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Mathematical model for BMP4 induced differentiation therapy in glioblastoma

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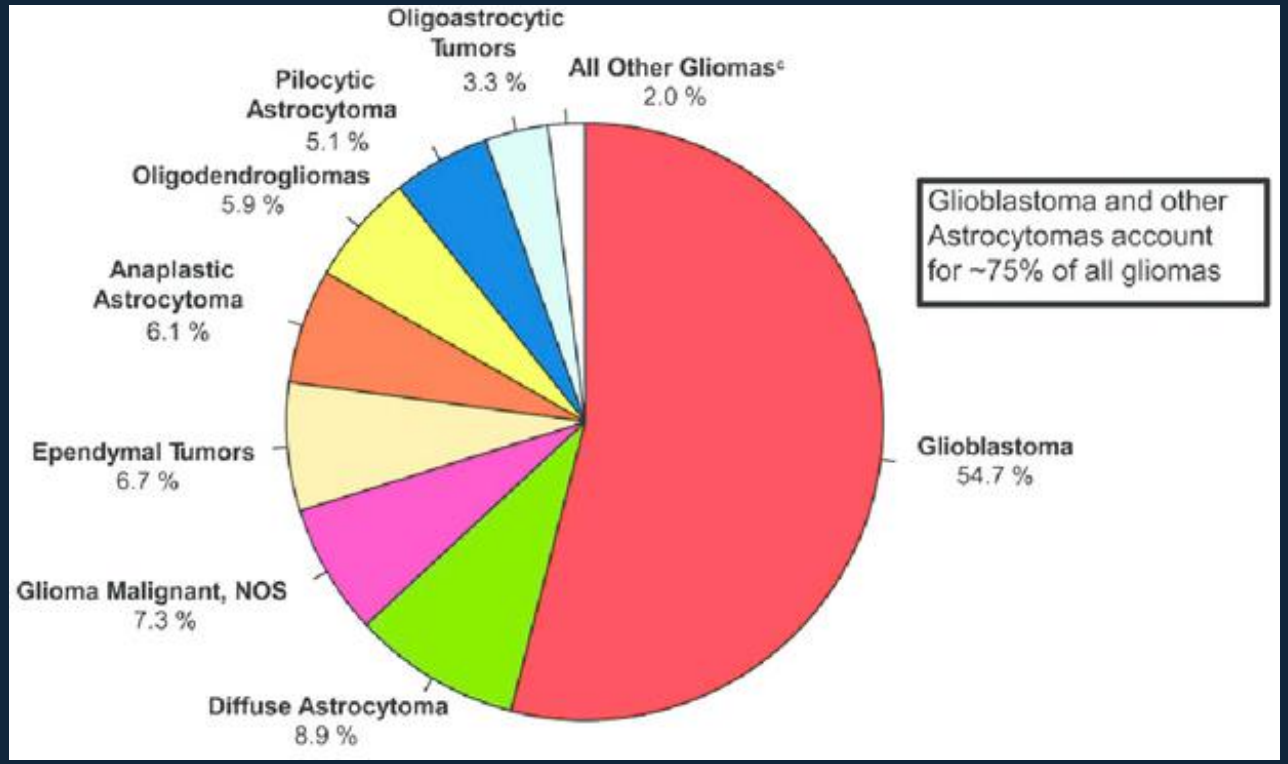
MAYO CLINIC

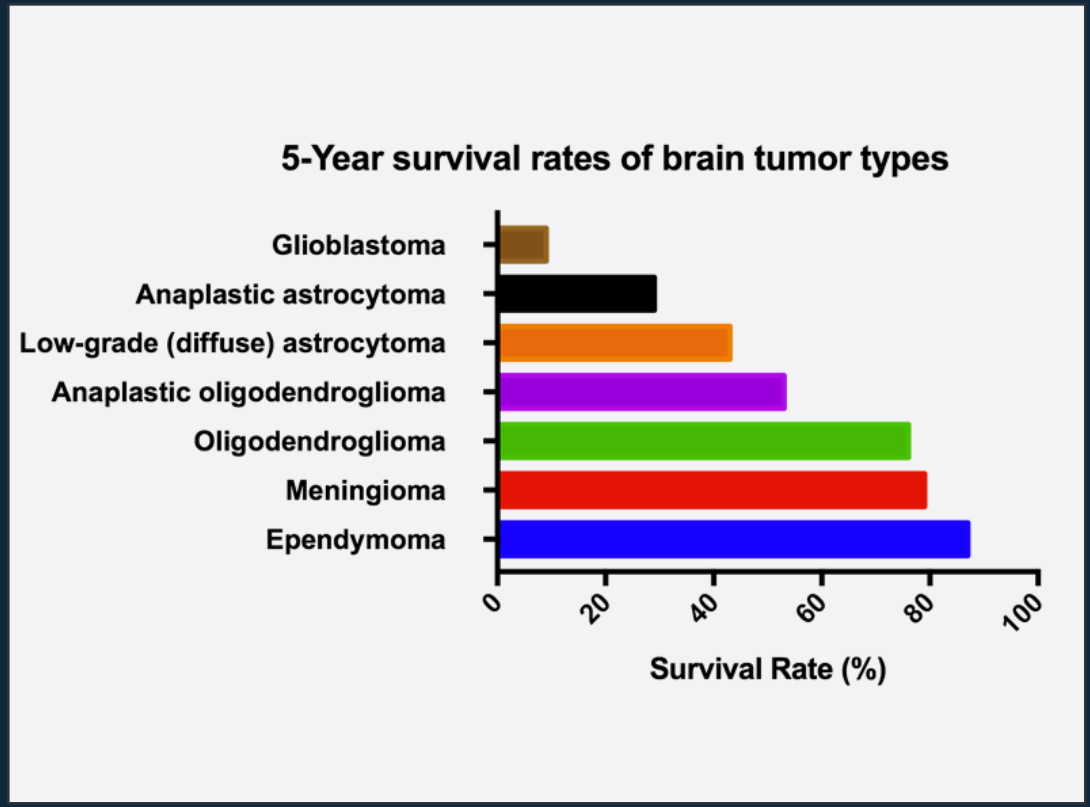
Glioblastoma (GBM)

GBM is the most common primary malignant brain tumour (USA 2007-2011)



10.1093/neuonc/nou223

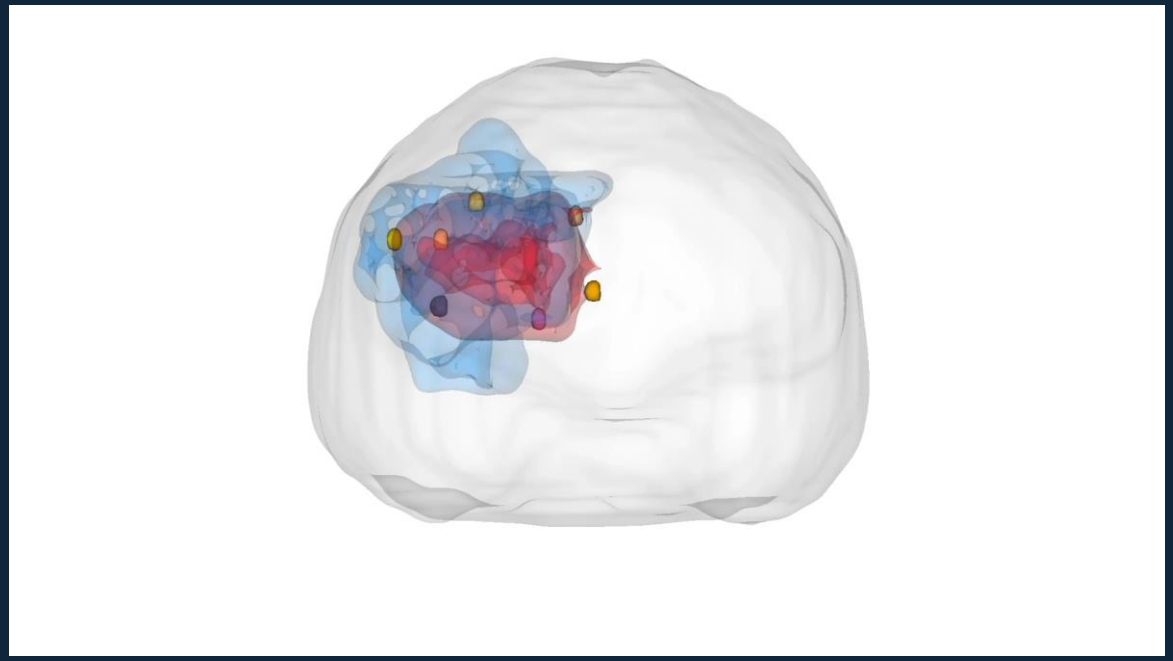
GBM has 5-year survival rate of only 5%

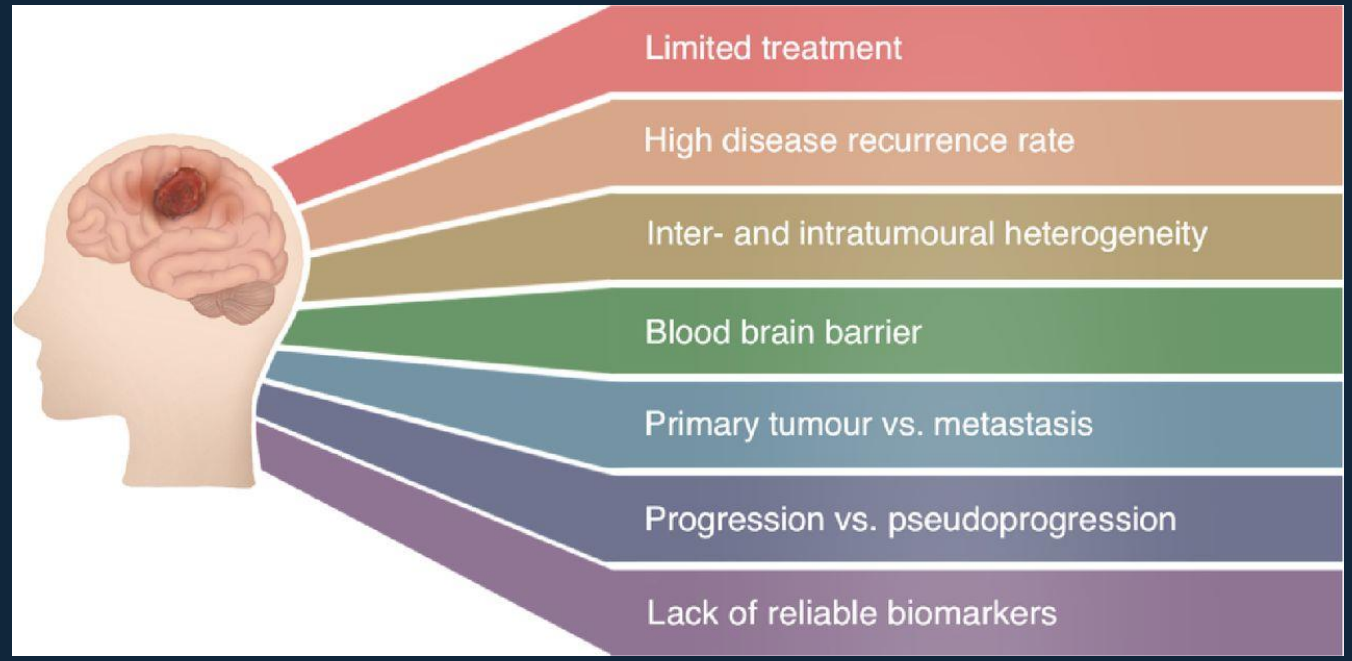


Glioblastoma — Laboratory for Precision Cancer Medicine (lpcm.be)

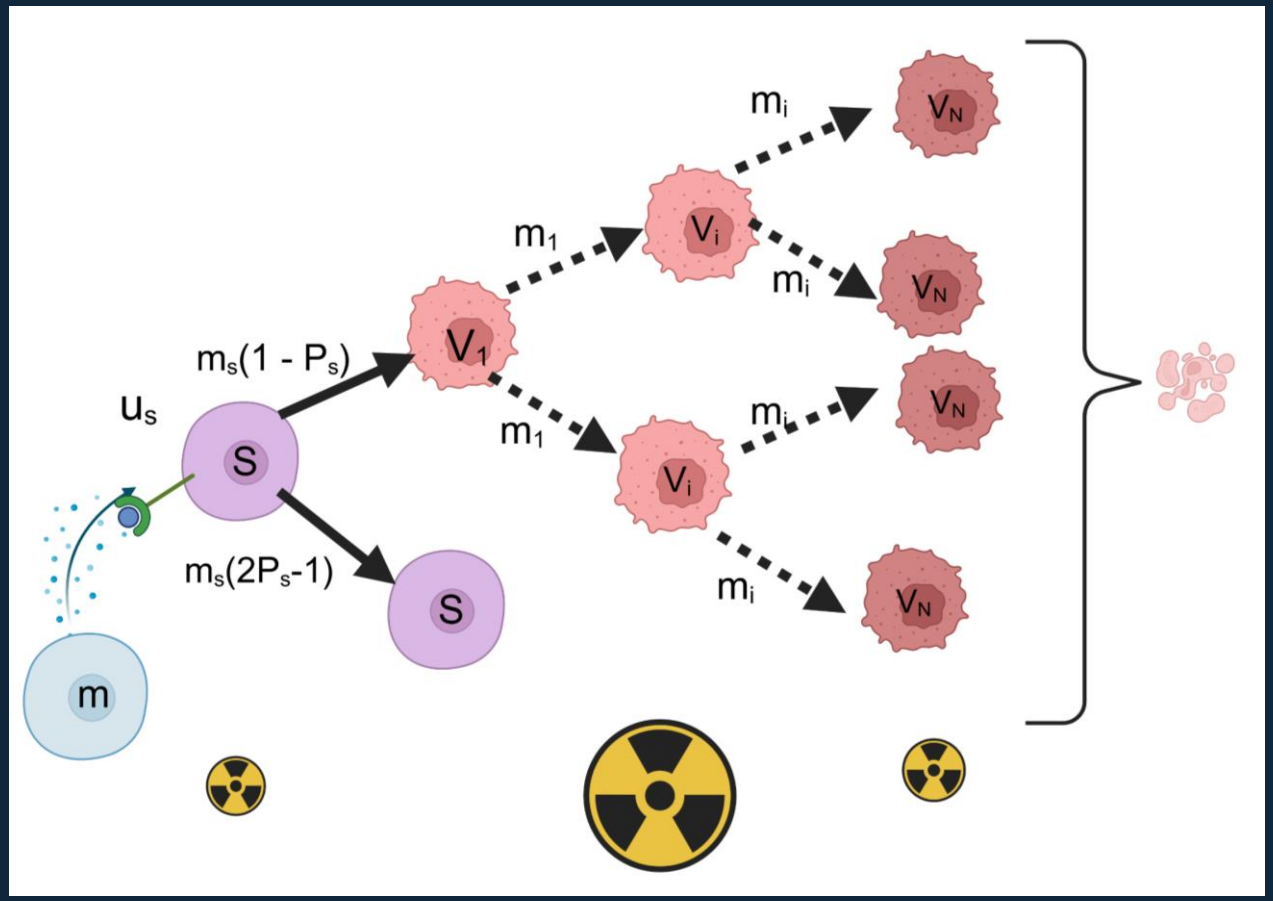
Why does standard of care fail

1) GBM is highly diffuse – complete surgical resection is impossible
2) GBM is heterogenous – In particular a critical subpopulation, the glioma stem cells (GSCs) are highly resistant to both radio and chemo therapy.





Glioma stem cell mathematical



- GSCs divide asymmetrically to produce progenitor cells (PCs)
- Balance of GSC symmetric. and asymmetric division set up an equilibrium with a small fraction of GSC (~2%).
- GSCs have unlimited self-renewal.
- PCs have a limited number of divisions before they become terminally differentiated.
- GSCs are less sensitive to RT than PCs.
- BMP4 promotes differentiation of GSCs.

GSC model

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

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

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

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

GSC reduced model

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

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

Where

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

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

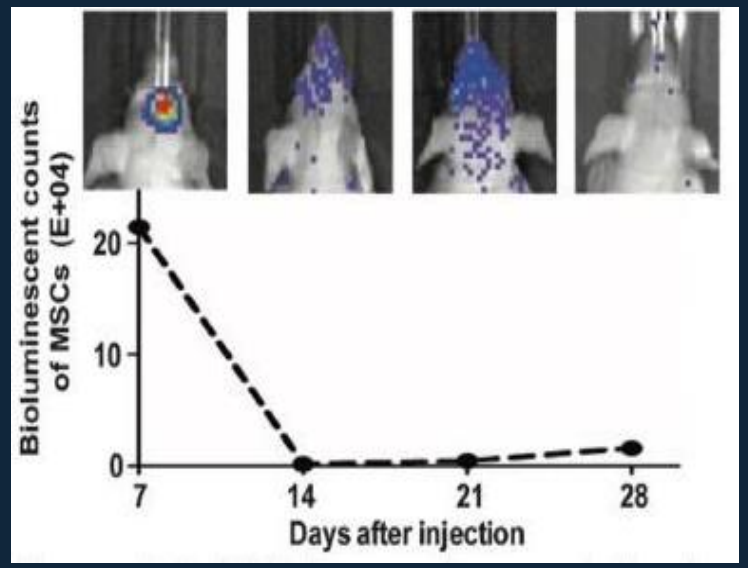
$$\alpha_j = \frac{2m_{i-1}\left(1 - {}^{N}/_{k}\right)}{\delta_i + m_i\left(1 - {}^{N}/_{k}\right)}$$

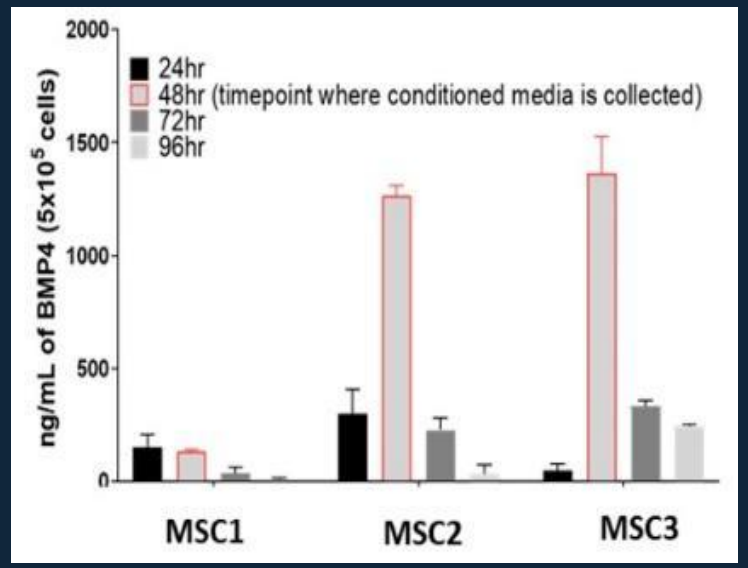
https://doi.org/10.1007/s11538-012-9798-x (Hillen, Enderling, Hahnfeldt)

AMSCs delivery of BMP4 model

$$\frac{dm}{dt} = -\underbrace{\delta_m m}_{Decay\ of\ AMSC}$$

$$\frac{dB}{dt} = \underbrace{Cm}_{Release\ of\ BMP4} - \underbrace{u_s S}_{Uptake\ by\ GSCs}$$

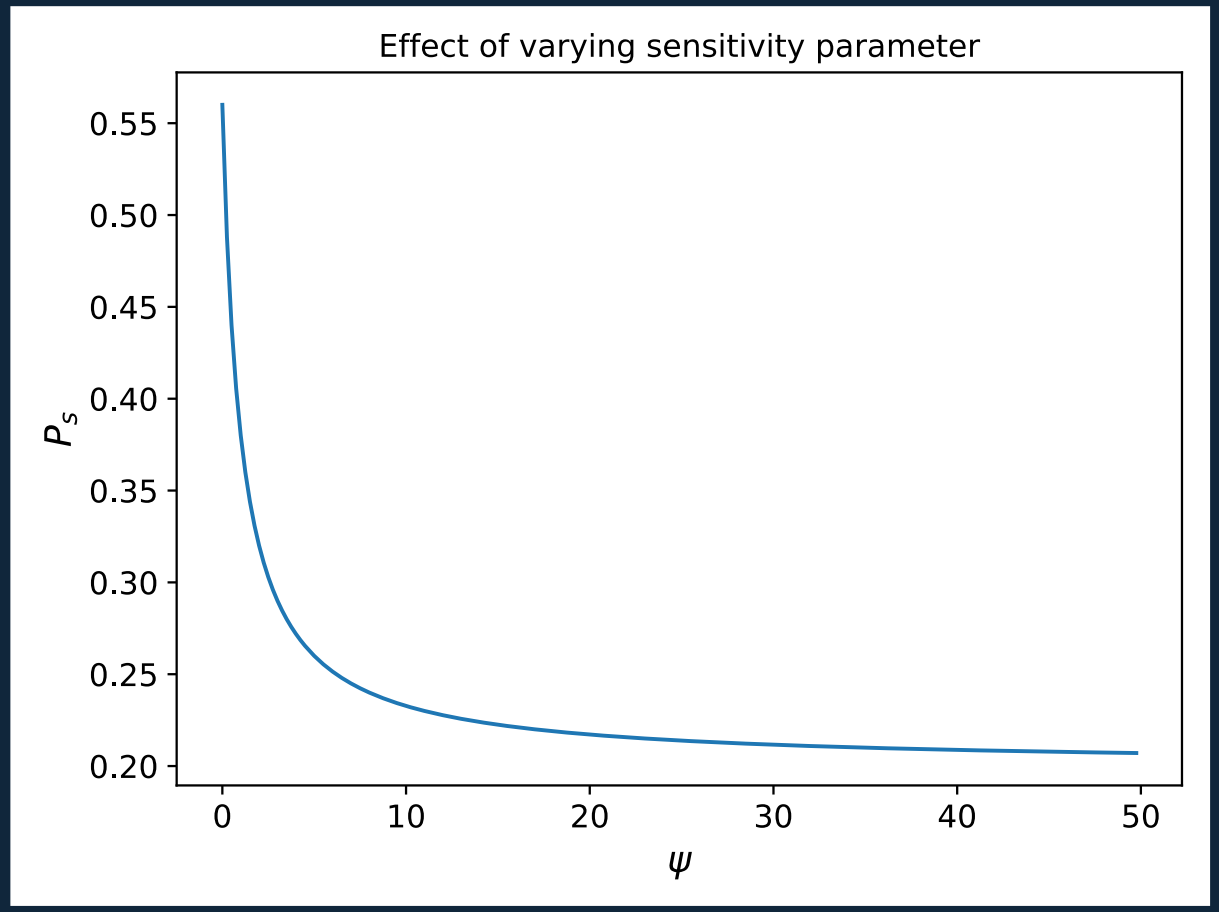




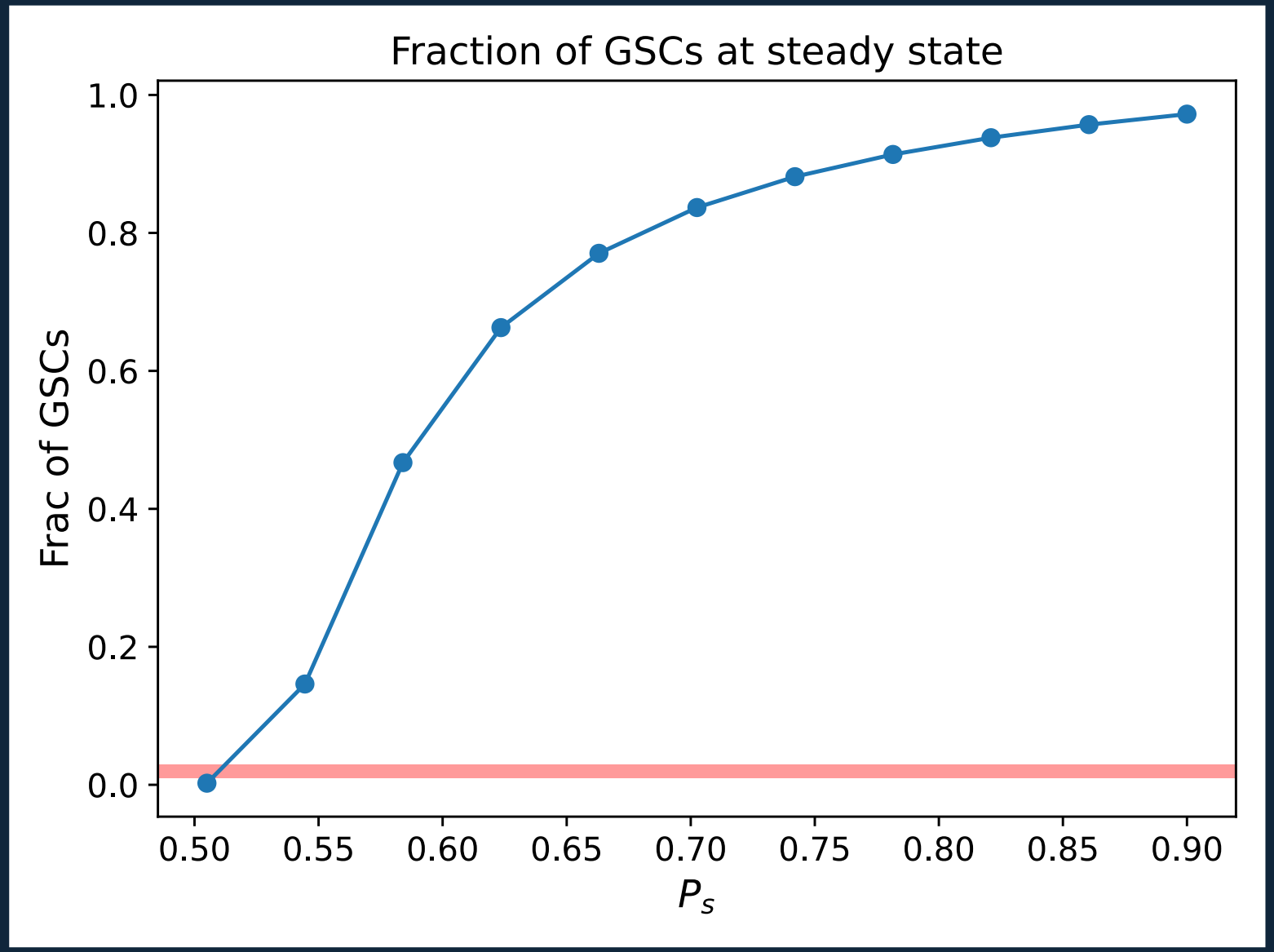
10.1158/1078-0432.CCR-13-1415

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

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



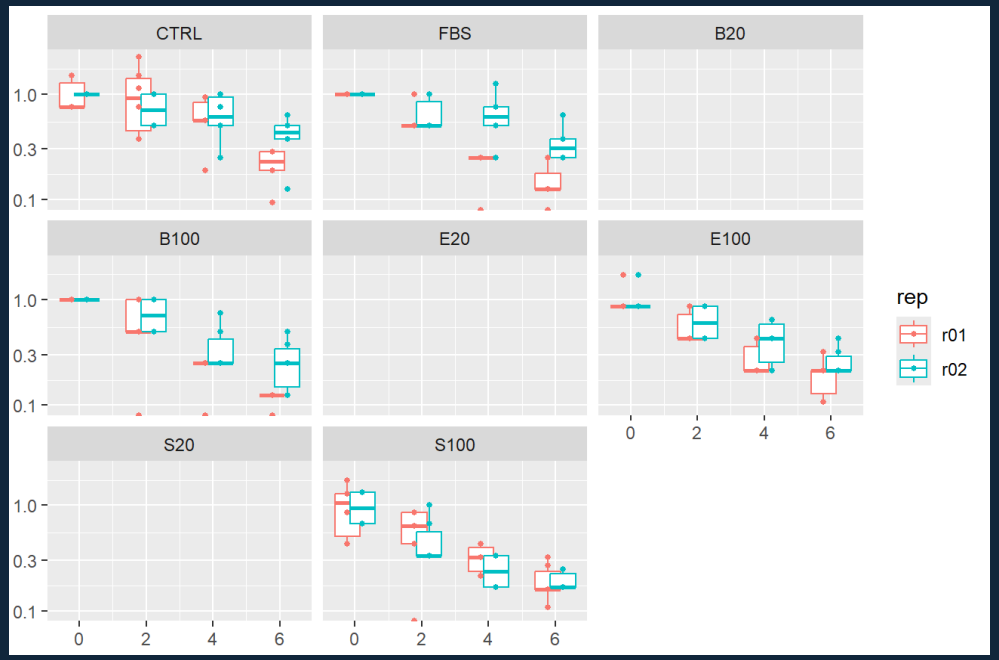
Work out a reasonable value of P_{max}



RT data wrangling

- Clonogenic assay to determine RT effect.
- Normalised each cell line by treatment group (CTRL, B100, S100) and by biological replicate by its mean at dose 0 Gy.
- Only include replicates that have measurements at 0,2,4,6 Gy.

QNS120

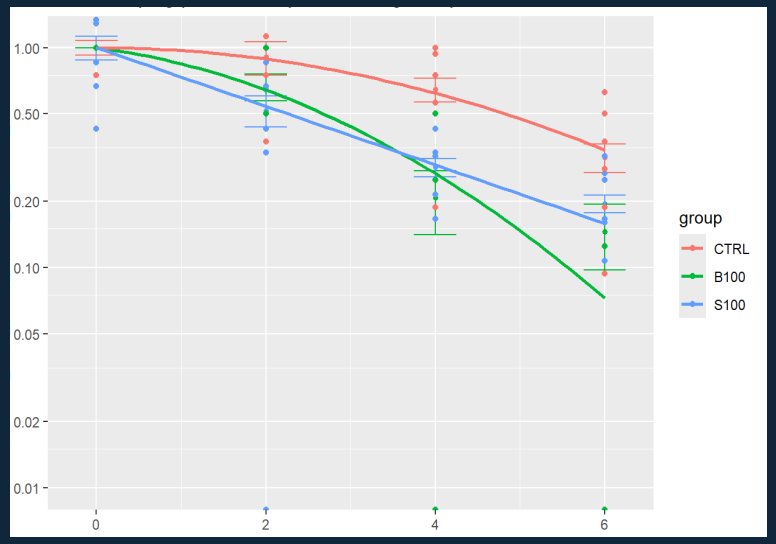


GBM1a

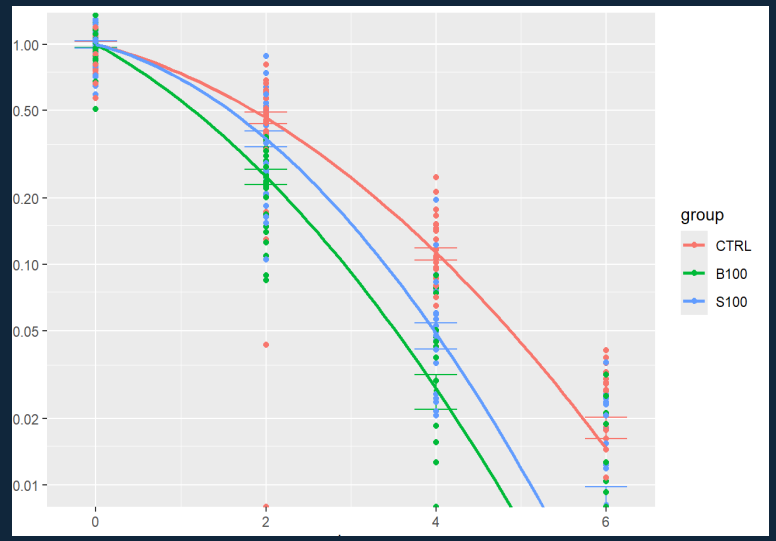
LQ model fits

$$S(d) = \exp(-(\alpha d + \beta d^2))$$

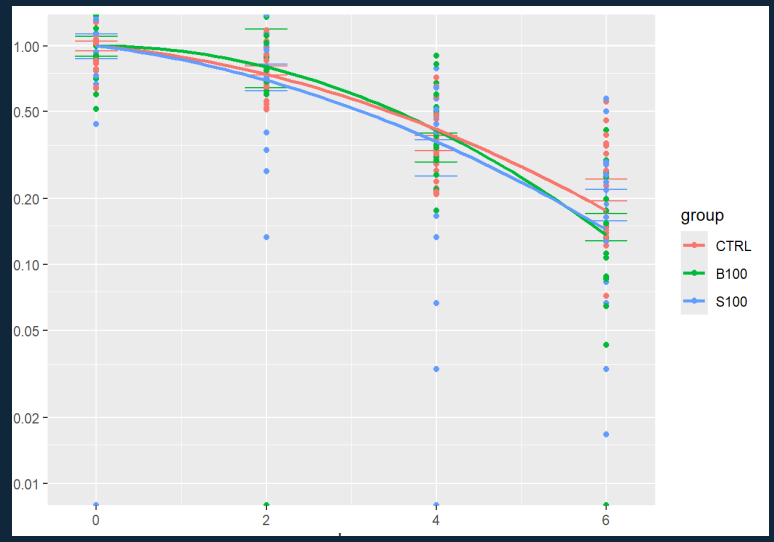
QNS120



GBM1a



GBM965



dose

Dual linear quadratic model to capture the fraction of GSCs.

$$S(d) = \exp(-(\alpha d + \beta d^2))$$

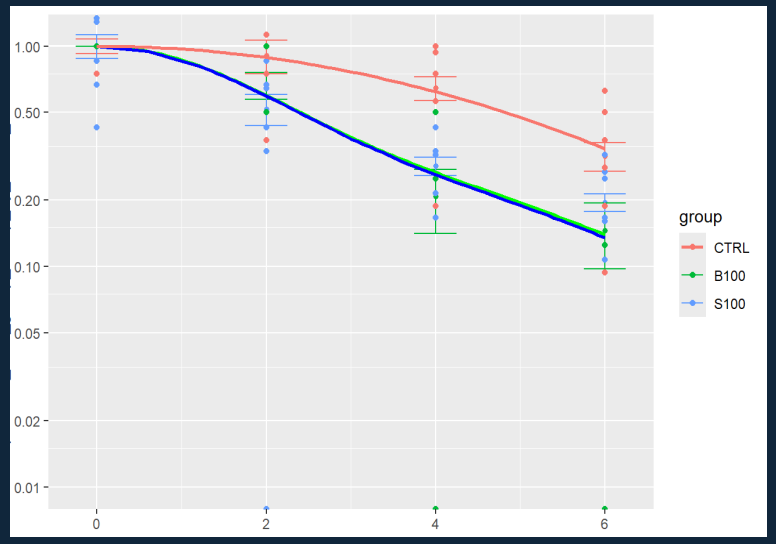
$$S(d) = F\exp\left(-(\alpha d + \beta d^2)\right) + (1 - F)\exp(-\gamma(\alpha d + \beta d^2))$$

- F = Fraction of GSCs
- γ = The difference in radiosensitivity between GSCs and non-GSCs, taken to be around 6 (Gao et al. 2013).
- This allows us to get an estimate for how much differentiation was induced by treatment (BMP4).

https://doi.org/10.1016/j.ijrobp.2014.12.004

DLQ model fits

QNS120



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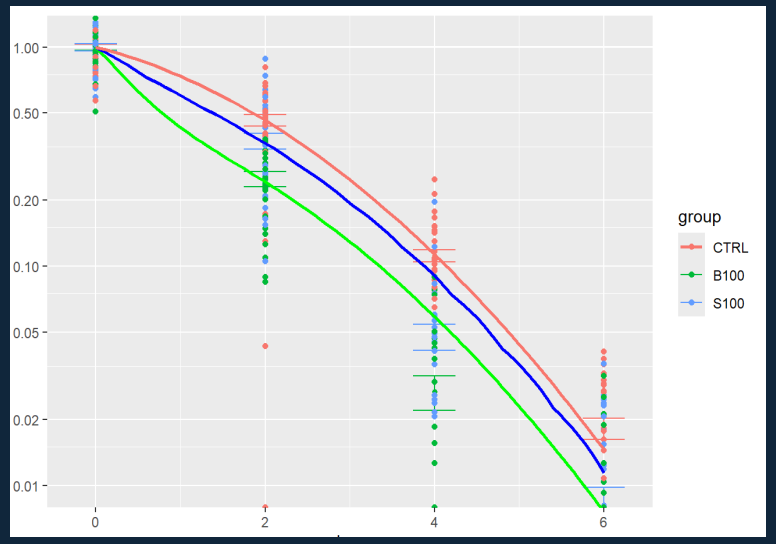

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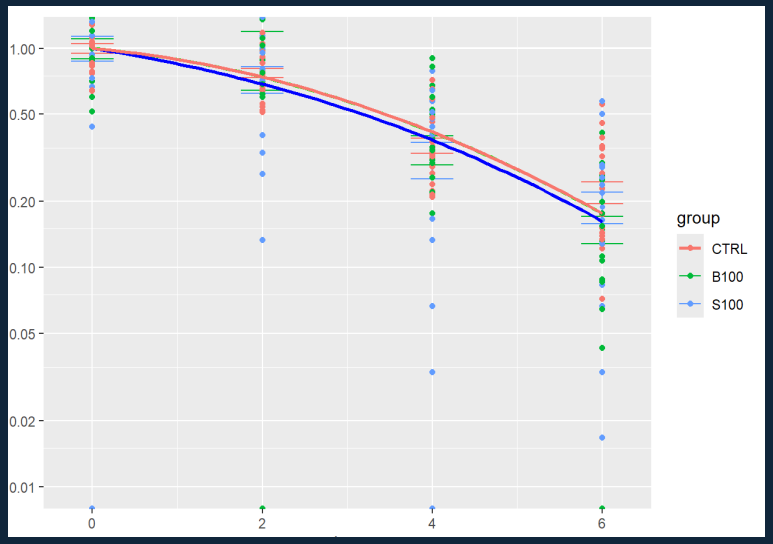
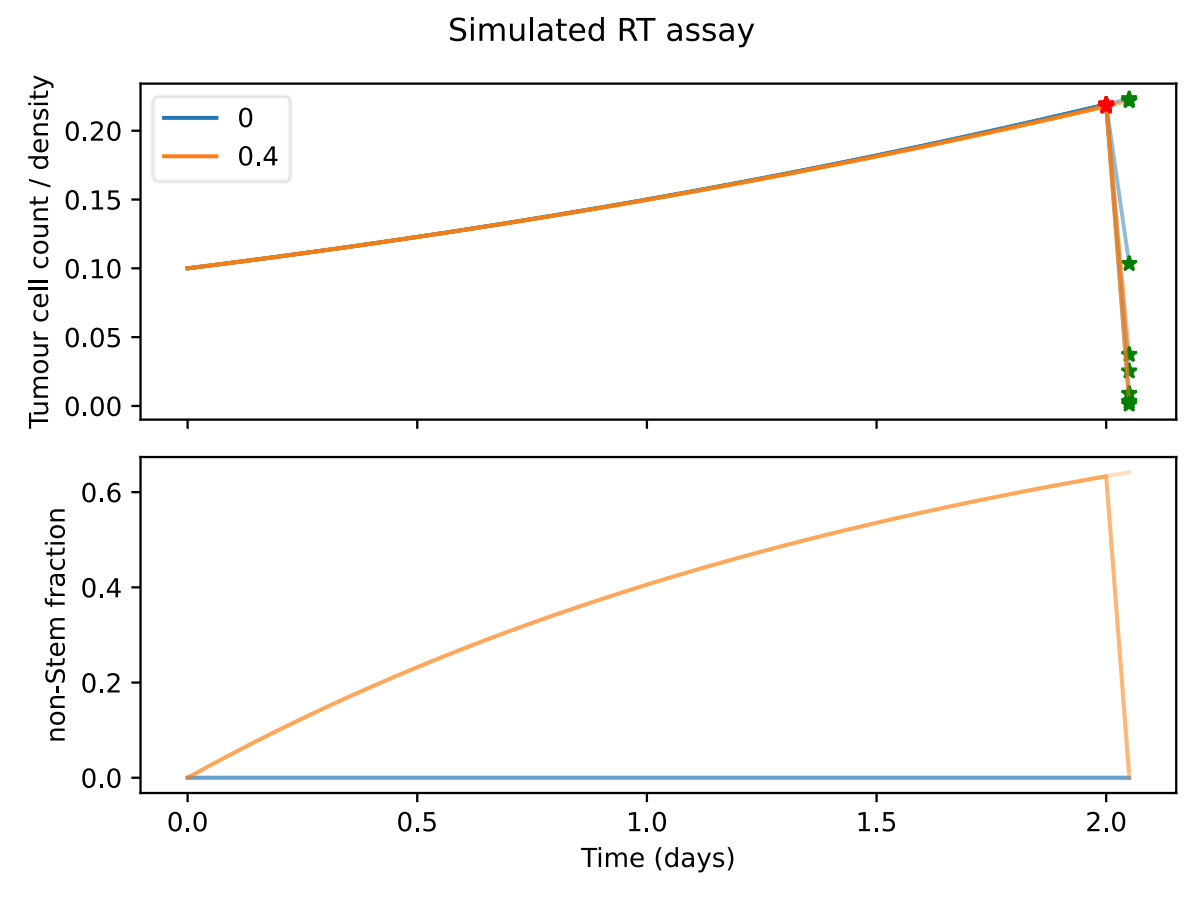


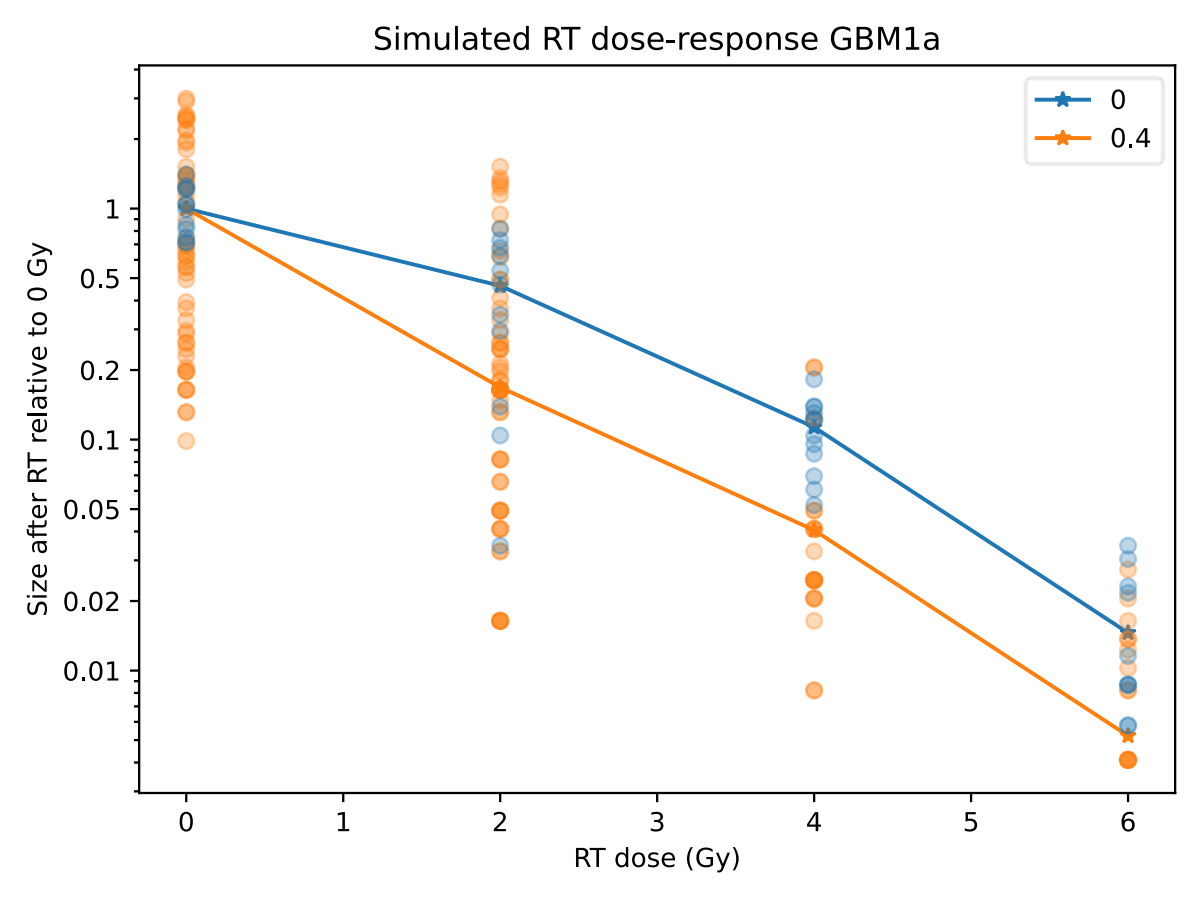
Frac GSCs (F):
- CTRL = 1
- B100 = 0.40
- S100 = 0.39

Frac GSCs (F):
- CTRL = 1
- B100 = 0.52
- S100 = 0.78

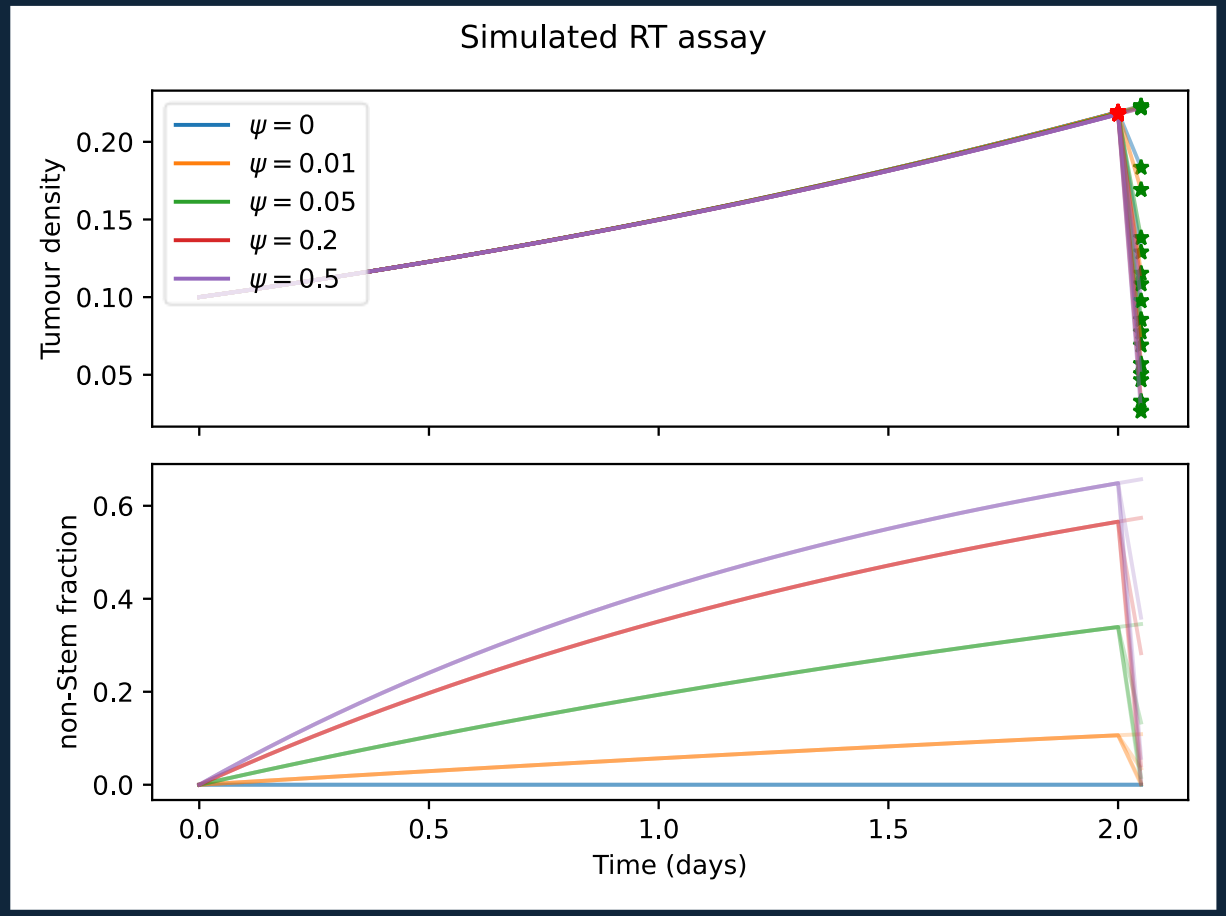
Frac GSCs (F):
- CTRL = 1
- B100 = 0.99
- S100 = 0.92

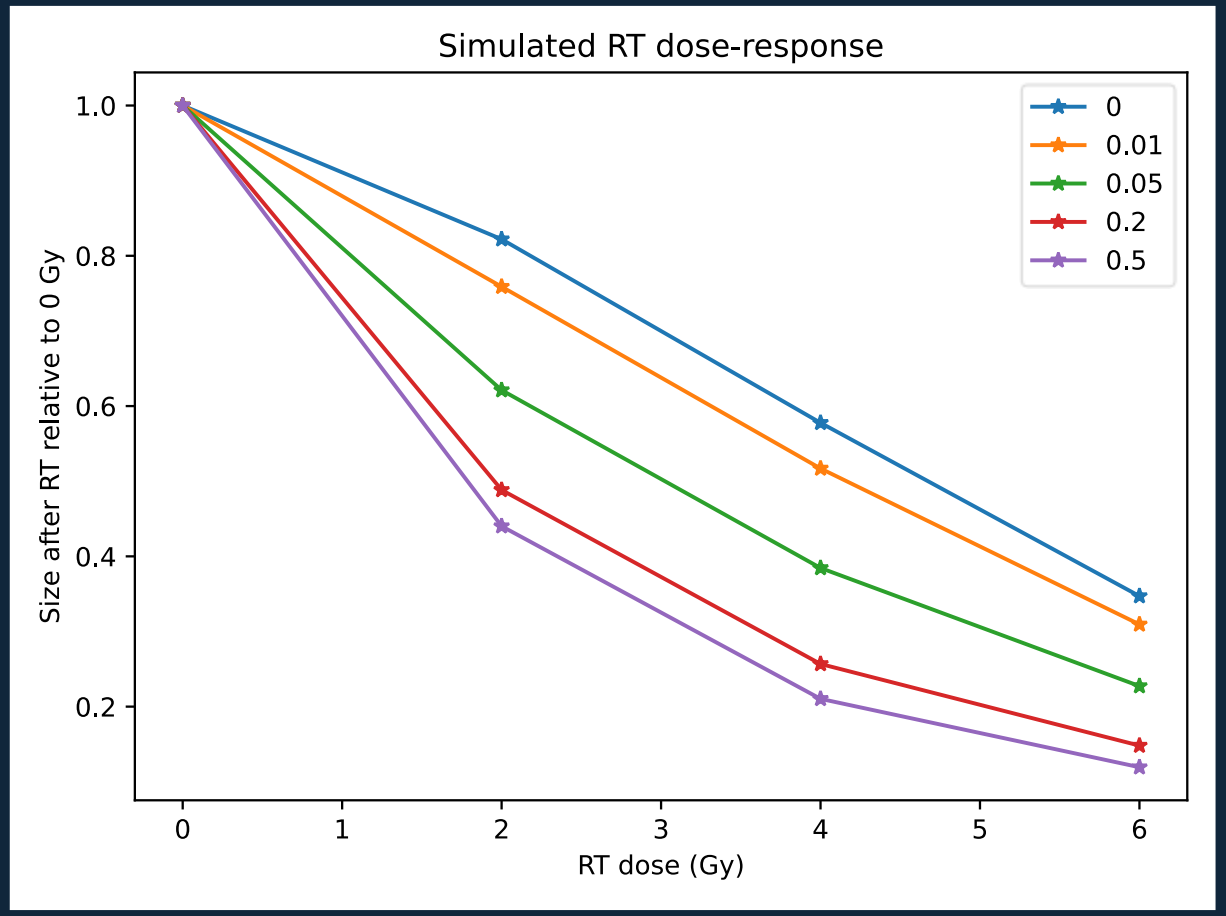
Model simulations of the clonogenic assay



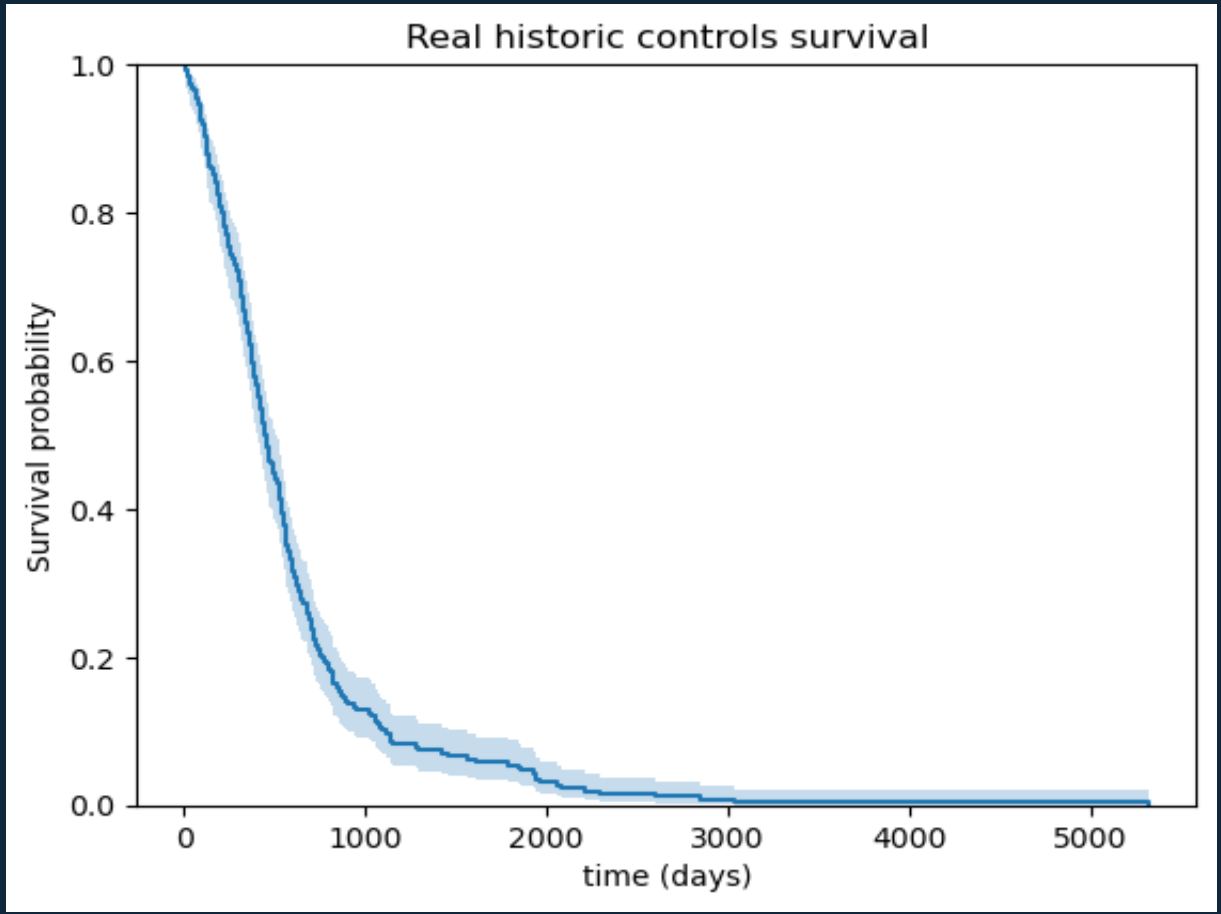


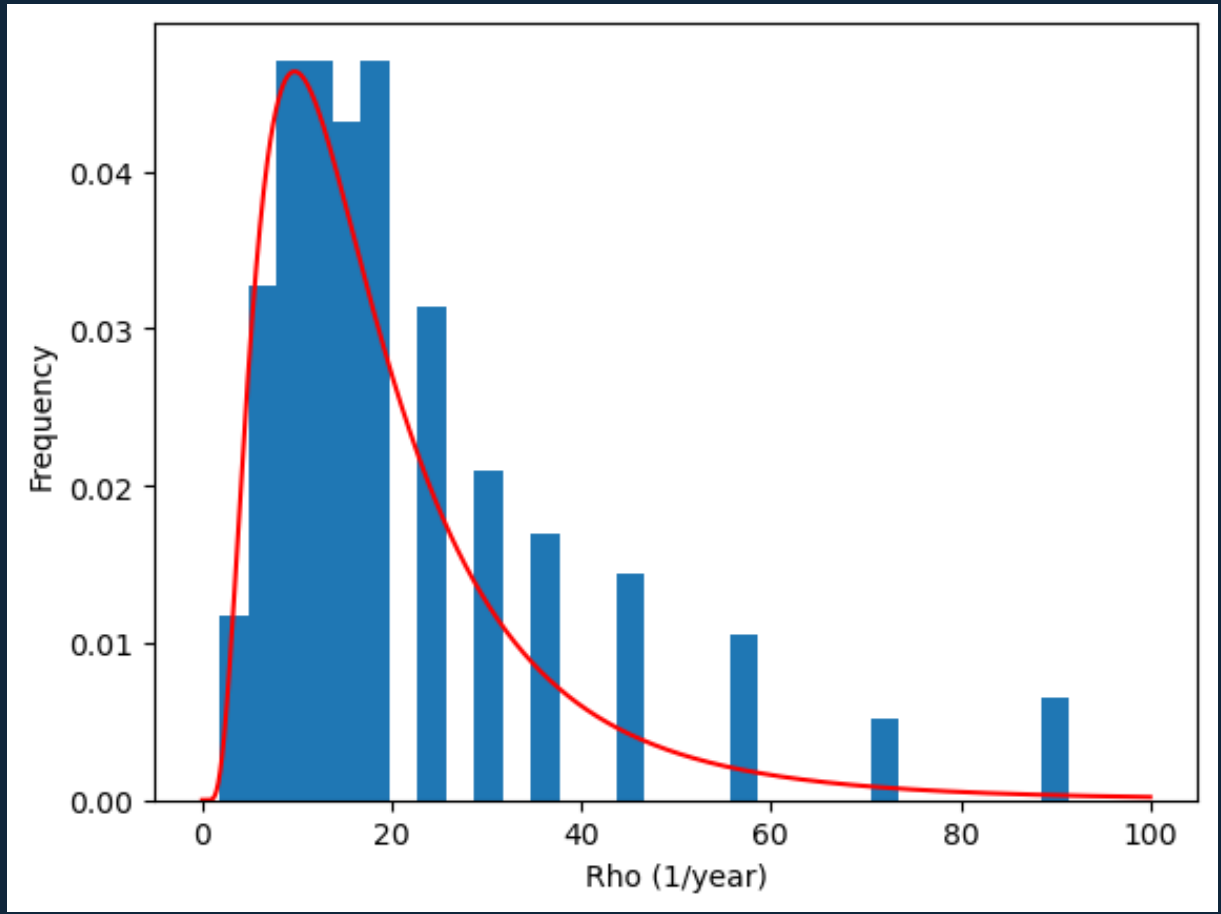
Model simulations of the clonogenic assay





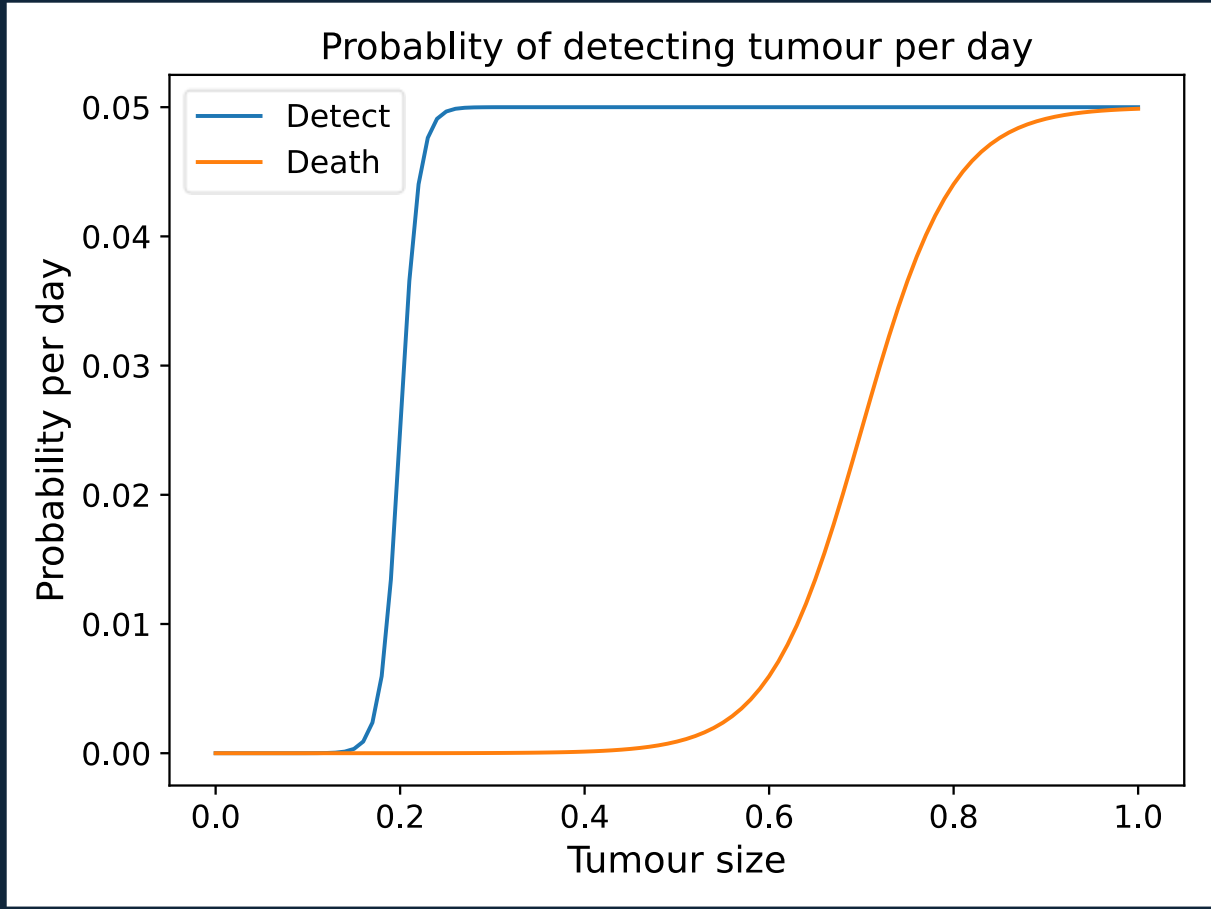
In silico trials: Patient data

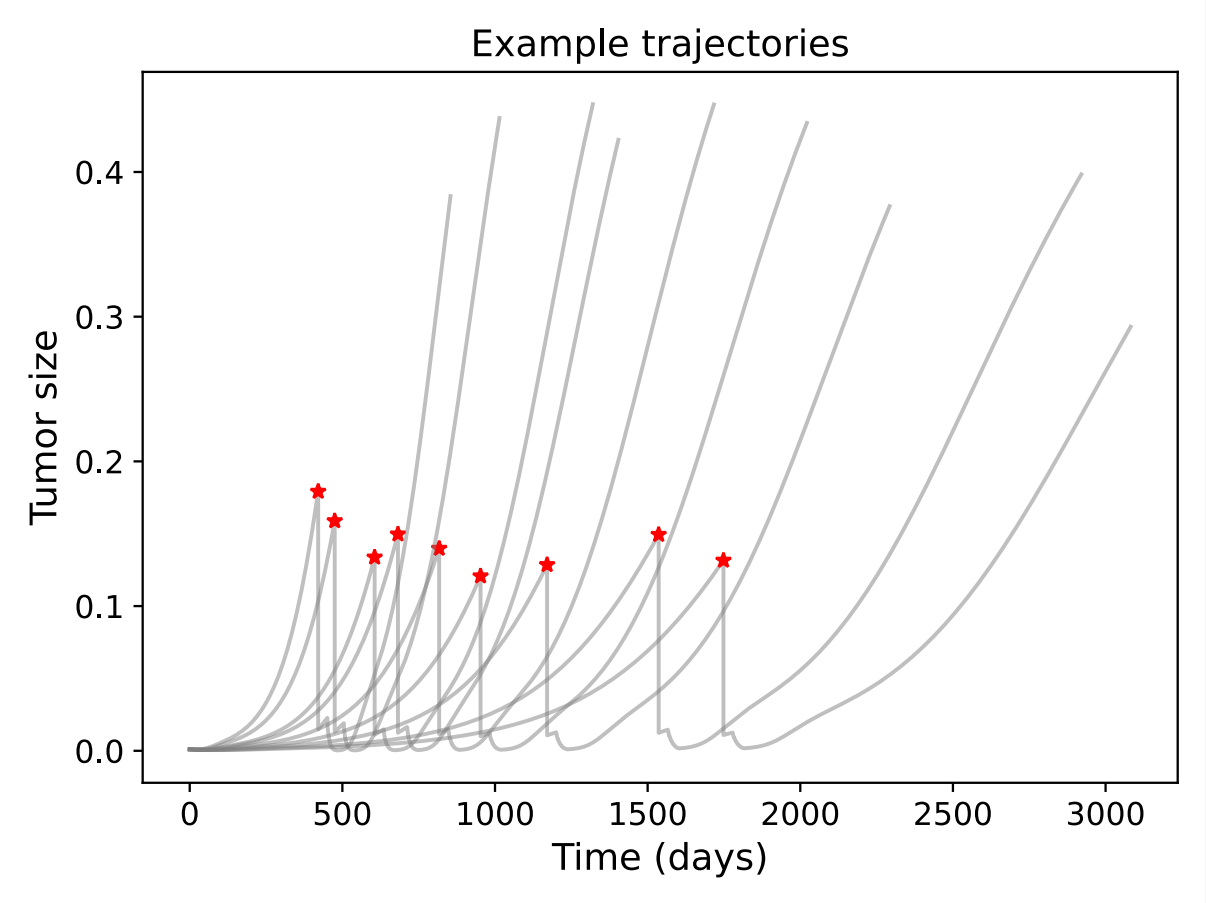




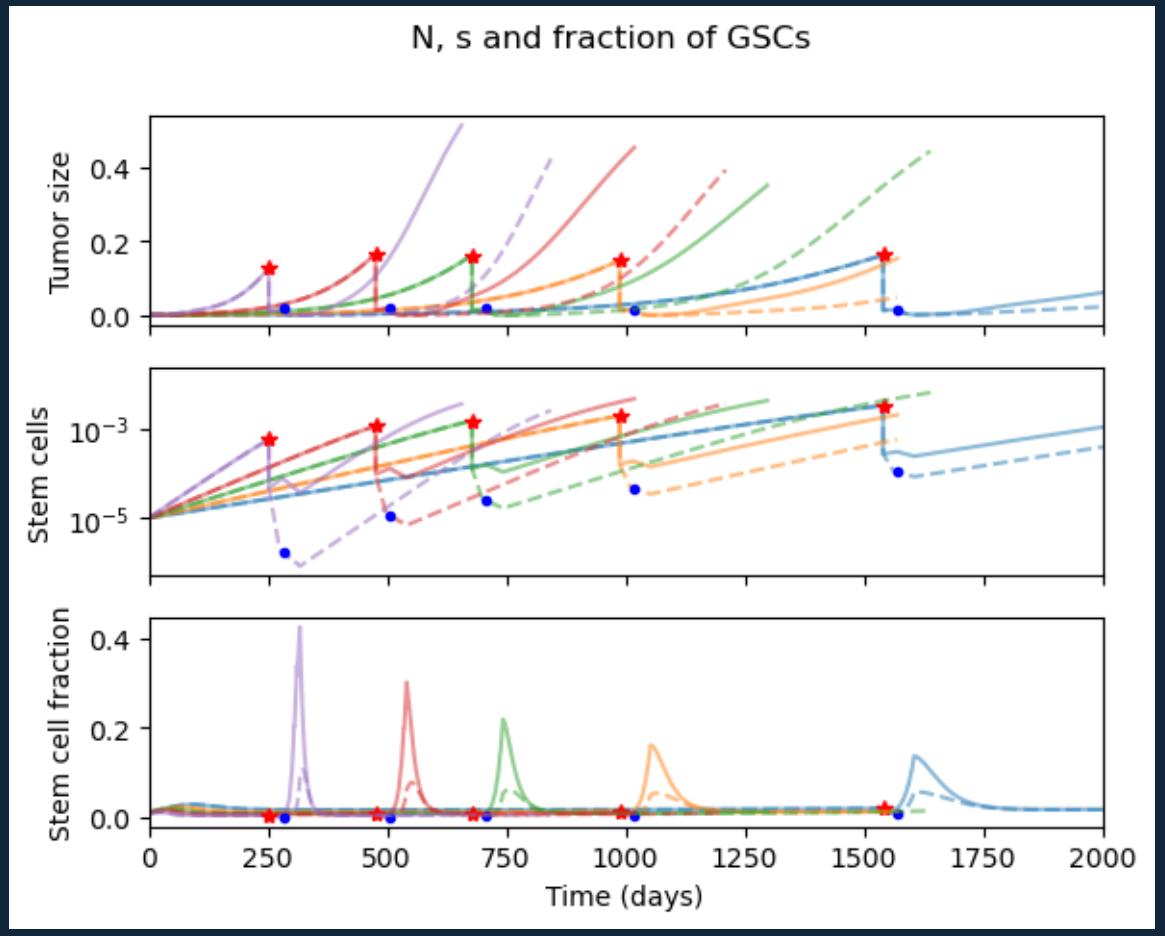
Yang et al. 2019 (https://doi.org/10.1126/scitranslmed.aao5253)

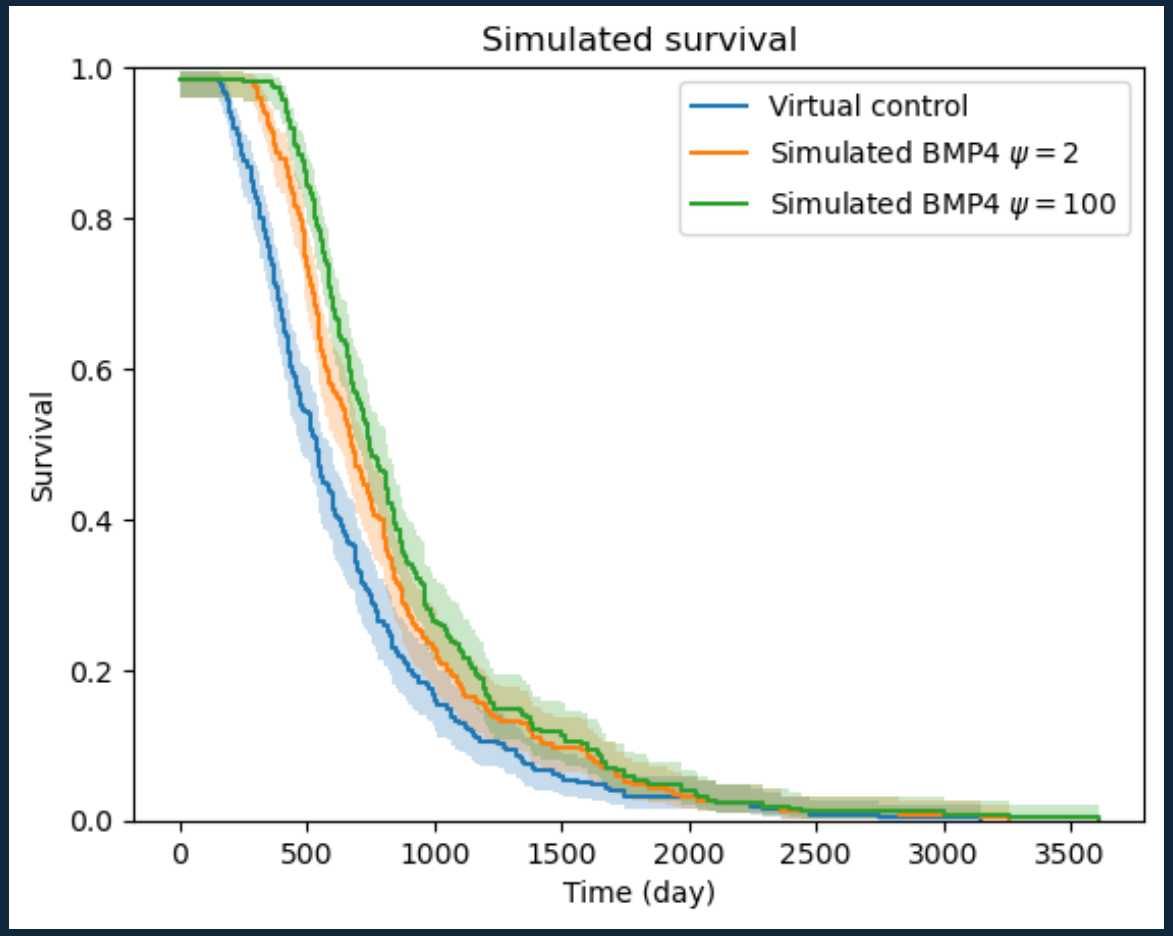
Uncertainty in death and detection



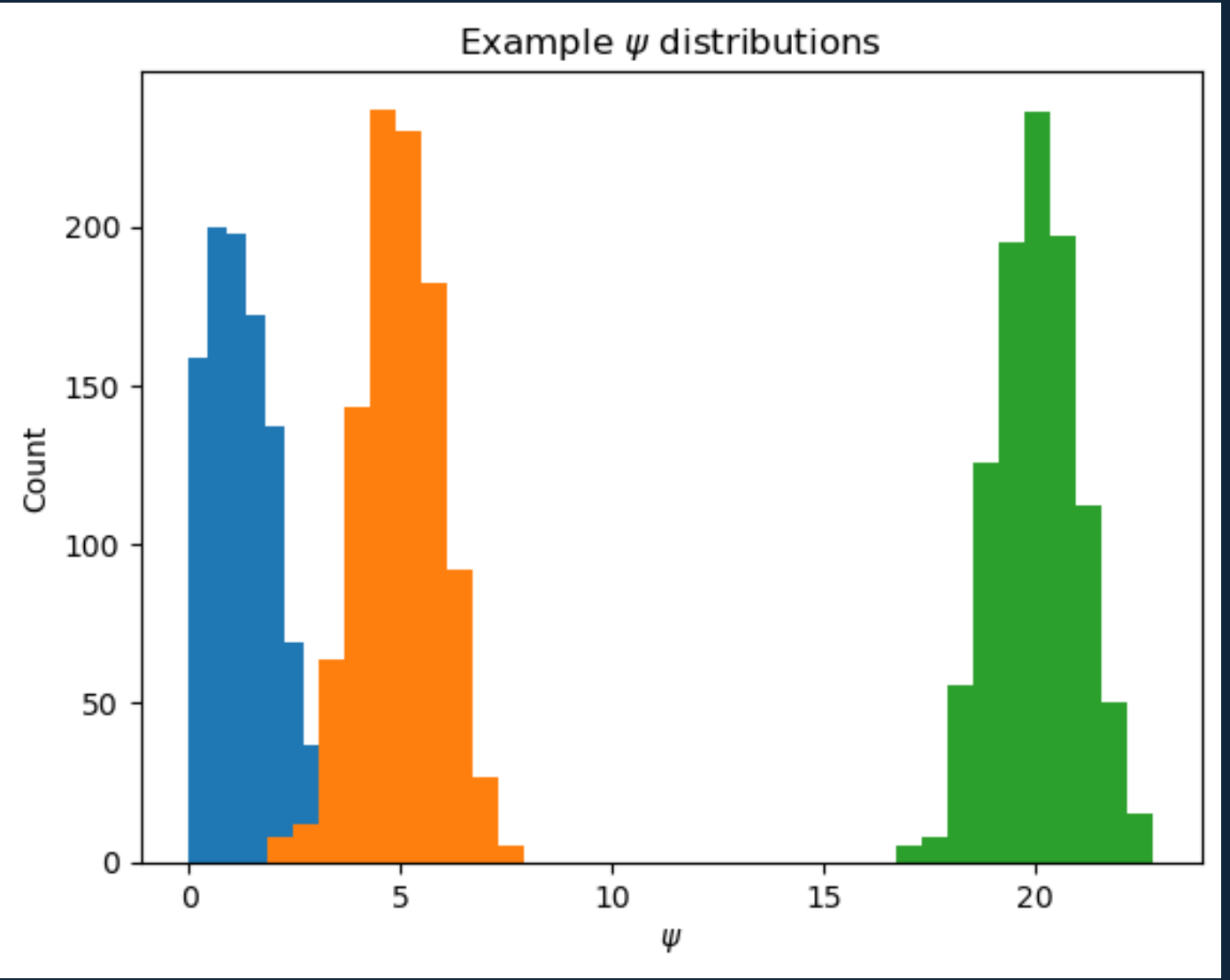


Simulating treatments: resection + RT vs resection + BMP4 + RT

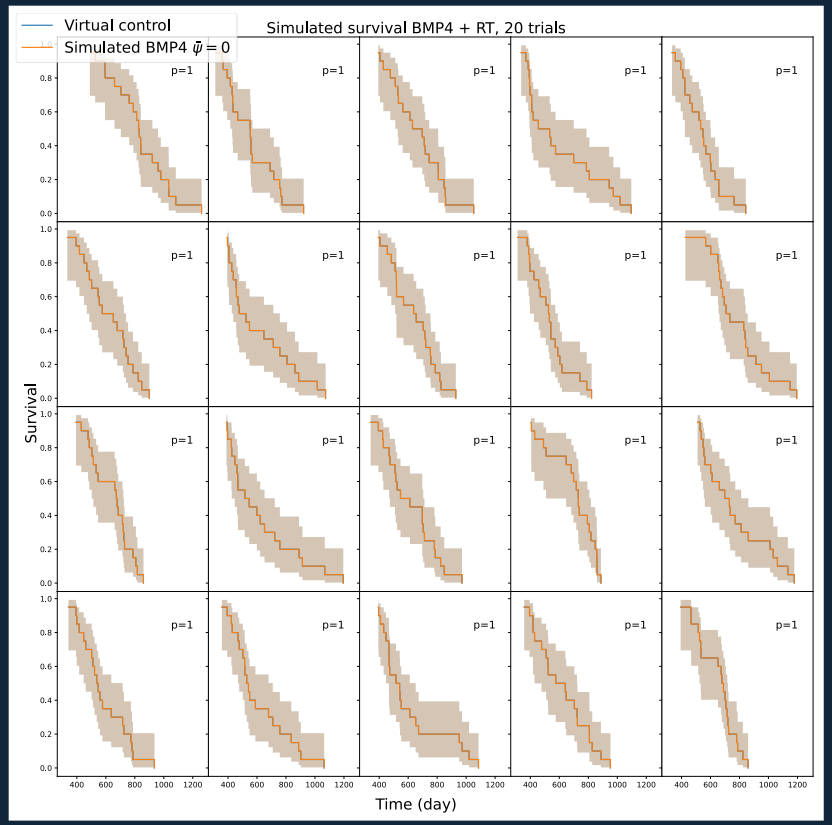


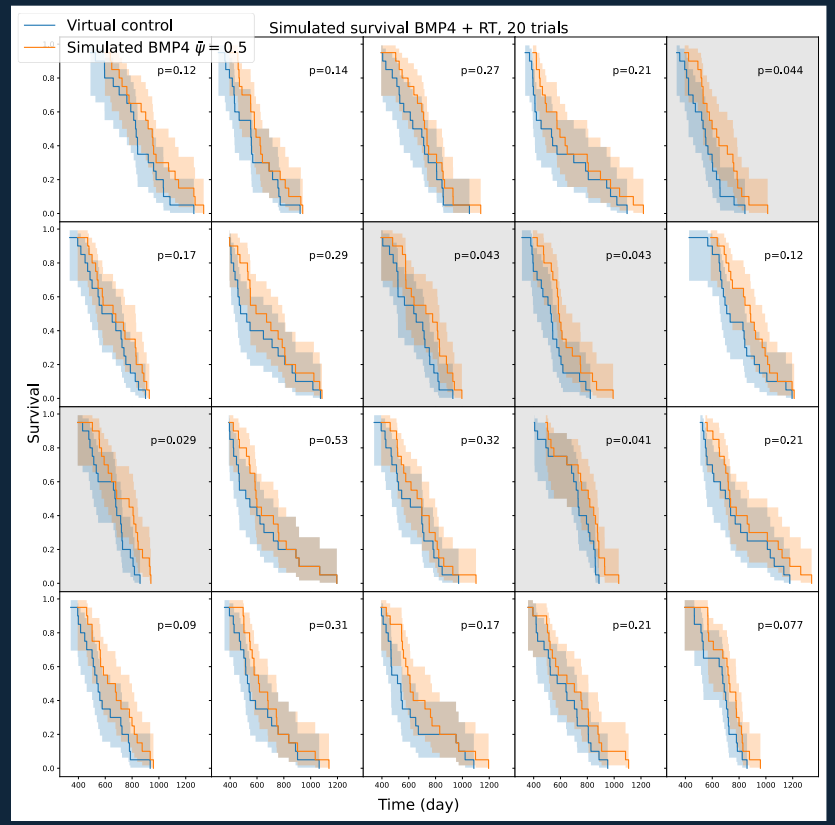


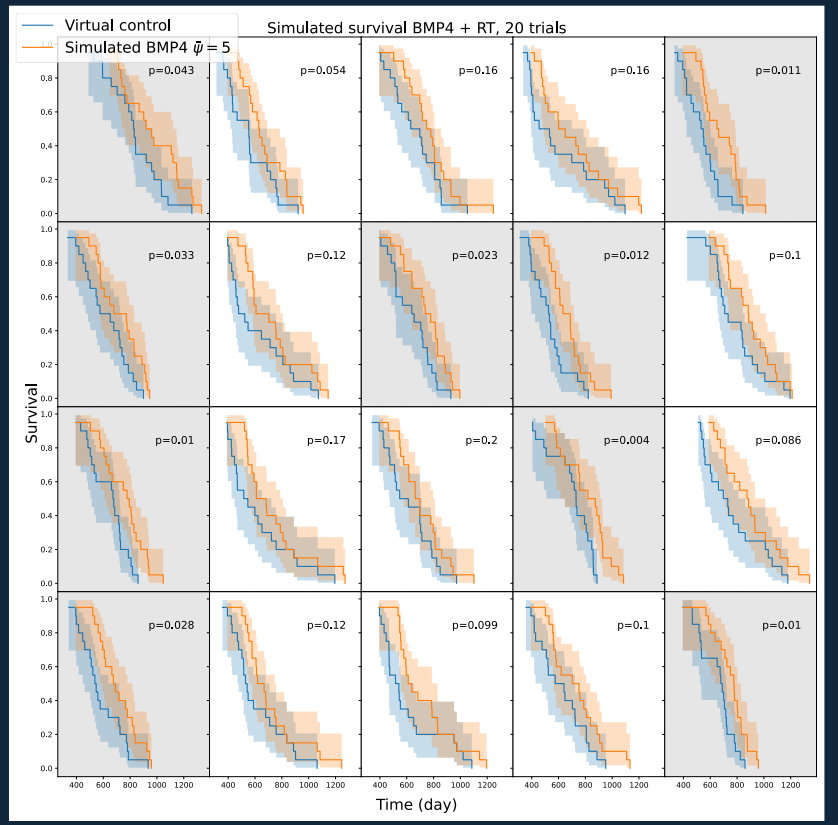
Phase 2 trials



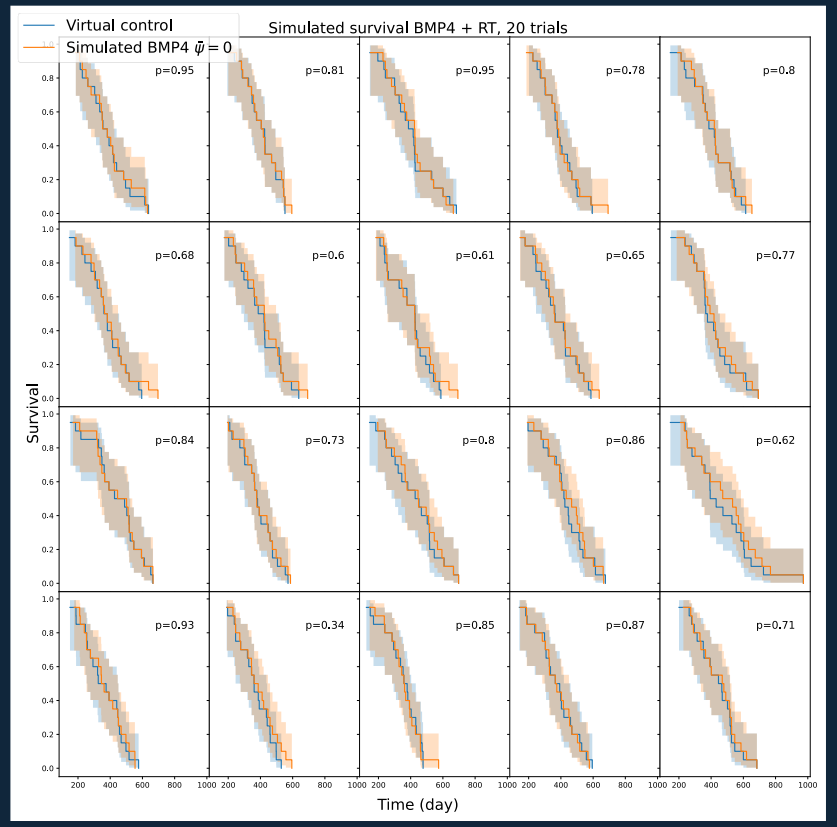
Phase 2 trial: identical populations

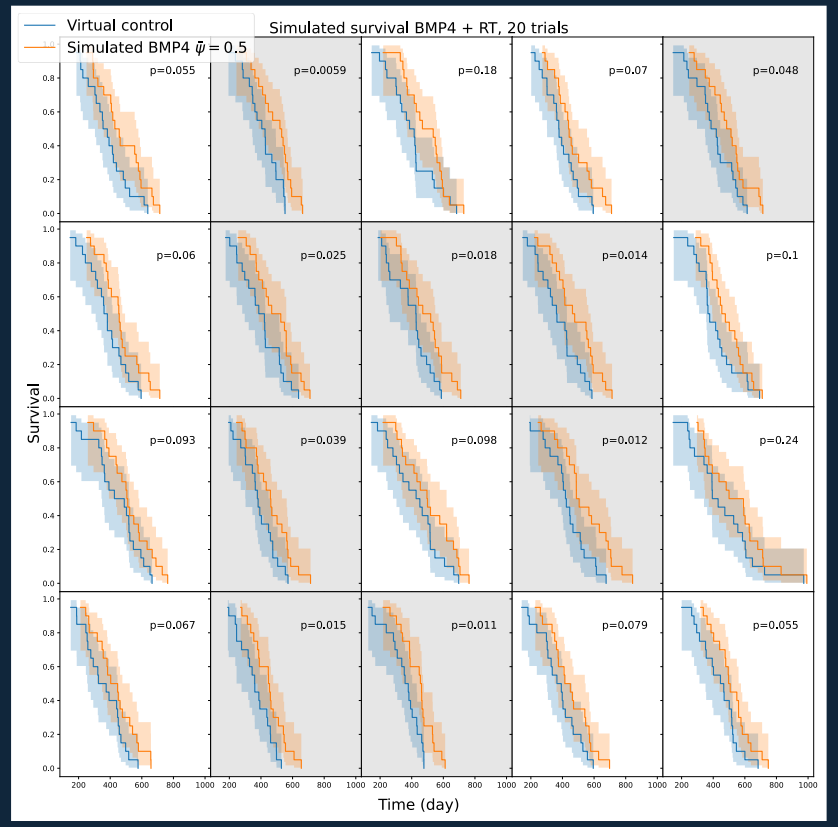


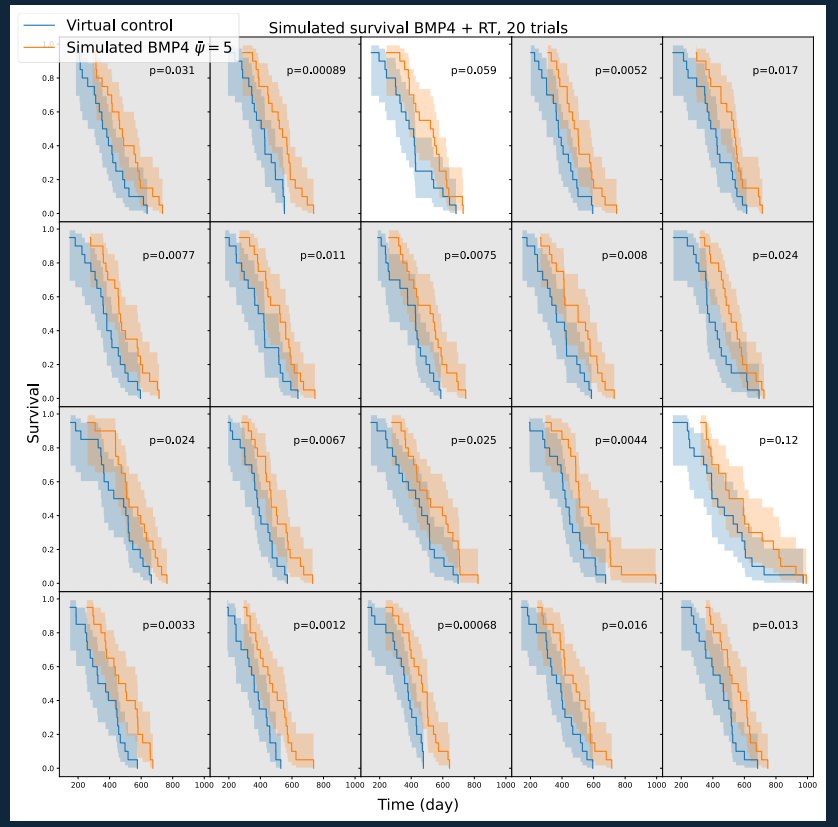




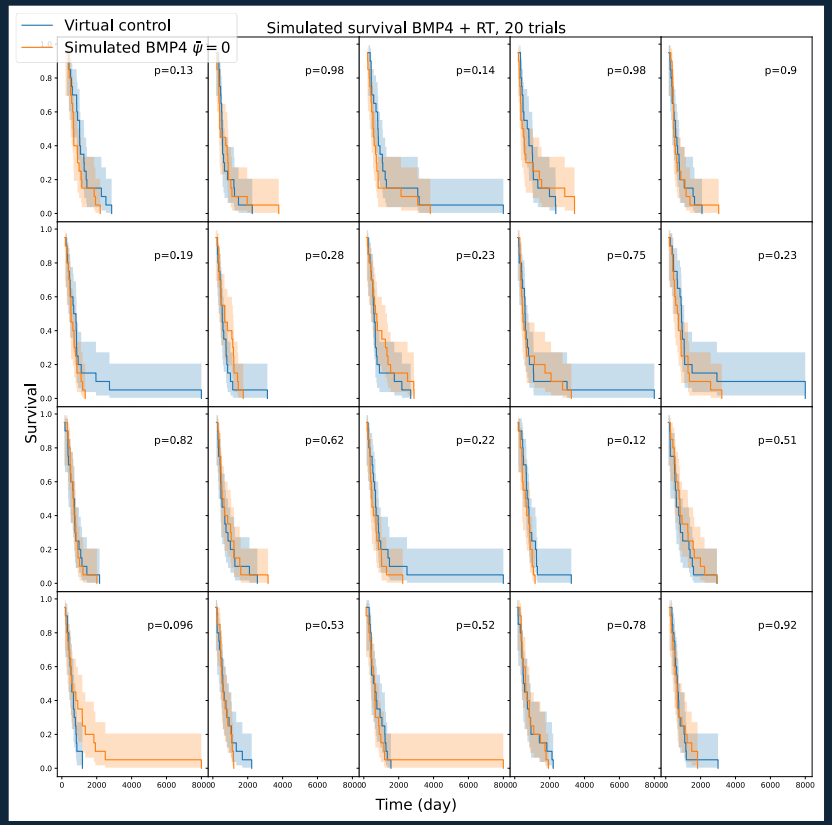
Phase 2 trial: fast proliferation rate

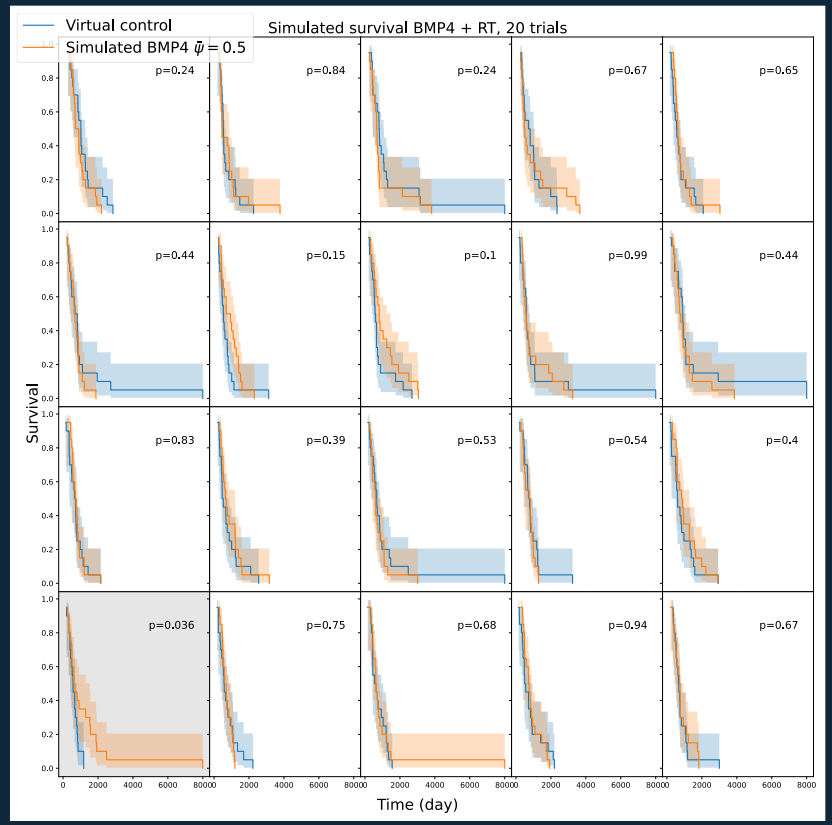


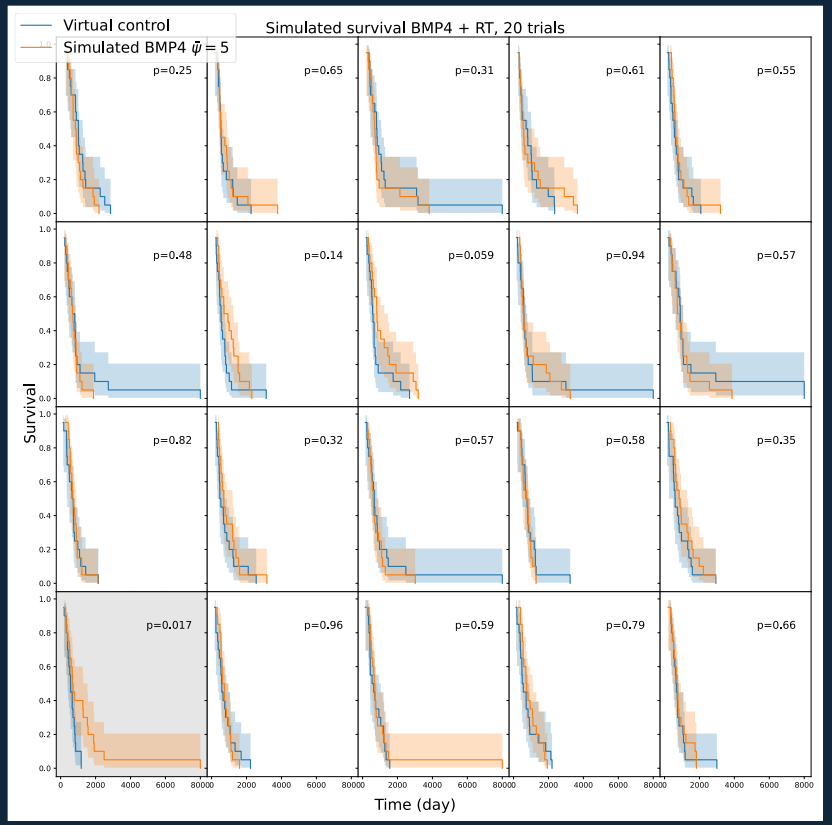




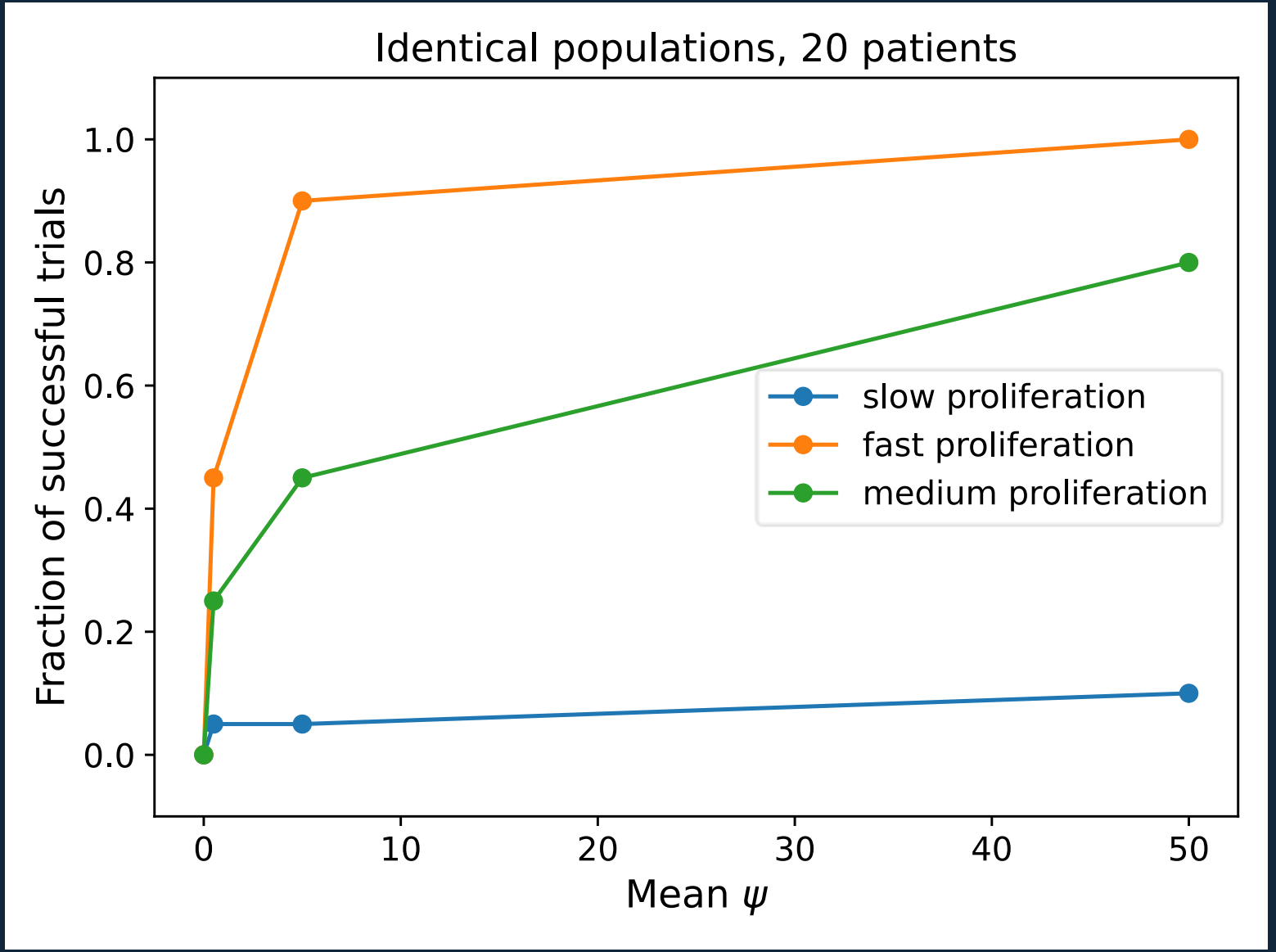
Phase 2 trial: slow proliferation rate







Phase 2 trial



Conclusions

- Mathematical modelling can be used to guide clinical trial design to increase the likelihood of observing a successful trial.
- Relative effect (“days gained”) is often more powerful than actual survival.

Acknowledgements

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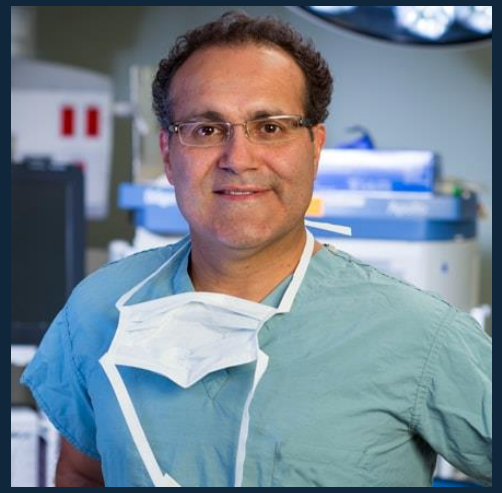

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