DETECTION AND AMPLIFICATION OF MOLECULAR SIGNALS USING COOPERATING NANO-DEVICES

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ABSTRACT

We analyze the performance of a network of very simple nano-devices that cooperate to detect and/or amplify the presence of target molecules. The nano-devices only have the capability to detect a single type of molecules and in response release molecules. Furthermore, each device has a binary operation, and releases all of its stored molecules in response to a single detection. Nevertheless, the network establishes a complex behavior through cooperation between the devices (without additional device complexity). Analysis reveals that depending on the network parameters, the network can implement a mass amplifier (that releases an amount of molecules that is proportional to the input mass) or a binary detector (that generates a macro level response to the presence of a small mass of target molecules). We characterize the network behavior and derive exact expressions for the variance of the response and the miss-detection probability.

Index Terms— Bionanotechnology, Network analysis, Nanoscale devices, nanorobots, Poisson point process.

1. INTRODUCTION

Nano-devices are just around the corner. These nanometer scale devices (sometimes also termed nano-robots) are going to open new frontiers in the sensing and manipulation at the molecular level.

Nano-devices with similar capabilities to those considered in this work have been demonstrated using various technologies. These include devices that are based on DNA molecules (e.g., [1]), hydrogels (e.g., [2]), mesoporous silica (e.g., [3]) and more. However, due to size requirements and the current state of technology, all nano-devices (at least in the first few generations) will have very limited capabilities. Luckily, nano-devices come in very large numbers. Thus, even with limited capabilities per device, the network capabilities can be almost limitless, if the nano-devices are able to cooperate.

The need and potential of cooperating nano-devices is easily imagined, (e.g., [4–6]). Yet the details of such cooperation are far from obvious. So far, analyses of such cooperation were mostly focused on swarm ideas, and assumed some 'significant' communication between the nodes (e.g., [7, 8]). Such 'significant' communication that can deliver data values from one device to another requires protocols, addressing, modulations synchronization and so on.

This type of communication is termed nano - communications and has been studied extensively (e.g., [9–11]). However, it is not feasible at the current technology in devices at the scale of nanometers (or even micrometers). Such devices do not have enough (if any) memory and processing capabilities.

Thus, so far, no theoretical performance analysis had considered the behavior of a complete network of cooperating nano-devices with feasible complexity.

In this work we study the cooperation of very simple nano-devices, where each device is only capable of sensing a specific type of molecule and in response to release molecules (of the same type or different than the sensed molecules). Such devices are feasible using various technologies as mentioned above [1–3]. By choosing one type of molecules to be communication molecules (CM), these molecule are used to achieve cooperation between the nano-devices in the network. This type of communication, where devices communicate indirectly by modifying the environment, was termed stigmergic [12] communications,

While such a network can be used for multitude of applications, in this work we focus on the network ability to operate as a detector. That is, we study the ability of the network to detect target molecules and amplify the response enough such that an external detector (at the macro level) will be able to sense it. We note that this analysis can be easily adapted to networks in which the released molecules have a desired effect on the environment.

2. SYSTEM MODEL

We consider a (set of) very simple nano-devices, which only has a capability to detect a specific types of molecules and make a single action. The only action that is considered is releasing all the molecules stored at the device. We further assume that each device is binary, i.e., it either detects molecules or not, and its reaction for a detection is always to release all stored molecules.

The network is composed of two types of devices. Devices of type T have sensors that can detect the target molecules (TM) and in response release communication molecules (CM). Devices of type C detect CM and release CM.

The TM are considered the input of the system, i.e., the network is designed to detect their presence. The CM is used to coordinate the cooperation between the devices and are also considered as the system output. Thus, the network is characterized by the release of CM in response to the presence of TM. Obviously, we assume also that at the macro level, there are sensors that are capable to detect the CM density and use such measurements to characterize the presence of TM.

Denote the density of TM and CM at any given time, t, and location, $\underline{\mathrm{x}}$, by $m_u(\underline{\mathrm{x}}, t)$, where $u = '\mathrm{t}'$ for TM and $u = '\mathrm{c}'$ for CM. This density follows the diffusion equation [13]:

$$\frac{\partial m_u(\underline{\mathrm{x}}, t)}{\partial t} = -\frac{1}{\bar{\tau}_u} m_u(\underline{\mathrm{x}}, t) + D_u \nabla^2 m_u(\underline{\mathrm{x}}, t) \qquad (1)$$

where D_u is the diffusion coefficient and $\bar{\tau}_u$ is the average life time of molecules of type u[1].

On the other hand, we treat the nano-devices as distinct devices, and address the operation of each device separately. As the devices mobility is described by a random walk, in steady state, they are uniformly distributed over the system volume. To avoid the characterization of a specific system volume, we assume that the volume is very large, and model it as infinite. Thus, the device locations are modeled by a homogenous Poisson point process (HPPP).

HPPP processes were widely used both in communications [14–19] and in biology [20–22]. In HPPP, denoting the device density by λ devices per μm^3, the number of devices in any volume of size V is a Poisson variable with parameter λV. Conveniently, as the devices has no memory, the mobility of the nano-devices has no effect on the network, and we can treat the nano-devices as fixed in space.

Denote the initial TM density at time $t = 0$ as $m_0(\underline{\mathrm{x}})$. The density of TM at any time and place is given by:

$$m_{\mathrm{t}}(\underline{\mathrm{x}}, t) = \int_{\mathbb{R}^3} \frac{m_0(\underline{\mathrm{y}}) e^{-\frac{t}{\bar{\tau}_{\mathrm{t}}}}}{(4\pi t D_{\mathrm{t}})^{3/2}} \exp\left\{ -\frac{\|(\underline{\mathrm{x}} - \underline{\mathrm{y}})\|^2}{4tD_{\mathrm{t}}} \right\} d\underline{\mathrm{y}}. \quad (2)$$

This density affects the detection probability of type T devices.

We focus on simple sensors, in which the detection probability is linear with the molecule density. Thus, assuming that the device is still charged, the detection probability at short time interval $[t, t + dt)$ at a location $\underline{\mathrm{x}}$ is $\mu_{\mathrm{t}} \cdot m_{\mathrm{t}}(\underline{\mathrm{x}}, \underline{\mathrm{t}})dt$.

[1] We assume that the molecules degrade and disappear according to an exponential distribution. An analysis without degradation ($\bar{\tau}_u \to \infty$) is nearly identical, but then we have to consider a finite analysis time.

The sensor also has a false alarm probability, that can cause a false detection even in the absence of TM. However, due to lack of space, the false alarm is not addressed herein, and is left for the journal version of this work.

Denote the location of the i-th device by $\underline{\mathrm{x}}_i = [x_i, y_i, z_i]$, its type by $e_i \in \{\mathrm{c}, \mathrm{t}\}$ and its detection time by $\tau_i \in (0, \infty]$. For the sensors described above, if $e_i = \{\mathrm{t}\}$, we can write:

$$\Pr(\tau_i \le t) = \int_0^t (1 - \Pr(\tau_i < \tau)) \mu_{\mathrm{t}} m_{\mathrm{t}}(\underline{\mathrm{x}}, \tau) d\tau. \qquad (3)$$

Once a sensor is activated, the device releases its storage of a mass M of CM. Thus, the density of CM is given by:

$$m_{\mathrm{c}}(\underline{\mathrm{x}}, t) = \sum_i \frac{M e^{-\frac{t-\tau_i}{\bar{\tau}_{\mathrm{c}}}} U(t - \tau_i)}{(4\pi(t - \tau_i)D_{\mathrm{c}})^{3/2}} \exp\left\{ -\frac{\|(\underline{\mathrm{x}} - \underline{\mathrm{x}}_i)\|^2}{4(t - \tau_i)D_{\mathrm{c}}} \right\} \quad (4)$$

where $U(t)$ is the unit step function.

The description so far focused on the sensing in T type devices. The activation of type C devices is identical except for possible difference in the device parameters. Thus, this detection described by equation (3), with the replacement of μ_{t} and m_{t} by μ_{c} and m_{c}, respectively.

3. NETWORK ANALYSIS

In this work we focus on the analysis of the total response of the network in the low detection probability regime. The total response and the low detection probability regime are defined in the next two subsections, followed by our main results.

3.1. The low detection probability regime

The low detection probability regime describes the system conditions for which most of the devices remain inactive, i.e.,

$$\Pr(\tau_i \le t) \ll 1. \qquad (5)$$

This regime is typical in networks where the number of nano-devices is large, and only small part of them will participate in the reaction. Noting that the detection probability, (3), is described by an integral, guarantees that the low detection probability regime will describe any network for a short enough time.

Inequality (5), which will be termed in herein the *low probability assumption*, immediately simplifies the detection probability, (3), to:

$$\Pr(\tau_i \le t) \approx \int_0^t \left(\mu_{e_i} m_{e_i}(\underline{\mathrm{x}}, \tau) + q_{e_i} \right) d\tau. \qquad (6)$$

This equation is much easier to evaluate, and it allows a simpler characterization of the network. It also allows to characterize the limits of the low detection probability regime, as (5) is satisfied whenever (6) is much smaller than 1. We also note that the low probability assumption implies that the density of ready devices (devices that can release CM) can be considered constant throughout the analysis.

3.2. Total response analysis

The total response is defined as the integral over time and space of the density of CM in the system. That is:

$$R = \int_0^\infty \int_{\mathbb{R}^3} m(\underline{x}, t) d\underline{x} dt. \tag{7}$$

For simplicity, the total response is evaluated over infinite time. Thus, this type of analysis will be valid only if the network remain in the low detection probability regime for infinite time. This rules out some interesting cases. Yet, we will show that we can get much insight on the network from the total response analysis.

Substituting (4) in (7), we get:

$$R = NM\bar{\tau}_{\mathrm{c}} \tag{8}$$

where $N = \sum_i \mathbf{1}_{\tau_i < \infty}$ is the number of activated devices and $\mathbf{1}_{x=y}$ is the indicator function. Note that $\tau_i = \infty$ indicates that i-th device was not activated at all. Thus, evaluating the total response requires the evaluation of the number of activated devices.

3.3. Main results

The total response of the network can be characterized through the average device response

$$G = \lambda \mu_{\mathrm{c}} M \bar{\tau}_{\mathrm{c}} \tag{9}$$

and average input response

$$\eta = \lambda \mu_{\mathrm{t}} A \bar{\tau}_{\mathrm{t}} \tag{10}$$

where A is the initial (or input) mass of TM in the system, given by:

$$A = \int_{\mathbb{R}^3} m_0(\underline{x}) d\underline{x}. \tag{11}$$

The network analysis indicates that the network has two distinct behaviors. A mass amplifier behavior when $G < 1$ and a detector when $G > 1$. These two behaviors are characterized by Theorems 1 and 2.

Theorem 1 (Mass amplifier)**.** *If $G < 1$ then the total response of the network is bounded and satisfies:*

$$E[R] = \frac{G}{1-G}\frac{\mu_{\mathrm{t}}}{\mu_{\mathrm{c}}}\bar{\tau}_{\mathrm{t}} A, \quad \frac{\mathit{Std}(R)}{E[R]} = \sqrt{\frac{1}{(1-G)\eta}}\ . \tag{12}$$

Thus, the average total response grows linearly with the input mass, A, and we can say that the network amplifies the input mass. However, if the input mass is not large, the variance of the response will be significant, and the accuracy of the mass amplification will be poor. On the other hand, for large enough inputs, Theorem 1 shows that the standard deviation of the response will be much smaller than its mean, and we will get an accurate amplification. Thus, we can say that the amplifier is accurate if $\eta \gg 1/(1-G)$. To express this fact, we say that the amplification sensitivity level is $(\lambda\mu_{\mathrm{t}}\bar{\tau}_{\mathrm{t}})^{-1} \cdot (1-G)^{-1}$ and that the network serves as a good amplifier if the input mass, A, is significantly larger than the sensitivity. This amplification behavior is demonstrated in the numerical section below.

If $G > 1$ then the total response according to the approximation in (6) can be infinite. Thus, the network will not stay in the low detection probability regime for long, and our analysis may seem irrelevant. Nevertheless, as the low probaility assumption will hold until significant part of the devices will be activated, we can conclude that in such case the network will have a significant response to the input mass. Such a significant response can be detected at the macro level, and hence, the network acts as an intermediate detector, that detects the input mass and creates a significant enough response that can be observed at the macro level. Thus, we conclude that we can use the low probability analysis to understand wether the network response will be significant enough to be observed, or will fade off (when the low probability analysis shows a bounded response). The detection behavior is described by:

Theorem 2 (Detection)**.** *If $G > 1$ then the total response of the network under the low probability assumption (e.g., using* (6)*), can be bounded or unbounded. The probability of unbounded response is given by:*

$$P_{\mathrm{det}} = 1 - p_{\mathrm{bm}}^{\eta/G} \tag{13}$$

where p_{bm} is the solution of

$$p_{\mathrm{bm}} = e^{-G + G p_{\mathrm{bm}}} \tag{14}$$

that dose not equal 1.

Thus, Theorem 2 characterizes the miss detection probability of the network detection. This probability is also demonstrated in the next section.

Proof of Theorems 1 and 2. The proof of the theorems is too long to fit in the space constraints of this version. Hence, we give herein only the main idea: To characterize the total response, we group the activated devices according to conceptual activation stages. The devices that are activated directly by the input signal belong to stage 1, and a device belongs to stage k if it is activated by a device that belongs to stage $k-1$. Now, the total response can be characterized by the process that counts the number of devices in each stage. The proof is based on showing that the number of devices in stage k has a Poisson distribution with a parameter that equals G times the number of devices in stage $k-1$. Theorems 1 and 2 then follow from the analysis of this random process. □

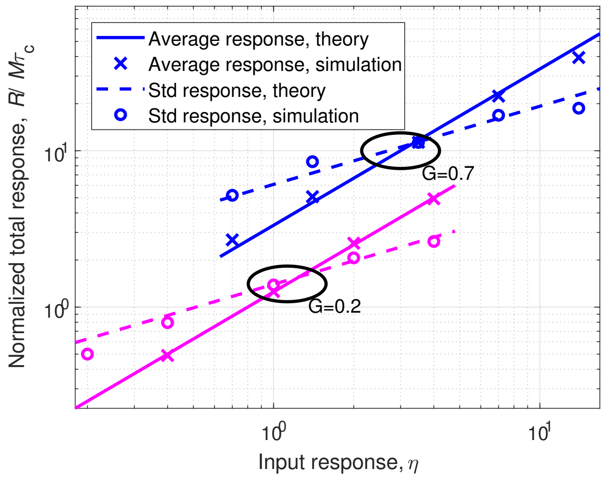

Fig. 1. Total response as a function of the input mass. The figure demonstrate the linear network gain and its standard deviation for various values of the device response, G.

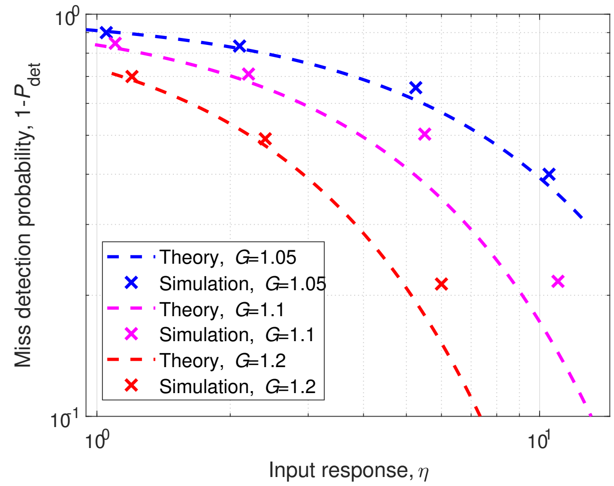

Fig. 2. Miss detection probability as a function of the input mass, for various values of device response, G.

4. NUMERICAL RESULTS

In this section we demonstrate the different network behaviors, and the accuracy of our analysis. To this end, we used Monte Carlo simulations, in a setup with an average number 30 million nano-devices, distributed over a 3-dimensional ball with a radius of 10mm ($\lambda = 7.16 \cdot 10^{-6}$ devices per $\mu\mathrm{m}^3$). For simplicity, we chose the same parameters for the TM and CM, with $D_\mathrm{t} = D_\mathrm{c} = 1000\mu\mathrm{m}^2/\mathrm{s}$ (which is a typical diffusion coefficient for small molecules in water) and $\tau_\mathrm{t} = \tau_\mathrm{c} = 20$ seconds. The values of $M\mu_\mathrm{c}$ were chosen to generate various values of the average device response, G (and $\mu_\mathrm{t} = \mu_\mathrm{c}$). The input mass was always inserted at time zero at the center of the system. The simulation emulated the devices activation with a time step of 2 seconds.

Fig. 1 depicts the normalized total response, defined as $R/M\tau_\mathrm{c}$, as a function of the input response $\eta = \lambda\mu_\mathrm{t}\bar{\tau}_\mathrm{t}A$ in the amplifying regime ($G < 1$). The figure demonstrates the linearity of the average total response with the input mass, and thus justifies the name 'amplifier'. The figure also depicts the standard deviation of the normalized total response, and shows that for large input mass, the standard deviation is much smaller than the mean.

The figure also shows the accuracy of the analytical results of Theorem 1, which are shown as lines in the figure. All measured responses (depicted by markers) lie almost exactly on the theoretical lines. Extending the measurement results using the derived expressions, we can say, for example, that an input mass that will lead to $\eta = 100/(1-G)$ will lead to a response with a standard deviation of only 10% of its mean.

Fig. 2 demonstrates the network behavior in the detection regime. The figure depicts the miss-detection probability as a function of the input response. For this simulation we decided that an activation of 200 devices is considered as detectable by the macro detector (mostly because the probability that the response will decay after reaching 200 devices is negligible).

The figure shows that the Miss-detection probability indeed decreases as G and η increase, and the accuracy of the analysis of Theorem 2 is very good[2].

5. CONCLUSIONS

In this work we studied the behavior of a network that consists of two simple device types: Devices of type T that can detect target molecules (TM) and in response release communication molecules (CM), and devices of type C that detect CM and release CM.

We showed that the network can exhibit different behaviors as a function of its parameters, and mainly the average device response, G. If $G < 1$, the network implements a mass amplifier, in which the amount of CM released is proportional to amount of input TM. If $G > 1$, the network implements a binary detector that releases a very large mass of a CM once the TM is detected in the system.

This complex behavior starts to reveal the potential of nano-device cooperation, and the importance of complete network analysis. Further research is required to further characterize the behavior of this interesting network, for example through characterization of the spatial distribution and the timing of the device activations. Even further research is needed to start the characterization of more complex networks that can result from small increase in the device capabilities.

[2]For low miss detection probabilities, the input mass deviate by up to 20% from the values predicted by theory. Further research is required to determine whether this is an analytical issue (e.g., the effect of the low probability assumption) or a simulation issue (e.g., too high time step).

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