Application of the projection operator formalism to non-Hamiltonian dynamics

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Abstract

Dimension reduction is a fundamental problem in the study of dynamical systems with many degrees of freedom. Extensive efforts have been made but with limited success to generalize the Zwanzig-Mori projection formalism, originally developed for Hamiltonian systems close to thermodynamic equilibrium, to general non-Hamiltonian and far-from-equilibrium systems. One difficulty lies in defining an invariant measure. Based on a recent discovery that a system defined by stochastic differential equations can be mapped to a Hamiltonian system, we developed a projection formalism for general dynamical systems. In the obtained generalized Langevin equations, the memory kernel and the random noise terms are connected by generalized fluctuation-dissipation relations. Lacking of these relations restricts previous application of the generalized Langevin formalism in general. Our numerical test on a chemical network with end-product inhibition demonstrates the validity of the formalism. We suggest that the formalism can find usage in various branches of science. Specifically, we discuss potential applications in studying biological networks, and its implications in network properties such as robustness, parameter transferability.

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It is common to study dynamics of a system with many degrees of freedom in almost every scientific field. In general it is impractical, and often unnecessary, to track all the dynamical information of the whole system. A common practice is projecting the dynamics of the whole system into that of a smaller subsystem through information contraction. The procedure leads to the celebrated Langevin and generalized Langevin dynamics. The Zwanzig-Mori formalism is a formal procedure of projection, especially for Hamiltonian systems [1, 2, 3, 4]. Inspired by its great success in irreversible statistical mechanics, Chorin and coworkers, have suggested a version of the Zwanzig-Mori formalism for higher-order optimal prediction methods for general dynamical systems [5, 6]. The difficulty lies in choosing an invariant measure in defining an inner product (see below for details). The choice is straightforward for a Hamiltonian system, but not clear for a general system.

Recently one of us has proved that one can map a system described by a set of stochastic differential equations

\[
\dot{x}_i = dx_i/dt = G_i(x) + \sum_{j=1}^{M} g_{ij}(x) \zeta_j(t), \quad i = 1, \cdots, N. \tag{1}
\]

to a Hamiltonian system [7]. In general \(M\) and \(N\) may be different, \(\zeta_i(t)\) are temporally uncorrelated, statistically independent Gaussian white noise with the averages satisfying \(\langle \zeta_i(t) \zeta_j(\tau) \rangle = \delta_{ij} \delta(t - \tau)\), \(g(x)\) is related to the \(N \times N\) diffusion matrix \(gg^T = 2D/\beta\), where the superscript \(T\) refers to transpose. For a statistical mechanical system \(\beta\) is the inverse temperature, \(1/k_BT\) with \(k_B\) the Boltzmann’s constant. For a non-physical systems, \(\beta\) is a parameter analogous to an effective inverse temperature. Eqn. (1) is widely used to describe dynamics in various fields of science from physics, ecology and cell biology, finance, geology, etc [8, 9, 10]. The mapping makes explicit the choice of an invariant measure, and thus derivation of the Zwanzig-Mori projection formulae straightforward. The mapping is only used as an auxiliary tool to derive the formula. One needs not to actually construct the mapping Hamiltonian.

In the remaining parts of the paper, we will first develop the theory, then present analytical results for a quasi-linear system and numerical tests on a small chemical network, and finally conclude with a general discussion.

1 Theory

1.1 Summary of the Zwanzig-Mori formalism

We follow the notation of Zwanzig here [4]. Consider a dynamic variable described by a Liouville equation in a \(N\) dimensional space,

\[
\frac{\partial}{\partial t} A(x(t), t) = L A(x(t), t) \tag{2}
\]
For a Hamiltonian system, the Liouville operator $L$ is defined as,

$$LA = \sum_i \left( \frac{\partial H}{\partial p_i} \frac{\partial A}{\partial q_i} - \frac{\partial H}{\partial q_i} \frac{\partial A}{\partial p_i} \right)$$  \hspace{1cm} (3)$$

where $H$ is the Hamiltonian, and $q_i$ and $p_i$ are the coordinates and conjugate momenta. Any dynamical quantity $A(q,p)$ is a vector in the Hilbert space. One can define the projection of another dynamical quantity $B$ on $A$ as,

$$PB = \sum_{ij} (B, A_i)(A, A_j)^{-1} A_j, i, j = 1, \cdots, m$$  \hspace{1cm} (4)$$

where $m$ is the number of components of the vector $A$. The inner product for two arbitrary variables $A$ and $B$ is defined as,

$$\langle A, B \rangle \equiv \langle A^\dagger B \rangle \equiv \int A^\dagger B \psi(x) dx$$  \hspace{1cm} (5)$$

where $\dagger$ means taking transpose and complex conjugate, and $\psi$ is a weighting function need to be defined. Any dynamic variable within the subspace can be expressed as a linear combination of the basis functions. The projected equations of an arbitrary dynamic variable $A$, which is defined within the projected subspace, are in the form of generalized Langevin equations (GLEs),

$$\frac{\partial}{\partial t} A(t) = PLA(t) - \int_0^t ds K(s) \cdot A(x(t - s)) + F(t)$$  \hspace{1cm} (6)$$

where

$$F(t) = \exp(t(1 - P)L)(1 - P)LA$$  \hspace{1cm} (7)$$

$$K(t) = -(LF(t), A) \cdot (A, A)^{-1}$$  \hspace{1cm} (8)$$

At time 0, $A$ is within the subspace. Time evolution of $A$ is splitted into the dynamics within the subspace and within the orthogonal subspace, which are treated explicitly and implicitly, respectively. Effects of the latter on the former are accounted for by the last two terms in the right hand side of Eqn. (6). If the Liouville operator is anti-Hermitian, one further obtains the generalized fluctuation-dissipation relation (GFDR) between the memory kernel and the random force term,

$$K(t) = (F(t), LA) \cdot (A, A)^{-1} = (F(t), F(0)) \cdot (A, A)^{-1}$$  \hspace{1cm} (9)$$

Eqn. (9) is mathematically equivalent to Eqn. (2) and assumes a form formally analogous to the phenomenological generalized Langevin equation. In principle, one can apply the projection formalism to general dynamical systems, and the choice of the Hilbert subspace expanded by $A$ and the weighting functions can be arbitrary. However, as Zwanzig pointed out, in general the procedure
is only a mathematical exercise with no practical usage. To be practically useful, one has to choose $\psi$ properly. With an invariant measure,

$$
\int f(x(t))\psi(x(0))dx(0) = \int f(x(t))\psi(x(t))dx(t) = \int f(x)\psi(x)dx,
$$

(10)

$A$ and $x$ can be viewed as random variables [2, 4, 5]. For a Hamiltonian system near equilibrium, one can choose the Boltzmann factor $\rho(q, p) = \exp(-\beta H)/\int \exp(-\beta H)dqd$ as $\psi$. The conservation of $H$ and the Liouville theorem ensures the choice is an invariant measure. The term $F(t)$ has ensemble average $\langle F(t) \rangle = 0$, and thus indeed behaves as a random force term. The memory kernel and the random force terms are not independent, but are constrained by the GFDR. For a general non-Hamiltonian system it is not clear how to choose the measure. Phenomenological generalized Langevin equations have been used to model dynamical systems such as financial market fluctuations [16]. However, lacking of the GFDR makes model construction very difficult [20].

### 1.2 Projection formalism for non-Hamiltonian systems

In a seminal paper, Ao showed that one can always construct a symmetric matrix $S$ and an anti-symmetric one $T$, and transform Eqn. 11 into [11],

$$
M \frac{dx}{dt} = M \cdot (G(x) + g(x)\zeta(t)) = -\nabla_x \phi(x) + g'(x)\zeta(t)
$$

(11)

where, $M = S + T$, $\phi$ is a scalar function corresponding to the potential function in a Hamiltonian system satisfying $(\partial \times \partial \phi)_{ij} \equiv (\partial_i \partial_j - \partial_j \partial_i)\phi = 0$, and $g'g'^T = 2S/\beta$. Then $S$ and $T$ are uniquely determined by

$$
\partial \times [M \cdot G(x)] = 0, (M)^{-1} + (M)^{-T} = 2gg^T,
$$

(12)

and proper choice of the boundary conditions. One may extend the above equation with an auxiliary momentum term,

$$
\dot{x} = \frac{\dot{p}}{m},
$$

(13)

$$
\dot{\dot{p}} = \left[ -T(x) \frac{\dot{p}}{m} - \nabla_x \phi(x) \right] + \left[ -S(x) \frac{\dot{p}}{m} + g'(x)\zeta(t) \right],
$$

(14)

which reduces to Eqn. 12 in the limit $m \to 0 (\dot{p} \to 0)$.

In [7], Xing showed that one can map the dynamics described by Eqn. 11 to a Hamiltonian system in the zero mass limit. The proof proceeds in two steps. First one can define a Lagrangian so the resultant Euler-Lagrange equation gives Eqn. 13 and 14 excluding the dissipative terms (the terms inside the second
bracket in Eqn. [14]. Second following a procedure similar to that adopted by Zwanzig [12], one can replace the dissipative terms by a bath Hamiltonian with a large number of harmonic oscillators coupled to the primary degrees of freedom $x$. The bath is initially in contact with a heat reservoir. That is, the initial conditions of the bath degrees of freedom are drawn from a canonical distribution. The overall Hamiltonian is

$$H = \frac{(p - A(x))^2}{2m} + \phi(x)$$

where $A$ is a vector potential satisfying $T_{ij} = \left[ \frac{\partial A_i}{\partial x_j} - \frac{\partial A_j}{\partial x_i} \right]$, $p \equiv m\dot{x} + A = \tilde{p} + A$ is the conjugate momentum. The last term in Eqn. [15] is the bath Hamiltonian, and its form is determined by $S$ [7]. The Hamiltonian describes a massless particle, coupled to a set of harmonic oscillators, moving in a hypothetical $n$-dimensional conservative scalar potential and magnetic (the vector potential) field. The mapping permits applying techniques and results for Hamiltonian systems to dissipative systems [7,13]. For the current purpose, the property of Hamiltonian dynamics suggests the inner product definition,

$$(A, B) \equiv \int A^\dagger B \exp(-\beta H)dxdp$$

Alternatively, one can also replace the integration over $p$ by $\tilde{p}$. Both definitions ensure the requirement of invariant measure [14]. As will be clear from the following theoretical developments and examples, in real applications one needs not to actually perform the mapping. The mapping merely serves as an auxiliary tool to derive the projection formulae and the GFDR.

In this work for simplicity we only consider projecting to a subspace composed by the first $m$ components of $x$ and the corresponding velocity components. Generalization to collective coordinates is straightforward, and is given in Appendix A (see also [2,17,18]). In the following discussion we denote them as $\mathbf{X} = \{x_1, x_2, \ldots, x_m\}$, and $\mathbf{\dot{X}} = \{\dot{x}_1, \dot{x}_2, \ldots, \dot{x}_m\}$. Let’s define a nonlinear projection operator [2,5,18],

$$P_h = \frac{1}{\bar{\rho}(\mathbf{X}, \mathbf{\dot{X}})} \int h\rho(x,p)\delta(\mathbf{\dot{X}} - \mathbf{X})\delta(\mathbf{\dot{X}} - (p - A)/m)dxdp$$

where $h$ is an arbitrary function, and

$$\bar{\rho}(\mathbf{\dot{X}}, \mathbf{\dot{X}}) = \int \rho(x,p)\delta(\mathbf{\dot{X}} - \mathbf{X})\delta(\mathbf{\dot{X}} - (p - A)/m)dxdp$$
Then (see Appendix A for detailed derivation),

\[ PLX_j = \dot{X}_j \quad (19) \]

\[ PL\dot{X}_j = -\frac{1}{m\beta} \frac{\partial}{\partial X_j} \ln \bar{\rho}(X) - \sum_{k \neq j} \dot{X}_k \left( < \frac{\partial A_k}{\partial X_j} > x - < \frac{\partial A_j}{\partial X_k} > x \right) \quad (20) \]

where,

\[ \bar{\rho}(\bar{X}) = \int dx \exp(-\beta \phi) \delta(\bar{X} - X) \quad (21) \]

\[ < B >_{\bar{X}} = \frac{1}{\bar{\rho}(\bar{X})} \int dx B(x) \exp(-\beta \phi) \delta(\bar{X} - X) \quad (22) \]

and we have omitted the bar on the variables. The projected equation of motion is,

\[ m \frac{\partial^2}{\partial t^2} X_j(t) = -\frac{\partial}{\partial X_j} W(X) + \sum_i \left[ \bar{T}_{ij} + \int_0^t ds \gamma_j(s) \dot{X}_i(t - s) \right] + mF_j(t) \quad (23) \]

where \( W(X) = -\ln \bar{\rho}(X)/\beta \) is the potential of mean force, and \( \bar{T}_{ij} = < \frac{\partial A_j}{\partial x_i} - \frac{\partial A_i}{\partial X_j} > \) is the renormalized antisymmetric matrix in the reduced space. The memory kernel and the random force are related by the generalized fluctuation-dissipation relation,

\[ < F_i(t)F_j(t') >= K_{ij}(t - t')/(m\beta) \quad (24) \]

Taking the ansatz \( mK_{ji}(t) = \frac{1}{2}(2\gamma_{ji}^0 \delta(t) + \gamma_{ji}(t)) \) (see discussion below and the analytical examples in Supporting text for reasons), and take the zero-mass limit, one has,

\[ 0 = \left[ -\frac{\partial}{\partial X_j} W(X) - \sum_i (\bar{S}_{ji} + \bar{T}_{ji}) \dot{X}_i(t) \right] \]

\[ - \left[ \sum_i \int_0^t ds \gamma_{ji}(t - s) \dot{X}_i(s) \right] + m\beta F_j(t) \quad (25) \]

Where \( \bar{S}_{ij} = \gamma_{ij}^0 \), Eqn. 25 is in the form of the generalized Langevin equation (GLE), and together with the GFDR Eqn. 24 is the main result of this work. Physically the terms in the first brackets are related to the direct interactions (or fluxes) within the projected subspace and between the subspace and the surroundings. That is why we need to introduce the singular part of \( K_{ij} \) in
general. The terms in the second brackets refer to the retarded interactions mediated by the implicit surroundings. Notice that we never actually perform the complicated nonlinear transformation prescribed by Ao and by Xing [7, 11].

In the case we project to a 1-D system, the equation is,

\[ 0 = -\frac{\partial}{\partial X_j} W(X) - \int_0^t ds \Gamma(s) \dot{X}(t-s) + m \beta F(t) \]  \hspace{1cm} (26)

with \( \Gamma(t) = 2\gamma_0 \delta(t) + \gamma_1(t) \)

2 Analytical and numerical examples

Let’s first consider an \((N+1)\)-dimensional quasi-linear system in the transformed representation,

\[
\begin{align*}
0 &= -\phi(x) - M_0 \dot{x}_0 - \Phi_{0x} \cdot x - M_{0x} \cdot \dot{x} + \xi_0(t) \\
0 &= -\Phi \cdot x - M \cdot \dot{x} - \Phi_{x0} x_0 - M_{x0} \dot{x}_0 + \xi(t)
\end{align*}
\]

or in the original representation,

\[
\frac{d}{dt} \begin{pmatrix} x_0 \\ x \end{pmatrix} = \begin{pmatrix} M_0 & M_{0x} \\ M_{x0} & M \end{pmatrix} \cdot \begin{pmatrix} -\phi(x) - \Phi_{0x} \cdot x + \xi_0(t) \\ -\Phi \cdot x - \Phi_{x0} x_0 + \xi(t) \end{pmatrix}
\]

or in the transformed representation. We will project out the degrees of freedom \( x = (x_1, \cdots, x_N) \), and retain only the degree of freedom \( x_0 \). In the supporting text for a 2-D system we derived analytical expressions of the GLEs with the above two sets of equations, and showed that for the latter but not for the former the memory kernel and the random noise term are indeed connected by the GFDR. We also derived the GLE for the general \((N+1)\)-dimensional system. This model can be regarded as generalization of the well studied system-bath model in Hamiltonian systems [4].

In most applications of the projection formalism including previous work on Hamiltonian systems, it is impractical to perform the projection analytically. Extensive related methodology studies exist for Hamiltonian systems, which can be generalized to non-Hamiltonian systems due to the mapping. We will leave these for future studies. Here for illustrative purpose we will demonstrate the validity of the projection only through a simple chemical network. The network is an end-product inhibition motif commonly found in metabolic and other biological regulatory networks (see Fig. 1a) [19]. Each reaction is governed by irreversible Michaelis-Menten kinetics,

\[ \dot{x}_1 = \frac{v_m}{K_m + x_1} - \frac{v_m x_1}{K_m + x_1} + g \zeta_1(t) \]  \hspace{1cm} (27)

and similar expressions for other species concentrations. We used \( v_m = 1, K_m = 0.5, g = 0.005 \) in our simulations.

The system is initially at the steady-state. At time 0, the concentration of \( x_1 \) is set to a value \( x_1(0) \). The relaxation dynamics \( \bar{x}_1(t) \) is monitored. We used...
Figure 1: Determination of the GLE parameters. (a) The network with end-product inhibition. (b) Potential of mean force calculated from the steady-state distribution of the full model. (c) The memory kernel used for fitting. (d) The fitted and simulated relaxation curve of $x_1$ with $x_1(0) = 2 < x_1 >_{ss}$. We didn’t fully optimize the fitting.
Figure 2: Comparison of the predicted and simulated relaxation functions with $x_1(0)/\langle x_1 \rangle_{ss} = 1.2(a), 0.8(b), 0.5(c)$. The model parameters are the same as used in Fig.1.
the result of one simulation on the full model, that with $x_1(0) = 2 < x_1 >_{ss}$, as the known information to fit the parameters for the GLE Eqn. 26. The term $< x_1 >_{ss}$ refers to the steady-state average. Fig 1b-d show the fitting results and parameters. The potential of mean force is calculated from the steady-state distribution. We modeled the nonsingular part of the memory kernel, $\gamma_1$ with a Gaussian basis set. Physically one may understand the fitted memory kernel as follows: the change of $x_1$ is propagated to $x_4$ through a series of reactions, and acts back on $x_1$ at a later time. The first portion of $\gamma_1$ with negative values (as modeled by two Gaussian functions) accounts for most of the effect. Some remnant effect propagates one more cycle to act on $x_1$ with an opposite sign (inhibition of inhibition), doubled delay time, and reduced amplitude. We neglected further higher order effects. In this work we focused on illustrating validity of the method, and thus made no effort to fully optimize the fitting. We then used the set of parameters to simulate the GLE with different values of $x_1(0)$, and compared with simulation results of the full model. Fig 1d shows remarkable agreement even without fully optimizing the parameters, supporting the validity of Eqn. 26.

3 Discussions and concluding remarks

In this work we developed a generalized Zwanzig-Mori projection formalism for dissipative non-Hamiltonian systems. Because of the mapping between a dissipative non-Hamiltonian system and a conservative Hamiltonian system, we expect that the large number of existing methods on applying the projection method to Hamiltonian systems can be readily applied to non-Hamiltonian systems. We suggest that an important direction for future researches is to develop a number of standard ansatz (function forms for the potential of mean force, the memory kernel, etc) for different situations. Analytical results for the quasi-linear systems may serve as the starting points.

In most applications of the projection formalism including previous work on Hamiltonian systems, it is impractical to perform the projection procedure analytically. For heuristic purpose we tested the formalism through projecting systems with two and three dimensions to one dimension. The formalism, however, can be applied to arbitrary high dimensional systems. In the supporting text, we derived the analytical formula for projecting an $(N+1)$-dimensional quasi-linear system to one dimension. In real applications, information about a system is usually incomplete. Instead one can obtain the potential of mean force, the matrices $\mathbf{S} + \mathbf{T}$ and $\gamma$ from available data, following the well-established procedures developed for Hamiltonian systems. On multiplying $(\mathbf{S} + \mathbf{T})^{-1}$ on both sides of Eqn. 25, one transforms back to the original representation with direct physical meaning for each term.

Given the broad range of problems Eqn. 1 describes, we expect that the method discussed in this work will find applications in many fields of science. Here we will discuss its usage and implications in the field of mathematical modeling of biological networks, or systems biology in a broader sense.
On modeling a complex dynamic system, a common problem is that there is insufficient information to identify a large number of parameter values in the model. For example in the field of systems biology, one frequent criticism of mathematical modeling is that one sometimes attempts to fit several data points with dozens or even hundreds of parameters. Fortunately, analysis shows that for many systems, the quality of the data fitting is usually largely affected by a small number of composite parameters, and insensitive to others [22]. A mathematical model with many variables and parameters is also computationally expensive. The present projection formalism provides a systematic method to construct a reduced model with a small number of variables and parameters important for the dynamics under study. It also provides a method for performing multi-scale modeling, using information obtained from finer level simulations for constructing a more coarse-grained model.

Network robustness is a related problem. It has been suggested that robustness is a general property for many biological networks. As illustrated by Barkai and Leibler using the bacterial chemotaxis network model, a system is robust if its function is determined by one or a small number of composite quantities, and values of the latter are insensitive to variation of most control parameters [23]. The projection method provides a natural framework for quantifying network robustness under perturbations.

There are extensive discussions on whether one can use the parameters measured in vitro on modeling processes in vivo [24]. For the latter, there are inevitably interactions between the subsystem one examines and the remaining part of the living system, which are not present in the system in vitro. The projection method provides a theoretical explanation why in general the two sets of parameters should be different. Even in the case that the memory kernel can be approximated by a delta function so the retarded memory term $\gamma_{ij} = 0$, the interactions between the subsystem one models and the remaining degrees of freedom affect the dynamics of the subspace through renormalizing the model parameters [26]. The projection method can suggest a controlled approximation linking the two sets of parameters.

[A] Here we derive a more general projection formula, which reduces to Eqn. 20. The procedure resembles that of Lange and Grubmüller [17]. Let’s suppose that we project to a manifold,

$$c = f(x), \dot{c} = \nabla f(x) \cdot \dot{x} = \nabla f(x) \cdot (p - A) \frac{1}{m}$$

(28)

The Liouville operator is

$$L = \sum_{i=1}^{N} \left( \frac{\partial H}{\partial p_i} \frac{\partial}{\partial x_i} - \frac{\partial H}{\partial x_i} \frac{\partial}{\partial p_i} \right)$$

$$+ \sum_{i=1}^{N} \sum_{a=1}^{N_a} \left( \frac{\partial H}{\partial p_{ia}} \frac{\partial}{\partial q_{ia}} - \frac{\partial H}{\partial q_{ia}} \frac{\partial}{\partial p_{ia}} \right)$$

(29)

Notice that $c_j$ and $\dot{c}_j$ have no explicit dependence on the bath variables. We
define the projection operator as,

\[ Ph = \frac{1}{\bar{\rho}(c, \dot{c})} \int h\rho(x, p)\delta(c - f)\delta(\dot{c} - \nabla f(x) \cdot \dot{x}) dx dp \]  (30)

where \( h \) is an arbitrary function, and

\[ \bar{\rho}(c, \dot{c}) = \int \rho(x, p)\delta(c - f)\delta(\dot{c} - \nabla f(x) \cdot \dot{x}) dx dp \]  (31)

The projection of \( c_j \) is simple since it is still within the subspace,

\[ Lc_j = \sum_{i=1}^{N} \left( \frac{\partial H}{\partial p_i} \frac{\partial c_j}{\partial x_i} - \frac{\partial H}{\partial x_i} \frac{\partial c_j}{\partial p_i} \right) = \sum_{i} \frac{\partial H}{\partial p_i} \frac{\partial f_i}{\partial x_i} = \dot{c}_j \]  (32)

The projection of \( \dot{c}_j \) is given by,

\[ P\dot{c}_j = \sum_{i=1}^{N} \frac{1}{\beta \bar{\rho}(c, \dot{c})} \int dx dp \delta(c - f)\delta(\dot{c} - \nabla f(x) \cdot \dot{x}) \]

\[ \exp(-\beta H) \left( \frac{\partial H}{\partial \dot{c}_j} \frac{\partial \dot{c}_j}{\partial x_i} - \frac{\partial H}{\partial \dot{x}_i} \frac{\partial \dot{c}_j}{\partial p_i} \right) \]

\[ = \sum_{i=1}^{N} \frac{1}{\beta \bar{\rho}(c, \dot{c})} \int dx dp \delta(c - f)\delta(\dot{c} - \nabla f(x) \cdot \dot{x}) \]

\[ \left( \frac{\partial}{\partial p_i} \exp(-\beta H) \frac{\partial \dot{c}_j}{\partial x_i} - \frac{\partial}{\partial x_i} \exp(-\beta H) \frac{\partial \dot{c}_j}{\partial p_i} \right) \]

\[ = \sum_{i=1}^{N} \frac{1}{\beta \bar{\rho}(c, \dot{c})} \int \left( \exp(-\beta H) \frac{\partial \dot{c}_j}{\partial x_i} \right) \]

\[ \frac{\partial}{\partial p_i} \left[ \delta(c - f)\delta(\dot{c} - \nabla f(x) \cdot (p - A) \frac{1}{m}) \right] dx dp \]

\[ - \sum_{i=1}^{N} \frac{1}{\beta \bar{\rho}(c, \dot{c})} \int \left( \exp(-\beta H) \frac{\partial \dot{c}_j}{\partial p_i} \right) \]

\[ \frac{\partial}{\partial x_i} \left[ \delta(c - f)\delta(\dot{c} - \nabla f(x) \cdot (p - A) \frac{1}{m}) \right] dx dp \]
\[
\sum_{i=1}^{N} \frac{1}{\beta \rho(c, \dot{c})} \int dxdp \exp(-\beta H) \left( \frac{1}{m} \frac{\partial}{\partial x_i} (\nabla f_j(x) \cdot (p - A)) - \frac{1}{m} \nabla f_j(x) \cdot \frac{\partial}{\partial x_i} A \right) \\
\left\{ \sum_k \delta(c - f) \frac{1}{m} \frac{\partial f_k}{\partial x_i} \frac{\partial}{\partial c_k} \left[ \delta(c - \nabla f(x) \cdot (p - A) \frac{1}{m}) \right] \right\}
\]

\[
-\sum_{i=1}^{N} \frac{1}{\beta \rho(c, \dot{c})} \int dxdp \exp(-\beta H) \frac{1}{m} \frac{\partial f_j}{\partial x_i} \left\{ \sum_k \frac{\partial f_k}{\partial x_i} \delta(c - f) \delta(c - \nabla f(x) \cdot (p - A) \frac{1}{m}) \right\}
\]

\[
-\sum_{i=1}^{N} \frac{1}{\beta \rho(c, \dot{c})} \int dxdp \exp(-\beta H) \frac{1}{m} \frac{\partial f_j}{\partial x_i} \frac{1}{m} \nabla f_j \cdot (p - A) \frac{1}{m} \frac{\partial}{\partial \dot{c_k}} \left[ \delta(c - f) \delta(c - \nabla f(x) \cdot (p - A) \frac{1}{m}) \right] \}
\]

\[
= -\frac{1}{\beta \rho(c, \dot{c})} \sum_k \frac{\partial}{\partial c_k} \int dxdp \exp(-\beta H) \left[ \delta(c - f) \delta(c - \nabla f(x) \cdot (p - A) \frac{1}{m}) \right] \left\{ \sum_i \frac{1}{m} \frac{\partial f_j}{\partial x_i} \frac{\partial f_k}{\partial x_i} \right\}
\]

\[
-\frac{1}{\beta \rho(c, \dot{c})} \sum_{k \neq j} \frac{\partial}{\partial c_k} \int dxdp \exp(-\beta H) \left[ \delta(c - f) \delta(c - \nabla f(x) \cdot (p - A) \frac{1}{m}) \right] \left\{ \frac{1}{m} \sum_i \frac{\partial f_j}{\partial x_i} \frac{\partial f_k}{\partial x_i} \left( \frac{1}{m} \nabla f_j \cdot (p - A) \right) \right\}
\]

\[
-\frac{\partial f_k}{\partial x_i} \frac{\partial}{\partial x_i} \left( \frac{1}{m} \nabla f_j \cdot (p - A) \right) \}
\]

To derive the above expression, we performed integration by parts, and used
the relations,
\[
\nabla_x \delta (c - f) = \nabla_x f \partial_f \delta (x - f) = \nabla_x f \partial_c \delta (x - f)
\]
\[
\nabla_x (\nabla_x f \cdot (p - A)/m)
\]
\[
\partial_c \delta (\dot{c} - \nabla_x f \cdot (p - A)/m)
\]
\[
\nabla_p \delta (\dot{c} - \nabla_x f \cdot (p - A)/m) = \frac{1}{m} \nabla_x f \partial_c \delta (\dot{c} - \nabla_x f \cdot (p - A)/m)
\]
\[
\partial_c \delta (\dot{c} - \nabla_x f \cdot (p - A)/m)
\]
\[
\nabla \delta (\dot{c} - \nabla_x f \cdot (p - A)/m) = \nabla (\nabla_x f \cdot (p - A)/m)
\]
\[
\partial_c \delta (\dot{c} - \nabla_x f \cdot (p - A)/m)
\]

We have neglected possible surface terms while performing integration by parts. For example, If \(x_i\) represent concentrations, one expects that \(\rho(0, p) \approx 0\) so mathematically one can extend the integration to \(x \to -\infty\). Otherwise Eqn. 1 is not a good representation of the system dynamics in the first place. With \(f_j = X_j = x_j\) the final result of Eqn 33 reduces to Eqn. 20.

\[B\] For the full model, the Langevin equations were propagated by
\[
x_i(t_N) = x_i(t_{N-1}) + \Delta t G_i(x) + \sqrt{2g \Delta t / \beta} \zeta_i(t),
\]
where \(\zeta_i(t)\) is generated from a Gaussian distribution with zero mean and unit variance, and we have set \(\beta = 1\) throughout the work. We used \(\Delta t = 0.005\) in all calculations. The potential of mean force was obtained from the steady-state distribution histogram. All the relaxation curves are average over 40000 trajectories.

To solve Eqn. 20 numerically, we first integrate both sides from \(t_i = (i-1)\Delta t\) to \(t_{i+1} = i\Delta t\),
\[
0 = -\int_{t_{i-1}}^{t_i} dt' \frac{\partial}{\partial X_j} W(X(t')) - 2 \int_{t_{i-1}}^{t_i} dt' \Gamma_0 \dot{X}
\]
\[
- \int_{t_{i-1}}^{t_i} dt' \int_0^{t'} ds \Gamma_1(s) \dot{X}(t' - s) + m \beta \int_{t_{i-1}}^{t_i} dt' F(t')
\]
\[
\approx -\frac{\partial}{\partial X_j} W(X(t_{i-1})) \Delta t - \Delta t \Gamma_0 (X(t_i) - X(t_{i-1}))
\]
\[
- \sum_{k=0}^i \Gamma_1((k + 1/2)\Delta t)(X(t_{i-k}) - X(t_{i-k-1}))
\]
\[
+ m \beta \int_{t_{i-1}}^{t_i} dt' F(t')
\]
We used the method of Berkowitz et al. to generate the random forces [25].
Then one realization of the random force is,

\[
\int_{i\Delta t}^{(i+1)\Delta t} dt f(t) = \sum_{k=1}^{M} \left( \sqrt{J_K(2\pi k/P)} \right) \left[ \frac{\xi_{ak}}{\omega_k} \sin(\omega_k (i + 1)\Delta t) - \sin(\omega_k i\Delta t) \right] - \frac{\xi_{bk}}{\omega_k} \cos(\omega_k (i + 1)\Delta t) - \cos(\omega_k i\Delta t) \right] \tag{37}
\]

where \(\xi_{ak}\) and \(\xi_{bk}\) are random numbers drawn from independent normal Gaussian distributions, \(\omega_k = 2\pi k/P\), and \(P = M\Delta t\) is the time interval that the random force doesn’t repeat. The spectral density is determined by the memory kernel through the Wiener-Khintchine theorem,

\[
J_K(\omega) = 4 \int_{0}^{\infty} dt \Gamma \cos(\omega t) \tag{38}
\]

In all the simulations, we used \(\Delta t = 0.1, M = 4000\), and all results are averaged over 40000 trajectories. We use the following fitting parameters for the memory kernel: \(\gamma_0 = 28; \gamma_1\) is represented by four Gaussian functions in the form \(\lambda_i \exp\left(-0.5((t-b_i)/a_i)^2\right)\), with \(\lambda = (-5.2, -3, 1.56, 0.9)\), \(a = (1.5, 1.5, 1.5, 1.5)\), \(b = (8, 10, 16, 18)\).

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Supporting information

A Linear and nonlinear projection

As Zwanzig pointed out, the term "nonlinear projection" is actually misleading. Both linear and nonlinear projections work with linear Hilbert space. They differ only by the size of the Hilbert subspace. The formal theoretical development discussed in the section "Summary of the Zwanzig-Mori formalism" apply for both cases. As an example, let's consider a 1-D Hamiltonian system. If one chooses the subspace as expanded by \( \{ x_1, p_1 \} \) (the quantity \( A \) in the main text), the projection is linear. The projection is called "nonlinear" if the basis is expanded by including higher order functions of \( x_1 \). Especially, Zwanzig presented a choice of the subspace by including all the possible function forms of the projected degrees of freedom. The Hilbert subspace has infinite dimension. For this specific example, the basis is composed of \( \{ x_1, x_1^2, \cdots, p_1 \} \). In [18], we demonstrated the equivalence of the two procedures with an explicit model system.

B About the term \((A, A)^{-1}\)

Both the memory kernel and the GFDR contain the term \((A, A)^{-1}\). Here we will use the above mentioned 1-D system to derive the needed elements of \((A, A)^{-1}\). Generalization to multi-dimensions is straightforward. For a Hilbert space with basis \( \{ x_1, x_1^2, \cdots, x_1^n, p_1 \} \), notice that \((x_1, p_1) = 0\). Therefore, the matrix \((A, A)\) has the block form,

\[
(A, A) = \begin{pmatrix}
(x_1, x_1) & \cdots & (x_1^n, x_1^n) & 0 \\
\vdots & \ddots & \vdots & \vdots \\
(x_n, x_1) & \cdots & (x_n, x_n) & 0 \\
0 & \cdots & 0 & (p_1, p_1)
\end{pmatrix}
\]

(39)

Especially the momentum-containing term is block diagonal. In the projected equations, one needs only the momentum-containing term \(((A, A)^{-1})_{n+1,n+1}\), which is \((p_1, p_1)^{-1} = 1/m\).

C 2D example

Here we use an analytically solvable model to demonstrate how the transformation reveals some hidden relation between the memory kernel and the noise term,

\[
\begin{align*}
\dot{x}_1 &= -a_{11}x_1 - a_{12}x_2 + g_1\zeta_1(t) \\
\dot{x}_2 &= -a_{21}x_1 - a_{22}x_2 + g_2\zeta_2(t)
\end{align*}
\]

(40)
or

\[
\dot{x} = -a \cdot x + g \zeta \tag{41}
\]

C.1 Direct projection

First, let’s integrate out degree 2 directly. Notice that,

\[
x_2(t) = \exp(-a_{22}t)x_2(0) + \int_0^t \exp(-a_{22}\tau)(-a_{21}x_1(t - \tau) + g_2 \zeta_2(t - \tau))d\tau
\]

\[
= \exp(-a_{22}t) \left( x_2(0) + \frac{a_{21}}{a_{22}}x_1(0) \right) - \frac{a_{21}}{a_{22}}x_1(t)
\]

\[
+ \int_0^t \exp(-a_{22}\tau)(-\frac{a_{21}}{a_{22}}\dot{x}_1(t - \tau) + g_2 \zeta_2(t - \tau))d\tau \tag{42}
\]

and,

\[
\dot{x}_1 = -a_{11}x_1 + \int_0^t \left\{ \exp(-a_{22}\tau)a_{12}a_{21} \right\} x_1(t - \tau)d\tau
\]

\[
+ \left\{ -a_{12} \exp(-a_{22}t)x_2(0) + g_1 \zeta_1(t)
\right.
\]

\[
- \int_0^t \exp(-a_{22}\tau)a_{12}g_2 \zeta_2(t - \tau)d\tau \right\}
\]

\[
= -\left( a_{11} - \frac{a_{12}a_{21}}{a_{22}} \right) x_1(t)
\]

\[
+ \int_0^t \left\{ \exp(-a_{22}\tau)\frac{a_{12}a_{21}}{a_{22}} \right\} \dot{x}_1(t - \tau)d\tau
\]

\[
+ \left\{ -a_{12} \exp(-a_{22}t) \left( x_2(0) + \frac{a_{21}}{a_{22}}x_1(0) \right) + g_1 \zeta_1(t)
\right.
\]

\[
- \int_0^t \exp(-a_{22}\tau)a_{12}g_2 \zeta_2(t - \tau)d\tau \right\} \tag{43}
\]

Both eqns 43 and 44 have the generalized Langevin equation form, with the memory and noise terms identified as those in the curled brackets. However, the relation between the memory kernel and the noise is not transparent in any of these two equations. This is a major obstacle for applying the generalized Langevin equation formalism in general dynamic systems.

C.2 Projection after transformation

Let us transform Eqn 40 by multiplying \( M = S + T \) on both sides,

\[
0 = -M_{11}\dot{x}_1 - M_{12}\dot{x}_2 - \phi_{11}x_1 - \phi_{12}x_2 + \xi_1(t)
\]

\[
0 = -M_{21}\dot{x}_1 - M_{22}\dot{x}_2 - \phi_{12}x_1 - \phi_{22}x_2 + \xi_2(t) \tag{45}
\]
or by introducing the zero mass limit,
\[
\begin{align*}
\dot{x}_1 &= p_1/m \\
\dot{x}_2 &= p_2/m \\
\dot{p}_1 &= -\frac{1}{m}M_{11}p_1 - \frac{1}{m}M_{12}p_2 - \phi_{11}x_1 - \phi_{12}x_2 + \xi_1(t) \\
\dot{p}_2 &= -\frac{1}{m}M_{21}p_1 - \frac{1}{m}M_{22}p_2 - \phi_{21}x_1 - \phi_{22}x_2 + \xi_2(t)
\end{align*}
\]
(46)
where,
\[
\phi = M \cdot a, \xi = M \cdot g\zeta
\]
The matrix \( \phi \) is symmetric, and one can obtain the analytical expression of \( M \) following the procedure by Kwon et al.

**C.2.1 Approach 1**

Taking the Laplace transform on both sides of Eqn. 45,
\[
\begin{align*}
0 &= -M_{11}(s\ddot{x}_1 - x_1(0)) - M_{12}(s\ddot{x}_2 - x_2(0)) - \phi_{11}\ddot{x}_1 - \phi_{12}\ddot{x}_2 + \ddot{\xi}_1 \\
0 &= -M_{21}(s\ddot{x}_1 - x_1(0)) - M_{22}(s\ddot{x}_2 - x_2(0)) - \phi_{21}\ddot{x}_1 - \phi_{22}\ddot{x}_2 + \ddot{\xi}_2
\end{align*}
\]
(46)
Solve \( \ddot{x}_2 \) from the second equation, and substitute into the first one,
\[
\begin{align*}
0 &= -\left(M_{11} - \frac{M_{12}M_{21}}{M_{22}}\right)(s\ddot{x}_1 - x_1(0)) - \left(\phi_{11} - \frac{\phi_{21}M_{12}}{M_{22}}\right)\ddot{x}_1 \\
&\quad - \left(\phi_{12} - \frac{\phi_{22}M_{12}}{M_{22}}\right)\left(-\frac{M_{21}(s\ddot{x}_1 - x_1(0)) + \phi_{21}\ddot{x}_1}{sM_{22} + \phi_{22}} + \frac{M_{22}\ddot{x}_2(0) + \ddot{\xi}_2}{sM_{22} + \phi_{22}}\right) \\
&\quad + \ddot{\xi}_1 - \frac{M_{12}}{M_{22}}\ddot{\xi}_2 \\
&\quad = -\left(M_{11} - \frac{M_{12}M_{21}}{M_{22}}\right)(s\ddot{x}_1 - x_1(0)) - \left(\phi_{11} - \frac{\phi_{21}\phi_{12}}{\phi_{22}}\right)\ddot{x}_1 \\
&\quad + \phi_{21}\left(M_{12} - \frac{\phi_{12}}{\phi_{22}}\frac{sM_{22} + \phi_{22}}{sM_{22} + \phi_{22}}\ddot{x}_1\right) \\
&\quad + \phi_{22}\left(\frac{\phi_{12}}{\phi_{22}} - \frac{M_{12}}{M_{22}}\right)\left(-\frac{M_{21}(s\ddot{x}_1 - x_1(0)) + \phi_{21}\ddot{x}_1}{sM_{22} + \phi_{22}} + \ddot{\xi}_1 - \frac{M_{12}}{M_{22}}\ddot{\xi}_2\right) \\
&\quad = -\left(M_{11} - \frac{M_{12}M_{21}}{M_{22}}\right)(s\ddot{x}_1 - x_1(0)) - \left(\phi_{11} - \frac{\phi_{21}\phi_{12}}{\phi_{22}}\right)\ddot{x}_1 \\
&\quad - \phi_{22}\left(M_{12} - \frac{\phi_{12}}{\phi_{22}}\frac{M_{21}(s\ddot{x}_1 - x_1(0)) + \phi_{21}\ddot{x}_1}{s + \phi_{22}/M_{22}}\right) \\
&\quad - \left(\phi_{12} - \frac{M_{12}}{M_{22}}\right)\left(-\frac{\phi_{22}M_{12}}{M_{22}}\frac{M_{22}\ddot{x}_2(0) + \ddot{\xi}_2}{s + \phi_{22}/M_{22}} + \ddot{\xi}_1 - \frac{M_{12}}{M_{22}}\ddot{\xi}_2\right)
\end{align*}
\]
(47)
Therefore,

\[
0 = \left\{ \left( -\phi_{11} + \frac{\phi_{12}\phi_{12}}{\phi_{22}} \right) x_1(t) \right\} \\
\quad - \int_0^t d\tau \left\{ \frac{2}{m} \left( M_{11} - \frac{M_{12}M_{21}}{M_{22}} \right) \delta(t) \right\} \\
\quad + \phi_{22} e^{-\frac{\phi_{22}}{m} t} \left( \frac{M_{12}}{M_{22}} - \frac{\phi_{12}}{\phi_{22}} \right) \left( \frac{M_{21}}{M_{22}} - \frac{\phi_{21}}{\phi_{22}} \right) p_1(t - \tau) \\
\quad + \left\{ e^{-\frac{\phi_{22}}{m} t} \left( \frac{M_{12}}{M_{22}} - \frac{\phi_{12}}{\phi_{22}} \right) (\phi_{21} x_1(0) + \phi_{22} x_2(0)) + \xi_1(t) - \frac{M_{12}}{M_{22}} \xi_2(t) \right\} \\
\quad + \int_0^t d\tau e^{-\frac{\phi_{22}}{m} \tau} \phi_{22} \left( \frac{M_{12}}{M_{22}} - \frac{\phi_{12}}{\phi_{22}} \right) \xi_2(t - \tau) \right\}
\]

(48)

Comparing the above final expression with the projected equation of motion derived in the main text (Eqn. ), one can identify the terms in the fou r curled brackets correspond to the derivative of the potential of mean force, the memory term, and the random force term.

As one important observation, while Eqns. ?? and 45 are different only by a matrix transformation, there is no simple relation between Eqns. 44 and 48.

C.2.2 Approach 2

Here we will start with Eqn. 46. The derivation is mathematically more complex, but can provide further understanding of the zero mass limit,

\[
u(t) = e^{Kt} u(0) + \int_0^t e^{K\tau} v(t - \tau) d\tau
\]

(49)

where,

\[
u = (x, p)^T
\]

\[
K = \begin{pmatrix} 0 & -\frac{1}{m} \frac{M_{21}}{M_{22}} \\ -\phi_{22} & -\frac{1}{m} \end{pmatrix}
\]

\[
v = \begin{pmatrix} -\frac{1}{m} M_{21} p_1 - \phi_{12} x_1 + \xi_2(t) \\ 0 \end{pmatrix}
\]

\[
\exp(Kt) = \begin{pmatrix} -\frac{1}{2} \alpha - \beta - \frac{1}{2} \alpha + \beta + \frac{1}{2} \alpha + - \frac{1}{2} \alpha + - \frac{1}{2} \alpha + - \frac{1}{2} \alpha + & \frac{1}{2} \alpha - - \frac{1}{2} \alpha + - \frac{1}{2} \alpha + - \frac{1}{2} \alpha + \\
\alpha - \phi_{22} m - \alpha + \phi_{22} m & \frac{1}{2} \alpha - - \frac{1}{2} \alpha + - \frac{1}{2} \alpha + - \frac{1}{2} \alpha + \end{pmatrix}
\]

(50)
where,

\[
\begin{align*}
\alpha_+ &= e^{i\left(\sqrt{-4\phi_{22} m + M_{22}^2} - M_{22}\right)} \sqrt{-4\phi_{22} m + M_{22}^2} \\
&\approx e^{-\frac{M_{22} t}{M_{22}}} \sqrt{-4\phi_{22} m + M_{22}^2} \\
\alpha_- &= e^{i\left(-\sqrt{-4\phi_{22} m + M_{22}^2} - M_{22}\right)} \sqrt{-4\phi_{22} m + M_{22}^2} \\
&\approx e^{-\frac{M_{22} t}{M_{22}}} \sqrt{-4\phi_{22} m + M_{22}^2} \\
\beta_+ &= M_{22} + \sqrt{-4\phi_{22} m + M_{22}^2} \approx 2M_{22} \\
\beta_- &= M_{22} - \sqrt{-4\phi_{22} m + M_{22}^2} \approx 2\phi_{22} m / M_{22}
\end{align*}
\]  

(51)
Therefore,

\[ x_2(t) = \frac{1}{2}(\alpha_+\beta_+ - \alpha_-\beta_-)x_2(0) + (\alpha_+ - \alpha_-)p_2(0) \]

\[ + \int_0^t d\tau (\alpha_+(\tau) - \alpha_-(\tau)) \left[ -\frac{1}{m}M_{21}p_1(t - \tau) - \phi_{12}x_1(t - \tau) + \xi_2(t - \tau) \right] \]

\[ \approx e^{-\frac{\phi_{22}}{M_{22}}t}x_2(0) + \frac{1}{M_{22}} \left( e^{-\frac{\phi_{22}}{M_{22}}t} \right) p_2(0) \]

\[ + \int_0^t d\tau \left( e^{-\frac{\phi_{22}}{M_{22}}\tau} - e^{-\frac{\phi_{22}M_2}{m}} \right) \frac{1}{M_{22}} \left[ -\frac{1}{m}M_{21}p_1(t - \tau) - \phi_{12}x_1(t - \tau) + \xi_2(t - \tau) \right] \]

\[ = e^{-\frac{\phi_{22}}{M_{22}}t}x_2(0) + \frac{1}{M_{22}} \left( e^{-\frac{\phi_{22}}{M_{22}}t} \right) p_2(0) \]

\[ - \left( e^{-\frac{\phi_{22}}{M_{22}}t} \frac{M_{22}}{\phi_{22}} - e^{-\frac{\phi_{22}M_2}{m}} \frac{m}{M_{22}} \right) \frac{1}{M_{22}} [-\phi_{12}x_1(0)] \]

\[ + \left( \frac{M_{22}}{\phi_{22}} - \frac{m}{M_{22}} \right) \frac{1}{M_{22}} [-\phi_{12}x_1(t)] \]

\[ + \int_0^t d\tau e^{-\frac{\phi_{22}}{M_{22}}\tau} \left[ -\frac{1}{m} \left( \frac{M_{21}}{M_{22}} - \frac{\phi_{12}}{\phi_{22}} \right) p_1(t - \tau) + \frac{1}{M_{22}} \xi_2(t - \tau) \right] \]

\[ - \int_0^t d\tau e^{-\frac{\phi_{22}}{M_{22}}\tau} \left[ -\frac{1}{m} \left( \frac{M_{21}}{M_{22}} - \frac{\phi_{12}m}{\phi_{22}} \right) p_1(t - \tau) - \frac{1}{M_{22}} \xi_2(t - \tau) \right] \]

\[ \approx e^{-\frac{\phi_{22}}{M_{22}}t}x_2(0) + \frac{1}{M_{22}} e^{-\frac{\phi_{22}}{M_{22}}t} p_2(0) - e^{-\frac{\phi_{22}}{M_{22}}t} \left[ -\phi_{12}x_1(0) \right] \]

\[ + \left[ -\frac{\phi_{12}}{\phi_{22}}x_1(t) \right] + \int_0^t d\tau e^{-\frac{\phi_{22}}{M_{22}}\tau} \left[ -\frac{1}{m} \left( \frac{M_{21}}{M_{22}} - \frac{\phi_{12}}{\phi_{22}} \right) p_1(t - \tau) + \frac{1}{M_{22}} \xi_2(t - \tau) \right] \]

\[ + \int_0^t d\tau e^{-\frac{\phi_{22}}{M_{22}}\tau} \left[ \frac{1}{M_{22}}p_1(t - \tau) + \frac{1}{M_{22}} \xi_2(t - \tau) \right] \]

\[ = 1 \]  \hspace{1cm} \text{(52)}
\[ p_2(t) = (\alpha \phi_{22}m - \alpha_+ \phi_{22}m)x_2(0) + (\frac{1}{2}(\alpha_- \beta_+ - \frac{1}{2}(\alpha_+ \beta_-))p_2(0) \]
\[ + \int_0^t d\tau \left[ \frac{1}{2}(\alpha_-(\tau)\beta_+(\tau) - \alpha_+(\tau)\beta_-(\tau)) \right] \left[ -\frac{1}{m}M_{21}p_1(t - \tau) \right. \]
\[ - \phi_{12}x_1(t - \tau) + \xi_2(t - \tau) \]
\[ \approx -e^{-\frac{\alpha \phi_{22}m}{M_{22}}}M_{22}x_2(0) + \int_0^t d\tau \left( e^{-\frac{\alpha \phi_{22}m}{M_{22}}} - e^{-\frac{\alpha \phi_{22}m}{M_{22}}} \phi_{22}m \right) \]
\[ \left[ -\frac{1}{m}M_{21}p_1(t - \tau) - \phi_{12}x_1(t - \tau) + \xi_2(t - \tau) \right] \]
\[ \approx -e^{-\frac{\alpha \phi_{22}m}{M_{22}}}M_{22}x_2(0) - \frac{m}{M_{22}} \left( e^{-\frac{\alpha \phi_{22}m}{M_{22}}} - e^{-\frac{\alpha \phi_{22}m}{M_{22}}} \right) [-\phi_{12}x_1(0)] \]
\[ + \int_0^t d\tau e^{-\frac{\alpha \phi_{22}m}{M_{22}}} \left[ -\frac{1}{m}M_{21}p_1(t - \tau) + \xi_2(t - \tau) \right] \]
\[ - \int_0^t d\tau e^{-\frac{\alpha \phi_{22}m}{M_{22}}} \left[ -\phi_{22} \left( \frac{M_{21}}{M_{22}} - \frac{\phi_{12}}{\phi_{22}} \right) p_1(t - \tau) \right. \]
\[ + \phi_{22}m \xi_2(t - \tau) \]
\[ \approx -e^{-\frac{\alpha \phi_{22}m}{M_{22}}}M_{22}x_2(0) \text{ } (53) \]
Then,

\[
\dot{p}_1(t) = -\frac{1}{m} M_{11} p_1(t) - \phi_{11} x_1(t) + \xi_1(t) \\
- \frac{M_{12}}{m} \left\{ -e^{-\frac{\phi_{22} t}{M_{22}}} \frac{m \phi_{22}}{M_{22}} x_2(0) - \frac{m}{M_{22}} \left( e^{-\frac{\phi_{22} t}{m}} - e^{-\frac{\phi_{22} t}{M_{22}}} \right) [-\phi_{12} x_1(0)] \right. \\
+ \int_0^t dr e^{-\frac{\phi_{22} r}{M_{22}}} \left[ -\frac{1}{m} M_{21} p_1(t - r) + \xi_2(t - r) \right] \\
- \frac{M_{22}}{m} \left\{ \phi_{22} \int_0^t dr e^{-\frac{\phi_{22} r}{M_{22}}} \left[ \phi_{22} \left( M_{21} - \frac{\phi_{12}}{\phi_{22}} \right) p_1(t - r) \right. \\
+ \int_0^t dr e^{-\frac{\phi_{22} r}{M_{22}}} \left[ -\frac{1}{m} \left( M_{21} - \frac{\phi_{12}}{\phi_{22}} \right) p_1(t - r) \right] \\
\left. \left\{ \phi_{12} + \frac{\phi_{12} \phi_{21}}{\phi_{22}} \right\} x_1(t) \right\} \\
\approx \left\{ \left( -\frac{1}{m} M_{11} p_1(t) \right) \left( -\frac{M_{12}}{m} \phi_{22} \left( \frac{M_{21}}{M_{22}} - \frac{\phi_{21}}{\phi_{22}} \right) p_1(t - r) \right) \right. \\
+ \left\{ e^{-\frac{\phi_{22} t}{M_{22}}} \left( \frac{M_{12}}{M_{22}} - \frac{\phi_{21}}{\phi_{22}} \right) \left( \frac{M_{21}}{M_{22}} - \frac{\phi_{12}}{\phi_{22}} \right) p_1(t - r) \right\} \\
\left. \left\{ e^{-\frac{\phi_{22} t}{M_{22}}} \left( \frac{M_{12}}{M_{22}} - \frac{\phi_{21}}{\phi_{22}} \right) \left( \frac{M_{21}}{M_{22}} - \frac{\phi_{12}}{\phi_{22}} \right) p_1(t - r) \right\} \\
\left. \left\{ \phi_{12} e^{-\frac{\phi_{22} t}{M_{22}}} p_2(0) + \xi_1(t) - \frac{M_{12}}{m} \int_0^t dr e^{-\frac{\phi_{22} r}{m}} \xi_2(t - r) \right. \\
+ \int_0^t dr e^{-\frac{\phi_{22} r}{M_{22}}} \left( \frac{M_{12}}{M_{22}} - \frac{\phi_{12}}{\phi_{22}} \right) \left( \frac{M_{21}}{M_{22}} - \frac{\phi_{21}}{\phi_{22}} \right) \left( \frac{M_{21}}{M_{22}} - \frac{\phi_{12}}{\phi_{22}} \right) \xi_2(t - r) \right\} \right) \\
(54)
\]

Noticing,

\[ \lim_{m \to \infty} \int_0^t dr e^{-\frac{\phi_{22} r}{m}} h(t - r) \approx h(t) \frac{m}{M_{22}} \]

then one obtains (55).
C.2.3  Proof of the generalized F-D relation

To confirm the generalized fluctuation-dissipatin relation, let’s consider that $t' \leq t$. We have,

\[
< p_i x_i > = 0 \\
< p_i^2 > = m \\
< x_i \xi_j(t) > = 0 \\
< \xi_i(t) \xi_j(t') > = (M_{ij} + M_{ji}) \delta(t - t') \\
< (\phi_{21} x_1 + \phi_{22} x_2)^2 > = \frac{\int dy \left( \phi_{22} + \frac{\partial^2}{\partial x^2} \right) e^{-\frac{1}{2} y^T \cdot \nabla \phi \cdot \nabla \phi \cdot y}}{\int dy e^{-\frac{1}{2} y^T \cdot \nabla \phi \cdot \nabla \phi \cdot y}} = \phi_{22}
\]

Then,

\[
< \left( \xi_1(t) - \frac{M_{12}}{M_{22}} \xi_2(t) \right) \left( \xi_1(t') - \frac{M_{12}}{M_{22}} \xi_2(t') \right) > \\
= 2 \left[ M_{11} + \frac{M_{12} M_{12}}{M_{22}} - 2 \frac{M_{12}}{M_{22}} S_{12} \right] \delta(t - t') \\
= 2 \left[ M_{11} - \frac{M_{12} M_{21}}{M_{22}} \right] \delta(t - t')
\]

\[
< \left( \int_0^t d\tau' e^{-\frac{\phi_{22}}{M_{22}} (t - \tau')} \left( M_{22}^2 \phi_{22} M_{12} - \frac{\phi_{12}}{M_{22}} \right) \right) \left( \int_0^{t'} d\tau' e^{-\frac{\phi_{22}}{M_{22}} (t' - \tau')} \left( M_{22}^2 \phi_{22} M_{12} - \frac{\phi_{12}}{M_{22}} \right) \right) > \\
= 2 \left[ \frac{\phi_{22} M_{12}}{M_{22}^2} - \frac{\phi_{12}}{M_{22}} \right]^2 M_{22} \cdot \frac{\phi_{22} M_{12}}{M_{22}^2} - \frac{\phi_{12}}{M_{22}} \left[ e^{-\frac{\phi_{22}}{M_{22}} (t' + t)} - e^{-\frac{\phi_{22}}{M_{22}} (t' - t')} \right] \\
= -2 \left[ \frac{\phi_{22} M_{12}}{M_{22}^2} - \frac{\phi_{12}}{M_{22}} \right]^2 \phi_{22} \left[ e^{-\frac{\phi_{22}}{M_{22}} (t' + t)} - e^{-\frac{\phi_{22}}{M_{22}} (t' - t')} \right]
\]

\[
< \left( \xi_1(t') - \frac{M_{12}}{M_{22}} \xi_2(t') \right) \left( \int_0^t d\tau' e^{-\frac{\phi_{22}}{M_{22}} (t - \tau')} \left( M_{22}^2 \phi_{22} M_{12} - \frac{\phi_{12}}{M_{22}} \right) \right) > \\
= e^{-\frac{\phi_{22}}{M_{22}} (t - t')} \left[ \frac{\phi_{22} M_{12}}{M_{22}^2} - \frac{\phi_{12}}{M_{22}} \right] \left( M_{22} - M_{12} \right) \left( 1 - \frac{1}{2} \delta(t - t') \right) \\
= -e^{-\frac{\phi_{22}}{M_{22}} (t - t')} \phi_{22} \left( \frac{M_{12}}{M_{22}} - \frac{\phi_{12}}{\phi_{22}} \right) \left( \frac{M_{12}}{M_{22}} - \frac{M_{21}}{M_{22}} \right) \left( 1 - \frac{1}{2} \delta(t - t') \right)
\]
<\left( \xi_1(t) - \frac{M_{12}}{M_{22}} \xi_2(t) \right) \left( \int_0^{t'} d\tau e^{-\frac{\phi_{22}}{M_{22}} \tau} \left[ \frac{\phi_{22} M_{12}}{M_{22}^2} - \frac{\phi_{12}}{M_{22}} \right] \xi_2(t' - \tau) \right) > \\
= -\phi_{22} \left( \frac{M_{12}}{M_{22}} - \frac{\phi_{12}}{\phi_{22}} \right) \left( \frac{M_{12}}{M_{22}} - \frac{M_{21}}{M_{22}} \right) \frac{1}{2} \delta(t - t') \quad (59)

e^{-\frac{\phi_{22}}{M_{22}} (t+t')} \left( \frac{M_{12}}{M_{22}} - \frac{\phi_{12}}{\phi_{22}} \right)^2 <\phi_{21} x_1(0) + \phi_{22} x_2(0) + \phi_{23} x_3(0) >^2 \\
= e^{-\frac{\phi_{22}}{M_{22}} (t+t')} \left( \frac{M_{12}}{M_{22}} - \frac{\phi_{12}}{\phi_{22}} \right) \phi_{22} \quad (60)

Bu summing the above expressions, one has the generalized fluctuation-dissipation relation,

\begin{align*}
< F_1(t) F_1(t') >^2 & = K_{11} \quad (61)
\end{align*}

One can not exchange the order of the limits \( m \to 0 \) and \( t \to 0 \). That is,

\begin{align*}
\lim_{m \to 0} \int_0^t d\tau e^{-\frac{M_0}{M_{22}} \tau} \delta(t - t' - \tau) = \frac{1}{2} \frac{m}{M_{22}} \delta(t - t') & \quad (62)
\end{align*}

**D \quad Projection with a quasi-linear system**

Let’s consider an \((N + 1)\)-dimensional quasi-linear system,

\begin{align*}
0 &= -\phi(x_0) - M_0 \dot{x}_0 - \Phi_0 x_0 - \dot{x}_0 + \xi_0(t) \\
0 &= -\Phi \cdot x - M \cdot \dot{x} - \Phi x_0 x_0 - M x_0 \dot{x}_0 + \xi(t) \quad (63)
\end{align*}

Then,

\begin{align*}
x(t) &= e^{-M^{-1} \Phi' t} x(0) + \int_0^t e^{-M^{-1} \Phi' \tau} \left( -M^{-1} \cdot \Phi x_0 x_0(t - \tau) - M^{-1} \cdot M x_0 \dot{x}_0(t - \tau) + M^{-1} \cdot \xi(t - \tau) \right) d\tau \\
&= e^{-M^{-1} \Phi' t} x(0) + e^{-M^{-1} \Phi' t} - \Phi^{-1} \cdot \Phi x_0 x_0(0) \\
&+ \int_0^t d\tau e^{-M^{-1} \Phi' \tau} M^{-1} \cdot \xi(t - \tau) - \Phi^{-1} \cdot \Phi x_0 \dot{x}_0(t) \\
&- \int_0^t d\tau e^{-M^{-1} \Phi' \tau} \left( \Phi^{-1} \cdot \Phi x_0 + M^{-1} \cdot M x_0 \right) \dot{x}_0(t - \tau) \quad (64)
\end{align*}
\[ \ddot{x}(t) = -M^{-1} \cdot \Phi \cdot \left[ e^{-M^{-1}\Phi t} \dot{x}(0) + e^{-M^{-1}\Phi t} \cdot \Phi^{-1} \cdot \Phi_x x_0(0) \right] \\
+ \int_0^t d\tau e^{-M^{-1}\Phi \tau} M^{-1} \cdot \xi(t - \tau) - \Phi^{-1} \cdot \Phi_x x_0(t) \]
\[ - \int_0^t d\tau e^{-M^{-1}\Phi \tau} \left( \Phi^{-1} \cdot \Phi_x + M^{-1} \cdot M_{x0} \right) \dot{x}_0(t - \tau) \]
\[ -M^{-1} \cdot \Phi_x x_0 - M^{-1} \cdot M_{x0} \dot{x}_0 + M^{-1} \cdot \xi(t) \]
\[ = -M^{-1} \cdot \Phi \cdot e^{-M^{-1}\Phi t} \dot{x}(0) - e^{-M^{-1}\Phi t} \cdot M^{-1} \cdot \Phi_x x_0(0) \]
\[ - \int_0^t d\tau e^{-M^{-1}\Phi \tau} \cdot M^{-1} \cdot \Phi \cdot M^{-1} \cdot \xi(t - \tau) + M^{-1} \cdot \xi(t) \]
\[ + \int_0^t d\tau e^{-M^{-1}\Phi \tau} \cdot M^{-1} \cdot (\Phi_x + \Phi \cdot M^{-1} \cdot M_{x0}) \dot{x}_0(t - \tau) \]
\[ -M^{-1} \cdot M_{x0} \dot{x}_0 \] (65)

and,
\[ 0 = -\phi(x_0) - M_0 \ddot{x}_0 - \Phi_{0x} \cdot \dot{x} - M_{0x} \cdot \dot{x} + \xi_0(t) \]
\[ = -\{ \phi(x_0) - \Phi_{0x} \cdot \Phi^{-1} \cdot \Phi_x x_0(t) \} \]
\[ - \int_0^t d\tau \dot{x}_0(t - \tau) \left\{ 2 \left[ M_0 - M_{0x} \cdot M^{-1} \cdot M_{x0} \right] \delta(t) \right\} \]
\[ + \left[ M_{0x} \cdot M^{-1} \cdot \Phi - \Phi_{0x} \right] \cdot e^{-M^{-1}\Phi \tau} \cdot M^{-1} \cdot (\Phi_x + \Phi \cdot M^{-1} \cdot M_{x0}) \right\} \]
\[ + \left\{ \xi_0(t) - M_{0x} \cdot M^{-1} \cdot \xi(t) \right\} \]
\[ + \left[ M_{0x} \cdot M^{-1} \cdot \Phi - \Phi_{0x} \right] \cdot \int_0^t d\tau e^{-M^{-1}\Phi \tau} M^{-1} \cdot \xi(t - \tau) \]
\[ + \left[ M_{0x} \cdot M^{-1} \cdot \Phi - \Phi_{0x} \right] \cdot e^{-M^{-1}\Phi \tau} \dot{x}(0) \]
\[ + \left[ M_{0x} \cdot M^{-1} \cdot \Phi - \Phi_{0x} \right] \cdot e^{-M^{-1}\Phi \tau} \Phi_x x_0(0) \} \] (66)

The terms in the curled brackets are the derivative of potential of mean force, the memory kernel, and the random force terms, respectively.