Endovascular Mobile Sensor Network for Detecting Circulating Tumoral Cells

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ABSTRACT

This paper analyzes the communications and medical potentials arising from establishing nano-scale communications making use of the stent tubular structures in blood vessels. Most of stent implants (both bare metal and drug eluiting stents) happens in coronary arteries for supporting weak endothelial points and counteracting the obstructing effects of arthrosclerosis. Such structures have continuously inspired researchers for introducing additional functions to the mere mechanical sustain of vessels. After a review of the current literature, we propose an original use of stents for monitoring CD47 receptors bearing cells and provide effective diagnostic and prognostic information. We can also perform the detection of different cancer markers, and then integrate this information. These monitoring functions and the event notifications makes used of nano-scale communications. Through a well established simulator of biological nano-scale communications, we will gain significant insights about the establishment of these types of communications happening between different sections of the stent structure. The information exchanges is assumed to be collected by nano-sensors of tumor cells. The outcome of the research is the characterization of the channel transmission capabilities. When considering cost benefit of these expensive smart stents, we suggest a wider perspective where oncologists may join the team of future interventional cardiologists. Thus, our system creates a link between cancer detection, stent devices, and body area networks to P5 medicine.

Categories and Subject Descriptors

I.6.3 [**Simulation and Modeling**]: Applications.

General Terms

Design, Performance, Theory.

Keywords

Biological Nano-Communications, Tumor detection, Simulation, Biomarkers.

1. INTRODUCTION

The interaction between rapidly growing fields often produces burst of advancements. One of such field is the development of complexly structured stent devices which allow sensoring and communication of large number of body parameters. Another such field is the detection of circulating tumor cells (CTCs) [1], which is widely recognized as fundamental component of the P5 medicine [41]. The approaches used in P5 Medicine (Personalized, Predictive, Preventive and Participatory, Population) require a radical change in mentality and a close collaboration between physicians, patients and computer scientists from a variety of research areas. P5 Medicine will shape the four previous "P"s address medical problems in more encompassing integrative ways, creating complete Population perspectives. In fact CTCs, originated from a primary tumor site, can metastasise and reach any part of the body, thus exploring different molecular and tissue environment , and spreading the disease. The number of CTCs in the bloodstream is not precisely correlated with the survival. The presence of specific proteins on the surface of the circulating tumor cell provide an effective correlation with the survival to specific cancer. For example recently Trumpp group [40] have identified a set a genetic markers in CTCs which are key players in establishing bone metastasis (metastasis-initiating cells, MICs) and largely in influencing outcomes and patient's survival (the presence of EPCAM+; CD44+; CD47+; MET+ in CTCs is associated with lower secondary cancer (bone) survival).

Recently, some researchers have implemented a micro-fluidic chip capable of capturing CTCs with 90% success rate [2]. This achievement, and similar ones in the field [3][4], have stimulated further the research activities. Here we design a device that in principle could be used for detecting different types of surface proteins carrying information on CTC risk posing, i.e. possible metastasis and secondary tumors in a variety of organs. For sake of space we focus on the most important task for a CTC which consists in evading the adaptive immune system. This capability is the most important factor correlating with the cancer survival.

Essentially, tumors try to evade the immune system by exploiting the regulatory mechanisms that protect healthy cells from immune-mediated attacks [34]. In particular, the CD47 protein, an immunoglobulin (Ig)-like receptor, is exposed by many cell types cells on their surface in order to indicate to macrophages that they should not be destroyed. Most or all cancers over-expresses CD47. The binding of CD47 expressed on the cell surface with the signal regulatory protein-α (SIRP-α) protein carried by macrophages allows tumor cells to escape the macrophage's mediated innate immune response. Tackling this mechanism through modifying the mutual relationship between CD47 and

BODYNETS 2014, September 29-October 01, London, Great Britain

DOI 10.4108/icst.bodynets.2014.256917

SIRP-α is an active research area [35]. Current nanomedicine approaches consider RNA interference (RNAi) technology by means of liposomes made with protamine-hyaluronic acid and loaded with anti-CD47 siRNA. This has resulted in an efficient silencing of CD47 and tumor regression [36].

Another important research direction, which is combined with the treatment of tumor cell detection and phagocytosis in our proposal, consists of enhancing the stent capabilities. Stents are cylindrical structures typically introduced in coronary arteries and, possibly, in other blood vessels, having primary aim of both supporting weak endothelial points and counteracting the obstructing effects of arthrosclerosis. Such structures have continuously inspired researchers over time for introducing additional functions to the mere mechanical support of weak endothelial tissues.

The two medical research areas mentioned above can be successfully merged through biological nano-communication technologies. This is a quite novel research areas [8][10][11][16][17][33][39], the development of which requires the combined expertise of ICT and biological researchers.

Our proposal contributes to the research objectives mentioned above, and consists of a CTC detection and communication system, which can be view as a *body area network*, including:

- Micro-scale CTC detectors, made of biodegradable components, circulating in the bloodstream. Their role is to increase the system's sensitivity of identifying CTCs at very low density. when their density is still small enough in order to allow defining a successful treatment.
- A smart stent inner surface able to capture the circulating CTC detectors. Since the number of captures cannot be very large, it is necessary to use them to stimulate a more powerful process having the aim of transferring the available information to the external.
- For this purpose, a biological communication system is needed in order to distribute the point-wise information collected from the captured sensors to a larger stent surface.
- A radio communication system attached to the stent able to convey the available information to the external.

As shown in Section 2, the current state of art and potentialities of the involved technologies in the areas of micro-scale sensors [9], stent implementation [23], biodegradable materials [14], and radio communication technologies [18][19][20][21][22] make the proposal feasible within a timeframe of few years. Our proposal is illustrated is some details in Section 3. The expected behavior and properties of the system have been investigated by means of computer simulations. Simulating a biological environment is a challenging task due to the enormous number of involved particles and their interactions. For this reason, we have used a simulator, named BiNS2 [5][6][32], specifically targeted to the biological environment, developed through a continuous experimental evaluation of its results. Its setting described in Section 4, along with the specific results of the analysis of our proposal. The description includes the basic processing mechanisms, from a computer science viewpoint, which highlights the functions needed to simulate molecular communications within blood vessels. These communications are based on the diffusion principles combined with drift. The combined effects produce the movement of particles, such as white and red blood cells, platelets, and the molecule types involved in communication mechanisms, and their interaction. Some comments summarizing our achievement are included in the final Section 5.

2. BACKGROUND AND NOVELTIES

2.1 Background on molecular communications

In molecular communications, the typical signal propagation occurs by way of particle diffusion through a fluid medium, which is usually modeled as a Brownian motion. Mathematical models of transmitter, receiver, and channel, and are proposed in [16], where nodes are assumed to be fixed. Information is associated with the concentration of the emitted particles. Noise components affecting the diffusion-based molecular communications are analyzed in [8]. The number of the so-called bound receptors, which are receptor-ligand pairs, or complexes, is considered the input signal to the receiver. All these papers consider diffusion-based propagation only, which is a model that cannot be used in our reference environment.

A slightly different model is illustrated in [10], where the transmitter is assumed to sit within a fluid and emits a burst of molecules, which diffuse in the fluid through a Brownian motion, until they are absorbed by a receiver capable of measuring their arrival times. The particle release time is associated with the transmitted information as in a pulse position modulation. The scenario shown in [17] is slightly different. Two communicating nanomachines and emitted molecules propagate through a fluid medium. Their motion includes both a drift velocity and Brownian component. The communication model consists of the release of one or two molecules within the medium. The same authors show in [11] that the additive inverse Gaussian noise model is appropriate for molecular communication channels in fluid media with drift. They derived an upper bound and a lower bound of channel capacity and proposed a maximum likelihood receiver model. Nevertheless, the propagation model does not include the collisions, which are of paramount importance in our scenario, as observed also in [12].

2.2 Novelties on molecular communications

In our case the communication environment is quite complex. It essentially consists of three components, to be simultaneously considered:

- particle diffusion, which is typically modeled as a Brownian motion [7];
- positive drift caused by the bloodstream, the extent of which depends on the distance of the considered particle from the longitudinal axis of the vessels. Clearly, the drift is maximum on the axis and minimum at the vessel walls. Two well known drift models are the Poiseuille or Casson laws [13]);
- interactions(collisions)between particles in blood vessels and between particles and vessel walls.

Whilst different theoretical diffusion models have been proposed [7]; also including the effects of drift (see [13] and references therein), a comprehensive analysis of all these effects has been published only in recent times [12]. It was made evident that the red blood cells are those that most influence the particle motion, due to their number and size. The latter is slightly inferior to only that of the white blood cells. The resulting effect is that smaller particles, such as platelets, are pushed close to the vessel walls

2.3 Stent technologies and embedded-sensors

Over one million of stents are implanted every year. In its basic version, a stent consists of a mechanical cylindrical device inserted into an obstructed blood vessel. Once positioned in the right place, it is expanded in order to keeps arteries open, and to restore circulation.

Recent advances in ICT, has allowed producing miniaturized electronic devices, including radio communication capabilities, that can be integrated within the stent structure. This way, it is possible to design stent devices that, in addition to have the necessary mechanical properties, can integrate micro sensors, thus providing additional features. For this reason, even if the cardio circulatory conditions do not require a stent implantation for restoring blood circulation, the new advanced features may well justify it. For example, they could implement monitoring functions, likewise in the proposal illustrated in this paper, or remotely controlled drug release to block cell proliferation through a biodegradable coating (such as the drug-eluting stents).

Possible drawbacks of stent implantation are restenosis, which happens when the vessel narrows again after the stent implantation, immune response against this non-self object, and scan tissue which grows through the stent graph.

Introduction of pressure sensors in stents dates back to 1998. Pressure measurements were converted into capacitance, which modulate RF signals generated by specific Application Specific Integrated Circuit (ASIC), with a signal range of 1m. The approved frequency bands include 900 MHz, 2.4 GHz, and 5.8 GHz. Exposure limits to protect against electromagnetic fields exposure are specified by IEEE C95.1 [37], and ICNIRP [38].

The possibility of using passive UHF-RFID technology for exchanging information between a stent and the external was explored in [18]. The objective of the research was to monitor abnormal accumulation of tissue inside the lumen of an implanted stent.

Experiments made us of a test antenna implemented as a dipole placed on the longitudinal axis of the vessel. The effects of restenosis were analyzed by varying the dielectric properties of the tissue inside the vessel.

Due to the possible drawback of stent implantations, a lot of research activities have been focused on implementation of non invasive monitoring systems for diagnosing restenosis and the relevant communication techniques of the developed status to the external, on which we can rely for our proposal. For example, the use of wireless telemetry systems in conjunction with stents hosting capacitive pressure sensors was investigated in [19] and [20]. Though the values of the blood pressure at the two ends of the stent the status of restenosis can be monitored. The problem emerged is that the size of the pressure sensors could not be compliant with most of critical blood vessels, such as coronary arteries.

The use of implantable sensors powered by batteries was proposed in [21]. Nevertheless, even this solution was hampered by the unpractical battery size. Thus, a passive approach, based in an inductive stent is proposed in [22]. In particular, a thinned integrated circuit (IC), with two on-chip oscillators was supposed to be implanted on the stent structure. These oscillators are assumed to be powered wirelessly through the stent, acting as an inductor. Since the blood pressure on each end of the stent alter the capacitance of the relevant sensor, it can change the transmitted frequency. Active telemonitoring using an integrated circuit embedded on the stent structure is proposed in [23], which shows that a power of 56 μW delivered through a signal at a frequency of 0.8 GHz is sufficient to supply an IC embedded on the stent for monitoring purposes.

3. SYSTEM MODEL

The typical concentration of tumor cells in the early stages of a disease, or relapse of it, makes their detection from a fixed receiving point extremely difficult. For this reason a fundamental component of our proposal, inspired by the state of the art in the relevant technologies, consists of making use of mobile nano-sensors free to move within the blood vessels. Since the capture of CTCs is assumed to happen by a mechanism that can be assimilated to a cell particle absorption, the size of the freely moving sensors cannot cause obstruction of vessels. In addition, they can be implemented by using bio-degradable material. In our experiment we assume that these sensors, pushed through the blood flow, can detect the cells having their surface populated by the CD47 protein, since it can be put in relation with a number of tumors. In fact, it was shown that blocking CD47 can reduce tumor growth by enabling macrophages to eliminate cancer cells [31]. In simply words, expression of the CD47 by a cell has the effect of communicating to macrophages a “don’t eat me” signal [31][34]. In fact, macrophages can recognize CD47 molecules by a signal regulatory protein-α (SIRPα), also known as SHPS1. It acts as a receptor for CD47, thus blocking the phagocytosis of macrophages, as schematically shown in Figure 1.

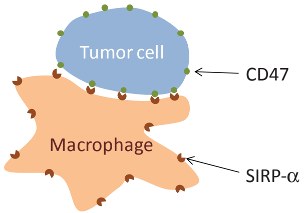


Figure 1. Tumor cell blocking phagocytosis though CD47 exposure.

Hence, the antibodies able to block CD47–SIRPα interactions can allow phagocytosis of tumour cells by macrophages [34][35].

In order to allow such treatments, detection of cells exposing the CD47 is of paramount importance. This detection happens through a physical contact of the tumor cells and sensors.

Detection of sensors can be implemented by exploiting the RNA interference (RNAi) technology [36]. We can assume the usage of RNAi to implement the detection mechanisms in mobile sensors of the CD47 proteins, by associating it to the antibody of CD47.

Each time a sensor detects a tumor cell, it updates the stored information by comparing the number and the frequency of detections against a number of thresholds and a decision tree. This way, the current status of the sensor reflects the likelihood of the tumor growth. The key aspect is that this information could regulate /trigger the further release of liposomes-loaded siRNA anti CD47.

Flowing through the blood circulatory system, these sensors happen to pass through the stent. Given the the small size of the sensors, they are pushed towards the endothelium by larger blood cells, such as white cells, as it typically happens to platelets. This way, sensors move close to the stent graph, over which a number of sensor receptors are attached. When a sensor is captured by a receptor, the stored information is released to it and the sensor status is reset. Clearly, the energy associated with the released signal is not enough to drive any future actions. For this reason, it is used as a switch to trigger a local communication, the scope of which is limited to the stent structure, having the task of triggering a large number of receptors and collect a sufficient energy to make the information available to the external. These receptors are located over receivers that are stick to stent graph, and their number is sufficiently high that it can be assumed that the inner cylindrical structure of stent is fully covered by them. This behavior is sketched in Figure 2.

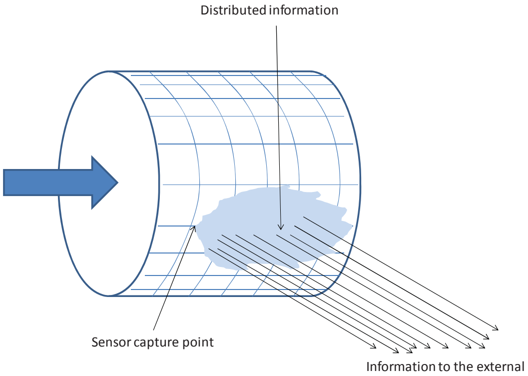


Figure 2. Sketch of the proposed smart stent solution.

Possible solutions for communicating the information to the external are:

- Release from the sensor capture point of a substance that generates an allergic reaction on the skin surface.
- Release from the sensor capture of a substance that modifies the stent composition, detectable through the use of infrared rays (local temperature of the skin) or by ultrasound.
- Through the use of passive responders such as RFID tags, the response of which can be altered by a dielectric change of the transmission medium. For example, the dielectric change can be stimulated between the passive RFID tag surface and the external active RFID sensor, which form a variable capacitor, by stimulating the release of adhesive molecules by the endothelium, such as the VCAM. This way, a local and time limited change of the RFID response may be associated with tumor cells (see Figure 3).

The objective of numerical analysis shown in what follows is to investigate the communication system from the sensor capture point to the receivers to be activated on the stent structure. This communications happens through the emission of a burst of biodegradable particles, referred to as information carriers, which are involved in the blood flow. The objective of the communication system is to activate the maximum number of receivers, in order to enable a reliable following communication with the external. To this aim, it is necessary to determine the suitable value of the system parameters, such as the transmitter distance from the stent inner surface, the number of particles transmitted by a single burst, and the receiver detection rules. These rules have to detect the incoming signal in a reliable manner, by avoiding false positives due to the possible presence of particles in the blood flow that are not part of the ongoing communication process. In addition, the frequency of detection of common markers of normal cells makes it possible to calibrate the detector or figure out if there are malfunctions

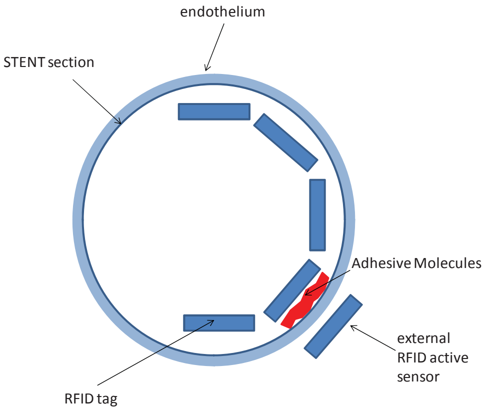


Figure 3. RFID sensor communicating though a variable capacitor, by stimulating the release of adhesive molecules by the endothelium.

4. COMMUNICATION MODEL AND NUMERICAL ANALYSIS

4.1 Model of particles motion in blood vessels

Blood vessels under consideration are assumed to be at a distance from the heart so as to allow modeling the bloodstream without turbulences. This way, the flow properties, such as velocity and pressure, can be considered constant over time, and the resulting motion laminar. In particular, in the longitudinal direction the vessel can be viewed as a set of concentric cylinders. The space between concentric cylinders is a lamina, and a laminar flow consists of fluid particles moving in straight lines in each lamina.

The velocity profile v of this laminar flow was shown to be parabolic, and is expressed by the well known Hagen–Poiseuille equation, which can be derived from the Navier-Stokes equations [24][25][26]:

$$v(r)=\frac{1}{4\mu}\frac{\Delta P}{L}\left(R^{2}-r^{2}\right) \qquad (1)$$

where R is the vessel radius, μ is the dynamic fluid viscosity, ΔP is the pressure decrease happening through a vessel section of length L, and r is the transversal distance from the longitudinal axis of the vessel. Table 1 reports some known parameters for a sample blood vessel, whose values we have used in the simulation study presented in Section 4.

It is worth to note that this velocity profile needs some adaptation when large vessels are considered. In particular, some authors consider the Casson profile more accurate [13].

This model generalizes the motion model of the fluid particles, typical of blood vessels, suspended in a fluid. As overall particle flow carries fluid particles along, thus creating drag. The drag force F_d is given by the Stokes Law [26] and can be applied on a particle with a low Reynolds number (such as red blood cells) in a continuous viscous fluid [27]:

$$F_d = 6\pi\mu R v_p \qquad (2)$$

where v_p is the relative velocity of the particle with respect to the flow, given by (1). By using this value of the drag force, it is possible to estimate the acceleration and thus the velocity of particles. Also a diffusion component must be considered. It is modeled by the Brownian diffusion coefficient D_m of a quiescent fluid [7][28]:

$$D_m = \frac{k_B T}{6\pi\mu a} \qquad (3)$$

where k_B is Boltzmann constant, a is particles radius, and T is the temperature in Kelvin degrees.

Since the Reynolds number for nano particles is high, equation (2) cannot be used as it is. It is necessary to consider both convection and diffusion effects in addition to the velocity component (1), governed by the following equation [12][13]:

$$\frac{\partial C}{\partial t} + v \cdot \nabla C = D_m \nabla^2 C \qquad (4)$$

where C is the particle concentration, v is the fluid velocity vector, and D_m is the diffusion coefficient. A similar model, alternative to solving equation (4), has been proposed in 1950s and further investigated in other papers, such as [13] and [29]. It consists of the using an effective longitudinal diffusion coefficient D_{eff}, applied only along the propagation direction. A recent study, [12], considers the presence of the blood cells. This study consists of a numerical analysis validated also by experimental results. It shows that these cells can significantly influence nano-particle propagation and assimilations, so it is proposed to include them explicitly in the model.

In fact, what happens is that larger and heavier cells move essentially along the longitudinal vessel axis, whilst the smaller elements, such as platelets, when collide with red blood cells are pushed towards the vessel walls. They remain confined close to walls since they find a less obstructed propagation path. The collisions between particles or between particles and endothelium, can be modeled as inelastic, by using the values of the coefficient of restitution reported in [30]. Thus, the simulation analysis presented in what follows adopts the approach suggested in [12], by modeling collisions between nano particles and white and red blood cells, in addition to the laminar and brownian motion contributions. This is clearly a significant step forward for suitably modeling the propagation of the information carriers in molecular communications.

4.2 Simulation Results

The section begins with an analysis of the carrier propagation towards the receiver, which is followed by the numerical evaluation of the receiving capabilities of any single cell. What emerges is that if the number of carriers received by a single receiver is significantly lower than the number of receptors present on the cell surface the channel shows a linear and stationary behavior. Hence, in order to evaluate the impulse response of such a channel we emulate the transmission of a burst of carriers, as the closest approximation of an impulse. Table 1 reports the simulation parameters. These parameter values have been estimated experimentally [6][39] for a specific ligand, the CD40L [15]. Receivers include mechanisms similar to those present over endothelial cells, which receive sCD40L particles as information carriers by means of the CD40 receptor. Nonetheless, the resulting communication is general, since it can be associated with any other type of molecular exchange by simply adapting the parameter values.

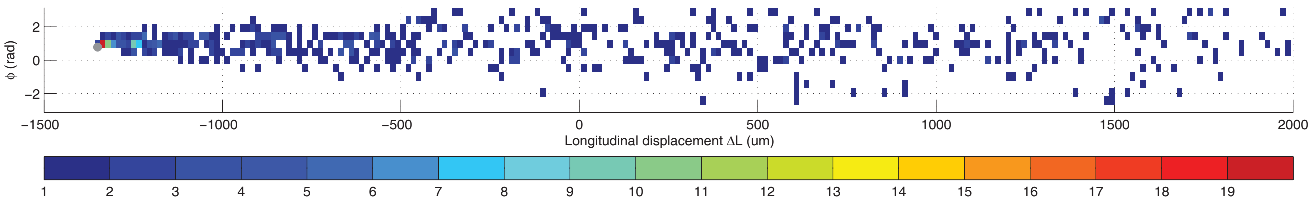
We have placed the transmitter in two positions very close to the vessel walls. We describe the environment by using the cylindrical system of coordinates (ϕ, d, L), where the first coordinate ϕ is phase displacement, the second is the distance d from the cylinder axis, and the third coordinate L is the displacement along the axis of the cylinder. The cylindrical coordinates $\mathbf{X_0}$ of these positions, are (0, d_1, 0) and (0, d_2, 0), where d_1=2495µm and 2490 µm. The position corresponding to d_1 is adjacent to the vessel wall. The blood flow pushes particles towards positive values of the third coordinate L.

Figure 4 shows the number of carriers received by receivers during 8 seconds of simulated time. The transmitter position X_0 is shown by a grey circle. Figure 4.a and Figure 4.b are relevant to the transmitter positions adjacent to the endothelium (d_1) and at a small distance from it (d_2), respectively. What emerges is that, when the distance between the transmitter and the endothelium increases, the carriers are received over a very long area in the direction of the longitudinal axis. Therefore, a larger number of cells can receive a lower number of carriers. In terms of signal strength, this is the same as to say that the signal results to be more attenuated, analogously to a directional antenna footprint where the antenna distance is increased. Essentially, the maximum value of the total number of received carriers is bit higher in Figure 4.a, and a small number of carriers are received just below the transmitter. In Figure 4.b, carries are distributed over a bit larger ϕ range. In addition, the cells able to receive the signal may have a larger longitudinal coordinate value.

Table 1. Parameter values used in the simulation analysis.

General parameters	
Vessel length	4.0 mm
Vessel diameter (venule)	60 µm
Mean flow velocity	0.5 mm/s
Viscosity	1.3 mPa×s
Temperature	310° K
Rest. coeff. of vessel wall [30]	0.6
Rest. coeff. of particles collisions [30]	0.9
Simulation time step	100 µs
Fixed RXs on smart probe	
Side (square shape)	14.5 µm
Receptor radius	8 nm
# receptors	10000
# fixed RXs	3055
Transmitter nodes	
Radius	1.0 µm
Carrier burst	3000
Carrier radius	1.75 nm
Red blood cells (RBC)	
Conc.	4×10^6 U/mm^{-3}
Radius	3.5 µm
White blood cells (WBC)	
Conc.	4×10^3 U/mm^{-3}
Radius	5 µm
Receptor radius	8 nm
# receptors	5000

(a) TX node at d_1



(b) TX node at d_2

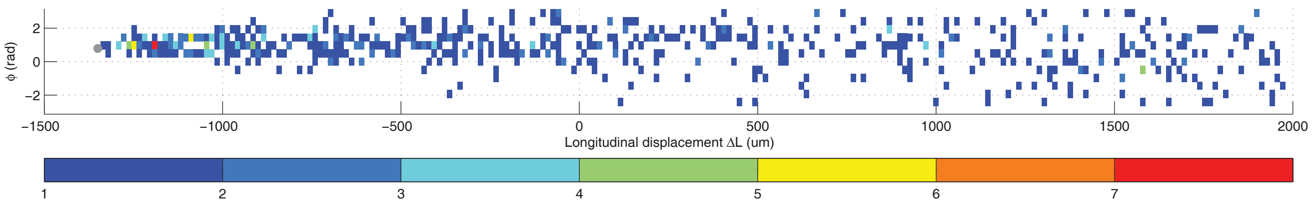


Figure 4. Assimilation of carriers as a function of the distance of the transmitter from the vessel axis.

5. CONCLUSION

This paper explores the achievements coming from the introduction of a biological communication system embedded in smart stents. In our proposal, this communication system integrates a medical system designed for capturing tumor cells circulating through the cardio-circulatory system. The analyzed communication system is activated when the smart stent becomes aware of the existence of tumor cells by means of freely circulating sensors. The detection of tumor cells acts as a switch which triggers the analyzed communication system that can spread the available information over a significant portion of the stent. This information diffusion has the scope of modulating some electrical parameters of radio communication devices used to communicate with the external.

The biological communication system within the stent has been analyzed in some details by using a sophisticated simulator, developed and experimentally evaluated in our laboratories, specifically targeted to biological environments.

The results achieved are promising. In addition to showing the actual feasibility of the proposal, they have also inspired further studies towards the exchange of more structured information and, in the longer term, towards the experimental evaluation of the proposal. In fact, body area networks seems to be of paramount importance in P5 and, in general, in the personalised oncology medicine.

6. ACKNOWLEDGMENTS

L. Felicetti, M. Femminella, and G. Reali have been supported by Fondazione Cassa di Risparmio di Perugia, project code *2013.0055.021 RICERCA SCIENTIFICA E TECNOLOGICA*.

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