# Path-integral Hamiltonian of non-equilibrium gene regulatory network

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We rigorously derived the path-integral Hamiltonian to describe the landscape that governs the dynamics of non-equilibrium gene regulatory network. We start from the simplest case—the self-regulating gene in the adiabatic limit, where only two gene states are present and binding of transcription factors are fast compared with gene switch. Then we extend the model to multiple gene states. A more general model for regulatory network that contains multiple genes is also derived. Lastly, we further discuss the model to the regime of non-adiabatic dynamics, where the DNA binding should also be taken into account.

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## I. INTRODUCTION

Gene regulation is stochastic. This is not only because of the single-molecule nature of gene itself but also due to the fact that gene is regulated by a small finite number of transcription factors [1, 2]. The whole process of the regulation of gene expression is rather complicated, involving the interplay of various genes, RNA, proteins, multiprotein complexes, etc., which can be pictured as a gene regulatory network (GRN) [3, 4]. GRN is defined as a comprehensive collection of all kinds of factors that are involved in the process of gene regulation, and the interactions among different components in the network encode important cellular processes, e.g. cell differentiation. Considering the complexity of the players exist in the GRN, the entire network system is typically far from equilibrium [5].

In order to have a faithful description of the stochastic dynamics of GRN, statistics of at least several factors should be explicitly considered: 1) DNA transcription and translation into proteins, 2) protein dimerization, 3) binding/unbinding rate of the proteins on to the target genes, 4) gene state switches and 5) degradation rate of proteins.

Due to the complexity of the factors in the network abovementioned, a handful of reasonable assumptions are often, and also some in the context of this paper, been made regarding different processes with distinct time scales [6]. First, the diffusion-limited DNA binding process is assumed to be much faster than the process of DNA transcription together with protein translation. This is the so-called adiabatic limit, which means there is a quasi-equilibrium been reached for the transcription factors bind to the DNA as regulatory factors so that the dynamics of the gene expression is governed by the average production/degradation rates of protein that depend on the protein concentrations. What should be emphasized here is that perhaps being valid in some simplest case, this assumption, however, might not be a universal rule for all GRNs. The reasons are quite obvious, one of which is probably because the highly compacted 3D organization of the chromatin may significantly slow down the protein binding rate *in vivo*, as well as the different structural environment may let the protein binding rates become considerably different in distinct regions on the chromosome. Second, the time for protein dimerization is neglected compared to other more time-limiting processes in this regulatory network. The detailed dynamics of the dimerization process is not explicitly considered since it is assumed that if a gene is regulated, what really takes effects are protein dimers under most of the cases so that we do not have to worry about the monomers. Third, dimers are assumed to be homodimers in this model. As we mentioned above, this is also not always true considering the existence of mediators, i.e., multiprotein complexes in the real biological systems. Lastly, the transcription factors are assumed to be well-mixed in the nucleus and the unbinding rate of transcription factors from DNA and the degradation rate of proteins are assumed to be the same for simplicity.

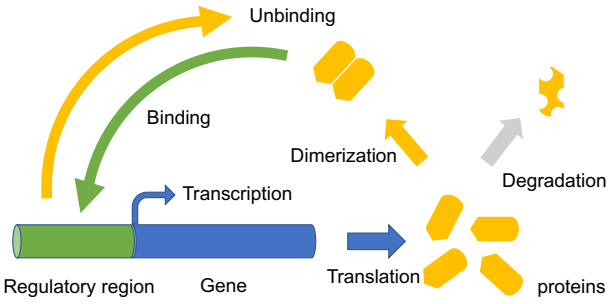


FIG.1. Schematic figure of the circus showing dynamics of the self-regulating gene.

Theoretical frameworks on adiabatic and non-adiabatic non-equilibrium dynamics have been shown to have promising potential in the applications to the studies of GRN [6–8]. One of the very inspiring ideas, which was proposed a few years ago, was to study the regulatory networks by borrowing some analytical approaches from

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quantum statistical mechanics [9]. Under this regime, the stochastic gene expression can be viewed as a quantum many-body problem, where the number of transcription factors can be thought through the bosonic coherent state while the fluctuations of the protein number correspond to the creation/annihilation operators. In addition, the gene states (e.g. binary states, open and closed) can be described by the quantum spin operator. By having this transformation, a complex GRN can be understood as a spin-boson problem, which possesses rigorous analytical solution that can be mathematically and physically interpreted, instead of stagnating on a vague and phenomenological picture. This idea has been brought up and utilized to study various properties of gene regulation through computational models, but none of them provides a step-by-step rigorous mathematical derivation, which is the main purpose of this paper. And we will also generalize the model starting from two gene states to multiple gene states, and to multiple genes under the adiabatic limit. Finally, the theoretical framework under non-adiabatic regime will also be discussed.

## II. THEORETICAL FRAMEWORK

Here we present detailed step-by-step derivations of the theoretical framework for GRN. We will start from the simplest GRN for the self-regulating gene in the adiabatic limit.

### A. Master equation for network dynamics

We start from the simplest casethe self-regulating gene in the adiabatic limit (see Fig.1). Two distinct gene states are represented by unbound state ($s = 1$) and bound state ($s = 0$). The number of transcription factors is represented as $n$. The rate of protein synthesis at gene state $s$ is represented as $g_s$. The binding and unbinding rates of the regulatory protein to the target gene are represented as $h$ and $f$, respectively. Since the regulatory protein is taking effect in the form of dimer, we have: $h(n) = h_0 \cdot n(n-1)$. The degradation rate of the regulatory protein is represented as $k$.

In the system of self-regulating gene, the protein produced by the gene is acting back on to the gene. So, we can write down the following master equation to describe the dynamics of the system:

$$\begin{aligned}\frac{\partial \mathbf{P}(n,t)}{\partial t} = &\begin{pmatrix} g_1 & 0 \\ 0 & g_0 \end{pmatrix} [\mathbf{P}(n-1,t) - \mathbf{P}(n,t)] \\ &+ k(n+1)\mathbf{P}(n+1,t) - kn\mathbf{P}(n,t) \\ &+ \begin{pmatrix} -h(n) & f \\ h(n) & -f \end{pmatrix} \mathbf{P}(n,t)\end{aligned} \tag{1}$$

where $\mathbf{P}(\mathbf{n})$ is a two-component vector:

$$\mathbf{P}(n,t) = \begin{pmatrix} P_1(n,t) \\ P_0(n,t) \end{pmatrix} \tag{2}$$

The $P_s(n)$ is the probability of having $n$ number of protein in gene state $s$. Matrix $\begin{pmatrix} g_1 & 0 \\ 0 & g_0 \end{pmatrix}$ is a diagonal matrix with the element being the protein synthesis rate at individual gene state. The first term describes the probability change due to the protein translation. The second and third terms are related to rate constant $k$, which describe the probability change due to the protein degradation. The last term simply describes the probability exchange because of the binding and unbinding of the transcription factors to the gene with the rate constants aforementioned.

If we then define the probability wavefunction:

$$|\Psi\rangle = \begin{pmatrix} \sum_n P_1(n,t)\,|n\rangle \\ \sum_n P_0(n,t)\,|n\rangle \end{pmatrix} \tag{3}$$

with normalization constrain: $\forall t$, $\sum_s \sum_n P_s(n) = 1$, and creation and annihilation operators:

$$\begin{cases} a^\dagger\,|n\rangle = |n+1\rangle \\ a\,|n\rangle = n\,|n-1\rangle \end{cases} \tag{4}$$

with $[a, a^\dagger] = 1$.

We can then write the Eq.(1) in a second quantized form:

$$\frac{\partial}{\partial t}\,|\Psi\rangle = \mathcal{H}\,|\Psi\rangle \tag{5}$$

where the Hamiltonian carries the form:

$$\mathcal{H} = \begin{pmatrix} g_1 & 0 \\ 0 & g_0 \end{pmatrix}(1 - a^\dagger) + k(a^\dagger a - a) + \begin{pmatrix} -h(n) & f \\ h(n) & -f \end{pmatrix} \tag{6}$$

By defining the parameters in the formula:

$$\begin{aligned} X &= (g_1 + g_0)/(2k) \\ \delta X &= (g_1 - g_0)/(2k) \\ K &= h_0/f \\ \omega &= f/k \end{aligned} \tag{7}$$

Eq.(6) can be rewritten in the form:

$$\begin{aligned}\mathcal{H} = &\begin{pmatrix} X + \delta X & 0 \\ 0 & X - \delta X \end{pmatrix}(1 - a^\dagger) \\ &+ a^\dagger a - a + \omega \begin{pmatrix} -K(a^\dagger)^2 a^2 & 1 \\ K(a^\dagger)^2 a^2 & -1 \end{pmatrix}\end{aligned} \tag{8}$$

### B. Path-integral formalism of transition probability

$P(n_f, \tau | n_i, 0)$ is defined as the probability to start from $n_i$ at time 0, to arrive at the state with $n_f$ at time $\tau$. We can easily write down the form of $P(n_f, \tau | n_i, 0)$ with a time-dependent operator acts on the braket:

$$P(n_f, \tau | n_i, 0) = \frac{1}{n_f!}\,\langle n_f |\, exp\left[-\int_0^\tau \mathcal{H} dt\right] |n_i\rangle \tag{9}$$

*a. Bosonic subspace.* As mentioned above, the transition probability can be represented in terms of the spin-boson formalism. We first build the resolution of identity in bosonic subspace.

$$\mathbb{1}_{\mathcal{B}} = \sum_{n_0} |n_0\rangle \langle n_0| \otimes \sum_{n_1} |n_1\rangle \langle n_1| \tag{10}$$

The coherent state is defined as $|z\rangle$, where:

$$a|z\rangle = z|z\rangle \tag{11}$$

so that we have (see Appendix):

$$\begin{aligned} |z\rangle &= exp(a^\dagger z)|0\rangle = exp\left(\sum_i a_i^\dagger z_i\right)|0\rangle \\ \langle z| &= \langle 0| exp\left(\sum_i a_i \bar{z}_i\right) \end{aligned} \tag{12}$$

If we make use of the relationship:

$$\begin{aligned} \langle z'|z\rangle &= \langle 0| exp\left(\sum_i a_i \bar{z_i'}\right)|z\rangle \\ &= exp\left(\sum_i z_i \bar{z_i'}\right)\langle 0|z\rangle = exp\left(\sum_i z_i \bar{z_i'}\right) \end{aligned} \tag{13}$$

we can easily infer that the norm of a coherent state is given as:

$$\langle z|z\rangle = exp\left(\sum_i z_i \bar{z}_i\right) \tag{14}$$

so that we have the resolution of identity formed by bosonic coherent states in Fock space:

$$\mathbb{1}_{\mathcal{B}} = \int \prod_i \frac{dz_i d\bar{z_i}}{\pi} exp\left(-\sum_i z_i \bar{z}_i\right)|z\rangle \langle z| \tag{15}$$

*b. Fermionic subspace.* Next, we build the resolution of identity in fermionic subspace.

$$\mathbb{1}_{\mathcal{S}} = |\uparrow\rangle\langle\uparrow| + |\downarrow\rangle\langle\downarrow| \tag{16}$$

The coherent state is defined as $|\theta,\phi\rangle$, where:

$$|\theta,\phi\rangle = cos\frac{\theta}{2}e^{i\frac{\phi}{2}}|\uparrow\rangle + sin\frac{\theta}{2}e^{-i\frac{\phi}{2}}|\downarrow\rangle \tag{17}$$

and it is easy to prove the resolution of identity formed by the spin coherent state is:

$$\mathbb{1}_{\mathcal{S}} = \int \prod_i \frac{sin\theta_i d\theta_i d\phi_i}{4\pi^2}|\theta,\phi\rangle\langle\theta,\phi| \tag{18}$$

*c. Spin-boson Fock space.* Now if we combine these two things in order to discuss the regulatory effect of the entire network under spin-boson Fock space, we can have the resolution of identity:

$$\begin{aligned} \mathbb{1}_{\mathcal{F}} &= \mathbb{1}_{\mathcal{B}} \otimes \mathbb{1}_{\mathcal{S}} \\ &= \int \prod_i dz_i d\bar{z_i} sin\theta_i d\theta_i d\phi_i \cdot \\ &\quad exp\left(-\sum_i z_i \bar{z}_i\right)|z\rangle\langle z| \otimes |\theta,\phi\rangle\langle\theta,\phi| \end{aligned} \tag{19}$$

Having Eq.(9), if we discretize the time by defining $\Delta\tau = \tau/N$, we can rewrite the transition probability in the following form:

$$P(n_f,\tau|n_i,0) = \frac{1}{n_f!}\langle n_f| \prod_i e^{-\Delta\tau\mathcal{H}}|n_i\rangle \tag{20}$$

Note that here the index $i$ in $\prod_i$ is the discretized steps while the index $i$ in $|n_i\rangle$ stands for the initial state.

Then by inserting the identity, we have the form of transition probability in the spin-boson Fock space:

$$\begin{aligned} &P(n_f,\tau|n_i,0) \\ &= \int \prod_i dz_i d\bar{z_i} sin\theta_i d\theta_i d\phi_i \cdot exp\left(-\sum_i z_i \bar{z}_i\right)\cdot \\ &\langle z_i| \otimes \langle\theta_i,\phi_i| e^{-\Delta\tau\mathcal{H}}|\theta_{i-1},\phi_{i-1}\rangle \otimes |z_{i-1}\rangle \end{aligned} \tag{21}$$

where:

$$\begin{aligned} &\mathcal{E}_i = \langle z_i| \otimes \langle\theta_i,\phi_i| e^{-\Delta\tau\mathcal{H}}|\theta_{i-1},\phi_{i-1}\rangle \otimes |z_{i-1}\rangle \\ &\sim \langle z_i|z_{i-1}\rangle \langle\theta_i,\phi_i|\theta_{i-1},\phi_{i-1}\rangle \\ &\quad - \Delta\tau \langle z_i| \otimes \langle\theta_i,\phi_i| \mathcal{H}|\theta_{i-1},\phi_{i-1}\rangle \otimes |z_{i-1}\rangle \\ &= exp(\bar{z}_i z_{i-1}) \cdot exp\left[ln\langle\theta_i,\phi_i|\theta_{i-1},\phi_{i-1}\rangle\right] \\ &\quad \cdot \left[1 - \Delta\tau\mathcal{H}(z_i,\bar{z}_i,\theta_i,\phi_i)\right] \\ &\sim exp\left[\bar{z}_i z_{i-1} + ln\langle\theta_i,\phi_i|\theta_{i-1},\phi_{i-1}\rangle - \Delta\tau\mathcal{H}(z_i,\bar{z}_i,\theta_i,\phi_i)\right] \end{aligned} \tag{22}$$

So the transition probability can be rewritten into:

$$\begin{aligned} &P(n_f,\tau|n_i,0) \\ &= \int \prod_i dz_i d\bar{z_i} sin\theta_i d\theta_i d\phi_i \cdot exp\left(-\sum_i z_i \bar{z}_i\right)\mathcal{E}_i \\ &= \int \prod_i dz_i d\bar{z_i} sin\theta_i d\theta_i d\phi_i \cdot \\ &exp\left[\sum_i (-z_i\bar{z}_i + \bar{z}_i z_{i-1})\right. \\ &\left. + \sum_i ln\langle\theta_i,\phi_i|\theta_{i-1},\phi_{i-1}\rangle - \Delta\tau\sum_i \mathcal{H}(z_i,\bar{z}_i,\theta_i,\phi_i)\right] \end{aligned} \tag{23}$$

Now if we look at each individual term:

$$\begin{aligned}\sum_i -z_i\bar{z}_i + \bar{z}_i z_{i-1} &= -\sum_i \Delta\tau\left(\bar{z}_i + \frac{z_i - z_{i-1}}{\Delta\tau}\right) \\ &= -\int d\tau \bar{z}\partial_t z\end{aligned} \tag{24}$$

$$\begin{aligned}&\sum_i ln\left\langle\theta_i,\phi_i|\theta_{i-1},\phi_{i-1}\right\rangle \\ &= i\int d\tau\partial_\tau\phi(1-cos\theta) \\ &\equiv Berry\ Phase\end{aligned} \tag{25}$$

$$-\Delta\tau\sum_i \mathcal{H}\left(z_i,\bar{z}_i,\theta_i,\phi_i\right) = -\int d\tau\mathcal{H}\left(z_i,\bar{z}_i,\theta_i,\phi_i\right) \tag{26}$$

To explicitly write down the Hamiltonian:

$$\begin{aligned}\mathcal{H} &= X(1-a^\dagger) + a - a + \delta X(1-a^\dagger)\sigma_z \\ &+ \omega\cdot\left(\frac{-K(a^\dagger)^2a^2+1}{2}\sigma_z + \frac{-K(a^\dagger)^2a^2-1}{2}\right. \\ &\left.+\frac{K(a^\dagger)^2a^2+1}{2}\sigma_x + \frac{K(a^\dagger)^2a^2-1}{2i}\sigma_y\right)\end{aligned} \tag{27}$$

where $\sigma_s, s \in x,y,z$ are Pauli matrices. And since we have the relationship with spin coherent states (see Appendix):

$$\begin{aligned}\left\langle\theta,\phi\right|\sigma_x\left|\theta,\phi\right\rangle &= sin\theta cos\phi \\ \left\langle\theta,\phi\right|\sigma_y\left|\theta,\phi\right\rangle &= -sin\theta sin\phi \\ \left\langle\theta,\phi\right|\sigma_z\left|\theta,\phi\right\rangle &= cos\theta\end{aligned} \tag{28}$$

and when the creation/annihilation operators act on boson coherent states, the $z$ and $\bar{z}$ are given, respectively, so that we have the final form of effective Hamiltonian:

$$\begin{aligned}\mathcal{H}\left(z,\bar{z},\theta,\phi\right) &= X(1-\bar{z}) + \bar{z}z + \delta X(1-\bar{z})cos\theta \\ &+\omega\cdot\left(\frac{-K(\bar{z}z)^2+1}{2}cos\theta\right. \\ &+\frac{-K(\bar{z}z)^2-1}{2} + \frac{K(\bar{z}z)^2+1}{2}sin\theta cos\phi \\ &\left.-\frac{K(\bar{z}z)^2-1}{2i}sin\theta sin\phi\right) \\ &\sim\omega\cdot\left(\frac{-K(\bar{z}z)^2+1}{2}cos\theta\right. \\ &+\frac{-K(\bar{z}z)^2-1}{2} + \frac{K(\bar{z}z)^2+1}{2}sin\theta cos\phi \\ &\left.-\frac{K(\bar{z}z)^2-1}{2i}sin\theta sin\phi\right)\end{aligned} \tag{29}$$

The final approximation is valid under the adiabatic limit, where $\omega\to\infty$. And hence the transition probability can be expressed in terms of the path-integral form:

$$\begin{aligned}&P(n_f,\tau|n_i,0) \propto \int\mathcal{D}z\mathcal{D}\bar{z}\mathcal{D}\theta\mathcal{D}\phi exp\left(-\int\mathcal{L}dt\right) \\ &\mathcal{L} = \bar{z}\partial_t z + i\partial_\tau\phi(1-cos\theta) + \mathcal{H}\left(z,\bar{z},\theta,\phi\right)\end{aligned} \tag{30}$$

where $\mathcal{L}$ is the effective Lagrangian.

### C. Generalization to multiple gene states

We have explicitly solved the situation of two gene states above, however, conditions need to be reconsidered when there are more than two gene states that are present. For example, there are in total $N_{TF}$ types of transcription factors get involved in regulating the gene, which will make the total number of available gene states to $N_s = 2^{N_{TF}}$. Under this regime, the boson subspace in the formalism we built for two-state model still remains the same. However, it is apparent that we need to extend the two-spin model to a multi-spin one.

The probability vector is extended to $N-$dimensional space:

$$\mathbf{P}(n,t) = \begin{pmatrix} P_1(n,t) \\ \vdots \\ P_N(n,t)\end{pmatrix} \tag{31}$$

together with the wavefunction:

$$\left|\Psi\right\rangle = \begin{pmatrix} \sum_n P_1(n,t)\left|n\right\rangle \\ \vdots \\ \sum_n P_0(n,t)\left|n\right\rangle\end{pmatrix} \tag{32}$$

with normalization constrain: $\forall t, \sum_s\sum_n P_s(n) = 1$,
Now we will define the new spin coherent state as:

$$\left|\theta,\phi\right\rangle_R = \begin{pmatrix} \frac{2}{N}cos\frac{\theta}{N}e^{i\frac{\phi}{2}}\left|z_1\right\rangle \\ \vdots \\ \frac{2}{N}cos\frac{\theta}{N}e^{i\frac{\phi}{2}}\left|z_N\right\rangle\end{pmatrix} \tag{33}$$

$$\left|\theta,\phi\right\rangle_L = \left(\left\langle z_1\right|\frac{2}{N}sin\frac{\theta}{N}e^{-i\frac{\phi}{2}},\cdots,\left\langle z_N\right|\frac{2}{N}sin\frac{\theta}{N}e^{-i\frac{\phi}{2}}\right) \tag{34}$$

And all the other operations should be transformed under $N-$dimensional space.

### D. Generalization to multiple genes

Up to now, we are still discussing the dynamics of only a single gene. If we were to enter the regime of multiple

genes, we would add another level of complexity that shows as:

$$|\Psi\rangle = |\Psi_1\rangle \otimes |\Psi_2\rangle \cdots \otimes |\Psi_m\rangle \tag{35}$$

where $m$ represents the total number of genes. And the master equation will show up as:

$$\frac{\partial}{\partial t}|\Psi\rangle = \mathcal{H}_m |\Psi\rangle \tag{36}$$

where the Hamiltonian is effective under the space with the total $m \times N$ degree of freedom (gene states).

### E. Discussion on adiabaticity

Attention might already be drawn on the interpretation of the physical meaning of the parameter $\omega$, which is defined as $\omega = f/k$ in Eq.(7). The $\omega$ is actually the parameter to measure the adiabaticity of the system. When $\omega$ is sufficiently large, the binding/unbinding processes are considered to be much faster than the synthesis/degradation of proteins, where the system is in the adiabatic limit. However, when $\omega$ is small, the two processes are comparable, where the system is non-adiabatic and thus the first few terms in Eq.(27) cannot be ignored.

So far, we have discussed the methodology of using spin-boson model and path-integral formalism from the quantum many-body problem to understand the GRN under several cases. We started from the self-regulating gene with two gene states with detailed step-by-step derivations, then generalized to multiple gene states, and finally generalized to multiple genes.

Due to very limited time, derivations taking into account of some more realistic cases to GRN are not fully realized as well as simulations that based on the model are also not explicitly performed, which will be certainly viewed as further steps.

The author would like to thank Professor Mirny and Professor Kardar for giving a very inspiring and fruitful lecture series.

## III. APPENDIX

### A. Derivation to Eq.(12)

The coherent state $|z\rangle$ is generated from the vacuum state $|0\rangle$ through the displacement operator.

$$\begin{aligned} |z\rangle &= D(z)|0\rangle = e^{a^\dagger z - a\bar{z}}|0\rangle \\ |z\rangle &= \sum_n |n\rangle\langle n|z\rangle \end{aligned} \tag{37}$$

and we immediately have:

$$\begin{aligned} a^\dagger|n\rangle = \sqrt{n+1}\,|n+1\rangle &\Rightarrow \langle n|\,a = \sqrt{n+1}\,\langle n+1| \\ \sqrt{n+1}\,\langle n+1|z\rangle &= \langle n|\,a\,|z\rangle = z\,\langle n|z\rangle \\ \langle n+1|z\rangle &= \frac{z}{\sqrt{n+1}}\langle n|z\rangle \\ \Rightarrow \langle n|z\rangle &= \frac{z^n}{\sqrt{n!}}\langle 0|z\rangle \end{aligned} \tag{38}$$

and then it would be easy to get:

$$\begin{aligned} |z\rangle &= \sum_n |n\rangle\langle n|z\rangle = \sum_n |n\rangle \frac{z^n}{\sqrt{n!}}\langle 0|z\rangle \\ &= \langle 0|z\rangle \sum_n \frac{z^n}{\sqrt{n!}}|n\rangle \end{aligned} \tag{39}$$

where $\langle 0|z\rangle$ can be calculated:

$$\begin{aligned} \langle 0|z\rangle &= \langle 0|\,D(z)\,|0\rangle = \langle 0|\,e^{a^\dagger z - a\bar{z}}\,|0\rangle = 1 \\ \Rightarrow |z\rangle &= \sum_n \frac{z^n}{\sqrt{n!}}|n\rangle = \sum_n \frac{(a^\dagger z)^n}{\sqrt{n!}}|0\rangle \\ &= exp\left(a^\dagger z\right)|0\rangle \end{aligned} \tag{40}$$

### B. Derivation to Eq.(28)

We use $\sigma_y$ to show as an example:

$$\begin{aligned} \sigma_y|\uparrow\rangle &= i\,|\downarrow\rangle \\ \sigma_y|\downarrow\rangle &= -i\,|\uparrow\rangle \\ \sigma_y|\theta,\phi\rangle &= i\left[cos\frac{\theta}{2}e^{i\frac{\phi}{2}}|\downarrow\rangle - sin\frac{\theta}{2}e^{-i\frac{\phi}{2}}|\uparrow\rangle\right] \\ \langle\theta,\phi|\,\sigma_y\,|\theta,\phi\rangle &= isin\theta\left[\frac{1}{2}e^{i\phi} - \frac{1}{2}e^{-i\phi}\right] = -sin\theta sin\phi \end{aligned} \tag{41}$$


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