Computable Functionalized Human Phantoms for Medical Device Modeling

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Overview

• introduction

• functionalized anatomical models

• MRI with implant
  - safety assessment

• MRI induced heating
  - V&V
  - uncertainty analysis
  - effect assessment

• EM-neuron interactions
  - V&V
  - effect assessment

• conclusions
Background
Computational Modeling for MedTech & LS

- application areas of computational modelling in MedTech & Life Sciences:
  - mechanism analysis
  - investigation of novel treatment
  - device design & optimization
  - safety & efficacy assessment (regulatory)
  - personalized treatment planning

- benefits of computational modeling:
  - analyse (insight beyond experimentally accessible, well controlled, dense information, visualization)
  - optimize (device design, performance, safety)
  - understand & troubleshoot (mechanism investigation, problem identification)
  - reduce time-to-market (*in silico* prototyping & testing)
  - perform trials (*in silico* trials, reduce bench/animal/human trials)
  - personalize (image-based anatomy, patient specific properties/processes, treatment planning)
Computational Modeling for Regulatory Submissions

- regulatory requirement: demonstration of safety & efficacy
- use of computational modelling increasingly pushed by regulators (FDA white-paper)
- efforts underway to standardize reporting, V&V (FDA, ASME V&V40, MDIC)
- computational modelling used to:
  - identify worst-case configuration for subsequent experiments
  - compare device performance
  - make absolute predictions
  - increase population coverage
  - drive device (algorithms)
- CFD safety assessment examples:
  - mechanical failure risk
  - blood damage assessment (pumps)
  - clotting risk assessment
  - wall shear-stress assessment
  - EM exposure safety
V&V Standard (ASME, FDA)

- verification: process of ascertaining that the intended model/algorithm is correctly implemented

- validation: process of ascertaining that the proposed model adequately reproduces the relevant behavior and quantities of interest within the intended context of use

- assess:
  - risk: function of modelling impact on decision process & severity of consequences
  - credibility: degree & quality of V&V activity performed
    - code & solution verification, computational model and applicator validation (e.g., configuration, governing equations, properties, conditions, coverage), agreement and applicability assessment

- effort inspired by methodology from engineering community
## V&V Standard (ASME, FDA)

<table>
<thead>
<tr>
<th>LEVEL</th>
<th>SYSTEM CONFIGURATION</th>
<th>GOVERNING EQUATIONS</th>
<th>SYSTEM PROPERTIES</th>
<th>SYSTEM CONDITIONS</th>
<th>EVIDENCE-BASED COMPARATOR</th>
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**The Purpose of Fast SAR Evaluations**

Basingstoke, June 11, 2015
V&V & UA: Multi-Physics & In Vivo - Issues

- frequent need for multi-physics (coupled modelling) in life sciences & medtech
  - typically insufficient to perform V&V for the individual modalities only
  - coupling introduces additional complexity

- frequent need to consider human body in device environment
  - complex geometry, difficult material property assignment
  - often complex behaviour dependence on body model
  - large inter/intra-person variation (geometry & properties), posture changes -> population coverage needed within CoU, or demonstration that worst-case covered

- frequently includes not only physics modalities but also physiological/biological models
  - particularly for effect assessment when no threshold limits exist or are applicable (need to understand assumptions behind thresholds)
  - poor knowledge about parameters, large variation, dynamic behaviour
  - equations typically not as well known/defined as for physics

- frequently in vivo is less accessible to measurements for experimental valid.
V&V

- **benchmarks** required:
  - analytical (simple, well defined)
  - reference solutions (e.g., comparison with different numerical approach, increased complexity, wealth of accessible information)
  - experimental measurements (model correctly represents real behaviour)

- **code verification** must be documented

- code verification always related to **validity range** which must encompass CoU (e.g., staircasing errors in FDTD not caught by rectangular benchmark) user/regulator must be aware of degree of validation, gaps in validation

- code verification must also cover **coupling** implementation, **post-processing**

- validation always has an **application specific** aspect (demonstration that relevant feature(s) of reality correctly reproduced)

- validation of **coupled phenomena** (especially strong coupling) can typically not be reduced to validation of individual components
Uncertainty / Sensitivity Analysis

- agreement cannot be judged without proper uncertainty determination (‘agreement within the expected combined uncertainty’ vs. ‘simulations and measurements agree well’)

- strength of validation only apparent from sensitivity analysis (e.g., B1+ example)

- validity range requires knowledge about uncertainty

- sensitivity analysis required to identify critical parameters

- conservativeness / safety margins can typically not be ascertained without uncertainty analysis

- no validation / submission is complete without uncertainty assessment
Functionalized Anatomical Models
**Functionalized Models**

- need to develop functionalized anatomical models
  - range of models to cover anatomical variations
  - parameterized (posing, breathing, morphing…)
  - tissue parameters
  - integration of image-based property information (e.g., density/perfusion maps; spatial / spatio-temporal)
  - integration of dynamic models (e.g., vasculature networks with flow information, neuronal dynamics)

- go beyond static models for geometry information
- increase realism, enable physiological/biological level
- next step: personalization
Personalized Models / Virtual Population
Posing / Morphing
Example: FDA Critical Path Initiative

- high-resolution (0.5mm isotropic) head model based on multi-modal image data
- integration of deep brain structures (Morel atlas), vasculature
- co-registration of DTI data:
  - inhomogeneous, anisotropic properties
  - help with neuron placement
- integration of selected dynamic neuron models (ongoing)
- surface extraction & processing, discretization routines, specialized solvers
Example: FDA Critical Path Initiative
Example: MRI Implant Safety
RF Coupling Mechanisms w/ External Fields

Safety Assessment of EM Exposed Implants

- determination of EM field enhancement by
  - measurement (homogeneous, tissue simulating-media filled phantom)
  - simulation (w/wo whole-body/regional anatomical models, simplified)
AIMD Exposure Safety Assessment

- exposure is defined by the H-field induced field inside the body
- function of: coil, polarization, anatomy, trajectory, posture…
- typical AIMD are long, whereas internal structures are small, with respect to the wavelength
- wavelength varies with surrounding tissue
- exposure cannot be predicted safely by experimental or simulation methods without high overestimation
AIMD Exposure Safety Assessment

- approach (JWG):
  - generate numerical lead model w/ uncertainty budget
  - experimentally validate the lead model with sufficient excitation variations
  - test if the numerical and experimental results agree within the combined uncertainty
  - determine the incident field distribution by simulation with known uncertainty
  - assess confidence interval for the entire assessment for the power deposition at the electrode
πX \textit{ex vivo} Model Generation

The Purpose of Fast SAR Evaluations

Basingstoke, June 11, 2015

\[ E_{\text{induced},p1} = \int_0^l h_{\text{AIMD}}(l) E_{\tan}(l) \, dl \]

\[ h_{\text{AIMD}}(l) = E_{\text{induced},p1} \quad \text{where} \quad E_{\tan}(l) = 1 \]
πX ex vivo Model Validation

TLe78c0.47
Tier 3 ex vivo analysis
The Purpose of Fast SAR Evaluations

Basingstoke, June 11, 2015

πX model validation process
Tier 3 incident analysis
Human Modeling: *in vivo* RF Exposure from MRI
Human Modeling: *in vivo* Excitation to AIMD
Tier 3 incident analysis
in vivo - ex vivo comparison / concept validation
in vivo - ex vivo comparison / concept validation
Example: MRI Induced Heating
Illustrating Example: MRI RF Exposure

- MRI RF-coil exposure safety (without implant) considering:
  - local hot-spots
  - tissue heating & thermoregulation
  - tissue sensitivity
  - pTx technology

- measurements provide information about: incident fields, B1+, (T)

- simulations provide information about: \textit{in vivo} power deposition distributions, current distributions, temperature increase, induced effects
Illustrating Example: MRI RF Exposure

- verification of EM solver implementation – IEEE standard

- validation:
  - coil model
  - local SAR prediction
  - local T prediction
  - in-vivo heating

- uncertainty analysis:
  - psSAR, pT
  - experimental validation

- effect assessment:
  - SAR induced heating
  - heating induced effect
MR RF Safety Background: Limits

- based on core and local temperatures (IEC60601-2-33)

<table>
<thead>
<tr>
<th>Operating mode</th>
<th>Rise of body core temperature °C</th>
<th>Spatially localised temperature limits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Head °C</td>
</tr>
<tr>
<td>NORMAL</td>
<td>0.5</td>
<td>38</td>
</tr>
<tr>
<td>FIRST LEVEL CONTROLLED</td>
<td>1</td>
<td>38</td>
</tr>
<tr>
<td>SECOND LEVEL CONTROLLED</td>
<td>&gt;1</td>
<td>&gt;38</td>
</tr>
</tbody>
</table>

- derived wbSAR10g values: 2W/kg (4W/kg); headSAR: 3.2 W/kg

  - assumption: local limits automatically satisfied if wbSAR met
MR RF Safety Background: Exposure

MR RF Safety Background: psSAR & T

MR RF Safety Background: T Distrib. (4W/kg)

MR RF Safety Background: pTx vs CP

Validation
Verification: Coil Modeling with Huygens vs Direct

- additional coil model validation:
  - compare resonance frequency & mode
  - B field measurements
Validation: Incident E/B-Field
Validation: Local Field - Requirements

• measurements are well controlled and sensitive

• relevant scanning situations are mimicked
  - loading conditions
  - steering parameters

• sufficient number of excitations to account for:
  - coverage of all relevant scanning situations
  - particularly high local field enhancements compared to CP-mode (safety)
  - particularly high local SAR values (scan limiting)

• measurement locations should cover regions of high sensitivity with respect to steering parameters

• comprehensive uncertainty budget for both measurement and simulation to assess the quality of the validation
Validation: Local Fields – Experimental Setup
Validation: Local Fields – Results

![Graph showing CP enhancement factor for different field configurations.](image)
Validation: Local Fields – Results

[Diagram showing CP enhancement factor for various orientations and conditions.]
Validation: EM Induced Heating – Setup

- basis of FDA benchmark, standard

Validation: EM Induced Heating – Results

- agreement within determined uncertainty
Validation: EM Induced Heating – Results

- agreement within determined uncertainty
Validation: *In Vivo* Heating

- agreement only when thermoregulation considered

Uncertainty Analysis
Uncertainty / Sensitivity Analysis: Approach

- based on [Taylor&Kuyatt, NIST1994], GUM [JCGM 100:2008]
- decide if relative/absolute uncertainties appropriate
- decompose uncertainty (numerics, model, measurement) into independent contributions
- determine sensitivity of quantity of interest (simulations offer perfect control)
- combine knowledge about uncertainty distribution of underlying variable with sensitivity to obtain uncertainty contribution
- combine uncertainties (root sum squares)
- expanded uncertainty (k=2) should cover 95%
- be creative (e.g., when factors cannot be treated independently -> MC…)
- for validation: combined measurement & simulation uncertainty
- for hybrid models: combined measurement & simulation uncertainty
Uncertainty Assessment: pTx psSAR – Factors

- numerical methods (spatial resolution, convergence, Huygens’ box, SAR averaging algorithm)
- coil model (geometry, tuning, mode)
- coil steering
- anatomy (model quality, inter-person variation, postures)
- tissue properties (dielectric contrast/losses)
- patient positioning

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Quantity</th>
<th>Val1</th>
<th>Val2</th>
<th>Stddev</th>
<th>Factor</th>
<th>Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\varepsilon_{r,\text{gel}})</td>
<td>0.1gSAR</td>
<td>56</td>
<td>50</td>
<td>2.8</td>
<td>0.24%/%</td>
<td>1.2%</td>
</tr>
<tr>
<td>(\sigma_{\text{gel}}) (S m(^{-1}))</td>
<td>0.1gSAR</td>
<td>0.82</td>
<td>0.74</td>
<td>0.041</td>
<td>1.01%/%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Phant. pos (x) (mm)</td>
<td>0</td>
<td>10</td>
<td>2/\sqrt{3}</td>
<td>0.77%/%</td>
<td>0.89%</td>
<td></td>
</tr>
<tr>
<td>Phant. pos (y) (mm)</td>
<td>0</td>
<td>10</td>
<td>2/\sqrt{3}</td>
<td>0.77%/%</td>
<td>0.89%</td>
<td></td>
</tr>
<tr>
<td>Phant. pos (z) (mm)</td>
<td>0</td>
<td>10</td>
<td>2/\sqrt{3}</td>
<td>0.69%/%</td>
<td>0.80%</td>
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<tr>
<td>Implant pos (x) (mm)</td>
<td>0</td>
<td>1</td>
<td>1/\sqrt{3}</td>
<td>2.4%/mm</td>
<td>1.4%</td>
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<tr>
<td>Implant pos (y) (mm)</td>
<td>0</td>
<td>1</td>
<td>1/\sqrt{3}</td>
<td>1.0%/mm</td>
<td>0.58%</td>
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<tr>
<td>Implant pos (z) (mm)</td>
<td>0</td>
<td>1</td>
<td>1/\sqrt{3}</td>
<td>0.6%/mm</td>
<td>0.35%</td>
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<tr>
<td>Subuncertainty SAR</td>
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<td></td>
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<td>5.6%</td>
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Uncertainty Assessment: Infinite Possibilities…

- factors assessed for each spatial point, every model and every position, by taking the biggest EV of the difference of the corresponding matrices:
  - small shifts (x,y,z)
  - dielectric properties of major tissues and entire model
  - phase and amplitude uncertainties (analytical calculation)
  - convergence

- factors assessed for psSAR of selected excitations:
  - grid resolution
  - Huygens’ box method
  - inter-model variations
  - coil modeling
Uncertainty Assessment: Infinite Possibilities…

- Example: phase and amplitude uncertainty

\[
\begin{pmatrix}
1 & 0 \\
0 & e^{-\Delta \phi}
\end{pmatrix}
\begin{pmatrix}
a & c \\
c^* & b
\end{pmatrix}
\begin{pmatrix}
1 & 0 \\
0 & e^{\Delta \phi}
\end{pmatrix}
= 
\begin{pmatrix}
a & c \cdot e^{\Delta \phi} \\
(c \cdot e^{\Delta \phi})^* & b
\end{pmatrix}
\]

\[\lambda_{max} = \left| c \left( e^{\Delta \phi} - 1 \right) \right| \quad \text{(maximal EV of difference matrix)}\]

\[
\begin{pmatrix}
1 & 0 \\
0 & f
\end{pmatrix}
\begin{pmatrix}
a & c \\
c^* & b
\end{pmatrix}
\begin{pmatrix}
1 & 0 \\
0 & f
\end{pmatrix}
= 
\begin{pmatrix}
a & c \cdot f \\
c^* \cdot f & b \cdot f^2
\end{pmatrix}
\]

\[\lambda_{max} = \frac{b \left( f^2 - 1 \right) + \sqrt{b^2 \left( f^2 - 1 \right)} + 4 |c|^2 (f - 1)^2}{2}\]

- evaluate for each single averaging volume (per model and position) and take spatial peak

- worst-case uncertainty of all possible excitations, overestimating psSAR
Uncertainty Assessment: Population Coverage

- independent ‘Virtual Population’ models to acquire data (male/female, large age variation, obese models…)

- additional postures, & morphing (BMI, shape) to extend coverage

- independent models for testing the predictions in the end

- 10 positional shifts
Uncertainty Assessment: Population Coverage

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- 10 positional shifts
Uncertainty Assessment: Population Coverage

- determine stddev for each position over simulated models and extend to relevant population coverage
- difference between extended coverage and envelope must be added to safety margin
Uncertainty Assessment: Tissue Parameters

- uncertainty contribution requires knowledge of:
  - sensitivity
  - uncertainty for underlying parameter

  - literature review of densities, thermal properties, perfusion rates, dielectric properties (incl. LF); coming: acoustic, flow
  - information about range, stddev
### Uncertainty Assessment: *In Vivo* T Validation

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<thead>
<tr>
<th>Parameter</th>
<th>Range</th>
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<tbody>
<tr>
<td>(a) EM Simulation</td>
<td></td>
<td>psSAR10g per wbSAR$^a$</td>
</tr>
<tr>
<td>Convergence</td>
<td>Simulation length: $+100%$</td>
<td>0.03 dB</td>
</tr>
<tr>
<td>Model discretization</td>
<td>Voxel size: 0.5 mm, 3 mm</td>
<td>0.26 dB</td>
</tr>
<tr>
<td>Dielectric parameter</td>
<td>$\sigma$: $\pm 10%$</td>
<td>0.05 dB</td>
</tr>
<tr>
<td>Dielectric parameter</td>
<td>$\varepsilon$: $\pm 10%$</td>
<td>0.17 dB</td>
</tr>
<tr>
<td>Dielectric contrast</td>
<td>$\sigma$: $\pm 10%$, in single tissue</td>
<td>0.09 dB</td>
</tr>
<tr>
<td>Density contrast</td>
<td>$\rho$: $\pm 10%$, in single tissue</td>
<td>0.08 dB</td>
</tr>
<tr>
<td>Anatomical model accuracy</td>
<td>According to (29)</td>
<td>0.28 dB</td>
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<tr>
<td>RSS: Local SAR uncertainty</td>
<td></td>
<td>0.51 dB ($-11%; +12%$)</td>
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(b) Thermal Simulation (worst case scenario, steady-state)

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<th>Parameter</th>
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<tbody>
<tr>
<td>Local SAR uncertainty</td>
<td>from (a)</td>
<td>pT, Thermoregulated</td>
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<tr>
<td>Convergence</td>
<td>Simulation length and time step</td>
<td>0.40 dB$^b$</td>
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<tr>
<td>Model discretization</td>
<td>Voxel size: 0.5 mm, 3 mm</td>
<td>0.04 dB$^b$</td>
</tr>
<tr>
<td>Thermal parameter</td>
<td>$c$: $\pm 10%$</td>
<td>0.19 dB$^b$</td>
</tr>
<tr>
<td>Thermal parameter</td>
<td>$k$: $\pm 20%$</td>
<td>0.00 dB$^b$</td>
</tr>
<tr>
<td>Thermal parameter</td>
<td>$Q$: $\pm 20%$</td>
<td>0.05 dB$^b$</td>
</tr>
<tr>
<td>Blood heat capacity</td>
<td>$\rho_b$-$c_b$: $\pm 10%$</td>
<td>0.08 dB$^b$</td>
</tr>
<tr>
<td>Thermal boundary cond.</td>
<td>$h$: $\pm 50%$</td>
<td>0.16 dB$^b$</td>
</tr>
<tr>
<td>Basal (constant) perfusion</td>
<td>$B_0$: $\pm 50%$ (all tissues)</td>
<td>0.12 dB$^b$</td>
</tr>
<tr>
<td>Perfusion increase</td>
<td>$L_b$: $\pm 50%$</td>
<td>0.26 dB$^b$</td>
</tr>
<tr>
<td>RSS: Peak temperature increase uncertainty</td>
<td>Estimated value and resulting uncertainty</td>
<td>0.90 dB$^b$, 42.8°C (41.7°C; 44.1°C)</td>
</tr>
<tr>
<td>Corresponding max. scan time uncertainty</td>
<td>(in defined worst-case scenario for CEM43 = 15 min limit)</td>
<td>0.70 dB$^b$, $n.a.$</td>
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<thead>
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<tr>
<td>Convergence</td>
<td></td>
<td>2.1 dB$^b$, 25 min (16 min; 41 min)</td>
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<tr>
<td>Model discretization</td>
<td></td>
<td>1.2 dB$^b$, 4 min (3 min; 5.3 min)</td>
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*FOUNDAION*
Uncertainty: Validation Experiment

<table>
<thead>
<tr>
<th>Source of Uncertainty</th>
<th>Uncertainty Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature probe uncertainty</td>
<td>&lt; 0.1 dB</td>
</tr>
<tr>
<td>Incidence B1 field assessment</td>
<td>0.6 dB</td>
</tr>
<tr>
<td>Probe placement (20 mm)</td>
<td>1.0 dB</td>
</tr>
<tr>
<td>Probe thermal contact</td>
<td>0.5 dB</td>
</tr>
<tr>
<td>Volunteer positioning (100 mm)</td>
<td>0.3 dB</td>
</tr>
<tr>
<td>Differences between Duke and the actual volunteer</td>
<td>0.3 dB</td>
</tr>
<tr>
<td>Thermal equilibration</td>
<td>0.5 dB</td>
</tr>
<tr>
<td>RSS: Thermal validation measurement uncertainty, actual estimated value and uncertainty interval</td>
<td>1.4 dB, 39.5°C (38.8°; 40.5°)</td>
</tr>
<tr>
<td>RSS (b) + (d):</td>
<td>1.6 dB (k = 1); 3.2 dB (k = 2)</td>
</tr>
</tbody>
</table>

*Relative local SAR uncertainty, as exposure is normalized to wbSAR.

*Highly nonlinear model. Values only valid for this specific worst-case (Fats, pelvis position, and first level om).

Stated uncertainty values are standard deviations (k = 1) in the assumed log-normal probability distribution. Since they are uncorrelated, they can be combined by root-sum-square (RSS) procedures.

Effect Assessment
Thermal Dose-Based Limits

- required safety margins can be reduced if quantities closer to safety relevant effect are evaluated

- JWG Thermal Workshop has proposed CEM43-based thresholds for MRI:
  - local hot-spots
  - transient effects
  - tissue specific thresholds
  - literature-based multi-tier thresholds (controlled?, compromised perfusion?, pregnant?)
Thermal Dose-Based Limits

Example: EM-Neuron Interaction
Illustrating Example: EM Induced Neuron Stim.

- MRI gradient coil switching induced nerve stimulation considering:
  - inhomogeneity/anisotropy
  - nerve models

- question of suitable safety thresholds
  - standards all based on E-field limits, typically derived based on SENN

- necessity of understanding how thresholds were derived (assumptions)
  - e.g., assumptions regarding relation wbSAR-psSAR not valid for pTx

- typically biology/physiology-based thresholds:
  - larger variability
  - not always obvious which effects are safety limiting
  - interaction mechanism frequently poorly established
    - role of modelling goes beyond task of providing detail on physical interaction difficult to obtain by measurements
    - enhanced need for validation to ascertain critical aspects captured
Effect Assessment: EM Induced Neuron Stimulation –

- Integration of sciatic nerve model with SENN dynamics in Ella (ViP v3.0)
- Coupled EM-NEURON modeling
- RF induced heating on/off
Effect Assessment: EM Induced Neuron Stimulation – Results

issues with standard limits:

- importance of inhomogeneity
  - affects threshold (even when end-node stimulation)
  - results in local foci

- threshold for center-type stimulation similar as end-node
  - E-field not sole criterium

- impact of temperature on dynamics
V&V: EM Induced Neuron Stimulation

- analytically solvable cases
- reproduction of published results:
  - results produced with widely employed, conservative SENN model
  - results published in Model DB on rat hippocampus stimulation
  - results produced by groups working on DBS modeling and measurement
- experiments (ongoing):
  - retinal ganglion cell activity measurements
  - rat sciatic nerve recruitment by neuroprosthetic device
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Selectivity for the right side of the TIME electrode, simulated vs experimental data
Conclusions
Conclusions

• computational modelling is valuable for device design/optimization, interaction analysis, safety assessment, trials, personalization

• it is increasingly demanded & standardized by regulatory agencies

• regulatory submission requires safety & efficacy, risk & credibility assessment

• V&V (code&model) must be documented and range must cover the CoU

• no V&V or submission is complete without uncertainty assessment
  ▸ establish detailed uncertainty budgets, after careful identification of factors
  ▸ linked to sensitivity analysis & to identification of worst-case

• multi-physics & in vivo bring additional challenges:
  - need of considering anatomical complexity & variability
    ▸ parameterized family of anatomical models
  - increased uncertainty of properties, dynamical behaviour
    ▸ increased need for validation
    ▸ material database; functionalized models
  - coupling needs V&V too
  - safety relevant interaction must be identified
    ▸ ascertain that modelling reproduces behaviour of interest, or
    ▸ identify suitable safety limits/margins – but be aware of underlying assumptions