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FORMAL VERIFICATION OF A MICROFLUIDIC DEVICE FOR BLOOD CELL SEPARATION

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Abstract. Blood cell separation microdevices are designed in biomedical engineering for separation of cancer cells from blood. The movement of cancer cells particles in a continuous flow microfluidic device is a challenging problem since there are several forces incorporated. For instance, forces due to inertia, gravity, buoyancy, dielectrophoresis and virtual mass are accounted for in this system. Understanding the cell particle movement and behavior at high level of abstraction is necessary in order to avoid fundamental errors in the design of systems that can make use of this behavior. In this paper we use formal analysis in order to formalize and validate the movement of microparticles under DEP forces for blood cell separation microdevice. This is achieved by modeling the dynamic behavior that can predict the trajectory of microparticles as a transition state based system. The model is used to validate the correctness of the microdevice at early stages of the design process.

Key words: Reliability Analysis, Medical System, Microfluidic Device, Blood Cell Separation

AMS subject classifications. 92C17, 92C50, 92-08, 68Q60

1. Introduction. Dielectrophoresis (DEP) is the phenomenon in which neutral but polarizable particles, dispersed in a medium, transverse when subjected to a non-uniform electric field. The particles transverse towards either the field maxima or minima; the preference of maxima/minima depends on electrical properties, specifically conductivity and permittivity, of the microparticles and medium as well as applied frequency. DEP is used very frequently in order to design techniques that are used for separating microparticles in a heterogeneous mixture. In these microdevices, the sample containing microparticles is subjected to a DEP field, applied normal to the direction of flow, thereby repelling the microparticles away from the electrodes. In most microfluidic devices the DEP field is generated in the vertical direction and this leads to the microparticles being distributed along the height when subjected to DEP. The height to which each microparticle is repelled depends on the properties such as conductivity, permittivity and density of the medium and the microparticle itself.

Existing microparticles separation techniques are usually validated through a set of experimental data, and then results are compared to the theoretical model. Simulation however, cannot provide full coverage for complex systems, since huge number of test cases are needed. Therefore, other complementary testing and verification techniques such as formal method are often used. Formal methods, in particular, model checking, involve a systematic analysis that is based on mathematical reasoning to verify that design specifications comprehend certain design requirements. They have been successfully used for the precise analysis of various complex systems [10], therefore, they can be efficiently used to validate the separation of microparticles in a continuous flow microdevice at high level of abstraction. NuSMV model checking method is used in this work in order to formalize and validate the movement of blood cells under DEP in a microfluidic device employing dielectrophoresis for purposes of blood cell separation.

Model checking [7] (or sometimes called property checking) is a formal verification technique that verifies whether a model of a system meets a given specification. The method provides exhaustive coverage for the system and is conducted automatically. It examines all possible system states in a brute-force manner in order to show that a given system model truly satisfies a certain property. Model checking approach has a limitation related to the size of system states that can be checked, therefore, abstraction methods are used to enable the verification of complex and large systems. In this, paper we use the NuSMV model checker, which provides cutting-edge formal verification methods based on optimized techniques. It supports both temporal model checking including CTL and LTL temporal logics, and safety assessment, and has been used in several industrial contexts. Therefore, we will use NuSMV [13] in order to model and verify the microdevice used for blood cell separation.

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This paper extends the work in [19] by using model checking for the formal analysis of the movement of blood cells in microdevices within a heterogeneous mixture of human blood for cell separation. This formalization helps in identifying certain features about the behavior of these blood cells, for instance, whether they are affected by specific design parameters, such as microchannel height, while in the transient state. This model also provides an early understanding of the behavior of the system at high level of abstraction, and therefore can provide early feedback to the designers of DEP microdevice.

2. Related Work. The first attempt for modeling the trajectory of cells in a DEP microfluidic device, employing IDT electrodes, is credited to Huang *et al.* [22]. In this work the authors developed an analytical static model for determining the levitation height of cells subjected to nDEP in a microfluidic device. As with static models the model developed by Huang *et al.* is valid only under steady state conditions. The model accounts for forces due to DEP, gravity, buoyancy and hydrodynamic lift. For purposes of developing an analytical equation the force due to DEP is modified from its original form, in terms of gradient of the square of the magnitude of electric field, to a function in applied voltage (RMS). They did not consider the forces due to inertia, drag and virtual mass. The authors experimentally validated this model using data from their own experiments.

Kralj *et al.* [24] modeled the trajectory of microparticles in a continuous flow nDEP based microfluidic device, with IDT electrodes, they developed for sorting of microparticles. The electrodes are located at the bottom of the microchannel but aligned at an angle to side walls of the microchannel. The purpose of this microdevice is to sort the microparticles in the lateral direction, i.e. along the width of the microchannel. Unlike traditional DEP microdevices where microparticles are sorted based on material properties alone, the microdevice of Kralj *et al.* can achieve sorting based on the size of microparticles as well. This is because the sorting is achieved in the lateral direction rather than in the vertical direction. The authors modeled the trajectory of microparticles only in the lateral direction for which they considered the forces due to drag and DEP. In this model the electric field is approximated using a trigonometric function for realizing an analytical equation of the trajectory of the microparticles. Crews *et al.* [14] carried out a numerical study of the IDT electrodes for the purpose of developing an approximate mathematical equation of the gradient of square of the magnitude of electric field inside the microchannel for use in estimating the force due to DEP. This equation is a function of electrode and gap length; in addition, it implicitly accounts for the height of the microchannel. According to Crews *et al.* (2007) their equation is applicable only for voltages lower than 8 V (peak-to-peak) as well for electrode/gap lengths smaller than $80\mu m$.

Cao *et al.* [11] developed a model for describing the levitation of microparticles in a DEP microfluidic device employing IDT electrodes. The work only considered the forces due to DEP, gravity, buoyancy and drag in their model. The influence of electrothermal flow on the trajectory of microparticles is accounted though the drag force. Leu and Weng [26] developed an analytical equation for the predicting the levitation height of microparticles in a DEP-FFF microdevice. They considered the forces due to DEP, gravity and buoyancy. In this model they used an existing analytical equation for electric field for calculating the square of the magnitude of electric field.

Neculae *et al.* [30] carried out a numerical study of the trajectory of nanoparticles subjected to DEP, both pDEP and nDEP, in a continuous flow microfluidic device with IDT electrodes. The electric potential inside the microchannel is determined numerically. This is followed by the calculation of the nanoparticle trajectory by equating the forces associated with drag and DEP; the force due to DEP is approximated using a mathematical expression to simplify the calculation. The authors did not consider the influence of forces due to inertial, gravity and buoyancy. In addition, they observed that a specific nanoparticle, when subjected to nDEP, translated towards the same final location irrespective of its initial location along the height of the microchannel. Lam *et al.* [25] developed a three dimensional model of the trajectory of cells in a microfluidic device employing DEP for purposes of sorting cells; the model is numerically solved and experimentally validated. The work in [5], used a microfluidic device that employs interdigitated electrodes, on the bottom surface of the microchannel, for separation of cancer cells from blood.

To overcome the above-mentioned inaccuracy limitations of simulations, formal methods have been proposed as a viable solution[20]. They are primarily based on computer-based mathematical analysis methods to model and analyse the given system. A lot of work has been done in the domain of analyzing heathcare systems

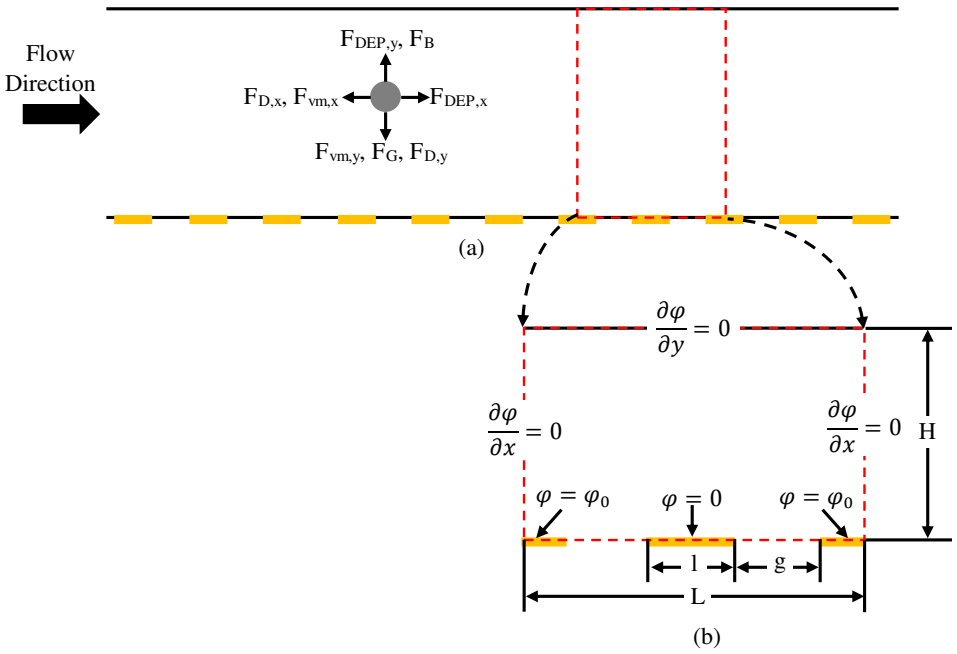

FIG. 3.1. *(a) Schematic of a section of the microchannel embedded with electrodes and forces acting on the microparticle; dashed line represents the repeating unit with respect to the electrodes; (b) detailed schematic of repeating unit with boundary conditions.*

using formal methods. Some notable examples include the verification of electrocardiogram (ECG) biosensors in event-B [2, 1]. The work is then extended to formalize the rules that reflects the construction of the ECG wave specifications [3, 4]. In addition, reliability analysis of FHIR standard based e-health system was addressed in [31, 32]. Other works include the verification of software components in medical devices [6, 16] and [29, 15], ambient assisted systems [8] or healthcare requirements [17] and the verification of collaborative and agent based workflows in healthcare [9, 21]. Other work related to managing medical wrokflow was presented in [28] and [12].

Medical devices are considered critical, since faults and errors in the medical system may lead to loss of lives, and in the best cases, loss of money and reputations [18]. To the best knowledge of the authors, this work presents the only effort at dynamic modeling of the trajectory of microparticles in a microdevices at high level of abstraction. The model presented in this work includes all forces relevant to the translation of microparticles in a microdevice, including that due to inertia, drag, DEP, virtual mass, gravity and buoyancy. In contrast to a static model a dynamic model is necessary for relating the time duration associated with the blood cell to reach the steady state position as well as the corresponding axial displacement. Moreover, the presented model can be used for parametric study of the microdevices with different positions of electrodes, which can be beneficial to designers of such microdevice.

3. Specification of Blood Cell Separation Device. Existing microparticles separation techniques are usually validated through a set of experimental data, and then results are compared to the theoretical model. In previous work, we used a microfluidic device that employs interdigitated electrodes, on the bottom surface of the microchannel, for separation of microparticles. We have also derived mathematical models for modeling movement particles in microchannels under the influence of DEP. Figure 3.1 represents the schematic of the microchannel considered in this work, where the IDT electrodes are located on the bottom surface of the microchannel. Under steady state conditions, the electric field and electric potential inside this repeating unit are provided by Khoshmanesh *et al.* 2011 [23] and Zhang *et al.* 2010 [33]. The system specifications assumes

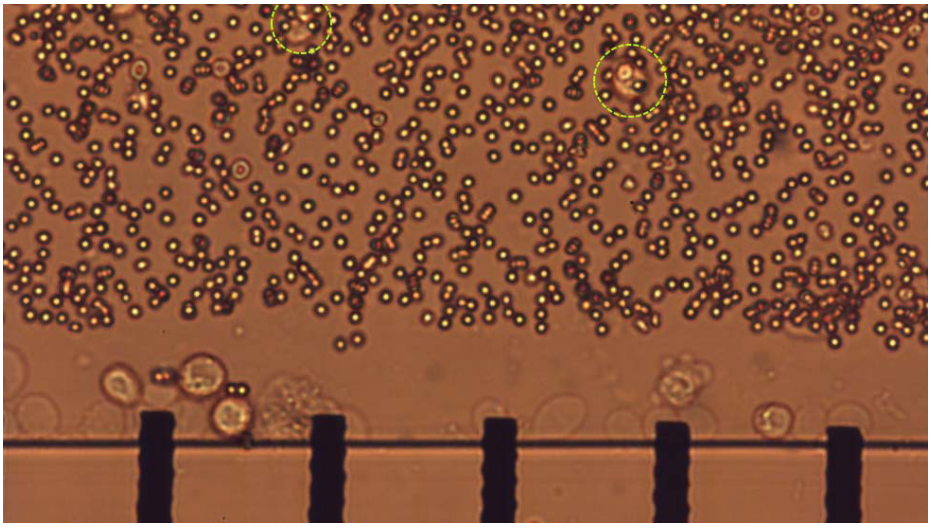

FIG. 3.2. *Blood cell separation image from microdevice shows that certain cancer cells could not be captured.*

that there are no electric charges inside the microchannel. The force due to DEP depends on the gradient of the Electric field and thus the need for non-uniform electric field. The force due to DEP also depends on the radius and electrical properties of the microparticles, the electrical properties of the medium and the applied frequency. The forces in Figure 3.1 are defined as drag F_D, DEP force F_{DEP}, virtual mass force F_{vm}, gravity force F_G and buoyancy force F_B.

Several assumptions were considered in this model, most were were initially provided by Loth (2000) [27]. First, blood cell particles are assumed to be spherical and rigid. It is also assumed that there is only one way coupling between particles and the medium as well as between particles and the electric potential. The particles are also assumed to be much smaller than the depth of the microchannel. There are no interactions between different particles, and no interactions between particles and the wall. Finally, the microparticle is not subjected to rotation about its axis while in transition.

According to Figure 3.1, a particle flows in the blood is affected by eight different forces. Some of these forces are of constant value, such as, F_G, other forces are imposed by the fluid flow, such as F_{vm}. The main force that will be used to guide the particle into the separation path is enforced through F_{DEP}. In our formal analysis, we assume that F_{DEP} is controlled by the separation device, and the rest are controlled by other factors, such as blood flow and location of the blood cell particle. In the next section, we provide formal modeling and analysis for the separation system.

Figure 3.2 shows a view of separated blood cell from the flow. We observed that some infected blood cells could not be captured in the separation process. Therefore, in the next step, we intend to conduct performance analysis on the system, that will help providing statistical information about the ability of the microdevice to capture infected cells. This can help in improving the performance of the microdevice by changing certain design parameters such as Electric field strength, frequency or electric cathode position and dimensions.

4. Formal Analysis of Microparticle Separation Device. Formal methods has proved to provide a complete coverage, and are becoming fundamental for the certification of such different types of systems. Model checking [7] or property checking is a formal verification technique where we check exhaustively and automatically whether a model of a system meets a given specification. Model checking examines all possible system states in a brute-force manner in order to show that a given system model truly satisfies a certain property. The main drawback of model checking approach is the limited size of number of system states that can be checked, therefore, abstraction methods are used to enable the verification of complex and large systems. In this paper we use the NuSMV model checker, which provides cutting-edge formal verification methods based on optimized techniques. It supports both temporal model checking including CTL and LTL temporal logics,

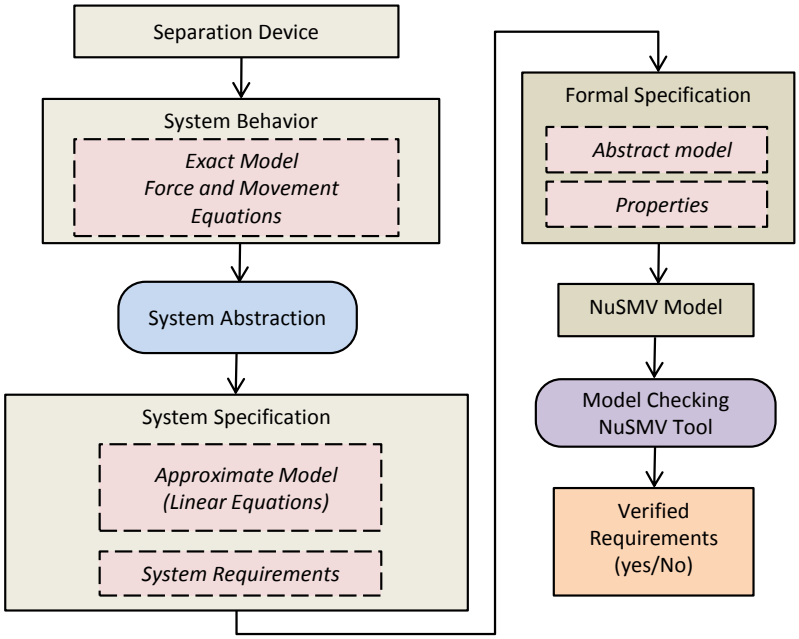

FIG. 4.1. *Separation Device Formal Verification Methodology*

and safety assessment, and has been used in several industrial contexts. Therefore, we will use NuSMV in order to model and verify the microparticle separation device.

Figure 4.1 illustrates the verification method for blood cell separation systems, where the behavior of the given system is usually described using an exact model with a set of system equations that describes particle movement and applied forces. In order to conduct formal reliability analysis of such a system, we first apply abstraction in order to simplify the system behavior. This results in a linear model of the system with a set of system requirement to be satisfied. It shall be noted here that system approximation is not intended to be used for design purposes, but only for the transformation of the system into a model that can be formally analyzed. Then, a NuSMV model is obtained, along with the desired system properties. The underlying verification tool is used in order to validate whether the requirement is satisfied or not.

In order to be able to describe the system under verification using NuSMV language, the system needs to be described as a transition based system, where variables are abstracted within finite integer ranges. This abstraction should be in conformance with the above system specifications. The blood cell separation system is described using several state variables that represent the particle behavior and characteristics including, its position, speed and forces that affect its movement. In fact, all variables are normalized with regard to the formal analysis model. First we define the set of ranges for variables of the blood cell septation system in NuSMV as shown below, where $MAXF1$, for instance, represents the upper bound of $FDEp$ force in both x and y directions.

```
MODULE main
VAR
  FDEPy : 0.. MAXF1;      FDEPx : 0.. MAXF1;
  Fvmx  : 0.. MAXF2;      Fvmy  : 0.. MAXF2;
  FDx   : 0.. MAXF3;      FDy   : 0.. MAXF3;
  posx  : 0.. MAXPx;      posy  : 0.. MAXPy;
  FB    : 0.. MAXF4;      PSx   : 0.. MAXSx;
```

Next, we model the state variables of the separation device. First we show how F_{DEP_x} and F_{DEP_y} are updated by changing the force level incrementally or detrimentally according to the microparticle movement. This models the application of Electrical field on the fluid flow, where value of the electrical field change according to the distance inside the fliud device.

```
next(FDEPy) := case
 (posx > POSxT & posy < TARyL & FDEPy < MAXF1 - 1):
       FDEPy + 2;
 (posx > POSxT & posy < TARyL ) : MAXF1;
 (posy < TARyL & FDEPy < MAXF1) : FDEPy + 1;
 (posx > POSxT & posy > TARyH & FDEPy > 2):
       FDEPy - 3;
 (posx > POSxT & posy > TARyH ) : 0;
 (posy > TARyH & FDEPy > 0)     : FDEPy - 1;
 (FDEPy < MAXF1) : FDEPy + 1;
 TRUE            : FDEPy;
esac;

next(FDEPx) := case
 (posy >= TARyL &  posy <= TARyH) : FDEPx;
 ((posy < TARyL |  posy <= TARyH) & posx > POSxT &
       FDEPx > 2) : FDEPx - 2;
 ((posy < TARyL |  posy <= TARyH) & FDEPx > 0) :
                    FDEPx - 1;
 (FDEPx > MAXF1 / 2) : FDEPx - 1;
 TRUE            : FDEPx;
esac;
```

Next, we show how the particle speed in both directions, x and y are calculated based on the total forces enforced on the particle, where C represent a constant related to the particle mass and force normalization.

```
next(PSx) := case
 (PSx + (FDEPx - Fvmx - FDx)*C) < MAXSx &
     (PSx + (FDEPx - Fvmx - FDx)*C) > 0 :
              PSx + (FDEPx - Fvmx - FDx)*C;
 (PSx + (FDEPx - Fvmx - FDx)*C) >= MAXSx:
             MAXSx;
 (PSx + (FDEPx - Fvmx - FDx)*C) <= 0 : 0;
 TRUE          : PSx;
esac;

next(PSy) := case
 (PSy + (FDEPy + FB - Fvmy - FDy - FG)*C) < MAXSy &
   ((FDEPy + FB - Fvmy - FDy - FG)*C) > 0 :
            PSy + (FDEPy + FB - Fvmy - FDy - FG)*1;
 (PSy + (FDEPy + FB - Fvmy - FDy - FG)*C) >= MAXSy:
            MAXSy;
 (PSy + (FDEPy + FB - Fvmy - FDy - FG)*C) <= 0 : 0;
 TRUE          : PSy;
esac;
```

Next, we show how the particle coordinates are calculated based on the speed of the particle in both directions, where DX represent the difference in distance from previous location, and is equal to particle speed multiplied by time unit.

```
next(posx) := case
  (posx + DX < MAXPx & posx + DX > 0) : posx + DX;
  posx + DX >= MAXPx  : MAXPx;
  TRUE          : 0;
esac;

 next(posy) := case
  (posy + DY < MAXPy & posy + DY > 0) : posy + DY;
  posy + DY >= MAXPy  : MAXPy;
  TRUE          : 0;
 esac;
```

In order to validate the model of the particle movement considered in this work, we formalize a property about particle separation in the microdevice as follows:

Property. *The microparticle will eventually move in the* x *direction under the application of a positive electric field. The particle will be successfully separated in it hits the target x coordinate between upper threshold y_h and*

lower threshold $y - l$ on the y-coordinate. This property is modeled in NuSMV as follows:

```
SPEC AG((posx = TARx) ->   posy >= TARyL & posy <= TARyH)
```

In order to conduct analysis on the microdevice, we assumed discrete sets of possible values for particle parameters, and we also assumed that all parameters are normalized to one. Table 4.1 below shows the results of the analysis of microparticle movement using different parameters for particles and results of verification, where separation is successful or unsuccessful. The value $True$ illustrates that the particle with the given parameters will be separated successfully, while the value $False$ states the opposite. P_{y_0} represents particle initial position in the y-coordinate, P_{x_0} is assumed to be 0 for all particles, since it is the beginning of the device microchannel where the fluid flows. PS_{x_0} and PS_{y_0} represents particle initial speed in x and y coordinates, respectively. Table 4.2 shows the results for different location of the separation unit. The results shows that the separation success depends on several issues, first the location of the separation unit, second the particle initial position and speed in both directions. In addition, the results show that separation will be unsuccessful only if particles enter the flow at specific positions with certain initial speeds. While the used model checking framework can show correctness of the property for all given values, it cannot be used to provide statistical analysis about the behavior of the microdevice. This is an open issue that can be addressed at later stage of the work.

TABLE 4.1
Analysis of particle separation at first location

P_{y_0}	PS_{x_0}	PS_{y_0}	Separation
$\{0, 0.01, \ldots, 0.60\}$	$\{0, 0.1, \ldots, 1\}$	$\{-1.0, -0.8, \ldots 1.0\}$	True
$\{0.61, 0.62, \ldots, 0.80\}$	$\{0, 0.2\}$	$\{-1.0, -0.8, \ldots 1\}$	False
$\{0.61, 0.62, \ldots 0.80\}$	$\{0.3, 0.4, \ldots, 1\}$	$\{-1.0, -0.8, \ldots, 1.0\}$	True
$\{0.81, 0.82, \ldots, 1\}$	$\{0.0, 0.1\}$	$\{-1.0, -0.8, \ldots, 1.0\}$	True
$\{0.81, 0.82, \ldots, 1\}$	$\{0.2\}$	$\{-1.0, -0.8, \ldots, 0.8\}$	False
$\{0.81, 0.82, \ldots, 1\}$	$\{0.2\}$	$\{1.0\}$	True
$\{0.81, 0.82, \ldots, 1\}$	$\{0.3, 0.4, \ldots, 0.6\}$	$\{-1.0, -0.8, \ldots, 1.0\}$	True
$\{0.81, 0.82, \ldots, 1\}$	$\{0.7, 0.8, \ldots, 1.0\}$	$\{-1.0, -0.8, \ldots, 1.0\}$	True

TABLE 4.2
Analysis of particle separation at second location

P_{y_0}	PS_{x_0}	PS_{y_0}	Separation
$\{0, 0.01, \ldots, 1.0\}$	$\{0, 0.1\}$	$\{-1.0, -0.8, \ldots 1.0\}$	True
$\{0, 0.01, \ldots, 1.0\}$	$\{0.2\}$	$\{-1.0, -0.8, \ldots, 0.4\}$	False
$\{0, 0.01, \ldots, 1.0\}$	$\{0.2\}$	$\{0.6, 0.8, 1.0\}$	True
$\{0, 0.01, \ldots, 1.0\}$	$\{0.3, 0.4, \ldots, 0.7\}$	$\{-1.0, -0.8, \ldots, 1.0\}$	True
$\{0, 0.01, \ldots, 1.0\}$	$\{0.8\}$	$\{-1.0, -0.8, \ldots, 0.8\}$	True
$\{0, 0.01, \ldots, 0.2\}$	$\{0.8\}$	$\{-1.0\}$	False
$\{0.21, 0.22, \ldots, 1.0\}$	$\{0.8\}$	$\{-1.0\}$	True
$\{0, 0.01, \ldots, 1.0\}$	$\{0.9, 1.0\}$	$\{-1.0, -0.8, \ldots, 1.0\}$	True

5. Conclusion and Discussion. Existing microparticles separation techniques are used frequently within health domain for cancer cell separation in human blood. These techniques are usually validated through a set of experimental data, and then results are compared to the theoretical model. However, there is a lack of modeling the behavior of these particles within microfluidic device at high level of abstraction, where the movement of cells and particles in microchannels under the influence of DEP is affected by several factors and forces such as inertia, gravity, buoyancy, dielectrophoresis and virtual mass. In this work, we formalize the movement of microparticles under DEP in a microfluidic device using NuSMV model checker in order to

provide formal analysis for the microdevice. We first modeled the system specifications including all types of forces in NuSMV language. This is achieved by modeling the dynamic behavior of the microdevice as a state based system. We then formalized the correct separation of blood cells as a CTL property. Finally, we used NuSMV tool to analyze the behavior of the system for different sets of parameters. The results show that the microdevice will successfully separate large portion of particles, while at the same time, there will be specific scenarios where cells with particular parameters might not be separated successfully.

As a future work, we intend to extend the work using probabilistic model checking which can provide statistical analysis about the behavior of the microdevice. This model can provide early understanding of the behavior of the system at high level of abstraction, and therefore can help to validate several aspects of the design which is beneficial to designers of similar microdevices at early stages of the design process.

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