Adiabatic coarse graining and stochastic path integrals in reactive networks

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Gillespie algorithms are one means to ascertain the behavior of complicated reaction networks. However, such approaches are costly as they require one to keep track of each individual reaction. The goal of this study is to determine closed form analytic solutions for certain functions of interest, such as the moment generating function for a random variable Q_p corresponding to the number of products of a complicated reaction network in a given time interval, T. First, we show that we can make an adiabatic approximation to find such a function for a Michaelis Menten reaction scheme. Then, we coarse-grain an entire network by hierarchically integrating out fast degrees of freedom, analogous to integrating out large wavevectors in the RG procedure. We do this by studying the stochastic path integral, a functional integral over the space of time series densities for molecules in a reactive network.

I. BACKGROUND

First, we review MM kinetics. The system of equations is as follows:

$$\begin{aligned} &E + S \overset{k_1[S]}{\to} C^* \overset{k_2}{\to} E + P \\ &C^* \overset{k_{-1}}{\to} E + S \end{aligned} \tag{1}$$

Formulating the two states of the enzyme (bound, denoted by C^*, and unbound, denoted by E) as a 2-state Markov process, we write the master equation as:

$$\frac{d}{dt}\begin{bmatrix} P_u \\ P_b \end{bmatrix} = -\begin{bmatrix} k_1[S] & -k_{-1} - k_2 \\ -k_1[S] & k_{-1} + k_2 \end{bmatrix}\begin{bmatrix} P_u \\ P_b \end{bmatrix} \tag{2}$$

Canonical MM kinetics comes from making a steady-state approximation in the intermediate concentration (C^*), and setting the overall rate of the reaction to $k_2[C^*]$, where we obtain the concentration of intermediate by setting $\frac{d[C^*]}{dt} = 0$, which implies (since all of the above are elementary reactions):

$$k_1[S][E] + k_2[C^*] = k_{-1}[C^*] \tag{3}$$

and substituting $[E] = [E]_0 - [C^*]$ where $[E]_0$ is the total enzme concentration (bound and unbound) yields:

$$[C^*] = \frac{[S][E]_0}{k_m + [S]} \tag{4}$$

with k_m equal to $\frac{k_{-1}-k_2}{k_1}$. Thus the overall rate is:

$$k_2[C^*] = \frac{k_2[S][E]_0}{k_m + [S]} \tag{5}$$

Such coarse-graining fails to take into account stochasticity, and the methods presented now are a first stab at analytic functions that account for randomness in the chemical network.

II. INTERACTION PICTURE ANALYSIS

Now, we seek to recast MM using an 'interaction picture' Schrodinger-like equation, and thus find the cumulant generating function for δQ, the number of reactions of the type $S \to P$ in a given time interval. From above, we adopt the notation:

$$\frac{d}{dt}\overrightarrow{P} = -\mathbf{H}\overrightarrow{P} \tag{6}$$

We wish to write an expression for the probability that no transition will occur into the product state. We will write a revised markov-chain rate matrix that expresses this probability. Note that the diagonal elements of the rate matrix (in the bound/unbound or C^*, E basis)are defined to be $-\sum \lambda_i$ over all rates entering the state, and these elements will not change in our revised matrix. However, as rates into the unbound state, we will only allow the $k_{-1}[C^*]$ term, but not the $k_2[C^*]$ term as the latter contributes to product formation. Thus (in keeping with the standard notation of interaction picture quantum mechanics) we write:

$$\mathbf{H}_0 = \begin{bmatrix} k_1[S] & -k_{-1} \\ -k_1[S] & k_{-1} + k_2 \end{bmatrix} \tag{7}$$

and $\mathbf{H} = \mathbf{H}_0 - \mathbf{V}$ for $\mathbf{V}$:

$$\begin{bmatrix} 0 & k_2 \\ 0 & 0 \end{bmatrix} \tag{8}$$

Now, we are in a position to write a time-evolution operator for the unperturbed Hamiltonian $U(t, t_0)$, which in this case has the nice interpretation of translating the 2-tuple pdf of bound and unbound states in time from t_0 to t subject to the constraint that no product form in this time interval. As above, the equation of motion for the 2-pdf of bound and unbound states subject to this constraint satisfies [1]:

$$\frac{d}{dt}\overrightarrow{P} = -\mathbf{H}_0\overrightarrow{P} \tag{9}$$

and thus $\overrightarrow{P}(t) = \hat{T}e^{-\int_{t_0}^{t}\mathrm{d}t'\mathbf{H}_0(t'-t_0)}\overrightarrow{P}(t_0) \equiv U_0(t,t_0)\overrightarrow{P}(t_0)$ where $\hat{T}$ is the time-ordering operator.

Now, the task of writing a pdf for the number of events of the sort $S \to P$ is simple, which is conventionally denoted $P(\delta Q|T)$ to represent the probability for δQ reactions to occur in a time interval T. For example the probability for one such event to occur $P(1|T)$ is the sum of all probabilities for the one event to occur in this time interval T. The probability for the event to occur at one specific time t_1 is given by the probability for no event to occur from t_0 to t_1 multiplied by the probability for the event to occur at t_1 multiplied by the probability for no event to occur in the remainder of the duration. We get the total probability by integrating over all possible times for the event to occur:

$$P(1|T) = \begin{bmatrix}1 & 1\end{bmatrix}\left[\int_{t_0}^{T} U_0(t,t_1)\mathbf{V}U_0(t_1,t_0)\mathrm{d}t_1\right]\overrightarrow{P}(t_0) \tag{10}$$

The outer product with vector of ones is simply to account for the fact that we have an initial pdf over both states (bound, unbound). The general equation for $P(\delta Q = n|T)$ is given by:

$$\begin{aligned}&P(\delta Q = n|T) = \begin{bmatrix}1 & 1\end{bmatrix}\\ &\left[\int_{t_0}^{T}\mathrm{d}t_n\int_{t_0}^{t_n}\mathrm{d}t_{n-1}\cdots\int_{t_0}^{t_2}\mathrm{d}t_1 U_0(T,t_n)\mathbf{V}U_0(t_n,t_{n-1})\mathbf{V}\ldots\right.\\ &\left.\mathbf{V}U_0(t_1,t_0)\right]\overrightarrow{P}(t_0)\end{aligned} \tag{11}$$

This can be written compactly using the time ordering operator for the Dyson-like integral expansion:

$$P(\delta Q = n|T) = \begin{bmatrix}1 & 1\end{bmatrix}\frac{1}{n!}\hat{T}\left[\int_{t_0}^{T}\mathrm{d}tU_0(T,t)\mathbf{V}\right]^n\overrightarrow{P}(t_0) \tag{12}$$

Also, note that the time evolution operator of the unperturbed Hamiltonian is time independent in the large $[S]$ regime, and thus we see that:

$$\begin{aligned}P(1|T) &= \begin{bmatrix}1 & 1\end{bmatrix}\left[\int_{0}^{T} U_0(T-t)\mathbf{V}U_0(t)\mathrm{d}t\right]\overrightarrow{P}(0)\\ &= \begin{bmatrix}1 & 1\end{bmatrix}U_0 * \left[\mathbf{V}U_0\right]\overrightarrow{P}(0)\end{aligned} \tag{13}$$

for convolution operator $*$. This easily extends to [1]:

$$P(\delta Q = n|T) = \begin{bmatrix}1 & 1\end{bmatrix}U_0\left[*\mathbf{V}U_0\right]^n\overrightarrow{P}(0) \tag{14}$$

We can write an operator equation of motion for the time evolution operator also by noting that:

$$\begin{aligned}\frac{d}{dt}\overrightarrow{P}(t) &= -\mathbf{H}_0\overrightarrow{P}(t) = \left[-\mathbf{H}_0U_0(t)\right]\overrightarrow{P}(0)\\ &= \left[\frac{d}{dt}U_0(t)\right]\overrightarrow{P}(0)\end{aligned} \tag{15}$$

where we note that only the time evolution operator has active (t) dependence in the $\overrightarrow{P}(t) = U_0(t)\overrightarrow{P}(0)$.

Now, for $S(\chi,T)$ the cumulant-generating function, note that:

$$\begin{aligned}e^{S(\chi,T)} &= \sum_{n=0}^{\infty}P(\delta Q = n|T)e^{i\chi n}\\ &= \begin{bmatrix}1 & 1\end{bmatrix}\sum_{n=0}^{\infty}\frac{1}{n!}\hat{T}\left[\int_{t_0}^{T}\mathrm{d}tU_0(T,t)\mathbf{V}e^{i\chi}\right]^n\overrightarrow{P}(t_0)\\ &= \begin{bmatrix}1 & 1\end{bmatrix}\sum_{n=0}^{\infty}U_0\left[*\mathbf{V}e^{i\chi}U_0\right]^n\overrightarrow{P}(0)\end{aligned} \tag{16}$$

Note that the initial conditions dictate $e^{S(\chi,0)} = \overrightarrow{P}(0)$. We seek to find an explicit formula for $f(\chi,t) = e^{S(\chi,t)}$ the moment generating function. Note that due to the derivative property of convolution, $(f*g)' = f'*g = g'*f$, we can write an equation of motion for the moment generating function:

$$\begin{aligned}\dot{f}(\chi,t) &= \begin{bmatrix}1 & 1\end{bmatrix}\sum_{n=0}^{\infty}\dot{U}_0\left[*\mathbf{V}e^{i\chi}U_0\right]^n\overrightarrow{P}(0)\\ &= \begin{bmatrix}1 & 1\end{bmatrix}\sum_{n=0}^{\infty}-\mathbf{H}_0U_0\left[*\mathbf{V}e^{i\chi}U_0\right]^n\overrightarrow{P}(0)\end{aligned} \tag{17}$$

From this, we see that [1]:

$$\dot{f}(\chi,t) = \begin{bmatrix}1 & 1\end{bmatrix}\left[-\mathbf{H}_0 + \mathbf{V}e^{i\chi}\right]f(\chi,t) \tag{18}$$

This implies that

$$f(\chi,t) = \begin{bmatrix}1 & 1\end{bmatrix}\hat{T}e^{\left[\int -\mathbf{H}_0 + \mathbf{V}e^{i\chi}\right]}\overrightarrow{P}(0) \tag{19}$$

III. ADIABATIC APPROXIMATION

We have thus reduced the problem to one in which our effective hamiltonian (-$\mathbf{H}_{eff} = -\mathbf{H}_0 + \mathbf{V}e^{i\chi}$) has time-dependent parameters, namely the concentration of substrate. Here we make an adiabatic approximation, and assume that the stationary states of the hamiltonian will evolve with the parameters slowly as a function of time. More precisely, following Sakurai, if we know the time dependent eigenvalues and eigenvectors of the hamiltonian, $\mathbf{H}_{eff}(t)|n;t\rangle = E_n(t)|n;t\rangle$, and we have a Schrodinger equation of the form in eqn. (18), we expand $\overrightarrow{P}$ in the set of hamiltonian eigenvectors as $\overrightarrow{P} = \sum_{n=1,2}c_n(t)e^{-\int E_n(t)\mathrm{d}t}|n;t\rangle$.

Further analysis shows the time-dependent expansion coefficients to be [2]:

$$c_n(t) = \exp\left[\int\langle n;t|\partial_t|n;t\rangle\mathrm{d}t\right]c_n(0) \tag{20}$$

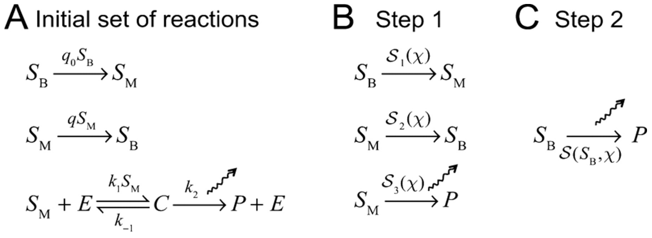

FIG. 1. We apply stochastic path integral techniques and adiabatic coarse graining in successive stages to the network pictured above

In fact, this term only contributes a geometrical factor relating to the curve traced out in parameter space. Its effects are second order and can be neglected for the purposes of this study (see Appendix B).

The second approximation we make here is in expanding the vector $\overrightarrow{P}$ in terms of hamiltonian eigenvectors. After the adiabatic approximation, and dropping the geometric berry phase-like terms, we rewrite eqn. (19) as:

$$f(\chi,t) = \sum c_n(0) e^{-\int E_n(t)\mathrm{d}t} \tag{21}$$

where we embed all information about the initial state and the decomposition of vector $\mathbf{1}^T$ in terms of the $\mathbf{H}_{eff}$ eigenvectors into the expansion coefficients $c_n(0)$. Now, we assume that over the time intervals of interest, we lose all information about the initial state and the expansion in (21) is dominated by the eigenvalue $E_n(t)$ with smallest real component, from which we get that [3]:

$$\begin{aligned} e^{S(\chi,T)} &\approx e^{-E_0 T} \Rightarrow \\ S(\chi,T) &\approx -E_0 T \end{aligned} \tag{22}$$

Thus, the crux of the argument rests in finding time scales T such that we can ignore geometrical factors, and also approximate the substrate concentration as slowly varying and therefore replace the integral in the exponent in eqn. (21) with its instantaneous value times the length of the interval.

Explicitly, reading the value from Sinitsyn et. al, we get [3]:

$$\begin{aligned} S(\chi,T) = S_{geom} &+ \frac{T}{2}\Big[-(k_{-1} + k_2 + [S]\,k_1) \\ &+ \sqrt{(k_{-1} + k_2 + [S]\,k_1)^2 + 4\,[S]\,k_1 k_2 (e^{i\chi} - 1)}\Big] \end{aligned} \tag{23}$$

IV. STOCHASTIC PATH INTEGRAL

Now, we seek to coarse grain the network pictured in figure one. This network was chosen because of its versatility in capturing the general scheme of signaling reactions, in either vision or immune signaling [3]. Step one shows a substrate molecule adsorbing to a membrane, and the reverse (desorption) is also allowed. The third step is precisely the step we have analyzed previously, namely the MM step.

The method presented here is unique in that it allows hierarchical coarse graining of fast variables. In fact, the aim is to eliminate fast variables altogether. This is similar to the RG procedure of integrating out large wavevectors. We consider three time-scales, τ_B, τ_M and τ_E. The first two represent fluctuations in the densities of bulk (B) and adsorbed membrane (M) molecules. The time scale τ_E represents the time scales of single MM reactions. Thus, generalizing the earlier notation, $P(\delta Q_\mu|T)$ will represent the probability for δQ reactions of type $\mu = 1,2,3$ in a time increment T, where $\mu = 1,2,3$ refer to the respective reactions above.

The first two steps, binding and desorption, will be Poissonian since they are elementary reactions, and if we consider time scales such that S_M and S_B are constant or slowly-evolving, they are Poisson with rates $q_0 S_B(t)$ and $q S_M(t)$ respectively [3]. Their moment generating functions (for number of events to occur in time T) are consequently given by $e^{S_\mu(\chi_\mu)} = \exp q T S_\mu(t)(e^{i\chi} - 1)$ (Appendix A). While we can treat the first two reactions as Poissonian because they are elementary, the MM step must be treated differently. It is coarse-grained according to the procedure outlined in sections $2, 3$. Now, we seek to coarse-grain the rest of the reactions to obtain a CGF for the reaction $S_B \rightarrow P$. In this step, we must consider time-scales of the order of τ_B, i.e. the $[S]$ (which is $S_M(t)$) is no longer constant, but slowly varying. For these time scales, however, we can still approximate the bulk concentration $[S_B]$ as constant.

First, we introduce the stochastic path integral. In this case, the field we integrate over is the time-series density of membrane bound protein, $[S]$. From here on out the brackets are dropped, but we will make explicitly clear that $S(t)$ is the substrate concentration as a function of time, whereas the $S_\mu(\chi_\mu)$ are the cumulant generating functions. Under the stochastic path integral, we define the expectation value of a certain operator as follows [3]:

$$\langle \mathcal{O} \rangle = \int \mathcal{D}S(t) \prod_{\mu=1,2,3} \left[\int \mathcal{D}\delta Q_\mu(t) P\left[\delta Q_\mu\right] \right] \mathcal{O} \tag{24}$$

To write down the moment generating function for the number of products formed in a time interval $T \approx \tau_B$, which is given by $e^{S_p(\chi_p)} = \langle e^{i\chi_p Q_p} \rangle$ (where Q_p is the discrete random variable representing the number of products formed), we first note the following. We can discretize the total time interval into small intervals t_k of duration δt, and note then that the number of products formed will be $Q_p = \sum_k \delta Q_3(t_k)$, since it is only the MM step (reaction 3) that produces product molecule.

Further, we will have to obey the conservation law in integrating over all forms of the substrate concentration as a function of time. That is to say, the number of substrate molecules at a given time, plus the number that adsorb in that time increment, minus the number that desorb in that time increment and minus the number that form product (MM step) in that time increment will have to equal the number of substrate molecules at the next step. As in the non-linear sigma model, we have to explicitly include the conserved quantity as a delta function: $\delta\left(S(t_k)+\delta Q_1(t_k)-\delta Q_2(t_k)-\delta Q_3(t_k)-S(t_{k+1})\right)$

In fact, it proves easiest to write the probability distributions for various reactions in terms of the inverse fourier transform of their MGF. In other words, the probability of δQ_μ reactions of type μ in time t_k is written as:

$$P\left[\delta Q_\mu(t_k)\right]=\frac{1}{2\pi}\int_{-\pi}^{\pi}\mathrm{d}\chi_\mu e^{-i\chi_\mu\delta Q_\mu(t_k)}e^{S_\mu(\chi_\mu)} \tag{25}$$

Also, we can rewrite the delta function for the conservation law as well:

$$\delta(\dots)=\frac{1}{2\pi}\int_{-\pi}^{\pi}\mathrm{d}\chi_M e^{i\chi_M\cdots} \tag{26}$$

where we note that now each of the δQ_μ terms is multiplied by the variable χ_M from the delta function for conservation law, and also its own variable χ_μ from the inverse fourier transform of the μ probability distribution.

The stochastic path integral for the MGF of total number of reactions (from bulk to product) then will look like:

$$\begin{aligned}\langle e^{i\chi_p Q_p}\rangle=\int\mathcal{D}S(t)\int\prod_{i=1,2,3,M}\mathrm{d}\chi_i\\ \prod_{k,\mu=1,2,3}\int\mathcal{D}\delta Q_\mu(t_k)e^{i\chi_p\sum_k\delta Q_3(t_k)}\dots\end{aligned} \tag{27}$$

Thus, in writing the path integral this way, we will get simplifications of the following form:

$$\begin{aligned}&\int_{-\pi}^{\pi}\mathrm{d}\chi_\mu\int\mathcal{D}\delta Q_\mu e^{-i(\chi_\mu+\chi_M)\delta Q_\mu}e^{S_\mu(\chi_\mu)}\\ &=\int_{-\pi}^{\pi}\mathrm{d}\chi_\mu\delta(\chi_\mu+\chi_M)e^{S_\mu(\chi_\mu)}\\ &=e^{S_\mu(-\chi_M)}\end{aligned} \tag{28}$$

Thus, after all simplifications, the only variables that remain are the χ_M which we introduced for the conservation law, and also the χ_p which we introduced for the random variable Q_p.

We next take the continuum limit to replace $S(t_{k+1})-S(t_k)\approx\delta t\dot{S}$, and the simplified result is:

$$\langle e^{i\chi_p Q_p}\rangle=\int\mathcal{D}S(t)\mathrm{d}\chi_M e^{\int_0^T\mathrm{d}t\left[i\chi_M S\dot{(t)}+\mathcal{H}(S(t),\chi_p,\chi_M)\right]} \tag{29}$$

In the above, the functional $\mathcal{H}$ is related to the CGF's for each of the individual reactions [3]:

$$\begin{aligned}&\mathcal{H}(S(t),\chi_M,\chi_p)=\\ &=S_1(-\chi_M,S(t))+S_2(\chi_M,S(t))+S_3(\chi_M+\chi_p,S(t))\\ &=q_oS_B(e^{-i\chi_M}-1)+qS(t)(e^{i\chi_M}-1)\\ &+\frac{1}{2}\left[-(k_{-1}+k_2+S(t)k_1)\right.\\ &\left.+\sqrt{(k_{-1}+k_2+S(t)k_1)^2+4S(t)k_1k_2(e^{i(\chi_M+\chi_p)}-1)}\right]\end{aligned} \tag{30}$$

Finally, we make a saddle point approximation to argue that the path integral will be dominated by the 'classical' path, that is, a constant substrate field: $\dot{S}=0$. As for the magnitudes, we denote $S_{cl}(\chi_p)$ and $\chi_{cl}(\chi_p)$ to be the simultaneous solutions to:

$$\frac{\partial\mathcal{H}}{\partial\chi_M}=\frac{\partial\mathcal{H}}{\partial S_M}=0 \tag{31}$$

Then, the final result is [3]:

$$\langle e^{i\chi_p Q_p}\rangle=e^{T\mathcal{H}(S_{cl},\chi_{cl},\chi_p)} \tag{32}$$

V. FUTURE PLANS

We have shown that closed form analytic solutions can be found for equations of interest in complicated chemical reaction networks, such as the CGF/MGF for the number of events of the sort $S_B\to P$ to occur in a time interval T. The first several cumulants predicted by this result agree with Gillespie simulations to within 1% [3]. This implies that stochastic effects can be captured effectively by coarse-graining. Costly computer simulations may not be necessary in certain cases.

We note that coarse graining complicated reaction networks to a single random variable Q_p allows for many exciting areas of pursuit. For example, if a membrane could be partitioned into N independent segments (assuming negligible interaction at boundaries), as N grows large the law of large numbers tells us that the sum of $Q_{p,i}$ for $i\in(1,\dots,N)$ will converge with probability 1 to the expected value of Q_p under the distribution derived above.

Further, Sanov's theorem gives us a simple method for computing the probability of large deviations from the sample mean. For example, to find the probability that the membrane will reach some concentration C_0 of product, one computes an I-projection by tilting the distribution to one with a mean of C_0. The probability is governed to first order in the exponent by N times the KL divergence between the actual pdf and the I-projection.

One can take into account spatial variations in the membrane as follows. Assume that k membrane patches have a certain clustering pattern causing a different set of initial concentrations than the remaining $N-k$ patches. To find the probability in this case of reaching a threshold concentration of $C_0 > \mathbf{E}[Q_p]$, Sanov's theorem predicts that we must compute the probability for the k patches to hit a concentration of n_1 and the $N-k$ remaining patches to hit a concentration of n_2 such that the total concentration is C_0.The exponential behavior will be dictated by the n_1 and n_2 that minimize the KL divergence.

These are experiments that could be tested against Gillespie simulations.

APPENDIX A: CGF FOR POISSON DISTRIBUTION

Here we review the derivation for the cumulant generating function of the poisson distribution, which is a one parameter distribution:

$$P_\lambda(y) = \frac{e^{-\lambda}\lambda^y}{y!} \tag{33}$$

The characteristic function is given by

$$\begin{aligned} \langle e^{i\chi y}\rangle &= e^{-\lambda}\sum_{y=0}^{\infty}\frac{(\lambda e^{i\chi})^y}{y!} \\ &= \exp\lambda(e^{i\chi}-1) \end{aligned} \tag{34}$$

The CGF as we have seen produces the connected averages, and comes from taking the logarithm of the characteristic function. In this study, it is denoted $S(\chi)$:

$$S(\chi) = \log\langle e^{i\chi y}\rangle = \lambda(e^{i\chi}-1) \tag{35}$$

APPENDIX B: BERRY PHASE IN QUANTUM MECHANICS AND CHEMICAL KINETICS

In quantum mechanics, we aim to solve equations of the form $\partial_t|f\rangle = -\mathbf{H}(t)|f\rangle$. We use an ansatz solution of the form $|f\rangle = \sum_n c_n(t)e^{\int E_n(t')dt'}|n,t\rangle$ where $\mathbf{H}(t)|n,t\rangle = E_n(t)|n,t\rangle$ and solve for the time dependent coefficients by substituting the ansatz into the Schrodinger equation to yield:

$$\begin{aligned} &\sum_n e^{\int E_n(t')dt'}\left[\partial_t c_n|n,t\rangle - c_n(t)E_n(t)|n,t\rangle + c_n(t)\partial_t|n,t\rangle\right] \\ &= \sum_n -e^{\int E_n(t')dt'}c_n(t)E_n(t)|n,t\rangle \Rightarrow \\ &\sum_n e^{\int E_n(t')dt'}\left[\partial_t c_n|n,t\rangle + c_n(t)\partial_t|n,t\rangle\right] = 0 \end{aligned} \tag{36}$$

Next, we take the outer product of the above equation with $\langle m,t|$ and invoke orthonormality of the eigenvectors to get:

$$\partial_t c_m(t) = -\sum_n c_n(t)e^{\int E_n(t')-E_m(t')dt'}\langle m,t|\partial_t|n,t\rangle \tag{37}$$

In fact, our effective Hamiltonian in this study is not hermitian, but as shown by Sinitsyn et. al, we can choose the two instantaneous eigenvectors for our system to be properly normalized such that $\langle n,t|m,t\rangle = \delta_{n,m}$ [4].

Then, following the traditional quantum mechanical derivation [2], we must construct $\langle m,t|\partial_t\mathbf{H}|n,t\rangle$ by taking:

$$\partial_t\left[\mathbf{H}|n\rangle = E_n|n\rangle\right] \Rightarrow \partial_t\mathbf{H}|n\rangle + \mathbf{H}\partial_t|n\rangle = E_n\partial_t|n\rangle \tag{38}$$

Again taking an outer product with $\langle m|$ and noting that (even though our Hamiltonian is not hermitian) $\langle m|\mathbf{H} = \langle m|E_m$, we arrive at:

$$\begin{aligned} \langle m|\partial_t\mathbf{H}|n\rangle &= (E_n - E_m)\langle m|\partial_t|n\rangle \Rightarrow \\ \langle m|\partial_t|n\rangle &= \frac{\langle m|\partial_t\mathbf{H}|n\rangle}{(E_n-E_m)} \end{aligned} \tag{39}$$

Substituting into eqn. 37:

$$\begin{aligned} \partial_t c_m(t) &= -c_m(t)\langle m|\partial_t|m\rangle \\ &\quad + \sum_{n\neq m} c_n(t)e^{\int E_n(t')-E_m(t')dt'}\frac{\langle m|\partial_t\mathbf{H}|n\rangle}{(E_n-E_m)} \end{aligned} \tag{40}$$

The adiabatic approximation is to say that the parameters are changing very slowly in time, and thus $\partial_t\mathbf{H}_{nm} \approx 0$. We arrive at the desired result for the time dependent expansion coefficients:

$$c_m(t) = \exp\left[\int\langle m;t|\partial_t|m;t\rangle \mathrm{d}t\right]c_m(0) \tag{41}$$

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