Predator-Prey Adaptive Control for Exosome-based Molecular Communications Glioblastoma Treatment

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***Abstract*—Glioblastoma Multiform (GBM) is known as one of the most malignant tumours in the brain, and challenges remain in developing effective therapeutic solutions. This paper addresses an open-loop control molecular communication system using an adaptive algorithm that controls engineered induced Neural Stem Cells (iNSCs) to release therapeutic exosomes for treating GBM. The adaptive algorithm is based on the Lotka-Volterra Predator-Prey model, and virtually monitors the tumour growth from an external Brain-Machine Interface to control the release of the exosomes for the treatment. We developed the model to incorporate the control from an external RF signal that controls the production of exosomes as well as the diffusion propagation of exosomes through a 3D simulated Extracellular Space tissue. Based on numerical analysis coupled with simulations, we found that factors such as stochastic propagation of exosomes influence the aggressiveness of the model to tackle the tumour. This work can lay the foundation for future adaptive Brain-Machine Interface that controls molecular communication system for GBM treatment.**

***Index Terms*—Lotka-Volterra Predator-Prey, Control Theory, Exosomes, Glioblastoma, Molecular Communications, Theranostics.**

I. Introduction

The field of *Theranostics* (therapy + diagnostics) has been advancing rapidly in the past few years, and has provided a new alternative for the treatment of various diseases. The newly emerging field of molecular communications can play a major role in theranostics, where it aims to create engineered biological-based communication systems that can be implanted into the human body [1]. Example applications of such a system, and is the focus of this paper, is for systemic and targeted drug delivery for brain tumour known as *Glioblastoma Multiform* (*GBM*). These introduced engineered bio-nanomachines, which are part of the molecular communication system, can be controlled to release therapeutic molecules against the tumor, where they can be engineered from induced Neural Stem Cells (iNSCs). These bio-nanomachines, herein defined as *therapeutic organoids* are designed to function as a transmitter, responding to activation by an external signal to *Exosomes* that serve as extracellular vesicles to transport therapeutic molecules [2].

There are many mathematical models in the area of targeted drug-delivery and its impact on tumour, which are based on population modelling. These models describe the relationships between the physiological structure of the tumour that is under the exposure of the drug molecules [3] [4]. The population-based models offer a means to increase understanding of the complex dynamics of cellular functions that involves numerous biochemical, mechanical, and biophysical factors [3]. Targeted cancer drug-delivery using exosomes is promising for cancer treatment, attributed to their organotropic properties. Tumor-derived exosomes, for example, can target and reach cancer cells to deliver the drug or the therapeutic molecules, behaving as tumor-homing carriers of the drug [5]. Another fundamental property of the exosomes as ideal solutions for targeted drug-delivery is their composition, as extracellular vesicles (EVs), where they can encapsulate host cell-derived proteins or nucleic acids to be delivered to the target cells. The recipient cells can receive the EVs either by receptor-ligand interactions or receptor-mediated endocytosis [4],[2]. Advanced Brain-Machine Interface (BMI) systems of the future can control the production of exosomes using an adaptive algorithm that controls the iNSCs from an external device.

In this work, we present an adaptive algorithm that controls the molecular communication exosome transport through the Extracellular Space (ESC) tissue using the Lotka-Volterra Predator-Prey population model [6]. The algorithm will be placed on an external BMI device and will virtually model the treatment process while controlling the release of the exosomes for the treatment, representing an open-loop control system. Our motivation for using the Predator-Prey model is its equivalence to the therapeutic organoids functioning as a predator while the glioblastoma tumor cells represent the prey. The dynamics are defined by the growth and regression of the tumor as a function of the exosomes transmitted through the molecular communication system.

The paper is organized as follows. In section II, the mathematical model for the interactions between the exosomes and the glioblastoma tumor cells are formulated based on the Lotka-Volterra predator-prey model. Our proposed adaptive algorithm is presented in section III, introducing the mathematical descriptions for the external control signal, and the addition of a proportional controller. Section IV presents the simulations for the adaptive algorithm. Lastly, section V presents the Conclusion.

II. Exosome-based molecular communication system model: A Predator-Prey formulation

The interactions between the iNSCs, exosomes and the glioblastoma can be represented as a molecular communication system, as illustrated in Fig. 1. The iNSCs represent the transmitter, releasing the exosomes or the therapeutic bio-nanomachines through the brain ECS, which in this case is the propagation channel. The target of the exosomes will be the GBM that serves as the receiver in this communication system. As shown in Fig. 1 the external BMI device will emit a Radio Frequency (RF) signal in order to interact with the iNSCs to trigger the release of the exosomes, acting as the control input in the molecular communication system.

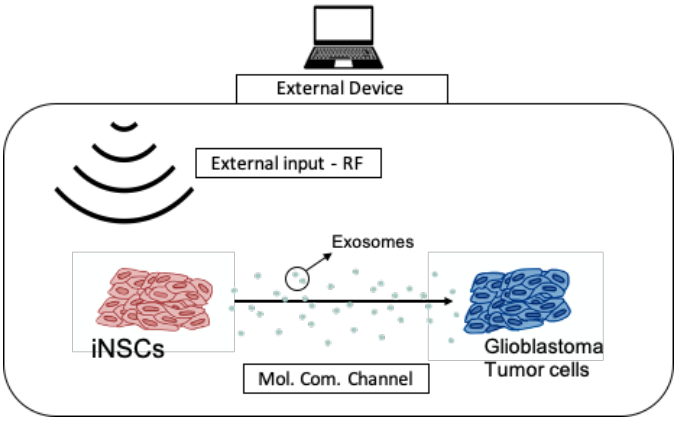


Fig. 1: Diagram of the Molecular Communication system of iNSC releasing the exosomes to the GBM, where the iNSC are controlled from an external RF signal.

The Predator-Prey model [6] represents the dynamic interactions between iNSCs and the glioblastoma tumor, where this relationship is based on the dependency of the growth or regression of the tumor to the rate of increase or decrease of the exosomes being released by the iNSCs. This is determined by the adaptive control algorithm of the Predator-Prey model. The Predator-Prey model can be described mathematically as follows [6]:

$$\frac{dG}{dt} = aG - bE, \tag{1}$$

$$\frac{dE}{dt} = \sigma EG - dE, \tag{2}$$

where G represents the number of glioblastoma tumor cells (prey population); E represents the number of exosomes (predator) being released from iNSCs; a represents the growth rate of the glioblastoma tumor cells, b is the aggressiveness rate of the predator population or in this situation, the exosomes efficiency in killing the tumor cells; σ represents the signalling factor or the parameter associated with the increase of exosomes due to the contributions resulted from the interactions between the exosomes and the glioblastoma, and d is the death rate of the predator population, which in this case means the rate of loss or half-life of exosomes.

A. Steady-State Scenario

According to [7], we can find the steady-state where the tumor will remain stable, not growing nor shrinking in size, and the number of exosomes will also stay the same with no net changes. The steady-state case can be described as follows

$$\frac{dG}{dt} = aG_0 - b_0E_0 = 0; G_0 = 1; b = \frac{a}{E_0}. \tag{3}$$

The same can be described for the number of exosomes in the steady-state scenario:

$$\frac{dE}{dt} = \sigma_0 E_0 G_0 - dE_0 = 0, \tag{4}$$

where $\sigma_0 = d$. The constant values will then be used as initial conditions for the simulations of the Eq. (1) and Eq. (2) as shown in the following section.

B. Parameters Estimation

In this paper, we will focus specially on the influence of the σ parameter, since it is our control signal, defined by the contributions due to the interactions between the exosomes and the glioblastoma cells, that will be determined by the ECS channel and this will affect the quantity of exosomes to be released. The other initial parameters will be estimated from experimental observations, similar to the approach in [7].

1) Estimation of the growth rate of the glioblastoma tumor: Stensjøen et al. [8] was able to show that the growth rate of the glioblastoma tumor has a median of 1.4% per day, doubling its equivalent volume every 49.6 days. This growth rate can be represented as follows

$$\frac{dG}{dt} = aG. \tag{5}$$

In this case we consider that there is no exosomes killing the tumor. The solution for this first-order differential equation is represented as

$$G(t) = e^{at}. \tag{6}$$

If we double the time $t = t_2$, the relationship is represented as follows

$$2 = e^{at_2}; a = \frac{ln(2)}{t_2}, \tag{7}$$

and therefore $a = 0.69/t_2$. Knowing that the volume of the tumor will double its volume every 49.6 days, we will have the growth rate $a = 0.69/49.6$, which results in approximately 1.4% per day.

2) Initial values for glioblastoma tumor cells, G_0, and exosomes, E_0: In order to normalize the Eqs. (1)(2), let $G = G/G_0$, where G_0 is the initial number of glioblastoma tumor cells or can also represent the total size, and let $E = E/G_0$ represent the number of exosomes relative to the tumor cells. Therefore, the initial tumor cell count will be $G_0 = 1$. The parameter E_0 represents the relative density of exosomes compared to the tumor cells.

The research on exosomes has been advancing at a fast pace offering promising solutions in the area of precision medicine and cancer therapy and diagnostics, with exosomes being considered as liquid biopsies for cancer detection and monitoring [9]. However, the identification of exosomes in terms of concentration is still not very precise, mostly due to

their nanoscale sizes ($30 - 100$ nm). Nevertheless, exosomes can be identified and characterized biochemically through the identification of exosome-specific markers such as tetraspanins (CD63, CD81, CD9), antigen presentation molecules (MHC I and MHC II) [10]. In this study, we will consider an arbitrary value for the relative number of exosomes compared to the tumor cells to be $E_0 = 1/100$ or $E_0 = 0.01$, a similar approach was taken by Babbs et al. [7] with their model on immune and tumor cells.

3) Estimation of Aggressiveness Rate b: According to the steady-state scenario previously described, aggressiveness rate b is defined by the Eq. (4), where $b = a/E_0$. The growth rate of the tumor, a, is 1.4% per day or $a = 0.0014$, and the relative density of exosomes, $E_0 = 0.01$, which leads to the value of $b = 0.14$. This value means that 0.14 tumor cells are killed per exosome per day.

4) Estimation of death rate d of predator population: There are many studies attempting to analyze all the applications that can be performed with exosomes in the field of precision medicine or targeted drug delivery. One of the main challenges in this area is to prolong the half-life of the exosomes for specific applications [2]. It has been observed that the half-life of exosomes is dependent on the application and the localization in the body. In humans, the half-life of exosomes is region-specific, meaning that if they were injected in the bloodstream, it would have a half-life shorter compared to the brain ECS. In this work, we will consider the half-life of the exosomes for this application to be one day.

In order to determine the parameter d, we have to analyse Eq. (2) without any increase or stimulation. Hence Eq. (2), will become $dE/dt = -dE$, which can be turned into $E = e^{-dt}$. In order to determine the half-life, the equation becomes $1/2 = e^{-dt_{1/2}}$, and this can be transformed into $d = ln(2)/t_{1/2}$. Applying the value for the half-life into d, gives the result of approximately 0.7, or $d = 0.7$.

TABLE I: Parameters of the model and its respective values

Parameter	Initial values
G_0	1
E_0	0.01
a	0.0014 days^{-1}
b	0.14 days^{-1}
c	0.7 days^{-1}
d	0.1 days^{-1}

III. Adaptive Control Algorithm

The dynamics of the glioblastoma tumor growth or remission as well as the number of exosomes are based on the Predator-Prey system as described in the previous section. As observed, the behavior of the system depends on the parameters of Eqs. (1) and (2), which are biological models not linked to external signals. However, for the application of this work, having an external RF signal interacting with the iNSCs, making these cells release more exosomes to target the glioblastoma tumor cells, means that the σ parameter that represents the contribution factor to E due to the interactions between the glioblastoma and the exosomes can be controlled. Consequently, the population of exosomes will increase or decrease depending on the external input, according to the Eq. (8).

For our adaptive control algorithm, we are using an open-loop control system illustrated in Fig. 2, since we are not using a feedback response or signal in order to adjust the control signal. The control system will analyze the behaviour of the model with the input of a control signal and determine a more efficient way of eradicating the tumor, and therefore, an open-loop control system is established. There will be two cases to be considered. The first assumes that the parameter σ can be modified by the application of the external input into the system, thus having different outcomes by controlling σ. The second case takes into consideration all variables in the Eqs. (1), (2) to be independent of external inputs, and therefore cannot be modified by such external input. In this case, the controller input will be added into the system by the introduction of another variable, which is the proportional controller kp, and this will determine the increase in the exosomes population by the Amplitude Modulation of such input.

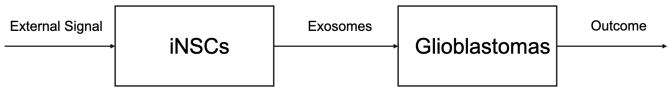


Fig. 2: Open-loop control system.

1) Case 1: Adaptive σ from external signal: As observed in the Fig. 1, the exosomes will be released through the interaction of the iNSCs and the external RF signal. The adaptive control algorithm aims to use the parameter σ by changing the concentration of exosomes in the brain ECS through the modulation of the amplitude of the external signal to interact with the iNSCs. The Eqs. (8)-(11) below describe the RF signal that will interact with the iNSCs, having the concentration as a function of the amplitude modulation of the external signal, the proportional controller or input, kp, and the new value of the parameter σ dependent on the function of the signal input.

$$S(t) = Asin(\omega t), \tag{8}$$

$$c'(t) = \frac{A}{A_{max}} c(t), \tag{9}$$

$$kp = \left| \left(\frac{c'(t)}{c_{max}(t)} \eta \right) \sigma_{max} - \sigma \right|, \tag{10}$$

$$\sigma' = kp + \sigma. \tag{11}$$

The value of σ_{max} is assumed to be the maximum value or a threshold, that the variable σ can take given the biological limitations of the system. For the simulations in this paper, an arbitrary value of approximately three times the value of σ in the equilibrium state was chosen, hence $\sigma_{max} = 2$. The variable c' represents the concentration of exosomes in the ECS as a function of the amplitude modulation and c_{max} represents the maximum concentration when the maximum

amplitude is being emitted by the external signal. The value of η represents a proportional constant connecting the ratio of the concentration of exosomes and their influence on σ_{max}. If $\eta = 1$, for example, the ratio between the concentration of exosomes will represent the exact fraction of σ_{max}. The variable A represents the value of the amplitude of the signal, and A_{max} represents the maximum amplitude that can be emitted.

Our proposed open-loop control system requires an input signal into the Molecular Communication system with its dynamics defined by the Eqs. (1) and (2). The input of the RF signal will be determined by σ as the parameter to control, and the adaptive changes in the virtual tumour model will determine the adaptations of σ.

Substituting Eq. (10) and Eq. (11) into Eq. (2) will result as follows

$$\frac{dE}{dt} = \left(\left| \left(\frac{c'(t)}{c_{max}(t)} \eta \right) \sigma_{max} - \sigma \right| + \sigma \right) EG - dE, \quad (12)$$

or simply

$$\frac{dE}{dt} = \sigma' EG - dE. \quad (13)$$

2) Case 2: Constant σ: In this scenario, all the parameters in Eq. (1) and Eq. (2) are biologically dependent. The parameter σ, in this case, is associated with the signalling factor due to the interactions between the exosomes and glioblastoma. This could represent feedback given by such interactions that could be used in a closed-loop control system to fine-tune the controller and consequently, the release of exosomes into the system. In our open-loop control system, we consider how the controller will influence the outcome and make it more efficient in this case for constant values of the parameter σ. Taking this into consideration, we use the same principles of control theory to add a proportional controller to control the exosomes production based on Eq. (10) and (15). The production of exosomes will depend on the amplitude modulation of the RF signal, aiming to control the output of the system that corresponds to the size of the glioblastoma or the total number of tumor cells. Eq. (14) below, describes the insertion of the proportional controller, kp, into the Eq. (2)

$$\frac{dE}{dt} = \sigma EG - dE + kpE, \quad (14)$$

The proportional controller, kp, will be a function of the external signal and the respective resulting concentration of exosomes when applied to Eq. (9) can be described as

$$kp = \frac{c(t)}{c_{max}(t)} \sigma_{max} 10^{-3}. \quad (15)$$

For this scenario, kp needs to be scale down a few orders of magnitude, since it is a new system variable that will be directly linked with the increase of exosomes into the ECS.

IV. Exosomes-release Concentration Simulations

The exosomes release and its diffusion in the extracellular matrix can be modelled by the following Eq. (16) based on the works of Tao et al. [11] and Sykova et al. [12]. The equation will determine the concentration as a function of time and radius distance from its origin, and is represented as follows:

$$c(r,t) = \frac{N_0}{(4\pi D^* t)^{3/2}} e^{\frac{-r^2}{4D^* t}}, \quad (16)$$

where the diffusion coefficient is represented by D, the number of molecules released as a point source or in this case from the therapeutic bio-nanomachines, exosomes is defined by N_0, the time is defined by t and the distance from the point source is represented by r. The interaction of the external signal with the iNSCs will result in more or less exosome release into the ECS, which will increase or decrease the concentration of the exosomes. Taking into consideration this feature of the system, we can model the concentration of exosomes using the modulation of amplitude for the controller input. This will be represented as follows:

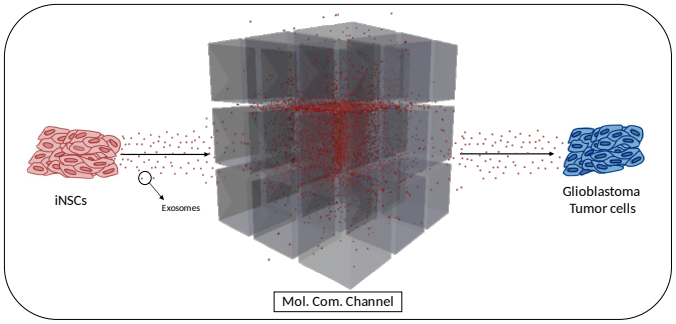


Fig. 3: Diagram of the simulations of the molecular diffusion through the brain ECS.

$$c(r,t) = \left(\frac{A}{A_{max}} \right) \frac{N_0}{(4\pi D^* t)^{3/2}} e^{\frac{-r^2}{4D^* t}}, \quad (17)$$

Fig. 4 illustrates the concentration of exosomes based on the Eq. (17) as a function of the amplitude modulation for a radial distance of 5 microns.

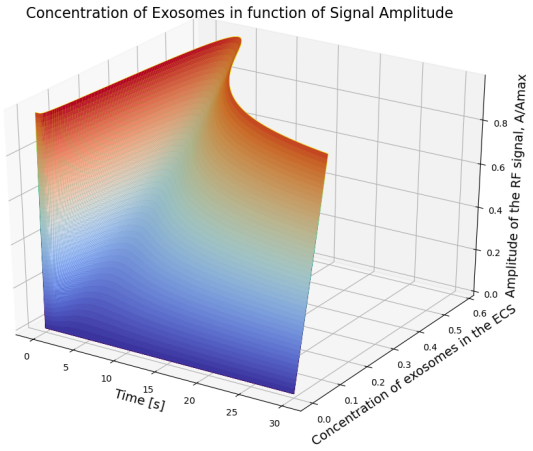


Fig. 4: Concentration of exosomes based on (17) for a distance of r = 5 microns and diffusion coefficient $D = 15x10^{-6} cm^2/s$.

The diagram of Fig. 3 illustrates the molecular communication system defined by the iNSCs transmitters, the propagation channel represented as the brain ECS, as well as the receivers, which are the glioblastoma tumor cells. Simulations for the molecular diffusion through a reconstructed brain ECS made of cubic cells were performed to observe the number of molecules as a function of time and radial distance. The reconstructed brain ECS is made of an ensemble of cubic cells put together in a volume with interstitial space between the cubes. The ECS volume in the reconstructed neural tissue is built to occupy 20% of the total volume. The reconstructed ECS serves as a tool to study the molecular diffusion in such space, as defined by Eq. (18).

$$N(t) = N_0 \left[erf\left(\frac{a}{2\sqrt{D^* t}}\right)\right]^3, \tag{18}$$

where N_0 is the number of molecules being released; a represents half the size of the cube; D^* is the effective diffusion coefficient and t is the time variable. The simulations performed had 1000 molecules being released from a point source, diffusing across the tissue at a diffusion constant of $D = 1.0$ x 10^{-6} (the parameters for the tissue are defined in Fig. 5). The results can be observed in the Fig. 5, showing the number of molecules with respect to time within the sampling cubes of 2, 3, 4 and 5 micrometers of size. The simulations for the molecular diffusion are based on the Monte Carlo simulations in a 3D environment based on the tool *Mcell* [13],[14] [11]. The equation that accounts for the number of molecules diffusing through a propagation channel can be obtained by integrating the Eq. (16) over a cubic volume of side $2a$ as demonstrated by [11].

The diffusion of molecules as demonstrated in Fig. 5 was obtained by simulations with the reconstructed ECS and is mathematically described by Eq. (16). Therefore, we can analyze the concentration of molecules for a specified radial distance as a function of the amplitude of the external signal, as illustrated in Fig. 4, as well as how the molecules will diffuse in such space depending on the tortuosity, which can be described as the hindrance or the obstacles in the ECS influencing how the molecules diffuse, and the volume fraction occupied by the ECS as illustrated in Fig. 5. These simulations serve as a tool to assist in the understanding of the exosomes diffusion in the ECS determining the concentration of the exosomes through time and space for specific configurations of the ECS, consequently influencing the parameter σ, and therefore the output of the system.

Fig. 6a illustrates the tumor growth and decay through time dependent on the parameter σ as defined by Eqs. (1)(2). This variable was changed from its initial steady-state value of 0.7, to arbitrary values by increments of 0.2. For different values of σ, oscillations start to occur, which is expected from the predator-prey dynamical systems. It is important to note that it is fundamental that the tumor is completely eradicated, because for many values of σ the tumor is close to being eradicated but it starts to grow again presenting recurrences

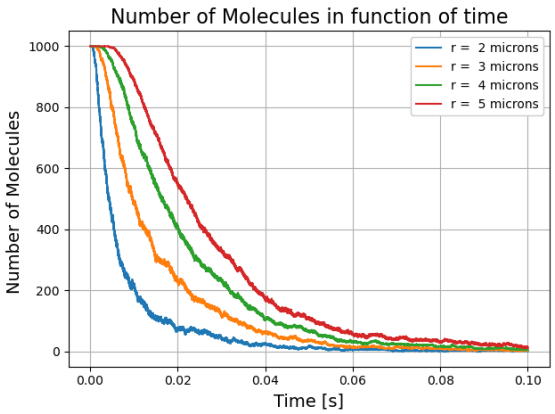


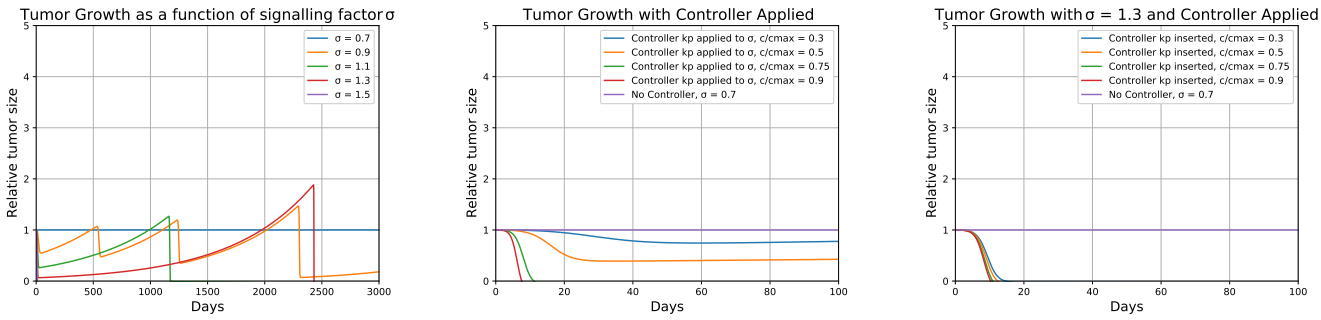
Fig. 5: Diffusion of molecules through the reconstructed neural tissue defined by 10x10x10 cubic cells with length size of $2a$ = 0.5 μm with a spacing between them of w = 42.9 nm. The number of molecules were recorded using extra cubes as sampling boxes of length size r as illustrated in the figure.

due to the oscillatory behavior of these systems. Experimental results giving more precise and accurate parameters for the model may allow for the fine-tuning of the controller to eradicate the tumor much sooner.

The Fig. 6b illustrates the results for the application of the proportional controller for the first case, where the parameter σ is variable. We observe the influence of the controller in decreasing the time or number of days to eradicate the tumor efficiently. In some cases, the controller can also increase the time to eradicate the tumor, depending on the amplitude modulation value. This happens, because in this scenario, applying different modulations will produce different values for the variable σ and as observed in Fig. 6a, some values of σ can result in a longer time to eliminate the tumor than lower values of σ. This means that high values of σ are not necessarily the best values, the best choices for σ are the ones shown in the simulations to eradicate the tumor faster. The second case, the proportional controller, kp, is added into the model, while the parameter σ is fixed in one value. The influence of the controller in the model is similar to the first case, being able to drastically reduce the number of days to eliminate the tumor efficiently. Although, the difference between the two cases is that the second is more dependent on the value of the parameter σ. This can be observed in Fig. 6c, where the results are closer almost independently to the amplitude modulation. This is explained by the fact that the controller cannot change the value of the variable σ, which means that the controller as defined by the amplitude modulation will make all new values oscillate around the fixed variable σ. The results of this system can become more precise and accurate, once the biological parameters relative to the exosomes and the glioblastoma tumor are more studied and modelled further.

V. Conclusion

In this paper, we model the interactions between exosomes and the glioblastoma tumor cells mathematically, as a dy-



(a) (b) (c)

Fig. 6: a) Tumor growth and decay as a function of σ. b) Case 1: Tumor Size for parameter σ variable and controller applied. c) Tumor Size for parameter σ fixed and controller added for $\sigma = 1.3$.

namical predator-prey system, where the exosomes represent the predator, and the glioblastoma tumor cells represent the prey. Additionally, we present an adaptive control algorithm for brain-machine interfaces in the context of molecular communication systems theranostics and targeted drug delivery. An external RF signal is used as an input control signal to control the dynamics of the model, and consequently, eradicate the tumor more efficiently by the application or addition of a proportional controller into the system. We analyze two possible cases for this control system taking. The first one takes into consideration the potential of the control system to modify one of the biological parameters of the system. The second one considers that these biological variables cannot be changed by the external input and so the controller has to be added into the model as another variable of the system. We consider the molecular communication established between the exosomes and glioblastoma tumor cells as well as the propagation of the exosomes through the ECS channel and how this will be influence and be influenced by the adaptive control algorithm. The results were able to show that the controller is efficient in eradicating the tumor by drastically reducing the required time. This work paves the way to novel biotechnology solutions to tumour theranostics using principles of molecular communications.

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