Liquid Biopsy Using Intra-Body Nanonetworks: Perspective and Approach

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I. Motivation and Problem Statement

Traditional disease screening methods, e.g., tissue biopsy, have a median of thirty days to get lab results (turnaround delay) and are invasive. Recently, an alternative screening technique called liquid biopsy (LB) has been gaining broad interest because of its shorter turnaround delays and minimally invasive nature. It involves taking samples of fluids, such as blood or saliva, to look for disease biomarkers using nano-biosensors [1]. A biomarker can be a protein, a fragment of a protein, DNA/RNA, or an organic chemical made by abnormal cells that indicate the physiological state of a disease. For instance, in the case of cancer disease, the prominent biomarkers, namely, circulating tumor cells (CTC) and circulating tumor DNA (ctDNA), are found in the blood. CTCs are intact cancer cells, and ctDNA refers to small DNA fragments. with LB, the blood sample undergoes a series of ex vivo processes to isolate, enrich, detect, and characterize CTCs, or to isolate and detect ctDNAs. These processes cause a turnaround delay of around 7 days (≈ 10000 minutes) [2]. In addition, the samples contain only a tiny percentage of the total biomarkers available in the bloodstream. For example, approximately 0.3 % of total ctDNA is found in a 15 ml blood sample [3]. This is inefficient, given that in the early phases of a disease, biomarkers are already in extremely low concentrations. Overall, the sampling approach and lengthy turnaround delay render LB ineffective.

In vivo techniques, such as functionalized probes to detect CTCs directly from the bloodstream, have been developed, such as fibers [4]. Such techniques validate the viability of in vivo sensing. However, a majority of the expensive ex vivo steps remain, meaning no reduction in turnaround delays has been reported. The next natural step in innovation would be to reduce turnaround delays from the present best of 10000 minutes to just a few tens. Such short delays would not only enable rapid diagnosis but also real-time monitoring. In addition, it is critical to make these technologies lightweight and mobility-friendly so that patients can use them daily without discomfort. In that regard, the current in vivo approaches for LB are limited.

In this context, **I**ntra-**B**ody **N**anonetworks (IBN) (*cf.* Fig. 1), comprising in-body **B**loodstream **C**irculating **N**anonetwork (BCN) and on-body gateways, hold immense promise [5]. BCN is the inter-network of nanomachines (NMs), which can perform sensing and communication. Given their nano- to micro-meter size, NMs can be deployed with minimal intrusion into the bloodstream, with the ability to detect biomarkers down to a single molecule [6]. This makes them extremely attractive for detecting biomarkers that are in very low numbers. BCNs are further envisioned to communicate with the outside world (through the gateways), enabling real-time health-related data transfers to medical personnel or the patient. These remarkable properties make IBN the ideal technology for next-generation minimally invasive, early diagnosis, and real-time monitoring of disease applications.

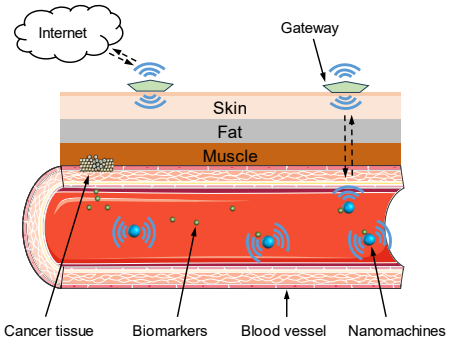

Fig. 1: Schematic representation of intra-body nanonetworks.

At this point, it is essential to note that Mosayebi *et al.* carried out pivotal work in this direction [7]. A model of cancer cells and biomarker generation was developed under the assumption of uniform flow across the cross-section of a blood vessel. The number of biomarkers that the NMs count determines the activation level of an NM, which is what the gateway detects to determine the detection of a biomarker. It was reported that both the density of biomarkers and NMs affected the probability of detection. Due to space constraints, we omit the discussions on the closely related topic of in-body anomaly detection.

In this short paper, using a particle-based simulator, AcCoRD [8], we present two preliminary analyses for IBNs for in vivo detection of biomarkers. 1) Detection probability of biomarkers. Unlike the uniform flow assumed in [7], we consider a laminar flow, which is a realistic representation of the blood flow in blood vessels. 2) **C**ontact-**b**ased **c**ommunication (CbC). As the availability of biomarkers is extremely low, it reduces the possibility that each NM can detect a biomarker. Hence, CbC, in which communication occurs via physical contact, is investigated to improve detection reliability. This opportunistic communication approach also ensures that the information is not lost during transmission, which could happen in a wireless communication setup.

II. Simulation Set Up, Results, and Discussions

As shown in Fig. 2a, without loss of generality, we approximate the blood vessel as a rectangular prism, which matches

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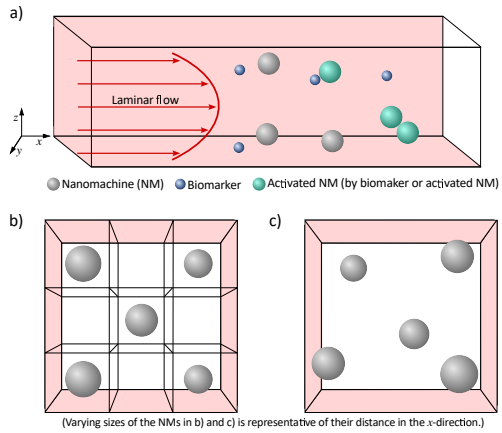

Fig. 2: a) Rectangular prism approximation of a cylindrical blood vessel. Cross-sectional view of the blood vessel b) laminar flow and static NMs c) uniform flow and mobile NMs.

the channel shape in the AcCoRD simulator. The radius of the NM is $1\,\mu\mathrm{m}$, simulation duration is $1\,\mathrm{s}$, and Monte Carlo repetition is 100.

A. Detection probability of biomarkers

The biomarkers enter the prism from the left and propagate toward the other end of the prism via advection-diffusion. Similarly, the NMs are mobile. However, we consider the mobile NMs static, implying that the biomarkers move with an effective diffusion coefficient [9]. To realize the laminar flow, the prism ($100\,\mu\mathrm{m} \times 12\,\mu\mathrm{m} \times 12\,\mu\mathrm{m}$) consists of nine sub-prisms, each with a dimension of $100\,\mu\mathrm{m} \times 4\,\mu\mathrm{m} \times 4\,\mu\mathrm{m}$ (*cf.* Fig. 2b). The velocity at the central prism is $1.5\,\mathrm{mm/s}$. In contrast, that of the surrounding prisms is $0.5\,\mathrm{mm/s}$, reflecting the parabolic profile of laminar flow, where velocity is the smallest along the walls and largest at the center of the blood vessel. Five static NMs are located at $(40, 2, 2)$ µm, $(40, 2, 10)$ µm,$(50, 6, 6)$ µm,$(60, 10, 2)$ µm, and $(60, 10, 10)$ µm.

Fig. 3 illustrates how the detection probability of biomarkers varies with different conditions. As observed, the absorption probability and the number of biomarkers impact this probability. The relationship between these variables is crucial for understanding the efficiency of the in vivo biomarker detection process. This is because the number of biomarkers correlates with the size of cancer tissue and the half-life of the biomarker, and the absorption probability captures the NMs' biosensor properties, such as specificity and sensitivity.

B. Contact-based communication

For analyzing CbC, a uniform flow velocity of $1.5\,\mathrm{mm/s}$ is used, and the NMs travel along the length of the prism via advection-diffusion (*cf.* Fig. 2c). At the beginning of the simulation, only one NM is randomly activated by a biomarker. (In future work, the detection probability will be correlated with activating an NM.) The remaining NMs are activated via CbC over the simulation duration. That said, contact does not necessarily result in activation because of various unforeseen and unknown forces; hence, the *activation on contact probability* is defined as the probability that an inactivated NM is activated by an activated NM.

Fig. 4 shows the relationship between the number of activated NMs and two key variables: the number of NMs and the

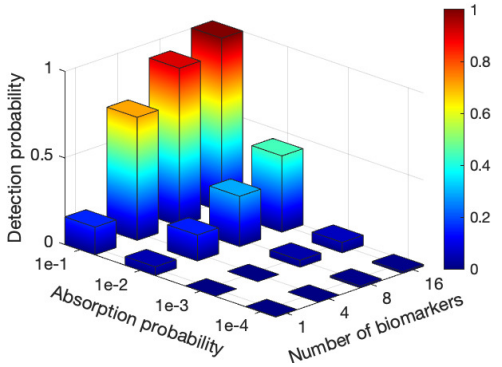

Fig. 3: Detection probability of biomarkers.

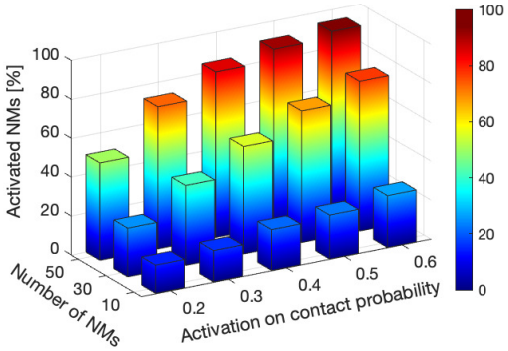

Fig. 4: Percentage of activated NMs.

probability of activation upon contact. We can infer that CbC is an effective strategy in this context, especially considering the low availability of biomarkers. The results indicate the potential for optimizing the deployment and activation strategies of NMs for efficient disease biomarker detection.

Future efforts will focus on simultaneously integrating biomarker detection and CbC events within a unified simulation framework. Additionally, we aim to develop a SAR-compliant and human-safe wireless communication system for efficient data collection from activated NMs. A comprehensive exploration of the system's design space will be undertaken to uncover the fundamental principles guiding the design of IBN for early disease diagnosis and real-time monitoring.

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