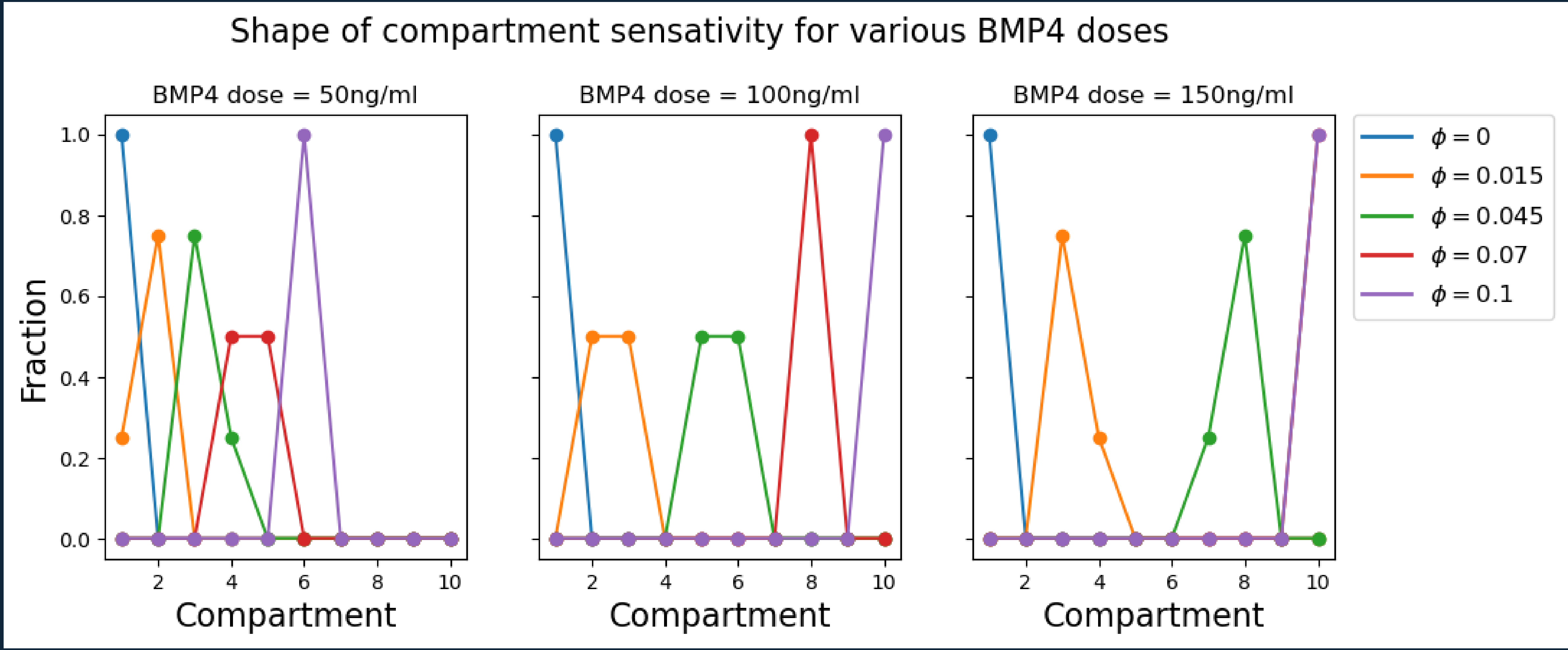
Bachman and Hillen 2013

$$P_s(t) = P_{min} + (P_{max} - P_{min})\left(\frac{1}{1 + \psi B(t)}\right)$$

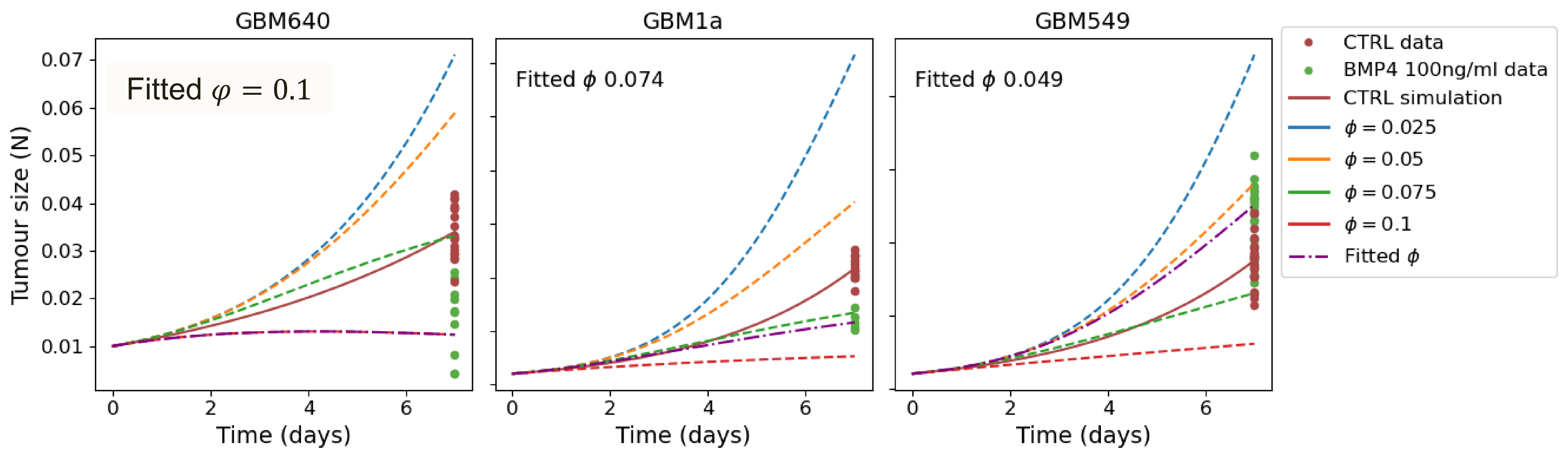




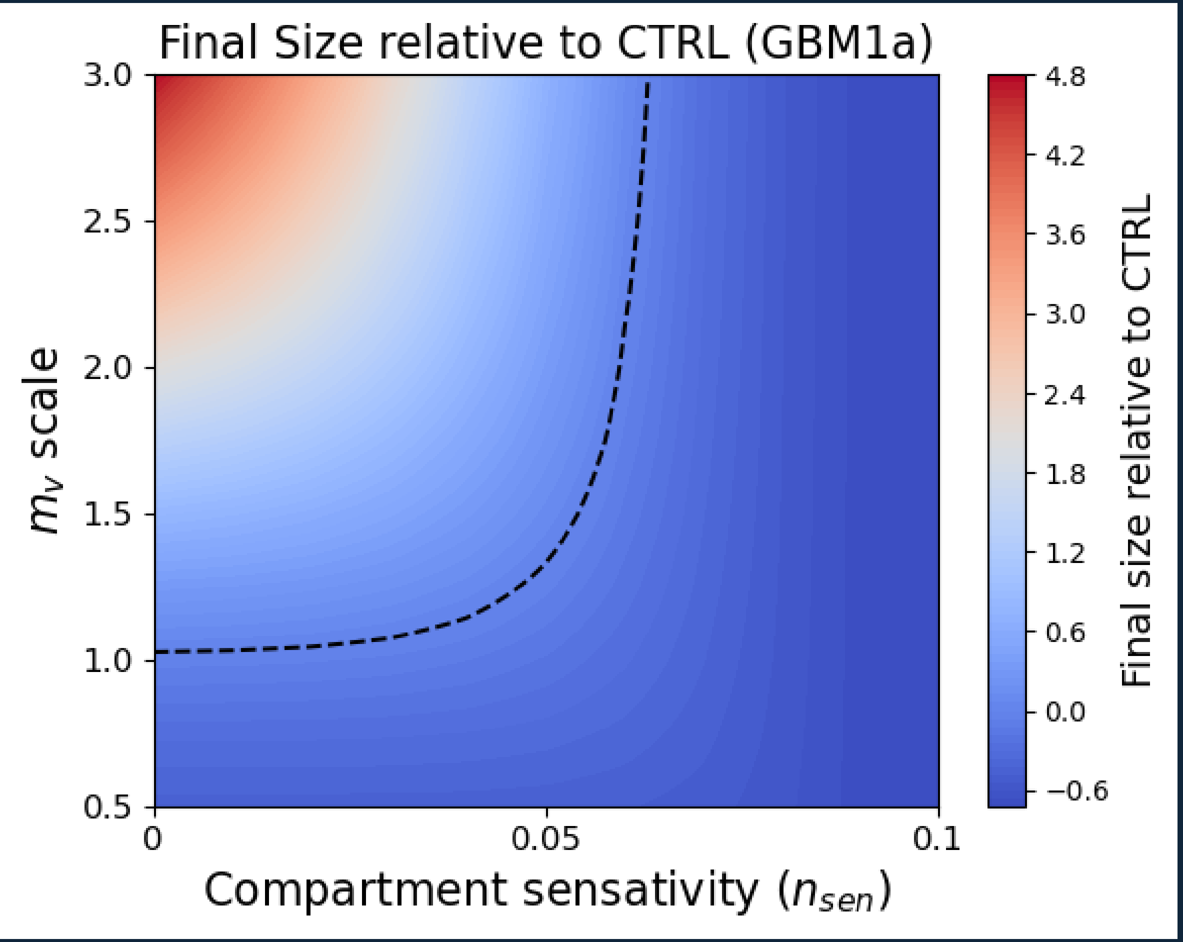
Compartment sensitivity

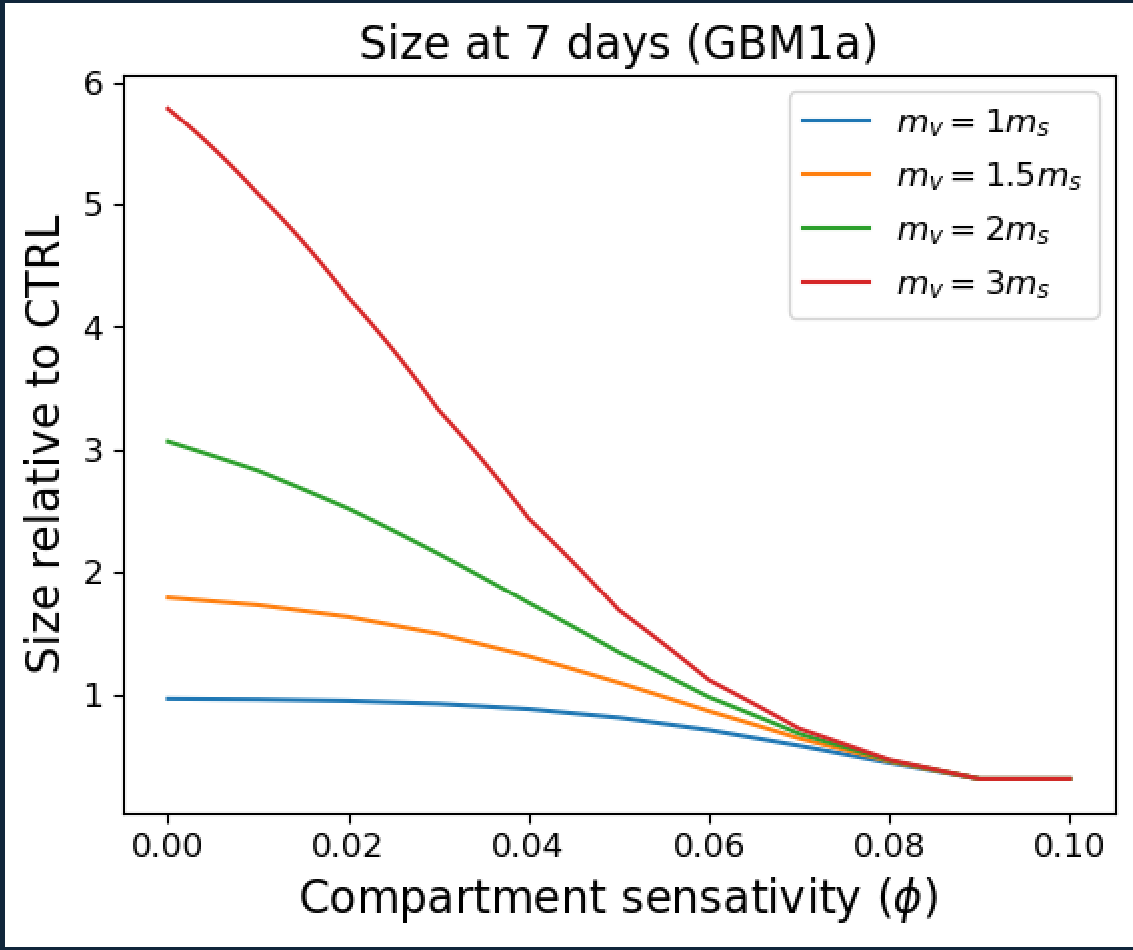


Fit compartment sensitivty

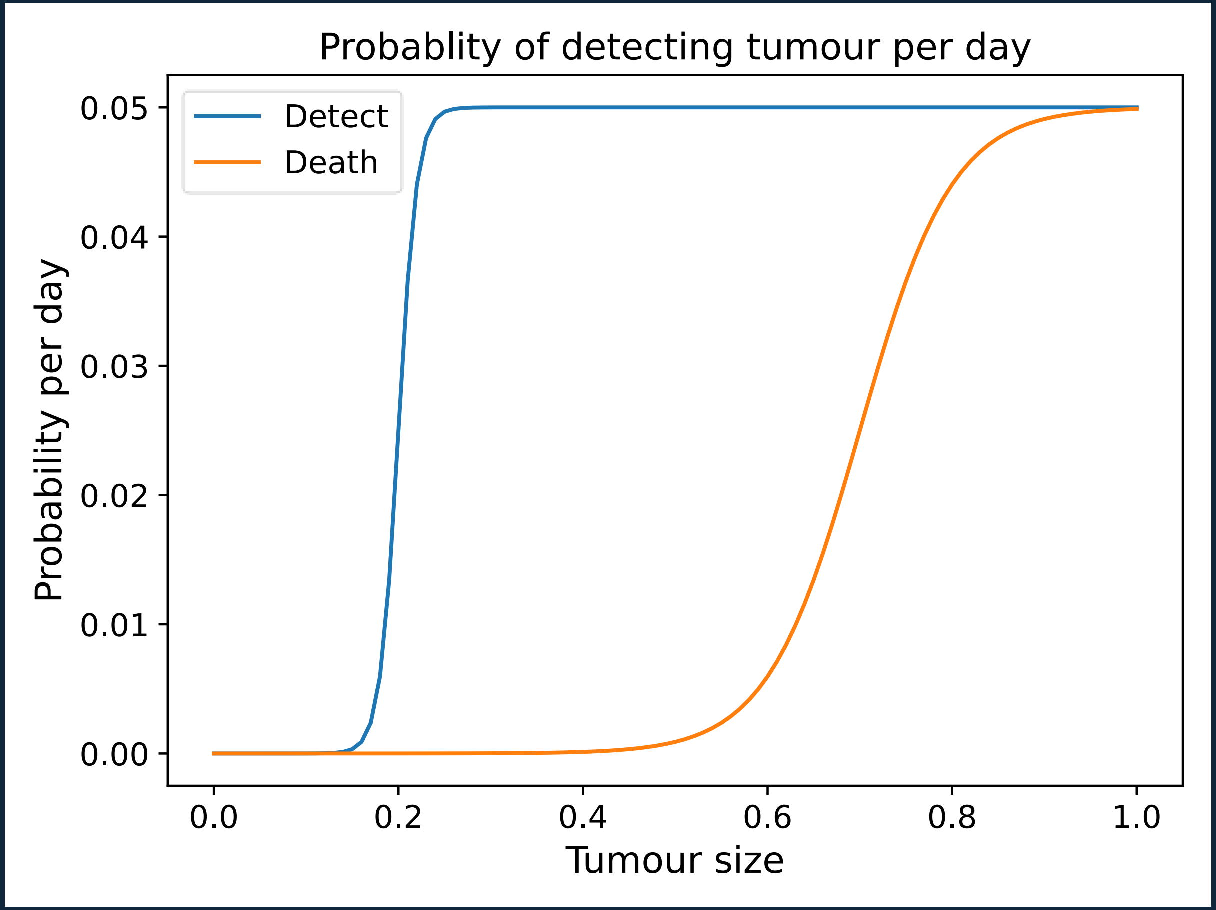


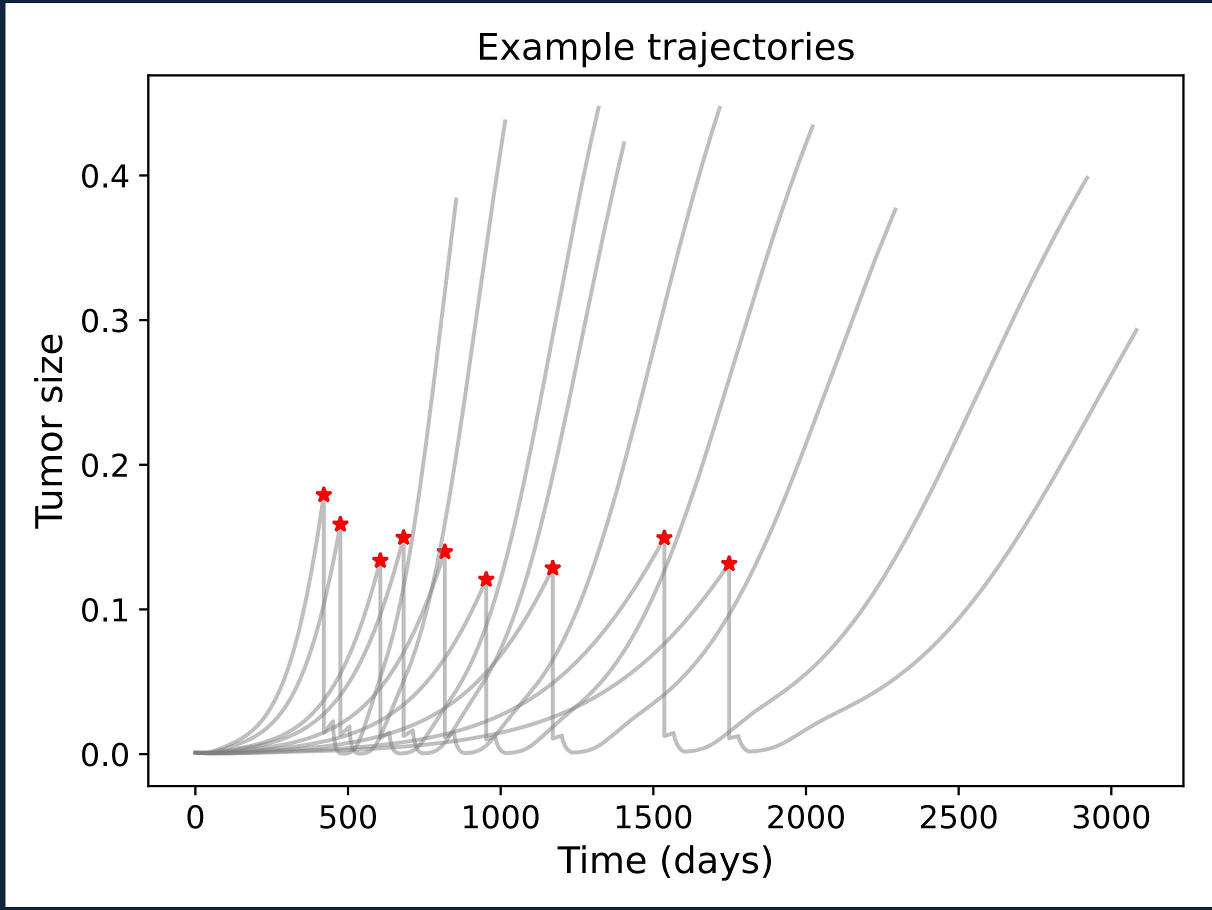
Compartment sensitivity visualised



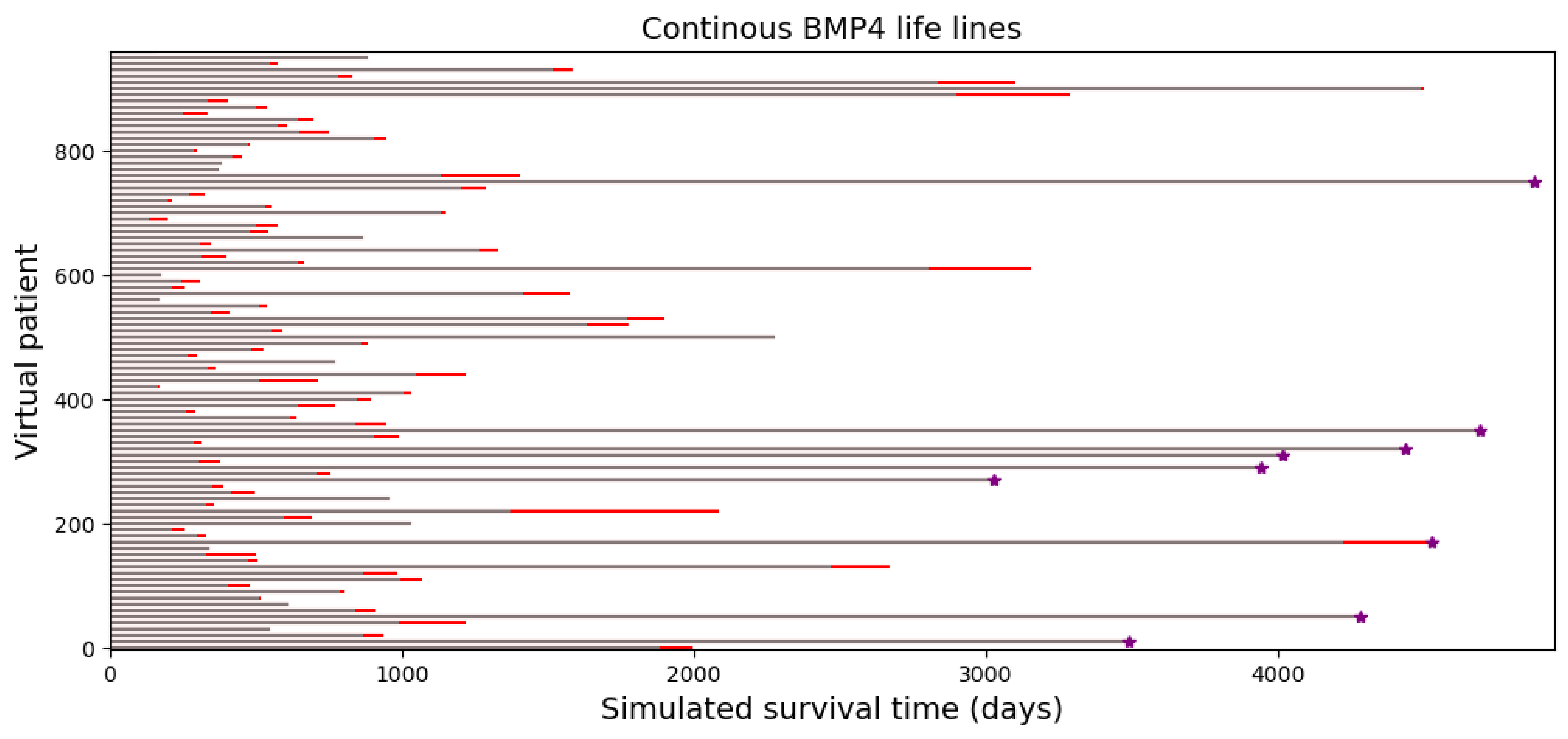


Uncertainty in death and detection

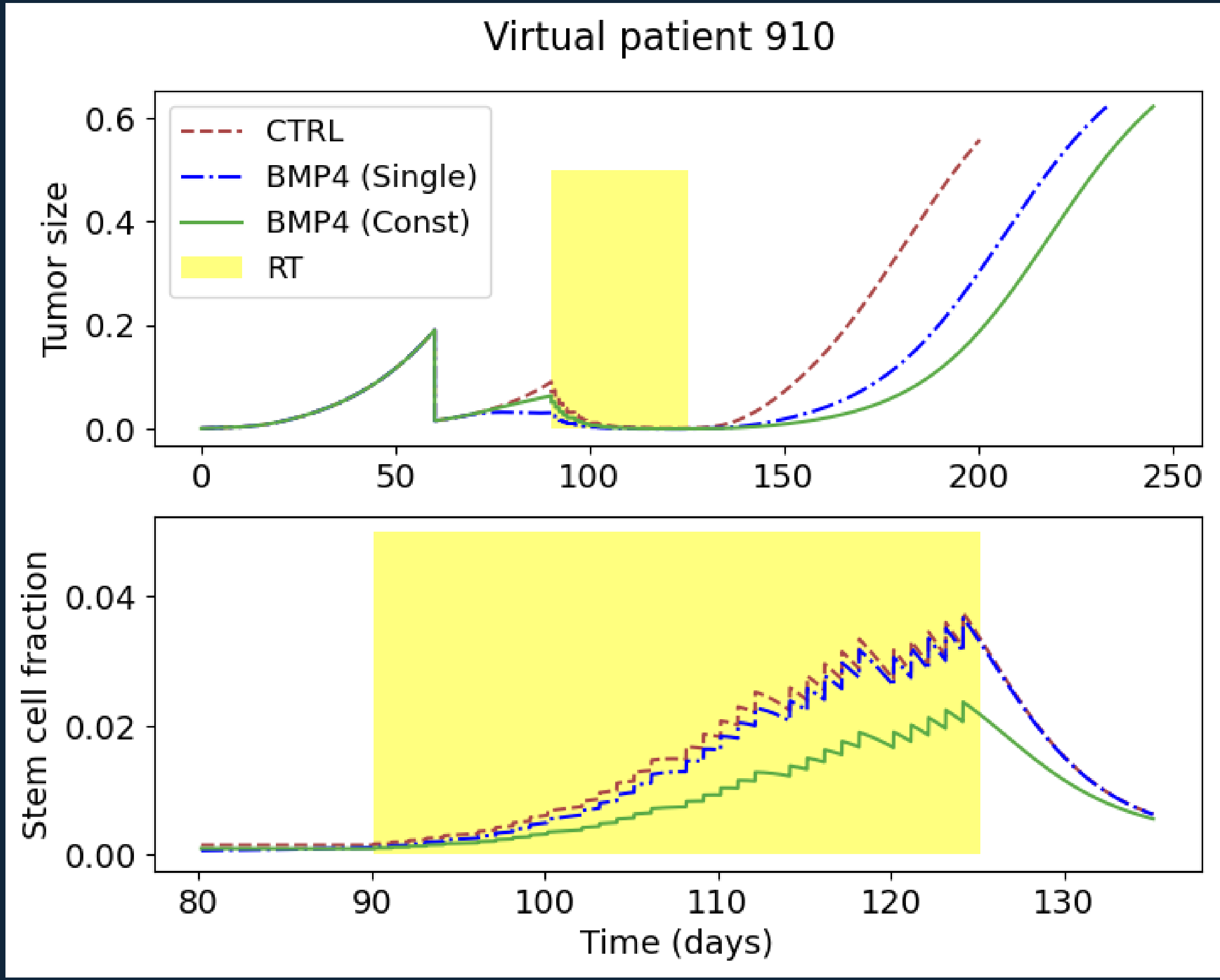


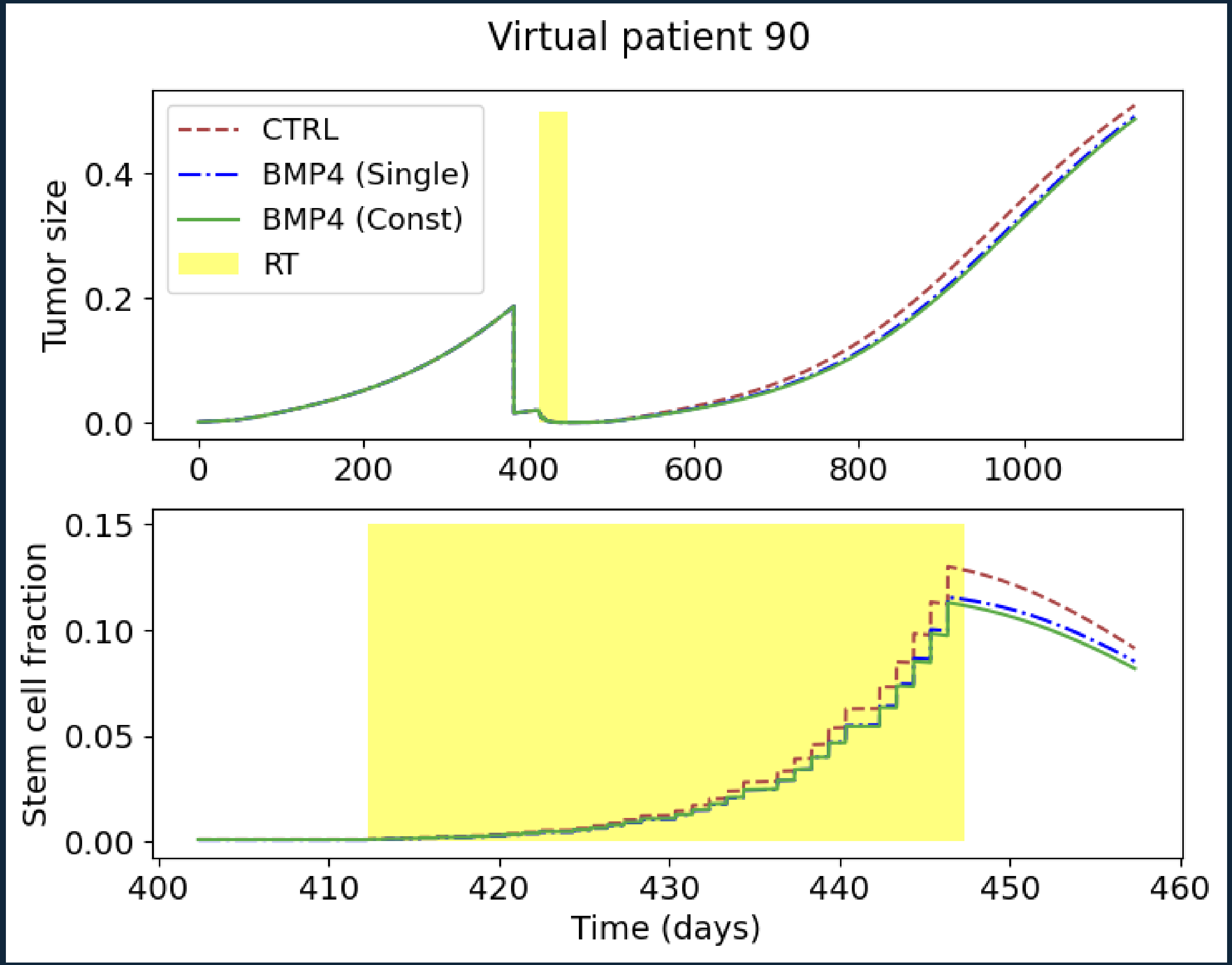


Global sensitivity analysis

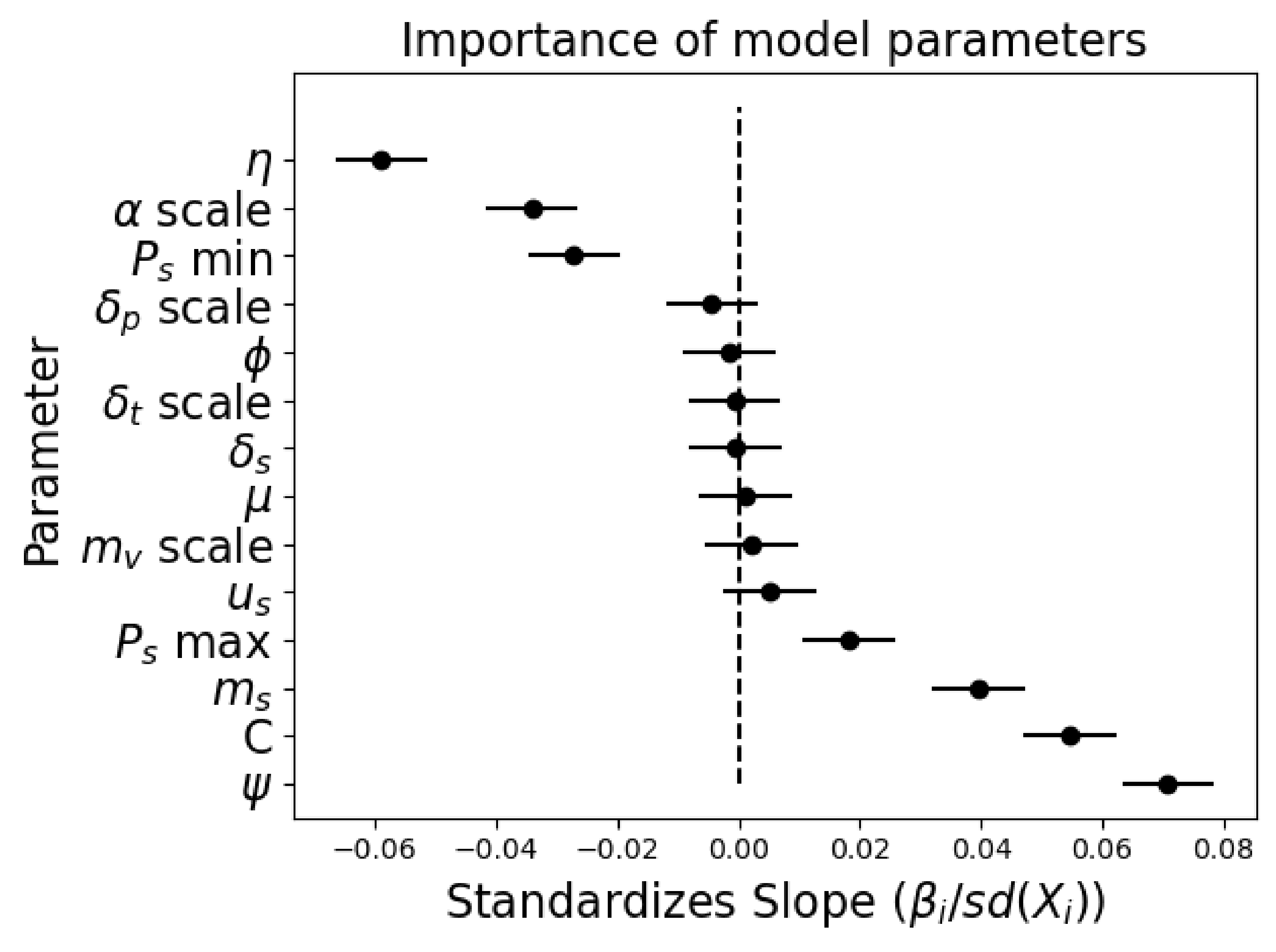


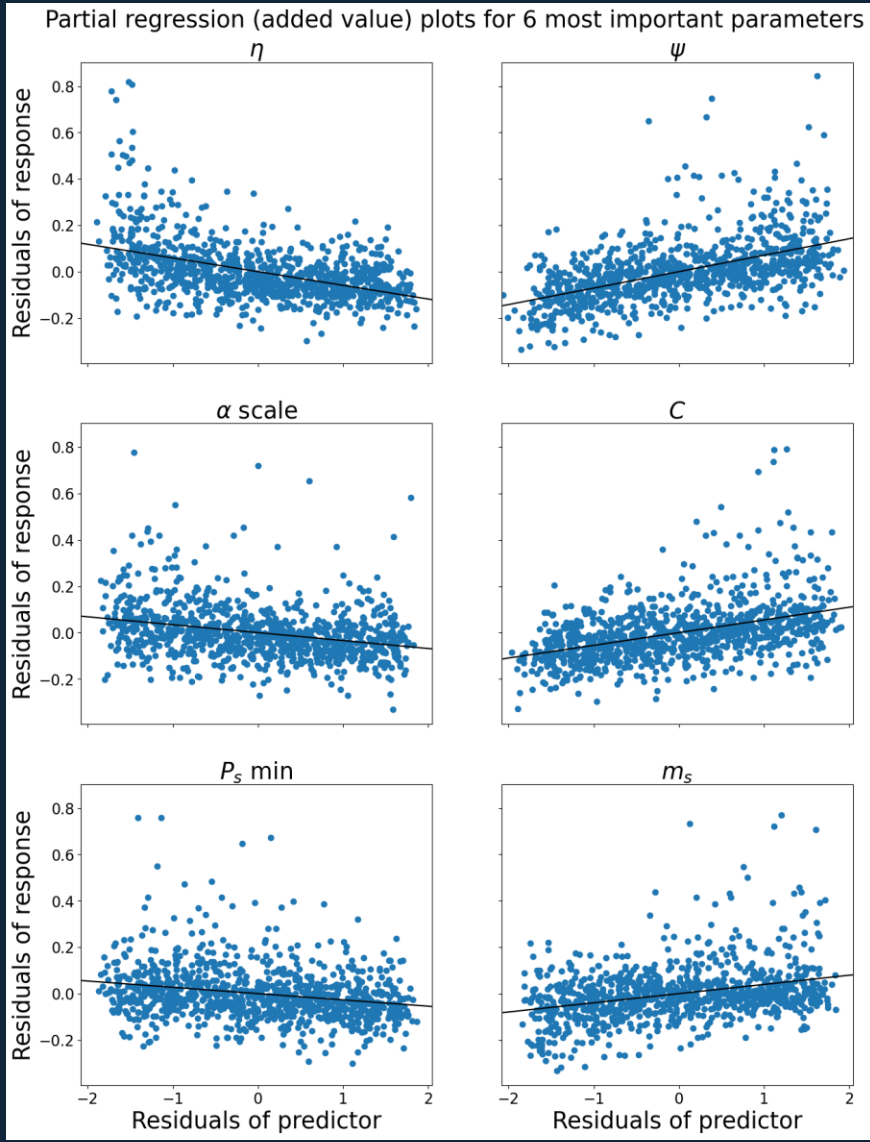
GSA – Example trajectories



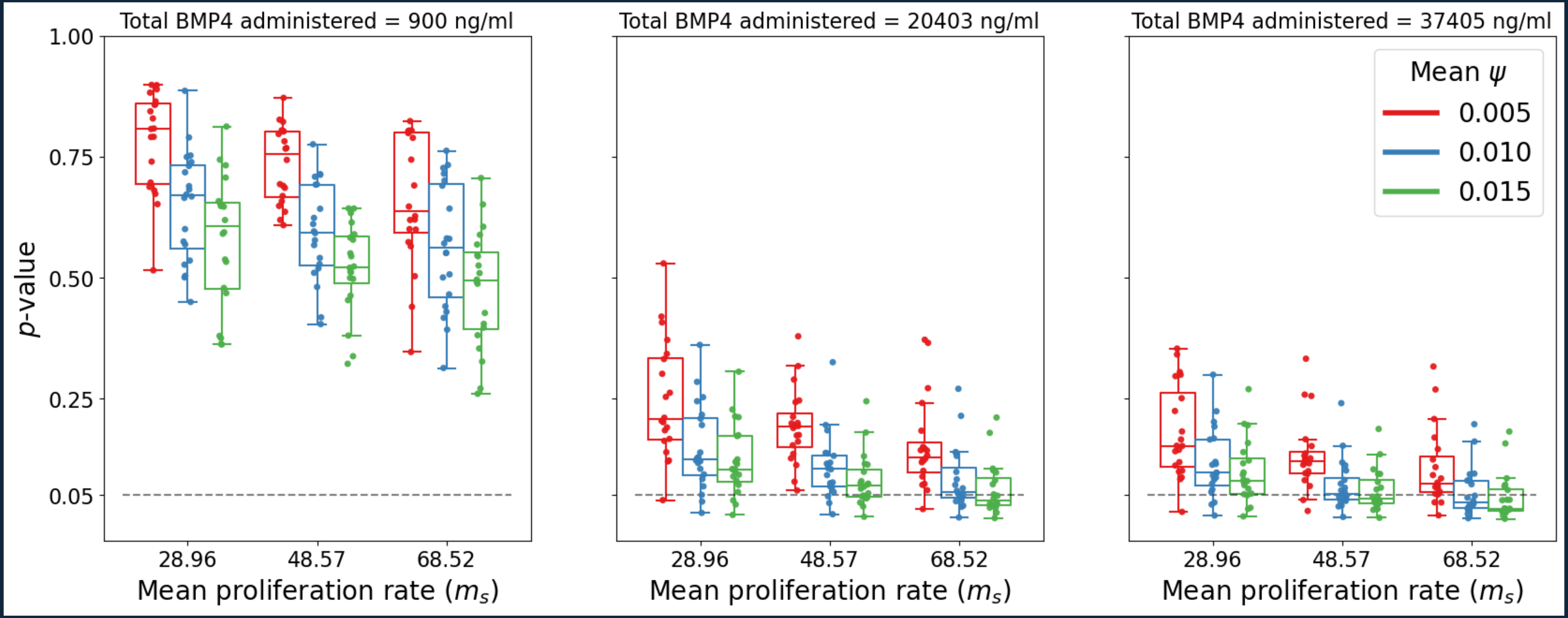


GSA – Important parameters

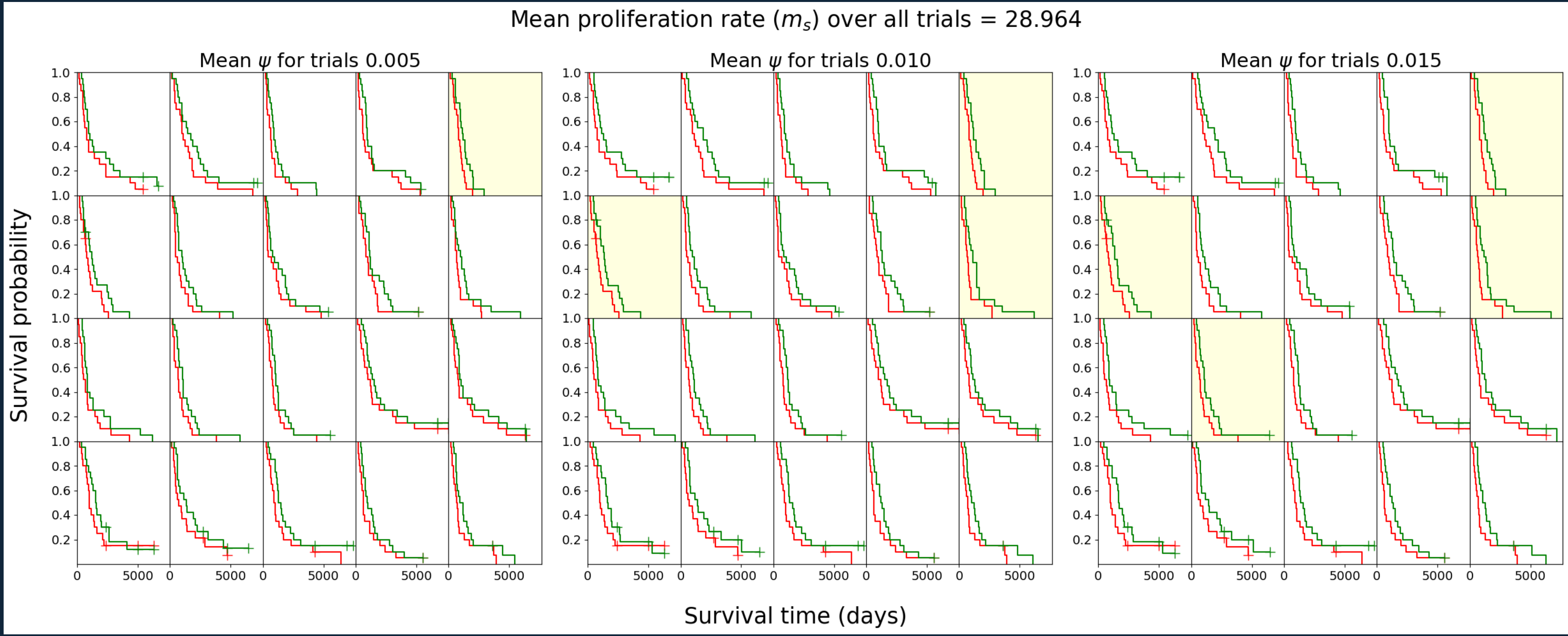




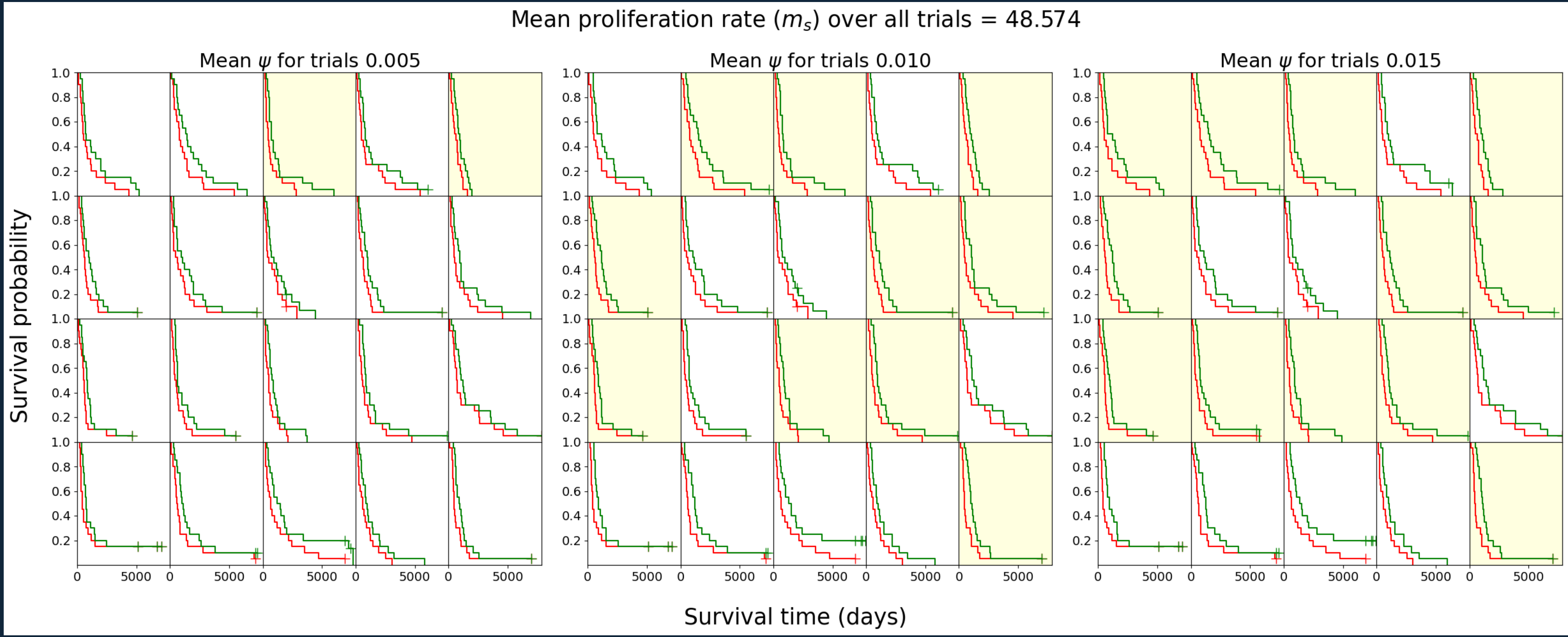
Stratified virtual clinical trials



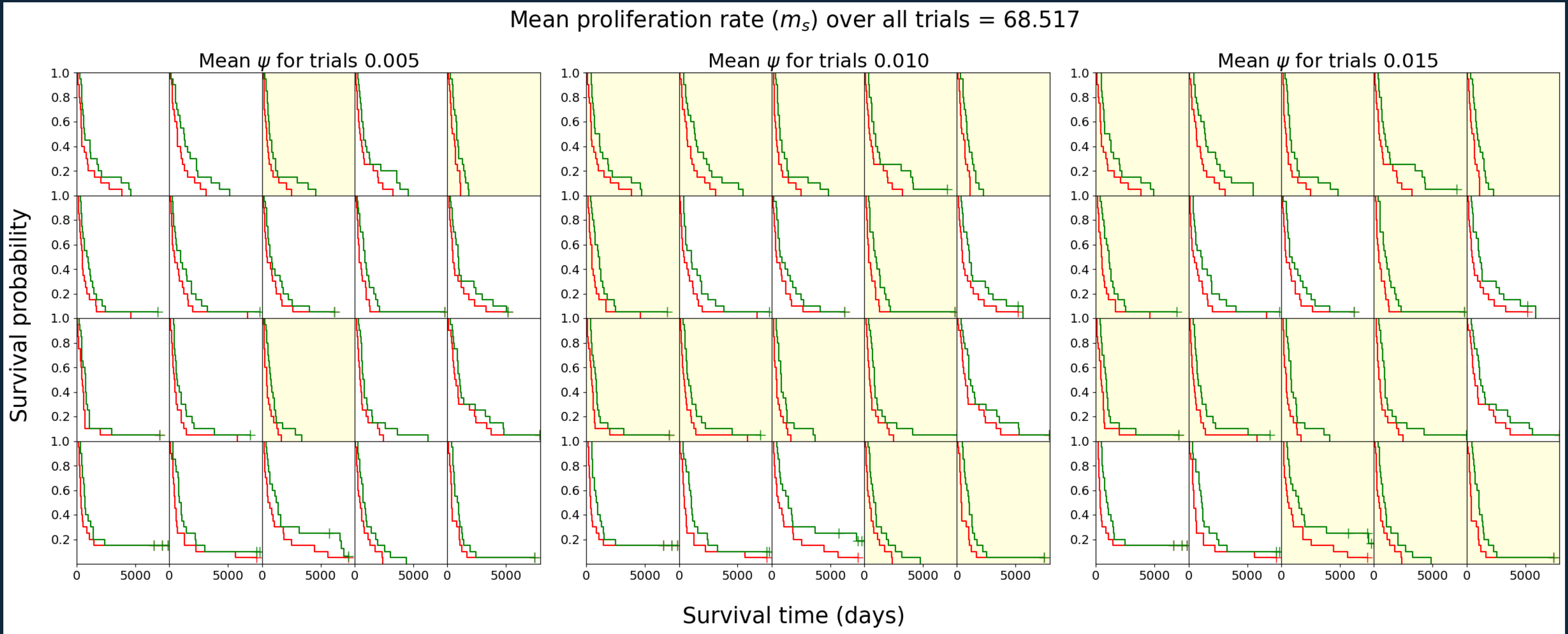
Slow proliferation rate



Medium proliferation rate



Fast proliferators



Acknowledgements

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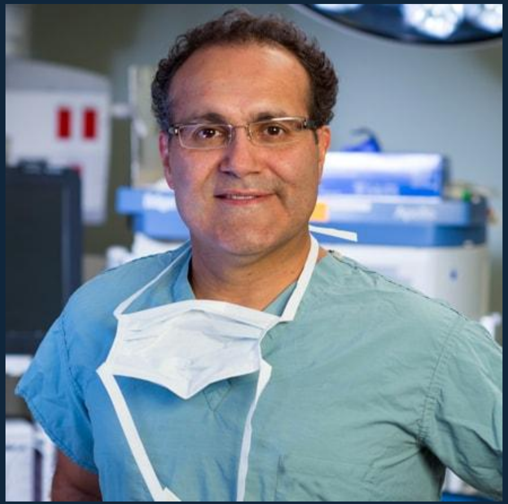

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