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Single Event Molecular Signalling for Estimation and Control

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Abstract— **Cell biology is characterised by low molecule numbers and coupled stochastic chemical reactions with intrinsic noise permeating and dominating the interactions between molecules. Recent work [9] has shown that in such environments there are hard limits on the accuracy with which molecular populations can be controlled and estimated. These limits are predicated on a continuous diffusion approximation of the target molecule (although the remainder of the system is non-linear and discrete). The principal result of [9] assumes that the birth rate of the signalling species is linearly dependent on the target molecule population size. In this paper, we investigate the situation when the entire system is kept discrete, and arbitrary non-linear coupling is allowed between the target molecule and downstream signalling molecules. In this case it is possible, by relying solely on the event triggered nature of control and signalling reactions, to define non-linear reaction rate modulation schemes that achieve improved performance in certain parameter regimes. These schemes would not appear to be biologically relevant, raising the question of what are an appropriate set of assumptions for obtaining biologically meaningful results.**

I. Introduction

Noise is an integral and prevalent feature of molecular and systems biology. Whether due to intrinsic fluctuations in small molecular populations or extrinsic uncertainties caused by random upstream events in reaction circuits, noise is largely influential on biological mechanisms. Coordination of genetic expression, neural signalling, enzymatic dynamics, ion-channel gating and evolutionary diversity are among the many biological processes shaped by noise [3]. Given the widespread impact of noise, biological systems have had to evolve schemes that attenuate, filter, utilise or tolerate its stochastic effects [9] in order to achieve complex and effective functionality.

Despite a decade of research the question of how biology is able to achieve precise, seemingly ordered and intricate behaviours in the presence of random molecular fluctuations largely remains unsolved [12]. Although regulatory reaction circuits and negative feedback control loops are known essential noise management network motifs [3], their biological capabilities and contributions to complex cell functionality are still open research questions.

Lestas et al [9] provided insight into these motifs by proving that the noise suppression attainable via feedback control is limited by constraints imposed by reaction channel information capacities. In particular they derive a slack bound, $d_{\min}$ for general coding and a tight quartic bound for linear encoding. However, these bounds are not absolute as they are predicated on a continuity approximation. This paper illustrates that, if arbitrary non-linear coupling is allowed and the fully discrete system description is used, noise performance superior to $d_{\min}$ is achievable. It is believed, however, that the central quartic bound of [9] still holds in the fully discrete case. Since the non-linear codes developed seem biologically implausible, one questions what coding assumptions must be imposed to truly examine noise performance in a biologically meaningful manner.

Two key problems in cellular noise management, denoted as the estimation and control problems, form the basis of this paper. The estimation problem aims to determine good schemes for measuring the population of a target molecular species, X_1, at some time, t, given only observations of another correlated (signalling) species X_2 until t. The correlation between the two species is embedded in the X_2 birth reaction rate f which can be regarded as an information theoretic encoding function.

The control problem extends the estimation problem by using an estimate of X_1 to control the actual X_1 population characteristics in accordance with control objectives. The negative feedback control is implemented by modulating the X_1 birth rate, u.

The source of noise in both problems is intrinsically due to the stochastic nature of X_1 and X_2 reactions which, given the usually low copy number of such molecules, results in non-negligible population fluctuations. The solution of estimation and control problems involves finding feasible f and u functions which achieve good performance despite the noise. Absolute performance is described by an appropriate mean squared error index, denoted mse. As the minimum distortion bound, $d_{\min}$ applies to all estimation-control problems [9] relative performance is described by the ratio $\psi = \text{mse}/d_{\min}$. Consequently this paper presents solutions that achieve $\psi < 1$ over some parameter set.

The importance of estimation and control problems is undoubted when considered in the context of biological noise regulation circuits. Such circuits inevitably involve networks of signalling and control molecules with fluctuating populations due to random births and deaths. Feedback loops and molecular estimation cascades are integral and prevalent structural components of such networks [13] thus emphasising the significance of exploring the limits to accuracy.

This paper is structured as follows: the preliminaries de-

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scribes existing theory applied in this paper while section III proposes and analyses an encoding scheme which betters the estimation bound analytically in the pure birth setting. Sections IV and V focus on the full control problem, providing schemes which outperform the bound for pure birth and birth-death processes respectively. The main results are then discussed in the conclusion.

II. Preliminaries

Birth-death processes, Cox processes, Poisson channels and the distortion bound are the main concepts used in this paper. A birth-death process is a stochastic process which has a countably infinite discrete state space $S = 0,1,2,... = \mathbb{Z}_0^+$ and allows transitions only between neighbouring states [8]. If $X(t_n) = x_n = j, j \in S$ is the n^{th} state of such a process then $X(t_{n+1}) = x_{n+1} \in \{j-1,\ j+1\}$. All chemical reactions considered here are birth-death processes with the population $x_i(t)$ representing the continuous time discrete state of the process and x_i^+, x_i^- representing births and deaths respectively. Control and estimation use rate functions u, f which depend on the stochastic populations of signalling or controlled molecules. This results in Cox process descriptions for the molecular species which are driven by u and f. Cox processes (or doubly stochastic Poisson processes) are Poisson processes with stochastic intensity functions.

Poisson channels are point process information channels which are modulated by an intensity process with the receiver registering a count proportional to the modulating intensity, $\lambda(t)$ [2]. In such channels this count is represented as a Cox process which has a rate determined by the input process. The capacity of Poisson channels is dependent on the constraints applied to the channel inputs. As derived in [7] the feedback invariant capacity under mean constraint $\mathbb{E}[\lambda(t)] = m$ and maximum constraint $0 \le \lambda(t) \le c$ is $C = m\log(c/m)$. Importantly Davis [2] shows that stationary random telegraph signals defined by piecewise continuous processes which switch between 0 and a maximum are able to achieve this capacity. These results for channel capacity and the telegraph signal will have an important bearing on the choice of encoding strategy applied in this paper.

The general distortion bound establishes an information theoretic lower limit on the accuracy attainable in molecular estimation and control. In the chemical framework used to derive the bound u is an optimal control signal, dependent only on X_2, that minimises $\mathrm{var}(x_1)$. Since f is a finite signalling rate and X_2 reacts probabilistically, $x_1(t)$ cannot be determined exactly from the x_2 time series. This corresponds to an information loss that is induced by the intrinsic noise.

A key development of [9] is to treat reaction pathways as Poisson channels. This formalises the information transfer between X_1 and X_2 in terms of the finite channel capacity. As information about X_1 only enters X_2 via f then f acts as the constrained channel input. The channel capacities can then be obtained as in [7].

Further [9] uses a continuous stochastic differential equation to approximate X_1 dynamics while maintaining the discrete nature of the signalling and control processes. Coupled with causality constraints, the minimum distortion bound is derived as below with minimum distortion $d_{\min}$, channel capacity, C and death rate $1/\tau_1$. Under the Poisson channel interpretation f is an encoding function. Constraints on f imply a limit on the capacity of the channel between X_1 and X_2 which imposes a bound on the distortion between these molecular species.

$$dx_1 = (u - x_1/\tau_1)dt + \sqrt{\frac{2\langle x_1\rangle}{\tau_1}}dw \tag{1}$$

$$x_2 \xrightarrow{f=f(x_1{}_0^t,\, x_2{}_0^t)} x_2 + 1 \tag{2}$$

$$d_{\min} = \frac{u}{2(C + 1/\tau_1)} \tag{3}$$

Given its formulation, $d_{\min}$ is thought to be a conservative lower limit on feasible noise suppression performance under these assumptions. However, its achievability remains unexamined. This paper will, via manipulation of the above equations and through construction of sensible non-linear codecs, prove that $d_{\min}$ can be beaten if the discrete form of the equation for x_1 is retained. As this paper focuses on non-linear coupling, the tight quartic bound of [9] which is thought to be valid in the fully discrete case (due to the linear encoding constraint), is not examined. Verifying the validity of this tight bound thus remains an open research problem.

III. Fundamental estimation problem

Consider the simplest non-trivial reaction scheme shown below with x_1 and x_2 representing the X_1 and X_2 molecular populations.

$$x_1 \xrightarrow{u=\text{const}} x_1 + 1 \qquad x_2 \xrightarrow{f=f(x_1{}_0^t,\, x_2{}_0^t)} x_2 + 1 \tag{4}$$

Here the estimation molecule X_2 has an encoding intensity or rate function f which depends on the time history of X_1 and has knowledge of X_2. As there are no death reactions then x_1 follows a homogeneous Poisson process while x_2 admits a Cox process.

The aim of this section is to specify a feasible f under mean and maximum channel constraints which compares favourably with the bound and achieves good estimation accuracy. If f were not maximally constrained, the estimation error could be made zero by forcing a single X_2 birth infinitely quickly in response to every X_1 birth - a result that corresponds to the Poisson channel having infinite capacity. Analysing this initial coupled reaction set is fundamentally important as more complicated reaction systems are examinable using the general concepts derived subsequently.

Since random telegraph signals achieve Poisson channel capacity, a mechanism using this concept would have a high likelihood of good performance. Thus the birth-following encoding scheme, which ignores the x_1 time history, is defined as below.

- If x_1^+ is detected, set $f = f_{\max}$ until x_2^+ occurs
- If further x_1^+s occur before x_2 transitions, keep f high until x_2 overcomes the deficit
- Otherwise set $f = 0$

The state transformation from x_1 and x_2 to $e(t) = x_1(t) - x_2(t)$ is integral to solving the birth-following scheme. The pseudo-molecular behaviour of $e(t)$ can be described as:

$$e \xrightarrow{u=\text{const}} e+1 \qquad e \xrightarrow{f=f(e(t))} e-1 \tag{5}$$

$$f(e) = \begin{cases} f_{max} & : e > 0 \\ 0 & : e \leq 0 \end{cases} \tag{6}$$

This description corresponds to a M|M|1 queue and thus e has the geometric distribution at equilibrium shown below. The interpretation is that every x_1 birth is a customer requiring estimation and every estimator jump represents a service. The number of customers in the queueing system at any time (including the one currently being served) is then $e(t)$. The queue utilisation is defined as ρ below and allows one to non-dimensionalise the birth-following scheme to any biological settings provided the queue is stable. The M|M|1 solution forces a mean rate equivalence $\langle f \rangle = \langle u \rangle = u$.

$$\rho = \frac{u}{f_{\max}} = \frac{\langle f \rangle}{f_{\max}} < 1 \tag{7}$$

$$P(e = k) = (1-\rho)\rho^k, \; k \in \mathbb{Z}_0^+ \tag{8}$$

Using the above results $d_{\min}$ can be redefined in terms of ρ, and the mse expressed analytically from the second raw moment of the e distribution, $\mathbb{E}(e^2) = \text{var}(e) + \mathbb{E}(e)^2$. The resulting expressions are given below.

$$C = u \log\left(\frac{1}{\rho}\right) \tag{9}$$

$$d_{\min} = \frac{1}{2\log(\frac{1}{\rho})} \tag{10}$$

$$\text{mse} = \frac{\rho}{(1-\rho)^2} + \left(\frac{\rho}{1-\rho}\right)^2 = \frac{\rho(1+\rho)}{(1-\rho)^2} \tag{11}$$

Examining $d_{\min}$ and mse, the analytical expressions of which are plotted in figure 1, it is clear that the birth-following mechanism outperforms the bound in the light traffic or low ρ regime. This result is significant as it proves the bound can be easily beaten up to $\rho = 0.166$ without even requiring an optimal history dependent decoding scheme. At higher utilisations large queueing delays cause rapid information loss which results in $\psi \gg 1$. This poor heavy traffic performance, however, while not treated in this paper, will form the subject of subsequent research. It is worth noting that both measures are unstable at $\rho = 1$.

Interestingly the optimal decoder is derivable for this simple scheme. As stated in [14] the optimal estimator of a random process x_1 given the time history of a Cox process, x_2, is described by the causal minimum mean square error (mmse) estimator, $\hat{x}_{1\text{opt}}$ with mmse:

$$\hat{x}_{1\text{opt}} = \mathbb{E}\left\{x_1(t) | x_{2_0}^t\right\} \tag{12}$$

$$\text{mmse} = \mathbb{E}\left\{\left(x_1(t) - \mathbb{E}\left\{x_1(t) | x_{2_0}^t\right\}\right)^2\right\} \tag{13}$$

Substituting $e(t) = x_1(t) - x_2(t)$ the mmse expression then becomes:

$$\text{mmse} = \mathbb{E}\left\{\left(x_1(t) - \mathbb{E}\left\{x_2(t) + e(t) | x_{2_0}^t\right\}\right)^2\right\} \tag{14}$$

$$\text{mmse} = \mathbb{E}\left\{\left(x_1(t) - \mathbb{E}\left\{x_2(t) | x_{2_0}^t\right\} - \mathbb{E}\left\{e(t) | x_{2_0}^t\right\}\right)^2\right\} \tag{15}$$

$$\text{mmse} = \mathbb{E}\left\{\left(x_1(t) - x_2(t) - \mathbb{E}\left\{e(t) | x_{2_0}^t\right\}\right)^2\right\} \tag{16}$$

$$\text{mmse} = \mathbb{E}\left\{\left(e(t) - \mathbb{E}\left\{e(t) | x_{2_0}^t\right\}\right)^2\right\} \tag{17}$$

The result of the transformation is significant as now the mmse is interpreted as the expected square error between the current number of customers in the queue system and the expected number at that time given the history of departures from the queue until that time. Burke's theorem [1] states that M|M|c queues with input Poisson process of rate u have homogeneous Poisson output processes which are also of rate u. An important corollary of this theorem is that via time reversibility, as the state of the queue system $e(t)$ is not dependent on future arrivals in reversed time then in normal time $e(t)$ is not dependent on past departures. Consequently the mmse equation simplifies as follows.

$$\text{mmse} = \mathbb{E}\left\{(e(t) - \mathbb{E}\{e(t)\})^2\right\} \tag{18}$$

$$\text{mmse} = \text{var}(e) = \frac{\rho}{(1-\rho)^2} \tag{19}$$

The optical decoding scheme given the encoder is thus $\hat{x}_{1\text{opt}}(t) = x_2(t) + \mathbb{E}(e(t))$. Figure 1 quantifies the differences between the mmse and the original birth-following mse. When compared to the original mse, the mmse has a larger region over which it beats the distortion bound and an improved optimal performance point (where the mse or mmse is maximally below $d_{\min}$).

The birth-following estimation scheme, when applied to a system including molecular deaths, appears unable to defeat the bound (unpublished results). While the scheme is able to achieve $1 < \psi \leq 2$, over a small parameter set, its generally poor performance is attributable to the death reactions acting as additional noise sources.

IV. Estimation and Control of a Birth Process

Previous discussions have detailed solutions to the molecular estimation problem with the aim of exploring codecs which achieve good performance. This section extends this form of analysis to the more complicated control scenario. The x_1 birth rate, u, is now a Cox process that serves as the control signal. The solution to this problem

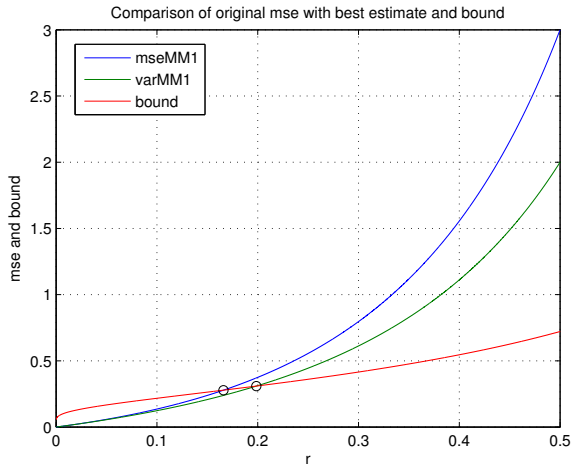

Fig. 1. Comparison of mmse (var(e)) and mse across ρ with bound

involves finding a good u which based on knowledge of an estimate of x_1, $\hat{x}_1$, is able to achieve performance comparable to that stipulated by $d_{\min}$. The following investigations tackle the simplest version of the control problem, ramp tracking, and show how solutions to the estimation problem provide useful insight into the implementation of control laws.

The simplest application of molecular control involves only birth reactions and is analogous to the estimation problem solved in section III. The relevant reactions are:

$$x_1 \xrightarrow{u=u(\hat{x}_1{}_0^t)} x_1 + 1 \qquad x_2 \xrightarrow{f=f(x_1{}_0^t,\, x_2{}_0^t)} x_2 + 1 \tag{20}$$

The estimator encoder f is constrained in mean and maximum. The control signal u is unconstrained but is only able to respond to an estimate of x_1. The control aim is to achieve accurate tracking of some reference, $x_{\text{ref}}(t)$, such that at steady state there exists a parameter regime in which there is: zero steady state error: $\mathbb{E}(x_{\text{ref}} - x_1) = 0$, small error variance: min $\{\text{mse} = \mathbb{E}\left[(x_{\text{ref}} - x_1)^2\right]\}$ and good relative performance: $\psi < 1$.

To properly define this problem a suitable reference must be used. Since the reaction set involves only discrete state births, setting $x_{\text{ref}}(t) = \lfloor \alpha t \rfloor$, $\alpha \in \mathbb{R}^+$, properly accounts for the best imaginable form x_1 could take - that of a deterministic birth process.

Given its good performance in pure birth estimation, birth-following was retained for encoding and decoding. However, as u is not constant a M|M|1 queue no longer results. As before the history-less decoder $\hat{x}_1(t) = x_2(t)$ will be used. Better decoders are possible but it will be shown that this treatment is sufficient for achieving the desired control aim. To maintain a reaction based approach the reference is interpreted as a molecular species which deterministically has a birth every $1/\alpha$ time units. The control problem is therefore an incomplete information floor ramp tracking problem.

The full closed loop control scheme involves Cox processes and is analytically intractable. In contrast to the pure estimation case where a constant u allowed Markov interpretations, no such simplifications can be applied. Further the perturbations caused by the estimation error on the control signal input are difficult to characterise. Nevertheless a sensible control scheme is attainable by reinterpreting the control problem in terms of estimation. This key step treats tracking as equivalent to the estimation of the deterministic pseudo-molecule $x_{\text{ref}}(t)$ by the controlled species $x_1(t)$.

Given this interpretation it would be sensible to apply a birth-following scheme between x_1 and x_{ref} in addition to that already operating between x_1 and x_2. Defining the estimation error as $e_e = x_1(t) - x_2(t)$, the control error as $e_c = x_{\text{ref}}(t) - x_2(t)$ and the tracking error as $e_t = x_{\text{ref}}(t) - x_1(t)$ leads to the following description of the estimator encoding and control laws:

$$f(e_e) = \begin{cases} f_{\max} & : e_e > 0 \\ 0 & : e_e \le 0 \end{cases} \tag{21}$$

$$u(e_c) = \begin{cases} u_{\max} & : e_c > 0 \\ 0 & : e_c \le 0 \end{cases} \tag{22}$$

The control algorithm is:

- Observe the e_c queue at every event time (event driven control)
- If $e_c > 0$ set the control signal to $u_{\max}$ until e_c is observed to be 0
- If $e_c \le 0$ set $u = 0$ - wait until x_{ref} is above $\hat{x}_1$

Using this law the expected best performance would be achieved when the dynamics of the x_1 births are fast in comparison to the reference birth rate so that the perceived tracking error, e_c is removed with minimum delay. Here the term dynamics refers to the non-zero rate values, which are the maxima in this scheme. Further to ensure that e_c matches e_t closely, the dynamics of x_2 births must be faster than those of x_1 births - an insight derived from the pure birth estimation problem. Due to the birth-following type schemes operational in both control and estimation the average rates of all molecular species naturally converge (a requirement of stable equilibrium and the principle of local balance [6]). This results in the first control objective being automatically satisfied. Thus three dynamical constraints are required for good performance: $\frac{\langle u \rangle}{\alpha} = \frac{\langle f \rangle}{\langle u \rangle} = 1$, $\frac{u_{max}}{\alpha} >> 1$ and $\frac{f_{\max}}{u_{\max}} >> 1$.

The $f_{\max}/u_{\max}$ constraint is reminiscent of the concept in linear control theory of designing observer dynamics to be faster than desired system dynamics [4]. The relations above require that u have a constant maximum in order to achieve accurate estimation.

Using the developed scheme and describing relevant system dynamical ratios by the dimensionless quantities $q = \frac{\alpha}{u_{\max}}$, $r = \frac{\alpha}{f_{\max}}$ the control problem was formulated as a

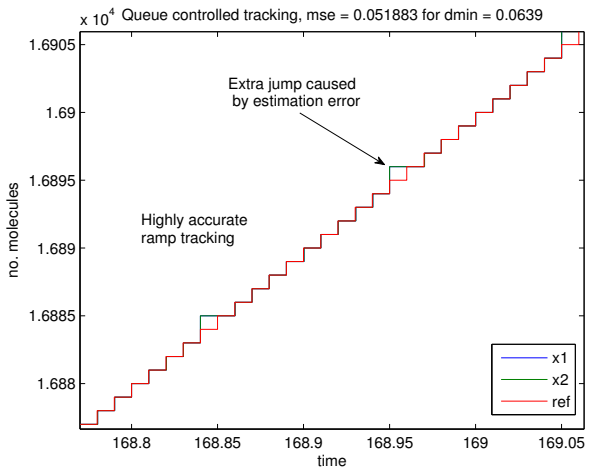

Fig. 2. Single realisation of accurate ramp tracking

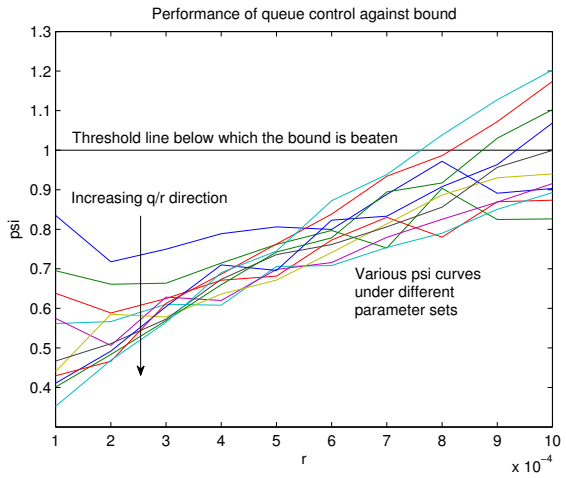

Fig. 3. Control system relative performance across r for various q

search across q and r to determine if there exists a set that achieves $\psi < 1$. The bound used is exactly that from the corresponding estimation problem [9] and is reproduced below using the new notation.

$$C = \langle f \rangle \log\left(\frac{f_{\max}}{\langle f \rangle}\right) = \alpha \log\left(\frac{f_{\max}}{\alpha}\right) \tag{23}$$

$$d_{\min} = \frac{\langle u \rangle}{2C} = \frac{\alpha}{2C} = \frac{1}{2\log(\frac{1}{r})} \tag{24}$$

Since this doubly stochastic non-linear control is analytically complex, the mse was obtained directly from stochastic simulations which treated the reference as a deterministic molecule. The simulations were performed in accordance with Gillespie's algorithm [5].

It was found that $d_{\min}$ can be beaten and all control objectives achieved if r and q are made small enough. Results for one such parameter set, $[r \;\; q \;\; \alpha] = [0.0004 \;\; 0.01 \;\; 100]$, are given in figure 2 for which mse = 0.0519 and $d_{\min} = 0.0639$. Figure 3 explores the parameter set in which the control scheme performance rivals and beats the distortion bound. Thus the bound is outperformed in the low r and high q/r regime.

V. Estimation and Control of a Birth-Death Process

Extending the previous control problem to include exponential deaths leads to the reaction set below. The control objectives remain the same as previously but now $x_{\text{ref}} = \beta$ is a step reference, which is a natural response to track for the equilibrium birth-death processes considered. As birth-following appeared unable to overcome $d_{\min}$ in the estimation with deaths case, a different methodology was applied to this control problem. Since event triggered, threshold based policies have been used to successfully implement control strategies over constrained information channels [10] [11], it was thought sensible to apply such a scheme for this problem.

$$x_1 \xrightarrow{u=u(\hat{x}_1{}_0^t)} x_1 + 1 \qquad x_2 \xrightarrow{f=f(x_1{}_0^t,\, x_2{}_0^t)} x_2 + 1 \tag{25}$$

$$x_1 \xrightarrow{x_1(t)/\tau_1 = k_1 x_1(t)} x_1 - 1 \qquad x_2 \xrightarrow{x_2(t)/\tau_2 = k_2 x_2(t)} x_2 - 1 \tag{26}$$

Using the signalling species $x_2(t)$, the toggle based control scheme below was implemented. The major error signals and appropriate encoding and control functions are also defined subsequently with $\hat{x}_1(t) = x_2(t)$. The main difference between this and the birth-following methodology is that while the latter focuses on actual molecular numbers, the former observes molecular number transitions and is thus more complex theoretically. The notation $h(t-)$ indicates the previous value of function $h(t)$.

$$f(x_1{}_0^t, x_2{}_0^t) = \begin{cases} f_{\max} : \beta - x_1(t) > 0 \wedge u(t-) = 0 \;\wedge \\ \qquad\qquad x_2(t) - x_2(t-) \le 0 \\ f_{\max} : \beta - x_1(t) \le 0 \wedge u(t-) = u_{\max} \;\wedge \\ \qquad\qquad x_2(t) - x_2(t-) \le 0 \\ 0 \qquad : \text{otherwise} \end{cases} \tag{27}$$

$$u(x_2{}_0^t) = \begin{cases} u_{\max} & : x_2(t) - x_2(t-) > 0 \wedge u(t-) = 0 \\ 0 & : x_2(t) - x_2(t-) > 0 \wedge u(t-) = u_{\max} \\ u(t-) & : \text{otherwise} \end{cases} \tag{28}$$

The control scheme above uses a threshold based encoder which forces x_2 births if the last control signal is zero and x_1 is below its reference threshold or if x_1 is above its reference and the last control signal is maximal. If an x_2 birth has been recorded or any other combination of x_1 and u occur then the encoder switches off. Therefore the encoder accounts for both the position and velocity of the controlled molecule since it signals every time x_1 is below β and not rising or above β and not falling.

The control function toggles the control signal on every x_2 birth else it remains unchanged. Thus from the control perspective x_2 events are indicative of control switching times. Note that while the encoder is mean and maximum

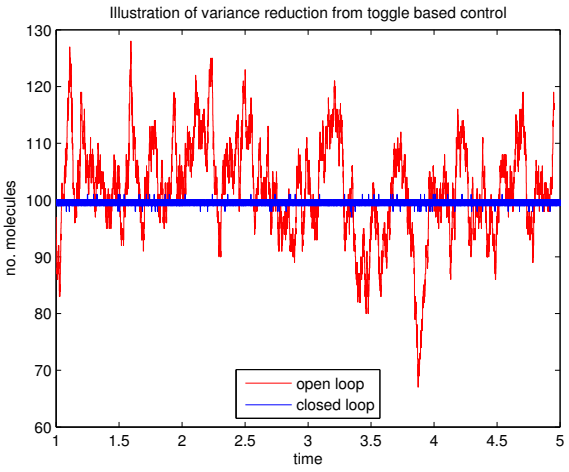

Fig. 4. Improvement of tracking from open loop to closed loop

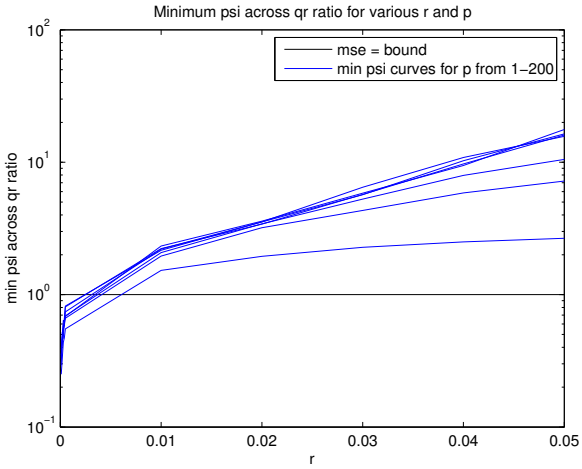

Fig. 5. Minimum ψ curves across q/r for r and p

constrained the control signal, while having a defined maximum, is not truly constrained.

Using the dimensionless parameters $q = \frac{k_1\beta}{u_{\max}}$ and $r = \frac{k_1\beta}{f_{\max}}$ and $p = \beta$, the estimation-control problem devolved to finding a parameter set which met the control objectives and outperformed the distortion bound below [9]:

$$C = \langle f \rangle \log \frac{f_{\max}}{\langle f \rangle} \tag{29}$$

$$d_{\min} = \frac{\langle x_1 \rangle}{C\tau_1 + 1} \tag{30}$$

From simulations, it was found that the region $q \ll 1$, $r \ll 1$ allowed tracking of various p settings with accuracy that improves on $d_{\min}$. A typical controlled trajectory with $[r\ q\ p] = [0.0001\ 0.01\ 100]$ is compared with the open loop case in figure 4. Note the substantial variance reduction that the control scheme achieves. For these settings the toggle based method achieves $\psi = 0.365$. The choice of $k_1 = 10$, $k_2 = 1000$ is arbitrary and inconsequential to performance. Figure 5 indicates that there is a clear region of parameter settings over which $\psi < 1$ is achieved.

The defeat of the distortion bound with deaths by the toggle based scheme implies that $d_{\min}$ would also be outperformed in the corresponding estimation problem, since estimation simplifies the control problem by setting u constant. However, this is not shown since there are no analytical insights to be gained.

VI. Conclusion and Outlook

This paper has investigated the limits of estimation and control accuracy as applied to fundamental stochastic chemical reactions and shown that diffusion approximations, though analytically tractable, can seriously affect one's notions of the maximal noise suppression achievable. While it is clear that codecs involving single event signalling can defeat the distortion bound in both control and estimation over some parameter regime, the schemes achieving this performance are unlikely to be biologically implementable. Consequently, before one can truly characterise the limits of biological noise suppression in the absence of continuity approximations, it is necessary to determine what conditions, beyond Poisson channel constraints, guarantee biologically meaningful codecs.

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