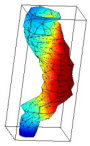
The relevance of the spatial distribution of dose for complications after prostate RT and head-and-neck RT



Florian Buettner

fbuettner.phys@gmail.com

HelmholtzZentrum münchen
German Research Center for Environmental Health

THE ROYAL MARSDEN

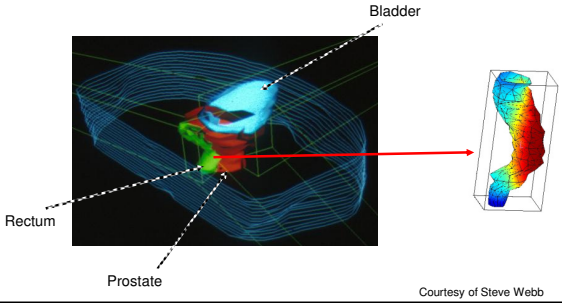
ICR
The Institute of Cancer Research

Radiotherapy and side-effects

- Challenge of radiotherapy: maximise dose to the tumour and spare healthy tissue
- Wide range of dose-distributions possible
- Which dose-distribution has the highest therapeutic ratio?
- Understand dose-response of normal tissue
- Analyse radiotherapy trials

Side-effects after prostate radiotherapy

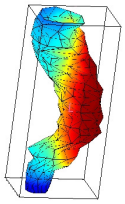
- Rectal complications because of anatomical proximity of rectum to prostate



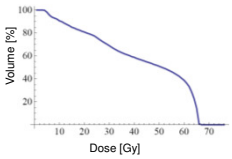
Courtesy of Steve Webb

Understanding side-effects

- Usual approach: Summarize dose distribution in dose-volume-histogram



3D dose-distribution



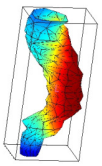
Dose-volume-histogram

A novel approach to understand side-effects

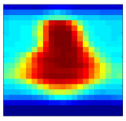
- Hypothesis: Information on spatial distribution is important
- Preferable dose patterns?
- Analyse data from prostate radiotherapy trial RT01
  - 388 prostate cancer patients
  - rectal bleeding, loose stools

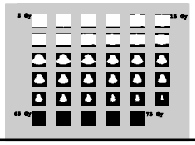
Describing the dose to the rectum

- Processing the 3D dose-distribution



3D distribution of radiation-dose

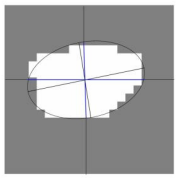




- Map dose on 2D dose-surface-map
- Extract a limited set of interpretable features
  - Describe arbitrary dose patterns
- Consider binary maps for feature extraction

Describing the dose to the rectum

- Extracting geometrical features



Typical binary image with ellipse fitted around it: lateral and longitudinal extent are shown in blue

For 35 threshold doses determine:

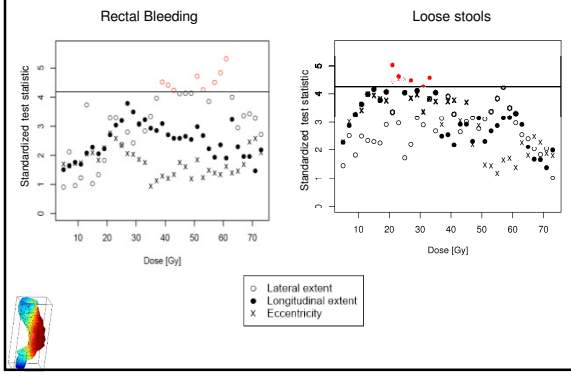
- Longitudinal extent (Irradiated length of the rectum)
- Lateral extent (Irradiated circumference of the rectum)
- Eccentricity of dose pattern
- DSH (Irradiated surface)

Statistical analysis

- Perform cut-point analysis to assess strength of correlation as well as type of relationship
  - Allows generation of spatial dose constraint
  - Threshold every variable at all possible values so that every split of the data is considered
- Quantify correlations between variables and outcomes by maximally selecting Wilcoxon rank sums:
  - Generate joint linear test statistic **T** by calculating Wilcoxon rank sum for every split
  - Standardise **T** by mean and variance
  - Take randomization to 64Gy/74Gy into account by block-wise calculations
  - Calculate significance-levels using resampling methods
  - Select maximal standardised T of each variable

Buettner *et al* 2009 PMB

Results



Validation of Results

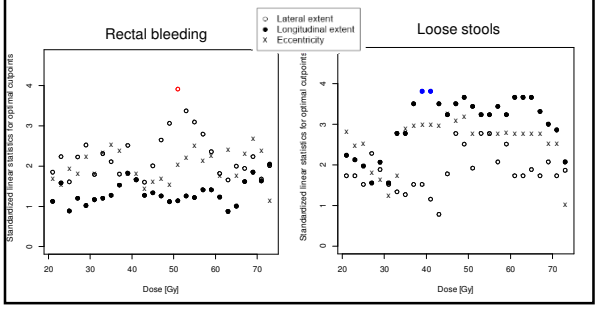
- Analyse data from independent patient cohort
- 88 patients treated in Nijmegen, Holland
- All patients treated with endorectal balloon
- Repeat statistical analysis on Nijmegen data only
- Combine RT01 patients and Nijmegen patients to establish constraint

Endorectal Balloon, photo E. van Lin

van der Geest *et al* in submission

Validation of results

- Similar trends from Nijmegen and RT01 patient cohort

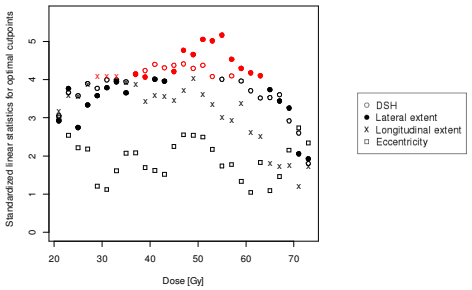


Validation of results

- Similar trends from Nijmegen and RT01 patient cohort
- Rectal bleeding: lateral extent between 50 Gy and 60 Gy most important
- Loose stools: longitudinal extent at low doses most important

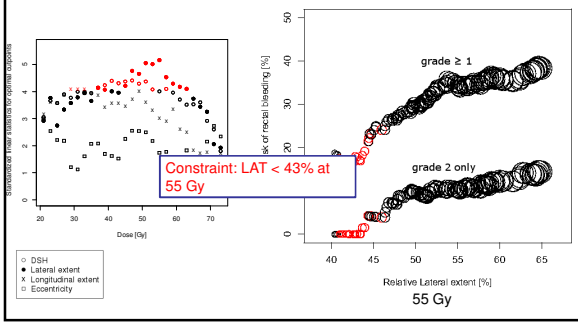
A geometric constraint for prostate RT

- Combine Nijmegen data and 74 Gy data from RT01 trial



A geometric constraint for prostate RT

- Combine Nijmegen data and 74 Gy data from RT01 trial



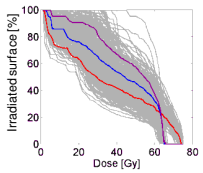
Probabilistic Models

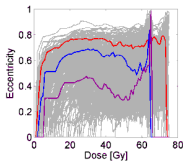
- Requirements of a normal-tissue-complication-probability model:
  - Ability to include dose and non-dose features
  - Capture interactions (non-linear model)
  - support vector machines (kernel-based machine learning algorithm)
- Dose features describing dose to the rectal wall
  - Small number of features
  - Volumetric as well as spatial features

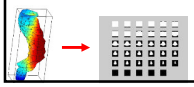
Buettner et al 2011, PMB

Description of the dose distribution

- Use dose-measure-histograms







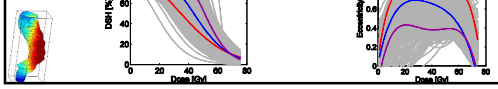
- Problems:
  - Strong correlations between the bins
  - High number of features
  - Difficult to choose suitable subset

Parameterizing the dose distribution

- Fit sigmoid function to dose-surface-histogram, dose-lateral extent-histogram and dose-longitudinal extent-histogram

$$\mathrm{M}(D) = M_{\max} - \frac{M_{\max}}{1 + a\exp(\frac{-D+b}{c})}$$

- Fit polynomial to eccentricity
- Low dimensional description of the dose-distribution



Predictive power of parameterized dose distribution

- Quantify predictive power by 10-fold cross-validation and AUC using support vector machines

Rectal Bleeding

	AUC
LAT[a]	0.66
LAT[b]	0.65
LONG,LAT, DSH and ECC[a]	0.64
DVH[a]	0.59
DVH[b]	0.59

Loose Stools

	AUC
LONG[a]	0.58
LONG,LAT, DSH and ECC[a]	0.63
LONG and ECC[a]	0.61
DSH[a]	0.60
DVH[a]	0.61
DVH[b]	0.59

[a] Parameterized representation
[b] Conventional representation using bins

External validation

- Generate NTCP model based on RT01 patients (74 Gy only)
- Calculate NTCPs of Nijmegen patients and determine AUCs

Model	AUC RT01	AUC Nijmegen
Lateral extent (parameterised)	0.69	0.63
DSH (bins)	0.58	0.53
LKB (QUANTEC)	0.58	--
Cluster model (Tucker et al)	0.59	0.51

Rectal bleeding

Inside the black box

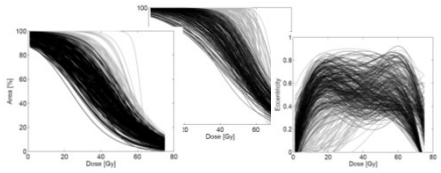
- Discovering beneficial 3D dose-patterns
- Rank patients according to their NTCP
- Extract rules for patients in the bottom of the ranking (low NTCP)
  - Rules with broad coverage and sharp differentiations
  - Quantify by leverage measure

$$R : \alpha \in [\alpha_1, \alpha_2] \& \beta \in [\beta_1, \beta_2] \& \gamma \in [\gamma_1, \gamma_2] \rightarrow \text{low risk}$$

Beneficial dose-patterns

- Identify rules for rectal bleeding and loose

	Leverage	Rule
Rectal bleeding	0.25	$\text{LAT}_a \in [-6.2, 40.1]$
Global toxicity score	0.17	$\text{DSH}_b \in [-6.1, 17.9]$
Loose Stools	0.22	$\text{ECC}_3 \in [-0.008, -0.001]$ AND $\text{DSH}_b \in [-16.3, 28.9]$

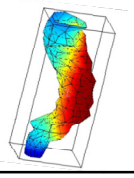


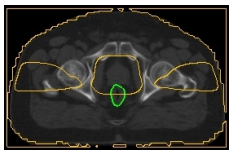
Even more possibilities to deal with spatial information…

- Use set of hybrid constrains comprising volumetric and spatial information: Buettner *et al* 2010 Med Phys
- Consider dose to anal canal separately to limit loss of subjective sphincter control: Buettner *et al* 2012 R&O
- Use endorectal devices to alter shape of the dose distribution: Buettner *et al* Poster T-255

Conclusion (rectal complications)

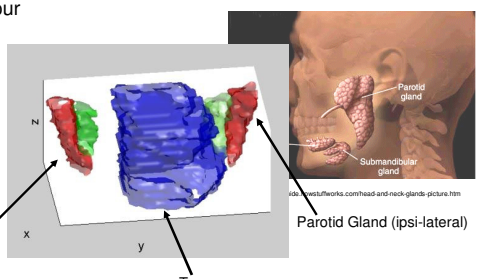
- Shape of the dose-distribution on the rectal surface is important
- Different aspects are important for different endpoints
- Integrate new knowledge in treatment-planning process
  - Constraints (Lateral extent at 55 Gy)
  - NTCP model





Side-effects after head and neck radiotherapy

- Reduced salivary flow and dry mouth (xerostomia) because of anatomical proximity of salivary glands to tumour



Motivation

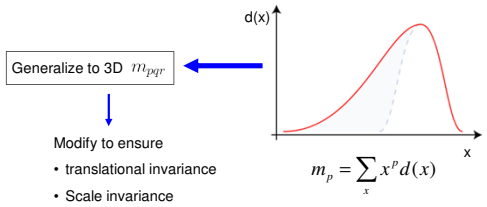
- Dose to parotid glands can result in xerostomia
- Standard NTCP models based on mean dose only
- Experiments in animal models suggest that spatial information may be important
- Generate NTCP model allowing for regional variations of radiosensitivity of parotid gland
- Analyse data from parotid-sparing PARSPORT trial:
  - 36 IMRT patients
  - Grade 2 Xerostomia after 12 months (LENTSOM)

van Luijk et. al. 2009 Bath and shower effects in the rat parotid gland explain increased relative risk of parotid gland dysfunction after IMRT, IJROBP, 74(4), 1002-1005

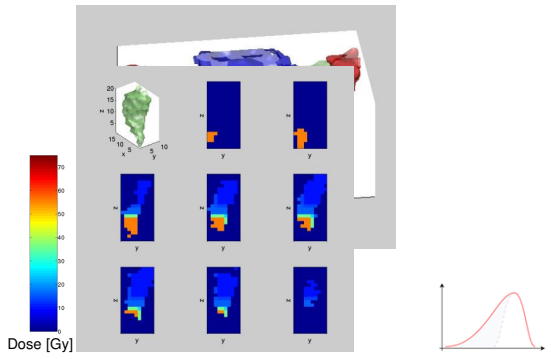
Describing the 3D dose distribution

- Extract a limited set of interpretable features
- Use scale-invariant statistical moments
  - Characterize the layout of voxels
    - Spread (p=2)
    - Skewness (p=3)

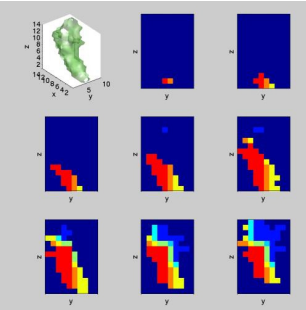
1D Example



m_{003} : Skewness in z-direction



m_{011}: Dose-concentration in cranial-lateral part of parotid



Dose response models

- Model xerostomia using multivariate logistic regression
- High number of potential predictors
  - m_{pqr} ipsi-lateral gland
  - m_{pqr} contra-lateral gland
  - m_{pqr} for deep and superficial lobes
  - Volume of the glands
  - Mean dose to submandibular gland
  - Surgical removal of ipsi-lateral submandibular gland
  - Clinical factors: gender, age, site, chemotherapy, hypertension
- Use variable selection algorithm to avoid over-fitting and over-complex models

Bayesian variable selection

- Use Bayesian framework for model-selection
  - View model as whole and treat number of variables as additional parameter
- Use Reversible Jump Markov Chain Monte Carlo algorithm
  - Calculate probability of being the best model for all potential models given the data
  - Determine marginal probabilities that a variable should be in the model

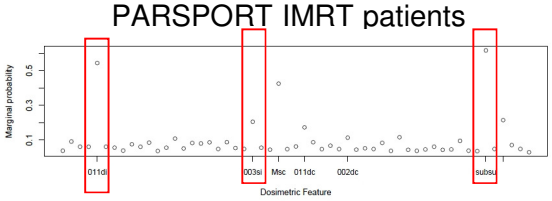
Lunn *et al.*,2006, *Genetic Epidemiology*
Lunn *et al.*,2009, *Statistics and Computing*

Evaluate dose response models

- Logistic regression based on predictors chosen by variable selection algorithm
- Model xerostomia
- Evaluate models by leave-one-out cross-validation and ROC analysis
- Compare performance to several mean-dose models
- Validate models using independent data

Buettner *et al* 2012 Radiother Oncol

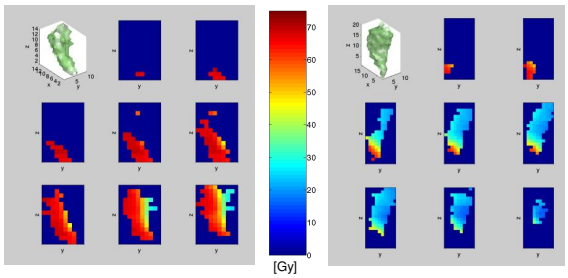
PARSPORT IMRT patients



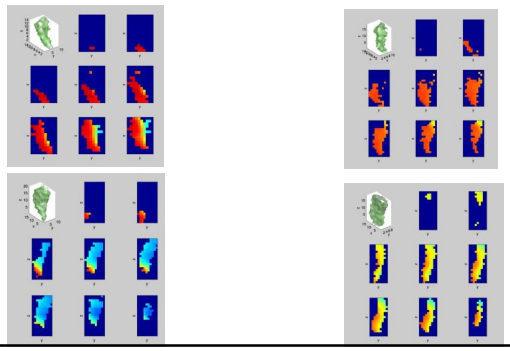
Predictive power of models

Model ID	Predictors	AUC
1	MsComb	0.70
2	Msc	0.69
3	MdComb	0.5
4	MWhole	0.66
5	$\eta_{011}di$, $\eta_{003}si$, subsu	0.88
6	$\eta_{011}di$, subsu	0.85
7	$\eta_{011}di$, $\eta_{003}si$	0.81
8	$\eta_{020}c$, $\eta_{003}c$, subsu	0.84

Beneficial dose patterns for IMRT patients



Beneficial dose patterns for IMRT patients



Validation of NTCP model

- Fit regression coefficients using PARSPORT data
- Use two independent patient cohorts to calculate NTCPs and AUCs
  - 19 Nasopharynx patients treated at RMH
  - 29 patients from PARSPORT II study treated at RMH

Independent validation

	Spatial model	Mean whole	Mean contra	Mean sup comb
Nasopharynx	0.80	0.50	0.56	0.50
PARSPORT II	0.69	0.54	0.39	0.54

RTOG

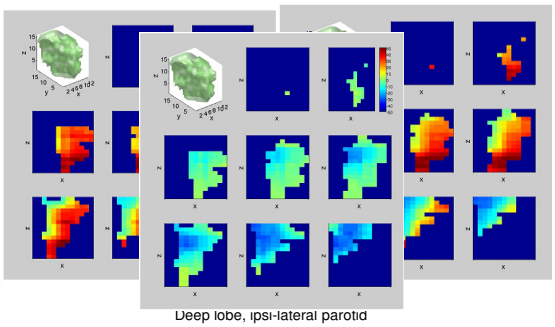
	Spatial model	Mean whole	Mean contra	Mean sup comb
PARSPORT	0.77	0.63	0.68	0.64
Nasopharynx	0.81	0.57	0.59	0.57
PARSPORT II	0.96	0.36	0.19	0.48

Outlook: morphological optimisation

- In-house TPS (AutoBeam) can do biological optimisation
- Implement morphological NTCP model
- Include additional objective in objective function (minimise morphological NTCP)
- Generate treatment plans for head and neck patients with and without morphological optimisation

Does it work?

- Test with 3 patients with midline tumours
- For 2 patients standard plans resulted in very low NTCPs (< 3%)
- Morphological optimisation resulted in little change
- For the 3rd patient NTCP was reduced from 14.5% to 8.9%



Deep lobe, ipsi-lateral parotid

Conclusions (parotid)

- Statistical moments are a good morphometric descriptor
- Dose-response models taking spatial information into account are consistently better
- Best models: Take shape and information on removal of submandibular gland into account

Summary

- Spatial distribution of dose is relevant for complications after RT
  - For different organs
  - A variety of clinically relevant endpoints
- Beneficial dose patterns could be identified
- Tools allowing integration into clinical practice
  - Spatial constraints (rectum: lateral extent at 55 Gy < 45%)
  - NTCP models

Acknowledgements

- Sarah Gulliford, Mike Partridge and Steve Webb
- Jervoise Andreyev, David Dearnaley, Aisha Miah, Chris Nutting, Kevin Harrington, Emma Alexander, Annelies van der Geest, Emile van Lin
- Matt Sydes, Emma Hall

MRC Clinical Trials Unit

Contact me: fbuettner.phys@gmail.com

Validation of results

- Similar trends from Nijmegen and RT01 patient cohort