

Cellular Response in Modulated Radiation Beams: three Types of Bystander Effect

Natalka Suchowerska

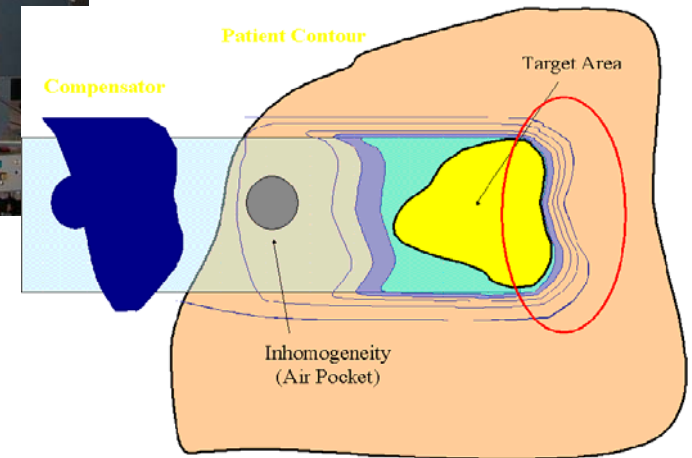


Royal Prince Alfred Hospital
University of Sydney
Australia

Dr Mazal



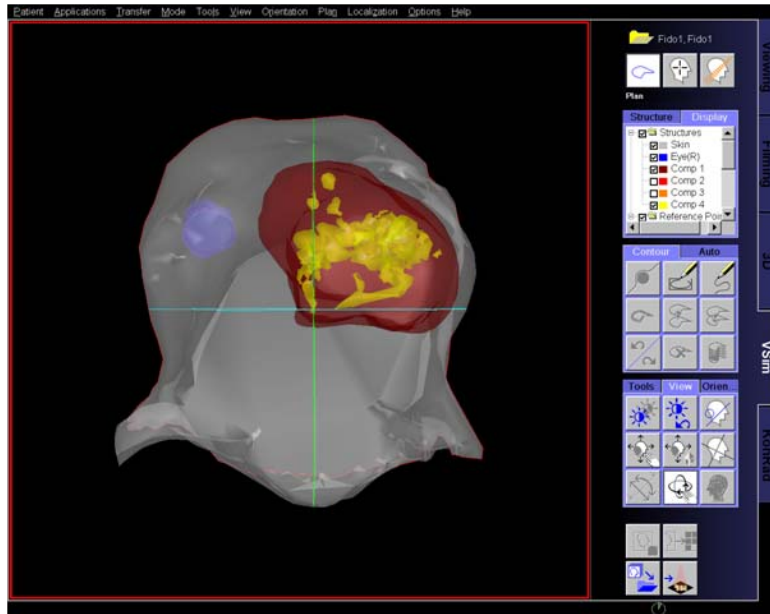
Magritte



“Dose is a surrogate
for clinical response”

Michael Goitein

Tumor and hypoxic compartment



Predicting treatment outcome of biologically optimised IMRT for hypoxic tumours

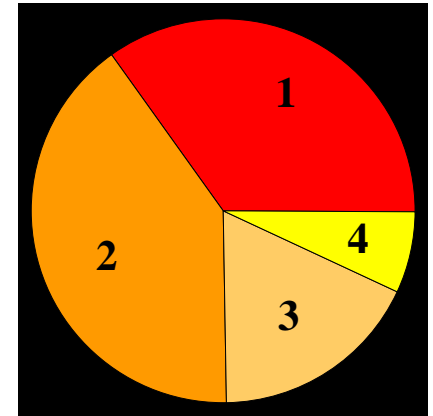
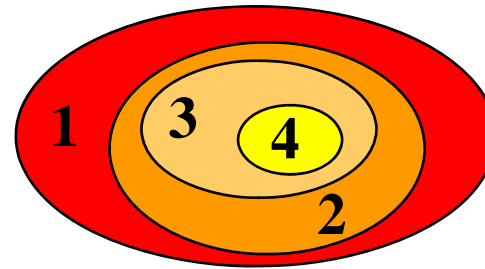
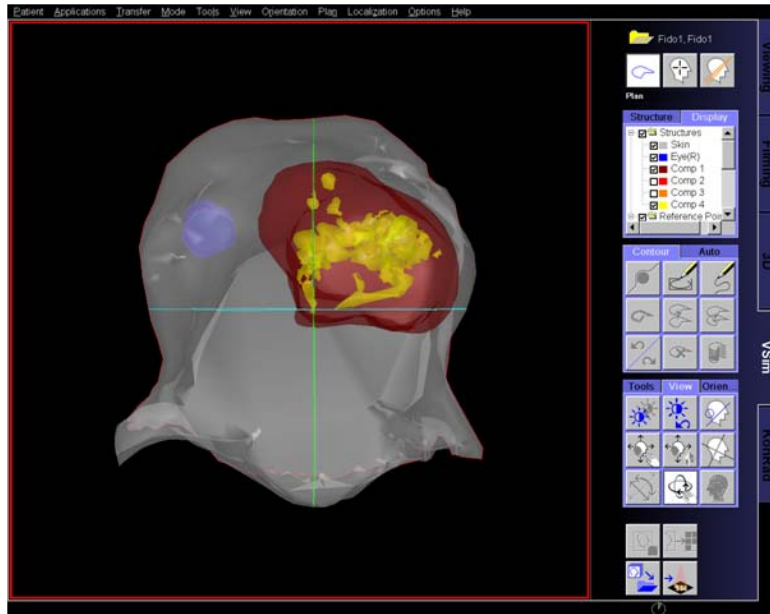
E. Malinen¹, Å. Søvik^{2,3}, D. R. Olsen¹

1 - *Institute for Cancer Research,
The Norwegian Radium Hospital, Oslo, Norway*

2 - *Department of Physics,
University of Oslo, Norway*

3 - *Department of Medical Physics and Technology,
The Norwegian Radium Hospital*

Tumor and hypoxic compartment



volume fractions

Predicting treatment outcome of biologically optimised IMRT for hypoxic tumours

E. Malinen¹, Å. Søvik^{2,3}, D. R. Olsen¹

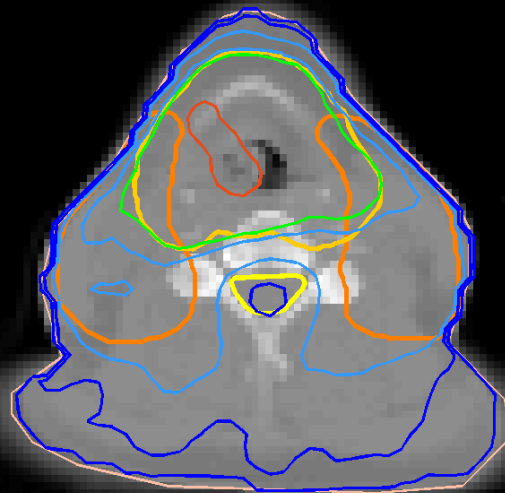
- 1 - *Institute for Cancer Research,
The Norwegian Radium Hospital, Oslo, Norway*
- 2 - *Department of Physics,
University of Oslo, Norway*
- 3 - *Department of Medical Physics and Technology,
The Norwegian Radium Hospital*

Absorbed dose map - Biological response?

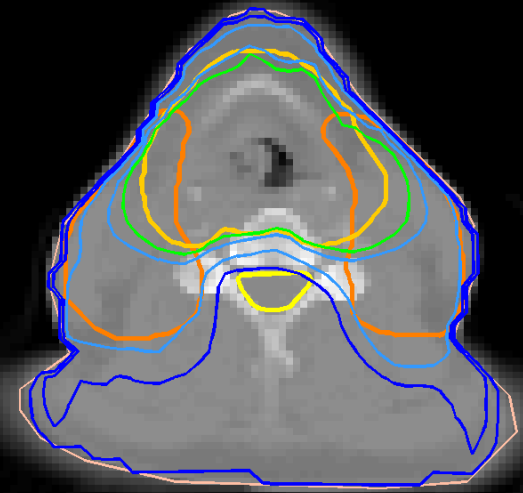
TARGET defn.



IMRT plan



PROTON plan



***In vitro* response of tumour cells to non-uniform irradiation**

N Suchowerska^{1,2}, M A Ebert^{3,4}, M Zhang¹ and M Jackson^{1,2}

¹ Department of Radiation Oncology, Royal Prince Alfred Hospital, Camperdown, NSW,

***In vitro* response of tumour cells to non-uniform irradiation**

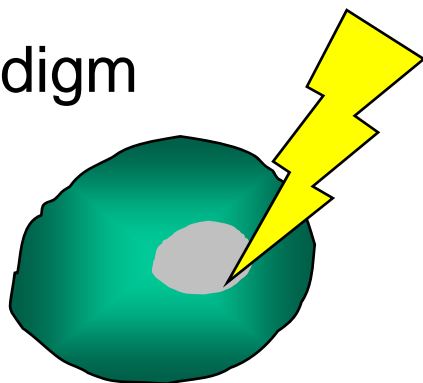
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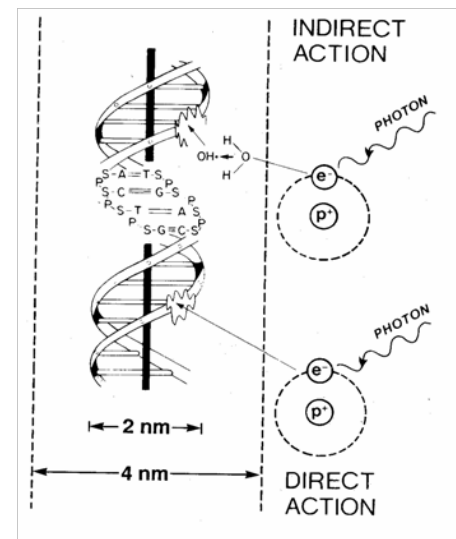
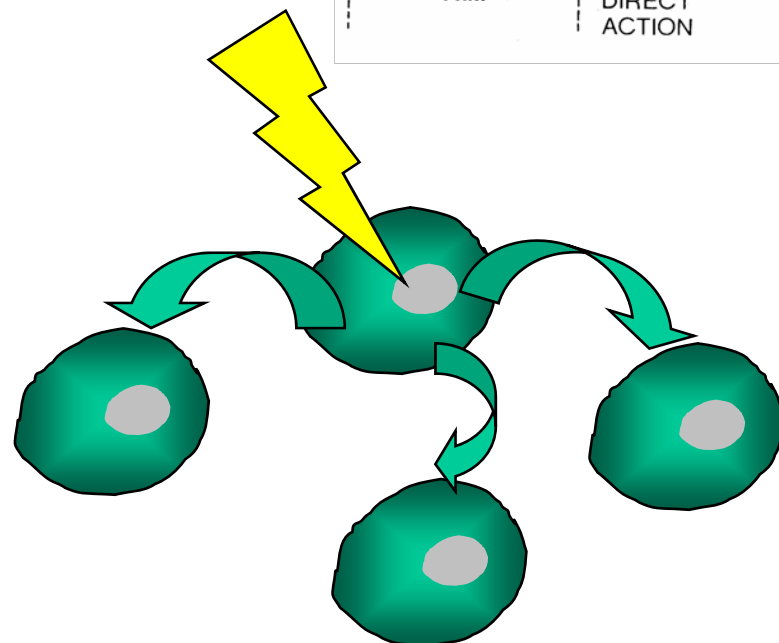
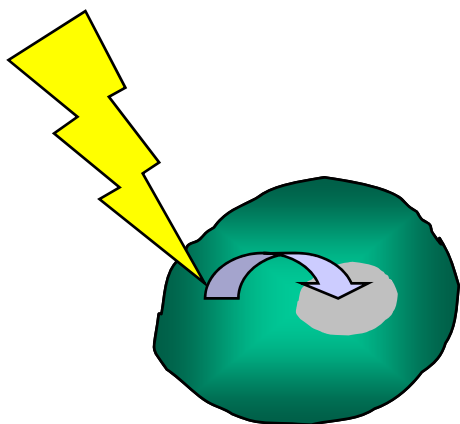
**Cell survival is affected by the
fate of neighbouring cells**

Non-Local Effects in Cellular Response

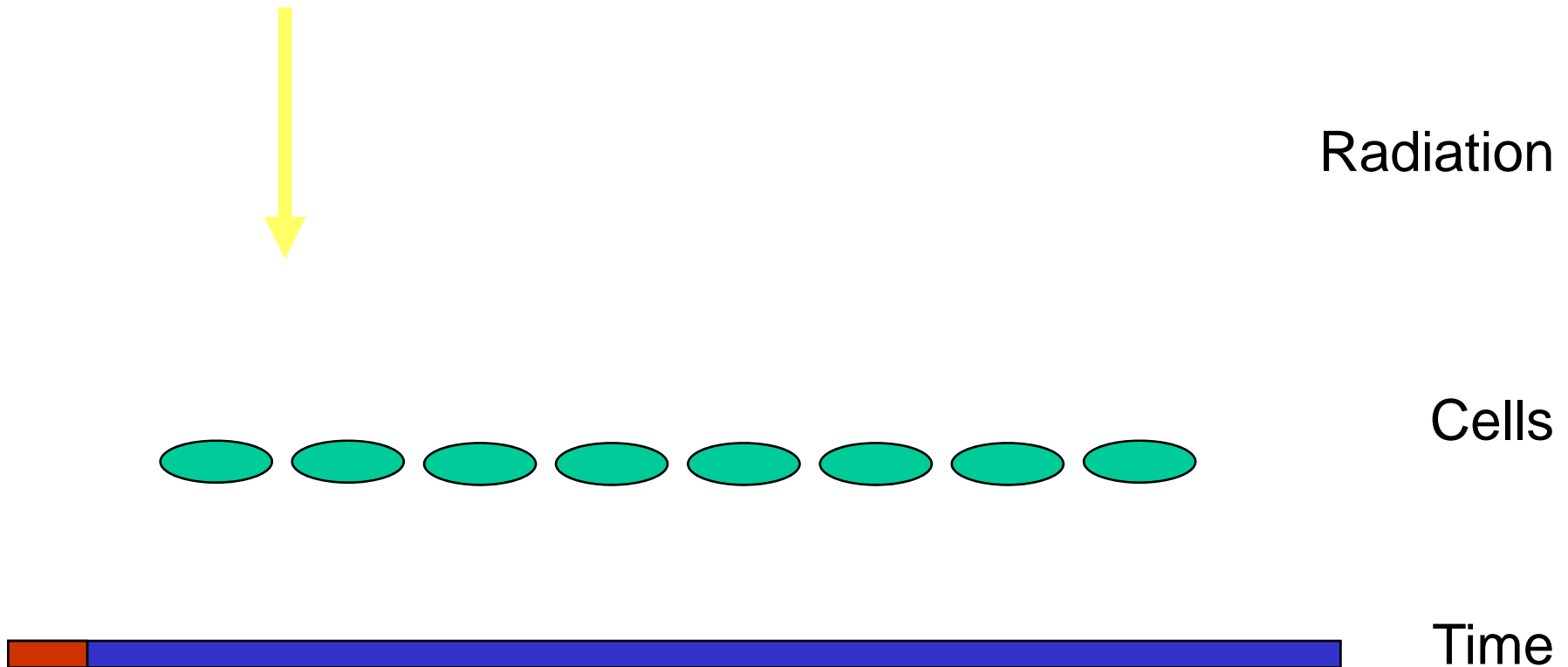
Old Paradigm



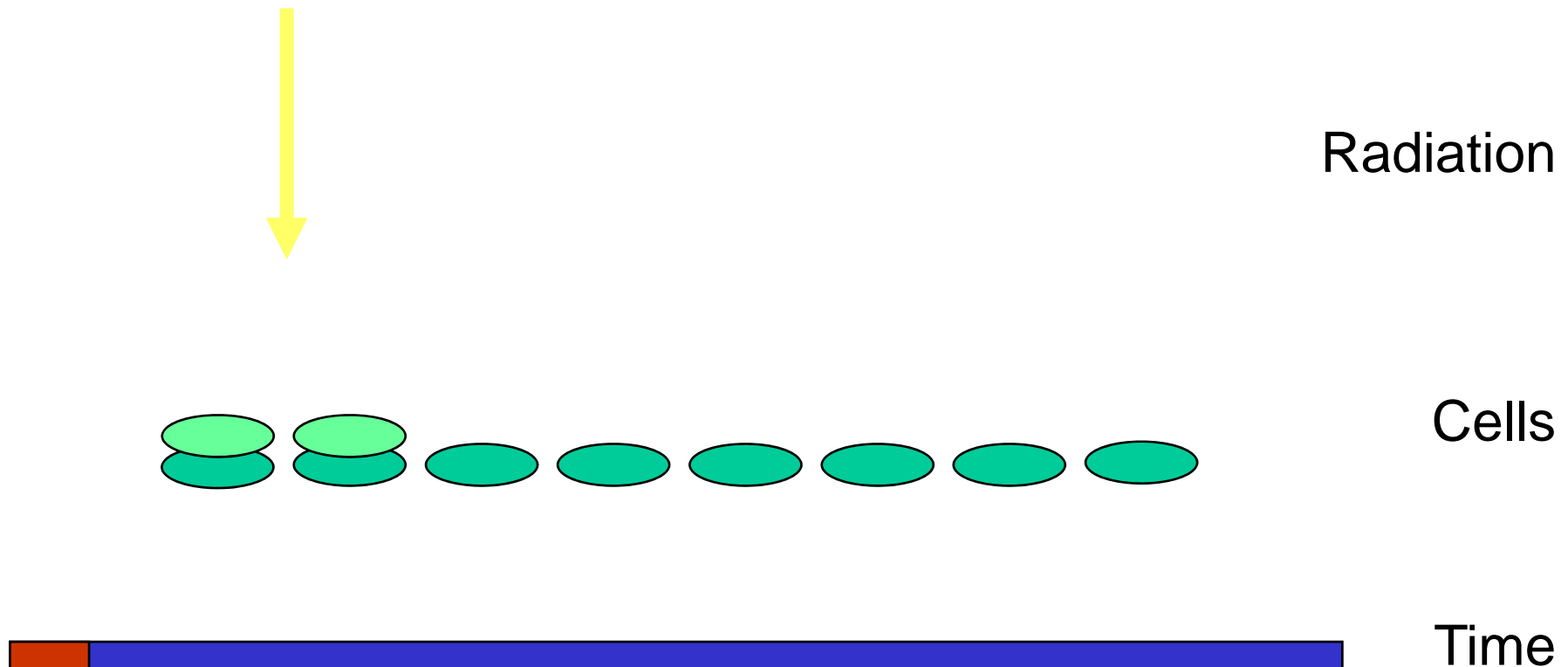
New Paradigm



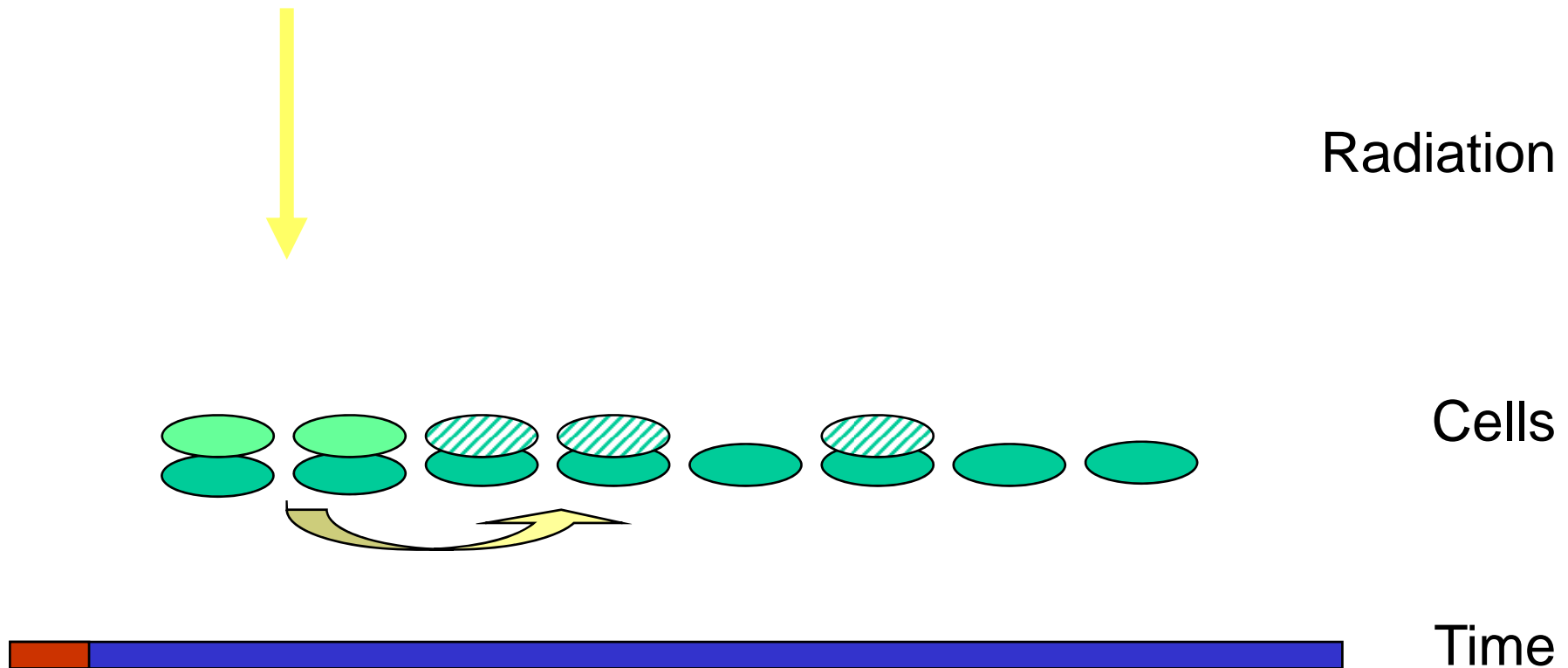
IMRT treatment - Cell's Perspective



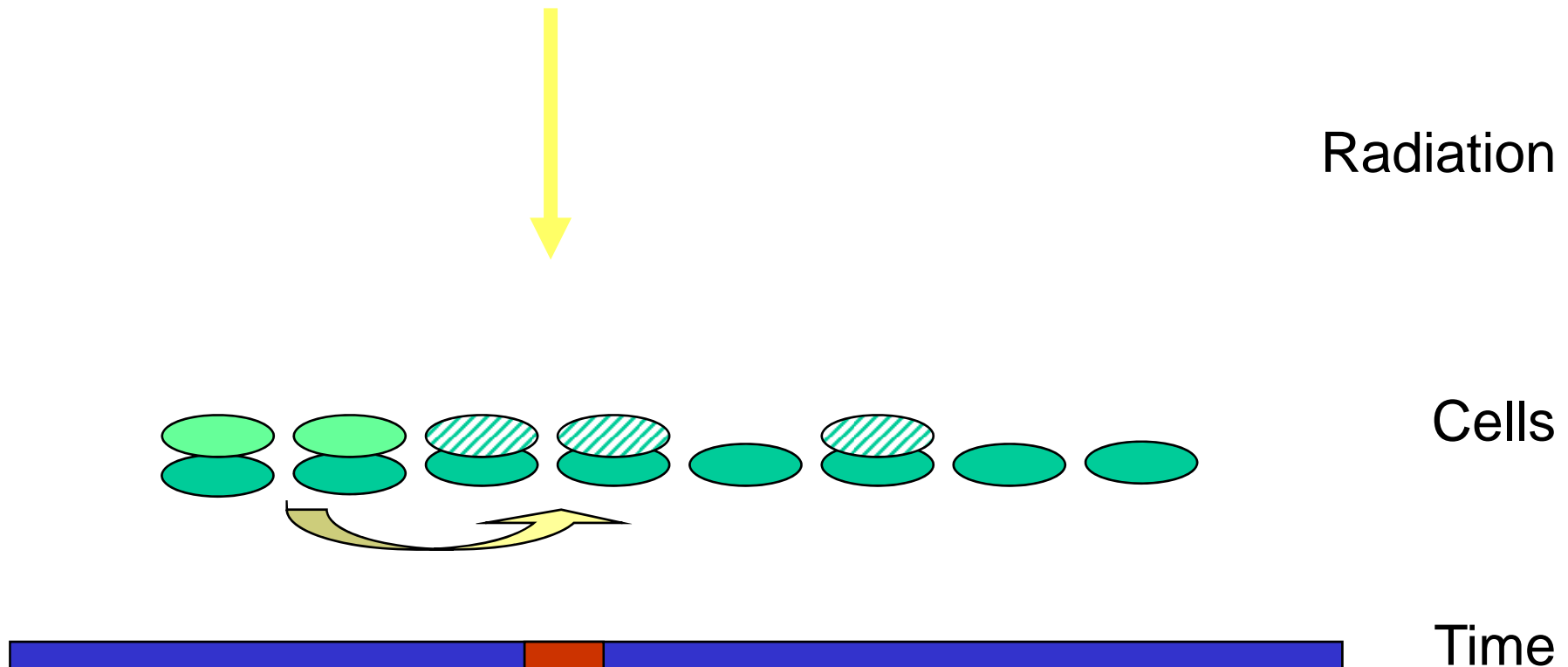
IMRT treatment - Cell's Perspective



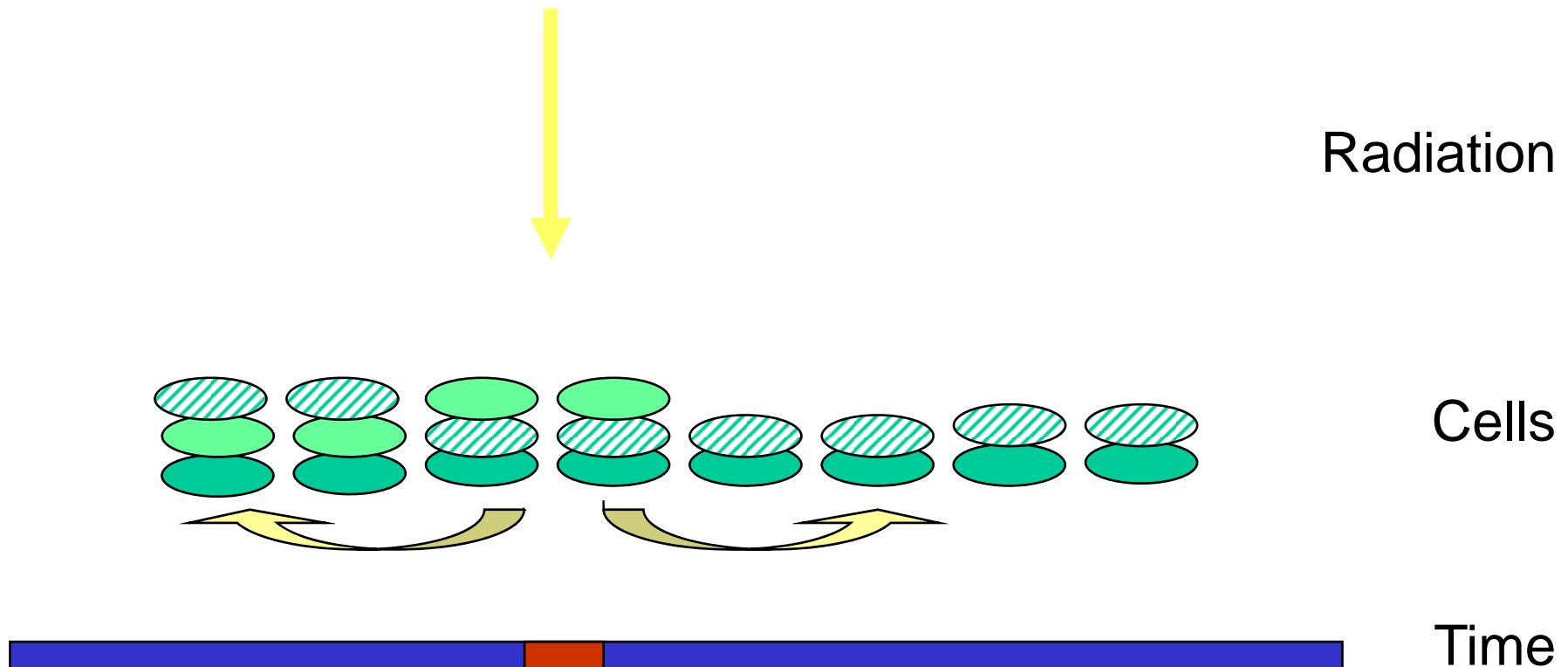
IMRT treatment - Cell's Perspective



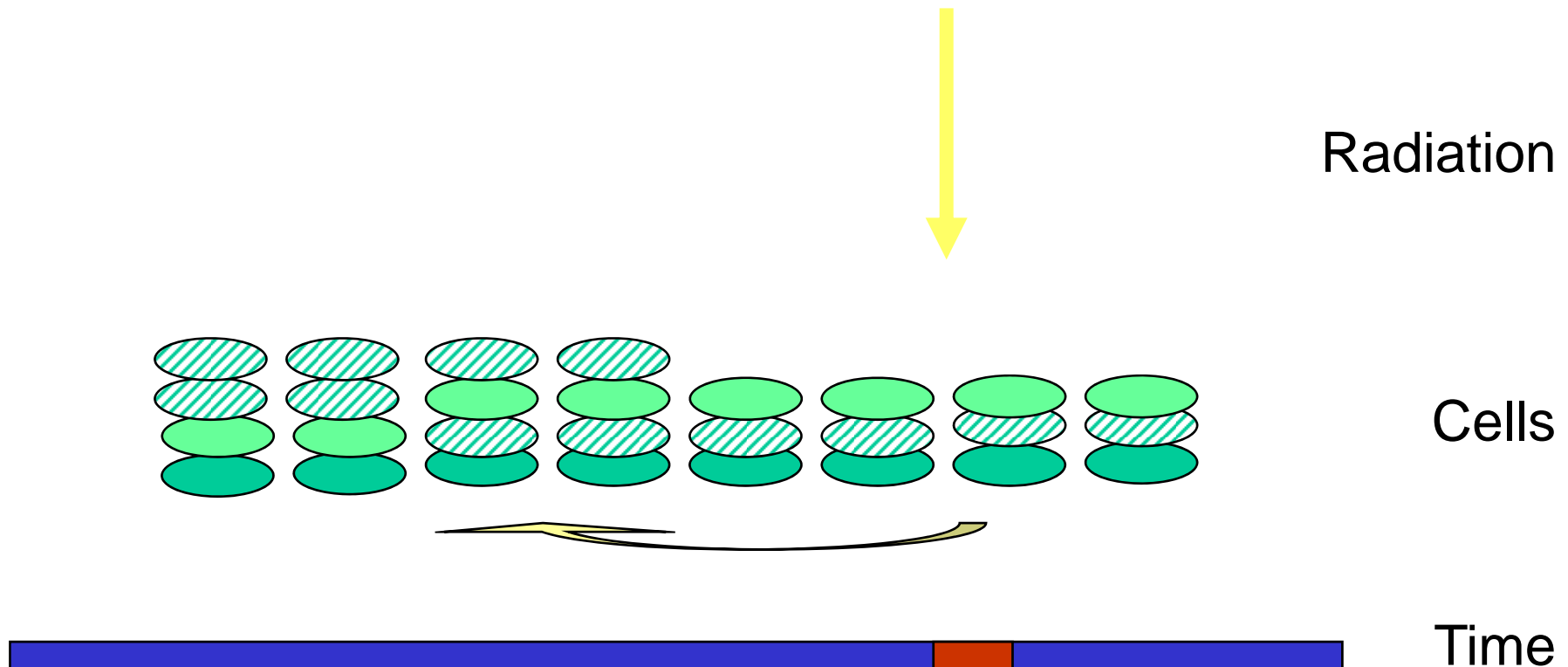
IMRT treatment - Cell's Perspective



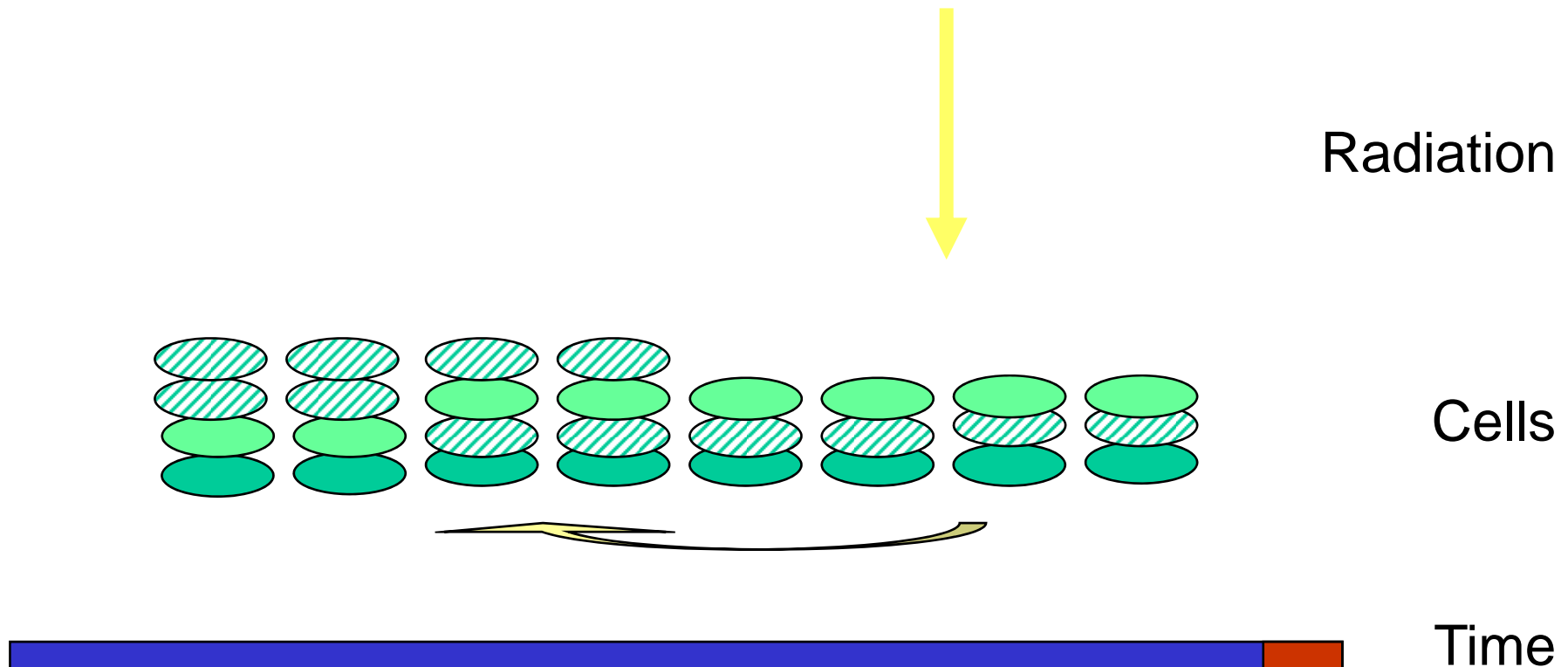
IMRT treatment - Cell's Perspective



IMRT treatment - Cell's Perspective



IMRT treatment - Cell's Perspective



Cancer signaling pathways

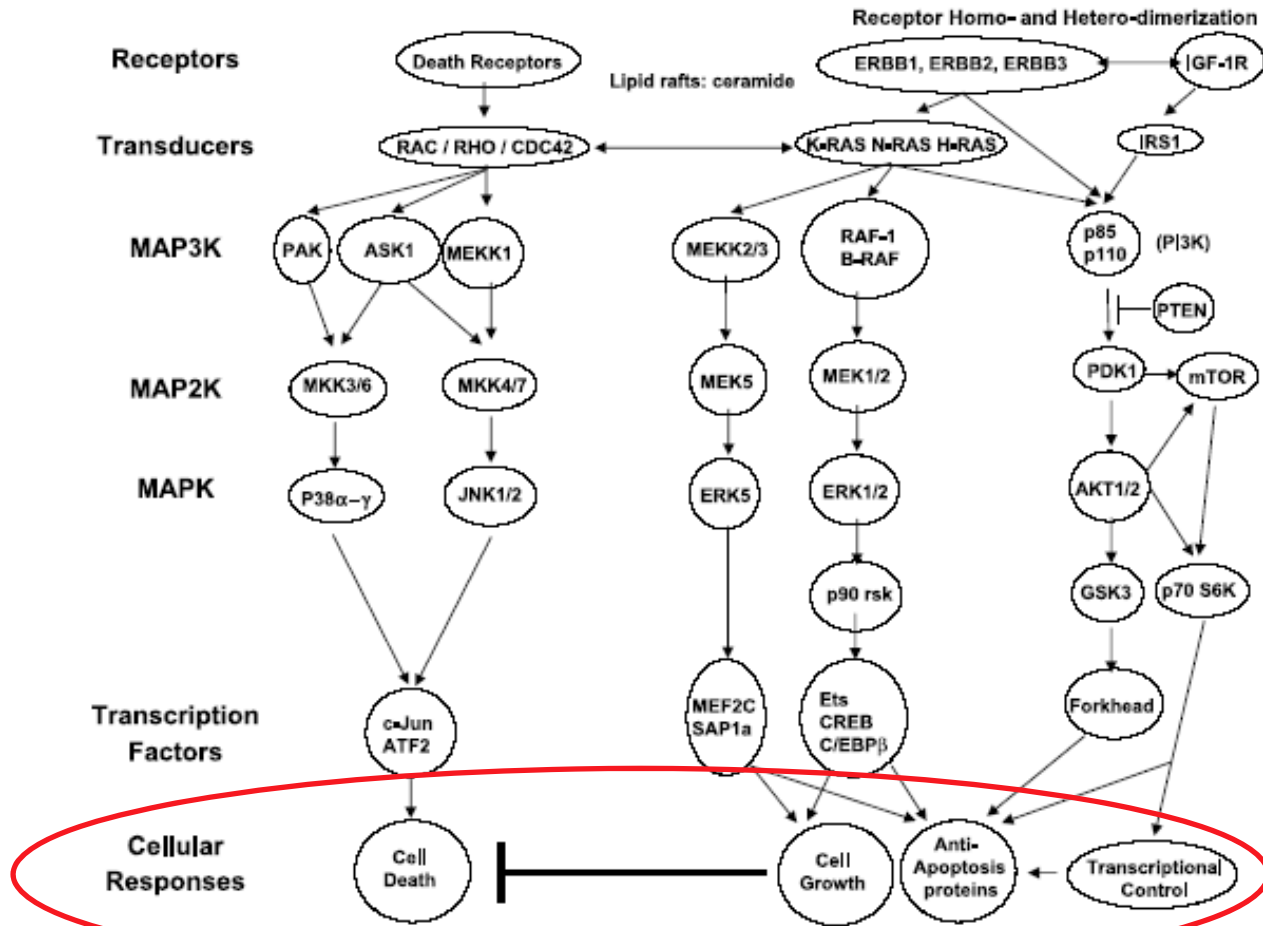


Figure 1. MAPK and PI3K signal transduction pathways in human carcinoma cells.

Research Question

Can radiation beam modulation
affect cell survival?

Method

Melanoma Cell line MM576

Cells plated as mono-layer

1000 cells/ flask [T75]

Irradiate – modulated fields

Irradiate - uniform dose

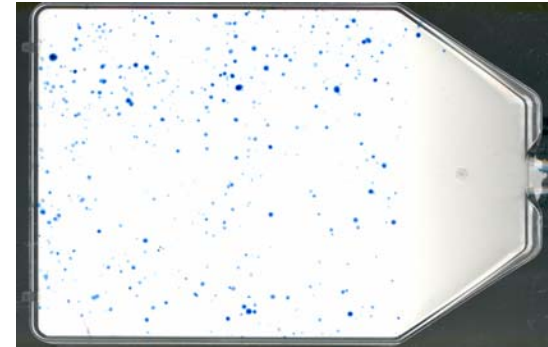
Unirradiated controls

Incubate 10 - 14 days

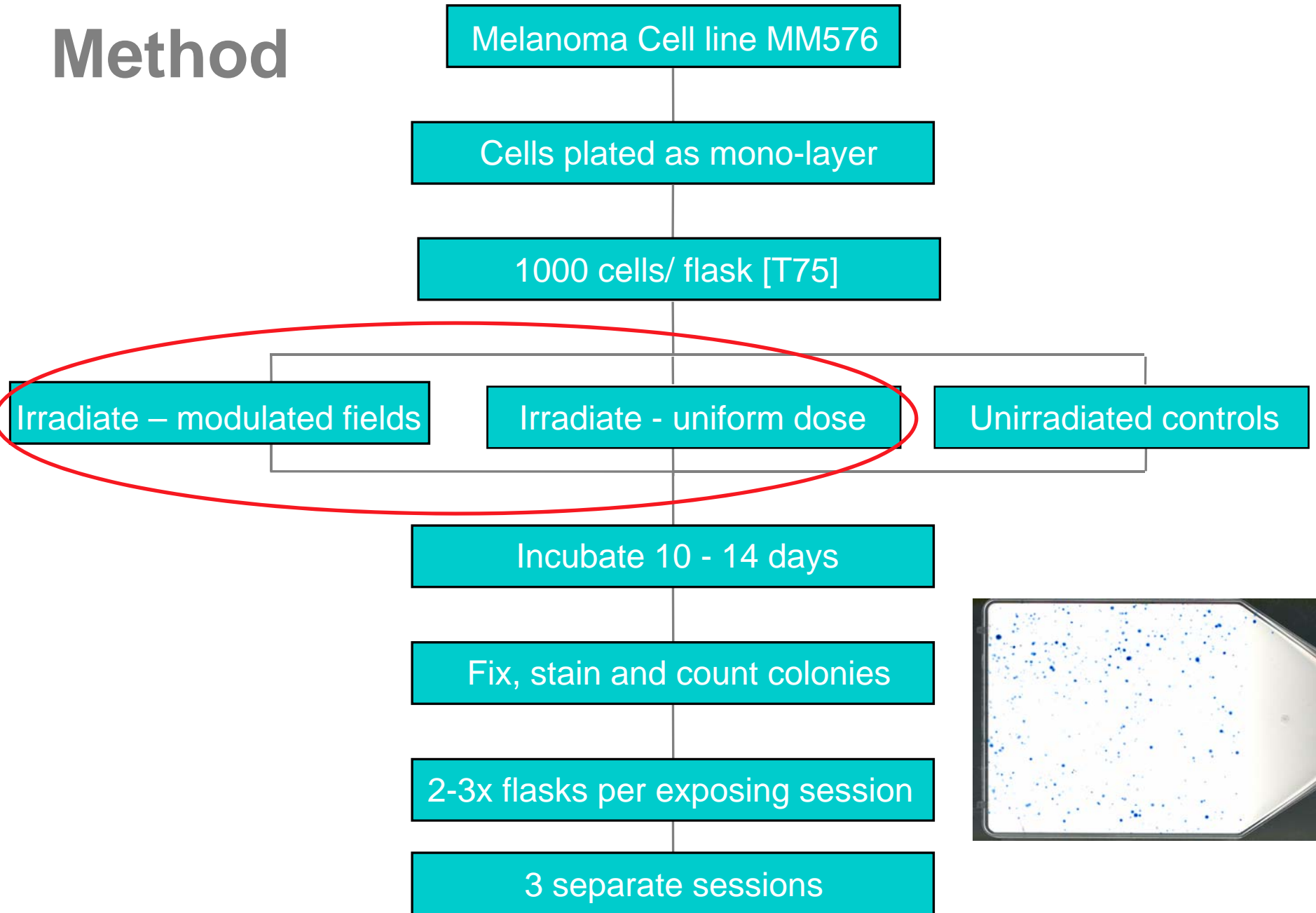
Fix, stain and count colonies

2-3x flasks per exposing session

3 separate sessions



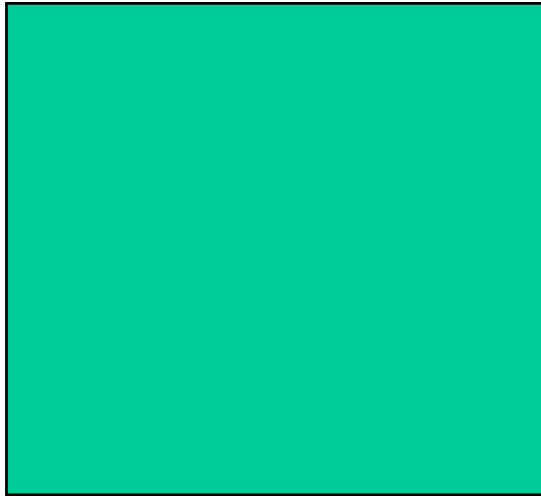
Method



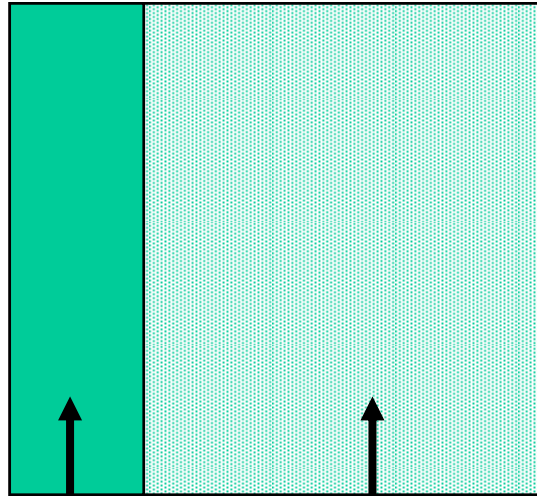
Modulated Fields

- 25% of the field is irradiated and 75% is shielded by MLCs

Open



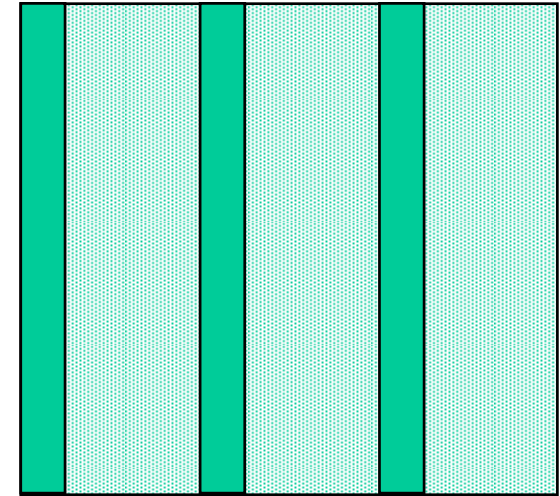
Quarter



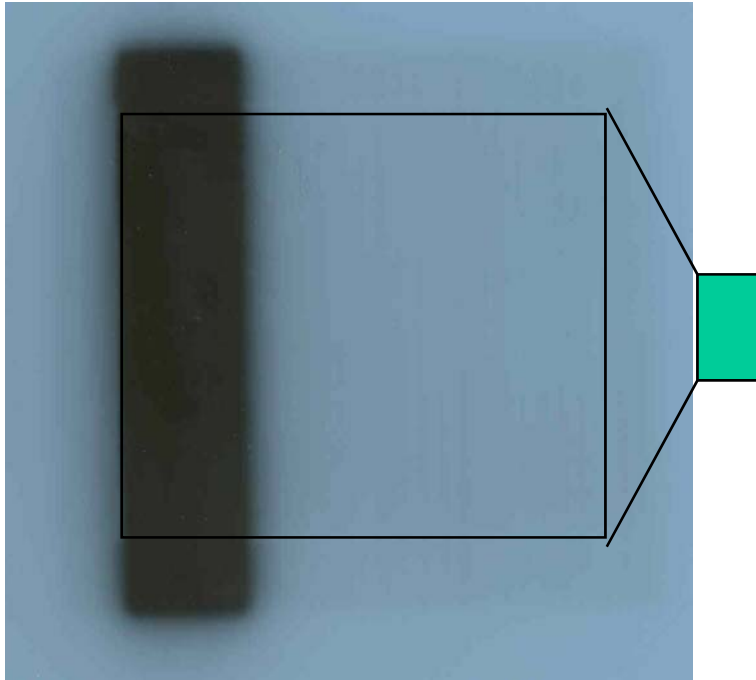
Irradiated region

Shielded region

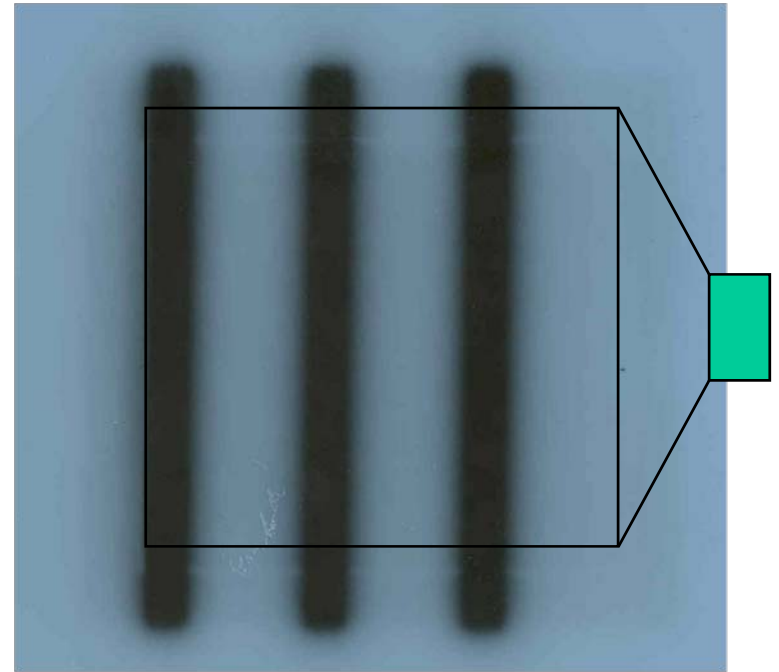
Striped



Positional and Dosimetric Verification



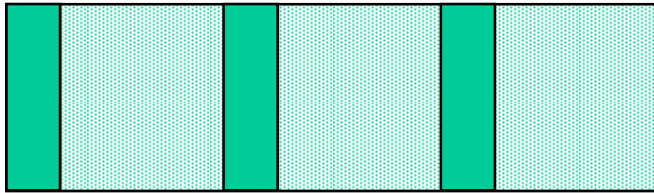
Kodak X-Omat V



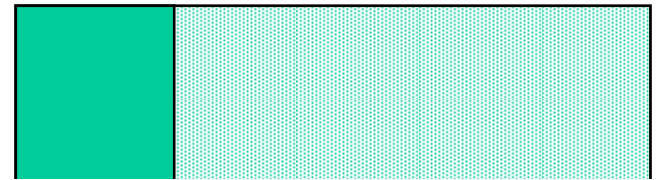
- Strips of GafChromic EBT film
- X-rite 301 densitometer
- Monitor units for each field were adjusted to give an equal dose to the open section of the field

Dosimetric Verification

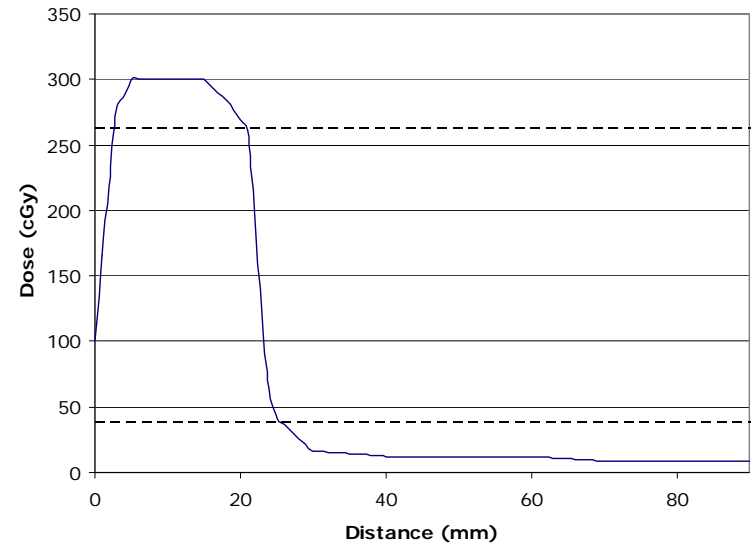
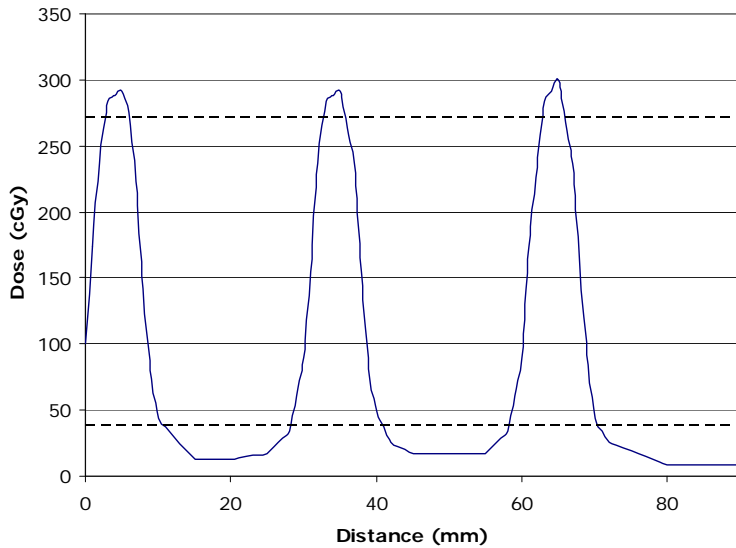
GafChromic EBT results



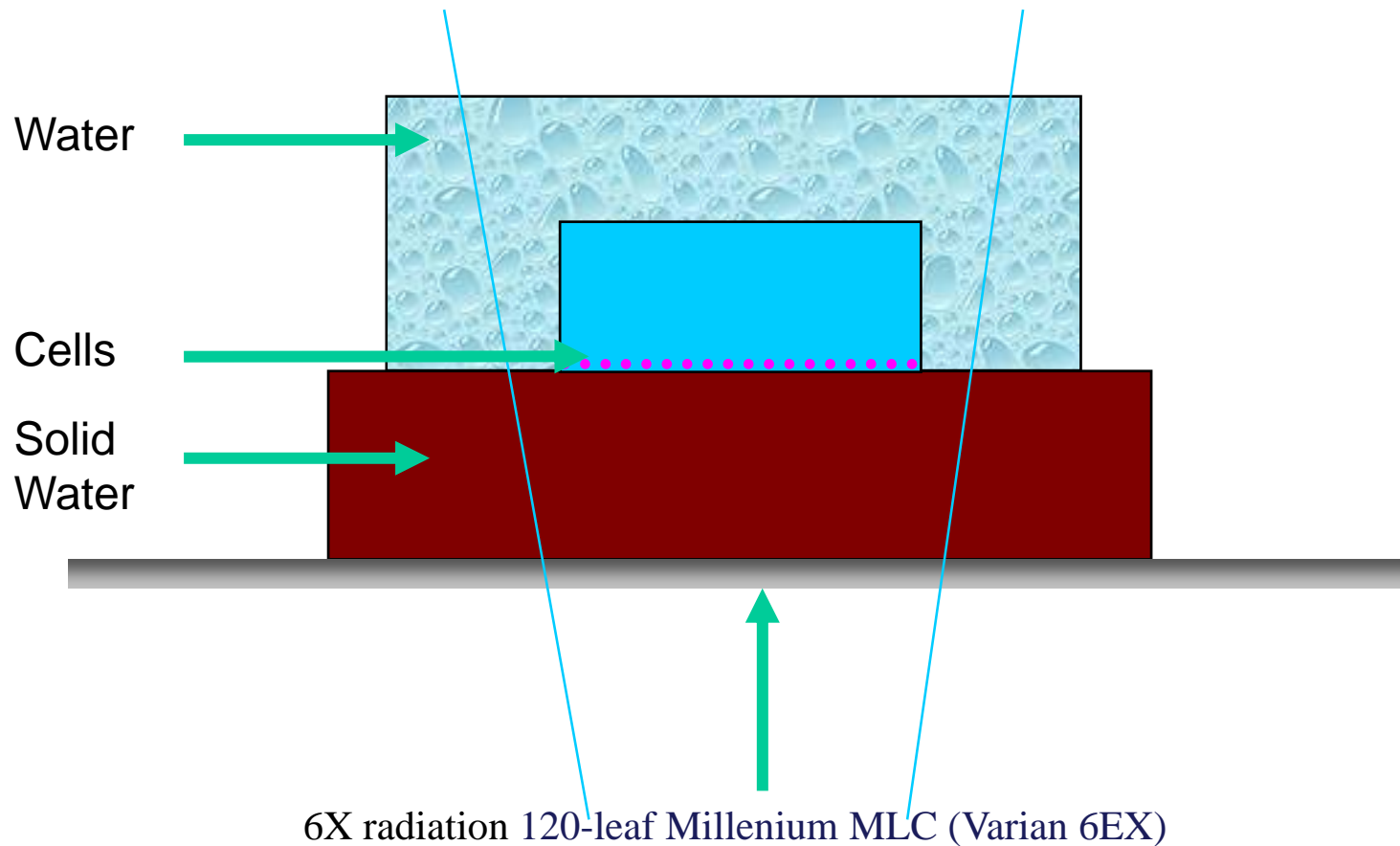
Striped Dose Profile



Quarter Dose Profile



Irradiation Setup



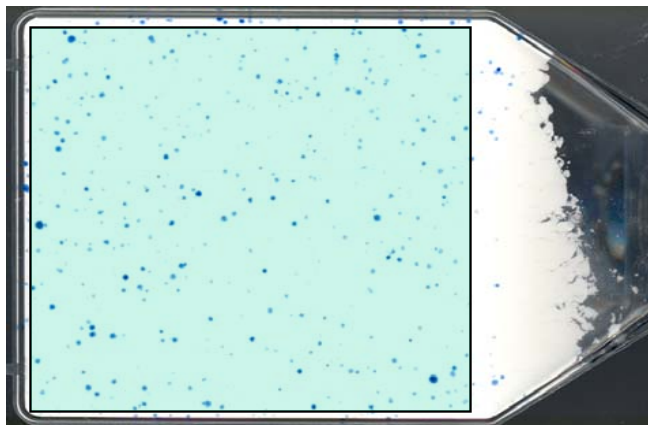


Cell Survival Fraction

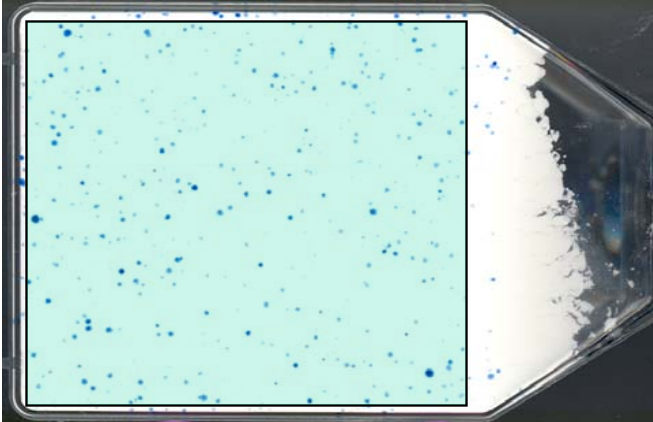
$$\text{Survival fraction (SF)} = \frac{\text{\# colonies [treated]}}{\text{\# colonies [control]}}$$

Error bars calculated from standard error in survival fraction between individual flasks

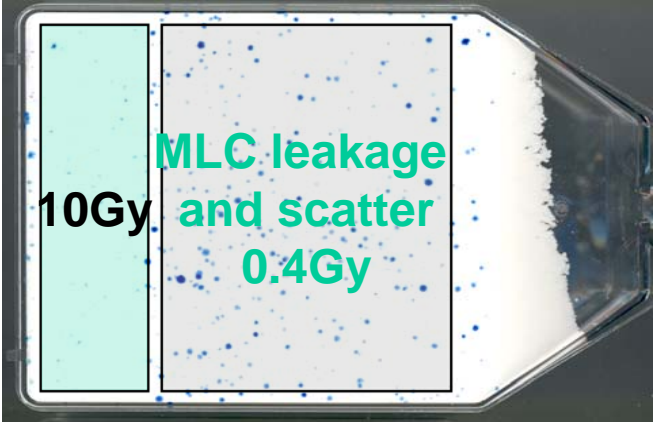
Open Field



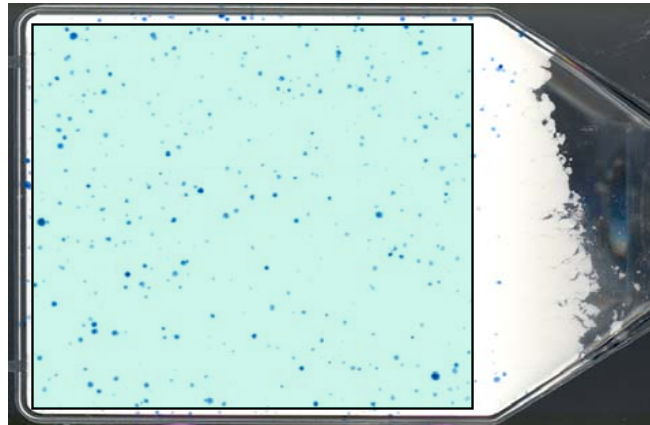
Open Field



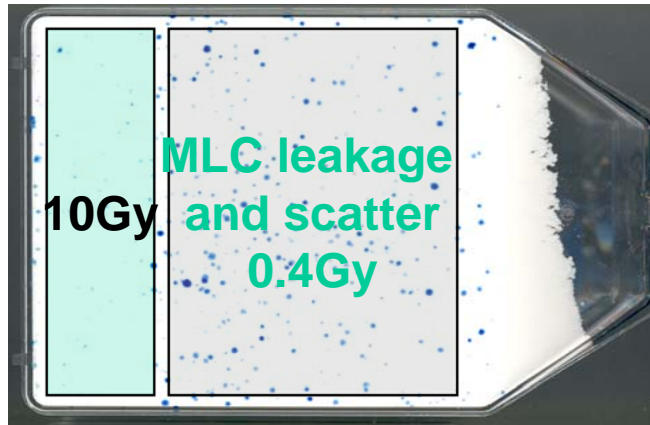
Quarter



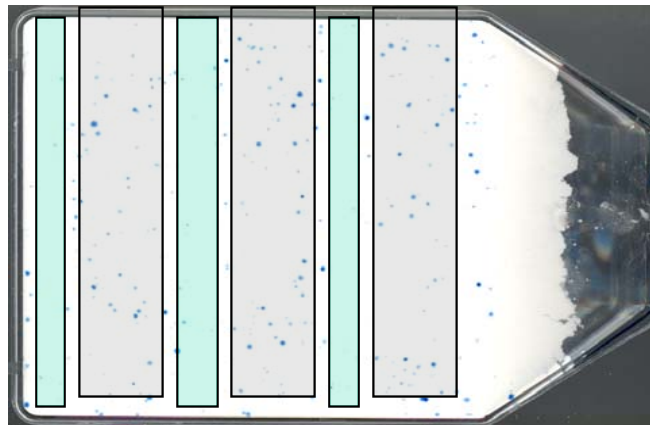
Open Field



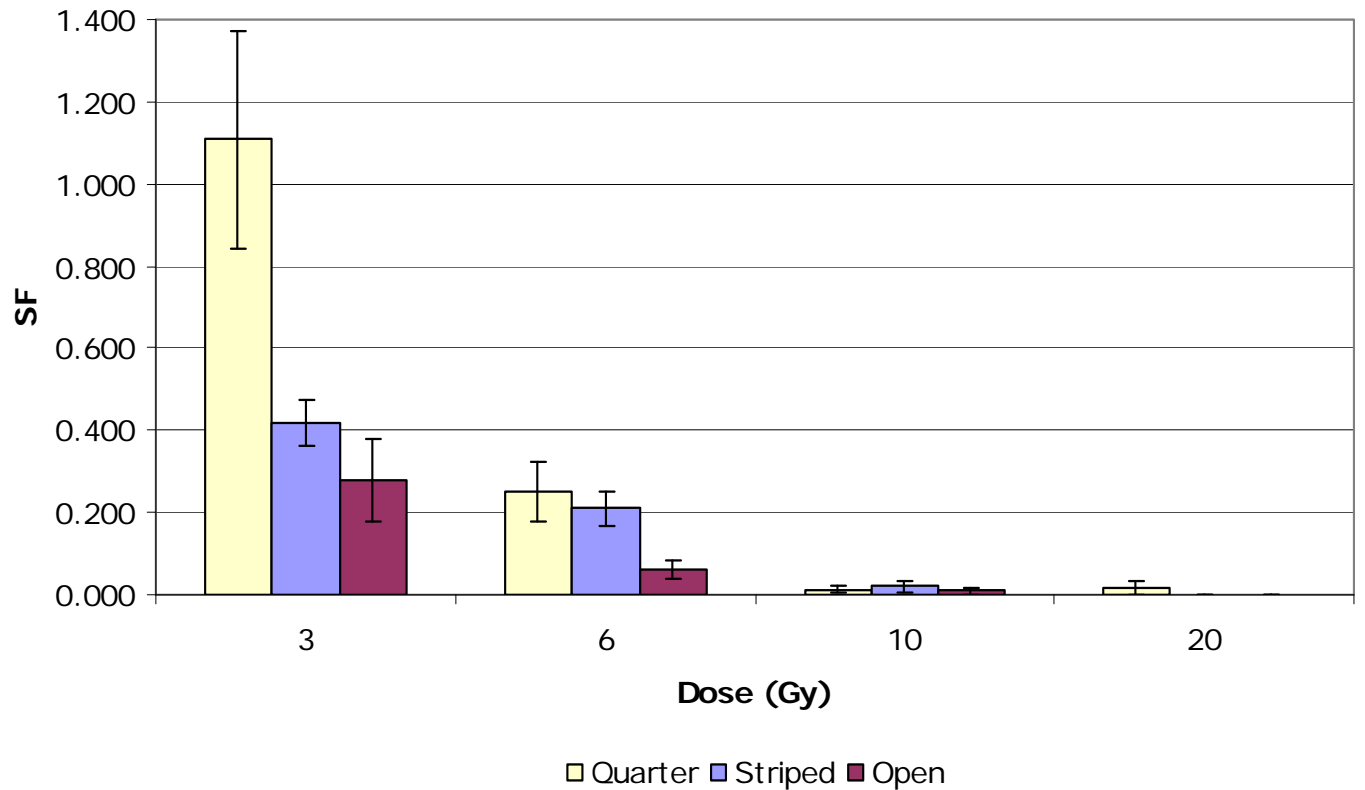
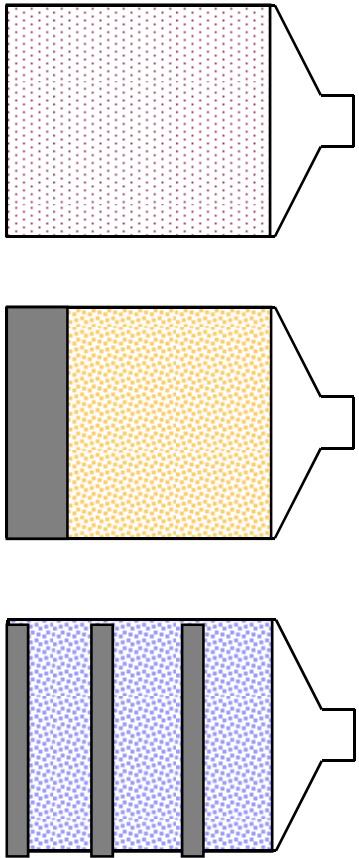
Quarter



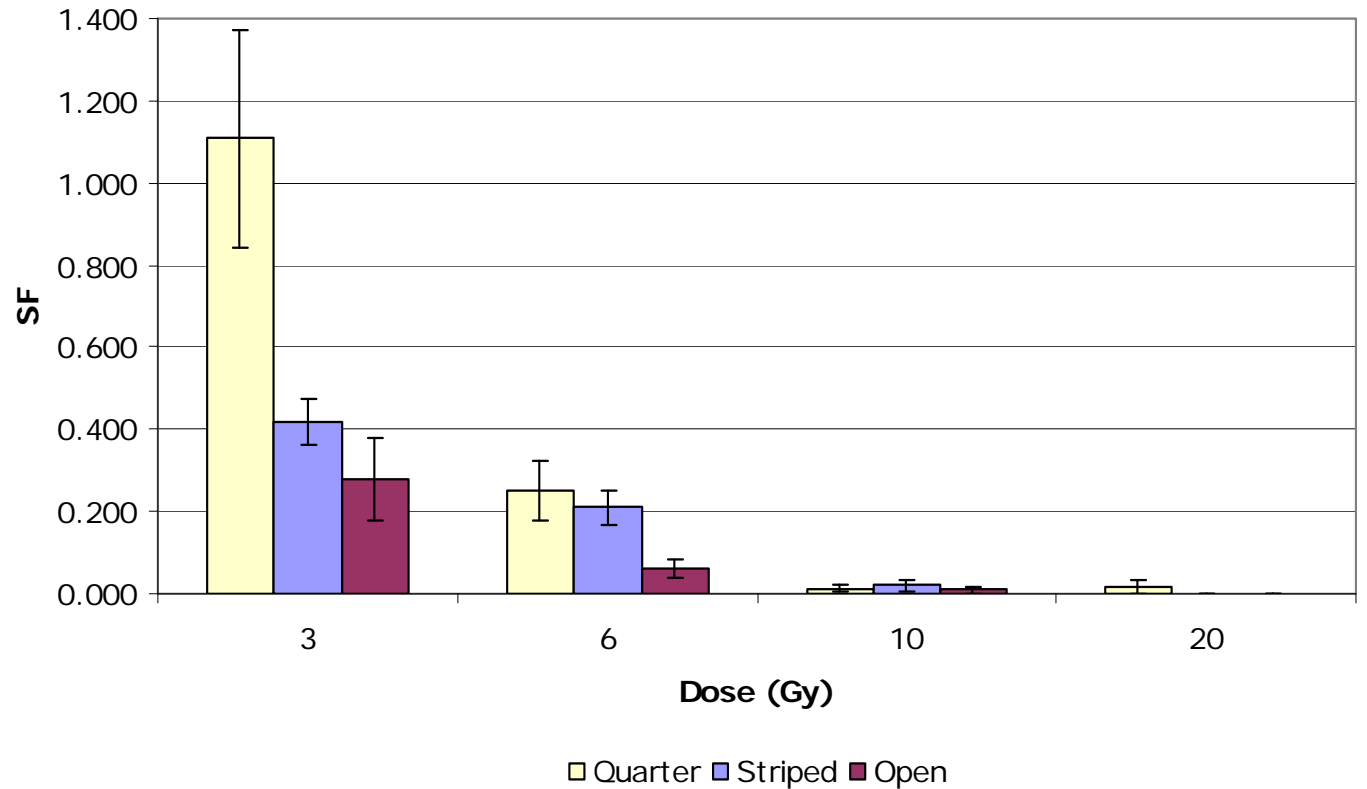
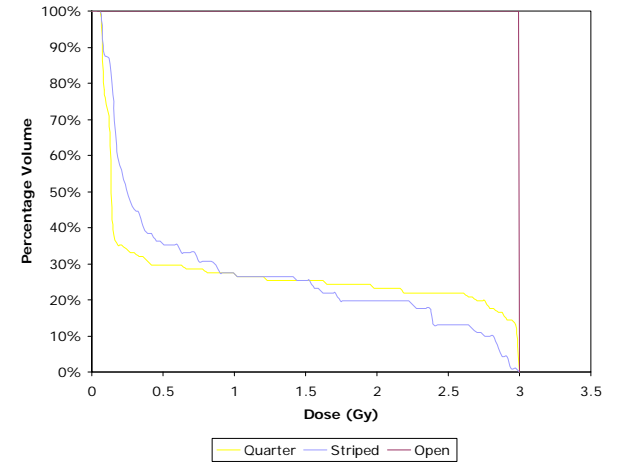
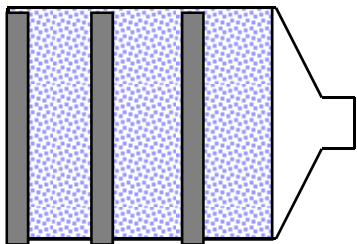
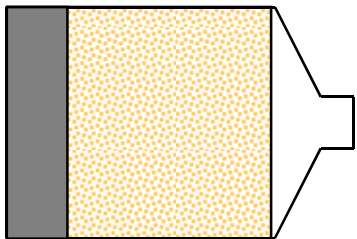
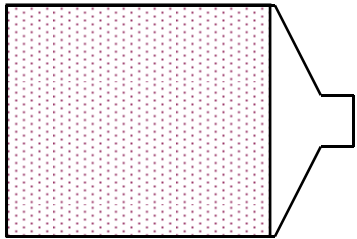
Striped



Open Region



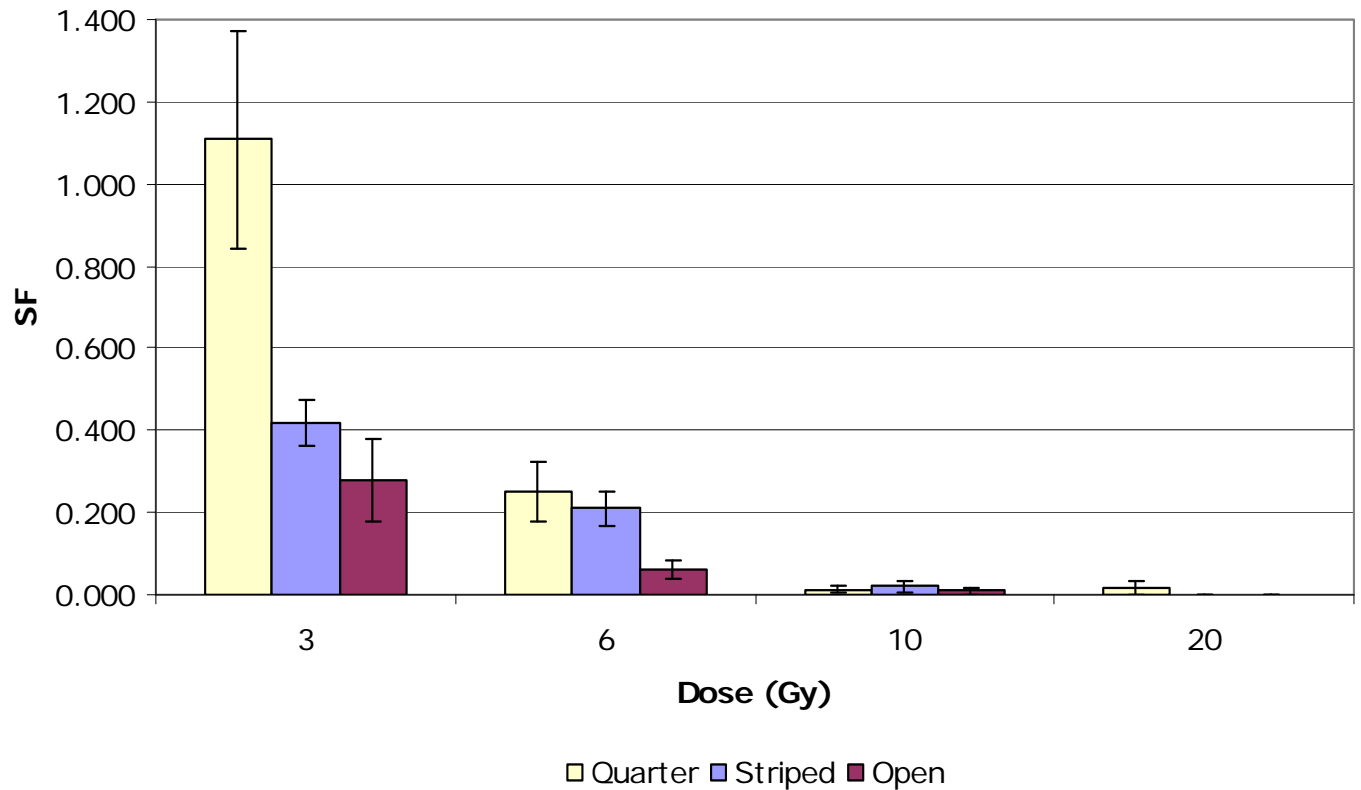
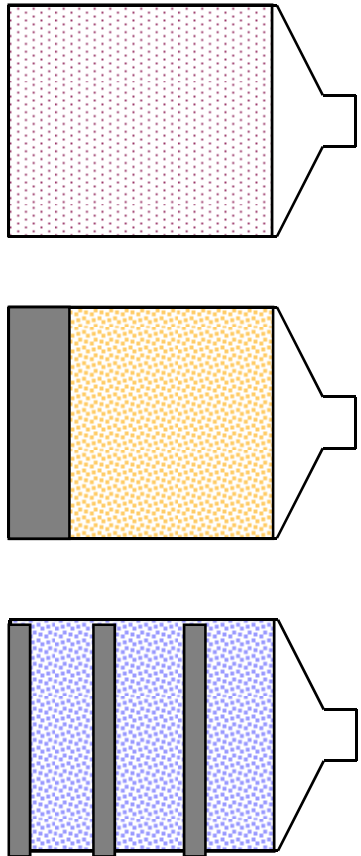
Open Region



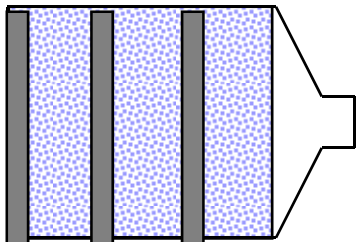
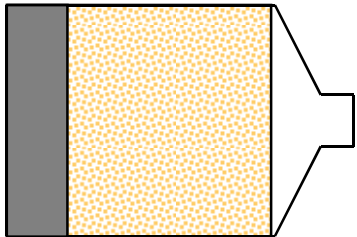
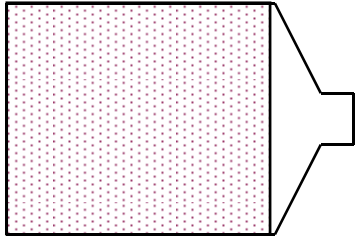
Open Region

Type 3 bystander effect

↑ survival of cells, when
neighbours receive a reduced dose



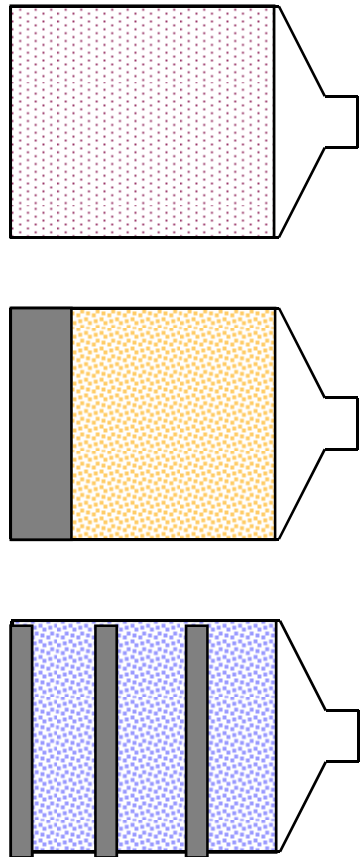
Open Region Significance



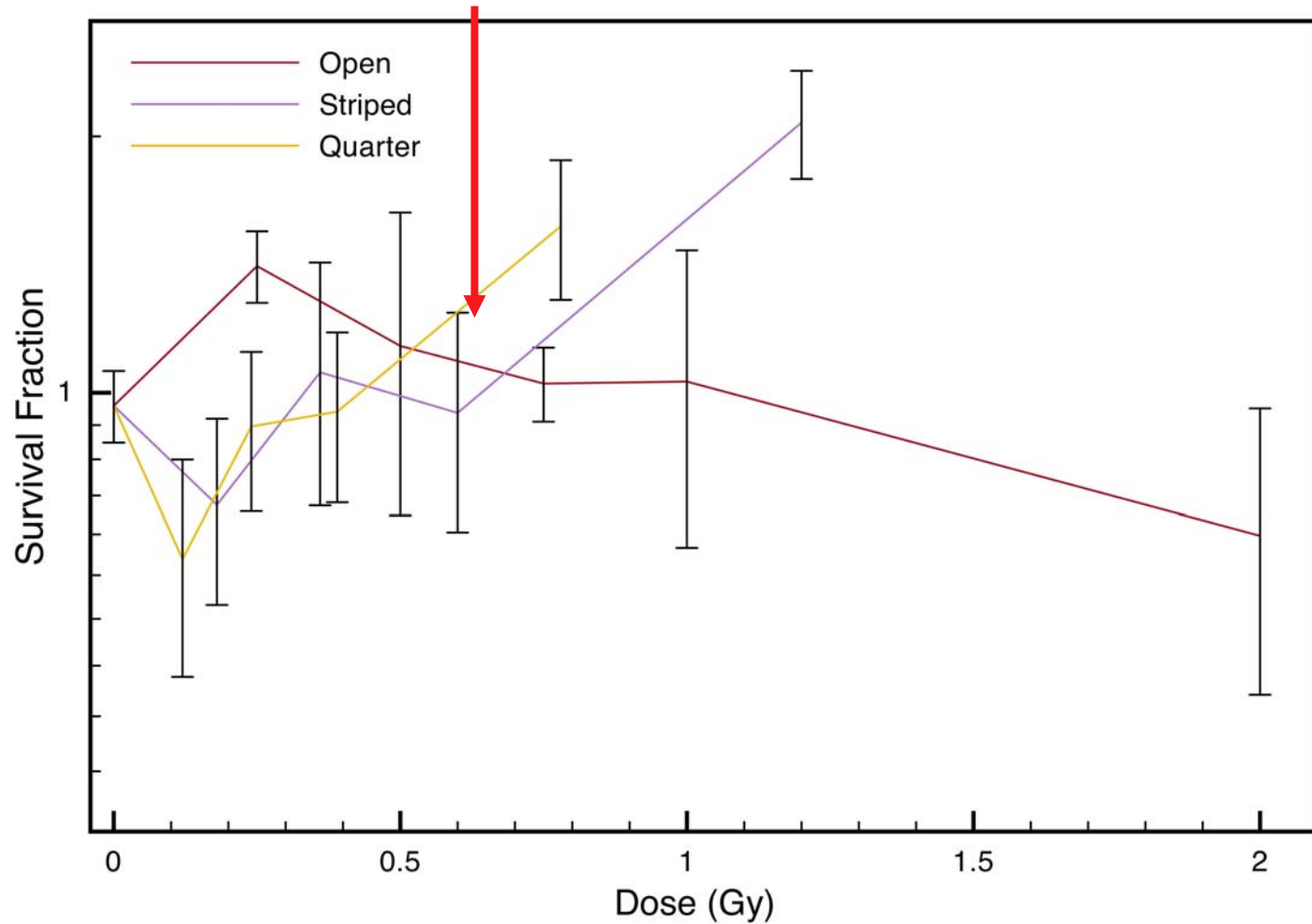
Student t-test for 3Gy irradiations

Quarter	Striped	>98%
Quarter	Open	>95%
Open	Striped	>90%

Shielded Region

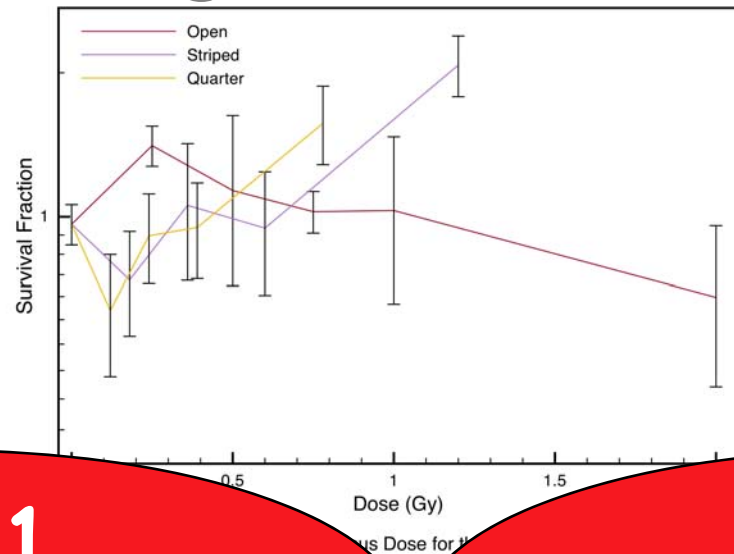


10Gy open field



Survival Fraction versus Dose for the Shielded Regions

Shielded Region



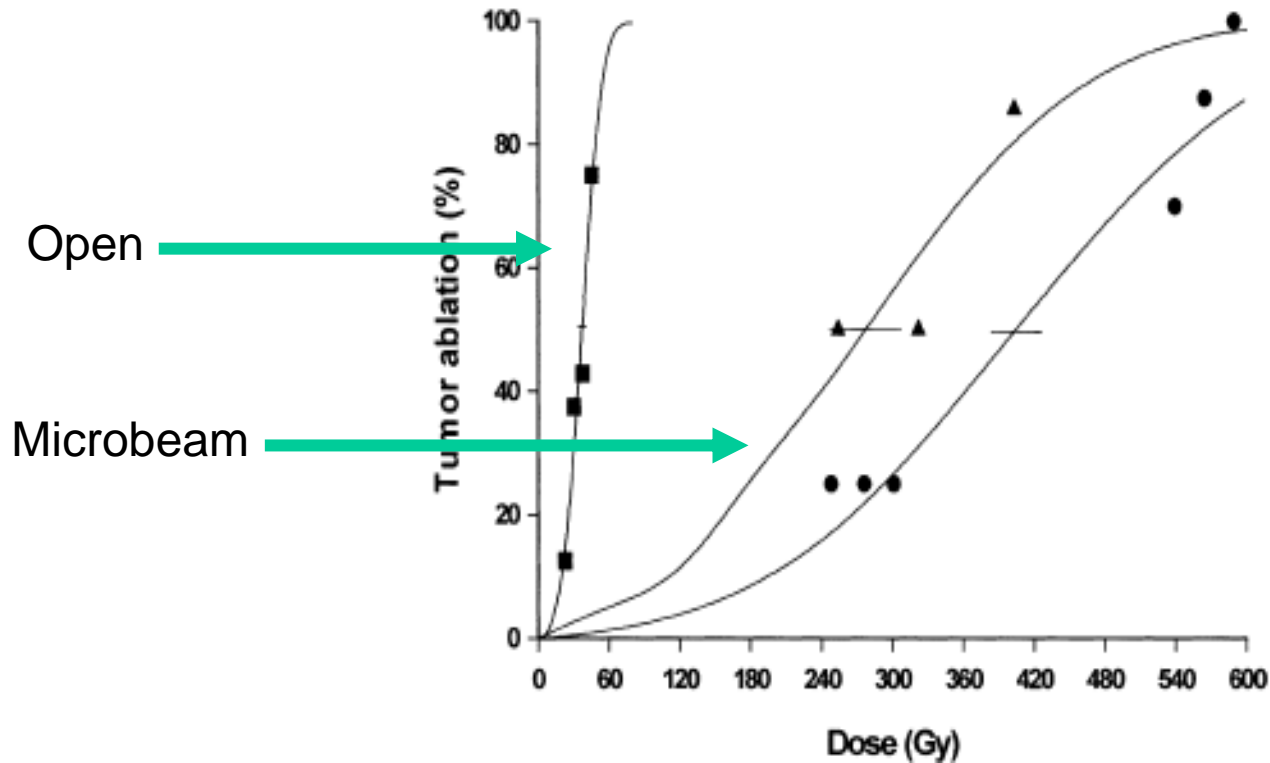
**Type 1
bystander effect**

↓ survival of shielded cells,
when neighbours receive a
high but not lethal dose
(3-6 Gy)

**Type 2
bystander effect**

↑ survival of shielded cells,
when neighbours receive a
lethal dose (10-20 Gy)

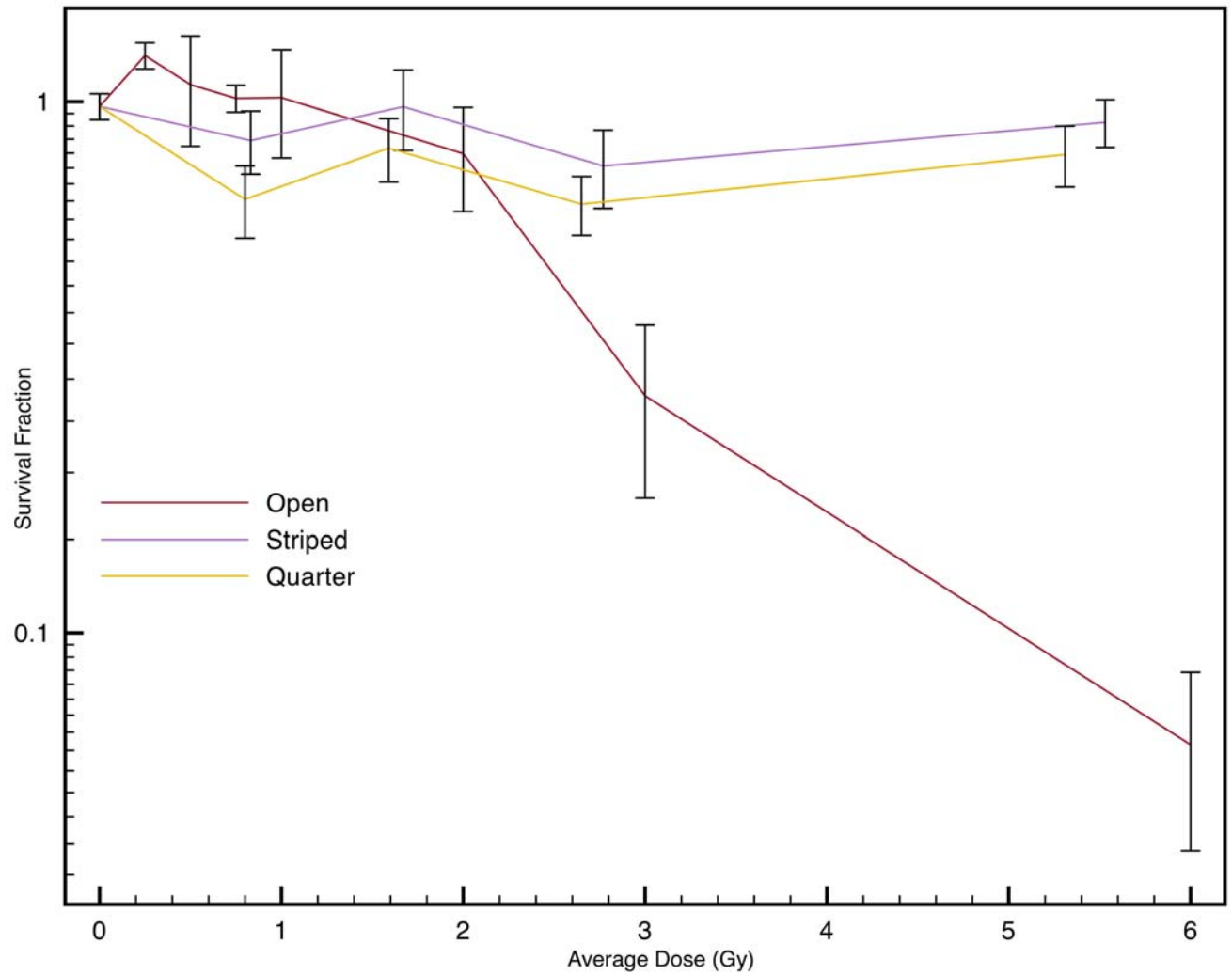
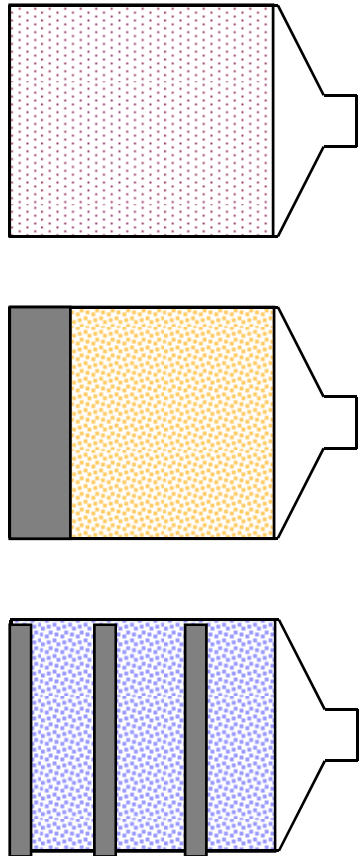
Microbeam results



Dilmanian et al., 2003,
Radiation Research, 159,
pp 632-641

FIG. 3. Dose-related changes in the percentage of mice exhibiting tumor ablation after treatment with microbeam radiation or broad-beam radiation; doses for microbeam radiation are expressed as integrated doses. Lines were fitted using probit analysis. (●) Co-planar microbeam radiation; (▲) cross-planar microbeam radiation; (■) broad beams. Horizontal lines are the standard errors of the LD₅₀'s.

Mean dose



***In vitro* study of cell survival following dynamic MLC intensity-modulated radiation therapy dose delivery^{a)}**

Vitali Moiseenko^{b)} and Cheryl Duzenli

Vancouver Cancer Centre, British Columbia Cancer Agency, 600 West 10th Avenue, Vancouver, British Columbia V5Z 4E6, Canada, and Department of Physics and Astronomy, University of British Columbia, 6224 Agricultural Road, Vancouver, British Columbia V6T 1Z1, Canada

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V. CONCLUSIONS

A persistent increase in cell survival from IMRT fields compared to acute dose delivery was observed. This increase, while not always statistically significant, was reproducible for all three studied cell lines. The obtained data set

Conclusion

- ! Dose distribution and pattern affect cell survival

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- ! This effect is seen in the open and shielded regions

Conclusion

- ! Dose distribution and pattern affect cell survival
- ! This effect is seen in the open and shielded regions
- ! Evidence of increased tolerance to radiation in modulated fields

Future work

A new cell response model is being developed,
using experimental data,
to include
intercellular communication effects

Understanding the
Bystander Effect is critical for
Radiobiological Optimisation
in modulated fields

Acknowledge

- Dr Michael Jackson
- A/Prof Chris Milross
- **Ms Elizabeth Claridge**
- Dr Mei Zhang
- Prof David McKenzie
- A/Prof Martin Ebert



