A SIMULATION ANALYSIS OF NANOMACHINES COMMUNICATION IN BLOOD VESSELS

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OUTLINE

• Introduction

• The biological scenario

• Design of new features of the simulation framework

• Analysis of simulations results

• Conclusions
INTRODUCTION

The general simulation framework

Previous work
Analysis of the Immune System communication scenario

Current research
Analysis of the Blood Vessels communication scenario

Main Features
- Discrete Time Steps
- Nano Objects modeling
- Fine grained approach
  - Positions on 3D space
  - Check Collisions
- Customized output
- 3D animated views
THE BIOLOGICAL SCENARIO

Blood cells as nano-nodes

Cellular interactions through the **cytokines release**

The assimilation of a particular type of cytokine can trigger **different behaviors** in the receiving cells

Circulatory system
Analysis of the communications between **Endothelial Cells** and **Platelets**

The Endothelial cells covers the **inner layer** of the blood and lymphatic vessels

It is the **interface** between circulating blood and lymph in the lumen and the rest of the vessel wall
THE BIOLOGICAL SCENARIO

Study of the “response-to-injury” theory

Damaged blood vessel (Endothelial cell injury)

Circulating Platelets are recruited to the site of injury

Platelets release molecules (sCD40L)

Activation of the Endothelial Cells

Exposure of adhesion molecules (VCAM) and recruitment of macrophages and other white blood cells

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Simulate a system of communication between nanomachines inside blood vessels.

- Information is represented by pulses of carriers released by a single transmitter (response to a single pulse).

- There is a vast literature about the propagation of nanoparticles in the blood vessels.

- A recent study that evaluates the presence of red blood cells inside the vessels invalidate previous studies. So, from the communication-network point of view, previous approaches are rough.

- It's need to perform simulations taking into account the presence of blood cells within the blood vessels.
MOTIVATIONS

Vast literature about the **propagation** of nanoparticles in the **blood vessels**


A recent study that evaluates the presence of red blood cells inside the vessels invalidate previous studies.

From the communication-network point of view:

Previous approaches:
- Coarse\(^{(1)}\)

A recent study:
- Take into account the presence of blood cells in the blood vessels\(^{(2)}\)

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(1) Sachin Kadloor, Raviraj S. Adve, and Andrew W. Eckford, “Molecular Communication Using Brownian Motion with Drift”, IEEE TRANSACTIONS ON NANOBIOSCIENCE, VOL. 11, NO. 2, JUNE 2012

Particle distribution profile at time $t = 7.5$ s. (A) NPs with RBCs case; (B) NPs without RBCs.

NEW FEATURES OF THE FRAMEWORK

General Framework

New features

Abstract Domain

Cylindric Domain

Cubic Domain

Specific simulator classes

NanoObj

NodeObj

CarrierObj

Blood Cells

sCD40L Cytokine

Mobility Model

Flow Model
1. DESIGN OF NEW SW DOMAINS

Two type of new Domains

- Cylindrical
  - Blood Vessels
- Cubic
  - Endothelial Cells

Hierarchical placement
Customized Mobility Model
Customized Collisions Handling for inner and outer NanoObjs

Endothelial cells
1. PLACEMENT OF THE SW ENDOTHELIAL CELLS

1. 1000 receptors are disposed on the exposed side of every cube.

2. The external surface of the cylinder is covered by cubes.

3. Each receptor is projected on the curvilinear surface of the cylinder.

Endothelial cell

Blood vessel
2. A NEW SW MOBILITY MODEL – THE FLOW MODEL

Fluid Mechanics

Fluid Statics

Fluid Dynamics

Newtonian Fluids

Navier-Stokes

Velocity field (or flow field)

Drag Force

If sufficiently dense to be a continuum

The viscosity depends linearly by velocity gradients and pressure
2. A SW NEW MOBILITY MODEL – THE FLOW MODEL

Turbulent Flow regime

- High Reynolds Number

Laminar Flow regime

- Low Reynolds Number

Hagen-Poiseuille Flow

Parabolic Velocity Profile

\[ v(r) = \frac{1}{4\eta} \frac{\Delta P}{L} (R^2 - r^2) \]

\( \eta \) = dynamic viscosity, \( \Delta P \) = pressure drop, 
\( L \) = pipe length, \( R \) = pipe radius, \( r \) = distance from pipe center
2. A NEW MOBILITY MODEL – THE FLOW MODEL

Drag force exerted on a particle

\[ F_d = 6\pi \eta a v_p \]

\( \eta = \text{viscosity}, \ a = \text{particles radius}, \ v_p = \text{relative velocity} \)

**Small molecules (Carriers)**

The **final velocity** is the sum of two contributions:
1. Hagen-Poiseuille flow
2. Effective longitudinal diffusion \( D_{eff} \) \(^{(1)}\)

**Blood cells (Nodes)**

The **final velocity** is the sum of two contributions:
1. Hagen-Poiseuille flow
2. Brownian motion

**Along the longitudinal component of the flow**

\[ D_{eff} = \frac{k_B T}{6\pi \eta a} + \frac{R_c^2 u(r)^2}{8k_B T \pi \eta a} \]

- Brownian
- convective

**Along the cross component of the flow**

\[ D_{eff} = \frac{k_B T}{6\pi \eta a} \]

Brownian

\( k_B = \text{Boltzmann Constant}, \ T = \text{temperature}, \ \eta = \text{viscosity}, \ a = \text{particles radius}, \ Re = \text{pipe radius}, \ u(r) = \text{fluid velocity} \)

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\(^{(1)}\) P. Decuzzi, F. Causa, M. Ferrari, P.A. Netti, “The Effective Dispersion of Nanovectors Within the Tumor Microvasculature”, Annals of Biomedical Engineering, Vol. 34, No. 4, April, DOI: 10.1007/s10439-005-9072-6
3. DESIGN OF THE NEW NANO OBJECTS

New NanoObjects to model the Blood Cells and the released molecules

Transmitter nodes
(release a burst of 1000 carriers)

Passive nodes

Can be receiver nodes...

Platelets
Red Blood Cells
Macrophages

Blood Cells

NanoObj
NodeObj
CarrierObj

sCD40L Cytokine
**SIMULATIONS SETUP**

### Venule

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>length</td>
<td>2 mm</td>
</tr>
<tr>
<td>diameter</td>
<td>60 μm</td>
</tr>
<tr>
<td>mean velocity</td>
<td>0.5 mm/s</td>
</tr>
<tr>
<td>viscosity</td>
<td>0.0013 Pa·s</td>
</tr>
<tr>
<td>temperature</td>
<td>310°K</td>
</tr>
<tr>
<td>Red Cells concentration</td>
<td>$4 \cdot 10^6$ mm$^3$</td>
</tr>
<tr>
<td>Macrophages concentration</td>
<td>$4 \cdot 10^3$ mm$^3$</td>
</tr>
<tr>
<td>Platelets concentration</td>
<td>$2 \cdot 10^5$ mm$^3$</td>
</tr>
</tbody>
</table>

### Blood cells & Endothelial cells

<table>
<thead>
<tr>
<th>Component</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red Blood Cell Radius</td>
<td>3.5 μm</td>
</tr>
<tr>
<td>Macrophage Radius</td>
<td>5 μm</td>
</tr>
<tr>
<td>#Receptors</td>
<td>1000</td>
</tr>
<tr>
<td>Receptors Radius</td>
<td>4 nm</td>
</tr>
<tr>
<td>Platelets Radius</td>
<td>1 μm</td>
</tr>
<tr>
<td>#Receptors</td>
<td>1000</td>
</tr>
<tr>
<td>Receptors Radius</td>
<td>4 nm</td>
</tr>
<tr>
<td>Burst emission</td>
<td>1000</td>
</tr>
<tr>
<td>sCD40L Radius</td>
<td>1.75 nm</td>
</tr>
<tr>
<td>Endothelial cells side</td>
<td>15 μm</td>
</tr>
<tr>
<td>#Receptors</td>
<td>1000</td>
</tr>
<tr>
<td>Receptors Radius</td>
<td>4 nm</td>
</tr>
</tbody>
</table>
SIMULATIONS SETUP

Buffer volume

Creation volume

Active simulated volume

Boundary surface

Void volume

Create new blood cells with realistic concentration

Collisions handling on domain surface

Finalize the outgoing Nano Objects

A single Platelet as TX node
(carriers release after 2.5 s!)

Endothelial Cells as RX nodes
SIMULATIONS SETUP

\[ \bar{E} = (E_x, E_y, E_z) \]

\[ \bar{r} = (0, r, 0) \]

\[ \bar{E} = (\bar{E}_z + \bar{E}_r) \]

\[ \bar{E}_z = (0, 0, E_z) \]

\[ \varphi = \arccos \left( \frac{\bar{E}_r \cdot \bar{r}}{\|\bar{E}_r\| \cdot \|\bar{r}\|} \right) \]
**Emissions near vessel wall allows an higher number of assimilations**

**Emissions near the longitudinal axis allows to cover an higher area along the longitudinal distance**
LAST ACHIEVEMENTS: GRID COMPUTING

Cubes on:
- X-axis: 3
- Y-axis: 2
- Z-axis: 1

Overall simulation 3D space

Splitted simulation space

Parallel sub-simulations
LAST ACHIEVEMENTS: WHY GRID COMPUTING?

- Bigger simulations
- Large Volumes
- A very large amount of nano objects

Sharing of CPUs and Memory from multiple computers

Main criticities:

- Splitting algorithm
- Synchronization of the nodes of the grid
- Objects' transition between the grid nodes

- Performance loss
- Retain the objects uniqueness and their consistency
CONCLUSIONS

• We created a tool for the detailed simulation of molecular communications within the blood vessels focusing on a specific dyad receptor/ligand
FUTURE WORKS

• Assessment of results through in vivo experimentation in collaboration with a medical team of the University of Perugia that is making a research on atherothrombotic diseases.

• Grid performance evaluation and optimization