

A nanocommunication system for endocrine diseases

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Abstract Nanotechnology is a new and very promising area of research which will allow several new applications to be created in different fields, such as, biological, medical, environmental, military, agricultural, industrial and consumer goods. This paper focuses specifically on nanocommunications, which will allow interconnected devices, at the nano-scale, to achieve collaborative tasks, greatly changing the paradigm in the fields described. Molecular communication is a new communication paradigm which allows nanomachines to exchange information using molecules as carrier. This is the most promising nanocommunication method within nanonetworks, since it can use bio-inspired techniques, inherit from studied biological systems, which makes the connection of biologic and man-made systems a easier process. At this point, the biggest challenges in these type of nanocommunication are to establish feasible and reliable techniques that will allow information to be encoded, and mechanisms that ensure a molecular communication between different nodes. This paper focus on creating concepts and techniques to tackle these challenges, and establishing new foundations on which future work can be developed. The created concepts and techniques are then applied in an envisioned medical application, which is based on a molecular nanonetwork deployed inside the Human body. The goal of this medical application is to automatously monitor endocrine diseases using the benefits of nanonetworks, which in turn connects with the internet, thus creating a Internet of NanoThings system. The concepts and techniques developed are evaluated by performing several simulations and comparing with other researches, and the results and discussions are presented on the later sections of this paper.

Keywords Molecular · Nanocommunication · Nanonetwork · Nanomedicine · Addressing · Routing

1 Introduction

The ideas and concepts of nanoscience and nanotechnology started in December 29, 1959 in the California Institute of Technology (CalTech), where the physicist Richard Feynman gave a talk entitled "There's Plenty of Room at the Bottom", in a meeting of the American Physical Society. In his talk, Feynman described a process in which scientists would be able to manipulate and control individual atoms and molecules to create more functional and powerful man-made devices. During that same talk, he realized that several scaling issues would require the engineering community to totally rethink the way in which nano-devices and nano-components are created [1].

Nanotechnology has a broad range of research applications and can be classified in four main areas: *Industrial* and Consumer Goods Applications (for example, devel-

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opment of intelligent functionalized materials and fabrics, new manufacturing processes and distributed quality control procedures, food and water quality control systems), that can be known as Nanomaterials, which are materials which often have specific properties due to their small particle size; *Biomedical Applications* (for example, intrabody health monitoring and drug delivery systems (DDS), immune system support mechanisms, and artificial biohybrid implants); *Environmental Applications* (biological and chemical nanosensor networks for pollution control, bio-degradation assistance, and animal and biodiversity control); *Military Applications* (nuclear, biological and chemical defenses and nano-functionalized equipment).

Nanotechnology enables the miniaturization and fabrication of devices in a scale ranging from 1 to 100 nanometers. At this scale, a nanomachine can be considered as the most basic unit. Some nanomachines such as chemical sensors, nano-valves, nano-switches, or molecular elevators [2], cannot execute complex tasks by themselves. However, nanomachines can be interconnected to execute collaborative tasks in a distributed manner. Exchanging information between them will allow a cooperative and synchronous way to perform more complex operations such as in-body drug delivery or disease treatments. Resulting nanonetworks are envisaged to expand the capabilities and applications of single nanomachines in innumerous ways [3]. Nanonetworks will allow dense deployments of interconnected nano-machines enabling larger application scenarios.

With the idea of a nanonetwork, a new communication paradigm appeared. For a nanonetwork to be able to operate, a communication between the nanomachines is needed. At this scale the communications concepts of regular computer networks, cannot be applied as easily. The way the information is exchanged at nano scale has not been defined yet, but different approaches have been presented, ranging from downscalling well-established communication means based on electromagnetic, optical, acoustic, or mechanical communication, to defining completely new paradigms based on biology, like molecular communication.

Molecular communication can be described as the use of molecules as messages between the transmitter and the receiver. This mode of communication is the most promising for general applications. An example of this communication method is the communication between neighbouring cells in the human body, which is conducted by means of diffusion of different types of molecules that encode different types of messages [4].

Molecular communication allows biological and artificial-created nanomachines to communicate over a short distance using molecules. In molecular communication, senders encode information onto molecules (called information molecules). Information molecules are then loaded onto carrier molecules and propagate to a receiver. The receiver,

upon receiving the information molecules, reacts biochemically to the incoming information molecules.

Carrier molecules are neurotransmitters, hormones, molecular motors, viruses and more are being discovered and studied. The information molecules are proteins, ions, or even DNA strands. Studies show that this method of communication is a lot more suitable for communication from nano to nano scale than electromagnetic waves communication method. The latter is described with great potential for other applications, but due to the size of the nanomachines is not as feasible as molecular communication [4]. Molecular communication is being specially attractive for some different reasons:

- Molecular communications in a nano scale that already occur in nature. Communication between cells and bacteria are a great natural phenomena which give studies a groundwork to model nanonetworks and to develop solutions:
- Molecular communications allows nanonetworks to be deployed into naturally occurring phenomena, consequently providing fast engineering pathways to viable solutions;
- Diverse medical applications require biocompatibility, properties that are already provided by nanonetworks using molecular communication.

In molecular communications there are several processes, which differ in the way molecules propagate through the communication channel from a network node to another. Since this method of communication is inspired by phenomena seen in nature, most of these processes mimic those phenomenons and there are active researches trying to master each new molecular communication process. Some relevant method being researched nowadays are: Calcium signalling, Chemical molecule diffusion, Molecular motors, Bacteria signalling, Flagellated bacteria communication and Pheromone signalling.

Each one of these different methods of molecular communication has its advantages and drawbacks. In this paper these methods were researched and studied in order to find the ones that seem most promising, thus envisioning new concepts where they would be applied and where their advantages could be more relevant. This paper contributes with new concepts and techniques in a molecular nanocommunication scenario, original routing and addressing mechanisms concepts to increase the effective range of a molecular nanonetwork and a full molecular nanocommunications based system which integrates several techniques and mechanisms. Additionally, the paper evaluates the overall performance of the proposed architecture and evaluates the possibility of an endocrine disease monitoring system in a nanothings environment.



The remaining part of this paper is structured as follows. In Sect. 2 a brief showcase of the most important researches that influenced the design the system architecture is presented. The envisioned system architecture is detailedly explained by describing all concepts, techniques and discussing all the decisions made in Sect. 3. In the case study presented in Sect. 4, the designed system is applied in a medical scenario, and its goal is to automatously monitor endocrine diseases. In Sect. 5, the system is evaluated by performing several simulation scenarios and discussing and comparing the results obtained with other researches. Finally, in Sect. 6, the paper is concluded with some final thoughts, discussions and some future work that could continue to expand the work described in the paper.

2 Related work

In this section, current researches on this field are carefully described by firstly referring several papers that provide useful insights on the basics of nanocommunication and molecular communication. In [1], the authors make a complete description of the basics of nanocommunications starting providing a brief history on nanotechnology, where it stands in the present and the direction it is heading. Additionally, it is explained the nanomachine manufacturing approaches and how they work, then a detailed analysis and explanation of the main methods of nanocommunication is structurally provided. The paper is concluded with a breakdown of protocols for nanonetworking, referring some of the challenges for different methods of nanocommunication. In addition to the basic concepts, in [3], an architecture concept for nanomachines to be used in nanorobots and bio-applications is described. Then the authors explain how wide the application window for nanonetworks is, giving several examples for biomedical, industrial, military and environmental applications.

Moving to the research area focused by this paper, i.e., molecular communication, there are several relevant papers that need to me mentioned. In [5] a great insight on molecular communication is provided by presenting notable information on communication with several nodes, the information capacity on the channel is explained and some processes for analysis are shown, a detailed study on protocols for molecular communication is given by describing architectures and techniques for protocols design and abstractions needed on this type of protocols. The authors go even further and explain their vision for a experimental platform based on communication among bacteria using quorum sensing. In [4] a clean description of molecular communications is given, making some intelligent arguments when comparing molecular communications to regular ones, and providing valuable information for Drug/DNA delivery systems (DDS). On [6]

a complete analysis of molecular nanocommunications for long range is provided. The authors give a great insight on different methods of communication for long range dividing them into groups of wireless and wired communications. In addition to describing the most commonly known wireless method, i.e., pheromone communication, they explain how other methods can be studied further, such as pollen and spores, and using light transduction.

On [7] it is presented a very detailed study on the information capacity on the channel using a diffusion process. The paper makes a thorough mathematical approach demonstrating that selecting appropriate molecular communication parameters such as temperature of environment, concentration of emitted molecules, distance between nanomachines and duration of molecule emission, it can be possible to achieve high capacity for the molecular communication between two nanomachines. The authors also establish that the molecular communication capacity between two nanomachines is heavily affected from the environmental factors such that appropriate coding and error control mechanisms for molecular communication must consider the environmental factors. On [8] the authors revise concentration encoding, by creating a new technique to encode the information, that accordingly to the paper, can increase the transfer rate and doesn't require a synchronous communication. In this new concept the information is encoded into an array of different types of molecules. Alternating the molecules in the array the information is encoded. This also resembles the natural encoding of genetic information, i.e., DNA arrays consisting of different base pairs.

Although the research papers mentioned so far provide essential information to understand how nanocommunication techniques work and some challenges involved in this research area, applications need to be envisioned in order to target specific challenges and discover new ones. Doing so will force the community to advance the technology, reaching breakthroughs. There are several important research papers that focus on nanocommunications applications. In [9], the term Internet of Nano-Things (IoNT) was introduced and the authors outlined a general architecture for electromagnetic nanomachine communication, including challenges in channel modeling, information's encoding, and protocols creation for channel sharing, nanomachine's addressing and information routing. The authors present the architecture for the IoNT in two different applications, one being a intrabody nanonetwork for healthcare, which is a common concept, and the other being a future interconnected office work area. Healthcare applications are the most obvious and is the subject gaining more attention from the community. Most researches envisage a sensing nanonetwork, capable of monitoring the health of the recipient. One of the most important research paper on this matter is [10], which creates a full assessment of nanocommunication techniques and designs



example architectures for a sensing nanonetwork for both molecular communication and electromagnetic communication. The authors created a silicon sensing component of the nanomachine, i.e., a nanosensor. This paper offers a great in depth look at sensing nanonetwork systems for healthcare, and achieve the conclusion that molecular communication seems to be the most promising technique to use in healthcare applications, although there is still much work needed to achieve an implementation of these systems in the real world.

Another important aspect that several researchers focus in the healthcare field is the drug delivery, i.e., DDS. The objective of the DDS is to dispatch a drug where the medication is needed, whilst preventing the drug from affecting other healthy parts of the body. In [11] a thorough description of DDS is explained. The authors created and designed a DDS by developing a molecular communication channel model of the drug particle propagation through the cardiovascular system, i.e., the bloodstream. Mixing these two concepts, sensing and drug delivery, an advanced medical tool is created, and that is what the authors of [12] envisioned. They described a route towards an effective methodology to control nanorobots, which they envision to be nanocomputers capable of doing several tasks, in order to create a valuable medical tool. Medical target identification, improving diagnosis and providing new therapeutic procedures are some of the tasks a nanorobot is expected to accomplish in a healthcare application.

Although healthcare applications are the most popular research field, nanonetworks can be applied in several other fields. In [3] a concise description of several applications for nanonetworks is presented and categorized by application areas. In applications for industrial and consumer goods, the authors describe an application in which nanonetworks monitor food and water quality, detecting small bacteria and toxic components that cannot be detected by traditional sensing technologies. In the same field, they describe an application in which nanonetworks are included in fabrics and materials to add new and improved functionalities, such as antimicrobial and stain-repeller textiles. In military applications, nanonetworks can be deployed over the battlefield or targeted areas to detect aggressive chemical or biological agents, additionally, similarly to consumer good, nanonetworks can be implemented in military equipment, enabling advanced camouflage, self-regulating temperature mechanisms underneath soldiers clothes, or even detect where a soldier has been injured. In the environmental field, the authors express an application that address an existing problem with garbage disposal, in this application a nanonetwork can help the biodegradation process in garbage dumps by sensing and tagging different materials that can be later located and processed by smart nanoactuators. Another application described for this field uses nanonetworks to control animals and biodiversity by using pheromones to trigger behaviours on animals. This process can allow interaction with those animals and also control their presence in particular areas.

Although most of these applications implementations in the real world is still in a far future, the theoretical possibility of creating such systems motivate researchers all over the world to continue working until an implementation is possible. One of the most important challenges to overcome is the ability to have a nanonetwork with addressing and routing capabilities. Published researches on addressing and routing mechanisms for molecular communication systems are very limited but there are a few theoretical approaches, that take advantage of features from some communication techniques, to create these mechanisms.

- Diffusion Communication

Communication via Diffusion (CvD) is one of the most researched methods of molecular communication due to the process's simplicity, therefore it is important to understand in what way routing can be implemented using this method. In [13] a very interesting study is presented, pin pointing CvD features that can be used to establish a routing mechanism and to what degree it affects the nanonetwork. In this molecular technique, waves of molecules leave the transmitter and propagate through the environment via a probabilistic motion, i.e., Brownian Motion/Diffusion. If the information can be encoded on the type of molecules sent from the transmitter, one can imagine a simple routing technique in which different types of molecules are used to target different destinations. However, when using CvD one aspect to have in mind is that nanomachines other than the receiver affect the propagation behaviour of the information molecules, hence when using an addressing structure embedded to the molecule type, nanomachines outside from the communication act as impenetrable barriers. However, these intermediary nanomachines can be designed to serve as signal repeaters or as signal guiders. In [13] the authors compare a free diffusion environment with one transmitter and receiver and a multi-node topology using molecule type addressing mechanism and show that the probability of hit at the receiver increases in the multi-node environment. On [13] the authors performed tests to see the impact that the release point has on communication by establishing a scenario of communication between two nodes and the transmitter node would swap releasing point in a 30° angle intervals. The results authors provided show that the probability of hit clearly decrease when the angle is greater than 30° and after 60° the probability is less than 50%. The results also show that the average delay of information molecules is influenced by the angle of the releasing point, when the angle



is larger than 30°, the average delay increases considerably as the angle increases. So, in a routing mechanism perspective, the selection of the releasing point would be different based on the target of the transmission, for a given node. In [13], the authors propose and analyse some different schemes for a routing mechanism using different release points.

There are other important researches papers that approach the challenges of addressing and routing in diffusion based molecular communication. In [14] the authors explain how gap junctions between cells can be used and manipulated in order to create pathways and cell switches in a calcium signalling molecular communication scenario. Although, the concepts described on those papers were not applied in the work developed in this paper.

- Molecular motors

To this point researches mentioned are based on diffusion of molecules but other methods of communication, such as molecular motors, are also being researched. On this method rail molecules, or microtubules, are deployed creating a connection between nanomachines. The information is encoded into vesicles which travel along the rail molecules through molecular motors, such as kinesin. The vesicle travels on the molecular motors until it reaches the destination, which can be specified by protein tag that only binds to a certain receptor. The authors of [15] describe molecular communication through molecular rails with some detail, and acknowledge that they focus primarily on single hop communication, however they describe a few mechanisms that will allow implementation of multiple hop communication. The mechanisms described help convert the signals from nano to macro scale, send molecules over a long-distance or even multicast to target nanomachines, allows the receiver to respond to a request and addressing nanomachines, which allows the transmitter to target different destinations.

One molecular motor based research that is relevant for this paper is [16], where the authors envisage a new technique for molecular communication, which mixes features from molecular diffusion and molecular motors. The authors create a hybrid communication technique in which several star-shaped molecular rails converge into the receiver, having their direction lead to the receiver. In this hybrid technique, the transmitter is not directly connected to the receiver, hence information molecules diffuse from the transmitter, propagating in the environment, until they hit one of the molecular rails that belong to the receiver. The information molecules upon being bound onto the molecular rails, they will travel along the rail until they reach the receiver. With this simple

manipulation of existing techniques, the authors created a technique that inherits the best from both diffusion and molecular motors communications. With this hybrid scheme, the receptor affinity (area around the receptor that captures molecules) is increased, thus increasing the probability of hit, therefore increasing the reliability of transmission.

Routing in molecular communications is still a very tricky subject, and there are still many challenges ahead, but there is one concept that different researches are converging to. This concept is based on the idea that for the ideal routing scheme, different techniques of communication will have to merge together and create a standard, in order to establish a communication and route information in different ranges. In [16] the diffusion and molecular motors techniques have been merged creating a hybrid method of communication that takes some features from each technique, creating a new one that will certainly have its use in specific applications.

- Bacteria communication

One method of molecular communication which has been proposed and presents itself as a very promising approach is the use of bacteria to establish communication. This method offers several attractive properties found in bacteria, such as the biased motility, i.e., the random walk towards the destination through chemotaxis process and the ability to transfer information, in this case genetic information, between each other using bacterial conjugation. Through the use of different chemoattractants the motility of a bacteria can be controlled, achieving the possibility to direct bacteria in the environment.

In [17] the authors propose an opportunistic routing process for a bacteria communication network by using the properties described above. The bacterial conjugation is the process of transferring DNA from a donor to a recipient cell. Although this feature seems very attractive, the conjugation process has the disadvantage of being a very slow process because of the complexity of protein machinery and occasionally the security and trust procedures that reside inside the recipient bacteria [18]. Moreover, the time that takes to complete the process depends on the amount of information on the gene that is being transferred, additionally, the transfer process takes several minutes to start due to the structural bounding required. In order to implement a routing scheme with bacteria communication, the authors applied both bacterial conjugation process and bacteria chemoattractants enabling them to implement a Delay Tolerant Network (DTN) routing scheme on a bacteria communication nanonetwork. A multi-hop system can be envisaged when considering these features, and the authors of [18] created several scenarios in which they study the performance of



such systems. By further manipulating these techniques, bacteria communication can be used to created addressing and routing mechanisms. In Sect. 3 these features are used in the proposed created mechanisms.

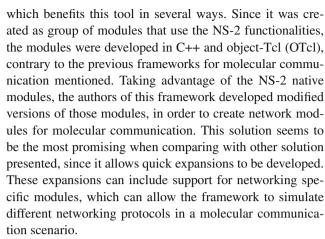
Most of the researches mentioned so far provide some simulation's results from mathematical models, while only a few use simulation frameworks created for nanocommunications. Although the mathematical simulations can provide helpful support to verify a performance of these systems, there is a need for a simulation framework, which allows researches to quickly perform simulations to validate their concepts. Simulation frameworks like this exists for regular computer networks, which help small researches validate small projects or new concepts. Being a new paradigm in communications, there are only some simulation frameworks focused for nanonetworks developed to date, targeting different types of nanocommunications.

In [19], the authors present a framework based on electromagnetic communication in the Terahertz band, designed for simulate wireless nanosensor networks (WN SN). The *Nano-sim* is a module of the well known Network Simulator 3, in which the authors implement the main types of nodes that are used in WNSN, MAC and PHY protocols, network layers, as well as channel access procedures.

On the other hand, simulation frameworks like *N3Sim* [20], *NanoNS* [21], and the one proposed in [22] have been designed for molecular communications, which is the most promising communication method. The *N3Sim* was design in order to simulate a set of nanomachines that communicate through molecular diffusion, in which information is encoded into the variation of the concentration. This framework is a very simple tool which implements a set of mathematical equations, but creates a level of transparency for the user, since the only requirement is to define the topology and the parameters, and a simple graphic output is generated.

Although this framework is similar to the one in [22], since both are a Java implementation, the latter offers a overall solider solution by including important features that distinguish itself from other solutions. While in *N3Sim* the simulations are done in a 2D environment, this tool calculate simulation in a 3D environment, which produce simulation results closer to the real-world. Additionally, while other framework tools use a Brownian motion model to describe the diffusion process, this tool uses a lattice position scheme, i.e., the authors use a multiparticle lattice gas automata algorithm, which divides the medium into latices sides. Hence, the exact position of a molecule is not necessary, since only its lattice position is required.

One of the most important simulation framework for nanocommunication, specifically molecular communication, is the *NanoNS* [21]. This tool was developed as an expansion to the commonly used Network Simulator 2 (NS-2),



This section creates a brief showcase of several researches that, in some way, influenced the work developed in this paper. The research papers described reach a high variety of subjects important for this field, however the mentioned research papers that describe communication techniques that allow addressing and routing mechanisms to be envisaged are the most important, since the designed system greatly focuses on these main networking components.

3 System architecture

In this section a system architecture for molecular nanonetworks is designed and carefully described. This system concept was envisaged according to current researches presented in the previous section, however, it is a new and unique approach for a nanonetwork system. Since this field of research is still very recent, and researches are still trying to find the optimal way of composing a nanonetwork, the system concept in this section tries to answer several challenges mentioned by other researches, and aggregate positive features from several aspects, to create an optimum system.

The motivation behind this concept was to create a nanocommunications system that would resolve popular problems and challenges, by manipulating existing and known features. The challenges that were targeted focused in the transmission performance, the ability to address individual nodes in the nanonetwork and give the nanonetwork some addressing and routing capabilities. Due to lack of resources and the early stages of research in this field, the most favorable approach is to use the inherited features from molecular communications, in order to address the challenges described.

3.1 Topology and communication techniques

The first thing to understand in this concept is the importance and the impact the topology has on the system's performance. The selected molecular communication techniques



individual features have an important role in the envisioned topology, since those features are manipulated in order to take advantage from them and thus, increasing the performance of the system.

- Communication techniques

In the interest of expanding nanonetworks effective range and create building blocks for future communication from nano-scale to micro-scale, allowing IoNT systems to be a reality, a communication mechanism that would provide those capabilities was envisioned. With that in mind, the specified mechanism utilizes different molecular communication techniques, which co-operate to achieve communication between different range levels.

The use of bacteria to establish communication in the medium-range was almost immediate, since the features it offers makes it one of the most promising molecular communication techniques. Since the bacteria communication uses a DNA encoding, which also offers very promising features, described in the next subsection, the objective was to select a short-range communication technique that would also use and benefit from DNA encoding. In the initial concept the molecular motor technique was considered, but then the paper [16] analysed in the previous section, envisaged a clever approach in which a hybrid system between molecular motors and molecular diffusion is created. Using these two approaches, the communication techniques used in this system are established. A hybrid approach between molecular motors and diffusion is used for communications at a short-range level, while a bacteria communication approach is used to establish communication at a medium-range level. An unification between the different range levels is met by using the same DNA encoding process. A message created in the short-range level, i.e., small nanomachines and nanosensors, can be directed through the network until it reaches a nanogateway, a nanointerface, that possibly connects to, for instance, a personal area network, which is connected to the internet.

In this system is considered that the nanogateways in the medium-range level can be individually targeted using different chemoattractants. On the other hand, to efficiently control the reliability of the transmission in the short-range, additional efforts have to be made. In the previous section it was described how important is the release point when using a diffusion-based communication, so, in order to maximize the efficiency, a static release point was defined but the proposed approach allows a prediction of where that release point will be pointing to, so the topology would have to be built accordingly.

In this concept the proposed solution forces the simple nanomachines, nanosensors, to assume a position. The manufacturing process of these devices would have to include a gömböc proportional to their size, which will force the nanomachine to assume a specific position. A gömböc is a mono-monostatic body, which is a convex three-dimensional homogeneous body, which when resting in a surface has one stable and unstable point of equilibrium, which is a similar behaviour to the commonly known balancing toys called "comeback kid". The gömböc was proven in 2006 by the mathematicians Gábor Domokos and Péter Várkonyi [23,24], and they discovered that there is no specific shape for a gömböc, but after ten years of research they found the equations that defines one, so it it feasible to manufacture a nanogömböc.

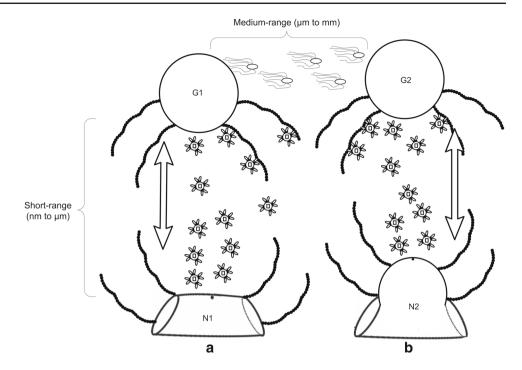
Mono-monostatic body nanomachines or nanomachines with a gömböc integrated would force them to always stand in the same position, so if the releasing point is placed in the apex of the nanomachine, the transmission will always be upwards. It is possible to manipulate the density of the nanomachines in order to make some "heavier" to sink in the environment, and some that "float in the middle" of the environment. Hence, the simple nanomachines, nanosensors, would sink and only transmit upwards, where the gateways nanomachines would hover around, receive the information, and communicate with each other by means of bacteria.

In Fig. 1 it is possible to see everything described in this subsection, there are two levels of communication illustrated, the bacteria communication in the medium-range to support communication between nano-gateways and the hybrid method described in [16], which utilizes both features of molecular motors and diffusion based communications. The hybrid method diffuses vesicle molecules with several molecular motors attached, the nodes that take part in this communication contain several molecular rails, that have the direction configured to converge to the node. The diffused vesicles will travel the channel until they reach either the destination receptors or one of the molecular rails that will guide it to the receiver. This short-range communication can be design to support bi-directional or uni-directional communication, the only requirement is that the nanogateway must be able to diffuse downwards.

Also illustrated in Fig. 1 are some example approaches to the nanomachine body manufacture. In Fig. 1a approach, the nanomachine entire body is a gömböc, i.e., a monomonostatic body, while in Fig. 1b the body is modified in order to have a gömböc in the bottom and the nanomachine itself is appended. With the method (B) some characteristic of the mono-monostatic body could be lost, depending on the manufacturing process, but with accurate construction most properties could remain unaltered.



Fig. 1 Illustration of the communication techniques used in this concept. a Mono-monostatic body manufacture approach. b Modified mono-monostatic body manufacture approach



- Topology

The concept topology selected was targeted at a sensoring network, for a biological or medical application. Since most efforts in molecular communications are for bio-medical applications, the motivation was to design a system that could be used in these applications. The topology is based on a hierarchy topology, common to sensor networks, but it needed to be adapted for a three dimensional environment. The first level to be described is the bottom level of the topology, which is composed by simple nanomachine with nanosensors and/or nanoactuators, etc. When the system is deployed, these will sink, as mention in the previous section, creating the first layer of the topology, as seen in Fig. 2a.

Using the approach described in the previous section, these nanomachines will communicate upwards to the closest nanogateway they encounter. These nanogateways are above the nanomachines, and communicate with one another using bacteria, establishing the mediumrange level. In Fig. 2b is possible to see an illustration of the two levels stacked, in which the hybrid communication between levels is represented by the cones and bacteria represent the communication within the medium-range. It is possible for several applications to place more layers of communication on top of the medium-range layer, thus creating a more complex nanonetwork system or IoNT systems. At the micro-scale the nanointerfaces are a closer reality, so a transduction from molecular signals to electromagnetic signals become possible, additionally, a nanointerface is able to, theoretically, transform the DNA information into a pheromone

signal, hence extending the range of the nanonetwork to the meter-scale, and maintaining its molecular nature. Some of the possible applications are illustrated in Fig. 2. In case of (c), the nanonetwork uses a molecular-toelectromagnetic nanointerface to communicate with a user device (bracelet, smart-phone, etc.), which in turn transfer the information to a web server. This type of application could be used in a fitness or mobile monitoring medical application. In this case, the nanonetwork can also directly connect to a small local server, possibly being a local information sink, or a relay server that transmits the information to a web server, which can be used in medical devices, like advanced imaging machines, medical condition monitoring for people that are bedridden at hospitals or their homes. In the case (d) the nanonetwork uses a nanointerface that transform the DNA information of bacteria into pheromone signalling, expanding the range of communication to the long-range. In theses scenarios, the best applications could be used in environmental situations, like water and air quality control, agricultural situations like livestock and pest control, military application, like offensive/defensive measures, and several more applications which are still to be envisioned. On the other hand, the use of pheromones in medical applications is not very common, and most certainly will not have a great impact in the medical field.

The proposed concepts resolve important challenges in the molecular communication methods used and increase the efficiency of the nanonetwork overall. The designed base topology takes advantage of the concepts described and sev-



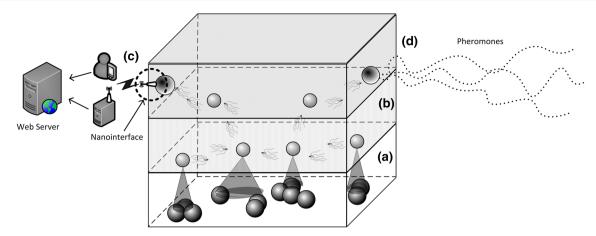


Fig. 2 Full molecular nanonetwork illustration. a Short-range layer, with simple nanomachines with nanosensors and/or nanoactuators. b Medium-range layer, with complex nanogateways capable of routing information bacteria. c Applications possible through a nanointerface

that transduces molecular information into electromagnetic waves. **d** Applications possible through a nanointerface that transforms DNA information into pheromones signalling

eral alternatives that can be placed on top of the base topology for different ranges of applications. However, for these applications to operate as intended, the information gathered from the nanomachines needs to have an encoding process in order to reach the destination safely.

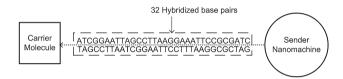


Fig. 3 Example DNA sequence loaded into a carrier molecule. Each nucleotide has his base mirrored with the corresponding pair nucleotide

3.2 Information's encoding

A DNA encoding was selected due to promising results in researches studied, and it can offer high flexibility, allow a larger quantity of data to be encoded, and with these features the performance of the designed concept benefits greatly. Additionally, with this encoding technique the system can easily decode information into ASCII characters, allowing a external user to directly interact with it. This encoding process is possible by using the four bases used in DNA: adenine (A); cytosine (C); guanine (G) and thymine (T). These four DNA bases can form a base-4 encoding, which can be used in long sequences in DNA strands. There are different methods of DNA encoding, but researches shows promising results using a DNA hybridization [25], in which a DNA encoded molecule is double-stranded and it is composed of two polymers of nucleotides, with each nucleotide from one polymer bonded to one in the other forming a base pair (bp). Each nucleotide contains one of the four possible bases mentioned, and the base in one nucleotide determines the base in the paired nucleotide, in which the pairs are either AT or CG, as shown in Fig. 3, where an example sequence is loaded into a carrier molecule. According to [26], each base pair can encode 2 bits, since each nucleotide has four possibilities and the paired nucleotide is determined by the first, and in [27] states that is possible to encode up to 1.6 mbp (mega base pairs), which, by doing the math, brings an approximate of 3.2 megabits per DNA molecule.

When using bacteria based communication there are some features worth to mention, like the ability to load several plasmids, i.e., DNA encoded messages, into a single bacteria, which makes bacteria communication ideal to aggregate information from several sources, and transmit a larger quantity of data at a time. In a bacteria communication, the information can be transferred from bacteria to bacteria or bacteria to receiver through a bacterial conjugation process. However, this process can be interrupted and the information in the new bacteria would be corrupted. To ensure only complete messages arrive at destination, the authors of [28] envisage a technique to remove this problem in the communication, in which targeted antibiotics are released into the environment removing bacteria. In order to only remove corrupted bacteria, the authors appended a antibiotic resistant gene to the encoded message. So if a complete bacterial conjugation takes places, the cloned bacteria will also inherit the resistant gene, so only defective bacteria will be removed with the antibiotics. In Fig. 4 an example of a plasmid construction using this technique is illustrated, the other genes are common genes found in plasmids. Hence, with this technique an error detection mechanism is implemented into the





Fig. 4 Illustration of appended antibiotic resistant gene to the message in the construction of the plasmid that will be loaded into the bacteria. The other genes in this illustration are common genes that are present in plasmids

system, and the number of defective bacteria arriving to the destination is reduced.

The packet envisioned for this system is very simple, containing three information blocks regarding destination and source, and one block for the information itself. There are three blocks for destination and source because it is required one block for the source and two for the destination, since one targets the destination nanogateway, and the other the destination nanomachine. The length, in base pairs, of each block is not rigid, since the total length for the message also depends on the type of molecules and plasmids the system uses, but a reasonable number would be 4–8 base pairs each to define the source and the destinations. The rest of the available length would be for the message, although this directly depends on the size of the network, as the number of nodes increases, the number of base pairs needed to identify source and destination would have to increase as well.

Considering that the message is encoded in a sequence of base pairs, and there are different blocks of information, it is important to differentiate them from other information in the plasmid. In order to achieve this communication requirement, a technique must be implemented in the system which manipulates different restriction enzymes. A restriction enzyme is an enzyme that recognizes a specific base pair sequence, and cuts the DNA in that specific site, the restriction site. These enzyme are commonly found in different bacteria, and they were created as a defense mechanism against invading viruses. There are several restriction enzymes discovered, and the sequences they react to, so when the sender nanomachine encodes the information, the sequences can be inserted between the information blocks in order to differentiate them. The only drawback is that the sequences and the enzymes to use must be integrated within the system, and cannot be changed on demand.

In this system concept two different restriction enzymes are used in order to wrap all blocks of information, as seen in Fig. 5, in order to differentiate them from other information in the plasmid. The length of the sequence each enzyme reacts to, depends on the enzyme itself, so the selection of the enzymes had in mind the length they would require, choosing enzymes with short sequences. The picked enzymes are the *SmaI*, isolated from the *Serratia marcescens* bacteria, and the *HaeIII*, isolated from *Haemophilus aegyptius* bacteria. Both of these enzyme create a "blunt" cleave, i.e., the cut performed leaves the same amount of nucleotides in each side.

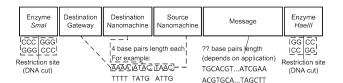


Fig. 5 Example DNA packet encoded into the carrier plasmid

In Fig. 5 it is possible to see the base pairs sequences which these enzymes react to, and the "blunt" cleave they create. Although the use of two enzymes and length for addresses were defined in this example design, they are not a constraint in the design, so this architecture is open for other enzymes and address lengths to be used.

A nanogateway after cleaving the message from the plasmid, can read the headers blocks in order to decide where to guide the message. In this design the scope was not how gateway nanomachines will handle enzymes, but researchers studied the behaviour of these enzymes, and have used them in experimental scenarios, and the progress in DNA computing and nanotechnology will allow for complex nanogateways to be created, with capability for automated enzyme actuation, which will allow systems similar to the one presented to be a closer reality. However, these system require addressing and routing mechanisms to be able to operate efficiently.

3.3 Routing and addressing mechanisms

Addressing and routing mechanisms allows several nodes to easily share information and participate in distributed tasks, achieve complex applications which would not be possible by a single node. These features are even more important in a nanonetwork than traditional computer networks. Although lot of the paradigms change from one to another, these features would allow nanonachines which, due to their small size and low complexity, cannot even achieve simple tasks by themselves, to form a real nanonetwork which would place the research of nanocommunications a huge step forward. Although molecular communication has several behaviours that pose as obstacles when trying to establish a nanonetwortk, it also have features that can benefit the nanonetwork. An example of an inherit behaviour that benefits a nanonetwork, in this case by proving a routing and addressing mechanism, is the use and manipulation of different bacteria and chemoattractants.

- Addressing mechanisms

In order to address different nanogateways and route the information accordingly, the system controls different chemoattractants, while each nanogateway has the properties to create bacteria that will only react to a specific chemoattractant. These chemoattractants can be trans-



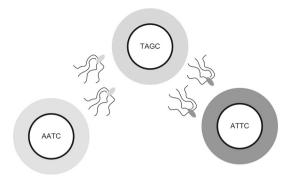


Fig. 6 Illustration of communication between nanogateways using different chemoattractants

lated to a value address, for example if a nanogateway has the address AATC, the nanogateways that want to reach it will use bacteria that will react to the AATC chemoattractant. A translation table or a procedure which determines what type of bacteria to use in order to react to a specific address is needed. How nanogateways will achieve these functionalities is not the scope of this work, being the target of big research teams which focus in advancing nanotechnology and the manufacturing process. In Fig. 6 it is possible to see a scenario where several nanogateways share information through bacteria and target different destinations using bacteria that will only react to the chemoattractants released by the targeted destination.

In this system concept the nanogateways can be compared with the base stations in a telecommunication system, while the simple nanomachines nodes can be compared with the cell-phones terminals. When the nanonetwork is deployed the nanomachines will proceed to look for a nanogateway, associating themselves with the first nanogateway they find. The nanogateway upon receiving a request from a nanomachine, will start a procedure in which it will designate an address for that nanomachine based on its own address, and answers the nanomachine with a message saying that acknowledged his request and containing the nanomachine address. The nanomachine will associate to the nanogateway which answer arrived first, which can mean that it is the closest nanogateway or the closest nanogateway which was able to attend his request, as illustrated in Fig. 2a, b. Several nanomachines can be associated with a single nanogateway, and when the nanogateway later on transmits information by diffusing molecules downwards, there will be molecules arriving at the wrong destination. When using this hybrid method of communication it is not possible to target a specific nanomachine, however the diffusion technique used will only affect a few nanomachines, which most likely are associated with that nanogateway. Nevertheless, the nanomachines

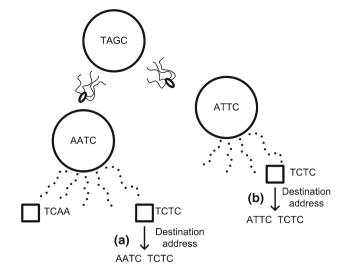


Fig. 7 Illustration of communication between nanogateways using different chemoattractants

will need to have a mechanism to discard packets which do not contain their address.

Two addressing schemes were described, a chemoattractant based addressing in the medium-range that would enable to identify different nanogateways, and a short-range addressing scheme that enables nanomachines to have an unique address based on the address of the nanogateway they are associated with. Herewith, the destination address is composed of two blocks illustrated in the previous section, destination nanogateway plus the destination nanomachine. For example, a nanomachine with address TCTC can exist in several points of the network, as Fig. 7a, b shows, but the nanomachine TCTC that is associated with the nanogateway AATC is unique, as seen in Fig. 7a. So messages that want to target that nanomachine are composed of the nanogateway address plus the nanomachine address, and these two block together can be objectively called the destination address, or destination nanomachine address.

With these mechanisms it is possible to uniquely identify individual members of the nanonetwork, and they provide the capability for a routing mechanism to be created in order to guide information within the network from a source to a destination.

- Routing mechanisms

In this concept it is considered that nanogateways have capabilities to store information, like a translation table, or a routing table that will be generated. The envisioned mechanism that would allow a routing table to be formed considers that all nanogateways have the same specific neutral chemoattractant, besides the individual chemoattractant, which can allow them to broadcast in



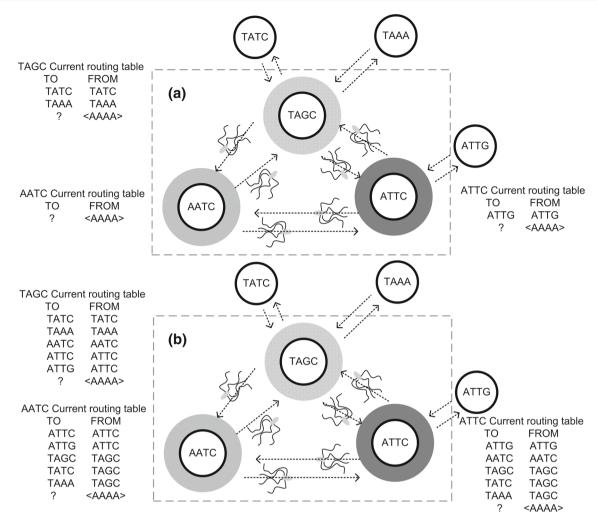


Fig. 8 Routing tables generation mechanism in two steps. The *black lines* in the chemoattractant fields represent the neutral chemoattractant common to every node. In **b** the updated routing tables are presented after **a** is completed

the environment, similar to a broadcast address in computer networks.

When the nanonetwork is deployed the nanogateways will broadcast to the environment, using the neutral chemoattractant sensitive bacteria, their address, which is a value that translates to a specific chemoattractant. The neighboring nanogateways upon receiving that information will update their routing tables, and broadcast their routing table information. Consequently, the neighboring nanogateways will receive the routing table, and update their own, and proceed to re-broadcast their routing table. This process will go on, until a nanogateway receives a routing table from a neighbor and it realizes that no new information was given, so an update of its routing table is not needed, and he will not broadcast his routing table. This process is similar to a process used in ad-hoc networks, because the network nanogateways will form is objectively an ad-hoc network. This process is illustrated in Fig. 8, in which the routing tables are shared with neighboring nodes, and those nodes updates their tables. After step (b) the routing tables would remain unaltered since all possible targets were in all routing tables, although the nodes would still share their routing tables on that iteration.

When a nanogateway receives a message and processes it, it will read the destination nanogateway, if the address is his own, the message its diffused downwards to his associated nanomachines, otherwise it will check its routing table, look for that destination address and determine to which gateway it has to transfer the message. Once it knows where the message needs to be transferred next, it will determine what type of bacteria it needs to use, by querying the translation table, encode the message in the bacteria, and transmit the bacteria (Fig. 9a). This process continues until the message reaches the destination gateway, which transfer the message to the associated nanomachines (Fig. 9b), however the mes-



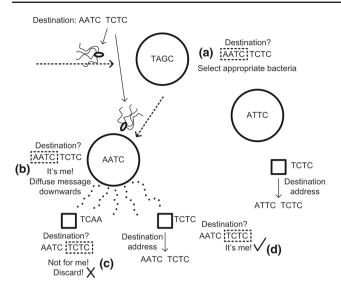


Fig. 9 Illustration of a message reaching a destination. The procedures presented are the main components that enable the routing of messages. a Nanogateways route the information until it reaches destination nanogateway. b Message arrives at destination nanogateway, it reacts to it and diffuses the message downwards to his associated nanomachines. c Message reaches a nanomachine which is not the destination, so the message is discarded. d Message reaches the final and correct destination nanomachine

sage will reach all nanomachines he can reach, and when using a diffusion process is not possible to exactly target a specific nanomachine. So the nanomachines, upon receiving a message, will read the nanomachine address, if it does not belong to it, the message is immediately discarded (Fig. 9c), otherwise it continues to read the message (Fig. 9d).

In this section several concepts are introduced to nanonetworking and some techniques are modified in order to achieve the required capabilities to allow the information routing. This section is very important to understand the synergy between all elements of the designed system, since they all come together and individually provide features that allow the envisioned mechanisms to function.

The solutions presented to solve the challenges on addressing and routing in nanonetworks, originally modify and integrate several mechanisms from other systems in a nanonetworking scenario, which also transmits an important message. Even though this is a new field of research, and researches from all over the world are trying to conceive new techniques which can allow nanonetworks to be closer to the reality, there are several mechanisms already implemented on other fields which, when modified correctly can be integrated in a nanonetworking scenario.

4 Case study

Molecular communications tend to be applied in biomedicine applications due to its characteristics. In [25] a good

description of a future health care system is given, using motor based nanomachines and DNA hybridization transport. Molecular communications supplies means to send, to transport, and to receive molecules and allows biological and artificially-created components such as sensors and reactors to communicate with each other using molecules. Consequently molecular communication provides a tremendous potential to enable future health care applications such as drug/DNA delivery systems [29], and monitoring of health conditions using implanted biochemical sensors.

The endocrine system is responsible for secreting hormones directly into the bloodstream. And, in some individuals, can malfunction. Generating either too much or too less hormones, these are called endocrine diseases. This condition has a vast range of specific illnesses, which include some well-known diseases, such as diabetes, the Cushing's syndrome, hyperthyroidism, and hypothyroidism [30]. Unfortunately these diseases don't have a cure, but they do have a treatment to keep them stable. These treatments function is to keep the levels of a specific hormone within threshold limits. Nowadays individuals that suffer from diabetes, for instance, have to constantly measure their levels with a simple blood sample test, however, this monitoring could be made by an automatous system, using a molecular communication bio-nanosensor network.

The nanomachines used in this kind of application, are molecular scale objects that are able of performing simple tasks such as actuation and sensing [4]. Although nanomachines are able to complete tasks such as drug delivery, in this type of application it is too early to think in an actuation system due to the risks involved. But a sensing-only system can be theoretical hypothesized. If a number of nanomachines were deployed, scattering around the body, providing a continuous reading of certain hormone levels, through bio-sensors, it would be possible to monitor these levels automatously and continuously. This nanosystem would then communicate with a remote computer, through a nanointerface. This nanointerface would allow a conversion from molecular signalling to electromagnetic waves, as it shown in Fig. 10.

5 Architecture evaluation

After envisioning and designing a system, a validation process must occur in order to gather data that can move the project to a implementation state. As mention in the previous sections, this is a new field of research and the simulation framework tools developed by the community are still very limited. In order to obtain experimental results of an original system, these tools need to support several features, which they don't have at the moment. Thus, the existing tools need to be developed further and modified to achieve the required



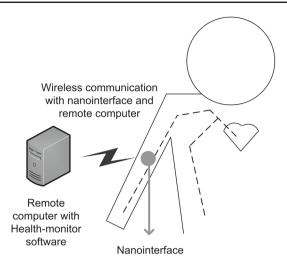


Fig. 10 Health-monitoring system illustration

features that allow these envisioned systems to quickly be tested and validated. In order to evaluate this architecture and, at the same time, create specific scenarios that would help to better understand and validate some concepts, several simulations were performed in available tools.

Unfortunately, there are no simulation framework tools available that support bacteria communication, and all their features. On the other hand, the community seems to be focusing on diffusion based communications and already developed some simulation tools that support it. Since molecular diffusion technique is often described as unreliable, unpredictable and not very efficient, several simulation scenarios were created in order to better understand this technique. The simulation tool described in Sect. 2 by the name of *NanoNS* was the tool that better fitted the requirements, and Özgür Barış Akan, one of the authors, was kind enough to share the tool so these simulation could be performed.

On all simulation scenarios created the environment parameters were maintained in order to achieve fair and comparable results. In [31] a study was conducted which explored the optimal environmental parameters for a diffusion communication, so in the scenarios simulated the environmental parameters were set to be as close to the values mentioned in [31] as possible. Additionally, on all simulations the amount of molecules sent from the transmitter was set at one thousand molecules.

The first simulation scenario presented in this section is the baseline scenario created, in which all other scenarios can be compared. In this simple scenario a transmission between two nanomachines was configured, in which the distance between them is 100 nm and they are located in a three dimensional environment. The Fig. 11 shows the results obtained from this simulation and it is possible to see that the molecules that reach the receiver quickly scale up, but after 0.1 s the number of molecules received stabilizes and keeps

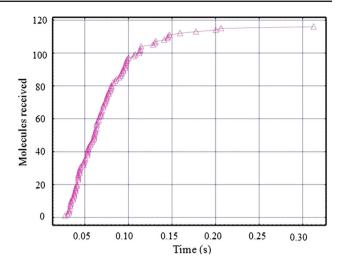


Fig. 11 Baseline simulation result, molecules received measured as a function of time

more or less constant until the simulation time is depleted. However, it is possible to see that the number of molecules received doesn't even reach 120, having in mind that 1000 molecules were transmitted, a surprising result of a loss rate 88% is achieved. The expected results weren't very promising, but the results obtained were negatively suprisingely, and demonstrate how this communication technique is unreliable.

In the first scenario the molecular reaction were represented by direct hit on the receiver nanomachine, so by applying a stochastic equation to calculate a statistical reaction of molecules, like the Gillespie algorithm, another simulation scenario was created. In this simulation scenario is possible to see the impact receptor affinity, described in chapter 3, has in molecule reception. In Fig. 12 it is possible to see that more molecules were received when comparing with the baseline scenario. Although there is only a slight increase, that is explained by the distance between nanomachines, since the distance from the baseline scenario was kept, the randomness factor of diffusion still is the most prominent element in the transmission. Comparing this scenario with the baseline, the differences in overall behaviour are very slim, however it can be observed an increase in molecules received and thus a decrease in loss rate, being around 86%.

It was already described in previous chapters the influence distance between nodes has in a diffusion based transmission. In this next scenario the distance between the two nanomachines was reduced by 70%, in order to evaluate the impact this parameter has in the transmission loss rate. Since the distance was reduced by 70% it was expected a dramatically decrease of loss rate, however the simulation results show that although the loss rate decreased, it wasn't a substantial decrease as expected, as shown in Fig. 13. It is possible to



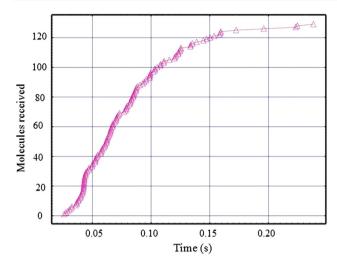


Fig. 12 Gillespie algorithm simulation result, impact of receptor affinity, molecules received measured as a function of time

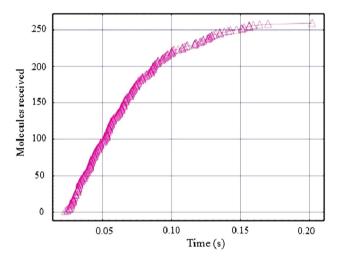


Fig. 13 Impact of distance between nanomachines simulation result, 70% reduced distance when comparing with baseline, molecules received measured as a function of time

see in Fig. 13 that the loss rate reached around 74%, although when comparing with previous scenarios it is possible to see that about one hundred more molecules were received.

The simulation scenarios described so far use equally sized nanomachines, and as described in previous chapters, the increased surface perimeter of nanomachines can increase the receiving efficiency of the nanomachines. In order to evaluate this feature a simulation scenario was created in which the radius of the receiving nanomachine was increased by 50%, in order to maximize the gathering capabilities of the receiver. Figure 14 shows the simulation results of this scenario, and it is possible to observe that the loss rate decrease to 15%. A closer look shows that in this scenario, there are over seven hundred molecules gathered, which is more than 70% of molecules sent, in 0.04 s. From this result it is easy to see that in a molecular nanonetwork based

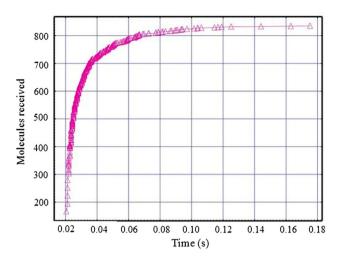


Fig. 14 Increased radius in receiving nanomachine simulation result, molecules received measured as a function of time

on diffusion, it would benefit the transmission if receiving nanomachines would be slightly larger than other nodes.

Finally, to evaluate a simple concept, which consists on the idea that if a transmitter diffuses molecules in the environment, the transmission can always be one-to-many, i.e., broadcasting. Hence, a receiving node can be composed by a cluster of receiving nanomachines which are strategically positioned, in order to increase the efficiency of molecule reception. A simulation scenario was created in which two receiver nanomachines are strategically deployed, in order to simulate a receiving node composed of several receiving nanomachines. In Fig. 15 its shown that with two receiving nanomachines the loss rate is around 70%, which means that the decrease in loss rate is a little better than a direct proportion to the number of receiving nanomachines. It is also possible to observe that in the first 0.1s the number of molecules captured is almost the double, when comparing with the baseline simulation result.

By observing Fig. 16, it is possible to compare all simulation results, and better identify the features that allow the loss rate to be minimized. The result for increasing the receiver nanomachine radius clearly stands out, and it possible to see the impact this feature can have on diffusion based transmissions. Although this type of transmission is very susceptible to environmental factors, if the nanonetwork is configured correctly and some features could be implemented on that system, it is possible to achieved working applications. These features can be simple solution like decreasing the distance between nanomachines, creation of cluster nodes composed of several nanomachines in order to increase the reception potential, although in Fig. 16 a slight decrease in loss rate is seen, the results show promising results that motivate these features to be further investigated.



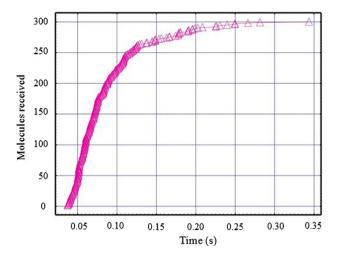


Fig. 15 Two receiver nanomachines simulation result, molecules received measured as a function of time

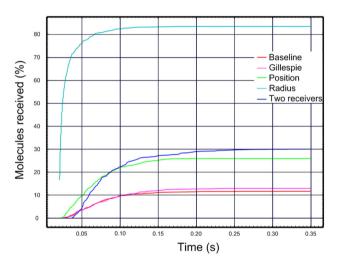
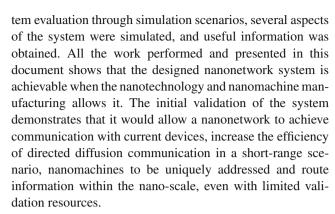


Fig. 16 Comparison between all simulation results obtained, % molecules received measured as a function of time

6 Conclusions

The advances in nanotechnology and other research areas directly connected to it will continue and will have a great impact in almost every field of our lives, mainly increasing the quality of life of mankind around the world. The developments in this field will allow applications to be born that can help save lives by early disease detection and disease monitoring, the quality control of the environment will increase, the consumer goods will get better quality and agricultural applications will allow a better control of livestock and plantations fields. These new applications will completely change the paradigm in these fields, consequently changing the lives of every human being.

A solution for a nanonetwork system that offers the required capabilities that allow new applications to be created was conceived. In spite of not accomplishing a full sys-



This document describes new techniques that are able to support the research community designing and developing new systems, increasing the efficiency of transmissions and design new routing mechanisms. Additionally, this document passes a message on the mentality that is needed while working on this field. The paradigm changes so much from what networking specialists are used to, that the same methods cannot be applied. Also, this document offers a great foundation in which future projects can be based on.

In the future, this project could continue the development of new modules, expanding a promising simulation framework tool. Firstly new nanocommunication techniques must be implemented, like molecular motors and bacteria communication. Afterwards, it is imperative that protocol support in a simulation framework for nanocommunication is implemented. These modules would enable the researchers to envisage new addressing mechanisms, routing protocols or MAC protocols, and quickly evaluate their performance.

Although, in this research field, the future work for the scientific community has still many decades of researching and developing ahead, a small and important step would be the creation of stable simulation tools, and that is why it makes perfect sense to expand the work performed so far, and continue the development of new modules that step by step makes a complete simulation framework a reality. When this barrier is defeated, this research field is going to leap forward, and certainly enter a new phase of research, where new advances will be even more frequent and real applications will be in our grasp.

References

- Akyildiz, I.F.: Nanonetworks—a new frontier in communications. In: Proceedings of the 2010 International Conference on Signal Processing and Multimedia Applications (SIGMAP), pp. IS-5–IS-5, 26–28 July 2010
- Badjic, J.D., Balzani, V., Credi, A., Silvi, S., Stoddar, J.F.: A molecular elevator. Science 303, 1845–1849 (2004)
- Akyildiz, I.F., Brunetti, F., Blázquez, C.: Nanonetworks: a new communication paradigm. Comput. Netw. 52(12), 22 (2008)



- Hiyama, S., Moritani, Y., Suda, T., Egashira, R., Enomoto, A., Moore, M., Nakano, T.: Molecular communication. In: Proceedings of NSTI Nanotech 2005, Anaheim, California, USA
- Akyildiz, I.F., Fekri, F., Sivakumar, R., Forest, C.R., Hammer, B.K.: Monaco: fundamentals of molecular nano-communication networks. Wirel. Commun. 19(5), 12–18 (2012)
- Parcerisa Giné, L., Akyildiz, I.F.: Molecular communication options for long range nanonetworks. Comput. Netw. 53(16), 2753–2766 (2009)
- Atakan, B., Akan, O.B.: An information theoretical approach for molecular communication. In: Bio-inspired Models of Network, Information and Computing Systems, 2007. Bionetics 2007, vol. 2, pp. 33, 40, 10–12 December 2007
- Atakan, B., Galmes, S., Akan, O.B.: Nanoscale communication with molecular arrays in nanonetworks. IEEE Trans. NanoBiosci. 11(2), 149–160 (2012)
- Akyildiz, I.E., Jornet, J.M.: The Internet of nano-things. IEEE Wirel. Commun. 17(6), 58–63 (2010)
- Agoulmine, N., Kim, K., Kim, S., Rim, T., Lee, J.-S., Meyyappan, M.: Enabling communication and cooperation in bio-nanosensor networks: toward innovative healthcare solutions. IEEE Wirel Commun 19(5), 42–51 (2012)
- Chahibi, Y., Pierobon, M., Song, S.O., Akyildiz, I.F.: A molecular communication system model for particulate drug delivery systems. IEEE Trans. Biomed. Eng. 60, 3468–3483 (2013)
- Cavalcanti, A., Shirinzadeh, B., Freitas, R.A.: Nanorobot architecture for medical target identification. Nanotechnology 19, 015103 (2008)
- Kuran, M.S.; Yilmaz, H.B.; Tugcu, T.: Effects of routing for communication via diffusion system in the multi-node environment. In: 2011 IEEE Conference on Computer Communications Workshops (INFOCOM WKSHPS), pp. 461, 466, 10–15 April 2011
- Nakano, T., Suda, T., Moore, M., Egashira, R., Enomoto, A., Arima, K.: Molecular communication for nanomachines using intercellular calcium signaling. In: 5th IEEE Conference on Nanotechnology, vol. 2 pp. 478, 481, 11–15 July 2005
- Moore, M., Enomoto, A., Nakano, T., Egashira, R., Suda, T., Kayasuga, A., Kojima, H., Sakakibara, H., Oiwa, K.: A design of a molecular communication system for nanomachines using molecular motors. In: Proceedings of the Fourth Annual IEEE International Conference on Pervasive Computing and Communications (PerCom'06) (2006)
- Moore, M.J., Enomoto, A., Watanabe, S., Oiwa, K., Suda, T.: Simulating molecular motor uni-cast information rate for molecular communication. In: 43rd Annual Conference on Information Sciences and Systems, 2009. CISS 2009, pp. 859, 864, 18–20 March 2009
- Lio', P., Balasubramaniam, S.: Opportunistic routing through conjugation in bacteria communication nanonetwork. Nano Commun. Netw. 3(1), 36–45 (2012)
- Frost, L.S., Koraimann, G.: Regulation of bacterial conjugation: balancing opportunity with adversity. Future Microbiol. 5(7), 1057–1071 (2010)
- Piro, G., Grieco, L.A., Boggia, G., Camarda, P.: Nano-Sim: simulating electromagnetic-based nanonetworks in the network simulator 3. In: Proceedings of the 6th International ICST Conference on Simulation Tools and Techniques (SimuTools '13) (2013)
- Llatser, I., Pascual, I., Garralda, N., Cabellos-Aparicio, A., Alarcon, E.: N3sim: a simulation framework for diffusion-based molecular communication. In: IEEE Technical Committee on Simulation (2011)
- Gul, E., Atakan, B., Akan, O.B.: NanoNS: a nanoscale network simulator framework for molecular communications. Nano Commun. Netw. 1(2), 138–156 (2010)
- 22. Felicetti, L., Femminella, M., Reali, G.: A simulation tool for biological nano-communication systems. In: Proceedings of the

- 4th International Symposium on Applied Sciences in Biomedical and Communication Technologies (ISABEL'11), ACM, New York, NY, USA, Article 23 (2011)
- Várkonyi, P.L., Domokos, G.: Static equilibria of rigid bodies: dice, pebbles and the Poincare-Hopf Theorem. J. Nonlinear Sci. 16, 255– 281 (2006)
- 24. Várkonyi, P.L., Domokos, G.: Mono-monostatic bodies: the answer to Arnold's question. Math. Intell. **28**(4), 34–38 (2006)
- Hiyama, S., Isogawa, Y., Suda, T., Moritani, Y., Sutoh, K.: A design of an autonomous molecule loading/transporting/unloading system using DNA hybridization and biomolecular linear motors. In: European Nano Systems, Paris, France, pp. 75–80 (2005)
- Cobo-Rus, L.C., Akyildiz, I.E.: Bacteria-based communication in nanonetworks. Nano Commun. Netw. 1(4), 244–256 (2010)
- Finan, T.M., Weidner, S., Wong, K., Buhrmester, J., Chain, P., Vorhölter, E.J., Hernandez-Lucas, I., Becker, A., Cowie, A., Gouzy, J., Golding, B., Pühler, A.: The complete sequence of the 1,683-kb pSymB megaplasmid from the N2-fixing endosymbiont *Sinorhizobium meliloti*. Proc. Natl. Acad. Sci. USA 98(17), 9889–9894 (2001)
- Balasubramaniam, S., Lio', P.: Multi-hop conjugation based bacteria nanonetworks. IEEE Trans. NanoBioscience 12(1), 47–59 (2013)
- Moritani, Y., Hiyama, S., Suda, T.: Molecular communication for health care applications. In: Proceedings of IEEE PERCOMW 2006, Italy (2006)
- 30. Hoy, C., Beecroft, C.: The patient with endocrine disease. Surgery (Oxford) 31(8), 404–409 (2013)
- Atakan, B., Akan, O.B.: On channel capacity and error compensation in molecular communication. Transaction on Computational System Biology. Springer, Berlin (2008)



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