Supplement for "Dynamical Analysis on Gene Activity in the Presence of Repressors and an Interfering Promoter"

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Detailed derivations for the mathematical expressions in the text are given.

I. ELONGATION INITIATION INTERVAL AND CORRELATION

Let $C(t)$ be the time-dependent activity after the clearance of both the promoter and the operator. Then it can also be regarded as a correlation function of the transcription initiation, and it is related to the initiation interval distribution $p(\tau)$ as

$$\begin{aligned}C(t) &= p(t) + \int_0^\infty d\tau_1 \int_0^\infty d\tau_2\, \delta(t-\tau_1-\tau_2)\, p(\tau_1)p(\tau_2) \\ &\quad + \int_0^\infty d\tau_1 \int_0^\infty d\tau_2 \int_0^\infty d\tau_3\, \delta(t-\tau_1-\tau_2-\tau_3)\, p(\tau_1)p(\tau_2)p(\tau_3) \\ &\quad + \cdots . \end{aligned} \tag{1}$$

Since each term in the right hand side is a convolution of $p(\tau)$, the Laplace transformation

$$\tilde{C}(s) \equiv \int_0^\infty C(t) e^{-st} dt \tag{2}$$

can be obtained easily as a sum of geometrical series;

$$\tilde{C}(s) = \sum_{n=1}^\infty \tilde{p}(s)^n = \frac{\tilde{p}(s)}{1-\tilde{p}(s)} \tag{3}$$

with $\tilde{p}(s)$ being the Laplace transform of $p(\tau)$.

II. BARE PROMOTERS

In this section, the explicit expressions for $p(\tau)$ and $C(t)$ for a bare promoter of each model are derived within the approximation that the self-occlusion effect is ignored.

A. Single step model

For the single step model, the elongation initiation is a simple Poissonian process with the rate Ω_0, thus we have

$$p(\tau) = \Omega_0 e^{-\Omega_0 \tau}, \qquad \tilde{p}(s) = \frac{\Omega_0}{s+\Omega_0}, \tag{4}$$

and

$$\tilde{C}(s) = \frac{\Omega_0}{s}, \qquad C(t) = \Omega_0. \tag{5}$$

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B. Two step model

In the two step model, each elongation interval consists of an off-state period and an on-state period, whose length distributions, $p_{\rm off}(\tau_{\rm off})$ and $p_{\rm on}(\tau_{\rm on})$, are Poissonian given by

$$p_{\rm off}(\tau_{\rm off}) = k_{\rm on} e^{-k_{\rm on}\tau_{\rm off}}, \quad \text{and} \quad p_{\rm on}(\tau_{\rm on}) = k_e e^{-k_e \tau_{\rm on}}, \tag{6}$$

respectively. Since the elongation interval is the sum of the off-period length and the on-period length, the elongation interval distribution $p(\tau)$ for the two step model is given by

$$p(\tau) = \int_0^\infty d\tau_{\rm off} \int_0^\infty d\tau_{\rm on}\, \delta(\tau - \tau_{\rm off} - \tau_{\rm on}) p_{\rm off}(\tau_{\rm off}) p_{\rm on}(\tau_{\rm on}). \tag{7}$$

Again, the right hand side is a convolution of $p_{\rm off}(\tau_{\rm off})$ and $p_{\rm on}(\tau_{\rm on})$, thus in the Laplace transform, we have

$$\tilde{p}(s) = \tilde{p}_{\rm off}(s)\, \tilde{p}_{\rm on}(s) = \frac{k_{\rm on} k_e}{(s + k_{\rm on})(s + k_e)}, \tag{8}$$

which gives

$$p(\tau) = \begin{cases} k_{\rm on} k_e \dfrac{e^{-k_e \tau} - e^{-k_{\rm on}\tau}}{k_{\rm on} - k_e} & \text{for } k_{\rm on} \neq k_e \\ k_e^2\, \tau\, e^{-k_e \tau} & \text{for } k_{\rm on} = k_e \end{cases}. \tag{9}$$

Then, the correlation function is given by

$$\tilde{C}(s) = \frac{k_{\rm on} k_e}{s(s + k_{\rm on} + k_e)}, \quad C(t) = \Omega_0 \left(1 - e^{-(k_{\rm on} + k_e)t}\right) \tag{10}$$

with Ω_0 being the bare activity for the two step model:

$$\Omega_0 = \frac{k_{\rm on} k_e}{k_{\rm on} + k_e} = \frac{1}{\tau_{\rm on} + \tau_e}; \qquad \tau_{\rm on} \equiv \frac{1}{k_{\rm on}}, \quad \tau_e \equiv \frac{1}{k_e}. \tag{11}$$

Note that the last expression simply represents that the average interval between elongation $1/\Omega_0$ is the sum of the average waiting time to become the on-state $\tau_{\rm on}$ and the time for the elongation τ_e.

C. Three step model

In the three step model, the initial transition between the off-state and the closed complex state is reversible, which means that the closed state goes either back to the off-state or forward to the open complex state with the branching ratios k_u and k_o, or with the probabilities

$$p \equiv \frac{k_u}{k_u + k_o}, \quad \text{and} \quad q \equiv \frac{k_o}{k_u + k_o} = 1 - p, \tag{12}$$

respectively. Therefore, the promoter may get into the closed state many times before an RNAP starts elongation. Let n be the number of times that the promoter gets in the closed state before elongation, then the sequence of states and their probabilities are

n	state sequence	probability
1	(off - closed) $\bullet$ open - elong	q
2	(off - closed) $\circ$ (off - closed) $\bullet$ open - elong	$p\,q$
	$\cdots$	
n	(off - closed $\circ)^{n-1}$(off - closed) $\bullet$ open - elong	$p^{n-1}q$
	$\cdots$	

, (13)

where $\circ$ and $\bullet$ represent the branching probabilities p and q, respectively.

Let $p_n(\tau)$ be the elongation interval distribution for the interval during which the promoter goes through the closed state n times, then it is given by a convolution of the life time distribution of the off-state $p_{\rm off}(\tau)$, the closed state $p_{\rm cl}(\tau)$, and the open state $p_{\rm op}(\tau)$; For example, $p_1(\tau)$ is given by

$$p_1(\tau) = \int_0^\infty d\tau_{\rm off} \int_0^\infty d\tau_{\rm cl} \int_0^\infty d\tau_{\rm op}\, \delta(\tau - \tau_{\rm off} - \tau_{\rm cl} - \tau_{\rm op}) p_{\rm off}(\tau_{\rm off}) p_{\rm cl}(\tau_{\rm cl}) p_{\rm op}(\tau_{\rm op}). \tag{14}$$

In the same way, the Laplace transform of $p_n(\tau)$ for general n is given by

$$\tilde{p}_n(s) = \Big(\tilde{p}_{\rm off}(s)\tilde{p}_{\rm cl}(s)\Big)^n \tilde{p}_{\rm op}(s) \tag{15}$$

with

$$\tilde{p}_{\rm off}(s) = \frac{k_b}{s + k_b}, \quad \tilde{p}_{\rm op}(s) = \frac{k_u + k_o}{s + k_u + k_o}, \quad \tilde{p}_{\rm cl}(s) = \frac{k_e}{s + k_e}. \tag{16}$$

The elongation interval distribution $p(\tau)$ is the average over $p_n(\tau)$ with the probability given by (13), and can be calculated as follows;

$$\tilde{p}(s) = \sum_{n=1}^\infty \tilde{p}_n(s)\, p^{n-1} q \quad = \frac{\tilde{p}_{\rm off}(s)\tilde{p}_{\rm cl}(s)}{1 - \tilde{p}_{\rm off}(s)\tilde{p}_{\rm cl}(s) p}\, \tilde{p}_{\rm op}(s)\, q \quad = \frac{k_b k_o k_e}{(s + k_+)(s + k_-)(s + k_e)} \tag{17}$$

with

$$k_\pm \equiv \frac{1}{2}\Big[(k_b + k_u + k_o) \pm \sqrt{(k_b + k_u + k_o)^2 - 4 k_b k_o}\Big], \tag{18}$$

from which we obtain

$$p(\tau) = \frac{k_b k_o k_e}{(k_e - k_+)(k_e - k_-)} e^{-k_e \tau} + \frac{k_b k_o k_e}{\sqrt{(k_b + k_o + k_e)^2 - 4 k_b k_o}} \left[\frac{e^{-k_- \tau}}{k_e - k_-} - \frac{e^{-k_+ \tau}}{k_e - k_+}\right]. \tag{19}$$

From eqs.(3) and (17), we have

$$\tilde{C}(s) = \frac{k_b k_o k_e}{s(s + k_+^C)(s + k_-^C)}; \quad k_\pm^C \equiv \frac{1}{2}\left[(k_b + k_u + k_o + k_e) \pm \sqrt{(k_b + k_u + k_o - k_e)^2 - 4 k_b k_o}\right], \tag{20}$$

which leads to

$$C(t) = \Omega_0 \left[1 - \frac{k_+^C e^{-k_-^C t} - k_-^C e^{-k_+^C t}}{k_+^C - k_-^C}\right] \tag{21}$$

where Ω_0 is the bare activity for the three step model:

$$\Omega_0 = \frac{k_b k_o k_e}{k_+^C k_-^C} \quad = \frac{1}{\tau_b + \tau_o^* + \tau_e}; \qquad \tau_b \equiv \frac{1}{k_b}, \quad \tau_o^* \equiv \frac{1}{k_{\rm on}^*} = \frac{1}{k_o} + \frac{k_u}{k_o} \cdot \frac{1}{k_b}, \quad \tau_e \equiv \frac{1}{k_e}. \tag{22}$$

The average interval between elongations, $1/\Omega_0$, are the sum of the three times: (1) τ_b, the time for RNAP to bind and form the closed complex for the first time, (2) τ_o^*, the time for RNAP to form the open complex after the first binding, and (3) τ_e, the time to start elongation. Note that the validity of this expression is *not* limited to the case within the two step approximation, where $k_{\rm on}^*$ can be interpreted as the effective on-rate.

The time τ_o^* consists of two parts: (i) $1/k_o$, the time to go forward to the open state, and (ii) the re-binding time $1/k_b$ after unbinding multiplied by the average number of unbindings k_u/k_o. Mathematical derivation of this expression is given in the appendix. We will encounter similar expressions in the following.

III. REGULATED PROMOTERS

Now, we derive the expressions for $p(\tau)$ and $C(t)$ for each model of a bare promoter in the case where the promoter is repressed by a transcription factor (TF). In the case where the suppression is strong by a slow binding TF, the transcription activity occurs in bursts. The averaged activity is given by the long time limit $t \to \infty$ of $C(t)$.

A. Single step model

The state sequence between elongations can be classified according to the number of TF bindings, and the probability and the interval distribution for each case are obtained as

n	state sequence	probability	interval distribution
0	off • elong	q	$\tilde{p}_{\rm off}(s)$
1	(off ∘ TF) - off • elong	$p\,q$	$\tilde{p}_{\rm off}(s)\tilde{p}_{\rm TF}(s)\tilde{p}_{\rm off}(s)$
2	(off ∘ TF)^2 - off • elong	p^2q	$\big(\tilde{p}_{\rm off}(s)\tilde{p}_{\rm TF}(s)\big)^2\tilde{p}_{\rm off}(s)$,
	. . .		
n	(off ∘ TF)^n - off • elong	p^nq	$\big(\tilde{p}_{\rm off}(s)\tilde{p}_{\rm TF}(s)\big)^n\tilde{p}_{\rm off}(s)$
	. . .		

(23)

where TF represents the state with TF at the operator site and

$$\tilde{p}_{\rm off}(s) \equiv \frac{k_b^{\rm TF}+\Omega_0}{s+k_b^{\rm TF}+\Omega_0}, \quad \tilde{p}_{\rm TF}(s) \equiv \frac{k_u^{\rm TF}}{s+k_u^{\rm TF}}, \qquad p \equiv \frac{k_b^{\rm TF}}{k_b^{\rm TF}+\Omega_0}, \quad q \equiv \frac{\Omega_0}{k_b^{\rm TF}+\Omega_0}. \tag{24}$$

Thus, we have

$$\tilde{p}(s) \;=\; \sum_{n=0}^{\infty} p^n q\big(\tilde{p}_{\rm off}(s)\tilde{p}_{\rm TF}(s)\big)^n\tilde{p}_{\rm off}(s) \;=\; \frac{\tilde{p}_{\rm off}(s)q}{1-\tilde{p}_{\rm off}(s)\tilde{p}_{\rm TF}(s)p} \;=\; \frac{(s+k_u^{\rm TF})\Omega_0}{(s+k_+)(s+k_-)}; \tag{25}$$

$$k_\pm \equiv \frac{1}{2}\Big[k_b^{\rm TF}+k_u^{\rm TF}+\Omega_0 \pm \sqrt{(k_b^{\rm TF}+k_u^{\rm TF}+\Omega_0)^2-4k_u^{\rm TF}\Omega_0}\Big] \tag{26}$$

and

$$C(t) = \frac{\Omega_0}{k_b^{\rm TF}+k_u^{\rm TF}}\Big(k_u^{\rm TF}+k_b^{\rm TF}e^{-(k_b^{\rm TF}+k_u^{\rm TF})t}\Big). \tag{27}$$

Thus, the steady state activity $\Omega_{\rm TF}$ for the single step model is given by

$$\Omega_{\rm TF} = \lim_{t\to\infty} C(t) = \frac{k_u^{\rm TF}}{k_b^{\rm TF}+k_u^{\rm TF}}\,\Omega_0 \quad = \frac{n_{\rm bst}}{\tau_{\rm bst}+\tau_{\rm TF}} \tag{28}$$

with

$$\tau_{\rm bst} \equiv \frac{1}{k_b^{\rm TF}}, \qquad n_{\rm bst} \equiv \Omega_0\tau_{\rm bst}, \qquad \tau_{\rm TF} \equiv \frac{1}{k_u^{\rm TF}}\,. \tag{29}$$

The last expression for $\Omega_{\rm TF}$ allows a simple interpretation in terms of bursting activity; $\tau_{\rm bst}$ and $\tau_{\rm TF}$ are the bursting time and the quiescent time, respectively, and $n_{\rm bst}$ is the number of transcriptions during the bursting time.

B. Two step model

For the two step model, the state sequences, their probabilities, and the interval distributions are

n	state sequence	probability	interval distribution
0	off • on - elong	q	$\tilde{p}_{\rm off}(s)\tilde{p}_{\rm on}(s)$
1	(off ∘ TF) - off • on - elong	$p\,q$	$\tilde{p}_{\rm off}(s)\tilde{p}_{\rm TF}(s)\tilde{p}_{\rm off}(s)\tilde{p}_{\rm on}(s)$
2	(off ∘ TF)^2 - off • on - elong	p^2q	$\big(\tilde{p}_{\rm off}(s)\tilde{p}_{\rm TF}(s)\big)^2\tilde{p}_{\rm off}(s)\tilde{p}_{\rm on}(s)$,
	. . .		
n	(off ∘ TF)^n - off • on - elong	p^nq	$\big(\tilde{p}_{\rm off}(s)\tilde{p}_{\rm TF}(s)\big)^n\tilde{p}_{\rm off}(s)\tilde{p}_{\rm on}(s)$
	. . .		

(30)

with

$$\tilde{p}_{\rm off}(s) = \frac{k_b^{\rm TF} + k_{\rm on}}{s + k_b^{\rm TF} + k_{\rm on}}, \quad \tilde{p}_{\rm TF}(s) = \frac{k_u^{\rm TF}}{s + k_u^{\rm TF}}, \quad \tilde{p}_{\rm on}(s) = \frac{k_e}{s + k_e}, \qquad p \equiv \frac{k_b^{\rm TF}}{k_b^{\rm TF} + k_{\rm on}}, \quad q \equiv \frac{k_{\rm on}}{k_b^{\rm TF} + k_{\rm on}}. \tag{31}$$

From these, we obtain

$$p(\tau) = k_e k_{\rm on}\left[\frac{k_u^{\rm TF} - k_e}{(k_+ - k_e)(k_- - k_e)} e^{-k_e\tau} + \frac{1}{k_+ - k_-}\left(\frac{k_u^{\rm TF} - k_-}{k_e - k_-} e^{-k_-\tau} - \frac{k_u^{\rm TF} - k_+}{k_e - k_+} e^{-k_+\tau}\right)\right] \tag{32}$$

$$k_\pm \equiv \frac{1}{2}\left[k_b^{\rm TF} + k_u^{\rm TF} + k_{\rm on} \pm \sqrt{(k_b^{\rm TF} + k_u^{\rm TF} + k_{\rm on})^2 - 4k_u^{\rm TF}k_{\rm on}}\right] \tag{33}$$

$$C(t) = \frac{k_e k_{\rm on} k_u^{\rm TF}}{k_+^C k_-^C} + \frac{k_e k_{\rm on}}{k_+^C - k_-^C}\left[\frac{k_-^C - k_u^{\rm TF}}{k_-^C} e^{-k_-^C t} - \frac{k_+^C - k_u^{\rm TF}}{k_+^C} e^{-k_+^C t}\right] \tag{34}$$

$$k_\pm^C \equiv \frac{1}{2}\left[(k_b^{\rm TF} + k_{\rm on} + k_u^{\rm TF} + k_e) \pm \sqrt{(k_b^{\rm TF} + k_{\rm on} + k_u^{\rm TF} + k_e)^2 - 4(k_{\rm on}k_u^{\rm TF} + k_u^{\rm TF}k_e + k_b^{\rm TF}k_e)}\right] \tag{35}$$

The steady state activity $\Omega_{\rm TF}$ is now

$$\Omega_{\rm TF} = \lim_{t\to\infty} C(t) \quad = \frac{k_e k_{\rm on} k_u^{\rm TF}}{k_+^C k_-^C} \quad = \frac{k_e k_{\rm on}}{k_{\rm on} + k_e + (k_b^{\rm TF}/k_u^{\rm TF})k_e} \quad = \frac{n_{\rm bst}}{\tau_{\rm bst} + \tau_{\rm TF}}, \tag{36}$$

with

$$n_{\rm bst} \equiv \frac{k_{\rm on}}{k_b^{\rm TF}}, \qquad \tau_{\rm bst} \equiv \frac{1}{k_b^{\rm TF}} + n_{\rm bst}\frac{1}{k_e}. \tag{37}$$

The number of transcriptions during a bursting period is given by the winning ratio of RNAP to TF.

It is interesting to see that eq.(36) can be also put in the form,

$$\Omega_{\rm TF} = \frac{1}{\tau_{\rm on} + \tau_e}; \qquad \tau_{\rm on}({\rm TF}) \equiv \tau_{\rm on} + \frac{k_b^{\rm TF}}{k_{\rm on}}\tau_{\rm TF}, \quad \tau_{\rm on} = \frac{1}{k_{\rm on}}, \quad \tau_e = \frac{1}{k_e}, \tag{38}$$

which is similar to the expression for the bare promoter (11). The expression for $\tau_{\rm on}({\rm TF})$ allows a similar interpretation with that for eqs.(22); the time to reach the on-state from the off-state, $\tau_{\rm on}({\rm TF})$ is the sum of the two times: (1) $\tau_{\rm on}$, the time to reach the on-state without TF binding, and (2) the TF unbinding time, $\tau_{\rm TF}$, multiplied by the number of TF bindings, $k_b^{\rm TF}/k_{\rm on}$, before an RNAP binds.

In the case $k_b^{\rm TF} \gg k_e \gg k_u^{\rm TF} \approx 0$, the correlation function $C(t)$ shows a plateau. As the lowest order estimate, we put simply $k_u^{\rm TF} = 0$, then we obtain

$$C(t) \approx \frac{k_e k_{\rm on}}{k_b^{\rm TF} + k_{\rm on}}\left(e^{-k_-^C t} - e^{-k_+^C t}\right); \qquad k_+^C \approx k_b^{\rm TF} + k_{\rm on}, \quad k_-^C \approx \frac{k_b^{\rm TF}k_e}{k_b^{\rm TF} + k_{\rm on}}. \tag{39}$$

therefore, $C(t)$ behaves as

$$C(t) \approx \begin{cases} k_{\rm on}k_e t & \text{for} \quad t \lesssim (k_b^{\rm TF} + k_{\rm on})^{-1} \\ \dfrac{k_e k_{\rm on}}{k_b^{\rm TF} + k_{\rm on}} & \text{for} \quad (k_b^{\rm TF} + k_{\rm on})^{-1} \lesssim t \lesssim t_{\rm pl} \\ \dfrac{k_e k_{\rm on}}{k_b^{\rm TF} + k_{\rm on}} \exp\left[-\dfrac{k_b^{\rm TF}k_e}{k_b^{\rm TF} + k_{\rm on}}t\right] & \text{for} \quad t \gtrsim t_{\rm pl} \end{cases}$$

with the plateau time

$$t_{\rm pl} \equiv \frac{1}{k_e}\left(1 + n_{\rm bst}\right) \tag{40}$$

and the plateau value

$$C_{\rm max} \approx \frac{k_{\rm on}}{k_b^{\rm TF} + k_{\rm on}} \cdot k_e = \frac{n_{\rm bst}}{t_{\rm pl}}. \tag{41}$$

C. Three step model

For the three step model, additional complication is that there are two reversible transitions, i.e. the transition between the off-state and the closed state, and the transition between the off-state and TF binding state, thus there exist two sequences of transitions within each elongation interval. This can be nicely represented by a binominal expansion;

state sequence	interval distribution with probability
off ⊙ cl • op - elong,	$\tilde{p}_{\rm off}(s)q_1\tilde{p}_{\rm cl}(s)q_2\tilde{p}_{\rm op}(s)$
((off⊗TF-)+(off⊙cl ∘)) off ⊙ cl • op - elong,	$\big(\tilde{p}_{\rm off}(s)p_1\tilde{p}_{\rm TF}(s)+\tilde{p}_{\rm off}(s)q_1\tilde{p}_{\rm cl}(s)p_2\big)\tilde{p}_{\rm off}(s)q_1\tilde{p}_{\rm cl}(s)q_2\tilde{p}_{\rm op}(s)$
((off⊗TF-)+(off⊙cl ∘))^2 off ⊙ cl • op - elong,	$\big(\tilde{p}_{\rm off}(s)p_1\tilde{p}_{\rm TF}(s)+\tilde{p}_{\rm off}(s)q_1\tilde{p}_{\rm cl}(s)p_2\big)^2\tilde{p}_{\rm off}(s)q_1\tilde{p}_{\rm cl}(s)q_2\tilde{p}_{\rm op}(s)$
...	
((off⊗TF-)+(off⊙cl ∘))^n off ⊙ cl • op - elong,	$\big(\tilde{p}_{\rm off}(s)p_1\tilde{p}_{\rm TF}(s)+\tilde{p}_{\rm off}(s)q_1\tilde{p}_{\rm cl}(s)p_2\big)^n\tilde{p}_{\rm off}(s)q_1\tilde{p}_{\rm cl}(s)q_2\tilde{p}_{\rm op}(s)$
...	

with the period length distributions

$$\tilde{p}_{\rm off}(s)=\frac{k_b^{\rm TF}+k_b}{s+k_b^{\rm TF}+k_b},\quad \tilde{p}_{\rm TF}(s)=\frac{k_u^{\rm TF}}{s+k_u^{\rm TF}},\quad \tilde{p}_{\rm cl}(s)=\frac{k_u+k_o}{s+k_u+k_o},\quad \tilde{p}_{\rm op}(s)=\frac{k_e}{s+k_e},$$

and the branching probabilities

$$p_1=\frac{k_b^{\rm TF}}{k_b^{\rm TF}+k_b},\quad q_1=1-p_1,\qquad p_2=\frac{k_u}{k_u+k_o},\quad q_2=1-p_2,$$

which are represented by the marks: ⊗ for p_1, ⊙ for q_1, ∘ for p_2, and • for q_2. This gives

$$\tilde{p}(s)=\frac{\tilde{p}_{\rm off}(s)q_1\tilde{p}_{\rm cl}(s)q_2\tilde{p}_{\rm op}(s)}{1-\big(\tilde{p}_{\rm off}(s)p_1\tilde{p}_{\rm TF}(s)+\tilde{p}_{\rm off}(s)q_1\tilde{p}_{\rm cl}(s)p_2\big)},\tag{42}$$

and the expression for $p(\tau)$ is

$$p(\tau)=k_bk_ok_e\left[\frac{k_u^{\rm TF}-k_e}{(k_1-k_e)(k_2-k_e)(k_3-k_e)}e^{-k_e\tau}+\sum_{i=1}^{3}\frac{k_u^{\rm TF}-k_i}{(k_{i+1}-k_i)(k_{i-1}-k_i)(k_e-k_i)}e^{-k_i\tau}\right]\tag{43}$$

with $-k_i$ $(i=1,2,3)$ being the solution of the cubic equation

$$s^3+As^2+Bs+C=0\tag{44}$$

with the coefficients

$$\begin{aligned}A&\equiv k_b^{\rm TF}+k_b+k_u^{\rm TF}+k_u+k_o\\ B&\equiv k_u^{\rm TF}(k_u+k_b+k_o)+k_b^{\rm TF}(k_u+k_o)+k_bk_o\\ C&\equiv k_bk_ok_u^{\rm TF}.\end{aligned}$$

Note that we define k_i as a decay rate with a positive real part.

From eqs.(3) and (42), the correlation function $C(t)$ is given by

$$C(t)=\frac{k_bk_ok_ek_u^{\rm TF}}{k_1^Ck_2^Ck_3^C}-k_bk_ok_e\sum_{i=1}^{3}\frac{(k_u^{\rm TF}-k_i^C)e^{-k_i^Ct}}{k_i^C(k_{i+1}^C-k_i^C)(k_{i-1}^C-k_i^C)},\tag{45}$$

with $-k_i^C$ $(i=1,2,3)$ being the solution of the cubic equation

$$s^3+Ds^2+Es+F=0\tag{46}$$

with the coefficients

$$\begin{aligned}D&\equiv k_b^{\rm TF}+k_b+k_u^{\rm TF}+k_u+k_o+k_e\\ E&\equiv (k_b^{\rm TF}+k_u^{\rm TF})(k_u+k_o+k_e)+k_b(k_u^{\rm TF}+k_o+k_e)+(k_u+k_o)k_e\\ F&\equiv k_u^{\rm TF}k_b(k_o+k_e)+(k_b^{\rm TF}+k_u^{\rm TF})(k_u+k_o)k_e.\end{aligned}$$

The steady state activity $\Omega_{\rm TF}$ is

$$\Omega_{\rm TF} = \lim_{t\to\infty} C(t) = \frac{k_b k_o k_e k_u^{\rm TF}}{k_u^{\rm TF} k_b (k_o + k_e) + (k_b^{\rm TF} + k_u^{\rm TF})(k_u + k_o) k_e} \tag{47}$$

$$= \frac{n_{\rm bst}}{\tau_{\rm bst} + \tau_{\rm TF}} = \begin{cases} \Omega_0 & \text{for } \frac{k_b^{\rm TF}}{k_u^{\rm TF}} \to 0 \\ \frac{n_{\rm bst}}{\tau_{\rm TF}} & \text{for } \frac{k_b^{\rm TF}}{k_u^{\rm TF}} \to \infty \end{cases}, \tag{48}$$

with

$$n_{\rm bst} \equiv \frac{k_b}{k_b^{\rm TF}} \frac{k_o}{k_o + k_u}, \qquad \tau_{\rm bst} \equiv \frac{1}{k_b^{\rm TF}} + n_{\rm bst} \left(\frac{1}{k_o} + \frac{1}{k_e} \right), \qquad \tau_{\rm TF} = \frac{1}{k_u^{\rm TF}}, \tag{49}$$

and Ω_0 being the bare activity of the three step model (22). The number of transcriptions $n_{\rm bst}$ in a burst is now given by the winning ratio of RNAP $k_b/k_b^{\rm TF}$ multiplied by the branching ratio in the closed state $k_o/(k_o + k_u)$.

The expression for $\Omega_{\rm TF}$ can also be put in the form analogous to eq.(22),

$$\frac{1}{\Omega_{\rm TF}} = \left[\frac{1}{k_b} + \frac{k_b^{\rm TF}}{k_b} \cdot \frac{1}{k_u^{\rm TF}} \right] + \left[\frac{1}{k_o} + \frac{k_u}{k_o} \cdot \left(\frac{1}{k_b} + \frac{k_b^{\rm TF}}{k_b} \cdot \frac{1}{k_u^{\rm TF}} \right) \right] + \frac{1}{k_e} \quad = \tau_b({\rm TF}) + \tau_o^*({\rm TF}) + \tau_e \tag{50}$$

with

$$\tau_b({\rm TF}) \equiv \tau_b + \frac{k_b^{\rm TF}}{k_b} \cdot \tau_{\rm TF}, \quad \tau_o^*({\rm TF}) \equiv \tau_o + \frac{k_u}{k_o} \cdot \tau_b({\rm TF}), \qquad \tau_b = \frac{1}{k_b}, \quad \tau_o = \frac{1}{k_o}. \tag{51}$$

This allows a similar interpretation with that for eq. (38); The average interval of elongation $1/\Omega_{\rm TF}$ is the sum of three times: (1) $\tau_b(TF)$, the time for RNAP to bind the promoter, (2) $\tau_o^*(TF)$, the time to form a open complex for the first time after RNAP binding, and (3) τ_e, the time to elongate after forming the open complex. The time $\tau_b(TF)$ is the sum of (i) τ_b, the RNAP binding time, and (ii) the unbinding time, $\tau_{\rm TF}$, multiplied by the number of TF bindings, $k_b^{\rm TF}/k_b$, before an RNAP binds. Similarly, the time $\tau_o^*(TF)$ is the sum of (i) τ_o, the time to form an open complex, and (ii) the binding time $\tau_b(TF)$ multiplied by the average number of RNAP unbindings, k_u/k_o, before it forms an open complex.

IV. PROMOTER INTERFERENCE

If there is another promoter, pA, competing with the promoter pS in the parallel or converging position, then their activities interfere with each other. Here, we consider only the interference effect on pS by pA. The activity of pA is given by the elongation interval distribution $p_A(\tau)$.

We consider two effects for the transcription interference: occlusion and sitting duck interference. The occlusion is the effect that an RNAP cannot bind to the promoter site of pS while the RNAP from pA is passing over the promoter site. The time that RNAP needs to pass through the promoter site is the occlusion time $\tau_{\rm occ}$. The sitting duck interference is that the RNAP sitting on the promoter site pS is removed by the RNAP from pA comes to pS.

Under the interference of pA, the pS activity is limited within the elongation intervals from pA. Therefore, the average activity of pS under these effects $\Omega_{\rm TI}$ is the average over the activity within the interval τ and the average by the probability that a time is in the interval of the length τ; This is given by

$$\Omega_{\rm TI} = \frac{\displaystyle\int_{\tau_{\rm occ}}^{\infty} p_A(\tau)\, \tau \left(\frac{1}{\tau} \int_0^{\tau - \tau_{\rm occ}} C(t)\; dt \right) d\tau}{\displaystyle\int_0^{\infty} p_A(\tau)\, \tau\, d\tau}, \tag{52}$$

using the transcription initiation correlation function $C(t)$ without interference effects.

A. Interference with unregulated promoters

First, we consider the cases where the promoter pS is not regulated by TF. In this case, the correlation function $C(t)$ is rather simple and the interference effect can be represented by a simple factor χ, that is the averaged fraction of time that is not occluded:

$$\chi \equiv \frac{\displaystyle\int_{\tau_{\rm occ}}^{\infty} p_A(\tau)\,\tau \left(\frac{\tau-\tau_{\rm occ}}{\tau}\right) d\tau}{\displaystyle\int_0^{\infty} p_A(\tau)\,\tau\, d\tau}. \tag{53}$$

If we assume the simple Poissonian for pA with the activity Ω_A,

$$p_A(\tau) = \Omega_A e^{-\Omega_A \tau}, \tag{54}$$

then χ is given by

$$\chi_P = e^{-\Omega_A \tau_{\rm occ}}. \tag{55}$$

(i) In the case that pS can be described by the single step model, $C(t)$ is given by the constant $k_e = \Omega_0$ as has been calculated (5), thus eq.(52) gives

$$\Omega_{\rm TI} = \frac{\displaystyle\int_{\tau_{\rm occ}}^{\infty} p_A(\tau)\,\tau \left(\frac{1}{\tau}\int_0^{\tau-\tau_{\rm occ}} \Omega_0\, dt\right) d\tau}{\displaystyle\int_0^{\infty} p_A(\tau)\,\tau\, d\tau} = \chi\Omega_0, \tag{56}$$

which means that the interference effects reduce the activity by the factor χ.

(ii) In the case of the two step model with the Poissonian pA, eq.(52) can be estimated as

$$\Omega_{\rm TI} = \chi_P \Omega_0 \frac{k_{\rm on}+k_e}{k_{\rm on}+k_e+\Omega_A} \tag{57}$$

using eq.(10). Here, Ω_0 is the bare activity (11) for the two step model[1].

B. Interference with regulated promoters

Only difference from the cases above is that we use the correlation $C(t)$ under the effect of TF. We give explicit expressions only for the Poissonian pA (54).

For the single step promoter pS, using eqs.(28) and (52), we obtain

$$\Omega_{\rm TI} = \chi_P\, \Omega_0 \left[\frac{k_u^{\rm TF}}{k_u^{\rm TF}+k_b^{\rm TF}} + \frac{k_b^{\rm TF}}{k_u^{\rm TF}+k_b^{\rm TF}} \cdot \frac{\Omega_A}{\Omega_A + k_u^{\rm TF}+k_b^{\rm TF}}\right] = \chi_P \frac{n_{\rm bst}}{\tau_{\rm bst} + \dfrac{\tau_{\rm TF}\Omega_A^{-1}}{\tau_{\rm TF}+\Omega_A^{-1}}} \tag{58}$$

with χ_P given by eq.(55) and $n_{\rm bst}$ and $\tau_{\rm bst}$ by eq.(29). The last expression simply shows that the quiescent period is interrupted to be Ω_A^{-1} when $\Omega_A^{-1} < \tau_{\rm TF}$.

For the two step promoter, we give the expression only for $\tau_{\rm occ} = 0$, namely, without the occlusion effect:

$$\begin{aligned}
\Omega_{\rm TI} &= \frac{k_e k_{\rm on} k_u^{\rm TF}}{k_+^C k_-^C} + \frac{k_e k_{\rm on}}{k_+^C - k_-^C}\left[\frac{k_-^C - k_u^{\rm TF}}{k_-^C}\frac{\Omega_A}{\Omega_A + k_-^C} - \frac{k_+^C - k_u^{\rm TF}}{k_+^C}\frac{\Omega_A}{\Omega_A + k_+^C}\right] \\
&= \Omega_{\rm TF}\left[1 - \frac{\Omega_A(\Omega_A + k_+^C + k_-^C - k_+^C k_-^C/k_u^{\rm TF})}{(\Omega_A + k_-^C)(\Omega_A + k_+^C)}\right]
\end{aligned}$$

with $k_\pm^C$ given by eq.(35) and $\Omega_{\rm TF}$ being the steady activity under TF by eq.(36).

In the same approximation as eq.(39), $k_b^{\rm TF} \gg k_e \gg k_u^{\rm TF} \approx 0$, using the approximate form of $k_\pm^C$, we obtain

$$\begin{aligned} \Omega_{\rm TI} &\approx k_{\rm on} \frac{k_e}{\Omega_A + k_b^{\rm TF} k_e/(k_b^{\rm TF}+k_{\rm on})} \cdot \frac{1}{1+(k_b^{\rm TF}+k_{\rm on})/\Omega_A} \quad = \frac{n_{\rm bst}}{t_{\rm pl}+\Omega_A^{-1}} \cdot \frac{k_b^{\rm TF}+k_{\rm on}}{k_b^{\rm TF}+k_{\rm on}+\Omega_A} \\ &\approx \begin{cases} n_{\rm bst}\Omega_A & \text{for } \Omega_A \ll 1/t_{\rm pl} = \frac{k_b^{\rm TF}}{k_b^{\rm TF}+k_{\rm on}} k_e \\ \dfrac{n_{\rm bst}}{t_{\rm pl}} & \text{for } 1/t_{\rm pl} \ll \Omega_A \ll (k_b^{\rm TF}+k_{\rm on}) \\ \dfrac{n_{\rm bst}}{t_{\rm pl}} \dfrac{k_b^{\rm TF}+k_{\rm on}}{\Omega_A} = \dfrac{k_{\rm on}k_e}{\Omega_A} & \text{for } (k_b^{\rm TF}+k_{\rm on}) \ll \Omega_A \end{cases} \end{aligned}$$

with $n_{\rm bst}$ (37) and $t_{\rm pl}$ (40). The maximum value of $\Omega_{\rm TI}$ is achieved at $\Omega_A \approx \sqrt{k_b^{\rm TF} k_e}$. The behavior of $C(t)$ in (39) and $\Omega_{\rm TI}$ as a function of Ω_A correspond to each other by the correspondence $t \sim 1/\Omega_A$.

For the three step model, we give only a formal solution for Poissonian pA:

$$\Omega_{\rm TI} = \frac{k_b k_o k_e k_u^{\rm TF}}{k_1^C k_2^C k_3^C} - k_b k_o k_e \sum_{i=1}^{3} \frac{(k_u^{\rm TF} - k_i^C)}{k_i^C (k_{i+1}^C - k_i^C)(k_{i-1}^C - k_i^C)} \frac{\Omega_A}{\Omega_A + k_i^C}, \tag{59}$$

with the same k_i^C $(i = 1, 2, 3)$ with those in eq.(45).

APPENDIX: MATHEMATICAL EXPLANATION FOR τ_o^* IN (22)

In this appendix, we will give a mathematical explanation for the expression of τ_o^* in eq.(22).

This is the time for RNAP and promoter to form the open complex after the first binding of RNAP. Since the initial binding/unbinding process is reversible, after the first binding, the system may either go forward to form the open complex, or may go backward to unbind with the probabilities,

$$q = \frac{k_o}{k_o + k_u} \quad \text{and} \quad p = \frac{k_u}{k_o + k_u}, \tag{A.1}$$

respectively. The average waiting time for either of the cases to happen is

$$\frac{1}{k_o + k_u}. \tag{A.2}$$

If the system goes backward to unbind the RNAP, then after the time

$$\frac{1}{k_b}, \tag{A.3}$$

another RNAP binds to form the closed complex again, and the situation becomes the same as before.

If the system goes backward to unbind n times before it proceeds to form the open complex, the times that the system spends and the probabilities that should occur are given

$$\begin{array}{lcc} n & \text{time} & \text{probability} \\ \hline 1 & \dfrac{1}{k_o+k_u} & q \\ 2 & \dfrac{1}{k_o+k_u} + \dfrac{1}{k_b} + \dfrac{1}{k_o+k_u} & p\,q \\ & \cdots & \\ n & \left(\dfrac{1}{k_o+k_u} + \dfrac{1}{k_b}\right) n + \dfrac{1}{k_o+k_u} & p^n\,q \\ & \cdots & \end{array} \tag{A.4}$$

thus the average time is given by

$$\sum_{n=0}^{\infty} \left[\left(\frac{1}{k_o+k_u} + \frac{1}{k_b} \right) n + \frac{1}{k_o+k_u} \right] p^n\, q = \frac{1}{k_o} + \frac{k_u}{k_o} \frac{1}{k_b} \tag{A.5}$$

which is τ_o^* in eq.(22).

---

[1] Eq.(57) disagrees with the corresponding expression

$$\Omega_{\mathrm{TI}} = \Omega_0 \, \frac{\chi(k_{\mathrm{on}} + k_e)}{\chi k_{\mathrm{on}} + k_e + \Omega_A}$$

of eq.(4) and Figure 1(d) in Sneppen *et al.* [*J. Mol. Biol.* **346** (2005) 399–409](the notations have been changed from the original ones). It is not difficult, however, to see that this expression cannot be correct because this does not reduce to that for the single step case (56) in the $k_{\mathrm{on}} \to \infty$ limit. In its derivation, only the on-rate was reduced by the factor χ, and it was not taken into account that the total probability of the states available to RNAP is limited by the factor χ.