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3D Simulation of Platelet Aggregation in Cryosurgery

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***Abstract*— In cryosurgery for cancer treatment, cells are injured not only by freezing but also by vascular stasis. The vascular stasis caused by thrombosis necrotizes the surrounding non-targeted cells due to the lack of oxygen and nourishment. Inhibition of thrombus formation, which is the former phase of the vascular stasis, is required to prevent damaging normal cells around a tumor. Foregoing studies simulated platelet aggregation based on distance between platelets. However, in cryosurgery, temperature dependency of blood-clotting factors' activity is required to be considered. The authors constructed a three-dimensional model consisting of vascular and extra-vascular tissues, and simulated heat transform and platelet aggregation. Heat transform was analyzed by boundary fitted coordinates method, and platelet aggregation was analyzed by particle method. The probability of bonding between platelets is derived from chemical reaction kinetics. The results showed larger size of simulated thrombus on higher temperature. The simulation with varied temperature around destructed area showed platelet aggregation depending on temperature.**

I. Introduction

Cryosurgery is a cancer treatment which destructs cells by freezing. Cryosurgery has an advantage of being performed under local anesthesia over other treatment methods. However, it has a difficulty in identification of cell necrosis area because cell necrosis mechanism by freezing is complex[1].

Most of foregoing cryosurgery simulations consider only mechanical cell destruction by intracellular and extracellular ice crystal[2], [3] without considering cell necrosis due to vascular stasis. The vascular stasis caused by thrombosis necrotizes the surrounding non-targeted cells due to the lack of oxygen and nourishment[4], [5]. To identify necrosis area by vascular stasis, the former phase of the vascular stasis needs to be analyzed. Since thrombus formation is a chemical reaction, temperature dependency of blood-clotting factors' activity is required to be considered.

The authors analyzed primary thrombus formation in 2D in a foregoing study[6]. The study showed temperature dependency of thrombus formation in 2D. However, geometrical representation of the model was 2D square grid, and remained to be improved to 3D grid.

In this paper, we extend the analysis to 3D primary thrombus formation, and examine the effect in 3D space. We constructed a 3D model consisting of vascular and extra-vascular tissues, and simulate heat transfer by the boundary-fitted coordinates (BFC) method. Vascular endothelial cell necrosis is estimated by temperature. The authors also simulate platelet aggregation to vascular endothelial cell necrosis area.

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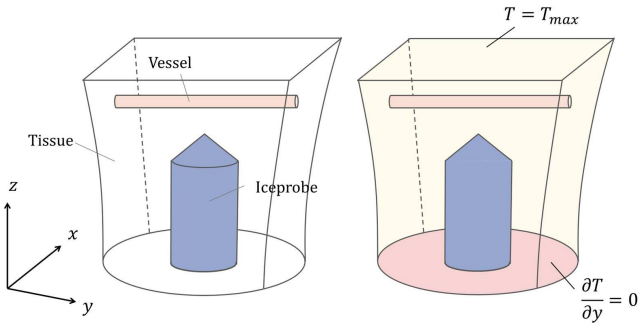
II. Thrombosis formation simulation

Thrombosis formation is simulated in the following procedure.

- Heat transfer simulation
  Fluid energy equation is calculated to analyze temperature distribution by BFC method. (section II-A)
- Estimation of endothelial cell necrosis area based on temperature
  Death of endothelial cell is judged from calculated temperature to estimate cell necrosis area.
- Simulation of platelet aggregation to cell necrosis area
  Platelet aggregation to estimated cell necrosis area is analyzed. Bondings between platelet and necrosis area and also between platelets are represented as a spring and a dumper. Probability of bonding between platelets is derived from chemical reaction kinetics. (section II-B)

A. Heat transfer model

Analytical object is 3D model consisting of vascular and tissue. Fig.1 (a) illustrates heat transfer model, and Fig.1 (b) illustrates boundary condition. Thermal parameters of rat's liver and human blood are set in the parameters of tissue and blood in the model, respectively[2].



(a)Proposed model (b)Boundary condition

Fig. 1. Proposed model and boundary condition

In vessel and tissue outside vessel, energy equation in 3D is calculated by BFC method. Blood flow in vessel is laminar in case Reynolds number is less than 2000[7]. In this model, blood flow in arteriole is laminar because its Reynolds number is about 300. In BFC method, a boundary-fitted grid is generated numerically in Cartesian coordinates[8]. Then, the boundary-fitted grid in Cartesian coordinates is transformed to a simple rectangular grid in

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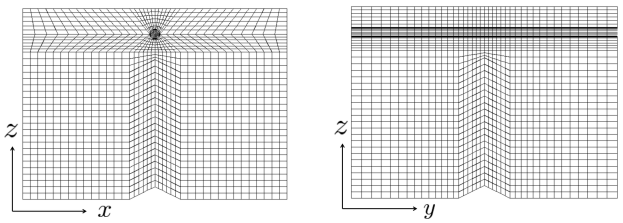


(a)BFC mesh(x-z plane) (b)BFC mesh(y-z plane)

Fig. 2. Generated boundary-fitted grid

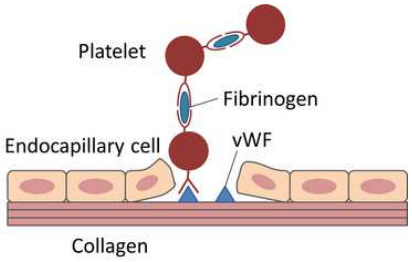


Fig. 3. Formation of primary thrombus

the boundary-fitted coordinates. The governing equations are also transformed from the Cartesian coordinates to the boundary-fitted coordinates. Finally, the solution is obtained in the computational space by means of the finite difference method. Fig.2 illustrates generated boundary-fitted grid. In case that blood is Newtonian fluid and non-compressed fluid, fluid energy equation in 3D is written in the following equation:

$$\rho C_V \left(\frac{\partial T}{\partial t} + u_x \frac{\partial T}{\partial x} + u_y \frac{\partial T}{\partial y} + u_z \frac{\partial T}{\partial z} \right) = \lambda \left(\frac{\partial^2 T}{\partial x^2} + \frac{\partial^2 T}{\partial y^2} + \frac{\partial^2 T}{\partial z^2} \right) \quad (1)$$

where T is temperature, t is time, u_x is x axial fluid velocity, u_y is y axial fluid velocity, u_z is z axial fluid velocity, ρ is density, C_v is specific heat at constant volume, and λ is thermal conductivity[8].

Equation 1 is transformed to the following equation in BFC system ((ξ, η, ζ) coordinates).

$$\begin{aligned} &\rho C_P \left[\frac{\partial T}{\partial t} + u_x \left(\frac{\partial \xi}{\partial x} \cdot \frac{\partial}{\partial \xi} + \frac{\partial \eta}{\partial x} \cdot \frac{\partial}{\partial \eta} + \frac{\partial \zeta}{\partial x} \cdot \frac{\partial}{\partial \zeta} \right) T \right. \\ &+ u_y \left(\frac{\partial \xi}{\partial y} \cdot \frac{\partial}{\partial \xi} + \frac{\partial \eta}{\partial y} \cdot \frac{\partial}{\partial \eta} + \frac{\partial \zeta}{\partial y} \cdot \frac{\partial}{\partial \zeta} \right) T \\ &\left. + u_z \left(\frac{\partial \xi}{\partial z} \cdot \frac{\partial}{\partial \xi} + \frac{\partial \eta}{\partial z} \cdot \frac{\partial}{\partial \eta} + \frac{\partial \zeta}{\partial z} \cdot \frac{\partial}{\partial \zeta} \right) T \right] \\ &= \lambda \left[\left(\frac{\partial \xi}{\partial x} \cdot \frac{\partial}{\partial \xi} + \frac{\partial \eta}{\partial x} \cdot \frac{\partial}{\partial \eta} + \frac{\partial \zeta}{\partial x} \cdot \frac{\partial}{\partial \zeta} \right)^2 T \right. \\ &+ \left(\frac{\partial \xi}{\partial y} \cdot \frac{\partial}{\partial \xi} + \frac{\partial \eta}{\partial y} \cdot \frac{\partial}{\partial \eta} + \frac{\partial \zeta}{\partial y} \cdot \frac{\partial}{\partial \zeta} \right)^2 T \\ &\left. + \left(\frac{\partial \xi}{\partial z} \cdot \frac{\partial}{\partial \xi} + \frac{\partial \eta}{\partial z} \cdot \frac{\partial}{\partial \eta} + \frac{\partial \zeta}{\partial z} \cdot \frac{\partial}{\partial \zeta} \right)^2 T \right] \end{aligned} \quad (2)$$

B. Model of thrombosis formation in cell necrosis area

In this study, platelet aggregation is represented as particles bonding to cell necrosis area. The following part describes the mechanism of thrombosis formation, bonding probability derived from chemical reaction kinetics, bonding force, blood flow, and vascular model.

1) Mechanism of thrombosis formation: When vascular wall is injured, platelets rapidly aggregate to vascular wall through various chemical substances. Aggregated platelets form thrombosis. It is called as a primary thrombus, as illustrated in Fig.3.

The possibility of a platelet aggregation depends on temperature because a platelet aggregation is a chemical reaction. The foregoing model of platelet aggregation is based on distance between platelets[11]. However, in cryosurgery, temperature dependency of blood-clotting factors' activity is required to be considered. In this paper, the primary thrombus formation is analyzed considering temperature dependency.

2) Chemical reaction kinetics: A thrombus is formed through many processes. Each process is considered as a chemical reaction.

The substance P_{AB} is generated by the reaction that the substance A binds to substance B. The reaction rate of the substance P_{AB} is written in the following equation:

$$\frac{d[P_{AB}]}{dt} = -\frac{d[A]}{dt} = -\frac{d[B]}{dt} = k[A][B] \quad (3)$$

where $[P_{AB}]$, $[A]$, $[B]$ are the concentration of the substance P_{AB}, A, B, respectively, and k is the reaction rate constant.

A chemical reaction is considered as a collision between chemical molecules. The constant of reaction rate in x, y, z axis are equally derived from collision theory:

$$k = \sigma_s L \sqrt{\frac{k_B T}{2\pi \mu_m}} e^{-\frac{\varepsilon}{RT}} \quad (4)$$

where σ_s is reaction cross-sectional area, L is Avogadro number, k_B is Boltzmann constant, μ_m is reduced mass, ε is activation energy, and R is gas constant[9]. In case the velocity distribution obey Maxwell distribution, the relative velocity in x axis direction is written in the following equation:

$$|v_A - v_B| = \sqrt{\frac{k_B T}{2\pi \mu_m}} \quad (5)$$

where v_A and v_B are the velocity of molecule A and B in x axis direction, respectively.

In case molecule A and B flow in the x axially laminar flow, the relative velocity including the molecular motion velocity and the flow velocity are written in the following equation:

$$\begin{aligned} |v'_A - v'_B| &= \left(v_A + u_{max} \left(1 - \frac{y_A^2}{H^2} \right) \right) \\ &\quad - \left(v_B + u_{max} \left(1 - \frac{y_B^2}{H^2} \right) \right) \\ &= \left(\sqrt{\frac{k_B T}{2\pi \mu_m}} + u_{max} \left(\frac{y_A^2 - y_B^2}{H^2} \right) \right) \end{aligned} \quad (6)$$

where v'_A is the velocity of molecule A and v'_B is the velocity of molecule B, both of them in x axis direction

including the molecular motion velocity and the flow velocity. Therefore, the constant of reaction is derived as follows:

$$k = \sigma_s L \left(\sqrt{\frac{k_B T}{2\pi\mu_m}} + u_{max} \left(\frac{y_A^2 - y_B^2}{H^2} \right) \right) e^{-\frac{\varepsilon}{RT}} \quad (7)$$

3) The reaction probability based on chemical reaction kinetics: The reaction probability is derived from the reaction rate divided by the molar number and multiplied volume and reaction time. The reaction probability is represented as

$$v \frac{L}{N_a} V_P t \quad (8)$$

where v is the reaction rate, L is Avogadro number, N_A is the molar number, and V_P is volume.

In spring and mass model, a platelet represented as a mass point is connected to other platelets with a spring and a damper in the derived reaction probability.

4) The force subjecting to a platelet: A platelet in blood flow is subject to the forces from endothelial cell necrosis area, from activated platelets, and from blood flow. Fig.4 shows the force subjecting to a platelet and the affected area for activation. A non-activated platelet is activated in case the distance between platelet and endothelial cell necrosis area is smaller than the threshold R_1, or in case the distance between platelet and activated platelets is smaller than the threshold R_2. The activated platelet is subject to the force F_1 from endothelial cell necrosis area, the force F_2 from other activated platelets, and the force F_f from blood flow. These chain reactions generate primary thrombus from platelets.

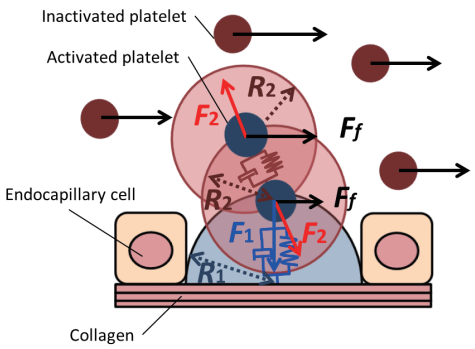


Fig. 4. Interaction between platelets

- The force from cell necrosis area F_1
  The force subjecting to a platelet from cell necrosis area is written as:

$$F_1 = -k_1((R_1 - r_1) - l_1) \quad (r_1 < R_1) \quad (9)$$

  where k_1 is a spring constant, r_1 is a distance between platelet and cell necrosis area, R_1 is threshold distance for activation, and l_1 is a natural length of spring.
- The force from activated platelets F_2
  The interactive force subjecting to a platelet from an activated platelet is described as:

$$F_2 = -k_2((R_2 - r_2) - l_2) \quad (r_2 < R_2) \quad (10)$$

  where k_2 is a spring constant, r_2 is a distance between a platelet and a activated platelet, R_2 is threshold distance for activation, and l_2 is a natural length of spring.
- The force from blood flow F_f
  In case Reynolds number is small, the force subjecting to a sphere in fluid flow is approximated as Stokes drag[10]. Therefore, the force subjecting to a platelet from blood flow can be represented as Stokes drag, such that:

$$F_f = 6\pi\rho\nu r_0 V \quad (11)$$

  where ρ is a density, ν is a kinematic viscosity, and r_0 is a platelet's diameter.

5) The platelet aggregation model in vessel: Platelet aggregation to cell necrosis area is analyzed by representing platelets as mass points and calculating the force subjecting to platelets. Fig.5 shows three-dimensional vascular model, and Fig.6 shows its boundary condition.

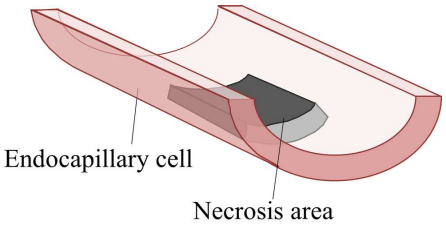


Fig. 5. Vascular model in platelet aggregation simulation

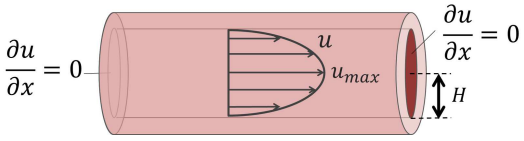
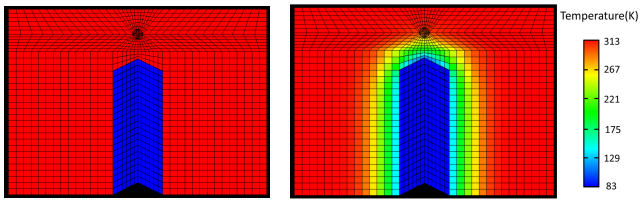


Fig. 6. Boundary condition in vascular model

III. Result

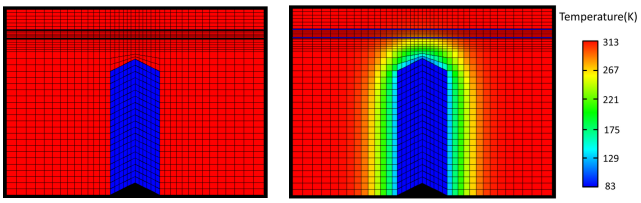
A. Heat transfer simulation

Temperature distribution is analyzed in body tissue model as described in section II-A by BFC method. Boundary condition is shown in Fig.1 (b). Time step is 10 ms. Initial temperature in tissue and blood is 313 K and in iceprobe is 83 K. Fig.7 and Fig.8 show results of heat transfer simulation at 0 s and 270 s. Fig.9 shows the cell necrosis area as black color cell at 270 s.



(a)0 s (b)270 s

Fig. 7. Temperature distribution around iceprobe($x - z$ plane at $y = 0$)



(a)0 sec (b)270 sec

Fig. 8. Temperature distribution around iceprobe($y-z$ plane at $x=0$)

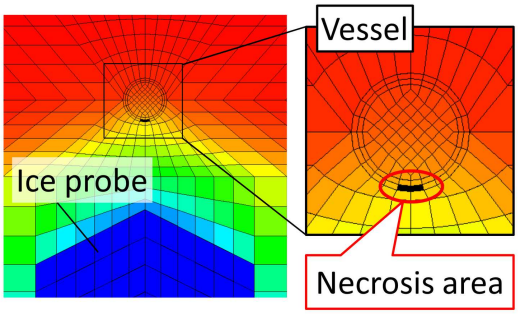


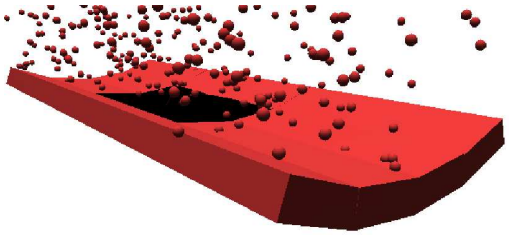
Fig. 9. Cell necrosis area (after 270 ms)

B. Platelet aggregation simulation

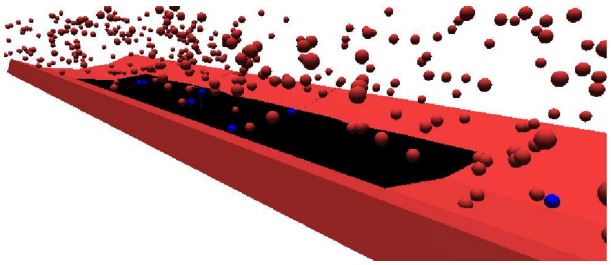
Platelet aggregation is analyzed in the model as described in section II-B.5. Time step is 1 ms. Fig.10 shows simulation results on 268 K at 50 ms and 800 ms. Fig.11 shows simulation results on 310 K at 800 ms. As time goes on, cell necrosis area expands and more platelets aggregate to cell necrosis area. Fig.12 shows number of aggregated platelets in different temperature(310 K, 289 K, and 268 K). The results showed that thrombus becomes bigger on higher temperature because platelet aggregation is a chemical reaction.

IV. Conclusion

In this paper, the authors constructed three-dimensional model and simulated platelet aggregation for cryosurgery. Temperature distribution is analyzed by calculation of energy equation in BFC method. In platelet aggregation simulation, platelet was bound to necrosis area and activated platelets in probability on the basis of chemical reaction kinetics. The experimental results showed that the size of generated thrombus becomes bigger in case of higher temperature.



(a)50 ms



(b)800 ms

Fig. 10. Platelet aggregation simulation result(268K)

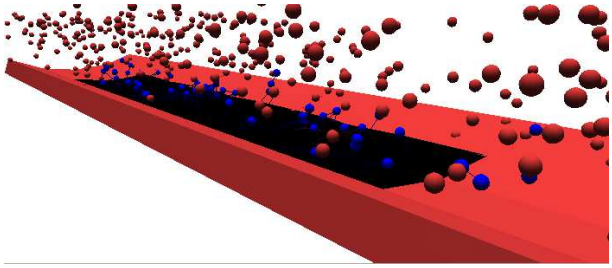


Fig. 11. Platelet aggregation simulation result(310 K-after 800 ms)

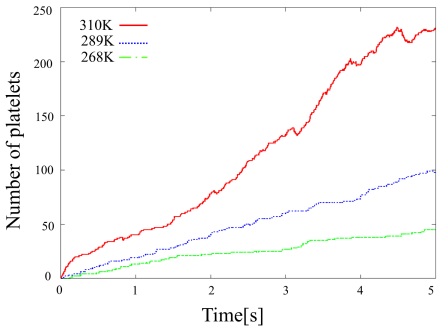


Fig. 12. Number of aggregated platelets in different temperature

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