Supporting Information

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I. STOCHASTIC DYNAMICS AND FOKKER-PLANCK EQUATION

The stochastic dynamics for the dynamical systems can be quantified in continuous spaces by the *Langevin* equations (in *Ito*'s form):

$$\dot{x}_\mu = F_\mu(\vec{x}) + \sum_a B^a_\mu(\vec{x})\xi^a(t) \tag{1}$$

where $F_\mu(\vec{x})$ is the driving force, $\xi_a(t)$ represents the Gaussian distributed white noise unit fluctuations and $B^a_\mu(\vec{x})$ represents the strength or magnitude of the variable dependent fluctuations: $\langle \xi^a(t)\xi^b(t')\rangle = \delta^{ab}\delta(t-t')$. Rather than each individual trajectory, we should focus on the underlying probability evolution to quantify the stochastic dynamics. The corresponding probability evolution $P(\vec{x},t)$ obeys the *Fokker-Planck equation*: with the diffusion coefficient $\varepsilon_{\mu\nu}(\vec{x}) = \sum_{a,b} B^a_\mu(\vec{x})B^b_\mu(\vec{x})\delta^{ab}$.

$$\frac{dP}{dt} = \sum_\mu \partial_\mu(-F_\mu P) + \sum_{\mu,\nu}\frac{1}{2}\partial_\mu\partial_\nu(\varepsilon_{\mu\nu}P) \tag{2}$$

II. QUASISTATIONARY DENSITY AND ESCAPING RATE

For general stochastic processes, when the fluctuations $\varepsilon_{\mu\nu}(\vec{x})$ are small, the escaping rate is determined by the quasistationary density, i.e., the principal eigenfunction ϕ^0 of operator L: $L\phi^0 = \lambda^0\phi^0$, ϕ^0 (L is the Fokker-Planck operator $\frac{dP}{dt} = -LP$ represents the slowest decaying eigenmode [1–3]. The escaping rate (inverse of the Mean First Passage Time (MFPT)) is proportional to the principal eigenvalue λ^0: $r_K^{noneq} = (E\tau)^{-1} \sim \lambda^0$. Therefore, near the bottleneck region connecting the two destinies (one stable state to another) with absorbing boundary condition, we obtain

$$\begin{aligned} \int_\Omega (L\phi^0)dx = \int_\Omega \partial\cdot J^0 dx = \int_\Omega \lambda^0\phi^0 dx \\ \Longrightarrow \int_{\partial\Omega}\sum_\mu J^0_\mu(\vec{x})n_\mu(\vec{x})dx = \lambda^0\int_\Omega \phi^0(\vec{x})dx \end{aligned} \tag{3}$$

where J^0_i is the current or the flux of ϕ^0: $J^0_\mu = F_\mu\phi^0 - \sum_\nu \frac{1}{2}\partial_\nu(\varepsilon_{\mu\nu}\phi^0)$ and $n_\mu(\vec{x})$ is the outward unit vector normal to the absorbing boundary $\partial\Omega$ at $\vec{x}$. Then, the escaping rate from a stable basin state to a bottleneck with absorbing boundary condition $\partial\Omega$ ("saddle" point included) can be evaluated as

$$r_K^{noneq} = (E\tau_\epsilon)^{-1} \sim \lambda^0_\epsilon = \frac{\int_{\partial\Omega}\sum_\mu J^0_\mu(\vec{x})n_\mu(\vec{x})dx}{\int_\Omega \phi^0(\vec{x})dx} \tag{4}$$

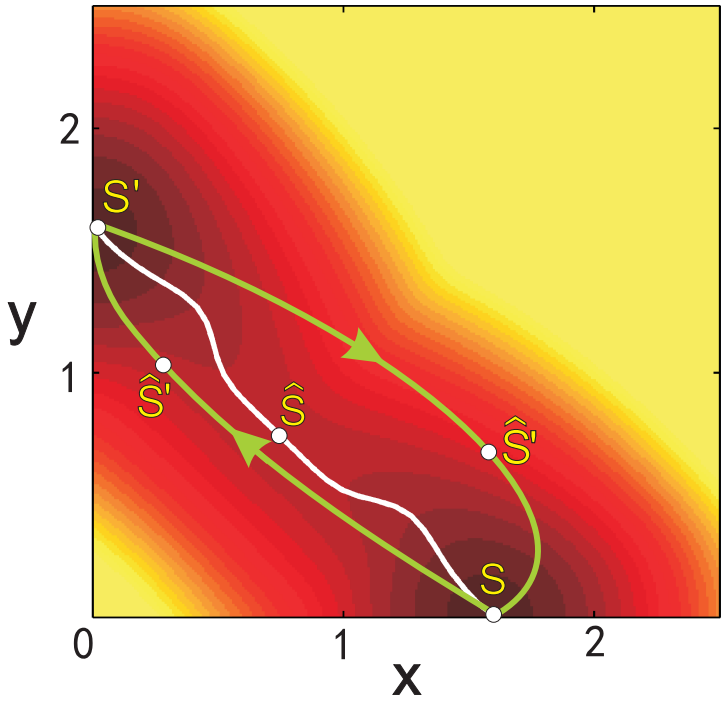

FIG. 1: 2D illustration of non-equilibrium landscape with the irreversible dominant transition paths between basins S and S' (green lines with arrows) and the gradient path (white line). Here, $\hat{S}$ is the saddle point and $\hat{S}'$ is "the global maximum along the dominant path".

where $\int_\Omega \phi^0(\vec{x})dx$ in the denominator gives the correct normalization factor for connecting solutions of ϕ^0 in different regions and numerator of the rate formula is determined by the flux through the bottleneck area at the boundary on the way to the destiny (another stable state).

Furthermore, we can approximate ϕ^0 as a solution of

$$L\phi^0 = \sum_\mu \partial_\mu [F_\mu \phi^0] - \sum_{\mu\nu} \frac{1}{2}\partial_\mu \partial_\nu [\varepsilon_{\mu\nu}\phi^0] = 0 \tag{5}$$

because when $\varepsilon_{\mu\nu}(\vec{x}) \to 0$, $\lambda^0 \to 0$ exponentially fast. Therefore, up to exponential small errors, the solution $L\phi^0$ gives lowest order approximation for the solution $L\phi^0 = \lambda^0\phi^0$ [3]. In equ. (4), since we only integrate the flux $J^0_\mu(\vec{x})$ on the bottleneck boundary $\partial\Omega$ near "the saddle point " $\hat{S}'$, the numerator will not be zero even we use the solution $L\phi^0 = \lambda^0\phi^0 = 0$ for obtaining the $J^0_\mu(\vec{x})$ at the bottleneck boundary.

Here, instead of choosing the saddle point of the force or the associated non-equilibrium

potential landscape as the absorbing boundary $\partial\Omega$ [1–3], we choose "the global maximum along the dominant path" as the bottleneck region with the absorbing boundary condition $\partial\Omega$, as shown in Fig. 1. Given this boundary, we can use the method of matching asymptotic expansions to approximate ϕ^0 for the small fluctuations in three asymptotic regions:

1. ϕ^0_S at the local stable region centered around the stable state S;

2. $\phi^0_{\hat{S}'}$ at the boundary region $\partial\Omega$ centered on "the global maximum along the dominant path" $\hat{S}'$;

3. $\phi^0_{\Omega'}$ at the rest of the region of Ω: Ω' between the stable basin S and "the global maximum along the dominant path" $\hat{S}'$.

In the equ. (4), we will substitute ϕ^0_S to the denominator because ϕ^0_S is the solution in the neighbor of the stable state S and contributes the most to the integral $\int_\Omega \phi^0(\vec{x})dx$. However, the contribution of ϕ^0_S on the bottleneck boundary $\partial\Omega$ near "saddle point" $\hat{S}'$ can be ignored because it is the solution away from $\hat{S}'$. Therefore, we will substitute $\phi^0_{\hat{S}'}$ to the numerator, since $\phi^0_{\hat{S}'}$ dominates near the "saddle point" $\hat{S}'$ and gives the major contribution of the integral $\int_{\partial\Omega}\sum_\mu J^0_\mu(\vec{x})n_\mu(\vec{x})dx$. In addition, the $\phi^0_{\Omega'}$ between S and $\hat{S}'$ will contribute and give the right normalization for $\phi^0_{\hat{S}'}$ and ϕ^0_S matching the solution of ϕ^0 in different regions. We propose an analytical approximation of the escaping rate for general non-equilibrium systems with small but finite fluctuations as

$$r_K^{noneq} = \kappa e^{-S} \tag{6}$$

In the next section, we will review the WKB approximation of ϕ^0 in the region of Ω', which leads to the exponential term e^{-S} in the rate of equ. (6) in the zero noise limit. After that, in the following sections, we will quantify ϕ^0 using the path integral formalism, which gives new transition state theory for general nonequilibrium systems.

III. TRANSITION STATE RATE OF ZERO NOISE LIMIT

In the weak-noise ($\epsilon \to 0$), the existing problem is also determined by the quasistationary density as given by equation (4). However, it is assumed that transition path always go through the original saddle of the force $\hat{S}$. $\phi^0_{\Omega'}$ at the rest of the region of Ω: Ω' between the stable point S and the saddle $\hat{S}$ is calculated by WKB formalism. Assuming $v^0_\epsilon =$

$K(x)e^{-M(x)/\epsilon}$, we have equation:

$$H(x_\mu, \partial_\mu M) = 0 \tag{7}$$

$$H(x,p) = \frac{1}{2}\varepsilon_{\mu\nu}(x)p_\mu p_\nu + F_\mu(x)p_\mu \tag{8}$$

$$\Big[\frac{\partial H}{\partial p_\mu}(x_\mu, \partial_\mu M)\Big]\partial_\mu K = -\Big[\frac{\partial^2 H}{\partial p_\mu \partial x_\mu}(x_\mu, \partial_\mu M) + \frac{1}{2}\frac{\partial^2 M}{\partial x_\mu \partial x_\nu}(x)\frac{\partial^2 H}{\partial p_\mu \partial p_\mu}(x_\mu, \partial_\mu M)\Big]K \tag{9}$$

The solution of above equations are given as

$$M(x) = \int^x p_\mu dx_\mu \tag{10}$$

$$\frac{dM_{\mu\nu}(x)}{dt} = \frac{\partial^2 H}{\partial p_\xi \partial p_{\xi'}}M_{\mu\xi}M_{\nu\xi'} - \frac{\partial^2 H}{\partial x_\nu \partial p_\xi}M_{\mu\xi} - \frac{\partial^2 H}{\partial x_\mu \partial p_\xi}M_{\nu\xi} - \frac{\partial^2 H}{\partial x_\mu \partial x_\nu} \tag{11}$$

$$\frac{dK}{dt} = -\Big[\sum_\mu \frac{\partial^2 H}{\partial x_\mu \partial p_\mu} + \sum_{\mu\nu}\frac{1}{2}\frac{\partial^2 S}{\partial x_\mu x_\nu}\frac{\partial^2 H}{\partial p_\mu \partial p_\nu}\Big]K \tag{12}$$

with x and p following dynamics equations

$$\dot{x}_\mu = \varepsilon_{\mu\nu}p_\nu + F_\mu \tag{13}$$

$$\dot{p}_\mu = (\partial_\mu \varepsilon_{\nu\nu'})p_\nu p_{\nu'} + (\partial_\mu F_\nu)p_\nu \tag{14}$$

On the stable state $S(S')$ or the saddle point $\hat{S}$, momentum $p_\mu \to 0$, we have the stationary solution from equation (11).

$$\sum_{\xi\chi}\varepsilon_{\xi\chi}M_{,\mu\xi}M_{,\nu\chi} + \sum_\xi M_{,\mu\xi}F_{\nu,\xi} + \sum_\xi M_{,\nu\xi}F_{\mu,\xi} = 0 \tag{15}$$

Near the stable basin state S , we do a linear expansion of the force for quantifying the fluctuations around that state in addition to the mean: $F_\mu(X_1, X_2) = F_{\mu,\nu}(X_\nu - S_\nu) \equiv \frac{\partial F_\mu}{\partial x_\nu}(X_\nu - S_\nu)$ and the equation $L\phi^0 = 0$ can be written as

$$0 = \sum_{\mu\nu}\partial_\mu[-F_{\mu,\nu}(S)(x_\nu - S_\nu)\phi^0] + \sum_{\mu\nu}\frac{1}{2}\varepsilon_{\mu\nu}(S)\partial_\mu\partial_\nu\phi^0 \tag{16}$$

The solution is in the form of steady state solution of Ornstein-Uhlenbeck process [3, 9], which is a Gaussian function:

$$\phi_S^0 \sim exp[-\sum_{\mu\nu}(x_\mu - S_\mu)M_{,\mu\nu}(x_\nu - S_\nu)] \tag{17}$$

with the matrix M satisfying equation (15). ε is the diffusion matrix and F is the driving force. Then, the integral in the denominator of equ. (4) near stable state gives

$$\int_{\Omega} \phi^0(x)dx = [detM(S)]^{-1/2} \tag{18}$$

Here, $\sqrt{detM(S)}$ in equ. (17) above measures the degree or strength of the second order fluctuations around stable basin S, which is the product of stable frequencies at stable state S.

While, near the saddle point $\hat{S}$, with the linear expansion of the force $F_\mu(X_1, X_2) = F_\mu + \sum_\nu F_{\mu,\nu}(X_\nu - \hat{S}_\nu)$ and the boundary condition $\phi^0(\partial\Omega) = 0$, the equation $L\phi^0 = 0$ has the approximation solution [3],

$$\begin{aligned} \phi^0_{\hat{S}}(X_1, X_2) \sim\ & K(S, \hat{S})e^{-M(S,\hat{S})/\epsilon} e^{-\sum_{\mu\nu}(x_\mu - \hat{S}_\mu)M_{,\mu\nu}(x_\nu - \hat{S}_\nu)/2\epsilon} \\ & \times erf[\lambda_u(\hat{S})^{1/2} \sum_{\mu\nu} n_\mu \epsilon_{\mu\nu}(x_\nu - \hat{S}_\nu)/\epsilon^{1/2}] \end{aligned} \tag{19}$$

where $\lambda_u(\hat{S})$ is the positive eigenvalue of matrix $F_{\mu,\nu}(\hat{S})$ at the saddle point $\hat{S}$ and the erf function $erf(z)$ is defined as

$$erf(z) = \frac{2}{\sqrt{\pi}} \int_{s=0}^{z} e^{-s^2} ds \tag{20}$$

Here, the normalization factor $K(S, \hat{S})e^{-M(S,\hat{S})/\epsilon}$ is included to match the solution in the region Ω': $\phi^0_{\Omega'}(x_f) \sim K(S, \hat{S})e^{-M(S,\hat{S})/\epsilon}$, as in equation. (11) and (12), from the point S to $\hat{S}$. In the neighborhood of the stable point S, however, because the weight action from S to S for the dominant path is zero: $S_{HJ}(S, S) = \int_S^S p \cdot dx = 0$, the normalization factor for the solution ϕ^0_S near stable point S is $K(S, S)e^{-M(S,S)/\epsilon} = 1$.

Together, the transition state rate in the zero noise limit can be written as [1–3]

$$r_K^{noneq} = (E\tau)^{-1} = \frac{\lambda_u(\hat{S})}{2\pi} \sqrt{\frac{detM(S)}{|detM(\hat{S})|}} K(\hat{S}) e^{-\int_S^{\hat{S}} \sum_\mu p_\mu dx_\mu} \tag{21}$$

Here, matrix M satisfies the equation (15) and the frequency factor $K(\hat{S})$ multiplies the frequency of excursions to the vicinity of $\hat{S}$, which satisfies equation (12).

IV. EXPONENTIAL FACTOR AND PATH INTEGRAL WITH INTRINSIC NOISE

When the diffusion coefficients are constants, which do not depend on the location $\vec{x}$, the weight action in the path integral formalism can be written as [4, 5]:

$$S = \int_{t_i}^{t_f} dt\mathcal{L} \tag{22}$$

with the *Lagrangian*

$$\mathcal{L} = \sum_{\mu\nu} \frac{\varepsilon_{\mu\nu}^{-1}}{2}(\dot{x}_\mu - F_\mu)(\dot{x}_\nu - F_\nu) + \sum_\mu \frac{1}{2}\partial_\mu F_\mu \tag{23}$$

However, the general weight action when the diffusion coefficients $\varepsilon_{\mu\nu}(\vec{x})$ do depend on the location $\vec{x}$ is still challenging. Here, we will derive this path integral weight action and the corresponding equation of motion for the dominant path for general stochastic dynamics under inhomogeneous location dependent diffusion.

By defining the momentum operator: $\partial_\mu = i\hat{p}_\mu$, as in general *Quantum Mechanics*, the general *Fokker-Planck equation* (2) can be rewritten in a form of the operators:

$$\frac{dP}{dt} = -i\hat{H}P \tag{24}$$

In Ito's formalism, we keep all operators $\hat{p}_\mu$ on the left side and it gives

$$-i\hat{H} = -(\sum_\mu i\hat{p}_\mu)F_\mu - \sum_{\mu\nu}\frac{1}{2}\hat{p}_\mu\hat{p}_\nu\varepsilon_{\mu\nu} \tag{25}$$

Therefore, the transition probability from initial state $\vec{x}_i$ at t_0 to the final state $\vec{x}_f$ at time t is expressed as [5]:

$$P(\vec{x}_f, t|\vec{x}_i, t_0) = \int_{x_f=x_n} \prod_{j=1}^{n-1} d\vec{x}_j \prod_{j=1}^{n} \langle\vec{x}_j|1 - i\hat{H}\delta t|\vec{x}_{j-1}\rangle \tag{26}$$

Following the path integral formalism, for a small time interval δt, we can insert the identity $I = \int d\vec{p}|\vec{p}\rangle\langle\vec{p}|$ and obtain

$$\begin{aligned}\langle\vec{x}_j|1 - i\hat{H}\delta t|\vec{x}_{j-1}\rangle &= \int d\vec{p}\langle\vec{x}_j|\vec{p}\rangle\langle\vec{p}|1 - i\hat{H}\delta t|\vec{x}_{j-1}\rangle \\ = \int \frac{d\vec{p}}{2\pi} exp[i\vec{p}\cdot(\vec{x}_j - \vec{x}_{j-1}) \\ &- \sum_{\mu\nu}\frac{\delta t}{2}p_\mu p_\nu\varepsilon_{\mu\nu}(\vec{x}_{j-1}) - i\sum_\mu \delta t p_\mu F_\mu(\vec{x}_{j-1})]\end{aligned} \tag{27}$$

Gaussian integrating out the p_μ's gives the weight action in the coordinate space:

$$P(\vec{x}_f,t|\vec{x}_i,t_0)=\int_{x_f=x_n}\prod_{j=1}^{n-1}d\vec{x}_j\prod_{j=1}^{n}\frac{1}{\sqrt{2\pi\delta t[det\varepsilon(\vec{x}_{j-1})]}}$$
$$\times exp\Big(\delta t\sum_{j=1}^{n}\{-[\frac{\vec{x}_j-\vec{x}_{j-1}}{\delta t}-\vec{F}(\vec{x}_{j-1})]\frac{\varepsilon^{-1}(\vec{x}_{j-1})}{2}$$
$$[\frac{\vec{x}_j-\vec{x}_{j-1}}{\delta t}-\vec{F}(\vec{x}_{j-1})]\}\Big) \tag{28}$$

In the continuous limit of $\delta t\to 0$, we have

$$P(\vec{x}_f,t|\vec{x}_i,t_0)=\int_{t_i}^{t_f}\frac{\mathcal{D}[\vec{x}(t)]}{\sqrt{det\varepsilon(\vec{x}(t))}}e^{-S} \tag{29}$$

with the weight action

$$S=-\frac{1}{2}\int dt[\sum_{\mu\nu}\dot{x}_\mu\varepsilon^{-1}_{\mu\nu}\dot{x}_\nu+\sum_{\mu\nu}F_\mu\varepsilon^{-1}_{\mu\nu}F_\nu]$$
$$+(I)\int\sum_{\mu\nu}F_\nu\varepsilon^{-1}_{\mu\nu}dx_\mu \tag{30}$$

where (I) indicates the Ito's integral. If we define $\hat{F}_\mu(\vec{x})=\sum_\nu F_\nu(\vec{x})\varepsilon^{-1}_{\mu\nu}(\vec{x})$, according to *Ito's* calculus, we have

$$(I)\int\sum_{\mu\nu}F_\nu\varepsilon^{-1}_{\mu\nu}dx_\mu=\lim_{n\to\infty}\sum_{j=1}^{n}[\sum_\mu\hat{F}_\mu(\vec{x}_{j-1})(x^\mu_j-x^\mu_{j-1})]$$
$$=\lim_{n\to\infty}\sum_{j=1}^{n}\sum_\mu[\frac{\hat{F}_\mu(\vec{x}_{j-1})+\hat{F}_\mu(\vec{x}_j)}{2}$$
$$-\sum_\chi\frac{\partial_\chi\hat{F}_\mu(\vec{x}_{j-1})}{2}(x^\chi_j-x^\chi_{j-1})][(x^\mu_j-x^\mu_{j-1})]$$
$$=\int\sum_\mu\hat{F}_\mu(\vec{x})dx_\mu-\sum_{\mu\chi}\frac{1}{2}\int\frac{d[\hat{F}_\mu(\vec{x})]}{dx_\chi}\varepsilon_{\mu\chi}(\vec{x})dt \tag{31}$$

Here, in the first step, we did the Taylor expansion: $\hat{F}_\mu(\vec{x}_j)=\hat{F}_\mu(\vec{x}_{j-1})+\sum_\chi\partial_\chi\hat{F}_\mu(\vec{x}_{j-1})(x^\chi_j-x^\chi_{j-1})$. In the second step, $\lim_{n\to\infty}\sum_{j=1}^{n}\sum_\mu\frac{\hat{F}_\mu(\vec{x}_{j-1})+\hat{F}_\mu(\vec{x}_j)}{2}[(x^\mu_j-x^\mu_{j-1})]$ is the Stratonovich integral which holds the same fundamental theorem of Newtonian calculus and can be written as the first term: $\int\hat{F}_\mu(\vec{x})dx_\mu$. In addition, we apply *Ito's* calculus: $dx_\mu(t)dx_\nu(t)=\varepsilon_{\mu\nu}(\vec{x})dt$ to obtain the second term.

According to *Ito's lemma* in *Ito's* calculus and *Langevin* equations in Equ. (1), for a function of $\vec{x}$: $H(\vec{x})$, we have

$$\begin{aligned} dH &= \frac{\partial H}{\partial x_\mu} dx_\mu + \frac{1}{2}\frac{\partial^2 H}{\partial x_\mu \partial x_\nu} dx_\mu dx_\nu \\ &= \frac{\partial H}{\partial x_\mu} dx_\mu + \frac{1}{2}\frac{\partial^2 H}{\partial x_\mu \partial x_\nu} \varepsilon_{\mu\nu} dt \end{aligned} \tag{32}$$

Integrating on both sides from x_i to x_f along any particular path l, we have

$$\begin{aligned} \int_l dH &= H(\vec{x}_f) - H(\vec{x}_i) \\ &= (I)\int_l \frac{\partial H}{\partial x_\nu} dx_\nu + \int_l \frac{1}{2}\frac{\partial^2 H}{\partial x_\nu \partial x_\chi}\varepsilon_{\nu\chi} dt \end{aligned} \tag{33}$$

In general, $\hat{F}_\mu(\vec{x}) = F_\nu(\vec{x})\varepsilon^{-1}_{\mu\nu}(\vec{x})$ can not necessary be written the gradient of the a general potential $H(\vec{x})$. However, along any particular path l, which is a 1 dimensional line, we can always define a function H as the inverse derivative of the component of $\hat{F}_\mu$ along the l: $\frac{\partial_l H(\vec{x})}{\partial_l x_\mu} = \hat{F}^l_\mu(\vec{x})$. Then, substitute the H into equ. (33), we found that the *Ito's* integral along any path l in the second term of equ. (30) becomes

$$\begin{aligned} (I)\int_l \hat{F}^l(\vec{x}) dl &= (I)\int_l F_\mu(\vec{x})\varepsilon^{-1}_{\mu\nu}(\vec{x}) dx_\nu \\ = \int_l F_\mu(\vec{x})\varepsilon^{-1}_{\mu\nu}(\vec{x}) dx_\nu &- \frac{1}{2}\int_l \frac{d[F_\mu(\vec{x})\varepsilon^{-1}_{\mu\nu}(\vec{x})]}{dx_\chi}\varepsilon_{\nu\chi}(\vec{x}) dt \end{aligned} \tag{34}$$

Therefore, the whole weight action is

$$S = \int_{t_i}^{t_f} dt\mathcal{L} \tag{35}$$

with the *Lagrangian*

$$\mathcal{L} = \sum_{\mu\nu} \frac{\varepsilon^{-1}_{\mu\nu}}{2}(\dot{x}_\mu - F_\mu)(\dot{x}_\nu - F_\nu) + \sum_{\mu\nu\chi}\frac{1}{2}\varepsilon_{\mu\chi}\partial_\chi(F_\nu\varepsilon^{-1}_{\mu\nu}) \tag{36}$$

A new effective contribution to the potential can be introduced: $V = \sum_{\mu\nu\chi}\frac{1}{2}\varepsilon_{\nu\chi}\partial_\chi(F_\mu\varepsilon^{-1}_{\mu\nu})$. If diffusion coefficients $\varepsilon_{\mu\nu}$ are constants and independent on the location $\vec{x}$, we get $V = \sum_\mu \frac{1}{2}\partial_\mu F_\mu$, which agrees with the previous results for constant noise condition, as shown in equ. (22).

Here, we derived the path integral weight action for general non-equilibrium stochastic processes with location dependent fluctuations (diffusion). Taking functional variations

of the weight action S with respect to $x_\mu(t)$'s, we obtain the equation of motion for the dominant path which satisfies the Euler-Lagrangian equation $\frac{d}{dt}\frac{\partial \mathcal{L}}{\partial \dot{x}_\alpha} = \frac{\partial \mathcal{L}}{\partial x_\alpha}$ as:

$$\begin{aligned}
&\sum_\nu \varepsilon^{-1}_{\mu\nu}(\ddot{x}_\nu - \sum_\chi \frac{\partial F_\nu}{\partial x_\chi}\dot{x}_\chi) + \sum_{\nu\chi}\frac{\partial \varepsilon^{-1}_{\mu\nu}}{\partial x_\chi}(\dot{x}_\nu - F_\nu)\dot{x}_\chi \\
= &\sum_{\nu\chi}\frac{1}{2}\frac{\partial \varepsilon^{-1}_{\nu\chi}}{\partial x_\mu}(\dot{x}_\nu - F_\nu)(\dot{x}_\chi - F_\chi) \\
&- \sum_{\nu\chi}\varepsilon^{-1}_{\nu\chi}(\dot{x}_\chi - F_\chi)\frac{\partial F_\nu}{\partial x_\mu} + \frac{\partial V}{\partial x_\mu}
\end{aligned} \tag{37}$$

The dominant path approach gives the lowest order approximation of the full path integral weight action. When the fluctuation level is relatively small, it provides a practical way to quantify the process in the large dynamical systems, since the dominant path equations reduces the computational task significantly from the original exponential complexity to the polynomials complexity [6].

V. HAMILTONIAN-JACOBI APPROACH TO DOMINANT PATHS

Instead of solving the equation of motion as in equ. (37) directly, we can evaluate the dominant kinetic path by minimizing the weight action S in path integral formalism. Define canonical momentum

$$p_\mu = \frac{\partial \mathcal{L}}{\partial \dot{x}_\mu} = \sum_\nu \varepsilon^{-1}_{\mu\nu}(\dot{x}_\nu - F_\nu), \tag{38}$$

the total energy should be expressed as

$$\begin{aligned}
-E = -H &= \mathcal{L} - p_\mu \dot{x}_\mu \\
&= \sum_{\mu\nu} -\frac{1}{2}\varepsilon^{-1}_{\mu\nu}(\dot{x}_\nu - F_\nu)(\dot{x}_\mu + F_\mu) + V
\end{aligned} \tag{39}$$

which will conserve along the dominant path. For a symmetric $\varepsilon_{\mu\nu}$ and $\varepsilon^{-1}_{\mu\nu}$, we have

$$E = \sum_{\mu\nu}\frac{1}{2}\varepsilon^{-1}_{\mu\nu}(\dot{x}_\mu\dot{x}_\nu - F_\mu F_\nu) - V \tag{40}$$

By defining an effective potential $V_{eff} = -\sum_{\mu\nu}\frac{1}{2}\varepsilon^{-1}_{\mu\nu}F_\mu F_\nu - V$, we obtain

$$\begin{aligned}
&\sum_{\mu\nu}\frac{1}{2}\varepsilon^{-1}_{\mu\nu}\dot{x}_\mu\dot{x}_\nu = E - V_{eff} \\
&\Rightarrow dt = \sqrt{\frac{\frac{1}{2}\sum_{\mu\nu}\varepsilon^{-1}_{\mu\nu}dx_\mu dx_\nu}{E - V_{eff}}} = dl\sqrt{\frac{1}{2(E - V_{eff})}}
\end{aligned} \tag{41}$$

where $dl = \sqrt{\sum_{\mu\nu} \varepsilon^{-1}_{\mu\nu} dx_\mu dx_\nu}$ is the length in a curved space with distance measure $\varepsilon^{-1}_{\mu\nu}$. So the dynamics becomes effectively one dimensional along the length l.

For fixed energy, the *HJ weight action*, which should be minimized to find the dominant path, can be written as [7]:

$$\begin{aligned} S_{HJ}(x_i, x_f) &= \int_{x_i}^{x_f} p \cdot dx = \sum_{\mu\nu} \varepsilon^{-1}_{\mu\nu} (\dot{x}_\nu - F_\nu) dx_\mu \\ &= \int_{x_i}^{x_f} \sum_{\mu\nu} \varepsilon^{-1}_{\mu\nu} dx_\mu dx_\nu / dt - \int_{x_i}^{x_f} \sum_{\mu\nu} \varepsilon^{-1}_{\mu\nu} F_\nu dx_\mu \\ &= \int_{x_i}^{x_f} 2(E - V_{eff}) dt - \int_{x_i}^{x_f} \sum_{\mu\nu} \varepsilon^{-1}_{\mu\nu} F_\nu dx_\mu \\ &= \int_{x_i}^{x_f} \sqrt{2(E - V_{eff})} dl - \int_{x_i}^{x_f} \sum_{\mu\nu} \varepsilon^{-1}_{\mu\nu} F_\nu dx_\mu \end{aligned} \tag{42}$$

which is further simplified to a line integral along a particular one dimensional path l. In this Hamilton-Jacobian (HJ) approach, we switch from the time-dependent to the effective Hamiltonian-dependent description (in length space).

Minimizing the the *HJ weight action* $S_{HJ}(x_i, x_f)$, we can obtain the dominant transition path and the associated weight action $S^{DOM}_{HJ}(x_i, x_f)$. This *HJ weight action* gives the ϕ^0 in the the region of Ω' between the stable basin of attraction and saddle on the dominant path:

$$\phi^0_{\Omega'}(x_f) \sim e^{-S^{DOM}_{HJ}(x_i, x_f)} \tag{43}$$

exponential term of the escaping rate for general non-equilibrium systems with finite intrinsic noise as in equ. (6): $e^{-S^{DOM}_{HJ}}$. In the next section, we are going to derive the pre-factor κ. As we will see, it will give the contribution for the exponential part (factor) in the expression of the escape rate.

Numerically, the optimal path and its weight action can be obtained by minimizing the discretized target function (HJ weight action):

$$\begin{aligned} S_{HJ} \;=\; & \sum_{n=0}^{N-1} \big[\sqrt{2(E - V_{eff}(x_n))} \Delta l_{n,n+1} \\ & - \sum_{\mu\nu} \varepsilon^{-1}_{\mu\nu}(x(n)) F_\nu(x(n)) \Delta x_\mu(n) \big] + \lambda P \end{aligned} \tag{44}$$

with $P = \sum_{n=0}^{N-1} (\Delta d_{n,n+1} - \langle \Delta d \rangle)^2$ and $V_{eff}(x(n)) = -\sum_{\mu\nu} \frac{1}{2} \varepsilon^{-1}_{\mu\nu}(x(n) F_\mu(x(n)) F_\nu(x(n)) - V(x(n))$. $\Delta d_{n,n+1} = \sum_\mu [x_\mu(n+1) - x_\mu(n)][x_\mu(n+1) - x_\mu(n)]$ is the Euclidean measure of

the nth elementary step on the path and P is a penalty function which numerically keeps all the length elements close to their average and becomes irrelevant in the continuum limit $\Delta d_{n,n+1} \to 0$. In addition, $(\Delta l)^2_{n,n+1} = \sum_{\mu\nu} \varepsilon^{-1}_{\mu\nu}(n)[x_\mu(n+1)-x_\mu(n)][x_\nu(n+1)-x_\nu(n)]$ is the measure of the nth elementary path step in the curved space determined by concentration dependent diffusion (fluctuations) with distance measure $\varepsilon^{-1}_{\mu\nu}$.

VI. PRE-FACTOR

For the pre-factor, we follow the similar solution as the case of zero noise limit [3], as reviewed in section III. Near the stable state S, we have the same stationary solution as equation (17)

$$\phi^0_S \sim exp[-\sum_{\mu\nu}(x_\mu - S_\mu)M_{,\mu\nu}(x_\nu - S_\nu)] \tag{45}$$

with the matrix M satisfying equation (15).

Near "the global maximum along the dominant path" $\hat{S}'$, we have similar solution as equation (19)

$$\begin{aligned}\phi^0_{\hat{S}'}(X_1, X_2) \;\sim\; & e^{-S^{DOM}_{HJ}(S,\hat{S}')} e^{-\sum_{\mu\nu}(x_\mu-\hat{S}'_\mu)M_{,\mu\nu}(x_\nu-\hat{S}'_\nu)/2\epsilon} \\ & \times erf[\lambda_u(\hat{S}')^{1/2}\sum_{\mu\nu} n_\mu \epsilon_{\mu\nu}(x_\nu - \hat{S}'_\nu)/\epsilon^{1/2}]\end{aligned} \tag{46}$$

Here, since "the global maximum along the dominant path" $\hat{S}'$ is not a fixed point with force $F = 0$, equation (46) is not a stationary solution and matrix M satisfies the dynamic equation (11).

Again, the normalization factor $e^{-S^{DOM}_{HJ}(S,\hat{S}')}$ is included to match the solution in the region Ω': $\phi^0_{\Omega'}(x_f) \sim e^{-S^{DOM}_{HJ}(x_i,x_f)}$, as in equ. (43), from the point S to $\hat{S}'$. In the neighborhood of the stable point S, however, because the weight action from S to S for the dominant path is zero: $S_{HJ}(S,S) = \int_S^S p \cdot dx = 0$, the normalization factor for the solution ϕ^0_S near stable point S is $e^{-S^{DOM}_{HJ}(S,S)} = 1$.

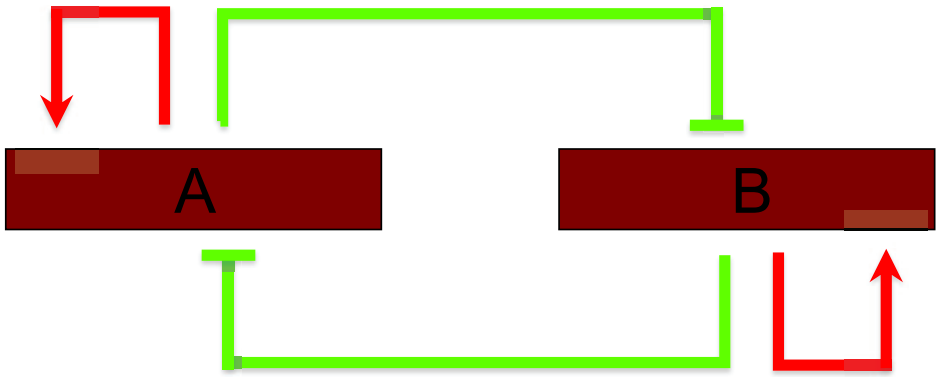

FIG. 2: Network diagram of canonical gene regulatory circuit of two mutually opposing proteins that positively self-regulate themselves.

VII. NEW TRANSITION STATE OR KRAMERS' RATE FOR NON-EQUILIBRIUM SYSTEMS

In the equ. (4), we substitute ϕ_S^0 in equ. (17) to the denominator and $\phi_{\hat{S}'}^0$ in equ. (19) to the numerator, we can write the escaping rate for the general non-equilibrium systems as:

$$r_K^{noneq} = (E\tau)^{-1} = \frac{1}{2\pi}[detM(S)]^{1/2}\sqrt{\frac{\hat{F}_{1,1}}{|\hat{F}_{2,2}|}}e^{-S_{HJ}^{DOM}} \tag{47}$$

After transforming back to an arbitrary coordinate system, we have the final analytical expression for our kinetic rate formula (theory) for non-equilibrium systems as

$$r_K^{noneq} = (E\tau)^{-1} = \frac{\lambda_u(\hat{S}')}{2\pi}\sqrt{\frac{detM(S)}{|detM(\hat{S}')|}}e^{-S_{HJ}^{DOM}} \tag{48}$$

which is given in the main text. Here, $\lambda_u(\hat{S}')$ is the positive eigenvalue of matrix $F_{\mu,\nu}(\hat{S}')$ at "the global maximum along the dominant path" $\hat{S}'$, and the matrix $M(S)$ and $M(\hat{S}')$ satisfy the stationary equation (15) and dynamic equation (11) at the basin S and $\hat{S}'$, respectively.

VIII. MASTER EQUATIONS

In the gene regulatory circuit, as shown in Fig. 2, there are two types of genes, A and B, to be translated into proteins A and B respectively. This gene circuit with two genes mutually repress each other while self-activate themselves. The proteins $A(B)$ can bind to the promoter of the same gene $A(B)$ to self activate the synthesis rate of $A(B)$, which

makes a self-activation feedback loop. Protein $A(B)$ can bind to the gene $B(A)$ to repress the synthesis rate of $B(A)$, which makes a mutual repression loop. Here, both protein A and protein B bind to promoters as a tetrameter with the binding rate $h_A = hx_1^4$ and $h_B = hx_2^4$, disassociate rate f_A and f_B, respectively. Therefore, each gene has 4 states (self activated or not combined with mutually repressed or not) and the whole circuit with two genes has $4 \times 4 = 16$ gene states in total. Chemical reactions are as following:

$$\mathcal{O}_\alpha^{11} + 4A \underset{f_A}{\overset{h_A}{\rightleftharpoons}} \mathcal{O}_\alpha^{01}, \quad \mathcal{O}_\alpha^{10} + 4A \underset{f_A}{\overset{h_A}{\rightleftharpoons}} \mathcal{O}_\alpha^{00} \tag{49}$$

$$\mathcal{O}_\alpha^{11} + 4B \underset{f_B}{\overset{h_B}{\rightleftharpoons}} \mathcal{O}_\alpha^{10}, \quad \mathcal{O}_\alpha^{01} + 4B \underset{f_B}{\overset{h_B}{\rightleftharpoons}} \mathcal{O}_\alpha^{00} \tag{50}$$

$$\mathcal{O}_A^{ij} \xrightarrow{g_{ij}^A} A, \quad \mathcal{O}_B^{ij} \xrightarrow{g_{ij}^B} B, \quad A \xrightarrow{k_A} \emptyset \quad B \xrightarrow{k_B} \emptyset \tag{51}$$

with $\alpha = A$ or B representing gene A or B. For the gene state index ij of gene O_α, the first index $i = 1(0)$ stands for the activator protein unbound(bound) to the promoter α; the second index $j = 1(0)$ stands for the repressor protein unbound(bound) to the promoter α. g_A^{ij} (g_B^{ij}) is the synthesis rate of the protein A (B) when the gene A (B) is in state ij. The probability distribution of the microstate is indicated as $P_{ijkl}(x_1, x_2)$ ($x_1 = n_A/V, x_2 = n_B/V$ are concentrations of the protein A and B, V is the cell volume). The index $i(j)$ represents the gene A occupation state by the protein $A(B)$ and the index $k(l)$ represents the gene B occupation state by the protein $A(B)$. Corresponding 16 Master equations for this gene regulatory circuit are given as following:

$$\begin{aligned}
&\frac{dP_{1111}(x_1,x_2)}{dt} = \\
&-hx_1^4 P_{1111}(x_1,x_2) + fP_{0111}(x_1,x_2) - hx_2^4 P_{1111}(x_1,x_2) + fP_{1011}(x_1,x_2) \\
&-hx_1^4 P_{1111}(x_1,x_2) + fP_{1101}(x_1,x_2) - hx_1^4 P_{1111}(x_1,x_2) + fP_{1110}(x_1,x_2) \\
&+k_A[(x_1+\frac{1}{V})P_{1111}(x_1+\frac{1}{V},x_2) - x_1 P_{1111}(x_1,x_2)] + g_{11}^A[P_{1111}(x_1-\frac{1}{V},x_2) - P_{1111}(x_1,x_2)] \\
&+k_B[(x_2+\frac{1}{V})P_{1111}(x_1,x_2+\frac{1}{V}) - x_2 P_{1111}(x_1,x_2)] + g_{11}^B[P_{1111}(x_1,x_2-\frac{1}{V}) - P_{1111}(x_1,x_2)]
\end{aligned} \tag{52}$$

$$\frac{dP_{1011}(x_1,x_2)}{dt} =$$
$$-hx_1^4 P_{1011}(x_1,x_2) + fP_{0011}(x_1,x_2) + hx_2^4 P_{1111}(x_1,x_2) - fP_{1011}(x_1,x_2)$$
$$-hx_1^4 P_{1011}(x_1,x_2) + fP_{1001}(x_1,x_2) - hx_2^4 P_{1011}(x_1,x_2) + fP_{1010}(x_1,x_2)$$
$$+k_A[(x_1+\frac{1}{V})P_{1011}(x_1+\frac{1}{V},x_2) - x_1 P_{1011}(x_1,x_2)] + g_{10}^A[P_{1011}(x_1-\frac{1}{V},x_2) - P_{1011}(x_1,x_2)]$$
$$+k_B[(x_2+\frac{1}{V})P_{1011}(x_1,x_2+\frac{1}{V}) - x_2 P_{1011}(x_1,x_2)] + g_{11}^B[P_{1011}(x_1,x_2-\frac{1}{V}) - P_{1011}(x_1,x_2)] \tag{53}$$

$$\frac{dP_{0111}(x_1,x_2)}{dt} =$$
$$+hx_1^4 P_{1111}(x_1,x_2) - fP_{0111}(x_1,x_2) - hx_2^4 P_{0111}(x_1,x_2) + fP_{0011}(x_1,x_2)$$
$$-hx_1^4 P_{0111}(x_1,x_2) + fP_{0101}(x_1,x_2) - hx_2^4 P_{0111}(x_1,x_2) + fP_{0110}(x_1,x_2)$$
$$+k_A[(x_1+\frac{1}{V})P_{0111}(x_1+\frac{1}{V},x_2) - x_1 P_{0111}(x_1,x_2)] + g_{01}^A[P_{0111}(x_1-\frac{1}{V},x_2) - P_{0111}(x_1,x_2)]$$
$$+k_B[(x_2+\frac{1}{V})P_{0111}(x_1,x_2+\frac{1}{V}) - x_2 P_{0111}(x_1,x_2)] + g_{11}^B[P_{0111}(x_1,x_2-\frac{1}{V}) - P_{0111}(x_1,x_2)] \tag{54}$$

$$\frac{dP_{0011}(x_1,x_2)}{dt} =$$
$$+hx_1^4 P_{1011}(x_1,x_2) - fP_{0011}(x_1,x_2) + hx_2^4 P_{0111}(x_1,x_2) - fP_{0011}(x_1,x_2)$$
$$-hx_1^4 P_{0011}(x_1,x_2) + fP_{0001}(x_1,x_2) - hx_2^4 P_{0011}(x_1,x_2) + fP_{0010}(x_1,x_2)$$
$$+k_A[(x_1+\frac{1}{V})P_{0011}(x_1+\frac{1}{V},x_2) - x_1 P_{0011}(x_1,x_2)] + g_{00}^A[P_{0011}(x_1-\frac{1}{V},x_2) - P_{0011}(x_1,x_2)]$$
$$+k_B[(x_2+\frac{1}{V})P_{0011}(x_1,x_2+\frac{1}{V}) - x_2 P_{0011}(x_1,x_2)] + g_{11}^B[P_{0011}(x_1,x_2-\frac{1}{V}) - P_{0011}(x_1,x_2)] \tag{55}$$

$$\frac{dP_{1110}(x_1,x_2)}{dt} =$$
$$-hx_1^4 P_{1110}(x_1,x_2) + fP_{0110}(x_1,x_2) - hx_2^4 P_{1110}(x_1,x_2) + fP_{1010}(x_1,x_2)$$
$$-hx_1^4 P_{1110}(x_1,x_2) + fP_{1100}(x_1,x_2) + hx_2^4 P_{1111}(x_1,x_2) - fP_{1110}(x_1,x_2)$$
$$+k_A[(x_1+\frac{1}{V})P_{1110}(x_1+\frac{1}{V},x_2) - x_1 P_{1110}(x_1,x_2)] + g_{11}^A[P_{1110}(x_1-\frac{1}{V},x_2) - P_{1110}(x_1,x_2)]$$
$$+k_B[(x_2+\frac{1}{V})P_{1110}(x_1,x_2+\frac{1}{V}) - x_2 P_{1110}(x_1,x_2)] + g_{10}^B[P_{1110}(x_1,x_2-\frac{1}{V}) - P_{1110}(x_1,x_2)] \tag{56}$$

$$\frac{dP_{1010}(x_1,x_2)}{dt} =$$
$$-hx_1^4 P_{1010}(x_1,x_2) + fP_{0010}(x_1,x_2) + hx_2^4 P_{1110}(x_1,x_2) - fP_{1010}(x_1,x_2)$$
$$-hx_1^4 P_{1010}(x_1,x_2) + fP_{1000}(x_1,x_2) + hx_2^4 P_{1011}(x_1,x_2) - fP_{1010}(x_1,x_2)$$
$$+k_A[(x_1+\frac{1}{V})P_{1010}(x_1+\frac{1}{V},x_2) - x_1 P_{1010}(x_1,x_2)] + g_{10}^A[P_{1010}(x_1-\frac{1}{V},x_2) - P_{1010}(x_1,x_2)]$$
$$+k_B[(x_2+\frac{1}{V})P_{1010}(x_1,x_2+\frac{1}{V}) - x_2 P_{1010}(x_1,x_2)] + g_{10}^B[P_{1010}(x_1,x_2-\frac{1}{V}) - P_{1010}(x_1,x_2)] \tag{57}$$

$$\frac{dP_{0110}(x_1,x_2)}{dt} =$$
$$+hx_1^4 P_{1110}(x_1,x_2) - fP_{0110}(x_1,x_2) - hx_2^4 P_{0110}(x_1,x_2) + fP_{0010}(x_1,x_2)$$
$$-hx_1^4 P_{0110}(x_1,x_2) + fP_{0100}(x_1,x_2) + hx_2^4 P_{0111}(x_1,x_2) - fP_{0110}(x_1,x_2)$$
$$+k_A[(x_1+\frac{1}{V})P_{0110}(x_1+\frac{1}{V},x_2) - x_1 P_{0110}(x_1,x_2)] + g_{01}^A[P_{0110}(x_1-\frac{1}{V},x_2) - P_{0110}(x_1,x_2)]$$
$$+k_B[(x_2+\frac{1}{V})P_{0110}(x_1,x_2+\frac{1}{V}) - x_2 P_{0110}(x_1,x_2)] + g_{10}^B[P_{0110}(x_1,x_2-\frac{1}{V}) - P_{0110}(x_1,x_2)] \tag{58}$$

$$\frac{dP_{0010}(x_1,x_2)}{dt} =$$
$$+hx_1^4P_{1010}(x_1,x_2) - fP_{0010}(x_1,x_2) + hx_2^4P_{0110}(x_1,x_2) - fP_{0010}(x_1,x_2)$$
$$-hx_1^4P_{0010}(x_1,x_2) + fP_{0000}(x_1,x_2) + hx_2^4P_{0011}(x_1,x_2) - fP_{0010}(x_1,x_2)$$
$$+k_A[(x_1+\frac{1}{V})P_{0010}(x_1+\frac{1}{V},x_2) - x_1P_{0010}(x_1,x_2)] + g_{00}^A[P_{0010}(x_1-\frac{1}{V},x_2) - P_{0010}(x_1,x_2)]$$
$$+k_B[(x_2+\frac{1}{V})P_{0010}(x_1,x_2+\frac{1}{V}) - x_2P_{0010}(x_1,x_2)] + g_{10}^B[P_{0010}(x_1,x_2-\frac{1}{V}) - P_{0010}(x_1,x_2)] \tag{59}$$

$$\frac{dP_{1101}(x_1,x_2)}{dt} =$$
$$-hx_1^4P_{1101}(x_1,x_2) + fP_{0101}(x_1,x_2) - hx_2^4P_{1101}(x_1,x_2) + fP_{1001}(x_1,x_2)$$
$$+hx_1^4P_{1111}(x_1,x_2) - fP_{1101}(x_1,x_2) - hx_2^4P_{1101}(x_1,x_2) + fP_{1100}(x_1,x_2)$$
$$+k_A[(x_1+\frac{1}{V})P_{1101}(x_1+\frac{1}{V},x_2) - x_1P_{1101}(x_1,x_2)] + g_{11}^A[P_{1101}(x_1-\frac{1}{V},x_2) - P_{1101}(x_1,x_2)]$$
$$+k_B[(x_2+\frac{1}{V})P_{1101}(x_1,x_2+\frac{1}{V}) - x_2P_{1101}(x_1,x_2)] + g_{01}^B[P_{1101}(x_1,x_2-\frac{1}{V}) - P_{1101}(x_1,x_2)] \tag{60}$$

$$\frac{dP_{1001}(x_1,x_2)}{dt} =$$
$$-hx_1^4P_{1001}(x_1,x_2) + fP_{0001}(x_1,x_2) + hx_2^4P_{1101}(x_1,x_2) - fP_{1001}(x_1,x_2)$$
$$+hx_1^4P_{1011}(x_1,x_2) - fP_{1001}(x_1,x_2) - hx_2^4P_{1001}(x_1,x_2) + fP_{1000}(x_1,x_2)$$
$$+k_A[(x_1+\frac{1}{V})P_{1001}(x_1+\frac{1}{V},x_2) - x_1P_{1001}(x_1,x_2)] + g_{10}^A[P_{1001}(x_1-\frac{1}{V},x_2) - P_{1001}(x_1,x_2)]$$
$$+k_B[(x_2+\frac{1}{V})P_{1001}(x_1,x_2+\frac{1}{V}) - x_2P_{1001}(x_1,x_2)] + g_{01}^B[P_{1001}(x_1,x_2-\frac{1}{V}) - P_{1001}(x_1,x_2)] \tag{61}$$

$$\frac{dP_{0101}(x_1,x_2)}{dt} =$$
$$+hx_1^4 P_{1101}(x_1,x_2) - fP_{0101}(x_1,x_2) - hx_2^4 P_{0101}(x_1,x_2) + fP_{0001}(x_1,x_2)$$
$$+hx_1^4 P_{0111}(x_1,x_2) - fP_{0101}(x_1,x_2) - hx_2^4 P_{0101}(x_1,x_2) + fP_{0100}(x_1,x_2)$$
$$+k_A[(x_1+\frac{1}{V})P_{0101}(x_1+\frac{1}{V},x_2) - x_1 P_{0101}(x_1,x_2)] + g_{01}^A[P_{0101}(x_1-\frac{1}{V},x_2) - P_{0101}(x_1,x_2)]$$
$$+k_B[(x_2+\frac{1}{V})P_{0101}(x_1,x_2+\frac{1}{V}) - x_2 P_{0101}(x_1,x_2)] + g_{01}^B[P_{0101}(x_1,x_2-\frac{1}{V}) - P_{0101}(x_1,x_2)] \tag{62}$$

$$\frac{dP_{0001}(x_1,x_2)}{dt} =$$
$$+hx_1^4 P_{1001}(x_1,x_2) - fP_{0001}(x_1,x_2) + hx_2^4 P_{0101}(x_1,x_2) - fP_{0001}(x_1,x_2)$$
$$+hx_1^4 P_{0011}(x_1,x_2) - fP_{0001}(x_1,x_2) - hx_2^4 P_{0001}(x_1,x_2) + fP_{0000}(x_1,x_2)$$
$$+k_A[(x_1+\frac{1}{V})P_{0001}(x_1+\frac{1}{V},x_2) - x_1 P_{0001}(x_1,x_2)] + g_{00}^A[P_{0001}(x_1-\frac{1}{V},x_2) - P_{0001}(x_1,x_2)]$$
$$+k_B[(x_2+\frac{1}{V})P_{0001}(x_1,x_2+\frac{1}{V}) - x_2 P_{0001}(x_1,x_2)] + g_{01}^B[P_{0001}(x_1,x_2-\frac{1}{V}) - P_{0001}(x_1,x_2)] \tag{63}$$

$$\frac{dP_{1100}(x_1,x_2)}{dt} =$$
$$-hx_1^4 P_{1100}(x_1,x_2) + fP_{0100}(x_1,x_2) - hx_2^4 P_{1100}(x_1,x_2) + fP_{1000}(x_1,x_2)$$
$$+hx_1^4 P_{1110}(x_1,x_2) - fP_{1100}(x_1,x_2) + hx_2^4 P_{1101}(x_1,x_2) - fP_{1100}(x_1,x_2)$$
$$+k_A[(x_1+\frac{1}{V})P_{1100}(x_1+\frac{1}{V},x_2) - x_1 P_{1100}(x_1,x_2)] + g_{11}^A[P_{1100}(x_1-\frac{1}{V},x_2) - P_{1100}(x_1,x_2)]$$
$$+k_B[(x_2+\frac{1}{V})P_{1100}(x_1,x_2+\frac{1}{V}) - x_2 P_{1100}(x_1,x_2)] + g_{00}^B[P_{1100}(x_1,x_2-\frac{1}{V}) - P_{1100}(x_1,x_2)] \tag{64}$$

$$\frac{dP_{1000}(x_1,x_2)}{dt} =$$
$$-hx_1^4 P_{1000}(x_1,x_2) + fP_{0000}(x_1,x_2) + hx_2^4 P_{1100}(x_1,x_2) - fP_{1000}(x_1,x_2)$$
$$+hx_1^4 P_{1010}(x_1,x_2) - fP_{1000}(x_1,x_2) + hx_2^4 P_{1001}(x_1,x_2) - fP_{1000}(x_1,x_2)$$
$$+k_A[(x_1+\frac{1}{V})P_{1000}(x_1+\frac{1}{V},x_2) - x_1 P_{1000}(x_1,x_2)] + g_{10}^A[P_{1000}(x_1-\frac{1}{V},x_2) - P_{1000}(x_1,x_2)]$$
$$+k_B[(x_2+\frac{1}{V})P_{1000}(x_1,x_2+\frac{1}{V}) - x_2 P_{1000}(x_1,x_2)] + g_{00}^B[P_{1000}(x_1,x_2-\frac{1}{V}) - P_{1000}(x_1,x_2)] \tag{65}$$

$$\frac{dP_{0100}(x_1,x_2)}{dt} =$$
$$+hx_1^4 P_{1100}(x_1,x_2) - fP_{0100}(x_1,x_2) - hx_2^4 P_{0100}(x_1,x_2) + fP_{0000}(x_1,x_2)$$
$$+hx_1^4 P_{0110}(x_1,x_2) - fP_{0100}(x_1,x_2) + hx_2^4 P_{0101}(x_1,x_2) - fP_{0100}(x_1,x_2)$$
$$+k_A[(x_1+\frac{1}{V})P_{0100}(x_1+\frac{1}{V},x_2) - x_1 P_{0100}(x_1,x_2)] + g_{01}^A[P_{0100}(x_1-\frac{1}{V},x_2) - P_{0100}(x_1,x_2)]$$
$$+k_B[(x_2+\frac{1}{V})P_{0100}(x_1,x_2+\frac{1}{V}) - x_2 P_{0100}(x_1,x_2)] + g_{00}^B[P_{0100}(x_1,x_2-\frac{1}{V}) - P_{0100}(x_1,x_2)] \tag{66}$$

$$\frac{dP_{0000}(x_1,x_2)}{dt} =$$
$$+hx_1^4 P_{1000}(x_1,x_2) - fP_{0000}(x_1,x_2) + hx_2^4 P_{0100}(x_1,x_2) - fP_{0000}(x_1,x_2)$$
$$+hx_1^4 P_{0010}(x_1,x_2) - fP_{0000}(x_1,x_2) + hx_2^4 P_{0001}(x_1,x_2) - fP_{0000}(x_1,x_2)$$
$$+k_A[(x_1+\frac{1}{V})P_{0000}(x_1+\frac{1}{V},x_2) - x_1 P_{0000}(x_1,x_2)] + g_{00}^A[P_{0000}(x_1-\frac{1}{V},x_2) - P_{0000}(x_1,x_2)]$$
$$+k_B[(x_2+\frac{1}{V})P_{0000}(x_1,x_2+\frac{1}{V}) - x_2 P_{0000}(x_1,x_2)] + g_{00}^B[P_{0000}(x_1,x_2-\frac{1}{V}) - P_{0000}(x_1,x_2)] \tag{67}$$

In the adiabatic limit, the binding/unbinding processes are much faster than the synthesis/degradation. Therefore, the binding/unbinding processes reach equilibrium faster than the other processes and the probability of the gene state P_{ij}^A is determined as the function

of the concentrations x_1 and x_2: $hx_1^4 P_{1j}^A = fP_{0j}^A$, $hx_2^4 P_{i1}^A = fP_{i0}^A$, which lead to

$$P_{00}^A = \frac{1}{1 + \frac{x_1^4}{S^4} + \frac{x_2^4}{S^4} + \frac{x_1^4}{S^4}\frac{x_2^4}{S^4}} \tag{68}$$

$$P_{01}^A = \frac{\frac{x_2^4}{S^4}}{1 + \frac{x_1^4}{S^4} + \frac{x_2^4}{S^4} + \frac{x_1^4}{S^4}\frac{x_2^4}{S^4}} \tag{69}$$

$$P_{10}^A = \frac{\frac{x_1^4}{S^4}}{1 + \frac{x_1^4}{S^4} + \frac{x_2^4}{S^4} + \frac{x_1^4}{S^4}\frac{x_2^4}{S^4}} \tag{70}$$

$$P_{11}^A = \frac{\frac{x_1^4}{S^4}\frac{x_2^4}{S^4}}{1 + \frac{x_1^4}{S^4} + \frac{x_2^4}{S^4} + \frac{x_1^4}{S^4}\frac{x_2^4}{S^4}} \tag{71}$$

with $S^4 = f/h$. If $g_{00}^A = g_0^A + b_1$, $g_{01}^A = g_0^A$, $g_{10}^A = g_0^A + a_1 + b_1$, $g_{11}^A = g_0^A + a_1$, the total effective synthesis rate of protein A from these 4 gene states is: with

$$g^A(x_1, x_2) = g_0^A + \frac{a_1 x_1^4}{S^4 + x_1^4} + \frac{b_1 S^4}{S^4 + x_2^4} \tag{72}$$

Similarly, we can have effective synthesis rate of protein B as:

$$g^B(x_1, x_2) = g_0^B + \frac{a_2 x_2^4}{S^4 + x_2^4} + \frac{b_2 S^4}{S^4 + x_1^4} \tag{73}$$

Then, in the adiabatic limit, we can finally reach an effective chemical master equation in concentration space as (as compared to the general 16 chemical master equations without the adiabaticity assumption of faster binding/unbinding of regulatory proteins to the genes):

$$\begin{aligned} \frac{dP(x_1, x_2)}{dt} &= g^A(x_1, x_2)[P(x_1 - \frac{1}{V}, x_2) - P(x_1, x_2)] \\ &+ k_A[(x_1 + \frac{1}{V})P(x_1 + \frac{1}{V}, x_1) - x_1 P(x_1, x_2)] \\ &+ g^B(x_1, x_2)[P(x_1, x_2 - \frac{1}{V}) - P(x_1, x_2)] \\ &+ k_B[(x_2 + \frac{1}{V})P(x_1, x_2 + \frac{1}{V}) - x_2 P(x_1, x_2)] \end{aligned} \tag{74}$$

Here a_1, a_2 are self-activation coefficients, b_1 and b_2 are mutual repression coefficients, g_0^A and g_0^B are basel synthesis rates of A and B.

When the number of the molecules become large, one can do large volume expansion for the master equation (74). The Taylor expansion of chemical master equations equ. (74) up to the second order will lead to the Fokker-Planck equation as

$$\frac{dP}{dt} = \sum_\mu \partial_\mu(-F_\mu P) + \sum_{\mu,\nu} \frac{1}{2}\partial_\mu\partial_\nu(\varepsilon_{\mu\nu} P) \tag{75}$$

with the driving force $\vec{F} = \frac{1}{V}(g^A - k_A x_1, g^B - k_B x_2)$ and diffusion coefficients $\varepsilon_{11} = \frac{1}{V^2}(g^A + k_A x_1), \varepsilon_{22} = \frac{1}{V^2}(g^B + k_B x_2), \varepsilon_{12} = \varepsilon_{21} = 0$. It represents a stochastic process with intrinsic noise where the diffusion coefficients depend on the location (x_1, x_2) [8].

IX. TABLE OF MFPT RESULTS

The numerical values of $MFPT = 1/r_K^{noneq}$ from our theory (Nonequilibrium TST), Langevin dynamics simulations, the zero fluctuation approximations, and equilibrium transition state or Kramers' theory for differentiation and reprogramming are given in following tables.

TABLE I: Differential rate

V	Nonequilibrium TST	Simulation	zero noise approximation	Equilibrium
25	6127.6	6675.0	2385.4	509.62
30	13502.5	13590.4	5541.6	1208.0
35	31923.0	24375.6	12952.6	2716.1
40	67216.2	46081.2	25663.3	6000.3
45	1.3571e5	93247.0	55385.3	12942.0
50	2.7072e5	1.8806e5	1.1725e5	27496.3

TABLE II: Reprogramming rate

V	Nonequilibrium TST	Simulation	zero noise approximation	Equilibrium
25	2390.8	3142.1	1261.2	452.10
30	4603.1	5345.6	2025.8	875.19
35	8532.4	9215.8	4183.8	1599.2
40	15893.1	15873.6	7134.3	2898.4
45	28330.6	24914.9	12587.5	5098.0
50	49218.9	44115.7	21126.2	8840.1

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