COMPUTATION OF ELECTROMAGNETIC FIELDS IN ASSEMBLAGES OF BIOLOGICAL CELLS USING A MODIFIED FINITE DIFFERENCE TIME DOMAIN SCHEME

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***Abstract*— When modeling objects that are small compared with the wavelength, for example biological cells at radio frequencies, the standard Finite-Difference Time-domain (FDTD) method requires extremely small time-step sizes, which may lead to excessive computation times. The problem can be overcome by implementing a quasi-static approximate version of FDTD, based on transferring the working frequency to a higher frequency and scaling back to the frequency of interest after the field has been computed. An approach to modeling and analysis of biological cells, incorporating the Hodgkin and Huxley membrane model, is presented here. Since the external medium of the biological cell is lossy material, a modified Berenger absorbing boundary condition is used to truncate the computation grid. Linear assemblages of cells are investigated and then Floquet periodic boundary conditions are imposed to imitate the effect of periodic replication of the assemblages. Thus, the analysis of a large structure of cells is made more computationally efficient than the modeling of the entire structure. The total fields of the simulated structures are shown to give reasonable and stable results at 900MHz, 1800MHz and 2450MHz. This method will facilitate deeper investigation of the phenomena in the interaction between EM fields and biological systems.**

***Index Terms*— Finite-Difference Time Domain (FDTD), quasi-static method, Floquet Periodic Boundary Conditions.**

I. Introduction

Research into possible mechanisms of interaction of electromagnetic (EM) fields with biological tissues and cells in culture has motivated a growing need for accurate models describing the EM behavior of cells exposed to these fields. Therefore, several numerical models have been created in order to study the interaction between EM fields and biological entities, at tissue level, cell level and ionic level. In this area, the most frequently used technique for computing the EM field is the finite-difference time-domain (FDTD) method [1,2], due to its independence from the material parameters.

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The original Finite-Difference Time-Domain (FDTD) method requires extremely small time-step sizes when modeling electrically-small regions (much smaller than a wavelength): this is especially the case when modeling biological cells, since they have maximum dimensions of a few tens of micrometers. Thus, it can become impractical due to the unaffordable computation times required. This problem can be solved by implementing a quasi-static approximate version of FDTD. This approach is based on transferring the working frequency to a higher frequency, to reduce the number of time steps required. Then, the generated internal field at the higher frequency can be scaled back to the frequency of interest [3-6].

Cells are surrounded by thin membranes, typically a few nanometres thick [7]. They are the major barrier in the cell, separating the inside of the cell from the exterior medium. It is this structure which allows cells to selectively interact with their environment. Therefore, the cell membrane has been identified as the primary target for the study of possible actions of EM fields on biological structures. Since the thickness of the membrane is about 1000 times smaller than the width of a typical biological cell, if the standard FDTD procedure were to be blindly applied to model detail in the membrane within a complete cell model, this would cause some millions of iterations to be required to complete one cycle of simulation. This again would cause excessive computation time. To overcome this drawback in standard FDTD, the lumped element finite different time domain method [8-11] was implemented to model the behavior of the membrane, based on the Hodgkin-Huxley model [12-16] on the surface of the biological cell.

This paper presents the new approach to modeling and analysis of the Hodgkin and Huxley membrane model, which is represented as an electrical circuit on the surface of the biological equivalent cells. For the sake of simplicity, the analyzed structure has been represented with spherical or cubical cells and Floquet periodic boundary conditions [17-20] have been applied to the border of the analyzed structure in order to mimic the presence of the surrounding cells. Although cellular tissues are not perfectly periodic and living cells are not

precisely spheres or cubes, these approximations allow a reasonable approach to the modeling of biological tissue using only a small part of the structure, while alleviating the problem of the huge requirement of computer resources for the simulation of a complete body of tissue. Since the external medium of the biological tissue is lossy fluid, the modified Berenger perfectly matched layer (PML) absorbing boundary condition [21-24] is used to truncate the computation grid, in order to reduce the reflections on the interface layers: this is more accurate than the Mur boundary condition [25,26], used in other recent work [4].

A further difficulty is the limited extent of studies on the dielectric properties of cell tissues [27]; thus, the complex permittivity of each cell tissue is not clearly established for radio frequencies. However, in this study, an analytical method for estimating the electrical properties of cell tissues in the RF band [28] will be adopted throughout the analysis. Earlier work only considered two media (water and membrane) [4], but the procedure adopted here enables the tissue model to consist of three media (lossy medium, membrane and cytoplasm). In addition, a mass of connected biological tissue is simulated by creating an equivalent stack of compacted cells (both spherical, with interstices, and fully-compacted cubical). The total electric fields along the central axes of rows of these spherical and cubical cellular structures will be investigated.

II. SUMMARY OF METHOD

A. *Quasi-Static FDTD Scheme*

The interaction between animals and humans exposed to extremely low frequency electric fields was investigated by Kaune and Gillis [29] and Guy et al. [30] in 1981 and 1982 respectively. Their research outcomes furnish valuable analytical and experimental verification of the concept of quasi-static coupling at power-line frequencies. Later authors [5,6,31] implemented the same principles using finite difference time domain to study the numerical dosimetry of anatomically-based models. Recently, the same idea was further extended to modeling the interaction between electromagnetic fields and biological tissue at mobile communication frequencies, i.e. GSM900 and GSM1800 [4].

In order to implement the quasi-static approximation to analyze scattering problems, the maximum dimension of the structure under investigation must be less than about one-tenth of the wavelength in the surrounding medium [29,30]. According to the scaling relationship between the fields at frequencies f and f' that was derived in [5,30], a higher working frequency (f') that still falls within the quasi-static regime can be chosen to excite the model, to reduce the computation time.

B. *Modified Berenger PML*

The Perfectly Matched Layer (PML), introduced by Berenger [21] in 1994, allowed boundary reflections below -80dB to be realised. PML is based on surrounding the FDTD problem space with a highly lossy and matched non-physical absorber. It has been found to be the most accurate technique of the absorbing boundary conditions available and has become standard in most current FDTD implementations [32]. For the case of PML layers with conductivities increasing geometrically, the geometric grading factor (g) can be modified in order to reduce the reflection on the interface layer when the problem space is entirely within a lossy-medium environment. An empirical expression from which g can be found, and which has been found to give good results [23,24] is:

$$\sigma = -\frac{\varepsilon c}{2\Delta x}\frac{\ln g}{g^N - 1}\ln R(0) \qquad (1)$$

where Δx is the spatial increment of the FDTD mesh, $R(0)$ is the normal reflection coefficient, N is the number of the cells in the PML thickness, and c is the velocity of EM waves in the environment concerned.

C. *Floquet Periodic Boundary Condition*

Many structures of electromagnetic interest are electrically very large and hence pose great difficulties for computational simulation. One approach that can be used to reduce the size of the computational task is to exploit any periodicity in the structure, in one or more dimensions: this concept will be exploited here, assuming that a sample of tissue is formed from a periodic grid of biological cells. In order to perform EM analysis on these types of structure with reasonable computational time, the structures are assumed to be an infinite grid and the problem can then be reduced to a unit-cell analysis via use of the Floquet boundary condition to simulate the effect of the periodic replication.

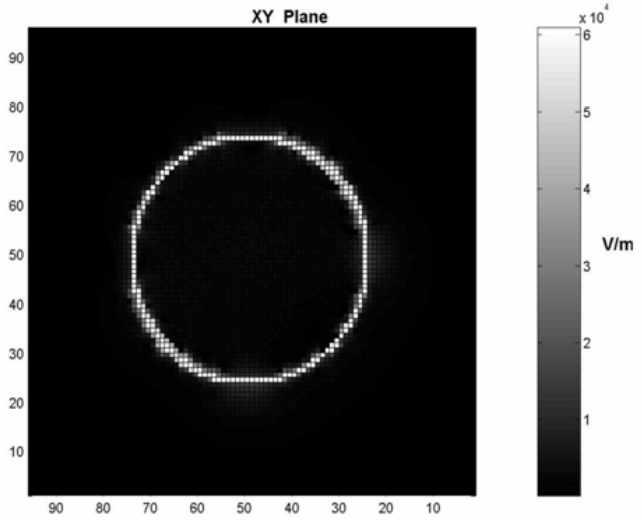

Fig. 1: Field distribution in and around a single isolated cell.

The FDTD technique was applied to the basic structure due to its simplicity and flexibility. FDTD has already been successfully extended to incorporate the Floquet theorem for the case of normal [17,33] and oblique incidence [34,35] for two- and three-dimensional problems. The techniques used to combine FDTD with the Floquet periodic boundary condition can be classified into two categories, direct field methods and field transformation methods [2].

D. *Hodgkin and Huxley Membrane Model*

Cells are surrounded by a thin membrane, which is the major barrier separating the cell from its environment (normally a liquid). Since the cell needs to get nutrients in and waste out, the membrane must be able to accommodate this. Therefore, the membrane has to act as a selective barrier, allowing nutrients to pass in but keeping out many substances harmful to the cell, and acting as a dynamic barrier medium, constantly adapting to changing environmental conditions (e.g. different concentrations of ions).

The dimensions of a biological cell are around a few tens of micrometers and the thicknesses of the membranes are in the scale of a few nanometers, strongly depending on the type of the tissue. Depending on the type of the cell, voltages in the range of 20-200mV can arise across the membrane. When the cell is in a resting state, the current across the membrane averages zero, but more generally it depends on the variation of the membrane voltage [12].

Hodgkin and Huxley gave a general description of the time course of the current which flows through the membrane of the squid giant axon when the potential difference across the membrane was suddenly changed from its steady state. The results in [12] suggest that the behaviour of membrane may be represented by an electric circuit [4,12]. Current can be carried through the membrane either by charging the membrane capacitance or by movement of ions through the nonlinear conductance in parallel with the membrane capacitance. A set of equations governing the model is given in [4,12].

III. IMPLEMENTATION AND VALIDATION

A. *Hodgkin-Huxley model implementation*

To verify the correctness of the implementation of the Hodgkin-Huxley model within the FDTD framework, the results of the analytically computed solution have been used for comparison. The Hodgkin-Huxley model was implemented on a spherical structure with diameter 50 μm and discretised with 1 μm steps, in order to check for the expected polarization voltage of 60.27 mV on the membrane [4]. The Hodgkin-Huxley model was included on the surface of the cell, while the regions internal and external to the sphere were considered as cytoplasm and lossy medium respectively. It should be noted that the lumped-element FDTD method has been successfully modified in order to allow arbitrary positioning of lumped elements inside FDTD elements representing the membrane, not necessarily aligned with the FDTD grid [4], so that they represent the structure more exactly than simple FDTD. Fig. 1 depicts the expected polarization voltage of 60.27mV, appearing on the membrane of the spherical structure without any external excitation.

B. *Quasi-static FDTD validation*

In this section, a simple example will be given to illustrate this method: the results will be compared with the Mie series analytical solution [36,37]. A two-layer sphere simulating a biological cell inside a lossy medium was considered, for which the assumed properties were as follows [38]: cytoplasm (internal) $\varepsilon_r = 48.699$, $\sigma = 1.412$ S/m; membrane $\varepsilon_r = 11.3$, $\sigma = 0.0$ S/m; external lossy medium $\varepsilon_r = 70.87$, $\sigma = 2.781$ S/m. The radius of the internal region was 25 μm and the membrane thickness was set to 2 μm. The operating frequency was 2.45 GHz, whereas the interim transformed frequency used in this example was 30 GHz. From equation (1), the optimum grading factor g is 6.07 for an FDTD cell size of 1 μm. It should be noted that this model in the FDTD computation domain is excited by a standard plane wave of amplitude 1 V/m, propagating in the z-direction and polarized in the x-direction. The field distributions along the two central axes of the layered cell are depicted in Figs. 2 and 3. As can be seen, the numerical results are in good agreement with the analytical ones. It should be noted that the method was executed for a total time equal to four cycles.

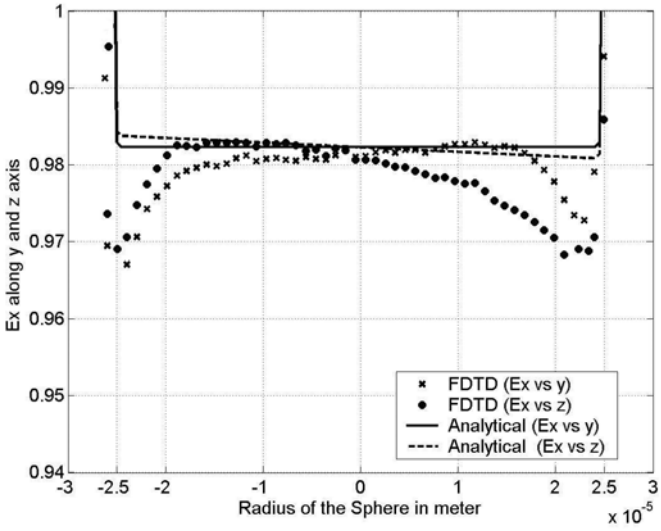

Fig. 2: Electric Field (E_x) distribution along principal axes of a double-layer sphere in lossy medium, excited by a plane wave of 1 V/m at 2450 GHz.

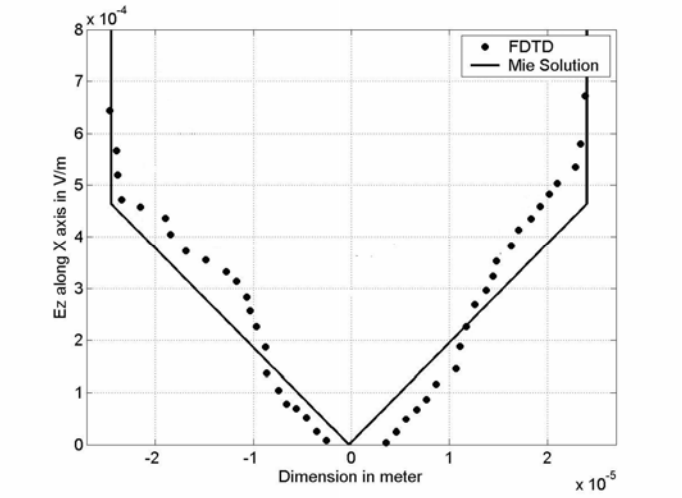

Fig. 3: Electric Field (E_z) distribution along the x-axis for double-layer sphere in lossy medium, excited by plane wave of 1 V/m at 2450 GHz.

C. *Implementation of Floquet Boundary Condition*

This section demonstrates the implementation of Floquet boundary conditions, quasi-static FDTD and the present modified PML for a lossy medium excited by a 100 V/m plane wave at an operating frequency of 900 MHz. The lossy medium properties were $\varepsilon_r = 1.0$, $\sigma = 25$ S/m. The problem space and cell sizes were 21×21×121 and 10μm respectively. The Floquet boundary conditions were imposed on four sides of the lossy medium. The remaining two sides were each terminated by a PML of 6 cells. The analyses were performed at 10, 15 and 20GHz and then transferred back to the desired operating frequency of 900MHz. As can be observed in Fig. 4, the analytical and computed results are in good agreement.

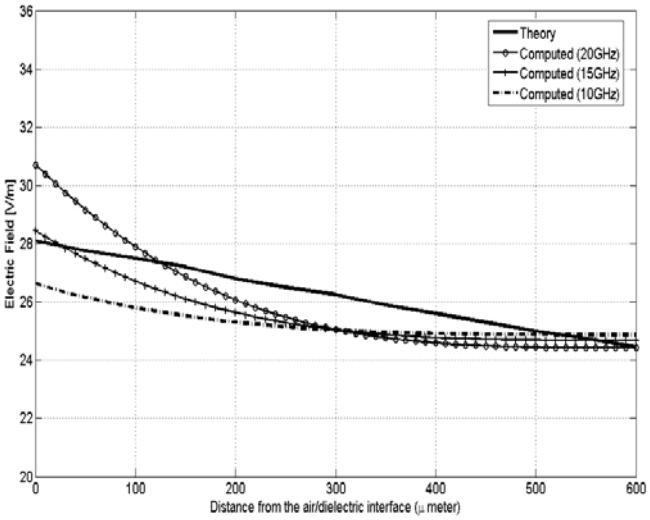

Fig. 4: Electric Field along the centre of the lossy medium.

IV. SIMULATION AND RESULTS

A. *Connected Tissue Model Using Spherical Cells*

A stack of ten spherical cells was investigated, as shown in Figs. 5 and 6. The radius of the each cell was 10 μm. The model contained three media, cytoplasm, membrane and extracellular medium, and the dielectric properties of these were obtained from [28], as tabulated in Table I. A plane wave of 100 V/m, propagating in the z-direction and polarized in the x-direction was used as the excitation. Note that the incident plane wave excitation was applied on a plane lying between the PML region and the outer limit of the FDTD grid. In addition, in order to reduce high-frequency transients [39,40] and DC offsets [41,42] sometimes associated with unramped sine wave excitations, the ramped sinusoidal source in equation (2) was adopted, multiplying the excitation source of 100 V/m with the f(t) functions given [41].

$$f(t)=\begin{cases}0 & t<0\\ 0.5\left[1-\cos(\omega_r t)\right]\sin(\omega_r t) & 0\le t\le \dfrac{T_r}{2}\\ \sin(\omega_r t) & t>\dfrac{T_r}{2}\end{cases} \qquad (2)$$

Where T_r is the duration of the ramped cosine regime, which is about 3 source cycles.

TABLE I.
ELECTRICAL PROPERTIES OF THE SIMULATED MEDIA AT RELEVANT FREQUENCIES

	900 MHz	1800MHz	2000MHz	2450MHz	10GHz
ε_i	72.2003	71.956	71.88	71.6806	63.5023
σ_i	0.4168	0.7656	0.8742	1.1590	12.8384
ε_m	1.6526	1.5680	1.5621	1.5536	1.5371
σ_m	0.0217	0.0232	0.0233	0.0234	0.0237
ε_e	72.2003	71.956	71.88	71.6806	63.5023
σ_e	1.3168	1.6656	1.7742	2.0590	13.7384

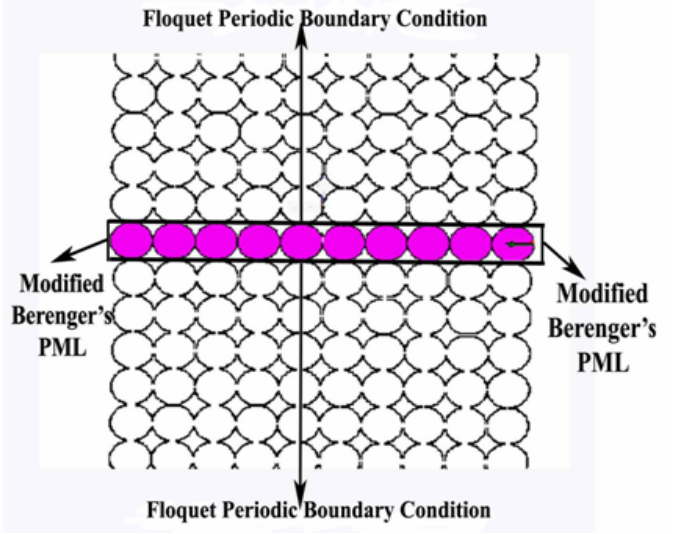

Fig. 5: Two-dimensional view of the simulated periodic structure in the FDTD computational domain, extended by the Floquet boundary condition.

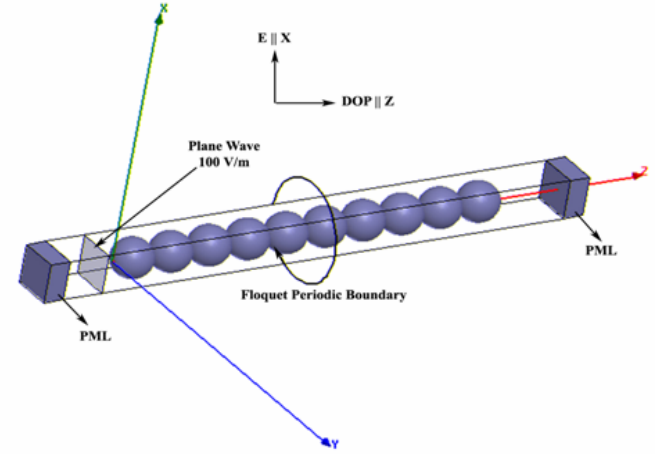

Fig. 6: Three-dimensional view of the basic simulated spherical structures in the FDTD computational domain.

The PML, shown in Fig. 6, was 6 FDTD elements wide, the grading factor g was 10.1383 and the grid structure was effectively extended to infinity in the x- and y-directions, by imposing the Floquet boundary condition along the x and y axes. The Floquet periodic boundary condition plays an important role to mimic the presence of an extended 3-dimensional structure of biological cells, simulating

connected tissue. This can be easily imagined in two dimensions, as shown in Fig. 5. The FDTD problem space was 220×20×20 FDTD elements of size 1μm while a discretization time step δt of 1.3 femtoseconds was chosen to drive the FDTD computation, to meet the requirements of the Courant stability criterion.

Before implementing the Hodgkin-Huxley model into the simulated structure, the effect of moving the Floquet boundaries gradually away from the simulated structure was studied. Figs. 7 and 8 depict the field distribution through the centre of the simulated structure at 10GHz with varying locations of the Floquet boundaries, where Ncell is the number of FDTD elements between the Floquet boundaries and the boundaries of the biological cells, in the x and y directions. Fig. 9 shows the field distribution on the xz-plane of the simulated structure for the case of Ncell = 10. When the Floquet boundaries are exactly adjacent to the simulated structure (Ncell = 0), the strongest coupling effect between cells can be obtained: the highest induced field on the membrane and lowest induced field in the cytoplasm of the cell can be observed. Conversely, when the Floquet boundaries are far away from the simulated structure (Ncell = 10), the lowest induced field on the membrane and highest induced field in the cytoplasm of the cell are observed. It should be noted that all the following analysis will be based on Ncell = 0, which is assumed to be the most appropriate model for the real living biological tissues or cells in this micro-dosimetry study.

The simulations were performed at the transformed intermediate frequency of 10GHz and the overall model was then transformed to the intended lower frequencies. Table II reports the transformation factors at 900MHz, 1800MHz, 2000MHz and 2450MHz that were used in the analysis [43].

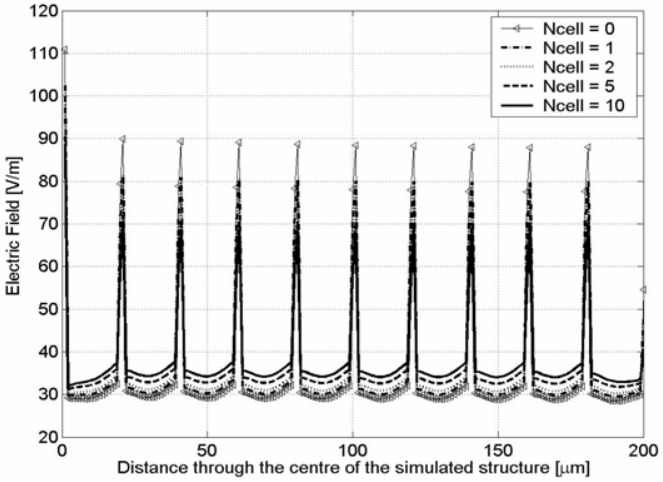

Fig. 7: Electric field distribution along z-axis, through the centre of the simulated structure, showing effect of different spacings to the Floquet boundary condition (Ncell is the number of FDTD elements from the biological cell wall to the boundary).

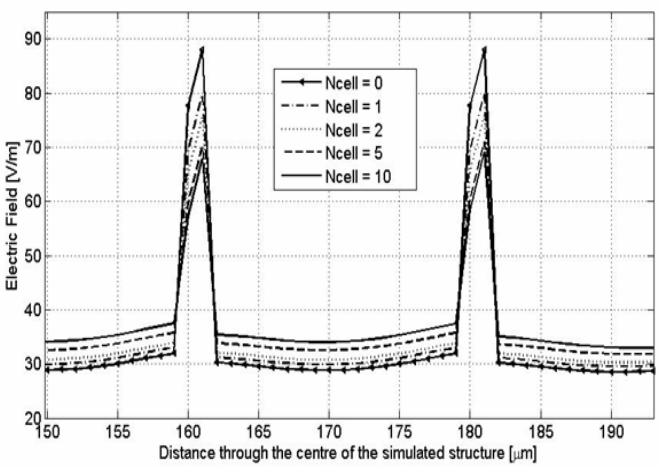

Fig. 8: Electric field distribution (Enlargement of Fig.7)

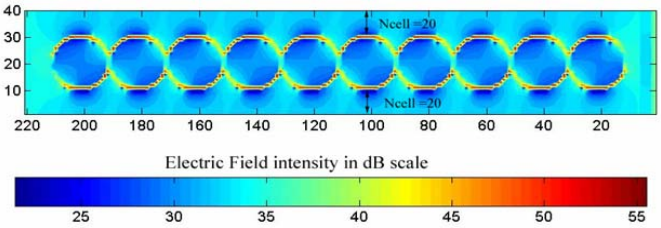

Fig. 9: Modulus of the electric field on the xz-plane at intermediate frequency 10GHz, with Floquet boundary spaced 20 FDTD elements from the biological cell walls.

TABLE II.
FREQUENCY SCALING TRANSFORMATION FACTOR FROM 10GHZ TO THE MOBILE COMMUNICATION FREQUENCIES GIVEN

Parameter	900MHz	1800MHz	2000MHz	2450MHz
Cytoplasm	0.9296	0.9337	0.9344	0.9360
Membrane	0.9	0.97	0.9756	0.9838
Extracellular medium	0.8867	0.9226	0.9254	0.9301

Fig. 10 illustrates the 10GHz field distribution on the xz-plane of the simulated structure. The distributions of the electric field through the centre of the simulated structure, along the incident wave propagation direction, at 900MHz, 1800MHz, 2000MHz and 2450MHz are given in Figs. 11 and 12, where Fig. 12 is an enlarged version of Fig. 11. From inspection of Fig.12, the field inside the cells is not constant and the induced field intensity is directly proportional to the frequency. In the other words, the higher the operating frequency that is used to excite the model, the higher the electric field intensity that will be induced within the analyzed structures.

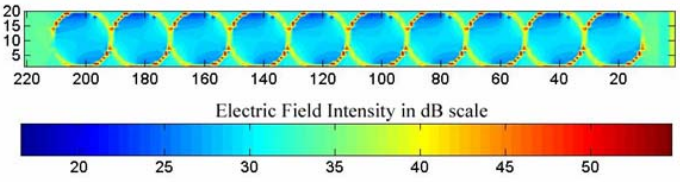

Fig.10: Modulus of the electric field on xz-plane at intermediate frequency 10GHz, with Floquet boundary adjacent to the biological cell walls.

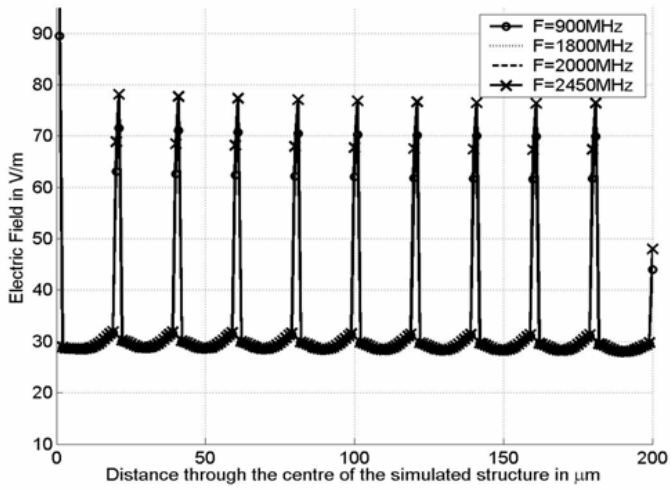

Fig. 11: Electric field distribution along z axis, through the centre of the simulated structure in Fig. 10.

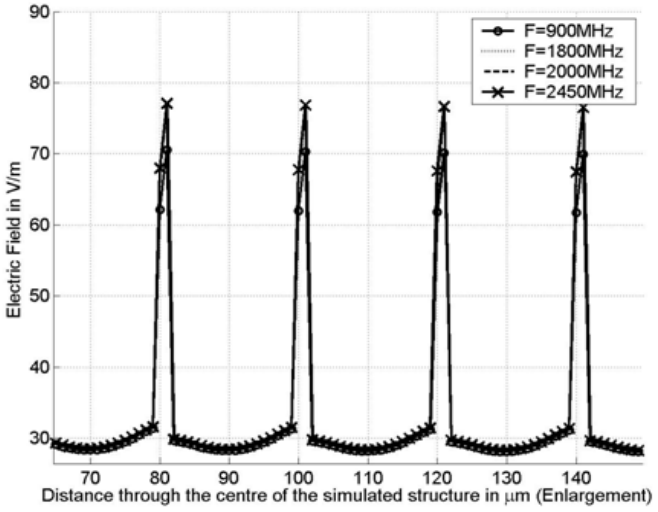

Fig. 12: Electric field distribution along z axis through the centre of the simulated structure in Fig. 11 (Enlargement).

To complete the simulation, the Hodgkin-Huxley models were embedded in the surface of the spherical cells, in a direction normal to the surface, to represent the membrane effect of the tissue model. Versions including this were studied at frequencies of 900MHz and 2450MHz. As can be seen in Figs. 13 and 14, there is a difference of approximately 15% in the field strength due to the contribution of the membrane effect from the Hodgkin-Huxley model: these variations were in good agreement with expectations [4,12,28].

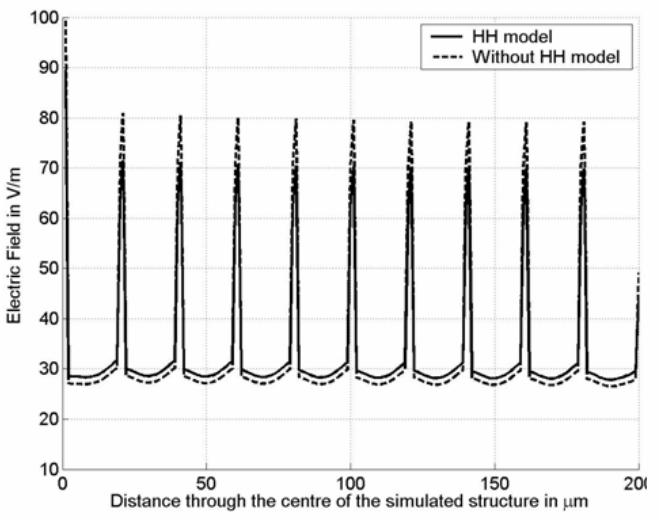

Fig.13: Electric field distribution along z-axis, through the centre of the simulated spherical structure in Fig.10, incorporating Hodgkin-Huxley model and driven at 900MHz.

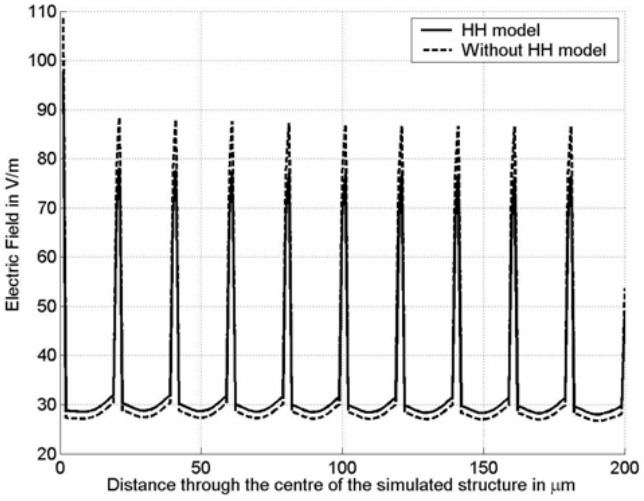

Fig. 14: As Fig. 13, driven at 2450MHz.

B. *Connected Tissue Model Using Cubical Cells*

Since living cells, when compacted into connected tissue, are not perfect spheres, a cluster of cubical cells was chosen for study on the foundation of the previous spherical-cells analysis. Fig. 15 depicts the proposed cluster of cubical cells in a three dimensional view of the FDTD computational domain. In order to compare the results obtained from the previous model with this analysis, an FDTD simulation was executed, keeping the same parameter values as in the previous configuration. The 2D view of the electric field inside the cubical-cell tissue is shown in Fig. 16. The field distributions along the propagation direction of the incident wave, through the centre of the simulated structure at various frequencies, are illustrated in Figs. 17 and 18. The contribution of the Hodgkin-Huxley model to the cubical tissue model has also been investigated, as shown in Figs. 19 and 20. The effect of adding the Hodgkin-Huxley model is about 15% difference in field, as can be seen from the figures.

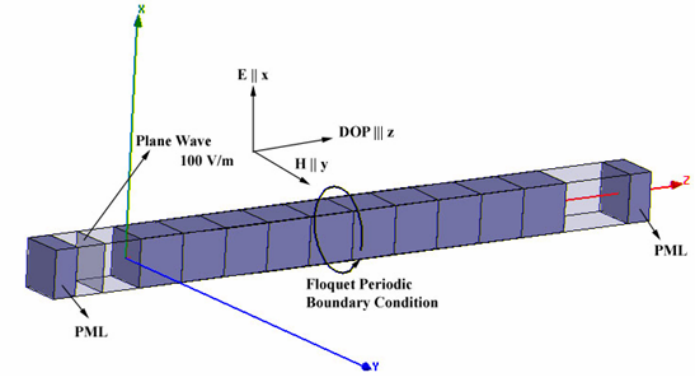

Fig. 15: Three-dimensional view of the simulated cubical structures in the FDTD computational domain.

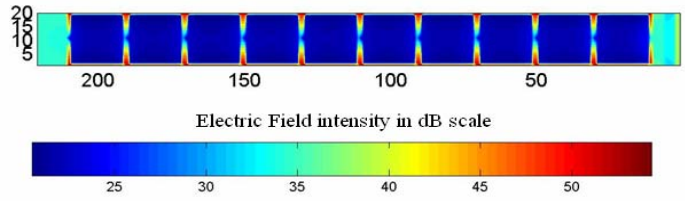

Fig.16: Modulus of the electric field on xz-plane at intermediate frequency 10GHz with Floquet boundary adjacent to the biological cell walls.

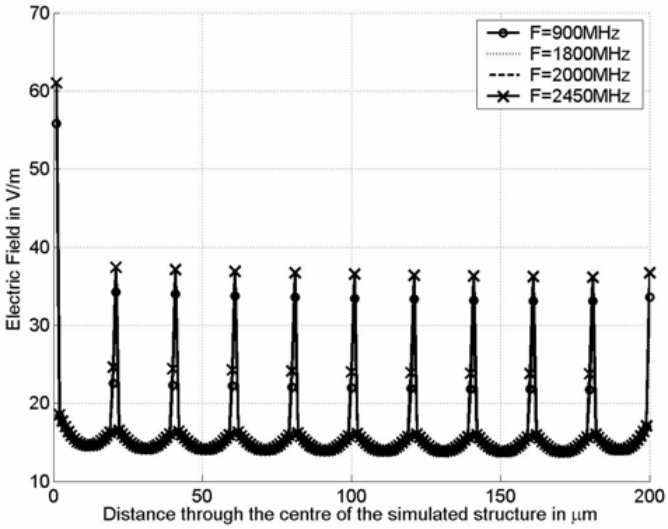

Fig.17: Electric field distribution along z-axis, through the centre of the simulated cubical structure

The peak field on the membrane of the cubical structure is observed to be about three times higher than in the cytoplasm, which agrees well with the results from the structure based on spherical cells. However, the absolute field strength is approximately doubled in the spherical-cell case, presumably because of the curvature at the points studied: it is to be expected that much higher fields would be observed at the corners of the cubical cells, but it might be argued that, as a localised matter, these points do not correspond well with biological reality.

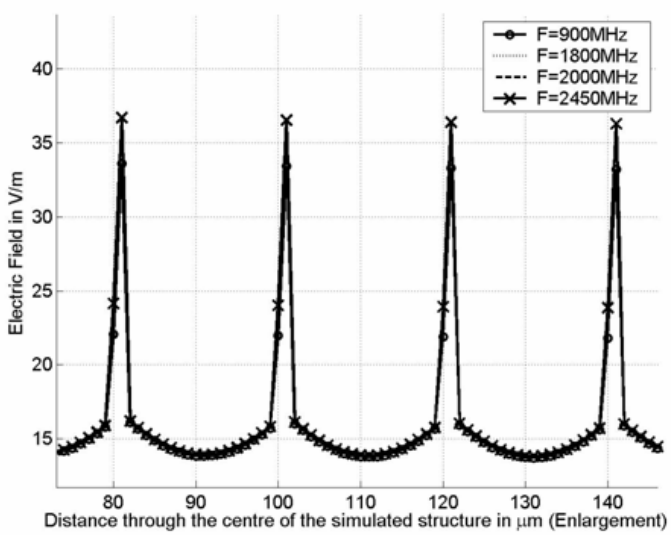

Fig.18: Electric field distribution along z-axis, through the centre of the simulated cubical structure (Enlargement of Fig. 17)

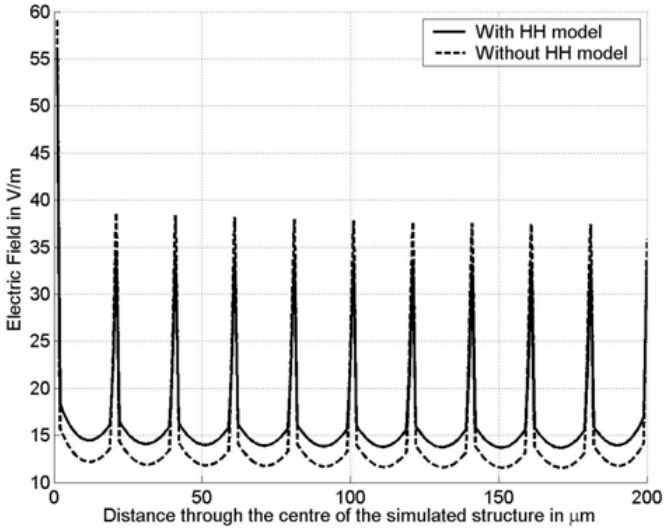

Fig.19: Electric field distribution along z-axis, through the centre of the simulated cubical-cell structure in Fig. 16, incorporating Hodgkin-Huxley model and driven at 900MHz.

V. CONCLUSION

An approach to microdosimetric modeling of bioelectromagnetic interactions at the cellular level has been presented. This uses the FDTD method, combined with an arbitrarily-oriented implementation of the Hodgkin-Huxley cell-membrane model and the Floquet periodic boundary condition. By implementing a frequency-scaling approach, the number of FDTD time steps for such an electrically-small structure can be reduced from several millions to a few tens of thousands. The reflection on the interface layers inside the FDTD computation domain has also been successfully reduced, even though it is within lossy penetrable media, by using a modified version of Berenger's absorbing boundary condition. The accuracy of the FDTD scaling approach was verified with idealized models of spherical cells in lossy media. The feasibility of the inclusion of the HH model inside the FDTD computation domain was demonstrated. This leads to the

conclusion that the application of the HH model allows cells of arbitrary geometries to be handled and demonstrates the viability of embedding other types of lumped-element model for membrane behavior. It can be argued that the HH model is imperfect for microwave frequencies, but it is reasonable to use it as a working hypothesis (as have others [4]) to develop modeling techniques while operational versions of improved models are still in development.

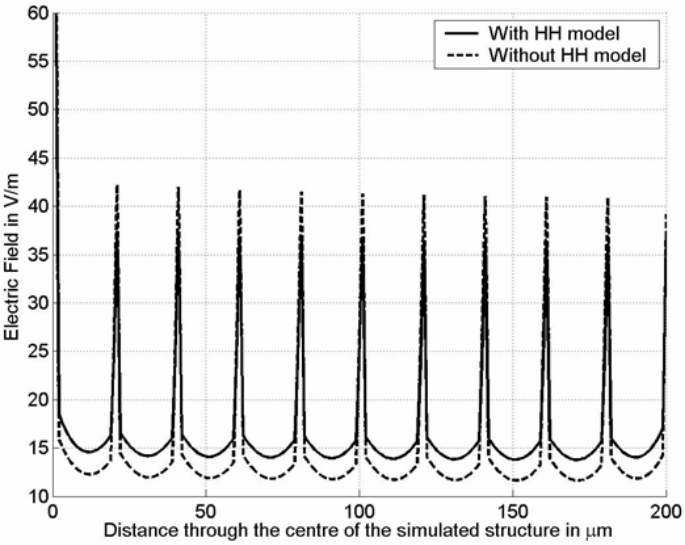

Fig.20: As Fig. 19, driven at 2450MHz.

Use of the Floquet boundary condition enables a non-trivial region of connected biological tissue to be simulated. Such a tool will facilitate deeper investigation of the phenomena in the interaction between EM fields and biological systems at various levels of spatial definition. The combination of quasi-static FDTD with an arbitrarily-oriented lumped element membrane model, the modified Berenger absorbing boundary condition and the Floquet periodic boundary condition represents a significant advance in verisimilitude of biological cell modeling.

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