On Semantic Information in Drug Delivery Systems

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I. Background

The development of drug delivery systems (DDSs), designed to adapt to physiological conditions and disease progression, faces challenges due to the complexity of the human body and numerous interacting phenomena. DDS optimization typically focuses on criteria such as precision targeting, controlled release, therapeutic efficacy, minimal side effects, patient compliance, cost-effectiveness, and personalization. However, the inability to adequately quantify drug effects limits precise optimization and hampers the potential for personalized treatments.

The integration of computational methods in drug delivery reduces reliance on costly and time-consuming experiments but faces challenges in accurately measuring and interpreting drug effects due to biological variability. By drawing parallels between drug delivery and information transmission, drug delivery problems can be analyzed using molecular communication (MC) framework [1]. A critical limitation in current MC approaches lies in their abstraction of molecular information, which occurs at three levels: syntactic (statistical correlations), semantic (meaning of messages), and effectiveness (induced actions) [2]. Traditional syntactic measures, like Shannon's information theory, focus on accurate message transmission but ignore meaning.

Given the poor syntactic performance (e.g., low data rates) and strong semantic/effectiveness performance of MC systems, syntactic information is likely less relevant [3]. Instead, semantic information may be a more suitable measure, particularly in DDS optimization efforts.

Semantic information, introduced by Kolchinsky and Wolpert, refers to information that is meaningful to a system, rather than being purely correlational [4]. Their framework is rooted in the intrinsic dynamics of a physical system and its environment. This perspective emphasizes the importance of a system's internal states, performance, or existence as determined by its exchange of information with the environment. Recently, this concept has been applied to the information-theoretic analysis of bacterial chemotaxis [2] and drug delivery via synthetic cells [5].

In the ongoing work, we hypothesize that applying the concept of semantic information theory to drug delivery also helps distinguish portions of system parameters that are 'meaningful' and 'meaningless' in affecting target cells. For instance, in an overdose scenario, the 'meaningless' portion of the drug dose as system parameter is the excess that, if removed, would not impact the therapeutic outcome. Identifying such inefficiencies can potentially reduce dosage while preserving therapeutic efficacy, optimizing the chemical budget, and improving cost-effectiveness.

II. Proposed Semantic Information Framework

The definition of semantic information relies on the specification of a viability function, the formulation of so-called counter-factual interventions (intervened distributions), and the syntactic information measure [4].

We consider a drug-delivery model composed of a target cancer cell system $\mathcal{X}$ and an environment $\mathcal{Y}$. We aim to establish a robust framework for quantifying: 1) the degree of existence of system $\mathcal{X}$, 2) the interaction between the system $\mathcal{X}$ and environment $\mathcal{Y}$, and 3) the semantic information (measure) of the system.

A viability function $V(\tau)$ quantifies the system's 'degree of existence' at a given time τ [4]. A natural definition of the viability function is the probability that the system's state is in the viability set. Given this, we tailor $V(\tau)$ to our system model as quantifying the natural physiological tendency of cancer cell to remain in a living state. Precisely, we define the viability function in terms of the probability that the treated cancer cell remains viable after exposure to varying particle release rate λ as follows

$$V(\tau) = (1 - P_{\mathrm{r}}(\tau|r_0))^{N(\lambda,\tau)}, \tag{1}$$

where $P_{\mathrm{r}}(\tau|r_0)$ is the probability that a drug molecule released at $r_0 = (x_0, y_0, z_0)$ and time $t_0 = 0$ is received by a cancer cell at τ, and $N(\lambda, \tau) = \lfloor \lambda\tau \rfloor$ particles are available to be released at the beginning of each time slot.

To evaluate the interaction between the system $\mathcal{X}$ and environment $\mathcal{Y}$, we define counter-factual interventions which scramble some of the syntactic information between the system and its environment. In our case of study, we observe controlled counter-factual interventions where specific parameters of the DDS are altered as a way to scramble the correlation between $\mathcal{X}$ and $\mathcal{Y}$ on the initial configuration ($t = 0$). These alterations present a transformation of an actual (non-intervened) distribution into an intervened distribution [4]. We define an actual distribution by the default set of system parameters (omitted due to space constraints).

While mutual information is a prevailing syntactic information measure for deriving the semantic information of the system, alternatives like transfer entropy [2], [4], [6] may

also be suitable. The choice should align with the measure's ability to capture the system's dynamics effectively. As we consider DDS as a (molecular) communication system, our goal is to provide semantic information results at the upper boundary. Building on measures from [2], [4], [5], we focus on maximized mutual information, i.e., channel capacity to meet our analysis requirement(s).

To apply semantic information theoretic framework to the DDS, we utilize the MC model of the particle intensity channel (PIC) [7]. The proposed PIC presents the detection probability $P_{\mathrm{r}}(\tau|r_0)$, modeled using the binomial distribution, which represents the probability of receiving a certain number of particles (successes) from a fixed total number of released particles (trials), N [7]. This model enables the analysis of channel capacity limits, defined as the maximum mutual information over all possible input distributions. We leverage this capability to derive semantic information in the observed drug delivery scenario under the optimal input distribution. The resulting semantic information measure - equivalent to the channel capacity of the PIC [7] - is developed under simplifying assumptions to facilitate analysis. The derived channel capacity formula for the binary input PIC is

$$\mathcal{C} = \frac{1}{\tau}\log_2\left[1 + (1 - V(\tau))V(\tau)^{\frac{V(\tau)}{1-V(\tau)}}\right]. \qquad (2)$$

Due to space constraints, detailed derivation and model description are omitted.

Finally, we derive the semantic information at time τ, $S_\epsilon(\tau)$, as the minimum channel capacity among the calculated set of counter-factual interventions $\mathcal{I}$ for which $V_{\mathrm{i}}(\tau)$, $\mathrm{i} \in \mathcal{I}$ is not significantly higher than the minimum achievable viability. The allowed variations in viability, considered negligible in practice, are defined by ϵ. This value depends on the specific intervention, MC system under study, and the acceptable sensitivity and efficacy requirements of the treatment. This definition is adopted from [2]. Notably, the computation of semantic information is inherently tied to the specific time instant τ at which both viability and channel capacity are evaluated [4].

III. Initial Results

To demonstrate the proposed semantic information framework, we consider counter-factual interventions by modifying the particle release rate (λ) at the initial configuration ($t = 0$). The actual distribution corresponds to $\lambda = 0$ particle s^{-1}, while interventions use λ values of $\{5, 10, 15, 20, 30, 40, 50, 100\} \times 10^3$ particle s^{-1} to achieve the lowest possible cancer cell viability value. For each λ intervention, we first estimate PIC dynamics $P_{\mathrm{r}}(\tau|r_0)$ at $\tau = 1$ ms using the default system parameters. Then we compute the viability function $V(\tau)$ in (1) and the channel capacity $\mathcal{C}$ in (2) to derive semantic information S_ϵ of the considered DDS.

Fig. 1 illustrates the viability/channel capacity curve under different λ interventions evaluated at $\tau = 1$ ms. The non-intervened case ($\lambda = 0$) is marked by a dark orange dot, while other dots represent interventions. The curve shows viability decreasing as λ increases, consistent with expectations that higher particle release rates (drug concentrations) reduce cancer cell survival. With a minimum achievable viability near 0, we define S_ϵ as the channel capacity value required to achieve ϵ + minimum achievable viability and set $\epsilon = 0.05$. From Fig. 1, S_ϵ corresponds to $\lambda = 20 \times 10^3$ particle s^{-1} intervention, identifying portion of λ system parameter that is effectively 'meaningful' in terms of impact on DDS optimization. The higher particle release rates would produce the same effect as $\lambda = 20 \times 10^3$ particle s^{-1}. The pink-shaded area highlights the difference between S_ϵ and the maximal achievable channel capacity reflecting the difference between the semantic and syntactic information in the considered scenario. In conclusion, the proposed semantic information framework evaluates how information transmission influences the system's ability to achieve the goal, thereby demonstrating potential for DDS optimization.

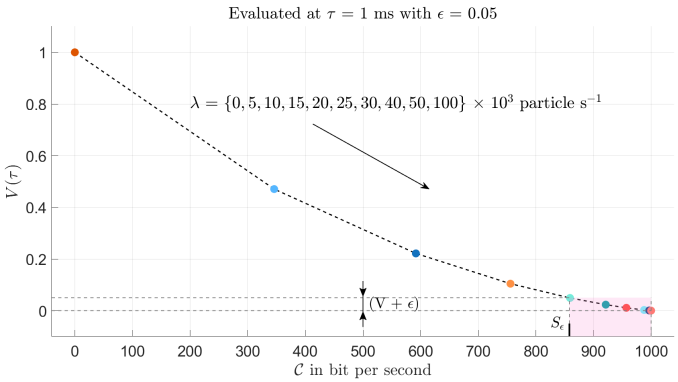

Fig. 1: Channel capacity vs. viability at $\tau = 1$ ms for ten particle release rates λ as different counter-factual interventions. The shaded area highlights channel capacity of interventions resulting in (nearly) constant viability values characterized by ϵ.

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