Development of a pH-Responsive Bio-robotics for Targeted Drug Delivery to Lung Cancer in the Vascular System

Phuwich Uthansakul,[1†] Pichchaya Petchsritong,[1‡] and Adis Khetubol[2]

[1] Kamnoetvidya Science Academy, Rayong, Thailand
[2] Department of Physics and Astronomy, Kamnoetvidya Science Academy, Rayong, Thailand
phuwich.u@kvis.ac.th, pichchaya.p@kvis.ac.th, and adis.k@kvis.ac.th
[†] P.U. and [‡]P.P. contributed equally to this work.

Abstract. Targeted drugs are widely used and developed as they reduce side effects for cancer patients. However, the turbulent blood flow may reduce their precision from their target, causing negative effects on other tissues. This research aims to overcome such limitations by developing a bio-robot with a turtle-like shape, which maintains stability in turbulent flow and moves in a direction responsive to the acidity of cancer cells. The robot is designed to effectively move towards cancer cells relying on two types of muscles: 1) a self-activated muscle that maintains the robot's stability in turbulent flow, mimicking the movement of sea turtle fins, and is controlled by muscle cells with different activation phases. The optimal coefficient of calcium diffusion for their activation is found at approximately 0.01 $\mu m^2/s$; and 2) a pH-responsive muscle that generates force to pull the robot towards cancer cells in the direction of increasing acid concentration by varying activation strength differently in the horizontal and vertical planes. The precision is compared with other delivery methods. It was found that in a system with turbulence and blood pumping, the robot could deliver drugs to cancer cells more successfully than MOFs by 5.8 times at a pH operation range of 5.4, more than liposomes by 6.24 times at an operation range of 150 micrometers, and more than nanoparticles by 13.7 times at an operation range of 100 micrometers, confirming the successful design of both muscles that not only maintain stability but also enhance movement accuracy towards the target.

Keywords: Drug delivery; Cancer; Bio-robotics; Tissue engineering

1 Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide, according to the International Agency for Research on Cancer (IARC). A distinct feature of tumor cells is their more acidic surroundings, caused by the Warburg effect [1], which

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scientists are exploring as a target for drug delivery. Although treatments like chemotherapy, radiation, and surgery are common, they often cause serious side effects that lower patients' quality of life. Targeted drug delivery aims to send medication directly to cancer cells, reducing these side effects, but challenges remain. Drugs can still leak into healthy tissues, leading to issues like skin rashes and fatigue [2].

Blood flow turbulence, particularly in narrowed vessels, makes targeted delivery even more difficult. Tan et al. [3] showed that unstable blood flow can cause drugs to miss their targets, increasing side effects and lowering treatment success. This underlines the need for delivery systems that can operate accurately even in turbulent conditions.

Bio-robotics offers a potential solution by combining biology and robotics to create machines that mimic natural movements. Fish-like soft robots [4] and 3D-printed muscle tissue using bioink [5] demonstrate how flexible, adaptable designs can navigate complex environments. Park et al. [6] advanced this concept by creating a stingray-inspired robot powered by light-sensitive rat heart cells.

Despite these advances, no bio-robot has yet been built to navigate the human bloodstream for drug delivery. This study focuses on designing a sea turtle-inspired robot to handling turbulent blood flow. Using computer simulations, we examine how flow patterns affect drug delivery, aiming to optimize drug delivery and minimize side effects, bring us closer to real-world applications of bio-robotics in cancer treatment.

2 Methodology

To replicate dynamic blood flow conditions, OpenFOAM was used to simulate turbulent blood flow with pumping effects. A bio-robotics motion equation and a force-pH relationship were developed by analyzing simulation data exported as EDF files and using Python to examine the relationships between blood flow and muscle contraction.

Hill's Model, linking calcium dynamics throughout Fick's law to force production, was used to model muscle activation. Myocyte position, activation phase, and diffusion coefficients were considered to define activation patterns and pH-driven force. Turbulent and laminar flow models were created to estimate muscle movement.

To confirm the validity and applicability of our bio-robotics model, we compared it with previous studies involving substances released into the environment. Validation was conducted based on Root Mean Square Error (RMSE) method.

3 Computational Results and Discussion

3.1 Vascular System Model

Effect of blood pumping: Effect of Blood Pumping: From the OpenFOAM simulation conducted to study the effects of blood flow within blood vessels due to heart pumping, it was found that blood velocity fluctuations at different time intervals exhibit significant turbulence variations. As shown in Fig. 1, at 0.25 seconds, when the highest

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blood ejection force occurs, the blood velocity reaches its peak. In contrast, at 0.5 seconds, during the phase of minimal blood ejection, the velocity within the blood vessel demonstrates a vortex-like swirling motion. The flow then gradually returns to normal at approximately 1.0 seconds. This study provides similar contents as many works [7-8].

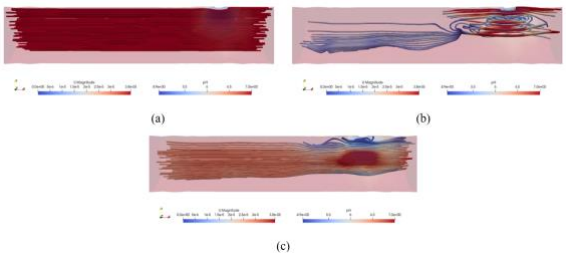

Fig. 1 Blood flow considering blood pumping effects at (a) 0.25s (b) 0.5s and (c) 1.0s

Proposed Drug Delivery Movement: Initially, the researchers focused on studying the size of blood vessels connected to cancer cells. Generally, blood vessels in the human body are classified into three main types: the aorta (the largest artery), arterioles (small arteries), and capillaries (the smallest blood vessels).

This classification is widely accepted in biology and physiology. In previous sections, the results presented were based on the aorta. To provide a more comprehensive understanding of the vascular system, this project expanded the study by conducting additional experiments using arterioles, selecting a blood vessel system with a diameter of 500 micrometers. A bio-robot smaller than the vessel was used to assess drug delivery precision to cancer cells, comparing it with other research studies in a more realistic physiological environment. The size of the bio-robotic device can be adjusted, as we are able to determine the optimal alpha value for each robot size. In this case, the robot was set at 150 µm wide, 100 µm long, and 50 µm high. The bio-robot operates based on pH-responsive propulsion, as represented by the force versus pH relationship in Fig. 2(a). It utilizes the pH gradient between healthy and cancerous tissue. OpenFOAM simulations integrated with a muscle-driven mechanism demonstrated targeted movement toward cancer cells (Fig. 2b).

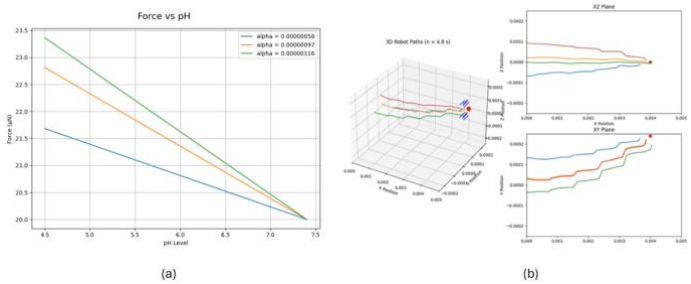

Fig. 2 (a) Force–pH relationship for each muscle. (b) Movement of 5 bio-robots toward cancer cells under turbulent flow with pumping effects in xyz-coordinate, xz-plane, and xy-plane.

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3.2 Muscle Model

To model the behavior of the two types of artificial muscles for the bio-robotic system, we developed a computational framework that integrates partial differential equation (PDE) modeling, nonlinear system optimization, and activation mechanisms. Both models were utilizing numerical integration and optimization tools from the SciPy library, along with NumPy for vectorized operations and Matplotlib for visualization.
Self-Activated Muscle used in the bio-robot's flippers mimics the motion of a turtle's flippers, stabilizing motion in turbulent environments. Each muscle unit (myocyte) was represented as a discrete cell within a two-dimensional calcium concentration grid. By comparing trajectories, we selected configurations that produced the sweeping motion observed in turtle locomotion (Fig. 3a), with simulations confirming the expected movement (Fig. 3b).

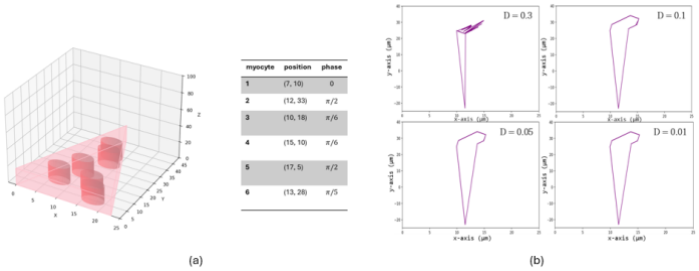

Fig. 3 (a) Position and phase of activation of each myocyte. (b) Muscle tip movement's path at difference diffusion coefficients (D)

The result shows that, when D is large, the pattern of movement becomes irregular due to overstimulation and muscle movement, but it balances out in the long term. However, when D is small, the movement becomes regular. Therefore, D = 0.01μm^2/s was used. We then analyzed the motion under turbulent and normal flow conditions in both small and large arteries, as shown in Fig. 4. Large arteries possess a Reynolds number of at most 10,000; thus, we considered this condition, and the results are presented in Fig. 5.

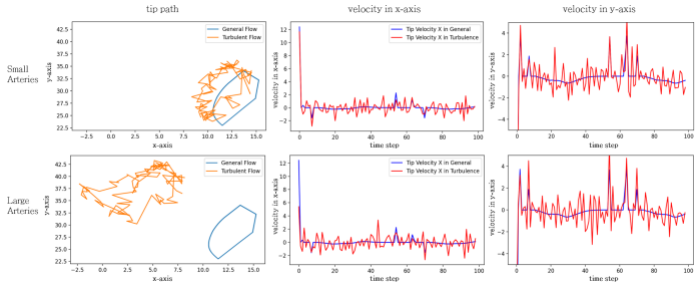

Fig. 4 Comparison of the muscle tip movement's paths and the velocities along the x and y axes under normal (general) blood flow and turbulent flow, in large artery and small artery.

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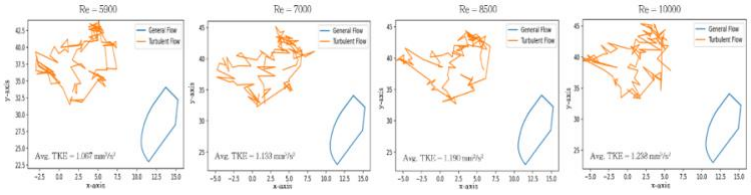

Fig. 5 Comparison of muscle tip movement's paths under normal (general) blood flow and turbulent flow at different Reynolds numbers in the large artery.

Despite the turbulent flow causing instability or oscillation at the tip of the muscle, the velocity in both the x and y directions follows the same pattern observed in normal blood flow tending toward zero over time. This suggests that the overall motion of the robot remained stable; that is, no rotational motion was observed in either normal or turbulent flow, and the robot moved along with the fluid.

pH-Responsive Muscle is designed to generate force that pulls the bio-robot toward cancer cells. We designed the muscle structure and positioned the myocytes as shown in Fig. 6, and solved the equation (Hill's model), with the force–pH relationship from Fig. 2(a). Optimization was performed using the L-BFGS-B algorithm to minimize the error between the simulated and target force. We obtained the optimized values for both the diffusion coefficient and activation strength, as presented in Fig. 7.

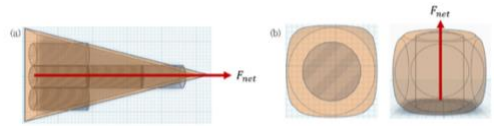

Fig. 6 Muscle models for force generation in: (a) y-axis, (b) z-axis.

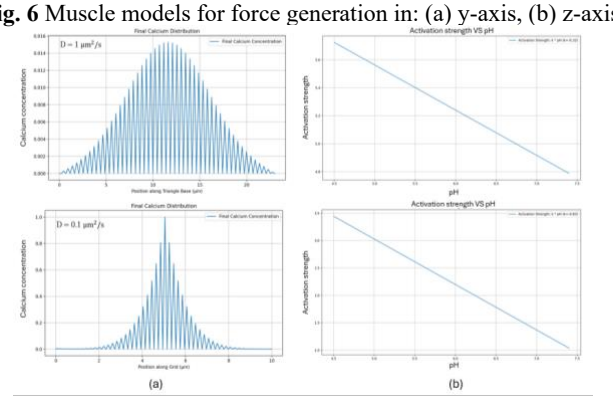

Fig. 7 (a) Calcium concentration via distance of the base of muscle for y and z-axis. (b) Relation between activation strength and pH

3.3 Comparison on Cancer Drug Delivery with Various Research Studies

Nanoparticles: M. A. Beach [9] discussed the use of polymeric nanoparticles for targeted drug delivery in diseases such as cancer, highlighting the challenges of

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understanding biological barriers and technology. Drugs are typically released within 50-200 micrometers of acidic sources, triggered by pH changes.

A. N. Al-Thani [10] investigated nanoparticles in cancer therapies, using gold and iron oxide to reduce side effects and improve drug targeting. Drug delivery accuracy ranges between 10% and 60%, with additional improvements required for full precision.

MOFs: E. Mashayekh [11] investigated the use of Metal-Organic Frameworks (MOFs) for targeted Cisplatin delivery, addressing side effects and resistance. The porous structures of MOFs allow for specific drug binding, followed by release at acidic pH conditions. Blood flow and membrane penetration both have an impact on drug delivery.

Liposomes: Z. Li [12] reviewed studies on nanomaterials for cancer treatment, including: Liposomes: Lipid-based structures that encapsulate and protect drugs, ensuring targeted release at specific locations. Polymers: Used to construct nanoparticles that control drug release. The study concluded by discussing the challenges in enhancing drug delivery precision to cancer cells.

Most targeted medication delivery studies overlook the significance of blood turbulence, which can carry drugs away from target sites. These limitations motivate this research, aiming to develop a bio-robot-assisted delivery system integrated with advanced technologies.

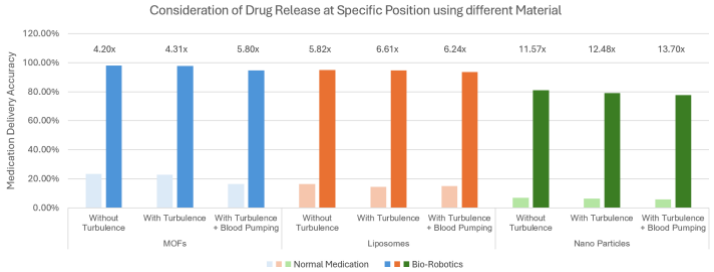

Fig 8. Consideration of Drug Release at Specific Position using different Material.

From the bar charts assessing the accuracy of drug delivery to cancer cells in Fig. 8, it was found that utilizing a bio-robot with a turtle inspired movement significantly improves drug delivery efficiency by about 7.86 times compared to conventional methods. This increase translates to a greater chance of effective cancer treatment for patients while also reducing unintended drug distribution to non-target organs.

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4 Validation

After simulation, we validate our model, including both blood vessel model and blood environment conditions, toward the effect on the muscle motion by using RMSE, which the results summarized as illustrated in Fig. 9.

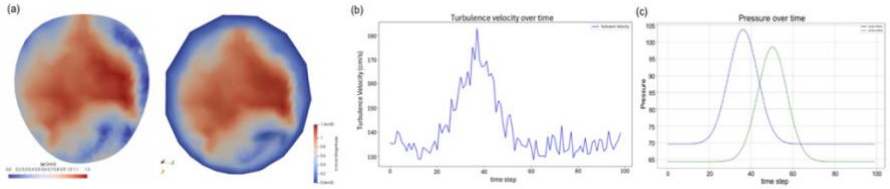

Fig. 9 (a) Cross-sectional blood velocity images: Left, from S. Katz [8]; right, from OpenFOAM in this project, RMSE = 0.173. (b) Velocity-time: RMSE = 0.736 compared to [12]. (c) Pressure-time in Large artery: RMSE = 0.577 and Small artery: RMSE = 0.545 compared to [13] and [1] respectively.

From the results, we can conclude that our experimental conditions are comparable to the previous simulations and data from actual blood vessels, suggesting reliability of our model and acceptable results.

5 Conclusion

Our bio-robotics deliver cancer drugs 7.86 times more efficiently, reducing organ damage. It accounts for blood flow and turbulence, which were ignored in previous studies, while maintaining stable muscle movement under a variety of conditions. Additional research is required to simulate branched and non-uniform blood vessels to better reflect real vascular systems and test robot navigation under complex flow. We will also model drug dispersion after delivery to optimize local concentration and reduce off-target effects.

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