**Workshop / *Radionica***

**"Innovation in engineering design"**

***"Inovacije u inženjerskom projektiranju"***

**27-28. January 2011, Rijeka**

**Engineering approach to biomedical applications**

*dr. Tomaž Šuštar C3M d.o.o.*

*Slovenia*

*Name/s of presenter/s*

This project has been funded with support from the European Commission



- Biomedical engineering
  - "Biomedical engineering is the application of engineering principles and techniques to the medical field. … It combines the design and problem solving skills of engineering with medical and biological sciences to improve healthcare diagnosis, monitoring and therapy" (source: Wikipedia)

This project has been funded with support from the European Commission



- Main application fields:
  - Medical imaging
    - visualization of MRI etc…
  - Rehabilitation engineering
    - design of equipment
  - Orthopedic engineering
    - implants – solutions for muscosceletal problems
  - Biomechanics
    - mechanical functioning of cells, circulation, muscles, limbs and bones and use the results to develop new treatments for a variety of medical problems
  - Tissue engineering
    - combination of mechanical equipment and biological materials to grow replacement organs

This project has been funded with support from the European Commission



- Challenges for engineers
  - Understanding of "medical language"
  - Complexity of the biological materials and processes
    - Large scatter of tissue properties (mechanical, electrical, etc …)
    - Large set of parameters influencing the experiments ( psychological, etc…)
    - Repeatability of experiments

This project has been funded with support from the European Commission



- C3M's story on biomedical applications
  - FP6 Nanobiotact
  - FP7 Nanobiotouch
  - ESA/SURE
  - Electroporation - Electrochemotheraphy

This project has been funded with support from the European Commission



- It all started from polymer modeling …
  - Development of sophisticated polymer models for behavior of deformation at high strain rates
    - Polymer-steel laminates (strain rates up to $10^{-4}$)
    - Leonov model
    - Arruda – Boyce model
    - Knauss – Emri model

This project has been funded with support from the European Commission

- from mechanics to biomechanics
  - Artificial skin polymers

**Silicone GLS 40 (Prochima):**

- Shore A: 11
- Viscosity: 28,000 mPa
- Elongation at break: 380%
- Color: pink

**Silicone Dragon Skin (Smooth-On):**

- Shore A: 10
- Viscosity: 23,000 mPa
- Elongation at break: 1000%
- Tensile strength: 475 psi
- Color: translucent clear

**Polyurethane Poly 74-45 (Polytek):**

- Shore A: 45
- Viscosity: 2,500 mPa
- Elongation at break: unknown
- Color: yellow

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"Innovation in engineering design"
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27-28. siječanj 2011, Sveučilište u Rijeci – Tehnički fakultet

- from mechanics to biomechanics
  - visco – elastic human skin tissue model

(Fung, 1993 Y.C. Fung, Biomechanics: Mechanical Properties of Living Tissues, Springer-Verlag, New York (1993) pp. 242–320.)

$$S_{ij}(t) = \int_0^t G_{ijkl}(t-\tau) \cdot \frac{\partial S_{kl}^{\infty}(E_{kl}(\tau))}{\partial \tau} \cdot d\tau$$

$$S_{ij}(t) = S_{ij}^{dev}(t) + S_{ij}^{vol}(t)$$

$$S_{ij}^{dev}(t) = \int_0^t G^{dev}(t-\tau) \cdot \frac{\partial S_{kl}^{dev}(E_{kl}(\tau))}{\partial \tau} \cdot d\tau$$

$$S_{ij}^{vol}(t) = \int_0^t G^{vol}(t-\tau) \cdot \frac{\partial S_{kl}^{vol}(E_{kl}(\tau))}{\partial \tau} \cdot d\tau$$

$$G^{dev}(\xi) = \sum_{i=0}^{n} G_i^{dev} \cdot Exp\left(-\frac{\xi}{\tau_i^{dev}}\right)$$

$$\tau_0^{dev} = \infty$$

$$W = \sum_{i=1}^{n} c_{i0} \cdot (\bar{I}_1 - 3)^i + \frac{K}{2} \cdot (J_{el} - 1)^2$$

$$S_{kl} = \frac{\partial W}{\partial E_{kl}}$$

$$G = \mu = 2 \cdot c_{10}$$

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**FP6-NMP-STREP-NANOBIOTACT**

**Nano-engineering biomimetic tactile sensors**

| | | | |
|---|---|---|---|
| Coordinator: | **University of Birmingham** | Psychophysical evaluation<br>NEMS transducers<br>Tissue engineering | **UK** |
| Companies: | **Unilever** | Synthetic materials | **UK** |
| | **Rockfield Software Ltd** | Numerical modelling | **UK** |
| | **C3M** | Sensitivity analyses and optimisation | **Slovenia** |
| Academics: | **Göteborg University** | Clinical Neurophysiology | **Sweden** |
| | **Universite catholique de Louvain** | Psychophysical measurements | **Belgium** |
| | **Technical University Munich** | Tactile information processing | **Germany** |
| | **Scuola Superiore Sant'Anna** | Humanoid robotics | **Italy** |

**Start:** December 2006
**Finish:** November 2009
**Budget:** 3,4 MEURO

This project has been funded with support from the European Commission

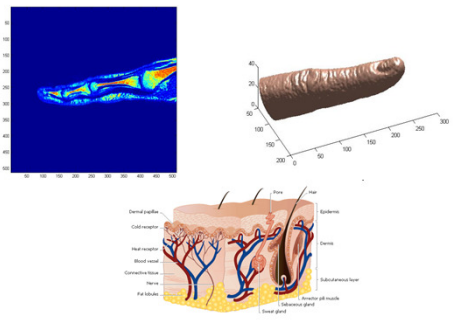
"Innovation in engineering design"
*"Inovacije u inženjerskom projektiranju"*
27-28. siječanj 2011, Sveučilište u Rijeci – Tehnički fakultet

**FP6-NMP-STREP-NANOBIOTACT**

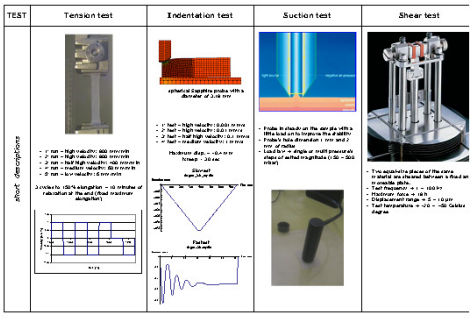
- "The objective of Nanobiotact is to design and construct an articulated artificial finger with a biomimetic sensor based on an array of MEMS force transducers that will mimic the spatial resolution, sensitivity and dynamics of human tactile neural sensors."
- C3M's role :
- finite element simulation of the fingerpad
- advanced optimisation procedures for obtaining the material models from improved mechanical measurements of the fingerpad
- neuromechanical coupling to simulate real tactile experiences.

This project has been funded with support from the European Commission

**Finger – modeling geometry**



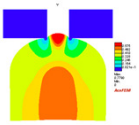
Material testing



## 2D modeling – different tactile stimuli

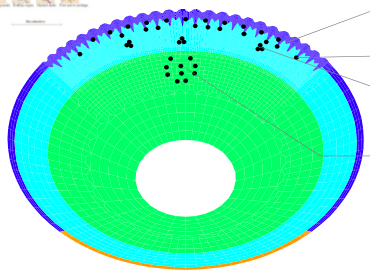
- Indentation

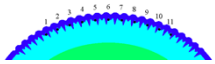
- Suction



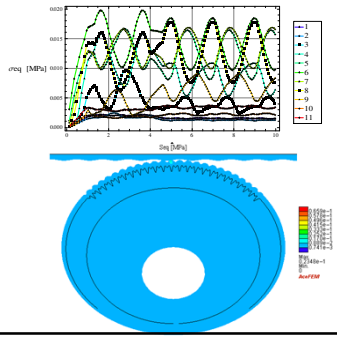
- Surface sliding (regular/irregular patterns)

## Mechanoreceptors

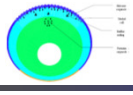


## Effective stress at MC

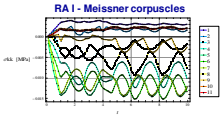




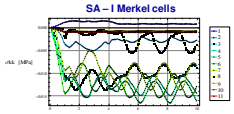


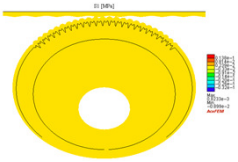
## Pressures at mechanoreceptors

RA I - Meissner corpuscles

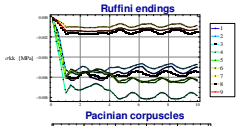


SA – I Merkel cells

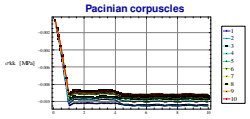




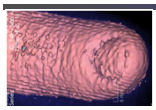
Ruffini endings

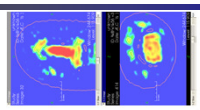


Pacinian corpuscles

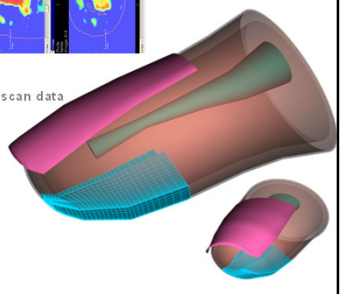


## Global Model Construction



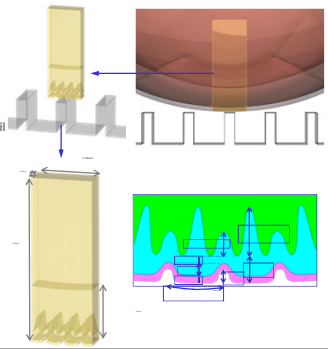


- Geometry extracted from MRI scan data
- Structured mesh
- Defined local region output
- Distal phalange
  - Extended and thickened
  - Representative stiffness

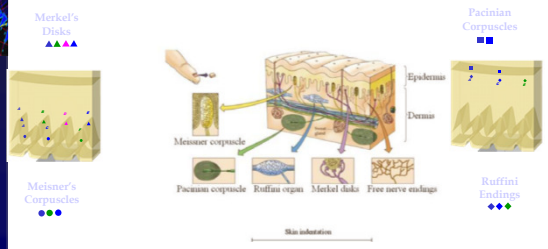


## Local Model Construction

- Enhance geometry
- Stratum corneum
  - Papillary ridges
  - Intermediate and limiting ridges
- Capturing greater response detail
- Extrusion of 2D local model
  - Structure of fingerprint
- Model loading
  - Displacement
  - Extracted from global model

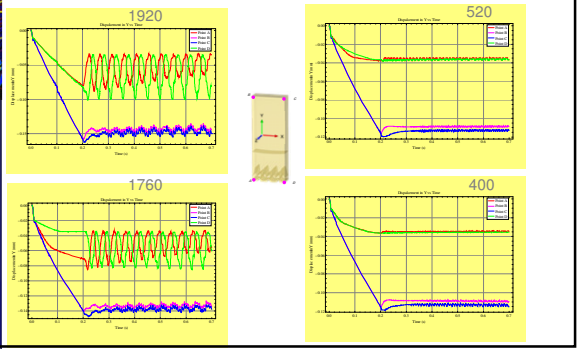


## Locations of mechanoreceptors



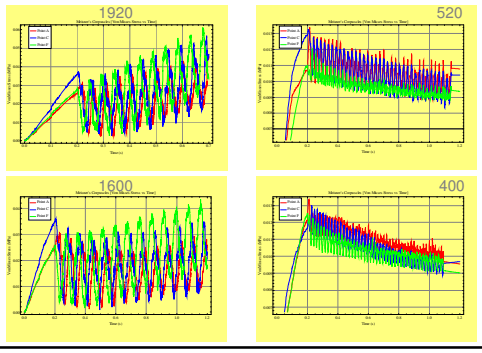

## Comparisons

**different grating same speed (40 mm/s)**



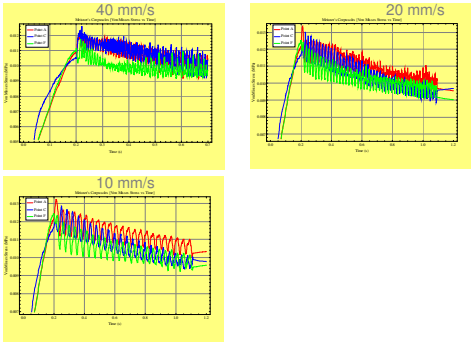

## Comparisons

**Meinser – different grating same speed (20 mm/s)**



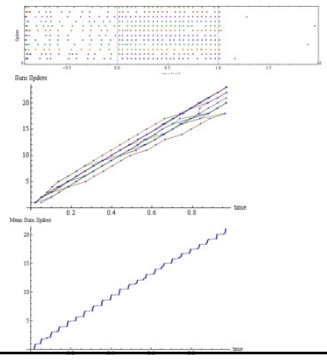

## Comparisons

**Meisner – grating 400 different speed (10, 20, 40 mm/s)**




## Neuro mechanical coupling

- Experiment
- Sum of spikes
- Averaged sum



## Neuro mechanical coupling

- Proposed equation for accumulated number of spikes N

$$N = a \cdot \left( \sum_i \Delta t_i \cdot \sigma_i^b \cdot \left| \Delta \varepsilon_i \right|^c \right)$$

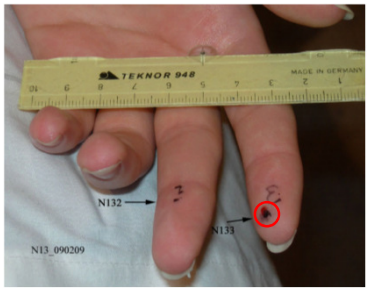
$\sigma_i$ ... Misses equivalent stress at time $t_i$

$\Delta \varepsilon_i$ ... Increment of equivalent strain at time $t_i$

$a, b, c$ ... parameters

## Neuro mechanical coupling

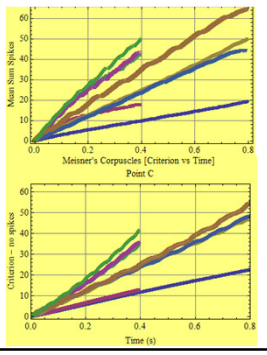
- N133 (RA) - rapidly adapting type (Meissner)

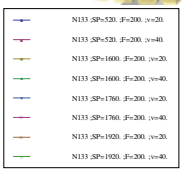



## Neuro mechanical coupling

- N133 (RA)
  Experiment

a = 25000
b = 0.8
c = 0.3



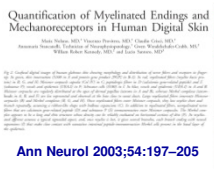

## Future developments – FP7 NANOBIOTOUCH

- FP7 Nanobiotouch : Nano-resolved multi-scale investigations of human tactile sensations and tissue engineered nanobiosensors

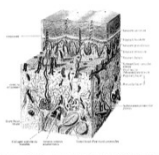
| Role | Partner No. | Name | Short name | Country |
|---|---|---|---|---|
| Coordinator | 1 | University of Birmingham | UB | UK |
| Industry & SME | 2 | C3M | C3M | Slovenia |
| | 3 | Rockfield Software Ltd. | RSL | UK |
| | 4 | CK Electronics | CKE | Germany |
| | 5 | Optaglio | OPT | Czech Republic |
| | 6 | Unilever R&D Port Sunlight | UNL | UK |
| Academic | 7 | University of Gothenburg | UG | Sweden |
| | 8 | Universite Catholique de Louvain | UCL | Belgium |
| | 9 | University of Ljubljana | UL | Slovenia |
| | 10 | University of Wales, Swansea | UW | UK |
| | 11 | Scuola Superiore Sant'Anna | SSSA | Italy |
| | 12 | Dalle Molle Institute for Artificial Intelligence | IDSIA | Switzerland |

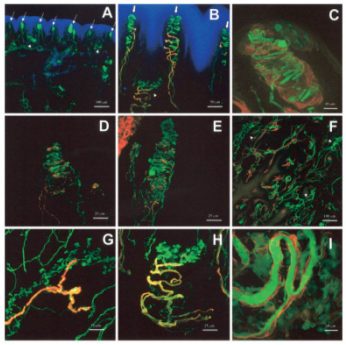
- C3M's role: Development of nano-resolved multiscale multiphysics model of mechanotransduction that will be capable of simulating responses of the artificial and human tactile sensation systems.

## Mechanoreceptor properties, size and locations ?


Quantification of Myelinated Endings and Mechanoreceptors in Human Digital Skin

Ann Neurol 2003;54:197–205






## Mechanoreceptor properties, size and locations ?

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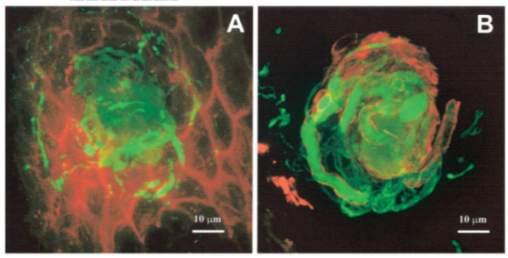
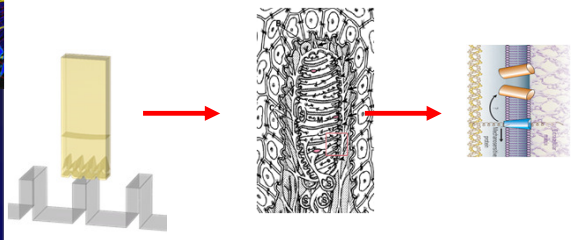
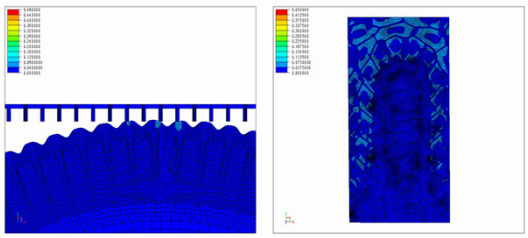



*Digital confocal images (A, B) at high magnification (100) of* ***Meissner corpuscles*** *from fingertip (horizontal cut) obtained from the projection of 60 1m-thick optical sections.*

## Nanobiotouch : Multi scale modeling



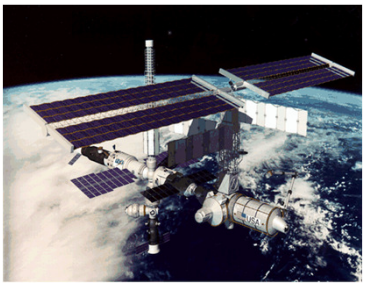

## Nanobiotouch : Multi scale modeling



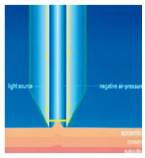
## C3M experiment on ISS

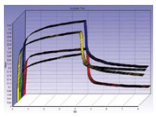
**SURE AO 021:** In vivo biomechanical measurements of human skin properties under accelerated aging conditions during ISS mission

The project approved by ESA



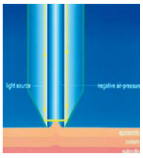
## Inverse modeling

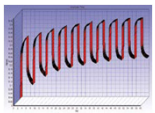




Experiment

## Inverse modeling

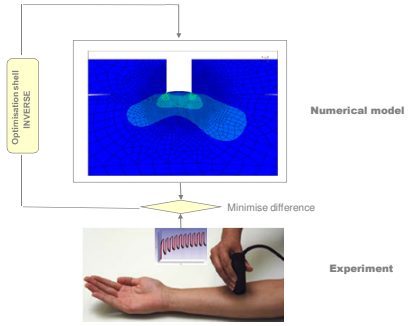




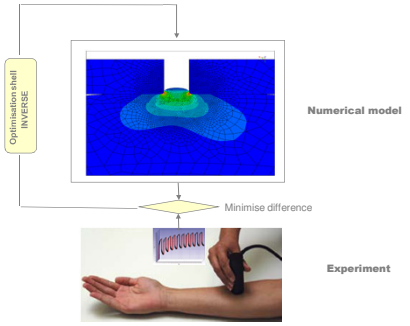
Experiment

Koln, 27 October 2006

## Inverse modeling




## Inverse modeling




## C3M ISS experiment

**Dermatology Experiment Unit** was installed on board the ISS in **2006** and has beed successfully tested during the **ESA Astrolab Mission**

**Based on the results from Astrolab mission decision was taken to perform pre and post fly measurements and to significantly extend the measurement protocol**

## Equipment

- **Dermatology Experiment Unit on ISS**
- Skin Hydration grade (Corneometer®)
- Transepidermal waterloss (Tewameter®)
- Skin microstructure (VisioScan®)

- **On-ground measurements by Cutometer**

## C3M ISS experiment

- **Updated protocol includes measurements of touch discrimination which will be performed by partners from Nanobiotact project: SSSA and UCL**
  - Dynamic platform – tactile investigation
  - Extended set of skin parameters
  - High precision camera

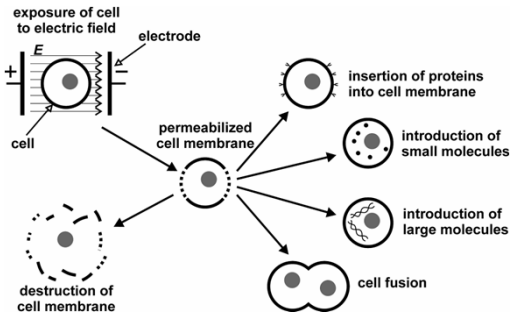
- **Current project status:**
  - stand by for BDC (base line data collection)
  - The experiment is scheduled for 2010/2011

## Electroporation

- “**Electroporation**, or electropermeabilization, is a **significant increase in** the electrical conductivity and **permeability of the cell plasma membrane** caused by an externally applied electrical field. It is usually used in molecular biology as a way of introducing some substance into a cell, such as loading it with a molecular probe, a drug that can change the cell's function, or a piece of coding DNA”

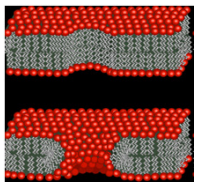
(source: wikipedia)

## Electroporation

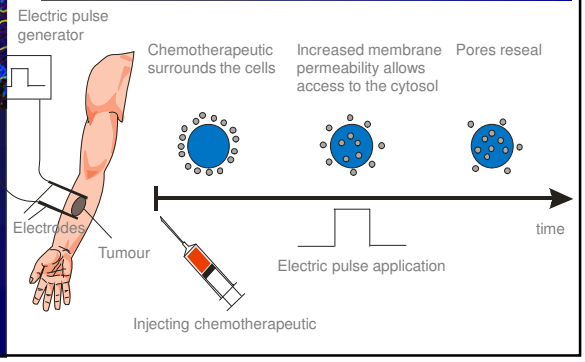



## Electroporation based Technologies and Treatments

- Molecular cell biology research
- Protein insertion into cell membrane
- Cell fusion
- Gene expression silencing by siRNA
- **Electrochemotherapy**
- Genetherapy based on electro genetransfer
- Transdermal drug delivery
- Tissue ablation
- Biotechnology
- Water and liquid food sterilisation



## Electrochemotherapy = chemotherapy + electroporation




## Electrochemotherapy

- **Consortium:**
  - University of Ljubljana, Faculty of electrical engineering (SI)
  - IGEA Medical (I)
  - Institute of Oncology Ljubljana (SI)
  - C3M (SI)
  - Clinical partners from EU
- **Objective : to develop EC treatment planning software featuring:**
  - determination of voltage
  - electrode positioning
  - electrode pairs
  - pulse parameters
- **EC is well established method for melanoma but has large potential also for deeper seated tumors (liver, bones etc…). The development of treatment planning software would strongly support application of EC in new areas**

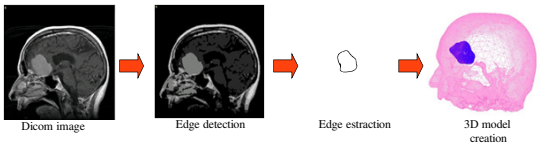
## Treatment planning : custom development of electroporation model

- **Scientific version of treatment planning software**
  - 3D Geometry extraction from DICOM images with automatic segmentation (tumor/tissue)
  - Insertion of the electrodes in 3D geometry
  - FEM mesh creation
  - FEM analysis
    - Stationary electric field
    - Transient electric filed
    - Coupling with thermal and diffusion model
  - Optimization of electrode positioning
- **Overview of the current status of the developments**
  - Geometry (segmentation, mesh generation)
  - Model (FE development)
  - Test cases (benchmarks, real patient cases)

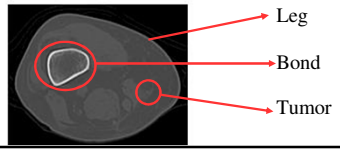
## Create 3D image data by a series of 2D dicom files of a leg

**WORK FLOW PHASES**

**Example:**




**Profile to detect in DICOM:**

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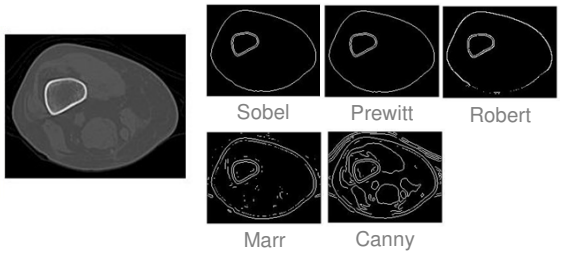
## Create 3D image data by a series of 2D dicom files of a leg

EDGE DETECTION

**EDGE DETECTION:**



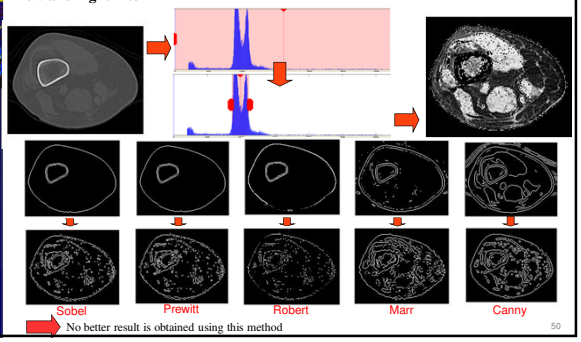

Using Sobel and Prewitt we are able to detect bond and leg edges in a very simple way.
Tumor is visible with Canny but is not well defined



## Create 3D image data by a series of 2D dicom files of a leg

TUMOR EDGE DETECTION

**Low and hight filter**



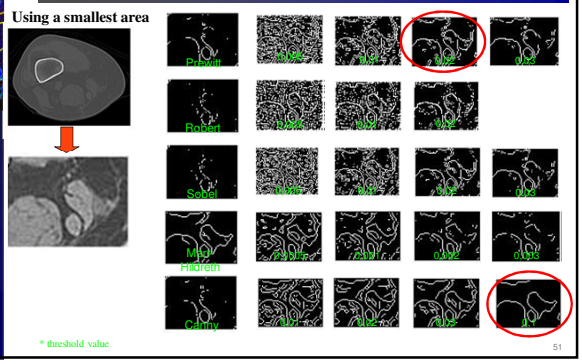

No better result is obtained using this method



## Create 3D image data by a series of 2D dicom files of a leg

EDGE DETECTION

**Using a smallest area**



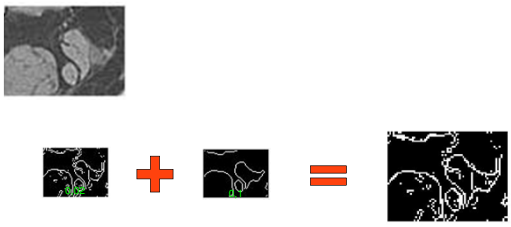

* threshold value



## Create 3D image data by a series of 2D dicom files of a leg

EDGE DETECTION

**Combining the two best results:**

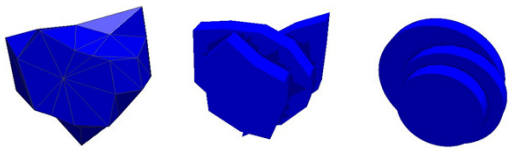




## Geometry preparation

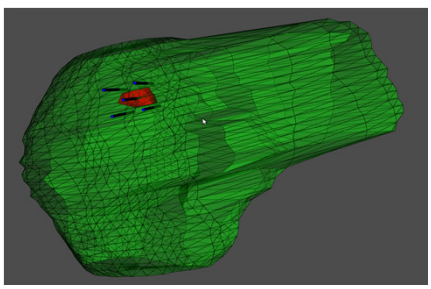
- Image segmentation – tumor slices:

- Approximation of tumor geometry:
  a) generation of STL surface  b) extrusion of profile  c) extrusion of cylinder



## Mesh generation

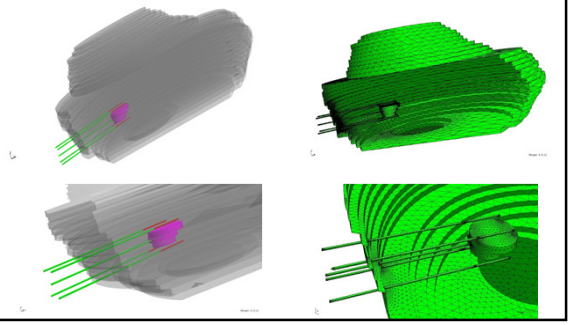
- Insertion of the electrodes into STL geometry and identification of domains



## Model : Liver – Tumor - Electrodes

- Geometry

FE mesh



## Stationary electrical field

Equations for stationary electrical field

$U$ .... Voltage [V]

$\vec{E} = -\nabla U$ .... Electric field [V/m]

$\sigma = \begin{bmatrix} \sigma_{xx} & \sigma_{xy} & \sigma_{xz} \\ \sigma_{yx} & \sigma_{yy} & \sigma_{yz} \\ \sigma_{zx} & \sigma_{zy} & \sigma_{zz} \end{bmatrix}$ .... Electrical conductivity [S/m]

$\sigma = \sigma(E)$

$E = \sqrt{\vec{E}.\vec{E}}$ .... Electric field strength

$\vec{J} = \sigma.\vec{E}$ .... Current density[A/m2]

$\Pi = \int_{\Omega} \frac{1}{2} \vec{J}.\vec{E}\, d\Omega$ .... Free energy [VA]

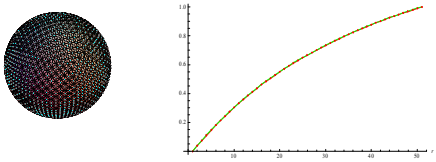
using FEM we are searching for minimum of free energy on domain Ω

## Finite element development

Convergence tests

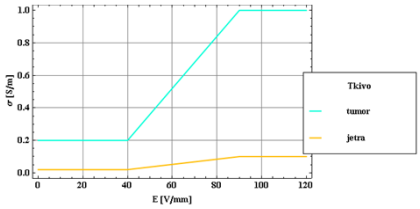
Verification against analytical solution

(solution for full and hollow sphere)



## Material data

| Tkivo | Tip poracije | Povečanje | Pragovi poracije (V/m) | Naklon funkcije | Začetna spec. Prevodnost (S/m) |
|---|---|---|---|---|---|
| tumor | $1-e^{X}$ | 5 kratno | rev.:40.000; irev.:90.000 | B=15000 | 0,2 |
| jetra | $1-e^{X}$ | 5 kratno | rev.:40.000; irev.:90.000 | B=15000 | 0,02 |
| Prevodnost elektrod | | 60 000 000 S/m | | | |

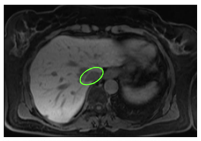


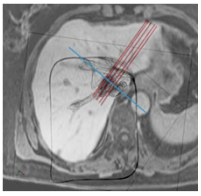

## Patient description

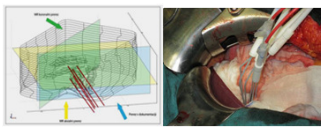
A patient with single metastasis in Sg1, on the inferior caval vein, between the right hepatic vein and the common trunk

Considering specific location RFA could not be effective because of cooling effect of the veins.

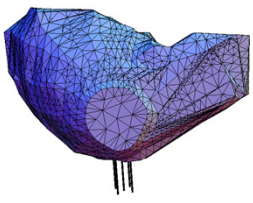
Radical resection was potentially possible with right trisectionectomy (leaving only lateral part of the left liver – to small liver remnant)





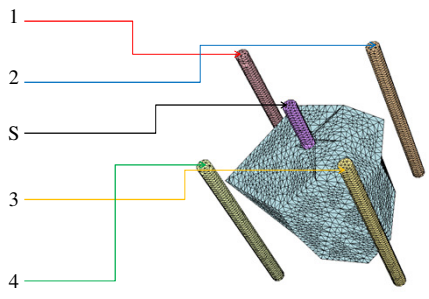


## FE mesh



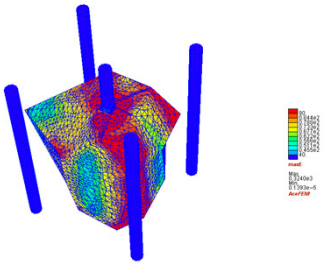
| No.Nodes | No.Elements |
|---|---|
| 34757 | 187969 |

## Tumor with conductive part of the electrodes



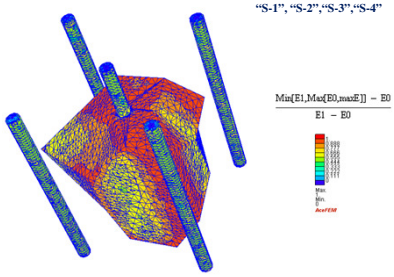

## Maximal electrical fied

Voltage: 3000V
Electrode pairs:
"S-1", "S-2","S-3","S-4"



## % of electroporation

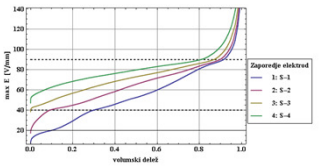
Voltage: 3000V
Electrode pairs:
"S-1", "S-2","S-3","S-4"



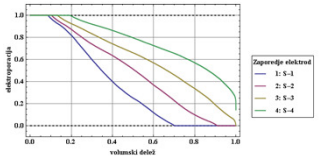
$$\frac{\mathrm{Min}[E1,\mathrm{Max}[E0,\mathrm{max}E]] - E0}{E1 - E0}$$

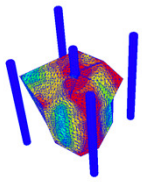
## Results

Voltage: 3000V




| par | I [A] |
|---|---|
| S-1 | 19.7163 |
| S-2 | 18.8957 |
| S-3 | 18.3701 |
| S-4 | 21.4731 |



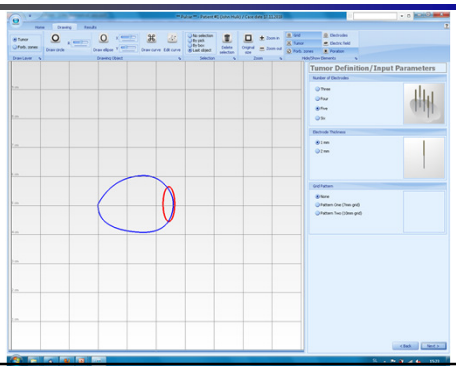
## Custom development of electroporation model

**Pulsar application – based on semi analytical solution for clinical use**

- Geometry based on surgeon access view
- Definition of forbidden zones
- Insertion mask options
- Fast solution for field calculation
- Determination of the optimal number of electrodes
- Optimal placing of electrodes
- Generation of treatment plan for target device

Commercial application

## Pulsar application



**Pulsar application**