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A perturbation analysis of rate theory of self-regulating genes and signaling networks

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A thorough kinetic analysis of the rate theory for stochastic self-regulating gene networks is presented. The chemical master equation kinetic model in terms of a coupled birth–death process is deconstructed into several simpler kinetic modules. We formulate and improve upon the rate theory of self-regulating genes in terms of perturbation theory. We propose a simple five-state scheme as a faithful caricature that elucidates the full kinetics including the "resonance phenomenon" discovered by Walczak *et al.* [Proc. Natl. Acad. Sci. U.S.A. **102**, 18926 (2005)]. The same analysis can be readily applied to other biochemical networks such as phosphorylation signaling with fluctuating kinase activity. Generalization of the present approach can be included in multiple time-scale numerical computations for large biochemical networks. © *2011 American Institute of Physics*. [doi:10.1063/1.3535561]

I. INTRODUCTION

State switching of a biochemical network exists widely in cell biology. Transitions, or jumps, between "macroscopic states" play important roles in crucial biological processes, such as gene expression regulation, epigenetic differentiation, signal transduction, etc. The stochastic properties in the kinetics of a genetic switch is the key part in understanding the function and mechanism of genetic switches. One of the switches that has been extensively studied is the self-activating gene, which is a simplified model originated from the bacteriophage λ.[1–7] Such a self-regulating genetic system resides in one of the two stable attractors, corresponding to two different phenotypes of the cell. The kinetic parameters that determine the characteristics of switching from one attractor to the other are the rates of binding and unbinding of activators and the rates for protein synthesis and degradation. The case that activator binding–unbinding is much faster than the protein synthesis and degradation is known as the *adiabatic* limit, while the case of rare binding–unbinding relative to protein number fluctuation is called the *nonadiabatic* limit. Biologically both scenarios may exist: Sometimes, the protein binding is only diffusion limited and thus is much faster than the complex protein expression process which involves multiple components and is energy consuming; while in other situations, especially in eukaryotic systems, transcription initiation itself requires a complex chromosome restructuring which could be considerably slower than the protein production. Finally but not the least, changing the rate of protein degradation is an important regulatory mechanism in cellular biology in general. Such a change will also result in a change of adiabaticity of the system. Therefore, the transition rate between stable attractors of a genetic switch in the whole range of adiabaticity parameter is biologically relevant; it is intimately related to the general issue of genetic stability. Furthermore, the existence of a maximum transition rate in the intermediate region of adiabaticity makes it a more interesting kinetic problem, and computing the transition rate in the entire range of adiabaticity attracts a great amount of attention in recent years.[3,8–14] While there have been a great many work on steady-state distributions and on numerical simulations of switching kinetics,[15–17] analytical treatment of the rate theory has not been fully developed. Toward this end, one of the most relevant work is Walczak *et al.*'s absolute rate theory.[8]

In our present work, we study the self-regulating gene problem using a systematic perturbation theory approach. We show that the leading terms of the asymptotic series solution, in terms of a dimensionless adiabatic parameter σ, coincide with approximation approaches assuming fast pre-equilibriums. One of the most interesting discoveries of the earlier work is a resonancelike behavior of the escape rate between the stable transcriptional states of the gene—the maximum of escape rate locates at the intermediate region of the adiabaticity parameter. Using the asymptotic series solution, we can define the condition of the existence of Walczak–Onuchic–Wolynes (WOW) resonance by the leading terms of the asymptotic series solutions. To further understand the mechanism of the resonance, we propose a five-state kinetic scheme as the minimum model that preserves the resonance kinetics. The analysis of the five-state model reveals the mechanism of the WOW resonance, and conclude that similar resonance exists for gene activations that requires multiple binding of a transcription factor. Finally, the simple five-state model can be fitted using leading terms of asymptotic series solution to obtain a full-range approximated escape rate, which predicts the maximum escape rate, as well as the location of the maximum.

We shall emphasize that the analysis on self-regulating gene networks can be generalized to self-regulating signaling networks directly. The resemblance between the self-regulating gene networks and phosphorylation–dephosphorylation signaling networks with feedback is shown in Fig. 1. The regulatory mechanisms of the two

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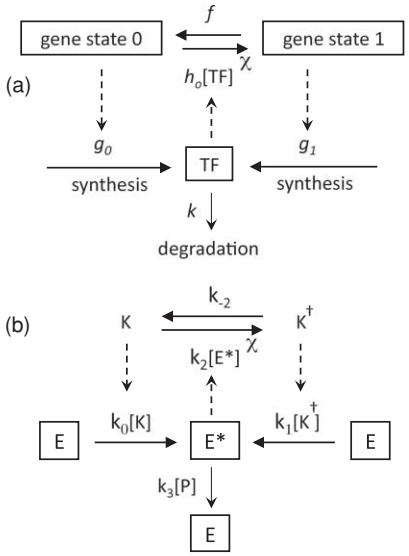

FIG. 1. Schematic diagrams showing kinetic isomorphism between a self-regulating gene network in (a) and a cellular signaling network based on phosphorylation–dephosphorylation cycle with feedback in (b). (a) Binding of a transcription factor (TF) monomer ($\chi = 1$) or dimer ($\chi = 2$) turns the gene state from 0 to 1; the gene states 0 and 1 determine the rate of TF synthesis with g_0 and g_1, respectively. The TF is degraded with rate k. (b) A phosphorylated enzyme E^* activates a kinase from state K to $K^\dagger$ by binding to the kinase; the K and $K^\dagger$ in turn are the enzymes responsible for the phosphorylation of E with rate constants k_0 and k_1. The dephosphorylation reaction has a rate of $k_3[P]$ where P is a phosphatase. The solid lines represent biochemical reactions while the dashed lines represent information flow.

systems are kinetically isomorphic: An active signaling protein (e.g., a phosphorylated enzyme or a GTP-bound GTPase) controls the state of a regulator protein (a kinase or a guanine nucleotide exchange factor, respectively), which in turn affects the concentration of the active signal proteins. Such a signaling kinetics can be found in both Src family kinase[18] and Rab5 GTPase.[19]

II. SELF-REGULATING GENE NETWORK AND WOW RESONANCE

While our perturbation approach is general, we focus in particular on the simple genetic switch model previously studied by Walczak *et al.*[6–8] The system is characterized by the "u" (up) or "d" (down) state of a single gene, corresponding to bound or unbound of the transcription factors (TF) onto the appropriate DNA binding sites, respectively, and the number of TF proteins in the cellular environment. The gene expression is regulated by the binding of two TF proteins (dimers), with the binding rate $h_{\text{bind}}n(n-1)/2$; the unbinding rate is f_{unbind}. In the d (unbound) state, the gene expresses the TF proteins at a basal level of g_d, while in the u (bound) state, the expression rate is changed to g_u. $g_u < g_d$ means the TF is a repressor while $g_u > g_d$ means the TF is an enhancer. The TF proteins at the meantime are continuously degraded at a constant rate k.

The essential biochemistry of this self-regulating gene system, shown in Fig. 1(a), can be represented by a discrete state continuous time Markov process illustrated in Fig. 2. The lines $m =$ d and $m =$ u correspond to the d ("off") and u ("on") states of the gene, respectively. Within each line, the states are the number of TF proteins in the system. In our specific model, the switching rates between $m =$ d and $m =$ u while the TF number being n, are $h(n) = h_{\text{bind}}n(n-1)/2$, and $f(n) = f_{\text{unbind}}$. More precisely speaking, this mathematical model is a coupled birth–death process. (See Ref. 21 for a recent review of coupled diffusion processes in which the stochastic motions along each line is continuous.) Coupled diffusion has many applications including fluctuating enzyme, ratchet model for motor protein, and protein unfolding by force.[22–26]

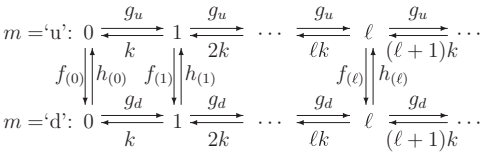

FIG. 2. The self-regulating gene model as a discrete state Markov process. In the theory of the chemical master equation (CME), this type of drawing is called a *chemical master equation graph* (Ref. 20).

In a coupled birth–death process, the steady-state probability distribution of the number of TF proteins characterizes macroscopic states of the gene regulatory system. In nonadiabatic limit ($f(n), h(n) \ll k$), each line ($m =$d,u) reaches its own (quasi) stationarity of birth–death process, so the total probability $P(n)$ (the probability that the system has n molecules and the gene in either u or d state) has two prominent peaks if the g_d and g_u are significantly different. In adiabatic limit ($f(n), h(n) \gg k$), the switching between u and d state of the gene reaches fast equilibrium, so the mean protein production rate is $\overline{g} = (f(n)g_d + h(n)g_u)/(f(n) + h(n))$, and the mean protein degradation rate is $\overline{k} = kn$. With certain parameters, the mean protein "flux" $\overline{g} - \overline{k} = (f_{\text{unbind}}g_d + h_{\text{bind}}n(n-1)g_u/2)/(f_{\text{unbind}} + h_{\text{bind}}n(n-1)/2) - kn$ can have three zeros. This can occur independent of the TF being activating or repressing. As a consequence, the steady-state distribution in adiabatic limit also has two peaks. From the perspective of a stochastic system, two separate peaks in the distribution $P(n)$ means two stable states (attractors) of the system. Therefore, the self-regulating gene forms a self-regulating bistable switch in the whole adiabaticity domain.

The switching rate between the attractors of the system under different adiabaticity is of great interest, as it reflects the stability of the switch. We define $\sigma = (h_{\text{bind}}g_u^2)/(2k^3)$ as the measurement of the adiabaticity of the process, and assume $h_{\text{bind}}/f_{\text{unbind}}$ is kept constant when the adiabaticity changes. Therefore, both h_{bind} and f_{unbind} are linear functions of the adiabaticity σ. Beyond this point of the paper, we use the notation $h_{\text{bind}} = \sigma h$, $f_{\text{unbind}} = \sigma f$, where $h = 2k^3/g_u^2$ and $f = hf_{\text{unbind}}/h_{\text{bind}}$ are the binding and unbinding rates of the TFs at adiabaticity $\sigma = 1$. As a result, $h(n) = \sigma hn(n-1)/2$, $f(n) = \sigma f$. The advantage of the above notation is that adiabaticity is isolated from other parameters of the model.

One well-established measure of switching rate is $k_{\text{on}} + k_{\text{off}}$, the sum of the two escape rates from one attractor to the other. With properly chosen parameter values, Walczak *et al.*

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have shown that the rate as a function of adiabaticity exhibits a maximum, which we shall call WOW resonance. More precisely, in terms of the adiabaticity parameter σ, in the nonadiabatic limit the rate $k_{\rm on}+k_{\rm off}$ is proportional to σ, in the adiabatic limit the rate is constant, and in intermediate domain, the rate reaches a maximum. In other words, the switching rate between the two stable macroscopic states of the system is not monotonic with respect to the gene regulator's binding and unbinding rates, and a resonancelike effect takes place when the binding–unbinding rate falls in a certain region of intermediate adiabaticity.

In both strong nonadiabatic and adiabatic limit, one can exploit the time scale separation in TF protein number fluctuation and gene states fluctuation to compute the steady-state probability distribution and mean first passage time between attractors. In the nonadiabatic limit, since the interconversions of the gene states are slow, one can safely assume that each gene state has a rapid "pre-equilibrium" for the protein copy numbers, in terms of a Poisson distribution

$$p(n|m)=\frac{1}{n!}\left(\frac{g_m}{k}\right)^n e^{-g_m/k}, \tag{1}$$

where $m=$ d, u is the gene state. With the rapid pre-equilibrium among the protein copy numbers within a gene state, one then have the transition rates, on a slower time scale, between two gene states d and u

$$\begin{aligned} q_{ud}&=\sum_{n=0}^{\infty} f(n)p(n|\mathrm{u})=\sigma f,\\ q_{du}&=\sum_{n=0}^{\infty} h(n)p(n|\mathrm{d})=\sigma\frac{hg_d^2}{2k^2}. \end{aligned} \tag{2}$$

When g_d, k, f, and h are fixed, the transition rate between two attractors are linear with respect to σ in non-adiabatic limit.

In the adiabatic limit, as the interconversions between the gene states are fast, the gene states reaches pre-equilibrium before protein number fluctuations. Let $p(n)$ be the probability of having n TFs in the system, then $p_d(n)=f(n)/(f(n)+h(n))$, and $p_u(n)=h(n)/(f(n)+h(n))$. Note that $f(n)$ and $h(n)$ are both linear in adiabaticity parameter σ, the adiabatic-limit distribution $p_d(n)$ and $p_u(n)$ are independent of σ. The two birth–death process can be represented by a single average birth–death process with mean protein production rate $\overline{g}(n)=(f(n)g_d+h(n)g_u)/(f(n)+h(n))$, and the mean protein degradation rate is $\overline{k}(n)=kn$, The steady-state distribution for the total probability of having n proteins in the system is

$$p(n)=\frac{\prod_{j=0}^{n-1}\overline{g}(j)}{n!k^n}\Bigg/\sum_{\ell=0}^{\infty}\frac{\prod_{j=0}^{\ell-1}\overline{g}(j)}{\ell!k^\ell}. \tag{3}$$

The transition rate can be obtained using the mean first passage time (MFPT) between states $n=a$ and $n=b$ in the average birth–death process[27]

$$\begin{aligned} T_{a\to b}&=\sum_{s=a+1}^{b}\sum_{j=0}^{s-1}\frac{1}{\overline{g}(j)}\left(\prod_{l=j+1}^{s-1}\frac{lk}{\overline{g}(l)}\right),\quad i=a,\ldots,b-1;\\ T_{b\to a}&=\sum_{s=a+1}^{b}\sum_{j=s}^{\infty}\frac{1}{jk}\left(\prod_{l=s}^{j-1}\frac{\overline{g}(l)}{lk}\right),\quad i=a+1,\ldots,b. \end{aligned} \tag{4}$$

And the transition rates are $q_{ab}=1/T_{a\to b}$, $q_{ba}=1/T_{b\to a}$.

Complications start to arise if the rates $f(n)$ and $g(n)$ are smaller but not sufficiently smaller than $g_{u,d}(n)$ and k. In this case, the time from n_0 state in β to n^* state in $(\alpha,\beta\in\{u,d\})$ still has a dominant term from $1/q_{\alpha\beta}$ [as in Eq. (2)], but not all the transitions from $\beta(n)\to\alpha(n)$ $(n\sim n_0)$ made to the n^*. This is the case that the survival probability of staying at state α after the gene state switching $(\beta\to\alpha)$ occurs need to be estimated and added as a correction to the linear transition rate formula.[8] As the TF binding–unbinding rates $h_{\rm bind}$ and $f_{\rm unbind}$ continue increasing, the survival probability of staying at either gene state becomes so small that a number of switching back and forth in the gene state occur before escaping from either attractors, which is the so-called "eddie motion" in the

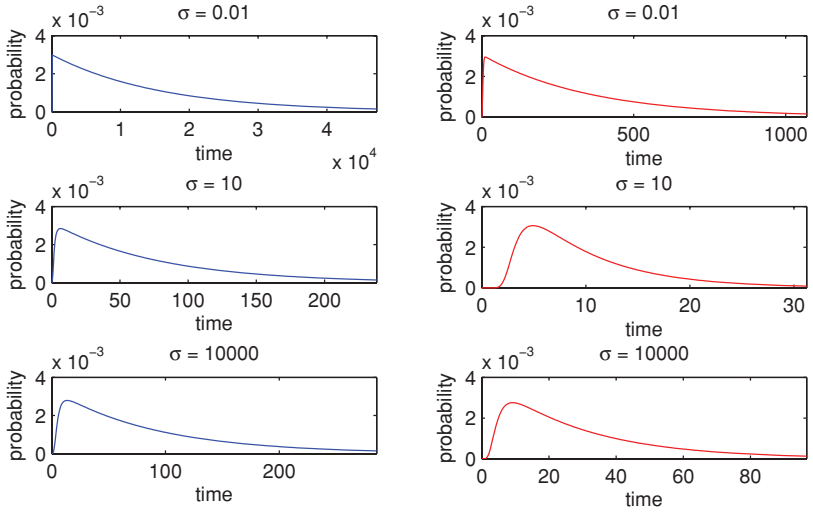

FIG. 3. First passage time distribution at nonadiabatic case ($\sigma=0.01$), intermediate adiabaticity ($\sigma=10$), and adiabatic case ($\sigma=10\,000$). Left panels: transition time distribution from d state to u state. Right panels: transition time distribution from u state to d state. The parameters used in this and all following computations, if not otherwise specified, are $g_u=100$, $g_d=8$, $k=1$, $h=0.0002$, $f=0.2852$.

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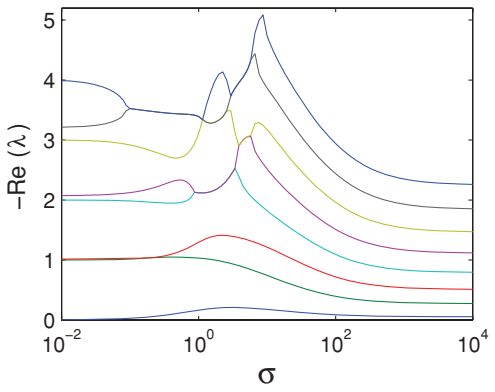

FIG. 4. Inverse of the real part of first eight nonzero eigenvalues (from bottom to top) of the coupled birth–death process as a function of adiabaticity parameter σ. All the eigenvalues show a resonancelike behavior as adiabaticity increases, which means the resonance happens in all time scales. The tangling of eigenvalues in intermediate region shows the dynamics in nonadiabatic region and adiabatic region are essentially different.

coupled birth–death process.[8] In such cases, there is no obvious time scale separation, and the system is the most complex. The transition rate between attractors in this region of adiabaticity is not well approximated by any existing analytical methods. Beyond this region, when adiabaticity becomes fairly large, the gene state switching dominates the fast time scale, and approximation based on absolute rate theory by Walczak *et al.* captures the decreasing behavior of transition rate versus increasing adiabaticity toward the adiabatic limit.[8]

To give an overview of the unique character of the interesting kinetic problem, we shall first present some results from numerically computations, including the transition rate between attractors, the escape time distribution, and the first few nonzero eigenvalues, all the above as functions of adiabaticity. In Fig. 6(a), the exact transition rate between d and u states of the gene (solid curve) exhibits a resonancelike behavior when adiabaticity increases. The fast-equilibrium approximations [diamond and circle curves in top graph of Fig. 6(a)] can capture the limiting behavior, but totally miss the intermediate region. In Fig. 3, the first passage time (FPT) distribution at three adiabaticity regions (nonadiabatic limit, intermediate region, adiabatic limit) shows that only at nonadiabatic limit, the first passage time distribution is approximately exponential. The nonexponentialness of the FPT distributions in adiabatic and intermediate region indicates that in these cases, the transition between attractors cannot be well approximated by a single barrier crossing event. Similar nonexponential first passage time distribution was discovered and discussed in a DNA-inversion genetic switch model, where the switching rates lie in an intermediate adiabaticity region.[28] In Fig. 4, computations show a significant separation between first and second nonzero eigenvalues in the nonadiabatic limit, but the gap shrinks as adiabaticity increases. This implies that outside the nonadiabatic region, the system has to be modeled as a multistep kinetic process.

Due to the complexity of this coupled birth–death process in the intermediate region of adiabaticity, we exploit a rigorous, powerful, and conceptually straightforward tool, the perturbation theory, to conduct an asymptotic analysis of the self-regulating gene transition rate problem. It turns out the leading terms of the asymptotic series solution coincide with approximation methods. By including more terms in the asymptotic series solutions, the region of close approximation is significantly extended.

III. ASYMPTOTIC SERIES SOLUTION

The approximation approaches we discussed in Eq. (1)-(4) are more or less based on physical assumptions that simplify the system. Both the nonadiabatic and adiabatic limiting cases assume fast pre-equilibrium in one of the two dimensions and reduces the problem to a one-dimensional problem. Physically, systems governed by chemical master equations with separated eigenvalues undergoes several processes of different time scales. Therefore, one can break the problem down to several smaller eigen-problems, each one corresponding to a major time scale. However, except for physically very simple problems, how to break down the problem is often not apparent.

Nevertheless, the perturbation theory as a mathematical tool can help deconstructing the whole system into solvable parts. Furthermore, asymptotic methods always give insights on the physics behind the equations. Here we develop a "robust, easy to follow" recipe based on perturbation theory. One of the advantage of this, in addition to being easy to apply to other system, and conceptually simple, is the possibility to go to higher orders. It is not clear, from the original treatment of Walczak *et al.*, how to further improve their approximation method. For demonstration, we carried out the calculation to second order, and the result gives significant improvement. The calculation is straight forward. Finally, this line of approach will also be useful in simplifying multiscale numerical computations[29] for large scale biochemical networks in the future.

We are interested in the relaxation time for a two stable attractor system defined by

$$T = T_{\text{on}} + T_{\text{off}}, \tag{5}$$

where T_{on} is the mean first passage times (MFPT) from the left attractor (gene off, d state) to the right attractor (gene on, u state), and T_{off} is the reverse MFPT from the right to the left. The adiabaticity parameter σ is explicitly expressed in the transition rate between u and d lines, $h(n) = \sigma h_n$, $f(n) = \sigma f_n$. In the current settings, we do not assume specific functional form of f_n and h_n, so the computation of T_{on} and T_{off} are symmetric, and the expressions for T_{on} can be applied directly to T_{off} by swapping g_u and g_d, f_n and h_n. Thus, to

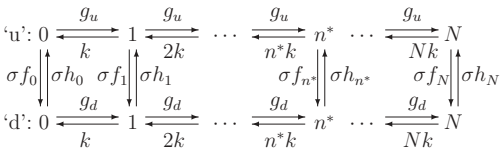

FIG. 5. Chemical master equation graph of the truncated self-regulating gene model which the perturbation equations [Eq. (6)] are based on. n^* is the number of proteins at the attractor at u state of the gene. N is the maximum allowed number of proteins in the system. In the computation of T_{on}, n^* at u line is the tination.

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avoid redundancy, we consider only T_{on}, the time from the left attractor located on lower line, to the right attractor located on upper line. We denote the destination as state n^* on upper line (Fig. 5). Let T_i^d be the MFPT from state i on lower line (d) to destination, and T_i^u be the MFPT from state i on upper line (u) to destination. For the compatibility of numerical computation, we set the maximum number of proteins as a large number N. Due to the exponentially decreasing tail of Poisson distribution, the effect of cut-off is negligible. The formal set up of the problem is

$$(\sigma h_i + g_d + ik)T_i^d = 1 + \sigma h_i T_i^u + g_d T_{i+1}^d + ikT_{i-1}^d \quad i = 0, 1, \ldots, N-1. \tag{6a}$$

$$(\sigma f_i + g_u + ik)T_i^u = 1 + \sigma f_i T_i^d + g_u T_{i+1}^u + ikT_{i-1}^u \quad i = 0, 1, \ldots, N-1, \quad i \neq n^*. \tag{6b}$$

with boundary conditions

$$T_{n^*}^u = 0, \qquad g_u|_{i=N} = g_d|_{i=N} = 0. \tag{6c}$$

The above set of equations is derived based on the Markovian assumption of the underlying process. At each state X ($X = i^u$ or i^d) in the network, the process of transition to the destination state can be decomposed as (1) waiting in state X for a random time, (2) instantaneous transition to one of the directly accessible states of X, and (3) transition from the new state to the destination state. Therefore, the MFPT to the destination state is the mean waiting time at state X plus the mean MFPT from the neighboring states Y, weighted by the probability $p_{X\to Y}$. The equation of T_i^d, as a result, is

$$T_i^d = \frac{1}{\sigma h_i + g_d + ik} + \frac{\sigma h_i}{\sigma h_i + g_d + ik} T_i^u + \frac{g_d}{\sigma h_i + g_d + ik} T_{i+1}^d + \frac{ik}{\sigma h_i + g_d + ik} T_{i-1}^d, \tag{7}$$

where the first term is the mean waiting time at state i^d, and the following three terms are the transition probability multiplied by the MFPT of the three directly accessible states of i^d. Similar derivation applies to T_i^u. By rearranging the terms, we obtain the desired Eq. (6).

A. Nonadiabatic situation

We first investigate the nonadiabatic case, where $\sigma \ll 1$. When $\sigma = 0$, T_i^u will be the MFPT of a birth–death process in one dimension, which is in normal time scale comparing to σ; while T_i^d is ∞, since there is no transition from d line to u line. Therefore, we write the variable in series of σ as

$$T_i^d = \frac{1}{\sigma} T_i^{d0} + T_i^{d1} + \sigma T_i^{d2} + \cdots, \tag{8}$$

$$T_i^u = T_i^{u0} + \sigma T_i^{u1} + \cdots. \tag{9}$$

Substituting these expressions into the master equation [Eq. (6)], we consider the equations in orders of σ^{-1}, 1, and σ.

$$\text{Order } \sigma^{-1}: (g_d + ik)T_i^{d0} = g_d T_{i+1}^{d0} + ikT_{i-1}^{d0}. \tag{10}$$

This is a homogeneous difference equation with Wronskian equals to zero. So there is no unique solution.[30] By induction,

$$T_i^{d0} = \text{const} = T^{d0}, i = 0, 1, \ldots, N.$$

This corresponds to the fast pre-equilibrium assumption in the nonadiabatic limit: The probability distribution along d and u line reaches fast pre-equilibrium before any inter-line transition occurs, so the whole line can be taken as one single state, where the MFPT on line d is the same for all position i.

To compute the value of T^{d0}, we need the next order equation.

$$\text{Order } \sigma^0(d): (g_d + ik)T_i^{d1} = 1 - h_i T_i^{d0} + g_d T_{i+1}^{d1} + ikT_{i-1}^{d1}, \tag{11}$$

with reflecting boundary condition on both ends. In this equation, $T_i^{d0} = T^{d0}$ is an undetermined equation parameter. As shown in detail in Appendix, this is a type I difference equation, and the consistency condition give rise to an equation about T^{d0},

$$\sum_{j=0}^{N} \frac{1}{j!} \left(\frac{g_d}{k}\right)^j \frac{1 - h_j T^{d0}}{g_d} = 0.$$

Plug in the expression of $h_j = hj(j-1)/2$, and let $N \to \infty$, we get

$$T^{d0} = \frac{2}{h} \left(\frac{k}{g_d}\right)^2,$$

so $T^d \approx T^{d0}/\sigma$, which is the same as $1/r$, where r is the escape rate k_{on} computed from Eq. (2), assuming fast pre-equilibrium is reached on both lines before the transition event occurs.

The leading order time T^{d0} governs the solution when σ is small. To get better results when σ approaches 10^{-2}–10^0, we continue to compute the second order time T_i^{d1}.

$$\text{Order } \sigma^0(u): (g_u + ik)T_i^{u0} = 1 + f_i T_i^{d0} + g_u T_{i+1}^{u0} + ikT_{i-1}^{u0}, \tag{12}$$

with an interior Dirichlet boundary condition at n^*, and Neumann boundary at both ends. T_i^{u0} can be computed inductively from n^* to the two ends. (This is a type II difference equation. Refer to Appendix for detail.)

$$T_i^{u0} = \sum_{l=i}^{n^*-1} \sum_{m=0}^{l} \frac{l!}{m!} \left(\frac{k}{g_u}\right)^{l-m} \frac{1 + f_j T^{d0}}{g_u}, \quad i = 0, 1, \ldots, n^* - 1, \tag{13}$$

$$T_i^{u0} = \sum_{l=n^*}^{i-1} \sum_{m=l+1}^{N} \frac{l!}{m!} \left(\frac{k}{g_u}\right)^{l-m} \frac{1 + f_j T^{d0}}{g_u}, \quad i = n^* + 1, \ldots, N. \tag{14}$$

The Eq. (12) is similar to the backward equation for a birth–death process, with an additional time delaying at each step, due to the probability of switching from u state of the gene back to d state before reaching the attractor at u state.

$$\text{Order } \sigma^1(d): (g_d + ik)T_i^{d2} = h_i(T_i^{u0} - T_i^{d1}) + g_d T_{i+1}^{d2} + ikT_{i-1}^{d2}. \tag{15}$$

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Applying the similar consistency condition, we get an equation for T_i^{d1},

$$\sum_{j=0}^{N} \frac{1}{j!} \left(\frac{g_d}{k}\right)^j \frac{h_j(T_j^{u0} - T_j^{d1})}{g_d} = 0. \tag{16}$$

And T_j^{d1} can be expressed in terms of only one unknown variable T_0^{d1},

$$T_j^{d1} = T_0^{d1} + \sum_{l=0}^{j-1} \sum_{m=l+1}^{N} \frac{l!}{m!} \left(\frac{k}{g_d}\right)^{l-m} \frac{1 - h_m T^{d0}}{g_d}.$$

In this way, Eq. (16) is in terms of one variable T_0^{d1}, and can be solved directly. The explicit expression for T_0^{d1} and $T_{n_d}^{d1}$ are shown in Appendix.

The above cycle of computing T^u and T^d alternatively can be carried on to higher orders. To give a clearer picture of this iterative process, we define type I and type II difference equations for the master equation of a one-dimensional birth–death process

$$(\alpha_i + \beta_i)T_i = r_i + \alpha_i T_{i+1} + \beta_i T_{i-1}, \quad 0 \le i \le N. \tag{17}$$

Both type I and type II equations have reflecting boundary at $i = 0$ and $i = N$, but type II equation has a fixed value Dirichlet boundary condition at an interior point while type I equation has no such constrains. Within cycle $k + 1$, the equation for $T^{d(k+1)}$ is a type I difference equation [as Eqs. (11) and (15)], which give rise to a consistency equation for T^{dk}. To solve it, we need to express T^{dk} in terms of one unknown variable, via the lower order equation of T^{dk} in previous computation cycle. Once T^{dk} is computed, the equation for T^{uk} is a type II equation [as Eq. (12)], which can be solved directly. Then the next cycle can be started.

After solving the equations via the cyclic iterations, the MFPT from d state to u state is actually the solution evaluated at the d state attractor n_d. With two leading terms computed, the MFPT is approximately

$$T_{\text{on}} \approx \frac{T^{d0}}{\sigma} + T_{n_d}^{d1}. \tag{18}$$

B. Adiabatic situation

In the adiabatic situation, σ is large, so the asymptotic series are written in the reverse order

$$T_i^d = T_i^{d0} + \frac{T_i^{d1}}{\sigma} + \frac{T_i^{d2}}{\sigma^2} + \cdots, \tag{19}$$

$$T_i^u = T_i^{u0} + \frac{T_i^{u1}}{\sigma} + \frac{T_i^{u2}}{\sigma^2} + \cdots. \tag{20}$$

Plugging into the master equation [Eq. (6)], the leading order (σ) equation is

$$h_i T_i^{d0} = h_i T_i^{u0}, \quad f_i T_i^{u0} = f_i T_i^{d0}. \tag{21}$$

So

$$T_i^{d0} = T_i^{u0} \triangleq T_i^0.$$

This means the MFPT is a function of only the number of proteins in the system, and irrelevant of the gene state, which is actually the direct result by assuming fast pre-equilibrium in transition between gene states.

In order σ^0, we have

$$(g_d + ik)T_i^0 + h_i T_i^{d1} = 1 + h_i T_i^{u1} + g_d T_{i+1}^0 + ikT_{i-1}^0, \tag{22}$$

$$(g_u + ik)T_i^0 + f_i T_i^{u1} = 1 + f_i T_i^{d1} + g_u T_{i+1}^0 + ikT_{i-1}^0, \quad i \ne n^*. \tag{23}$$

Use $f_i \times (22) + h_i \times (23)$, we get an equation about T_i^0,

$$\left[(f_i g_d + h_i g_u) + (f_i + h_i)ik\right] T_i^0 = f_i + h_i + (f_i g_d + h_i g_u)T_{i+1}^0 + (f_i + h_i)ikT_{i-1}^0, \tag{24}$$

with boundary condition at n^* that $T_{n^*}^0 = 0$. This is the same equation as the one dimension birth–death problem with expected forward rate $(f_i g_d + h_i g_u)/(f_i + h_i)$ and backward rate ik. So, the solution T_i^{u0} are actually the same as that of fast pre-equilibrium assumption [Eq. (4)].

Once T_i^0 is computed, according to Eq. (22), T_i^{u1} and T_i^{d1} will be related as

$$T_i^{d1} - T_i^{u1} = \frac{1 + g_d(T_{i+1}^0 - T_i^0) - ik(T_i^0 - T_{i-1}^0)}{h_i} \equiv \Delta_i^1.$$

In the next order σ^{-1},

$$(g_d + ik)T_i^{d1} + h_i T_i^{d2} = h_i T_i^{u2} + g_d T_{i+1}^{d1} + ikT_{i-1}^{d1}, \tag{25}$$

$$(g_u + ik)T_i^{u1} + f_i T_i^{u2} = f_i T_i^{d2} + g_u T_{i+1}^{u1} + ikT_{i-1}^{u1}, \quad i \ne n^*. \tag{26}$$

Similarly, $f_i \times (25) + h_i \times (26)$, we get

$$f_i(g_d + ik)T_i^{d1} + h_i(g_u + ik)T_i^{u1} = f_i g_d T_{i+1}^{d1} + f_i ikT_{i-1}^{d1} + h_i g_u T_{i+1}^{u1} + h_i ikT_{i-1}^{u1}. \tag{27}$$

Plug in $T_i^{d1} = T_i^{u1} + \Delta_i^1$, we get a type II equation for T_i^{u1},

$$\left[(f_i g_d + h_i g_u) + (f_i + h_i)ik\right] T_i^{u1} = f_i\left[-(g_d + ik)\Delta_i^1 + g_d\Delta_{i+1}^1 + ik\Delta_{i-1}^1\right] + (f_i g_d + h_i g_u)T_{i+1}^{u1} + (f_i + h_i)ikT_{i-1}^{u1}, \tag{28}$$

with boundary condition $T_{n^*}^{u1} = 0$. It can be solved using formula for type II equations (shown in Appendix).

Finally, the MFPT from d to u state in adiabatic case can be written in terms of the solution evaluated at d state attractor n_d, as a second order approximation

$$T_{\text{on}} \approx T_{n_d}^{d0} + \frac{T_{n_d}^{d1}}{\sigma}. \tag{29}$$

The iterative process of computing each terms of asymptotic series in adiabatic case is different from that in nonadiabatic case. In each order of σ, we have a pair of equation coupled with next order terms [as Eqs. (25) and (26)]: One equation has terms of T^{dk}, $T^{d(k+1)}$, and $T^{u(k+1)}$, the other equation has terms of T^{uk}, $T^{d(k+1)}$, and $T^{u(k+1)}$. The coupling is homogeneous, so by linear combination, we get one equation [as Eq. (27)] about T^{dk} and T^{uk}, while one can be

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expressed in terms of the other using previous order equations. The resulting equation is a type II difference equation, and is solvable.

The solutions with one, two, and three leading terms of the asymptotic series are shown in Fig. 6. As shown in the top graph, the series solution with only the first term is the same as the approximation solutions assuming fast equilibrium in strong nonadiabatic and strong adiabatic limit. The relative error of these asymptotic series solutions shows, with only one additional term, the error is significantly reduced. Due to the essential difference of the dynamics in nonadiabatic and adiabatic cases, no global asymptotic series representation is possible. For this reason, the asymptotic series does not converge in intermediate regions of adiabaticity, and optimal truncation of the series is needed. In nonadiabatic limit, truncating at two terms gives the most accurate result, and in adiabatic limit, three terms is the optimal.

C. Escape rate at intermediate region and the condition for WOW resonance

Now an interesting question arises: What is the condition of the model parameters such that the relaxation rate exhibits the WOW resonance? This question can be answered in terms of asymptotic series solutions, but due to the complication of the MFPT solution of a general birth–death process, explicit analytical boundary of the region of resonance in the parameter space is not available. However, we shall point out that the condition in terms of asymptotic series solution can be computed without looping through all adiabaticity value of σ, which is more efficient and accurate than computing the parameter region of resonance by numerically solving the original MFPT problem.

The second leading term of asymptotic series determines the escape rate at nonlimiting adiabaticity regions. In the nonadiabatic case, $\sigma \ll 1$,

$$T_{\text{on}} \approx \frac{T^{d0}}{\sigma} + T^{d1}_{n_d}.$$

The escape rate from the attractor at d state to the attractor at u state will be

$$k_{\text{on}} = \frac{1}{T_{\text{on}}} = \frac{\sigma}{T^{d0} + \sigma T^{d1}_{n_d}}.$$

As a function of adiabaticity σ, the escape rate increase linearly first, then the second term affects the trend. If $T^{d1}_{n_d} > 0$, then the escape rate will be smaller than the linear function predicted by assuming fast equilibrium; if $T^{d1}_{n_d} < 0$, then the escape rate will be larger than the linear rate.

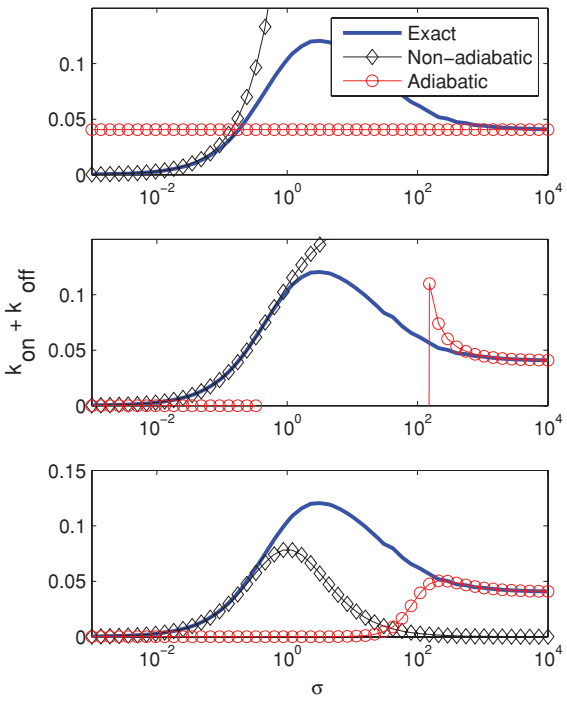
In the adiabatic case, $\sigma \gg 1$,

$$T_{\text{on}} \approx T^{d0}_{n_d} + \frac{T^{d1}_{n_d}}{\sigma}.$$

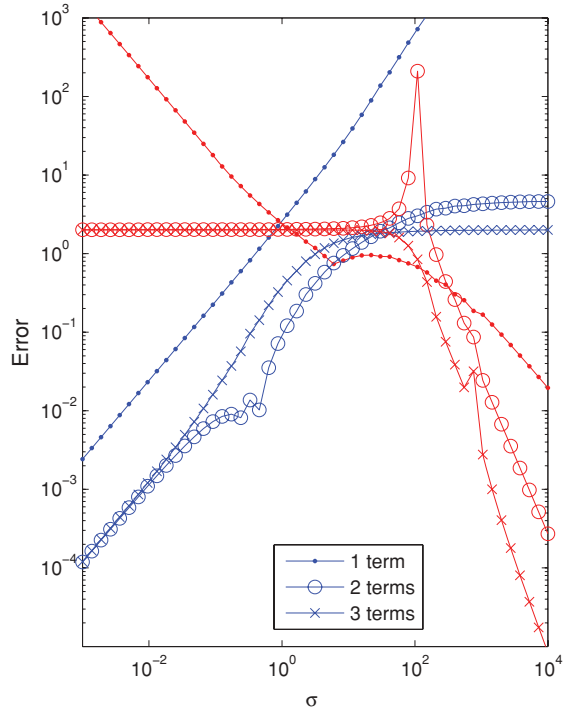
The approximated escape rate is

$$k_{\text{on}} = \frac{1}{T^{d0}_{n_d} + \dfrac{T^{d1}_{n_d}}{\sigma}}.$$

Using the second term in the adiabatic case asymptotic series solution, we can define the region of WOW resonance as



(a)



(b)

FIG. 6. (a) The nonadiabatic and adiabatic asymptotic series solution of the summation of transition rates $r = k_{\text{on}} + k_{\text{off}}$. The solid curve is the exact transition rate $k_{\text{on}} + k_{\text{off}}$. The diamond and circle curves are the asymptotic series approximation at non-adiabatic and adiabatic cases, respectively. From top to bottom, the first one, two, and three leading terms are used in the asymptotic series. Note that the solution with one leading term (top graph) is the same as the approximation solution using fast equilibrium. (b) The relative errors of the asymptotic series solution. Error is defined as $|k^{\text{ptb}}_{\text{on}} - k^{\text{true}}_{\text{on}}|/k^{\text{true}}_{\text{on}} + |k^{\text{ptb}}_{\text{off}} - k^{\text{true}}_{\text{off}}|/k^{\text{true}}_{\text{off}}$, where k^{ptb} is the perturbation solution of transition rate, k^{true} is the true transition rate.

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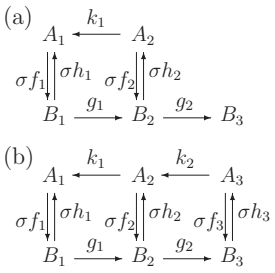

FIG. 7. (a) Kinetic schemes of five-state model. It exhibits the Walczak–Onuchic–Wolynes (WOW) resonance as well as all other features of the rate theory for self-regulating gene networks. (b) A six-state model that represents the full coupled birth–death process with two stable attractors. The transition from either attractor to the other is exactly a five-state model shown in (a).

following. If $T_{n_d}^{d1} > 0$, then when σ decreases from infinity and approaches 1, the escape rate will decrease; If $T_{n_d}^{d1} < 0$, the escape rate will increase as σ decreases. In the latter case, WOW resonance occurs. In later sections, we will study the condition of resonance via a reduced simplified model, which not only is analytically solvable, but also provides good insight of the problem.

IV. FURTHER INVESTIGATION OF WOW RESONANCE

For the self-regulating gene networks, between adiabatic and nonadiabatic limits, Walczak *et al.* have discovered a region in which the rate of gene switching exhibits a maximum.[8] In this section, we shall further investigate this "resonance" phenomenon, and show that a minimal of five-state model is able to provide an intuitive explanation for the interesting behavior. In self-regulating genes, there is only one major pathway from one attractor to the other. That is, the gene turns on or off first, and then the protein number crosses the energy barrier. The reverse order, i.e., protein number crosses the barrier before gene state switches, might happen but with a much smaller probability. Along this pathway, there are loops going backward. When σ is small, the pathway is slow; when σ is large, though the pathway is fast, the probability of going backward is larger too. So the maximum relaxation rate occurs in between where the trade-offs reach a balance.

A. Five-state model

To investigate the resonance phenomenon of the above mechanism, we consider a five-state model as shown in Fig. 7. A_1 and B_3 are two attractors: the birth–death process in upper line is dominated by the movement from A_2 to A_1, and the the movement in lower line is B_1 to B_2 to B_3. The coupling is controlled by the adiabaticity parameter σ. We omitted the transition from B_2 to B_1 and A_1 to A_2 to make the horizontal reactions unidirectional, because (1) the reverse rate is significantly smaller than g_1 and k_1, so adding them back would not change the physics, (2) the MFPT of simplified model can be computed analytically. We claim this five-state model is the minimum model that reveals the mechanism of resonance in the self-regulating gene problem. Here we only consider the escape rate from A_1 to B_3, so B_3 is an absorbing state, and the transition from B_2 to B_3 is set to be irreversible.

Let T_i^X be the MFPT of transition from A_i to B_3, $i = 1, 2$, $X = A, B$, then

$$\begin{aligned}
\sigma f_1 T_1^A &= 1 + \sigma f_1 T_1^B,\\
(\sigma h_1 + g_1) T_1^B &= 1 + \sigma h_1 T_1^A + g_1 T_2^B,\\
(\sigma h_2 + g) T_2^B &= 1 + \sigma h_2 T_2^A,\\
(\sigma f_2 + k_1) T_2^A &= 1 + k_1 T_1^A + \sigma f_2 T_2^B.
\end{aligned}$$

The desired MFPT from A_1 to B_3 is

$$T_1^A = \frac{\sigma h_1 + \sigma f_1 + g_1}{\sigma f_1 g_1} + \frac{\sigma f_2 + \sigma h_2 + k_1}{(\sigma f_2 + k_1) g} + \frac{h_2 k_1 (\sigma h_1 + \sigma f_1 + g_1)}{g f_1 g_1 (\sigma f_2 + k_1)}. \tag{30}$$

The expression can be rearranged as

$$T_1^A = \frac{1}{g} + \frac{h_1 + f_1}{f_1 g_1} + \frac{\sigma^2 (h_2 f_1 g_1 + h_1 h_2 k_1 + f_1 h_2 k_1) + \sigma g_1 (g f_2 + h_2 k_1) + g g_1 k_1}{\sigma (\sigma g g_1 f_1 f_2 + g g_1 f_1 k_1)}. \tag{31}$$

We can check this solution has all desired properties. At nonadiabatic limit, $\sigma \ll 1$, the leading order term of T_1^A is $1/(\sigma f_1)$, corresponding to the transition rate of σf_1, which is exactly the rate of switching gene state. At adiabatic limit, $\sigma \gg 1$, the leading order term is $(\alpha + \beta + \kappa)/(\alpha\beta)$, where

$$\alpha = \frac{f_1}{f_1 + h_1} g_1, \quad \beta = \frac{f_2}{f_2 + h_2} g, \quad \kappa = \frac{h_2}{f_2 + h_2} k_1.$$

This expression of leading term is actually the mean first passage time of a three state reaction

$$C_1 \underset{\kappa}{\overset{\alpha}{\rightleftharpoons}} C_2 \overset{\beta}{\to} C_3,$$

which is the resulting average system in adiabatic limit.

The condition that resonance happens is that in adiabatic limit, the term of σ^{-1} in series form solution being negative, so that when adiabaticity decreases, the mean first passage

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time decrease as well. This leads to the following condition:

$$g_1 f_2(g_2 f_2 + h_2 k_1) < (h_2 f_1 g_1 + h_1 h_2 k_1 + f_1 h_2 k_1) k_1. \quad (32)$$

To investigate the condition of resonance in the self-regulating gene problem, we consider a six-state system as shown in Fig. 7(b), in which A_1 and B_3 are two attractors. We choose parameters in the following way such that the six-state scheme resembles the original settings of the self-regulating gene. We map A_1 and B_3 to the u and d state attractors, respectively, and let

$$f_1 = f_2 = f_3, \quad h_1 > h_2 > h_3, \quad k_1 = g_2 < g_1 = k_2.$$

First of all, to be an appropriate reduced model of the self-regulating gene model, the six-state model need to have two stable attractors at adiabatic limit. In other words, the steady state distribution $A_1 \cup B_1$ and $A_3 \cup B_3$ should be greater than that in $A_2 \cup B_2$, i.e., the chemical potential in $A_2 \cup B_2$ is the highest. Let $C_i = A_i \cup B_i$ be the states of the slow dynamics, within which fast pre-equilibrium between A_i and B_i is reached due to strong adiabaticity, then the dynamics can be represented as

$$C_1 \underset{\frac{h_2}{f_2+h_2}k_1}{\overset{\frac{f_1}{f_1+h_1}g_1}{\rightleftharpoons}} C_2 \underset{\frac{h_3}{f_3+h_3}k_2}{\overset{\frac{f_2}{f_2+h_2}g_2}{\rightleftharpoons}} C_3$$

To ensure C_2 has the highest potential, we require

$$\frac{h_2}{f_2+h_2}k_1 > \frac{f_1}{f_1+h_1}g_1, \quad \frac{f_2}{f_2+h_2}g_2 > \frac{h_3}{f_3+h_3}k_2.$$

Under the assumptions of the parameters, these conditions can be rewritten as

$$\frac{h_1}{f_1} > \frac{\frac{g_1}{k_1}}{\frac{h_2}{f_2}} - 1 + \frac{g_1}{k_1}, \quad (33)$$

$$\frac{h_3}{f_3} < \frac{1}{\frac{g_1}{k_1}\left(1+\frac{h_2}{f_2}\right) - 1}. \quad (34)$$

Second, the parameters should satisfy the condition of resonance. As the transition from A_1 to B_3 and vise versa both follow the five-state kinetics we discussed above, we apply Inequality 32 to get the condition of resonance for each transition process. For A_1 to B_3, using $f_1 = f_2, k_1 = g_2$, we get

$$\frac{h_1}{f_1} > \frac{\frac{g_1}{k_1}}{\frac{h_2}{f_2}} - 1. \quad (35)$$

Together with the constrain $h_1 > h_2$ and potential constrain Inequality 33, the phase diagram of resonance region for the MFPT from A_1 to B_3 for parameter h_1/f_1 and h_2/f_2 is shown in right panel of Fig. 8. For B_3 to A_1, with the simplification using $k_1 = g_2$, $f_2 = f_3$, we have

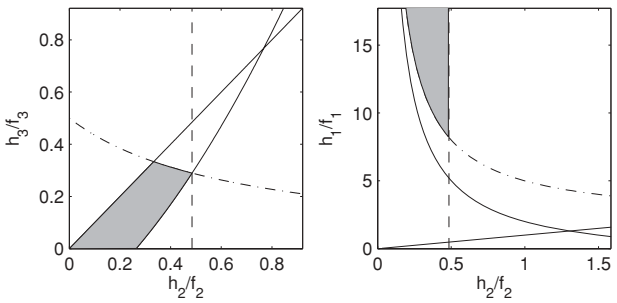

FIG. 8. Phase diagram of resonance region for reduced six-state scheme of self-regulating gene. The left panel is in parameter space of h_3/f_3 vs h_2/f_2, and the right panel is in parameter space of h_1/f_1 vs h_2/f_2. The vertical dash line in the left panel marks the maximum h_2/f_2 value, which in turn bounds the region in the right panel. The solid lines are conditions of resonance [inequalities (36), (35)], and the dotted-dashed lines are conditions of potential [inequalities (34), (33)]. The other parameters are set as $g_1/k_1 = 3$, $g_1 = k_2$, $g_2 = k_1$.

$$\frac{h_3}{f_3} > \frac{\frac{k_2}{g_2}}{1+\frac{k_2}{g_2}}\left(\frac{h_2}{f_2}\right)^2 + \frac{\frac{k_2}{g_2}}{1+\frac{k_2}{g_2}}\left(\frac{h_2}{f_2}\right) - \frac{1}{1+\frac{k_2}{g_2}}. \quad (36)$$

and the region of resonance for the MFPT from B_3 to A_1 in the parameter space of h_3/f_3 and h_2/f_2 is plotted in left panel of Fig. 8.

One interesting implication of the phase diagram of resonance region is that the WOW resonance exists for all polymer-regulated genes. First of all, in polymer activator cases, the number of attractors is always at most two. This is apparently true for nonadiabatic case, and is also true for adiabatic case, as the mean birth rate

$$\frac{f g_d + h(n) g_u}{f + h(n)},$$

where

$$h(n) = \frac{hn(n-1)(n-2)\cdots(n-p+1)}{p!},$$

is a sigmoidal shaped curve. The mean rate starts from g_d at $n = 0$, and ends with g_u when $n \to \infty$. With proper parameters, the mean birth rate will have three crosses with the mean death rate nk, which generates at most two attractors. Therefore, the six-state model that has two attractors and allows circular eddie motion is a reasonable model for polymer activator cases. Second, the higher number of TF proteins in the polymer, the larger ratio between the association rate at two attractors, i.e., $h(n_u)/h(n_d)$, where n_d and n_u is the attractor at d and u state, respectively. According to the phase diagram

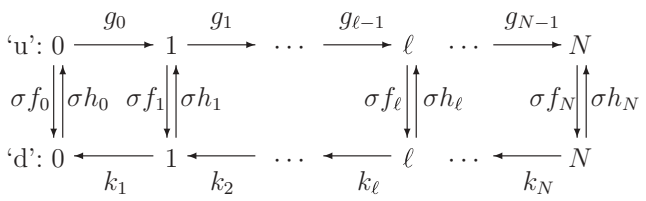

FIG. 9. The self-regulating gene model as a concatenation of a sequence of five-state model blocks. It is an approximation of the full self-regulating gene model, where the TF protein number fluctuation is unidirectional.

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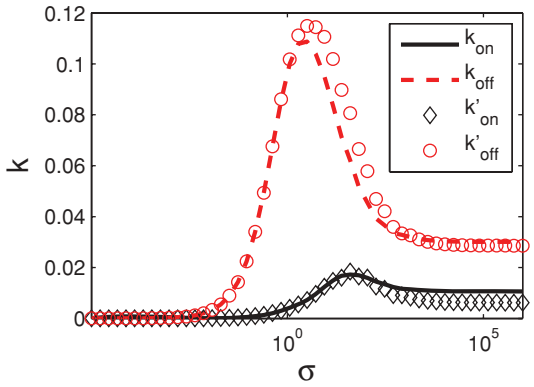

FIG. 10. The transition rate of approximate system approximates the true transition rate well. The solid and dash lines are numerical solutions of the transition rates from d state to u state and vise versa, respectively. The circles and diamonds symbols are transition rates between the same attractors in simplified system as shown in Fig. 9.

Fig. 8, with proper h_2/f_2 value, the h_3/f_3 (corresponding to the relative activator association and dissociation rate at d state attractor) can be as small as 0, and the h_1/f_1 (corresponding to the relative rate at u state attractor) can be as large as ∞. As a result, larger number of proteins in the polymer activator makes h_1/h_3 larger, so the parameters (h_1, h_2, h_3) are easier to fall in the resonance region. To confirm this conclusion, resonance with higher peaks is observed in our numerical experiments for trimer and tetramer activators.

B. Concatenation of five-state blocks

If we generalize the idea of the five-state model to the full coupled birth–death problem, assuming the fluctuation of TF number on each gene state is irreversible, then the resulting system as a sequential concatenation of the five-state model blocks, is an approximation to the original system. To match up with the mean drift in the original birth–death process, we use $g_u - kn$ as forward rate at gene u state and $kn - g_d$ as backward rate at gene d state. This approximation preserves the location of separatrix of the two attractors at adiabatic limit, but the overall dynamics is slower than the full system. The MFPT between attractors can be computed recursively due to the simplification. It not only shows the WOW resonance, which support as evidence that the five-state model captures the true mechanism, but also approximates the exact MFPT very well as shown in Fig. 10.

C. Use asymptotic series solution leading terms to fit five-state model parameters

Like Kramers' theory using quadratic energy landscape to approximate any stable chemical state, we use the five-state model to approximate the full coupled birth–death process. From the perspective of Kramers' theory, one uses the original parameters of the coupled birth–death process to estimate the shape of the quadratic attractor, and hereby compute the transition rate between stable states. Similarly, we use the same logic—fitting the full problem to a minimum mechanically representative model, and use the result of this solvable representative model to approximate the solution of original problem. We utilize the leading terms of asymptotic series solution to estimate the parameters of the five-state model, and reach a better global estimation of the transition rate as a function of adiabaticity.

The MFPT of five-state model can be written in the form of

$$\langle T\rangle = \frac{a\sigma^2 + b\sigma + c}{\sigma^2 + e\sigma}.$$

At nonadiabatic limit ($\sigma \ll 1$),

$$\begin{aligned}\langle T\rangle &= \left(\frac{a}{e}\sigma + \frac{b}{e} + \frac{c}{e\sigma}\right)\frac{1}{1+\frac{\sigma}{e}} \\ &= \left(\frac{a}{e}\sigma + \frac{b}{e} + \frac{c}{e\sigma}\right)\left[1 - \frac{\sigma}{e} + \left(\frac{\sigma}{e}\right)^2 + \cdots\right] \\ &= \frac{c}{e}\frac{1}{\sigma} + \left(\frac{b}{e} - \frac{c}{e^2}\right) + \left(\frac{a}{e} - \frac{b}{e^2} + \frac{c}{e^3}\right)\sigma + \cdots. \end{aligned} \quad (37)$$

At adiabatic limit ($\sigma \gg 1$),

$$\begin{aligned}\langle T\rangle &= \left(a + \frac{b}{\sigma} + \frac{c}{\sigma^2}\right)\frac{1}{1+\frac{e}{\sigma}} \\ &= \left(a + \frac{b}{\sigma} + \frac{c}{\sigma^2}\right)\left[1 - \frac{e}{\sigma} + \left(\frac{e}{\sigma}\right)^2 + \cdots\right] \\ &= a + (b - ae)\frac{1}{\sigma} + (c - be + ae^2)\frac{1}{\sigma^2} + \cdots. \end{aligned} \quad (38)$$

Since there are only four free parameters for a five-state model, we can use the first two terms of adiabatic and nonadiabatic limit asymptotic series to estimate the four parameters a, b, c, and e.

Suppose the leading terms of nonadiabatic and adiabatic asymptotic series are

$$T_{\text{nonadiabatic}} = x_{-1}\sigma^{-1} + x_0, \quad T_{\text{adiabatic}} = y_0 + y_1\sigma - 1,$$

then we can estimate the solution parameters of five-state model as

$$e = \frac{y_1 - x_{-1}}{x_0 - y_0}, \quad c = \frac{y_1 - x_{-1}}{x_0 - y_0}x_{-1},$$

$$a = y_0, \quad b = y_1 + \frac{y_1 - x_{-1}}{x_0 - y_0}y_0.$$

We also need to estimate the leading term of total rate, i.e., $k_{\text{on}} + k_{\text{off}}$, in terms of the leading term of one-sided MFPT. For nonadiabatic limit, suppose

$$T^u = \frac{x^u_{-1}}{\sigma} + x^u_0, \quad T^d = \frac{x^d_{-1}}{\sigma} + x^d_0,$$

then since

$$\frac{1}{T^u} + \frac{1}{T^d} = \frac{1}{T},$$

the leading terms of T will be

$$x_{-1} = \frac{x^u_{-1}x^d_{-1}}{x^u_{-1} + x^d_{-1}}, \quad (39)$$

$$x_0 = \frac{x^u_0 x^d_{-1} + x^d_0 x^u_{-1} - x_{-1}(x^u_0 + x^d_0)}{x^u_{-1} + x^d_{-1}}. \quad (40)$$

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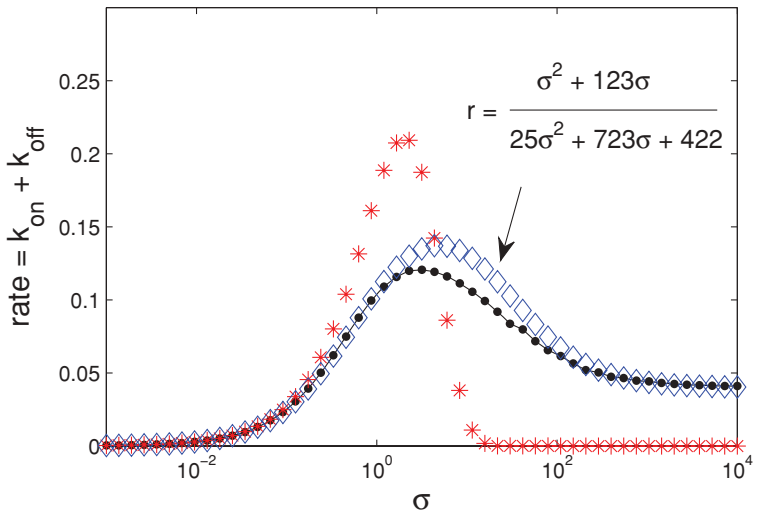

FIG. 11. Dotted line is exact numerical solution by solving the full MFPT backward equation. Diamonds are approximate solution by fitting the perturbation series to the five-state model, and the asterisks are the result of Walczak *et al* in nonadiabatic case (Ref. 8).

Similarly, in adiabatic limit,

$$T^u = y_0^u + \frac{y_1^u}{\sigma}, \quad T^u = y_0^d + \frac{y_1^d}{\sigma}.$$

Then the leading terms of T are

$$y_0 = \frac{y_0^u y_0^d}{y_0^u + y_0^d}, \tag{41}$$

$$y_1 = \frac{y_0^d y_1^u + y_0^u y_1^d - y_0(y_1^u + y_1^d)}{y_0^u + y_0^d}. \tag{42}$$

This approach yield an estimation of the rate as a function of adiabaticity parameter σ (Fig. 11),

$$k_{\text{on}} + k_{\text{off}} = \frac{\sigma^2 + 123\sigma}{25\sigma^2 + 723\sigma + 422}.$$

When $\sigma \ll 1$, the limit is $123\sigma/422 \approx 0.29\sigma$; when $\sigma \gg 1$, the limit is $1/25 = 0.04$.

V. DISCUSSION

The perturbation theory provides a rigorous and straightforward way to decompose the coupled birth–death problem into solvable subproblems. Due to the essentially different dynamics of the problem in nonadiabatic and adiabatic limit, the MFPT is expressed as two asymptotic series, and computed separately. In the computation of each term in the asymptotic series solution, one need to solve a MFPT problem in a one-dimensional birth–death process, which can be analytically solved. The second term in the series solution of MFTP at adiabatic case defines the parameter region of WOW resonance. This condition, though does not provide a closed form expression for the boundaries of the resonance region in parameter space, is computationally efficient and accurate. Furthermore, this condition can potentially reveal some properties of the boundaries of the resonance region.

As a complement to the rigorous but computationally cumbersome perturbation series solution, we propose a five-state model to explain the mechanism of the WOW resonance. In one word, the WOW resonance is the effect of the change in dynamics from nonadiabatic limit of the system to adiabatic limit. And the condition that resonance occurs is that the dynamics is faster when adiabaticity is away from both nonadiabatic and adiabatic limits. In nonadiabatic region, faster transition is achieved due to the faster gene switching rate, and in adiabatic region, when adiabaticity decreases, the transition is faster because slower gene state switching (i.e., smaller adiabaticity) allows easier movement in protein number direction. One important implication of the simplified models is that in cases of activation requiring multiple binding of an activator, i.e., the copies of the TF to activate a gene are greater than two, the WOW resonance all exists.

The asymptotic series solution and simplified five-state model both have the advantages and drawbacks. The asymptotic series have good accuracy, but no global representation is available, while the five-state model has a simple global analytical expression, but no direct estimation of the parameters can be made from original full coupled birth–death process. A combination of the two methods provide a global approximation of the transition rate as a function of adiabaticity. The rational function form is also simple enough for experimental data fitting.

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APPENDIX: METHODS

1. Equations of type I and II, and the solutions

The following two types of equations are the general form of difference equations we need to solve in perturbation theories approach.

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Equation of type I:

$$(\alpha_i + \beta_i)T_i = r_i + \alpha_i T_{i+1} + \beta_i T_{i-1},$$

with reflecting boundary conditions on both ends of the domain $[a, b]$,

$$\alpha_a T_a = r_a + \alpha_a T_{a+1}, \quad \beta_b T_b = r_b + \beta_b T_{b-1}.$$

We call it reflecting boundary condition because it is equivalent to

$$T_{a-1} = T_a, \quad T_{b+1} = T_b,$$

or no outgoing probability flux.

For type I equation, there is no unique solution. However, type I equation give rise to a consistency condition as a constrain on the equation coefficients α_i, β_i, r_i, which can be used to solve for undetermined parameters. And type I equation can be solved if other equations about T_i is provided.

To solve type I equation, we introduce first order difference variable

$$S_i = T_i - T_{i-1},$$

then S_i satisfies the equation

$$\alpha_i S_{i+1} - \beta_i S_i + r_i = 0$$

and boundary conditions yields

$$S_{a+1} = -\frac{r_a}{\alpha_a}, \quad S_b = \frac{r_b}{\beta_b}.$$

Starting from either end, and using deduction, we can get the expression of S_i,

$$S_i = -\sum_{j=a}^{i-1} \frac{r_j}{\alpha_j} \left(\prod_{l=j+1}^{i-1} \frac{\beta_l}{\alpha_l} \right)$$

or

$$S_i = \sum_{j=i}^{b} \frac{r_j}{\beta_j} \left(\prod_{l=i}^{j-1} \frac{\alpha_l}{\beta_l} \right).$$

To match the boundary condition at the other end, we have the consistency condition

$$\sum_{j=a}^{b} \frac{r_j}{\alpha_j} \left(\prod_{l=a}^{j} \frac{\alpha_l}{\beta_l} \right) = 0. \tag{A1}$$

Equation of type II:

$$(\alpha_i + \beta_i)T_i = r_i + \alpha_i T_{i+1} + \beta_i T_{i-1},$$

with reflecting boundary conditions on both ends of the domain $[a, b]$,

$$\alpha_a T_a = r_a + \alpha_a T_{a+1}, \quad \beta_b T_b = r_b + \beta_b T_{b-1}.$$

and Dirichlet fixed value condition at n^*,

$$T_{n^*} = t.$$

Using the same technique of difference variable, we have

$$T_i = t + \sum_{k=i+1}^{n^*} \sum_{j=a}^{k-1} \frac{r_j}{\alpha_j} \left(\prod_{l=j+1}^{k-1} \frac{\beta_l}{\alpha_l} \right), \quad i = a, \ldots, n^* - 1; \tag{A2a}$$

$$T_i = t + \sum_{k=n^*+1}^{i} \sum_{j=i}^{b} \frac{r_j}{\beta_j} \left(\prod_{l=i}^{j-1} \frac{\alpha_l}{\beta_l} \right), \quad i = n^* + 1, \ldots, b. \tag{A2b}$$

2. Nonadiabatic situation

We first investigate nonadiabatic case, where $\sigma \ll 1$. When $\sigma = 0$, T_i^u will be the MFPT of a birth—death process in one dimension, which is in normal time scale comparing to σ; while T_i^d is ∞, since there is no transition from d line to u line. Therefore, we write the variable in series of σ as

$$T_i^d = \frac{1}{\sigma} T_i^{d0} + T_i^{d1} + \sigma T_i^{d2} + \cdots, \tag{A3}$$

$$T_i^u = T_i^{u0} + \sigma T_i^{u1} + \cdots. \tag{A4}$$

Plug in equation, we consider the equations in orders of σ^{-1}, 1, and σ.

$$\text{Order } \sigma^{-1}(d)\text{: } (g_d + ik)T_i^{d0} = g_d T_{i+1}^{d0} + ikT_{i-1}^{d0}. \tag{A5}$$

This is a homogeneous difference equation with Wronskian equals to zero. So there is no unique solution. From $i = 0$, we get

$$g_d T_0^{d0} = g_d T_1^{d0} \quad \Rightarrow \quad T_0^{d0} = T_1^{d0}$$

and by induction

$$T_i^{d0} = \text{const} = T^{d0}, \quad i = 0, 1, \ldots, N.$$

To compute the value of T^{d0}, we need the next order equation.

$$\text{Order } \sigma^0(d)\text{: } (g_d + ik)T_i^{d1} = 1 - h_i T_i^{d0} + g_d T_{i+1}^{d1} + ikT_{i-1}^{d1}, \tag{A6}$$

which is a type I equation. According to formula (A1), we have an equation for T^{d0},

$$\sum_{j=0}^{N} \frac{1}{j!} \left(\frac{g_d}{k} \right)^j \frac{1 - h_j T^{d0}}{g_d} = 0,$$

So

$$T^{d0} = \frac{\sum_{j=0}^{N} \frac{1}{j!} \left(\frac{g_d}{k} \right)^j}{\sum_{j=0}^{N} \frac{1}{j!} \left(\frac{g_d}{k} \right)^j h^{\frac{j(j-1)}{2}}}.$$

Let $N \to \infty$,

$$T^{d0} = \frac{2}{h} \left(\frac{k}{g_d} \right)^2,$$

$$\text{Order } \sigma^0(u) : (g_u + ik)T_i^{u0} = 1 + f_i T_i^{d0} + g_u T_{i+1}^{u0} + ikT_{i-1}^{u0}, \tag{A7}$$

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with condition $T_{n^*}^{u0}=0$. This is a type II equation, and the solution is

$$T_i^{u0}=\sum_{l=i}^{n^*-1}\sum_{m=0}^{l}\frac{l!}{m!}\left(\frac{k}{g_u}\right)^{l-m}\frac{1+f_jT^{d0}}{g_u},\quad i=0,1,\ldots,n^*-1, \tag{A8}$$

$$T_i^{u0}=\sum_{l=n^*}^{i-1}\sum_{m=l+1}^{N}\frac{l!}{m!}\left(\frac{k}{g_u}\right)^{l-m}\frac{1+f_jT^{d0}}{g_u},\quad i=n^*+1,\ldots,N, \tag{A9}$$

Order $\sigma^1(d)$: $(g_d+ik)T_i^{d2}=h_i(T_i^{u0}-T_i^{d1})+g_dT_{i+1}^{d2}+ikT_{i-1}^{d2}$, (A10)

This type I equation give rise to consistency equation

$$\sum_{j=0}^{N}\frac{1}{j!}\left(\frac{g_d}{k}\right)^j\frac{h_j(T_j^{u0}-T_j^{d1})}{g_d}=0. \tag{A11}$$

And T_j^{d1} can be expressed in terms of only one unknown variable T_0^{d1},

$$T_j^{d1}=T_0^{d1}+\sum_{l=0}^{j-1}\sum_{m=l+1}^{N}\frac{l!}{m!}\left(\frac{k}{g_d}\right)^{l-m}\frac{1-h_mT^{d0}}{g_d}.$$

We can solve for T_0^{d1}

$$T_0^{d1}=\left[\sum_{j=0}^{n^*-1}\frac{h_j}{j!}\left(\frac{g_d}{k}\right)^j\sum_{l=j}^{n^*-1}\sum_{m=0}^{l}\frac{l!}{m!}\left(\frac{k}{g_u}\right)^{l-m}\frac{1+f_mT^{d0}}{g_u}+\sum_{j=n^*+1}^{N}\frac{h_j}{j!}\left(\frac{g_d}{k}\right)^j\sum_{l=n^*}^{j-1}\sum_{m=l+1}^{N}\frac{l!}{m!}\left(\frac{k}{g_u}\right)^{l-m}\frac{1+f_mT^{d0}}{g_u}\right.$$
$$\left.-\sum_{j=0}^{N}\frac{h_j}{j!}\left(\frac{g_d}{k}\right)^j\sum_{l=0}^{j-1}\sum_{m=l+1}^{N}\frac{l!}{m!}\left(\frac{k}{g_d}\right)^{l-m}\frac{1-h_mT^{d0}}{g_d}\right]\Bigg/\sum_{j=0}^{N}\frac{h_j}{j!}\left(\frac{g_d}{k}\right)^j \tag{A12}$$

$$T_{n_d}^{d1}=T_0^{d1}+\sum_{l=0}^{n_d-1}\sum_{m=l+1}^{N}\frac{l!}{m!}\left(\frac{k}{g_d}\right)^{l-m}\frac{1-h_mT^{d0}}{g_d}. \tag{A13}$$

Finally, the MFPT from d state to u state is

$$T_{\rm on}\approx\frac{T^{d0}}{\sigma}+T_{n_d}^{d1}.$$

3. Adiabatic situation

In the adiabatic situation, σ is large, so the asymptotic series are written in the reverse order

$$T_i^d=T_i^{d0}+\frac{T_i^{d1}}{\sigma}+\frac{T_i^{d2}}{\sigma^2}+\cdots, \tag{A14}$$

$$T_i^u=T_i^{u0}+\frac{T_i^{u1}}{\sigma}+\frac{T_i^{u2}}{\sigma^2}+\cdots. \tag{A15}$$

In order σ^1:

$$h_iT_i^{d0}=h_iT_i^{u0}\quad f_iT_i^{u0}=f_iT_i^{d0}. \tag{A16}$$

So

$$T_i^{d0}=T_i^{u0}=T_i^0.$$

In order σ^0:

$$(g_d+ik)T_i^0+h_iT_i^{d1}=1+h_iT_i^{u1}+g_dT_{i+1}^0+ikT_{i-1}^0, \tag{A17}$$

$$(g_u+ik)T_i^0+f_iT_i^{u1}=1+f_iT_i^{d1}+g_uT_{i+1}^0+ikT_{i-1}^0,\quad i\neq n^*. \tag{A18}$$

Use $f_i\times$(A17) $+h_i\times$(A18), we get an equation about T_i^0,

$$\left[(f_ig_d+h_ig_u)+(f_i+h_i)ik\right]T_i^0=f_i+h_i+(f_ig_d+h_ig_u)T_{i+1}^0+(f_i+h_i)ikT_{i-1}^0, \tag{A19}$$

with boundary condition at n^*, that $T_{n^*}^0=0$. Using formula for type II Eq. (A2), we have

$$T_i^0=\sum_{k=i+1}^{n^*}\sum_{j=0}^{k-1}\frac{f_j+h_j}{f_jg_d+h_jg_u}\left(\prod_{l=j+1}^{k-1}\frac{(f_l+h_l)lk}{f_lg_d+h_lg_u}\right),\quad i=0,\ldots,n^*-1; \tag{A20}$$

$$T_i^0=\sum_{k=n^*+1}^{i}\sum_{j=i}^{N}\frac{f_j+h_j}{f_jg_d+h_jg_u}\left(\prod_{l=i}^{j-1}\frac{f_jg_d+h_jg_u}{(f_l+h_l)lk}\right),\quad i=n^*+1,\ldots,N; \tag{A21}$$

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Using Eq. (A17), T_i^{u1} and T_i^{d1} are related as

$$T_i^{d1} - T_i^{u1} = \frac{1 + g_d(T_{i+1}^0 - T_i^0) - ik(T_i^0 - T_{i-1}^0)}{h_i} \equiv \Delta_i^1.$$

In the next order σ^{-1},

$$(g_d + ik)T_i^{d1} + h_i T_i^{d2} = h_i T_i^{u2} + g_d T_{i+1}^{d1} + ikT_{i-1}^{d1}, \quad \text{(A22)}$$

$$(g_u + ik)T_i^{u1} + f_i T_i^{u2} = f_i T_i^{d2} + g_u T_{i+1}^{u1} + ikT_{i-1}^{u1}, \quad i \neq n^*. \quad \text{(A23)}$$

Similarly, $f_i \times$(A22) $+ h_i \times$(A23), we get

$$f_i(g_d + ik)T_i^{d1} + h_i(g_u + ik)T_i^{u1} = f_i g_d T_{i+1}^{d1} + f_i ikT_{i-1}^{d1} + h_i g_u T_{i+1}^{u1} + h_i ikT_{i-1}^{u1}. \quad \text{(A24)}$$

Plug in $T_i^{d1} = T_i^{u1} + \Delta_i^1$, we get

$$\left[(f_i g_d + h_i g_u) + (f_i + h_i)ik\right] T_i^{u1} = f_i\left[-(g_d + ik)\Delta_i^1 + g_d\Delta_{i+1}^1 + ik\Delta_{i-1}^1\right] + (f_i g_d + h_i g_u)T_{i+1}^{u1} + (f_i + h_i)ikT_{i-1}^{u1}. \quad \text{(A25)}$$

with boundary condition $T_{n^*}^{u1} = 0$, which is again a type II equation, that can be solved by formula (A2).

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