



# A New Computerized Boundary Element Algorithm for Cancer Modeling of Cardiac Anisotropy on the ECG Simulation

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## Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

## Article Information

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## ABSTRACT

**Aims:** The main aim of this paper is to propose a new boundary element method (BEM) algorithm for cancer modeling of cardiac anisotropy on the electrocardiogram (ECG) Simulation.

**Study design:** Original research paper.

**Place and Duration of Study:** Jamoum laboratory, June 2018, Makkah, Saudi Arabia.

**Methodology:** a new boundary element algorithm was proposed and implemented for solving the governing equations of new cancer mathematical modeling in conjunction with the governing equations of ECG simulation.

**Results:** The effect of cardiac anisotropy on the ECG. Also, the effect of anisotropy on the relation between healthy and infected tissues.

**Conclusion:** For a known set of conductivities, numerical results show that the boundary element

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algorithm, for cancer modeling of cardiac anisotropy on the ECG simulation is very accurate, due to the excellent agreement of our results with the corresponding finite difference results, effects of anisotropic tissues that relate between people and (plants, insects and animals) are also studied as a new advantage for the proposed model.

**Keywords:** Boundary element algorithm; cardiac anisotropy; cancer mathematical modeling; electrocardiogram (ECG).

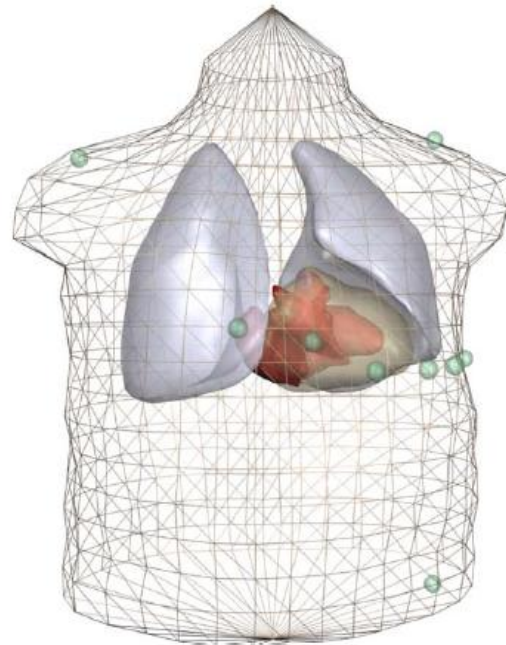
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## 1. INTRODUCTION

In the present paper, our cancer mathematical modeling investigates the interaction between tumour and immune cells. Also, it establishes the importance of combining immuno-oncology (IO) with ionizing radiation (IR) [1-4]. An understanding of behaviour of electrocardiographic resulted in computer models of ECG which is an important role that has been filled the knowledge gaps [5, 6].

Recently, the BEM [7-55] and BEM software [56] have been used as very important tools for ECG simulation to describe the torso, muscle layer, lungs and ventricular blood masses with thousand triangles as in the anatomic model shown in Fig. 1.

One of the important anti-cancer treatments is that which enable the immune system to attack the tumour and kill tumour cells [57], where CD4 T-cells, have been used for discover the tumour and CD8 cytotoxic T-cells have been used to seek out and destroy the cancer. Our cancer mathematical modeling investigates the relation between a growing cancer cells and the immune T-cells, we assumed that cancer cells are a homogeneous population, where the radiation therapy is the same on each cell, the T-cell population is unlimited, but its ability to kill tumour cells is limited. Also, Immunotherapy supports the ability of the immune system to recognise and kill the tumour. Roberts and Scher [58] presented analytic solution for studying the anisotropy effects on the intact heart. Stenroos and Haueisen [59] studied boundary element computations in the forward and inverse problems of electrocardiography and they focus on comparison of collocation and Galerking weightings Thivierge [60] studied intracellular anisotropy and neglecting extracellular anisotropy effects, which we are taken it into consideration in the present paper.



**Fig. 1. Boundary element anatomic model**

## 2. BEM FORMULATION AND IMPLEMENTATION

For real simulations, the torso surface has been replaced by the skeletal muscle layer's inner and outer surfaces, where electrodes are placed on the outer layer, we consider the anisotropic bidomain model of cardiac tissue [1]

$$\nabla \cdot (G_i \nabla \Psi_i) = -\nabla \cdot (G_e \nabla \Psi_e) \quad (1)$$

where  $\Psi_i$  and  $\Psi_e$  are potential fields related to  $J_i = G_i \nabla \Psi_i$  and  $J_e = G_e \nabla \Psi_e$ , respectively.

Making use of the following membrane potential  $V_m = \Psi_i - \Psi_e$ , we can write Eq. (1) as

$$\nabla \cdot ([G_i + G_e] \nabla \Psi_e) = -\nabla \cdot (G_i \nabla V_m) \quad (2)$$

In the current ECG study, the boundary element model of membrane and finite difference (FD) model of human torso are simulated.

Where current density and conductivity tensor are given by

$$J_c = -G_c \nabla V_m, \quad G_c = f_c G(R_c \sigma_{iT}, \sigma_{iT}) \quad (3)$$

The governing equation of reaction-diffusion model can be expressed as

$$C_m \frac{\partial V_m}{\partial t} = \beta^{-1} \nabla \cdot (G(\sigma_{mL}, \sigma_{mT}) \nabla V_m) - I_{ion} \quad (4)$$

where  $\sigma_{mL}$  and  $\sigma_{mT}$  are equivalent conductivities [4],  $\beta$ ,  $C_m$  and  $I_{ion}$  are membrane surface, capacitance and ionic currents summation, respectively.

The boundary integral equation corresponding to (4) can be written as

$$\Psi_e(r) = \frac{1}{2\pi(\sigma_\ell^- - \sigma_\ell^+)} \left[ \int J_c(r') \cdot \frac{r - r'}{|r - r'|^3} dV' + \sum_k \int_{S_k} (\sigma_k^- - \sigma_k^+) \Psi_e(r') dR_{rr'} \right] \quad (5)$$

where  $S_k$ ,  $\sigma$ ,  $\sigma_\ell^-$ ,  $\sigma_\ell^+$  and  $J_c$  are set of surfaces  $k$ , continuous isotropic conductivity, conductivity inside surface  $\ell$ , conductivity outside surface and source current density field, respectively. According to Potse and Dube [4] and using equation (2), the current model can be simulated as in the BEM model.

The mathematical cancer modeling of the considered problem (see Fig. 2) can be expressed as follows

$$\frac{dS}{dt} = g_1(S) - g_2(S, T, C) + g_7(S, C) \quad (6)$$

$$\frac{dT}{dt} = g_3(S, T, I, C) - g_4(S, T, C) \quad (7)$$

$$\frac{dI}{dt} = -g_5(S, I) \quad (8)$$

$$\frac{dC}{dt} = -g_6(S, C) \quad (9)$$

Where  $S$  is the tumour volume,  $T$  – cells is the tumour density which are only considered active against the cancer in our considered modeling,  $I$  is the concentration of immune-agent,  $C$  is the radioactivity administred,  $g_1$ ,  $g_2$ ,  $g_3$ ,  $g_4$ ,  $g_5$ ,  $g_6$

and  $g_7$  are tumour logistic growth, tumour death, T-cell activation, T-cell death, immunotherapy decrease, radiotherapy decrease and new function that contains anisotropic effects that relate between people and (plants, insects and animals), respectively and can be written as follows

$$g_1(S) = rS - \frac{rS^2}{S_{max}} \quad (10)$$

$$g_2(S, T, C) = \frac{\delta_1 TS}{T_{50} + T} + \delta_2 CS + \frac{\delta_3 S}{1 + k_1 T} \quad (11)$$

$$g_3(S, T, I, C) = \frac{\Psi(\beta_1 + \beta_2 I)S + \varphi_1 g_2 T}{1 + k_2 CS} \quad (12)$$

$$g_4(S, T, C) = \varphi_2 \frac{\delta_1 TS}{T_{50} + T} + \delta_4 TC + \delta_5 T \quad (13)$$

$$g_5(S, I) = \varphi_3 \frac{\beta_2 IS}{1 + k_2 CS} \quad (14)$$

$$g_6(S, C) = \varphi_4 \delta_2 CS \quad (15)$$

$$g_7(S, C) = \frac{\Psi(\beta_1 + \beta_2 I)S + \varphi_4 \delta_2 CS}{1 + k_2 CS} \quad (16)$$

where  $\Psi$  is the control function of healthy anisotropic tissue of people when eating plants or insects or animals with tumour.

Also, we used the following constants to obtain the numerical results [5]

$$r = 0.2 \text{ d}^{-1}, S_{max} = 3000 \text{ mm}^3, \delta_1 = 15 \text{ d}^{-1}, \delta_2 = 0.07 \text{ d}^{-1} \text{ G y}^{-1}, \delta_3 = 0 \text{ d}^{-1}, \delta_4 = 0.05 \text{ d}^{-1} \text{ G y}^{-1}, \delta_5 = 0.05 \text{ d}^{-1}, \beta_1 = 0.1 \times 10^9 \text{ cells}/(\text{L d mm}^3), \beta_2 = 0.3 \times 10^9 \text{ cells}/(\text{L d mm}^3 \mu\text{M}), \varphi_1 = 12.13 \text{ mm}^{-3}, \varphi_2 = 30 \times 10^9 \text{ cells}/(\text{L mm}^3), \varphi_3 = 0.0001 \mu\text{M}/(10^9 \text{ cells}/\text{L}), \varphi_4 = 0.0001 \text{ Gy}/\text{mm}^3, k_1 = 0 \text{ L}/10^9 \text{ cells}, k_2 = 0.001 \text{ mm}^{-3} \text{ G y}^{-1}, T_{50} = 100 \times 10^9 \text{ cells}/\text{L}.$$

We developed the matlab code of Chappell et al. [5] for the solution and simulation of our BEM model

### 3. NUMERICAL ALGORITHM, RESULTS AND DISCUSSION

The numerical modeling considered in the current paper based on the following algorithm

- 1) Solving the governing equation of monodomain reaction-diffusion which is replaced by the boundary integral equation

- (5) following the boundary element technique of Fahmy [12-15]
- 2) Solving the mathematical cancer modeling system (6) - (9) using the technique of Fahmy [8-11] and Houbolt's algorithm
- 3) Find the solution that satisfy steps (1) and (2) simultaneously
- 4) Find the effect of anisotropy

where tumour cells, T-cells and therapies are in black, blue and red colours, respectively. T-cells

in blue colour and therapies in red. Straight lines show direct interactions while dotted lines refer to indirect interactions

It can be noticed from Fig. 3 that the IR and IO when used as a single agents can't reduce the tumour mass, but when they are used in a combination, the number of activated T-cells is higher than the single agents using of them as shown in Fig. 4. Stability of the considered model was established by Chappell et al. [5].

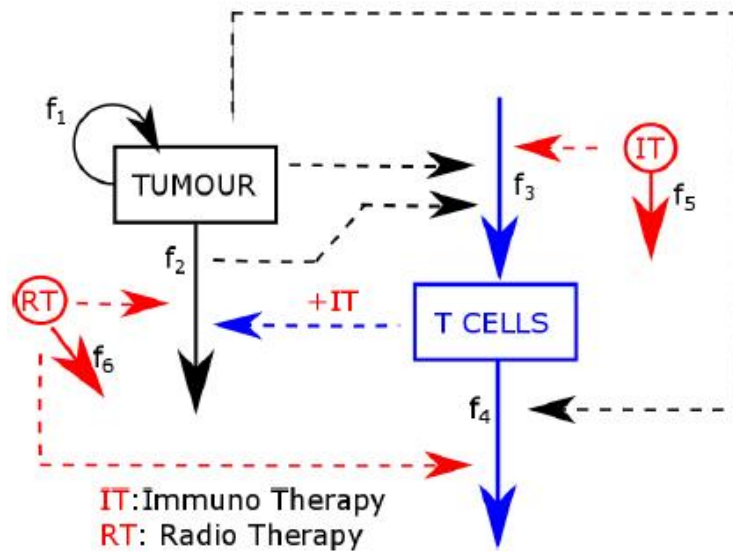


Fig. 2. Model scheme representation

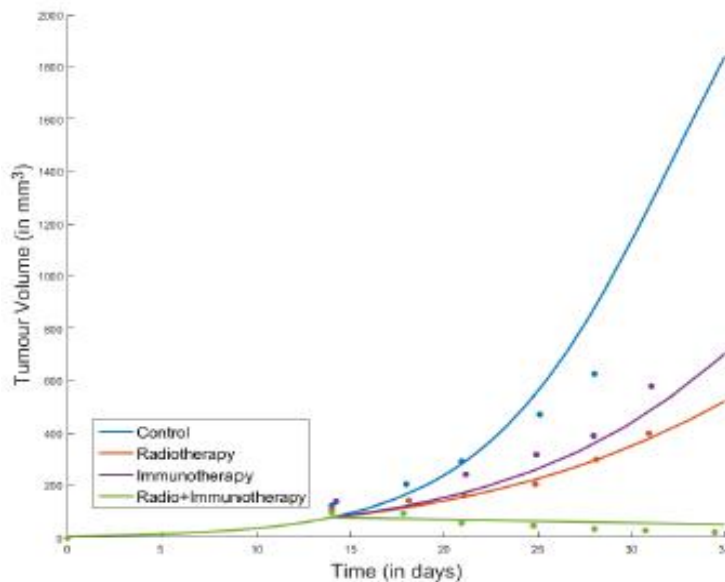
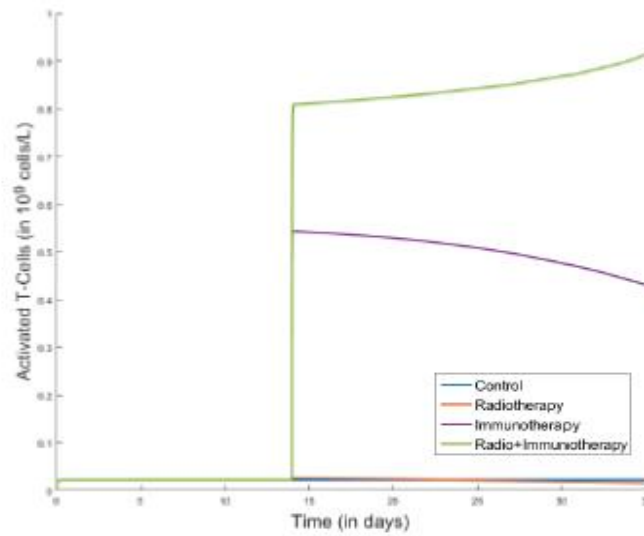


Fig. 3. Variation of the tumour volume with time



**Fig 4. Variation of the activated T-cells with time**



**Fig. 5. ECGs simulations for FDM and BEM.**

Also, from Fig. 5, it can be seen that our model results excellent agreement with results of [5] for anisotropic but at  $RD = 0.12$ , because at  $RD = 0.13$  there are significant differences due to the solution of ECG equations and Cancer modeling equations simultaneously.

A review of two promising classes of antibodies, antiCTLA-4 and antiprogrammed Death-Ligand 1 (antiPD-L1), used as monotherapy and in combination with cancer therapies can be found in [61].

It can be seen from considered study that our model results are in excellent agreement with Deng et al. [6] results shown in Fig. 6, where the PD-L1 and IR through T-cell dependent mechanism are reducing the tumour growth

Initial conditions used through our model are introduced in Table 1. as suggested by Chappell et al. [5] as a future work, we have seen from numerical results that the difference can be neglected between the two initial conditions cases. Also, we recommend to change  $C(0)$  to be 1.6 as a future work from our study.

**Table 1. Initial conditions used in the proposed model**

Variables	No treatments	Immunotherapy	Radiotherapy	Immuno & Radio-therapy
$S(0)$	5	5	5	5
$T(0)$	0	0	0	0
$I(0)$	0	6	0	6
$C(0)$	0	0	1.4	1.4

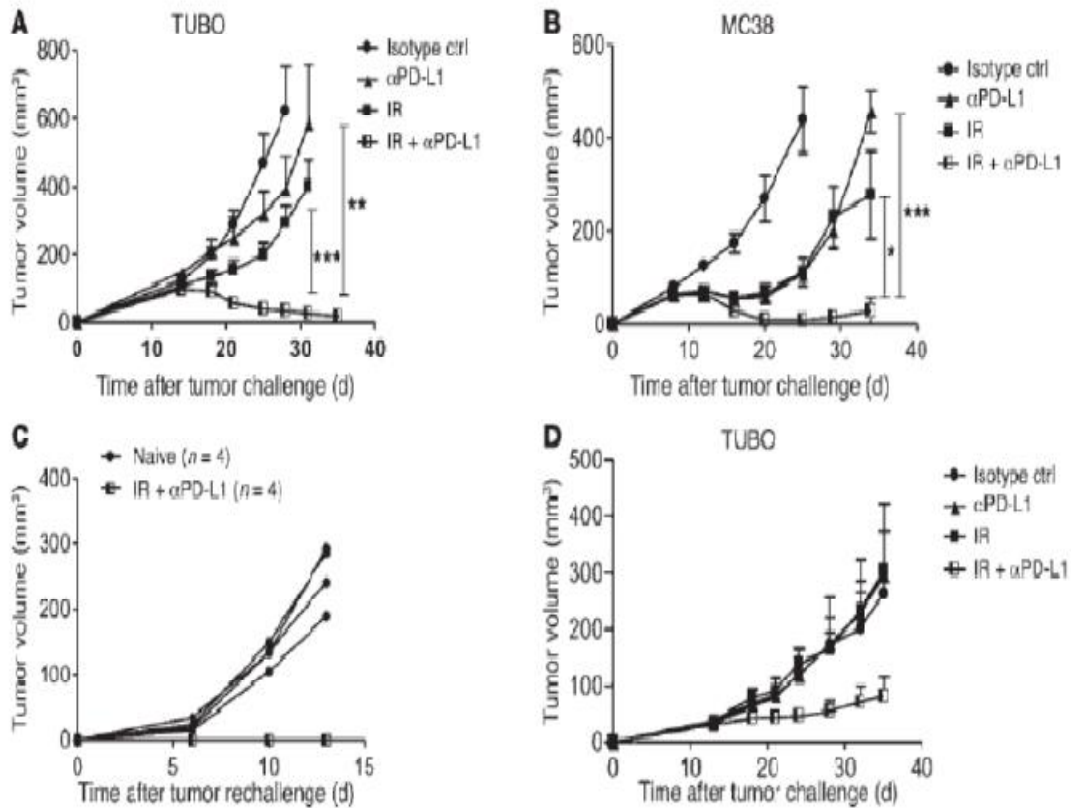


Fig. 6. Effects of IR and PD-L1 on tumour growth of Deng et al. [6]

#### 4. CONCLUSION

The boundary element algorithm for cancer modeling of cardiac anisotropy on the electrocardiogram (ECG) simulation. For a known set of conductivities, our results are in a very good agreement with the corresponding finite difference results. A lot of clinical applications neglect the effects of heart anisotropy, as an important result of our study, we analyse the new function  $g_7(S,C)$  that contains anisotropic effects that relate between people and (plants, insects and animals), we concluded that the cardiac anisotropy has a strong effect on ECG simulation in comparison with considered isotropy effect. Also, if we considered the anisotropy effects, we can detect the heart cancer in people infected with it. The peoples eating plants, insects and animals. When they are eating plants such as vegetables and fruit with cancer can easily transmit it to humans when he takes it. When we make a sauce from rotten tomatoes, this sauce also can

infect humans with heart cancer. Early detection of heart cancer can be difficult when we do not take into consideration cardiac anisotropy effect. It moves from infected tissues of organisms to healthy tissues of humans. For these reasons the anisotropy effect should be taken into consideration in clinical applications.

#### COMPETING INTERESTS

Author has declared that no competing interests exist.

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