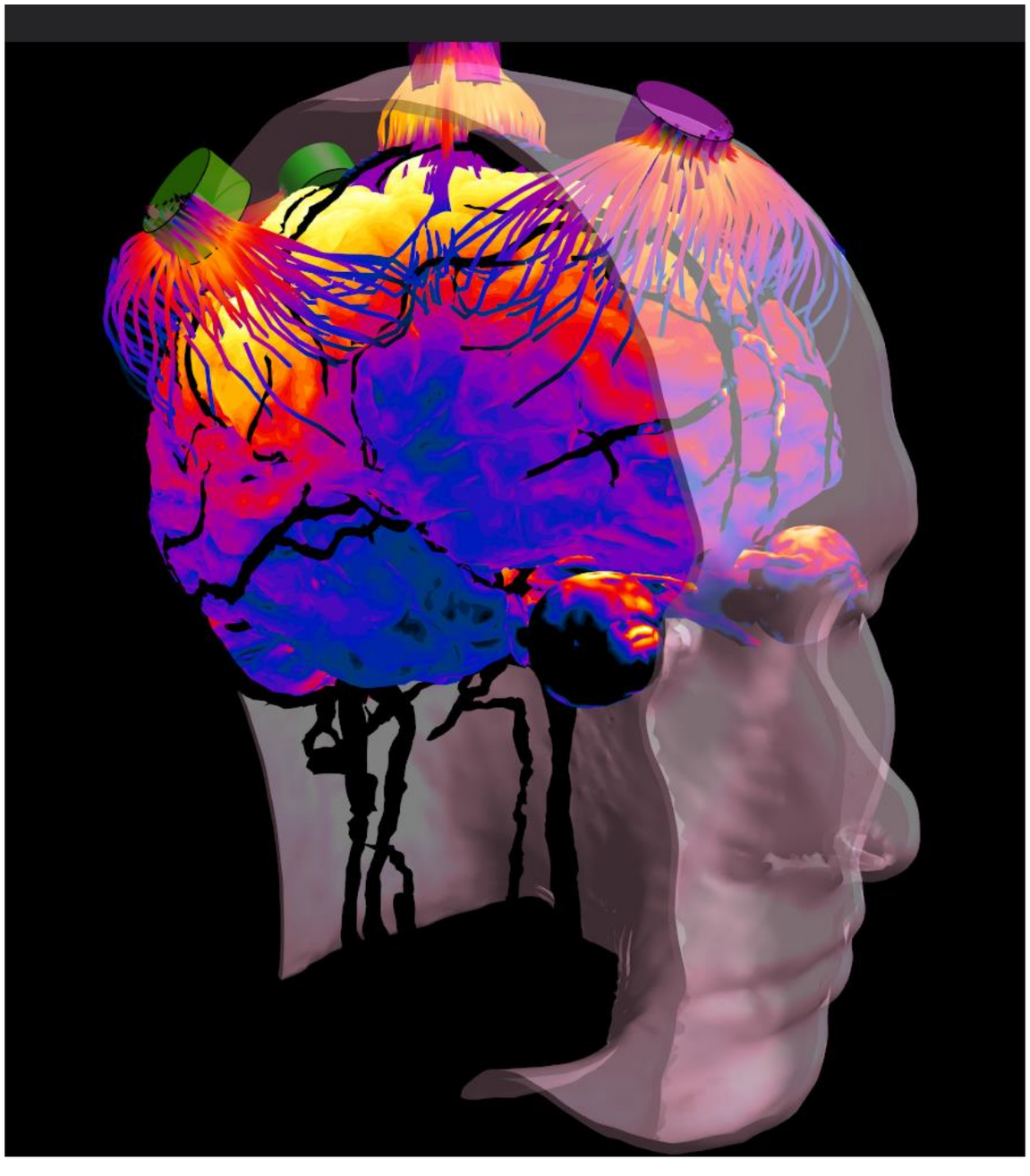
Sim4Life & Functionalized Anatomical Models:
MRI Safety, Thermal Therapies, and Neurostimulation

IT'IS Computational Life Sciences Group

Introduction

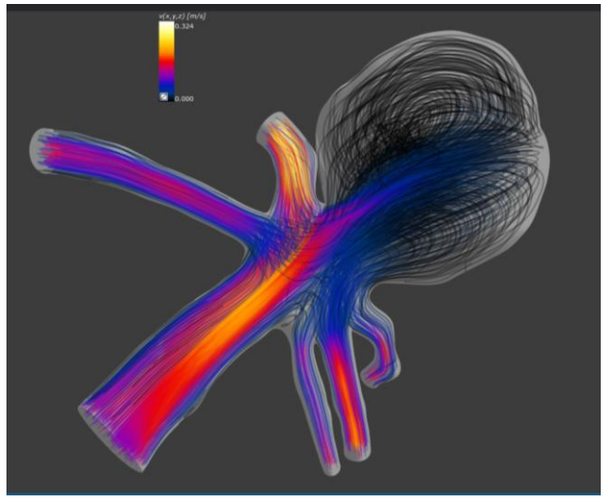
- advances in imaging and simulation technology permit the generation of functionalized (personalized) patient models
- this opens novel and powerful possibilities in:
  - device & therapy innovation
  - personalized medicine & treatment planning
  - *in silico* clinical trials (safety & effectivity assessment)
  - …
- Sim4Life is a computational life sciences platform optimized for the modeling physical and physiological/biological process in and around the human body

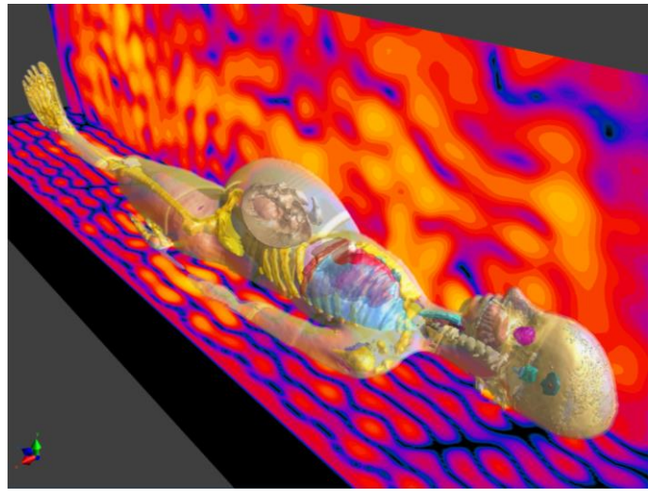


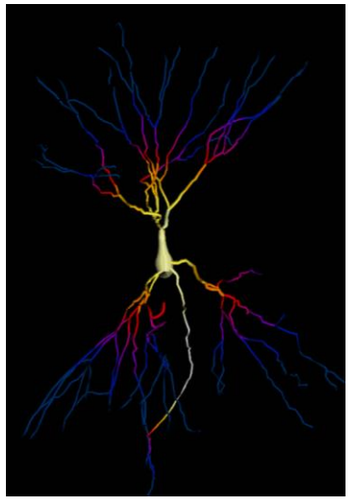
Solvers

physics

- electro-magnetics
- thermodynamics
- acoustics
- fluid dynamics



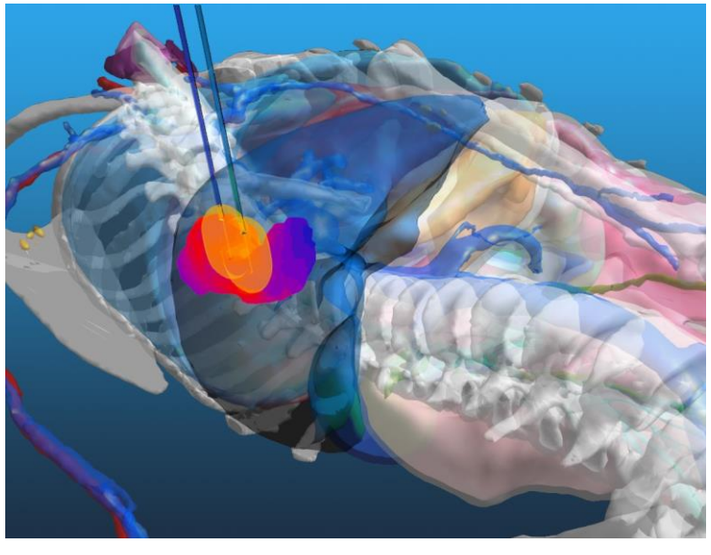


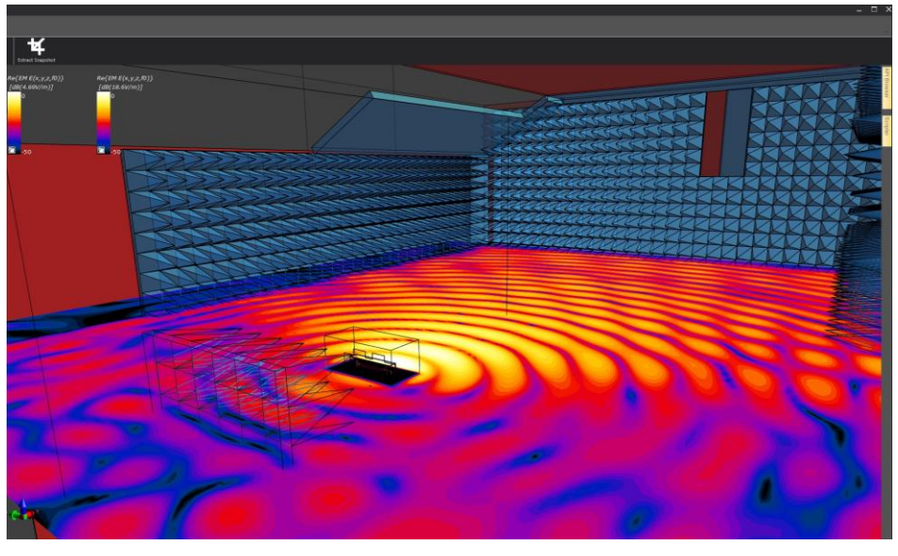


- CRD
- (mechanics

tissue models

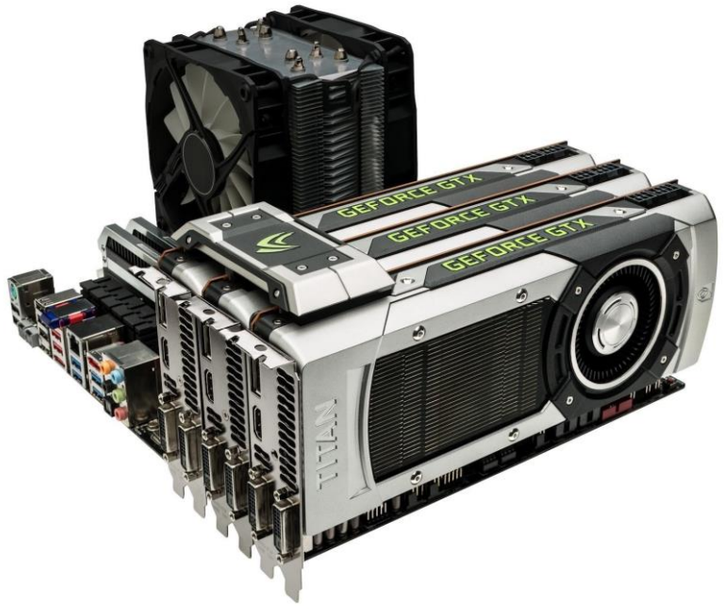
- neuronal dynamics
- perfusion models
- tissue damage / growth models

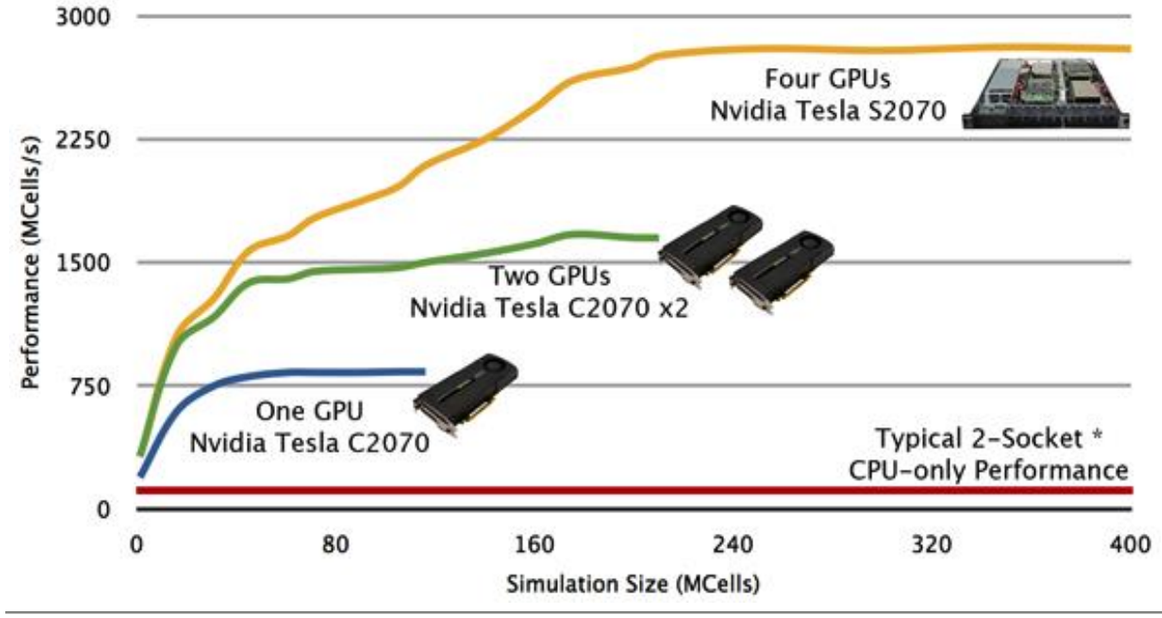


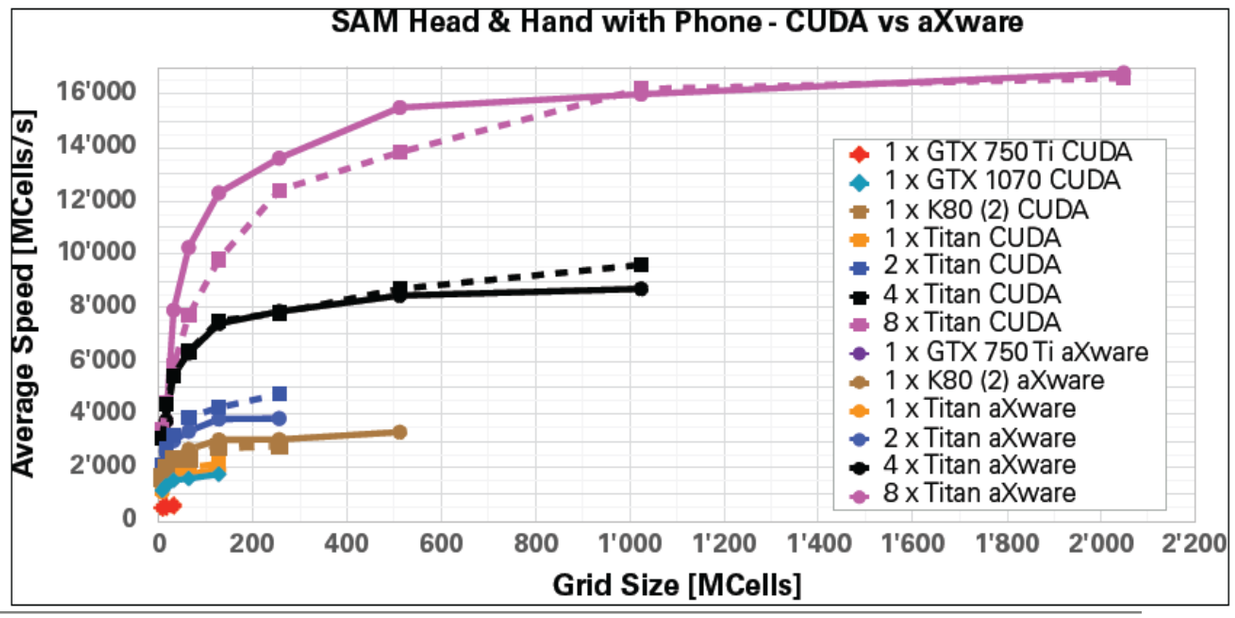


High Performance Computing

- (multi-)GPU HW acceleration
- MPI/OMP parallelization (clusters, supercomp.…)

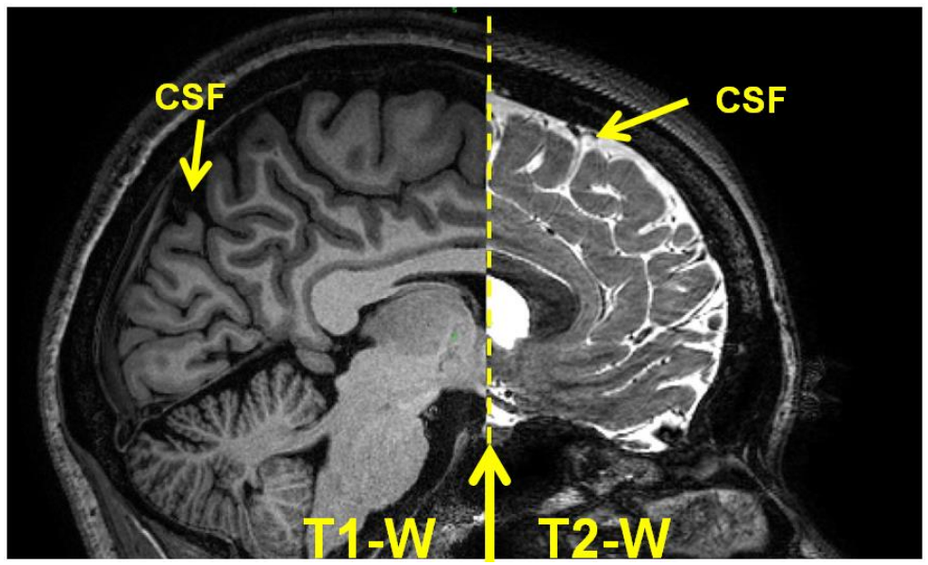


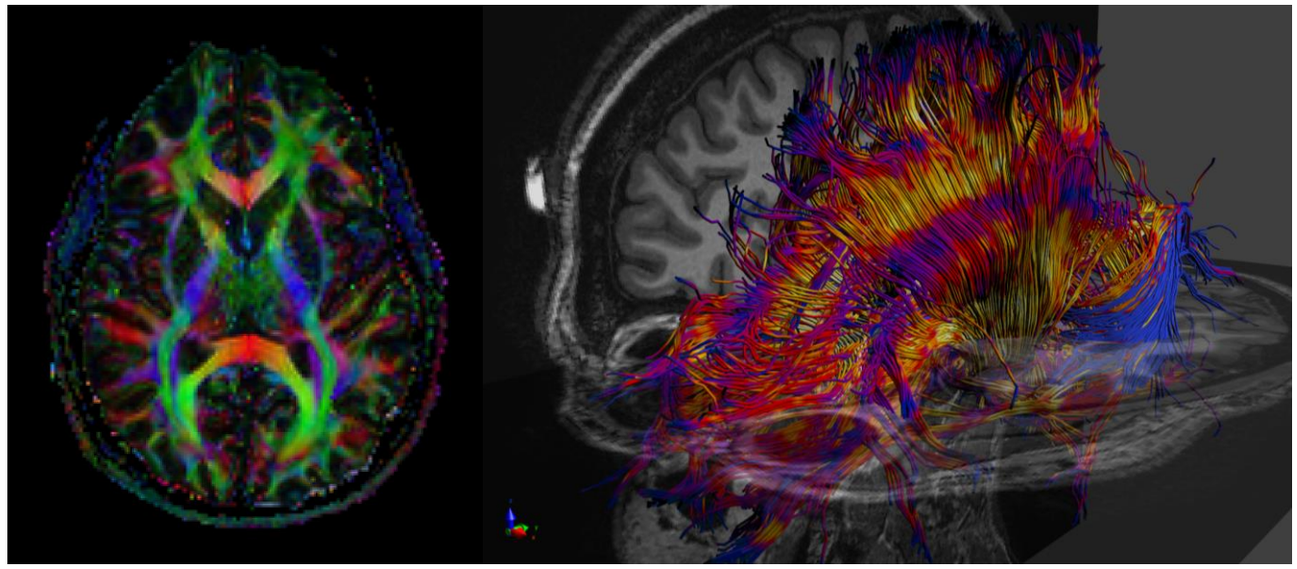


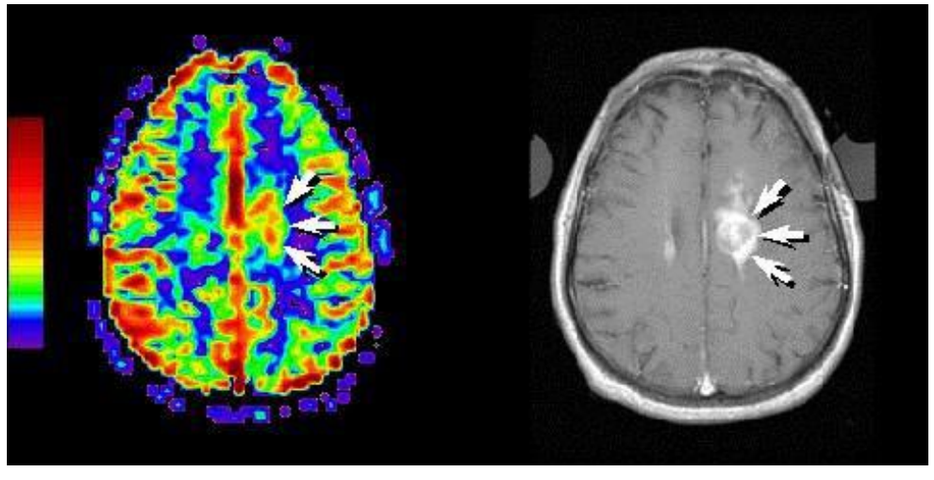


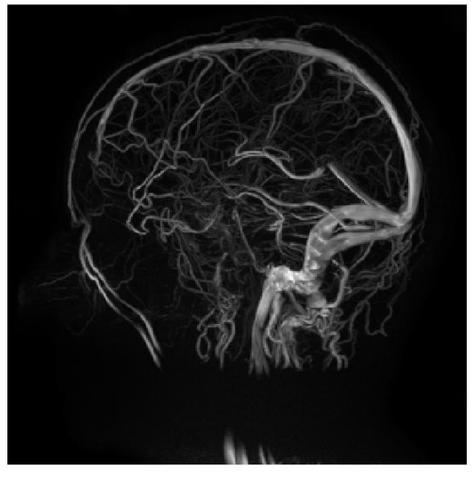
FUNCTIONALIZED ANATOMICAL MODELS

Medical Image Data (MRI)

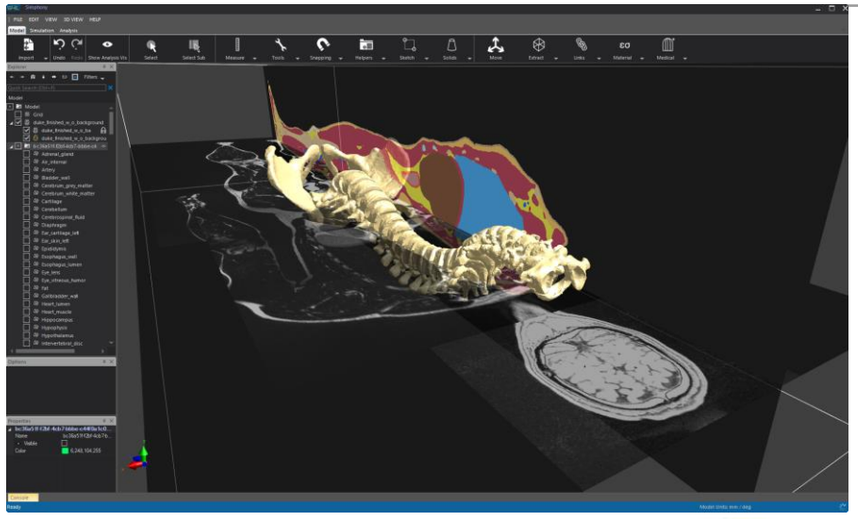


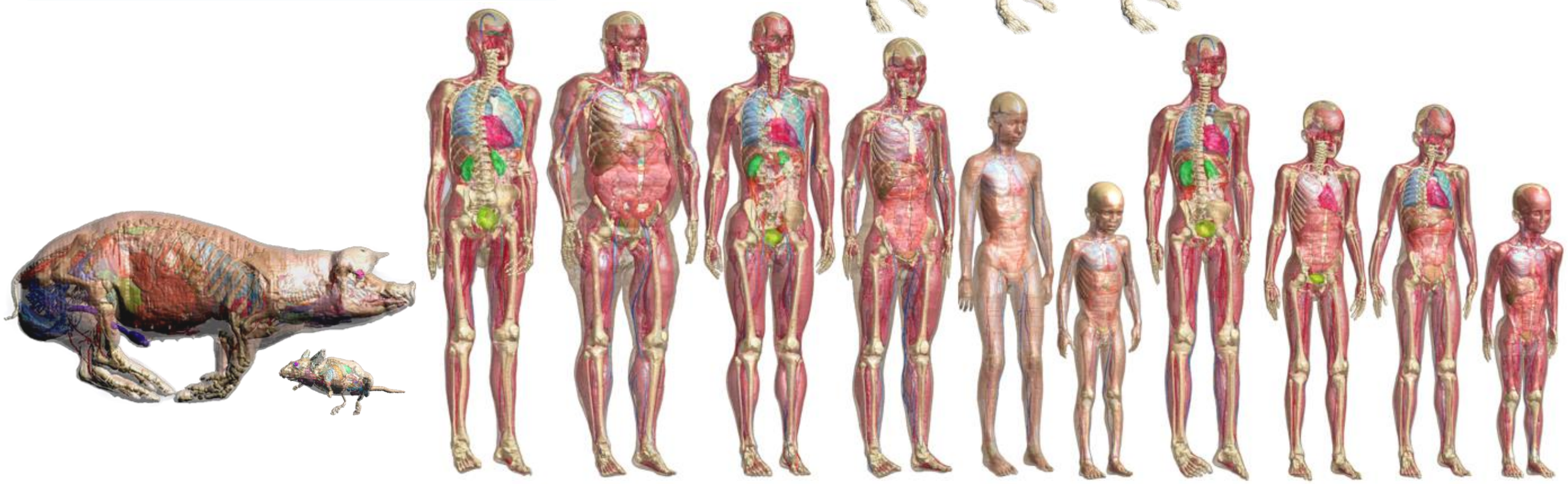




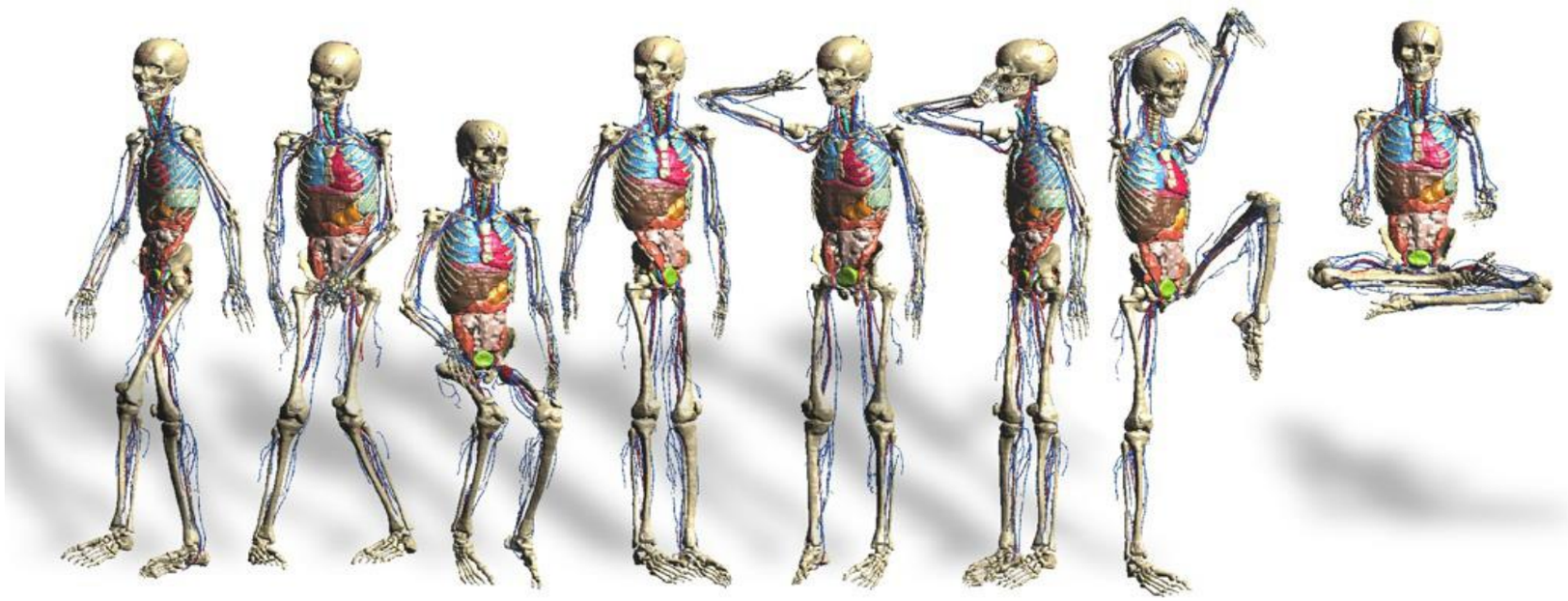


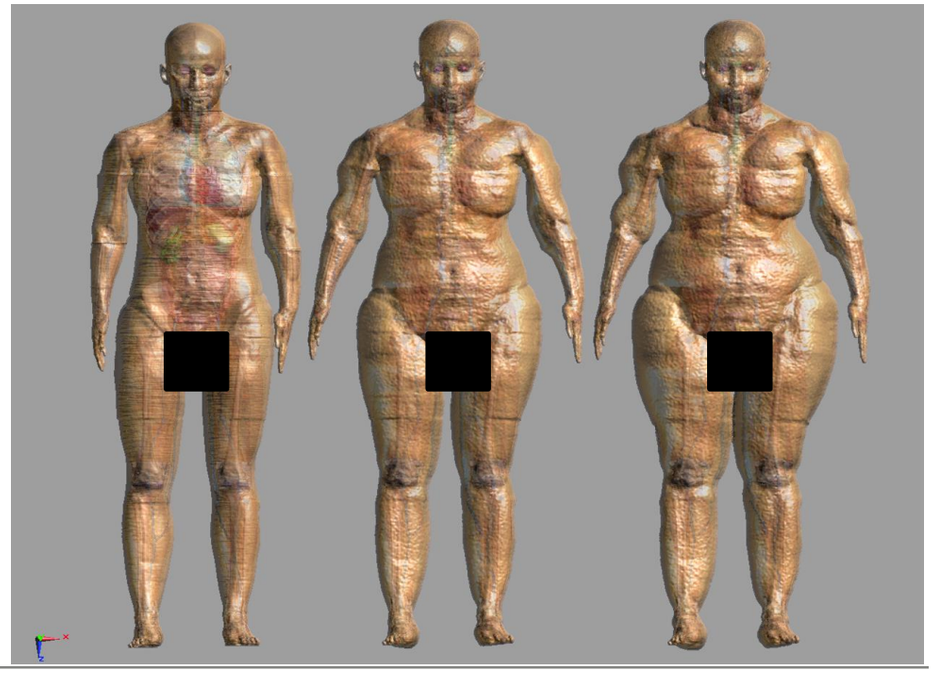
Virtual Population





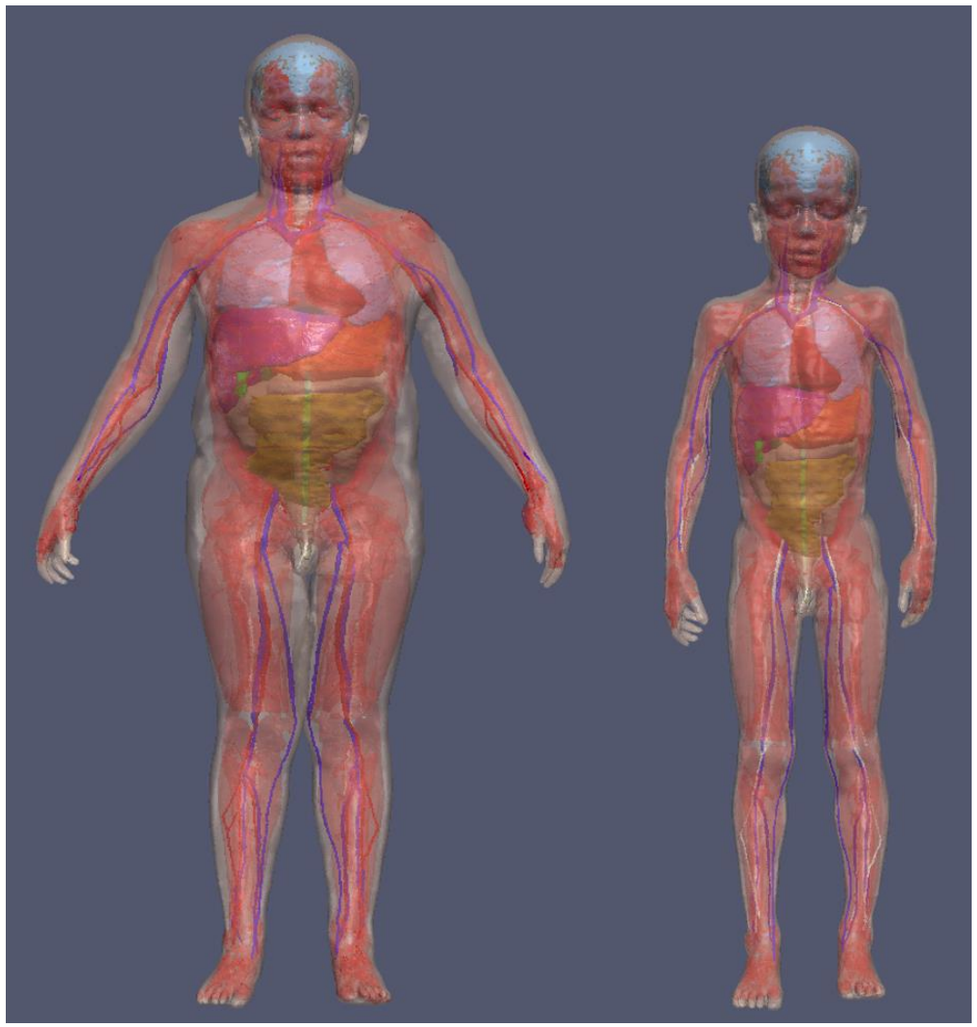
Parameterization for Comprehensive Coverage



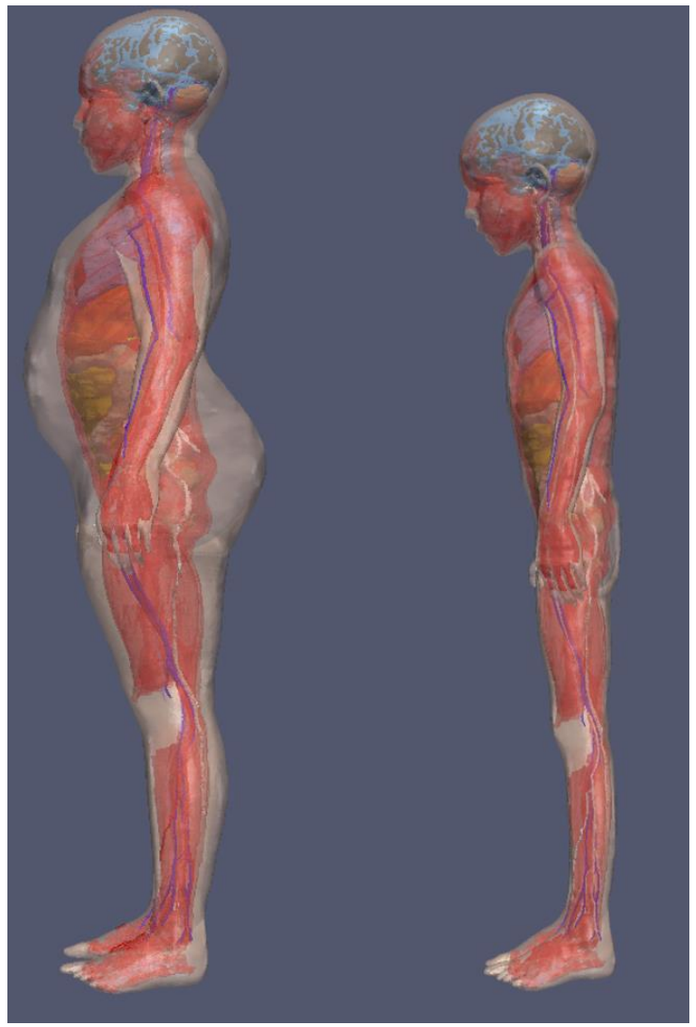


Morphing for Personalization

- surface-based (ICP) / image-based (registration) / physics-based (biomechanical)

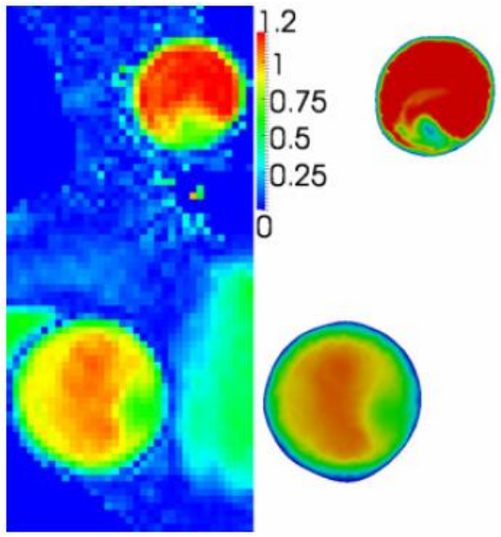


Obese Child Thelonious

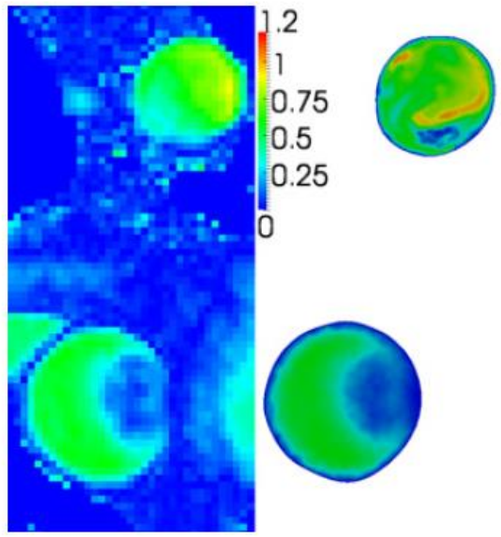


Obese Child Thelonious

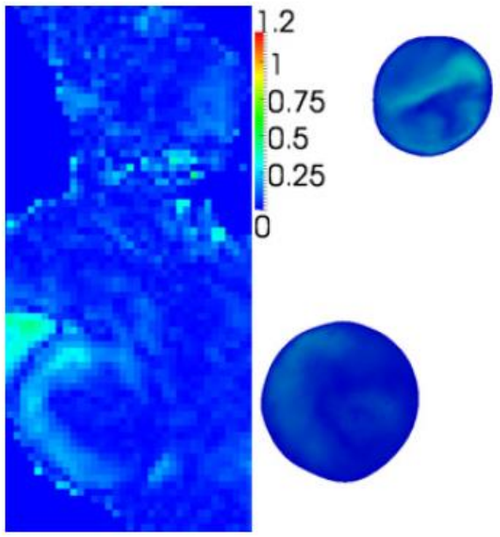
Images Provide more than Anatomy: MHD



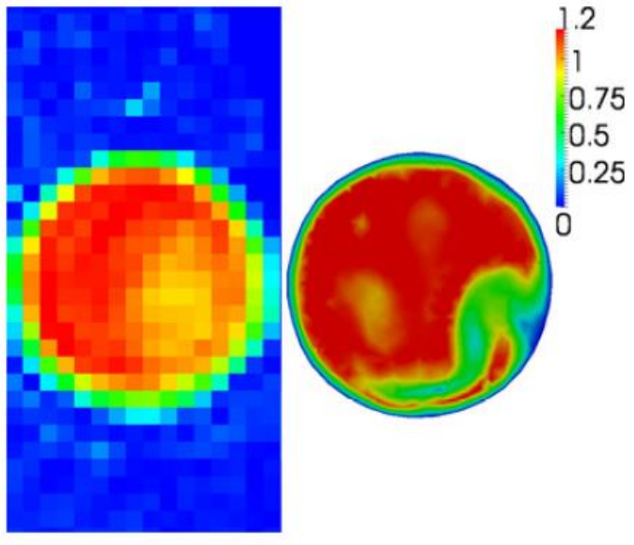
(a)



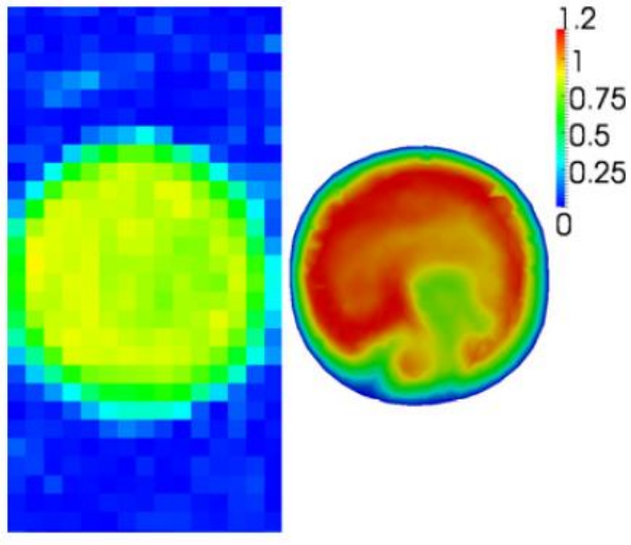
(b)



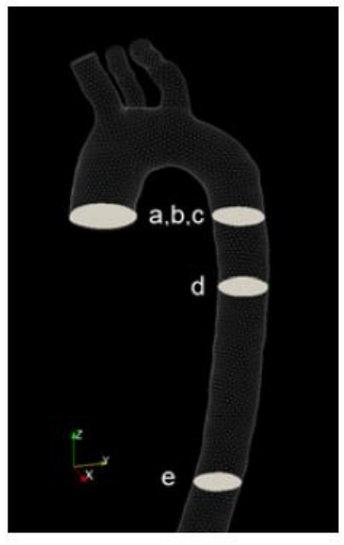
(c)



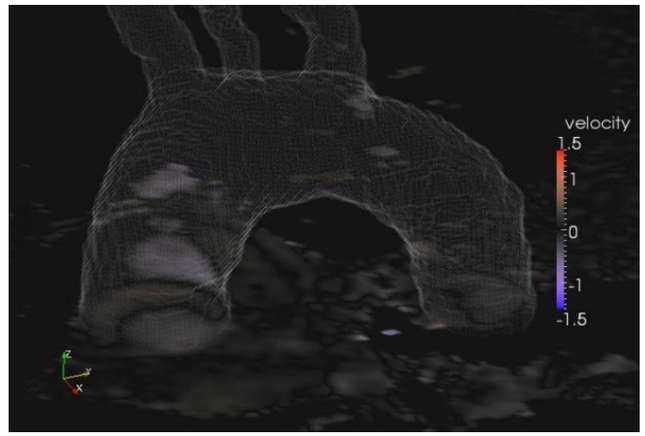
(d)



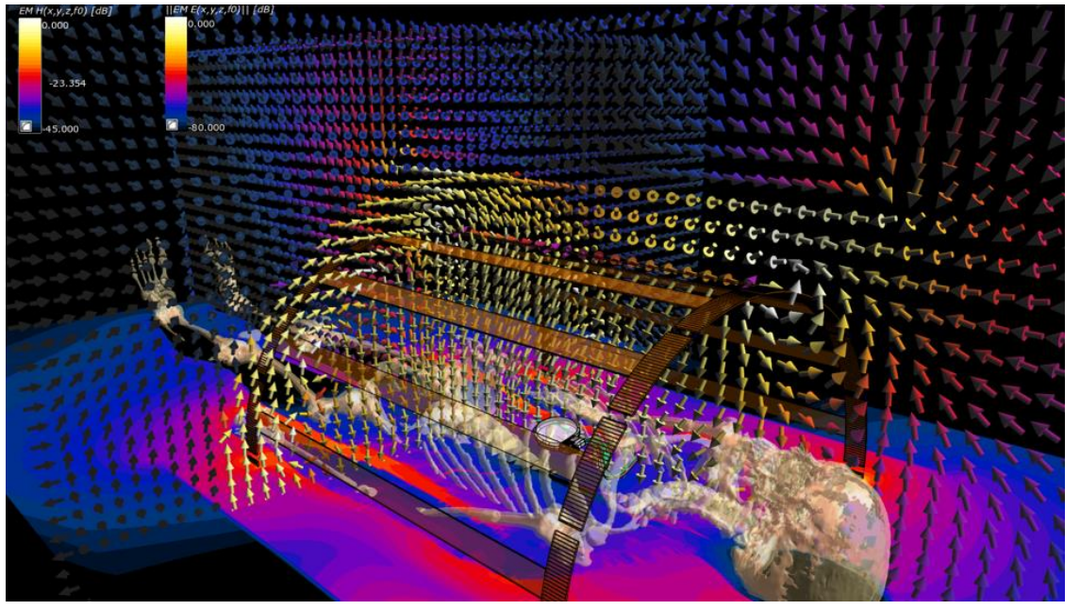
(e)

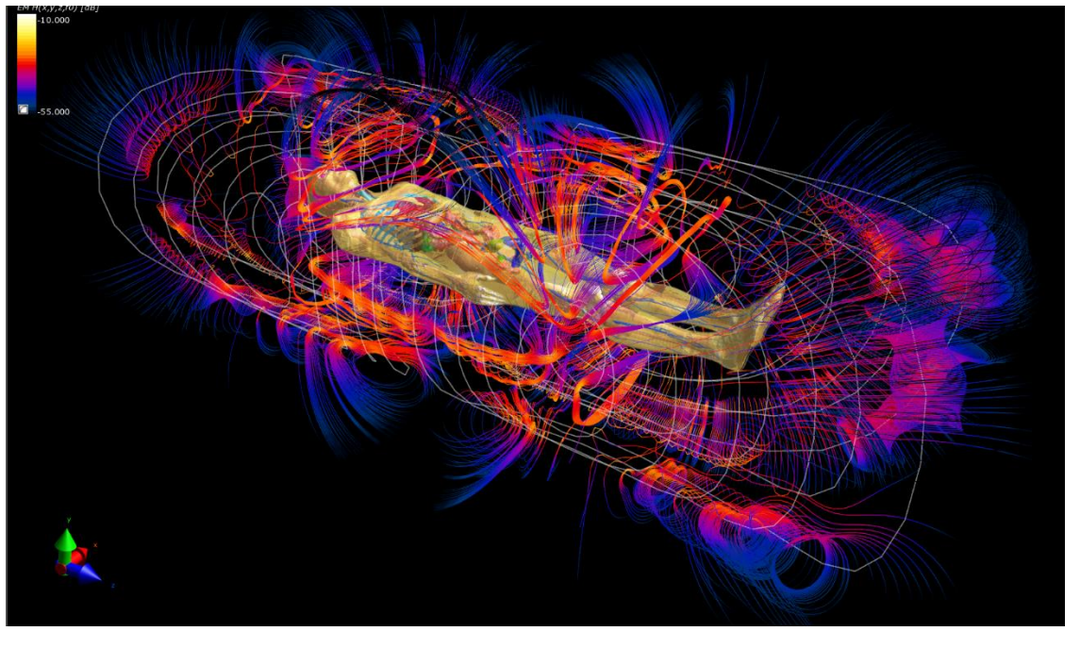


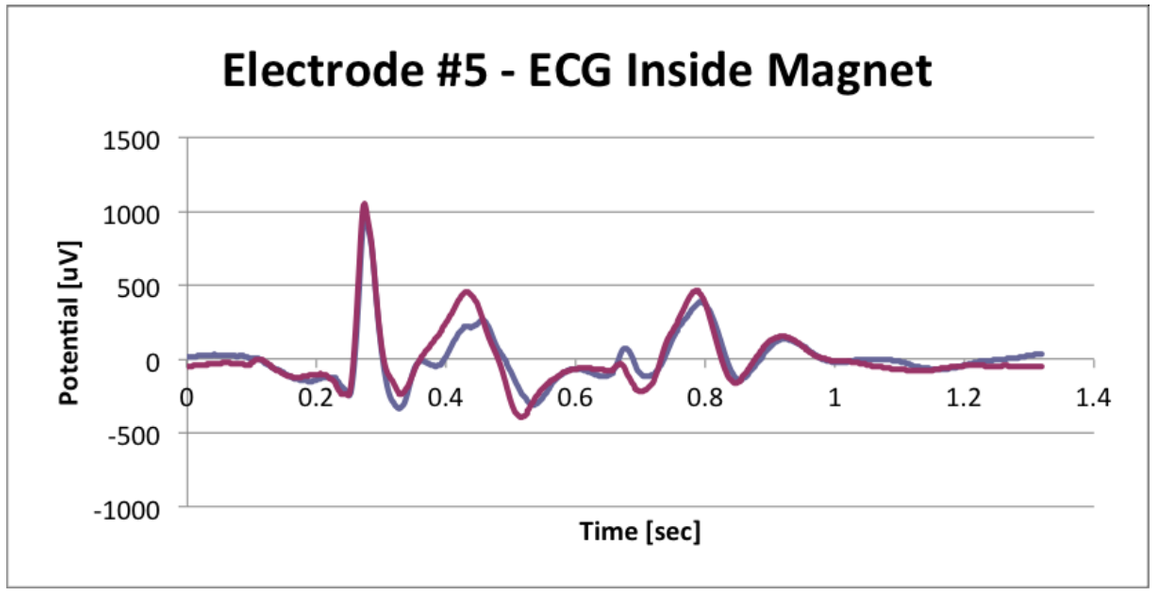
(f)

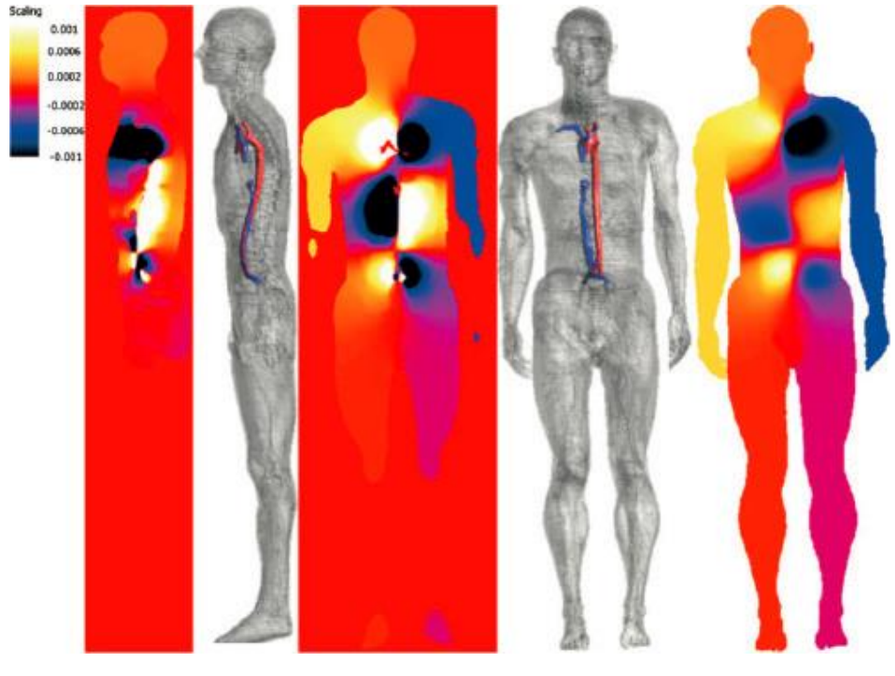


Images Provide more than Anatomy: MHD

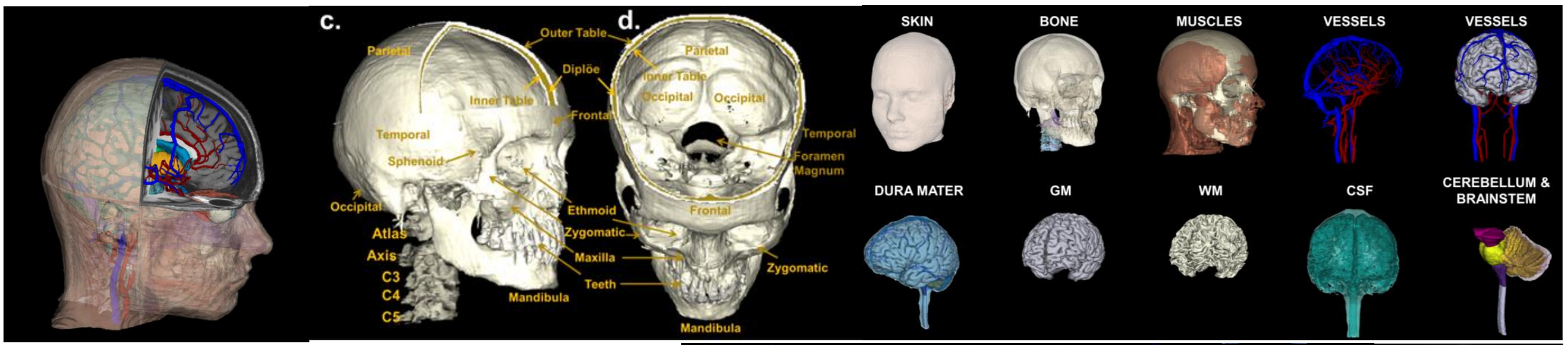


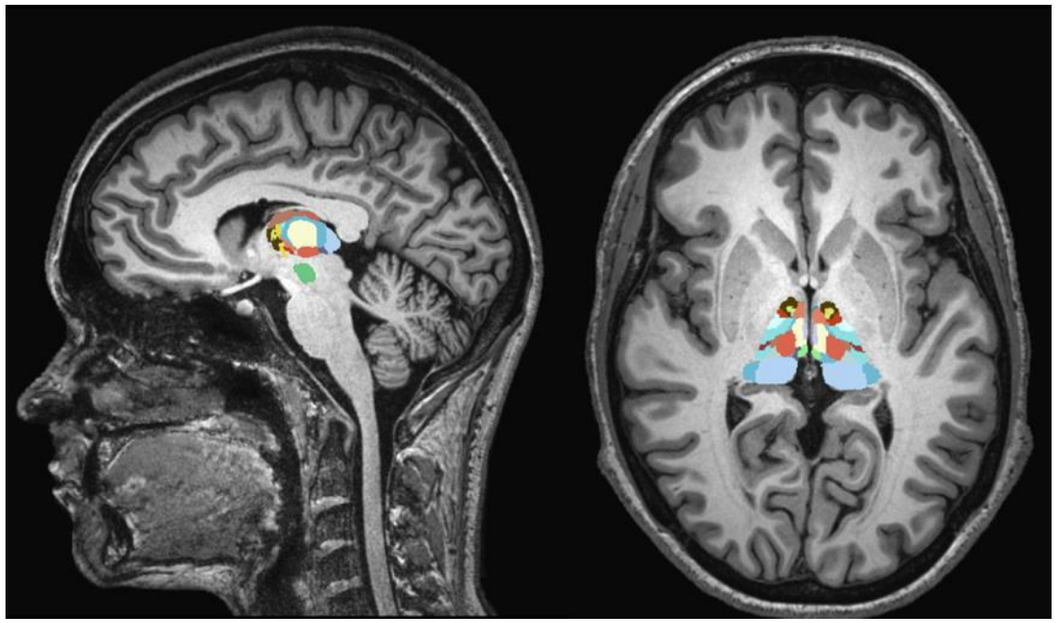


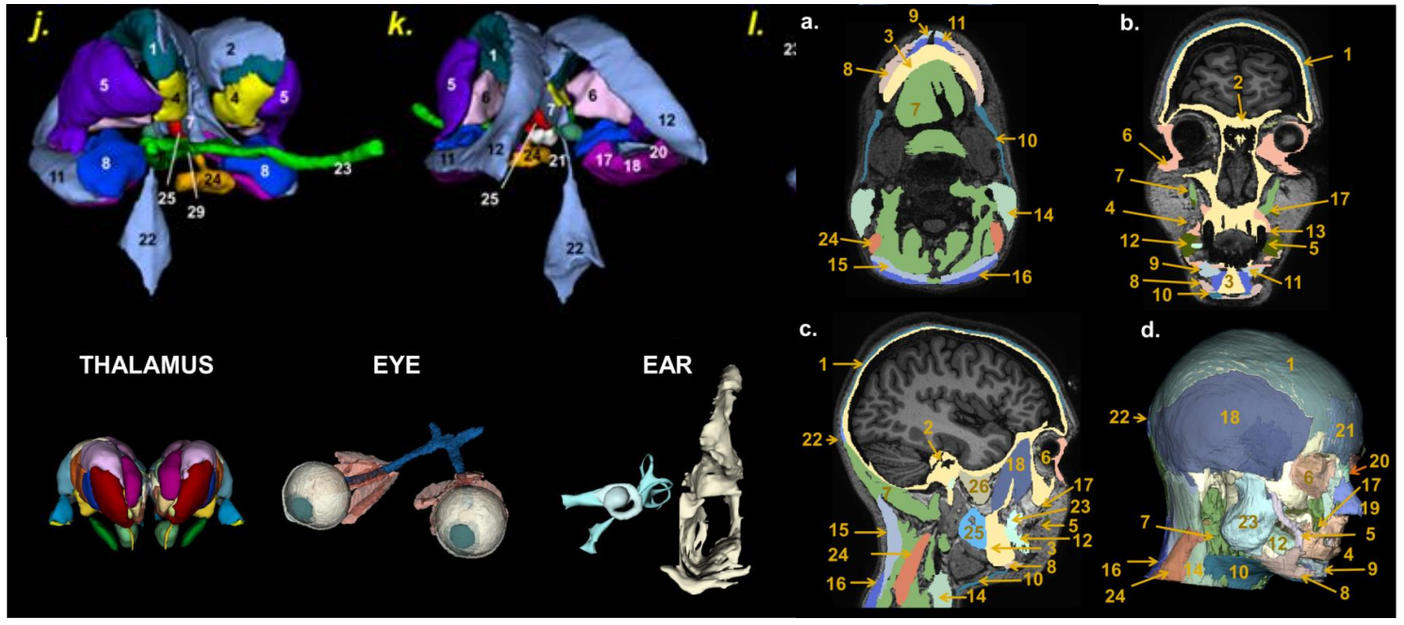




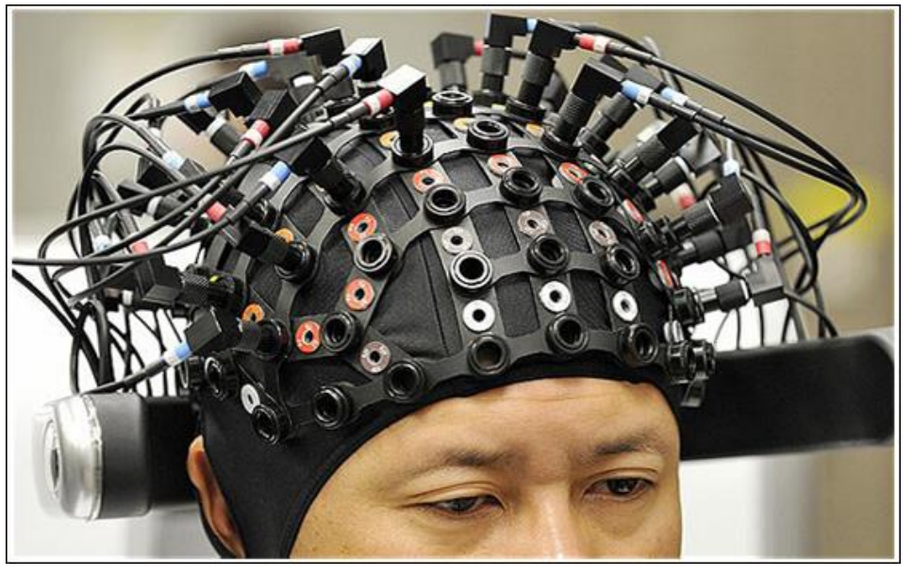
High Resolution MIDA Head Model (0.5mm, 160 struct.)

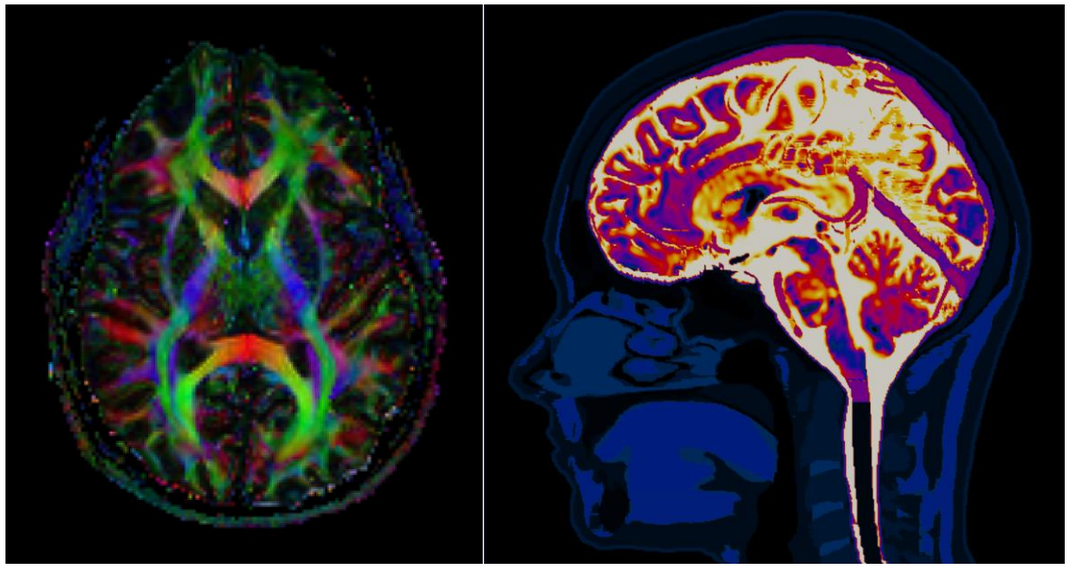


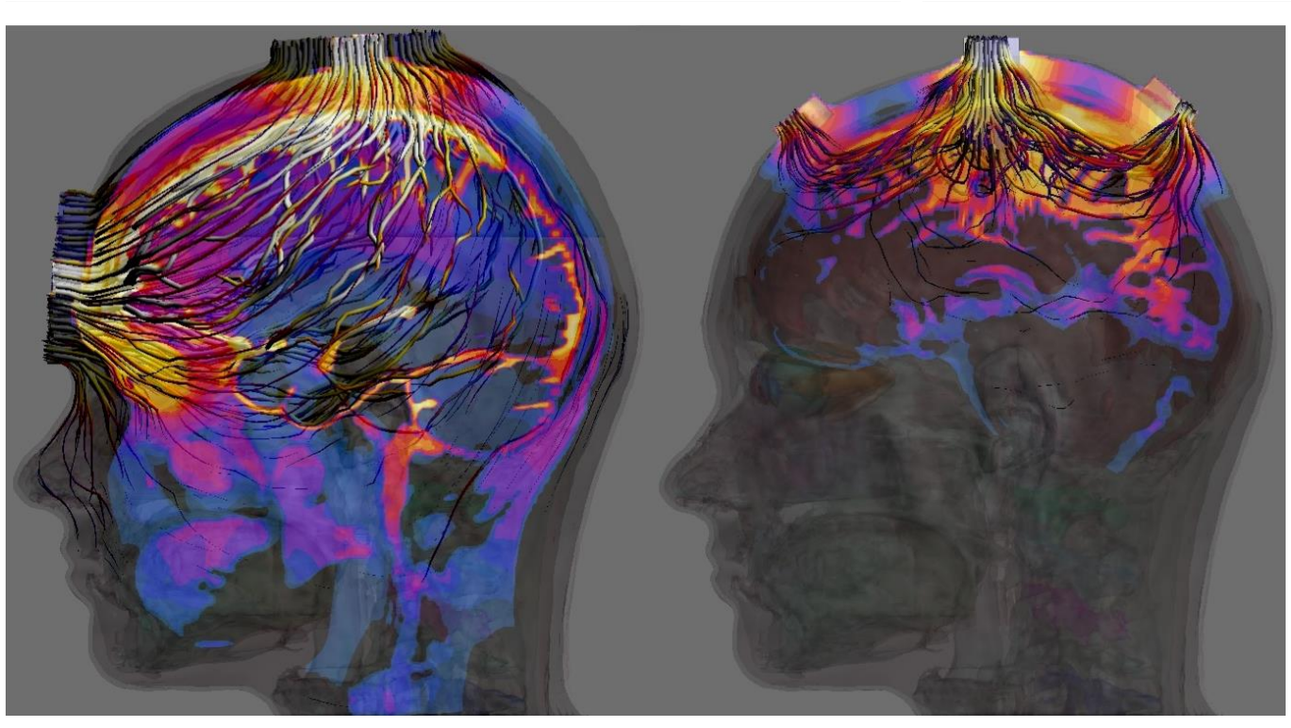


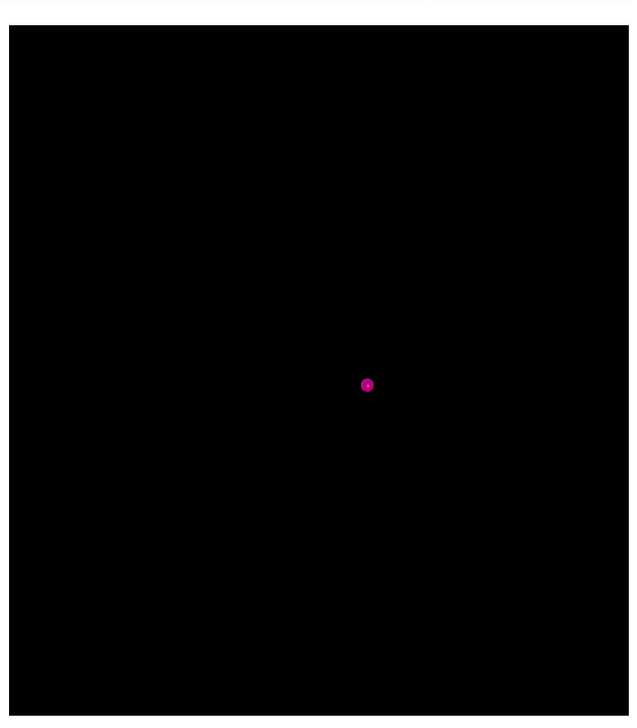


Images Provide more than Anatomy : TACS

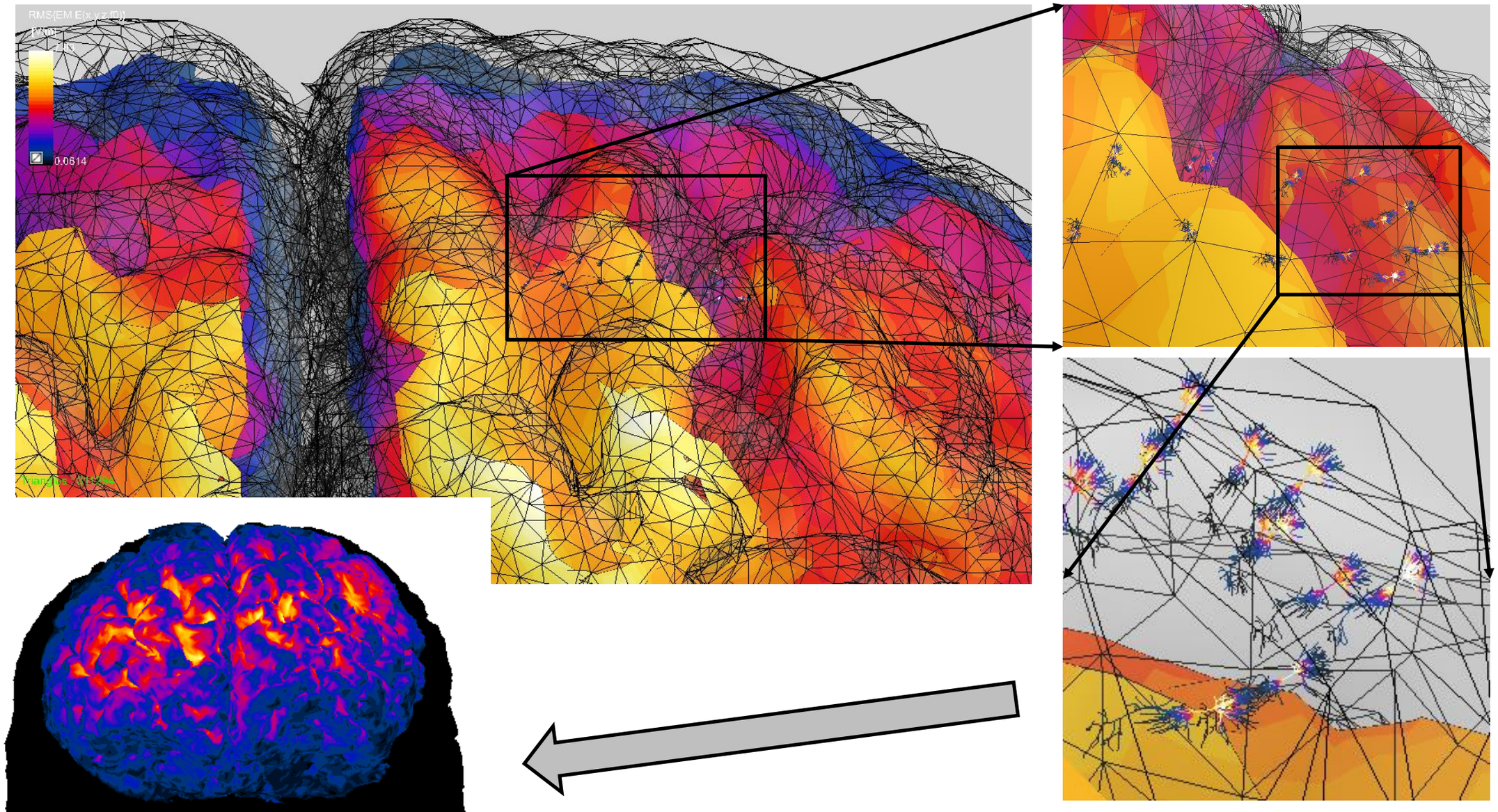






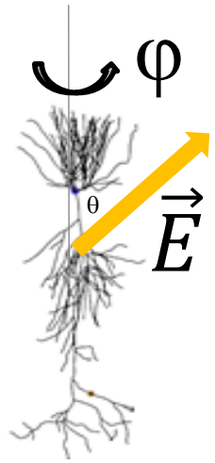


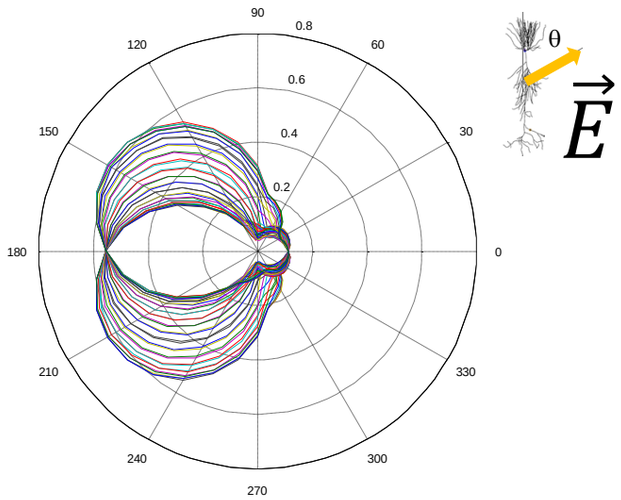
Images Provide more than Anatomy : TACS



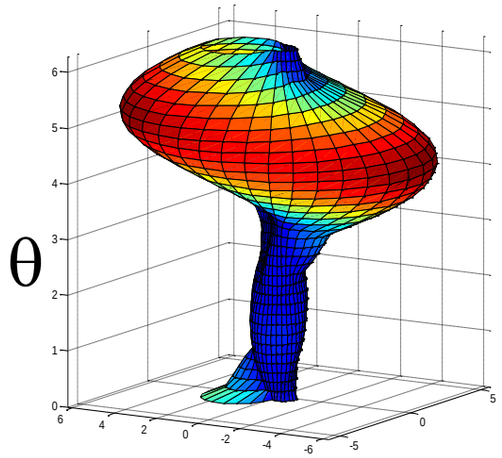
Multiscale: Top-Down

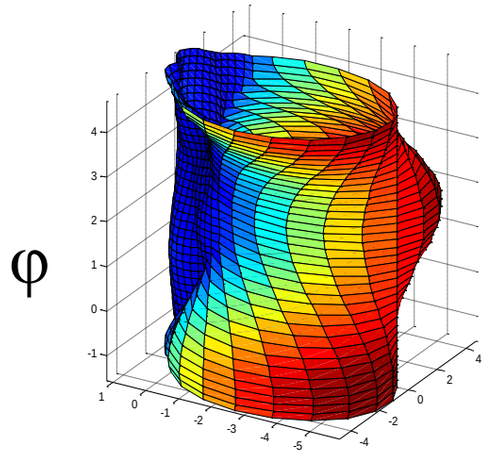
Neuronal Excitability: Anysotropy, Timing, Location



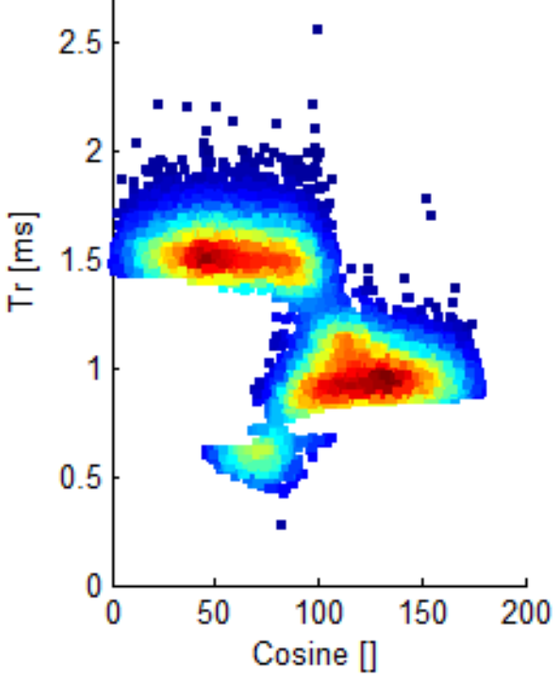


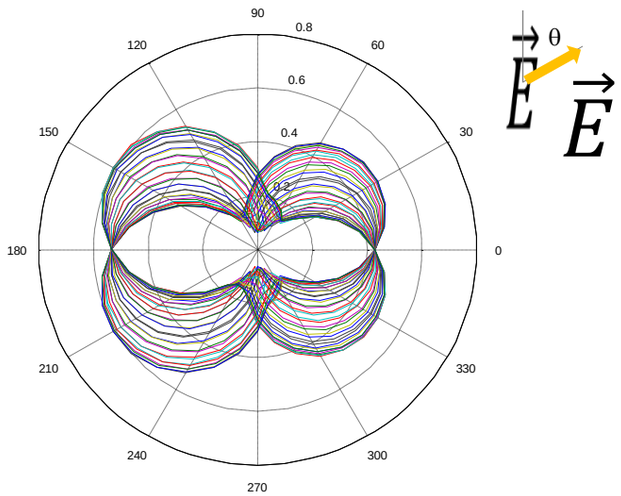
Monopolar Pulse

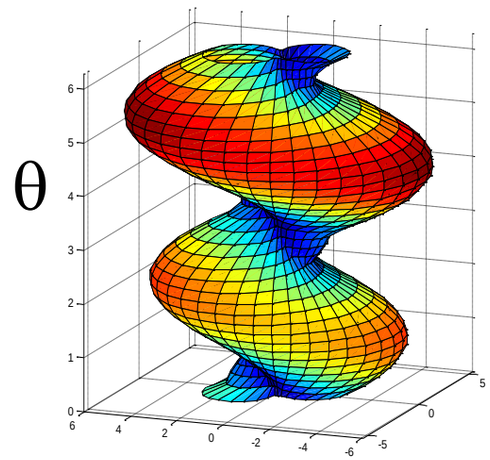


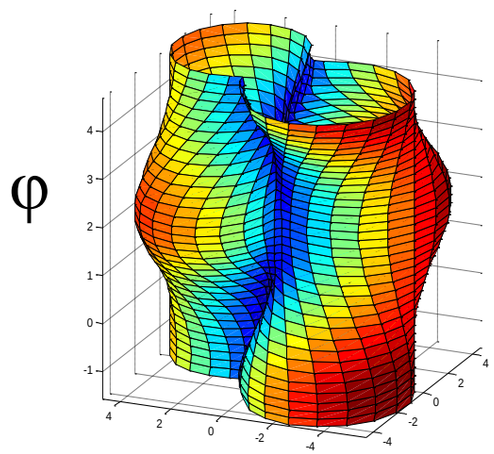


Bipolar Pulse







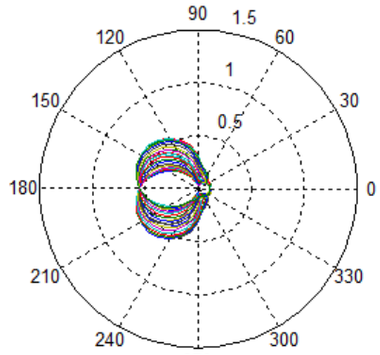


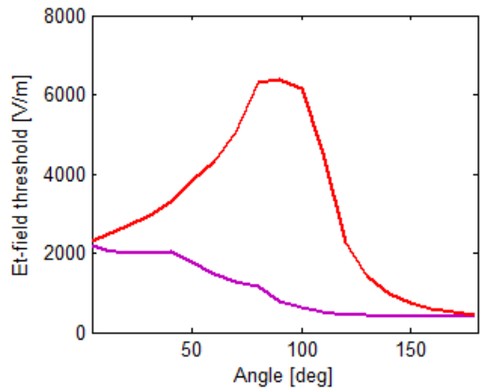
Multiscale Modeling

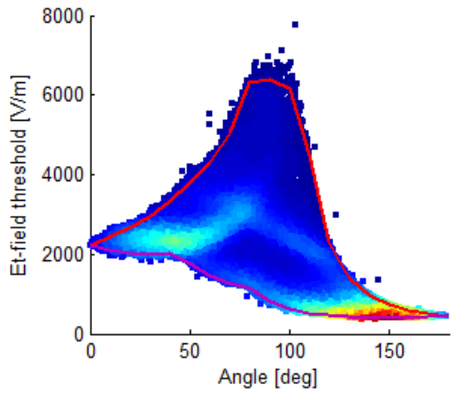
Single-Cell

In-Situ

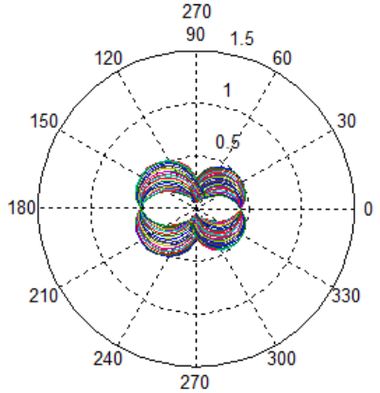
Monophasic

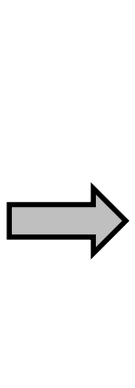


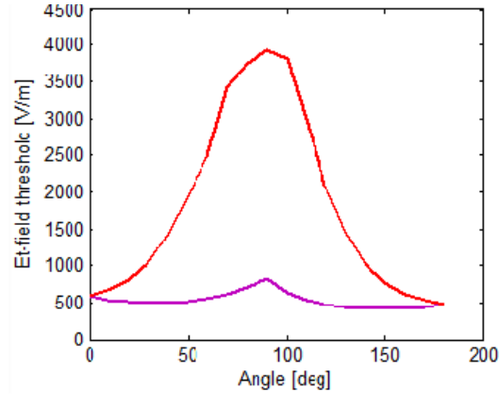


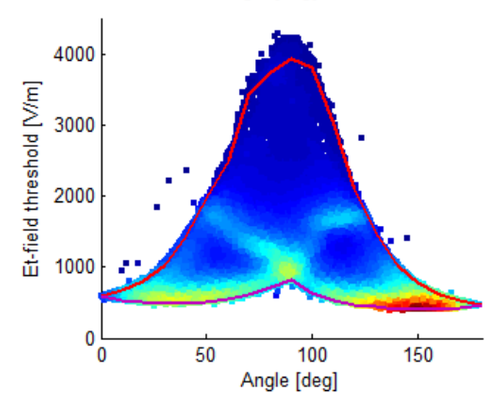


Biphasic

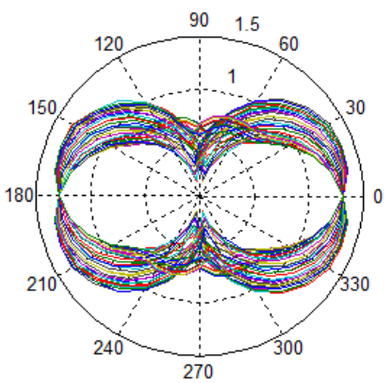


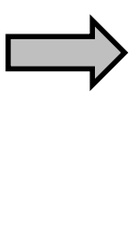


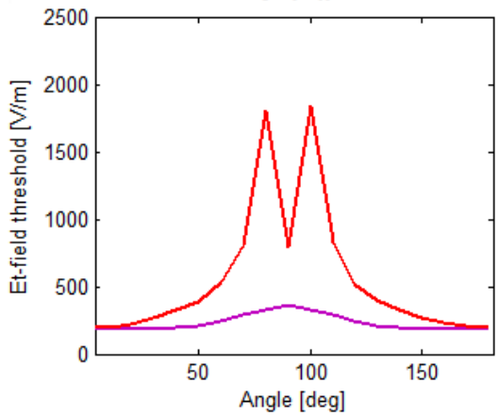


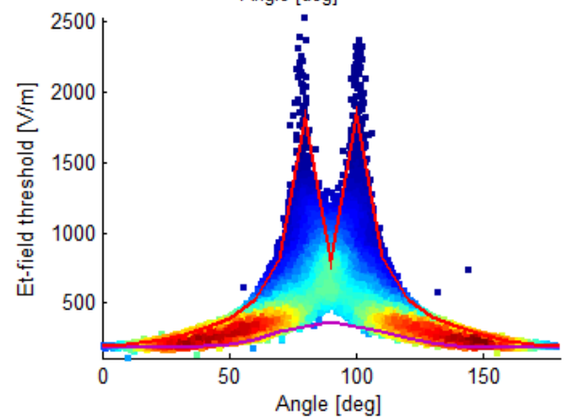


10 Hz



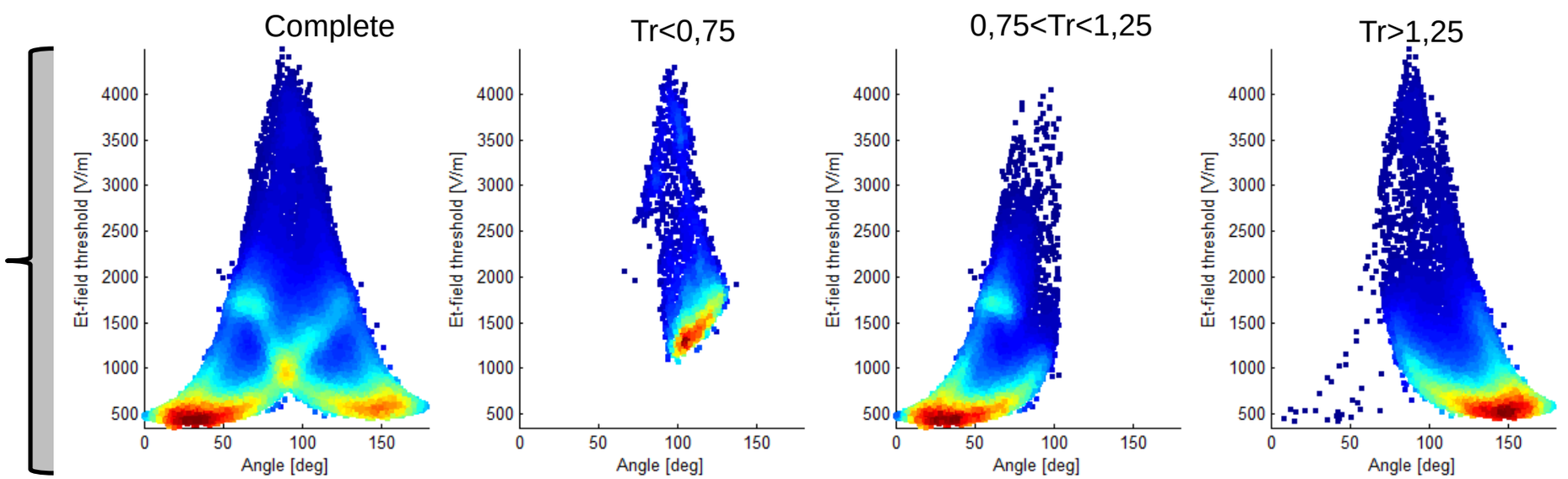




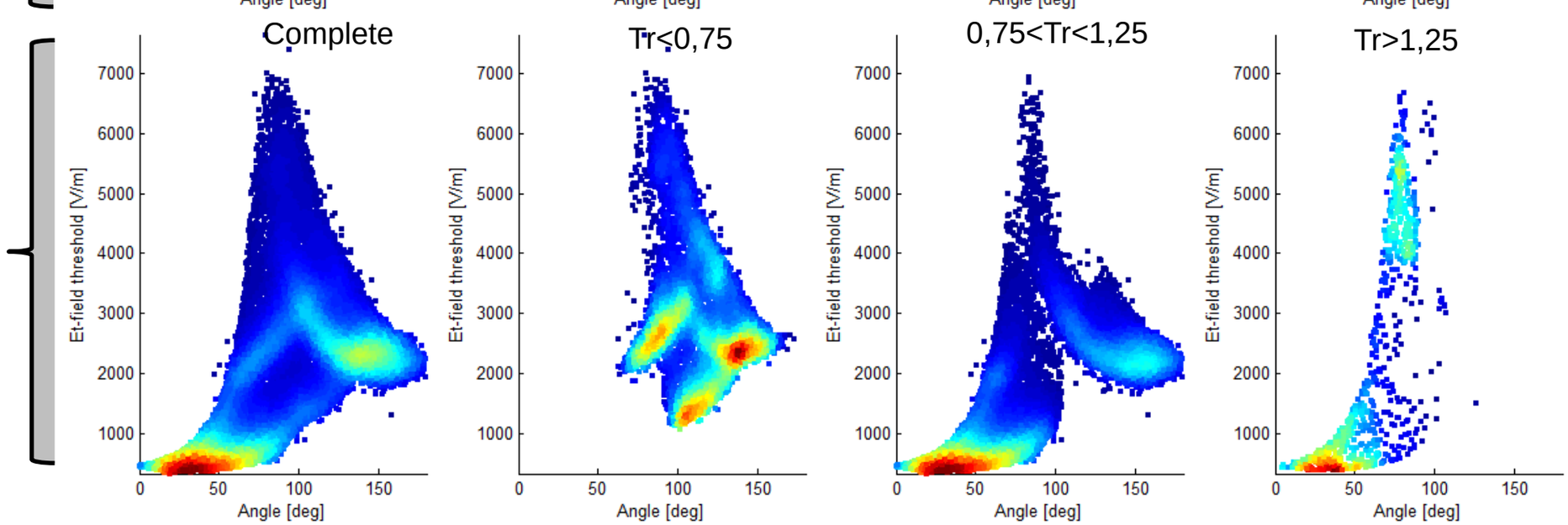


Neuronal Excitability: Anysotropy, Timing, Location

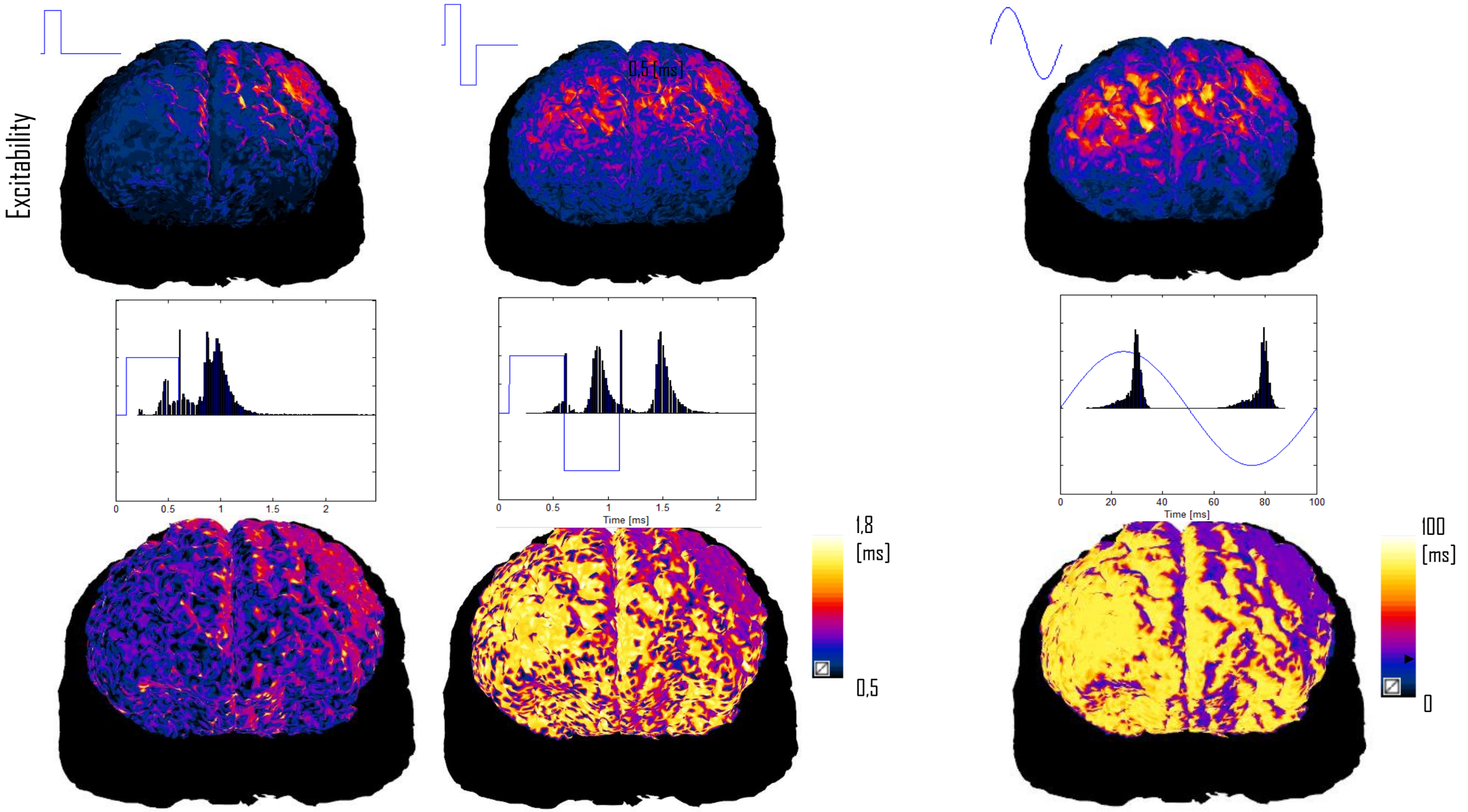
Biphasic



Monophasic Cathodic

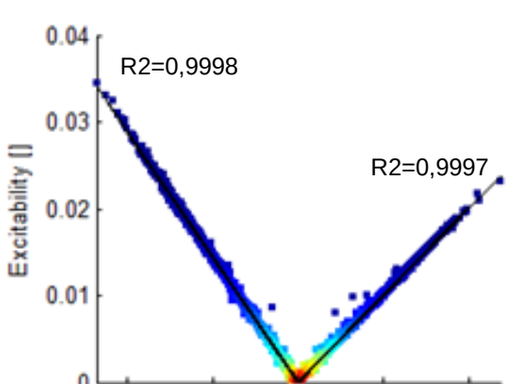


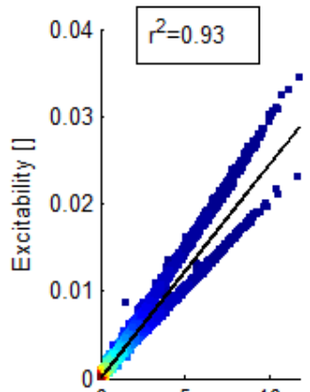
Stimulation Localization & Timing

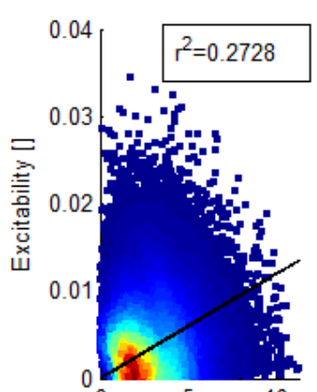


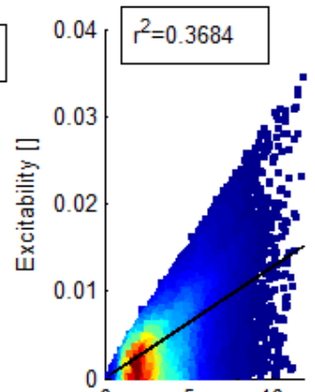
Field / Stimulation: Correlation

Ball and Stick

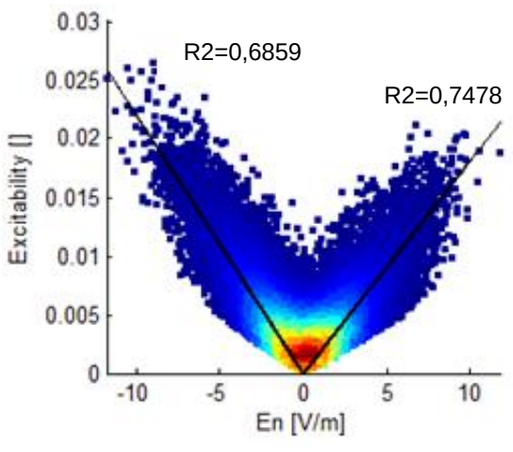


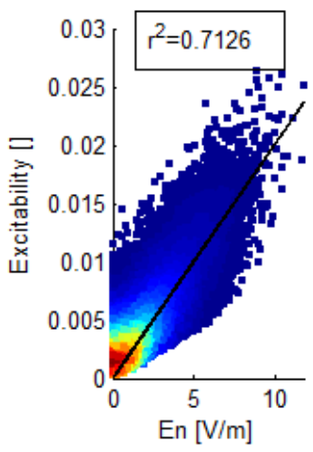


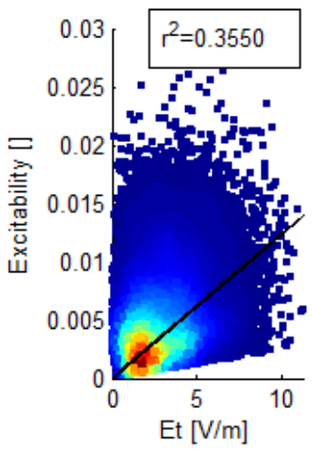


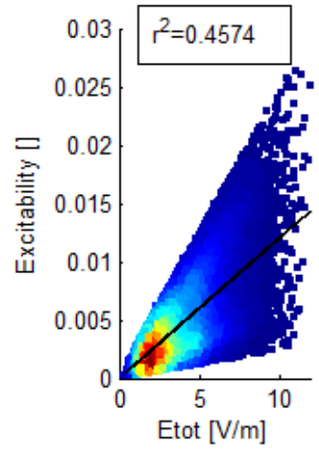


CA1



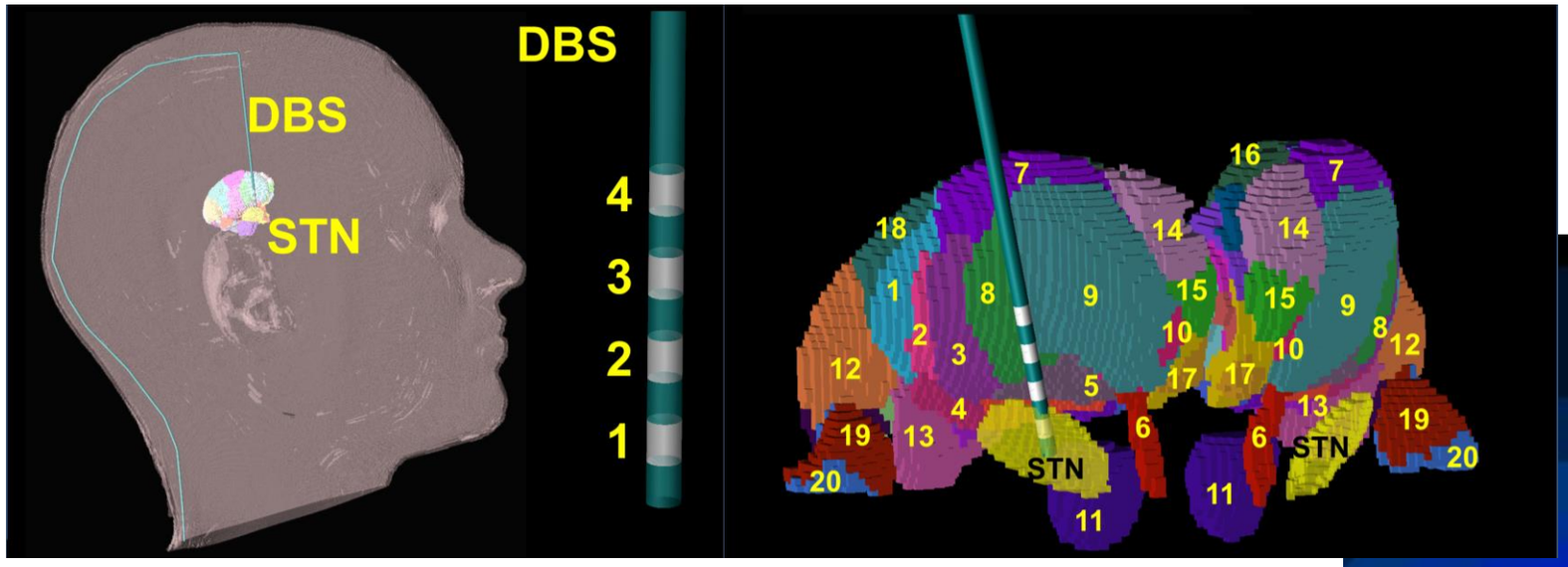


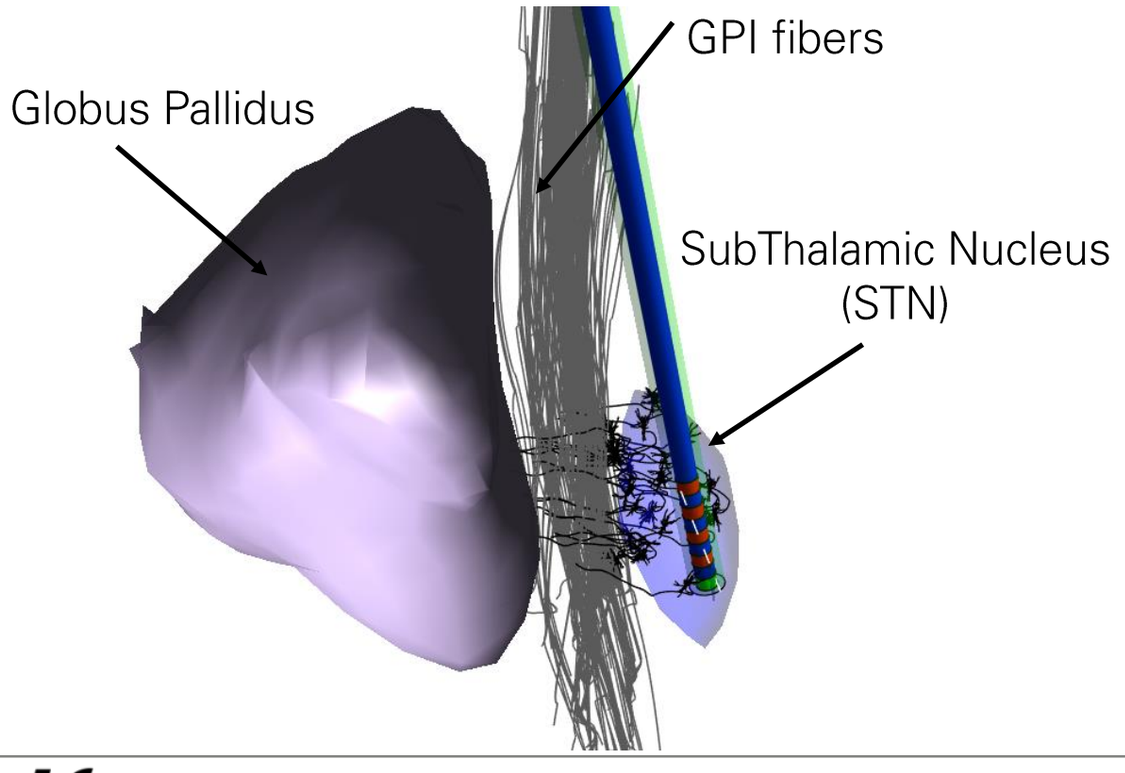


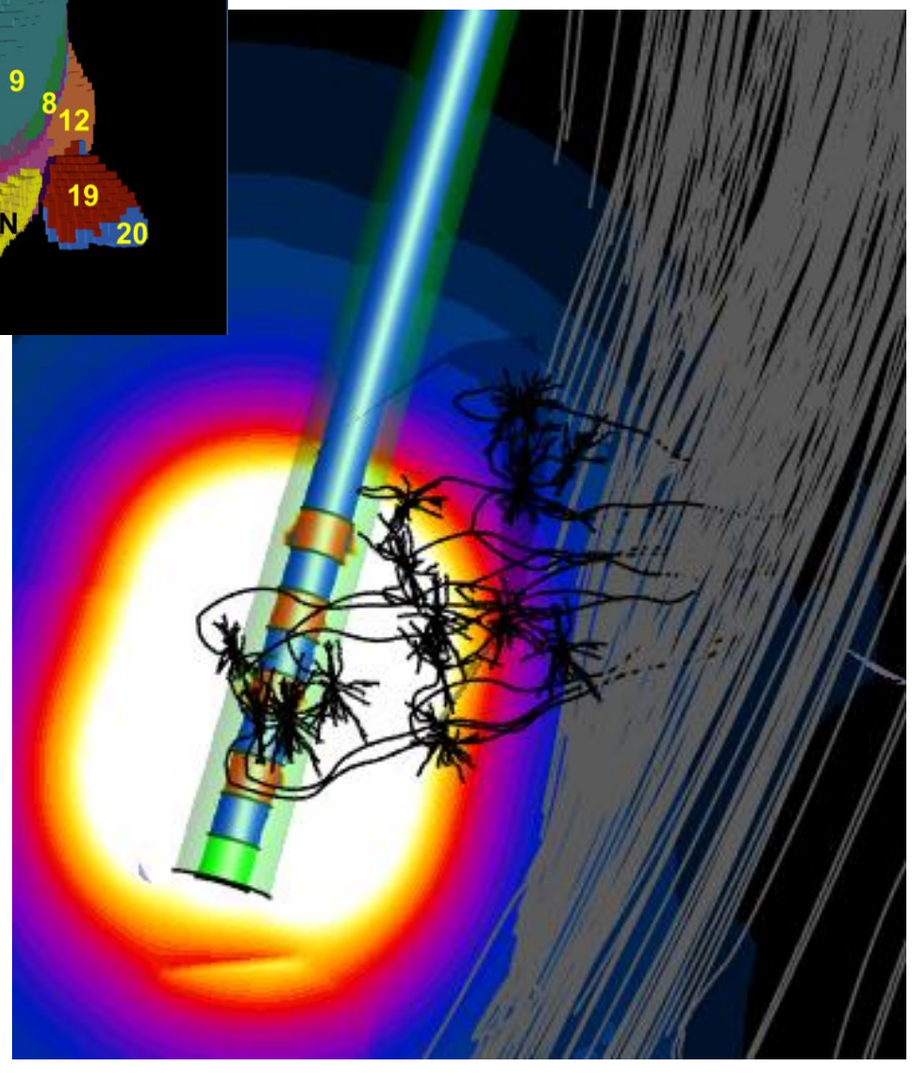


model	setup	stimulus	En_+	En_-	Ep	Et
CA1	TES	biphasic	0.7478	0.6859	0.3550	0.4574
CA1	TES	monophasic	0.7606	0.7259	0.5668	0.7210
CA1	TES	10Hz	0.8917	0.8950	0.3646	0.5289
CA1	TMS	biphasic	0.7701	0.8204	0.5294	0.6311
CA1	TMS	monophasic				
CA1	TMS	10Hz				
BS	TES	biphasic	0.999	0.998	0.2728	0.3684

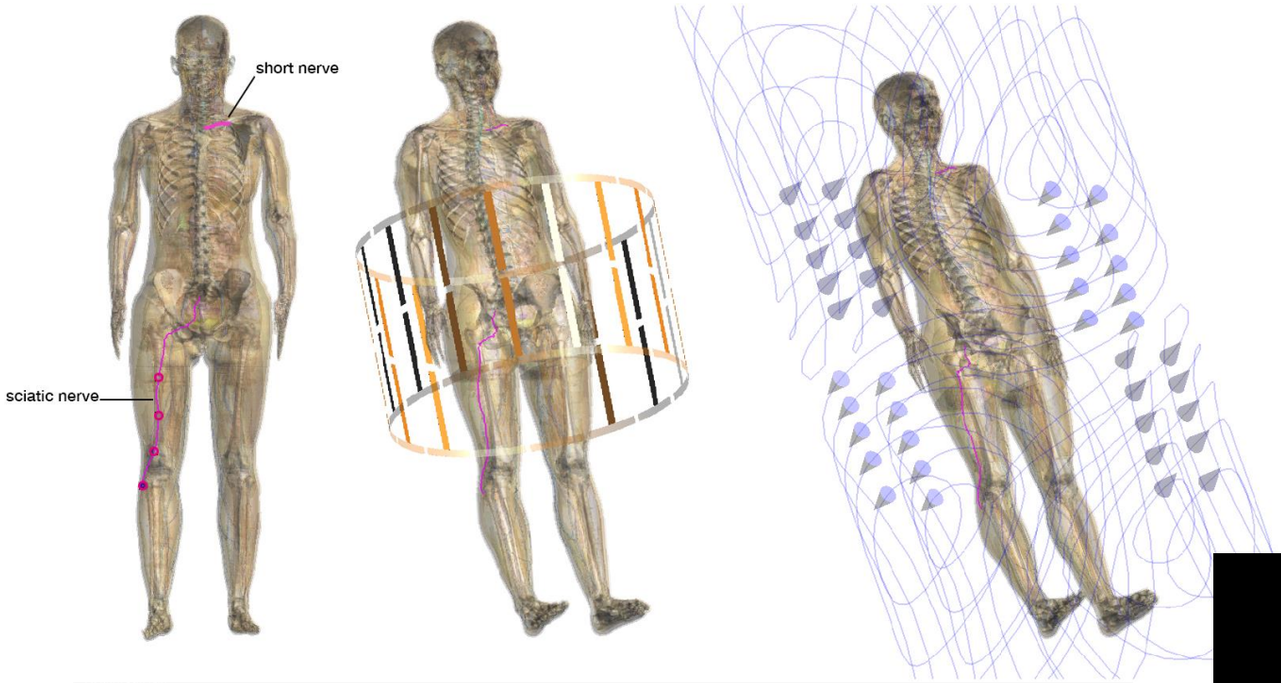
Image-Based Functionalization: Neurons with DTI

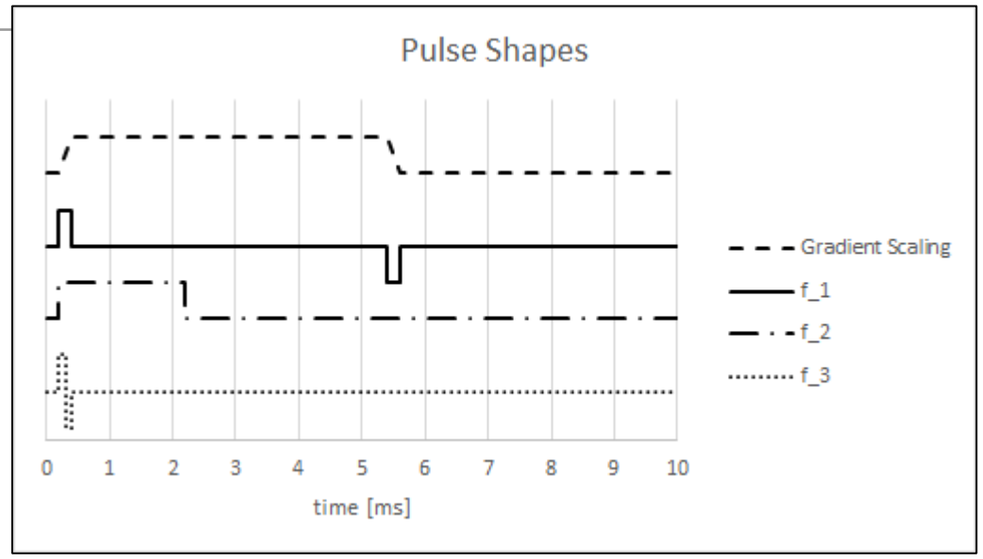


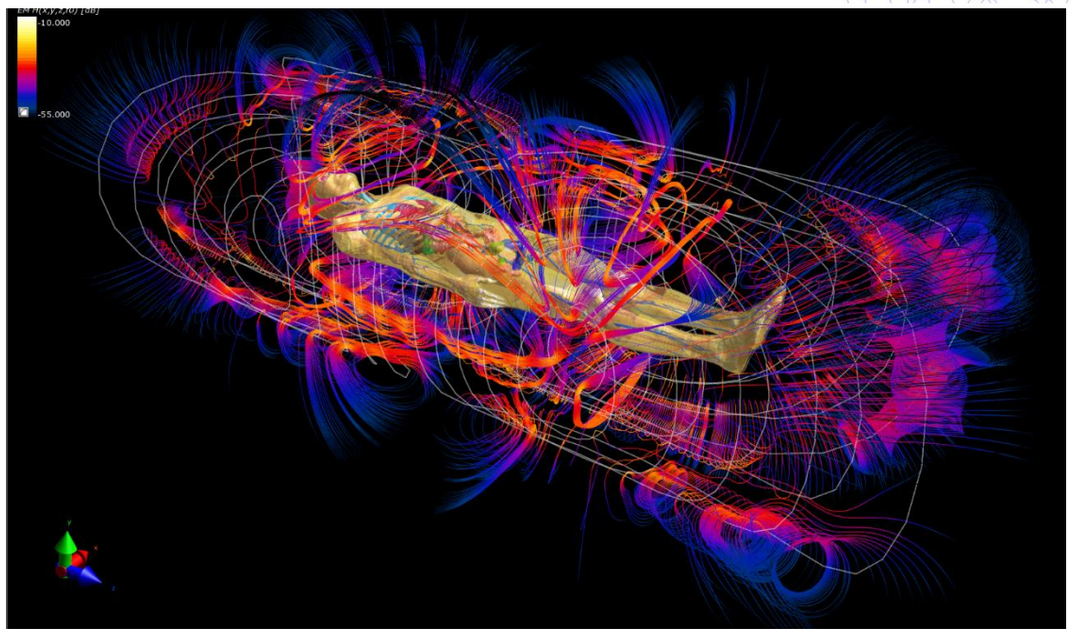


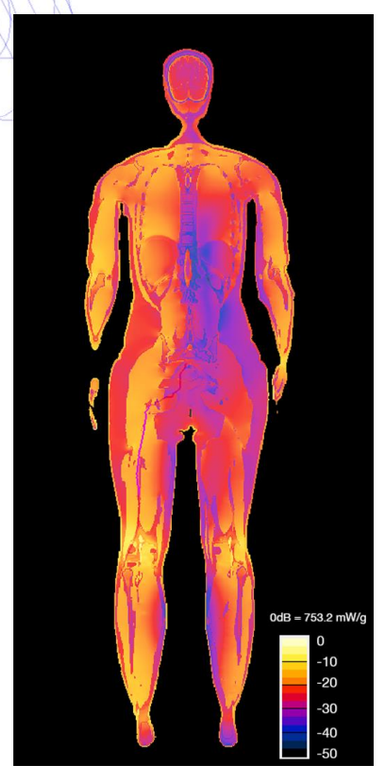


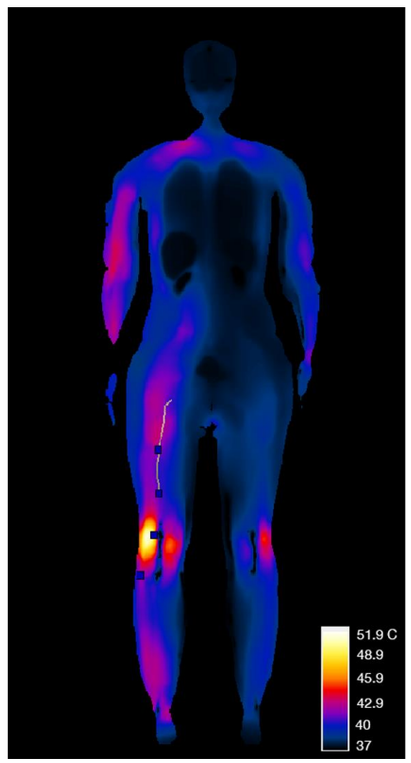
MRI Gradient Coil Safety

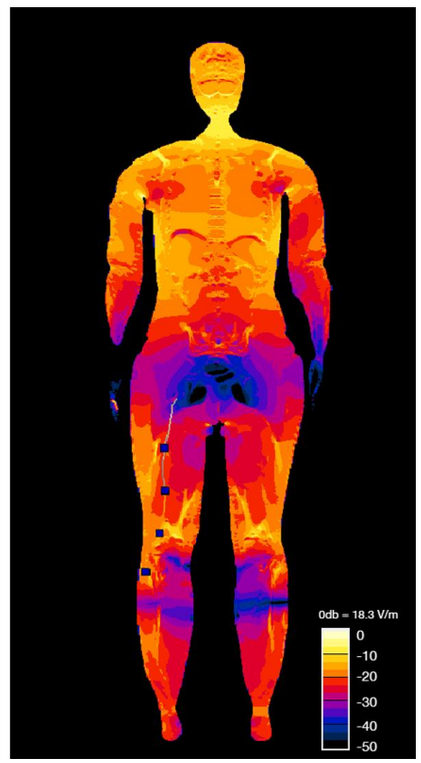






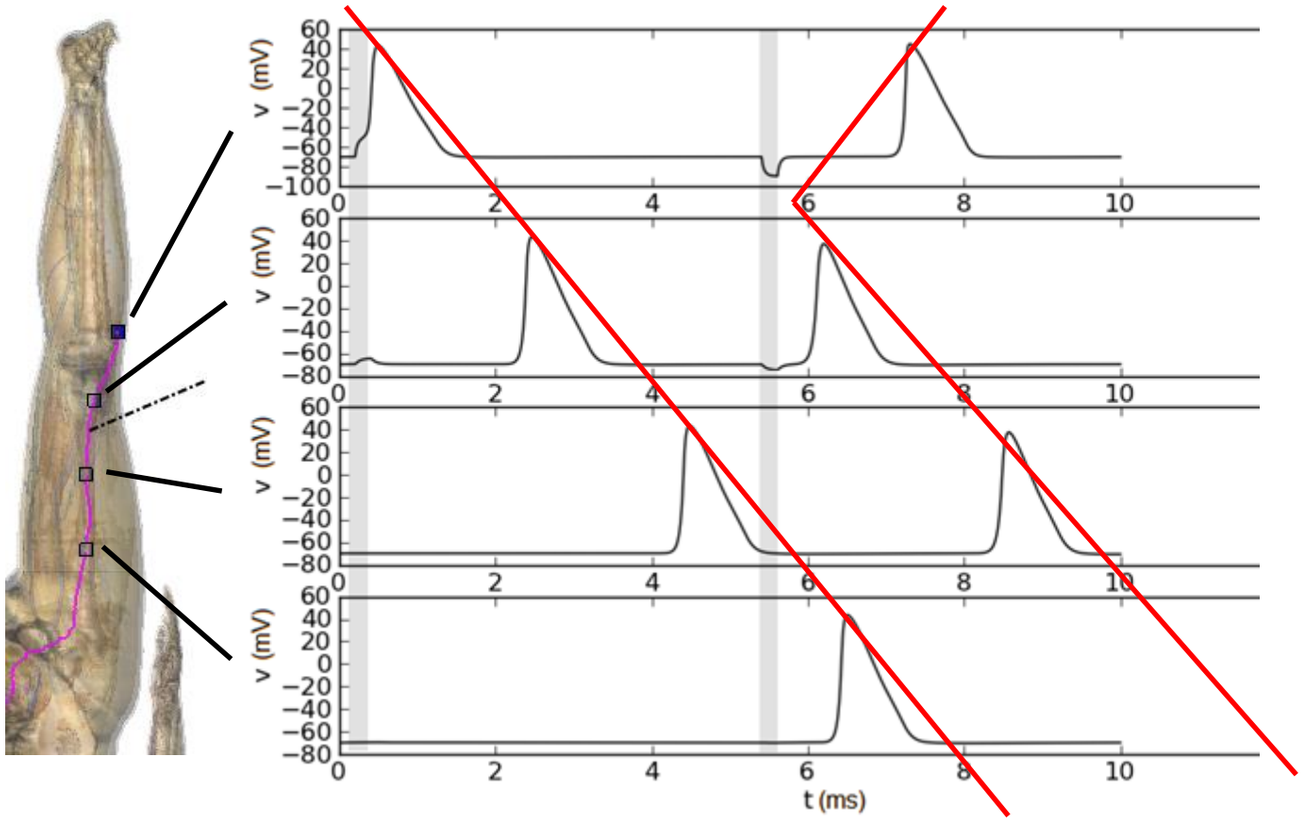




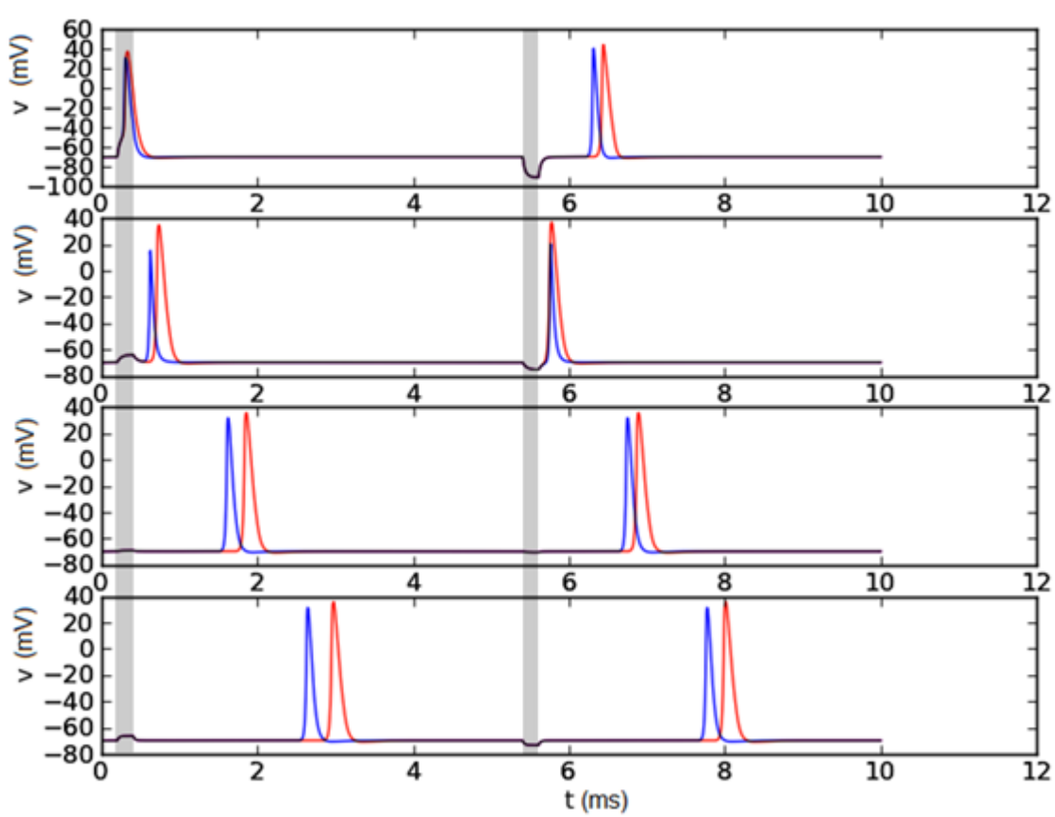


EM Induced Neuron Stimulation – Results

SENN22



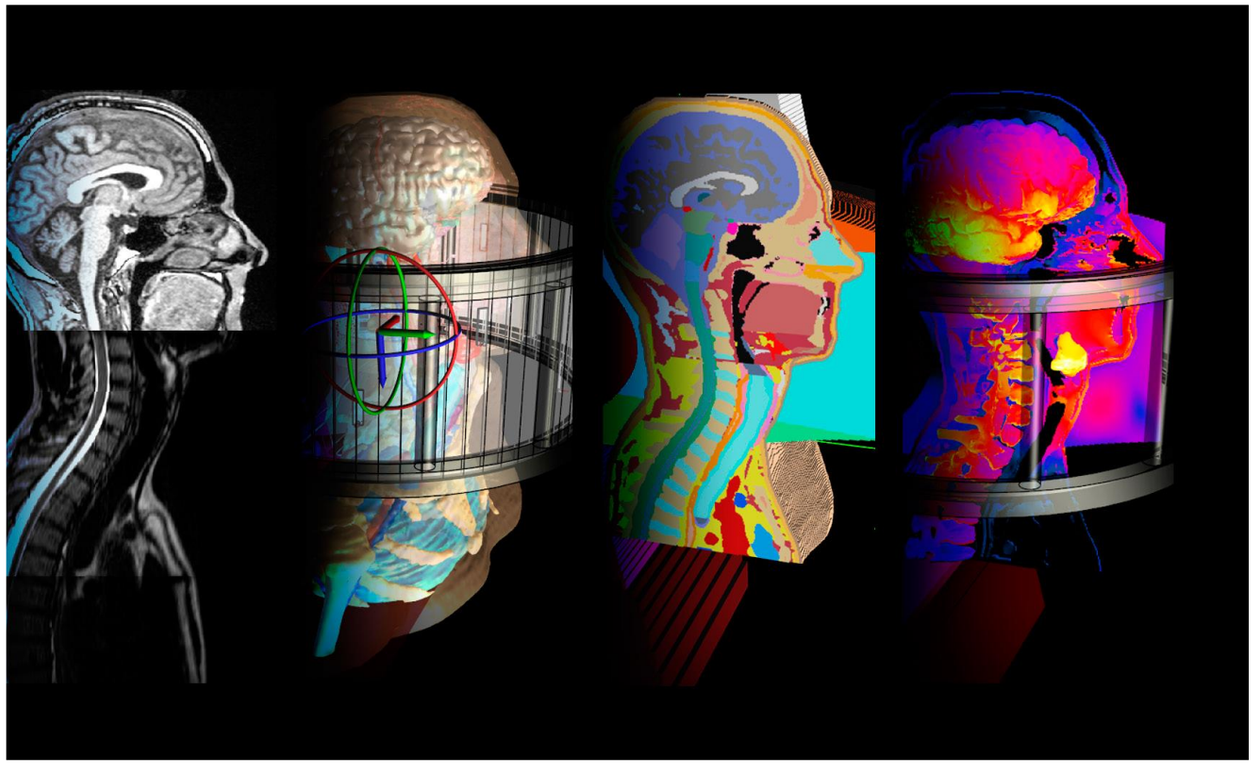
SENN37 & SENN(T)



end-node center-type

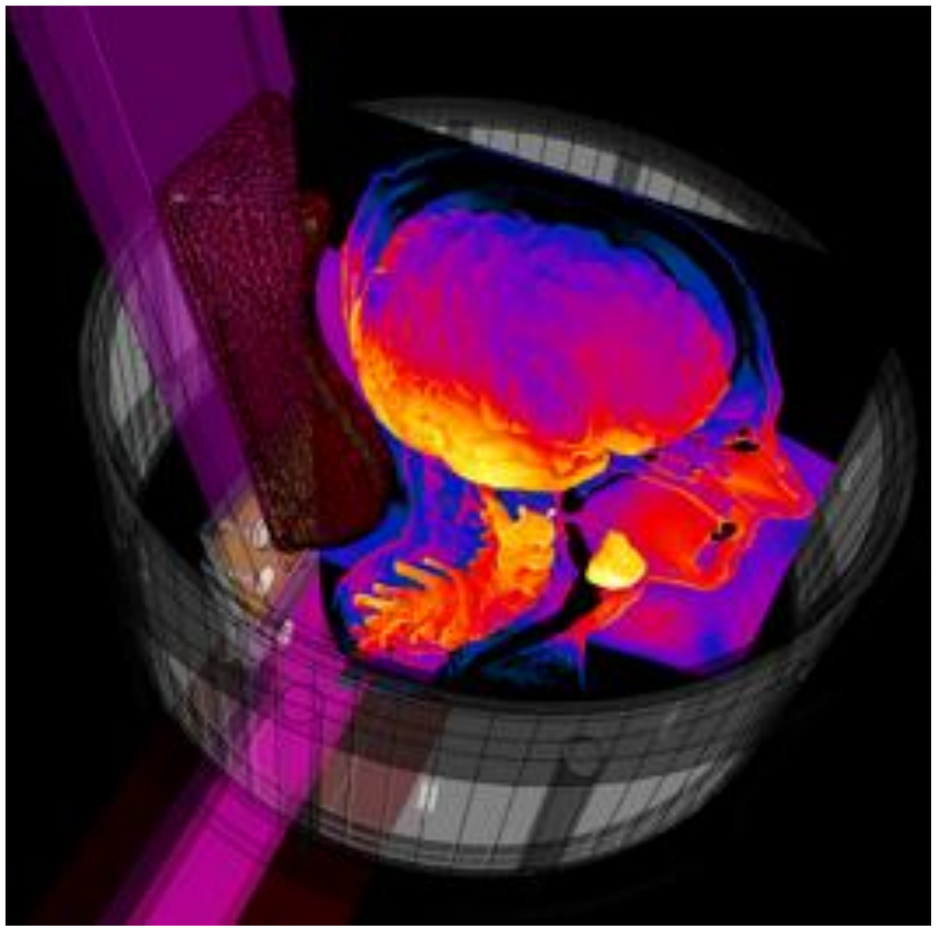
EM Induced Neuron Stimulation – Results

- calculated peak gradient coil E-field (in fat & overall), dB/dt comparable to previously reported values [Turk2012, So2004];
  slightly higher as expected due to increased resolution & detail [So2004]
- onset of stimulation slightly above realistically occurring switching rates
- end- and center-type stimulation occur at similar thresholds
  - E-field not sole criterium
- potential distribution along nerve has influence on stimulation threshold
- local foci occur and matter
- detailed motor neuron model has in some cases lower threshold than SENN
- temperature strongly affects dynamics, but only minimally threshold (<20% except for very short pulses)
- neuron trajectory should be smoothed to avoid falsely lowering predicted stimulation onset, but
- field smoothing should be avoided
- dielectric contrast at tissue interfaces related issues are naturally handled (sampling by nodes)



PERSONALIZED MEDICINE: THERMAL THERAPIES

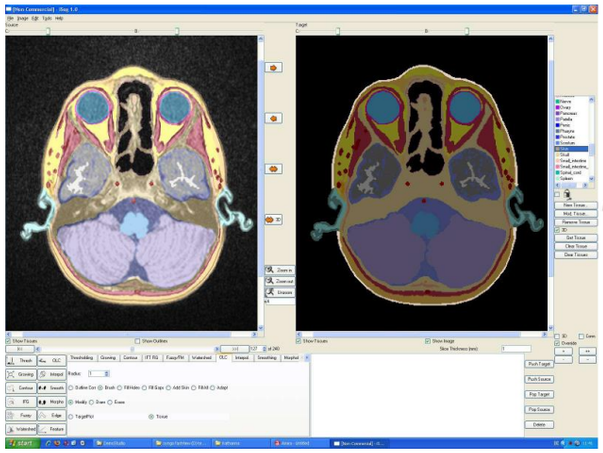
Thermal Therapies

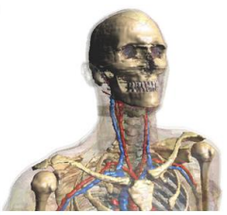


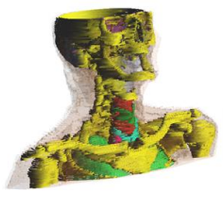
Erasmus MC, Rotterdam

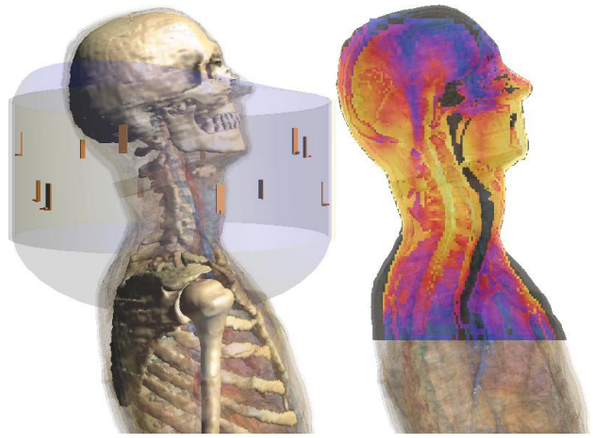
- hyperthermic oncology (aims at >42C, benefits shown at 40-42C)
- ablation (55 - >100C)

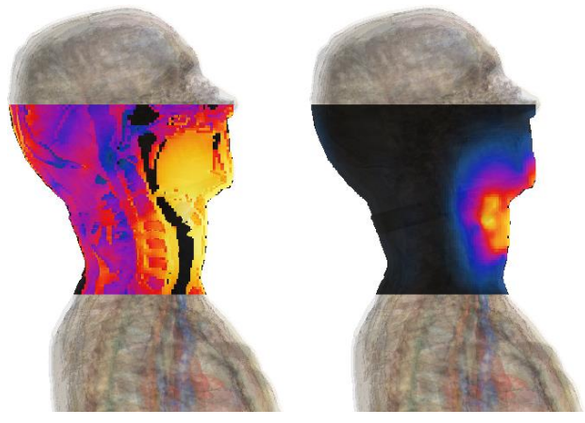
Personalized Treatment Planning

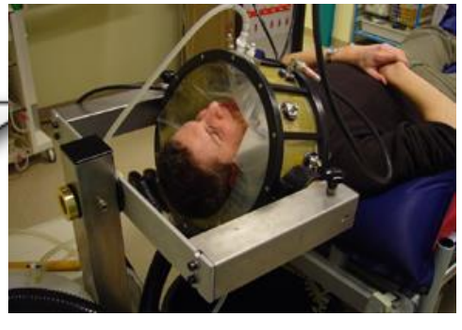




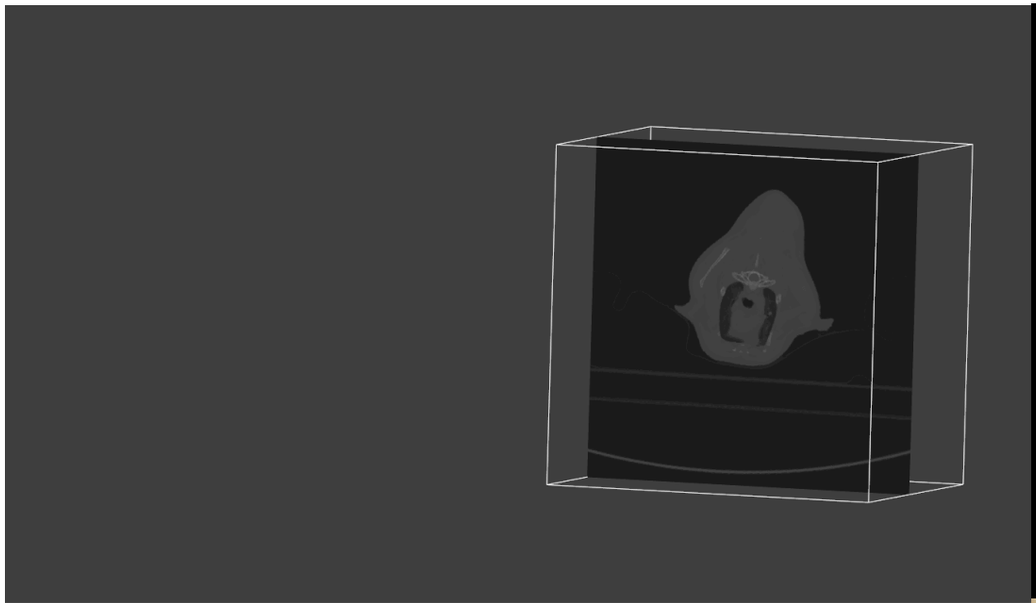
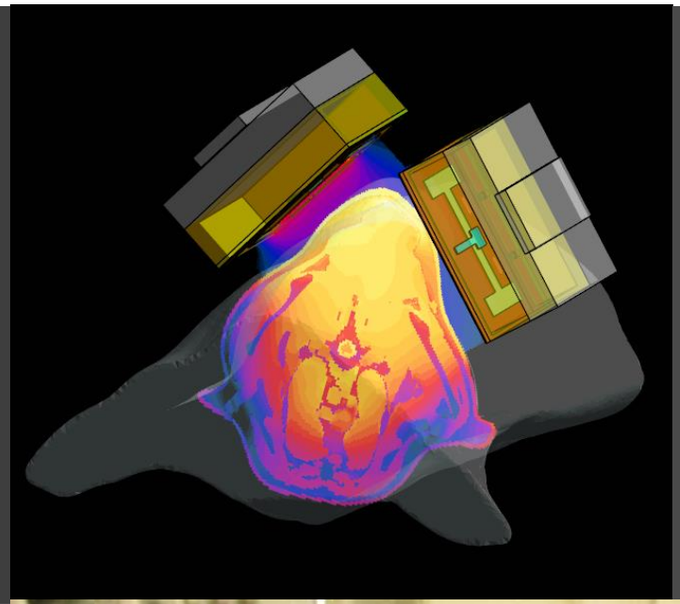
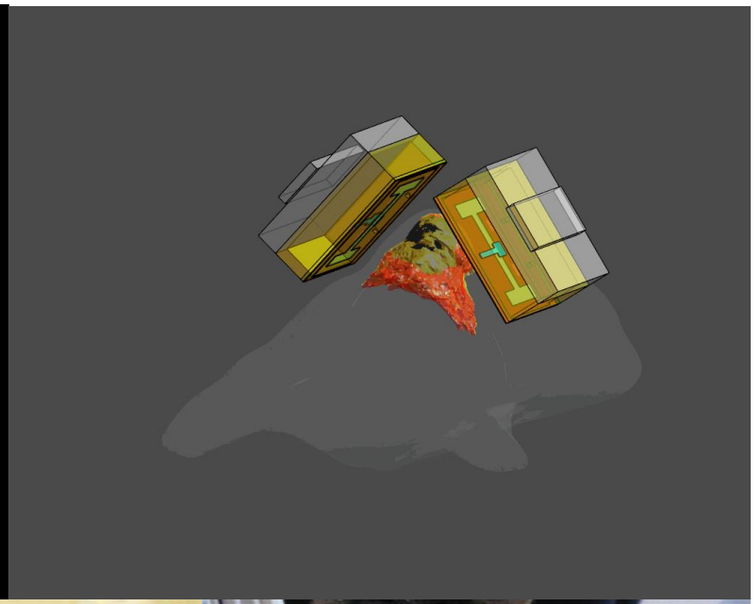
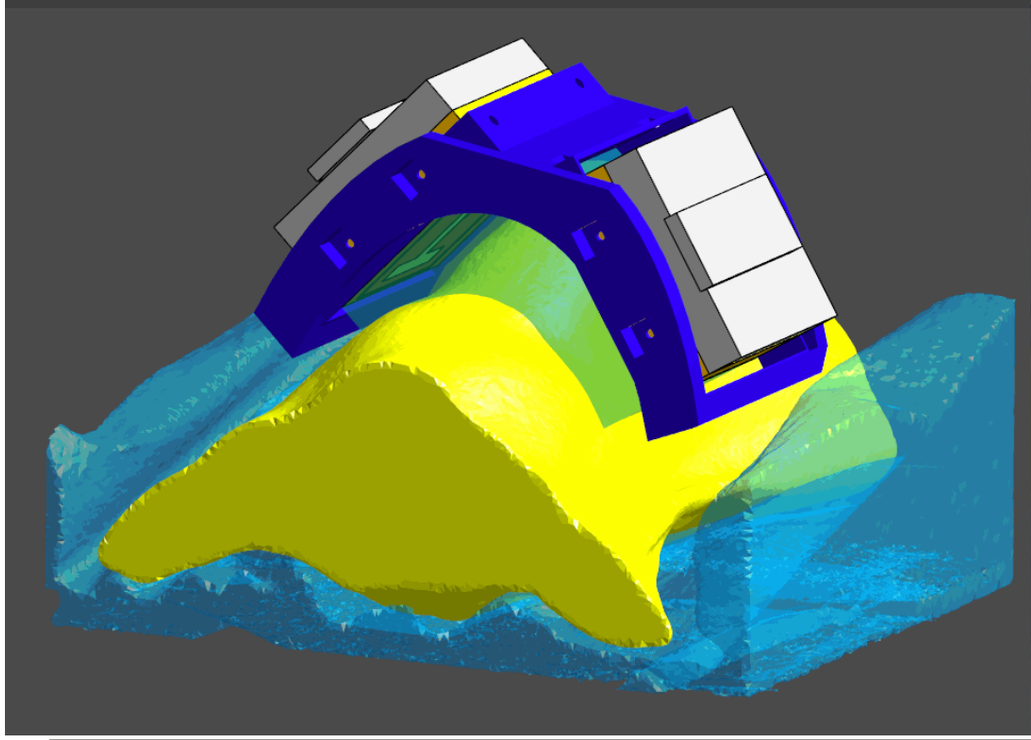






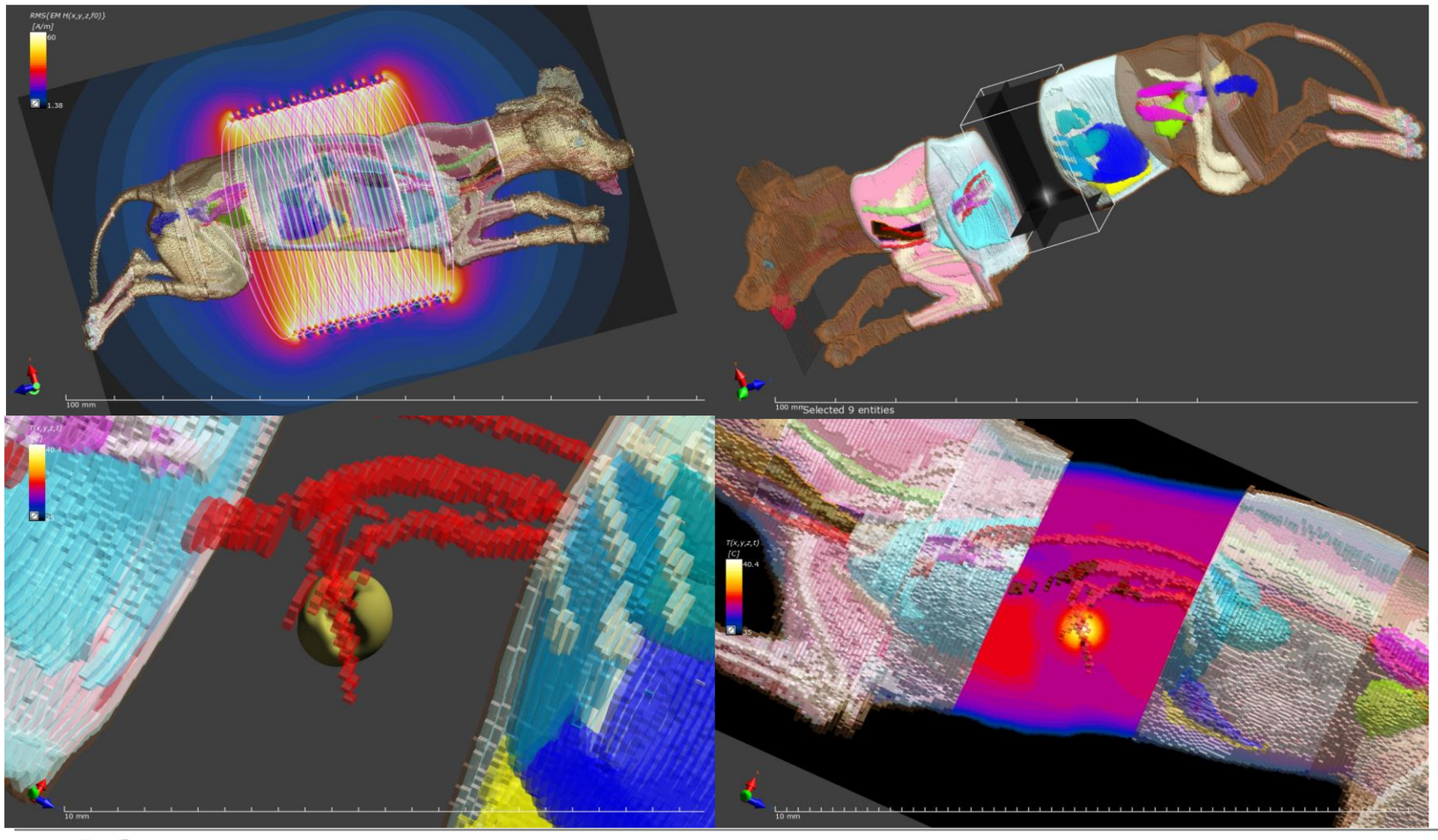


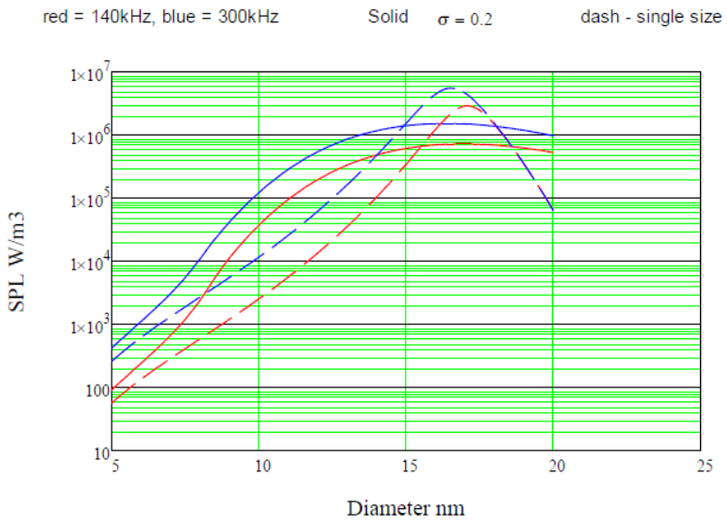
Novel Applicator, Design&QA&TP by Modeling

Superparamagnetic Nano-Particle HT

$$EPFL(f,d,H) := \mu_0 \cdot \pi \cdot M_S \cdot \left[\left(\frac{\cosh\left(\frac{\mu_0 \cdot M_S \cdot H \cdot V_M(d)}{k \cdot T} \right)}{\sinh\left(\frac{\mu_0 \cdot M_S \cdot H \cdot V_M(d)}{k \cdot T} \right)} - \frac{1}{\frac{\mu_0 \cdot M_S \cdot H \cdot V_M(d)}{k \cdot T}} \right) \cdot \frac{2 \cdot \pi \cdot f \cdot \tau_0 \cdot 1 \cdot e^{\frac{K \cdot V_M(d)}{k \cdot T}}}{1 + \left(2 \cdot \pi \cdot f \cdot \tau_0 \cdot 1 \cdot e^{\frac{K \cdot V_M(d)}{k \cdot T}} \right)^2} \cdot H \cdot f \right]$$





Multiscale:
Bottom-Up

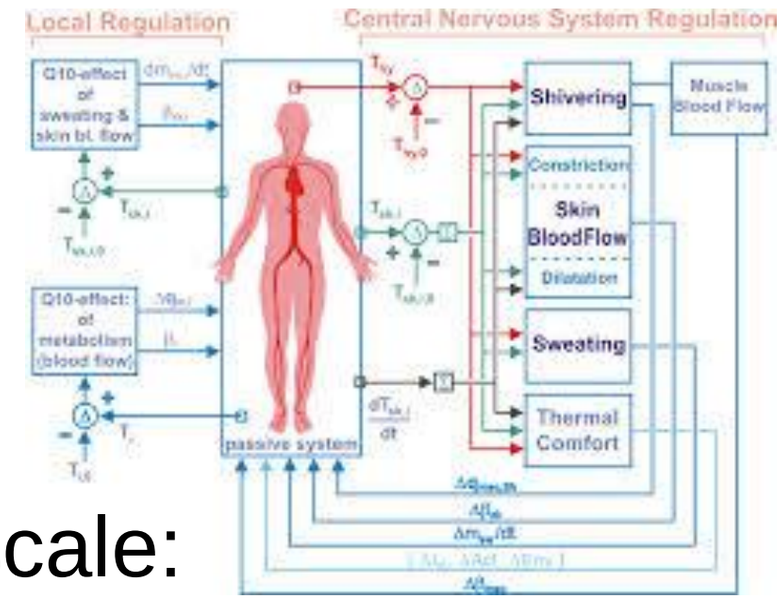
Thermal Modeling: From Physics to Physiology

- based on widely employed Pennes Bioheat Equation

$$\rho c \frac{\partial T}{\partial t} = \nabla \cdot (k \nabla T) + \rho Q + \rho S - \rho_b c_b \rho \omega (T - T_b)$$

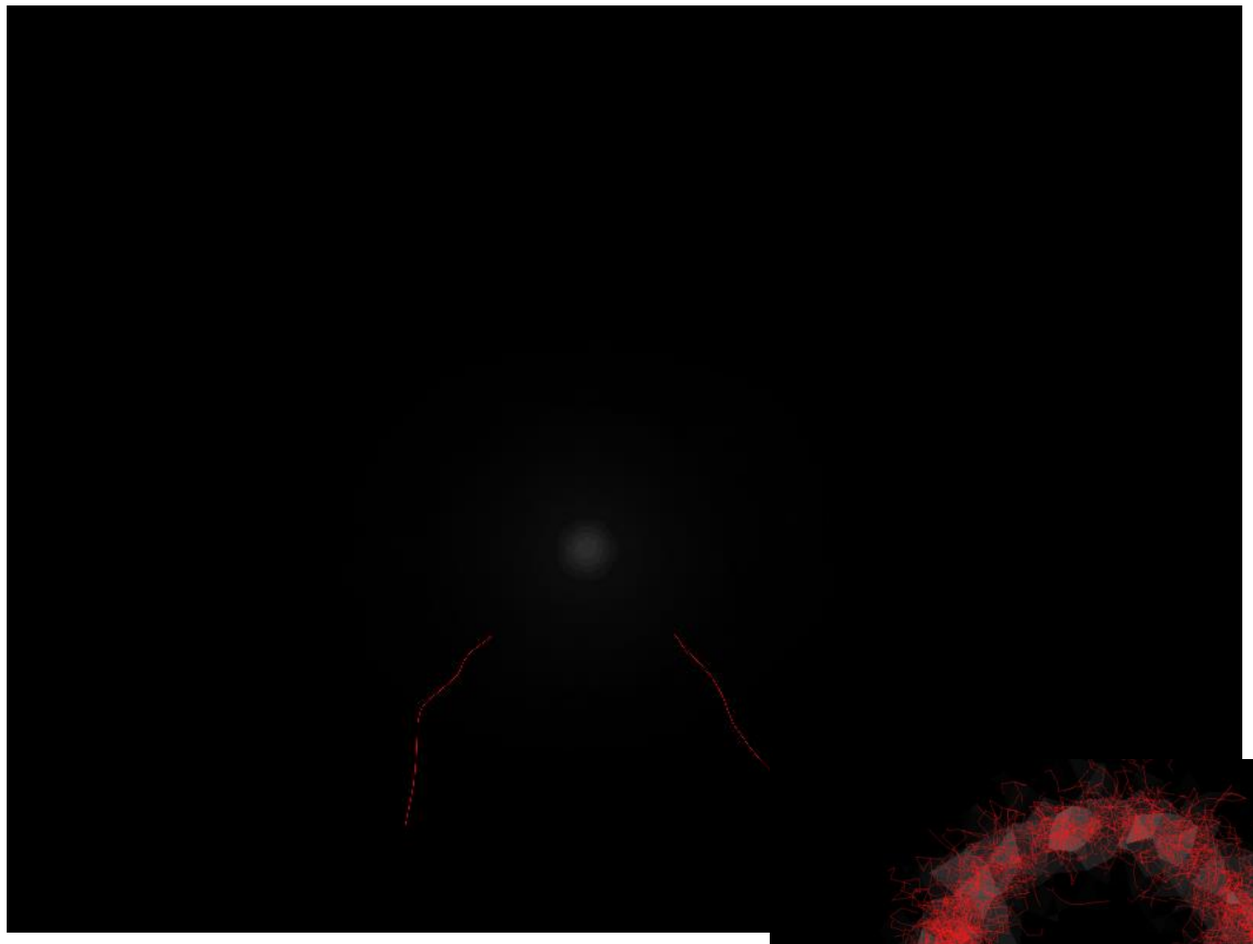
k: thermal conductivity, S: specific absorption rate
ω: perfusion rate, Q: metabolic heat generation rate

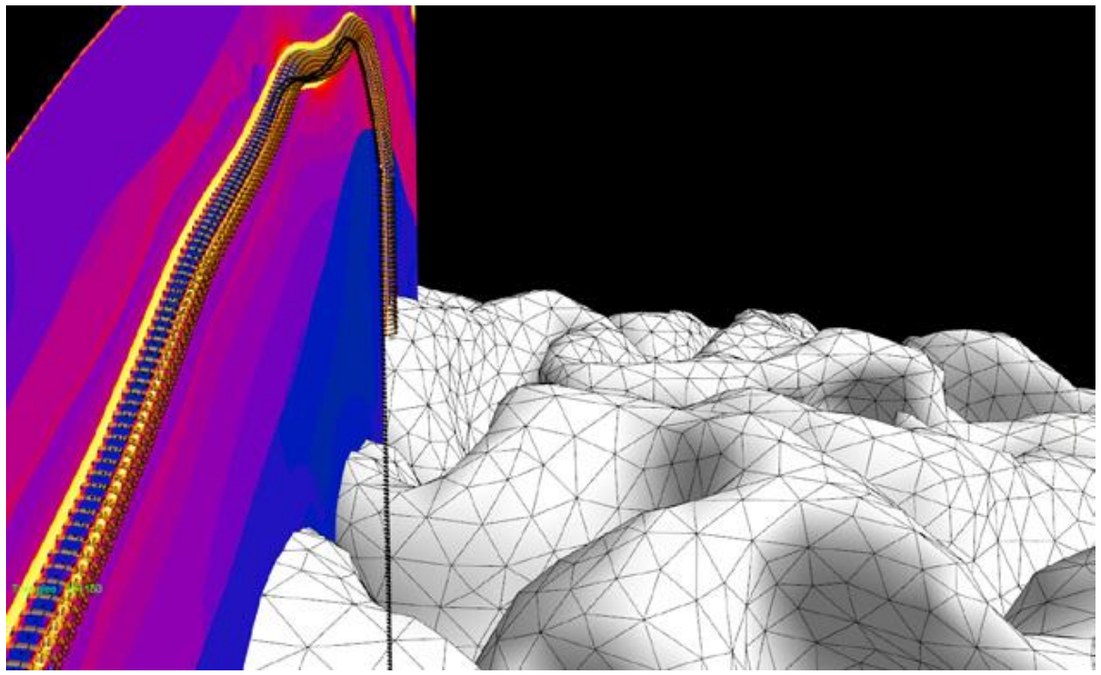
- extensions:
  - coupling to 1D vessel networks to account for directivity & discreteness of blood flow (increased accuracy & x100 acceleration)
  - local thermoregulation (vasodilation & vascular shut-down)
  - coupling to whole body thermoregulation model
  - accounting for body core temperature increase
  - supporting MR perfusion maps & MR flow field maps (personalization)
- for high T (ablation): evaporation, rehydration, coagulation

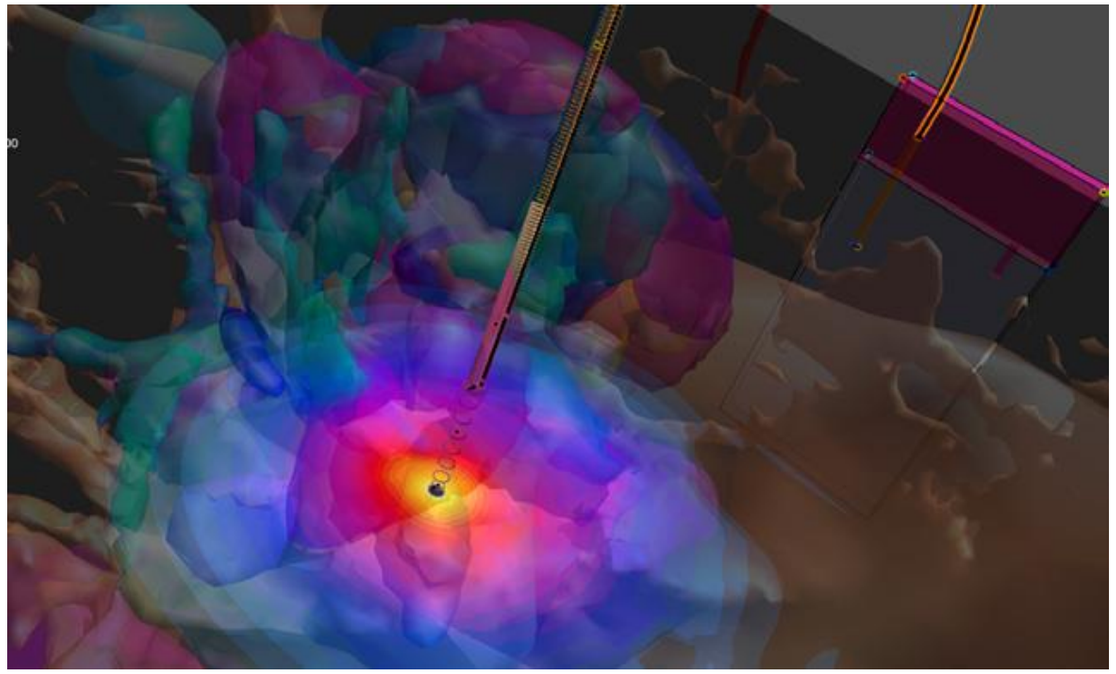


Multiscale: Hybrid/Parallel

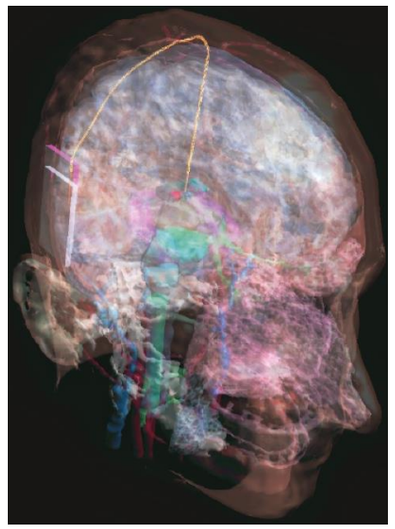
Treatment Effect on Tumor Evolution



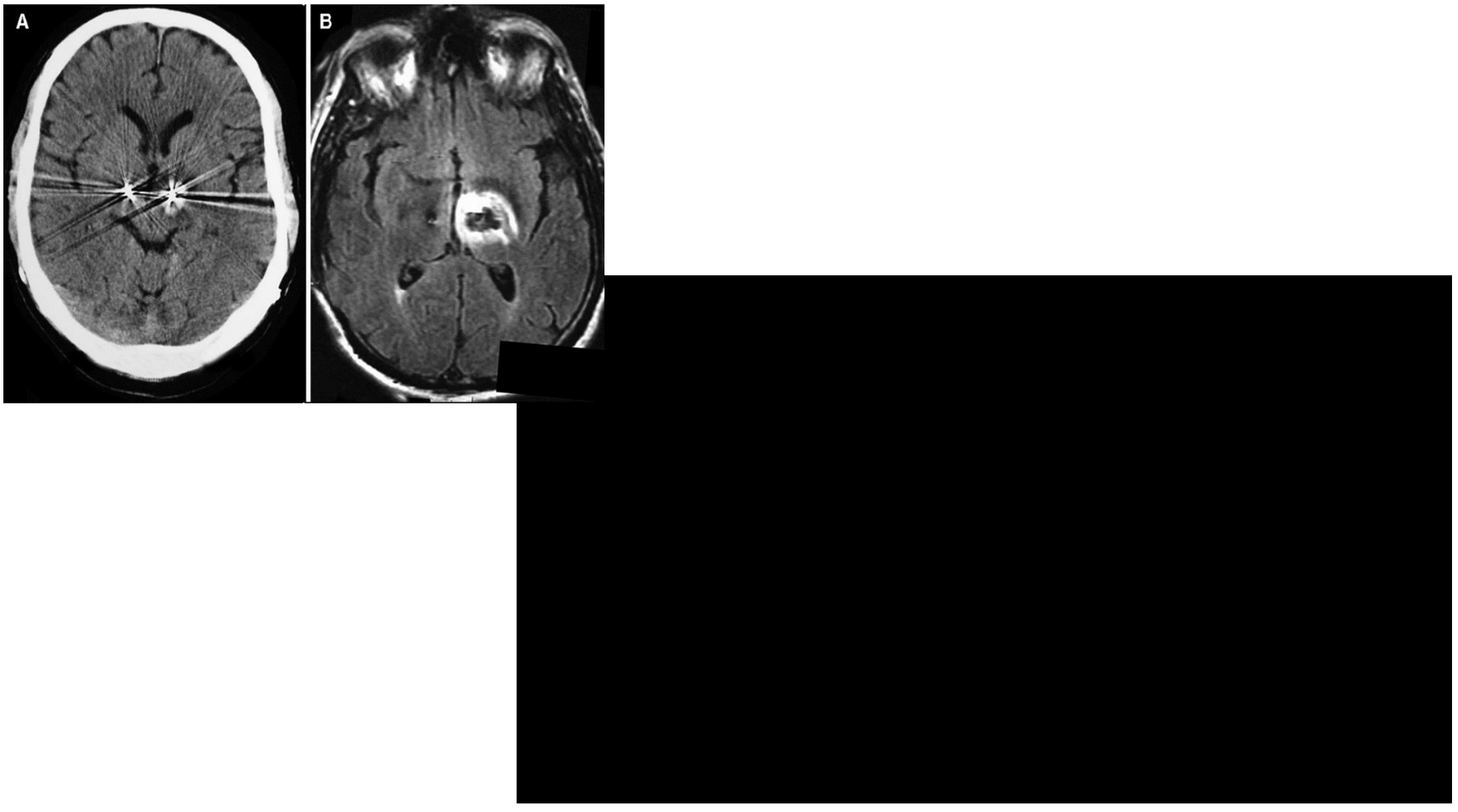




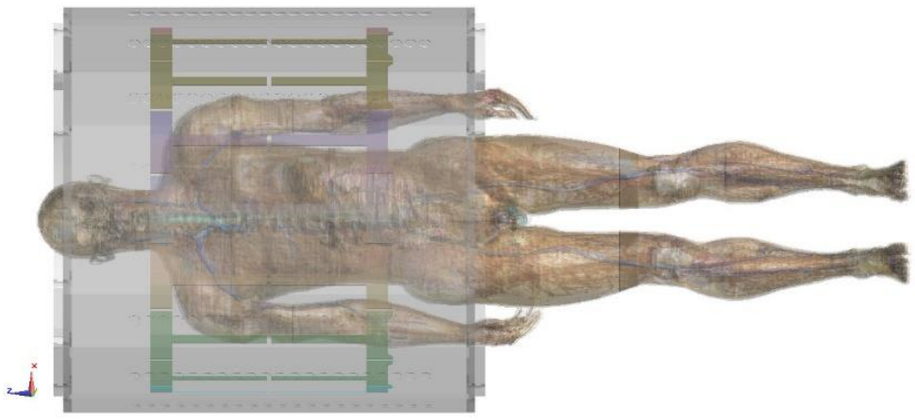
IN SILICO CLINICAL TRIALS: MRI IMPLANTATE SICHERHEIT

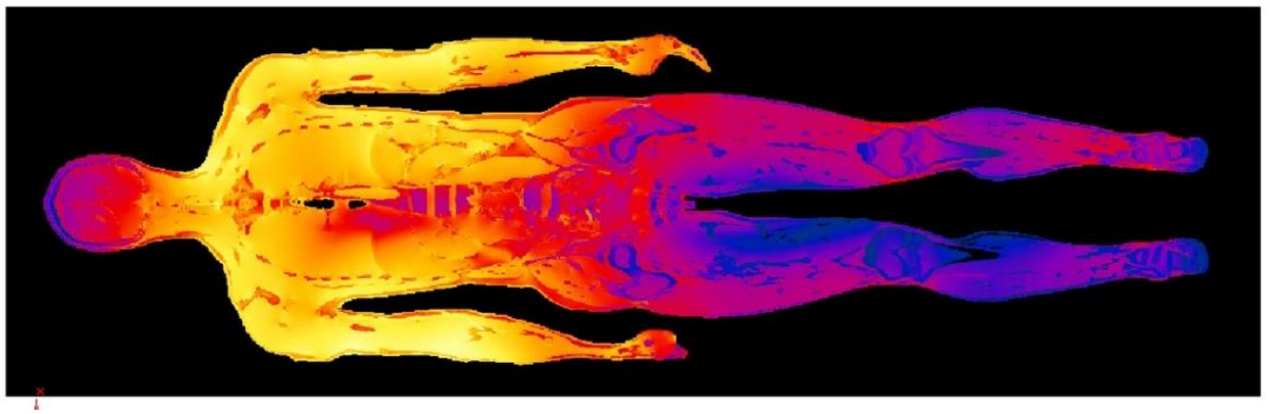


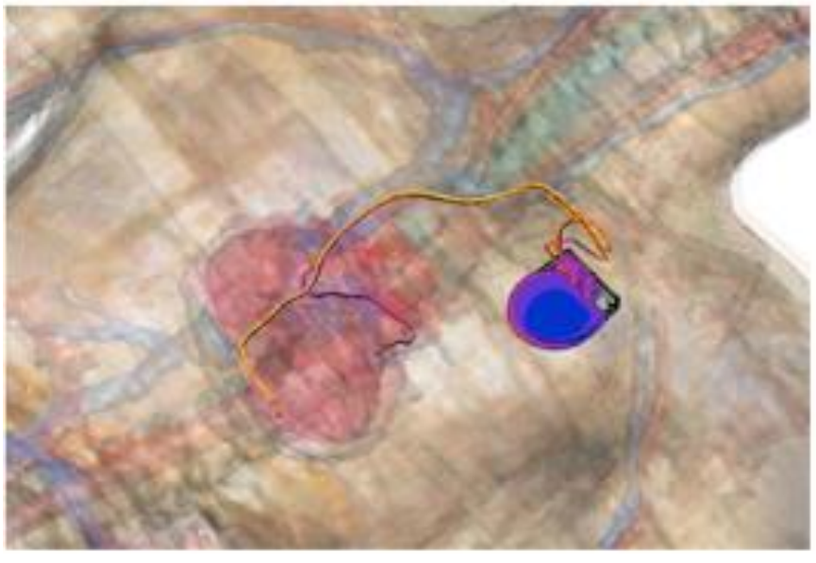
The Problem: MRI Implant Safety

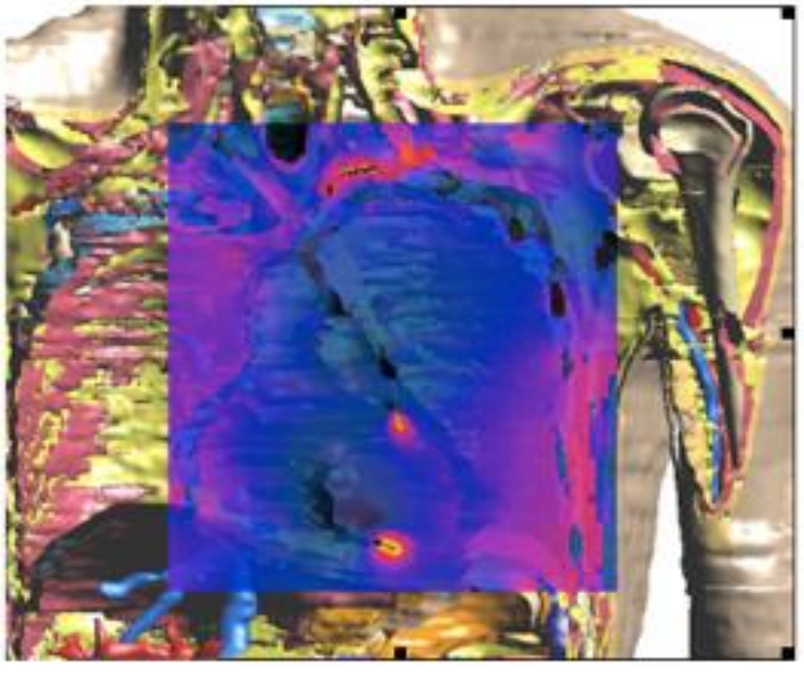


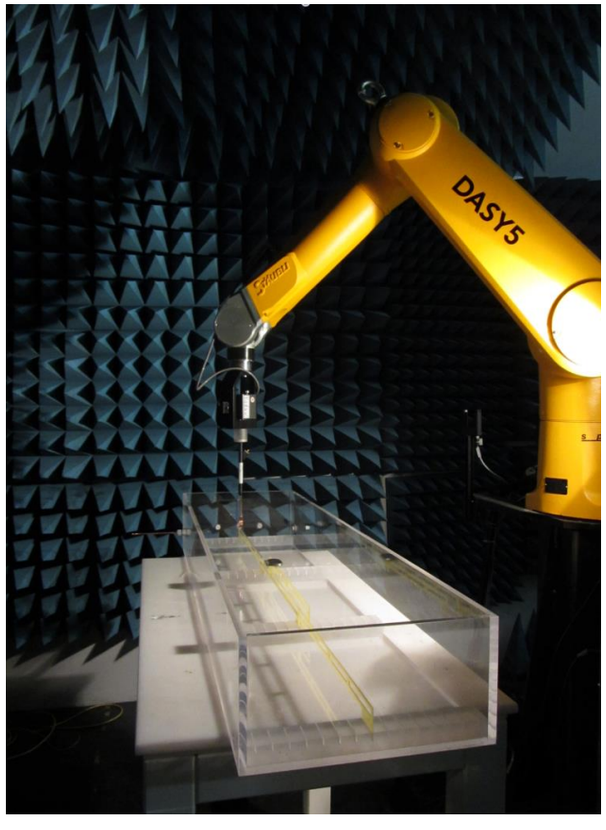
AIMD Expositionssicherheitsabklärung



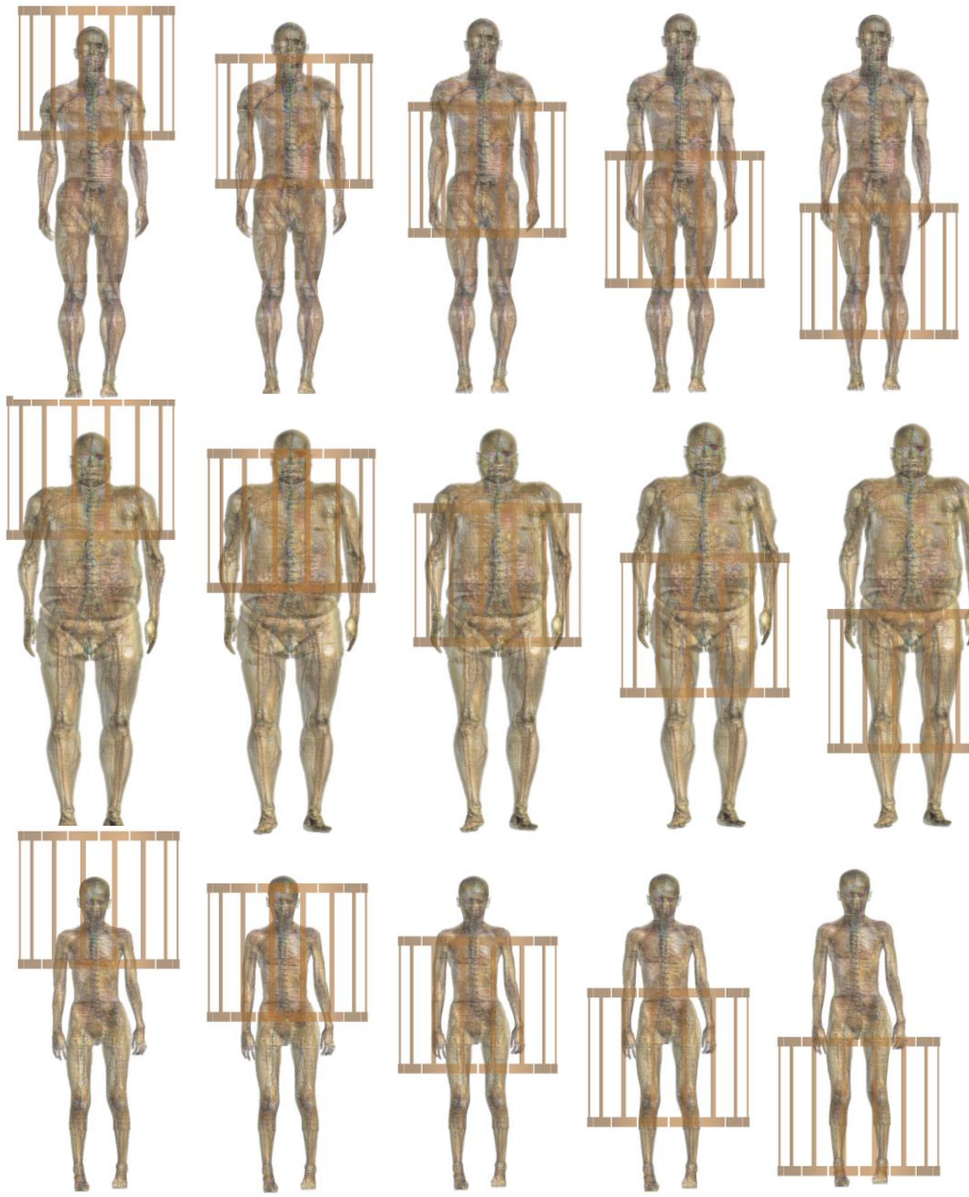


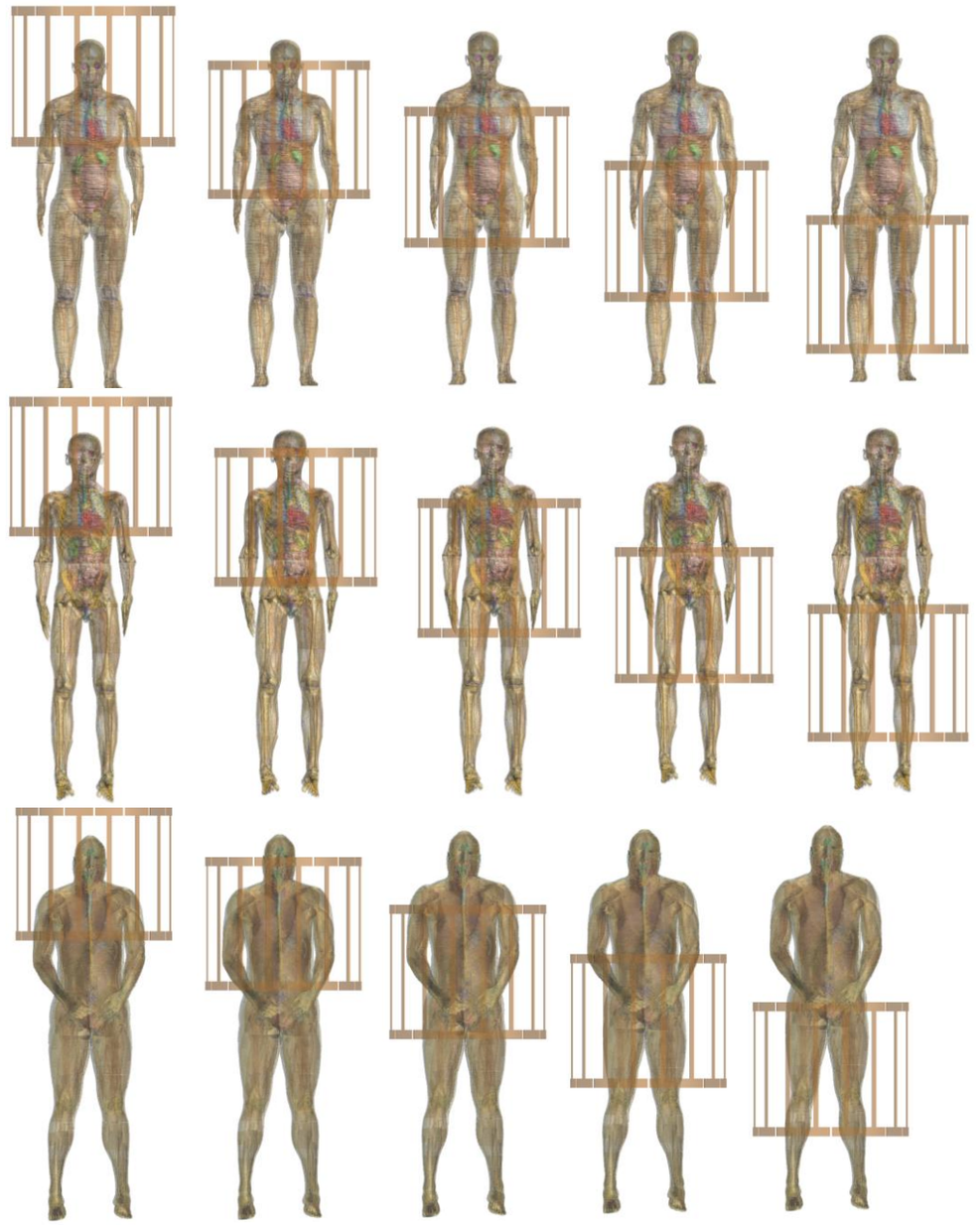




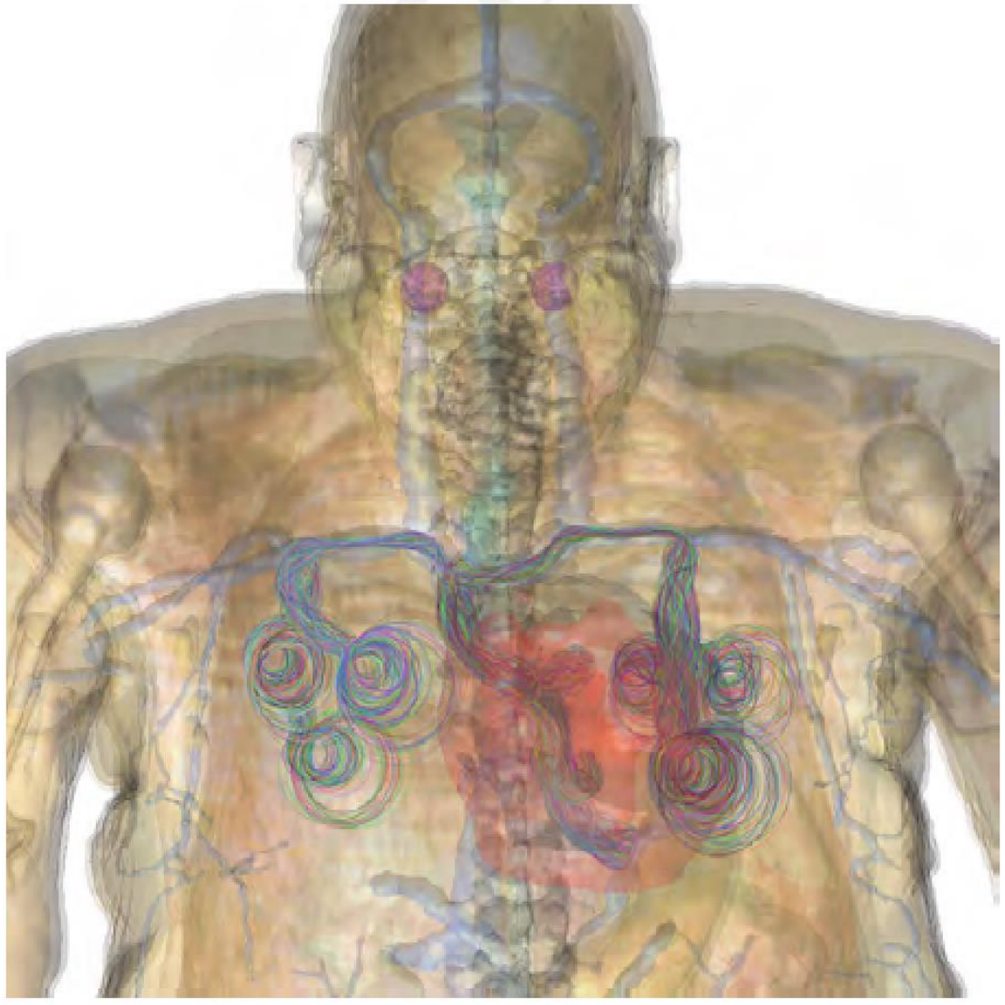


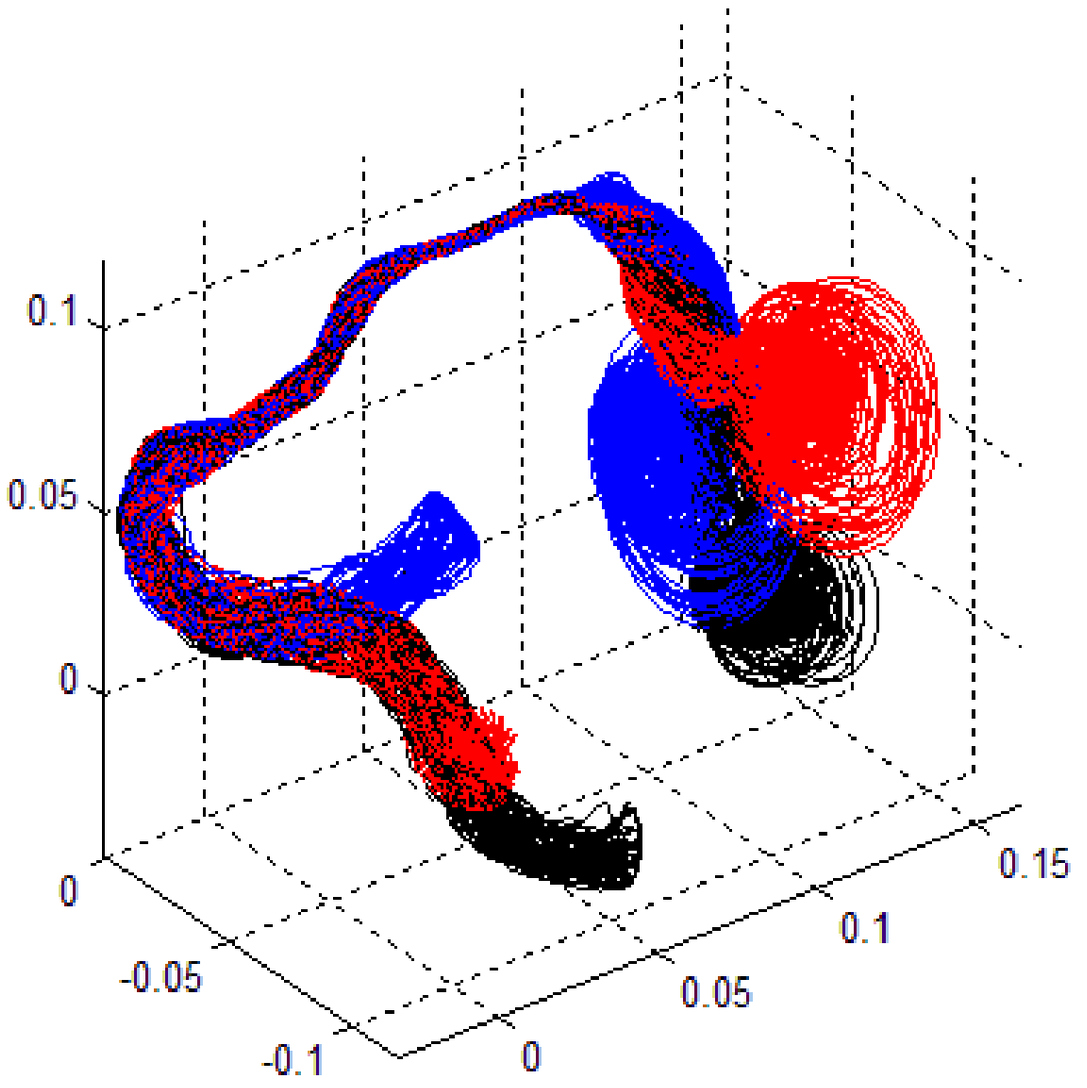
in vivo RF Feldverteilung: Populationsabdeckung



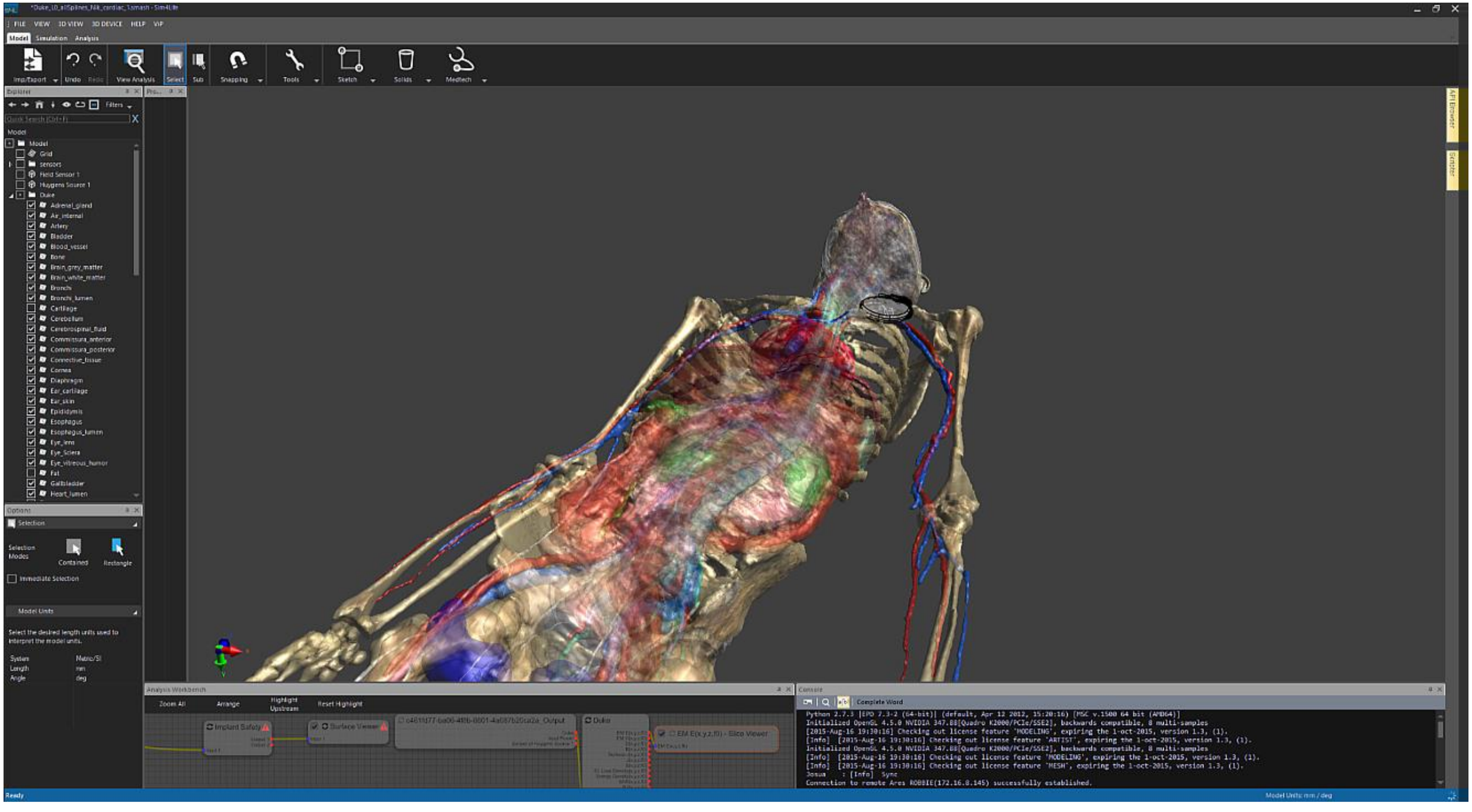


Trajektorienabdeckung

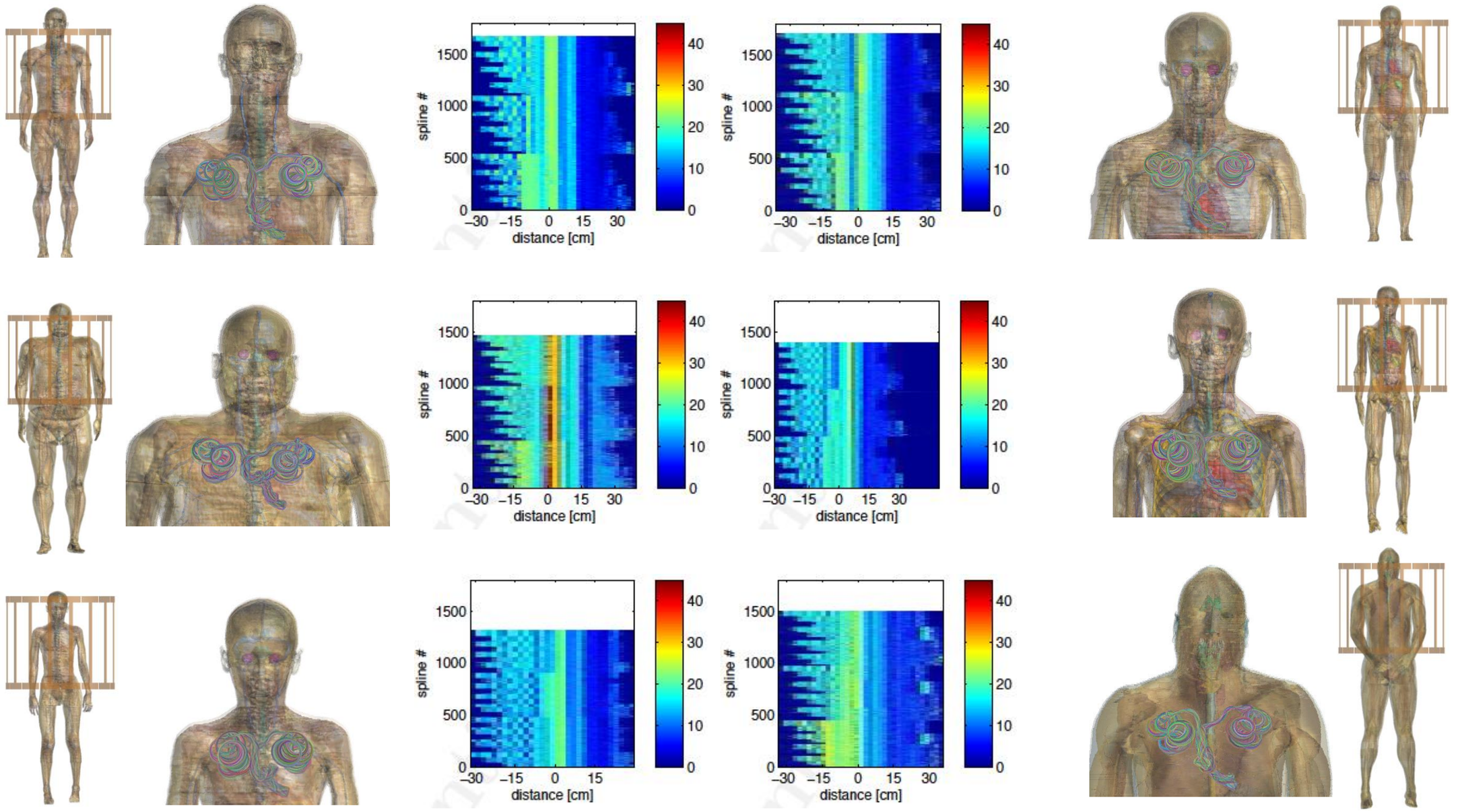




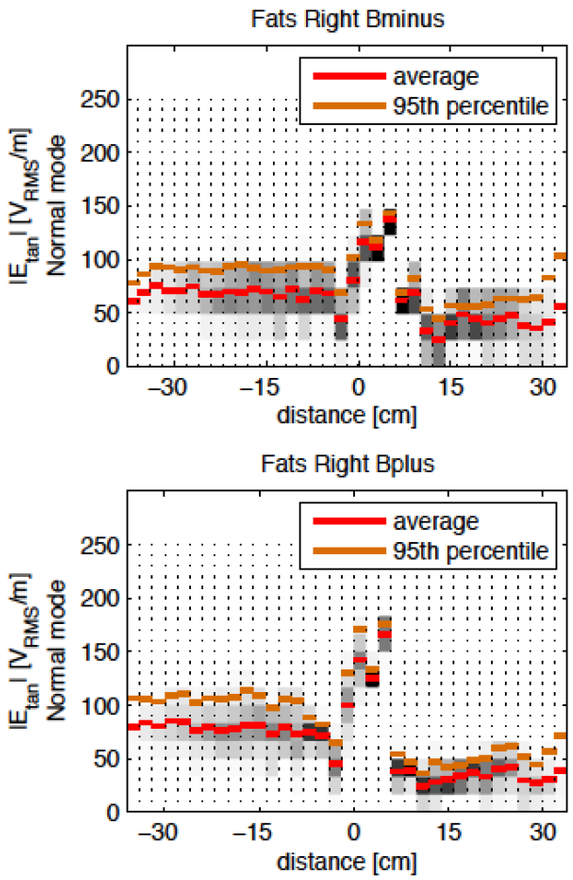
Kombination

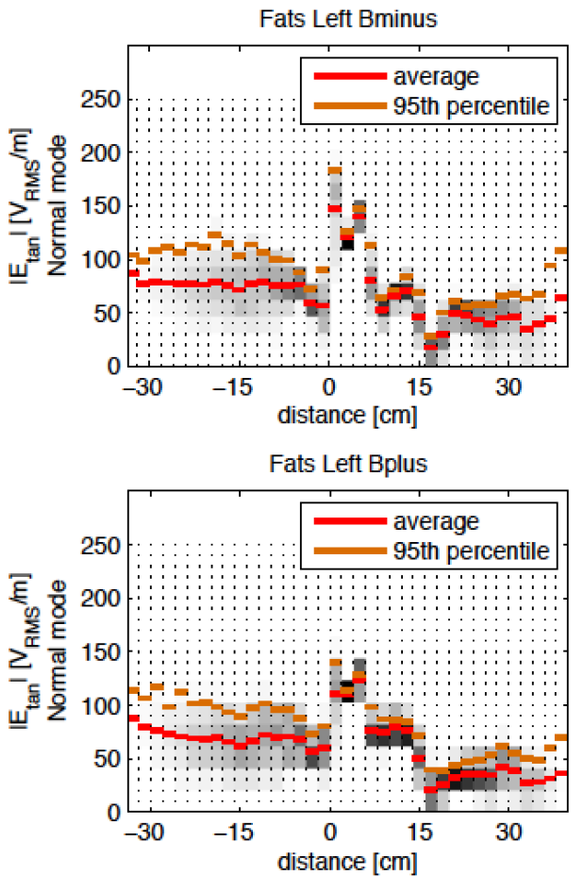


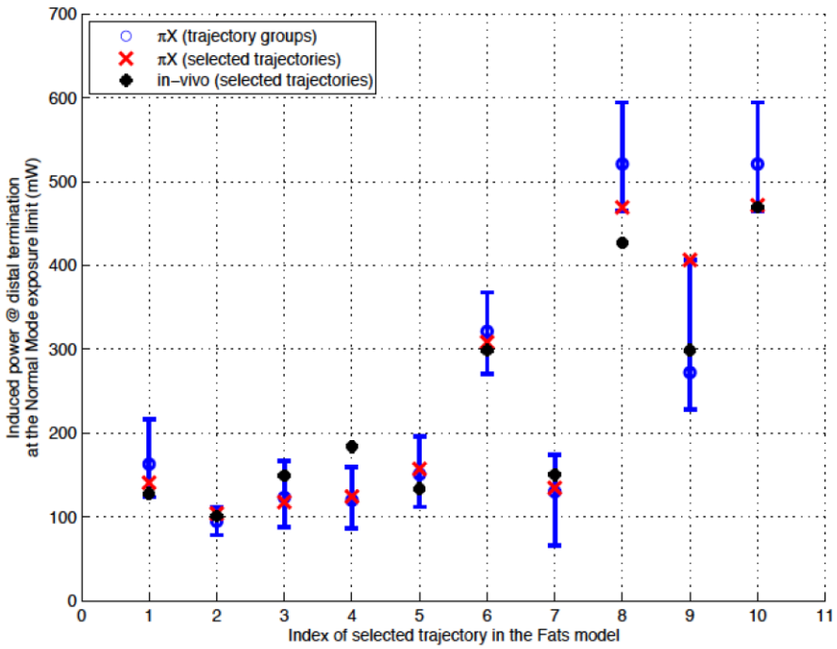
Kombination

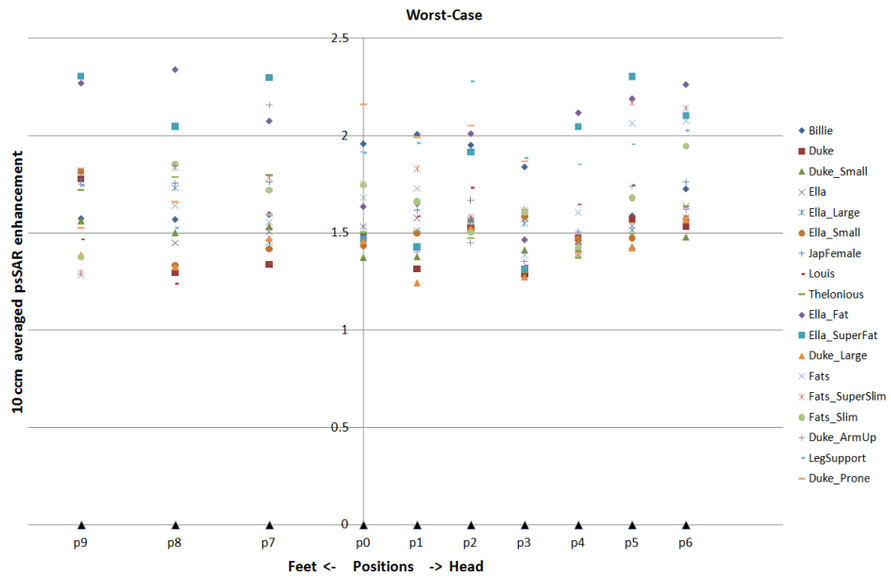


Statistische Auswertung









Auszug aus der Unsicherheitsanalyse

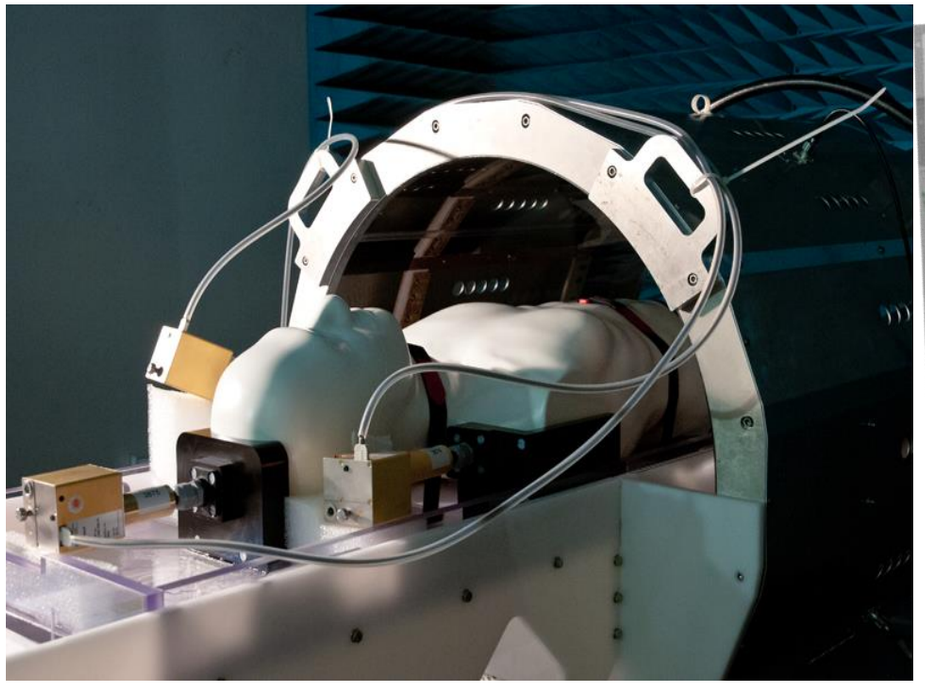
Parameter	Range	u_i	
(a) EM Simulation		psSAR10g per wbSAR[a]	
Convergence	Simulation length: +100%	0.03 dB	
Model discretization	Voxel size: 0.5 mm, 3 mm	0.26 dB	
Dielectric parameter	σ: ±10%	0.05 dB	
Dielectric parameter	ε: ±10%	0.17 dB	
Dielectric contrast	σ: ±10%, in single tissue	0.09 dB	
Dielectric contrast	ε: ±10%, in single tissue	0.08 dB	
Density contrast	ρ: ±10%, in single tissue	0.26 dB	
Anatomical model accuracy	According to (29)	0.28 dB	
RSS: Local SAR uncertainty		0.51 dB (−11%; +12%)	
(b) Thermal Simulation (worst case scenario, steady-state)		pT, Thermoregulated	pT, Constant perf.
Local SAR uncertainty	from (a)	0.40 dB[b]	0.40 dB
Convergence	Simulation length and time step	0.04 dB[b]	0.05 dB
Model discretization	Voxel size: 0.5 mm, 3 mm	0.19 dB[b]	0.26 dB
Thermal parameter	c: ± 10%	0.00 dB[b]	0.00 dB
Thermal parameter	k: ± 20%	0.05 dB[b]	0.26 dB
Thermal parameter	Q: ± 20%	0.08 dB[b]	0.02 dB
Blood heat capacity	$\rho_b \cdot c_b$: ± 10%	0.16 dB[b]	0.16 dB
Thermal boundary cond.	h: ± 50%	0.12 dB[b]	0.11 dB
Basal (constant) perfusion	B_0: ± 50% (all tissues)	0.26 dB[b]	1.14 dB
Perfusion increase	L_b: ± 50%	0.70 dB[b]	n.a.
RSS: Peak temperature increase uncertainty, actual estimated value and resulting uncertainty interval in peak temperature		0.90 dB[b], 42.8°C (41.7°; 44.1°)	1.28 dB, 60°C (54.1°; 67.9°)
Corresponding max. scan time uncertainty (in defined worst-case scenario for CEM43 = 15 min limit), actual estimated value and uncertainty interval		2.1 dB[b], 25 min (16 min; 41 min)	1.2 dB[b], 4 min (3 min; 5.3 min)

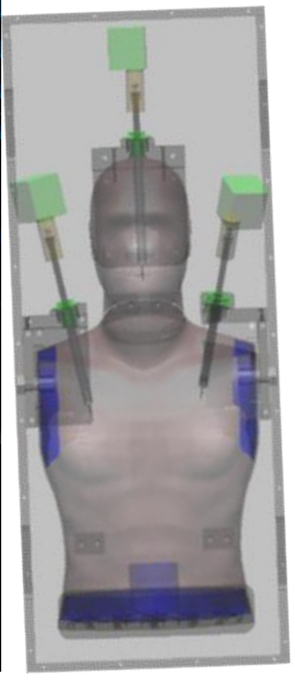
Auszug aus der Unsicherheitsanalyse

(d) Temperature increase validation measurement (assessment for T1 at high dose experiment)		
Temperature probe uncertainty	< 0.1 dB	
Incidence B1 field assessment	0.6 dB	
Probe placement (20 mm)	1.0 dB	
Probe thermal contact	0.5 dB	
Volunteer positioning (100 mm)	0.3 dB	
Differences between Duke and the actual volunteer	0.3 dB	
Thermal equilibration	0.5 dB	RSS (*b*) + (*d*):
RSS: Thermal validation measurement uncertainty, actual estimated value and uncertainty interval	1.4 dB, 39.5°C (38.8°; 40.5°)	1.6 dB ($k=1$); 3.2 dB ($k=2$)

[a]Relative local SAR uncertainty, as exposure is normalized to wbSAR.
[b]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.

Neufeld, et al., Phys. Med. Biol. ***54*** *(2009) 4151–4169*





VERIFICATION AND VALIDATION

Verification & Validation

Method of Manufactured Solutions, benchmarks, published data, measurements

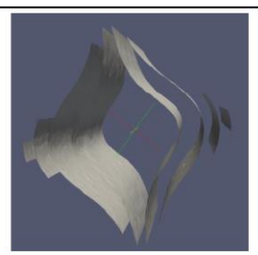


Fig 1. Expected solution

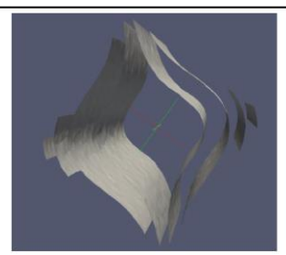


Fig 2. Numerical solution

$$\sigma = \begin{bmatrix} x^2+0.1 & 0 & 0 \\ 0 & (4x^2+1.2)\#1-(2z^2+1.1)(\#2-1) & \#1 \\ 0 & \#1 & (2z^2+1.1)\#2-(4x^2+1.2)(\#2-1) \end{bmatrix}$$

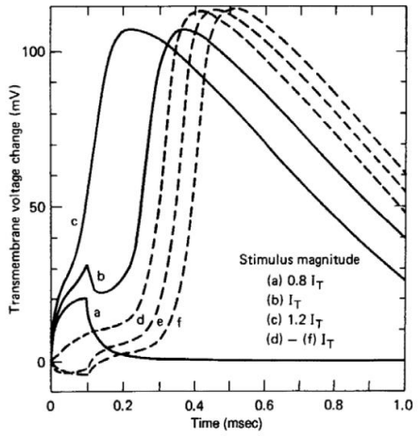
$$\#1 = \frac{\sqrt{(1-\#2)}\left(1000x^4+500x^2z^2-55x^2-500z^4+65z^2-2\right)}{250} \tag{5.1}$$

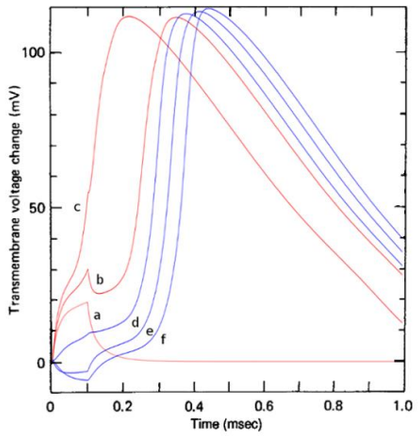
$$\#2 = \left(x^2+z^2-0.08\right)^2$$

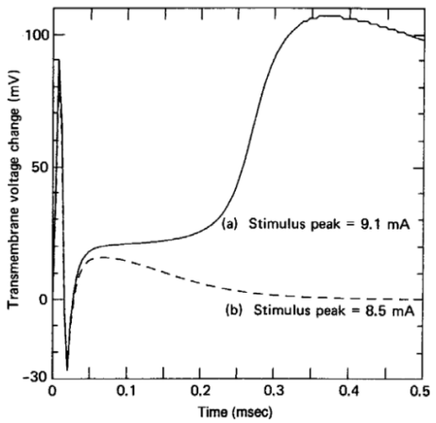
$$\phi = x+y+z \tag{5.2}$$

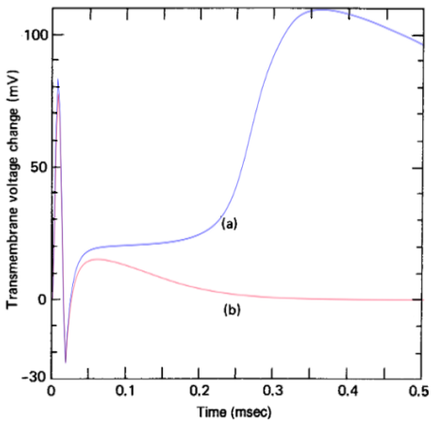
$$\begin{aligned} S_0 &= 2x+4z\#6^2-4z\#5\#6-4z\#4\#6+4z\#3\#6 \\ &= 2z\#4\#5-2z\#3\#5-\frac{2z\#4\#6^2}{\#5}+\frac{2z\#3\#6^2}{\#5} \\ \#3 &= 2z^2+1.1 \\ \#4 &= 4x^2+1.2 \\ \#5 &= \sqrt{1-\#6^2} \\ \#6 &= x^2+z^2-0.08 \end{aligned} \tag{5.3}$$

- sharp contrasts
- anisotropic tensorial conductivity
- conductivity inhomogeneity
- source term inhomogeneity

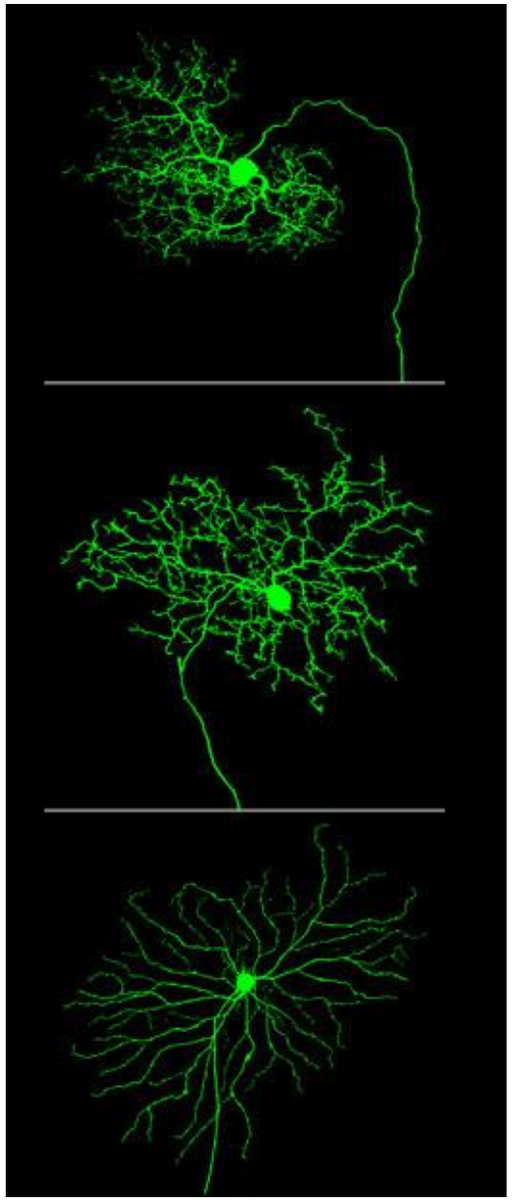




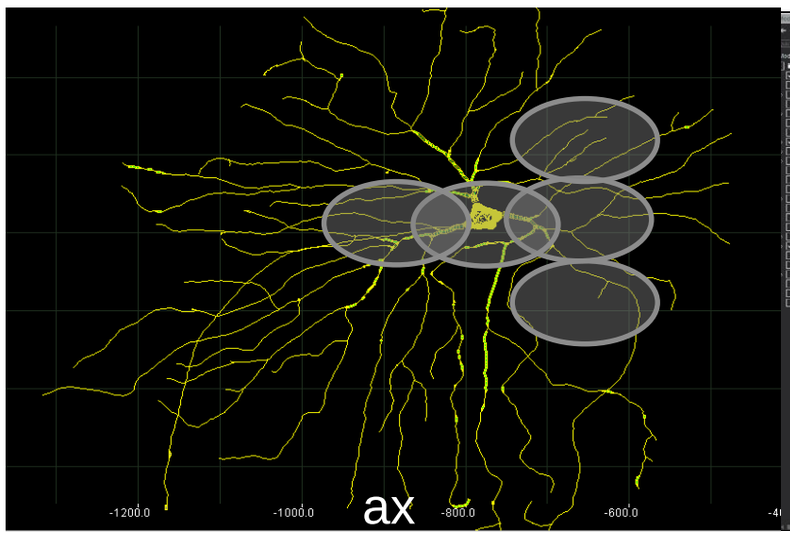


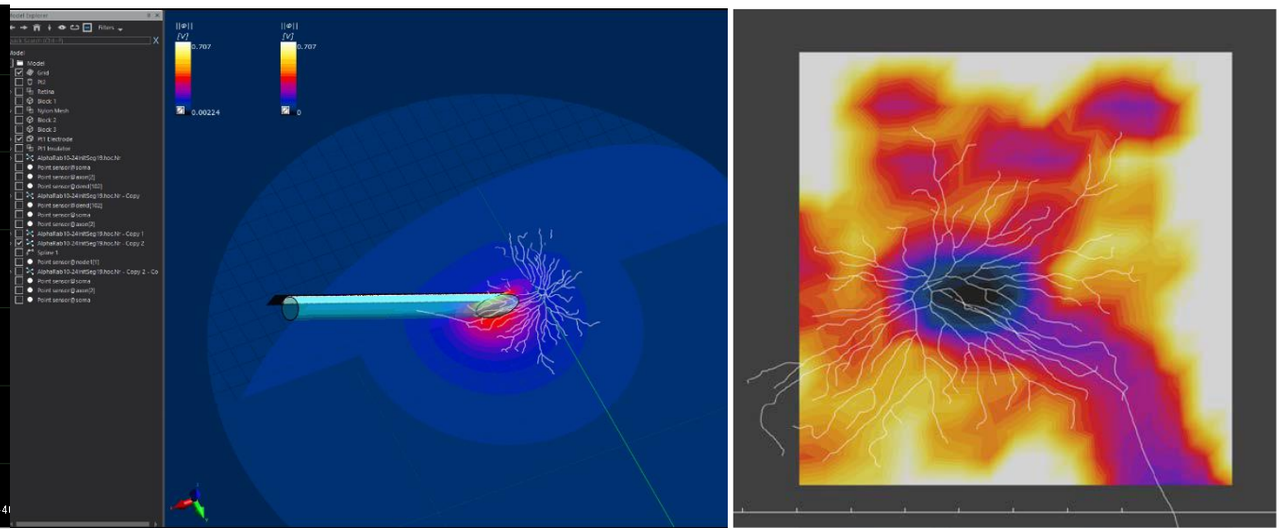


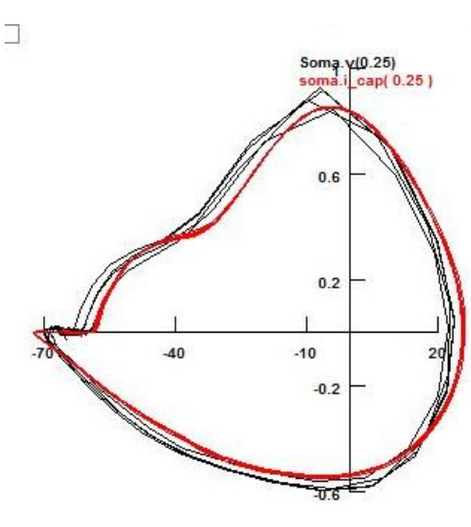
- pulse shape
- stimulation thresholds (center-type and end-node stimulation)



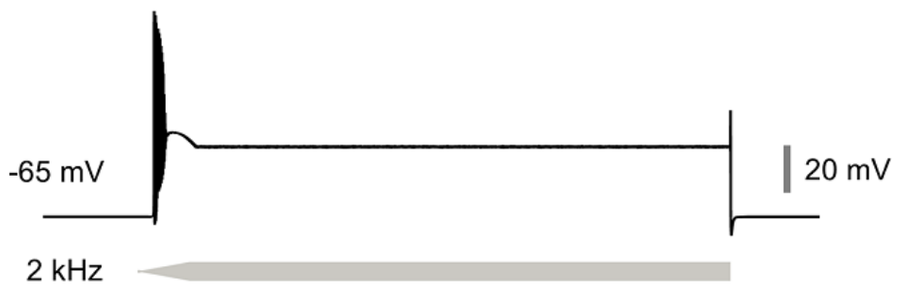
Patch Clamp Measurements

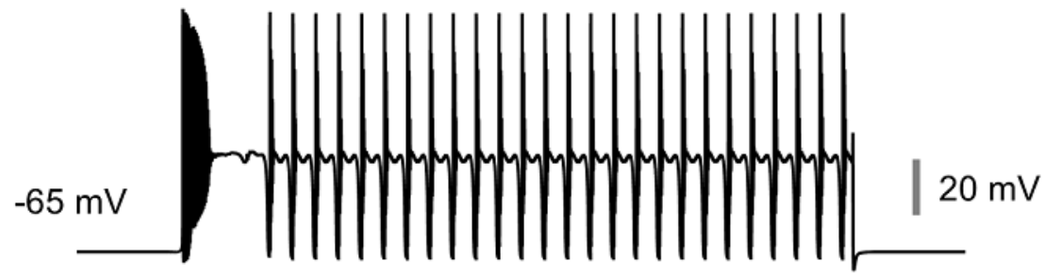




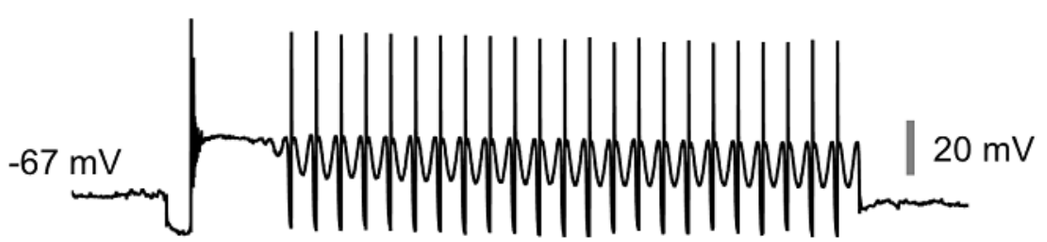


Simulation

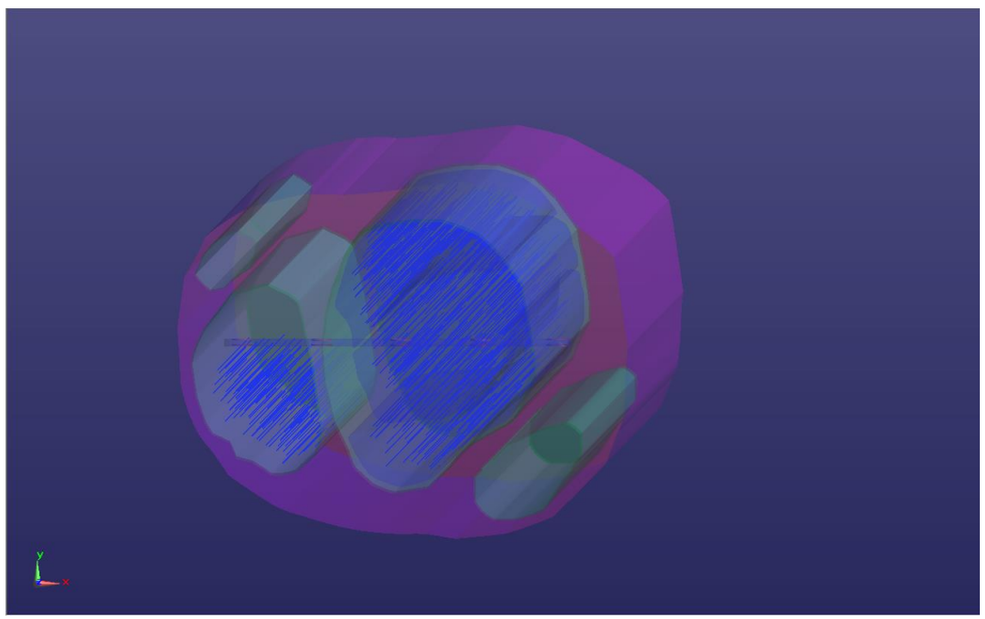


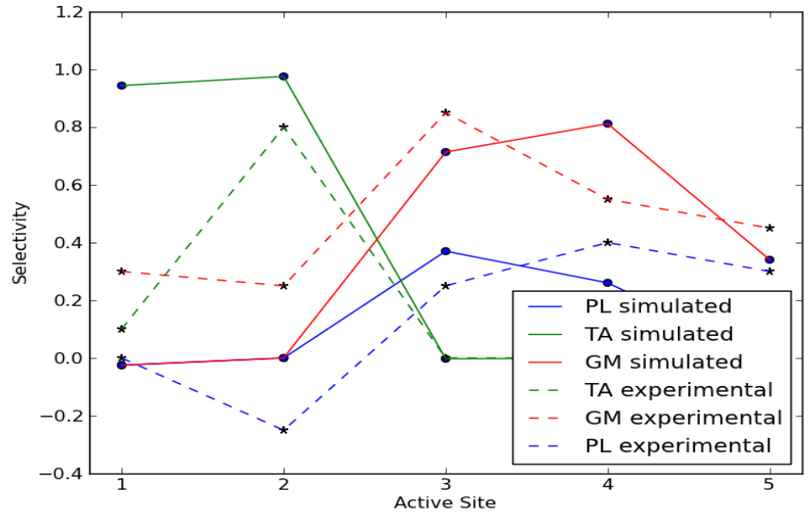


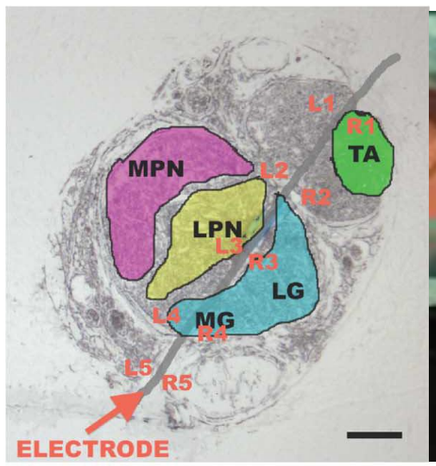
In-vitro measurements

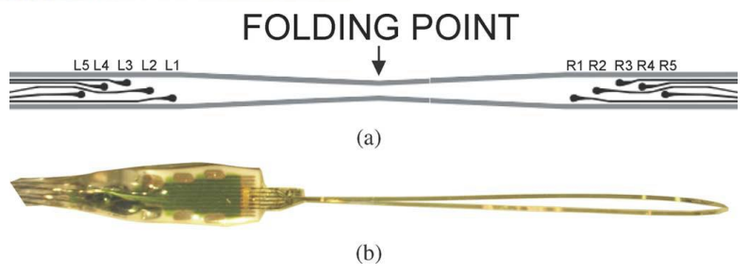


Neuroprosthetics: Selective Muscle Activation









Verification & Quality Assurance

- documented solver&algorithm verification (available for regulatory purposes)
  - following standards where available (e.g., IEC/IEEE 62704-1 for EM FDTD)
- automated test suit running nightly on large number of systems, unit tests
- quality assurance measures:
  - e.g., cross-checking & external expert review for ViP models,
  - automated checks (e.g., change of tissue property values, organ weight)
  - requirements & checklists & guidance documents
- bug & feature tracking system, version control

IT'IS FOUNDATION

Foundation for Research on Information Technologies in Society

Prof. Dr. Niels Kuster

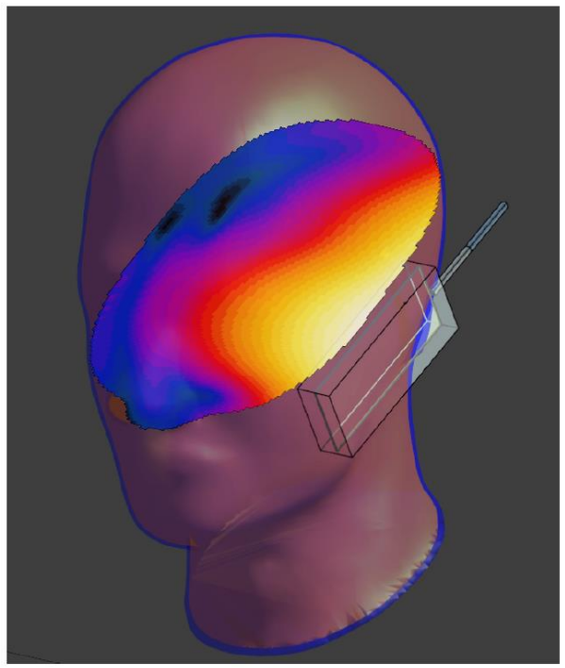
Director Foundation IT'IS
Professor of Swiss Federal Institute of Technology – ETH Z
Phone +41 44 245 9690 - kuster@its.ethz.ch

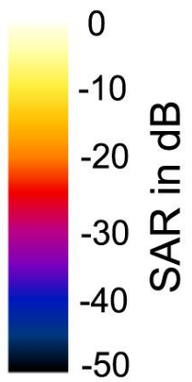
Verification Report FDTD001AA201507

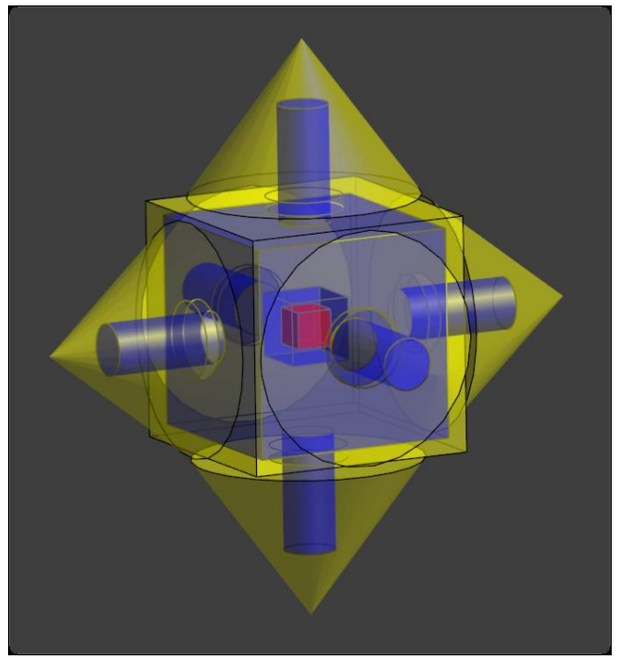
Sim4Life EM-FDTD Solver
Verification According to the Current Draft of IEC/IEEE 62704-1

Andreas Christ, Esra Neufeld and Niels Kuster

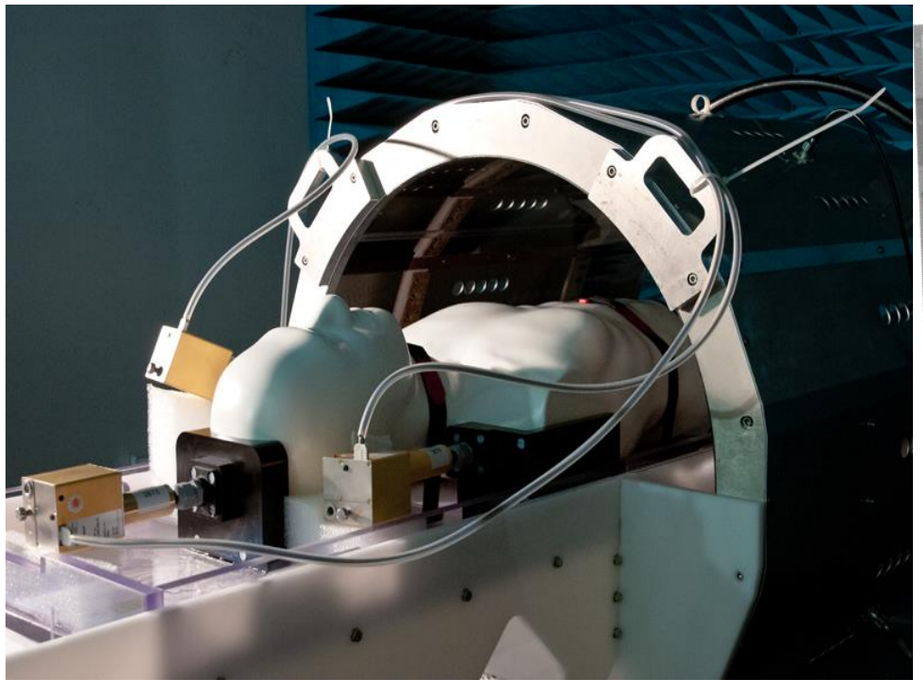
Zürich, July 2015

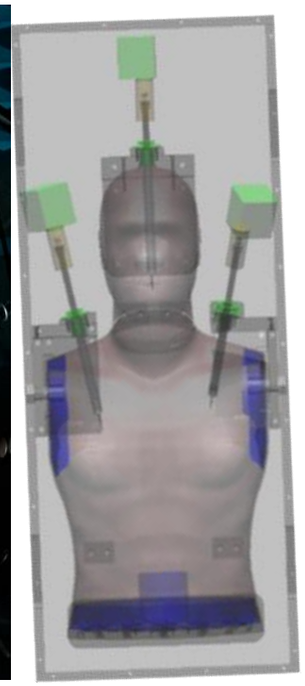




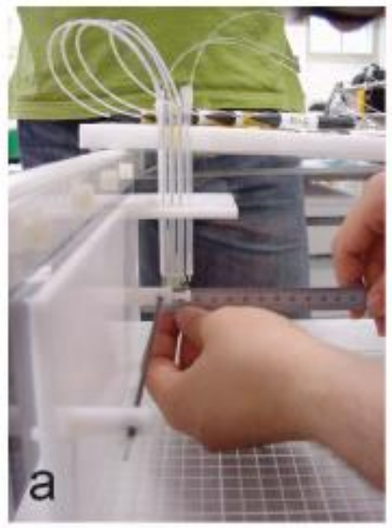


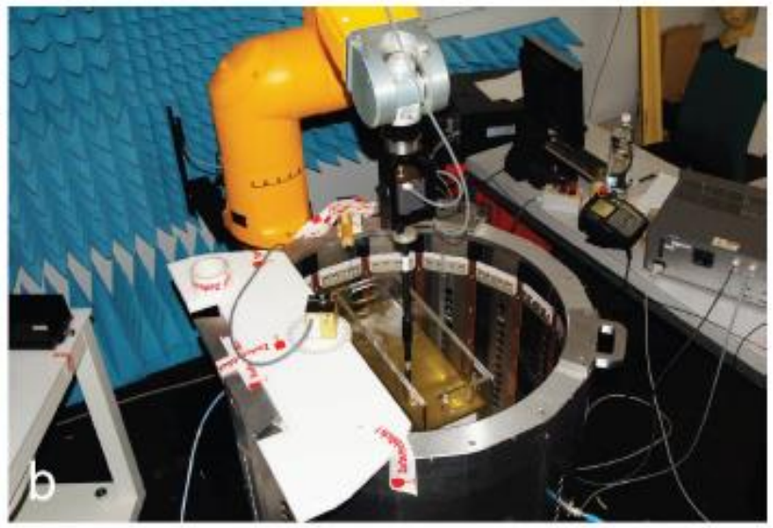
Torso Phantom and Model

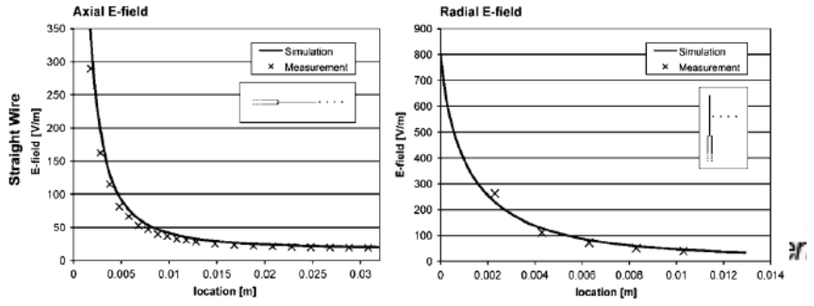


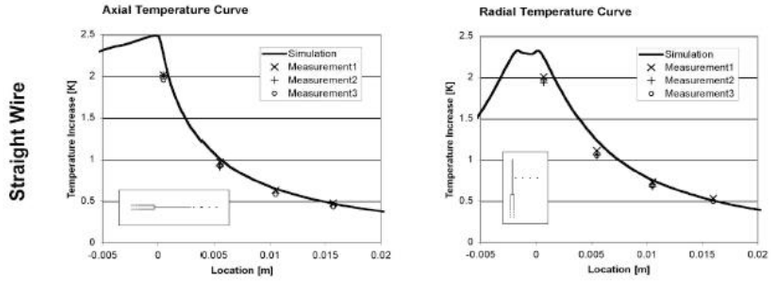


Generic (FDA) Implant

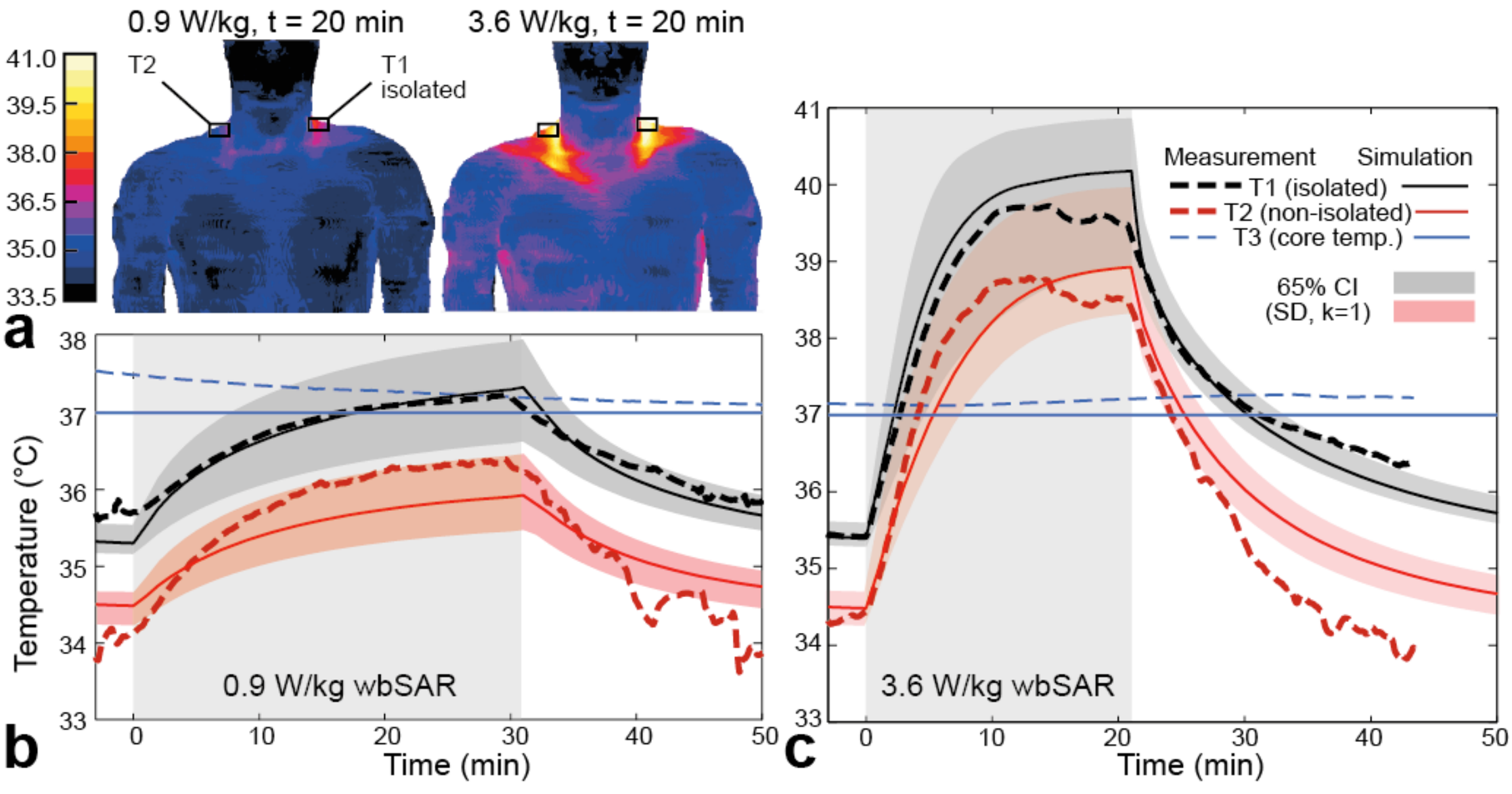




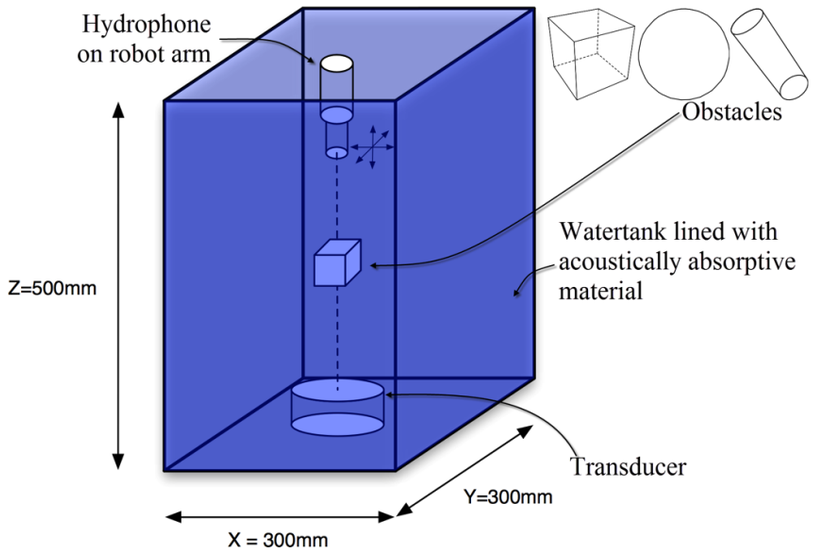


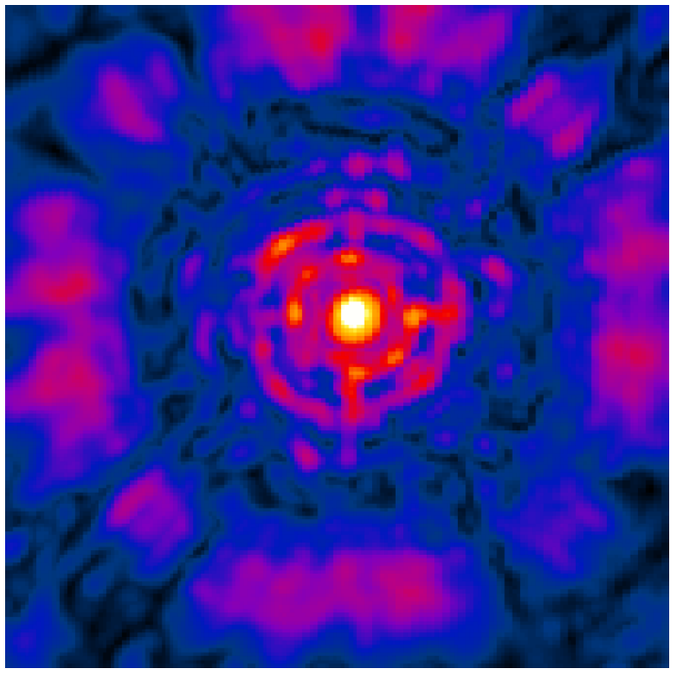


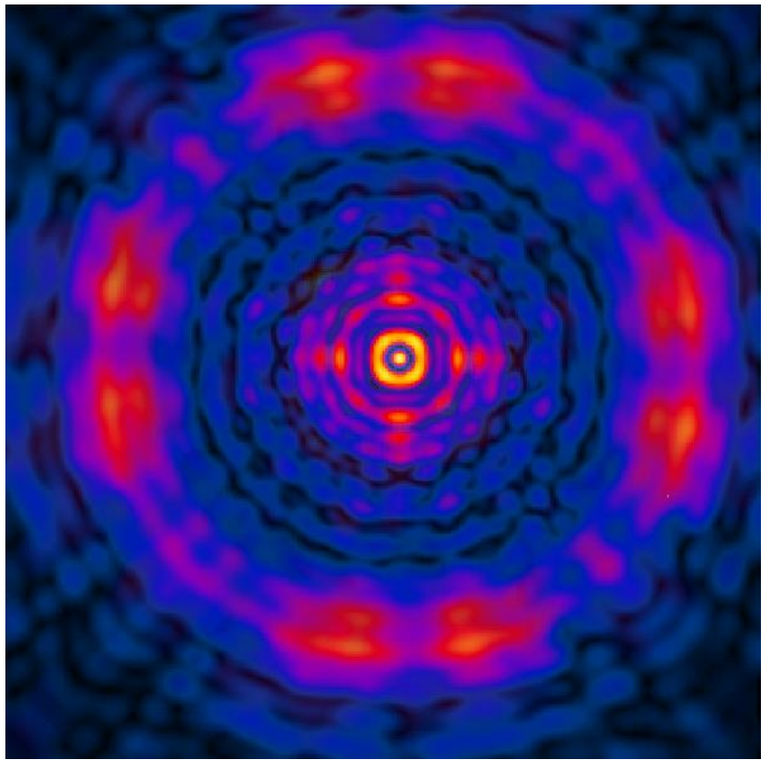
In Vivo Heating

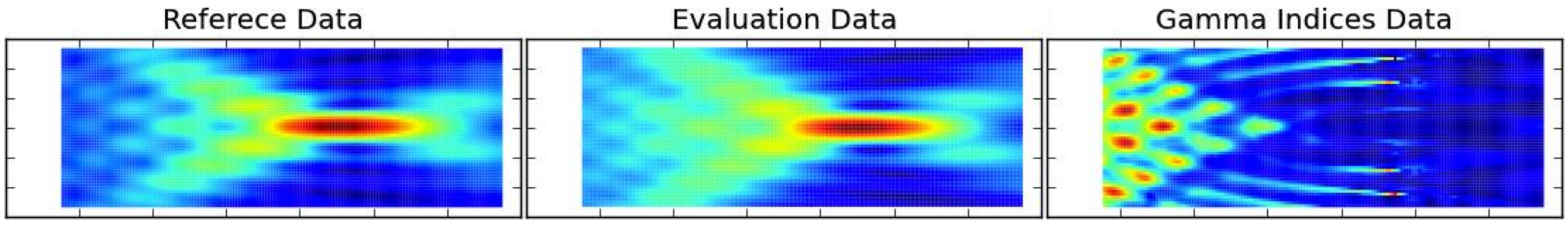


Validation: Gamma Method & GUM









CONCLUSIONS

Conclusions

- advances in imaging, HPC, and computational life sciences permit computable, functionalized anatomical phantoms
- these have been successfully applied for:
  - device & therapy innovation
  - personalized medicine & treatment planning
  - *in silico* clinical trials (safety & effectivity assessment)
- requires:
  - image-based generation of personalized / population-covering models
  - (image-based) functionalization (properties, BC, dynamics)
  - simulating physical interactions with living tissue within complex, inhomogeneous anatomy
  - modeling induced physiological/biological impact
  - identification of optimal therapy, worst-case configuration
  - quantification of confidence interval & V&V