Noisy Delay Denoises Biochemical Oscillators

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Genetic oscillations are generated by delayed transcriptional negative feedback loops, wherein repressor proteins inhibit their own synthesis after a temporal production delay. This delay is distributed because it arises from a sequence of noisy processes, including transcription, translocation, translation, and folding. Because the delay determines repression timing and, therefore, oscillation period, it has been commonly believed that delay noise weakens oscillatory dynamics. Here, we demonstrate that noisy delay can surprisingly denoise genetic oscillators. Specifically, moderate delay noise improves the signal-to-noise ratio and sharpens oscillation peaks, all without impacting period and amplitude. We show that this denoising phenomenon occurs in a variety of well-studied genetic oscillators, and we use queueing theory to uncover the universal mechanisms that produce it.

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Introduction.—Living organisms rely on periodic phenomena such as the cell cycle and circadian rhythms to survive and adapt. Biochemical interaction networks produce the oscillations in protein concentration and activity that drive such phenomena [1–3]. Negative feedback loops play an essential role in network topologies that generate periodic dynamics [4]. Generating oscillations requires sufficient temporal delay in this feedback [4,5], for the absence of delay results in convergence to a steady state. Delay is an inherent component of many biochemical reaction networks. It results from the sequential assembly of functional proteins via transcription, translation, folding, and phosphorylation [6–8] or arises when cytoplasmic proteins pass various obstacles and enter the nucleus to inhibit their own genes [9].

Modeling processes such as regulator protein formation and protein diffusion using explicit delays rather than intricate descriptions of the intermediate steps can be advantageous from analytical and inferential points of view [7,10]. When introducing explicit delay representing the cumulative timing of complex processes with many stochastic intermediate steps, it is realistic to use distributed (random) delay. Nevertheless, many studies have used fixed delay for simulation and analysis [11–14]. Oscillator studies that use fixed delay have found that fixed delay acts constructively, meaning that more delay enhances the stability of the oscillation.

By contrast, it is natural to conjecture that distributed delay weakens oscillations, based on the supposition that generating a strong oscillation necessitates precise timing of the repression signal. For instance, a partial repression signal received during the protein production phase could prevent sufficient buildup of protein level, thereby diminishing oscillation amplitude. This conjecture has been verified in some important cases. For instance, generating strong circadian rhythms requires PERIOD proteins to enter the nucleus to inhibit their own production at a precise time of day [15–17]. The distributed delay that results from the stochasticity associated with protein generation and travel weakens the circadian rhythm [15,18,19]. Consequently, biological filtering mechanisms to mitigate the heterogeneous nuclear entry time have been investigated [15,16]. Recent analysis has shown that increasing the average delay while maintaining the number of sequential processes that produce distributed delay can weaken oscillations [20].

Here, we demonstrate that distributed delay can act constructively by denoising a variety of well-studied stochastic genetic oscillators. This is surprising, because distributed delay accelerates signaling in feed-forward architectures [6], a phenomenon that can interfere with oscillation formation because of the need for sufficient delay in the negative feedback. We inject noise into the delay distribution by increasing the coefficient of variation (cv), defined as the ratio of the standard deviation of the distribution to its mean, while holding mean delay fixed. We find that until delay cv reaches a moderate level, this process improves the signal-to-noise ratio (SNR) and sharpens oscillation peaks, all without impacting period and amplitude. We use queueing theory to uncover the universal mechanisms that drive this unexpected denoising phenomenon: The aforementioned accelerated signaling

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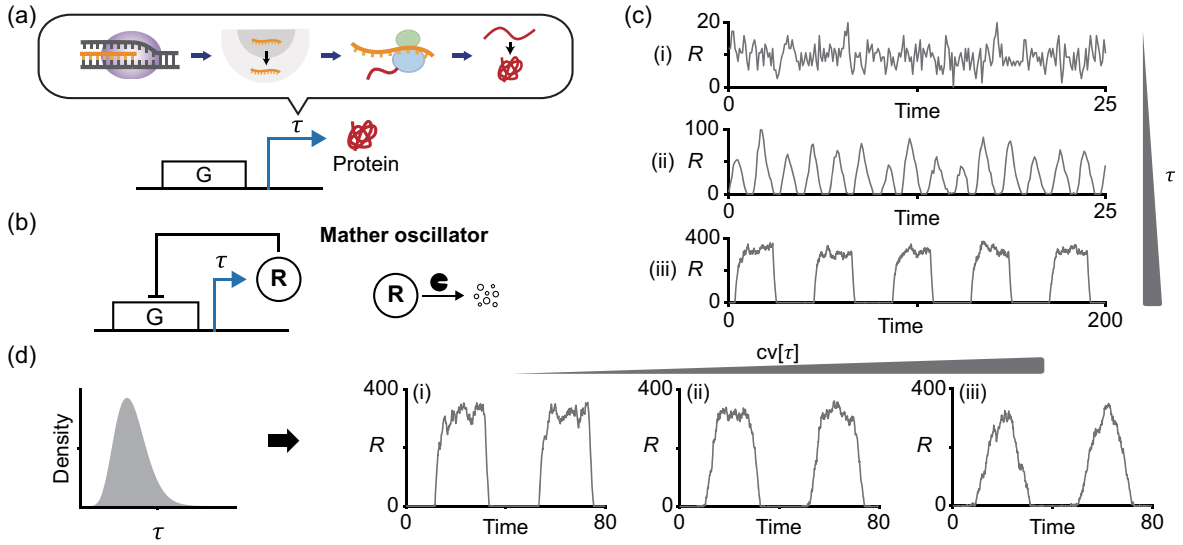

FIG. 1. Distributed delay sharpens peaks for the Mather oscillator. (a) Synthesizing mature regulator proteins requires a sequence of intricate processes, including transcription elongation, mRNA translocation, translation, and protein folding. Protein synthesis can be described by an effective delay τ. (b) The Mather oscillator consists of a delayed negative feedback loop, wherein mature repressor proteins repress transcription. Mature repressor proteins are cleared from the system by enzymatic degradation and dilution. (c) When τ is fixed, tuning it upward induces oscillations in mature repressor protein count $R(t)$. Without delay ($\tau = 0$), the Mather oscillator does not oscillate (i). As the delay increases ($\tau = 0.5$), oscillations emerge (ii), and a longer delay ($\tau = 20$) generates strong oscillations with plateaued peaks (iii). (d) When τ follows a gamma distribution with $E[\tau] = 20$, the peaks of the oscillation sharpen as $\mathrm{cv}[\tau]$ increases, while the period and amplitude of the oscillation appear to remain stable [(i)–(iii)]. From (i) to (iii), $\mathrm{cv}[\tau]$ values are 0.005, 0.1, and 0.2, respectively. The simulations were performed using a Gillespie-type stochastic simulation algorithm [26]. Trajectories show counts of mature repressor proteins, each of which requires a random individual delay time to produce.

induces sharper oscillation peaks, while a compensatory mechanism stabilizes the period of oscillation.

Results—Mather oscillator: Denoising phenomenon.— The production of mature proteins in genetic regulatory networks involves multiple sequential reactions [Fig. 1(a)], resulting in complex systems with numerous kinetic parameters. To simplify models of such networks, an effective delay τ is often used as a proxy for protein production [21–25]. Oscillatory dynamics can emerge when a mature transcription factor inhibits its own production and thereby creates a delayed negative feedback loop, provided the production delay is sufficiently long [4]. The degrade-and-fire oscillator [7] [Mather oscillator, Fig. 1(b)] is an important example that utilizes delayed negative feedback. It consists of a single gene that produces a repressor protein that down-regulates its own production and is cleared by dilution and enzymatic degradation. Delay is required for the production reaction, while the dilution and enzymatic degradation reactions occur instantaneously.

We use a delay birth-death (dBD) framework [27] to model the Mather oscillator, in particular, and investigate the effect of distributed delay on stochastic oscillators, in general. In this stochastic framework, each reaction comes equipped with a propensity function as well as a probability distribution that describes the (random) delay time between reaction initiation and reaction completion. We use a Gillespie-type stochastic simulation algorithm [26] to simulate stochastic oscillators. This algorithm accurately generates sample trajectories from the underlying stochastic process.

For the Mather oscillator, the birth reaction has propensity function $f_{\mathrm{birth}}(R) = (\alpha C_0^2)/[(C_0 + R)^2]$, where R denotes the number of mature repressor proteins. Dilution and enzymatic degradation propensities are given, respectively, by $f_{\mathrm{dil}}(R) = \beta R$ and $f_{\mathrm{deg}}(R) = (\gamma R)/(R_0 + R)$, where the functional form of f_{deg} captures Michaelis-Menten kinetics. (See Table S1 [28] for parameter details.)

We first verify that the stochastic dBD model of the Mather oscillator can generate oscillatory dynamics when the delay τ is fixed (i.e., $\mathrm{cv}[\tau] = 0$). The model does not oscillate when τ is small [Fig. 1(c)(i)], while a stable oscillation emerges as the production delay increases [Fig. 1(c)(ii)]. As τ increases beyond the level at which oscillatory dynamics appear, a strong oscillation with large amplitude, long period, and plateaued peaks emerges [Fig. 1(c)(iii)].

Although fixed delay has been widely used to investigate biological systems [11–14], assuming a distributed delay is more realistic due to the inherent stochasticity associated with the numerous reactions required for protein synthesis [24,25,29,30]. Thus, we now investigate the impact of distributed delay on the Mather oscillator by supposing that τ follows a gamma distribution. The gamma family can

capture the theoretical dynamics of various intracellular reaction networks [31] as well as effectively approximate biological delay distributions inferred from experimental data [32]. Writing $E[\cdot]$ for mathematical expectation, here we set $E[\tau] = 20$, a value for which fixed delay produces a strong oscillation with plateaued peaks [Fig. 1(c)(iii)]. This expected delay is a significant fraction of the oscillation period for our parameters. Such extended temporal delays can arise within genetic oscillators, accounting for factors such as protein trafficking times required for nuclear entry in eukaryotic cells [16], or intricate interactions involving many genes [33]. Indeed, the emergence of plateau-shaped oscillations has been empirically demonstrated in several synthetic oscillators that utilize multiple genes [33,34].

One might expect that delay noise weakens the oscillation, because delay noise accelerates signaling in feed-forward genetic circuits, thereby decreasing the apparent delay [6]. However, we see that, as $\mathrm{cv}[\tau]$ increases from low to moderate, the period and amplitude of oscillation remain stable [Figs. 1(d)(i)–1(d)(iii)]. Importantly, peaks become sharper, suggesting that increasing $\mathrm{cv}[\tau]$ to a moderate level may induce higher-resolution timing. Beyond moderate levels of $\mathrm{cv}[\tau]$, sufficiently strong delay noise will substantially weaken the oscillation.

Mather oscillator: Quantification of denoising.—To quantify the impact of delay noise on oscillation precision, we specify three quantification methods for the mature

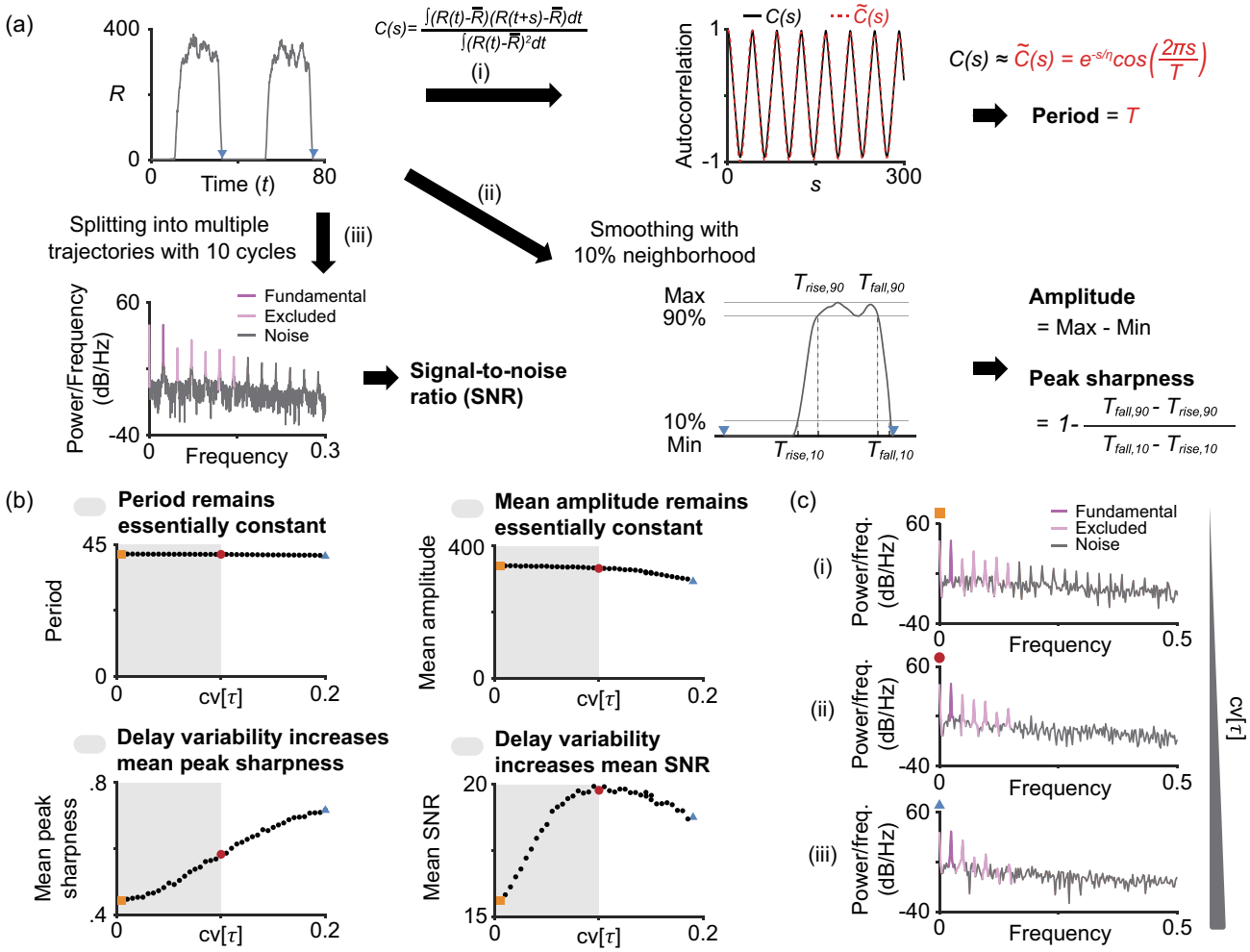

FIG. 2. Denoising phenomenon for the Mather oscillator: quantification and explanation. (a) We quantify the impact of distributed delay on the oscillation using period extracted from the autocorrelation function $[C(s)]_{s\geq 0}$ (i), amplitude and peak sharpness obtained from each cycle of the smoothed trajectory (ii), and mean SNR obtained by averaging over trajectory segments that contain ten cycles (iii). Here, the high-frequency harmonics of order greater than five are considered noise. Trajectories used for quantification contain more than 500 cycles. (b) As $\mathrm{cv}[\tau]$ increases from zero to 0.1 (gray regions), period and mean amplitude remain essentially constant, while mean peak sharpness and mean SNR increase. As $\mathrm{cv}[\tau]$ increases beyond 0.1 (white regions), mean amplitude and mean SNR slightly decrease. The orange square, red disk, and blue triangle correspond to the trajectories in Fig. 1(d). (c) Mean SNR increases, because peak sharpening suppresses high-frequency harmonics [(i) and (ii)], and then declines as $\mathrm{cv}[\tau]$ continues to grow, because fundamental signal power starts to decrease (iii).

repressor protein signal. First, we approximate the autocorrelation function of the trajectory $[R(t)]_{t\geq 0}$:

$$C(s) = \frac{\int [R(t) - \bar{R}][R(t+s) - \bar{R}]dt}{\int [R(t) - \bar{R}]^2 dt}, \tag{1}$$

with a damped cosine function, defined by $\tilde{C}(s) = e^{-s/\eta}\cos(2\pi s/T)$, and then estimate the period of oscillation T [Fig. 2(a)(i)]. Second, for each cycle [between blue triangles in Fig. 2(a), upper left], we smooth using a moving average filter (of length 10% of the cycle data point count) and then define amplitude by max − min and peak sharpness by $1-(T_{\text{fall},90}-T_{\text{rise},90})/(T_{\text{fall},10}-T_{\text{rise},10})$, where the ratio compares time spent above 90% to time spent above 10% [Fig. 2(a)(ii)]. Third, we partition the trajectory into blocks containing ten cycles, compute the power spectral density for each block, and average the resulting SNR over blocks to produce mean SNR [Fig. 2(a)(iii)]. Here, high-frequency harmonics of order greater than five are considered noise. See Supplemental Material [28] for details on how we define SNR and how this definition has been applied in previous work [35–38].

As $\text{cv}[\tau]$ increases away from zero [Fig. 2(b), gray regions], period and mean amplitude remain essentially constant, while mean peak sharpness and mean SNR increase. The favorable SNR behavior results from the suppression of high-frequency harmonics due to peak sharpening [Figs. 2(c)(i) and 2(c)(ii)]. Mean SNR initially increases for a range of values of h, the number of harmonics we exclude from the noise (see [28] for this result). When $\text{cv}[\tau]$ further increases [Fig. 2(b), white regions], mean amplitude and mean SNR decrease as fundamental signal power decreases [Fig. 2(c)(iii)], indicating that moderate delay noise yields optimal mean SNR.

Denoising biochemical oscillators: Generality and analysis.—We investigate the impact of distributed delay on several additional well-studied biochemical oscillators to verify that the denoising phenomenon we have discovered is not specific to the Mather oscillator (Fig. 3). We study the Kim-Forger model [39], wherein repression is based on protein sequestration [40] and enzymatic degradation is absent; the dual-feedback oscillator [7,41], an extension of the Mather oscillator that includes an activation loop, where the activator and repressor are cleared by coupled enzymatic degradation; and the repressilator, constructed by cyclically coupling three Mather oscillators. We model the oscillators using the dBD framework [27], as we did with the Mather oscillator. See Tables S2–S4 [28] for

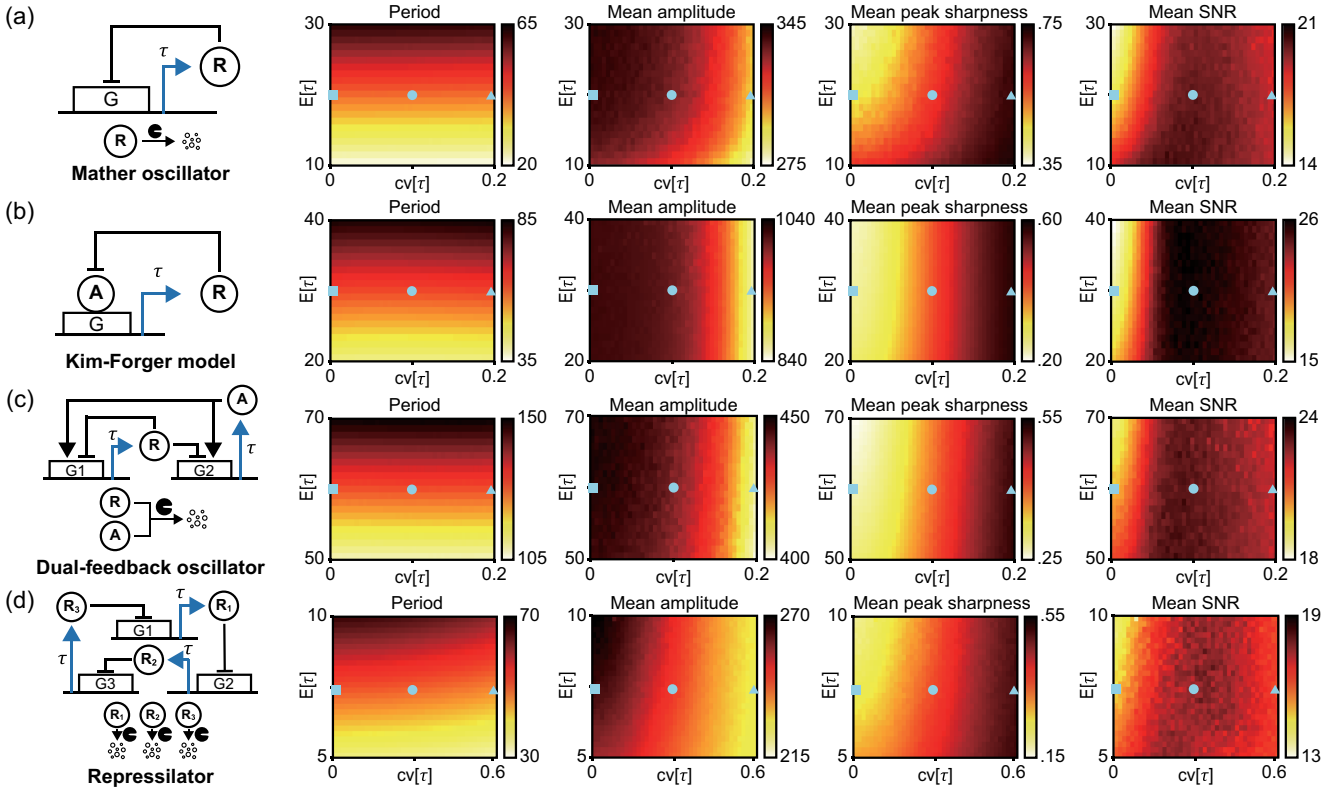

FIG. 3. Distributed delay denoises various oscillators built upon a core negative feedback loop. We demonstrate that distributed delay denoises the Mather oscillator (a), the Kim-Forger model (b), the dual-feedback oscillator (c), and the repressilator (d). For each model, we observe denoising over a range of $E[\tau]$ values: As $\text{cv}[\tau]$ increases from zero to moderate, period and mean amplitude remain essentially constant, while mean peak sharpness and mean SNR increase. See Fig. S1 [28] for trajectories corresponding to blue squares, circles, and triangles. The simulations were performed using a Gillespie-type algorithm [26]. Trajectories track mature protein counts.

model details and propensity functions. Each of the genetic oscillator models exhibits period robustness, mean amplitude robustness, and unimodal mean SNR profile across a range of values of $E[\tau]$. Unimodality results from the trade-off between mean peak sharpness and mean amplitude [Figs. 3(a)–3(d)]. These results suggest that distributed delay universally denoises genetic oscillators, regardless of transcriptional repression mechanism (e.g., Hill-type or protein sequestration), protein clearance mechanisms (e.g., presence of enzymatic degradation), or network structure (e.g., single or multiple feedback loops).

We introduce and analyze a two-phase model in order to uncover the universal mechanisms that denoise genetic oscillators (see [28]). The two-phase model is a simplification of the Mather oscillator that retains the core negative feedback loop. We obtain it by eliminating enzymatic degradation and replacing the birth propensity $f_{\text{birth}}(R)$ with a switch (α if R is below repression threshold L and 0 if R meets or exceeds L). To analyze the two-phase model, we use ideas from queueing theory [6,42] and combine stochastic analysis with deterministic techniques to show that the denoising phenomenon results from the following two harmonious effects.

First, injecting noise into the delay distribution induces faster signal formation [6], reducing the typical number of proteins produced per cycle and thereby sharpening oscillation peaks. Second, we express the time between transcription initiation and protein clearance in a convolutional manner and show that the support of the convolution essentially does not depend on $\text{cv}[\tau]$. This feature of the support explains why the period of oscillation is robust to increases in $\text{cv}[\tau]$. Our analysis assumes that protein clearance via dilution can be neglected during signal formation and is, therefore, valid when signaling threshold L is low and transcription initiation rate α is high. See [28] for the details that support this intuitive picture as well as a demonstration that the analysis accurately predicts mean period as a function of $\text{cv}[\tau]$.

Discussion.—In this Letter, we asked how distributed delay impacts the dynamics of biochemical oscillators. For a variety of well-studied genetic oscillators, we have established a counterintuitive result: Injecting moderate noise into the delay distribution sharpens oscillation peaks and improves SNR while affecting neither period nor amplitude.

Signals featuring sharp oscillation peaks provide high-resolution timing [43,44]. Examples include signals for plant growth [45] and starch degradation [46]. The value of sharp oscillation peaks may extend well beyond high-resolution timing. The mechanisms by which circadian oscillators maintain constant period over a range of temperatures remain unclear. Gibo and Kurosawa [47] argue that, for circadian oscillators to compensate for temperature, it is essential that circadian waveform shapes depend on temperature. In particular, higher temperatures correspond to more nonsinusoidal waveforms. Nonsinusoidal features of neural oscillations in the brain may provide crucial physiological information related to neural communication, computation, and cognition [48]. Ongoing development of adaptive, data-driven time-frequency analysis supports the study of exotic waveforms [49].

More work is needed to fully assess the impact of distributed delay on oscillatory systems. A systematic study of network topologies would be a natural next step. Connections between network topology and oscillator robustness have been extensively examined [50,51]. For instance, local structures that complement core topologies can significantly modulate the robustness of oscillations [50]. It would be interesting to extend such studies by including distributed delay. This could be done by introducing parametrized families of delay distributions and then studying an augmented parameter space that includes kinetic parameters and delay distribution parameters.

Beyond oscillators, the impact of distributed delay on the dynamics of biochemical systems with multiple metastable states remains to be assessed. It is known that introducing fixed delay can dramatically stabilize bistable gene networks [52]. Kyrychko and Schwartz [53] have found that broadening the width of the delay distribution reduces switching rates for a model system that admits a saddle point and a single metastable state. For stochastic systems, the interplay between distributed delay and large deviation asymptotics remains a fruitful research area.

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