Radiobiological modelling of individual radiosensitivity

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Radiobiological modelling accounting for radiosensitivity

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Modelling

- To simulate a process, a concept or the operation of a system (commonly with the aid of a computer).
  - Starting from ground principles and processes (mechanistic modelling)
  - Starting from observations (empirical modelling)
  - Combining observations and principles (semi-empirical/semi-mechanistic modelling)

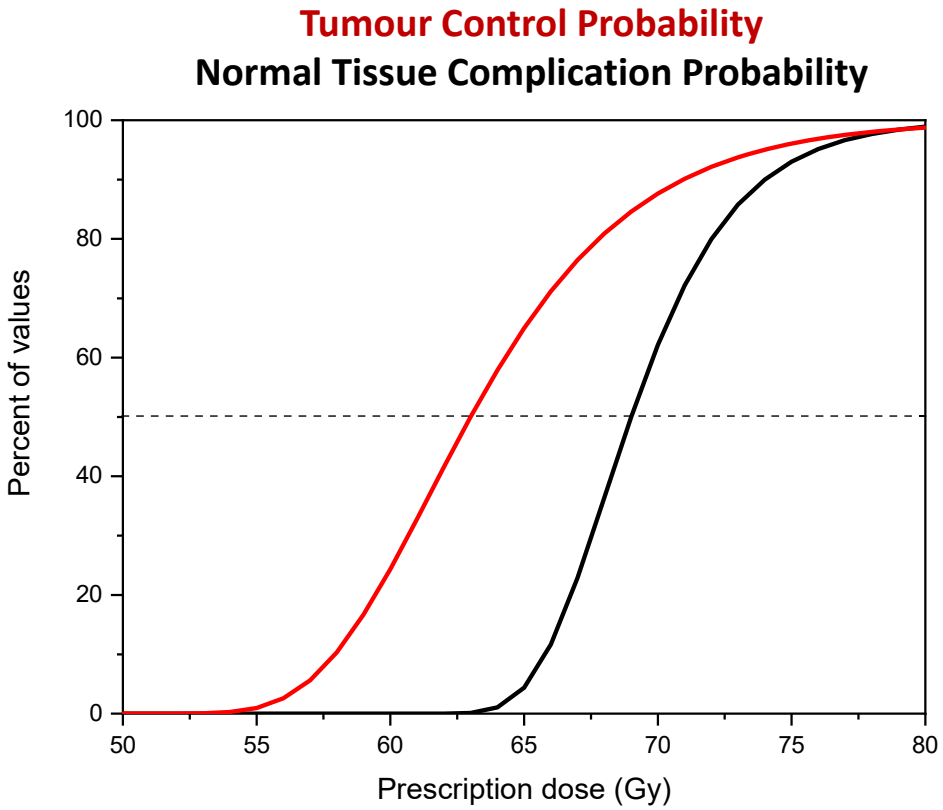
- The aims of modelling include:
  - Predicting the outcome of a system
  - Characterising the impact of one or several influence factors

Modelling in radiotherapy

- To simulate the impact of radiation on the response of biology systems

- The aims of modelling include:
  - Predicting the probability of complications in normal tissues
  - Predicting the probability of controlling tumours
  - Including the modulating effect of influence factors
  - Optimising the treatment by accounting for individual factors

Modelling in radiotherapy



- Characterising the therapeutic window between the sigmoid curves describing the probability of control and the incidence of complications.

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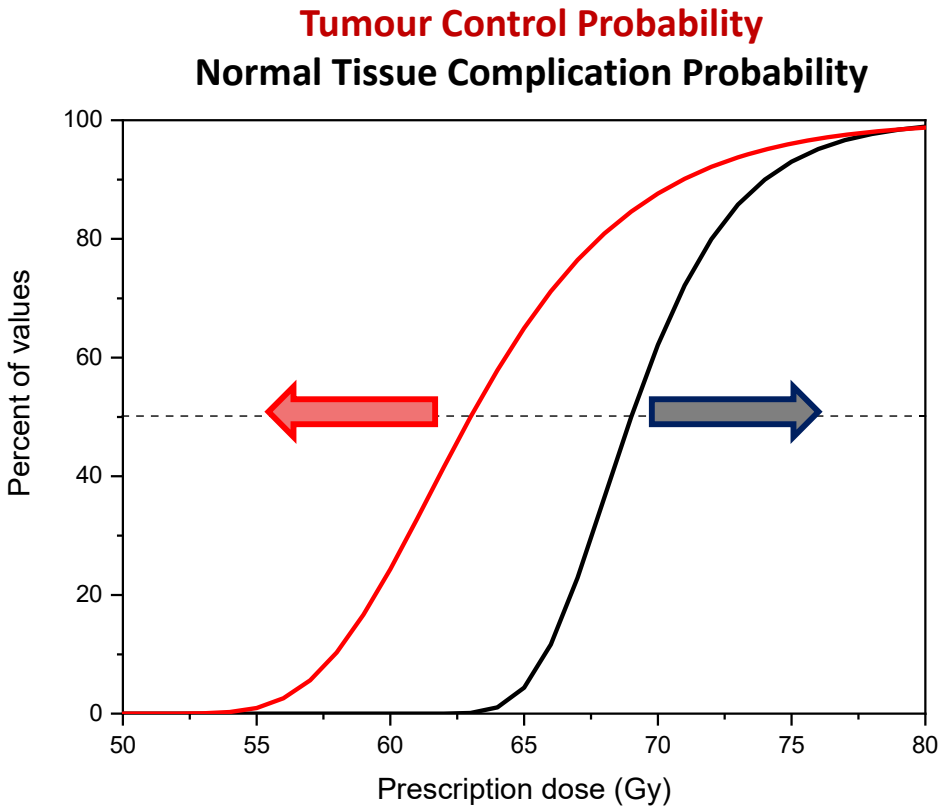
Modelling in radiotherapy



- Maximising the therapeutic window between the sigmoid curves describing the probability of control and the incidence of complications.

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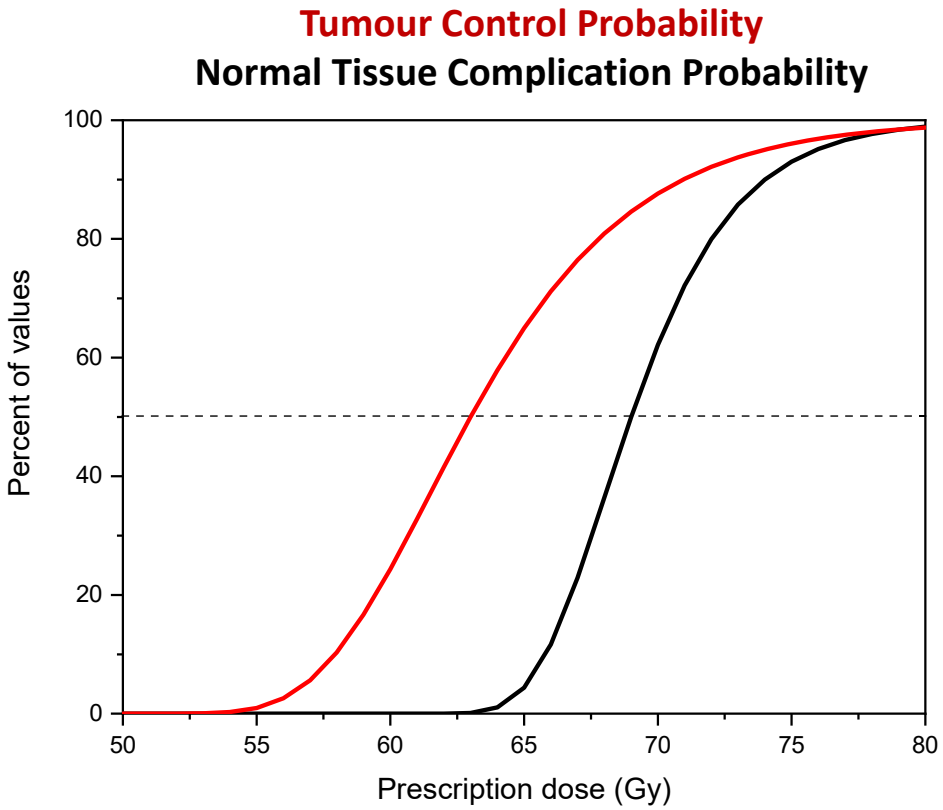
Modelling in radiotherapy



- Models to describe tissue response:
  - Mechanistic models
  - Dose response fitting (empirical/semi-mechanistic models)

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Mechanistic models

- Tissues organised in functional subunits (FSU) that perform a specific function
- The minimum number of FSU to ensure functionality of the tissue: tissue rescuing units (TRU)
- Number of surviving TRU = ***TRU·SF***
- The probability of tissue functioning failure = $\boldsymbol{(1\text{-}SF)^{TRU}}$

$$P = \exp(-TRU \cdot SF)$$

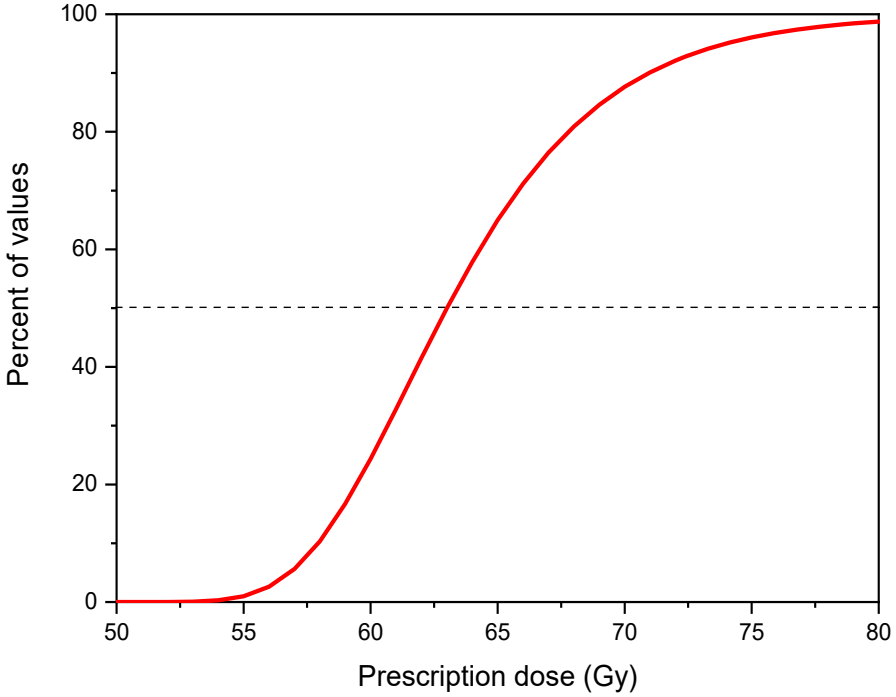
Mechanistic TCP models

- In tumours FSU ≡ 1 clonogenic cell!

$$TCP = \exp(-N_0 \cdot SF)$$

- where N_0 is the initial number of cells and SF is the surviving fraction of cells.

Mechanistic TCP models



$$TCP = \exp(-N_0 \cdot SF)$$

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Survival and proliferation

$$TCP = \exp(-N_0 \cdot SF)$$

Without repopulation

$$TCP = \exp\left(-N_0 \cdot SF \cdot F_{prolif}\right)$$

With accelerated repopulation

$$F_{prolif} = \begin{cases} 1 & \text{for } T \leq T_k \\ exp\dfrac{ln(2)(T - T_k)}{T_p} & \text{for } T > T_k \end{cases}$$

Modelling in radiotherapy

- Radiotherapy targets are never homogeneous.
  - GTV vs CTV
- Dose distributions in RT are seldom uniform
- Various processes can influence the result and can be targeted
- Various techniques and treatment modalities are available for clinicians, each with their own particular features
- Treatments are usually delivered over several days or weeks

TCP modelling in radiotherapy

- Modelling TCP and comparing of the outcome for:
  - Various tumours
    - different individual sensitivities
    - different proliferative capacities
    - different repair rates
    - different microenviromental conditions
  - Different types of particles
  - Different dose-rates
  - Different fractionated schedules
  - Different irradiation modalities
  - etc.

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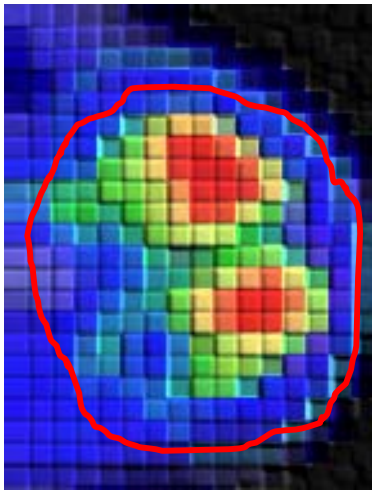
Accounting for heterogeneities

In case of intra-tumour heterogeneities:

$$TCP = \prod_{i}^{m} P_i$$



P_i is the control probability at the voxel level.

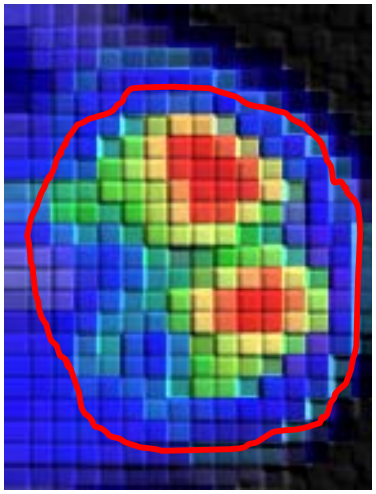
$$P_i = \exp[-\rho_i V_i SF_i]$$

where ρ_i is the density of clonogenic cells in the voxel *i* and V_i is its volume.

Accounting for dose distributions

In case of intra-tumour heterogeneities:

$$TCP = \prod_{i}^{m} P_i$$



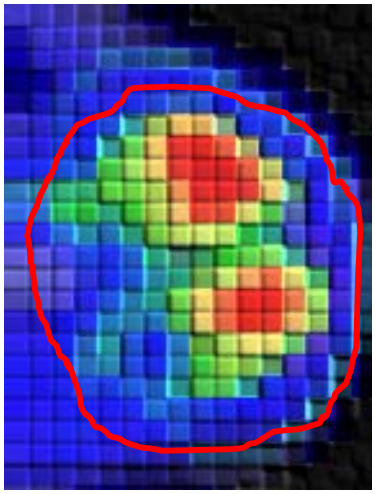
P_i is the control probability at the voxel level.

$$P_i = \exp\left[-\rho_i V_i exp\left(-n\left(\alpha d_i + \beta d_i^2\right)\right)\right]$$

where ρ_i is the density of clonogenic cells in the voxel *i* receiving dose d_i and V_i is its volume.

Accounting for heterogeneous radiosensitivities

In the case of non-homogeneous radiosensitivity in the tumour:



$$TCP = exp\left[-\int_{\mathbf{r}}^{\boldsymbol{m}} n_0 SF(\mathbf{r})d\mathbf{r}\right]$$

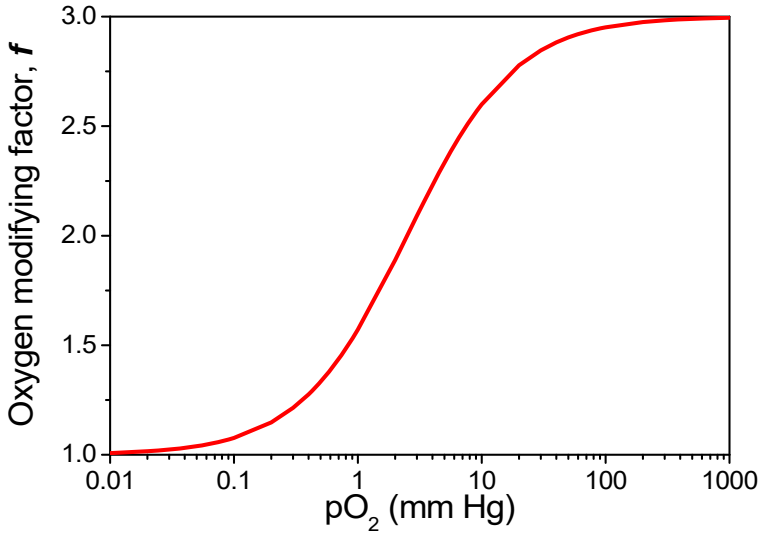
$$SF(\mathbf{r}) = \prod_{i=1}^{n} exp\left[-\alpha(\mathbf{r})d_i(\mathbf{r}) - \beta(\mathbf{r})d_i^2(\mathbf{r})\right] exp\left[\frac{Tln(2)}{TD(\mathbf{r})}\right]$$

Accounting for hypoxia

$$SF(\mathrm{r}) = \prod_{i=1}^{n} exp\left[-\alpha(\mathrm{r})d_i(\mathrm{r}) - \beta(\mathrm{r})d_i^2(\mathrm{r})\right] exp\left[\frac{Tln(2)}{TD(\mathrm{r})}\right]$$

$$\alpha(\mathrm{r}) = \frac{\alpha_{oxic}}{f(\mathrm{r})}$$

$$\beta(\mathrm{r}) = \frac{\beta_{oxic}}{[f(\mathrm{r})]^2}$$



$$f(\mathrm{r}) = \frac{OER_{max}\left(k + pO_2(\mathrm{r})\right)}{k + OER_{max}pO_2(\mathrm{r})}$$

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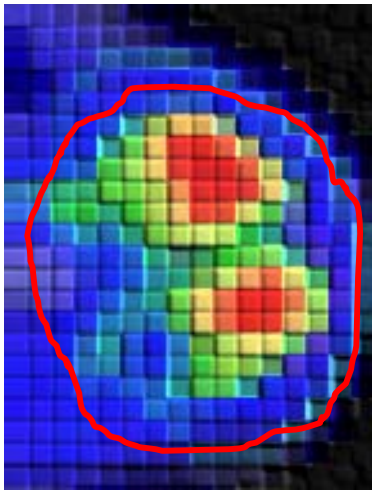
Accounting for several influencing factors

These expressions account for several influencing factors:



$$TCP = exp\left[-\int_{\mathbf{r}}^{m} n_0 SF(\mathbf{r})d\mathbf{r}\right]$$

Cell density

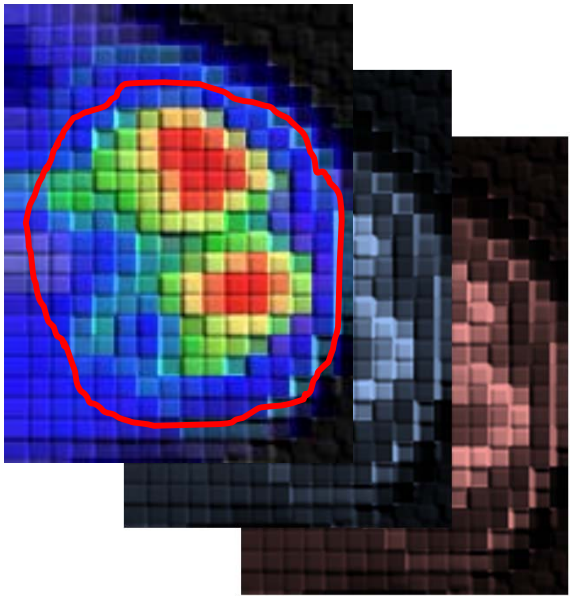
$$SF(\mathbf{r}) = \prod_{i=1}^{n} exp\left[-\alpha(\mathbf{r})d_i(\mathbf{r}) - \beta(\mathbf{r})d_i^2(\mathbf{r})\right] exp\left[\frac{Tln(2)}{TD(\mathbf{r})}\right]$$

Hypoxia

Proliferation

Accounting for several influencing factors

These expressions account for several influencing factors:



$$TCP = exp\left[-\int_{\mathbf{r}}^{m} n_0 SF(\mathbf{r})d\mathbf{r}\right]$$

FDG

$$SF(\mathbf{r}) = \prod_{i=1}^{n} exp\left[-\alpha(\mathbf{r})d_i(\mathbf{r}) - \beta(\mathbf{r})d_i^2(\mathbf{r})\right] exp\left[\frac{Tln(2)}{TD(\mathbf{r})}\right]$$

FMISO

FLT

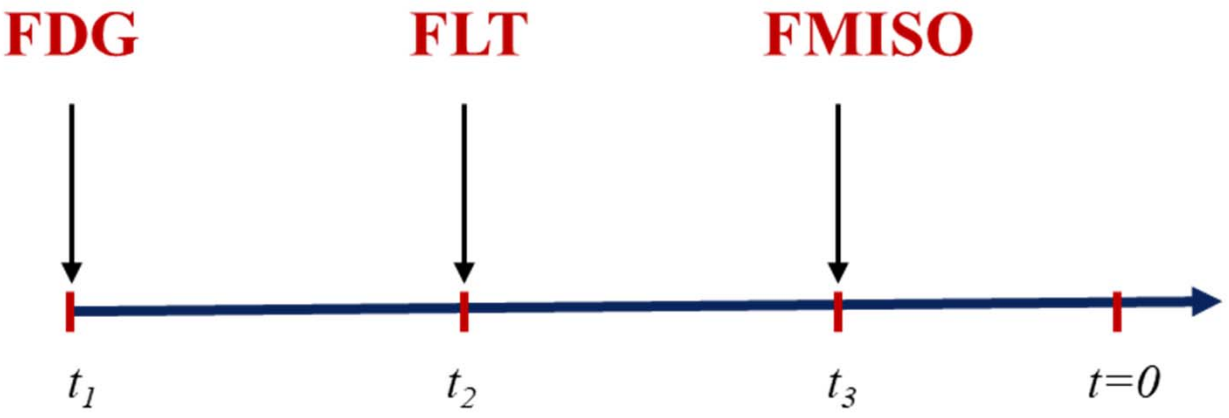
Accounting for several influencing factors

$$TCP = exp\left[-\int_{\mathbf{r}}^{\boldsymbol{m}} n_0(\mathbf{r},t_1)\left\{exp\left[-\alpha(\mathbf{r},t_3)d_i(\mathbf{r}) - \beta(\mathbf{r},t_3)d_i^2(\mathbf{r})\right]\right\}^{\boldsymbol{n}} exp\left[\frac{Tln(2)}{TD(\mathbf{r},t_2)}\right] d\mathbf{r}\right]$$

FDG

FMISO

FLT



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Accounting for radiation modality

$$SF(\mathrm{r}) = \prod_{i=1}^{n} exp\left[-\alpha(\mathrm{r})d_i(\mathrm{r}) - \beta(\mathrm{r})d_i^2(\mathrm{r})\right] exp\left[\frac{Tln(2)}{TD(\mathrm{r})}\right]$$

$$\alpha(\mathrm{r}) = \alpha_{photon}\, DMF_{\alpha}(L, \boldsymbol{r}, pO_2)$$

$$\beta(\mathrm{r}) = \beta_{photon}\, DMF_{\beta}(L, \boldsymbol{r}, pO_2)$$

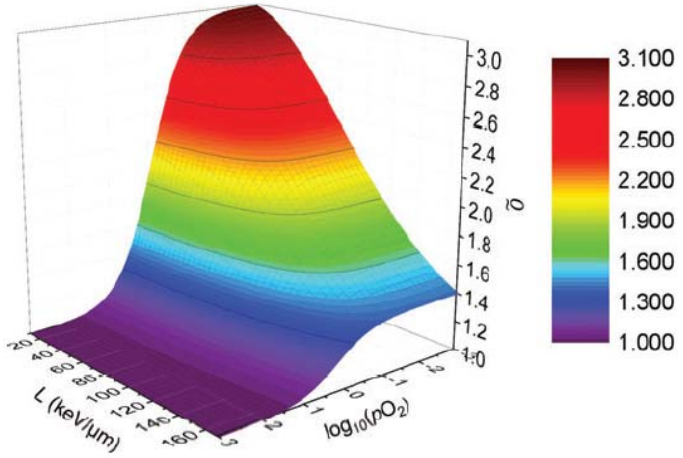

Fig. 6. The dose-modifying factor $\tilde{O}$ as a function of LET and oxygen tension.

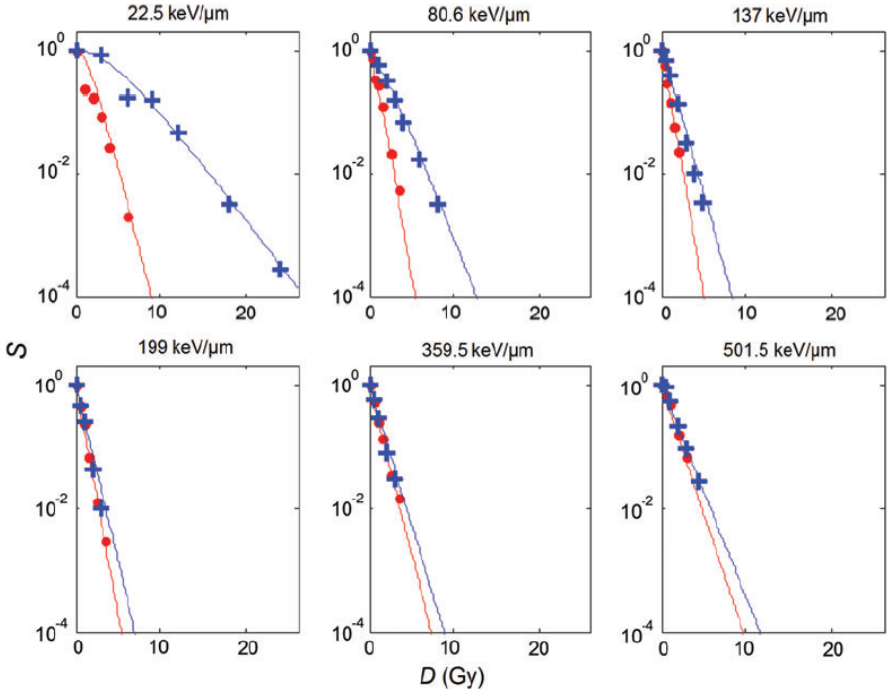

Fig. 5. Oxic (red lines) and anoxic (blue lines) cell-survival curves resulting from the fit to experimental human salivary gland tumor oxic (dots) and hypoxic (crosses) cell-survival data using the LET-parameterized RCR cell-survival model modified to take oxygenation into account. The experimental data was obtained from from Furusawa *et al* [2].

Antonovic et al (2015)

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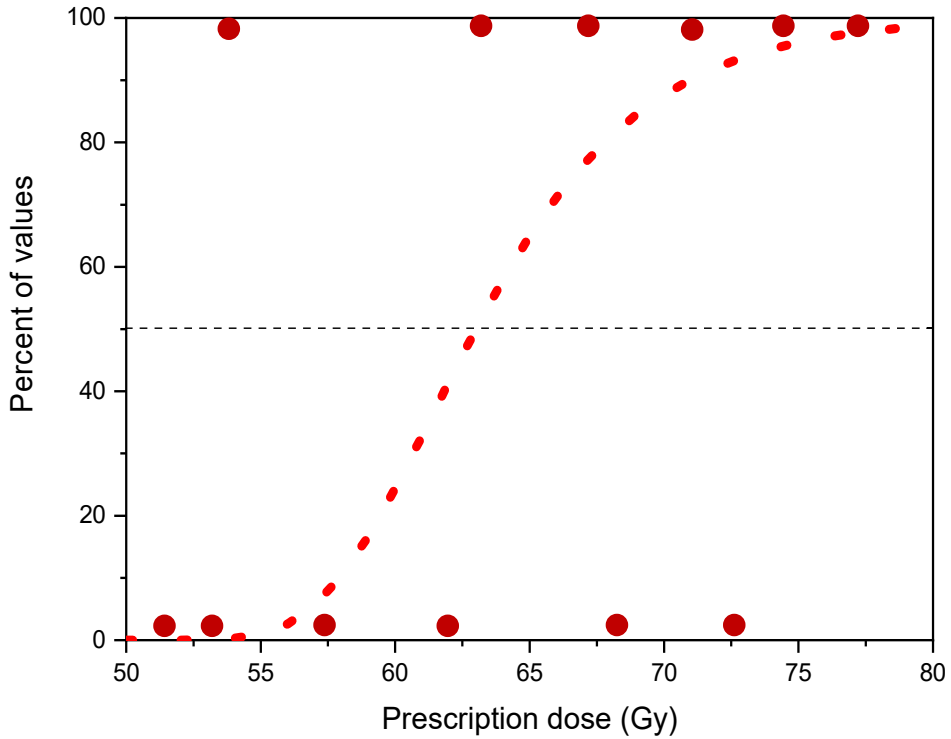
Mechanistic modelling

- It usually predicts very steep dose response curves
  - Supports the need for high homogeneity of dose distribution
  - Supports dose escalation
- Validation is difficult as predictions of response probabilities have to be materialised, usually in binary manner.
- Mechanistic model predictions might have to be reconciled with clinical outcome data and empirical modelling.

Outcome modelling

- Clinical outcome represent the aggregation of responses of individual patients in the clinical cohort.



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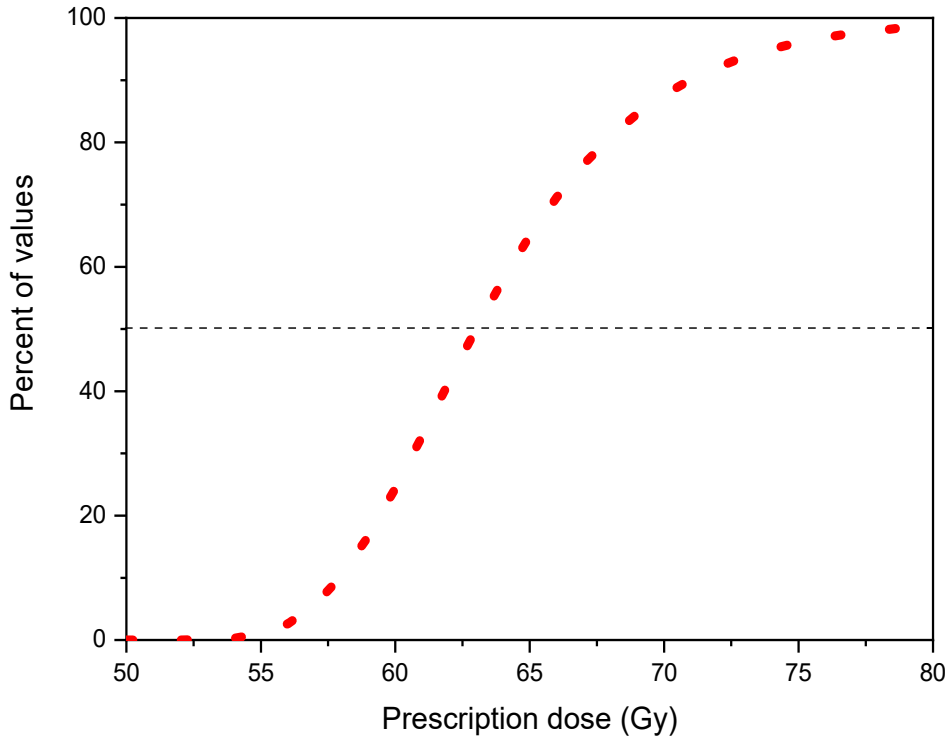
Empirical TCP modelling

- Deriving response parameters from fitting models to clinical outcome data



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Empirical TCP modelling

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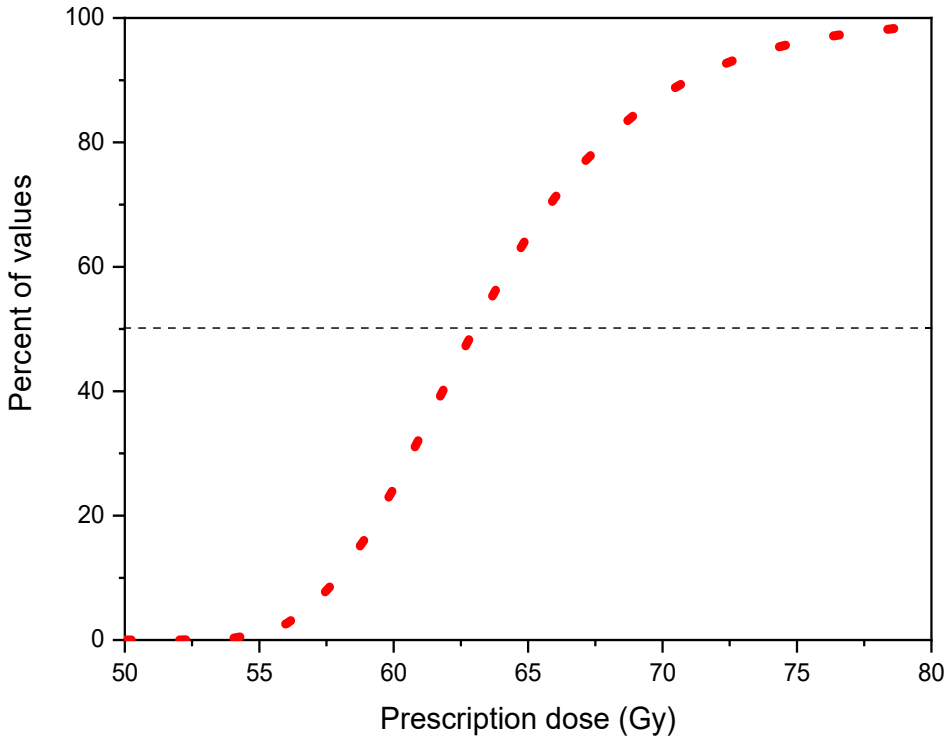

Sigmoid models are used:

(Poisson)

Logistic

Probit

etc.

Parameters may or may not have biological meaning.

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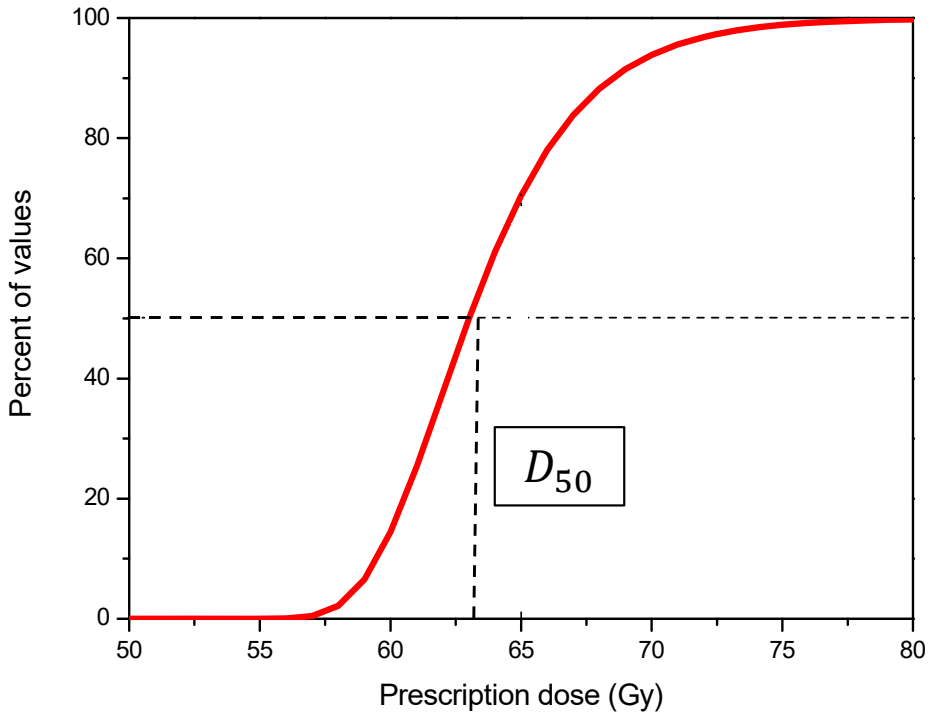
Empirical TCP modelling



Key parameters:

- D_{50}
- The slope of the TCP curve

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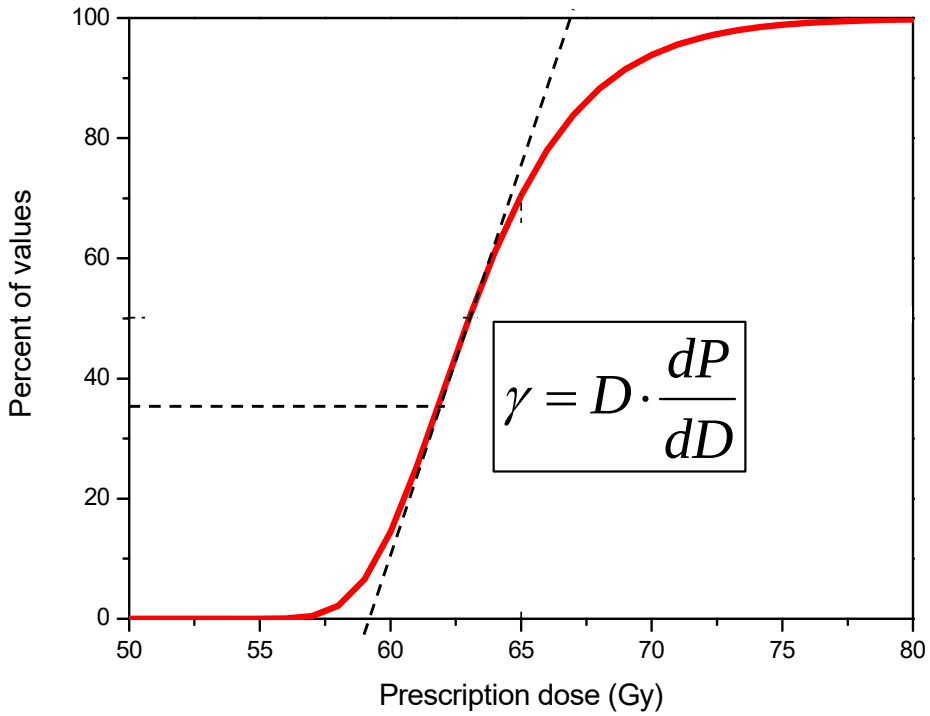
Empirical TCP modelling



Key parameters:

- D_{50}
- The slope of the TCP curve

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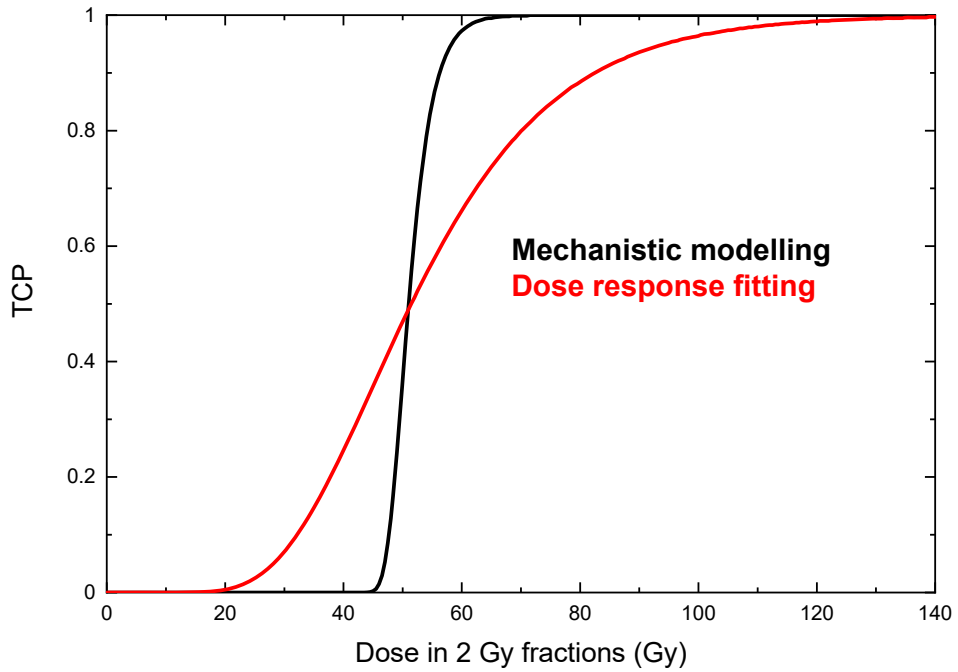
Mechanistic vs empirical modelling

- Reconciling mechanistic predictions with empirical outcome modelling.



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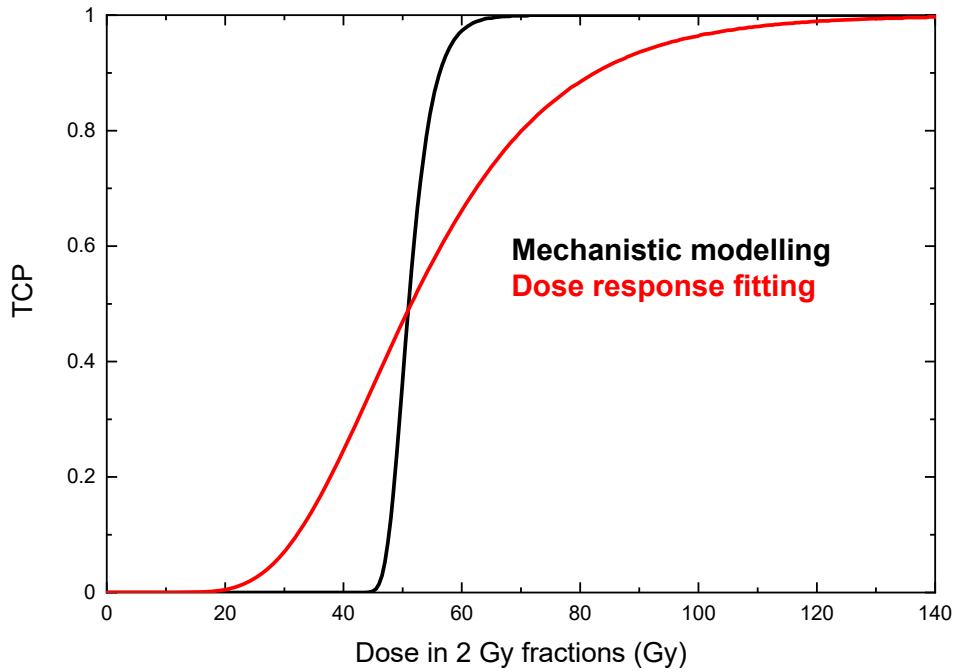
TCP modelling of clinical data

$$TCP = \exp[-N_0 exp(-\alpha D - \beta D^2)]$$



$$\gamma = \frac{ln(N_0)}{e}$$

$$\alpha = \frac{e\gamma - ln(ln2)}{D_{50}\left(1 + \frac{d}{\alpha/\beta}\right)}$$

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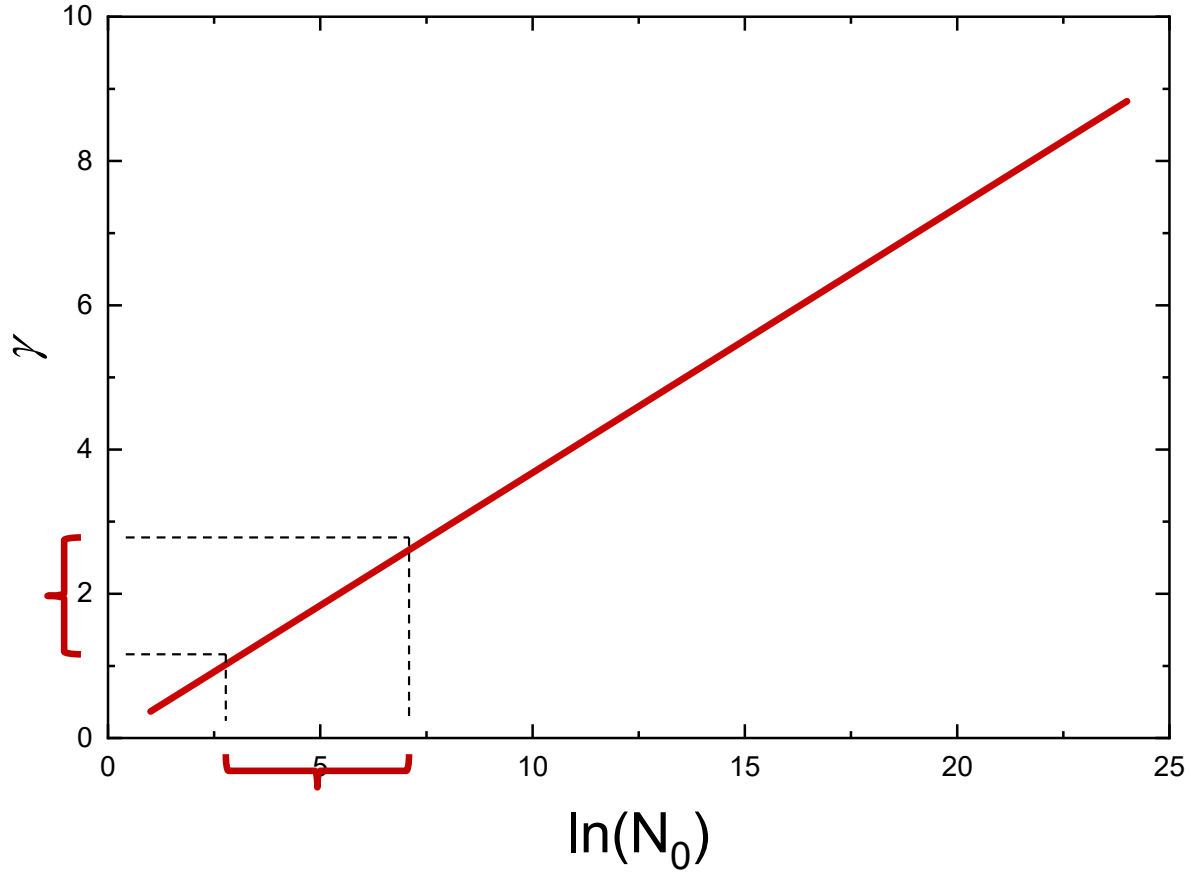
TCP modelling of clinical data



Clinically relevant values of 1.0-2.5 for *γ* are obtained only when there are extremely few tumour clonogens corresponding to $\ln(N_0)$ = 3-7

=> About 20 – 1000 clonogenic cells in the tumour?

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TCP modelling of clinical data

- Brenner and Hall (1999):

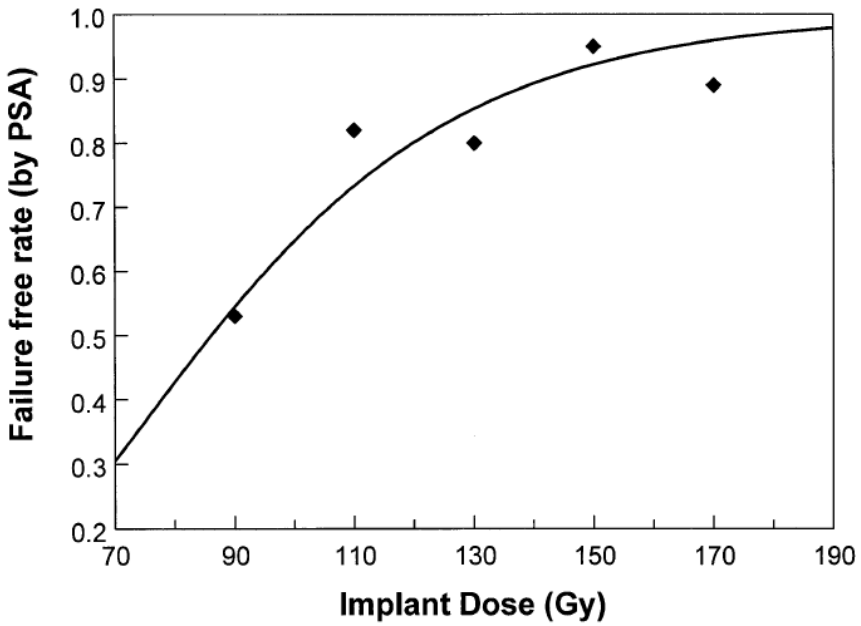

Fig. 1. Failure-free (assessed by PSA) rate at 3 years as a function of permanent implant (^{125}I) dose. Data points are from Stock *et al.* (8); the curve shows a fit to the data using Eqs. 1 and 3 with two free parameters, α and K.

- First report of a low alpha/beta for prostate cancers (1.5 Gy).
- The results were criticised for the ”clearly unbiological values of” clonogens, between 15.3 and 302, in the tumours (King and Mayo 2000).

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TCP modelling of clinical data

- Clinical outcome gives the combined responses from individuals in a population of patients.

TCP modelling of clinical data

- Clinical outcome data inherently includes inter-patient heterogeneities

- Each individual in the population represents the materialisation of a ’scenario’ regarding influence factors and their impact on the response.

TCP modelling of clinical data

- Accounting for tumour size and individual radiosensitivity

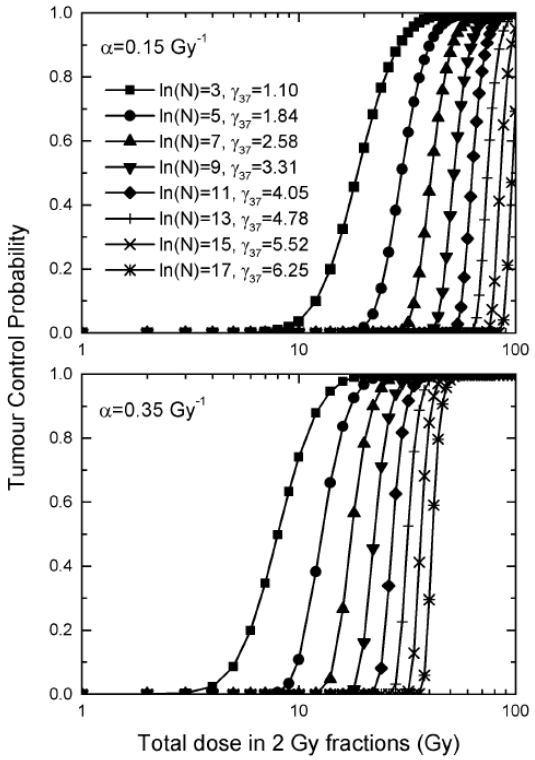

Figure 1. Calculated TCP curves for fixed α parameters and different numbers of clonogenic cells. The slope of the TCP curve and the total dose needed to achieve 37% control (D_{37}) decreases as the number of clonogens decreases.

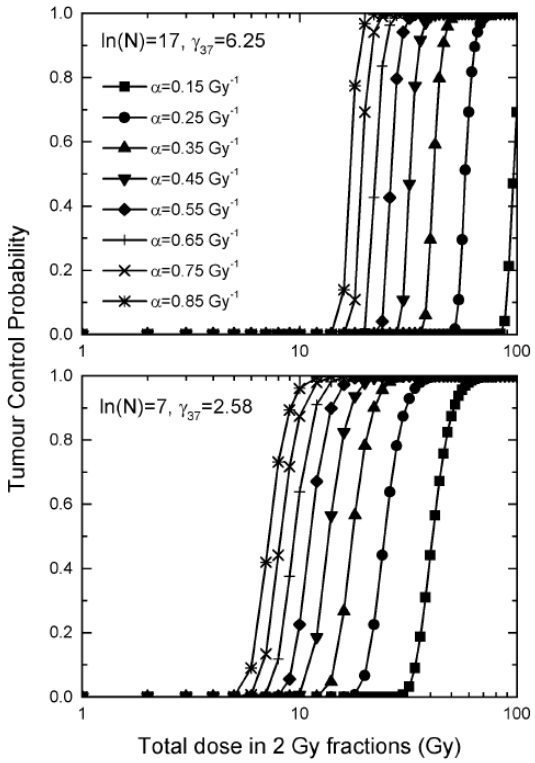

Figure 2. Calculated TCP curves for fixed numbers of clonogenic cells and different α parameters. The slope of the TCP curve is independent of the α parameter, but the total dose needed to achieve 37% control (D_{37}) is not.

Dasu et al (2003)

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TCP modelling of clinical data

- Increasing heterogeneity leads to shallower TCP curves

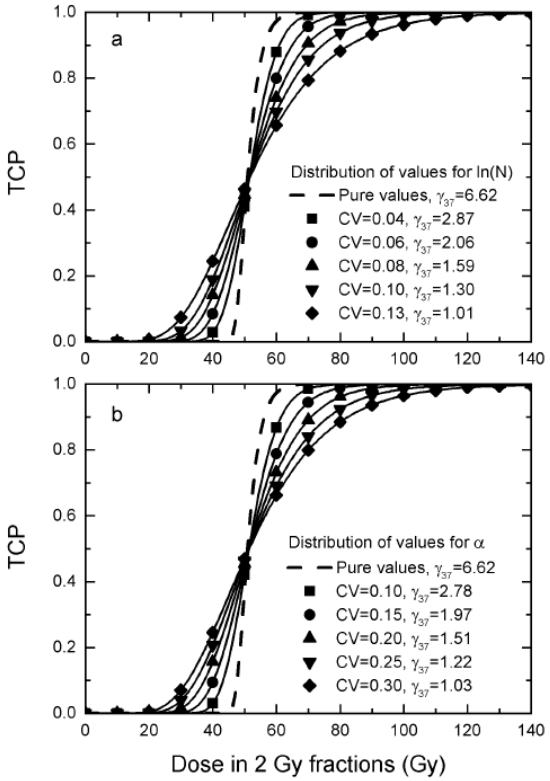

Figure 7. The influence of distributions of values. (a) TCP curves for distributions of the number of tumour clonogens. (b) TCP curves for distributions of values for α. Dashed lines—single values. Solid lines—distributions of values. As wider distributions of parameters are assumed, the TCP curves become progressively flatter.

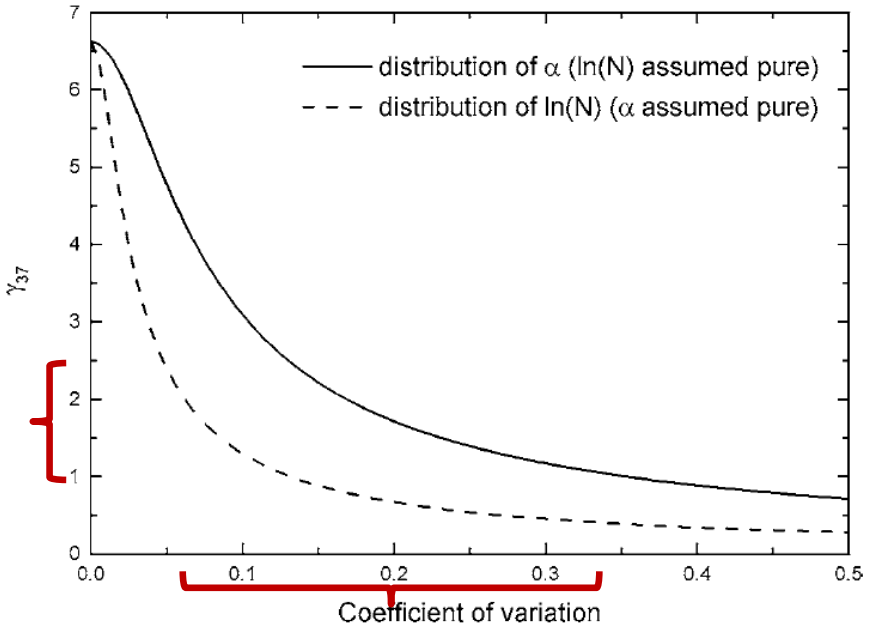

Figure 8. Relationship between γ_{37} and the width of the distribution of the parameters of the TCP curve. Reasonably wide distributions centred on biologically relevant values for the parameters yield clinically relevant values for γ_{37}.

Dasu et al (2003)

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TCP modelling of clinical data

- Assuming moderate heterogeneity leads to quite accurate TCP predictions from mechanistic models.

Table 11–1: Comparison between predicted tumor control probabilities for heterogeneous patient populations and control rates from clinical studies

Schedule	# of fx	Assumed CV		0 %	10 %	20 %	30 %	0 %	10 %	20 %	30 %	Reported TCP	Reference
		Dose per fx (Gy)	OTT (days)	Predicted TCP for small tumors (10^9 cells) (%)				Predicted TCP for large tumors (10^{10} cells) (%)					
Conventional	35	2	49	89.6	69.7	60.7	57.3	33.3	42.6	46.0	47.3	46%	Horiot et al. (1997)
EORTC 22851	45	1.6	35	99.5	93.3	79.3	71.0	95.0	77.7	65.7	60.7	59%	Horiot et al. (1997)
Conventional	33	2	46	74.5	58.9	54.6	53.1	5.2	30.9	39.5	42.9	50%	Dische et al. (1997)
CHART	36	1.5	12	69.5	57.9	54.1	52.8	2.6	24.7	35.5	40.0	54%	Dische et al. (1997)
Conventional	35	2	49	89.6	69.7	60.7	57.3	33.3	42.6	46.0	47.3	47%	Poulsen et al. (2001)
TROG	33	1.8	24	95.7	82.6	69.6	63.6	64.2	54.3	52.1	51.4	52%	Poulsen et al. (2001)
DAHANCA long	34	2	46	88.0	68.6	60.1	56.8	28.0	40.7	45.0	46.6	60%	Overgaard et al. (2003)
DAHANCA short	34	2	39	97.5	84.3	70.6	64.2	77.7	60.5	55.5	53.7	70%	Overgaard et al. (2003)
CAIR-1 short	38	1.89	38	99.5	92.8	78.6	70.4	94.8	76.9	65.1	60.3	75%	Skladowski et al. (2006)
CAIR-1 long	38	1.89	53	84.4	64.6	57.8	55.2	18.2	37.8	43.4	45.6	33%	Skladowski et al. (2006)
Conventional	20	2.55	25	62.5	53.8	51.9	51.2	0.9	22.3	34.0	39.0	51%	Cummings et al. (2007)
Hyperfractionated	40	1.45	25	81.7	65.7	58.6	55.8	13.2	32.9	40.5	43.5	59%	Cummings et al. (2007)
GORTEC 99-02	36	1.8	24	99.5	94.9	81.9	73.2	95.3	80.1	67.6	62.1	53%	Bourhis et al. (2012)

Fowler et al (2015)

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DAHANCA long	34	2	46	88.0	68.6	60.1	56.8	28.0	40.7	45.0	46.6	60%	Overgaard et al. (2003)
DAHANCA short	34	2	39	97.5	84.3	70.6	64.2	77.7	60.5	55.5	53.7	70%	Overgaard et al. (2003)
CAIR-1 short	38	1.89	38	99.5	92.8	78.6	70.4	94.8	76.9	65.1	60.3	75%	Skladowski et al. (2006)
CAIR-1 long	38	1.89	53	84.4	64.6	57.8	55.2	18.2	37.8	43.4	45.6	33%	Skladowski et al. (2006)
Conventional	20	2.55	25	62.5	53.8	51.9	51.2	0.9	22.3	34.0	39.0	51%	Cummings et al. (2007)
Hyperfractionated	40	1.45	25	81.7	65.7	58.6	55.8	13.2	32.9	40.5	43.5	59%	Cummings et al. (2007)
GORTEC 99-02	36	1.8	24	99.5	94.9	81.9	73.2	95.3	80.1	67.6	62.1	53%	Bourhis et al. (2012)

Fowler et al (2015)

TCP modelling of clinical data

- Assuming moderate heterogeneity leads to quite accurate TCP predictions from mechanistic models.

Table 11–1: Comparison between predicted tumor control probabilities for heterogeneous patient populations and control rates from clinical studies

Schedule	# of fx	Assumed CV		0 %	10 %	20 %	30 %	0 %	10 %	20 %	30 %	Reported TCP	Reference
		Dose per fx (Gy)	OTT (days)	Predicted TCP for small tumors (10^9 cells) (%)				Predicted TCP for large tumors (10^{10} cells) (%)					
Conventional	35	2	49	89.6	69.7	60.7	57.3	33.3	42.6	46.0	47.3	46%	Horiot et al. (1997)
EORTC 22851	45	1.6	35	99.5	93.3	79.3	71.0	95.0	77.7	65.7	60.7	59%	Horiot et al. (1997)
Conventional	33	2	46	74.5	58.9	54.6	53.1	5.2	30.9	39.5	42.9	50%	Dische et al. (1997)
CHART	36	1.5	12	69.5	57.9	54.1	52.8	2.6	24.7	35.5	40.0	54%	Dische et al. (1997)
Conventional	35	2	49	89.6	69.7	60.7	57.3	33.3	42.6	46.0	47.3	47%	Poulsen et al. (2001)
TROG	33	1.8	24	95.7	82.6	69.6	63.6	64.2	54.3	52.1	51.4	52%	Poulsen et al. (2001)
DAHANCA long	34	2	46	88.0	68.6	60.1	56.8	28.0	40.7	45.0	46.6	60%	Overgaard et al. (2003)
DAHANCA short	34	2	39	97.5	84.3	70.6	64.2	77.7	60.5	55.5	53.7	70%	Overgaard et al. (2003)
CAIR-1 short	38	1.89	38	99.5	92.8	78.6	70.4	94.8	76.9	65.1	60.3	75%	Skladowski et al. (2006)
CAIR-1 long	38	1.89	53	84.4	64.6	57.8	55.2	18.2	37.8	43.4	45.6	33%	Skladowski et al. (2006)
Conventional	20	2.55	25	62.5	53.8	51.9	51.2	0.9	22.3	34.0	39.0	51%	Cummings et al. (2007)
Hyperfractionated	40	1.45	25	81.7	65.7	58.6	55.8	13.2	32.9	40.5	43.5	59%	Cummings et al. (2007)
GORTEC 99-02	36	1.8	24	99.5	94.9	81.9	73.2	95.3	80.1	67.6	62.1	53%	Bourhis et al. (2012)

Fowler et al (2015)

TCP modelling of clinical data

- Deconvoluting the response of individuals from the population is not straightforward.
- The use of mechanistic or semi-mechanistic models with parameters from individual assays is required.

TCP modelling in radiotherapy

- How can modelling can be used for better radiotherapy plans?
  - Assessing the influence of various parameters on treatment outcome
  - Evaluating treatment plans
  - Optimising treatment plans

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TCP modelling in radiotherapy

- TCP modelling can be used to study the impact of individual factors:
  - Dose and beam quality
  - Intrinsic cellular sensitivity
  - Cellular proliferation
  - Density of clonogenic cells
  - Tumour microenvironment

Individualised RT

Conclusions

- TCP modelling is a powerful tool for the evaluation of treatment plan.
- It can easily accommodate intrinsic radiosensitivty as well as influencing factors in individual patients.
  - Intra-patient heterogeneities
- Can be combined with *in vitro* predictive assays and *in vivo* functional imaging for the optimisation of plans and treatments.
- Can easily account for inter-patient heterogeneities to reconcile mechanistic predictions with clinical outcome.
- Can also accommodate combination treatments.

Acknowledgements

- Iuliana Toma-Dasu

- Jack Fowler

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Thank you!

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