Semantic Information in Molecular Communication–Based Drug Delivery Systems

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***Abstract*—We are employing semantic information theory to quantify how much information about treatment parameters is functionally relevant for achieving a desired therapeutic outcome in a drug delivery system. The framework is evaluated through a simulation study of a focused ultrasound (FUS)–mediated drug delivery system.**

***Index Terms*—Semantic information theory, Molecular Communications, Drug Delivery Systems, Focused Ultrasound**

I. Introduction

Drug delivery systems (DDSs) can be viewed as molecular communication processes [1], in which therapeutic particles convey matter of interest through complex biological environments. In this perspective, particles act as messages and therapeutic outcomes define their meaning, in the sense of their contribution to achieving a specified treatment goal. This abstraction enables the parallelisation of particle transport and data transmission at the modelling level, which then provides an information and communication theoretic-based framework for analysing and optimising DDSs.

We view DDSs as goal-oriented molecular communication processes and adopt semantic information theory [2] to move beyond conventional statistical modelling. Semantic information theory distinguishes between syntactic information, which is the statistical correlation between variables, and semantic information, which quantifies how much of that information contributes to achieving and maintaining a specified goal. The framework has been applied to synthetic molecular communication systems, where engineered cells process the minimal amount of information required to trigger therapeutic responses [3], [4]. Specifically here, a DDS is interpreted as a goal-oriented communication process, in which the treatment setup (parameter configuration) affects a transport process (drug particle propagation and interaction), which ultimately produces a treatment outcome (therapeutic performance). Within this analogy, the treatment parameters constitute the message, and the achieved treatment outcome defines the meaning of treatment parameters. From this standpoint, semantic information theory is employed to determine how much each treatment parameter contributes to the treatment outcome and what level of control precision is minimally required to achieve it.

To demonstrate the framework's generality and practical relevance, we evaluate it through a simulation study of a focused ultrasound (FUS)-mediated DDS for brain tumours [5]. FUS-DDS offers a controlled and well-characterised platform for studying the effect of semantic relevance of parameters because it allows modulation of the blood-brain barrier and enables enhanced delivery of therapeutic agents that otherwise cannot reach the brain. The technique is inherently *multiparametric*, with multiple ultrasound parameters collectively determining the extent and duration of BBB opening. We introduce stochasticity to the deterministic model which couples FUS parameters with drug pharmacodynamics across the disrupted BBB and tumour microenvironment [5]. Variations in these parameters directly affect the transvascular transport rate k_{tv}, which governs drug delivery and uptake, further linking FUS control to treatment outcome. The stochastic model allows us to capture biological variability and apply information-theoretic measures that characterise how parameter uncertainty influences treatment outcomes. By embedding this FUS-DDS model into the proposed semantic information framework, we determine each FUS parameter's contribution to treatment outcome and evaluate how loss of resolution (implemented through coarse-graining procedures) degrades performance.

Understanding how each treatment parameter contributes to the treatment outcome and how robust treatment performance remains under informational uncertainty of treatment parameters is of direct significance for both clinical optimisation and treatment device design. The main contributions of this work are thus as follows:

- We develop a (general) semantic information framework for analysing the information bounds of treatment parameters in DDSs.
- We validate the proposed framework through a simulation study of the FUS-DDS characterising the impact of FUS parameters.
- We demonstrate that the semantic information framework quantifies the meaningful contribution of each parameter, distinguishing refinements that are therapeutically relevant from those that are redundant.

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II. Methodology

Five steps are required to operationalise semantic information in the context of DDS.

1) System partitioning: The system dynamics can be deterministic, stochastic, or a combination of the two, and continuous or discrete. This requires partitioning the system into two components: the agent and the environment. In our formulation, we designate the treatment outcome measure as the state of agent X, and the set of treatment parameters constitutes the environment Y.

2) Viability: The viability function relies on the key characteristics of the agent that contribute to its continued existence. The change in information granularity should be reflected in the viability of the agent state X. Each treatment setup corresponds to a particular set of parameters that yields a unique probability density function (PDF) representing the distribution of treatment outcomes. The ensemble of all possible treatment setups thus forms a space of possible treatment outcomes, which can itself be described by a composite PDF. When a restriction (e.g. coarse-graining) is applied to the set of treatment setups, such as reducing parameter variability or merging similar configurations, this restriction alters the corresponding PDF of possible treatment outcomes. In other words, each distinct level of parameter granularity produces a distinct distribution of outcomes, and hence a distinct PDF. To quantify how such changes in treatment information granularity affect the outcome space, we define a viability function based on the difference between the PDFs that characterize successive coarse-graining stages. This viability reflects how robust the agent's behaviour (or state X) remains as the treatment information is compressed. Several possible measures exist to quantify differences between probability distributions, including the Kullback–Leibler (KL) divergence, Hellinger distance, and total variation distance.

3) Syntactic Information Measure: We next consider the correlations between the agent and its environment, which can be extracted from the joint distribution $p_{X_\mathrm{t}Y_\mathrm{t}}$. Correlations between the agent and the environment prevent a factorisation of the joint distribution such that $p_{X_\mathrm{t}Y_\mathrm{t}} \neq p_{X_\mathrm{t}}p_{Y_\mathrm{t}}$. These correlations reflect the fact that the process of drug transport in the communication channel is shaped by the treatment parameters Y, also responsible for the treatment outcome X. To quantify this correlation at time t, we use the *mutual information* between the agent X_t and the environment Y_t.

4) Counter-factual Interventions: Mutual information reaches its minimum value of 0 if and only if X_t and Y_t are statistically independent under p_{XY}, i.e., when $p_{\mathrm{X}_t,\mathrm{Y}_t} = p_{\mathrm{X}_t}p_{\mathrm{Y}_t}$ [2]. This case corresponds to a full intervention that erases all correlations. To identify the meaningful portion of mutual information, we apply partial interventions that allow us to vary the amount of syntactic information preserved under different interventions, and then measure the resulting agent viability. While there are other ways to scramble the channel between the agent and environment, here we adopt a *coarse-graining* procedure from the information-theoretic perspective and apply it to the communication channel input.

5) Semantic Information Measure: The goal of the semantic information framework is to determine how the correlations identified in the previous steps contribute to the viability to distinguish which correlations are functionally relevant to the agent. This is achieved by applying a scrambling protocol that perturbs correlations and observing the resulting change in viability. The point at which the scrambled viability deviates from the actual viability defines the semantic threshold. This relationship can be represented through the information/viability curve as the achievable viability $D_{\mathrm{stored}}(R)$ under any intervention from the set of all possible coarse-graining functions Φ, that preserves a specified amount of mutual information R as:

$$D_{\mathrm{stored}}(R) := V(\hat{p}_X^{\phi}) \;\; \text{s.t.} \;\; I_{\hat{p}^{\phi}}(X_{\mathrm{t_{end}}}Y) = R. \qquad (1)$$

Finally, the (stored) semantic information S_{stored} is then the minimal amount of mutual information necessary to achieve the same viability as the actual distribution:

$$S_{\mathrm{stored}} := \min_{\hat{p}^{\phi}:\phi\in\Phi} I_{\hat{p}^{\phi}}(X_{\mathrm{t_{end}}};Y) \;\; \text{s.t.} \;\; V(\hat{p}_X^{\phi}) = V(p_X). \quad (2)$$

III. A Case Study: Focused Ultrasound-Mediated Drug Delivery

FUS treatment for central nervous system (CNS) diseases relies on FUS exposure to transiently open the BBB and to enhance the pharmacokinetics and pharmacodynamics (PK/PD) of the administered drug. Key factors in modelling BBB opening include the propagation of the ultrasound signal through the skull and brain tissue, as well as the timing and dosage of microbubble (MB) injection. BBB opening typically occurs within minutes of sonication and is followed by a closure phase that can last several hours. The dynamics of opening and closure are strongly influenced by FUS signal characteristics, the target location in the brain, and MB kinetics [5]. FUS provides a good platform for semantic analysis because it enables precise, controllable, and localised modulation of the BBB using controllable ultrasound signal parameters, such as pulse repetition frequency (PRF), pulse duration (PD), and mechanical index (MI), for treatment performance and robustness.

References

[1] Y. Chahibi, "Molecular communication for drug delivery systems: A survey," *Nano Communication Networks*, vol. 11, pp. 90–102, 2017.

[2] A. Kolchinsky and D. H. Wolpert, "Semantic information, autonomous agency and non-equilibrium statistical physics," *Interface Focus*, vol. 8, no. 6, p. 20180041, 10 2018.

[3] B. Ruzzante, L. Del Moro, M. Magarini, and P. Stano, "Synthetic Cells Extract Semantic Information from their Environment," *IEEE Transactions on Molecular, Biological, and Multi-Scale Communications*, vol. 9, no. 1, pp. 23–27, 2023.

[4] L. Del Moro, M. Magarini, and P. Stano, "Semantic Information as a Measure of Synthetic Cells' Knowledge of the Environment," in *Artificial Life and Evolutionary Computation*. Springer Nature Switzerland, pp. 98–110, 2024.

[5] M. Zoofaghari, M. Damrath, M. Veletić, and I. Balasingham, "Empirical Model of Focused Ultrasound-Mediated Treatment for Chemotherapy Delivery to Brain Tumors," *Ultrasound in Medicine & Biology*, vol. 51, no. 5, pp. 877–883, 2025.