# Interactions between cell populations in heterogeneous tumour spheroids

Vascular Tumour Journal Club

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# Motivation/Questions

- When radiotherapy is prescribed in the clinic it is usually assumed that tumours are homogeneous
- They are not… Tumours are composed of a number of different populations of cells with **different radiosensitivities**
- Could we exploit intratumour heterogeneity to obtain more accurate predictions of radiotherapy treatment?
  - Do subpopulations interact?
  - Are these interactions altered by radiation?
  - Is the spatial distribution of subpopulations altered by radiation?

# Materials and Methods

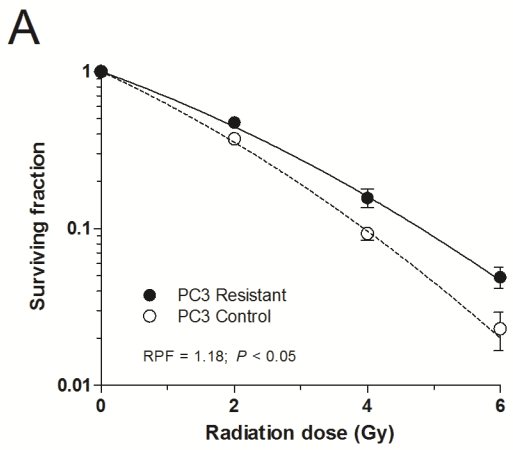
- Prostate cancer cell lines: PC3 and DU145
- These were repeatedly irradiated at low doses (50x2Gy) yielding stable resistant phenotypes
- Co-cultured control and resistant cell populations at different ratios: 1:0, 3:1, 1:1, 1:3 and 0:1
- Irradiated with a single dose of 6Gy
- Monitored their growth

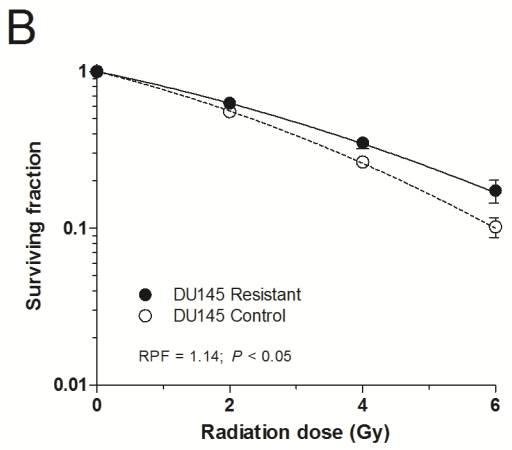
# Questions

- Do co-cultured control and resistant cell populations interact?
- What type of interactions occur between them?
- Are these interactions altered by radiation?

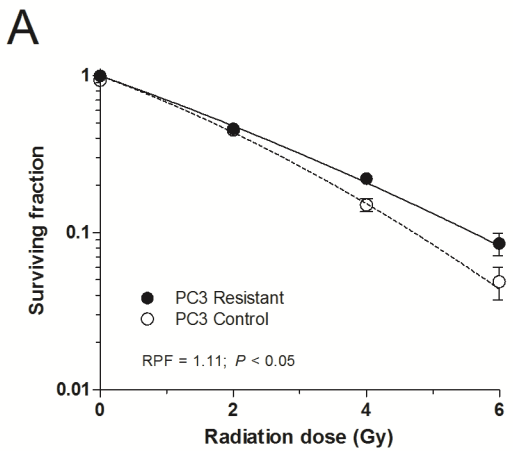
# Intrinsic radiosensitivity – clonogenic assays

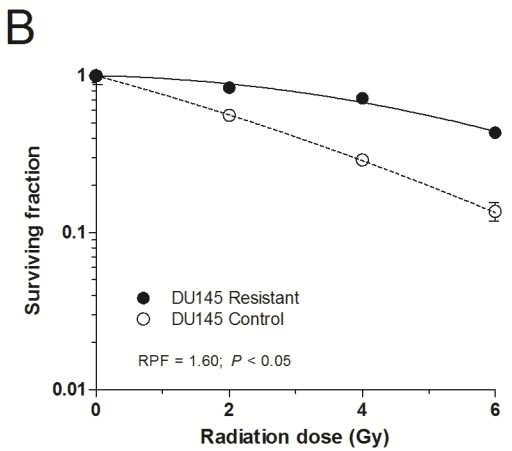
Normoxia



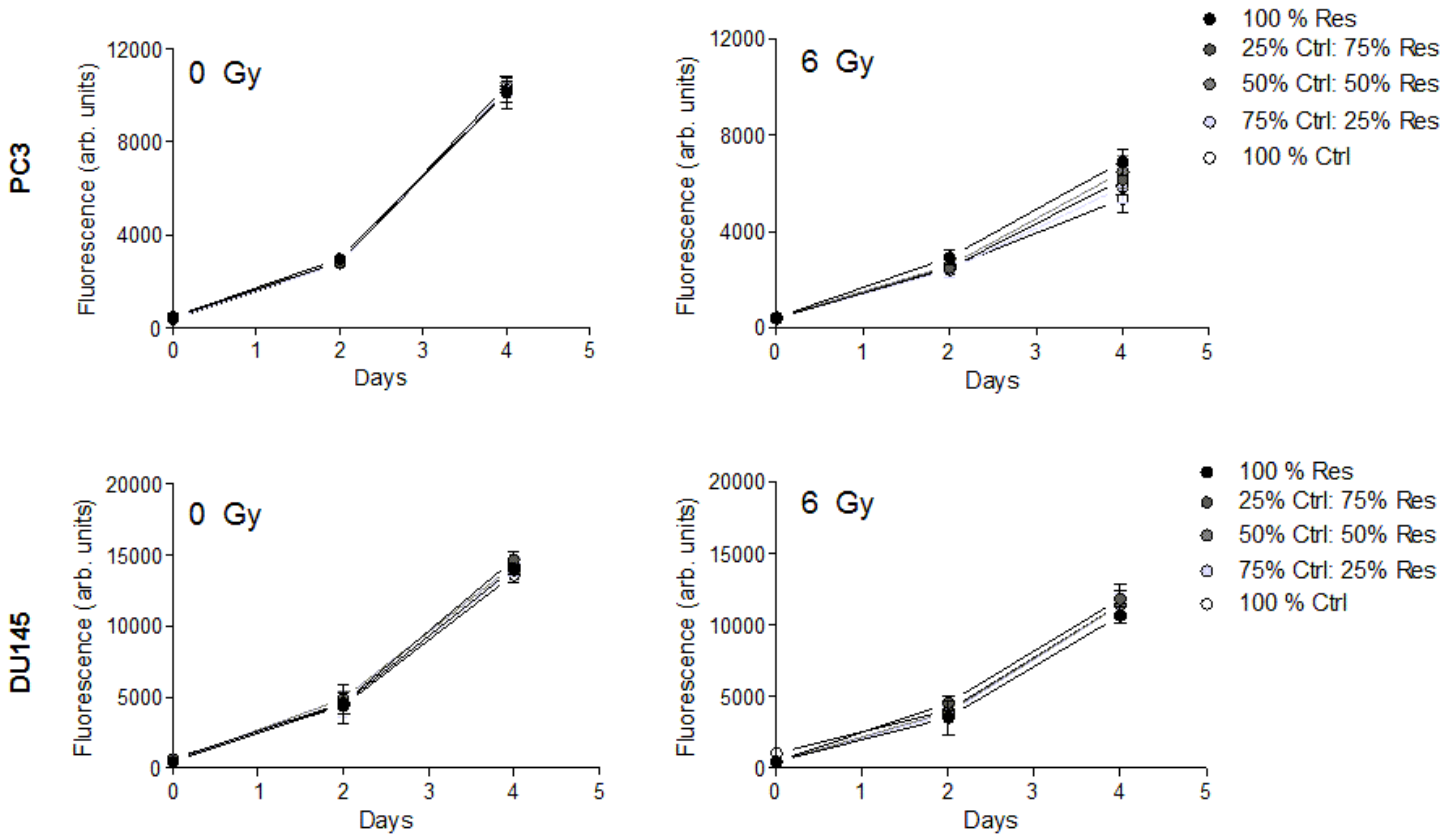




Hypoxia



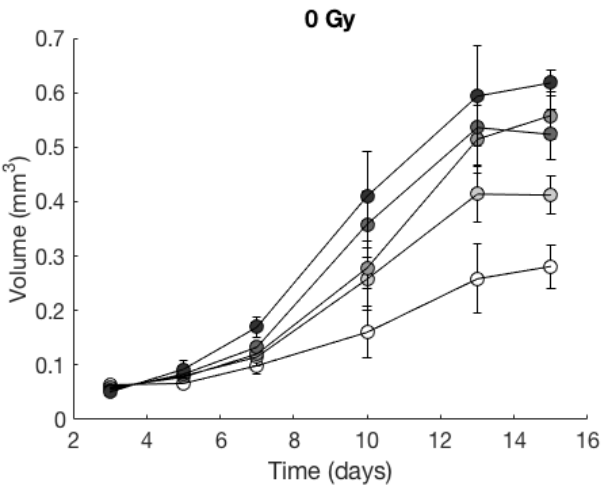
# Growth of heterogeneous populations in 2d

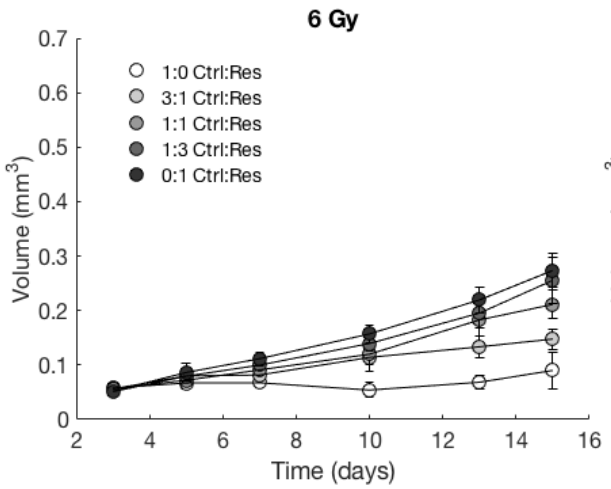



- Problem: confluence reached before any effect could be observed
- Solution: generate tumour spheroid by co-culturing cell populations and measure their volume

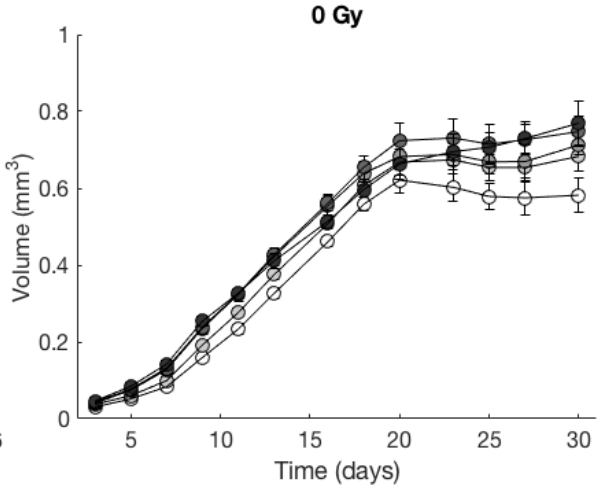
# Heterogeneous tumour spheroids

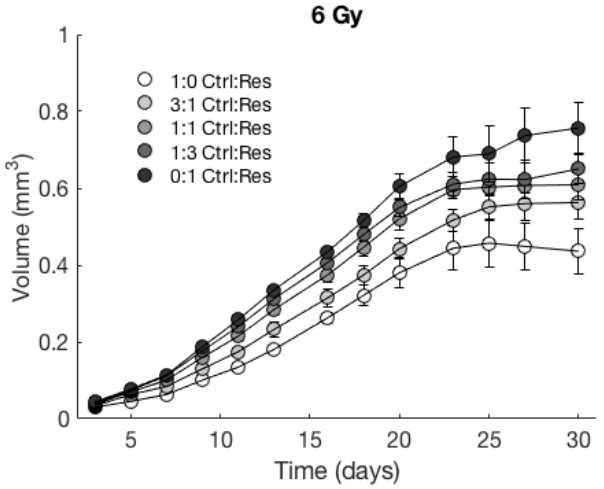
PC3




DU145




- Problem: looks like something is going on but cannot really say what
- Solution: use mathematical modelling

# Lotka-Volterra interactions model

$$\frac{dV_C}{dt} = V_C \left[ r_C \left( 1 - \frac{V_C}{K_C} \right) - \lambda_R V_R \right]$$
$$\frac{dV_R}{dt} = V_R \left[ r_R \left( 1 - \frac{V_R}{K_R} \right) - \lambda_C V_C \right]$$

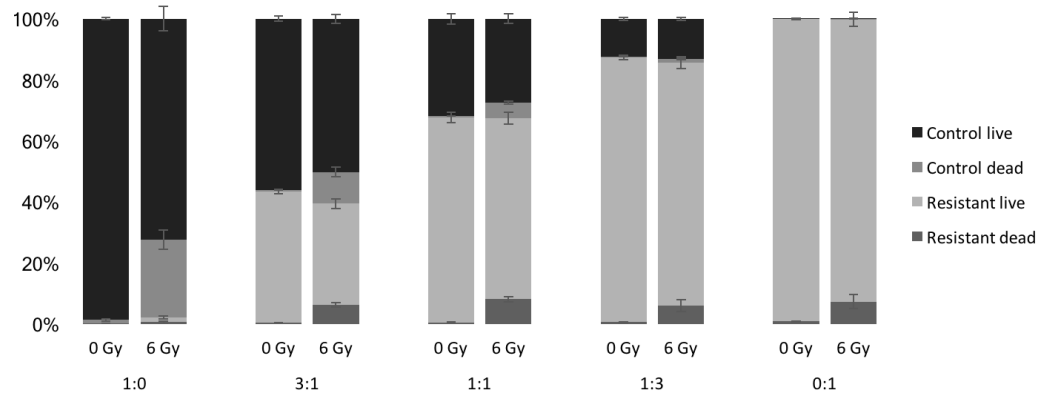
| Effect Ctrl cells have on Res cells | Effect Res cells have on Ctrl cells | Sign of $\lambda_C$ | Sign of $\lambda_R$ | Type of interaction |
|---|---|---|---|---|
| Detrimental | Detrimental | + | + | ***Competition*** |
| Detrimental | No effect | + | 0 | ***Amensalism*** |
| Detrimental | Beneficial | + | - | ***Antagonism*** |
| No effect | No effect | 0 | 0 | ***Neutralism*** |
| No effect | Beneficial | 0 | - | ***Commensalism*** |
| Beneficial | Beneficial | - | - | ***Mutualism*** |

- Problem: not possible to accurately estimate $\lambda_C$ and $\lambda_R$ using total volume measurements data alone
- Solution: Measure the proportions of the control and resistant cells populations.
- But when? It is an expensive and time-consuming experiment
- Perform experimental design study with synthetic data

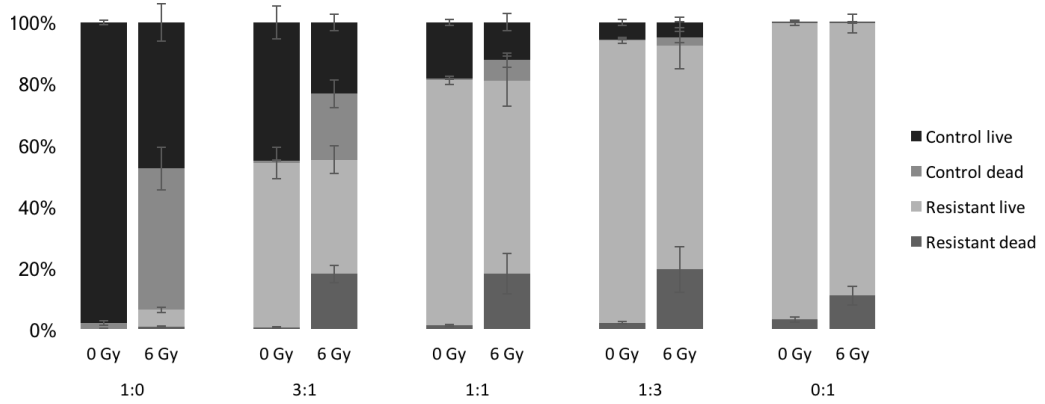
# Proportions of control and resistant cells

PC3

Day 10

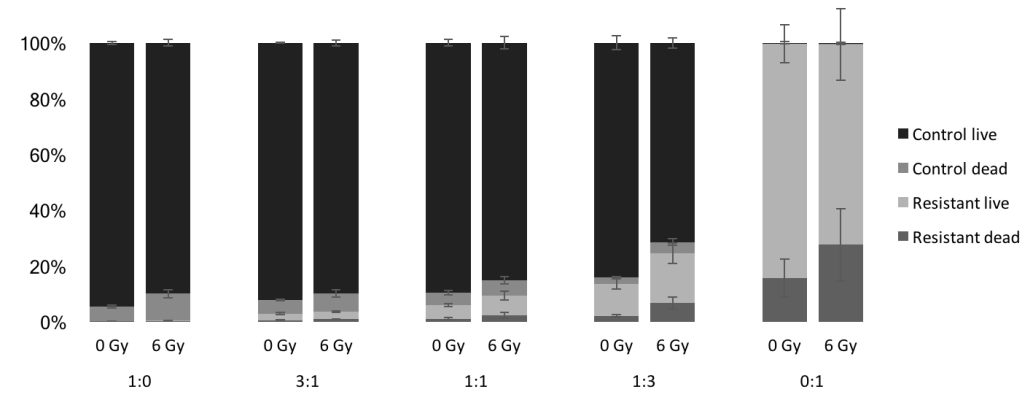



Day 15

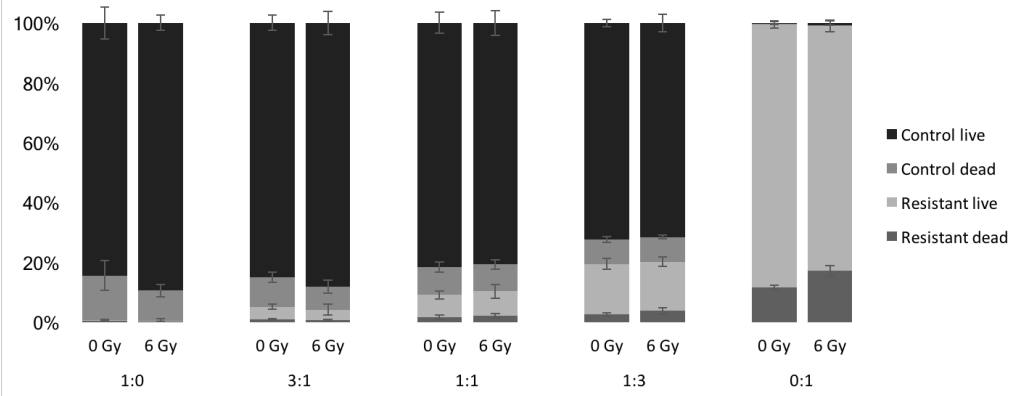



DU145

Day 16




Day 25

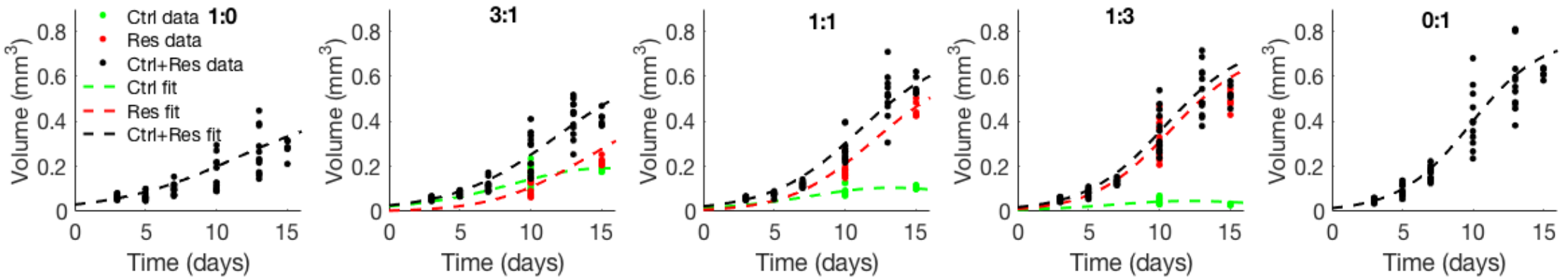


# Estimated parameter values

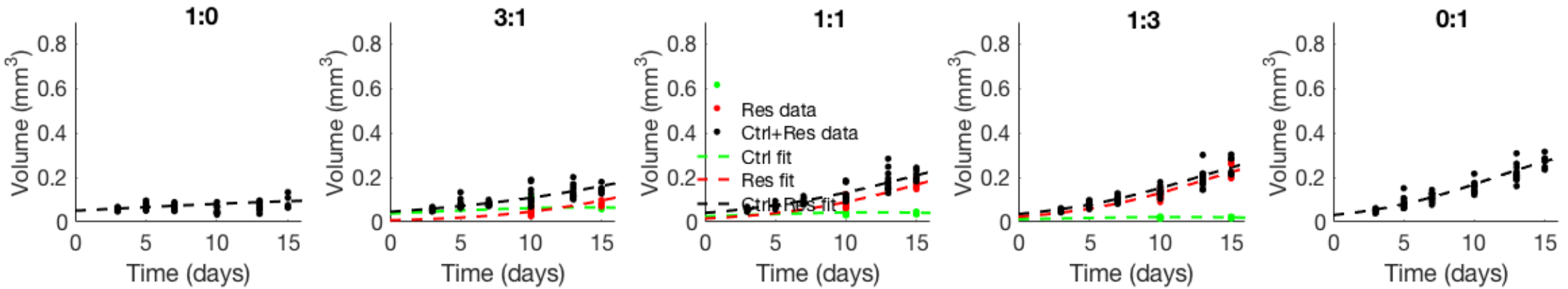
| | $r_C$ | $K_C$ | $V(0)_C$ | $r_R$ | $K_R$ | $V(0)_R$ | $\lambda_C$ | $\lambda_R$ |
|---|---|---|---|---|---|---|---|---|
| PC3 0Gy | **0.236** (0.201,0.271) | **0.473** (0.342,0.604) | **0.031** (0.026,0.036) | **0.401** (0.366,0.436) | **0.773** (0.673,0.873) | **0.015** (0.012,0.018) | **0.655** (0.434,0.875) | **0.480** (0.363,0.597) |
| PC3 6Gy | **0.112** (0.054,0.169) | **0.117** (0.087,0.146) | **0.051** (0.043,0.059) | **0.217** (0.169,0.265) | **0.393** (0.261,0.526) | **0.031** (0.026,0.037) | **0.516** (0.026,1.006) | **0.586** (0.199,0.974) |
| DU145 0Gy | **0.356** (0.343,0.370) | **0.605** (0.590,0.621) | **0.010** (0.009,0.011) | **0.251** (0.236,0.265) | **0.802** (0.756,0.849) | **0.027** (0.025,0.030) | **0.536** (0.504,0.567) | **-0.102** (-0.159,-0.044) |
| DU145 6Gy | **0.253** (0.242,0.265) | **0.496** (0.480,0.513) | **0.015** (0.013,0.016) | **0.195** (0.183,0.207) | **0.924** (0.838,1.009) | **0.032** (0.029,0.035) | **0.594** (0.555,0.632) | **-0.329** (-0.388,-0.269) |

# PC3 spheroids: best fits

0 Gy

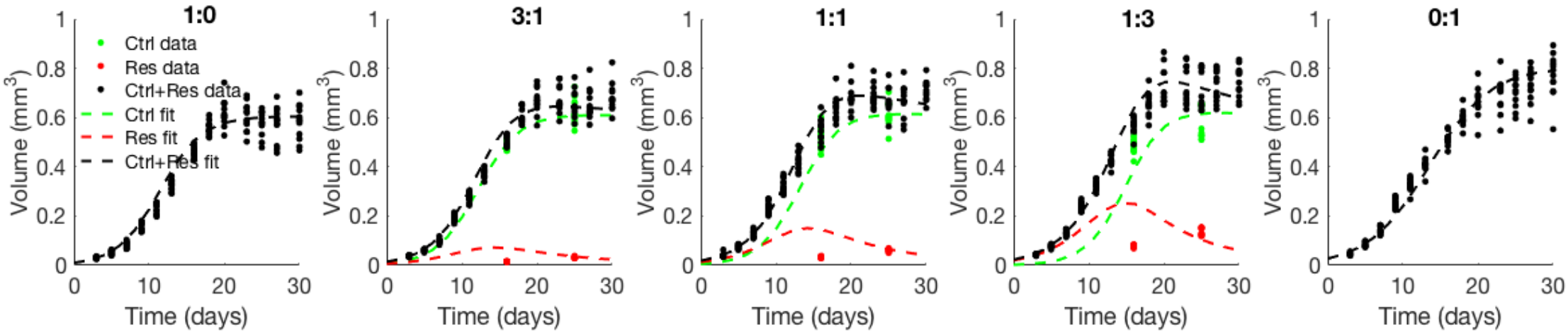



6 Gy

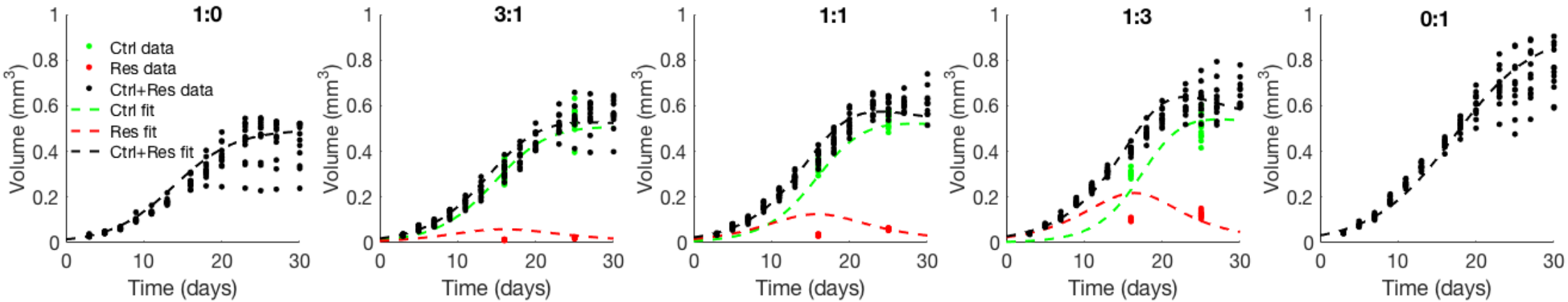


# DU145 spheroids: best fits

0 Gy




6 Gy



# Summary

- Do co-cultured control and resistant cell populations interact?
  - Yes, they do
- What type of interactions occur between them?
  - PC3– competition
  - DU145 – antagonism (predation?)
- Are these interactions altered by radiation?
  - The types of interactions do not change but their magnitudes do