The IST Programme
Project No. 10378

SimBio

SimBio - A Generic Environment for Bio-numerical Simulation

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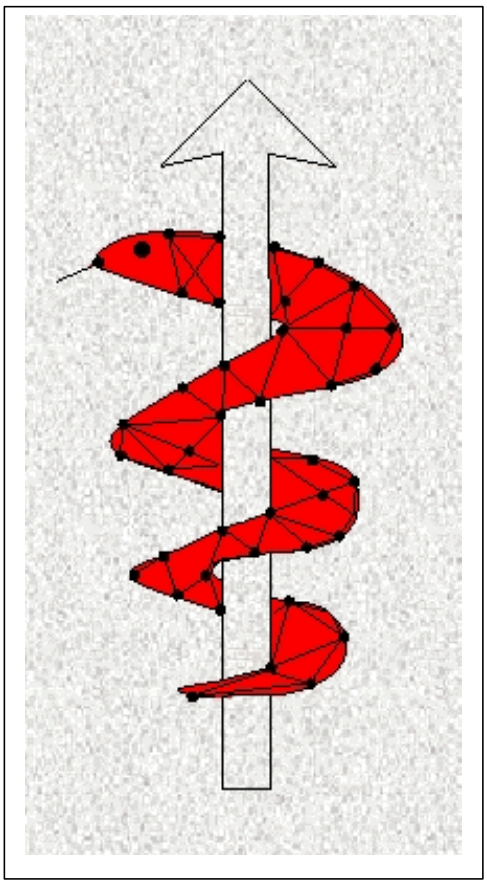

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NEC Europe Ltd. – UK
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Design report

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1 Introduction

1.1 The SimBio Project

The central objective of the SimBio project is the improvement of clinical and medical practices by the use of numerical simulation for bio-medical problems. The project builds on significant expertise and prior developments for specific applications to construct a generic environment, running on parallel and distributed computing systems, capable of handling a range of important problems relevant to the target community of clinical and medical service providers. This innovative development is an enabling technology for advanced clinical practice & health care leading to improvements in: non-invasive prognosis and diagnosis, pre-operative planning, design and implantation of prostheses and postoperative verification and evaluation of treatment success. The application evaluations in the project will demonstrate the effectiveness of the SimBio environment and thus accelerate the take-up of this IT technology within the medical area.

1.2 Validation and Evaluation

In electromagnetic source localization, it is our aim to include individual conductivity tensor information into routine noninvasive EEG/MEG-source localisation procedures. A typical example of improved health care and patient outcome in this regard is the presurgical magnetic source imaging (MSI) for tumour patients undergoing neurosurgery. It is known that most tumours are associated with changes in the tissue resistivity profile. Today’s standard modelling (boundary element) techniques do not take these changes into account. However, in these patients an accurate mapping of the location of primary sensory and motor functionality is crucial for the neurosurgeon in order to plan the surgery. An improved accuracy in presurgical MSI based on the patients individual conductivity tensor information will have a direct impact on the patient´s outcome.

2 Requirements

2.1 Focal physical source model

For this part of the study it is necessary to use a very small dipole because it will be used in the rabbits brain later on. In the following investigations we are going to stimulate nerves of the hindpaw and forepaw to activate the cortical neurones of the rabbits brain. The dipole should simulate these neuronal activities. The receptive field of the cortex of the hindpaw or forepaw are not larger than 1 to 1,5 mm. Thus, the dipole should have the size of not more then 1,5 mm. Since such dipoles are not available commercially we will design and produce such dipoles based an our previous experience with physical source models by Tenner et al.[16].

Dipole design criteria

- dipole size (length) equal to the size of the pyramidal cells of the cortical area
- easy handling in the animal with minimal tissue destruction by dipole implantation
- artefacts as small as possible

Dipole construction

- thicker twisted insulated copper wires shall be used as lead in wire for the dipole
- cutting of one part of the wire at the end and continue with a thin uninsulated copper wire
- thin wire shall be wrapped round the remaining part
- the wrap shall be soldered and insulated

Dipole layout

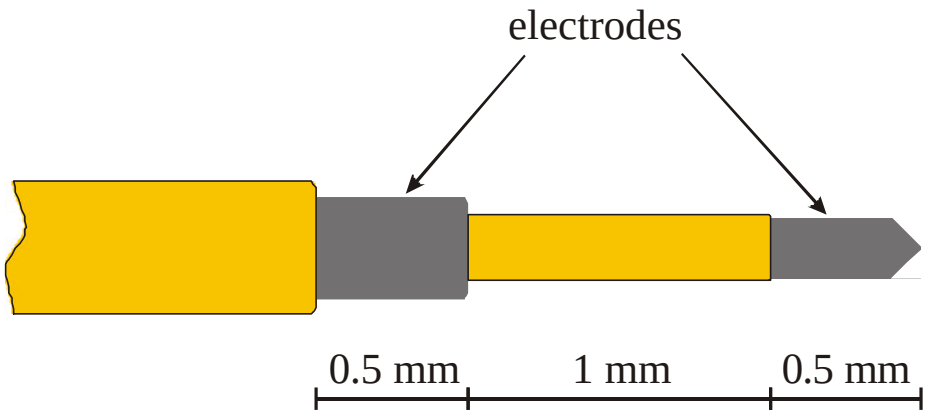

Figure 1: Dipole for inside brain position under the skull.

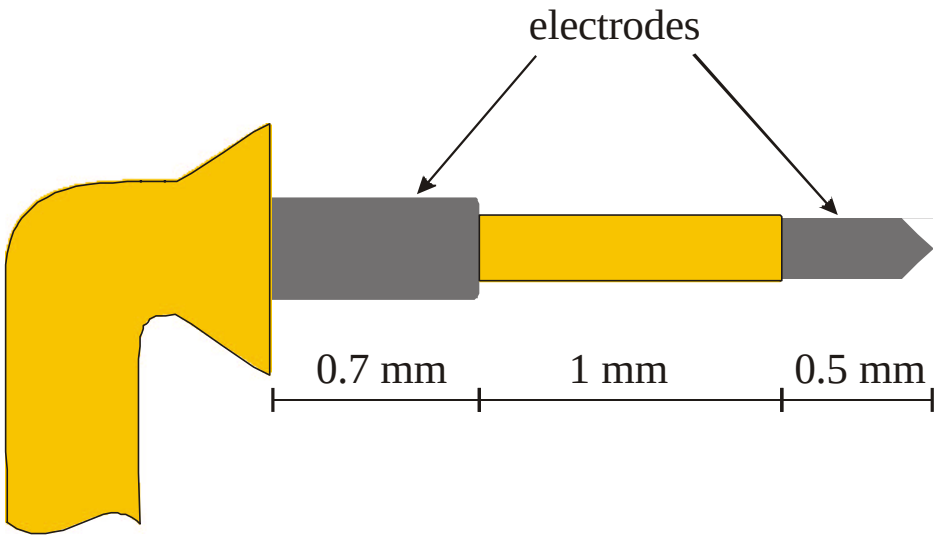

Figure 2: Dipole for position through the open skull in the brain.

2.2 Physiological stimulus modality

For the localisation and the determination of the strength of neuronal activity the stimulation of the rabbits hindpaw and forepaw nerves appears to be practical. The cortical areas of these nerves are situated in the upper part of the cortex directly under the skull (figure 3). Therefore we expect to obtain a high signal–to–noise ratio (SNR). To assure the reproducibility of the nerve irritation we will stimulate a certain nerve based on a small surgical intervention. The stimulation will be performed with silver electrodes adapted for animal investigations.

a) **b)**

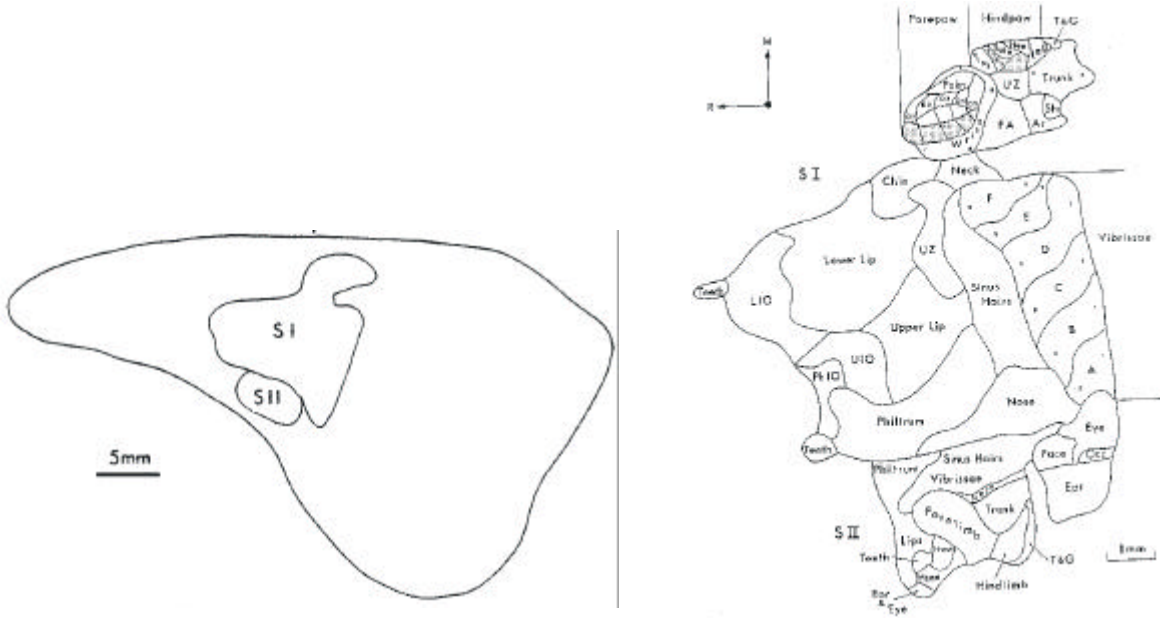

Figure 3 : Mapping of rabbit brain with areas of interest. SI indicates the primary somatosensory area in a). In b) this area is enlarged and further subdivisions are shown.

First investigations with anatomical preparation will show if it is possible to use the ulnar nerve and distal fibres of the ischiadic nerve depending on the surgical effort and the size of the nerve. Relating to the "Anatomy of small laboratory animals" by P.Popesko, V.Rajtova and J.Horak it seems to be possible.

Further tests are necessary to find out which stimulation parameters (current strength, frequency, stimulus duration, interstimulus interval) are useful to get the best magnetic signal. Furthermore, we have to investigate the dependency of the SNR of MEG, EEG and ECoG on the stimulation parameters. Thus, in the first tests, we have to uncover the nerves entirely to be able to irritate them ascending on several points with different currents.
The cortical areas of the ulnar and ischiadic nerve are adjacent with a distance of about 2 mm. This we will use to evaluate the precision of the spatial solution.

The localisation of neural excitation by MEG and EEG depends on the conductivity of several tissues according to investigations by Stok [15]. The measured electric potential on the skin surface is especially affected by the conductivity of the scalp and the skull (Haueisen et al.[5]). In contrast the magnetic field is changed by the white and grey matter and the cerebrospinal fluid (CSF). For certain tissues an anisotropic conductivity is known, e.g. the skull. To take into account such influences the MEG and the EEG will be recorded on several steps of the preparation. Recording will be done after taking off the different layers – hair, scalp skull and dura.
Partly, the steps of preparation have to be undertaken outside of the magnetically shielded room. This requires a possibility of an exact reposition. The use of at least 3 coils placed with cranial markers on the skull will be applied. Same markers filled with fat or Gadolinium will be used by MRI investigations later on.
The handling will be tested in one of the first investigations.

Furthermore, a positioning system was developed for transforming the gradiometer based co-ordinate system into the animal system. It consists of a set of 37 coils mounted on a plate below the animal. By subsequently measuring the fields originated by coils, the position of all gradiometers can be calculated by using a Levenberg – Marquardt algorithm [6].

Changes in body temperature and electrolyte balances influences the conductivity of neuronal tissue, therefore we have to keep this parameters constant during the whole investigation. A temperature sensor, a heating/warming pad, an infusion and the determination of blood gases and the electrolytes will support this process. The necessary arterial and venous approach will be made in the inguinal region.

The choice of the right anaesthetic agent is a very important part of this investigation due to the suppressive effect on somatosensory evoked potentials (SEP).
Most inhalation anaesthetic suppresses the SEP. Thus, we will use an inhalation anaesthetic with a short half-life period only for the beginning of the investigation and than an injection anaesthetic. For the application we will use the femoral vein like for the infusion. The small mouth and larynx complicate the normal intubation and the risk to develop a laryngospasmen is extremely high. Thus, artificial respiration will be ensured by intubation performed by tracheotomy.

The implantation of the dipole in the rabbits brain should be done over a small hole near the ear based on the work of Melcher and Cohen [4]. This way of implantation has the draw back that the problem of cell destruction possibly followed by a change in the brain conductivity might happen. During the process many cells of high concentration of potassium will be destroyed and the intercellular potassium concentration will increase. This will cause cell swelling and further disturbances of conductivity. Alternatively, we will use a small hole on the upper side of the head directly over the investigated area. The advantages are minimal cell destruction, exact localisation and easy handling. Under this performance we are not able to estimate the effect of the conductivity of different tissues (skull, scalp) in respect of the localisation.
Using FEM (finite element method) simulations will quantify the influence to the MEG data of this approach.
The final strategy depends on the results of the first investigations.

2.3 Computation of tissue conductivities from MEG/EEG/ECoG measurements

Computation of tissue conductivities from MEG/EEG/ECoG measurements will be realised with the resulting software of work package 4. This software will be especially tailored for the analysis of our work.

2.4 Diffusion tensor scans

The conductivity tensor describes the direction dependency of the conductivity, which is also known as anisotropy. Generally, it is an asymmetric second-rank tensor (3 x 3 matrix in the three-dimensional case). Ohm's law describes the coupling between the current density vector. It can be shown that for our application the conductivity tensor can be reduced to a symmetric tensor. Further, each symmetric second-rank tensor can be transformed to a diagonal form by choosing adequate co-ordinate axes.

The lack of a technique for robust measurement of the electrical conductivity tensor in vivo has discouraged the inclusion of anisotropic conductivity information in the electromagnetic source imaging forward model. Recently, however, investigators have proposed a framework for inferring the electrical conductivity tensor from the spin self-diffusion tensor as measured by diffusion tensor magnetic resonance imaging. The approach essentially derives the cross-property relationship between the conductivity and diffusion tensors through an effective medium representation of the tissue geometry. In the limit of small intracellular diffusion, the cross-property relation predicts a linear relationship between the conductivity and diffusion tensors. Hence, the first-order approximation to the full effective medium relation will be employed within the project.

Based on existing human diffusion tensor scan parameters we will adapt and optimise these parameters in order to perform diffusion tensor scans on rabbits.

2.5 Crossvalidation with the literature

The following values for cross validation with the existing literature have been extracted. Tissue resistivity depends on frequency and temperature. Thus, only resistivity values measured at or near body temperature and at low frequencies (d.c. up to 100 kHz) were taken into account. A brief summary of how the resistivity values for different types of tissues were estimated is given below. These values will be used in the simulations in WP 7.1. All resistivity values are in Ωcm.

1) Brain White Matter

   For the rabbit a value at 1 kHz of 746 was given by Crile et al.[2] and a value of 957 by van Harreveld et al.[17].
   For the cat 850 normal to fibres and 89 parallel to fibres at 20 Hz was given by Nicholson. Also for the cat a value of 333 using square pulses of 0.3 to 0.7 ms is given by Freygang and Landau [3].
   The mean value of the isotropic resistivity data was found to be 679.
   For the FEM computer model a mean value of 700 is chosen.

2) Brain Grey Matter

   A value of 222 was reported for the cat using square pulses of 0.3 to 0.7 ms by Freygang and Landau [3]. A value of 208 at 1 kHz was reported for the rabbit by van Harreveld et al.[17]. Also for the rabbit a value of 321 at 5 Hz was reported by Ranck [10] and a value of 438 at 1 kHz was reported by Crile [2].
   The mean value is 297 for the above studies and a rounded off mean value of 300 is chosen for the calculations.

3) Spinal Cord and Cerebellum

At 1 kHz a value of 576 was measured for the spinal cord and 730 for the cerebellum of the rabbit by Crile [2]. For the spinal cord of the cat a value of 175 parallel to the fibres and 1211 normal to the fibres was measured by Ranck et al.[11] at 5-10 Hz.
The mean value of the isotropic resistivity data is 653, thus for the calculations a mean value of 650 is chosen.

4) Cerebrospinal Fluid

A value of 65 at 1 kHz - 30 kHz is given by Geddes and Baker [4] for the human CSF.
A mean value of 65 is chosen for the calculations in our FEM model.

5) Hard Bone

A value of 16,000 at low frequencies was given by Geddes and Baker [4] for bones in the thorax. Reddy and Saha [12] have given a value of 16,600, 36,000, and 54,000 at 10 kHz for the axial, circumferential, and radial directions, respectively, of the wet, bovine, compact bone.
A mean value of 16,000 was chosen for the calculations and the upper bound of the resistivity is set to 50,000 for hard bone.

6) Soft Bone (substantia spongiosa)

There are no measurements of soft bone given in the literature to our knowledge. Since soft bone consists of a mixture of mainly fat and blood cells together with a spongy bone structure the same mean value of 2500 as for fat is selected.

7) Blood

A comparison of four investigations was made by Rush et al. [13] and it showed an agreement within ±3% The mean value was found to be 162 at low frequencies. We choose a mean value of 160 for our computations.

8) Muscle

A value of 150 and 2300 was given by Rush et al. for the longitudinal and transverse direction of the human arm muscles. This was measured with d.c. pulses of 0.1 sec duration. A value of 125 and 1800 was given by Burger and van Dongen [1]for longitudinal and transverse direction of rabbit muscles. More values can be found in Geddes and Baker [4]or in Polk and Postow [9] but all of them are within the range of the above values.
A mean value of 1000 and a lower and upper bound at ±80% of the mean value is selected to cover the whole range of values from the literature.

9) Fat

A mean value of 2500 was measured for anaesthetised animals by Rush et al using d.c. pulses of 0.1sec duration. Values from 1500 to 5000 were measured by Schwan and Kay [14] at 1 kHz for dogs.
A mean value of 2500 with lower and upper values of 1500 and 5000, respectively, are chosen.

10) Eye

A value of 198 at 300 kHz for bovine cortical eye, 285 at 500 kHz for bovine intermediate eye, and 530 at 500 kHz for bovine central eye was found in Geddes and Baker [4] . There are no data available for the human eye. In general, the resistivity

decreases with the increase of the frequency. Since these values for the eye are taken at higher frequencies it was assumed for calculations that a mean value of 200 with a lower bound of 100 and an upper bound of 400 is appropriate.

11) Scalp

In Geddes and Baker [4] a value of 230 at d.c. was given for the human scalp resistivity. For the calculations a mean value of 230 is taken.

12) Soft Tissue

To our knowledge there are no resistivity data on soft tissue available in the literature. Since soft tissue contains a high amount of water the value of the resistivity should be comparably low. From the structure of the soft tissue its resistivity should be in between those of body fluids (e.g. blood) and muscle.
Therefore, a mean value of 500 is chosen for the computations.

13) Internal Air

Internal air is used for the cavities in the head and since there are no resistivity data available a very high resistivity was assumed.
Therefore, the mean value is set to 50,000. An upper bound of 100,000 is used to check whether the mean value is high enough to represent a very good insulator. If the change in the resistivity from 50,000 to 100,000 leads to a significant change in the magnetic field or the surface potential than the higher value of 100,000 has to be used.

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