Fundamental limits and achievable performance in biomolecular control

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Abstract— Understanding how a biomolecular system achieves various control objectives via chemical reactions is of crucial importance in cell biology. However, unlike typical control problems where full information about the system is assumed to be known, typically, only a small portion of the entire biomolecular system can be characterized with certainty. In order to gain insights in these situations, we use control and information theory to derive the performance bounds when chemical species implement feedback control via the production rate or the degradation rate of chemical species. We expand the approach of the pioneering work Lestas et al. to treat more general scenarios and derive explicit lower bounds on the achievable Fano factor of the controlled species. Our results suggest that control and sensing via the degradation rates, compared with those via the production rates, benefit from the additional design freedom to choose degradation efficiencies, in addition to previously considered signal rate, which helps to lower the Fano factor of the controlled species. We compare our lower bounds with achievable performance via simulation of chemical master equations.

I. INTRODUCTION

Since the rise of systems biology and synthetic biology at the beginning of this century, a central objective has been to understand how biomolecular systems in a cell could perform complex control objectives, such as cell differentiation, homeostasis, and accurate timing of cell cycle [1]. Recent years have seen fruitful applications of established frameworks from control theory to biological systems [2]–[6]. The connection between complex biological systems and engineered ones became even more apparent with the advent of large scale engineered hardware and software systems [7], [8].

However, in contrast to engineered systems with full specifications in control theory [9], biomolecular systems encountered in biology are often a small part of a larger unknown network inside a cell. Adding to the difficulty, the stochasticity in the dynamics of molecules is considerable due to a cell's small size [10]. Finally, the state of the system is represented by discrete counts of molecules. Therefore, a deeper understanding of biomolecular systems necessitates the development of a robust control framework that takes stochasticity and discrete state into account.

One such approach was pioneered by Lestas et al. [11]. They considered the problem of centering the count of a chemical species X around a mean and suppressing the noise by controlling its production rate through other chemical species. By treating other parts of the network as an arbitrary control function with a constraint on communication, they were able to lower bound the variance of the species being

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controlled. Then, to connect to physical and measurable parameters of the biomolecular system, they expressed the communication constraint in terms of the channel capacity of a signaling chemical species C, whose production rate is influenced by X and therefore communicates information about X. This type of analysis proved to be highly insightful in applications, as discussed in [12], [13].

In this work we explore the approach of [11] further and provide more general results with fewer constraints, therefore enabling wider applications. First, we lift the constraint that control can only act through production rate and allow degradation rate control as well. Second, we also allow signaling species C to communicate information about X through its degradation rate. Third, we formulate the control action and stochasticity in a more comprehensive fashion, so as to genuinely represent possible actions of a biomolecular network with many unknown species, generalizing the approximate formulation in [11].

A. Related work in control and information theory

As the problem studied in this work arises in a biological context, we provide a brief discussion here connecting the control problem studied to the general field of control and information theory.

Control under communication constraints has been extensively studied. The comprehensive surveys [14]–[17] cover important issues in the field of networked control. The necessary and sufficient data rate through the feedback loop in order to achieve system stability in linear stochastic control is studied in [18]–[20]. The optimal controller structure, separation principles, performance bounds are studied in [21]–[29]. Some of the important results include separation principle between the controller design and communication protocols [22], [30], [31], and the relation between optimal cost and the causal rate-distortion function [32]–[34].

The amount of information can be quantified via mutual information [22], [35], anytime capacity [36], and directed information [27], [37], among others. In the classical setting of information theory, the source and channel codes can be designed separately without loss of optimality in the limit of infinite coding delay [38]. However, if the system has dynamics, then separating the design of source and channel can perform strictly worse compared with designing them jointly [39], [40]. The causal rate-distortion function on Polish spaces is also considered in [41], [42].

In this paper, communication via chemical reactions is modeled as Poisson-type channels [43]. The information capacity of various Poisson-type channels is shown in [11], [44], [45]. Relevant properties of the Poisson point process

are summarized in [46], [47]. In particular, the mutual information can be shown to be expressed by the Liptser–Shiryaev formula [47], which is the key to connecting the communication problem with the filtering (estimation) problem [48]–[50], and plays a major role in the proof of our main result (Theorem 2 in Section IV-B).

B. Notations

For a continuous time process $\{X(t)\}_{t \in \mathbb{R}_+}$, abbreviated as $X(t)$, we use the notations $X^T \triangleq \{X(t) : t \leq T\}$, $X^{T-} \triangleq \{X(t) : t < T\}$, and $X_{t_2}^{t_1} \triangleq \{X(t) : t_1 \leq t \leq t_2\}$. The expected value and the variance of $X(t)$ at time t are denoted by $\mathbb{E}[X(t)], \mathrm{Var}[X(t)]$ respectively; stationary mean and variance are denoted by $\mathbb{E}[X] \triangleq \lim_{t \to \infty} \mathbb{E}[X(t)]$, $\mathrm{Var}[X] \triangleq \lim_{t \to \infty} \mathrm{Var}[X(t)]$, provided that the said limits exist.

II. MOTIVATION: THE BIOMOLECULAR SYSTEM

In this section, we describe the biomolecular system studied in this paper.

A. Representation of chemical reactions

A biomolecular system in a cell may contain many molecular species. The evolution of the molecule counts $X(t)$ of a species X at time t can be modeled as a birth-death process,[1] defined as follows [51]:

- $X(t) \in \mathbb{Z}_+$, $t \in \mathbb{R}_+$, is a Markov chain taking values in the set of non-negative integers.
- The infinitesimal transition probabilities of $X(t)$ are given by[2]

$$\mathbb{P}\left[X(t+h) = n + m | X(t) = n\right]$$
$$= \begin{cases} \lambda(t)h + o(h) & \text{if } m = 1 \\ \mu(t)nh + o(h) & \text{if } m = -1 \\ o(h) & \text{if } |m| > 1, \end{cases} \quad (1)$$

where $n \in \mathbb{Z}_+$, $m \in \mathbb{Z}$, $\lambda(t) \geq 0$ is the production rate, $\mu(t) \geq 0$ is the degradation rate, and $\mu(t)X(t) \geq 0$ is the degradation propensity.

We use the following shorthand notation for the above process:

$$X \xrightarrow{\lambda} X + 1, \qquad X \xrightarrow{\mu X} X - 1. \quad (2)$$
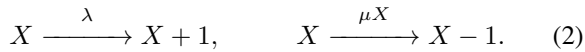
The degradation propensity is the product of the number of molecules $X(t)$ and the degradation rate $\mu(t)$ because a typical molecular degradation process acts on the whole population of species X.[3]

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[1]With slight abuse of notation, X represents both the species and the number of molecules of this species, interchangeably.

[2]The standard notation $f(h) = o(g(h))$ signifies that $f(h)/g(h) \to 0$ as $h \to 0$.

[3]This is according to a physical model of chemical dynamics called mass action. See [52] for a historical perspective with useful references about mass action.

B. Control via chemical reactions

The noise suppression process in a biomolecular system is implemented via chemical reactions among different species. We study the following basic scenario: one species, X, affects the production or degradation rate of another species, C, which in turn controls the production or degradation rate of X, possibly through other existing species (Fig. 1). Here, species X is the target of control, whereas species C and other species can aid the control process. The control objective is to center the stationary mean of $X(t)$ around a desired value $x^\star$ subject to a constraint on the stationary variance, i.e.,

$$\mathbb{E}[X] = x^\star, \qquad \mathrm{Var}[X] \leq D. \quad (3)$$

The stochastic process $\{X(t)\}$ is sensed by another species C, whose number of molecules $C(t)$ obeys the following birth-death process:

$$C \xrightarrow{\nu} C + 1, \qquad C \xrightarrow{\xi C} C - 1. \quad (4)$$
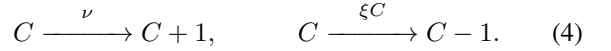
Species X transmits information to species C by setting either the production or the degradation rate of C to an arbitrary function $V(X^t)$ of X^t as follows:

- SP: sensing via the production rate by letting $\nu(t) = V(X^t)$ while keeping degradation rate $\xi(t) \equiv \xi$ fixed to a constant.
- SD: sensing via the degradation rate by letting $\xi(t) = V(X^t)$ while keeping production rate $\nu(t) \equiv \nu$ fixed to a constant.

Species C then acts on X through control action $\{U(t)\}$, and $U(t)$ is assumed to impact species X in either of the following manners:

- CP: control via the production rate $\lambda(t) = U(t)$ given a constant degradation rate $\mu(t) \equiv \mu$.
- CD: control via the degradation rate $\mu(t) = U(t)$ given a constant production rate $\lambda(t) \equiv \lambda$,

where λ, μ govern the transition probabilities of $\{X(t)\}$ according to (1). We assume that the only pathway by which species X can send information about X^t to the controller is via modifying the statistics of C^t, i.e.

$$P_{U(t)|U^{t-}, C^t, X^t} = P_{U(t)|U^{t-}, C^t}. \quad (5)$$

Any causal control policy is completely determined by specifying the probability kernels in (5).

Combining the signaling and control settings, the system described above can be categorized into four regimes, labeled by their acronyms:

SP/CP: sensing and control via production;
SD/CP: sensing via degradation and control via production;
SP/CD: sensing via production and control via degradation;
SD/CD: sensing and control via degradation.

Because the production rate and the degradation rate impact the transition probabilities differently, these four regimes lead to different limitations and tradeoffs, which are elucidated in Section V.
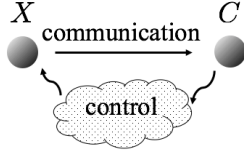
Fig. 1. The molecular control model studied. The control cloud may contain other chemical species.

C. Approximating chemical reactions

When the number of molecules $X(t)$ is sufficiently large, the number of birth events of species X in the time interval $[t, t+h]$ can be approximated by $\mathcal{N}(\lambda(t)h, \lambda(t)h)$; likewise, the number of death events can be approximated by $\mathcal{N}(\mu(t)X(t)h, \mu(t)X(t)h)$ [53].[4] Thus, we can approximate the dynamics of $X(t)$ as

$$dX = (\lambda - \mu X)dt + \sigma dW, \qquad (6)$$

where $\lambda \geq 0$, $\mu \geq 0$, and $\{W(t)\}$ is a Wiener process. The signal $\sigma(t)$ satisfies

$$\sigma(t)^2 = \lambda(t) + \mu(t)X(t). \qquad (7)$$

Equation (6) is known as the *chemical Langevin equation* [53].

If the expected value of $X(t)$ converges to a unique stationary value as $t \to \infty$ as required by the constraint in (3), then the time average of the production rate and that of the degradation propensity must be equal, i.e.,[5]

$$\ell^1\text{-}\lim_{T \to \infty} \frac{1}{T} \int_0^T \lambda(t)dt = \ell^1\text{-}\lim_{T \to \infty} \frac{1}{T} \int_0^T \mu(t)X(t)dt. \qquad (8)$$

Moreover, if the process $\lambda(t)$ is ergodic, then condition (8) further leads to

$$\ell^1\text{-}\lim_{T \to \infty} \frac{1}{T} \int_0^T \sigma(t)^2 dt = \ell^1\text{-}\lim_{T \to \infty} \frac{2}{T} \int_0^T \lambda(t)dt \equiv 2\mathbb{E}[\lambda], \qquad (9)$$

where recall that $\mathbb{E}[\lambda]$ denotes the stationary mean of $\lambda(t)$.

In the sequel, we analyze X in Section III using the continuous-state approximation in (6) and analyze C in Section IV without the approximation.

III. CONTROL PROBLEM

In this section, we consider an abstract control problem that includes the biomolecular control in Section II-B as a special case and characterize the minimum capacity of the channel between between the control action and the system state necessary to achieve the constraints on the first and second moments of $X(t)$.

[4] $\mathcal{N}(\mu, \sigma^2)$ denotes a Gaussian random variable with mean μ and variance σ^2.

[5] ℓ^1-lim denotes the limit *in mean*.

A. Fundamental limitations in feedback control

Consider the stochastic differential equation (SDE)

$$dY = FYdt + Gdt + \sigma dW, \qquad (10)$$

where $Y(t)$ is the state, and $W(t)$ is a Wiener process, as before. The variables $F(t) \in \mathbb{R}$ and $G(t) \in \mathbb{R}$ are deterministic functions of the control action $U(t)$, and the coefficient $\sigma(t)$ is allowed to depend on $Y(t)$, $F(t)$, and $G(t)$. We assume that

$$\lim_{T \to \infty} \frac{1}{T} \int_0^T \sigma(t)^2 dt = \Sigma, \qquad (11)$$

$$\lim_{T \to \infty} \frac{1}{T} \int_0^T F(t)dt = \mathcal{F}, \qquad (12)$$

for some constants $\Sigma > 0$ and $\mathcal{F}$. Furthermore, we assume that $\{F(t)\}$ is uniformly bounded, i.e., $|F(t)| \leq F_{\max}$ for some constant $F_{\max}$. We use the continuous-time *directed information* to quantify the amount of information that can be transmitted in a feedback loop.

Definition 1 ([50]): Let $Y(t), U(t), t \in \mathbb{R}_+$ be a pair of stochastic processes. The directed information from $Y(t)$ to $U(t)$ is defined as

$$I(Y^T \to U^T) = \inf_{\mathbf{t} \in \mathcal{T}(T)} \sum_{i=1}^n I(U_{t_{k-1}}^{t_k}; Y_{t_{k-1}}^{t_k} | U_0^{t_{k-1}}), \qquad (13)$$

where $\mathcal{T}(T)$ is the set of all finite partitions of the time interval $[0, T)$, i.e.

$$\mathcal{T}(T) = \{\mathbf{t} : 0 = t_0 < t_1 < \cdots < t_n = T, n \in \mathbb{N}\}. \qquad (14)$$

Definition 1 is the continuous-time version of the discrete-time directed information introduced by Massey [37], which can be thought of as the causal counterpart of Shannon's mutual information [35].

Our first goal is to characterize the minimum amount of directed information required for the existence of a control and communication policy that achieves

$$\mathbb{E}[Y] = 0, \qquad \text{Var}[Y] \leq D, \qquad (15)$$

where $\mathbb{E}[Y]$, $\text{Var}[Y]$ denote the stationary mean and variance of the process $Y(t)$. Towards that end, we introduce the *rate-cost functions* in continuous time.[6]

Definition 2: The rate-cost function in control for the continuous-time system in (10) is defined as

$$\mathbb{R}_c(D) = \inf \lim_{T \to \infty} \frac{1}{T} I(Y^T \to U^T), \qquad (16)$$

where the infimum is over all conditional distributions (control policies) $P_{U(t)|Y^t, U^{t-}}$ achieving (15).

Definition 3: The rate-cost function in estimation for the continuous-time system in (10) is defined as

$$\mathbb{R}_e(D) = \inf \lim_{T \to \infty} \frac{1}{T} I(Y^T \to \hat{Y}^T)$$

where the infimum is over all conditional distributions (estimation policies) $P_{\hat{Y}(t), U(t)|Y^t, U^{t-}}$ achieving

$$\mathbb{E}[Y - \hat{Y}] = 0, \qquad \text{Var}[Y - \hat{Y}] \leq D. \qquad (17)$$

[6] The discrete-time rate-cost function in control is proposed in [29].

The conditioning on U^{t-} in the optimization variable $P_{\hat{Y}(t),U(t)|Y^t,U^{t-}}$ allows the impact of control action on the state to be known by the estimator. The subscripts 'c' and 'e' in $\mathbb{R}_c(D)$ and $\mathbb{R}_e(D)$ stand for 'control' and 'estimation', respectively. The rate-cost function in control gives the normalized minimum directed information from the system state to the control action that is required to sustain the performance requirement (15) over the class of all causal communication policies, both stochastic and deterministic. The rate-cost function in estimation is the minimum directed information rate from the system state to the state estimate that is required to sustain the estimation accuracy over the class of all causal communication policies. Reminiscent of the separation between estimation and control, we record the following:

Proposition 1: The rate-cost function in control and the rate-cost function in estimation satisfies

$$\mathbb{R}_c(D) \geq \mathbb{R}_e(D). \tag{18}$$

Proof: See Appendix A. ∎

Proposition 1 essentially states that we can solve the rate-cost function in estimation in order to lower-bound the rate-cost function in control. Furthermore, the rate-cost function in estimation admits a closed-form formula.

Theorem 1: The rate-cost function in estimation is lower-bounded by

$$\mathbb{R}_e(D) = \frac{\Sigma}{2D} - \mathcal{F}. \tag{19}$$

Theorem 1 generalizes the result of [32], [33] to time-varying $F(t)$, which potentially depends on causal information on $Y(t)$. Due to the space limit, we outline the proof ideas of Theorem 1 below and refer to the supplementary material [54] for a complete proof. We first show the optimal estimator structure that achieves the rate-cost function in estimation. Relying on that structure, we then derive an explicit formula on the minimal amount of directed information as a function of the required estimation accuracy D and the statistics on $F(t)$ and $G(t)$.

Combining Proposition 1 and Theorem 1, we lower-bound the rate-cost function in control as

$$\mathbb{R}_c(D) \geq \frac{\Sigma}{2D} - \mathcal{F} \tag{20}$$

The bound (20) generalizes the discrete-time result of [22] to continuous time, and the continuous-time result of [11] to the scenario in which the control action acts via F instead of G, and/or the statistics of future disturbances depend on the control action chosen. Furthermore, it allows us to obtain the performance bounds in bimolecular control, which are presented in Section III-B and III-C.

B. Molecular control via production

Consider the regime of CP (control via production) in Section II-B. We perform the coordinate transformation

$$Y(t) = X(t) - x^\star, \qquad \tilde{U}(t) = U(t) - \mu x^\star. \tag{21}$$

From the chemical Langevin equation of $X(t)$ in (6), the dynamics of Y can be approximated using the stochastic differential equation

$$dY(t) = -\mu Y(t)dt + \tilde{U}(t)dt + \sigma(t)dW(t), \tag{22}$$

where $\sigma(t)$ is given in (7) and $W(t)$ is a Wiener process, as before. This corresponds to system (10) with

$$F(t) \equiv -\mu, \qquad G(t) = \tilde{U}(t), \qquad \mathcal{F} = \mu, \tag{23}$$

and the control objective given in (15).

Recall that $\mathbb{E}[\lambda]$ is the mean of the stationary distribution of $\lambda(t)$. If the control action $U(t) = \lambda(t)$ is chosen so that the random process $\lambda(t)$ is ergodic, then from (8), (9) and (11), we obtain

$$\Sigma = \ell^1\text{-}\lim_{T\to\infty} \frac{2}{T} \int_0^T \lambda(t)dt = 2\mathbb{E}[\lambda]. \tag{24}$$

Substituting (23) and (24) into (20), we obtain the minimum directed information from $X(t)$ to $U(t)$ in order to sustain the performance requirement (3) for the dynamics (22):

$$\lim_{T\to\infty} \frac{1}{T} I(X^T \to U^T) \geq \frac{\mathbb{E}[\lambda]}{D} - \mu, \tag{25}$$

when control is performed via the *production* rate. Additionally, there exist communication policies that attain the performance lower bound of (25) closely (see Example 1 in Section V-B). This extends the existing result [11] to the case when the control action $U(t)$ is not a deterministic function of C^t, allowing the control action to be generated by species in the system other than C.

C. Molecular control via degradation

Consider the regime of CD (control via degradation) in Section II-B. We perform the coordinate transformation

$$Y(t) = X(t) - x^\star, \qquad \tilde{U}(t) = U(t) - \frac{\lambda}{x^\star}. \tag{26}$$

The dynamics of $\{X(t)\}$ can be approximated using

$$dY(t) = -(U(t)Y(t) + \tilde{U}(t)x^\star)dt + \sigma(t)dW(t), \tag{27}$$

where $\sigma(t)$ is given in (7) and $W(t)$ is a Wiener process, as before. The dynamics of Y corresponds to system (10) with

$$F(t) = -U(t), \qquad G(t) = -\tilde{U}(t)x^\star, \qquad \Sigma = 2\lambda \tag{28}$$

and the control objective given in (15). If the control action $U(t) = \mu(t)$ is chosen so that the random process $\{\mu(t)\}$ is ergodic, then

$$\mathcal{F} = \ell^1\text{-}\lim_{T\to\infty} \frac{1}{T} \int_0^T \mu(t)dt = \mathbb{E}[\mu]. \tag{29}$$

Using the same argument as in Section III-B, a necessary amount of directed information to sustain the performance requirement (15) is

$$\lim_{T\to\infty} \frac{1}{T} I(X^T \to U^T) \geq \frac{\lambda}{D} - \mathbb{E}[\mu], \tag{30}$$

when control is performed via the *degradation* rate. The tightness of the bound in (30) and the structure of the optimal controller remain open problems.

IV. COMMUNICATION PROBLEM

Our results in Section III enable us to obtain minimum capacity of the feedback channel necessary to satisfy the constraints on the first and second moments of $X(t)$. In this section, we bound the capacity of the molecular channel that transmits information via modifying either the production rate or the degradation rate of species C.

A. Communication via production rate

Consider the regime of SP (sensing via production) in Section II-B. The information about species X is encoded in the production rate of species C, i.e., $\nu(t) = V(X^t)$, which defines the transition probabilities of $C(t)$ according to (4). The degradation rate of C can be an arbitrary process that is independent of X^t. Let $N_p(t)$ be the number of birth events of species C during time interval $[0,t]$. Then $N_p(t)$ evolves according to

$$N_p \xrightarrow{\nu} N_p + 1, \tag{31}$$

giving rise to a communication channel with input $\nu(t)$ and output $N_p(t)$. We further assume that

$$\mathbb{E}[\nu] = m_V, \qquad \mathrm{Var}[\nu] \leq \sigma_V^2, \tag{32}$$

where recall that $\mathbb{E}[\nu], \mathrm{Var}[\nu]$ denote the stationary mean and variance of the process $\nu(t)$. The constraints in (32) arise naturally in biomolecular systems, as the production and maintenance of the molecules in the system carry costs. The *channel capacity*, which quantifies the capability of a channel with feedback to deliver information, is defined as follows.

Definition 4 ([55]): The capacity of the communication channel from input $\nu(t)$ and output $N_p(t)$ is defined as

$$\mathbb{C}_{\nu,N_p} = \sup \lim_{T\to\infty} \frac{1}{T} I(\nu^T \to N_p^T), \tag{33}$$

where the supremum is taken over all distributions P_ν of the input process $\{\nu(t)\}_{t\in\mathbb{R}_+}$.

Definition 5: If the following condition holds,

$$\mathbb{P}_{\nu(t)|\nu^{t-}, N_p^t} = \mathbb{P}_{\nu(t)|\nu^{t-}}, \tag{34}$$

then we call that the channel is used *without feedback*. If the channel is used without feedback,[7] then the channel capacity in (33) equals the usual Shannon capacity [37]. The capacity of the channel in (31) satisfies

$$\mathbb{C}_{\nu,N_p} \leq \sup \lim_{T\to\infty} \frac{1}{T} I(\nu^T; N_p^T) \tag{35}$$

$$= m_V \log\left(1 + \frac{\sigma_V^2}{m_V^2}\right). \tag{36}$$

The first inequality holds because the the directed information is no greater than than the mutual information. The second equality is shown in [11, Appendix B].

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[7]In other words, the space over which the supremum in (33) is taken over cannot use feedback.

B. Communication via degradation rate

Consider the regime of SD (sensing via degradation) in Section II-B. The information about species X is encoded in the degradation rate of species C, i.e., $\xi(t) = V(X^t)$, which defines the transition probabilities of $C(t)$ according to (4). The production rate of C can be an arbitrary process that is independent of X^t. Let $N_d(t)$ be the number of death events of species C during time interval $[0,t]$. The process $N_d(t)$ evolves according to

$$N_d \xrightarrow{\xi C} N_d + 1, \tag{37}$$

giving rise to a communication channel with input $\xi(t)$ and output $N_d(t)$. Recall that in contrast to communication via the production rate, the degradation rate acts on the whole population of species C. We further assume that

$$\mathbb{E}[C] = \bar{C}, \ \mathbb{E}[\xi] = m_V, \ \mathrm{Var}[\xi] \leq \sigma_V^2. \tag{38}$$

Theorem 2: The capacity of the causal communication channel with input process $\xi(t)$ and output process $N_d(t)$ under constraints (38) is upper-bounded by

$$\mathbb{C}_{\xi,N_d} \leq m_V \bar{C} \log\left(1 + \frac{\sigma_V^2}{m_V^2}\right). \tag{39}$$

Proof: See Appendix E. ∎

V. TRADEOFFS IN MOLECULAR CONTROL

In this section, we combine the results on control in Section III and the results on communication in Section IV to obtain closed-form formulas that characterize the fundamental limitations in molecular control. Recall the biomolecular control system presented in Section II-B. We additionally assume for the rest of this section that the control policy is chosen so that the stochastic processes $X(t), C(t), U(t)$, and $V(t)$ have bounded first and second moments that are globally converging to their unique stationary values as $t \to \infty$; that the processes $U(t)$ and $C(t)$ are ergodic; that the SDEs (22) and (27) accurately approximate the actual transition dynamics of $\{X(t)\}$; and that the chemical reaction channel in (31) or (37) is used without feedback (see Definition 5).

A. Fundamental limits

We first define two biologically important quantities and then study their impact on the control performance. We define the *degradation efficiency* of X and μ as follows:

$$\gamma_X \triangleq \frac{\mathbb{E}[X]\mathbb{E}[\mu]}{\mathbb{E}[X\mu]} = \frac{\mathbb{E}[X]\mathbb{E}[\mu]}{\mathbb{E}[\lambda]} \tag{40}$$

$$\gamma_C \triangleq \frac{\mathbb{E}[C]\mathbb{E}[\xi]}{\mathbb{E}[C\xi]} = \frac{\mathbb{E}[C]\mathbb{E}[\xi]}{\mathbb{E}[\nu]} \tag{41}$$

where the second equalities in (40) and (41) follow from the assumption that the mean of $X(t)$ and $C(t)$ converge to their stationary values. If a species' degradation rate is fixed, then the degradation efficiency of that species takes the default value one. Otherwise, the degradation efficiency

is determined by the statistical dependence between the species' count and its degradation rate.

Let ℓ_X be the average lifetime of species X. If the degradation rate is constant, i.e., $\mu(t) \equiv \mu$, then μ^{-1} is the average lifetime for the molecules of species X. From Little's results [58], ℓ_X also satisfies

$$\ell_X = \frac{\mathbb{E}[X]}{\mathbb{E}[\lambda]}. \tag{42}$$

Let N_X and N_C be the average number of birth (or death) events of X and C, respectively, made during a time interval of length ℓ_X, the average lifetime of species X, i.e.,

$$N_X = \ell_X \mathbb{E}[\lambda] = \mathbb{E}[X] \qquad N_C = \ell_X \mathbb{E}[\nu]. \tag{43}$$

Counting the number of birth events is essentially the same as counting the number of death events because both numbers must be roughly equal in order to maintain constant $\mathbb{E}[X(t)]$ over time (see (8)). We define the *signal rate* to be N_C/N_X. The signal rate, originally proposed in [11], describes the sensing frequency of species C relative to the control frequency of species X.

Bounds for a general causal encoding function. The Fano factor of $X(t)$, $\mathrm{Var}[X]/\mathbb{E}[X]$ is bounded below as follows:[8]

SP: sensing via production

$$\frac{\mathrm{Var}[X]}{\mathbb{E}[X]} \geq \left\{ \frac{N_C}{N_X} \mathbb{E}[X] \log\left(1 + \mathrm{cv}(\nu)^2\right) + \gamma_X \right\}^{-1} \tag{44}$$

SD: sensing via degradation

$$\frac{\mathrm{Var}[X]}{\mathbb{E}[X]} \geq \left\{ \frac{N_C}{N_X} \mathbb{E}[X] \log\left(1 + \mathrm{cv}(\xi)^2\right) \gamma_C + \gamma_X \right\}^{-1} \tag{45}$$

The bounds in (44) and (45) quantify the variance reduction of species X in terms of the control effort by species C. Without feedback control, $\lim_{T \to \infty} \frac{1}{T} I(X^T \to (\lambda, \mu)) = 0$ and $\mathrm{Var}(X)/\mathbb{E}[X] = 1$ is the minimal achievable variance for any mean constraint $\mathbb{E}[X] = x^\star$. This performance can be achieved by setting the production rates λ, ν and the degradation rates μ, ξ in (2) and (4) to be constant over time. The stationary variance of $X(t)$ then becomes

$$\mathrm{Var}[X] = \frac{\lambda}{\mu} = x^\star = \mathbb{E}[X] \tag{46}$$

Under communication constraints and at the expense of fluctuations of the production or degradation rate of species C, from formulas (44)–(45), the stationary Fano factor $\mathrm{Var}[X]/\mathbb{E}[X]$ can be further reduced inverse-proportionally to the mean production rate (or mean degradation rate) of species C; inverse-logarithmically to the squared coefficient of variation of the production rate (or degradation rate) of C; and inverse-logarithmically to the degradation efficiency of species X or C.

Bounds for linear encoding functions. Now we constrain the encoding function to be a memoryless and linear function of X^t, i.e.,

$$V(t) = \alpha X(t). \tag{47}$$

[8]$\mathrm{cv}(Z)$ refers to the coefficient of variation of a random process $\{Z(t)\}$.

Combining (43) and (47) leads to $N_C = \alpha \ell_X \mathbb{E}[X]$ under the regime of SP (sensing via production), and $N_C = \alpha \ell_X \mathbb{E}[CX]$ under the regime of SD (sensing via degradation). Then, the Fano factor of $X(t)$ is lower-bounded by

$$\frac{\mathrm{Var}[X]}{\mathbb{E}[X]} \geq 2 \left\{ \gamma_X \left(1 + \sqrt{1 + 4\frac{\gamma_C}{\gamma_X^2}\frac{N_C}{N_X}} \right) \right\}^{-1} \tag{48}$$

$$= \begin{cases} (\gamma_X)^{-1} & \gamma_X \gg \gamma_C N_C/N_X \\ (N_X/\gamma_C N_C)^{1/2} & \gamma_X \ll \gamma_C N_C/N_X \end{cases}.$$

The bound in (48) includes the results of [11] as a special case: if sensing and control are performed via production rates, then the Fano factor of X is lower bounded by (48) with $\gamma_X = 1$, $\gamma_C = 1$. In contrast to control or sensing via the production rate, control or sensing via the degradation rate enjoys an additional design freedom to choose the degradation efficiency γ_X or γ_C in (40). The impact of degradation efficiency of species X is particularly salient at $\gamma_X \gg \gamma_C N_C/N_X$, and almost negligible at $\gamma_X \ll \gamma_C N_C/N_X$. Furthermore, if the policy of control or sensing via degradation is chosen so that $\gamma_\cdot \approx 1$, then its resultant performance bound with respect to the signal rate (48) is qualitatively similar to that via the production rate.

B. Achievable performance

Example 1: Consider the regime of SP/CP (control and sensing via production). The performance bound (25) in SDE approximation of $X(t) = Y(t) + x^\star$ can be attained arbitrarily closely using the following communication policy [27], [54]:

$$\begin{aligned} dN_p &= \alpha Y + \sqrt{\alpha Y}\, dW_c \\ d\hat{X} &= (\tilde{U} - \mu\hat{X})dt + L(dN_p - \alpha\hat{X})dt. \end{aligned} \tag{49}$$

The process $W_c(t)$ is a Wiener process independent of $W(t)$ in (22). The matrix L is the Kalman gain defined by $L = p/Y$, where the process $p(t)$ satisfies a Riccati differential equation $dp = -2\mu p - p^2\alpha/Y + \sigma(t)^2$, $p(0) = \mathbb{E}[Y^2]$. Using similar argument in Section V, we show that the policy (49) achieves

$$\frac{\mathrm{Var}[X]}{\mathbb{E}[X]} \approx 2 \left(1 + \sqrt{1 + 2\frac{N_C}{N_X}} \right)^{-1}. \tag{50}$$

Note that this requires the assumption that the number of molecules in species C, its production and degradation rates are large enough so that the dynamics of species C can be approximated using the chemical Langevin equation. In Fig. 2, we reversed the process in Section II-C to find the production rate of $C(t)$ (such that chemical Langevin equation of $C(t)$ matches (49)) and computed the Fano factor of $X(t)$ for different signal rate N_C/N_X. Although the performance formulas are derived for the continuous-state approximation, Fig. 2 suggests that they closely approximate the actual discrete-state performance. The approximation of C is accurate if C has high count, small noise, and fast dynamics [59].

Example 2: There are many ways to encode the information about $X(t)$ into $V(t)$. Assuming memoryless encoding,
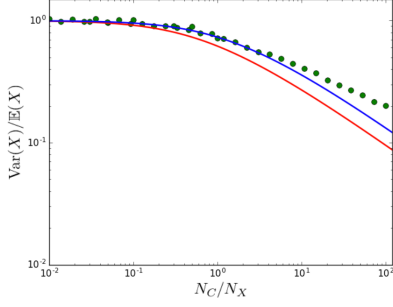
Fig. 2. Achievable performance and lower bound for $\mathrm{Var}[X(t)]/\mathbb{E}[X]$. Green dots represent the empirical statistics of each sample; blue line represents (50), the theoretically achievable values in the continuous-time approximation; the red line represents (48) with $\gamma_X = \gamma_C = 1$, the theoretical lower bound in the continuous-time approximation.

at one extreme, $V(X(t))$ can be a switching function of $X(t)$, i.e.,

$$V(t) = V(X(t)) = \begin{cases} a & X(t) \geq \ell \\ b & X(t) < \ell \end{cases} \qquad (51)$$

The proof of Theorem 2 suggests encoding by a switching function can be beneficial [54]. At another extreme, $V(X(t))$ can be a linear function of $X(t)$. What lies between the two extremes is the Hill function [9]

$$V(t) = V(X(t)) = (a - b)\left\{ \left(\frac{\ell}{X(t)} \right)^n + 1 \right\}^{-1} + b, \quad (52)$$

where $a, b > 0$. Linear encoding appears most often in biology, as it describes the case where X acts as a catalyst that produce or degrade C, e.g., X could be mRNAs that translates into proteins, C. The Hill function was first derived from chemical kinetic models to capture the cooperative effect of ligand binding with hemoglobin [60]. Since then, it has been used to describe other phenomena, such as transcription factors' effect on gene expression [61]. Furthermore, there exists a physical motivation for Hill-function-like dynamics based on thermodynamic models [62].

To test our bound on channel capacity in (35) and (39), we used the method in [63] to estimate the mutual information between C and X. In Fig. 3, we compared the empirical values of mutual information with the theoretical lower bounds in (35) and (39). In both cases, the bounds can be attained by a switching encoding function, while the decrement in mutual information by other classes of encoding functions remains small.

VI. CONCLUSION

In this paper, we study the fundamental limits and achievable performance in biomolecular control. The difficulty of analyzing discrete state CMEs is circumvented by

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[9]This is a smooth monotone function that takes the value $V(t) \to a$ as $X(t) \to 0^+$, and the value $V(t) \to b$ as $X(t) \to \infty$. At one end, as $n \to \infty$, the Hill function approximates the switching function in (51). Specifically, when $\ell/X(t) < 1$, $V(t) \to a$ as $n \to \infty$; when $\ell/X(t) > 1$, $V(t) \to b$ as $n \to \infty$. At the other end, as $n \to 1$, the Hill function approximates a linear function of $X(t)$ if $X(t)/\ell \ll 1$.
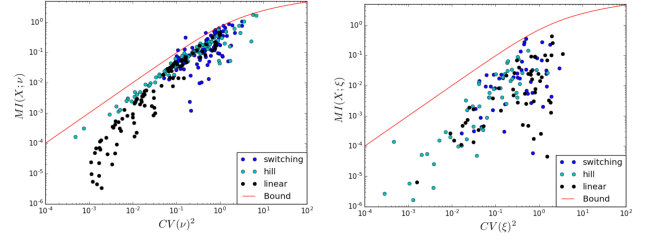

Fig. 3. Achievable performance $\frac{1}{T} I(\nu^T; N_p^T)$ (top) and $\frac{1}{T} I(\xi^T; N_d^T)$ (bottom). Each dot represents a randomly selected parameter in switching, linear, or hill functions. The red lines represent the lower bounds (35) and (39) in the top figure and the bottom figure, respectively.

continuous-state approximation using SDEs. Our analysis also takes into account the impact of control on future system noise and the nonlinearity arising from control via degradation. The derived performance bound also allows the sensing species (species C in Section V) to act on the target species indirectly via other species in the system. Consequently, our results extend the applicability of the pioneering work [11] to a wider range of biomolecular systems.

REFERENCES

[1] U. Alon, *An Introduction to Systems Biology, Design Principles of Biological Circuits*. London: CRC, 2006.

[2] T.-M. Yi, Y. Huang, M. I. Simon, , and J. Doyle, "Robust perfect adaptation in bacterial chemotaxis through integral feedback control," *Proceedings of the National Academy of Sciences*, vol. 97, no. 9, 2000.

[3] F. A. Chandra1, G. Buzi, and J. C. Doyle, "Glycolytic oscillations and limits on robust efficiency," *Science*, vol. 333, no. 6039, 2011.

[4] N. Li, J. Cruz, C. S. Chien, S. Sojoudi, B. Recht, D. Stone, M. Csete, D. Bahmiller, and J. C. Doyle, "Robust efficiency and actuator saturation explain healthy heart rate control and variability," *Proceedings of the National Academy of Sciences*, vol. 111, no. 33, 2014.

[5] D. D. Vecchio and R. M. Murray, *Biomolecular Feedback Systems*. Princeton University Press, 2014.

[6] C. Briat, A. Gupta, and M. Khammash, "Antithetic integral feedback ensures robust perfect adaptation in noisy biomolecular networks," *Cell systems*, vol. 2, no. 1, pp. 15–26, 2016.

[7] M. E. Csete and J. C. Doyle, "Reverse engineering of biological complexity," *Science*, vol. 295, no. 5560, 2002.

[8] J. C. Doyle and M. Csete, "Architecture, constraints, and behavior," *Proceedings of National Academy of Science*, vol. 108, no. s3, 2011.

[9] J. Doyle, "Robust and optimal control," in *Decision and Control, 1996., Proceedings of the 35th IEEE Conference on*, vol. 2, 1996, pp. 1595–1598.

[10] M. B. Elowitz, A. J. Levine, E. D. Siggia, and P. S. Swain, "Stochastic gene expression in a single cell," *Science*, vol. 5584, no. 297, 2002.

[11] I. Lestas, G. Vinnicombe, and J. Paulsson, "Fundamental limits on the suppression of molecular fluctuations," *Nature*, vol. 467, no. 7312, pp. 174–178, 2010.

[12] A. Hilfinger, T. M. Norman, and J. Paulsson, "Exploiting natural fluctuations to identify kinetic mechanisms in sparsely characterized systems," *Cell Systems*, vol. 4, no. 2, 2016.

[13] L. Potvin-Trottier, N. D. Lord, G. Vinnicombe, and J. Paulsson, "Synchronous long-term oscillations in a synthetic gene circuit," *Nature*, vol. 538, 2016.

[14] G. N. Nair, F. Fagnani, S. Zampieri, and R. J. Evans, "Feedback control under data rate constraints: An overview," *Proceedings of the IEEE*, vol. 95, no. 1, pp. 108–137, 2007.

[15] J. Baillieul and P. J. Antsaklis, "Control and communication challenges in networked real-time systems," *Proceedings of the IEEE*, vol. 95, no. 1, pp. 9–28, 2007.

[16] B. R. Andrievsky, A. S. Matveev, and A. L. Fradkov, "Control and estimation under information constraints: Toward a unified theory of control, computation and communications," *Automation and Remote Control*, vol. 71, no. 4, pp. 572–633, 2010.

[17] S. Fang, J. Chen, and I. Hideaki, *Towards integrating control and information theories*. Springer, 2017.

[18] S. Yuksel, "Stochastic stabilization of noisy linear systems with fixed-rate limited feedback," *IEEE Transactions on Automatic Control*, vol. 55, no. 12, pp. 2847–2853, 2010.

[19] G. N. Nair and R. J. Evans, "Stabilizability of stochastic linear systems with finite feedback data rates," *SIAM Journal on Control and Optimization*, vol. 43, no. 2, pp. 413–436, 2004.

[20] S. Tatikonda and S. Mitter, "Control over noisy channels," *IEEE Transactions on Automatic Control*, vol. 49, no. 7, pp. 1196–1201, 2004.

[21] Y. Bar-Shalom and E. Tse, "Dual effect, certainty equivalence, and separation in stochastic control," *IEEE Transactions on Automatic Control*, vol. 19, no. 5, pp. 494–500, 1974.

[22] S. Tatikonda, A. Sahai, and S. Mitter, "Stochastic linear control over a communication channel," *IEEE Transactions on Automatic Control*, vol. 49, no. 9, pp. 1549–1561, 2004.

[23] C. D. Charalambous and A. Farhadi, "LQG optimality and separation principle for general discrete time partially observed stochastic systems over finite capacity communication channels," *Automatica*, vol. 44, no. 12, pp. 3181–3188, 2008.

[24] J. S. Freudenberg, R. H. Middleton, and V. Solo, "Stabilization and disturbance attenuation over a Gaussian communication channel," *IEEE Transactions on Automatic Control*, vol. 55, no. 3, pp. 795–799, 2010.

[25] E. I. Silva, M. S. Derpich, and J. Ostergaard, "A framework for control system design subject to average data-rate constraints," *IEEE Transactions on Automatic Control*, vol. 56, no. 8, pp. 1886–1899, 2011.

[26] S. Yuksel, "Jointly optimal LQG quantization and control policies for multi-dimensional systems," *IEEE Transactions on Automatic Control*, vol. 59, no. 6, pp. 1612–1617, 2014.

[27] T. Tanaka, P. M. Esfahani, and S. K. Mitter, "LQG control with minimum directed information: Semidefinite programming approach," *arXiv preprint arXiv:1510.04214*, 2015.

[28] E. I. Silva, M. S. Derpich, J. Østergaard, and M. A. Encina, "A characterization of the minimal average data rate that guarantees a given closed-loop performance level," *IEEE Transactions on Automatic Control*, vol. 61, no. 8, pp. 2171–2186, 2016.

[29] V. Kostina and B. Hassibi, "Rate-cost tradeoffs in control. part i: lower bounds," in *arXiv:1612.02126*.

[30] T. Fischer, "Optimal quantized control," *IEEE Transactions on Automatic Control*, vol. 27, no. 4, pp. 996–998, 1982.

[31] M. Fu, "Lack of separation principle for quantized linear quadratic Gaussian control," *IEEE Transactions on Automatic Control*, vol. 57, no. 9, pp. 2385–2390, 2012.

[32] A. Gorbunov and M. S. Pinsker, "Nonanticipatory and prognostic epsilon entropies and message generation rates," *Problemy Peredachi Informatsii*, vol. 9, no. 3, pp. 12–21, 1973.

[33] R. Bucy, "Distortion-rate theory and filtering," in *Advances in Communications*. Springer, 1980, pp. 11–15.

[34] M. S. Derpich and J. Ostergaard, "Improved upper bounds to the causal quadratic rate-distortion function for Gaussian stationary sources," *IEEE Transactions on Information Theory*, vol. 58, no. 5, pp. 3131–3152, 2012.

[35] T. M. Cover and J. A. Thomas, *Elements of information theory*. John Wiley & Sons, 2012.

[36] A. Sahai and S. Mitter, "The necessity and sufficiency of anytime capacity for stabilization of a linear system over a noisy communication link - part i: Scalar systems," *IEEE Transactions on Information Theory*, vol. 52, no. 8, pp. 3369–3395, 2006.

[37] J. Massey, "Causality, feedback and directed information," in *Proceedings of the International Symposium on Information Theory and Applications (ISITA-90)*, 1990, pp. 303–305.

[38] C. E. Shannon, "A mathematical theory of communication," *ACM SIGMOBILE Mobile Computing and Communications Review*, vol. 5, no. 1, pp. 3–55, 2001.

[39] A. Khina, G. M. Pettersson, V. Kostina, and B. Hassibi, "Multi-rate control over awgn channels via analog joint source-channel coding," in *2016 IEEE 55th Conference on Decision and Control (CDC)*, 2016, pp. 5968–5973.

[40] B. Sinopoli, L. Schenato, M. Franceschetti, K. Poolla, M. I. Jordan, and S. S. Sastry, "Kalman filtering with intermittent observations," *IEEE Transactions on Automatic Control*, vol. 49, no. 9, pp. 1453–1464, 2004.

[41] F. Rezaei, N. Ahmed, and C. D. Charalambous, "Rate distortion theory for general sources with potential application to image compression," *International Journal of Applied Mathematical Sciences*, vol. 3, no. 2, pp. 141–165, 2006.

[42] C. D. Charalambous, P. A. Stavrou, and N. U. Ahmed, "Nonanticipative rate distortion function and relations to filtering theory," *IEEE Transactions on Automatic Control*, vol. 59, no. 4, pp. 937–952, 2014.

[43] S. Verdú, "Poisson communication theory," *International Technion Communication Day in Honor of Israel Bar-David*, vol. 66, 1999.

[44] Y. M. Kabanov, "The capacity of a channel of the Poisson type," *Theory of Probability & Its Applications*, vol. 23, no. 1, pp. 143–147, 1978.

[45] M. Davis, "Capacity and cutoff rate for Poisson-type channels," *IEEE Transactions on Information Theory*, vol. 26, no. 6, pp. 710–715, 1980.

[46] P. Br6maud, "Point processes and queues," 1981.

[47] R. Liptser and A. N. Shiryaev, *Statistics of random Processes II: Applications*. Springer Verlag, 2001.

[48] D. Snyder, "Filtering and detection for doubly stochastic Poisson processes," *IEEE Transactions on Information Theory*, vol. 18, no. 1, pp. 91–102, 1972.

[49] D. Guo, S. Shamai, and S. Verdú, "Mutual information and conditional mean estimation in Poisson channels," *IEEE Transactions on Information Theory*, vol. 54, no. 5, pp. 1837–1849, 2008.

[50] T. Weissman, Y.-H. Kim, and H. H. Permuter, "Directed information, causal estimation, and communication in continuous time," *IEEE Transactions on Information Theory*, vol. 59, no. 3, pp. 1271–1287, 2013.

[51] G. Grimmett and D. Stirzaker, *Probability and random processes*. Oxford university press, 2001.

[52] E. O. Volt, H. A. Martens, and S. W. Omholt, "150 years of the mass action law," *PLOS Computational Biology*, vol. 11, no. 1, 2015.

[53] D. T. Gillespie, "The chemical langevin equation," *Journal of Chemical Physics*, vol. 133(1), p. 297, 2000.

[54] Y. Nakahira, F. Xiao, and V. Kostina, "Fundamental limits and achievable performance in biomolecular control: supplementary material," 2014. [Online]. Available: http://users.cms.caltech.edu/ ynakahir/

[55] S. Tatikonda and S. Mitter, "The capacity of channels with feedback," *IEEE Transactions on Information Theory*, vol. 55, no. 1, pp. 323–349, 2009.

[56] S. L. Robert, *Statistics of random processes: II Applications*. Springer, 2001.

[57] W. Hoeffding, "The extrema of the expected value of a function of independent random variables," *The Annals of Mathematical Statistics*, pp. 268–275, 1955.

[58] J. D. Little, "A proof for the queuing formula: L= λ w," *Operations research*, vol. 9, no. 3, pp. 383–387, 1961.

[59] N. van Kampen, *Stochastic Processes in Physics and Chemistry*, 3rd ed. Amsterdam: Elsevier, 2007.

[60] A. V. Hill, "The possible effects of the aggregation of the molecules of hmoglobin on its dissociation curves," *Journal of Physiology*, vol. 40, no. 2, 1910.

[61] D. Chu, N. R. Zabeta, and B. Mitavskiy, "Models of transcription factor binding: Sensitivity of activation functions to model assumptions," *Journal of Theoretical Biology*, vol. 257, no. 3, 2009.

[62] L. Bintu1, N. E. Buchler, H. G. Garcia, U. Gerland, T. Hwa, J. Kondev1, and R. Phillips, "Transcriptional regulation by the numbers: models," *Current Opinion in Genetics and Development*, vol. 15, no. 2, 2005.

[63] S. A. Pasha and V. Solo, "Stochastic gene expression in a single cell," in *34th Annual International Conference of the IEEE EMBS*, 2012, pp. 4603–4606.

[64] S. Tatikonda, A. Sahai, and S. Mitter, "Stochastic linear control over a communication channel," *IEEE Transactions on Automatic Control*, vol. 49, no. 9, pp. 1549–1561, 2004.

[65] A. Gorbunov and M. S. Pinsker, "Prognostic epsilon entropy of a Gaussian message and a Gaussian source," *Problemy Peredachi Informatsii*, vol. 10, no. 2, pp. 5–25, 1974.