Computational Models for Trapping Ebola Virus Using Engineered Bacteria

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***Abstract*—The outbreak of Ebola virus in recent years has resulted in numerous research initiatives to seek new solutions to contain the virus. A number of approaches that have been investigated include new vaccines to boost the immune system. An alternative post-exposure treatment is presented in this paper. The proposed approach for clearing Ebola virus can be developed through a microfluidic attenuator, which contains the engineered bacteria that traps Ebola flowing through the blood onto its membrane. The paper presents the analysis of the chemical binding force between the virus and a genetically engineered bacterium considering the opposing forces acting on the attachment point, including hydrodynamic tension and drag force. To test the efficacy of the technique, simulations of bacterial motility within a confined area to trap the virus were performed. More than 60% of the displaced virus could be collected within 15 minutes. While the proposed approach currently focuses on *in vitro* environments for trapping the virus, the system can be further developed into the future for treatment whereby blood can be cycled out of the body into a microfluidic device that contains the engineered bacteria to trap viruses.**

***Index Terms*—Ebola virus, Genetically engineered bacteria, Microfluidic viral attenuator.**

I. Introduction

The recent outbreak of Ebola virus has resulted in concerns by the research community to develop new solutions that can curb and control their spreading process [1]. While the majority of Ebola virus outbreaks are currently found in Africa, their rate of spreading requires immediate attention. The spreading process of Ebola virus is through the exchange of fluids between individuals, animals, as well as within the environment where the virus lies. The poor sanitary conditions in the developing countries also fuel the spreading process, which has detrimental effects on lives and on the socio-economical stability of the affected regions.

Currently, there are preventive and post-exposure treatments available [2] [3]. Two vaccines were developed and are still being tested in Guinea: one developed by Merck Sharp and Dohme and another by Toyama Chemical [4], [5]. Other advanced research for solutions to the Ebola virus disease problem is in the domain of molecular biology and biotechnology [6]. Based on this, a number of therapeutic medications to treat Ebola virus disease has been developed and tested, and this includes TKM-Ebola, amiodarone, dronedarone, verapamil and ZMapp [3], [7], [8]. ZMapp is a cocktail of three monoclonal antibodies produced from Tobacco plants (*Nicotiana benthamiana* species) and provides immunity to the Ebola virus. Successful tests were made on mice and non-human primates [8], [9]. Also, monoclonal antibodies derived from a person who survived Ebola virus disease protected non-human primates when given as late as 5 days after the infection [10], [11]. Other treatments that have compounds capable of blocking Ebola virus-like particles from entry into the cells and a novel peptide vaccine have also been proposed to increase the range of available treatments [12], [13]. While the effectiveness of those vaccines in particular for large scale population is still under investigation, another outbreak can occur. Therefore, we propose an alternative post-exposure treatment using synthetic biology to engineer bacteria that can trap the virus, and utilize this solution through a microfluidic attenuator.

The field of *synthetic biology* has received tremendous attention in recent years, due largely to the potential impact of delivering new solutions for biotechnology [6], [14]. Synthetic biology enables genetic circuits to be designed and inserted into cells in order to create new properties as well as functionalities. For example the field of *molecular communication* [15], [16] aims to construct bio-compatible communication systems based on programming of cells. Engineered bacteria through synthetic biology have also been used as therapeutic agents in the past [17]. For example, HIV-1 infection in CD4+ T cells and macrophages were inhibited using *Lactobacillus jensenii* bacteria [17]. Bacteria have also been used to hunt down and eradicate human lymphomas [18].

In this paper, we propose synthetically engineered bacteria (*Escherichia coli*) that moves and traps Ebola virus in a sponge-like manner [19]. While our theoretical models and analysis presented in this paper are based on *in vitro* environments, the proposed approach has the potential to be used

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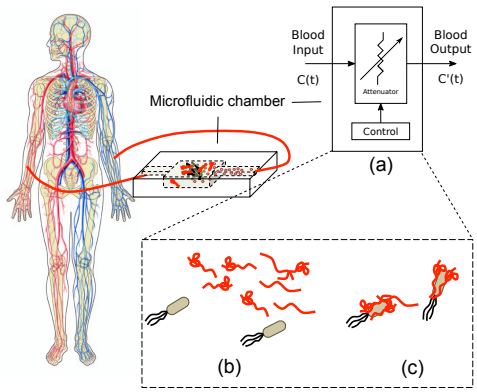

Fig. 1: Illustration of the proposed approach, where blood containing Ebola is passed through an external tube with a microfluidic chamber containing genetically engineered bacteria that are used to trap the Ebola virus, (a) the microfluidic chamber is represented as an attenuator (b) bacteria moves towards the Ebola virus scattered in the chamber, (c) bacteria after trapping the virus once they have bind to their surface membrane.

for treatments in the future as illustrated in Figure 1. The blood contaminated with Ebola virus are transported through a cyclic external tube that goes through a microfluidic attenuator, and back into the body again. Within the chamber are the engineered bacteria that will colide and trap the Ebola through the protein binding process on the surface membrane, resulting in the virus attachment. The proposed system can be described as

$$C'(t) = f_b(t)C, \tag{1}$$

where $C'(t)$ is the Ebola concentration in out-going blood flow, C is the incoming concentration of Ebola virus in the blood stream and $f_b(t)$ is the attenuation function described by the bacterial trapping performance.

The process of virus trapping has been investigated previously. For example, in [19] the red blood cells are used to trap viruses. The red blood cells are ideal for virus trapping due to the fact that they lose their DNA when grown in the bone marrow. Therefore, when the virus infects the red blood cell, it will have no capability of replicating itself due to the missing DNA, and hence, leading to a trapping process. Another example is in [20], where the authors specifically studied the *Phi-6* virus which typically invades *Pseudomonas phaseolica* cell. This particular bacterium attaches itself to the plants by using its hair like structure that extends from their body. The attachment is achieved when the bacteria contracts its body enabling the thick hair to grip onto the surface of the plant. This contracting process will also lead to the virus being able to infect the bacteria. In order to trap the virus, the authors engineered the bacteria to have excessive amount of hair on the surface leading to minimal amount of space to allow the virus to penetrate through the membrane but enough to embed and get stuck on the microbes [20].

The most common mechanism for virus binding on the cell's surface is through the polyvalent interactions between the proteins and the cell's receptors [21]. This process is similar to what we are proposing in this paper. However, there are a number of challenges to be addressed. First, compatible binding process is required between the virus and the bacterium. The compatible receptors on the bacteria can be

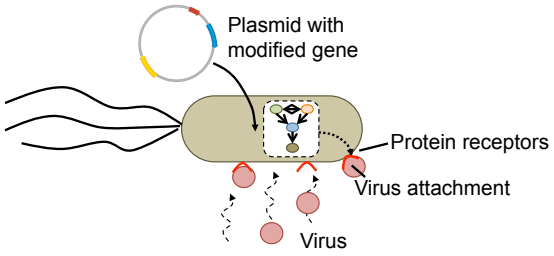

Fig. 2: Genetically engineered bacteria will produce proteins on the surface that will allow the virus to bind.

engineered through synthetic biology as illustrated in Figure 2, where genes that are inserted into the plasmid can lead to expression of proteins on the surface. Second, Ebola virus has a long filamentous structure unlike other types of virus, and usually with a higher molecular weight. Therefore, the binding process may not cover the entire length of the virus, leading to parts of the virus hanging from the bacterium after binding. This means that the binding process must be strong enough to support the momentum of the hanging virus body, and in particular when faced with hydrodynamic tension and drag.

The contributions of this paper include:

- **Design of Ebola virus microfluidic attenuator system**: a cleaning process is proposed, where the bacteria are used to collect and trap the Ebola virus. This trapping process will minimize the virus concentration in blood to curb them from replicating and spreading.
- **Binding force model:** Developed a protein binding force model to trap Ebola virus in free moving bacteria, considering their swimming and tumbling process, as well as opposing forces resulting from the hydrodynamic tension and drag and the weight of the hanging body of the virus.
- **Simulation evaluation:** Simulations of bacteria motility process are conducted to evaluate the effectiveness of trapping an Ebola virus population in a confined area.

The paper is organized as follows. Section II describes the physical properties of Ebola virus. The engineering of proteins on the bacteria surface to bind to the virus is presented in Section III. Section IV describes the binding force models between the bacteria and the virus. The simulation evaluation and results are presented and discussed in Section V. Lastly, Section VI presents the conclusion.

II. Background on Ebola Virus

Ebola virus belongs to the order *Mononegavirales* and the *Filoviridae* family. Upon infection, it can kill up to 50% of the patients within 6 to 16 days [22]. The virus has a filamentous shape, with a uniform width of nearly 80 nm and a length of approximately 970 nm, and its structure is illustrated in Fig. 3. As illustrated in Fig. 3, virus membrane consists of $GP_{1,2}$ (spike glycoprotein) and two other proteins, VP40 and VP24 (primary and secondary matrix proteins). $GP_{1,2}$ is a membrane-spanning protein, and VP40 and VP24 builds the inner matrix [23], [24]. The glycoprotein are 7 nm in diameter and have a spacing of 10 nm between each other. The glycoprotein enables the Ebola virus to bind and

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submerge itself into the host cells (process required for viral internalization) [23].

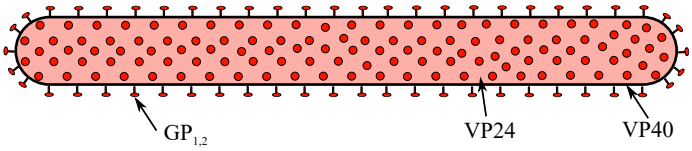

Fig. 3: Structure of an Ebola virus, including the membrane-spanning protein ($GP_{1,2}$) and the proteins that build the inner matrix (VP40 and VP24).

There are three infection routes for the Ebola virus: through mucosal surfaces (mouth, eyes, genitalia), skin abrasions or through the use of contaminated needles [24]. After the virus enters the body, it spreads rapidly [24]–[27], and is capable of overcoming responses from the immune system. The high rate of virus replication inside the immune system cells hinders the human body defenses [25]–[27]. Monocytes, macrophages and dendritic cells are the front door for the Ebola virus infection and preferred sites of replication [26]. In addition, these cells are used as vehicles to spread the Ebola virus through the lymphatic system [24]. Infected monocytes and macrophages secrete soluble factors to recruit other similar cells inside the lymph nodes to increase the infection. In latter stages, hepatocytes and adrenal cortical cells are infected and the production of coagulation factors is decreased which results in internal bleeding [28].

III. Engineering Protein Binding

A. Synthetic Protein Binding Receptors

The main challenge of lowering the concentration of the Ebola virus using bacteria lies in using synthetic biology to produce the required proteins on the surface membrane to bind the virus. In particular, careful understanding of viral entry and replication mechanisms into the host system is required before suitable genetic circuits can be developed. Past research have used dual color synthetic constructs to observe how a single virus affects the host bacterium and determine the level of infection [29]. Single-virus tracking methods have also been developed to observe the mode of interaction between *E. coli* and bacteriophage lambda [29]. In our proposed model, it is possible to construct a synthetic gene that could increase the expression of Ebola virus protein binding receptors. Facilitating the binding frequency between the viral proteins and over expressed membrane receptor proteins would be an advantage to harvest the target virus. Specifically, reports have suggested that the cell surface receptor *T-cell Immunoglobulin Mucin domain 1* (*TIM-1*) of epithelial cells favourably increases the binding of Ebola virus. A study on over expression of fluorescent tagged *TIM-3* protein in *E. coli* also confirms that TIM-like protein can have a functional property which allows viral protein recognition and binding [30]. Therefore, the TIM-like protein could be one of the possible targets to be expressed in *E. coli* to create engineered bacteria to trap the Ebola virus. Engineering the synthetic circuit of *EnvZ*/*OmpR*/*BolA* genes along with the TIM-like protein-coding genes will facilitate the binding of Ebola virus and simultaneously control the motility of *E.coli* during the binding and trapping of Ebola virus (*EnvZ* is the sensor-transmitter kinase that phosphorylates *OmpR*, a DNA-binding regulatory protein, under stress conditions) [31], [32]. Another requirement is the engineering of the bacteria to prevent the virus entry, and this could be achieved by considering the use of mutant *E.coli* as a host that carries membrane proteins (e.g., Porins) [33], [34].

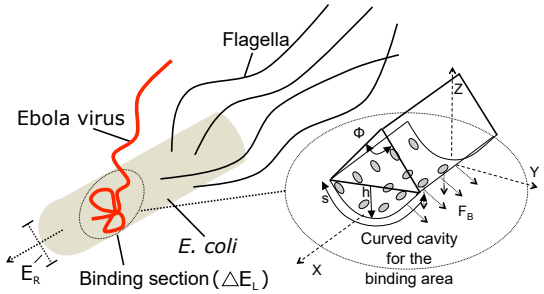

Fig. 4: Expanded view of the partial deformation on the bacterium's surface membrane when the virus binds on its surface.

B. Protein Binding Model

Our model is developed as a function of the binding among bacterial receptors and the viral glycoproteins. We analyse the produced binding force, and how it will counter the opposing forces (due to drag and weight of the virus) that can result in the attachment breakage. During the binding process, the virus deforms the bacterium's surface creating a curved cavity with a submergence angle ϕ (in radians) as shown in Fig. 4 [35]. The cavity segment consist of height h and arc length s. The attachment area B_{Area} between the virus and the bacterium can be evaluated as:

$$\begin{aligned} B_{Area} &= s\Delta E_L \\ &= \phi E_R \Delta E_L \end{aligned}$$

where E_R is the Ebola virus radius and ΔE_L is the length of Ebola virus that attaches to the bacterium. Therefore, the reaction between the bacterial receptors and virus proteins within B_{Area} can be represented as [35]:

$$\mathrm{n[V] + m[B] \overset{K_a}{\rightleftarrows} [B_m V_n]}, \tag{2}$$

where n is the number of viral proteins that binds to a single bacterial receptor; m is the number of bacterial receptors that binds to a single viral protein; $[\mathrm{V}]$ and $[\mathrm{B}]$ are the concentrations of viral proteins and bacterial receptors, respectively; and K_a is the association binding constant for the reaction. The initial values for the viral and bacterial proteins ($[\mathrm{V_0}]$ and $[\mathrm{B_0}]$) are the ratio between the minimum attachment area and the area occupied by the Ebola glycoprotein and TIM-1, respectively. Therefore, the fraction of the bacterial receptors that are bound by the viral proteins can be defined as p [36]:

$$p = \frac{[\mathrm{B_m V_n}]}{[\mathrm{V}] + [\mathrm{B_m V_n}]}. \tag{3}$$

The total binding energy resulting from the complex formation of the Ebola virus glycoprotein and the bacterium receptors is represented as [37]:

$$E_{Total} = (E_{Bind} + (p-1)T_a S_0)B_{Area}, \tag{4}$$

where T_a is the absolute temperature; S_0 is the translational and rotational entropy of binding for this complex. The affinity binding energy E_{Bind} can be evaluated as follows:

$$E_{Bind} = -pk_B T_a \ln K_a \tag{5}$$

where k_B is the Boltzmann constant. Based on the E_{Bind}, the binding force F_{Bind} for this process is represented as:

$$F_{Bind} = -\frac{\partial E_{Total}}{\partial \phi}. \tag{6}$$

Since each virus will occupy a small area of the bacterium, the surface area can accommodate a number of Ebola virus. The limit for the number of virus that can bind to each bacterium b_{limit} can be represented as:

$$b_{limit} = bac_{Area} - \sum_{i=0} B^i_{Area} \tag{7}$$

where bac_{Area} is the bacterium surface area and $i = 0, 1, 2, ...$ is the number of attached virus.

IV. Force Model for Virus Detachment

In general, to achieve the stability of attachment, the binding force will highly depend on the opposing forces that include hydrodynamic drag force as well as the tensions exerted on the Ebola virus. The equilibrium will depend on B_{Area} and the motion realized by both bodies. After binding, both bodies can move in a straight line or tumble in a fixed location. For each movement, different tensions will affect the attachment. In this section, we discuss the tensions and forces that are exerted onto the virus during the bacterium's movement.

A. Hydrodynamic Drag Force

The medium that we consider is the blood, where the Ebola virus will diffuse through brownian motion. Once the Ebola virus has attached itself to the bacterium, both are subjected to the same hydrodynamic force (drag force) as they mobilize. Since we model the shape of the bacterium as a cylinder, the $\mathbf{F_{Drag}}$ can be expressed as follows [38]:

$$\mathbf{F_{Drag}} = -\frac{1}{2}\rho_f v^2 A C_d, \tag{8}$$

where ρ_f is the fluid medium density, $v = v_b - v_f$ is the relative velocity between the bacterium (v_b) and the fluid (v_f), $A = \pi B_R^2$ is the bacterium's cross-section and B_R is the radius. The drag coefficient C_d is expressed as [38]:

$$C_d = \frac{24}{Re} + \frac{6}{1+\sqrt{Re}} + 0.4, \tag{9}$$

where the Reynolds number (Re) is expressed as [38]:

$$Re = \frac{D_v \rho_f v}{\eta_f}, \tag{10}$$

where η_f is the fluid viscosity, and D_v is the width of the microfluidic chamber.

B. Bacteria Motility

Bacteria have different types of motility, e.g., swarming, swimming, gliding [39]. For swimming, bacteria utilises their flagella to swim in a regular or biased motion towards a source (e.g., nutrients). Bacteria can also move in a coordinated manner across solid or semi-solid surfaces [39]. This motility process is known as swarming and it is performed by group of cells instead of single individuals. This form of motility also depends on the *pili* formation that helps the cells to aggregate into a population [39]. For our model, we consider that the bacteria will swim and will not be allowed to grow or attach onto other surfaces, which is based on the swarming and gliding process. Also our aim is to allow the bacteria the freedom of random movement to trap the Ebola virus, and this could be achieved through their swimming process.

The swimming process of the *E. coli* is based on their *flagella* movement. The flagella are tails that stem from the body of the *E. coli*. The swimming behavior of the bacteria is based on a cycle of run and tumble motion, and is governed by a random walk. During swimming, the flagella will wrap into a single body, and this will rotate as a propeller allowing them to swim forward. The bacteria swims in a straight line for an average period (λ_{Run}) that is based on an exponential distribution [40]. The binding between the bacterium and virus will occur when they come into contact with each other. After swimming for a short period, the flagella will unwrap into individual strands and this will lead to tumbling in a fixed location. Once again the average tumbling period is based on an exponential distribution (λ_{Tumble}) [40]. After the tumbling process, the bacterium will select a random angle to continue swimming.

C. Tension Force for Running Motion

The bacterium's running motion (see Figure 5) produces tension on the binding area that could break the attachment. In order to analyse the forces affecting the binding between two bodies, we use the approach presented in [41]. The description of each variable is as follows: ΔE_L is the length of the Ebola virus that binds to the bacterium's surface (we are assuming here that only a portion of the virus has bound), $\mathbf{F_M}$ is the force exerted by the bacterium's flagella that enables the movement, $\mathbf{W_h}$ is the weight for the hanging section of the Ebola virus, $\mathbf{W_{dl}}$ is the weight for the bound section of the Ebola virus, $\mathbf{T}$ is the tension exerted on the hanging portion of the Ebola virus that attempts to peel it from the bacterium due to resistance, l_1 is the distance between the bound mid-section of the Ebola virus and the bacterium's centre of mass, l_2 is the distance between the centre of the Ebola virus hanging section and its bound mid-section, θ_h is the angle between the hanging portion of the virus and the bacterium. We consider both the Ebola virus and bacterium as homogeneous bodies. Therefore,

$$\mathbf{W_{dl}} = \frac{m_e}{E_L} g \Delta E_L$$

and

$$\mathbf{W_h} = m_e g - \mathbf{W_{dl}} ,$$

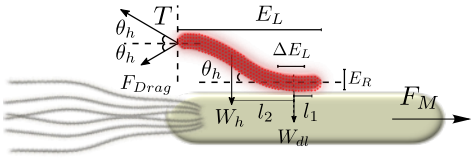

Fig. 5: The binding force representation model between an Ebola virus and the bacterium. The opposing tension force $\mathbf{T}$ is responsible for peeling the virus from the surface of the bacterium while the other forces act to maintain their attachment stability.

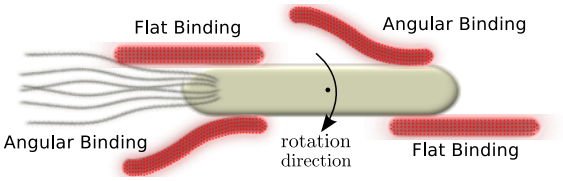

Fig. 6: Illustration of attachment points for angular and flat binding of Ebola virus on the bacterium as its going through a tumbling process. The positions of the flat and angular binding are dependent on the clockwise rotation of the bacterium.

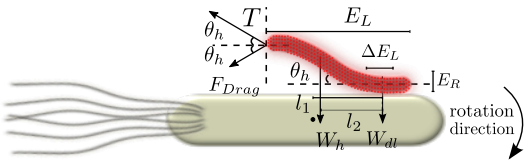

Fig. 7: The force model of an Ebola virus on the bacterium that is going through a tumbling process. This illustration shows the forces acting on the angular binding for Ebola virus. The angular binding only happens on locations of turns when the Ebola virus is being pulled outwards during the tumbling process.

where m_e is the Ebola virus' mass and g is the gravitational constant. In order for the body to move linearly in a particular direction, the sum of momentum has to be equal to zero. Therefore,

$$\sum M = M_{dl} + M_h + M_g + M_d - M_T = 0, \tag{11}$$

where $M_{dl} = \mathbf{W_{dL}} l_1$ is the momentum due to the force exerted on ΔE_L, $M_h = \mathbf{W_h}(l_2 + l_1)\cos\theta_h$ is the momentum due to the force exerted on the hanging section of the Ebola virus, $M_g = \int_0^{\Delta E_L} P_n \; x \; dx$ is the momentum due to the force exerted on the glycoprotein-receptor complexes on the bacterium (where P_n is the adhesive pressure of all the glycoproteins and x is the length of the Ebola virus binding area), $M_d = \mathbf{F_{Drag}} \sin\theta_h E_L$ is the momentum due to the drag force exerted on the edge of the Ebola virus ($\mathbf{F_{Drag}}$ is calculated from Eq. (8)), and $M_T = \mathbf{T} E_L \sin\theta_h$ is the momentum due to the tension exerted on the hanging section of the Ebola virus. Replacing these terms into Eq. (11) as well as the relationship of $l_2 = \left(\frac{E_L}{2} - \frac{\Delta E_L}{2}\right)$, which is the distance between the weights $\mathbf{W_{dL}}$ and $\mathbf{W_h}$, the tension $\mathbf{T}$ can be represented as:

$$T = \left(W_{dl} l_1 + W_h \left(\frac{E_L}{2} - \frac{\Delta E_L}{2} + l_1 \right) \cos\theta_h \right.$$
$$\left. + \frac{P \Delta E_L^2}{2} + F_{Drag} \sin\theta_h E_L \right) (E_L \sin\theta_h)^{-1}. \tag{12}$$

The adhesive pressure of glycoproteins (P) can be expressed as the force exerted within the bound area, and can be represented as follows [41]:

$$P = \frac{\left(F_n + \frac{m_e g}{n_G} \right) n_G \Delta E_L^2}{2\theta_h E_R \Delta E_L}.$$

where n_G is the concentration of glycoproteins required for the minimum attachment area. Inserting P into Eq. (12) will result in:

$$T = \left(W_{dl} l_1 + W_h \left(\frac{E_L}{2} - \frac{\Delta E_L}{2} + l_1 \right) \cos\theta_h \right.$$
$$\left. + \frac{\left(F_n + \frac{m_e g}{n_G} \right) n_G \Delta E_L}{2\theta_h E_R} + F_{Drag} \sin\theta_h E_L \right) (E_L \sin\theta_h)^{-1}. \tag{13}$$

D. Tension Force for Tumbling Motion

When a bacterium tumbles, depending on the position of the Ebola virus binding point, there will be two different types of force models, which are *angular* and *flat* binding. Figure 6 illustrates these binding points on the bacterium. As the bacterium rotates at the centre point of the body, the angular binding will occur when the Ebola virus encounters a pulling force (e.g., at the front of the bacterium when it tumbles clockwise), while the flat binding occurs at the tail end of the body when the virus is pushed through the circular motion. Figure 7 illustrates the force model for the angular binding, while the flat binding model is illustrated in Figure 8.

1) Angular Binding: Since the motion is a continuous rotational spin at a fixed point, the sum of the momentum is represented as follows:

$$\sum M = I\alpha, \tag{14}$$

where I is the inertial momentum of the bacterium as well as the Ebola virus, and the angular acceleration during the tumbling process, which is represented as:

$$\alpha = \frac{d\omega}{dt} = \frac{2\pi f_t}{\lambda_{Tumble}},$$

where f_t is the frequency of tumbling. Therefore, the inertial momentum is represented as:

$$I = \frac{m_B L^2}{12} + m_e \left(E_{hl} \cos\theta_h + \frac{\Delta E_L}{2} + l_1 \right), \tag{15}$$

where E_{hl} is the length of the virus that is hanging, m_B is the mass and L is the half length of the bacterium. For the angular binding, considering Eq. (14) and (15), Eq. (11) can be represented as:

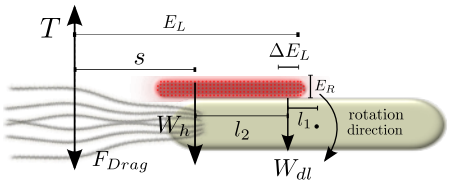

Fig. 8: The force model of the Ebola virus on the bacterium that is going through a tumbling process. This illustration shows the forces acting on the flat binding for the Ebola virus. The flat binding only occurs on locations of turns when the Ebola virus is being pushed up against the bacterium during the tumbling process.

$$I\alpha = W_{dl}l_1 + W_h\left(\frac{E_L}{2} - \frac{\Delta E_L}{2} + l_1\right)\cos\theta_h + \frac{\left(F_n + \frac{m_e g}{n_G}\right) n_G \Delta E_L}{2\theta_h E_R} + F_{Drag}\sin\theta_h E_L - TE_L\sin\theta_h,$$

and from the perspective of the tension $\mathbf{T}$, this is represented as:

$$T = \left(W_{dl}l_1 + W_h\left(\frac{E_L}{2} - \frac{\Delta E_L}{2} + l_1\right)\cos\theta_h + \frac{\left(F_n + \frac{m_e g}{n_G}\right) n_G \Delta E_L}{2\theta_h E_R} + F_{Drag}\sin\theta_h E_L - \frac{m_B L^2}{12} - m_e\left(E_{hl}\cos\theta_h - \frac{\Delta E_L}{2} - l_1\right)\alpha\right) * (E_L\sin\theta_h)^{-1}. \quad (16)$$

2) Flat Binding: For the flat binding during the tumbling process, Eq. (16) can be simplified because there is no angle of attachment between the Ebola virus and the bacterium. This means that a large part of the virus will lie flat on the bacterium during rotation. This scenario is presented in Figure 8. In this case, the tension $\mathbf{T}$ is represented as:

$$T = \left(W_{dl}l_1 + W_h\left(\frac{E_L}{2} - \frac{\Delta E_L}{2} + l_1\right) + \frac{\left(F_n + \frac{m_e g}{n_G}\right) n_G \Delta E_L}{2\theta_h E_R} + F_{Drag}E_L - \left(\frac{m_B L^2}{12} - m_e\left(E_{hl} - \frac{\Delta E_L}{2} - l_1\right)\right)\alpha\right)(E_L)^{-1}. \quad (17)$$

V. Analysis and Simulations

Firstly, we will present the analysis of the binding forces and tensions for the virus attachment to an individual bacterium. This will then be followed by simulations that will evaluate the microfluidic attenuator performance of the Ebola collection process. The values for all the parameters used in the binding force analysis and simulations are presented in Table I.

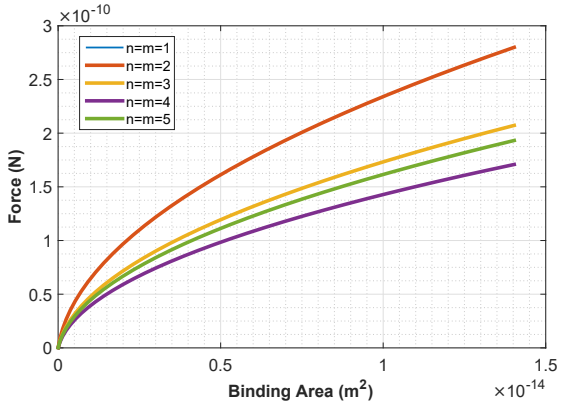

Fig. 9: Analysis of receptor binding force for five different valency configurations.

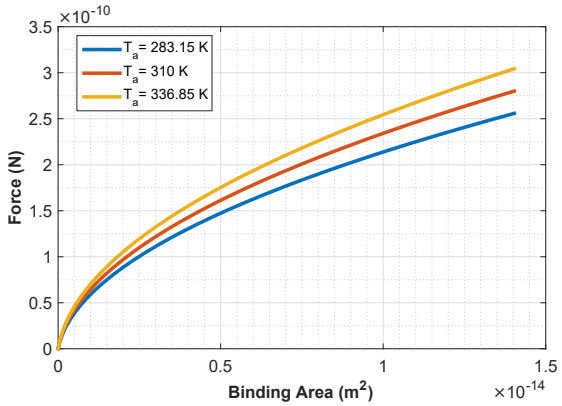

Fig. 10: Analysis of receptor binding force for two different temperatures. The temperature difference was not sufficient to produce significant changes in the attachment force.

A. Binding Force and Tensions Analysis

The aim of the analysis is to evaluate the effect of tension forces acting on the attachment point between the Ebola virus and the bacterium, and how this impacts on the protein binding force. The binding force analysis is presented in Figures 9 and 10, while the opposing forces analysis are presented in Figures 11, 12 and 13.

The binding force relies on the bacterial and viral proteins valency, and its models were presented in Eg. (2)-(6). Therefore, we considered different fixed values of n and m to evaluate their impact on the resulting binding force (see Figure 9). Even if the number of bonds increases, the ratio n/m will still remain the same. For $n = \{1, 2\}$ and $m = \{1, 2\}$, the binding force was almost the same with less than 1% difference, and this was the highest value achieved. The chosen protein, TIM-1, can bind to two or three proteins at same time (i. e. $1 \leq m \leq 3$) and as presented in Figure 9, this resulted in the highest binding force values for all possible attachment area, which also reflects the most suitable protein configuration. In Figure 10, we analysed the effect of temperature on the binding force. We considered three different temperatures to observe different behaviours that can arise. Normal human body temperature is 309.65 K and during fever this is elevated to 313 K. The latter value is also the average temperature of countries where the disease outbreak occurred. As we can observe, the temperature does not produce

TABLE I: Parameters used to evaluate the receptor binding force, tensions and drag force applied on the bacterium as well as the Ebola virus. * Refers to values chosen by the authors. ** Refers to standard values.

Variable	Value	References
E_R	47×10^{-9} m	[22], [23]
E_L	970×10^{-9} m	[22], [23]
B_R	0.5×10^{-6} m	[42]
B_L	1×10^{-6} m	[42]
v_b	20×10^{-6} m/s	[42]
m_e	5.45×10^{-19} kg	[22], [23]
m_b	1×10^{-18} kg	[42]
$[B_0]$	6.7×10^{-6} proteins/μm^2	*
$[V_0]$	2.8×10^{-2} proteins/μm^2	*
f_t	1.37 tumbles/s	[43]
ϕ	from $\pi/100$ rad to $\pi/10$ rad	*
T_a	310 K	*
k_B	0.00831446211 kJ/mol/K	**
ρ_{blood}	1060 kg.m^{-33}	[38]
g	9.8 m/s^2	**
μ_s	3×10^{-3} Pa.s	**
D_v	5 cm	*

significant changes in the receptor binding force behaviour, even for high temperatures such as $T_a = 336.85$ K.

The opposing forces acting on the attachment area can be increased or lowered depending on variations for a number of parameters: blood velocity, blood viscosity and angle of attachment between the Ebola virus and the bacterium. When the blood enters the microfluidic chamber, it will gain a certain velocity that could be high enough to increase the tension on the attachment point that can lead to breakage. In Figure 11 we considered three different velocities (v_f^1, v_f^2 and v_f^3) and evaluated their impact on the binding force when the bacterium is running in a straight line (worst case). As the velocity increases, we can observe that the tension increases as well. However, if the blood velocity is much higher than the bacteria velocity, this can become an issue. In this case, when the blood flows into the chamber, it will disrupt the bacterial movement by pushing them toward the opposite border of the compartment. To avoid this effect, the bacteria need to be placed inside the microfluidic chamber when the blood is at rest and removed before the blood is pumped back into the body.

The patient's blood can be more or less viscous depending on their health condition. Different viscosity values can produce significant changes on the drag force that could result in higher tension on the attachment point between the virus and the bacterium. Figure 12 shows the effect of three different viscosity values on the tension applied on B_{Area}. Higher viscous blood will have a larger impact when the bacteria is moving, and a less viscous blood will affect the tension when the bacteria is tumbling. For all cases presented in Figure 12, the changes to the tension on the attachment point is reasonably low. This result demonstrates that the blood viscosity will not impact on the proposed attenuator system performance. The same occurs if we change the attachment angle, as shown for both the running and angular binding analysis (Figure 13). For this analysis, we considered three

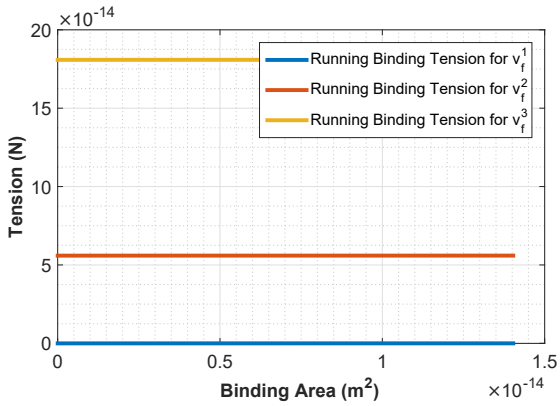

Fig. 11: Analysis of the effect of three different blood velocities on the tension exerted onto the attachment area. We evaluated the opposing forces for $v_f^1 = 0$ μm/s, $v_f^2 = 10$ μm/s and $v_f^3 = 20$ μm/s.

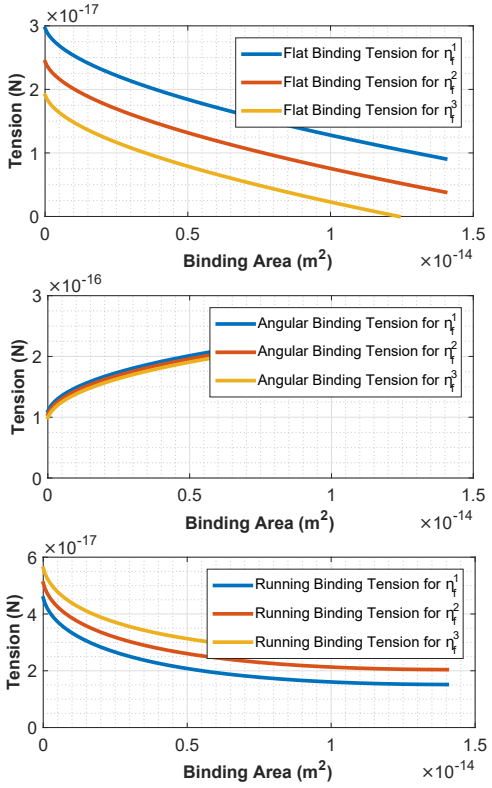

Fig. 12: Analysis of the effect of three different blood viscosities on the tension exerted onto the attachment area. We evaluated the opposing forces for $\eta_f^1 = 3 \times 10^{-3}$ Pa.s, $\eta_f^2 = 4 \times 10^{-3}$ Pa.s and $\eta_f^3 = 5 \times 10^{-3}$ Pa.s.

different attachment angles between the Ebola virus and the bacterium. As we can observe from the plots, when the angle increases, the tension applied to detach the virus from the bacterium decreases. Furthermore, for $\theta \geq 5$ rad, the angular binding tension enhances the attachment rather than oppose to detach the virus.

B. Microfluidic Attenuator Trapping Simulations

In order to validate the Ebola virus trapping process by the bacteria, we conducted several simulations for the different environments that the system could be exposed. We are interested in evaluating the attenuator model performance for

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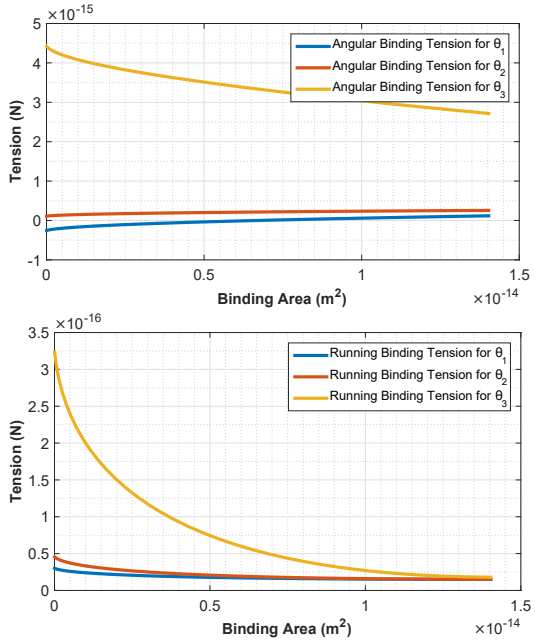

Fig. 13: Analysis of the angular and running binding tensions. Three different attachment angles were considered in this analysis $\theta_1 = 10$ rad, $\theta_2 = 5$ rad, $\theta_3 = 0.5$ rad

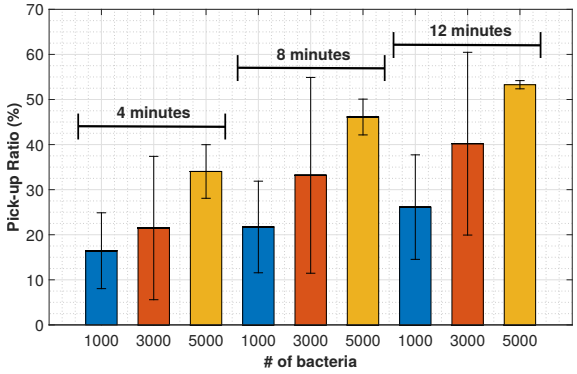

Fig. 14: The pickup ratio increased proportionally to the different simuation times. For 4 minutes more than 30% of the available virus were captured; for 8 minutes, more than 40%; and for 12 minutes, more than 50%.

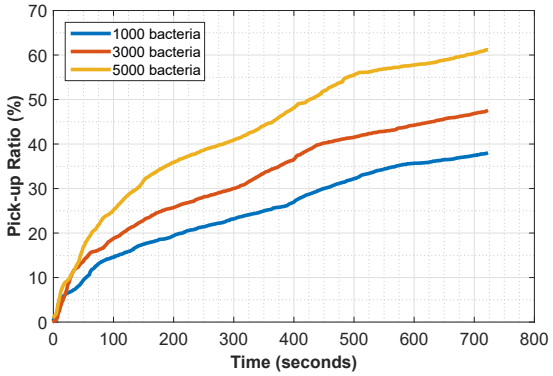

Fig. 15: The quantity of Ebola virus that are captured with respect to time as the quantity of bacteria are varied. The area considered is 5x5 cm.

the initial stage of the infection, where the number of Ebola is approximately 10^4 virus/ml of blood [44]. For all considered scenarios, the Ebola virus were randomly distributed in a microfluidic chamber square area with a size of 25 cm^2, while the bacteria are placed in an external compartment.

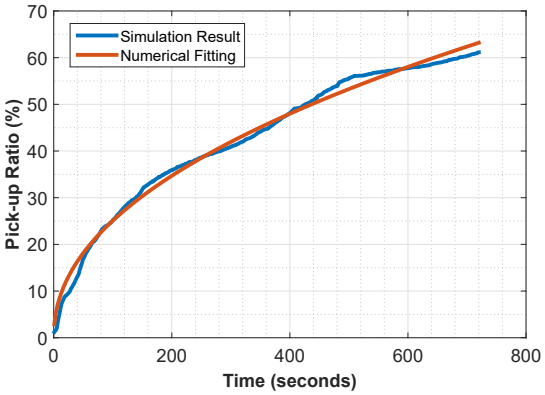

Fig. 16: The filter function $f_b(t)$ was numerically evaluated for 5000 bacteria. This function can be used to predict the time needed to reach the desired pick-up ratio.

The bacteria are released from the compartment ($x = 0$ and along the y-axis) swimming into the chamber to capture the Ebola virus. In our scenario, the number of Ebola virus is higher than the number of bacteria. To ensure a constant blood viscosity value (3×10^{-3} Pa.s), the simulation duration was limited by the amount of time before clotting naturally occurs, which is between 8 and 15 minutes [45]. We also considered a static blood flow ($v_f = 0$), small attachment angle ($\theta \leq 0.5$ rad) and the binding force was generated by a trivalent protein interaction ($n = m = 3$).

Based on the analysis presented in Section V-A, we found that the attachment area has an important effect on the reliability of the binding process. The area limit defined in Eq. (7) is used to determine the maximum number of virus that can attach to each bacterium (this is calculated by considering the bacteria shape as a cylinder, and determining the area of each virus that binds to the surface membrane). In our simulations, for each contact between a bacterium and a virus we evaluate Eq. (7). If the bacterium's area is already full of virus, or if the attachment area is larger than the area available, this means that there are no remaining space on the bacterium's surface. The results presented in Figures 9, 10 and angular binding tension in Figure 12, showed that an increase of B_{Area} resulted in larger binding force or opposing tensions. At the same time, the results presented in Figures 11, 12 (running and flat binding tensions) and 13 showed an inverse relationship with B_{Area}. Therefore, in order to simulate a realistic scenario, we consider various random attachment area between the Ebola virus and the bacteria.

The pick-up ratio was evaluated for different Ebola densities, simulation times and quantity of bacteria. Figure 14 presents the performance of the attenuator, which is the ratio of the average number of Ebola virus captured (10^4, 5×10^4 and 10^5 virus) by 1000, 3000 and 5000 bacteria within 4, 8 and 12 minutes. As we can see from the results, the quantity of virus is reduced with respect to the number of bacteria and duration allowed for the collection process.

Since each bacterium will have an attachment limit in terms of bound Ebola virus, after a certain amount of time the system

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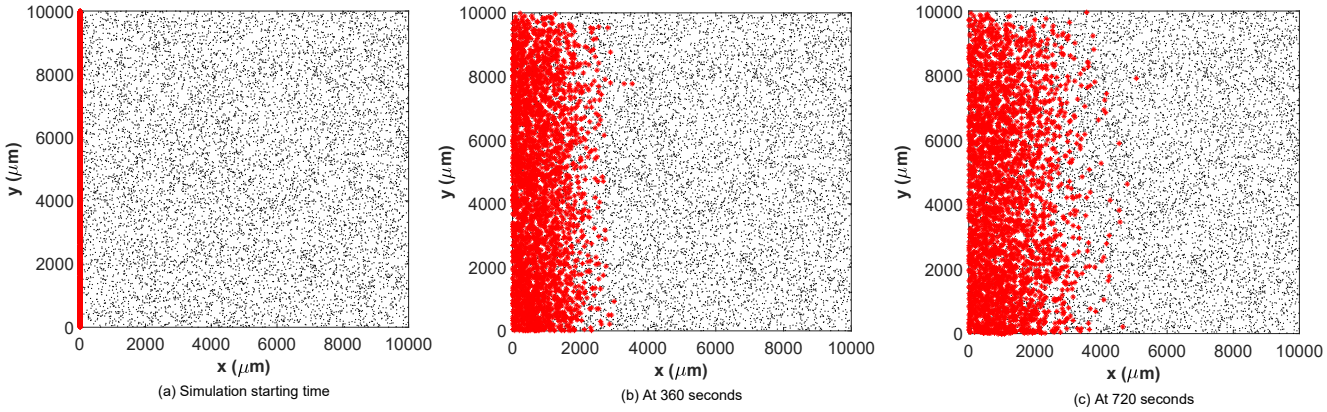

Fig. 17: The placement of bacteria have an impact on the spatial distribution of the virus. (a) At the start of the simulation, the bacteria where placed along the y-axis ($x = 0$) and the virus is randomly distributed within the chamber; (b) at 3600 seconds, bacteria could filter a small portion of the area; (c) at 7200 seconds, bacteria mobilized to more than 30% of the chamber's length.

is expected to became saturated. The next set of experiments is designed to measure the time required before saturation occurs. The number of Ebola virus were fixed at 10,000 and three quantities of bacteria were considered (1000, 3000, 5000), while the simulation time was fixed at a maximum of 720 seconds, and the simulations were executed for 10 cycles. The time 720 seconds is selected to avoid blood clotting. Figure 15 presents the average pick-up ratio, where after 720 seconds, 1000 bacteria achieved $37.89 \pm 12.6\%$ of the total number of virus, 3000 bacteria achieved $47.41 \pm 24.76\%$ and 5000 bacteria achieved $61.15 \pm 13.56\%$. We can also observe in Figure 15 that the bacteria do not achieve their saturation point within the considered period of 720 seconds. The considered number of Ebola (and their random placement) combined with the random nature of bacterial swimming process produce the high variance observed, and limits the bacteria from reaching their saturation point within 720 seconds. We previously defined the model for the attenuator in Eq. (1), which also includes the attenuator function $f_b(t)$ that determines the amount of Ebola virus to be picked up as a function of time. This function can be estimated from the saturation experiments. As an example, considering that 5000 bacteria achieved the highest pick-up ratio, we used this result to evaluate numerically the attenuator function $f_b(t)$ for 10,000 virus, and predict the time required to reach the desired pick-up ratio (see Figure 16), and this is represented as:

$$f_b(t) = 2.903t^{0.4682} \tag{18}$$

The pick-up process can also be observed spatially. In Figure 17, 10,000 Ebola virus were spread randomly within the chamber (with an area of 1 cm^2) and 3,000 bacteria were released along the y-axis ($x = 0$). Within 720 seconds, the number of bacteria reached approximately 5,000 μm. This also demonstates the speed the bacteria takes to move within the area and perform the Ebola pick-up. It can be also observed from Figure 17 that the bacteria is able to only cover a small portion of the area. This result suggest that a proper chamber design is important to optmise the pick-up process. The chamber geometry will depend on the concentration of the virus for the desired blood volume and the number of bacteria used to collect them. This is still a open problem that should be addressed during the attenuator design.

VI. Conclusion

The emergence of Ebola virus in recent years has motivated the need for effective treatment solutions to curb the spreading process. In this paper, we presented an approach where bacteria, genetically engineered, are capable of trapping Ebola virus that binds on its surface. The approach requires blood to be temporarily transported through an external tube that is connected through a microfluidic chamber containing the engineered bacteria. Our approach includes the engineering of receptors on the surface of the bacteria that are compatible to the glycoproteins found on the membrane of the Ebola virus. Our analysis found that the binding process of the Ebola virus on the bacteria is highly dependent on the valency of both viral and bacterial proteins as well as the attachment area. The paper also presented a simulation model of the bacteria hunting process of the Ebola virus within a confined area. The analysis includes the saturation time of the Ebola virus collection process, as well as the collection and trapping performance when the number of bacteria and Ebola virus varies. Our results show that for the considered simulation time, the bacteria can collect the virus without reaching its attachment limit, and the performance of the Ebola virus trapping quantity is highly dependent on the number of bacteria that are deployed. Although this paper only concentrated on the *E.coli* bacteria, the approach can also extend to other attenuated strains of bacteria such as *Salmonella* [46] and also to other virus that can bind to TIM-1. The proposed technique also shows the potential of using synthetic biology to build a biomedical machinery to clean human blood from virus.

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