Population Dynamics of Biosensors for Nano-therapeutic Applications in Internet of Bio-Nano Things

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***Abstract*—The development of nanomedical systems through the Internet of Bio-Nano Things (IoBNT) paradigm promotes designing of therapeutic models to facilitate drug transport and delivery. Such systems utilize microbial communities such as bacteria, which act as biosensors for molecular communication. We model the drug transport and delivery system by considering more realistic properties and characteristics of the biosensor community. We devise a Markov Decision Process (MDP) to model the biosensor lifecycle while considering division and death as parameters to regulate the model. This aids in estimating the required number of drug encapsulated biosensors. The proposed model indicates an increase in the number of instances of biosensor-target interactions that would be required for a better understanding of system dynamics. The proposed approach suggests a populace-aware coordination scheme with 3.5% increase in population, along with $20 - 50\%$ increase in information delivery. The solution proposed here can be harnessed in designing the number of optimum drug dosages. We show the effectiveness of our model with 90% increase in average biosensor lifetime, while highlighting the increase in the energy utilized in the network.**

***Index Terms*—Internet of Bio-Nano Things, Nano-healthcare system, Drug delivery system, System modeling, Biosensor estimation**

I. Introduction

The Internet of Bio-Nano Things (IoBNT) is a prominent paradigm for designing therapeutic methods of nanomedical system. Advances in nanotechnology and synthetic biology allow the design and engineering of biologically inspired nanosensors, referred to as biosensors, to suit size constraints in the order of nanometers. This attributes to an increase in bio-affinity and recognizes their use in non-intrusive *in vivo* organizations. The communication among bio-nano things involves sender biosensors encoding instructions in information molecules, which travel through the medium via chemical pathways or randomized diffusions [1] to receiver biosensors, where the information relayed is decoded. Typically, intra-body healthcare applications involve engineered bacterium loaded with drug molecules in detecting and tracking unhealthy cells [2], targeted drug delivery [3], and early detection of certain diseases [4]. A drug delivery system encourages estimated doses of therapeutic agents, which further dilutes unfavorable side effects, both at the exchange site and elsewhere in the body. Combination therapy allows for the simulataneous delivery of multiple salubrious agents and hence can be a cost effective solution to drug intensive care. Adding to the cost effectiveness of the approach, the adoption of genetically modified bacteria as biosensors precludes the need for drug refining and purification. The drug delivery system ensures to be one of the crucial applications towards IoBNT. We envision an IoBNT framework for targeted drug delivery system as

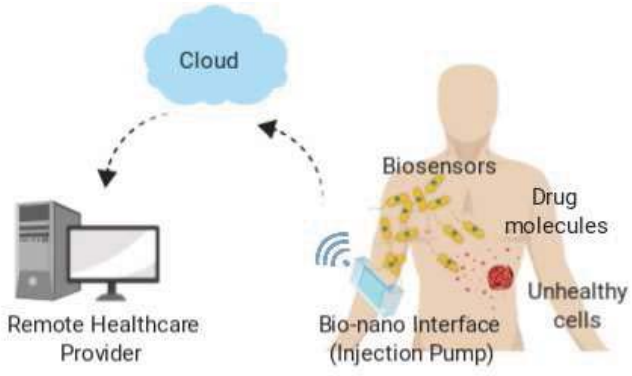

Fig. 1: Overview of Drug Delivery System towards Internet of Bio-NanoThings

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shown in Fig. 1. The IoBNT framework broadly includes the following networked elements:

1) Remote Healthcare Provider: This serves as the storage, maintenance, and management of the data pertaining to the quantity as well as timing of drug delivery. It helps in tracking the patient and analyse the collected data to predict the course of medications as well as any related risks or benefits.
2) Bio-nano Interface: It helps in connecting the macro domain with the nano domain, usually placed in the wrist of a patient. It includes a smart biosensor injection pump which controls the rate of injection of a set of therapeutic bio-nano sensors. These therapeutic biosensors are loaded with drug molecules that propagate through the complex network of blood vessels to the targeted unhealthy cells.
3) Biosensors: These are the genetically modified synthetic bacteria equipped with minimal processing power as well as drug molecules. They usually communicate through chemical signals in the biotic environment, which is referred to as Quorum Sensing (QS). Each bacterium comprehends its movement based on the concentration of the chemical compounds it perceives [5]. This locally networked decision process allows for a global effort in an otherwise globally unaware system. The process is harnessed as a signaling mechanism to address targeted drug delivery as well as target detection and tracking [6].
4) Unhealthy cells: These are the destinations (targets) in the IoBNT network architecture. They are disease causing, harmful cells which can be static as well mobile such as cancerous site. Once these are detected, the biosensors release the drug molecules in its environment so as not to harm any healthy site.

The controlled and networked biosensors is an essential factor towards efficient targeted drug management in IoBNT scenario. The significant parameter for drug management includes concentration of biosensors injected. One of the crucial challenges in the bio-nano therapeutic models involving engineered bacterium-based biosensors is considering the fact that a bacterium grows, divides, and proliferates dynamically. The focus on evaluating bacterial population changes in biosensor aided target tracking systems stems from the increasing recognition of the advantages presented in employing genetically engineered microbials in drug delivery. A semantic semblance can be drawn between wireless sensor networks (WSN) and bio-nano thing networks [7]. While a model based on WSN depends on the lifetime of the involved nodes, a bio-nano thing network relies on the mortality of constituent cellular structures. Upon failure, to some extent, a node can be replaced to resume communications in wireless sensor networks, but the same is not possible in nanonetworks, as the new node cannot be introduced at precisely the same location. This presses an exacting dependence on participating nodes in case of nanoscale communication systems. We lay emphasis on the mortality of biosensors in nanoscale interactions. As the focus on genetically engineered bacteria to play the role of biosensors for target tracking and drug delivery expands, it is essential to understand the dynamics of the microbial community to facilitate maximum utility and minimum detriment. This work elaborates on the population constraints in a bacterial community, thereby making the division and death rates as relevant parameters to evaluate the communication mechanism. The following constitutes the major research contributions of our work:

- To model a drug transport and delivery system capturing the lifecycle of biosensors.
- To model several stages of biosensor lifecycle through a Markov Decision Process (MDP).
- To analyze the network performance with varying concentration of the biosensors towards effective drug supply management.

A prospective promise of this work includes realizing an active environment targeted medication that will allow for a finer tuning in engineering bacteria aided delivery mechanisms. Dosage administrations can be regulated in both quantity and frequency. Dosage regulations related works would assist in eliminating excessive and unnecessary medication, and correspondingly suppressing drug side effects and wastage.

II. Related Work

IoBNT focuses on introducing genetically engineered bacteria in intra-body environments to be utilized for drug delivery in an advantageous manner [1], [3]. This further generates the need for a complete understanding of bacterial ecosystems for its utilization. Several works towards drug delivery systems designed for efficient target discovery and drug delivery focuses on cooperative signaling in the network [2], [8]. Other works modeled the population and proposed protocol to enhance the lifetime of drug encapsulated biosensors [9], [10]. More recent work focuses on minimizing the amount of drug released to ensure the desired rate of drug required for effective treatment during a specified time period [11]. The effect of division and proliferation in biosensor colonies acting as biomimetics to bacterial systems is necessary to analyse to allow for an effective drug measure. Our model is distinct in the attempt to analyze the dynamicity of proliferation in biosensor concentration based targeted drug delivery. Since excessive dosage of any medication can be both unnecessary and harmful, a constant focus is to target the mechanism effectively. Evolution and change in population are recognized as one of the future factors to refining current models on bacterial interactions [12]. This work elaborates on the growth and decline of biosensors in molecular communication towards IoBNT framework.

III. System Modeling

In order to realize a more realistic and dynamic drug delivery system, we model the binary fission in biosensors during drug transport. We consider the well-known approach of inducer-inhibitor mechanism for communication among biosensors. The drug delivery system involves directing biosensors towards target cells through two chemical

secretions; *inducers* that guide biosensors towards a target and *inhibitors* that dispell biosensors away from a congested target. Inducers and inhibitors, the obverse to inducers, are the chemical substances that are secreted by the bacteria to aid in the cooperative communication [13] . Upon locating a target, a biosensor secretes inducing molecules in the environment to signal other biosensors towards the target site. In case a target is approached by an excess of biosensors, biosensors perceive the congestion and secrete inhibiting molecules that repel the biosensors to approach the site. Upon injection into the system, the biosensors voyage to detect targets with the aid of inducer-inhibitor mechanism to deliver the information molecules. This work attempts to analyze characteristics of biosensor through variations in lifecycle during their voyage. We introduce $Division$ and $Death$ as parameters to monitor the change in biosensor population. We define division rate (α) as the average time interval for an engineered bacterium to split into two daughter cells. Death rate (β) is defined as the average lifetime for a bacterium. We devise the model via Markov Decision Process (MDP) by defining states for different stages in biosensor lifecycle. This model is developed on the following assumptions:

- We assume the genetically engineered bacteria to undergo binary fission, which implies a division into two cells only. Thus, every division leads to one more bacterium in the environment.
- We do not define a reward system for the MDP. Since this work seeks to simulate the effect of population change for a biosensor community in drug delivery, we define a termination or death state for the microorganisms based on β. The process functions till the death state is reached, thereby alleviating the need for an optimized solution as the working backbone.
- We neglect the multiplication phase for the targets.

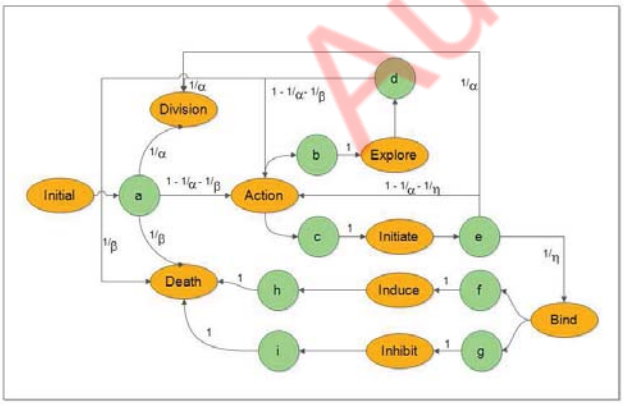


Fig. 2: State transition diagram

Fig. 2 illustrates the state transition diagram for the biosensors. The cycle begins at the initial state $S(Initial)$. $S(Initial)$ directs to only one action, a. The first decision involves division and death of the bacterium, the respective rates are denoted by α and β. Division state $S(Division)$ occurs with a probability of $1/\alpha$ for two new instances that begin with the same parameters as the parent process and the death state $S(Death)$ occurs with the probability of $1/\beta$ to terminate the process. The remaining process is forwarded to the action state $S(Action)$. $S(Action)$ phases out to two actions, b and c, depending on the biosensor's proximity to a target. In case a target has not been encountered (not in the T_r distance), the process proceeds with action b, leading to the explore state $S(Explore)$. $S(Explore)$ pertains to a motion based on sensed inducer-inhibitor concentrations. Inducer Detection Radius (I_r) and Inhibitor Detection Radius (IH_r) are defined as maximal distances till which a biosensor detects the signaling molecules. These aid in determining local concentrations. If inducer concentrations exceed a defined inducer-threshold (T_{ic}), the biosensor advances in the direction of the target cells. Similarly it tours away in case the inhibitor concentration surpasses the inhibitor threshold (T_{ihc}). In case these are absent in the local environment, a biosensor follows a random walk, implying traversal in a random direction. $S(Explore)$ further directs to action d, which allows the biosensor to divide, die or return to action states, depending on the birth and death rates. In the event that the biosensor is present within T_r distance of a target, the cycle transits to action c, which further directs to initial state $S(Initiate)$. The bind rate (η) is defined as the probability with which a biosensor binds with a receptor. $S(Initiate)$ pertains to this probability. It directs to action e that resolves to bind state $S(Bind)$ with a probability of $1/\eta$, $S(Division)$ with a probability of $1/\alpha$ and $S(Action)$ with a probability of $1 - 1/\alpha - 1/\eta$. This suggests that the biosensor interaction with the receptor is probabilistic. No exchange pertains to the biosensor returning to $S(Division)$ or $S(Action)$. At $S(Bind)$ the biosensor proceeds to assess its environment for inducer concentration. If it goes beyond the excess levels (I_{ec}), biosensors releases inhibitors, passing on to action g, else it releases inducers in the environment through action f. Both the actions f and g, transit to death state through state induce $S(Induce)$ and state inhibit $S(Inhibit)$ respectively. Algorithm 1 indicates the decision process followed by a biosensor. Taking the initial biosensor positions, the algorithm identifies the next state of the biosensor. This includes a binary delivery digit that pertains to checking whether the biosensor successfully deliveres the information molecules embedded within it. It also elaborates the position change in the biosensor location. Lastly, a state variable analyzes whether the biosensor contributes to a population change within the system, with 0 indicating no change, 1 indicating division, and -1 indicating death. The algorithm ascertains whether the biosensor is capable of interacting with a target based on the distance from the target. If so, then the interaction is facilitated with a probability η and the biosensor releases inducers and inhibitors depending on its environment. If not, the biosensor proceeds to explore the environment based on the local inducer-inhibitor concentrations. If an excess of inducer concentration is registered, the biosensor moves towards the nearest target $TowardsTarget(d)$. Like-

Algorithm 1 Biosensor MDP

Input: Position co-ordinates of biosensor (x,y)
Outputs: Delivery(0/1), Coordinates(x',y'), State(0/1/-1)

procedure BIOSENSORMDP($posx, posy$)
  $r \leftarrow random(0, 1)$
  if $r < \alpha$ **then return** (0, posx, posy, 1)
  else if $r < (\alpha + \beta)$ **then return** (0, posx, posy, -1)
  else
    $d \leftarrow NearestTarget$
    if $d < T_r$ **then**
      $r \leftarrow random(0, 1)$
      if $r < \eta$ **then**
        Exchange Information
        $I_c \leftarrow InducerConcentration$
        if $I_c > I_{ec}$ **then** Release Inhibitors
        elseRelease Inducers
        return (1, posx, posy, 0)
      else
        return (0, posx, posy, 0)
    else
      $I_c \leftarrow InducerConcentration$
      $IH_c \leftarrow InhibitorConcentration$
      if $I_c > T_{ic}$ **then**
        $(posx, posy) \leftarrow TowardsTarget(d)$
        return (0, posx, posy, 0)
      else if $IH_c > T_{ih}$ **then**
        $(posx, posy) \leftarrow AwayFromTarget(d)$
        return (0, posx, posy, 0)
      else
        $(posx, posy) \leftarrow RandomMovement$
        return (0, posx, posy, 0)
  return

wise, a plethora of inhibitors drives it away from the targets $AwayFromTarget(d)$. In case the biosensor perceives an absence of signaling regulators, its movement is randomized within the system. Assuming Q biosensors are introduced at $time = 0$, the biosensor population $N(t)$ at $time = t$ is represented as $N(t) = Q(1 + \alpha - \beta)$. Thus, $N(0) = Q$. We consider that biosensors follow the random walk model with drift [2]. The drift velocity (V_{Drift}) is defined as the velocity of the medium, like blood and lymph. Another factor called stepsize (SS) is defined as the single leap a biosensor takes. Direction of motion is analyzed by two factors θ and ϕ. θ pertains to the random orientation of the biosensor movement and is affected by inducer-inhibitor concentrations in the environment. It is randomly defined with respect to the direction of the nearest target (R_D). ϕ is interpreted as the angle made between the direction of biosensor motion and the drift velocity. We thus obtain biosensor motion as the following randomized function $F(x, y)$.

$$\begin{aligned} x_t &= x_{t-1} + (SS \times cos\theta) + (V_{Drift} \times cos\phi) \\ y_t &= y_{t-1} + (SS \times sin\theta) + (V_{Drift} \times sin\phi) \end{aligned} \tag{1}$$

$$\theta = \begin{cases} R_D & I_c >= T_{ic} \\ random((0, 2\pi) - R_D) & (IH_c >= T_{ih}) \ \& \ (I_c < T_{ic}) \\ random(0, 2\pi) & (IH_c < T_{ih}) \ \& \ (I_c < T_{ic}) \end{cases} \tag{2}$$

where ϕ is estimated as $random(0, 2\pi)$. Inducers are chemical compounds and clearly they do not follow a birth-death cycle, but since inducers can be lost in the stream through the current or the excessive diffusion, we define a iteration count (IC_i) to monitor the duration till which inducers may propagate in the system exceeding the same, they are assumed to terminate. Otherwise, the inducer molecules are directed to randomly phase out in the fluid. Further, an inhibitor-inducer threshold distance is defined to ensure that the inducer is suppressed in case of inhibitor proximity. In such a case, again inducer behavior is suppressed. Inhibitors are released by a biosensor when the latter detects an excessive inducer concentration around a target cell. Semantically, the function of a biosensor can be identified to halt the inducer effect for a congested target. They, thus, direct a biosensor away from a target. Inhibitors allow the biosensors to explore further in the medium and are thus essential to thorough delivery. Like inducers, inhibitors do not follow a birth-death cycle, but are lost in the medium through diffusion or current. Hence, we define the iteration count (IC_{ih}) to supervise the inhibitor circulation in the medium. Upon surpassing the same, inhibitors are terminated, otherwise, they continue to diffuse within the medium. Both the inducers and inhibitors follow a diffusion model analyzed using Fick's law of diffusion [2]. The law suggests that the rate of change of molecule concentration is proportional to the concentration curvature. To analyze the individual particle movement, the concentration parameter can conveniently be replaced with a probabilistic density function. $P_p(r, t)$ thus defines the displacement δ of the particle p at time t in the model. The diffusion coefficient (D) is introduced as the constant in this proportionality.

$$\frac{dP_p(\delta, t)}{dt} = D \bigtriangledown^2 P_p(\delta, t) \tag{3}$$

A solution to Eq. (3) presented in [13] assumes Gaussian distribution for displacement in a direction. It can be outlined as follows:

$$G(\Delta x) = \frac{1}{\sigma_p \sqrt{2\pi}} e^{\left(-\frac{\Delta x^2}{2\sigma_p^2}\right)} \tag{4}$$

where $\sigma_p = \sqrt{2D\Delta t}$ and $G_x(\Delta x)$ is the Gaussian distribution for particle p in a particular dimension, with mean μ = 0 and standard deviation σ is displacement for a movement. Since displacements in each direction stay independent of other directions, the corresponding probabilistic distribution for net displacement is obtained as below:

$$P_p(\delta + \Delta\delta, t + \Delta t) = G(\Delta x)G(\Delta y)G(\Delta z) \tag{5}$$

Elaborating on the individual dimensional displacement as shown in Eq. (5), the net displacement is computed as $\delta = \sqrt{\Delta x^2 + \Delta y^2 + \Delta z^2}$. By solving for δ, the diffusion process allows for a total stepsize of $\sqrt{6D\Delta t}$. Considering that targets are present in the blood stream for a time sufficient enough to be distributed evenly. This affirms that the targets commune at random and hence disallow their diffusion. Their motion is thus random, and is influenced by the drift in the medium. We elaborate the target motion with respect to a coordinate function $F_R(x, y)$ as below:

$$\begin{aligned} x_t &= x_{t-1} + (V_{Drift} \times cos\phi) \\ y_t &= y_{t-1} + (V_{Drift} \times sin\phi) \end{aligned} \tag{6}$$

where θ and ϕ are estimated as $random(0, 2\pi)$.

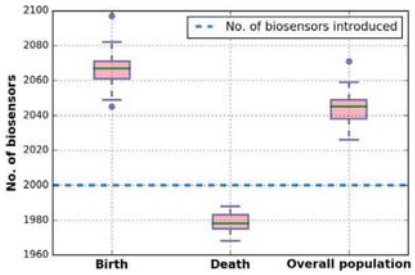


Fig. 3: Variation in biosensor population

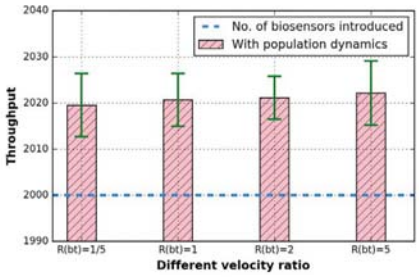


Fig. 4: Throughput of the network

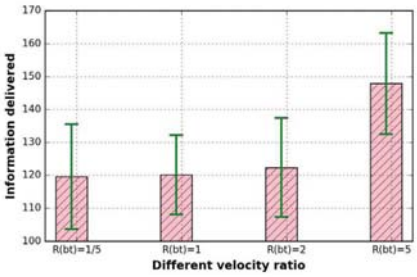
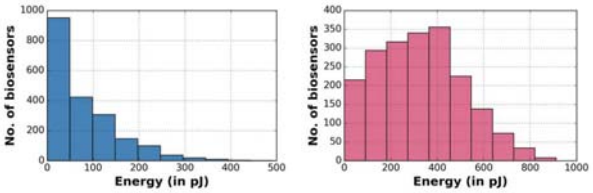


Fig. 5: Information Delivery in the network

IV. Numerical Analysis

In this section, we elaborate on the biosensor behavior for the proposed model of population dynamics due to biosensor lifecycle. We performed in-silico experiments to evaluate the performance of the model in terms of variation in population, latency, throughput, information delivered, energy and lifetime of the system. The Python-based simulations are carried out to numerically analyze the proposed model for varied parameters. The analysis considers an initial introduction of 2000 biosensors and 100 target cells as a base for the observations. The introduction of division and death parameters is specifically important for analyzing systems with non-extreme velocity ratio of biosensors and targets R_{bt}, suggesting chaotic behavior. Fig. 3 signifies the variation in population of biosensors in the proposed model. It shows the average number of biosensors that forms, extincts, and outlast in the system. The error bar further shows the maximum and the minimum values for the corresponding cases, while the box shows the variation around the median. We consider the mortality of biosensors in terms of birth and death rate, where birth signifies the division of a biosensor into two biosensors, pertaining to binary fission of a bacterium. The birth rate is estimated as the number of newly formed biosensors to the particular population of biosensors introduced per 20 minutes of simulation time. Likewise, the death rate is evaluated as the number of biosensors that face extinction in the process per 60 minutes of simulation time. We observe that the net population increases by considering the birth-death cycles. The behavior is natural for ecosystems to pertain to higher birth rates in comparison to death rates, otherwise, they face certain extinction. Fig. 4 illustrates the comparison of the basic and the proposed model for throughput of the system. The throughput is measured as the net number of biosensors that moved successfully to the targets per simulation period. We observe the throughput and the number of delivered information molecules for differing values for R_{bt}, namely $1/5$, 1, 2 and 5. With the introduction of 2000 biosensors in the medium, an absence of population dynamics as study parameters involves each biosensor in drug delivery. Considering the birth-death cycles in the proposed model, the bars denote the number of biosensors that move towards targets. A significant observation that results from the same is that the net successful interactions increase upon consideration of biosensor mortality. However, the observations indicate the need for an analysis in the context of information delivery since mortality induces a substantial difference between interactions for the basic model and the dynamic population model. We further analyze the proposed model with respect to the information delivered as shown in Fig. 5. A analogy similar to the variation in population is drawn contemplating information delivery in the system. We consider that each biosensor is packed with 5 information molecules which is delivered at the target site. A gradual increase in net deliveries is observed with an increase in R_{bt}, thereby leading to conclude that a robust biosensor response is an essential aid to conveyance. Since the rates of population changes remain constant for all the cycles, we can conclude that the behavior is due to an increase in robust target tracking. Clearly, an increased mobility in biosensors aids to rapid information delivery and an increased target interactions. It may also be noted that on an average $24-30$ biosensors reach the targets depicting that all the targets are successfully tracked in the system. We can thus establish that the consideration of birth and death rates in the system provides with a finer insight to throughput and information delivery, and aid in eliminating excessive dosage with proper optimization.



(a) Basic model (b) Proposed model

Fig. 6: Energy utilization

Figs. 6a and 6b elaborate on the energy utilized by the biosensor population in the system. Considering the energy contained in a biosensor to be $1000pJ$ [14], it was observed that around 70% of the biosensors utilized only 10% of their energy content in the basic model. A contrasting increase is seen in the proposed model with $70-80\%$ of the biosensors utilizing 50% of their energy content. Considering utilization of 30% of energy in division, 5% each in binding, induc-

tion, inhibition, and 1% in exploration, the increase in the energy utilization is justified with the state transitions of the biosensors. Correspondingly, the residual energy content in the biosensors for the basic model is more than 70% while it is around 50% for our proposed model as shown in Fig. 7. The conclusions also support that the variation in the number of biosensors introduced in the system contributes to smaller relative differences in the residual energy content.

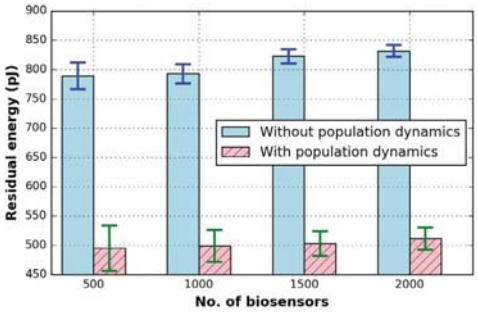


Fig. 7: Residual energy

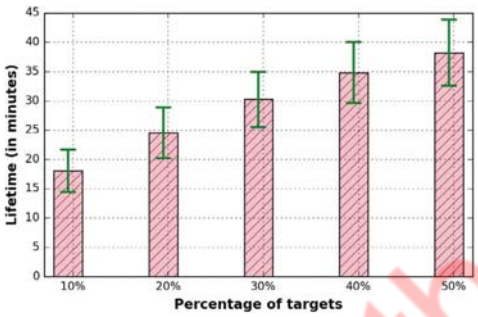


Fig. 8: Average lifetime of biosensors

Fig. 8 serves to highlight the average lifetime of biosensors for the proposed model with varying percentage of targets with respect to the number of introduced biosensors, which can be directly correlated with the reach of the network. A higher value of targets implies a lifetime of the biosensors in the system increases entailed to the need for successfully detecting the targets. Considering birth-death cycles for biosensors and a comparatively larger number of targets necessitate a longer exploration time, and hence, biosensors register 90% escalations in the average lifetime.

V. Conclusion

This work dwells into the effects caused by the change in biosensor lifecycle in drug delivery systems. Since the division and death parameters introduced are essentially natural in biotic systems, their presence in biomimetic sensor environments is transparent. Therefore, the birth-death cycles are essential to understanding the dynamics of biosensor aided drug deliveries. Our results indicate considerable hikes in biosensor population and information delivery in biosensor-target interactions. The potential associated with population changes can be harnessed to facilitate accurate drug dosages and targeted medication, thus eliminating excessive medicine portions, unwarranted side effects, and even prevent drug wastage. In the future, we intend to explore the effect of relative displacement of biosensors concerning the targets on the targeted drug delivery and the target tracking. We also plan to include time-varying model of population variation in the fluidic environment to get an in-depth insight of the microbial aided drug delivery inside the body.

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