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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

Customization

Main Features

- ✓ *Discrete Time Steps*
- ✓ *Nano Objects modeling*
- ✓ *Fine grained approach*
  - *Positions on 3D space*
  - *Check Collisions*
- ✓ *Customized output*
- ✓ *3D animated views*

Previous work

Analysis of the **Immune System** communication scenario

Current research

Analysis of the **Blood Vessels** communication scenario

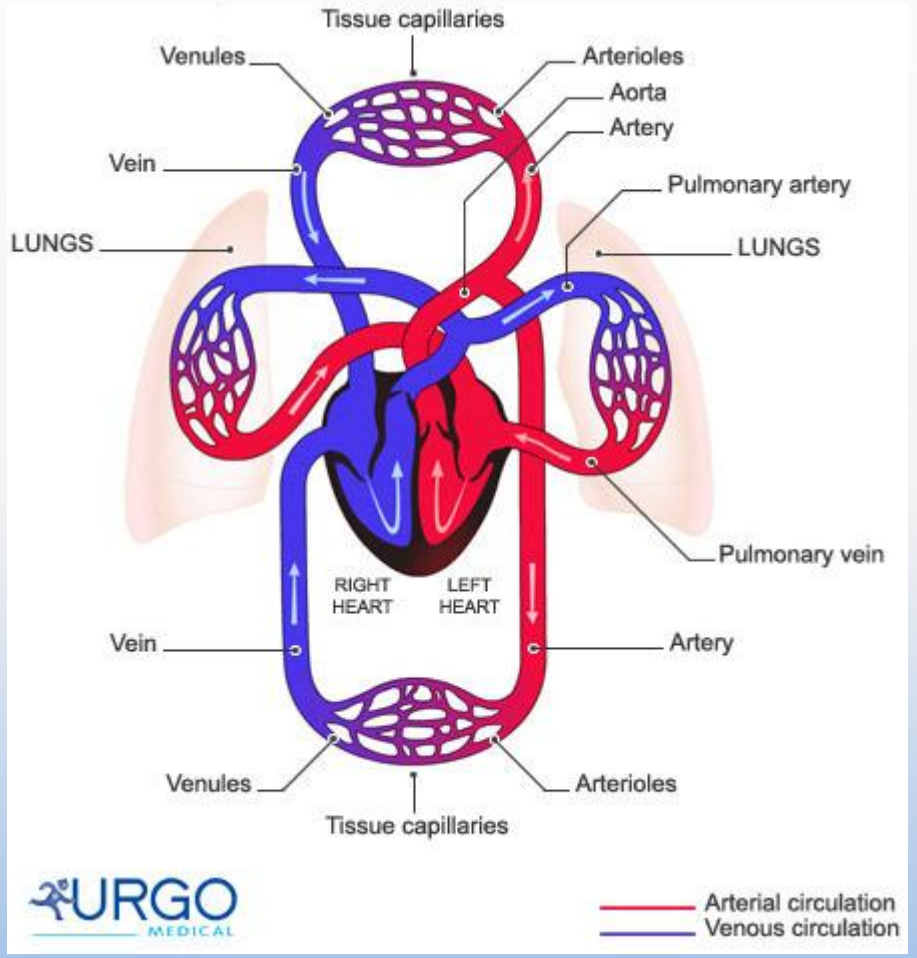
THE BIOLOGICAL SCENARIO

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

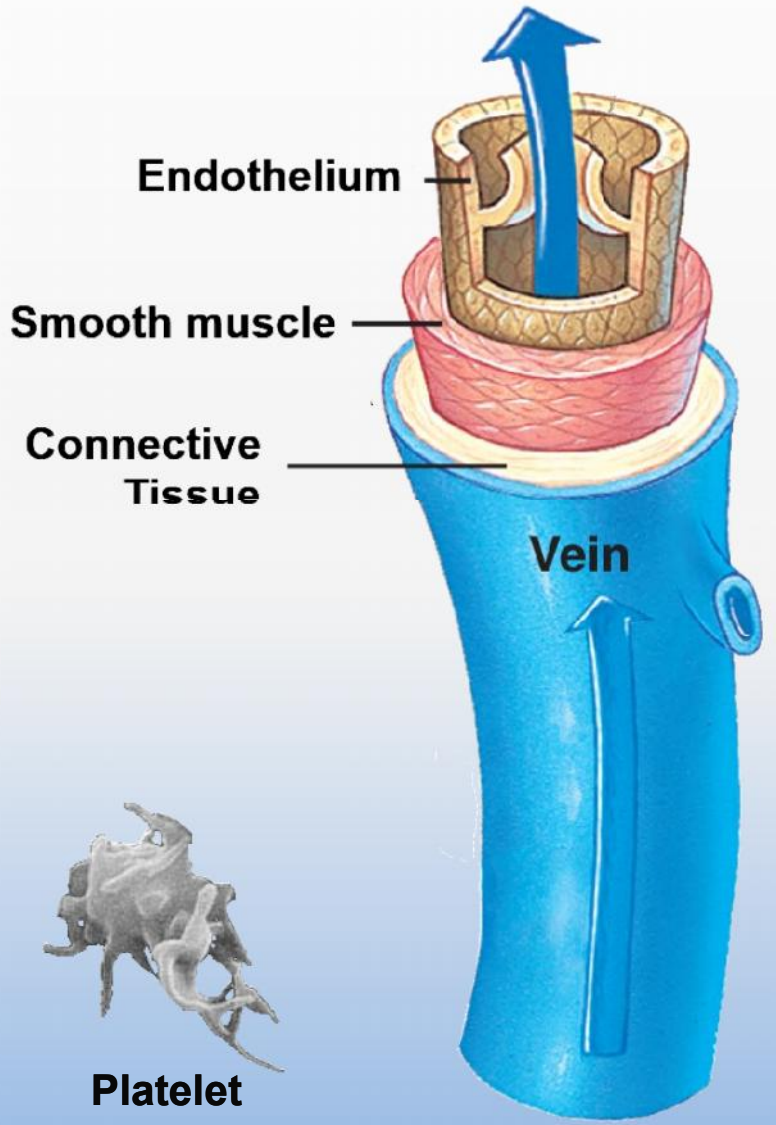


THE BIOLOGICAL SCENARIO

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

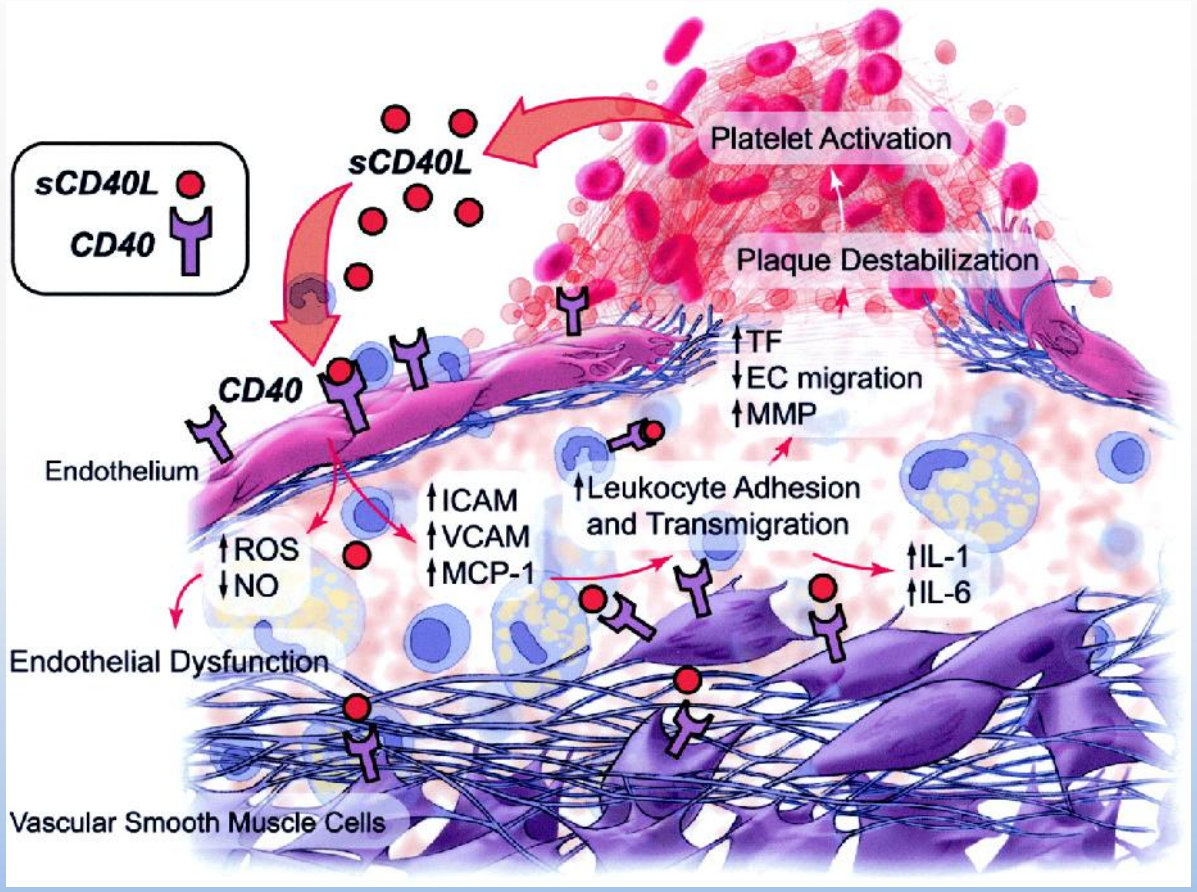
Damaged blood vessel (*Endothelial cell injury*)

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



Szmitko P E et al. Circulation 2003;108:1917-1923

MOTIVATIONS

Simulate a system of communication between nanomachines inside blood vessels

Moving Transmitters

vs

Static Receivers

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

MOTIVATIONS

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

1953

1956

1967

1970

2000

2006

2008

*[1] Geoffrey Taylor, "**Dispersion of Soluble Matter in Solvent Flowing Slowly through a Tube**", Proc. R. Soc. Lond. A 1953 219, 186-203, doi: 10.1098/rspa.1953.0139*

*[2] R. Aris, "**On the dispersion of a solute in a fluid flowing through a tube**", Proceedings of the Royal Society of London. Series A, Mathematical and Physical Sciences, Vol. 235, No. 1200. (Apr. 10, 1956), pp. 67-77.*

*[3] W. N. Gill, "**A note on the solution of transient dispersion problems**", Proc. R. Soc. Lond. A 298:335–339, 1967.*

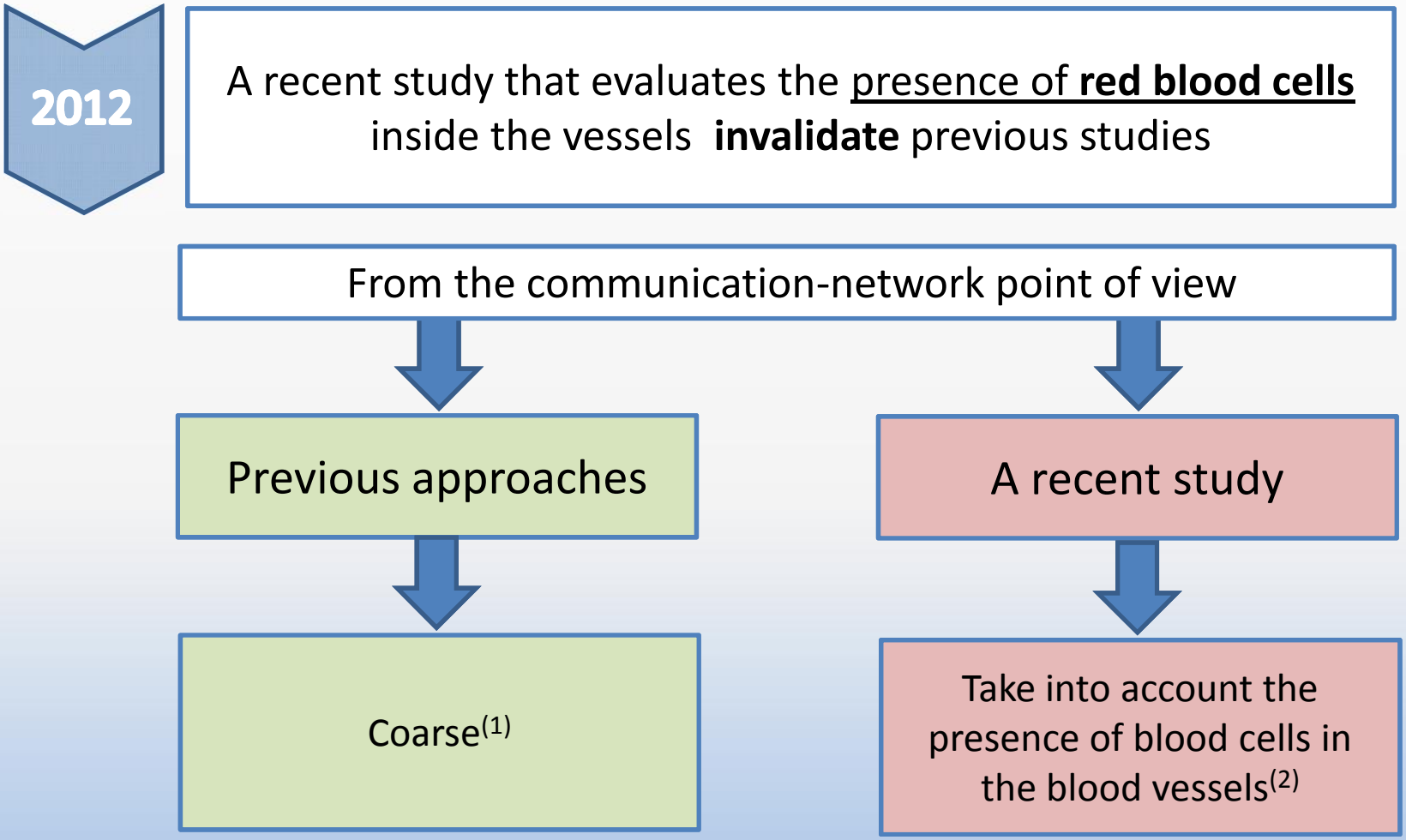
*[4] Gill, W. N., and R. Sankarasubramanian, "**Exact analysis of unsteady convective diffusion**", Proc. R. Soc. Lond. A 316:341–350, 1970.*

*[5] R. K. Dash, G. Jayaraman, and K. N. Metha, "**Shear Augmented Dispersion of a Solute in a Casson Fluid Flowing in a Conduit**", Annals of Biomedical Engineering, Vol. 28, pp. 373–385, 2000*

*[6] Decuzzi, P., F. Causa, M. Ferrari, and P. A. Netti. "**The effective dispersion of nanovectors within the tumor microvasculature**", Ann. Biomed. Eng. 34:633–641, 2006.*

*[7] F. Gentile, M. Ferrari, P. Decuzzi, "**The Transport of Nanoparticles in Blood Vessels: The Effect of Vessel Permeability and Blood Rheology**", Annals of Biomedical Engineering, Vol. 36, No. 2, pp. 254–261, February 2008.*

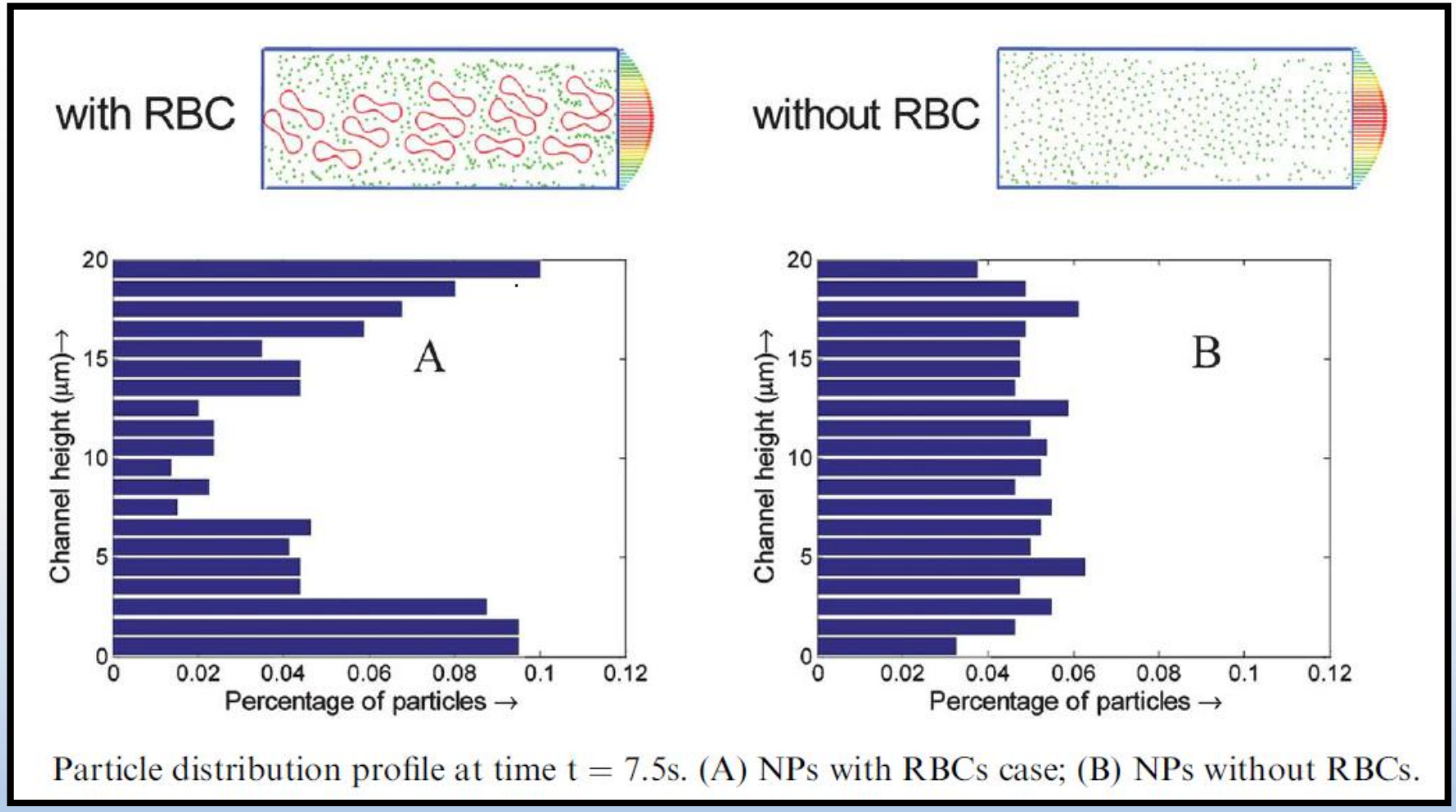
MOTIVATIONS



(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

(2) Jifu Tan, Antony Thomas, Yaling Liu, "Influence of red blood cells on nanoparticle targeted delivery in microcirculation", Soft Matter, The Royal Society of Chemistry 2012, DOI: 10.1039/c2sm06391c

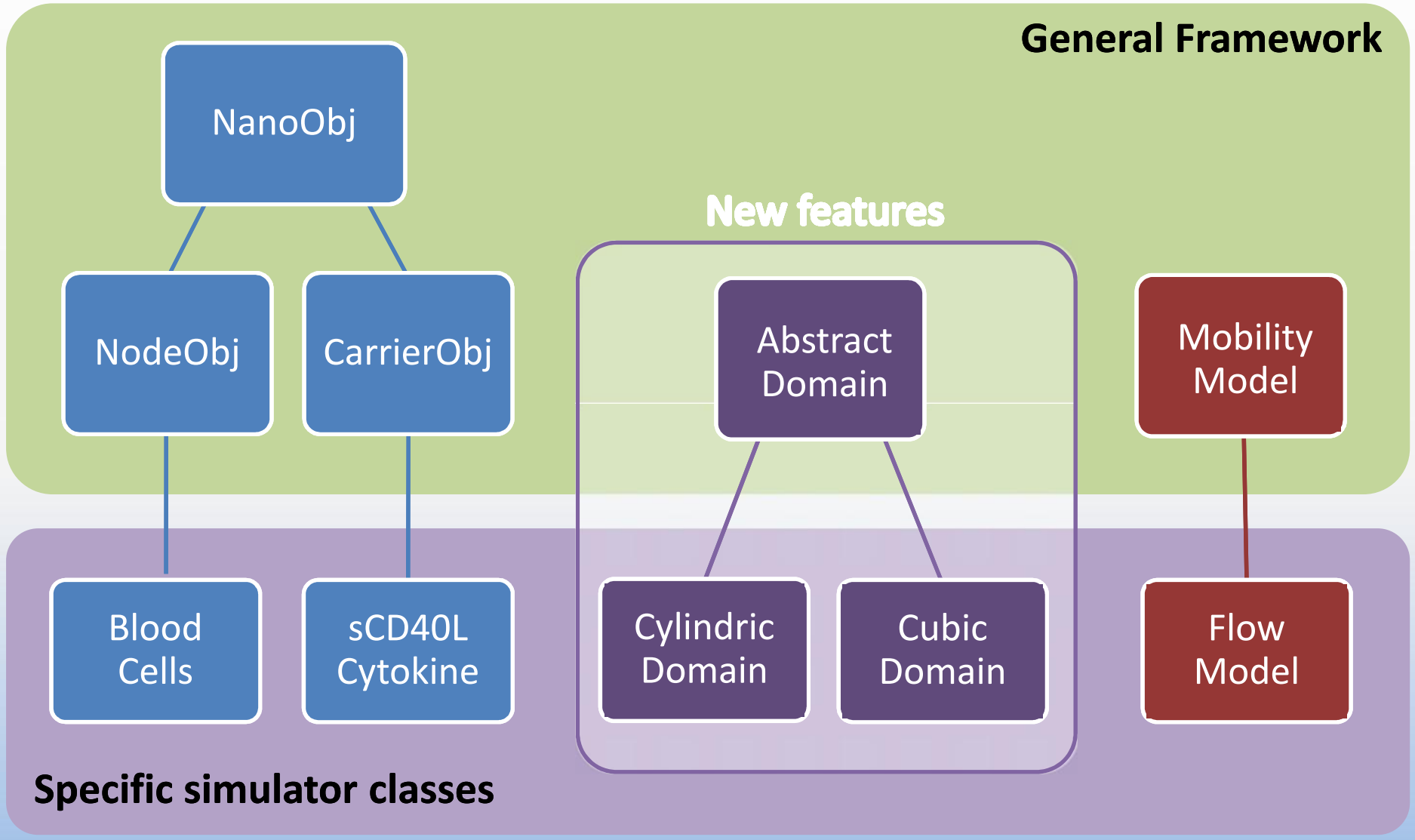
MOTIVATIONS



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

(*) Jifu Tan, Antony Thomas, Yaling Liu, "Influence of red blood cells on nanoparticle targeted delivery in microcirculation", Soft Matter, The Royal Society of Chemistry 2012, DOI: 10.1039/c2sm06391c

NEW FEATURES OF THE FRAMEWORK



1. DESIGN OF NEW SW DOMAINS

Two type of new **Domains**

Cylindrical

Blood Vessels

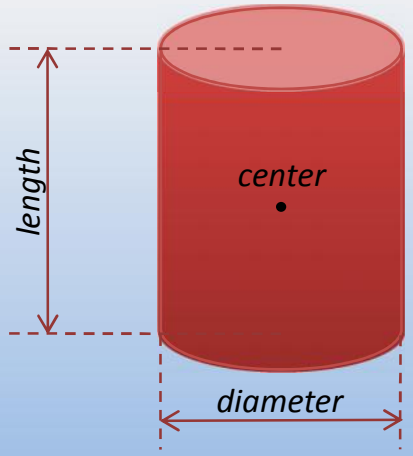
Hierarchical placement

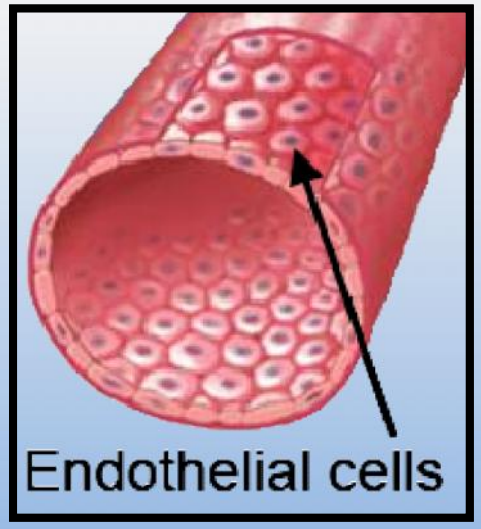
Customized **Mobility Model**

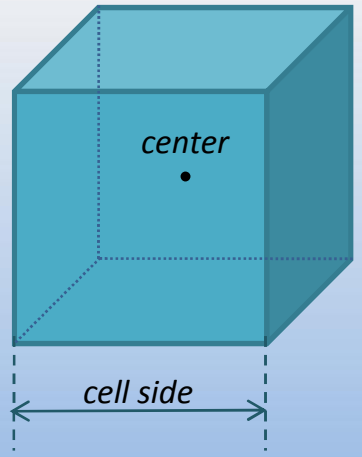
Customized **Collisions Handling** for inner and outer NanoObjs

Cubic

Endothelial Cells

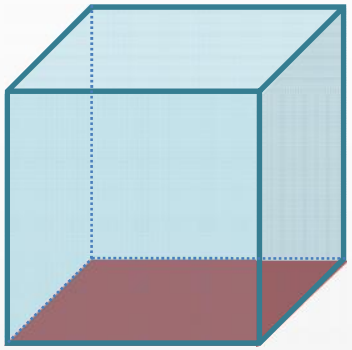






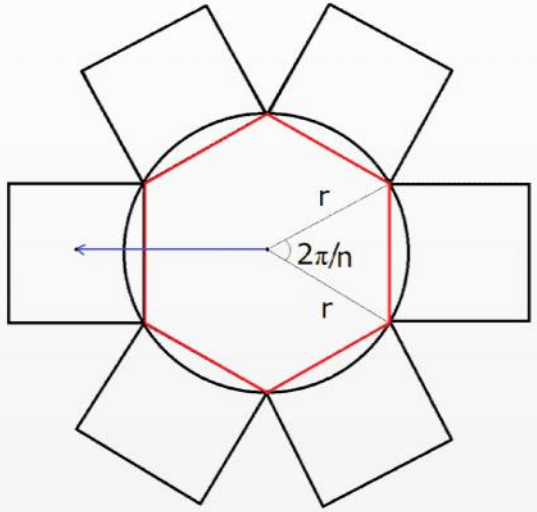
1. PLACEMENT OF THE SW ENDOTHELIAL CELLS

1



1000 receptors are disposed on the exposed side of every cube

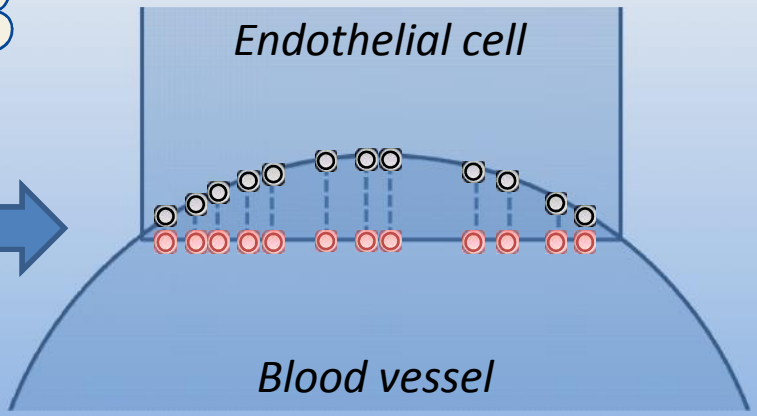
2



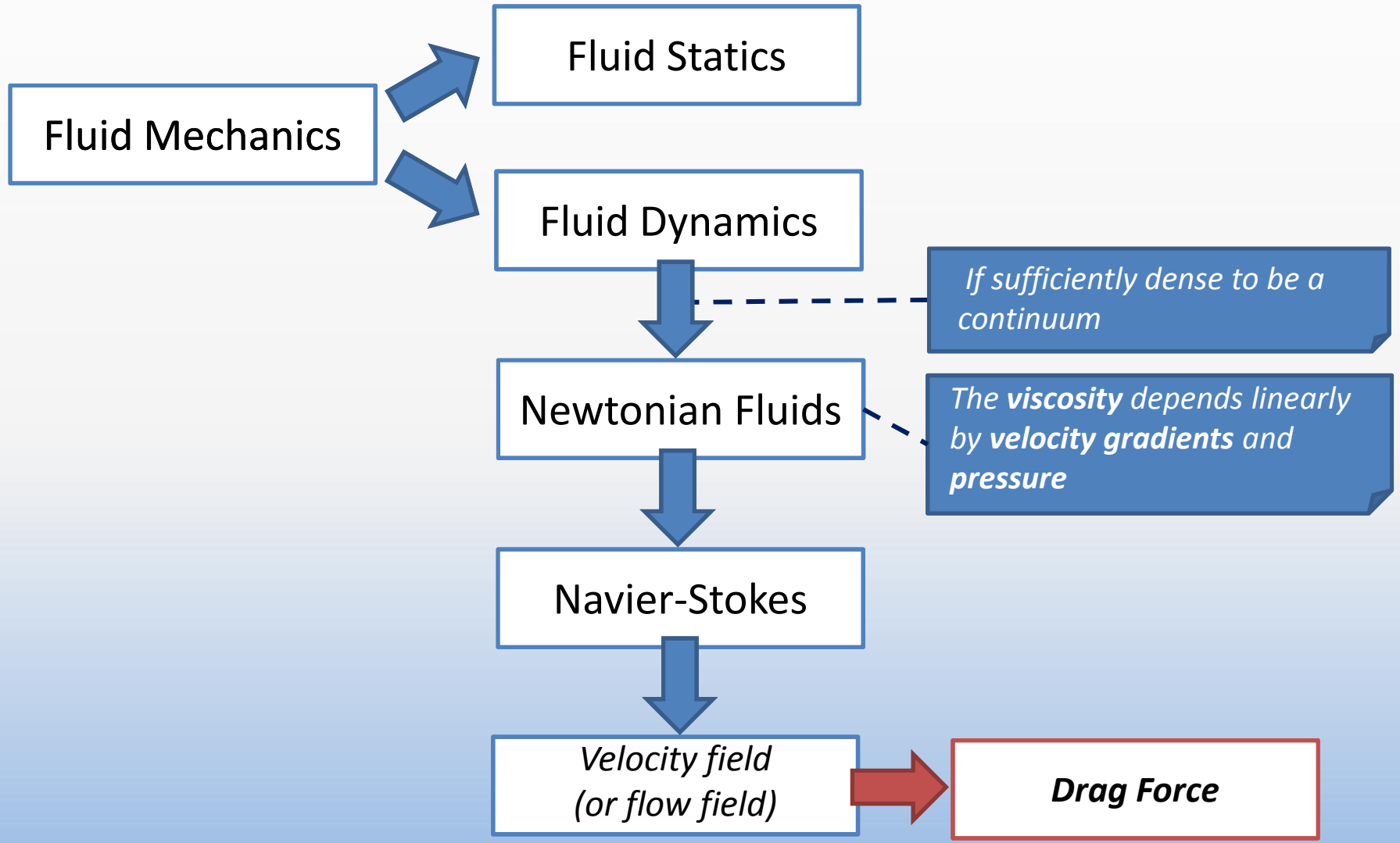
The external surface of the cylinder is **covered by cubes**

3

Each **receptor** is projected on the curvilinear surface of the cylinder



2. A NEW SW MOBILITY MODEL – THE FLOW MODEL



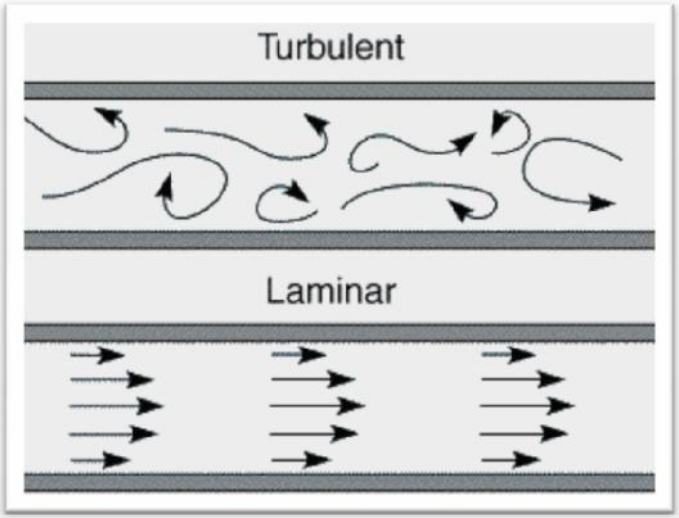
2. A SW NEW MOBILITY MODEL – THE FLOW MODEL

Turbulent Flow regime

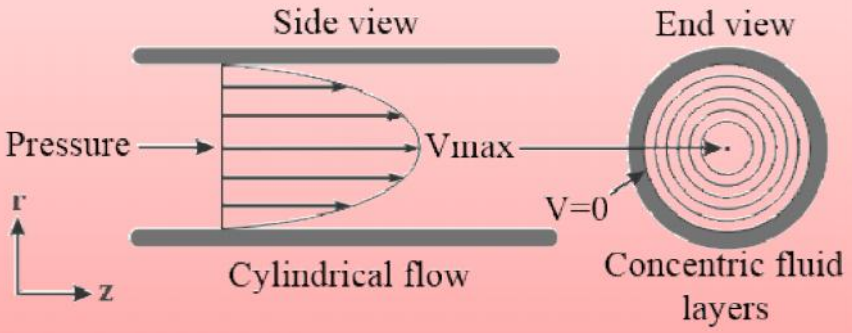
- *High Reynolds Number*

Laminar Flow regime

- *Low Reynolds Number*



Hagen-Poiseuille Flow



Parabolic Velocity Profile

$$v(r) = \frac{1}{4\eta}\frac{\triangle P}{L}(R^2 - r^2)$$

η = dynamic viscosity, $\triangle P$ = 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

$$F_d = 6\pi\eta a v_p$$

η = viscosity, a = particles radius, v_p = relative velocity

Small molecules (Carriers)

The **final velocity** is the sum of two contributions:

1. Hagen-Poiseuille flow
2. Effective longitudinal diffusion *Deff* [1]

Along the longitudinal component of the flow

$$D_{\text{eff}} = \underbrace{\frac{k_B T}{6\pi\eta a}}_{\text{Brownian}} + \underbrace{\frac{R_c^2 u(r)^2}{8 k_B T}\pi\eta a}_{\text{convective}}$$

Blood cells (Nodes)

The **final velocity** is the sum of two contributions:

1. Hagen-Poiseuille flow
2. Brownian motion

Along the cross component of the flow

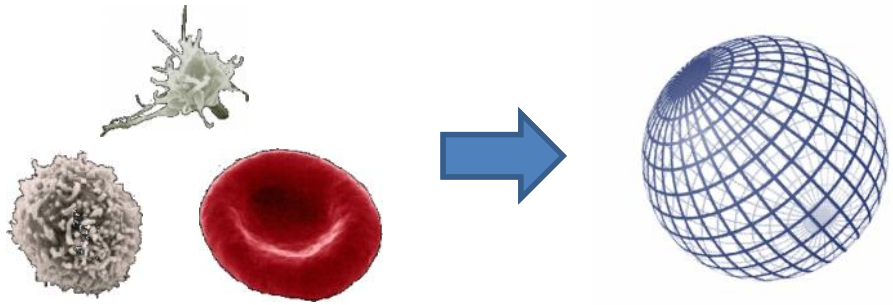
$$D_{\text{eff}} = \underbrace{\frac{k_B T}{6\pi\eta a}}_{\text{Brownian}}$$

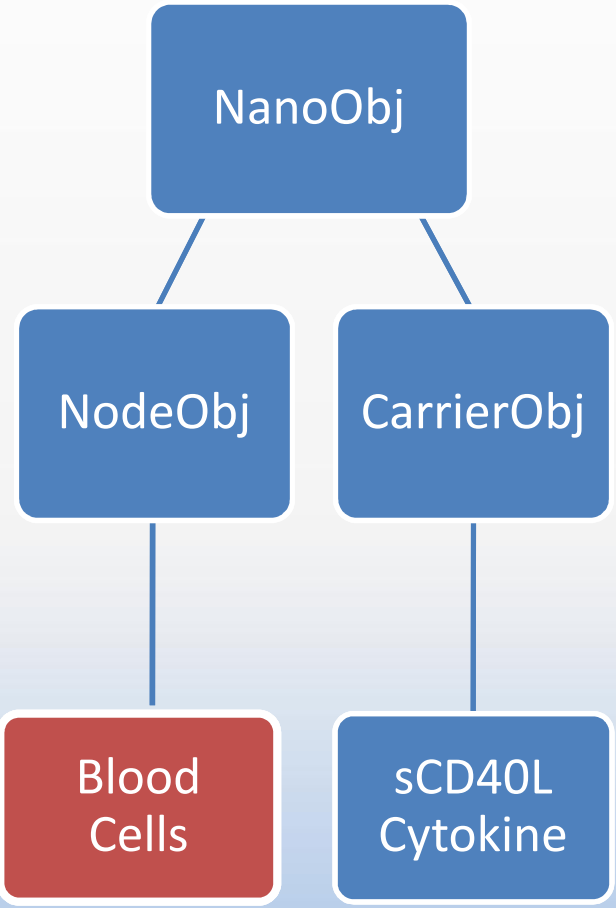
K_B = Boltzmann Constant, T = temperature, η = viscosity, a = particles radius, Re = pipe radius, u(r) = fluid velocity

(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



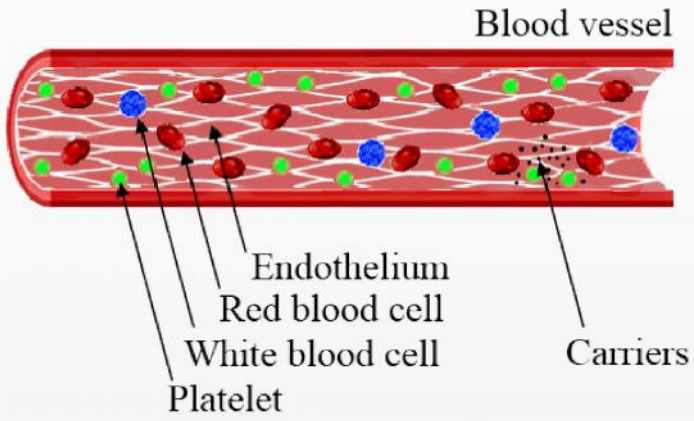


Transmitter nodes
(release a burst of 1000 carriers)

Passive nodes

Can be receiver nodes…

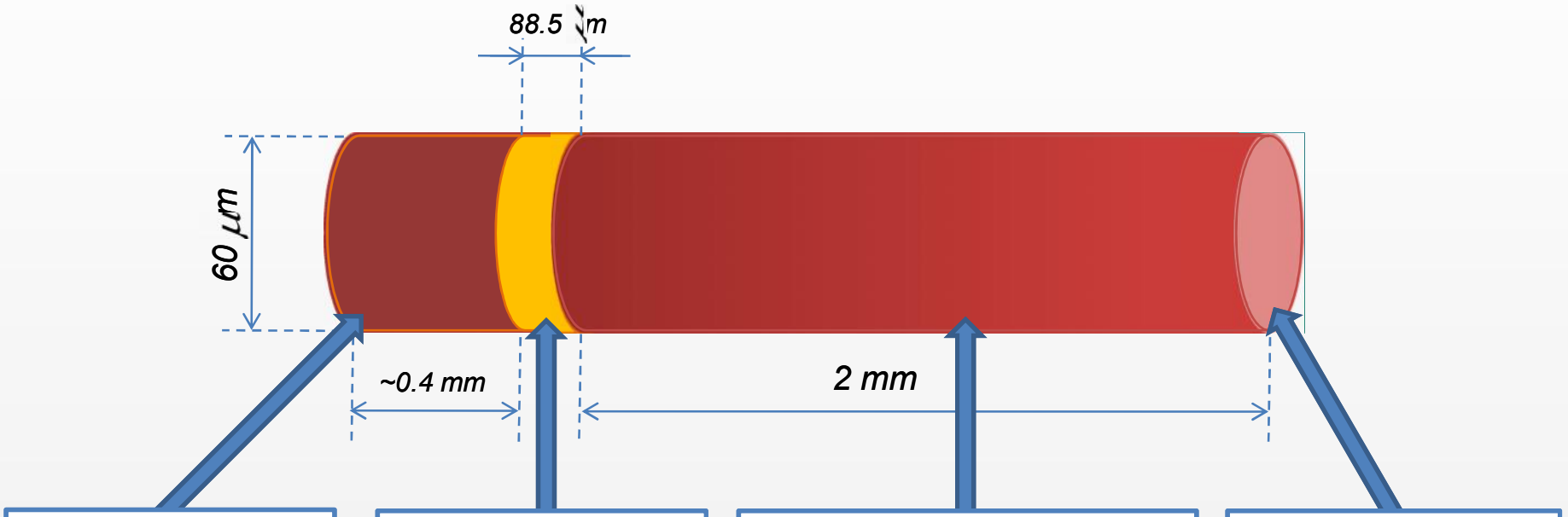
SIMULATIONS SETUP



Venule	
length	$2mm$
diameter	$60\mu m$
mean velocity	$0.5mm/s$
viscosity	$0.0013Pa \cdot s$
temperature	$310°K$
Red Cells concentration	$4 \cdot 10^6 mm^3$
Macrophages concentration	$4 \cdot 10^3 mm^3$
Platelets concentration	$2 \cdot 10^5 mm^3$

Blood cells & Endothelial cells	
Red Blood Cell Radius	$3.5\mu m$
Macrophage Radius	$5\mu m$
• ***#Receptors***	1000
• ***Receptors Radius***	$4nm$
Platelets Radius	$1\mu m$
• ***#Receptors***	1000
• ***Receptors Radius***	$4nm$
• ***Burst emission***	1000
sCD40L Radius	$1.75nm$
Endothelial cells side	$15\mu m$
• ***#Receptors***	1000
• ***Receptors Radius***	$4nm$

SIMULATIONS SETUP



Void volume

Create new blood cells with realistic concentration

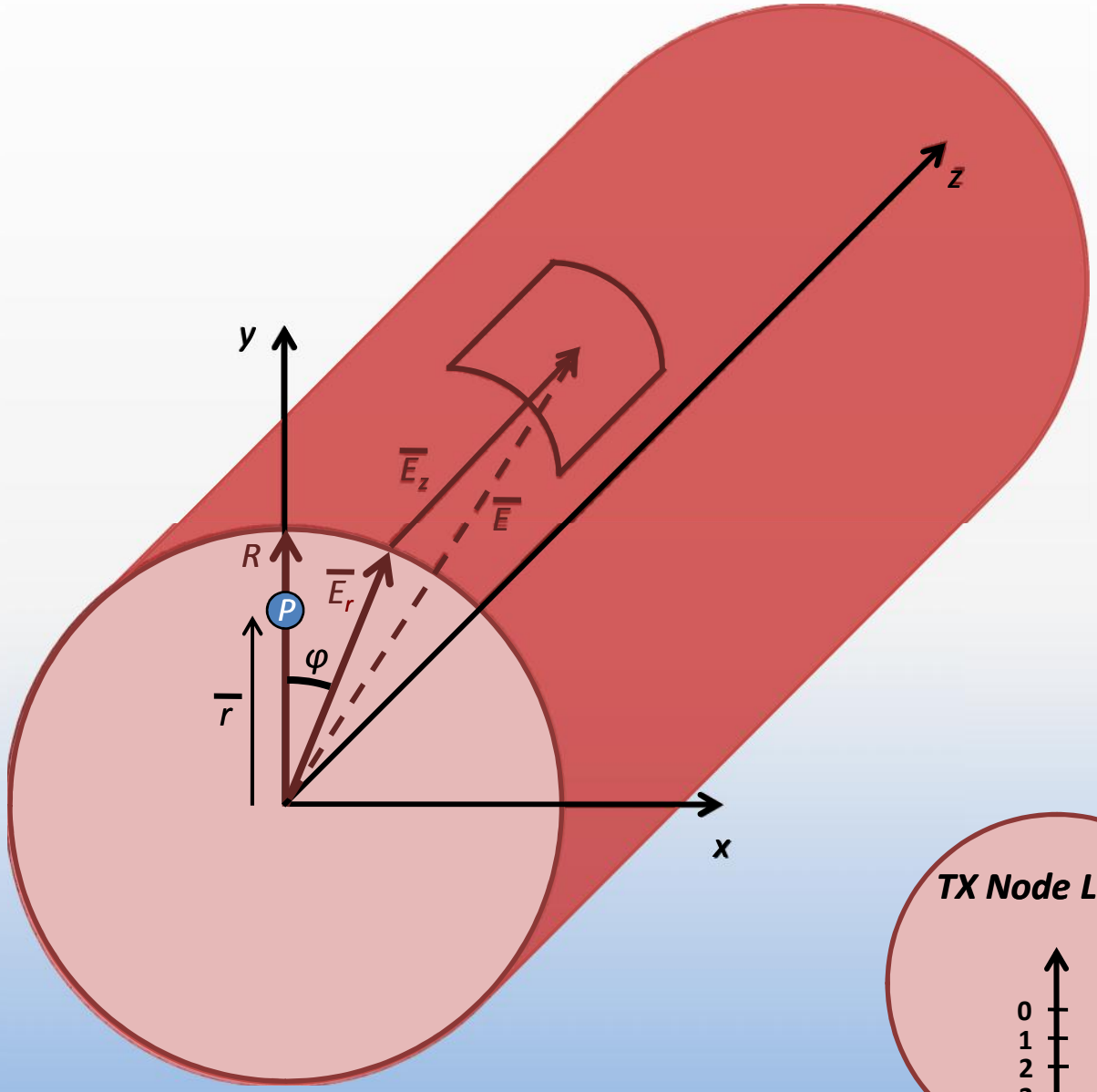
Collisions handling on domain surface

Finalize the outgoing Nano Objects

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

Endothelial Cells as RX nodes

SIMULATIONS SETUP



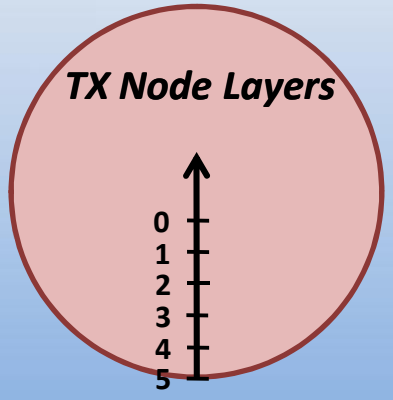
$$\bar{E} = (E_x, E_y, E_z)$$

$$\bar{r} = (0, r, 0)$$

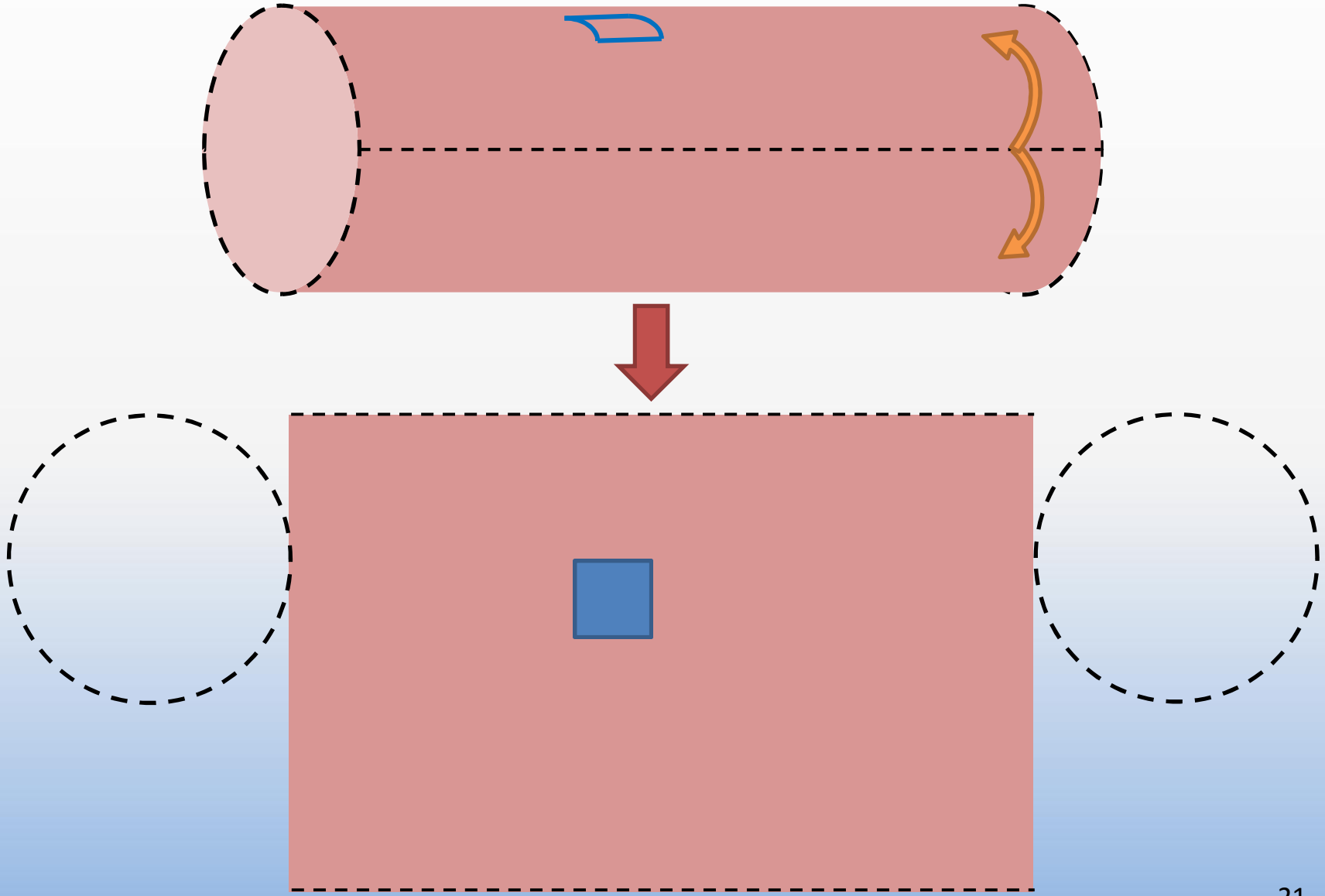
$$\bar{E} = (\bar{E}_z + \bar{E}_r)$$

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

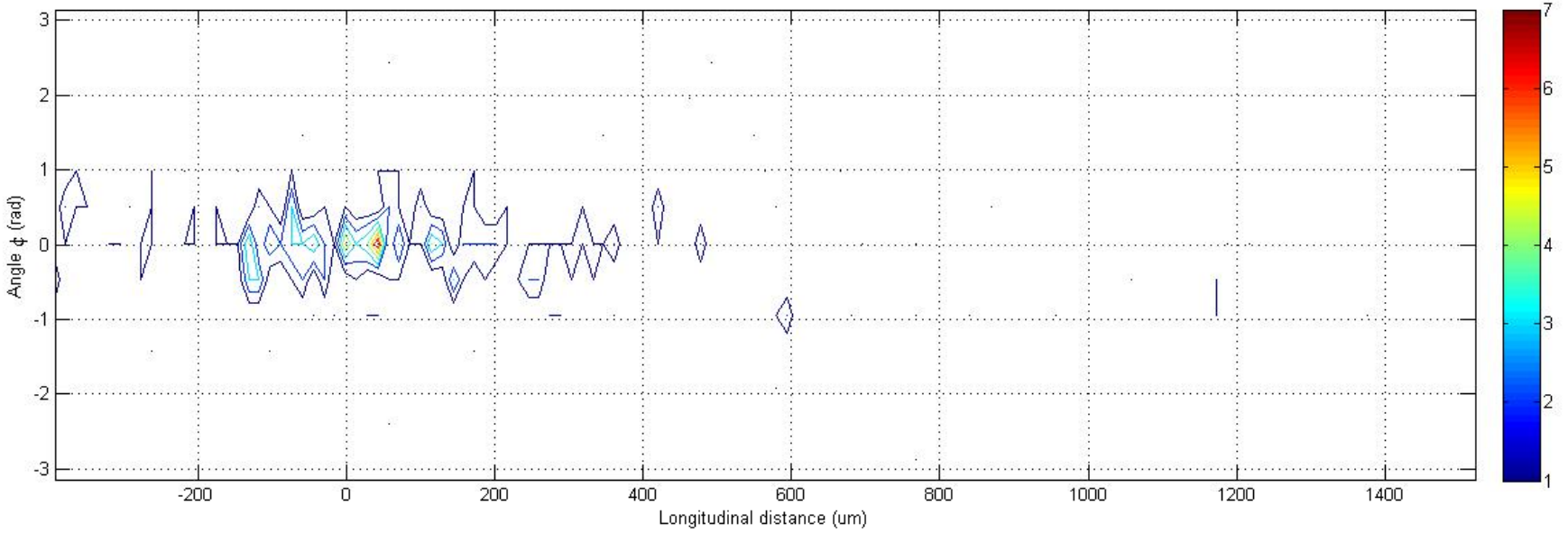
$$\varphi = a\cos\left(\frac{\bar{E}_r \cdot r}{\|\bar{E}_r\| \cdot \|\bar{r}\|}\right)$$

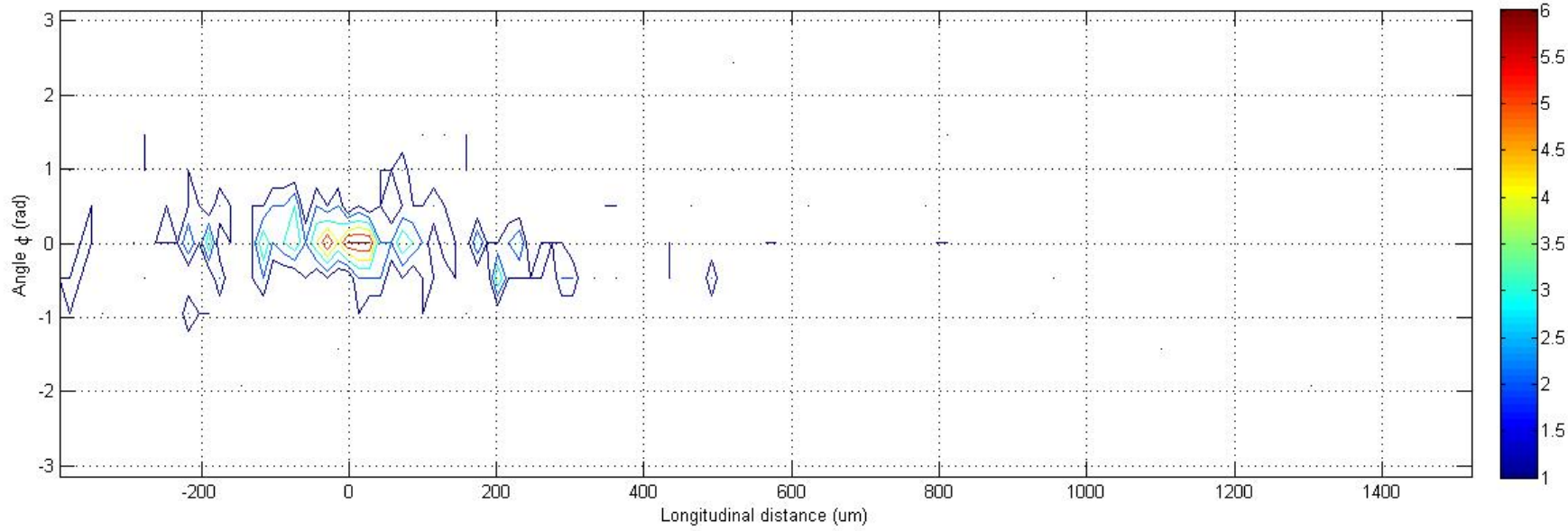


SIMULATIONS RESULTS

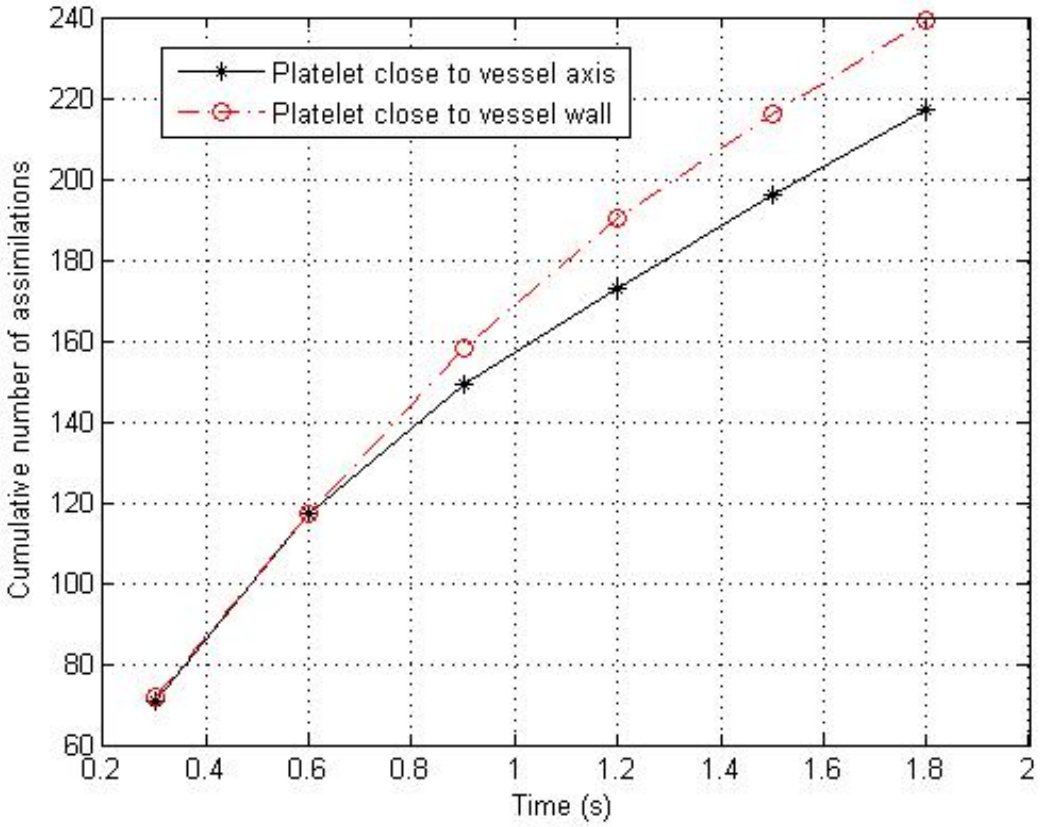


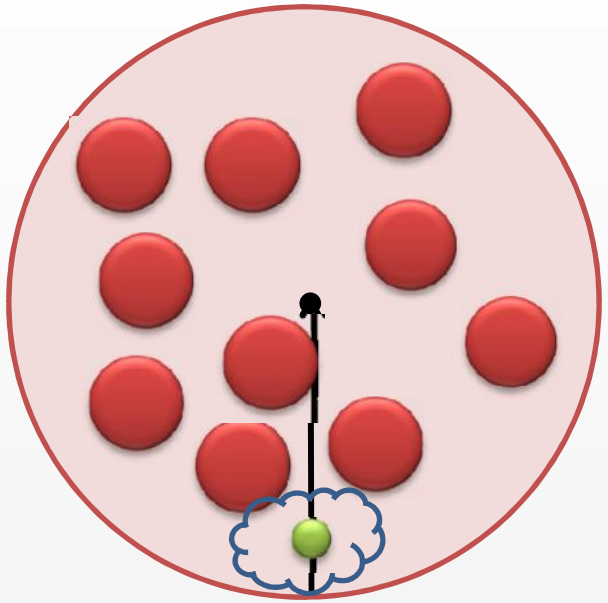
SIMULATIONS RESULTS

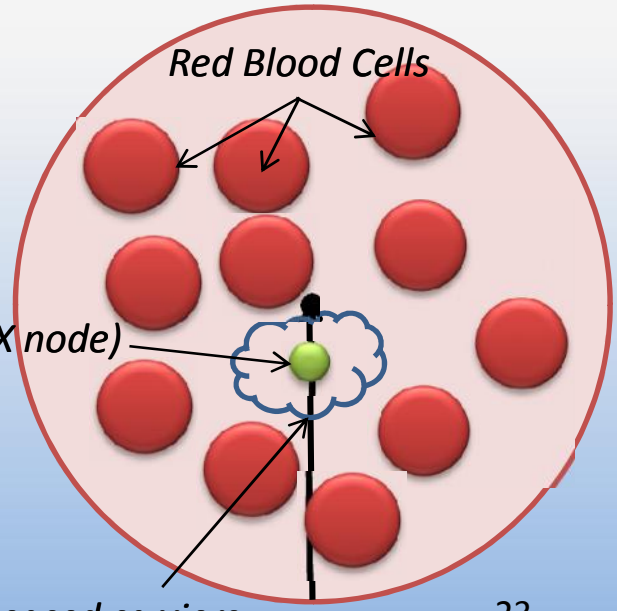




SIMULATIONS RESULTS



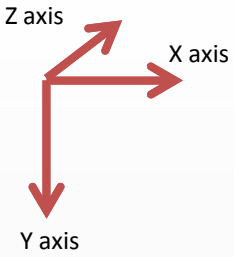


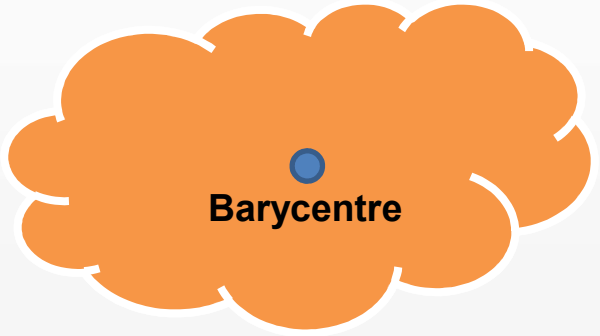


Emissions near vessel wall allows an higher number of assimilations

Emissions near the longitudinal axis allows to cover an higher area along the longitudinal distance

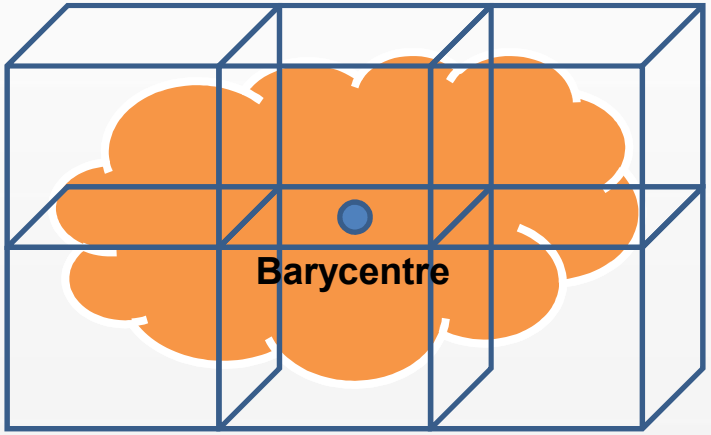
LAST ACHIEVEMENTS: GRID COMPUTING



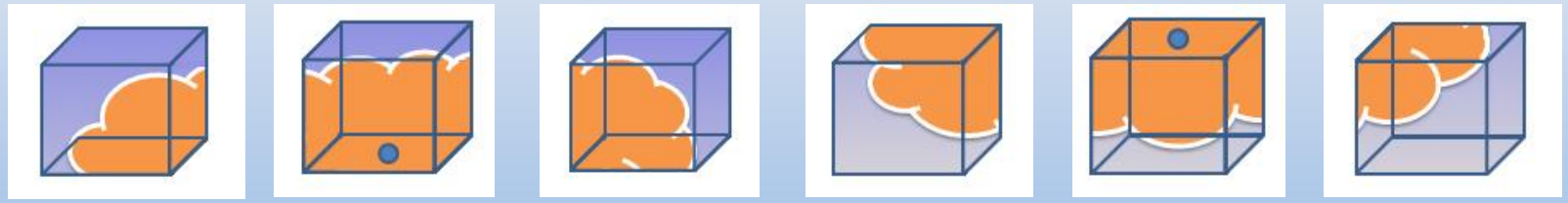


Overall simulation 3D space

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

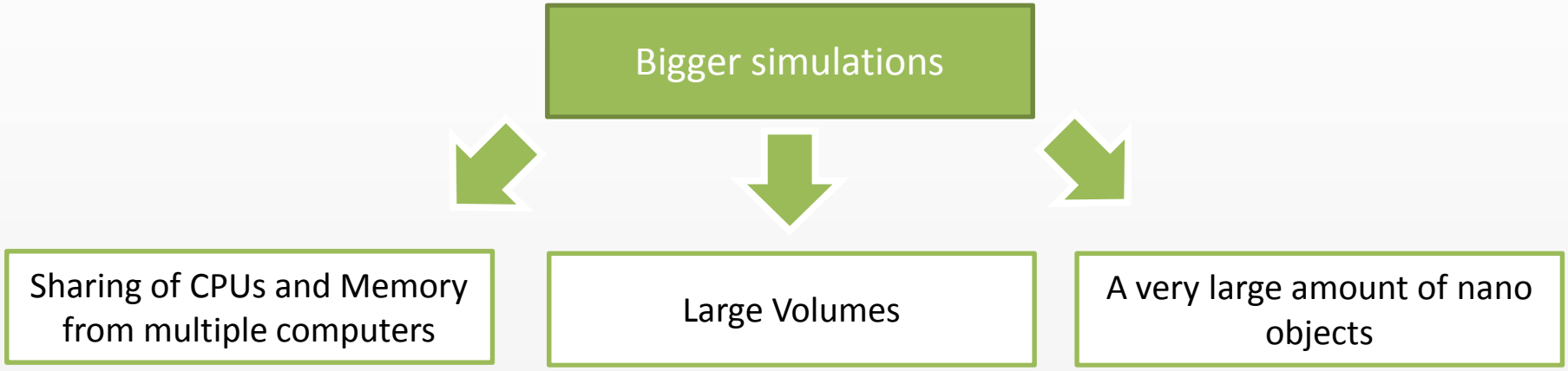


Splitted simulation space

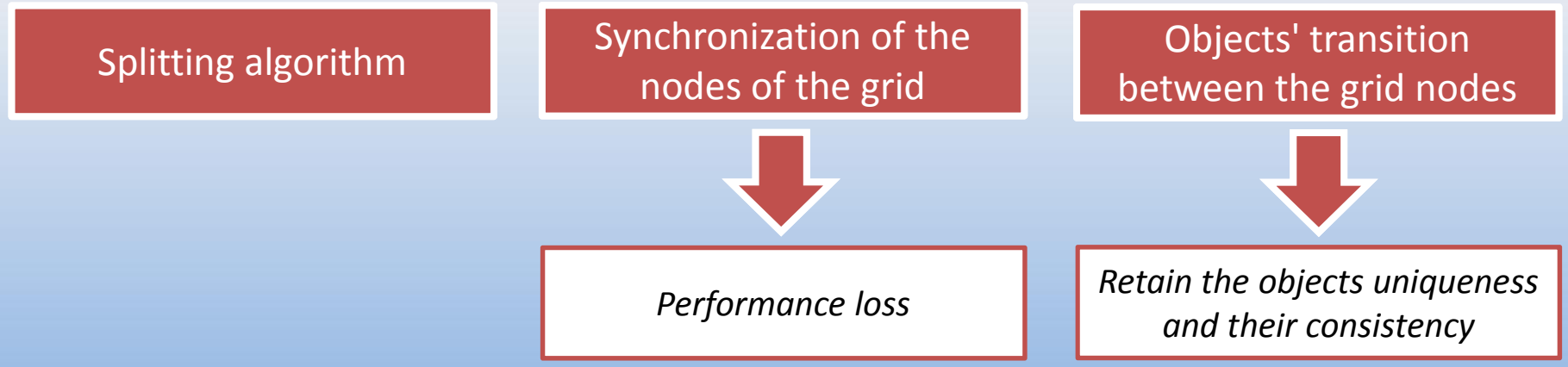


Parallel sub-simulations

LAST ACHIEVEMENTS : WHY GRID COMPUTING?



Main criticities:



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