Robust control of biochemical reaction networks via stochastic morphing

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Abstract: Synthetic biology is an interdisciplinary field aiming to design biochemical systems with desired behaviors. To this end, molecular controllers have been developed which, when embedded into a pre-existing ambient biochemical network, control the dynamics of the underlying target molecular species. When integrated into smaller compartments, such as biological cells in vivo, or vesicles in vitro, controllers have to be calibrated to factor in the intrinsic noise. In this context, molecular controllers put forward in the literature have focused on manipulating the mean (first moment), and reducing the variance (second moment), of the target species. However, many critical biochemical processes are realized via higher-order moments, particularly the number and configuration of the modes (maxima) of the probability distributions. To bridge the gap, a controller called stochastic morpher is put forward in this paper, inspired by gene-regulatory networks, which, under suitable time-scale separations, morphs the probability distribution of the target species into a desired predefined form. The morphing can be performed at the lower-resolution, allowing one to achieve desired multi-modality/multi-stability, and at the higher-resolution, allowing one to achieve arbitrary probability distributions. Properties of the controller, such as robust perfect adaptation and convergence, are rigorously established, and demonstrated on various examples. Also proposed is a blueprint for an experimental implementation of stochastic morpher.

1 Introduction

Synthetic biology is a growing interdisciplinary field of science and engineering which aims to design biochemical systems with predefined behaviors [1]. In the sub-field of nucleic-acid-based synthetic biology (also called DNA and/or RNA computing), biochemical systems are engineered using nucleic acids (DNA and/or RNA molecules). An advantage of this approach lies in the fact that nucleic acids have relatively well-understood biophysical properties, and their production is systematic and cost-effective. The key mechanism behind the excellent programmability properties of DNA and RNA, allowing for a controllable and dynamic change in the structure of these molecules, is the toehold-mediated strand-displacement mechanism [2, 3]. The strand-displacement mechanism involves a single-stranded nucleic acid displacing another one from a duplex, as a consequence of the Watson-Crick base-pairing principle, and allows one to realize dynamical systems [4, 5, 6, 7]. In particular, a large class of abstract mass-action biochemical reaction networks (see also Appendix A.1 for a background on reaction networks) can be physically realized using strand-displacement DNA computing [7]. A proof-of-concept is the displacillator - a purely DNA-based synthetic oscillator implemented in vitro [8]. Nucleic acids play some of the key roles inside living systems, involving storage and transfer of information, catalysis and a variety of regulatory functions. Consequently, nucleic-acid-based strand-displacement synthetic systems are desirable, as they can be more readily interfaced with a variety of key biochemical processes in living systems. Let us note that DNA and RNA strand-displacement is also hypothesized to take place in a number of native cellular processes, including the genetic recombination process [9] (see also Section 5), CRISPR-Cas systems [10] and co-transcriptional folding of RNA [4].
Depending on applications, synthetic systems can be implemented in a variety of different environments, each generally requiring different engineering approaches. In particular, synthetic systems may be integrated into larger-volume compartments (such as test-tubes in vitro), or smaller-volume compartments (such as biological cells in vivo, or cell-like vesicles in vitro). When integrated into larger-volume compartments, owning to the higher species copy-numbers, the task is to design reaction networks with desired deterministic dynamics, described by the reaction-rate equations \[11\]. Mathematical methods for achieving such goals have been developed in \[12, 13\]. On the other hand, when integrated into smaller-volume compartments, owning the lower species copy-numbers, intrinsic noise becomes an important dynamical feature \[14, 15, 16, 17, 18\], and the synthetic systems have to be constructed via a more-detailed stochastic approach \[19\] (see also Appendix A.2 for a background on the stochastic model of reaction networks). To this end, so-called noise-control algorithm has been developed in \[20\], which systematically re-designs a given reaction network to arbitrarily manipulate its intrinsic-noise profile and reshape its probability distribution, while preserving the desired underlying deterministic dynamics. Biochemical networks have been successfully implemented in vitro, displaying both desirable deterministic dynamics in test-tubes \[8, 21\], and stochastic dynamics in vesicles \[16, 17, 18\].

Another important feature of the compartments, aside from their volumes, is whether the compartments are biochemically active, i.e. infused with pre-existing biochemical processes (such as the native molecular machinery inside biological cells), or otherwise biochemically inactive (such as suitable test-tubes). When biochemically active environments are considered, of interest may be isolated synthetic systems, i.e. systems which, in an ideal case, execute predefined dynamics without altering their biochemical environment. On the other hand, one may also be interested in so-called controller networks, which are designed to couple to their active surroundings in order to manipulate the dynamics of some of the underlying ambient biochemical species. Controller networks, based on the RNA strand-displacement, have been successfully engineered to manipulate transcription and post-transcription stages of gene expression inside living cells, e.g. controlling the behavior of RNA polymerases \[22\] and editing the structure of messenger RNA (mRNA) molecules \[23\], respectively. Let us note that compiling abstract reaction networks into physical ones, and subsequent integrations into biochemically active environments, involves overcoming a number of challenges \[24, 25\], including undesirable cross-reactions inside individual, and between multiple, synthetic networks, and between the synthetic systems and their environments.

In this paper, we focus on controlling stochastic biochemical reaction networks, such as those forming biochemically active environments inside small-volume compartments, both in vitro (e.g. inside cell-like vesicles) and in vivo (e.g. inside living cells). We call a fixed ambient network, which we wish to control, an input (uncontrolled) network, shown in black in Figure 1. A critical assumption is that the input network is a black-box: its fixed structure and the induced dynamics are at most partially known. For example, if noisy time-series (sample paths) generated by a black-box network are experimentally available, dynamical features such as the average species abundance, time-scales of fluctuations and bifurcation structures may be inferable \[26, 27, 28\].

A key goal of biochemical control is to embed a suitable auxiliary network, called a controller, into a black-box input network, resulting in an output (controlled) network, which ensures that a desired subset of the input biochemical species have controlled stochastic dynamics in the output network. A controller consists of a sub-network governing its internal dynamics, and a sub-network specifying how the controller is interfaced with an input network, which are shown in green and red in Figure 1, respectively. We divide the input species into two mutually-exclusive sets: species which are explicitly (directly) targeted by the controller are called the target species, while the remaining species, which may be implicitly (indirectly) affected by the controller, are called the residual...
Figure 1: Schematic representation of biochemical control. A black-box input network, $\mathcal{R}_\alpha = \mathcal{R}_\alpha(\mathcal{X})$, is shown in black. The input species $\mathcal{X} = \{X_1, X_2, \ldots, X_N\}$ are divided into two mutually-exclusive sets: the target species $\mathcal{X}_\tau = \{X_1, X_2, \ldots, X_n\}$, and the residual species $\mathcal{X}_\rho = \{X_{n+1}, X_{n+2}, \ldots, X_N\}$, which are shown in white and yellow, respectively. The target and residual species are generally coupled, but the nature of the coupling is at most partially known. A known coupling between the species $X_1$ and $X_{n+2}$ is depicted as a white dashed double-arrow. A controller is shown, consisting of the sub-networks $\mathcal{R}_\beta = \mathcal{R}_\beta(\mathcal{Y})$ and $\mathcal{R}_\gamma = \mathcal{R}_\gamma(\mathcal{X}_\tau, \mathcal{Y})$, displayed in green and red, respectively. The network $\mathcal{R}_\beta$ specifies how the controlling species $\mathcal{Y} = \{Y_1, Y_2, \ldots, Y_M\}$, shown in purple, interact among themselves, which is depicted as the green double-arrows. On the other hand, the network $\mathcal{R}_\gamma$ specifies how the controlling species are interfaced with the target species, which is displayed as the red double-arrows. Embedding a controller $\mathcal{R}_{\beta,\gamma} = \mathcal{R}_\beta \cup \mathcal{R}_\gamma$ into an input network $\mathcal{R}_\alpha$ gives rise to an output network $\mathcal{R}_\alpha \cup \mathcal{R}_\beta \cup \mathcal{R}_\gamma$.

species. The target and residual species are shown in white and yellow in Figure 1, respectively, while the controlling species, introduced by the controller, are shown in purple. Control may be sought over the probability distributions of the input biochemical species (which we call weak control), or at the level of the underlying sample paths (which we call strong control). Of practical importance is weak control involving the long-time (stationary) statistics (expectations) of the input species. See Appendix A.3 for more details on biochemical control.

A controller network must satisfy a set of constraints in order to be useful and experimentally realizable. Structurally, it is desirable that the controller consists of up-to second-order (bi-molecular) reactions, i.e. reactions involving at most two reactant molecules [29], in order to be experimentally realizable [7]. Let us note that the composition of the bi-molecular reactions is arbitrary when implemented via the strand-displacement mechanism, i.e. the reactions may involve arbitrary product and reactant species. In particular, catalytic reactions, involving the same species as both a product and reactant, are allowed, as such non-elementary reactions are expanded into suitable elementary counterparts when compiled into physical networks [7, 30, 31, 32]. Kinetically, the rate coefficients of the reactions from a controller, realized via the strand-displacement mechanism, can be varied over at least six orders of magnitude [2, 33, 3], allowing one to achieve time-scale separations. Dynamically, when the controller is embedded into an input network, it is desirable that long-time dynamics of the corresponding output network satisfy the following two properties. Firstly, the stationary probability distribution of the target species is independent of the initial conditions for all of the species in the output network (a property known as ergodicity in mathematical literature). And, secondly, the controlled stationary statistic of the target species does not explicitly depend on the parameters (rate coefficients) from the input network. A controller satisfying these two properties is said to be robust, see also Appendix A.3.
The first property satisfied by a robust controller ensures that the dynamics of the target species reach a unique desired probability distribution in the long-run, even when the precise initial conditions for the biochemical species in the output network are unknown or experimentally difficult to control. For example, controlled synthetic systems may be split from a test-tube into a large number of cell-like vesicles [16, 17, 18], with each vesicle initially containing in general a different abundance of the underlying species. A similar effect occurs during the division of living cells, which induces an extrinsic noise into the initial conditions of the corresponding daughter cells [13]. A robust controller guarantees that, despite the difficult-to-control initial conditions, the long-time behavior of the system remains controlled.

The second property satisfied by a robust controller is necessary for systematically controlling the desired statistic, as the control may be reached by fine-tuning the parameters appearing in the controller, which can be experimentally manipulated, without the need to factor in the generally unknown and uncontrollable parameters from the underlying black-box input network. An output statistic which does not explicitly depend on the input parameters is said to display robust perfect adaptation [34, 35]. If such a property holds only in an asymptotic limit of some of the parameters from the controller (i.e. under suitable time-scale separation between the controller and the input network), then we say that the statistic displays asymptotic robust perfect adaptation. Perfect and near-perfect adaptations have been hypothesized to play important roles in systems biology, e.g. in cell signaling, glycolysis and chemokinesis [35, 36, 37, 38, 39]. These biochemical processes, and many others, involving multi-stability, oscillations, and bifurcations at both the deterministic and stochastic levels [14, 15, 10, 11, 12, 13, 20, 12], also often display time-scale separations (fast-slow dynamics) [43]. In some of the phenomenological models of such processes, the fast dynamics are eliminated (averaged out). Furthermore, the distinction between perfect and near-perfect adaptations may be difficult to infer, since the underlying experimental biochemical data is subjected to measurement errors. As a consequence, asymptotic robust perfect adaptation may play a greater role than its non-asymptotic counterpart in biochemical settings. In fact, robust perfect adaptation is a purely structural property of a reaction network and, as such, is fragile under network perturbations (e.g. addition of new reactions). An instance of the structural fragility has been investigated in [14], where it has been shown that robustness of the integral-feedback controller put forward in [45], under the addition of degradation reactions in the controlling species, is recovered only under an appropriate time-scale separation.

Biochemical controllers developed in the literature have been largely focused on manipulating the stationary mean (first-moment) of the target species [16, 17, 15], and reducing their stationary variance (second-moment) [48, 49]. Such an approach may be seen as a step forward from controlling the deterministic dynamics of the target species, to which the underlying stochastic dynamics converge in the thermodynamic limit [50]. However, many biochemical phenomena in systems biology, including cellular differentiation and memory, quorum sensing, bacterial chemokinesis and antibiotic resistance, are realized via higher-order moments of the underlying probability distributions [51, 40, 52, 41, 42, 20]. Particularly important is the number and configuration of the modes (maxima) of the probability distributions, and the timing and pattern of stochastic switching in the underlying sample paths. Such dynamically exotic and biochemically important phenomena cannot be achieved using controllers which target only the mean and variance. To bridge the gap, in this paper, we develop a robust controller called stochastic morpher, presented in Algorithm 1, which is inspired by the stochastic phenomenon called noise-induced mixing [42], which some gene-regulatory networks utilize for dynamical control in vivo [41]. As appropriate reactions from the stochastic morpher fire faster, overriding the reactions from the underlying black-box input network, the probability distribution of the target species, from the corresponding output network,
Input: Let the mass-action kinetics input network be given by
\[ R_\alpha = R_\alpha(X), \]  
where \( X = \{X_1, X_2, \ldots, X_N\} \), with the rate coefficients \( \alpha = (\alpha_1, \alpha_2, \ldots) \). Assume explicit control is sought over the stochastic dynamics of the target species \( X_\tau = \{X_1, X_2, \ldots, X_n\} \subseteq X, 1 < n \leq N \).

Stochastic morpher: Consider the controller, called the stochastic morpher, given by
\[ R_{\beta,\gamma}(X_\tau, Y, Z) = R_\beta(Y) \cup R_{\gamma}(X_\tau, Z; Y), \]  
depending on the target species \( X_\tau \), and two additional sets of species: the controlling and mediating species, \( Y \) and \( Z \), respectively. The sub-network \( R_\beta(Y) \) is given by
\[ R_\beta(Y) : 2Y_1 \overset{\beta_{1,1}}{\rightarrow} Y_1 \overset{\beta_{1,2}}{\rightarrow} Y_2 \overset{\beta_{2,3}}{\rightarrow} \ldots \overset{\beta_{M-1,M}}{\rightarrow} Y_M \overset{\beta_{M,1}}{\rightarrow} Y_1, \]  
with the \( M \) controlling species \( Y = \{Y_1, Y_2, \ldots, Y_M\} \), whose sum of copy-numbers is assumed to be initially non-zero, \( \sum_{i=1}^M Y_i(0) \neq 0 \). Consider two choices for \( R_{\gamma}(X_\tau; Z, Y) \):

(i) **Lower-resolution control.** \( R_{\gamma} = R_{\gamma}^\xi(X_\tau; Y) = R_{\gamma_0}(X_\tau; \emptyset) \cup_{i=1}^M R_{\gamma_i}(X_\tau; Y_i) : \)
\[ R_{\gamma_0}(X_\tau; \emptyset) : X_j \overset{\gamma_{0,j}/\xi}{\rightarrow} \emptyset, \text{ for } j \in \{1, 2, \ldots, n\}, \]
\[ R_{\gamma_i}(X_\tau; Y_i) : Y_i \overset{\gamma_{i,j}/\xi}{\rightarrow} Y_i + X_j, \text{ for } i \in \{1, 2, \ldots, M\}, j \in \{1, 2, \ldots, n\}, 0 < \xi \ll 1, \]  
with \( \gamma_{0,j} > 0 \) for \( j \in \{1, 2, \ldots, n\} \).

(ii) **Higher-resolution control.** \( R_{\gamma} = R_{\gamma}^\delta(X_\tau; Y) = R_{\gamma_0}^{\mu,\xi,\sigma}(X_\tau, Z; \emptyset) \cup_{i=1}^M R_{\gamma_i}^{\mu,\xi,\sigma}(Z; Y_i) : \)
\[ R_{\gamma_0}^{\mu,\xi,\sigma}(X_\tau; \emptyset) : \emptyset \overset{1/\xi}{\rightarrow} X_j, \quad X_j \overset{\gamma_{0,j,1}/\mu}{\rightarrow} Z_{j,1}, \]
\[ X_j + Z_{j,l} \overset{\gamma_{0,j,l+1}/\mu}{\rightarrow} Z_{j,l+1}, \text{ for } j \in \{1, 2, \ldots, n\}, l \in \{1, 2, \ldots, c_j - 1\}, \]
\[ R_{\gamma_i}^{\mu,\xi,\sigma}(Z; Y_i) : Y_i + Z_{j,x_i,j+1} \overset{\gamma_{i,j}/\xi}{\rightarrow} Y_i + Z_{j,x_i,j}, \text{ for } i \in \{1, 2, \ldots, M\}, j \in \{1, 2, \ldots, n\}, \{x_{i,j}\}_{i=1}^M \subseteq \{0, 1, \ldots, c_j - 1\}, \]  
where \( c = (c_1, c_2, \ldots, c_n) \in \mathbb{Z}_+^n \) is the truncation vector, \( Z = \{\{Z_{j,l}\}_{i=1}^n\}_{j=0}^{c_j} \) are the auxiliary species, with \( Z_{j,0} \equiv \emptyset \). The rate coefficients from (5) are assumed to satisfy the kinetic conditions given by (31) in Appendix B with \( 0 < \mu \ll \varepsilon, \sigma \ll 1 \).

Output: Embedding the stochastic morpher (2)–(5) into the input network (1), gives an output network
\[ R_{\alpha,\beta,\gamma}(X, Y, Z) = R_\alpha(X) \cup R_\beta(Y) \cup R_{\gamma}(X_\tau, Z; Y), \]  
whose species \( X_\tau \), under suitable assumptions, have controlled stochastic dynamics. In particular, the stationary PMF of \( X_\tau \) is a linear combination of Poisson distributions centered at the points \( (x_1, x_2, \ldots, x_n) = (\gamma_{i,1}/\gamma_{0,1}, \gamma_{i,2}/\gamma_{0,2}, \ldots, \gamma_{i,n}/\gamma_{0,n}) \), if \( R_\gamma = R_{\gamma}^\xi \), and Kronecker-delta distributions centered at the points \( (x_1, x_2, \ldots, x_n) = (x_{i,1}, x_{i,2}, \ldots, x_{i,n}) \), with \( x_{i,j} \in [0, c_j - 1] \), if \( R_\gamma = R_{\gamma}^\delta \), for \( i \in \{1, 2, \ldots, M\} \), see Theorem B.3 in Appendix B.

**Algorithm 1:** The algorithm for control of biochemical networks using the stochastic morpher.
gradually transforms (morphs) into a desired predefined form. More precisely, control may be achieved, under suitable time-scale separations, at two different levels of resolution: at the lower-resolution level, and at a lower biochemical cost, one may control the number and configuration of the modes in the target multi-modal probability distribution (weak control), and the mean timing and pattern of stochastic switching in the underlying multi-stable sample paths (strong control). At the higher-resolution level, and at a higher biochemical cost, one may achieve arbitrary target stationary distributions on bounded state-spaces (control over all of the stationary moments). The achieved probability distributions, and hence all of the underlying moments, display asymptotic robust perfect adaptation.

The rest of the paper is organized as follows. In Section 2, we introduce the lower- and higher-resolution control from Algorithm 1 by applying it on the one-species first-order (uni-molecular) production-degradation test network (7). In Section 3, we focus on the lower-resolution control in greater detail, by applying it on the three-species second-order (bi-molecular) test network (16). We explicitly jointly control two input biochemical species (target species), and outline how the remaining (residual) species is implicitly affected. In Section 4, we apply Algorithm 1 on the gene-expression network (20), and demonstrate how implicit control may be achieved. In particular, we explicitly influence the mRNA (target species) in a suitable way, ensuring that the translated protein (residual species) is implicitly controlled. In Section 5, we put forward a blueprint for an experimental realization of the stochastic morpher, using strand-displacement DNA nanotechnology. Finally, we conclude by presenting a summary and discussion in Section 6. The notation and background theory utilized in the paper are introduced as needed, and are summarized in Appendix A. General properties and convergence of the stochastic morpher, outlined via specific examples in Sections 2–4, are rigorously established in Appendix B.

2 Production-degradation input network

Consider the one-species uni-molecular input network $\mathcal{R}_{\alpha}^1 = \mathcal{R}_{\alpha}^1(X)$, under mass-action kinetics, given by

$$\mathcal{R}_{\alpha}^1 : \quad \emptyset \xrightleftharpoons{\alpha_1 \alpha_2} X,$$

where we adopt the convention of denoting two irreversible reactions (in this case, $\emptyset \to X$ and $X \to \emptyset$) jointly as a single reversible reaction (in this case, $\emptyset \rightleftharpoons X$), for notational convenience. In this paper, biochemical species, and their copy-numbers as a function of time $t$, are represented with upper-case letters (such as $X$, and $X(t)$, respectively), while the copy-number values are denoted by the corresponding lower-case letters (such as $x$), with the latter being elements of the set of non-negative integers, denoted by $\mathbb{Z}_\geq$. Symbol $\emptyset$ denotes biochemical species which are not explicitly taken into an account. Furthermore, for simplicity, we assume the non-negative rate coefficients, displayed above the reaction arrows, are dimensionless, and we denote them using the same letter as the sub-script of the corresponding reaction network. See also Appendix A for a summary of the notation used in this paper.

In what follows, we fix the (dimensionless) rate coefficients of the input network $\mathcal{R}_{\alpha}^1(X)$ to $\alpha = (\alpha_1, \alpha_2) = (1, 1/15)$. The stationary probability-mass function (PMF) of (7), describing the long-time dynamics of the input network and denoted by $p_\infty(x)$, is given by the Poisson distribution with mean $\alpha_1/\alpha_2$ (in this paper, we also say that the Poisson distribution is centered at $\alpha_1/\alpha_2$), denoted by $p_\infty(x) = \mathcal{P}(x; \alpha_1/\alpha_2)$. For the particular choice of the rate coefficients, the Poisson PMF is centered at $x = \alpha_1/\alpha_2 = 15$ and is shown as the black dots, interpolated with solid black
lines for visual clarity, in Figures 2, 3. In the rest of this section, we embed different controllers into the input network (7), in order to desirably influence the dynamics of the species X and showcase the capabilities of Algorithm I. Network (7) may be interpreted as a simplified model of genetic transcription, with X representing an mRNA species, being transcribed and degraded, see also Section 4 for a more-detailed model. Despite the simplicity of (7), it serves as a test network for biochemical control theory, outlining some of the advantages and disadvantages a controller may have. For example, the controller put forward in [45], when embedded into the test network (7), is unable to guide the stationary mean of the species X below the value $\alpha_1/\alpha_2$.

### 2.1 Lower-resolution control

**Uni-modality.** Consider the controller $\mathcal{R}_\beta \cup \mathcal{R}_\gamma^P = \mathcal{R}_\beta(Y_1) \cup \mathcal{R}_\gamma^P(X; Y_1)$, called a stochastic morpher, given by

$$
\mathcal{R}_\beta : 2Y_1 \xrightarrow{\beta_1} Y_1,
$$

$$
\mathcal{R}_\gamma^P : \begin{cases}
\mathcal{R}_{\gamma_0}^\varepsilon : X \xrightarrow{\gamma_0/\varepsilon} \emptyset, \\
\mathcal{R}_{\gamma_1}^\varepsilon : Y_1 \xrightarrow{\gamma_1/\varepsilon} Y_1 + X, & 0 < \varepsilon \ll 1,
\end{cases}
$$

where $X$ is the target species, while $Y_1$ is the controlling species. The controller (8) consists of two sub-networks: $\mathcal{R}_\beta(Y_1)$, describing a bi-molecular degradation of the controlling species $Y_1$, and $\mathcal{R}_\gamma^P(X; Y_1) = \mathcal{R}_{\gamma_0}^\varepsilon(X; \emptyset) \cup \mathcal{R}_{\gamma_1}^\varepsilon(X; Y_1)$ describing a degradation of the target species $X$, and a production of $X$ catalyzed by $Y_1$. To emphasize the catalytic role of $Y_1$ in $\mathcal{R}_{\gamma_1}^\varepsilon$, we write $\mathcal{R}_{\gamma_1}^\varepsilon = \mathcal{R}_{\gamma_1}^\varepsilon(X; Y_1)$ and, since $\mathcal{R}_{\gamma_0}^\varepsilon$ is not catalyzed by $Y_1$, we write $\mathcal{R}_{\gamma_0}^\varepsilon = \mathcal{R}_{\gamma_0}^\varepsilon(X; \emptyset)$. The super-script $\mathcal{P}$ appearing in $\mathcal{R}_\gamma^P$ stands for the Poisson distribution, as motivated shortly. See also Figure 1 and Appendices A.3 and B for more details on the notation.

In what follows, we analyze the output network $\mathcal{R}_\beta^a \cup \mathcal{R}_\beta \cup \mathcal{R}_\gamma^P$, obtained by embedding the stochastic morpher (8) into the input network (7), which we compactly denote by (7)∪(8). Assuming the copy-number of $Y_1$, denoted by $y_1 \in \mathbb{Z}_{\geq 2}$, is non-zero initially, the sub-network $\mathcal{R}_\beta(Y_1)$ fires until the stationary value $y_1 = 1$ is reached. On the other hand, the stationary marginal PMF of the target species $X$ from the output network (7)∪(8), denoted by $p_\varepsilon(x)$, reads $p_\varepsilon(x) = \mathcal{P}(x; (\gamma_1 + \varepsilon\alpha_1)/(\gamma_0 + \varepsilon\alpha_2))$, from which it follows that

$$
p_\varepsilon(x) = \begin{cases}
\mathcal{P}
\left( x; \frac{\alpha_1}{\alpha_2} \right), & \text{as } \varepsilon \to \infty, \\
\mathcal{P}
\left( x; \frac{\gamma_1}{\gamma_0} \right), & \text{as } \varepsilon \to 0.
\end{cases}
$$

(9)

In words, as the sub-network $\mathcal{R}_\gamma^P$ from the stochastic morpher $\mathcal{R}_\beta \cup \mathcal{R}_\gamma^P$, given by (8), fires faster, the input network $\mathcal{R}_\alpha^a$, given by (7), is over-ridden, and the stationary $x$-marginal PMF of the corresponding output network $\mathcal{R}_\alpha^a \cup \mathcal{R}_\beta \cup \mathcal{R}_\gamma^P$ is gradually transformed (morphed) from the Poisson PMF centered at $x = \alpha_1/\alpha_2$ to the Poisson PMF centered at $x = \gamma_1/\gamma_0$. Note that such a uni-modal morphing also controls the first-moment (mean) of the output network. This is numerically confirmed in Figure 2(a), where we display the stationary $x$-marginal PMFs of the output network (7)∪(8) for different values of $\varepsilon$, with the coefficients from $\mathcal{R}_\beta(Y_1)$ and $\mathcal{R}_\gamma^P(X; Y_1)$ fixed to $\beta_1 = 1$ and $\gamma = (\gamma_0, \gamma_1) = (1, 30)$, respectively. In particular, the stationary PMF is a Poisson distribution centered at $x = 24$ when $\varepsilon = 10$, shown as the purple squares, which, in accordance with (9), converges close to the Poisson distribution centered at $x = 30$ when $\varepsilon = 10^{-2}$, shown as the cyan histogram in Figure 2(a). A representative sample path, corresponding to the
Figure 2: Application of the lower-resolution control from Algorithm 1 on the input network (7). The stationary PMF of the input network is displayed as the interpolated black dots. Panel (a) shows the stationary x-marginal PMF of the output network (7) ∪ (8), with (γ_0, γ_1) = (1, 30), obtained numerically for two different values of the asymptotic parameter ε, shown as the interpolated purple squares and the cyan histogram. Panel (b) displays a representative sample path, obtained by applying the Gillespie algorithm, corresponding to the cyan histogram from panel (a). Analogous plots are shown for the output network (7) ∪ (10) with (γ_0, γ_1, γ_2) = (1, 5, 30) and (β_1,1, β_1,2, β_2,1) = (1, 1/2, 1/2) (as well as (β_1,1, β_1,2, β_2,1) = (1, 1, 1)) in panels (c)–(d), while with (β_1,1, β_1,2, β_2,1) = (1, 5/6, 1/6) in panels (e)–(f). Finally, panels (g)–(h) show the plots for the output network (7) ∪ (12) with (γ_0, γ_1, γ_2, γ_3) = (1, 5, 30, 15) and (β_1,1, β_1,2, β_2,3, β_3,1) = (1, 1/3, 1/3, 1/3). For simplicity, the sample paths have been generated with the controlling species initially satisfying $\sum_{i=1}^{M} Y_i(0) = 1$. 
histogram from Figure 2(a), is displayed in Figure 2(b), over a relatively short time-interval, allowing for the time-scale of the underlying fluctuations around the mean to be more readily visually discernible.

We say that the stochastic morpher (8), when embedded into (7), is a robust controller, due to the fact that the stationary $x$-marginal PMF of the resulting output network, given by (9), satisfies the following two properties: (a) it is independent of the initial conditions for X and non-zero initial conditions for $Y_1$, and (b) it is independent of the rate coefficients $\alpha$ from the input network in the limit $\varepsilon \to 0$. See also Definition A.3 from Appendix A.3 as well as Theorem B.3 from Appendix B.2 for a more general result. Note that, without the reaction $2Y_1 \to Y_1$ from (8), condition (a) would be violated, as in this case the stationary $x$-marginal PMF would depend on the initial condition for $Y_1$. However, under suitable experimental implementations of the stochastic morpher inside cell-like vesicles, one can achieve exactly one copy-number of $Y_1$ initially inside the vesicles, analogous to having one copy-number of a gene inside a living cell, hence eliminating the need for the reaction $2Y_1 \to Y_1$, see also Section 5. Note also that property (b) leads to asymptotic robust perfect adaptation for all of the underlying stationary statistics of the target species $X$.

The output network $(7) \cup (8)$ is obtained as a particular application of Algorithm 1 on the input network (7), with $R_{\beta}(Y_1)$ and $R_{\gamma}^P(X; Y_1)$ obtained by taking $M = 1$ controlling species $Y = \{Y_1\}$, and $N = 1$ target species $X_r = \{X = X_1\}$, in [8]–[10]. Before proceeding to further applications of Algorithm 1, let us note that the degradation reaction $X \to \emptyset$, introduced by the controller (8), may be seen as an approximation of the reaction $Y_0 + X \to Y_0$, where $Y_0$ is a suitable additional controller (buffer) species, assumed to be maintained at a constant copy-number. One may also replace $X \to \emptyset$ from (8) with (a possibly experimentally less elegant, see Section 5) reaction $Y_1 + X \to Y_1$, without changing the conclusions made in this section. More generally, in this paper, reactions present inside controllers, which depend explicitly only on the target species $X_r$, are assumed to implicitly depend on suitable additional auxiliary (buffer) species, see also Appendix B for a further discussion. Such simplifications have been employed for the purpose of exposition, and do not limit experimental implementations of the stochastic morpher. In fact, an introduction of suitable buffer species is a critical step in experimentally realizing biochemical reaction networks [7].

Bi-modality. Let us now apply Algorithm 1 on the input network (7), with the stochastic morpher $R_{\beta} \cup R_{\gamma}^P = R_{\beta}(Y_1, Y_2) \cup R_{\gamma}^P(X; Y_1, Y_2)$, given by

$$R_{\beta} : \quad 2Y_1 \xrightleftharpoons[\beta_{1,1}]{} Y_1 \xrightleftharpoons[\beta_{1,2}, \beta_{2,1}]{} Y_2,$$

$$R_{\gamma}^P : \quad R_{\gamma_0} : \quad X \xrightleftharpoons[\gamma_0/\varepsilon]{} \emptyset,$$

$$R_{\gamma_1} : \quad Y_1 \xrightleftharpoons[\gamma_1/\varepsilon]{} Y_1 + X,$$

$$R_{\gamma_2} : \quad Y_2 \xrightleftharpoons[\gamma_2/\varepsilon]{} Y_2 + X, \quad 0 < \varepsilon \ll 1. \quad (10)$$

Here, the sub-network $R_{\beta}(Y_1, Y_2)$ describes first-order conversion between the two controlling species $Y_1$ and $Y_2$, with the reaction $2Y_1 \to Y_1$ ensuring that the species $Y_1$ and $Y_2$ satisfy the conservation law $(y_1 + y_2) = 1$ in the long-run, independent of the non-zero initial conditions, i.e. the stationary (long-time) state-space is given by $(y_1, y_2) \in \{(1, 0), (0, 1)\}$. On the other hand, the sub-network $R_{\gamma}^P(X; Y_1, Y_2)$ involves two production reactions for the species $X$, one catalyzed by $Y_1$ and the other by $Y_2$. Ignoring the reaction $2Y_1 \to Y_1$, note that (10) may be interpreted as describing a gene, which switches between two different states $Y_1$ and $Y_2$, and produces an mRNA species $X$ at different rates, depending on the gene state [41, 42].

When $(y_1, y_2) = (1, 0)$, reaction $R_{\gamma_2}$ from the sub-network $R_{\gamma}^P(X; Y_1, Y_2)$ cannot fire, and the
remaining faster reactions $R_{\gamma_0} \cup R_{\gamma_1}$ generate the Poisson PMF centered at $x = \gamma_1/\gamma_0$, while when $(y_1, y_2) = (0, 1)$, the reaction $R_{\gamma_1}$ is switched off, and the active faster reactions $R_{\gamma_0} \cup R_{\gamma_2}$ induce the Poisson PMF centered at $x = \gamma_2/\gamma_0$. As the controlling species $Y_1$ and $Y_2$ convert between themselves, they mix the two Poisson PMFs from the faster network $R_{\gamma_1}(X; Y_1, Y_2)$, which override the PMF of the input network $R_{\gamma}(X)$. In the limit $\varepsilon \to 0$, the resulting stationary $x$-marginal PMF of the output network $\bigcup_{\gamma} R_{\gamma}$ is given by

$$p_0(x) = \left(1 + \frac{\beta_{1,2}}{\beta_{2,1}}\right)^{-1} \mathcal{P}(x; \gamma_1) + \left(1 + \frac{\beta_{2,1}}{\beta_{1,2}}\right)^{-1} \mathcal{P}(x; \gamma_2),$$

(11)

see also Theorem B.3 in Appendix B for a general result. Therefore, the controller (10) allows one remaining faster reactions $R_{\gamma}$ via a more-detailed fine-tuning of (the order of magnitude of) the rate coefficients (strong control). Furthermore, some of the properties of the underlying sample paths may also be controlled by a more-detailed fine-tuning of (the order of magnitude of) the rate coefficients (weak control). In particular, one may control the stationary marginal-PMF of the target species via appropriate ratios of the underlying rate coefficients (weak control). Furthermore, some of the properties of the underlying sample paths may also be controlled via a more-detailed fine-tuning of (the order of magnitude of) the rate coefficients (strong control). Given a fixed ratio $\beta_{1,2}/\beta_{2,1}$, the precise values of the coefficients may be fixed with the constraint $\beta_{1,2} + \beta_{2,1} = c > 0$. In what follows, when we do not wish to explicitly control the mean switching time, we arbitrarily set $c = 1$.

Let us fix two modes of the output network $\bigcup_{\gamma} R_{\gamma}$ to $x = \gamma_1/\gamma_0 = 5$ and $x = \gamma_1/\gamma_0 = 30$, which may be achieved by choosing $\gamma = (\gamma_0, \gamma_1, \gamma_2) = (1, 5, 30)$. In Figure 2(c), we display the corresponding stationary $x$-marginal PMFs for the output network for different values of $\varepsilon$, with $\beta = (\beta_{1,1}, \beta_{1,2}, \beta_{2,1}) = (1/2, 1/2)$ chosen so that the two Poisson distributions from (11) have equal weights, i.e. we take $\beta_{1,2}/\beta_{2,1} = 1$. One can notice that the uni-modal input PMF is morphed into the bi-modal output one, as predicted by (11), shown as the cyan histogram in Figure 2(c). A corresponding representative sample path is shown in the top sub-panel of Figure 2(d), over a suitable time-interval, where the time-scale of the noise-induced switching between the two modes is observable, with the mean time spent near each of the two modes given by $1/\beta_{1,2} = 1/\beta_{2,1} = 2$ time-units. Note that the time-scale of the fluctuations near each of the modes (determined by the parameter $\varepsilon$) matches the one shown magnified in Figure 2(b). Also shown, in the bottom sub-panel of Figure 2(d), is a sample path, over the same time-interval as in the top sub-panel, when $\beta = (\beta_{1,1}, \beta_{1,2}, \beta_{2,1}) = (1, 1, 1)$, which also corresponds to the stationary PMF shown as the histogram in Figure 2(c), but whose mean switching time is halved, $1/\beta_{1,2} = 1/\beta_{2,1} = 1$. More generally, instead of balancing the two Poisson PMFs by choosing $\beta_{1,2}/\beta_{2,1} = 1$, as in Figure 2(c)–(d), one
may control the weights of each of the two Poisson PMFs from (11) in a number of desirable ways. For example, in Figure 2(e)–(f), we set \( \beta_{1,2}/\beta_{2,1} = 2P(\gamma_1/\gamma_0; \gamma_1/\gamma_0) \approx 5 \), ensuring that the value of the stationary PMF at the mode \( x = \gamma_1/\gamma_0 = 30 \) is approximately twice the value at the mode \( x = \gamma_1/\gamma_0 = 5 \), which may be achieved by taking \( \beta = (\beta_{1,1}, \beta_{1,2}, \beta_{2,1}) = (1, 5/6, 1/6) \). Note that the intermediate PMFs from Figures 2(c) and (e), shown as the interpolated purple squares, and obtained when \( \varepsilon = 1 \), still partially achieve the goal of the control, demonstrating that the stochastic morpher may be useful even when not firing much faster than the input network.

**Tri-modality.** Algorithm 1 may be utilized to achieve multi-modality beyond bi-modality at the PMF level, and multi-stability and a controlled switching pattern at the underlying sample path level. For example, let us morph the stationary PMF of the input network (7) into a tri-modal one, with the modes \( x \in \{5, 15, 30\} \). Furthermore, let the underlying sample paths spend on average 3 time-units in the neighborhood of each of the modes, with the switching order 5 \( \rightarrow 30 \rightarrow 15 \), i.e. after being close to the mode \( x = 5 \), the system should jump near \( x = 30 \), then close to \( x = 15 \) and, finally, return back to \( x = 5 \). To this end, consider embedding into the input network \( R^1_\alpha(X) \) the stochastic morpher \( R_\beta \cup R_\gamma^P = R_\beta(Y_1, Y_2, Y_3) \cup R_\gamma^e(X; Y_1, Y_2, Y_3) \), given by

\[
R_\beta : \quad 2Y_1 \xrightarrow{\beta_{1,1}} Y_1 \xrightarrow{\beta_{1,2}} Y_2 \xrightarrow{\beta_{2,3}} Y_3 \xrightarrow{\beta_{3,1}} Y_1,
\]

\[
R_\gamma^P : \quad R_\gamma^e : \quad X \xrightarrow{\gamma_{0}/\varepsilon} \emptyset,
\]

\[
R_\gamma_{1} : \quad Y_1 \xrightarrow{\gamma_{1}/\varepsilon} Y_1 + X,
\]

\[
R_\gamma_{2} : \quad Y_2 \xrightarrow{\gamma_{2}/\varepsilon} Y_2 + X,
\]

\[
R_\gamma_{3} : \quad Y_3 \xrightarrow{\gamma_{3}/\varepsilon} Y_3 + X, \quad 0 < \varepsilon \ll 1.
\]

Analogous to Figure 2(a)–(f), in Figure 2(g)–(h) we display the stationary \( x \)-marginal PMF, and a representative sample path, of the output network \( R^1_\alpha(X) \cup R_\beta(Y_1, Y_2, Y_3) \cup R_\gamma^e(X; Y_1, Y_2, Y_3) \). With \( \gamma = (\gamma_0, \gamma_1, \gamma_2, \gamma_3) = (1, 5, 30, 15) \) and \( \beta = (\beta_0, \beta_{1,2}, \beta_{2,3}, \beta_{3,1}) = (1, 1/3, 1/3, 1/3) \). In the asymptotic limit \( \varepsilon \to 0 \), the stationary PMF is a linear combination of the three Poisson distributions centered at \( x = \gamma_1/\gamma_0 = 5 \), \( x = \gamma_2/\gamma_0 = 30 \) and \( x = \gamma_3/\gamma_0 = 15 \), each with equal weights (see also Theorem B.3 in Appendix B), which is in excellent agreement with the histogram from Figure 2(g), where the asymptotic parameter \( \varepsilon \) is two orders of magnitude larger than the rate coefficients from the networks \( R^1_\alpha(X) \) and \( R_\beta(Y_1, Y_2, Y_3) \). Note that the switching order of the sample path from Figure 2(h) mirrors the conversion \( Y_1 \rightarrow Y_2 \rightarrow Y_3 \rightarrow Y_1 \) from (12).

### 2.2 Higher-resolution control

In Section 2.1, we have applied the lower-resolution control from Algorithm 1, which consists of the networks \( R_\beta \) and \( R_\gamma^P \), given by (3) and (4), respectively, and may be used to achieve multi-modality/multi-stability. In this section, we replace the uni-molecular lower-resolution (Poisson-based) control network \( R_\gamma^P \) with its bi-molecular higher-resolution (Kronecker-delta-based) counterpart \( R_\gamma^\delta \), given by (5) in Algorithm 1, which may be used to morph input PMFs to arbitrary probability distributions on bounded state-spaces.

**Kronecker-delta distribution.** Consider the stochastic morpher \( R_\beta \cup R_\gamma^\delta = R_\beta(Y_1) \cup R_\gamma^\delta(X, Z_1, Z_2; Y_1) \),
Figure 3: Application of the higher-resolution control from Algorithm 1 on the input network (7) with \((\alpha_1, \alpha_2) = (1, 1/15)\). The stationary PMF of the input network is displayed as the interpolated black dots. Panel (a) shows the stationary \(x\)-marginal PMF of the output network \((7) \cup (13)\), taken in the limit \(\mu \to 0\) for computational efficiency (see also Theorem B.1 in Appendix B), with \(\beta_{1,1} = 1\) and two different values of the asymptotic parameters \((\varepsilon, \sigma)\), shown as the interpolated purple squares and the cyan histogram. Panel (b) displays an analogous plot for the output network \((7) \cup (15)\) with \((\beta_{1,1}, \beta_{1,2}, \beta_{2,3}, \beta_{3,1}) = (1,1/3,1/3,1/3)\). Panel (c) shows the stationary \(x\)-marginal PMF of the output network \((7) \cup (65)\) with \((\beta_{1,1}, \beta_{1,2}, \beta_{2,1}) = (1, 1/8, 7/8), (\gamma_1^P, \tilde{\gamma}_1^P) = (30, 1), (\gamma_0^P, \tilde{\gamma}_0^P) = (\mu^2 \varepsilon \sigma)^{-1/3}(\mu^{1/3}, \mu^{-1/6}, \mu^{-1/6})\), \(\mu = 10^{-10}\) and two different values for the pair \((\varepsilon, \sigma)\), while panel (d) displays a representative sample path corresponding to the histogram from panel (c).
given by

\[
\begin{align*}
R_\beta : & \quad 2Y_1 \xrightarrow{\beta_{1,1}} Y_1, \\
R_\gamma : & \quad R_{\gamma_7}^{\mu,\varepsilon,\sigma} : \begin{cases} \emptyset \xrightarrow{1/\varepsilon} X, \\
X \xrightarrow{\gamma_{0,1}} Z_1, \\
X + Z_1 \xrightarrow{1/\mu} Z_2, \end{cases} \\
R_{\gamma_1}^{\mu,\varepsilon,\sigma} : & \quad Y_1 + Z_2 \xrightarrow{\gamma_1} Y_1 + Z_1. \quad (13)
\end{align*}
\]

Network \( R_\gamma^\delta = R_{\gamma_7}^{\mu,\varepsilon,\sigma} \cup R_{\gamma_1}^{\mu,\varepsilon,\sigma} \) consists of two sub-networks: \( R_{\gamma_7}^{\mu,\varepsilon,\sigma} \) describes a production of \( X \), a reversible conversion of \( X \) into an auxiliary species \( Z_1 \), and a reversible conversion of \( X \) and \( Z_1 \) into another auxiliary species \( Z_2 \). On the other hand, \( R_{\gamma_1}^{\mu,\varepsilon,\sigma} \) describes an irreversible conversion of \( Z_2 \) into \( Z_1 \), catalyzed by \( Y_1 \). Note that the controlling species \( Y_1 \) does not react directly with the target species \( X \). Instead, \( Y_1 \) acts on \( X \) indirectly, via the species \( Z_1 \) and \( Z_2 \). For this reason, we call \( Z = \{Z_1, Z_2\} \) the mediating species, as they propagate the action of the controlling species \( Y_1 \) onto the target species \( X \).

The dynamics of the mediating species are assumed to be sufficiently fast. More precisely, it is assumed that the coefficients \( \gamma_{0,1}, \gamma_{0,2} \) and \( \gamma_1 \) from (13) satisfy the kinetic condition \( \mu^2 \gamma_{0,1} \gamma_{0,2} \gamma_1 = (\varepsilon \sigma)^{-1} \) with the asymptotic parameters \( 0 < \mu \ll \varepsilon, \sigma \ll 1 \). This ensures that the network \( R_\gamma^\delta \) fires sufficiently fast in a balanced way, see Theorem B.1 in Appendix B and [29]. Under the kinetic condition, species \( Z_1 \) and \( Z_2 \) formally satisfy \( Z_1 = X \) and \( Z_2 = X + Z_1 = 2X \) in the limit \( \mu \to 0 \), and the network \( R_\gamma^\delta \) from (13) reduces to

\[
\begin{align*}
R_{\gamma_7}^{\varepsilon} : & \quad \emptyset \xrightarrow{1/\varepsilon} X, \\
R_{\gamma_1}^{\varepsilon,\sigma} : & \quad Y_1 + 2X \xrightarrow{1/(\varepsilon \sigma)} Y_1 + X, \quad 0 < \varepsilon, \sigma \ll 1. \quad (14)
\end{align*}
\]

The first reaction from (14) provides a strong positive drift, which is overpowered by an even stronger negative drift, induced by the second reaction from (14), when the copy-number of the target species satisfies \( x > 1 \). As a consequence, the target species \( X \) from the output network \( \{7\} \cup \{13\} \) spends most of the time at the single state \( x = 1 \), i.e. the stationary \( x \)-marginal PMF is a Kronecker-delta distribution centered at \( x = 1 \), which we denote by \( \delta_{x,1} \). In Figure 3(a), we display the stationary \( x \)-marginal PMF of the output network \( \{7\} \cup \{13\} \), taken in the limit \( \mu \to 0 \) for computational efficiency. The PMF is shown in purple when the remaining two asymptotic parameters are fixed to \( \varepsilon = \sigma = 1 \), while as the cyan histogram when \( \varepsilon = \sigma = 10^{-2} \), which is in excellent agreement with the Kronecker-delta distribution \( \delta_{x,1} \).

Before proceeding to further applications of the higher-resolution control, let us explain briefly why the network \( R_\gamma^\delta \) from (13), involving the mediating species \( Z_1 \) and \( Z_2 \), has been put forward, as opposed to the dynamically similar network (14), which has been put forward to implement Kronecker-delta distributions in [54]. The former network is bi-molecular, and hence experimentally implementable in principle [7]. On the other hand, network (14) contains a third-order (tri-molecular) reaction which may not be directly experimentally implementable. As exemplified shortly, encoding Kronecker-delta distributions centered at higher values of \( x \) is achieved in our framework by simply adding more auxiliary species, which participate in up-to second-order reactions. On the other hand, this is achieved in networks of the form (14) by further increasing the order of some of the underlying reactions, thus making such networks experimentally less desirable.
Uniform distribution. Using multiple Kronecker-delta distributions, by applying the higher-resolution control from Algorithm 1, one may achieve arbitrary probability distributions on bounded domains. For example, having achieved a probability distribution concentrated at a single point, utilizing the controller (13), let us now morph the stationary PMF of the input network (7) into a uniform distribution on the state-space $x \in \{1, 2, 3\}$, via the controller

$$
\begin{align*}
R_\beta : & \quad 2Y_1 \xrightarrow{\beta_{1,1}} Y_1 \xrightarrow{\beta_{1,2}} Y_2 \xrightarrow{\beta_{2,3}} Y_3 \xrightarrow{\beta_{3,1}} Y_1, \\
R_\delta : & \quad R_{\mu,\varepsilon,\sigma}^{\gamma_1} : \quad \emptyset \xrightarrow{1/\varepsilon} X, \\
& \quad X \xrightarrow{\gamma_{0,1}} 1/\mu Z_1, \\
& \quad X + Z_1 \xrightarrow{\gamma_{0,2}} 1/\mu Z_2, \quad X + Z_2 \xrightarrow{\gamma_{0,3}} 1/\mu Z_3, \quad X + Z_3 \xrightarrow{\gamma_{0,4}} 1/\mu Z_4, \\
R_{\mu,\varepsilon,\sigma}^{\gamma_1} : & \quad Y_1 + Z_2 \xrightarrow{\gamma_1} Y_1 + Z_1, \\
R_{\mu,\varepsilon,\sigma}^{\gamma_2} : & \quad Y_2 + Z_3 \xrightarrow{\gamma_2} Y_2 + Z_2, \\
R_{\mu,\varepsilon,\sigma}^{\gamma_3} : & \quad Y_3 + Z_4 \xrightarrow{\gamma_3} Y_3 + Z_3, \quad 0 < \mu \ll \varepsilon, \sigma \ll 1.
\end{align*}
$$

(15)

Network (15) involves four mediating species, which, under suitable kinetic conditions (see Theorem B.1 in Appendix B), formally satisfy $Z_1 = X$, $Z_2 = 2X$, $Z_3 = 3X$ and $Z_4 = 4X$. Consequently, the fast production reaction $\emptyset \xrightarrow{1/\varepsilon} X$ and $R_{\mu,\varepsilon,\sigma}^{\gamma_1}$ generate the Kronecker-delta distributions centered at $x = i$, for $i \in \{1, 2, 3\}$, and the weight of each of the three Kronecker-delta distributions is controlled with the rate coefficients from the sub-network $R_\beta$, in the same manner as in network (12). In particular, a uniform distribution may be achieved by taking $\beta = (\beta_{1,1}, \beta_{1,2}, \beta_{2,3}, \beta_{3,1}) = (1, 1/3, 1/3, 1/3)$. Analogous to Figure 3(a), in Figure 3(b) we display the $x$-marginal PMF of the output network $(7)$ $\cup$ (15). Let us note that, while the weights of the Kronecker-delta distributions are encoded kinetically, in the rate coefficients from the sub-network $R_\beta$, the centers of the distributions are encoded stoichiometrically, i.e. they are determined by which mediating species is catalyzed by the controlling species.

Hybrid control. One may also wish to combine the lower- and higher-resolution networks $R_\gamma^P$ and $R_\delta^P$ from Algorithm 1, respectively, into a composite hybrid scheme for biochemical control. For example, one may wish to obtain a more-detailed control over regions of the state-space where the target species are in lower copy-numbers, while a less-detailed control may be sought over the state-space where the target species are in higher copy-numbers. Such a hybrid approach may be experimentally desirable, as biochemical realizations of the Kronecker-delta PMFs centered at lower copy-numbers of the species are less expensive to engineer, since a smaller number of the mediating species $Z$ is required. For example, in Figure 3(c), we embed a hybrid controller into the input network (7), and morph the PMF into a mixture of a Kronecker-delta distribution at $x = 1$ and a Poisson distribution at $x = 30$, with the underlying sample path shown in Figure 3(d). The hybrid controller is given as the network (65) in Appendix B.2.1.

3 Bi-stable input network

In Section 2, we have applied Algorithm 1 in order to control the one-species uni-molecular input network (7). In this section, we apply Algorithm 1 to a more complicated reaction network, involving bi-molecular reactions and multiple biochemical species. In particular, we highlight how
Algorithm [1] may be applied to simultaneously control multiple species, instead of only one species at a time. Furthermore, we analyze the dynamics of the species which are not explicitly controlled.

To this end, we put forward the three-species bi-molecular input network $\mathcal{R}_2^α = \mathcal{R}_2^α(X_1, X_2, X_3)$, under mass-action kinetics, given by

$$\mathcal{R}_2^α :  \quad \emptyset \xrightarrow{α_1} X_1, \quad \emptyset \xrightarrow{α_3} X_2, \quad \emptyset \xrightarrow{α_4} X_3, \quad X_3 \xrightarrow{α_5} X_1,$$

$$2X_1 \xrightarrow{α_6} 2X_1 + X_3, \quad X_1 + X_2 \xrightarrow{α_7} 2X_1, \quad X_1 + X_3 \xrightarrow{α_8} X_3. \quad (16)$$

For illustrative purposes, in what follows, we focus on controlling the target species $X_τ = \{X_1, X_2\}$, while the remaining species, called the residual species and denoted by $X_ρ = \{X_3\}$, is implicitly influenced, but not explicitly controlled (see also Figure 1 in Section 1 for a visualization of the target and residual species in a general setting). For a particular choice of the rate coefficients $α$, the stationary $(x_1, x_2)$-marginal PMF of the input network $\mathcal{R}_2^α$ is shown in Figure 4(a), while the underlying sample paths for $X_1$ and $X_2$ are shown in cyan and red in Figure 4(b), respectively. The $(x_1, x_2)$-marginal PMF is bi-modal, with the modes approximately given by $(x_1, x_2) = (10, 40)$ and $(x_1, x_2) = (40, 10)$, and with the species $X_1$ and $X_2$ being negatively correlated.

**Target species.** Let us now apply Algorithm 1 in order to morph the input PMF from Figure 4(a) into a bi-modal one, with the species $X_1$ and $X_2$ being positively correlated. More precisely, let us morph the input modes into the target modes given by $(x_1, x_2) = (10, 10)$ and $(x_1, x_2) = (40, 40)$, where the $(x_1, x_2)$-marginal PMF takes approximately the same values, and with the switching time between the two new modes being of the order $Ω(10)$ time-units. To this end, consider the stochastic morpher $\mathcal{R}_β \cup \mathcal{R}_γ^P = \mathcal{R}_β(Y_1, Y_2) \cup \mathcal{R}_γ^P(X_1, X_2; Y_1, Y_2)$, given by

$$\mathcal{R}_β : \quad 2Y_1 \xrightarrow{β_{1,1}} Y_1 \xrightarrow{β_{1,2}} Y_2$$

$$\mathcal{R}_γ^P : \quad \mathcal{R}_γ^{γ_0} : \quad X_1 \xrightarrow{γ_{0,1}/ε} \emptyset, \quad X_2 \xrightarrow{γ_{0,2}/ε} \emptyset,$$

$$\mathcal{R}_γ^{γ_1} : \quad Y_1 \xrightarrow{γ_{1,1}/ε} Y_1 + X_1, \quad Y_1 \xrightarrow{γ_{1,2}/ε} Y_1 + X_2,$$

$$\mathcal{R}_γ^{γ_2} : \quad Y_2 \xrightarrow{γ_{2,1}/ε} Y_2 + X_1, \quad Y_2 \xrightarrow{γ_{2,2}/ε} Y_2 + X_2, \quad 0 < ε \ll 1. \quad (17)$$

Controller [17] is a two-target-species analogue of the network [10], with each of the controlling species $Y = \{Y_1, Y_2\}$ now producing both of the target species $X_τ = \{X_1, X_2\}$. The stationary $(x_1, x_2)$-marginal PMF of the output network $\{16\} \cup \{17\}$ is given, in the limit $ε \to 0$, by

$$p_0(x_1, x_2) = \left(1 + \frac{β_{1,2}}{β_{2,1}}\right)^{-1} \mathcal{P}(x_1; \frac{γ_{1,1}}{γ_{0,1}}) \mathcal{P}(x_2; \frac{γ_{1,2}}{γ_{0,2}}) + \left(1 + \frac{β_{2,1}}{β_{1,2}}\right)^{-1} \mathcal{P}(x_1; \frac{γ_{2,1}}{γ_{0,1}}) \mathcal{P}(x_2; \frac{γ_{2,2}}{γ_{0,2}}), \quad (18)$$

see also Theorem 3.3 from Appendix 3.2. Note that (18) is a linear combination of a product of two Poisson distributions, which is a two-dimensional analogue of (11).

In order to achieve the desired modes, we fix $γ = (γ_1, γ_2) = ((γ_{0,1}, γ_{1,1}, γ_{2,1}), (γ_{0,2}, γ_{1,2}, γ_{2,2})) = ((1, 10, 40), (1, 10, 40))$. One the other hand, in order to ensure that the PMF takes approximately equal values at the two modes, and that the switching time is of the order $Ω(10)$ time-units, we set $β_{1,2}/β_{2,1} = 4$, and $(β_{1,2} + β_{2,1}) = 1/10$, respectively, which is achieved by taking $β = (β_{1,1}, β_{1,2}, β_{2,1}) = (1, 4/50, 1/50)$. In Figure 4(c)-(d), we display the stationary $(x_1, x_2)$-marginal PMF of the output network $\{16\} \cup \{17\}$, and the underlying representative sample paths, when the asymptotic parameter is fixed to $ε = 1$. One can notice that the two modes from the input PMF,
Figure 4: Application of the lower-resolution control from Algorithm 1 on the input network (16) with \( \alpha = (1, \alpha_2, \alpha_3, \alpha_4, \alpha_5, \alpha_6, \alpha_7, \alpha_8) = (2, 7/2, 2, 18, 3/2, 9/50, 1/200, 1/48) \). Panels (a), and (b), show the stationary \( (x_1, x_2) \)-marginal PMF of the input network (16), and the underlying representative sample paths for target species \( X_1 \) and \( X_2 \), respectively. Analogous plots are shown in panels (c)–(d), and (e)–(f), for the output network (16) \( \cup \) (17) with \( \beta = (\beta_{1,1}, \beta_{1,2}, \beta_{2,1}) = (1, 4/50, 1/50), \) \( \gamma = (\gamma_{1,1}, \gamma_{2,1}, \gamma_{1,2}, \gamma_{2,2}) = ((1, 10), (1, 10), (40)), \) and different values of the asymptotic parameter \( \epsilon \), as indicated in the plots. Panel (g) displays as the black dots, interpolated with the black lines, a plot of the \( l_1 \)-distance between the target PMF (18) and the long-time PMF of output network (16) \( \cup \) (17) as a function of the asymptotic parameter \( \epsilon \). Panel (h) shows the stationary \( x_3 \)-marginal PMFs of the input network (16), and the output network (16) \( \cup \) (17) with \( \epsilon = 10^{-2} \), as the black solid curve, and the cyan histogram, respectively. Also shown, as the dotted red curve, is the stationary \( x_3 \)-marginal PMF of the residual network (19).
shown in Figure 4(a), have already largely redistributed across the two target modes, concentrating more near \((x_1, x_2) = (40, 40)\). Broadly speaking, as the parameter \(\varepsilon\) is decreased, the input PMF is at first more attracted towards the target mode \((x_1, x_2) = (40, 40)\), than to \((x_1, x_2) = (10, 10)\), due to the fact that the former mode contains significantly more probability mass in the limit \(\varepsilon \to 0\), under the particular choice of \(\beta\). Note that the PMF already displays bi-modality and positive correlation between the target species for \(\varepsilon = 1\). As the parameter \(\varepsilon\) is further decreased, the PMF from Figure 4(c) gradually reshapes into the desired form. In Figure 4(e)–(f), we take the asymptotic parameter \(\varepsilon = 10^{-2}\), so that the largest rate coefficients from the input network (16) and the controller (17) are separated by two orders of magnitude, and one can notice that the stationary PMF has converged close to the target (18) when \(\varepsilon = 10^{-2}\). Comparing Figures 4(a)–(b) and (e)–(f), one can also notice that the marginal modes for the target species \(\mathcal{X}_t = \{X_1, X_2\}\) have been approximately preserved under the stochastic bifurcation induced by controller (17), while the correlation has been reversed from negative to positive, respectively. To gain a more quantitative information about the convergence, in Figure 4(g) we display the distance (error) \(|p_0 - p_\varepsilon|\), \(\varepsilon = 10^{-2}\), i.e. the error decreases linearly as a function of \(\varepsilon\) which also holds for more general input networks, see Theorem B.2 in Appendix B.1.1.

Residual species. The dynamics of the target and residual species, \(\mathcal{X}_t = \{X_1, X_2\}\) and \(\mathcal{X}_\rho = \{X_3\}\), respectively, are coupled. As a consequence, explicit control of the target species implicitly influences the dynamics of the residual species. In Figure 4(h), we display as the solid black curve, and the cyan histogram, the stationary \(x_3\)-marginal PMFs from the input network (16), and the output network \((16) \cup (17)\) with \(\varepsilon = 10^{-2}\), respectively. One can notice that, under the controller (17), the PMF of the residual species is redistributed across the two modes, which approximately remain fixed in this particular example.

The dynamics of the residual species \(X_3\), in the limit \(\varepsilon \to 0\), is governed by the so-called residual network, denoted by \(\mathcal{R}_\rho^2 = \mathcal{R}_\rho^2(X_3; Y_1, Y_2)\), which is given by

\[
\begin{align*}
\mathcal{R}_\rho^2 : & \quad \emptyset \xrightarrow{\alpha_5} X_3, \\
& \quad Y_1 \xrightarrow{\alpha_6(\gamma_1,1/\gamma_0,1)^2} Y_1 + X_3, \\
& \quad Y_2 \xrightarrow{\alpha_6(\gamma_2,1/\gamma_0,1)^2} Y_2 + X_3.
\end{align*}
\]

Network (19) is obtained by suitably eliminating the target species \(\mathcal{X}_t = \{X_1, X_2\}\) from the input network (16), see Appendix B.3 and equation (67) in particular, for more details. Note that the controlling species \(Y = \{Y_1, Y_2\}\), which play a catalytic role in the sub-network \(\mathcal{R}_\rho^2\) from (17), also play a catalytic role in the residual network (19). Note also that, as the black-box input network (16) is assumed to have an unknown structure, the residual network (19) is unknown from the control perspective.

In Figure 4(h), we show, as the dotted red curve, the stationary \(x_3\)-marginal PMF of the composite residual network \(\mathcal{R}_\rho^2 \cup \mathcal{R}_\beta\), where \(\mathcal{R}_\beta\) is given in (17), which is in good agreement with the cyan histogram, verifying the validity of the network (19). In fact, under the parameter choice in this paper, the conversion reactions from the network \(\mathcal{R}_\beta\) are significantly slower than the residual network \(\mathcal{R}_\rho^2\) and, as a consequence, the corresponding \(x_3\)-marginal PMFs is approximately given by a linear combination of two Poisson distributions (42) centered at \(x_3 = (\alpha_4 + \alpha_6(\gamma_1,1/\gamma_0,1)^2)/\alpha_5 = 24\) and \(x_3 = (\alpha_4 + \alpha_6(\gamma_2,1/\gamma_0,1)^2)/\alpha_5 = 204\), with weights identical to those from (18). Let us note that, more generally, the residual species do not necessarily inherit multi-modality, nor Poisson-based PMFs, from the target species.
4 Implicit control: Gene-expression input network

In Section 3, we have focused on controlling the target species, while ignoring the induced implicit effects on the underlying residual species. In this section, we shift our focus to an implicit control of the residual species, via appropriate manipulations of the target species. In particular, we exploit the time-scale separation between the residual network and the networking governing the dynamics of the controlling species in order to obtain a control over the residual species. To this end, consider the two-species uni-molecular reaction network, denoted by \( \mathcal{R}_\alpha^3 = \mathcal{R}_\alpha^3(X_1, X_2) \), and given by

\[
\mathcal{R}_\alpha^3 : \quad \emptyset \xrightarrow{\alpha_1} X_1, \quad X_1 \xrightarrow{\alpha_3} X_1 + X_2, \quad X_2 \xrightarrow{\alpha_4} \emptyset.
\]  

(20)

Network (20) may be interpreted as a simplified model for gene transcription and translation within a biological cell: \( X_1 \) represents an mRNA species, transcribed from a gene, and translated into a suitable protein species \( X_2 \), with each of the two species being degradable. For simplicity, many biochemical steps necessary for gene expression have been omitted [41] (e.g. a fixed abundance of genes and ribosomes is assumed, and incorporated as effective rate coefficients). Let us note that, while we have assumed that the black-box networks (7) and (16) have an unknown structure from the perspective of control, in this section we assume that the structure of the black-box input network (20) is partially known. More precisely, we assume that the only reactions which change the copy-number of \( X_2 \) are \( X_1 \rightarrow X_1 + X_2 \) and \( X_2 \rightarrow \emptyset \) (whose rate coefficients may be unknown), which is satisfied if e.g. \( X_2 \) is involved only as a catalyst in the remaining biochemical reactions within the cell, while the rest of the structure of (20), which may be embedded into a larger ambient network, is allowed to be unknown.

Assume one desires to control the protein species \( X_2 \) (and thereby the phenotype of the underlying cells), by utilizing a controller which is experimentally realized with RNA molecules [3, 23]. In this case, interfacing RNA controlling species with the protein \( X_2 \) may be a difficult task, as the two types of molecules have different biophysical properties. A more natural target for the RNA controlling species is the mRNA species \( X_1 \), as they may interact via the highly programmable toehold-mediated strand-displacement mechanism. This motivates one to consider the problem of explicitly influencing the target species \( X_1 \), in order to implicitly control the residual species \( X_2 \).

To this end, let us induce bi-modality into the probability distribution of \( X_2 \), by considering the stochastic morpher acting on \( X_1 \), given by

\[
\mathcal{R}_\beta : \quad 2Y_1 \xrightarrow{\beta_1} Y_1 + Y_2, \quad Y_1 \xrightarrow{\beta_2} Y_2,
\]

\[
\mathcal{R}_\gamma^p : \quad \mathcal{R}_\gamma^e : \quad X_1 \xrightarrow{\gamma_0/\varepsilon} \emptyset,
\]

\[
\mathcal{R}_\gamma^e : \quad Y_1 \xrightarrow{\gamma_1/\varepsilon} Y_1 + X_1,
\]

\[
\mathcal{R}_\gamma^e : \quad Y_2 \xrightarrow{\gamma_2/\varepsilon} Y_2 + X_1, \quad 0 < \varepsilon \ll 1.
\]  

(21)

In the limit \( \varepsilon \to 0 \), the stationary \( x_1 \)-marginal PMF from the output network [20] \( \cup \) [21], denoted by \( p_0(x_1) \), has the form [11]. On the other hand, the residual network, governing the dynamics of the species \( X_2 \), denoted by \( \mathcal{R}_\alpha^3 = \mathcal{R}_\alpha^3(X_2; Y_1, Y_2) \), is given by

\[
\mathcal{R}_\alpha^3 : \quad X_2 \xrightarrow{\alpha_4} \emptyset,
\]

\[
Y_1 \xrightarrow{\alpha_3(\gamma_{1,1}/\gamma_{0,1})} Y_1 + X_2, \quad Y_2 \xrightarrow{\alpha_3(\gamma_{2,1}/\gamma_{0,1})} Y_2 + X_2.
\]  

(22)
Bi-modality in the probability distribution of $X_2$ may be achieved by taking sufficiently slow conversion reactions from the network $R_\beta(Y_1, Y_2)$ \cite{12}. In particular, the stationary $x_2$-marginal PMF, in the limit $(\beta_{1,2} + \beta_{2,1}) = \epsilon_\beta \to 0$ with $\beta_{1,2}/\beta_{2,1}$ fixed, is given by

$$p_0(x_2) = \left(1 + \frac{\beta_{1,2}}{\beta_{2,1}}\right)^{-1} P \left(x_2; \frac{\alpha_3}{\alpha_4} \left(\frac{\gamma_{1,1}}{\gamma_{0,1}}\right)\right) + \left(1 + \frac{\beta_{2,1}}{\beta_{1,2}}\right)^{-1} P \left(x_2; \frac{\alpha_3}{\alpha_4} \left(\frac{\gamma_{2,1}}{\gamma_{0,1}}\right)\right).$$

(23)

Note that the assumption that the reactions which change the copy-numbers of $X_2$ are known, implies that the structure of the residual network \cite{22}, and the form of the $x_2$-marginal PMF \cite{23}, are also known.

The stationary PMF \cite{23}, describing the long-time dynamics of the residual species $X_2$, depends on the (generally) unknown input rate coefficients $\alpha_3$ and $\alpha_4$, in contrast to the stationary PMF of the target species, which does not depend on the input coefficients as $\epsilon \to 0$. Despite dependence on the input parameters, controllable bi-modality in species $X_2$ may be achieved. In particular, the ratio between the centers of the two Poisson distributions from \cite{23} is given by $\gamma_{2,1}/\gamma_{1,1}$, which is independent of the rate coefficients $\alpha_3$ and $\alpha_4$. Hence, relative distance between the two modes of the species $X_2$ is controllable with the ratio of the production rate coefficients of the species $X_1$ from the stochastic morpher \cite{21}. Taking the ratio $\gamma_{2,1}/\gamma_{1,1}$ sufficiently large ensures that the two Poisson distributions from \cite{23} are well-separated, and the probability mass at the two modes is controlled by the ratio $\beta_{1,2}/\beta_{2,1}$, as before. On the other hand, as opposed to before, in Sections \ref{2} and \ref{3}, where $(\beta_{1,2} + \beta_{2,1})$ was chosen to control the switching time of the underlying sample paths of the target species, in the current setting we exploit this degree of freedom by sufficiently slowing down the switching time by setting $(\beta_{1,2} + \beta_{2,1}) = \epsilon_\beta \ll 1$, ensuring validity of \cite{23}.

In Figure \ref{5}a and (b), we display, as the black interpolated dots, the stationary PMFs of the target and residual species, $X_1$ and $X_2$, respectively, of the input network \cite{20} with the rate coefficients fixed to $\alpha = (\alpha_1, \alpha_2, \alpha_3, \alpha_4) = (2, 1, 10, 1)$. Let us morph the input $x_2$-stationary PMF into a bi-modal one, of the form \cite{23}, with the larger mode being three times further away than the smaller mode, $\gamma_2/\gamma_1 = 3$, and with $\beta_{1,2}/\beta_{2,1} = 1$. To this end, we consider the output network \cite{20} with $\gamma = (\gamma_{0,1}, \gamma_{1,1}, \gamma_{2,1}) = (1, 1, 3)$, and $\beta_{1,2} + \beta_{2,1} = \epsilon_\beta \ll 1$. In Figure \ref{5}a, we display the stationary $x_1$-marginal PMF of the output network \cite{20} when $\epsilon = 10^{-2}$ as the cyan histogram, which is in an excellent agreement with the theoretical prediction \cite{11}. Note that the $x_1$-marginal PMF is uni-modal, as the two Poisson distributions from \cite{11} are not sufficiently well-separated for the chosen parameters, and that it is approximately independent of the value of $\epsilon_\beta$ (which only influences appropriate dynamical time-scales of the underlying sample paths). On the other hand, in Figure \ref{5}b, we display the stationary $x_2$-marginal PMF of the output network \cite{20} as the interpolated purple squares, and the cyan histogram, for $\epsilon = 10^{-2}$, and two different values of $\epsilon_\beta$, namely $\epsilon_\beta = 1$ and $\epsilon_\beta = 10^{-2}$, respectively. One can notice that, as the conversion reactions in the sub-network $R_\beta$ fire slower, the stationary $x_2$-marginal PMF converges to the desired bi-modal form, and an implicit control of the residual species is achieved.

5 Proposed experimental implementation

The stochastic morpher has been constructed to be experimentally implementable. At the structural level, both the lower- and higher-resolution controller networks from Algorithm \ref{1} consist of up-to second-order (and not higher-order) reactions, with any reaction which does not involve an auxiliary species being up-to first-order, allowing one to readily map the controller into nucleic-acid-based physical networks \cite{7}. At the dynamical level, as demonstrated in Sections \ref{2}--\ref{4} and established in Appendix \ref{13}, the operational precision and robustness of the stochastic morpher depend on
the appropriate orders of magnitude (time-scale separation) and ratios of the rate coefficients of the underlying reactions, rather than specific values. This is suitable for implementation via the strand-displacement mechanism, where the rate coefficients may be varied over at least six orders of magnitude [2, 33, 3], and where the speed of the overall biochemical dynamics may also be further increased with the addition of appropriate enzymes [21].

In this section, we put forward a blueprint for an experimental implementation of the stochastic morpher from Algorithm 1. More specifically, as a proof-of-concept, we focus on physically realizing the controller (10) from Section 2 which is capable of morphing the probability distribution of an input network into a desired bi-modal form. One way to realize the stochastic morpher (10) is via a physical network which satisfies the following two properties: (i) it contains two isomeric molecular species which may convert between themselves (realizing the controlling species $Y_1$ and $Y_2$, and the reaction $Y_1 \leftrightarrow Y_2$), each triggering a catalytic production of the target biochemical species $X$ at generally different rates (realizing the reactions $Y_1 \rightarrow Y_1 + X$ and $Y_2 \rightarrow Y_2 + X$), and (ii) the network is integrated into an environment ensuring the presence of exactly one copy-number of the two isomeric species at a time (realizing $y_1 + y_2 = 1$, and eliminating the need for the reaction $2Y_1 \rightarrow Y_1$). Such conditions may be experimentally achieved via suitable DNA-strand-displacement-based physical networks, enclosed in appropriate compartments [16, 17, 18, 53, 55], allowing for an experimental observation and validation of the stochastic morpher.

More specifically, we put forward a DNA complex, known as a Holliday junction molecule, encapsulated in a nano-scale chamber, known as a small unilamellar vesicle (SUV), as a realization of the stochastic morpher (10), schematically displayed in Figure 6(a). The SUV encapsulation is an experimentally demonstrated method for isolating and observing the dynamics of individual molecules, such as a single Holliday junction molecule, with minimal effect from the external environment [53]. The DNA Holliday junction complex consists of four double-stranded arms crossing at a branch point, which is designed to be fixed (non-migratory) for the purpose of our implementation. Let us note that the Holliday junction molecule with a migratory branch point is a central intermediate during genetic recombination process [9]. In the presence of magnesium ions, the Holliday junction can adopt two distinct orientations, known as stacked conformational iso-
mers [56], allowing one to physically realize the reversible reaction $Y_1 \rightleftharpoons Y_2$. In order to control the rate coefficient of the interconversion reactions $Y_1 \rightleftharpoons Y_2$, and the catalytic production reactions $Y_1 \rightarrow Y_1 + X$ and $Y_2 \rightarrow Y_2 + X$, we put forward suitable DNA overhangs involved in the associative (rather than dissociative) toehold activation [57]. More precisely, we tag three arms of the four-armed Holliday junction by extending them with distinct single-stranded DNA molecules (overhangs), which pairwise associate with each other and activate distinct toeholds, shown as the grey regions attached to $Y_1$ and $Y_2$ in Figure 6(b). The overhangs also partially hybridize with each other, forming duplexes next to the toeholds. By controlling the length, and therefore the binding energy, of the duplexes in the associated DNA overhangs, one can experimentally tune the interconversion rate between the two stacked conformational isomers. On the other hand, by controlling the length of the association-activated toeholds, one can independently tune the rates of the two subsequent strand-displacement reactions which produce the target species $X$ from a suitable precursor molecule, denoted by $\bar{X}$ in Figure 6(b). Once a molecule of $X$ is produced, the isomeric species $Y_1$ and $Y_2$ can be recovered via appropriate strand-displacement reactions, ensuring an effective catalytic role of $Y_1$ and $Y_2$ in the overall reaction cascade.

Figure 6: Proposed experimental scheme for the stochastic morpher [10]. Panel (a) displays a small unilamellar vesicle (SUV), immobilized onto a PEG or BSA passivated surface. The SUV encloses a single DNA Holliday junction molecule, which switches between two distinct orientations, denoted by $Y_1$ and $Y_2$, and catalytically produces the target species $X$. Panel (b) displays the underlying strand-displacement reactions, enclosed in the red quadrilateral in panel (a), in a greater detail. Here, three arms of the four-armed Holliday junction molecule are extended with single-stranded DNA overhangs (grey and blue strands on $Y_1$ and $Y_2$). The DNA overhangs pairwise connect with each other, forming associated DNA overhangs, which consist of a toehold and a branch-migration domain, shown in grey and blue on $Y_1$ and $Y_2$, respectively, which are separated by a duplex. The association-activated toeholds bind to an auxiliary double-stranded DNA, called the precursor species and denoted by $\bar{X}$, thus initiating the release of the target molecule $X$ via suitable strand-displacement reactions, whose rates are controlled by the toehold lengths. Species $Y_1$ and $Y_2$ are then recovered using additional suitable strand-displacement reactions.

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6 Discussion

In this paper, we have introduced a biochemical controller, called stochastic morpher and presented in Algorithm 1 in Section 1, which, when embedded into a black-box input reaction network with stochastic dynamics, overrides the input reactions and gradually transforms (morphs) the long-time probability mass function (PMF) of the target species into a desired predefined form. Morphing an input PMF consists of a sequence of intermediate probability distributions which increasingly resemble the desired output form, and which are parametrized by suitable time-scale separations between the stochastic morpher and the input network. We have put forward two forms of the stochastic morpher: the lower- and higher-resolution controllers, given by (3) ∪ (4) and (3) ∪ (5) in Algorithm 1 respectively. The lower-resolution controller morphs a given input PMF into the space spanned by non-negative linear combinations of the Poisson distribution basis, allowing one to achieve multi-modal PMFs (weak control), and to manipulate average timing and the mode-switching pattern of the underlying multi-stable sample paths (strong control). On the other hand, the higher-resolution controller allows one to achieve arbitrary PMFs defined on bounded-domains. General properties of the controller, including asymptotic robust perfect adaptation and convergence, are rigorously established in Appendix B using singular perturbation theory. The stochastic morpher is envisaged for experimental implementations involving cell-like vesicle in vitro, and biological cells in vivo, where the lower species copy-numbers can be exploited for gaining control over the dynamics of desired biochemical species.

In Section 2 the lower-resolution stochastic morpher has been applied on the one-species production-degradation test network (7), in order to achieve a desired uni-, bi- and tri-modality, as well as to control the timing and pattern of the stochastic switching in the underlying sample paths, as shown in Figure 2. We have also applied the higher-resolution controller, in order to achieve a PMF concentrated at a single state (Kronecker-delta distribution), a uniform PMF, and a hybrid combination of Poisson and Kronecker-delta distributions, which is displayed in Figure 3. In Section 3 we have focused on the lower-resolution control in greater detail, by considering the three-species test network (16), whose stationary PMF is bi-modal. The stochastic morpher has been utilized to jointly explicitly control two, out of three, input species. In particular, the input marginal-PMF of the target species has been suitably redistributed, ensuring that the correlation between the two target species reverses from negative to positive, as shown in Figure 4(a)–(f). The error between the output PMF and its target form has been numerically shown to decrease linearly with the underlying asymptotic parameter in Figure 4(g), in agreement with the theoretical convergence result established in Appendix B. Finally, the dynamics of the remaining, residual, species in the output network have been shown to match well with the theoretically derived residual network (19), as demonstrated in Figure 4(h). In Section 4 we have applied Algorithm 1 on the two-species test network (20), inspired by the process of gene expression, in order to obtain an implicit, rather than explicit, control. More specifically, the stochastic morpher has been used to explicitly influence a target species (interpreted as a transcribed mRNA), in order to implicitly control a residual species (interpreted as a translated protein). It has been shown that such an approach can be used to induce multi-modality into the residual species, with controllable relative separation between the modes, as displayed in Figure 5. Finally, in Section 5 as a proof-of-concept, we have put forward a blueprint for a DNA-strand-displacement-based experimental realization of the stochastic morpher (10), involving encapsulation of a suitable DNA complex inside nano-scale vesicles [9, 56, 53]. The experimental scheme, which may be seen as designing a synthetic cell, is outlined in Figure 6 and will be pursued in a future publication.
Let us complete this section with four remarks. Firstly, the stochastic morpher has been inspired by a design principle from systems biology, called noise-induced mixing [42], and its operation requires that the interfacing network $R^\gamma$, shown in red in Figure 1 in Section 1, fires sufficiently fast, with the controlling species, present at a single copy-number, being catalysts in $R^\gamma$. Such fast-slow dynamics (time-scale separations) are ubiquitous and central in many natural biochemical networks from systems biology [43, 14, 15, 10, 11, 12, 13, 20, 12]. It is then no surprise that time-scale separations are necessary when abstract biochemical networks are physically realized using molecules [7], and that fast-slow dynamics also play a role in other biochemical controllers developed in the literature [44, 45]. Furthermore, control achieved via single (or, more generally, low and tightly regulated) molecular copy-numbers is also utilized by some natural biochemical systems, such as gene-regulatory networks involving expression of a single copy-number of a gene, and it is then no surprise that such a property is also desirable in stochastic synthetic controllers. Secondly, the lower- and higher-resolution stochastic morphers from Algorithm 1 achieve PMFs that are linear combinations involving suitable bases. The bases are determined purely by the networks $R^\beta_P$ and $R^\delta_\gamma$, while the weights in the underlying linear combinations are determined purely by $R^\beta(\mathcal{Y})$, see also Appendix B.2. The latter network, which is given by [3], consists of the reaction $2Y_1 \rightarrow Y_1$, and a periodic chain of irreversible first-order conversion reactions between the controlling species $\mathcal{Y} = \{Y_1, Y_2, \ldots, Y_M\}$. However, one can replace [3] with more general weakly reversible chains of first-order conversion reactions between the species $\mathcal{Y}$, such as $2Y_1 \rightarrow Y_1 \rightleftharpoons Y_2 \rightleftharpoons \ldots \rightleftharpoons Y_M$. Such different choices of $R^\beta$ only modify the functional form of the weights in the PMFs achieved by Algorithm 1 and not the bases, and hence do not qualitatively change the weak control put forward in this paper. An advantage of the particular choice [3] is when strong control is desired, since it allows one to deterministically control the mode-switching pattern of the multi-stable sample paths underlying the achieved PMFs, see also Section 2 and Appendix B.2. Thirdly, the interfacing networks $R^\beta_P(\mathcal{X}_\tau; \mathcal{Y})$ and $R^\delta(\mathcal{X}_\tau, \mathcal{Z}; \mathcal{Y})$ from Algorithm 1 do not contain a feedback loop between the target species $\mathcal{X}_\tau$ and the controlling species $\mathcal{Y}$, making the stochastic morpher an open-loop controller in the control theory language [58]. One can straightforwardly create a feedback loop between $\mathcal{X}_\tau$ and $\mathcal{Y}$ by e.g. introducing some of the target species into the network $R^\gamma$, thus resulting in a closed-loop controller. Such feedback loops change only the weights of the PMFs achieved by the stochastic morpher, and not the bases in which the PMFs are expressed. However, in this case, the weights do not only depend on the rate coefficients from the network $R^\beta$, but also on the coefficients from the networks $R^\beta_P$ and $R^\delta$. Such mixed dependence may be seen as a disadvantage, since then e.g. the distribution of the modes and the values of the achieved PMF at the modes cannot be controlled independently. Finally, in the absence of an input network, $R_\alpha = \emptyset$, Algorithm 1 may be utilized to design, rather than control, biochemical reaction networks with predefined PMFs. Furthermore, noise-induced mixing can also be exploited for achieving other dynamical features, such multi-cyclicity (coexistence of multiple stable oscillations), see [42].

7 Acknowledgements

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A Appendix: Background

Notation. Set $\mathbb{R}$ is the space of real numbers, $\mathbb{R}_\geq$ the space of nonnegative real numbers, and $\mathbb{R}_>$ the space of positive real numbers. Similarly, $\mathbb{Z}$ is the space of integer numbers, $\mathbb{Z}_\geq$ the space of nonnegative integer numbers, and $\mathbb{Z}_>$ the space of positive integer numbers. Given two appropriate sequences $p(\cdot) : \mathbb{Z}_\geq^N \to \mathbb{R}$ and $u(\cdot) : \mathbb{Z}_\geq^N \to \mathbb{R}$, the $l^1$-norm of $p(x)$ is given by $\|p\|_1 = \sum x|p(x)|$, while the $l^2$ (Hilbert sequence space) inner-product of $p(x)$ and $u(x)$ is given by $(p,u)_1 = \sum x p(x) u(x)$. Euclidean row-vectors are denoted in boldface, $\mathbf{x} = (x_1, x_2, \ldots, x_N) \in \mathbb{R}^N = \mathbb{R}^{1 \times N}$. Given a function $f(\cdot) : \mathbb{Z}_\geq \to \mathbb{R}$, we define the product $\prod_{i=a}^{b} f(i) = f(a)f(a+1)\ldots f(b) \equiv 1$ if $a > b$. We also define $0^0 \equiv 1$. Given sets $\mathcal{A}_1$ and $\mathcal{A}_2$, their union is denoted by $\mathcal{A}_1 \cup \mathcal{A}_2$, their difference by $\mathcal{A}_1 \setminus \mathcal{A}_2$, while their Cartesian-product, abusing the notation slightly, by $\prod_{j=1}^{2} \mathcal{A}_j \equiv \mathcal{A}_1 \times \mathcal{A}_2$. The empty set is denoted by $\emptyset$.

A.1 Biochemical reaction networks

In this paper, we consider reaction networks $\mathcal{R}_\alpha$ firing in well-mixed unit-volume reactors under mass-action kinetics, involving $N$ biochemical species $\mathcal{X} = \{X_1, X_2, \ldots, X_N\}$, and $A$ reactions, given by [11]

$$\mathcal{R}_\alpha(\mathcal{X}) : \sum_{l=1}^{N} \nu_{j,l} X_l \xrightarrow{\alpha_j} \sum_{l=1}^{N} \bar{\nu}_{j,l} X_l, \quad j \in \{1, 2, \ldots, A\}. \quad (24)$$

Here, $\alpha_j \in \mathbb{R}_>$ is the rate coefficient of the $j$th reaction, and $\nu_{j,l}, \bar{\nu}_{j,l} \in \mathbb{Z}_\geq$ are the reactant and product stoichiometric coefficients of the species $X_l$ in the $j$th reaction, respectively. When all of the reactant (product) stoichiometric coefficients are equal to zero in a reaction, the reactant (product) is the zero-species, denoted by $\emptyset$, which represents species which are not explicitly modelled.

When convenient, we indicate dependence of a reaction network on species of interest, e.g. to emphasize that $\mathcal{R}_\alpha$ involves species $\mathcal{X}$, we have written $\mathcal{R}_\alpha = \mathcal{R}_\alpha(\mathcal{X})$ in [24]. We collect all of the rate coefficients into the vector $\alpha = (\alpha_1, \alpha_2, \ldots, \alpha_A) \in \mathbb{R}^A$. We follow the convention of denoting the (vector of the) rate coefficients of the reactions underlying a reaction network using the same letter as the network subscript. In addition, fixing a reaction coefficient to zero is defined as deleting the corresponding reaction from the underlying network. Furthermore, we define the reactant and product complexes of the $j$th reaction from [24] as the vectors $\nu_j = (\nu_{j,1}, \nu_{j,2}, \ldots, \nu_{j,N}) \in \mathbb{Z}_\geq^N$ and $\bar{\nu}_j = (\bar{\nu}_{j,1}, \bar{\nu}_{j,2}, \ldots, \bar{\nu}_{j,N}) \in \mathbb{Z}_\geq^N$, respectively, and, abusing the notation slightly, denote the $j$th reaction by $\nu_j \rightarrow \bar{\nu}_j \in \mathcal{R}_\alpha$, when convenient. Reactions with the same reactant and product complexes, $(\nu_j \rightarrow \bar{\nu}_j)$ (such as the one obtained by taking $M = 1$ in [3] from Algorithm [1]) are redundant, and are deleted from reaction networks. We denote two irreversible reactions $(\nu \rightarrow \nu) \in \mathcal{R}_\alpha$ and $(\nu \rightarrow \nu) \in \mathcal{R}_\alpha$ jointly as the single reversible reaction $(\nu \rightleftharpoons \bar{\nu}) \in \mathcal{R}_\alpha$, when convenient.

Reaction vector of the $j$th reaction is defined as $\Delta x_j = (\bar{\nu}_j - \nu_j) \in \mathbb{Z}^N$. The order of reaction $(\nu_j \rightarrow \bar{\nu}_j) \in \mathcal{R}$ is given by $(1, \nu_j) \in \mathbb{Z}_\geq$, with $1 = (1, 1, \ldots, 1) \in \mathbb{Z}^N$. The order of reaction network $\mathcal{R}_\alpha$ is given by the order of its highest-order reaction.

A.2 The stochastic model of reaction networks

We consider reaction networks with discrete species counts, and stochastic dynamics. Let $x = (x_1, x_2, \ldots, x_N) \in \mathbb{Z}_\geq^N$ denote the discrete state-vector of the species $\mathcal{X} = \{X_1, X_2, \ldots, X_N\}$ from [24], where element $x_l \in \mathbb{Z}_\geq$ denotes the copy-number values of the species $X_l$. Abusing the notation slightly, we denote the copy-numbers of the biochemical species $X_l$ as a function
of time using the same symbol, $X_t(t)$, where $t \in \mathbb{R}_\geq$ is the time-variable. A suitable stochastic description models the time-evolution of the species copy-number vector as a continuous-time discrete-space Markov chain $[19]$. The underlying probability-mass function (PMF) satisfies the partial difference-differential equation, called the chemical master equation (CME) $[59, 60, 61]$, given by

$$\frac{\partial}{\partial t} p(x, t) = \mathcal{L}_\alpha p(x, t) = \sum_{j=1}^{A} (E_x^{-\Delta x_j} - 1) (\lambda_j(x)p(x, t)), \quad (25)$$

where $p(x, t)$ is the PMF, i.e. the probability that the copy-number vector at time $t > 0$ is given by $x \in \mathbb{Z}_\geq^N$. Here, the step operator $E_x^{-\Delta x} = \prod_{l=1}^{N} E_{x_l}^{-\Delta x_l}$ is such that $E_x^{-\Delta x} p(x, t) = p(x - \Delta x, t)$. The function $\lambda_j(x)$ is the propensity (rate) function of the $j$-th reaction, and is given by

$$\lambda_j(x) = \alpha_j x^{\nu_j} \equiv \alpha_j \prod_{l=1}^{N} x_l^{\nu_{j,l}}, \quad x \in \mathbb{Z}_\geq^N, \quad \text{ (26)}$$

where $\alpha_j \in \mathbb{R}_\geq$ is the rate coefficient of the reaction $(\nu_j \rightarrow \bar{\nu}_j) \in \mathcal{R}_\alpha$. Here, $x^\nu = x(x-1)(x-2)\ldots(x-\nu+1) \in \mathbb{Z}_\geq^N$ for $x, \nu \in \mathbb{Z}_\geq$, denotes the $\nu$-th factorial power of $x$, with the convention that $x^0 \equiv 1$ for all $x \in \mathbb{Z}_\geq$.

The linear operator $\mathcal{L}_\alpha$ from $[25]$ is called the forward operator of the network $\mathcal{R}_\alpha(\mathcal{X})$, given by $[24]$. The $l^2$-adjoint operator of $\mathcal{L}_\alpha$, denoted by $\mathcal{L}_\alpha^*$ and called the backward operator $[62]$, is given by

$$\mathcal{L}_\alpha^* u(x) = \sum_{j=1}^{A} \lambda_j(x)(E_x^{+\Delta x_j} - 1) u(x). \quad \text{ (27)}$$

A function $p(x)$ satisfying $\mathcal{L}_\alpha p(x) = 0$, i.e. $p(x) \in \mathcal{N}(\mathcal{L}_\alpha)$, where $\mathcal{N}(\cdot)$ denotes the null-space of an operator, is called a stationary PMF of the network $\mathcal{R}_\alpha(\mathcal{X})$.

### A.3 Biochemical control

The aim of biochemical control theory $[46, 47, 24, 20, 12, 45]$ is to suitably modify a given reaction network in order to desirably influence the dynamics of a subset of the underlying species. It is implicitly assumed that the given network, which we wish to control, has at most partially known structure, and some of its rudimentary dynamical features, such as an averaged (mean) behavior or the time-scales at which the underlying reactions fire, may also be known.

**Definition A.1 (Black-box).** Reaction network $\mathcal{R}_\alpha(\mathcal{X})$, whose fixed structure (the set of reactions underlying the network) and the induced dynamics are at most partially known, is called a black-box network.

In this paper, it is assumed we are given a black-box reaction network under mass-action kinetics, denoted by $\mathcal{R}_\alpha = \mathcal{R}_\alpha(\mathcal{X})$, called an input (uncontrolled) network, which depends on $N$ biochemical species $\mathcal{X} = \{X_1, X_2, \ldots, X_N\}$, and has the form $[24]$. The input species are partitioned into $\mathcal{X} = \mathcal{X}_t \cup \mathcal{X}_r$, where $\mathcal{X}_t = \{X_1, X_2, \ldots, X_n\}$, $1 < n \leq N$, are the target species, whose dynamics we wish to explicitly control. On the other hand, the remaining species $\mathcal{X}_r = \mathcal{X} \setminus \mathcal{X}_t = \{X_{n+1}, X_{n+2}, \ldots, X_N\}$, are the residual species, whose dynamics may only be implicitly, but not explicitly, controlled.
In order to control a black-box input network $\mathcal{R}_\alpha(\mathcal{X})$, an auxiliary mass-action reaction network is embedded, called a controller network, and denoted by $\mathcal{R}_{\beta,\gamma} = \mathcal{R}_{\beta,\gamma}(\mathcal{X}_r, \mathcal{Y}, \mathcal{Z})$. The resulting composite network is denoted by $\mathcal{R}_{\alpha,\beta,\gamma} = \mathcal{R}_\alpha \cup \mathcal{R}_{\beta,\gamma}$, and called an output (controlled) network. Here, generally two sets of auxiliary species are introduced by the controller: $\mathcal{Y} = \{Y_1, Y_2, \ldots, Y_M\}$, called the controlling species, and $\mathcal{Z}$, called the mediating species. The controller can be decomposed into two sub-networks, $\mathcal{R}_{\beta,\gamma}(\mathcal{X}_r, \mathcal{Y}, \mathcal{Z}) = \mathcal{R}_\beta(\mathcal{Y}) \cup \mathcal{R}_\gamma(\mathcal{X}_r, \mathcal{Y}, \mathcal{Z})$, where $\mathcal{R}_\beta = \mathcal{R}_\beta(\mathcal{Y})$ specifies how the controlling species interact among themselves, while $\mathcal{R}_\gamma = \mathcal{R}_\gamma(\mathcal{X}_r, \mathcal{Y}, \mathcal{Z})$ specifies how the controller is interfaced with the input network. More precisely, the interfacing network $\mathcal{R}_\gamma(\mathcal{X}_r, \mathcal{Y}, \mathcal{Z})$ describes how the controlling species interact with the target species $\mathcal{X}_r$, either directly $(\mathcal{Z} = \emptyset)$, or indirectly via the mediating species $(\mathcal{Z} \neq \emptyset)$. Control of an input network in the absence of the mediating species is schematically depicted in Figure 1 in the main text.

We denote the vectors of the rate coefficients from the networks $\mathcal{R}_\alpha$, $\mathcal{R}_\beta$ and $\mathcal{R}_\gamma$ by $\alpha \in \mathbb{R}_+^A$, $\beta \in \mathbb{R}_+^B$ and $\gamma \in \mathbb{R}_+^C$, respectively. It is assumed that $\alpha$ is a given constant (fixed) vector (since the input network is a black-box), while $\beta$ and $\gamma$ are (variable) parameters (since we assume the kinetics of the controller are tunable). Furthermore, for fixed initial conditions, we denote the stationary marginal PMF of the target species from the output network $\mathcal{R}_{\alpha,\beta,\gamma}$, assumed to exist, by $p(x_r) = p(x_r, \beta, \gamma; \alpha)$, where $x_r = (x_1, x_2, \ldots, x_n) \in \mathbb{Z}_+^n$ are the copy-numbers of the target species $\mathcal{X}_r$.

**Controllability and robustness**

The objective of a controller network $\mathcal{R}_{\beta,\gamma}$, which is embedded into an input network $\mathcal{R}_\alpha$, is to ensure that the target species $\mathcal{X}_r$ from the resulting output network $\mathcal{R}_{\alpha,\beta,\gamma}$ have suitably controlled stochastic dynamics. Control may be sought at the level of the PMF (which we call weak control), or at the level of the underlying sample paths (which we call strong control). In this paper, we focus predominantly on the weak control over the stationary (long-time) dynamics, which is of most practical importance, and is achieved by manipulating the properties of the stationary marginal PMF of the target species, $p(x_r, \beta, \gamma; \alpha)$, such as the underlying means and modes. In particular, we consider linear functionals of the form $\mathbb{E}_{f_{x_r}} = \mathbb{E}_{f_{x_r}}(\beta, \gamma; \alpha) = \sum_{x_r} f_{x_r}(x_r)p(x_r, \beta, \gamma; \alpha)$, where $f_{x_r} : \mathbb{Z}_+^n \to \mathbb{R}$ is a suitable function of the target species, and $\mathbb{E}$ is the expectation operator with respect to the PMF $p(x_r, \beta, \gamma; \alpha)$.

**Definition A.2 (Controllability).** Consider an input network $\mathcal{R}_\alpha(\mathcal{X})$, a controller $\mathcal{R}_{\beta,\gamma}(\mathcal{X}_r, \mathcal{Y}, \mathcal{Z})$, and the corresponding output network $\mathcal{R}_{\alpha,\beta,\gamma}(\mathcal{X}, \mathcal{Y}, \mathcal{Z}) = \mathcal{R}_\alpha(\mathcal{X}) \cup \mathcal{R}_{\beta,\gamma}(\mathcal{X}_r, \mathcal{Y}, \mathcal{Z})$, where $\mathcal{X}_r = \{X_1, X_2, \ldots, X_n\} \subseteq \mathcal{X}$ are the target species. The range of the stationary statistic $\mathbb{E}_{f_{x_r}}(\beta, \gamma; \alpha)$ for each fixed $\alpha \in \mathbb{R}_+^A$ is denoted by $S_f^\alpha \subseteq \mathbb{R}$, i.e. $\mathbb{E}_{f_{x_r}}(\beta, \gamma; \alpha) : \mathbb{R}_+^B \times \mathbb{R}_+^C \to S_f^\alpha \subseteq \mathbb{R}$, and is called the set of admissible values of $\mathbb{E}_{f_{x_r}}(\beta, \gamma; \alpha)$. For a fixed $\alpha \in \mathbb{R}_+^A$, given a target value $f^* \in \mathbb{R}$, the statistic $\mathbb{E}_{f_{x_r}}(\beta, \gamma; \alpha)$ is said to be controllable if $f^* \in S_f^\alpha$.

The set of admissible values $S_f^\alpha$ depends on both the structure and rate coefficients $\alpha$ of the input network $\mathcal{R}_\alpha$. Given a suitable function $f_{x_r}(x_r)$, the goal is to find a controller with an appropriate structure, and suitably tuned rate coefficients, which manipulates the stationary $x_r$-marginal PMF so that the target value $f^*$ lies within the range of the underlying statistic of interest.

We are interested in the output networks which are experimentally implementable, which imposes a set of constraints on the controllers, some of which are captured in the following definition.

**Definition A.3 (Robustness).** A controller $\mathcal{R}_{\beta,\gamma}(\mathcal{X}_r, \mathcal{Y}, \mathcal{Z})$ is said to be robust, when embedded into an input network $\mathcal{R}_\alpha(\mathcal{X})$, if both of the following two conditions are satisfied:
(a) **Robustness with respect to the initial conditions.** The stationary marginal-PMF of the target species $\mathcal{X}_\tau$, from the output network $\mathcal{R}_{\alpha,\beta,\gamma}(\mathcal{X}, \mathcal{Y}, \mathcal{Z})$, exists and is unique, i.e. it is independent of the initial conditions for the species $\mathcal{X}$, $\mathcal{Y}$ and $\mathcal{Z}$, for a given fixed $\alpha$.

(b) **Robustness with respect to the input coefficients.** The controlled stationary statistic $\mathbb{E}_f_{x_{\tau}}$ of the target species $\mathcal{X}_\tau$, from the output network $\mathcal{R}_{\alpha,\beta,\gamma}(\mathcal{X}, \mathcal{Y}, \mathcal{Z})$, does not explicitly depend on the parameters $\alpha$ from the input network $\mathcal{R}_\alpha(\mathcal{X})$ (possibly only in an asymptotic limit of some of the rate coefficients from the controller), i.e. $\mathbb{E}_f_{x_{\tau}} = \mathbb{E}_f_{x_{\tau}}(\beta, \gamma)$.

Definition [A.3](a) demands that the marginal stochastic process, underlying the dynamics of the target species, is ergodic. On the other hand, Definition [A.3](b) ensures that the desired stationary statistics of the species $\mathcal{X}_\tau$ depend parametrically only on the rate coefficients appearing in the controller, which are experimentally tunable, allowing one to treat the underlying input network as a black-box. Let us note that if the stationary $x_{\tau}$-marginal PMF $p(x_{\tau}, \beta, \gamma; \alpha)$ is independent of the initial conditions, then the same is true for the stationary statistic $\mathbb{E}_f_{x_{\tau}} = \sum_{x_{\tau}} f_{x_{\tau}}(x_{\tau}) p(x_{\tau}, \beta, \gamma; \alpha)$, i.e. the stability condition (a) from Definition [A.3](a) also ensures stability of the underlying statistics. We allow non-uniqueness of the stationary marginal-PMF for the residual species $\mathcal{X}_\gamma$, thereby including a larger class of input networks $\mathcal{R}_\alpha$ into considerations, see also Example [B.2](a) in Appendix [B.3](b).

If condition (b) from Definition [A.3](b) is satisfied independently of the values of the rate coefficients from the controller, then the corresponding statistic is said to display **robust perfect adaptation** [34, 35]. On the other hand, if condition (b) from Definition [A.3](a) is satisfied only in an asymptotic limit of some of the rate coefficients from the controller, then we say that the statistic displays **asymptotic robust perfect adaptation.** Note that (asymptotic) robust perfect adaptation is experimentally implementable, and allows one to treat the input network as a black-box. This is in contrast to non-robust perfect adaptation, which requires fine-tuning of the rate coefficients $\beta$ and $\gamma$ of the controller to specific values, which depend on the unknown rate coefficients $\alpha$ of the black-box input network $\mathcal{R}_\alpha$.

**B Appendix: Dynamical analysis of the stochastic morpher**

In this paper, we consider controllers of the form $\mathcal{R}_{\beta,\gamma} = \mathcal{R}_{\beta,\gamma}(\mathcal{X}_\tau, \mathcal{Y}) = \mathcal{R}_{\beta,\gamma}(\mathcal{Y}) \cup \mathcal{R}_\gamma(\mathcal{X}_\tau; \mathcal{Y})$, giving rise the output networks

$$\mathcal{R}_{\alpha,\beta,\gamma}(\mathcal{X}, \mathcal{Y}) = \mathcal{R}_\alpha(\mathcal{X}) \cup \mathcal{R}_{\beta}(\mathcal{Y}) \cup \mathcal{R}_\gamma(\mathcal{X}_\tau, \mathcal{Y}).$$

(28)

The interfacing network $\mathcal{R}_\gamma = \mathcal{R}_\gamma(\mathcal{X}_\tau; \mathcal{Y})$ from [28] is assumed to take the following separable form

$$\mathcal{R}_\gamma(\mathcal{X}_\tau; \mathcal{Y}) = \mathcal{R}_\gamma(\mathcal{X}_\tau; \emptyset) \bigcup_{i=1}^{M} \mathcal{R}_\gamma(\mathcal{X}_\tau; \gamma_i),$$

(29)

where the sub-network $\mathcal{R}_\gamma = \mathcal{R}_\gamma(\mathcal{X}_\tau; \emptyset)$ depends on the species $\mathcal{X}_\tau$ and is independent of $\mathcal{Y}$, while each factor $\{\mathcal{R}_\gamma = \mathcal{R}_\gamma(\mathcal{X}_\tau; \gamma_i)\}_{i=1}^{M}$ consists exclusively of reactions which are catalyzed by the species $Y_i$. More precisely, the $j$th reaction from the sub-network $\mathcal{R}_\gamma$, denoted by $r_{ij}$, is given
by
\[ r_{0,j} : \sum_{l=1}^{n} \nu_{0,j,l} X_l \xrightarrow{\gamma_{0,j}/\varepsilon} \sum_{l=1}^{n} \bar{\nu}_{0,j,l} X_l, \]
\[ r_{i,j} : Y_i + \sum_{l=1}^{n} \nu_{i,j,l} X_l \xrightarrow{\gamma_{i,j}/\varepsilon} Y_i + \sum_{l=1}^{n} \bar{\nu}_{i,j,l} X_l, \quad 0 < \varepsilon \ll 1, \quad \text{for } i \in \{1, 2, \ldots, M\}. \] (30)

The rate coefficients \( \alpha, \beta, \) and \( \varepsilon^{-1} \gamma \) of the sub-networks \( \mathcal{R}_\alpha, \mathcal{R}_\beta, \) and \( \mathcal{R}_\gamma, \) respectively, are assumed to be of order one, \( \alpha, \beta, \gamma = \mathcal{O}(1), \) with respect to the small asymptotic parameter \( 0 < \varepsilon \ll 1. \)

In other words, we assume that the network \( \mathcal{R}_\gamma, \) which interfaces the controlling and the target species, fires much faster than the input network and the network governing the controlling species, \( \mathcal{R}_\alpha \) and \( \mathcal{R}_\beta, \) respectively.

Note that the target species \( \mathcal{X}_r \) interact directly with each other in the sub-network \( \mathcal{R}_\gamma^\varepsilon(\mathcal{X}_r; \emptyset), \) and that the auxiliary species \( \mathcal{Y} \) are interfaced directly with \( \mathcal{X}_r, \) as specified by the sub-network \( \bigcup_{i=1}^{M} \mathcal{R}_i^\varepsilon(\mathcal{X}_r; \mathcal{Y}_i). \) As outlined in Appendix A.3, we also consider a generalized case where the mediating species \( \mathcal{Z} \) are present. Such species may play a role of a buffer for indirect interactions between the species \( \mathcal{X}_r, \) or may serve as intermediate species, propagating the action of the controlling species \( \mathcal{Y} \) onto the target species \( \mathcal{X}_r. \) In this paper, we assume that the mediating species, when present, are sufficiently fast, and characterized by the dimensionless time-scale \( \mu, \) with \( 0 < \mu \ll \varepsilon \ll 1, \) and with the interfacing network given by \( \mathcal{R}_{\gamma_i}^{\mu,\varepsilon} = \mathcal{R}_{\gamma_i}^{\mu,\varepsilon}(\mathcal{X}_r; \mathcal{Z}; \emptyset) = \mathcal{R}_{\gamma_i}^{\mu,\varepsilon}(\mathcal{X}_r; \emptyset) \cup_{i=1}^{M} \mathcal{R}_{\gamma_i}^{\mu,\varepsilon}(\mathcal{X}_r; \mathcal{Y}_i). \) More specifically, we consider the interfacing network \( \mathcal{R}_\gamma \) from Algorithm 1 for which \( \mathcal{R}_{\gamma_i}^{\mu,\varepsilon} \to \mathcal{R}_\gamma^{\varepsilon} \) as \( \mu \to 0, \) i.e. the indirect coupling reduces to an effective direct coupling in the limit \( \mu \to 0, \) as we now establish.

**Theorem B.1.** Consider the network \( \mathcal{R}_\varepsilon(\mathcal{X}_r; \mathcal{Z}; \mathcal{Y}) = \mathcal{R}_{\gamma_0}^{\mu,\varepsilon}(\mathcal{X}_r; \mathcal{Z}; \emptyset) \cup_{i=1}^{M} \mathcal{R}_{\gamma_i}^{\mu,\varepsilon}(\mathcal{X}_r; \mathcal{Z}; \mathcal{Y}_i) \) given by (5) from Algorithm 1. Assume that the rate coefficients from (5) satisfy the kinetic conditions, given by

\[ \mu^{x_{i,j}+1} \left( \prod_{m=1}^{c_{i,j}+1} \gamma_{0,j,m} \right) \gamma_{i,j} = (\varepsilon\sigma)^{-1}, \quad \mu \gamma_{0,j,x_{i,j}}, \mu \gamma_{0,j,c_{j}}, \mu \gamma_{i,j} \ll 1, \]

for \( i \in \{1, 2, \ldots, M\}, \ j \in \{1, 2, \ldots, n\}, \ \{x_{i,j}\}_{i=1}^{M} \in \{1, 2, \ldots, c_{j} - 1\}. \) (31)

with \( c = (c_1, c_2, \ldots, c_n) \in \mathbb{Z}^n. \) Then, as \( \mu \to 0, \) with \( \varepsilon, \sigma = \mathcal{O}(1), \) the PMF of the network \( \mathcal{R}_\varepsilon(\mathcal{X}_r; \mathcal{Z}; \mathcal{Y}) \) converges to the PMF of the network \( \mathcal{R}_\varepsilon(\mathcal{X}_r; \mathcal{Z}; \emptyset) \cup_{i=1}^{M} \mathcal{R}_{\gamma_i}^{\varepsilon,\sigma}(\mathcal{X}_r; \mathcal{Y}_i), \) given by

\[ \mathcal{R}_\varepsilon: \emptyset \xrightarrow{1/\varepsilon} X_j, \quad \text{for } j \in \{1, 2, \ldots, n\}, \]
\[ \mathcal{R}_{\gamma_i}^{\varepsilon,\sigma}: Y_i + (x_{i,j} + 1)X_j \xrightarrow{1/(\varepsilon\sigma)} Y_i + x_{i,j}X_j, \quad \text{for } i \in \{1, 2, \ldots, M\}, \ j \in \{1, 2, \ldots, n\}, \ \{x_{i,j}\}_{i=1}^{M} \in \{0, 1, \ldots, c_{j} - 1\}. \] (32)

**Proof.** See [29]. \( \square \)

### B.1 Perturbation analysis: Limit \( \varepsilon \to 0 \)

The CME induced by the output network (28) is given by

\[ \frac{\partial}{\partial t} p_\varepsilon(x, y, t) = \mathcal{L}_\varepsilon p_\varepsilon(x, y, t) = \left( \frac{1}{\varepsilon} \mathcal{L}_\gamma + (\mathcal{L}_\alpha + \mathcal{L}_\beta) \right) p_\varepsilon(x, y, t), \] (33)
where $\mathcal{L}_\alpha$, $\mathcal{L}_\beta$, and $\mathcal{L}_\gamma$ are the forward operators of the sub-networks $\mathcal{R}_\alpha$, $\mathcal{R}_\beta$, and $\mathcal{R}_\gamma^1$, respectively. Here, $x = (x_1, x_2, \ldots, x_N) \in \mathbb{Z}_+^N$ and $y = (y_1, y_2, \ldots, y_M) \in \mathbb{Z}_+^M$ are the copy-number vectors of the input species $\mathcal{X} = \{X_1, X_2, \ldots, X_N\}$ and the controlling species $\mathcal{Y} = \{Y_1, Y_2, \ldots, Y_M\}$, respectively. Furthermore, we denote the copy-number vectors of the target and residual species, $\mathcal{X}_\tau = \{X_1, X_2, \ldots, X_n\}$ and $\mathcal{X}_\rho = \{X_{n+1}, X_{n+2}, \ldots, X_N\}$, by $x_\tau = (x_1, x_2, \ldots, x_n) \in \mathbb{Z}_+^n$ and $x_\rho = (x_{n+1}, x_{n+2}, \ldots, x_N) \in \mathbb{Z}_+^{N-n}$, respectively.

The CME (33) involves a singularly perturbed forward operator, which we now exploit by considering the following perturbation series (32):

$$p_\varepsilon(x, y, t) = p_0(x, y, t) + \varepsilon p_1(x, y, t) + \ldots + \varepsilon^i p_i(x, y, t) + \ldots, \quad \text{where } i \geq 2. \quad (34)$$

Here, $p_0(x, y, t)$ is required to be non-negative and normalized, and we call it the zero-order PMF, while we require $p_i(x, y, t)$, called an $i$th-order corrector, to be centered, $\langle p_i(x, y, t) \rangle_{x,y} = \sum_{x,y} p_i(x, y, t) = 0$, for $i \in \{1, 2, \ldots\}$. Substituting (34) into (33), and equating terms of equal powers in $\varepsilon$, the following system of equations is obtained:

$$\mathcal{O} \left( \frac{1}{\varepsilon} \right): \mathcal{L}_\gamma p_0(x, y, t) = 0, \quad (35)$$

$$\mathcal{O}(1): \mathcal{L}_\gamma p_1(x, y, t) = \left( \frac{\partial}{\partial t} - (\mathcal{L}_\alpha + \mathcal{L}_\beta) \right) p_0(x, y, t). \quad (36)$$

**Order $1/\varepsilon$ equation (35).** It follows from (29)–(30) that the operator $\mathcal{L}_\gamma$ may be written as the following linear combination

$$\mathcal{L}_\gamma = \mathcal{L}_{\gamma_0} + \sum_{i=1}^M y_i \mathcal{L}_{\gamma_i}, \quad (37)$$

where $\mathcal{L}_{\gamma_i}$ is the forward operator of the sub-network $\mathcal{R}_{\gamma_i}^1(\mathcal{X}_\tau; \emptyset)$ from (29), for $i \in \{0, 1, \ldots, M\}$. Here, $\mathcal{R}_{\gamma_i}^1(\mathcal{X}_\tau; \emptyset)$ is obtained by removing the catalyst $Y_i$ from the reactions underlying $\mathcal{R}_{\gamma_i}^1(\mathcal{X}_\tau; Y_i)$, for $i \in \{1, 2, \ldots, M\}$. Using the fact that $\mathcal{L}_\gamma$ acts only on the copy-numbers of the target species $x_\tau$, and depends parametrically on $y$, the definition of conditional probability implies that $p_0(x, y, t) = p_0(x_\tau|y)p_0(x_\rho, y, t)$, and (35) becomes

$$\left( \mathcal{L}_{\gamma_0} + \sum_{i=1}^M y_i \mathcal{L}_{\gamma_i} \right)p_0(x_\tau|y) = 0. \quad (38)$$

**Order 1 equation (36).** Applying the $l^2$ inner-product $\langle 1, \cdot \rangle_{x_\tau} = \langle \sum_{x_\tau} \cdot \rangle$ on equation (36), and using the fact that $\mathcal{L}_\beta$ acts and depends only on $y$, leads to the solvability condition in a form of an effective CME, describing the time-evolution of the $(x_\rho, y)$-marginal PMF, given by

$$\frac{\partial}{\partial t} p_0(x_\rho, y, t) = (\mathcal{L}_\alpha + \mathcal{L}_\beta) p_0(x_\rho, y, t), \quad \text{where } \mathcal{L}_\alpha = \langle 1, \mathcal{L}_\alpha p_0(x_\tau|y) \rangle_{x_\tau}. \quad (39)$$

This motivates the following definition.

**Definition B.1 (Residual network).** Consider an input network $\mathcal{R}_\alpha$ with the forward operator $\mathcal{L}_\alpha$, embedded into an output network $\mathcal{R}_\beta$. The operator $\mathcal{L}_\alpha = \langle 1, \mathcal{L}_\alpha p_0(x_\tau|y) \rangle_{x_\tau}$ is called the residual forward operator, where $p_0(x_\tau|y)$ satisfies (38). The reaction network induced by $\mathcal{L}_\alpha$ is called the corresponding residual network, and is denoted by $\mathcal{R}_\alpha = \mathcal{R}_\alpha(\mathcal{X}_\rho; \mathcal{Y})$.  

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The residual network $\tilde{\mathcal{R}}_\alpha(\mathcal{X}_\rho; \mathcal{Y})$ is obtained by averaging the input network $\mathcal{R}_\alpha(\mathcal{X})$ over the faster species $\mathcal{X}_\tau$ conditioned on the slower species $\mathcal{Y}$. Note that the controlling species $\mathcal{Y}$ play a catalytic role in the residual network, which we capture with the notation $\tilde{\mathcal{R}}_\alpha = \mathcal{R}_\alpha(\mathcal{X}_\rho; \mathcal{Y})$. See also Theorem B.3 and Section B.3 for more details on the residual networks.

The main object of interest in this paper is the zero-order marginal-PMF of the target species $\mathcal{X}_\tau$, denoted by $p_0(x_\tau, t)$, and given by

$$p_0(x_\tau, t) = \sum_y p_0(y, t)p_0(x_\tau|y).$$

Here, $p_0(x_\tau|y)$ is a solution of (38), while, applying the inner-product $(1, \cdot)_{x_\rho} = (\sum_{x_\rho} \cdot)$ on the equation (39), and using the fact that $\mathcal{L}_\alpha$ acts only on $x_\rho$, it follows that $p_0(y, t)$ satisfies

$$\frac{\partial}{\partial t}p_0(y, t) = \mathcal{L}_\beta p_0(y, t).$$

**B.1.1 Convergence**

We now provide conditions under which the PMF of the output network $\mathcal{R}_{\alpha,\beta,\gamma}$, given by (28), converges to its zero-order approximation from the perturbation series (34), thereby mathematically delineating the class of input networks $\mathcal{R}_\alpha$ which may be controlled with the stochastic morpher $\mathcal{R}_{\beta,\gamma}$.

**Theorem B.2.** Consider the output network $\mathcal{R}_{\alpha,\beta,\gamma} = \mathcal{R}_\alpha \cup \mathcal{R}_\beta \cup \mathcal{R}_\gamma$, given by (28)–(30), on a bounded state-space. Let $p_\varepsilon$ be the PMF of the output network, satisfying (33), and let $p_0$ be the zero-order PMF, satisfying (35). Assume there exists a function $p_1$, satisfying (36), which is bounded, and has a bounded time-derivative, for each time $t \geq 0$, and assume also that $p_\varepsilon = p_0$ initially, at time $t = 0$. Then, $p_\varepsilon \to p_0$ as $\varepsilon \to 0$ over any finite time-interval, with

$$\|p_\varepsilon(x, y, t) - p_0(x, y, t)\|_1 \leq c(T)\varepsilon, \quad \text{for} \ 0 \leq t \leq T, \quad \text{as} \ \varepsilon \to 0,$$

where $c(T)$ is a constant independent of $\varepsilon$.

**Proof.** Let us write the PMF of the output network in the following form:

$$p_\varepsilon(x, y, t) = p_0(x, y, t) + \varepsilon p_1(x, y, t) + r_\varepsilon(x, y, t),$$

where $p_0 = p_0(x, y, t)$ and $p_1 = p_1(x, y, t)$ are the zero-order PMF and a first-order corrector, respectively, satisfying (35)–(36), while $r_\varepsilon = r_\varepsilon(x, y, t)$ is a residual function. Substituting (43) into (33), and using (35)–(36), one obtains a linear non-homogeneous ordinary-differential equation governing the time-evolution of the residual function:

$$\frac{d}{dt}r_\varepsilon(t) - \mathcal{L}_\varepsilon r_\varepsilon(t) = \varepsilon \left( (\mathcal{L}_\alpha + \mathcal{L}_\beta) - \frac{d}{dt} \right) p_1(t),$$

where $p_1(t) = p_1(x, y, t)$ and $r_\varepsilon(t) = r_\varepsilon(x, y, t)$ are interpreted as column-vectors, while $\mathcal{L}_\varepsilon$ as a matrix, on a bounded state-space. Assuming that $p_\varepsilon(0) = p_0(0)$, equation (43) provides an initial condition for the residual function, given by

$$r_\varepsilon(0) = -\varepsilon p_1(0).$$

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The solution to the initial-value problem (44)–(45) is given by

\[ r_\varepsilon(t) = -\varepsilon e^{\mathcal{L}_{1\varepsilon} t} p_1(0) + \varepsilon \int_0^t e^{\mathcal{L}_{1\varepsilon}(t-s)} \left( (\mathcal{L}_\alpha + \mathcal{L}_\beta) - \frac{d}{ds} \right) p_1(s) ds. \]  

(46)

Let \( \| \cdot \|_1 \) denote the \( l^1 \)-norm over the bounded state-spaces of \( x \) and \( y \), as well as the induced matrix-operator norm. Applying \( \| \cdot \|_1 \) on (46), and using the fact that \( \| e^{\mathcal{L}_{1\varepsilon}t} \|_1 = 1 \) [62], one obtains

\[ \| r_\varepsilon(t) \|_1 \leq \varepsilon \left( \| p_1(0) \|_1 + t \sup_{0 \leq s \leq t} \left\| \left( (\mathcal{L}_\alpha + \mathcal{L}_\beta) - \frac{d}{ds} \right) p_1(s) \right\|_1 \right). \]  

(47)

Assuming a first-order corrector \( p_1(t) \) exists, which is bounded, with a bounded time-derivative \( dp_1(t)/dt \), for each fixed \( t \geq 0 \), it follows from (47) that \( r_\varepsilon(t) \to 0 \) as \( \varepsilon \to 0 \) for each fixed \( t \geq 0 \). Furthermore, the residual function is asymptotically given by \( \| r_\varepsilon(t) \|_1 = \mathcal{O}(\varepsilon) \) for sufficiently small \( 0 < \varepsilon \ll 1 \), which, together with equation (43), implies (42). \( \blacksquare \)

### B.2 Lower- and higher-resolution control

In Section B.1, we have established a weak convergence result: under suitable conditions, the time-dependent zero-order PMF approximates well the time-dependent PMF of the general output network \( \mathcal{R}_{\alpha,\beta,\gamma} \), given by (28)–(30), for \( 0 < \varepsilon \ll 1 \), over arbitrarily long (but finite) time-intervals. In what follows, we analyze the stationary (time-independent) zero-order PMF, which, under suitable conditions, approximates well the stationary PMF of the output network for \( 0 < \varepsilon \ll 1 \). Furthermore, we consider two particular classes of the controller: the lower- and higher-resolution stochastic morphers, given by \( \mathcal{R}_\beta(Y) \cup \mathcal{R}_\gamma^P(\mathcal{X}_r;Y) \) and \( \mathcal{R}_\beta(Y) \cup \mathcal{R}_\gamma^S(\mathcal{X}_r,Z;Y) \) in Algorithm 1, respectively. Note that one may also consider other choices for the sub-networks \( \mathcal{R}_\beta \) and \( \mathcal{R}_\gamma \), see [12].

**Network \( \mathcal{R}_\beta \).** Let us choose the sub-network \( \mathcal{R}_\beta \) to be given by [3] in Algorithm 1. The stationary \( y \)-marginal PMF is the normalized solution of \( \mathcal{L}_\beta p_0(y) = 0 \), obtained by setting the left-hand side of (41) to zero. The structure of [3] implies that, in the long-run, its state-space is given by \( \mathcal{S}_y = \{ y \in \{ e_i \}_{i=1}^M | e_i \in \mathbb{R}^M, \text{ for } i \in \{ 1, 2, \ldots, M \} \} \), where \( e_i \) denotes the \( i \)-th standard Euclidean basis vector, whose \( i \)-th element equals one, while the rest are zero. In other words, the long-time state space of [3] is constrained by the linear kinetic conservation law \( \sum_{i=1}^M y_i = 1 \). As a consequence, the stationary PMF of [3] is equivalent to the stationary PMF of the first-order conversion network, with an initial condition being element of \( \mathcal{S}_y \), given by

\[ Y_1 \xrightarrow{\beta_{1,2}} Y_2 \xrightarrow{\beta_{2,3}} Y_3 \xrightarrow{\beta_{3,4}} \ldots \xrightarrow{\beta_{M-1,M}} Y_M \xrightarrow{\beta_{M,1}} Y_1, \quad \text{with} \quad \sum_{i=1}^M Y_i(0) = 1, \]  

(48)

which takes a multinomial product-form [61, 12], given by

\[ p_0(y) = \left( \sum_{l=1}^M (\beta_{l,l+1}(1 - \delta_{l,M}) + \beta_{M,1}\delta_{l,M})^{y_l} \right)^{-1} \prod_{i=1}^M (\beta_{i,i+1}(1 - \delta_{i,M}) + \beta_{M,1}\delta_{i,M})^{y_i}, \]  

(49)

with \( \sum_{i=1}^M y_i = 1 \), and where \( \delta_{x,x_0} \) denotes the Kronecker-delta PMF centered at \( x = x_0 \).

Note that the convergence of \( p_0(y,t) \) to the stationary PMF (49) may be sped-up by increasing the rate coefficient \( \beta_{1,1} \) from the sub-network [3], i.e. by taking \( \beta_{i,j} \ll \beta_{1,1} \), for \( (i,j) \neq (1,1) \). If desired, the convergence rate may be further increased by adding suitable (faster) reactions to [3],...
which also constrain the state-space of the species \( Y \) to \( \mathcal{S}_y \), such as the reactions \( 2Y_i \xrightarrow{\beta_{i,1}} Y_i \) for \( i \in \{2,3,\ldots,M\} \). Note also that the sample paths of the network (48) may be readily characterized. In particular, given that the state of the network (48) is \( y = e_i \), the corresponding holding time (i.e. the time spent in the state \( y = e_i \)) is an exponentially distributed random variable with mean \( 1/\beta_{i,i+1} \) for \( i \in \{1,2,\ldots,M-1\} \) (and \( 1/\beta_{M,1} \) for \( i = M \)), after which the system jumps with probability one (deterministically) to the state \( y = e_{i+1} \) for \( i \in \{1,2,\ldots,M-1\} \) (and \( y = e_1 \) for \( i = M \)). Hence, while re-scaling the rate coefficient vector \( \beta \) does not influence the stationary PMF of the network (48) (this is equivalent to re-scaling the time-variable in (41)), it does modify the behavior of the underlying sample paths, by changing the holding times.

Substituting (49) into (40), one obtains

\[
p_0(x_r) = \sum_{i=1}^{M} p_0(e_i)p_0(x_r|e_i) = \sum_{i=1}^{M} a_i(\beta)p_{\gamma_i}(x_r),
\]

where \( a_i(\beta) \equiv p_0(e_i) \), i.e.

\[
a_i(\beta) = \left( \sum_{l=1}^{M} (\beta_{l,i+1}(1 - \delta_{l,M}) + \beta_{M,1}\delta_{l,M})^{-1} \right)^{-1} (\beta_{i,i+1}(1 - \delta_{i,M}) + \beta_{M,1}\delta_{i,M})^{-1},
\]

and \( p_{\gamma_i}(x_r) \equiv p_0(x_r|e_i) \) is a solution of (38) with \( y = e_i \), i.e.

\[
(L_{\gamma_0} + L_{\gamma_i})p_{\gamma_i}(x_r) = 0, \quad \text{for } i \in \{1,2,\ldots,M\}.
\]

Let us now consider the two choices for the network \( R_\gamma \) from Algorithm 1.

**Theorem B.3.** Consider the input network \( R_\alpha \) with the forward operator \( L_\alpha \), given by (24) and (25), respectively. Consider also a corresponding output network \( R_{\alpha,\beta,\gamma} = R_\alpha \cup R_\beta \cup R_\gamma \), given by (28)–(30), with the sub-network \( R_\beta \) fixed to (3). Then

(i) **Lower-resolution control.** If \( R_\gamma = R_\alpha^P(\mathcal{X}_r; Y) \), where \( R_\alpha^P(\mathcal{X}_r; Y) = R_{\gamma_0}(\mathcal{X}_r; \emptyset) \cup_{i=1}^{M} R_{\gamma_i}(\mathcal{X}_r; Y) \) is given by (4) in Algorithm 1, then the stationary zero-order \( x_r \)-marginal PMF (50) of the output network is given by

\[
p_0(x_r) = \sum_{i=1}^{M} a_i(\beta) \prod_{j=1}^{n} \mathcal{P}(x_j; \frac{\gamma_{i,j}}{\gamma_{0,j}}), \quad \text{for } 0 < \varepsilon \ll 1,
\]

where \( \mathcal{P}(x; \Lambda) \) denotes the Poisson distribution with mean \( \Lambda \), and the coefficients \( \{a_i(\beta)\}_{i=1}^{M} \) are given by (51). Furthermore, the residual forward operator \( \tilde{L}_\alpha^P = L_\alpha \), defined in Definition B.1, is given by

\[
\tilde{L}_\alpha^P = \sum_{j=1}^{A} \left( \mathcal{E}_{x_u}^{\Delta x_{j,\rho}} - 1 \right) \alpha_j \left( \sum_{i=1}^{\rho} \gamma_{i,j} \prod_{l=1}^{n} \left( \frac{\gamma_{l,j}}{\gamma_{0,l}} \right)^{\mu_{j,l}} \prod_{l=n+1}^{N} \frac{\mu_{j,l}}{x_{\rho,l}} \right),
\]

where \( \Delta x_{j,\rho} = (\Delta x_{j,n+1}, \Delta x_{j,n+2}, \ldots, \Delta x_{j,N}) \in \mathbb{Z}^{N-n} \).

(ii) **Higher-resolution control.** If \( R_\gamma = R_\alpha^\delta(\mathcal{X}_r, Z; Y) \), where \( R_\alpha^\delta(\mathcal{X}_r, Z; Y) = R_{\gamma_0}^\delta(\mathcal{X}_r, Z; \emptyset) \cup_{i=1}^{M} R_{\gamma_i}^\delta(\mathcal{X}_r, Z; Y) \) is given by (5) in Algorithm 1, with the truncation vector \( c = (c_1,c_2,\ldots,c_n) \in \)
$Z^n$, and if the kinetic conditions (31) are satisfied, then the stationary zero-order $x_r$-marginal PMF (50) of the output network is given by

$$p_0(x_r) = \sum_{i=1}^{M} a_i(\beta) \prod_{j=1}^{n} \delta_{x_{i,j},x_{i,j}}, \quad \text{for } \{x_{i,j}\}_{i=1}^{M} \in \{0,1,\ldots,c_{j}-1\}, \quad 0 < \mu \ll \varepsilon, \sigma \ll 1, \quad (55)$$

where $\delta_{x,x_0}$ denotes the Kronecker-delta distribution centered at $x = x_0$, and the coefficients $\{a_i(\beta)\}_{i=1}^{M}$ are given by (51). Furthermore, the residual forward operator $\bar{L}^\delta_\alpha = \bar{L}_\alpha$ is given by

$$\bar{L}^\delta_\alpha = \sum_{j=1}^{A} (E^{x_{j,r}-1}_{u} - 1) \alpha_j \left( \sum_{i=1}^{M} y_i \prod_{l=1}^{n} \frac{x_{\nu,j,l}^i}{x_{\nu,j,l}^i} \right) \prod_{l=n+1}^{N} \frac{x_{\nu,j,l}}{x_{\nu,j,l}}. \quad (56)$$

**Proof.** (i) **Lower-resolution control.**

If $R^\varepsilon_\gamma$ is given by (3), then the operators $\{L_{\gamma_i}\}_{i=0}^{M}$ from (37) read

$$L_{\gamma_0} = \sum_{j=1}^{n} (E_x^{n+1} - 1) \gamma_{0,j} x_j,$$

$$L_{\gamma_i} = \sum_{j=1}^{n} (E_x^{n-1} - 1) \gamma_{i,j}, \quad \text{for } i \in \{1,2,\ldots,M\}.$$  

The solution of the equation (52) may be written in the product-form, with each factor being a Poisson PMF:

$$p_{\gamma_i}(x_r) = \prod_{j=1}^{n} \mathcal{P}(x_{j}; \gamma_{i,j}^{\gamma}), \quad \text{for } i \in \{1,2,\ldots,M\}, \quad (57)$$

which, upon substitution into (50), leads to (53). Substituting (57) into the expression for $\bar{L}_\alpha$, given in Definition B.1, and using the fact that $y_iy_j = \delta_{i,j}$, one obtains the residual operator (54).

(ii) **Higher-resolution control.**

**Limit $\mu \rightarrow 0$.** Taking first the limit $\mu \rightarrow 0$, with $\varepsilon,\sigma = O(1)$, the network $R^\varepsilon_\gamma(X_r,Z;Y)$ reduces to the effective network $R^{\varepsilon,\sigma}_\gamma(X_r;Y) = R^{\varepsilon,\sigma}_\gamma(X_r;\emptyset) \cup_{i=1}^{M} R^{\varepsilon,\sigma}_{\gamma_i}(X_r;Y_i)$, given by (32), see Theorem B.1.

**Limit $\varepsilon \rightarrow 0$.** Taking the limit $\varepsilon \rightarrow 0$, with $\sigma = O(1)$, the $x_r$-marginal PMF of the effective output network $R_\alpha \cup R_{\beta} \cup R^{\varepsilon,\sigma}_\gamma$ is given by (50). Equation (52) may be written in the following form

$$\left( \frac{1}{\sigma} L_{\gamma_i} + L_{\gamma_0} \right) p_{\gamma_i}(x_r; \sigma) = 0, \quad \text{for } i \in \{1,2,\ldots,M\}, \quad (58)$$

with the operators $\{L_{\gamma_i}\}_{i=0}^{M}$ given by

$$L_{\gamma_0} = \sum_{j=1}^{n} (E_x^{n-1} - 1),$$

$$L_{\gamma_i} = \sum_{j=1}^{n} (E_x^{n+1} - 1) x_{j}^{(x_{i,j}+1)}, \quad \text{for } i \in \{1,2,\ldots,M\}.$$
Limit $\sigma \to 0$. Substituting the perturbation series:

$$p_{\gamma_i}(x_r; \sigma) = p_{\gamma_i}^0(x_r) + \sigma p_{\gamma_i}^1(x_r) + \ldots + \sigma^j p_{\gamma_i}^j(x_r) + \ldots,$$

where $j \geq 2$, into (58), and equating terms of equal powers in $\sigma$, one obtains

$$O\left(\frac{1}{\sigma}\right): \mathcal{L}_{\gamma_i} p_{\gamma_i}^0(x_r) = 0,$$

$$O(1): \mathcal{L}_{\gamma_i} p_{\gamma_i}^1(x_r) = -\mathcal{L}_{\gamma_0} p_{\gamma_i}^0(x_r).$$

Order $1/\sigma$ equation (59). It follows from the structure of the forward operator $\mathcal{L}_{\gamma_i}$ that the PMF $p_{\gamma_i}^0(x_r)$ takes the product-form

$$p_{\gamma_i}^0(x_r) = \prod_{j=1}^n p_{\gamma_i}^0(x_{j}; x_{i,j}), \quad \text{where } p_{\gamma_i}^0(x_{j}; x_{i,j}) = 0, \text{ for } x_j \geq (x_{i,j} + 1), \ i \in \{1, 2, \ldots, M\}. \quad (61)$$

Order 1 equation (60). The null-space of the backward operator $\mathcal{L}_{\gamma_i}^*$ is given by $\mathcal{N}(\mathcal{L}_{\gamma_i}^*) = \prod_{j=1}^n \{1_{x_j}, \delta_{x_{j},0}, \delta_{x_{j},1}, \ldots, \delta_{x_{j},x_{i,j}-1}\}$, where $1_{x_j}$ denotes functions independent of $x_j$. The Fredholm alternative theorem implies that the solvability conditions are given by $0 = \langle u_j(x_r), \mathcal{L}_{\gamma_0} p_{\gamma_i}^0(x_r) \rangle_{x_r}$, where $u_j(x_r) = u_j(x_1) u_j(x_2) \ldots u_j(x_n) \in \mathcal{N}(\mathcal{L}_{\gamma_i}^*)$. Taking $u(x_j) \in \{1_{x_j}, \delta_{x_{j},0}, \delta_{x_{j},1}, \ldots, \delta_{x_{j},x_{i,j}-1}\}$ and $\{u(x_m) = 1_{x_n}\}_{m=1,m \neq j}$ implies that

$$p_{\gamma_i}^0(x_{j}; x_{i,j}) = 0, \quad \text{for } x_j \leq (x_{i,j} - 1), \ i \in \{1, 2, \ldots, M\}. \quad (62)$$

Conditions (61), (62) jointly imply that $p_{\gamma_i}^0(x_{j}; x_{i,j}) = \delta_{x_{j},x_{i,j}}$, and $p_{\gamma_i}^0(x_r) = \prod_{j=1}^n \delta_{x_{j},x_{i,j}}$, which, upon substitution into (50), leads to (55), while substituting into the definition of $\mathcal{L}_{\alpha}$ leads to (56).

Under the assumption of suitably well-behaved residual networks, Theorem B.3 implies that the stochastic morphers $\mathcal{R}_{\beta}(\mathcal{Y}) \cup \mathcal{R}_{\gamma}^P(\mathcal{X}_r; \mathcal{Y})$ and $\mathcal{R}_{\beta}(\mathcal{Y}) \cup \mathcal{R}_{\gamma}^S(\mathcal{X}_r, \mathcal{Z}; \mathcal{Y})$ are robust, according to Definition A.3. In particular, the $\mathcal{X}_r$-marginal PMFs (53) and (55) depend only on the parameters $\beta$ and $\gamma$ from the controller in the asymptotic limit $\varepsilon \to 0$ (i.e. the $\mathcal{X}_r$-marginal PMFs are independent of the parameters $\alpha$ from the input network), so that the same is true for all of the stationary statistics of the target species $\mathcal{X}_r$.

Assuming convergence, Theorem B.3 ensures that, under the action of the stochastic morpher, the stationary-marginal-PMF of the target species $\mathcal{X}_r$ morphs into a PMF which is a linear combination of appropriate basis functions, whose form and centers depend on the stoichiometry and the rate coefficients $\gamma$ from the interfacing sub-network $\mathcal{R}_\beta^\xi$, while the weights depend on the stoichiometry and the rate coefficients $\beta$ from the sub-network $\mathcal{R}_\beta$. Furthermore, note that by choosing $\mathcal{R}_\beta$ to be given by (3), one also gains a control over the underlying long-time sample paths (strong control), which switch between the modes of the stationary PMF at exponentially distributed random times (whose average is controllable via the rate coefficients $\beta$), but in a predefined deterministic order, owning to the fact that each of the first-order conversion reaction from (3) is irreversible.

More specifically, choosing $\mathcal{R}_\gamma^\xi$ to be the first-order (uni-molecular) network $\mathcal{R}_\gamma^P(\mathcal{X}_r; \mathcal{Y})$, given by (4), allows one to design PMFs in the space spanned by the non-negative linear combinations of the Poisson-product functions. In this space of functions, one may construct PMFs with predefined modes (maxima of the PMFs): the $i$th summand from (53) peaks at $\gamma_i(x_1, x_2, \ldots, x_n) = (\gamma_{i,1}/\gamma_{0,1}, \gamma_{i,2}/\gamma_{0,2}, \ldots, \gamma_{i,n}/\gamma_{0,n})$ with the amplitude given by $a_i(\beta)$, as defined in (51), allowing for the design of reaction networks displaying multi-modality/multi-stability. On the other hand,
choosing $\mathcal{R}_\gamma^\delta$ to be the second-order (bi-molecular) network $\mathcal{R}_\gamma^\delta(\mathcal{X}, \mathcal{Z}; \mathcal{Y})$, given by \([5]\), allows one to construct arbitrary PMFs defined on a bounded-domain, $P(\cdot) : \prod_{i=1}^n [0, c_j - 1] \to [0, 1]$, with the state-space truncation vector $c = (c_1, c_2, \ldots, c_n) \in \mathbb{Z}_+^n$. More precisely, $P(\mathbf{x})$ may be realized with $M = \prod_{i=1}^n c_j$ species $\{\{Z_{j,l}\}_{i=1}^{n_j}\}$ and $\{Y_i\}_{i=1}^M$, and choosing $\beta$ such that $a_i(\beta) = P(\mathbf{x}_i)$ for all $\mathbf{x}_i = (x_{i,1}, x_{i,2}, \ldots, x_{i,n}) \in \prod_{i=1}^n [0, c_j - 1]$. Let us note that the centers of the Poisson distributions are encoded kinetically, i.e. they are determined by the rate coefficients from \([4]\), while the centers of the Kronecker-delta distributions are encoded stoichiometrically, i.e. they are determined by which species $\mathcal{Z}$ is catalysed by $\mathcal{Y}$ in \([5]\).

### B.2.1 Hybrid control

The lower- and higher-resolution networks, $\mathcal{R}_\gamma^P$ and $\mathcal{R}_\gamma^\delta$, respectively, may be combined into a composite hybrid scheme, capable of morphing input PMFs into a mixture of Kronecker-delta and Poisson distributions. In particular, consider the interfacing network $\mathcal{R}_\gamma^e = \mathcal{R}_\gamma^P \cup \mathcal{R}_\gamma^\delta(\mathcal{X}, \mathcal{Z}; \mathcal{Y}) = \mathcal{R}_\gamma^{\mu,\varepsilon,\sigma}(\mathcal{X}, \mathcal{Z}; \mathcal{Y}) \cup_{i=1}^{M_P} \mathcal{R}_\gamma^{\mu,\varepsilon,\sigma}(\mathcal{X}; Y_i) \cup_{i=M_P+1}^{M_P+M_\delta} \mathcal{R}_\gamma^{\mu,\varepsilon,\sigma}(\mathcal{Z}; Y_i)$, with $M_P, M_\delta \in \mathbb{Z}_+$, and

\[
\mathcal{R}_\gamma^{\mu,\varepsilon,\sigma} : \quad \begin{align*}
Z_{j,l} \xrightarrow{1/\mu} X_j, \\
X_j + Z_{j,l} \xrightarrow{\gamma_{j,l}^{\mu,\varepsilon}} Z_{j,l+1}, & \quad \text{for } j \in \{1, 2, \ldots, n\}, \ l \in \{1, 2, \ldots, c_j - 1\}, \\
Y_i \xrightarrow{\gamma_i^{\delta}/\varepsilon} Y_i + X_j, & \quad \text{for } i \in \{1, 2, \ldots, M_P\}, \ j \in \{1, 2, \ldots, n\}, \\
Y_i + X_j \xrightarrow{\gamma_j^{\mu,\varepsilon}} Y_i, & \quad \text{for } i \in \{1, 2, \ldots, M_P\}, \ j \in \{1, 2, \ldots, n\}, \\
Y_i + X_j \xrightarrow{1/\varepsilon} Y_i + Z_{j,1}, & \quad \text{for } i \in \{1, 2, \ldots, M_P\}, \ j \in \{1, 2, \ldots, n\}, \\
y_i + Z_{j,i+1} \xrightarrow{\gamma_{i,j}^{\delta}} Y_i + Z_{j,i+1}, & \quad \text{for } i \in \{M_P + 1, M_P + 2, \ldots, M_P + M_\delta\}, \ j \in \{1, 2, \ldots, n\}, \ \text{for } \{x_{i,j}\}_{i=M_P+1}^{M_P+M_\delta} \in \{0, 1, \ldots, c_j - 1\}. \quad (63)
\]

Assume the kinetic conditions \([31]\) are satisfied by the rate coefficient with the superscript $\delta$ from \([63]\). Then, one can readily show that the stationary zero-order $\mathbf{x}_r$-marginal PMF, on the domain bounded by the truncation vector $c = (c_1, c_2, \ldots, c_n)$, under the hybrid stochastic morpher $\mathcal{R}_\beta(\mathcal{Y}) \cup \mathcal{R}_\gamma^{P,\delta}(\mathcal{X}, \mathcal{Z}; \mathcal{Y})$, with $\mathcal{R}_\beta$ and $\mathcal{R}_\gamma^{P,\delta}$ given by \([3]\) and \([63]\), respectively, is given by

\[
p_0(\mathbf{x}_r) = \sum_{i=1}^{M_P} a_i(\beta) \prod_{j=1}^{n} \mathcal{P}(x_j; \gamma_{i,j}^{\mu,\varepsilon}) + \sum_{i=M_P+1}^{M_P+M_\delta} a_i(\beta) \prod_{j=1}^{n} \delta_{x_{i,j}, x_{i,j}}, \quad \text{for } \{x_{i,j}\}_{i=M_P+1}^{M_P+M_\delta} \in \{0, 1, \ldots, c_j - 1\}, \quad 0 < \mu \ll \varepsilon, \sigma \ll 1, \quad (64)
\]

with the coefficients $\{a_i(\beta)\}_{i=1}^{M_P+M_\delta}$ given by \([51]\). The hybrid controller $\mathcal{R}_\beta(\mathcal{Y}) \cup \mathcal{R}_\gamma^{P,\delta}(\mathcal{X}, \mathcal{Z}; \mathcal{Y})$ designs Poisson PMFs centered at the $M_P$ points $(x_{1}, x_{2}, \ldots, x_{n}) = (\gamma_{i,1}/\bar{\gamma}_{i,1}, \gamma_{i,2}/\bar{\gamma}_{i,2}, \ldots, \gamma_{i,n}/\bar{\gamma}_{i,n}) \in \prod_{i=1}^{n} [0, c_j - 1]$ for $i \in \{1, 2, \ldots, M_P\}$, and Kronecker-delta PMFs centered at the $M_\delta$ points $(x_{1}, x_{2}, \ldots, x_{n}) = (x_{i,1}, x_{i,2}, \ldots, x_{i,n}) \in \prod_{i=1}^{n} [0, c_j - 1]$ for $i \in \{M_P + 1, M_P + 2, \ldots, M_P + M_\delta\}$.

**Example B.1.** Consider the hybrid stochastic morpher $\mathcal{R}_\beta \cup \mathcal{R}_\gamma^{P,\delta} = \mathcal{R}_\beta(Y_1, Y_2) \cup \mathcal{R}_\gamma^{P,\delta}(X, Z_1, Z_2; Y_1, Y_2)$,
given by

\[ R_\beta : \quad 2Y_1 \xrightarrow{\beta_{1,1}} Y_1 \xrightarrow{\beta_{1,2}} Y_2, \]

\[ R_{\gamma,\delta}^P : \quad R_{\gamma_0}^{\mu,\varepsilon,\sigma} : \quad Z_1 \xrightarrow{1/\mu} X, \]

\[ X + Z_1 \xrightarrow{1/\mu} Z_2; \]

\[ \mathcal{R}_{\gamma_1}^\varepsilon : \quad Y_1 \xrightarrow{\gamma_1^P/\varepsilon} Y_1 + X, \]

\[ Y_1 + X \xrightarrow{\gamma_1^P/\varepsilon} Y_1, \]

\[ \mathcal{R}_{\gamma_2}^\mu,\varepsilon,\sigma : \quad Y_2 + X \xrightarrow{\gamma_0^\mu,\varepsilon,\sigma} Y_2 + Z_1, \]

\[ Y_2 \xrightarrow{\mu,\varepsilon,\sigma} Y_2 + X, \]

\[ Y_2 + Z_2 \xrightarrow{\gamma_0^\mu,\varepsilon,\sigma} Y_2 + Z_1, \quad 0 < \mu \ll \varepsilon, \sigma \ll 1. \quad (65) \]

which is obtained from [63] by taking one target species \( X \equiv X_1 \), two controlling species \( Y_1 \) and \( Y_2 \), and two mediating species \( Z_1 \) and \( Z_2 \). The species \( Y_1 \) is responsible for creating a Poisson distribution centered at \( x = (\gamma_1^P/\gamma_1^P) \), while \( Y_2 \) generates a Kronecker-delta distribution centered at \( x = 1 \). In particular, under the kinetic conditions, the controller (65) morphs an input PMF into a bi-modal one, given by

\[ p_0(x) = \left(1 + \frac{\beta_{2,1}}{\beta_{1,2}}\right)^{-1} P\left(x; \frac{\gamma_1^P}{\gamma_1^P}\right) + \left(1 + \frac{\beta_{1,2}}{\beta_{2,1}}\right)^{-1} \delta_{x,1}, \quad \text{for } 0 < \mu \ll \varepsilon, \sigma \ll 1. \quad (66) \]

See Figure 3(c)–(d) in the main text for the plots of the stochastic morphing induced when the hybrid controller (65) is embedded into the input network (7).

### B.3 Residual networks

The residual network under the lower-resolution control, denoted by \( \mathcal{R}_\alpha^P(\mathcal{X}_\rho; \mathcal{Y}) = \mathcal{R}_\alpha^P \), is induced by the effective forward operator (54), and given by

\[ \mathcal{R}_\alpha^P(\mathcal{X}_\rho; \mathcal{Y}) : \quad \sum_{l=n+1}^N \nu_{j,l} X_l + (1 - \delta_{\sum_{l=1}^n \nu_{j,l,0}})Y_i \xrightarrow{\alpha_j \prod_{l=1}^n (\gamma_{i,l}/\gamma_{0,l})^{\nu_{j,l}}} \sum_{l=n+1}^N \nu_{j,l} X_l + (1 - \delta_{\sum_{l=1}^n \nu_{j,l,0}})Y_i, \]

for \( i \in \{1, 2, \ldots, M\}, \quad j \in \{1, 2, \ldots, A\}. \quad (67) \]

In other words, if the reactant complex in the \( j \)th reaction from the input network \( \mathcal{R}_\alpha \) contains no target species \( \mathcal{X}_\tau \) (i.e. \( \delta_{\sum_{l=1}^n \nu_{j,l,0}} = 1 \), and \( \prod_{l=1}^n (\gamma_{i,l}/\gamma_{0,l})^{\nu_{j,l}} = 1 \) for each \( i \in \{1, 2, \ldots, M\} \)), then such a reaction becomes the \( j \)th reaction in the residual network, without any modifications. Otherwise, the \( j \)th reaction from the input network gives rise to a family of \( M \) reactions in the corresponding residual network, as given by (67).

Analogously, the residual network under the higher-resolution control, denoted by \( \mathcal{R}_\delta^\mu(\mathcal{X}_\rho; \mathcal{Y}) = \mathcal{R}_\delta^\mu \), is induced by (56), and reads

\[ \mathcal{R}_\delta^\mu(\mathcal{X}_\rho; \mathcal{Y}) : \quad \sum_{l=n+1}^N \nu_{j,l} X_l + (1 - \delta_{\sum_{l=1}^n \nu_{j,l,0}})Y_i \xrightarrow{\alpha_j \prod_{l=1}^n (\gamma_{i,l}/\gamma_{0,l})^{\nu_{j,l}}} \sum_{l=n+1}^N \nu_{j,l} X_l + (1 - \delta_{\sum_{l=1}^n \nu_{j,l,0}})Y_i, \]

for \( i \in \{1, 2, \ldots, M\}, \quad j \in \{1, 2, \ldots, A\}. \quad (68) \]
When going from the input to the residual network, the dynamics of the underlying residual species may undergo qualitative changes. For example, note that the $j$th reaction from the input network may be switched off in the corresponding residual network (68), and this occurs if there exist indices $l \in \{1, 2, \ldots, n\}$ such that $x_{i,l} < \nu_{j,l}$ for each $i \in \{1, 2, \ldots, M\}$. Such changes in the network structure may induce bifurcations in the dynamics of the underlying residual species, which may have biochemical significance. Let us note that the residual networks may display blow-ups, in which case the assumptions made in Theorem (B.2) from Appendix (B.1.1) may fail, so that the control imposed by the stochastic morpher may also fail. Explosivity of residual networks can be studied using the methods put forward in e.g. [63, 64]. On the other hand, the control remains successful if the residual networks display multiple stationary PMFs, as outlined in the following example.

Example B.2. Consider the input network

$$\mathcal{R}_{\alpha}: \varnothing \xrightarrow{\alpha_1/\alpha_2} X_1, \quad X_1 \xrightarrow{\alpha_3} X_1 + X_2, \quad X_1 + X_2 \xrightarrow{\alpha_4} X_1, \quad 2X_2 \xrightarrow{\alpha_5/\alpha_6} 3X_2,$$

(69)

with positive rate coefficients, $\alpha \in \mathbb{R}^6$. Let us control the target species $X_1$, by embedding into (69) the stochastic morpher

$$\mathcal{R}_{\beta}: 2Y_1 \xrightarrow{\beta_{1,1}} Y_1,$$

$$\mathcal{R}^P_{\gamma_0}: X \xrightarrow{\gamma_{0/\varepsilon}} \varnothing,$$

$$\mathcal{R}^P_{\gamma_1}: Y_1 \xrightarrow{\gamma_{1/\varepsilon}} Y_1 + X, \quad 0 < \varepsilon \ll 1,$$

(70)

with $\gamma_1 = 0$. In this case, the stationary $x_1$-marginal PMF is given by $p_0(x_1) = P(x_1; 0) = \delta_{x_1,0}$. On the other hand, it follows from (67) that the dynamics of the species $X_2$ is governed by the residual network

$$\mathcal{R}_{\alpha}: 2X_2 \xrightarrow{\alpha_5/\alpha_6} 3X_2.$$

(71)

The input network (69) is jointly ergodic in both of the species $X_1$ and $X_2$, with the third and fourth reactions, which are catalyzed by $X_1$, allowing $X_2$ to enter and exit the states $x_2 \in \{0, 1\}$. On the other hand, the output network $\mathcal{R}_{\alpha} \cup \mathcal{R}^P_{\gamma_0}$, in the limit $\varepsilon \to 0$, is only marginally ergodic in the target species $X_1$. In particular, the residual network (71) is non-ergodic, as the third and fourth reactions from (69) are switched off, resulting in a reducible state-space for $X_2$, with the three irreducible components given by $\{0\}$, $\{1\}$, and $\{x_2 | x_2 \geq 2\}$.

References

[1] Endy D., 2005. Foundations for engineering biology. Nature, 484: 449–453.

[2] Zhang, D. Y., Winfree, E., 2009. Control of DNA strand displacement kinetics using toehold exchange. Journal of the American Chemical Society, 131: 17303–17314.

[3] Šulc P, Ouldridge TE, Romano F, Doye JPK, Louis AA., 2015. Modelling toehold-mediated RNA strand displacement. Biophysical Journal, 108: 1238–1247.

[4] Hong, F., and Šulc, P., 2019. Strand displacement: a fundamental mechanism in RNA biology? Available as https://arxiv.org/abs/1811.02766.
[5] Ouldridge, T. E., 2015. DNA nanotechnology: understanding and optimisation through simulation. *Molecular Physics* **113**: 1–15.

[6] Yurke, B., Turberfield, A. J., Mills, A. P., Simmel, F. C., and Neumann, J. L., 2000. A DNA-fuelled molecular machine made of DNA. *Nature*, **406**: 605–608.

[7] Soloveichik D, Seeling G, Winfree E, 2010. DNA as a universal substrate for chemical kinetics. *Proceedings of the National Academy of Sciences*, **107**(12): 5393–5398.

[8] Srinivas, N., Parkin, J., Seeling, G., Winfree, E., Soloveichik, D., 2017. Enzyme-free nucleic acid dynamical systems. *Science*, **358**, eaal2052.

[9] Holliday, R., 1964. A mechanism for gene conversion in fungi. *Genetics Research*, **5**(2): 282–304.

[10] Jinek, M., Chylinski, K., Fonfara, I., Hauer, M., Doudna, J. A., and Charpentier, E., 2012. A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity. *Science*, **337**(6096): 816–821.

[11] Feinberg, M. *Lectures on Chemical Reaction Networks*, Delivered at the Mathematics Research Center, U. of Wisconsin, 1979.

[12] Plesa, T., Vejchodský, T., and Erban, R., 2016. Chemical Reaction Systems with a Homoclinic Bifurcation: An Inverse Problem. *Journal of Mathematical Chemistry*, **54**(10): 1884–1915.

[13] Plesa, T., Vejchodský, T., and Erban, R. Test Models for Statistical Inference: Two-Dimensional Reaction Systems Displaying Limit Cycle Bifurcations and Bistability, 2017. *Stochastic Dynamical Systems, Multiscale Modeling, Asymptotics and Numerical Methods for Computational Cellular Biology*, 2017.

[14] Kar S., Baumann W. T., Paul M. R., Tyson J. J., 2009. Exploring the roles of noise in the eukaryotic cell cycle. *Proceedings of the National Academy of Sciences* USA, **106**: 6471–6476.

[15] Vilar, J. M. G., Kueh, H. Y., Barkai, N., Leibler, S., 2002. Mechanisms of noise-resistance in genetic oscillators. *PNAS*, USA, **99**(9): 5988–5992.

[16] Hasatani, K., Leocmach, M., Genot, A. J., Estévez-Torres, A., Fujii, T., Rondelez, Y., 2013. High-throughput and long-term observation of compartmentalized biochemical oscillators. *ChemComm*, **49**: 8090–8092.

[17] Weitz, M., Kim, J., Kapsner, K., Winfree, E., Franco, E., Simmel, F. C., 2014. Diversity in the dynamical behaviour of a compartmentalized programmable biochemical oscillator. *Nature Chemistry*, **6**: 295–302.

[18] Genot, A. J., Baccouche, A., Sieskind, R., Aubert-Kato, N., Bredeche, N., Bartolo, J. F., et al, 2016. High-resolution mapping of bifurcations in nonlinear biochemical circuits. *Nature Chemistry*, 10.1038/nchem.2544.

[19] Gillespie, D. T., 1992. A rigorous derivation of the chemical master equation. *Physica A: Statistical Mechanics and its Applications*, **188**(1): 404–425.

[20] Plesa, T., Zygalakis, K. C., Anderson, D. F., and Erban, R., 2018. Noise control for molecular computing. *Journal of the Royal Society Interface*, **15**(144): 20180199.
[21] Fujii T, Rondelez Y., 2013. Predator-prey molecular ecosystems. ACS Nano, 7: 27–34.

[22] Chappell, J., Takahashi, M. K., and Lucks, J. B., 2015. Creating small transcription activating RNAs. Nature chemical biology, 11(3): 214–220.

[23] Isaacs, F. J., Dwyer, D. J., Ding, C., Pervouchine, D. D., Cantor, C. R., Collins, J. J., 2004. Engineered riboregulators enable post-transcriptional control of gene expression. Nature biotechnology, 22(7): 841–847.

[24] Boo, A., Ellis, T., Stan, G. B., 2019. Host-aware synthetic biology. Current Opinion in Systems Biology, 14: 66–72.

[25] Xiang, Y., Dalchau, N., Wang, B., 2018. Scaling up genetic circuit design for cellular computing: advances and prospects. Natural Computing, 17(4): 833–853.

[26] Liao, S., Vejchodský, T., Erban, R., 2015. Tensor methods for parameter estimation and bifurcation analysis of stochastic reaction networks. Journal of the Royal Society Interface, 12(108): 20150233.

[27] Tuza, Z. A., Stan, G. B., 2018. Characterization of Biologically Relevant Network Structures form Time-series Data. IEEE Conference on Decision and Control (CDC): 1089–1095.

[28] Kempter, S., Khmelinskaia, A., Strauss, M. T., Schwille, P., Jungmann, R., Liedl, T., and Bae, W., 2019. Single particle tracking and super-resolution imaging of membrane-assisted stop-and-go diffusion and lattice assembly of DNA origami. ACS Nano, 13(2): 996–1002.

[29] Plesa T., 2018. Stochastic approximation of high- by bi-molecular reactions. In the submission process. Available as https://arxiv.org/abs/1811.02766.

[30] King, G. A. M., 1983. Reactions for chemical systems far from equilibrium. Journal of the Chemical Society, Faraday Transactions 1, 79: 75–80.

[31] Deshpande, A., Ouldridge, T. E., 2019. High rates of fuel consumption are not required by insulating motifs to suppress retroactivity in biochemical circuits. Engineering Biology, 1(2): 86–99.

[32] Deshpande, A., Ouldridge, T. E., 2019. Optimizing enzymatic catalysts for rapid turnover of substrates with low enzyme sequestration. In the submission process. Available as https://arxiv.org/abs/1905.00555.

[33] Machinek, R. R., Ouldridge ,T. E., Haley, N. E., Bath, J., Turberfield, A. J., 2014. Programmable energy landscapes for kinetic control of DNA strand displacement. Nature communications 5, 5324.

[34] Drengstig, T., Ueda, H. R., Ruoff, P., 2008. Predicting perfect adaptation motifs in reaction kinetic networks. Journal of Physical Chemistry B, 112(51): 16752–16758.

[35] Ferrell, J. E., 2016. Perfect and near-perfect adaptation in cell signaling. Cell Systems, 2(2): 62–67.

[36] Chandra, F. A., Buzi, G., and Doyle, J. C., 2011. Glycolytic oscillations and limits on robust efficiency. Science, 333(6039): 187–192.
[37] Barkai, N., and Leibler, S., 1997. Robustness in simple biochemical networks. *Nature*, 387: 913–917.

[38] Spiro, P., Parkinson, J., and Othmer, H. G., 1997. A model of excitation and adaptation in bacterial chemotaxis. *PNAS, USA*, 94: 7263–7268.

[39] Yi, T. M., Huang, Y., Simon, M. I., and Doyle, J., 2000. Robust perfect adaptation in bacterial chemotaxis through integral feedback control. *PNAS, 97* (9): 4649–4653.

[40] Ghomi, M. S., Ciliberto, A., Kar, S., Novak, B., Tyson, J. J. 2008. Antagonism and bistability in protein interaction networks. *Journal of Theoretical Biology, 250*: 209–218.

[41] Kepler, T. B., Elston, T. C., 2001. Stochasticity in transcriptional regulation: Origins, consequences, and mathematical representations. *Biophysical Journal* 81: 3116–3136.

[42] Plesa, T., Erban, R., and Othmer, H. G, 2018. Noise-induced Mixing and Multimodality in Reaction Networks. *European Journal of Applied Mathematics*, 1-25. doi:10.1017/S0956792518000517.

[43] Qu, Z., Garfinkel, A., Weiss, J. N., Nivala, M., 2011. Multi-scale modeling in biology: How to bridge the gaps between scales? *Prog Biophys Mol Biol.*, 107(1): 21–31.

[44] Qian, Y., Vecchio, D., 2018. Realizing integral control in living cells: how to overcome leaky integration due to dilution? *Journal of the Royal Society Interface*, 15: 20170902.

[45] Briat, C., Gupta, A., and Khammash, M., 2016. Antithetic integral feedback ensures robust perfect adaptation in noisy bimolecular networks. *Cell Systems*, 2(1): 15–26.

[46] Del Vecchio, D., Dy, A. J., and Qian, Y., 2016. Control theory meets synthetic biology. *Journal of the Royal Society Interface*, 13(120): 3–43.

[47] Hsiao, V., de Los Santos, E. L. C., Whitaker, W. R., Dueber, J. E., and Murray, R. M., 2014. Design and implementation of a biomolecular concentration tracker. *ACS synthetic biology*, 4(2): 150–161.

[48] Briat, C., Gupta, A., and Khammash, M., 2016. Antithetic proportional-integral feedback for reduced variance and improved control performance of stochastic reaction networks. *Journal of the Royal Society Interface*, 15: 20180079.

[49] Laurenti, L., Kwiatkowska, M., Czikasz-Nagy, A., Cardelli, L., 2018. Molecular Filters for Noise Reduction. *Biophysical Journal*, 114(12): 3000–3011.

[50] Kurtz, T. G., 1972. The relationship between stochastic and deterministic models for chemical reactions. *Journal of Chemical Physics*, 57: 2976–2978.

[51] Bressloff, P. C., 2017. Stochastic switching in biology: from genotype to phenotype. *Journal of Physics A: Mathematical and Theoretical*, 50: 133001.

[52] Yates, C., Erban, R., Escudero, C., Couzin, I., Buhl, J., Kevrekidis, I., Maini, P., and Sumpter, D., 2009. Inherent noise can facilitate coherence in collective swarm motion. *PNAS, 106*(14): 5464–5469.

[53] Okumus, B., Wilson, T. J., Lilley, D. M. J., Ha, T., 2004. Vesicle encapsulation studies reveal that single molecule ribozyme heterogeneities are intrinsic. *Biophys Journal*, 87(4): 2798–2806.
[54] Cappelletti, D., Ortiz-Munoz, A., Anderson, D. F., and Winfree, E., 2018. Stochastic chemical reaction networks for approximating arbitrary probability distributions. Available as https://arxiv.org/abs/1810.02854.

[55] Cisse, I.I., Kim, H., Ha, T., 2012. A rule of seven in Watson-Crick base-pairing of mismatched sequences. Nature Structural & Molecular Biology, 19: 623-627.

[56] McKinney, S. A., Déclais, A.-C., Lilley, D. M. J., and Ha, T., 2003. Structural dynamics of individual Holliday junctions. Nature Structural Biology, 10: 93–97.

[57] Chen, X., 2012. Expanding the rule set of DNA circuitry with associative toehold activation. Journal of the American Chemical Society, 134: 263–271.

[58] Stubberud, A. R., Williams, I. J., and DiStefano, J. J. Schaum’s outline of theory and problems of feedback and control systems, second edition. McGraw Hill Professional, 1995.

[59] Van Kampen, N. G. Stochastic processes in physics and chemistry. Elsevier, 2007.

[60] Gardiner, C. Handbook of stochastic methods for physics, chemistry, and the natural sciences. Springer series in synergetics, Springer, New York, 2004.

[61] Anderson, D. F., Kurtz, T. G. Stochastic analysis of biochemical systems. Springer, 2015.

[62] Pavliotis, G. A., Stuart, A. M. Multiscale Methods: Averaging and Homogenization. Springer, New York, 2008.

[63] Engblom, S., 2012. On the stability of stochastic jump kinetics. Applied Mathematics, 5: 3217–3239.

[64] Gupta, A., Briat, C., and Khammash, M., 2014. A scalable computational framework for establishing long-term behavior of stochastic reaction networks. PLoS computational biology, 10(6): e1003669.