YITP International Workshop: Biological & Medical Science based on Physics (Nov.5-7) 14:00-15:00, Nov. 7, 2015

# Niche researches between computational image analysis and radiotherapy physics

#### Hidetaka Arimura, PhD

#### Professor, Computer-aided Diagnosis and Radiotherapy Laboratory

Division of Medical Quantum Science Department of Health Sciences Faculty of Medical Sciences Kyushu University

### Acknowledgements

My deep gratitude to :

All Organizers, especially Dr. Akihiro Haga (Unversity of Tokyo Hospital) and Dr. Jun'ichi Kotoku (Teikyo University)

My many co-researchers

My special thanks to :

All members of my laboratory

YITP International Workshop: Biological & Medical Science based on Physics (Nov.5-7) 14:00-15:00, Nov. 7, 2015

# Niche researches between computational image analysis and radiotherapy physics

#### Hidetaka N. Arimura

#### Computer-aided Diagnosis and Radiotherapy Laboratory

Division of Medical Quantum Science Department of Health Sciences Faculty of Medical Sciences Kyushu University

### What is medical physics?



## My policy

Knowing something about everything is much better than everything about something.

Multifaceted knowledge is best!

(一つの事柄についてすべてを知るよりも、すべての事柄に ついて何らかのことを知るほうがずっとよい.知識の多面 性が最上である.)(Blaise Pascal)

### What is radiation therapy?

# What are benefits of radiation therapy with "invisible knife"?

- Low-impact treatment without surgically cutting patient bodies, which can result in higher quality of life (QOL) of patients
- Considerably important for Japan, which have been rapidly moving toward an aging society (% of elderly people of 65 years old and over in Japan: around 23% in 2011\*)
- Preservation of organs' functions and reduction of the physical burden of patients with "invisible knife", particularly elderly patients (breast cancer, prostate cancer, tongue cancer, etc.)
  - \*Ministry of Internal Affairs and Communications (MIC). (2011) http://www.stat.go.jp/data/jinsui/pdf/201102.pdf.

# How are physical energies of "invisible knife" radiation



### **Goal of radiation therapy**

To deliver as high dose as possible to tumors (cancer or targets), and cause as little damage as possible to organs at risk (OAR\*) and normal tissues



\*OAR: organs whose radiation sensitivity may significantly influence treatment planning and/or prescribed dose

#### How is the radiotherapy procedure?



(1) Diagnosis



(2) CT imaging



(3) Radiation treatment planning (RTP)



10(4) Patient Setup



(5) Treatment in a fraction

Computational image analysis play indispensable roles in all aspects of radiation therapy.

### A nature on what medical physics is





## Because we have the uncertainties of patient positions due to "Uncertainty Principal"?

In 1927, Dr. Werner Heisenberg said, "The more precisely the momentum of a particle is determined, the less precisely the position can be known, and vice versa." (Uncertainty Principal)

$$\sigma_x \sigma_p \ge \frac{\hbar}{2}$$

 $\sigma_x$ : uncertainties (standard deviation) of position

 $\sigma_p$ : uncertainties of momentum

 $\hbar$ : Planck's constant/2 $\pi$ 

# Definition of target volumes in radiotherapy with taking into account the uncertainties

Margin to guarantee a sufficient dose to a target to take into account the uncertainties



**GTV: gross tumor volume**, defined as visible tumor volume in images

**CTV: clinical target volume**, defined as GTV + subclinical/invisible invasion

**ITV: internal target volume**, defined as CTV + IM (internal margin for organ motion)

**PTV: planning target volume**, defined as ITV + SM (setup margin for setup error)

### Several unavoidable uncertainties!

- Intra- and inter-observer variability of target delineations (drawing outlines of targets)
- Intra- and inter-fractional variation of the organ position (organ motion)
- Intra- and inter-observer variability of treatment plans
- Intra-fractional organ motion during treatment time



Safety margin (i.e, planning target volume (PTV) margin: geometrical margin to guarantee an enough dose to the target)

### Our challenges : To minimize these uncertainties

## That's why you need imaging techniques! OAR **Patient body** Target OAR

Why we need imaging techniques in RT:

- Recognition of regions of a target and OAR
- Understanding of relationship between dose distribution and organs of interests (tumor and OAR)

### Imaging on a treatment machine (linac)



# Visualization of target region during treatment time by using an EPID

**EPID : electronic portal imaging device** 

Therapeutic xray beam with higher energies (around 1MeV - )



### Niche researches in my lab



## Niche #1

## Computational anatomy

Automated determination of PTV margin

## We have not taken into account shape variations in determination of PTV margins

- Only target translations were considered for determination of PTV margins with respect to organ motion.
- We assumed that shape variations of CTV should be taken into account for determination of the PTV margins.



# A point computational anatomy in one dimensional space



a: A vector of a point anatomy

 $\mathbf{q} = (x)$ : A position vector of a point anatomy in one dimensional (1D) space

# A point computational anatomy with uncertainties in 1D space



#### A target of each patient is dealt with as a 3D vector of "a point" target (tumor) in radiation therapy



## M. van Herk said that 95% of a prescribed dose should cover 90% of position variations in all point CTVs



van Herk's safety margin model

PTV margin =  $2.5\sigma_s + 0.7\sigma_r$ 

- $\sigma_s$ : Quadratic sum of SD\* of all systematic errors
- $\sigma_r$  : Quadratic sum of SD of all random errors
- \*SD: Standard deviation

Fig. 3 in a paper of M. van Herk, et al. Red Journal, Vol. 47, No. 4, pp. 1121–1135, 2000

### **Computational anatomy with three points**



 $a = (q_1, q_2, q_3)^T$  $= (x_1, y_1, x_2, y_2, x_3, y_3)^T$ 

**a**: Vector of an anatomy consisting of three points

 $\mathbf{q}_i = (x_i, y_i)$ : 2D-space position vector (row vector) of an anatomy

### **Computational anatomy in 6D space**



Computational anatomy with a statistical model in multidimensional space

Each point on an anatomical shape may change by patient and/or fraction.



# **Computational anatomy with uncertainties in 6D space**



### Covariance matrix V and eigenvectors $e_i$

Covariance matrix for  $\mathbf{a}_{i} = (x_{1i}, x_{2i}, x_{3i}, y_{1i}, y_{2i}, y_{3i})^{T}$  is



V is  $M \times N$  matrix.  $x_i = (x_{1i} \cdots x_{\alpha i} \cdots x_{Mi})^T$  *i*: Patient number,  $1 \le i \le N$ N: Number of patients  $\alpha$ : Point number  $1 \le \alpha \le M$ M: Number of points

31

Eigenvectors,  $e_1, e_2, \dots, e_N$ , are calculated from this covariance matrix by a singular value decomposition (SVD).

# Statistical computational anatomy in multidimensional space

Computational anatomies may be useful for developing mathematical models with uncertainties <u>to predict something</u> <u>related to anatomy in radiotherapy such as organ translations</u> <u>and/or organ deformations</u> by patient and/or fraction.



# Definition of CTVs for prostate cancer radiation therapy

Risk group	PSA*	Gleason score	TNM	Definition of CTV	
Low risk	≤10	≤6	T1a - T2a	Prostate	
Intermediate risk	10.1 - 20	7	T2b	Prostate+Seminal vesicles 1cm	
High risk	20<	8 - 10	T2c -	Prostate+Seminal vesicles 2cm	





Intermediate-risk CTV



High-risk CTV

\*PSA: Prostate specific antigen/

## How to determine PTV margins including shape variations of CTVs





\*DICOM-RT: Digital imaging communications in medicine for radiation therapy \*\*SD: Standard deviation

### **Calculation of PTV margins**

Anisotropic PTV margins in three directions [LR(x), AP(y), SI(z)] were calculated by using a Yoda's PTV margin model\*. The PTV margin in x direction is shown below:

PTV margin 
$$(x) = 2.1\sigma_s(x) + 0.7\sigma_r(x)$$

$$\sigma_s(x) = \sqrt{\frac{1}{N} \sum_{i=0}^{N} \left( m_{ss}(x,i) - \overline{m_{ss}(x)} \right)^2} \qquad \sigma_r(x) = \sqrt{\sigma_{rs}^2(x) + \sigma_{rf}^2(x)}$$

 $\sigma_s(x)$ :Square root of quadratic sum of SD of all systematic errors $\sigma_r(x)$ :Square root of quadratic sum of SD of all random errors $\underline{m}_{ss}(x,i)$ :Systematic error vector of patient setup for *i*-th patient $\overline{m}_{ss}(x)$ :Mean systematic error vector of patient setup for all patients $\sigma_{rf}(x)$ :SD of random error for interfractional shape variation $\sigma_{rs}(x)$ :SD of random error of patient setupN:Number of patients

## How to obtain interfractional shape variations (Deviation of an organ's surface deformation)

Point distributions of all fractions (j=1 to M) for all patients (i=1 to N)







 $\boldsymbol{V}_{\boldsymbol{i}} = \frac{1}{M} \sum_{j=1}^{M} \boldsymbol{q}'_{ij} \boldsymbol{q}'_{ij}^{T}$ 

$$\sigma_{rf}(x) = \sqrt{\frac{1}{N} \sum_{i=0}^{N} \sigma_{rf}^{2}} (x, i)$$

$$\sigma_{rf}(x,i) = \sqrt{\frac{1}{P} \sum_{k=0}^{P} \sigma_{rf}^{2}} (x,i,k)$$

CTV surface position vector:

$$\boldsymbol{q}_{ij} = (x_{ij1}, \cdots, x_{ijP}, y_{ij1}, \cdots, y_{ijP}, z_{ij1}, \cdots, z_{ijP})^T$$
$$\boldsymbol{q}'_{ij} = \boldsymbol{q}_{ij} - \overline{\boldsymbol{q}}_i$$

No. of points on CTV surface : P

### **Computational approach for determination of PTV margins based on statistical shape analysis**



**Figure 3** An illustration of local SDs for shape variations projected on the surface of reference CTV for case No.1. (a), (b), and (c) are anterior-posterior view and (d), (e), and (f) are posterior-anterior view of low-risk, Intermediate-risk, high-risk CTV.

#### Shibayama Y, et al. AAPM 2015

## Niche #2

Principal component analysis

Inter-observer variation for tumor contouring

## Intra- and inter-observer variability of target delineations (or drawing contours)



Low-risk CTV





**High-risk CTV** 

Statistical shape modeling @ radiation treatment planning

Modeling of interobserver variations of CTV regions using a principal component analysis (PCA) for prostate cancer radiotherapy

**Modeling of interobserver variations of CTV** Shibayama S, Arimura H, et al. CARS 2014



Point distribution model

# What is a principal component analysis (PCA)?

Fourier series expansion (linear combination of cos and/or sin waves, which are orthogonal to each other like orthogonal vectors)



Principal component analysis (or Karhunen-Loève transform)



### What is the mathematical meaning of PCA?

$$J = \frac{1}{2} \| \boldsymbol{x} - (c_1 \boldsymbol{e}_1 + c_2 \boldsymbol{e}_2 + \dots + c_N \boldsymbol{e}_N) \|^2 \to \min$$

Take the derivative of J except for  $c_i$ 

$$\frac{\partial J}{\partial c_i} = \frac{1}{2} \frac{\partial J}{\partial c_i} \left( \mathbf{x} - \sum_{j=1}^n c_j \mathbf{e}_j, \mathbf{x} - \sum_{k=1}^n c_k \mathbf{e}_k \right) = \frac{\partial J}{\partial c_i} = c_i - (\mathbf{x}, \mathbf{e}_i)$$

 $\frac{s}{\partial c_i} = c_i - (\boldsymbol{x}, \boldsymbol{e}_i)$ 

 $c_i = \boldsymbol{e}_i^{\mathrm{T}} \left( \boldsymbol{q} - \overline{\boldsymbol{q}} \right)$ 

Therefor, coefficient vector **b** is

$$\boldsymbol{c} = \boldsymbol{U}^{\mathrm{T}} \left( \boldsymbol{q} - \overline{\boldsymbol{q}} \right)$$



$$\widehat{\boldsymbol{x}} = c_1 \boldsymbol{e}_1 + c_2 \boldsymbol{e}_2 + \dots + c_i \boldsymbol{e}_i + \dots + c_N \boldsymbol{e}_N$$

$$\boldsymbol{c} = (c_1 \ c_2 \ \cdots \ c_N)^{\mathrm{T}}$$
$$\boldsymbol{U} = (\boldsymbol{e}_1 \ \boldsymbol{e}_2 \ \cdots \ \boldsymbol{e}_N)$$

### Statistical computational anatomy

Statistical computational anatomy

a = m + Uc

- $= \boldsymbol{m} + c_1 \boldsymbol{e_1} + c_2 \boldsymbol{e_2} + \dots + c_N \boldsymbol{e_N}$
- Coefficient vector c
   for an unknwn anatomy

 $c = \mathbf{U}^{\mathrm{T}} (a' - m)$ 

a': an unknown anatomy

**a** : Arbitrary computational anatomy **m** : Mean CTV *N* : Number of eigenmodes  $\mathbf{c} = (c_1 \ c_2 \ \cdots \ c_N)^T$   $c_i$ : Coefficient  $\mathbf{U} = (\mathbf{e}_1 \ \mathbf{e}_2 \ \cdots \ \mathbf{e}_N)$ *i*: Eigenmode number

## Statistical CTV model of a high-risk group with respect to inter-observer variation of contours

Shape variations of statistical CTV model produced by the first and second largest modes.



45

## Niche #3

### Machine Learning

#### Automated contouring of tumor regions

#### Automated delineation framework of lung tumor regions using three types of images



FDG\*-PET image (annihilation radiation imaging)

> \*2-deoxy-2-[fluorine-18] fluoro-D-glucose

Arimura H, et al. Computational Intelligence in Biomedical Imaging, Springer Science+Business Media New York, Springer, 2013.

## SUV showing metabolic activities of cells including tumor cells

The SUV was calculated as a ratio of the radioactivity concentration of tissue at one time point to the injected dose of radioactivity concentration at that time point, divided by the body weight [*J Nucl Med* 2009;**50**(Suppl 1):11S-20S]:



$$SUV = \frac{C(kBq/ml)}{D(MBq)/W(kg)}$$

C : radioactivity concentration in kBq/ml obtained from the pixel value in the PET image multiplied by a cross calibration factor

*D* : injected dose of 18-FDG administered in MBq (decay corrected)

*W*: body weight of a patient in kilograms

#### Voxel-based image features obtained from multimodalities



$$f(x, y, z) = ax + by + cz + d$$

$$G = \sqrt{\left(\frac{\partial f}{\partial x}\right)^2 + \left(\frac{\partial f}{\partial y}\right)^2 + \left(\frac{\partial f}{\partial z}\right)^2} = \sqrt{a^2 + b^2 + c^2}$$

#### Multidimensional space of image features



50

#### How to classify objective data from all data



## Determination of a linear or non-linear discrimination function to classify objective data from all data

#### **Outputs of a machine learning system**



## Niche #4

Active contour model based on analytical mechanics

## Estimation of tumor contours

# Our basic idea for segmentation of lung tumors



\*Jin Z, Arimura H, et al. Journal of Radiation Research 2014

## What is a level set method? Ans. Active contour model



Definition of a curve:  $\mathbf{r}(t) = (x(t), y(t))$ 

This curve satisfies :  $\phi(\mathbf{r}(t), t) = 0$ 

By chain rule:  

$$\frac{\partial \phi(\boldsymbol{r}(t),t)}{\partial t} + \frac{\partial \phi(\boldsymbol{r}(t),t)}{\partial \boldsymbol{r}(t)} \frac{d\boldsymbol{r}(t)}{dt} = 0$$

Finally, the level set equation is obtained as a partial differential equation:

$$\frac{\partial \phi(\boldsymbol{r}(t), t)}{\partial t} + F |\nabla \phi(\boldsymbol{r}(t), t)| = 0$$

## What is the meaning of solving the level set equation?

Level set equation:

$$\frac{\partial \phi(\boldsymbol{r}(t), t)}{\partial t} + F |\nabla \phi(\boldsymbol{r}(t), t)| = 0$$

We can transform this equation as a Hamilton-Jacobi equation, which is equivalent to the Euler-Lagrange equation:

$$\frac{\partial \phi(\boldsymbol{r}(t),t)}{\partial t} + H(F,\phi(\boldsymbol{r}(t),t),t) = 0$$

where  $H(F, \phi(\mathbf{r}(t), t), t) = F |\nabla \phi(\mathbf{r}(t), t)|$ , which is considered as a Hamiltonian

Solving (Integration) of a Hamilton-Jacobi equation of a contour means the prediction of the contour with a minimum energy (i.e., stable contour) from the analytical mechanics standpoint.

### Principal of stationary action (least action)

The trajectory taken by an object between times  $t_1$  and  $t_2$  is the one in which the action is minimized.



57

Stationary action :  $\delta I = 0$ 

Action (integral of Lagrangian):  $I(\mathbf{r}) = \int_{t_1}^{t_2} L(t, \mathbf{r}(t), \mathbf{r}'(t)) dt$ 

Principal of Stationary Action = Variational Principal

Brachistochrone curve : curve of shortest path in time

### Optimum contour selection (OCS) method: searching for "global" minimum of mean of speed function





Initial contour

Contours during processing









Contours during processing

## Comparison in various tumors between results of proposed method and conventional method



#### Case 4





- **GTV** contours determined by radiation oncologists (red line)
  - **Estimated GTV contours (blue line)**
- **PM : Proposed method**
- **CM : Conventional method**

## Niche #5

#### **Similar cases**

## Treatment planning variability

## Variability of radiation treatment plans in stereotactic body radiation therapy (SBRT)

- Multiple (5-10) beams in coplanar and non-coplanar directions
- Highly conformal doses to tumors while minimizing doses to surrounding normal tissues
- Beam arrangements, which are manually determined by treatment planners
  - ✓ Reduce planning variation
  - ✓ Time-consuming
  - ✓ Difficult for less-experienced treatment planners



# Similar-case based treatment planning system



#### Feasibility of similar cases (Magome T, JRR 2013;54:569 BioMed Res. Int. 2013, SPIE 2014; 9039)



## How to determine beam directions based on similar cases



Beam directions of the objective case were automatically determined by registration of the similar case with the objective case.

### Five similar-case-based beam arrangements



## Comparison between original plans and optimized similar-case-based plans

	Original plan	Optimized similar- case-based plan	P value
D95 (Gy)	$45.5 \pm 0.47$	$46.0 \pm 0.60$	0.029
Homogeneity index	1.13 ± 0.03	1.13 ± 0.04	0.643
Conformity index	1.70 ± 0.15	1.72 ± 0.17	0.376
TCP (%)	$96.0 \pm 0.27$	96.1 ± 0.30	0.084
V5 (%)	$16.0 \pm 6.30$	14.7 ± 5.43	0.066
V10 (%)	9.96 ± 4.52	9.31 ± 3.53	0.161
V20 (%)	3.98 ± 1.46	4.03 ± 1.33	0.582
Lung mean dose (Gy)	3.03 ± 1.11	2.95 ± 1.03	0.152
NTCP_lung (%)	6.76 × 10 <sup>-3</sup> ± 1.22 × 10 <sup>-2</sup>	5.40 × 10 <sup>-3</sup> ± 9.33 × 10 <sup>-3</sup>	0.182
Spinal cord max dose (Gy)	6.13 ± 3.62	7.09 ± 5.95	0.465
NTCP_spinal cord (%)	1.12 × 10⁻⁵ ± 1.90 × 10⁻⁵	4.37 × 10 <sup>-4</sup> ± 9.51 × 10 <sup>-4</sup>	0.187

## Niche #6

### Machine Learning

Prediction of esophageal stenotic ratios

### Machine learning framework in artificial neural network (ANN)

Weights in a neural network are determined by using a backpropagation of errors between predicted outputs and teacher signals at a learning step.



# A computational model of biological neurons

#### Inputs





Input-output function y = f(s)  $S = \sum_{n=1}^{N} W_n X_n$  W : Connecting weight

## ANN-based approach for prediction of esophageal stenotic ratios in esophageal images



Predicted stenotic ratio: 80%

80

## Medical Physics: Actually niche field based on "colored" collaborations between it and the other fields



## Take-home message

I would be very happy if my presentation is helpful to understand *niche* researches or medical physics researches to improve the quality of medical cares.

Thanks a lot for your time and listening!

### H. N. Arimura