Sensitivity analysis of an in silico model of prostate tumour growth and response to radiotherapy

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Purpose or Objective

In silico models are appealing tools to understand and predict tumour growth and response to RT. A major issue of computational models is the large number of variables they may contain. The objective of this work was to perform a Morris sensitivity analysis on a prostate tumour growth and response to RT model, to identify the most relevant parameters and determine which ones can be negligible

Material and Methods

Histopathological specimens from 7 patients with localized prostate cancer, treated with radical prostatectomy, were used to initialise 21 computational tissues with different tumour and vascular densities. Tumour foci were delineated by a pathologist on the HES axial slides (figure 1.a) and a CD31 staining (figure 1.b) was carried out to identify the blood vessels. A multi-scale *in silico* model was generated, considering the prostate computational tissues, where each voxel corresponded to a cell of the following 7 types: healthy glandular/endothelial, tumour glandular/neo-created endothelial and dead (by apoptosis, hypoxic necrosis or mitotic catastrophe). Figure 1.c shows the corresponding initial computational tissue. The model integrated 5 biological processes: oxygenation of the tissue (Oxy.) using a reaction-diffusion equation (*Espinoza et al., Med Phys 2013*); proliferation of tumour cells, considering their life-cycle (Prolif.); angiogenesis based on the VEGF diffusion (Angio.) (*Harting et al., Phys. Med. Bio 2007)*; phase-and-oxygen-dependent response to irradiation, using the linear-quadratic model and considering cycle arrests and death by mitotic catastrophe (RespTolrr.) and resorption of dead cells (Resor). The table presents the 34 parameters of the model, indicating the process they intervene in. Every simulation considered a total dose of 80 Gy, administered every 24 h, from Monday to Friday.

Figure 1.d shows the computational prostate tissue after 80 Gy. The tumour density (number of tumour cells divided by the total number of cells) at the end of the treatment was used as output of the model. The Morris sensitivity method calculated, on the 21 computational tissues (73500 simulations in total), the mean and standard values ($\mu_i^* \pm \sigma_i$) of 100 elementary effects for each parameter. The Euclidean distance of the point (μ_i^*, σ_i) to the origin was the indicator of the impact of parameter i.

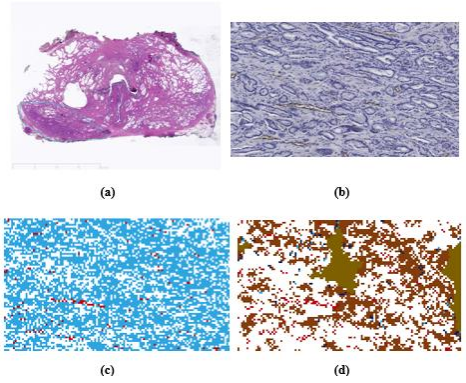

Figure 1. Example of an (a) histopathological cut; (b) CD31 staining; (c) initial computational tissue, where healthy cells are represented in white; tumour, in light blue and pre-existing endothelial in light red and (d) computational tissue after a 40 x 2 Gy RT treatment, where tumour cells with DNA damaged by irradiation are represented in dark blue; neo-created endothelial, in dark red and dead by hypoxic necrosis, in ochre and by mitotic catastrophe, in brown

Results

The table shows a ranking of the 34 parameters of the model, according to their mean Euclidean distances over the 21 tissues.

Parameter of the model	Biological process	Mean Euclidean distance
Duration of cycle of tumour cells	Prolif.	41.68 ± 3.90
Dose per fraction	RespToIrr.	41.62 ± 4.47
Dose threshold of immediate death by apoptosis	RespToIrr.	21.51 ± 4.45
Duration of arrest at checkpoints G1/S and G2/M due to irradiation	RespToIrr.	11.23 ± 2.10
O_2 Michaelis constant	Oxy.	7.53 ± 4.36
O_2 Michaelis-Menten maximum rate	Oxy.	7.25 ± 3.75
pO_2 threshold of hypoxia	Oxy.	6.64 ± 3.14
α of tumour cells in phase G1	RespToIrr.	5.52 ± 4.87
α of tumour cells in phase G2	RespToIrr.	4.43 ± 2.98
α of tumour cells in phase M	RespToIrr.	3.56 ± 1.17
pO_2 of pre-existing endothelial cells	Oxy.	3.26 ± 1.96
O_2 diffusion coefficient	Oxy.	2.66 ± 2.04
α of tumour cells in phase S	RespToIrr.	2.13 ± 1.55
α of tumour cells in phase G0	RespToIrr.	1.77 ± 1.52
α/β of tumour cells in phase G0	RespToIrr.	1.74 ± 1.09
α/β of tumour cells in phase M	RespToIrr.	1.70 ± 0.53
α/β of tumour cells in phase G1	RespToIrr.	1.52 ± 0.82
α/β of tumour cells in phase G2	RespToIrr.	1.47 ± 0.94
Duration of cycle of healthy cells	Resor.	1.29 ± 0.87
α of healthy cells	RespToIrr.	1.29 ± 1.12
VEGF of hypoxic cells	Angio.	1.28 ± 1.20
pO_2 of neo-created endothelial cells	Oxy.	1.26 ± 1.03
α/β of healthy cells	RespToIrr.	1.25 ± 0.70
α/β of neo created endothelial cells	RespToIrr.	1.24 ± 1.25
α/β of pre-existing endothelial cells	RespToIrr.	1.21 ± 0.67
pO_2 threshold of hypoxic necrosis	Oxy.	1.18 ± 0.45
α/β of tumour cells in phase S	RespToIrr.	1.10 ± 0.22
α of neo-created endothelial cells	RespToIrr.	1.09 ± 0.35
Duration of cycle of neo-created endothelial cells	Angio.	1.06 ± 0.34
VEGF threshold to trigger angiogenesis	Angio.	1.04 ± 0.22
α of pre-existing endothelial cells	RespToIrr.	1.02 ± 0.17
VEGF Michaelis-Menten maximum rate	Angio.	0.99 ± 0.15
VEGF Michaelis constant	Angio.	0.99 ± 0.24
VEGF diffusion coefficient	Angio.	0.98 ± 0.21

Table. Ranking of the 34 parameters of the model, according to their mean Euclidean distance to the origin

Conclusion

The Morris sensitivity analysis identified the duration of the cycle of tumour cells and the dose per fraction as the parameters having the greatest effect on the final tumour density after 80 Gy. The VEGF Michaelis-Menten maximun rate, the VEGF Michaelis constant and the VEGF diffusion coefficient had the lowest impact.

Poster: Physics track: Intra-fraction motion management