A Comparative Modeling Study on Intestinal Crypt Dynamics of Steady State and After Irradiation

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Background

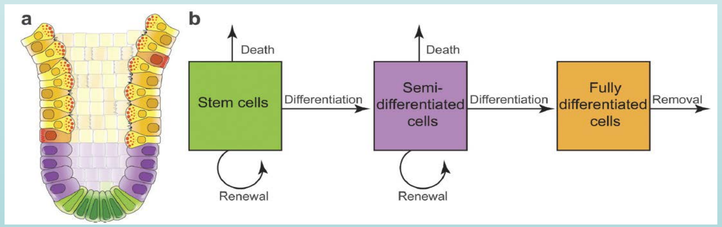
- The epithelium lining the small intestinal tract of mammals consists of a layer of columnar cells folded into villi and crypt that are renewed every few days and are sensitive to radiation.
- Over decades of study on the small intestine of BDF1 mice accumulated a large database of both cell kinetics and radiobiological response to various kinds of radiation exposure.
- Apoptosis can be observed in the proliferative cells at the bottom of crypt at dose of 0.01 Gy (Potten 2004), therefore the small intestine is an ideal target to study the effects at extreme low dose of radiation in space exploration.

Specific Aims

- Compare two modeling approaches to analyze the crypt dynamics of BDF1 mice in steady state and after acute radiation, so that the validated models can be extrapolated to other species.
- Incorporate the governing biological processes occurring at the subcellular, cellular, and tissue levels of crypt organization, to validate a multiscale tissue modeling framework for radiation research.
- Correlate the biological parameters in compartmental model with biological processes in spatial model of crypt dynamics, to investigate the parameter estimation procedure through experimental measurement.

Methods

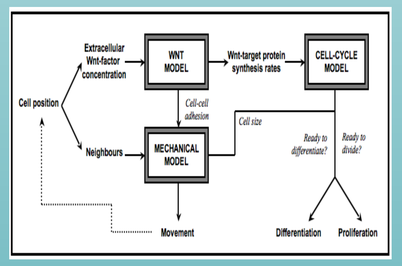
Compartmental model

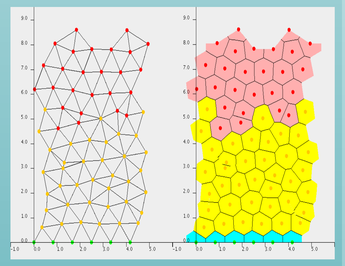


$$\frac{d\bar{x}^{ud}}{dt} = \gamma\bar{x}^{ud}(\bar{B}-1) - \frac{N}{D_x^0}\bar{x}^{ud},$$
$$\frac{d\bar{y}}{dt} = \delta\left[(1+l)\bar{x}^{ud} - (1+l\bar{B})\bar{y}\right],$$
$$\frac{d\bar{z}}{dt} = \psi\left[\frac{1+m}{1+l}(1+l\bar{B})\bar{y} - (1+m\bar{B})\bar{z}\right],$$
$$\frac{d\bar{x}^{d}}{dt} = \frac{N}{D_x^0}\bar{x}^{ud} - v\bar{x}^{d}.$$

- X: dividing cells
- Y: maturing cells
- Z: functional cells
- N: dose rate
- D^0: radiosensitivity parameter

Multiscale spatial model





Left: model scheme. By coupling Wnt signalling, cell cycle, and mechanical models, the spatio-temporal behavior of every cell can be simulated. **Right:** a Delaunay triangulation of a set of nodes and the corresponding Voronoi tessellation. The number of Delaunay triangles (mesh elements) that a node is involved in is equivalent to the number of sides that the cell has, as defined by the Voronoi tessellation.

Key assumptions for spatial model

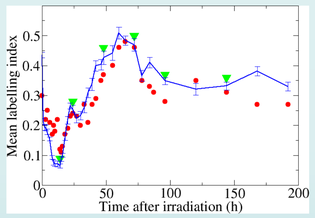
- Each cell is equipped with a cell cycle model governing proliferation and differentiation, and a mechanical model specifying interactions with neighbors.
- Extracellular Wnt concentration determines stem cell niche structure and the fate of each cell.
- Radiosensitivity parameters decide dose-dependent cell killing rates of proliferative cells.

Parameter changes due to irradiation

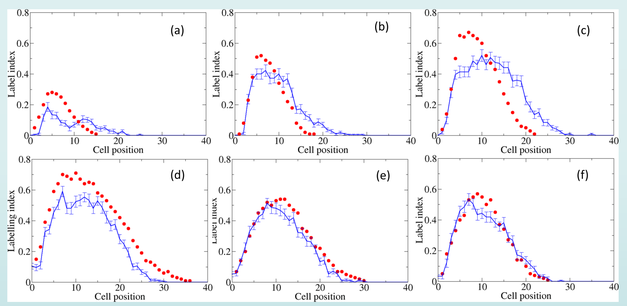
Model parameter	Steady state	After radiation
Transit cells G1, S, G2, M duration	3.5+1.5×N(0,1), 7.0+1.5×N(0,1), 0.75, 0.75 (h)	2.0+1.5×N(0,1), 6.0+1.5×N(0,1), 0.75, 0.75 (h)
Mitotic inhibition (G2 duration)	0.75 (h)	0.75 + 1.0×Dose (Gy) (h)
Colongeneic cell Wnt threshold	--	0.91
Delayed apoptosis	--	R(0,1) ×Dose (Gy) ×24.0 (h)

Results

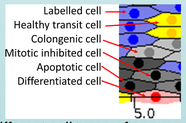
Labeling index dynamics after irradiation



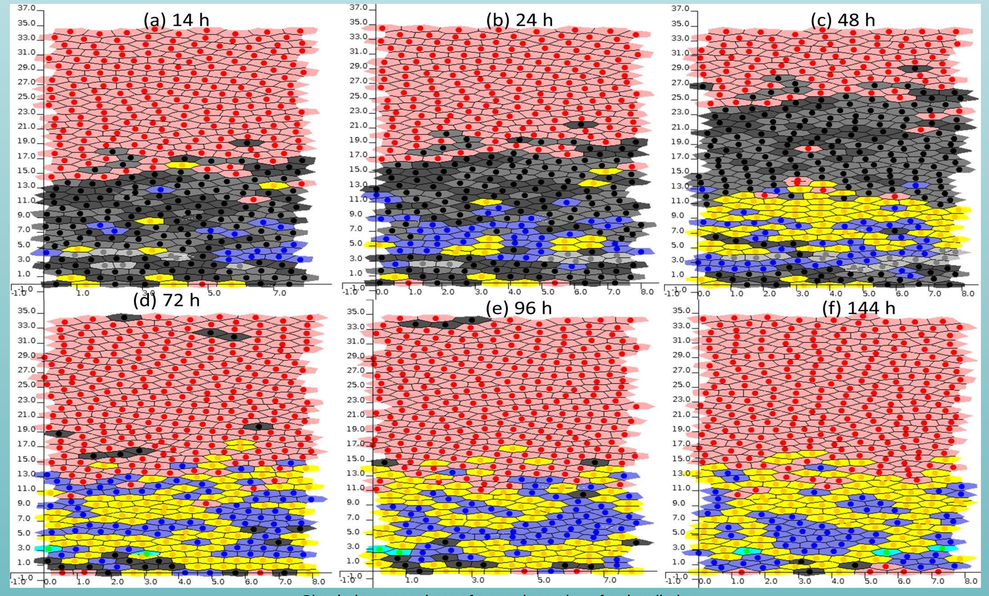
Comparison of experimental data and simulation results: overall label index after 8 Gy irradiation.



Comparison of experimental data and simulation results: positional label index after 8 Gy irradiation. (a) 12 h, (b) 24 h, (c) 48 h, (d) 72 h, (e) 96 h, (f) 144 h after exposure (• data, — simulation) (Gerike et al., 1998).

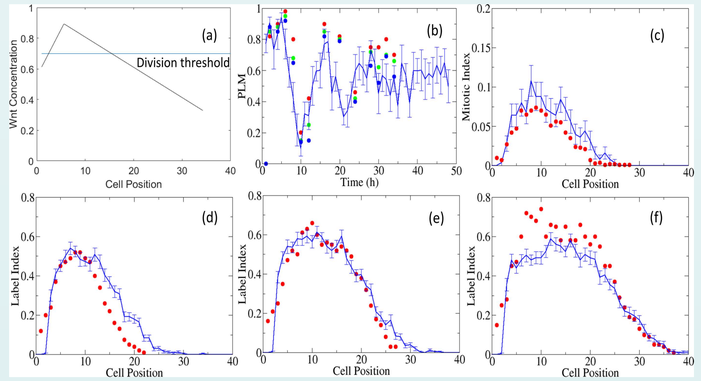


Different cell types after exposure



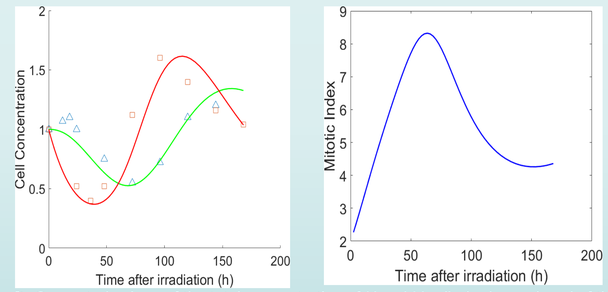
Simulation snapshots of crypt dynamics after irradiation

Steady state



(a) Positional Wnt concentration. Only cells with Wnt higher than the division threshold can divide. (b) Percentage of labelled mitosis (PLM) after pulse labelling. (c) Positional mitotic index. (d) Positional label index 40 min after pulse labelling (e) Positional label index 6 h after pulse labelling. (f) Positional label index 12 h after pulse labelling (• data, —simulation) (Gerike et al., 1998).

Cellular and mitotic index dynamics after irradiation



Left: Computed values of the total concentration of *X* and *Y* cells (red curve) and of the *Z* cell concentration (green curve), as well as experimentally measured concentrations of crypt cells (box) and villous cells (triangle) after 8 Gy exposure (Paulus et al., 1993).
Right: Computed mitotic index after 8 Gy exposure. Both with the compartmental model.

Conclusions and future work

- The "proof-of-concept" multiscale spatial model can simulate results compatible to experiments, however, the parameters governing various processes at different levels of crypt organization need to be finely tuned.
- Population kinetics and proliferation indices simulated by the simple compartmental model are consistent to those observed in chronically and acutely irradiated experiments.
- Spatial model has the potential to further incorporate the radiation effects at other biological scales such as radiation induced genetic mutation, chromosomal aberration, DNA damage, and radiation track structure.
- Both models can be extended to model radiation induced tumorigenesis at lower doses in colon and other organs.

References

1. Gerike et al. (1998) A dynamic model of proliferation and differentiation in the intestinal crypt based on a hypothetical intraepithelial growth factor, *Cell Proliferation*, 31, 93-110
2. Paulus et al., (1993) The differentiation and lineage development of goblet cells in the murine small intestinal crypt: experimental and modelling studies, *Journal of Cell Science* 106, 473-484
3. Potten C. S., (2004) Radiation, the ideal cytotoxic agent for studying the cell biology of tissues such as the small intestine, *Radiation Research* 161, 123-146
4. Smirnova O.A., (2009) Blood and small intestine cell kinetics under radiation exposures: mathematical modeling. *Advances in Space Research* 44,1457–1469.
5. van Leeuwen et al., (2009) An integrative computational model for intestinal tissue renewal. *Cell Proliferation* 42, 617-636.