FAST EVALUATION OF BIOPSY FOR PROSTATE CANCER DIAGNOSIS BY FRAUNHOFER IKTS

Joerg Opitz, Carola Gerich, Jürgen Schreiber, Andreas Lehmann
FAST EVALUATION OF BIOPSY FOR PROSTATE CANCER DIAGNOSIS BY FRAUNHOFER IKTS

- Fraunhofer IKTS in profile
- Optical Diagnostic Device
  - Motivation
  - Principle
  - Device Prototypes
  - OCD II
  - Clinical Results
- Cooperation models
The name giver: Joseph von Fraunhofer (1787 – 1826)

Researcher

➤ Discovery of the “Fraunhofer lines” in the solar spectrum

Inventor

➤ New methods for processing lenses

Entrepreneur

➤ Director and partner in a glassworks
The Fraunhofer-Gesellschaft at a Glance

The Fraunhofer-Gesellschaft undertakes applied research of direct utility to private and public enterprise and of wide benefit to society.

24,500 staff

69 institutes and research units

Finance volume 2016

€2.1 billion

Major infrastructure capital expenditure and defense research

Almost 30% is contributed by the German federal and Länder Governments

€1.9 billion

Contract Research

More than 70% is derived from contracts with industry and from publicly financed research projects.
Sites of the Fraunhofer IKTS

**Headquarters**
- Dresden, Winterbergstraße

**Other sites**
- Hermsdorf, Thuringia
- Dresden-Klotzsche

**Fraunhofer Center**
- for Energy Innovation CEI, USA

**Application Centers**
- Battery Technology Pleissa, Saxony
- Bioenergy Pöhl, Saxony
- Bio-Nanotechnology Application Lab, Leipzig, Saxony
- Membrane Technology Schmalkalden, Thuringia
- Tape Casting Lab, Hermsdorf, Thuringia
Fraunhofer IKTS in figures

<table>
<thead>
<tr>
<th>Sites</th>
<th>Headquarters</th>
<th>Hermsdorf site</th>
<th>Dresden-Klotzsche site</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personnel (heads)</td>
<td>374</td>
<td>150</td>
<td>151</td>
<td>675</td>
</tr>
<tr>
<td>- Scientists, technicians, admin. personnel</td>
<td>308</td>
<td>117</td>
<td>141</td>
<td>566</td>
</tr>
<tr>
<td>- PhD candidates, students, trainees</td>
<td>66</td>
<td>34</td>
<td>9</td>
<td>109</td>
</tr>
<tr>
<td>Overall budget in million €</td>
<td>28.7</td>
<td>13.6</td>
<td>11.3</td>
<td>53.6</td>
</tr>
<tr>
<td>Industrial revenues in million €</td>
<td>10.1</td>
<td>5.4</td>
<td>4.1</td>
<td>19.6</td>
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</tbody>
</table>

Latest update: December 31, 2016

Institute Director:
Prof. Dr. Alexander Michaelis
Our Business Divisions

- MATERIALS AND PROCESSES
- MECHANICAL AND AUTOMOTIVE ENGINEERING
- ELECTRONICS AND MICROSYSTEMS
- ENERGY

SYSTEMS EXPERTISE

MATERIALS DIAGNOSTICS
- Reliability
- Quality assurance

TECHNOLOGY EXPERTISE

WERKSTOFF-KOMPETENZ

ENVIRONMENTAL AND PROCESS ENGINEERING

BIO- AND MEDICAL TECHNOLOGY

OPTICS

MATERIALS AND PROCESS ANALYSIS
Business Division
Bio- and Medical Technology

Competencies

- Development, processing and integration of biomaterials
- Shaping and surface technologies
- Microsystems technology
- Sensors and actuators
- Integration of functional mechatronic components
- (Bio)medical analytics and diagnostics

Applications
Dental technology
Implants/endoprosthetics
Instruments
Medical components
Biosensors and actuators
Analytics and diagnostics
Motivation

Incidence of cancer

- In year 2010 477,300 people diseased on cancer in Germany
- For the year 2014, the scientists were expecting about 500,900 new cases of cancer
- Prostate cancer: common cancer and the third leading cause of cancer death of men in Germany
- The number of new cases of prostate cancer has risen steadily in recent years and in 2010 was about 65,800
- Forecast for 2014 was about 70,100
Motivation

Diagnostic of prostate cancer

- diagnostic of prostate cancer is varied
  - a lot of different methods but any method is 100 % satisfying
  - Long waiting time (about 10 days) for result => high psychological stress for patient
  - Biopsy removal is very unpleasant, recurring procedure is sometimes necessary
- situation in OP hall: OP has to be interuppted
- physical demand for patient
- saving of personnel and equipment

www.prostata.de
CLASSIFICATION OF CANCER DEVELOPMENT ACCORDING TO GLEASON

- Fractal dimension $D_F$ as a key parameter?
- Dynamics of fractals?
- Time-resolved fluorescence

$I(t) \sim \text{auto-correlation function, } I(t) = I(t_0) - [I(t_0) - I(t \to \infty)] \times C(t - t_0)$

$C(t) \sim t^{2H} \rightarrow D_F = 2 - H$

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P. Waliszewski et.al. Fractal dimension as a novel measure of prostate cancer grading, EAU-Congress (Barcelona, 2010)
USE OF FLUORESCENCE SPECTROSCOPY

Time-resolved single photon counting (TCSPC)

- Excitation: laser with high pulse rate (ps, fs)
- Detector: high-speed photon multiplier
- x-axis in histogram – time difference between excitation and detection; y-axis – number of counted photons
- Advantages of TCSPC – high time resolution and optimal signal-noise-ratio
USE OF FLUORESCENCE SPECTROSCOPY
Measurement results and evaluation
USE OF FLUORESCENCE SPECTROSCOPY

Measurement results and evaluation

Definition of maxima with model function

\[ C(t) := C_1(t-t_0)^{2H} - dC \]

Definition of auto-correlation function

\[ D_F := 2 - H \]
USE OF FLUORESCENCE SPECTROSCOPY

Measurement results and evaluation

- Data acquisition
  - Diode laser for excitation
  - TCSPC as method for detection
- Evaluation
  - Use of scale- and time rule, auto-correlation function
  - Result: value of fractal dimension $D_F$ (between 1 and 2)
  - Correlation: $D_F$-value – result
  - Statistical analysis
  - Classification: 2 classes benign – malignant
  - Threshold value TH

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laser wavelength</td>
<td>375 nm</td>
</tr>
<tr>
<td>Laser pulse frequenz</td>
<td>continuous wave (cw), 50 MHz</td>
</tr>
<tr>
<td>Laser pulse range</td>
<td>&lt; 90 ps</td>
</tr>
<tr>
<td>Laser intensity</td>
<td>&lt; 5 mW (cw), &lt; 0.5 mW (pulse)</td>
</tr>
<tr>
<td>Detection</td>
<td>DCC-camera (PMC 100, Hickl&amp;Becker)</td>
</tr>
<tr>
<td>Spectral detection range</td>
<td>490 – 510 nm</td>
</tr>
<tr>
<td>Focus range of the measurement</td>
<td>1 x 10 mm</td>
</tr>
</tbody>
</table>

![Graph showing fractal dimension vs. length of fit range](image-url)
DEVICE PROTOTYPES

CELIF

OCD-I

OCD-II

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## DEVICE PROTOTYPES: CELIF, OCD I, OCD II

<table>
<thead>
<tr>
<th></th>
<th>CELIF</th>
<th>OCD-01</th>
<th>OCD-02</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Size</strong></td>
<td>650 x 650 x 930 mm</td>
<td>760 x 640 x 490 mm</td>
<td>450 x 450 x 420 mm</td>
</tr>
<tr>
<td><strong>Measurement method</strong></td>
<td>Fluorescence spectrometer</td>
<td>TCSPC (time correlated single photon counting)</td>
<td></td>
</tr>
<tr>
<td><strong>Excitation wavelength</strong></td>
<td>337.1 nm</td>
<td>375 nm</td>
<td></td>
</tr>
<tr>
<td><strong>Excitation</strong></td>
<td>Nitrogen laser</td>
<td>Laser diode, pulsed 50MHz</td>
<td></td>
</tr>
<tr>
<td><strong>Evaluation method</strong></td>
<td>Algorithm fractal structure → DF-value</td>
<td>logistische Regression → Schwellwert (extern)</td>
<td></td>
</tr>
<tr>
<td><strong>Evaluation-SW</strong></td>
<td>extern</td>
<td>In the device</td>
<td></td>
</tr>
<tr>
<td><strong>Results of the measurements</strong></td>
<td>(earliest) 1 day later</td>
<td>Immediately after the measurement</td>
<td></td>
</tr>
</tbody>
</table>
OCD II

a) front view
b) top view
c) side view
d) holder for biopsy carrier
e) storage box
OCD II

Patient ID or biopsy number

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Study
Pathology Dresden – Material, Methods, Proceeding

- 60 Prostates after a total resection
- Removal of each 12 biopsies according to an urological scheme
- Per biopsy up to 15 measurement points → ca. 7900 measurements
- Recording of time resolved fluorescence spectra with TCSPC method (duration ca. 1.5 min per biopsy)
- Fractal Dimension $D_F$ as a value for the dignity
- Finding of each measurement points by the pathologists → Data sheet
- Correlation of the findings with the $D_F$-values → data model
- Analysis of the model with statistical methods: logistical regression, Box Plots, ROC-curves
- Transfer of the biopsies to the usual workflow for creating the instantaneous section
Study
Pathology Dresden – Material, Methods, Proceeding

Overview

<table>
<thead>
<tr>
<th></th>
<th>total</th>
<th>with tumour fraction</th>
<th>no tumour was found</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostates</td>
<td>60</td>
<td>53</td>
<td>7</td>
</tr>
<tr>
<td>Biopsies</td>
<td>499</td>
<td>167</td>
<td>332</td>
</tr>
<tr>
<td>Measurement points</td>
<td>5953</td>
<td>927</td>
<td>5026</td>
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</table>

Findings of the pathologist correlated with the values of the fractal dimension $D_F$
Study

Pathology Dresden – Material, Methods, Proceeding

- Clustering
  - 1. Cluster: 1 + 2 + 3 (normal, enflamed, BPH)
  - 2. Cluster: 4 + 5 (PIN, Tumour)
- Logistical regression for determination of the threshold TH

Regression equation for 2 Cluster (1+2+3), (4+5)

\[ D_F = \text{values of the fractal dimension} \]

\[ p = \text{probability} \]

\[ TH = 1.309, \ D_F > TH \rightarrow \text{tumour} \]
Study
Pathology Dresden – Material, Methods, Proceeding

- ROC-curve for Cluster (1+2+3), (4+5)

- Correct classification – probability of recognition of the tumour

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<th>predicted</th>
<th>Finding (Cluster)</th>
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<tr>
<td></td>
<td>normal</td>
<td>TN = 5001</td>
<td>99.5</td>
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<tr>
<td></td>
<td>Tumour</td>
<td>FN = 11</td>
<td>98.8</td>
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<tr>
<td>%</td>
<td></td>
<td></td>
<td>99.4</td>
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AUC = 0.9943

Optical Diagnostic Device
Study
Pathology Dresden – Material, Methods, Proceeding

- ROC-curve for Cluster (1+2+3), (4+5)

- Correct classification – probability of recognition of the tumour

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<tr>
<td>N_{TN}</td>
<td>5001</td>
<td>N_{FP} = 25</td>
</tr>
<tr>
<td>N_{FN}</td>
<td>11</td>
<td>N_{TP} = 916</td>
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</table>

ROC-Curve

AUC = 0.99143
Study
Pathology Dresden – Material, Methods, Proceeding

- ROC-curve for Cluster (1+2+3), (4+5) and box plots

- Correct classification – probability of recognition of the tumour

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TECHNOLOGY PROTECTION

3 Patent families:

✓ „Method and device for detecting tumorous living cell tissue“ granted in USA; filed in Europe (UK, F, GER, Nor) and South Korea (WO2010130254)

✓ „Biopsieplättchen, Einbettkassette und Diagnosevorrichtung“ filed in Germany (DE102011004449)

✓ „Prostate cancer diagnosis device using fractal dimension value“ granted in South Korea; filed in Europe (UK, F, GER, Nor) and USA (EP2699904)
Thank you for your attention!

You are invited to work with us on challenging topics in a city full of history and culture, with a high quality of life and an excellent surrounding.