A New Perspective on the Linear Noise Approximation

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A New Perspective on the Linear Noise Approximation

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ABSTRACT: Chemical reactions proceed stochastically at the microscopic level, and it is important to know to what extent deterministic approximations to the dynamics are useful, or otherwise misleading. The linear noise approximation (LNA) is widely known as the lowest-order correction to the deterministic chemical reaction rate equation (RRE) in van Kampen’s system-size expansion of the chemical master equation (CME). But the problematic character of the system-size expansion for some chemical systems, and the sometimes poor agreement of the LNA-corrected result with the exact solution of the CME, have raised concerns about the integrity and usefulness of the LNA. We argue here that those concerns can be resolved by viewing the LNA as an approximate solution, not of the CME, but of the chemical Langevin equation (CLE). The latter can be shown, independently of the system-size expansion, to be accurate for practical purposes whenever the system is sufficiently close to the thermodynamic (large-system) limit. We argue that the LNA should be viewed as describing the initial departure of the CLE from the RRE as we back away from the thermodynamic limit to a large but finite system. We show that this perspective of the LNA simplifies its derivation, clarifies its practical uses and limitations, and invites an easier way to deduce its solution.
1. Introduction

The chemical master equation (CME) describes the discrete-stochastic time evolution of the molecular populations in a well-stirred chemically reacting system. In the limit of an infinitely large system, the CME reduces to the reaction rate equation (RRE), the set of ordinary differential equations that has long been the cornerstone of deterministic chemical kinetics. Proposed proofs of this limit result have used a variety of arguments [1-6], the best known of which is the “system-size expansion” of van Kampen [4,5]. In the system-size expansion, the solution of the CME is, in effect, expanded about the solution of the RRE in a power series in the reciprocal of the square root of the size of the system. That expansion aims not only to establish the fact of the limit, but also to provide a systematic way of computing increasingly accurate solutions of the CME by adding perturbation terms to the solution of the RRE. But that goal can be achieved only if the coefficients of the successive terms in the series expansion are well behaved. That this is not always the case can be illustrated by two examples.

The first is a bistable chemical system, whose stable states $s_1$ and $s_2$ are separated by an unstable state $u$ so that $s_1 < u < s_2$. The RRE implies that this system will asymptotically approach $s_1$ if the initial state $s_0 < u$, or $s_2$ if $s_0 > u$. But the CME implies that the system will perpetually visit both stable states, fluctuating around each $s_i$ within some average range $\sigma_i$ for some average time $\tau_i$ before randomly transitioning to the other stable state. Clearly it will not be possible to represent those random transitions between the stable states as any kind of perturbation to the constant stable state value predicted by the RRE. But this failure of the system-size expansion does not invalidate the prediction that the solution of the CME approaches the solution to the RRE in the large-system limit. That’s because the CME also predicts that, in the limit of an infinitely large system, $\sigma_i/s_i \to 0$ and $\tau_i \to \infty$; thus, on any realistic spatiotemporal scale, the system’s behavior will appear just as described by the RRE.

A second counter-example is provided by any limit-cycle oscillator, such as for example the Brusselator [7,8], or the Wilson-Cowan equations of neural dynamics [9]. In the case of the Brusselator, the RRE predicts that the molecular populations $x_i(t)$ and
\( x_2(t) \) of its two time-varying species will evolve in such a way that the state point \((x_1(t), x_2(t))\) eventually traces out in the \(x_1-x_2\) plane a closed curve \(C\) (the limit cycle curve) with a fixed period \(T\). But the solution to the CME asymptotically approaches a time-independent “crater” over the \(x_1-x_2\) plane whose ridge is the curve \(C\). That happens because each trajectory, starting out at a given location on \(C\), will undergo fluctuations about the RRE prediction, and while fluctuations normal to the limit cycle will tend to be corrected, fluctuations tangential to the limit cycle will accumulate. After a sufficiently long time, it will be impossible to predict the phase of any particular trajectory. Clearly it would be folly to try represent the stationary crater predicted by the CME as a perturbation to the regularly orbiting point predicted by the RRE. However, the distribution of an ensemble of trajectories starting at the same location will relax from the sharp peak predicted by the RRE at a rate which is, roughly, inversely proportional to the system size. So by taking the species populations to be sufficiently large, the time required for the solution of the CME to relax from a sharp peak orbiting \(C\) with fixed period to the asymptotic time-stationary crater can be made so large that deviations from the behavior predicted by the RRE will be practically imperceptible over any realistic time frame.

In actual applications, only the first perturbation term in van Kampen’s system-size expansion has received much attention [10-12]. That lowest-order correction to the RRE has come to be called the linear noise approximation (LNA) [4,5]. In a recent study by Ferm, et al. [13], the LNA was applied to several specific systems. The results were mixed. In some cases the LNA provided an accurate approximation to the CME, while of course being computationally much more efficient; however, in other cases it proved to be a very inaccurate approximation to the CME.

All these considerations naturally raise questions about the practical usefulness of both the system-size expansion and the LNA. In this paper, we will argue that the LNA can play a useful though carefully circumscribed role in analyzing chemical systems in which stochasticity is important. But to fully appreciate that role, it is necessary to approach the LNA in a new way. The context of this new approach to the LNA is a relatively new proof of the theorem that the CME approaches the RRE in the large
system limit [6]. Since that proof does not rely on the system-size expansion, it establishes the RRE limit theorem regardless of whether or not the system-size expansion is well behaved.

In Sec. 2 we review this proof of the RRE limit theorem, and in the process establish our notation. In Sec. 3 we show how, from an intermediate result of the proof in Sec. 2, the LNA emerges remarkably easily through a well motivated approximation. In Sec. 4 and Appendix A, we note that an additional advantage of this approach to the LNA is the simpler way it suggests for solving the LNA. From the vantage point of this new perspective, we propose in Sec. 5 a new role for the LNA in the study of stochastically evolving chemical systems. In Sec. 6 we give some numerical examples that illustrate our thesis, and in Sec. 7 we briefly summarize our conclusions.

2. **The route from the CME to the RRE**

We consider a system of $N$ chemical species $S_1, \ldots, S_N$ whose molecules can undergo $M$ chemical reactions $R_1, \ldots, R_M$. If the molecules of the reactant species are *dilute* and *well stirred* inside some volume $\Omega$, it can be shown [6,14] that for each chemical reaction channel $R_m$ there should exist a function $a_m$ of $\mathbf{x} \equiv (x_1, \ldots, x_N)$, where $x_i$ is the current number of molecules of species $S_i$, that satisfies

$$a_m(\mathbf{x})dt \equiv \text{the probability that an } R_m \text{ reaction event will occur in the next infinitesimally small time interval } dt \quad (m = 1, \ldots, M). \quad (1)$$

This function is called the *propensity function* of reaction $R_m$, since it quantifies the likelihood that $R_m$ will “fire”. Equation (1) implies that the time-dependent state vector of the system, $\mathbf{X}(t) \equiv (X_1(t), \ldots, X_N(t))$ where $X_i(t)$ is the number of molecules of species $S_i$ at time $t$, is a jump Markov process.

There are two useful consequences of Eq. (1) that follow rigorously by applying the laws of probability theory. The first is the CME [15], which prescribes the time-evolution of the function $P(\mathbf{x}, t | \mathbf{x}_0, t_0) \equiv \text{the probability that } \mathbf{X}(t) \text{ will equal } \mathbf{x} \text{ given that } \mathbf{X}(t_0) = \mathbf{x}_0 \text{ for any } t \geq t_0$:
\[
\frac{\partial P(x,t|x_0,t_0)}{\partial t} = \sum_{m=1}^{M} [a_m(x - \nu_m)P(x - \nu_m,t|x_0,t_0) - a_m(x)P(x,t|x_0,t_0)].
\]  

(2)

Here \( \nu_m \equiv (\nu_{1m}, \ldots, \nu_{Nm}) \) is the state-change vector for reaction \( R_m \), with \( \nu_{im} \) being the change in the \( S_i \) molecular population caused by one \( R_m \) reaction. The other noteworthy rigorous consequence of Eq. (1) is the stochastic simulation algorithm (SSA) [16,17]. It enables us to construct unbiased realizations of \( X(t) \) by successively advancing the system from its current state by exactly one reaction event. More specifically, if \( X(t) = x \), then with \( a_0(x) \equiv \sum_{j=1}^{M} a_j(x) \), the time \( \tau \) to the next reaction will be a sample of the exponential random variable with mean \( a_0^{-1}(x) \), and the index \( m \) of that reaction will be a sample of the integer random variable with probability mass \( a_m(x)/a_0(x) \). With \( \tau \) and \( m \) chosen according to those specifications, the SSA advances the system from state \( x \) at time \( t \) to state \( x + \nu_m \) at time \( t + \tau \).

The journey from this discrete-stochastic CME/SSA description to the traditional continuous-deterministic description of the RRE begins with a formula that was originally proposed to speed up the SSA [18,19]. The idea was to advance the system from state \( x \) at time \( t \) by a preselected time \( \tau \) which encompasses more than one reaction event. If we take care to choose the time step \( \tau \) small enough that all the propensity functions remain approximately constant during \( \tau \), i.e., if

\[
a_m(x) \equiv \text{const in } [t,t+\tau), \ \forall m \quad \text{(first leap condition),}
\]  

then the state change in that step can easily be estimated: The Poisson random variable with mean \( a\tau \), \( P(a\tau) \), can be defined as the number of events that will occur in a time \( \tau \) given that \( a\, dt \), where \( a \) is a constant, is the probability that an event will occur in the next infinitesimal time \( dt \). This fact coupled with Eq. (1) implies that, under condition (3), the number of firings of reaction channel \( R_m \) in the next \( \tau \) will be the Poisson random variable \( P_m(a_m(x)\tau) \). Since each of those firings of \( R_m \) changes the system’s state by \( \nu_m \), the state of the system at time \( t + \tau \) can be computed as
\[ X(t + \tau) \doteq x + \sum_{m=1}^{M} P_m (a_m(x) \tau) \nu_m. \]  

This is called the *tau-leaping formula*. Its accuracy depends solely on how well condition (3) is satisfied, because that condition alone controls how accurately the number of \( R_m \) firings in time \( \tau \) can be approximated by \( P_m (a_m(x) \tau) \).

Although the tau-leaping formula (4) can often be used to simulate the evolution of a chemical system with acceptable accuracy faster than the SSA, our interest in Eq. (4) here is that it constitutes the first step in the journey from the CME/SSA to the RRE. The second step in that journey imposes a second condition on \( \tau \) in Eq. (4), namely that \( \tau \) also be large enough to satisfy

\[ a_m(x) \tau \gg 1, \forall m \text{ (second leap condition).} \]  

Since the mean of \( P(a \tau) \) is \( a \tau \), the physical import of requirement (5) is that each reaction channel will on average fire many more times than once in the next time step \( \tau \). Now, a well known result in random variable theory is that a Poisson random variable whose mean \( \mu \) is very large compared to 1 can be approximated by a normal random variable with mean \( \mu \) and variance \( \mu \). In symbols, with \( \mathcal{N}(\mu, \sigma^2) \) denoting the normal random variable with mean \( \mu \) and variance \( \sigma^2 \), \( P(\mu) \doteq \mathcal{N}(\mu, \mu) \) whenever \( \mu \gg 1 \). Therefore, if both leap conditions (3) and (5) are satisfied, we can use the identity \( \mathcal{N}(\mu, \sigma^2) \equiv \mu + \sigma \mathcal{N}(0, 1) \) to further approximate the tau-leaping formula (4) as follows:

\[
X(t + \tau) \doteq x + \sum_{m=1}^{M} \mathcal{N}_m (a_m(x) \tau, a_m(x) \tau) \nu_m \\
\doteq x + \sum_{m=1}^{M} \left[ a_m(x) \tau + \sqrt{a_m(x) \tau} \mathcal{N}_m (0, 1) \right] \nu_m \\
\doteq x + \sum_{m=1}^{M} \nu_m a_m(x) \tau + \sum_{m=1}^{M} \nu_m \sqrt{a_m(x)} \mathcal{N}_m (t) \sqrt{\tau}.
\]

In the last line, the \( \mathcal{N}_m (t) \) comprise a set of \( M \) statistically independent temporally uncorrelated normal random variables with means 0 and variances 1. Since \( \tau \) here is assumed to be small enough to satisfy the first leap condition yet also large enough to
satisfy the second leap condition, it has the character of a “macroscopic infinitesimal”, so as is often done in physics, we will denote it by \( dt \). Recalling that \( x \) stands for \( X(t) \), we finally obtain

\[
X(t + dt) - X(t) \approx \sum_{m=1}^{M} \mathbf{v}_m a_m(X(t)) dt + \sum_{m=1}^{M} \mathbf{v}_m \sqrt{a_m(X(t))} N_m(t) \sqrt{dt}.
\] (6)

Equation (6) is called the chemical Langevin equation (CLE) [1-3,20,21]. Two points about the CLE must be kept in mind: First, it will be valid only if the system admits a macroscopically infinitesimal time increment \( dt = \tau \) that satisfies both leap conditions (3) and (5). We should note that it is very easy to find model chemical systems for which that requirement cannot be met. Second, the CLE never accurately quantifies rarely occurring system trajectories. This is a consequence of the fact that the key approximation made in deriving the CLE, namely \( \mathcal{P}(\mu) \approx \mathcal{N}(\mu, \mu) \) for \( \mu \gg 1 \), although accurate for sample values of those two random variables that are within a few standard deviations \( \sqrt{\mu} \) of their means \( \mu \), is usually very inaccurate for sample values in the near-zero tails – the regions that give rise to unlikely events.

The question thus arises: Under what circumstances will both leap conditions be satisfied, so that the CLE will give an accurate description of typical system trajectories? For physically reasonable propensity functions and state-change vectors, it has been proven that both leap conditions will be satisfied if the system is sufficiently close to the thermodynamic limit [6]. The thermodynamic limit is the traditional “large-system” limit in statistical mechanics in which the molecular populations and the containing volume \( \Omega \) all approach infinity in such a way that the species concentrations

\[
Z_i(t) = \frac{X_i(t)}{\Omega}
\] (7)

stay constant (with respect to that limit, not with respect to \( t \)). The argument proving this result goes roughly as follows (see Ref. 6 for details): First it is established as an empirical fact that all physically reasonable propensity functions behave in the thermodynamic limit like

\[
a_m(x) \to \Omega \tilde{a}_m(z) \quad (m = 1, \ldots, M).
\] (8)
Here \( z \equiv x / \Omega \) is the concentration variable, and the functions \( \tilde{a}_m \) are independent of \( \Omega \) and are either the same as or nearly the same as the functions \( a_m \). Next we observe that the first leap condition (3) can always be satisfied simply by taking \( \tau \) sufficiently small. With \( \tau \) thus fixed, we then get close enough to the thermodynamic limit that the replacement (8) is justified, so that we can write the second leap condition (5) as \( \Omega \tilde{a}_m(z) \tau \gg 1 \). That condition can now be satisfied simply by continuing toward the thermodynamic limit until \( \Omega \) becomes large enough to secure the strong inequality. Thus we conclude that, by getting “close enough” to the thermodynamic limit, we can satisfy both leap conditions, and thereby assure that the CLE (6) holds.

In fact, being close to the thermodynamic limit is not only a sufficient condition for the validity of the CLE, but also a necessary condition. That’s because the time-varying molecular populations \( X_i(t) \), which are discretely varying integer variables, will not look like the continuously varying real variables in the CLE unless the \( X_i(t) \) are ranging over values that are \( \gg 1 \). It is therefore always permissible to make the replacement (8) in the CLE (6). Upon doing that, and then dividing through by \( \Omega \), we get the following “concentration form” of the CLE:

\[
Z(t + dt) - Z(t) \approx \sum_{m=1}^{M} v_m \tilde{a}_m(Z(t)) dt + \frac{1}{\sqrt{\Omega}} \sum_{m=1}^{M} v_m \sqrt{\tilde{a}_m(Z(t))} N_m(t) \sqrt{dt}. \tag{9}
\]

This equation makes it easy to see what happens to the CLE when we finally proceed fully to the thermodynamic limit: The two terms on the left side of Eq. (9), as well as the first term on the right, will all stay constant, but the second term on the right will go to zero. Therefore, in the full thermodynamic limit the CLE (9) reduces to

\[
Z(t + dt) - Z(t) \approx \sum_{m=1}^{M} v_m \tilde{a}_m(Z(t)) dt,
\]

which is equivalent to the ordinary differential equation

\[
\frac{dZ(t)}{dt} \approx \sum_{m=1}^{M} v_m \tilde{a}_m(Z(t)). \tag{10a}
\]
Equation (10a) is the RRE, expressed in terms of the species concentrations. If we multiply it through by $\Omega$ and again make use of the property (8), we obtain the RRE in terms of the molecular populations:

$$\frac{dX(t)}{dt} = \sum_{m=1}^{M} \nu_m a_m (X(t)).$$ (10b)

We have thus established, without making use of the system-size expansion, that the discrete-stochastic CME/SSA formalism reduces to the continuous-deterministic RRE formalism in the thermodynamic limit for physically realistic propensity functions.

3. Deriving the LNA

Having established that the CLE becomes the RRE in the thermodynamic limit, we will now derive the LNA as an approximation to the CLE (not the CME). Observing that the CLE (9) differs from the RRE (10a) by a term that is proportional to $1/\sqrt{\Omega}$, we make the provisional assumption that the solution $Z(t)$ to the CLE will differ from the solution $\hat{Z}(t)$ to the RRE by a term that is likewise proportional to $1/\sqrt{\Omega}$. Thus, we seek a solution to the CLE (9) of the form

$$Z(t) = \hat{Z}(t) + \frac{1}{\sqrt{\Omega}} \xi(t),$$ (11)

where $\hat{Z}(t)$ is the deterministic function that satisfies the RRE

$$\frac{d\hat{Z}(t)}{dt} = \sum_{m=1}^{M} \nu_m \tilde{a}_m (\hat{Z}(t))$$ (12)

and the initial condition

$$\hat{Z}(t_0) = Z(t_0).$$ (13)

To find the stochastic function $\xi(t)$ that makes (11) a solution of Eq. (9), we begin by substituting Eq. (11) into Eq. (9) to get

$$[\hat{Z}(t+dt) - \hat{Z}(t)] + \frac{1}{\sqrt{\Omega}} [\xi(t+dt) - \xi(t)].$$
\[
\begin{align*}
&= \sum_{m=1}^{M} v_m \tilde{a}_m \left( \dot{Z}(t) + \frac{1}{\sqrt{\Omega}} \xi(t) \right) dt \\
&+ \frac{1}{\sqrt{\Omega}} \sum_{m=1}^{M} v_m \sqrt{\tilde{a}_m \left( \dot{Z}(t) + \frac{1}{\sqrt{\Omega}} \xi(t) \right)} N_m(t) \sqrt{dt}.
\end{align*}
\]

Since \( \dot{Z}(t) \) satisfies the RRE (12), then \( \dot{Z}(t + dt) - \dot{Z}(t) \) on the left side of this equation can be replaced by \( \sum_m v_m \tilde{a}_m (\dot{Z}(t)) dt \). Doing that, and then multiplying through by \( \sqrt{\Omega} \), we get

\[
\xi(t + dt) - \xi(t) = \sqrt{\Omega} \sum_{m=1}^{M} v_m \left[ \tilde{a}_m \left( \dot{Z}(t) + \frac{1}{\sqrt{\Omega}} \xi(t) \right) - \tilde{a}_m (\dot{Z}(t)) \right] dt \\
+ \sum_{m=1}^{M} v_m \sqrt{\tilde{a}_m \left( \dot{Z}(t) + \frac{1}{\sqrt{\Omega}} \xi(t) \right)} N_m(t) \sqrt{dt}. \tag{14}
\]

This is the equation that \( \xi(t) \) must satisfy in order for \( Z(t) \) in Eq. (11) to exactly satisfy the CLE (9). But since we are near the thermodynamic limit where \( Z(t) \approx \dot{Z}(t) \), it is reasonable to expect that the term \( \xi(t)/\sqrt{\Omega} \) in Eq. (11) will be small compared to \( \dot{Z}(t) \); thus we can make the approximation

\[
\tilde{a}_m \left( \dot{Z}(t) + \frac{1}{\sqrt{\Omega}} \xi(t) \right) \approx \tilde{a}_m (\dot{Z}(t)) + \sum_{k=1}^{N} \frac{\partial \tilde{a}_m(z)}{\partial z_k} \left|_{z=\dot{Z}(t)} \right| \frac{1}{\sqrt{\Omega}} \tilde{\xi}_k(t) \\
\approx \tilde{a}_m (\dot{Z}(t)) + \frac{1}{\sqrt{\Omega}} \sum_{k=1}^{N} f_{mk}(t) \tilde{\xi}_k(t). \tag{15}
\]

In the last step, we have defined the deterministic functions

\[
f_{mk}(t) = \left. \frac{\partial \tilde{a}_m(z)}{\partial z_k} \right|_{z=\dot{Z}(t)} (m = 1, \ldots, M; k = 1, \ldots, N). \tag{16}
\]

Substituting Eq. (15) into Eq. (14), and then discarding all terms in \( 1/\sqrt{\Omega} \) of order \( \geq 1 \), as the approximation Eq. (15) implicitly requires, we finally obtain
\[ \xi(t + dt) - \xi(t) \doteq \sum_{k=1}^{N} \left( \sum_{m=1}^{M} \nu_m f_{mk}(t) \right) \xi_k(t) dt \]
\[ + \sum_{m=1}^{M} \nu_m \sqrt{\bar{a}_m(\hat{Z}(t))} N_m(t) \sqrt{dt} . \] (17)

Equation (17) is van Kampen’s *linear noise approximation* (LNA) [4,5]. In view of the definition (11) and the initial condition (13), Eq. (17) is to be solved subject to the initial condition

\[ \xi(t_0) = 0 . \] (18)

Although the LNA (17) might appear to be more complicated than the CLE (9) which it approximates, the LNA is in one important respect simpler: its stochastic term is independent of the process that it defines. That is not true of the CLE (9), nor of the mathematically equivalent equation (14).

We should comment here on the connection between the above derivation of the LNA and van Kampen’s original derivation [4,5]. Equation (11) is, at least in its mathematical form, exactly van Kampen’s ansatz for his system-size expansion. But van Kampen applied that ansatz to the CME, not to the CLE. Furthermore, van Kampen did not assume at the outset, as we did, that \( \hat{Z}(t) \) in Eq. (11) is the solution of the RRE. He inferred that result only later, through a computationally intensive procedure in which both sides of the CME were expanded in a Taylor series and terms of equal order in \( 1/\sqrt{\Omega} \) were then equated. Although the tactic of equating terms of the same order in an expansion parameter is common in analysis, the mathematical justification for doing that in this case is somewhat unclear, because the set of functions \( \{1, x, x^2, x^3 \ldots\} \) is not orthogonal. But in any case, there is *no* assurance that the resulting series expansion will be *well behaved*, as apparently it is not in the two examples described in Sec. 1. Our derivation of the LNA from the CLE avoids those difficulties, and has the additional advantage of being much simpler. Of course, we have not derived van Kampen’s full system-size expansion, but that was not our objective.
4. Solution of the LNA

The solution of the LNA (17) is known: [4,5] Each component \( \xi_i(t) \) of \( \xi(t) \) is a normal random variable with mean zero and variance \( \kappa_{ii}(t) \),

\[
\xi_i(t) \overset{\text{d}}{\sim} N\left(0, \kappa_{ii}(t)\right) \quad (i = 1, \ldots, N),
\]

and is statistically dependent on the other components through the covariances

\[
\text{cov}\{\xi_i(t), \xi_j(t)\} = \langle \xi_i(t)\xi_j(t) \rangle \equiv \kappa_{ij}(t) \quad (i, j = 1, \ldots, N).
\]

Here the (deterministic) functions \( \kappa_{ij}(t) \) are the solutions of the set of coupled, linear, ordinary differential equations

\[
\frac{d\kappa_{ij}(t)}{dt} = \sum_{k=1}^{N} \left( \sum_{m=1}^{M} V_{jm} f_{mk}(t) \right) \kappa_{kj}(t) + \sum_{k=1}^{N} \left( \sum_{m=1}^{M} V_{jm} f_{mk}(t) \right) \kappa_{ki}(t)
+ \sum_{m=1}^{M} V_{jm} \tilde{a}_m \left( \hat{Z}(t) \right) \quad (i, j = 1, \ldots, N)
\]

for the initial conditions

\[
\kappa_{ij}(t_0) = 0 \quad (i, j = 1, \ldots, N),
\]

where \( f_{mk}(t) \) is as defined earlier in Eq. (16), and \( \hat{Z}(t) \) is the solution of the RRE (12). Since any set of normal random variables is completely determined by their means, variances and covariances, the above constitutes a complete characterization of the solution \( \xi(t) \) of the LNA (17).

Hereetofore, the customary way of obtaining the above results was to solve the Fokker-Planck equation corresponding to the Langevin equation (17). In Appendix 10.1 we present a much simpler solution procedure which avoids the mathematical complexities of high-dimensional partial differential equations.

5. A new view of the LNA

We began this paper by calling attention to some shortcomings of the well known system-size expansion. We then reviewed in Sec. 2 an argument which proves,
independently of the system-size expansion, that any realistic chemical system that is sufficiently close to the thermodynamic limit will be well described by the chemical Langevin equation (CLE), and in the full thermodynamic limit will be well described by the traditional reaction rate equation (RRE).

To the obvious question of how large a system must be in order for the CLE or the RRE to be valid, no general answer can be given. The answer will depend on the forms of the propensity functions and the values of their parameters. There is, however, another less formidable question in this vein that we could pose: Suppose we start with the system effectively at the thermodynamic limit, and hence well described by its RRE, and then gradually move the system toward a smaller, finite size. What will be the first noticeable stochastic departures from the deterministic behavior predicted by the RRE? This less ambitious question can be answered by van Kampen’s linear noise approximation, provided we view it as an approximate solution of the CLE that is valid “sufficiently close” to the thermodynamic limit.

More specifically, by combining the result (19) with the solution form (11) to the CLE (9), we may conclude that the incipient stochastic behavior of the concentration of species $S_i$ is $Z_i(t) \doteq \hat{Z}_i(t) + \Omega^{-1/2} \mathcal{N}(0, \kappa_{ii}(t))$, or equivalently,

$$Z_i(t) \doteq \mathcal{N}(\hat{Z}_i(t), \Omega^{-1} \kappa_{ii}(t)) \quad (i = 1, \ldots, N).$$

(23)

Here, $\kappa_{ii}(t)$ is part of the solution to Eq. (21) for the initial condition (22). In words, as we back off from an infinitely large system to a finite system, the initial break from the purely deterministic behavior of the RRE (13) will be normal random fluctuations in the concentrations of species $S_i$ about the RRE values $\hat{Z}_i(t)$ with standard deviations $\sqrt{\kappa_{ii}(t)/\Omega}$. Therefore, as we move toward the thermodynamic limit, the sizes of the fluctuations in the concentrations will decrease in proportion to $\sqrt{1/\Omega}$. Multiplying Eq. (25) through by $\Omega$ gives us the population version of this result:

$$X_i(t) \doteq \mathcal{N}(\hat{X}_i(t), \Omega \kappa_{ii}(t)) \quad (i = 1, \ldots, N).$$

(24)
This says that the incipient stochastic behavior will manifest itself as normal random fluctuations in the populations of species $S_i$ about the RRE values $\hat{X}_i(t)$ with standard deviations $\sqrt{\Omega \kappa_i(t)}$. Thus, as we move toward the thermodynamic limit, the sizes of the fluctuations in the populations will increase in proportion to $\sqrt{\Omega}$, while the populations themselves will of course increase (more rapidly) in proportion to $\Omega$.

To see what is implied by the covariances $\kappa_{ij}(t)$ for $i \neq j$, we will make use of the easily proved identity

$$\text{cov}\{(a_1 + b_1 Y_1), (a_2 + b_2 Y_2)\} = b_1 b_2 \text{cov}\{Y_1, Y_2\}. $$

Applying this identity to Eq. (11), and then making use of the definition (20), we find that the covariance of the $S_i$ concentration with the $S_j$ concentration is

$$\text{cov}\{Z_i(t), Z_j(t)\} = (\Omega^{-1/2})^2 \text{cov}\{\xi_i(t), \xi_j(t)\} = \Omega^{-1} \kappa_{ij}(t). \quad (25a)$$

And multiplying this result through by $\Omega^2$ gives for the species populations,

$$\text{cov}\{X_i(t), X_j(t)\} = \Omega \kappa_{ij}(t). \quad (25b)$$

A more revealing indicator of the degree of coupling between any two random variables $X$ and $Y$ than their covariance is their correlation,

$$\text{corr}\{X, Y\} = \frac{\text{cov}\{X, Y\}}{\sqrt{\text{var}\{X\} \text{var}\{Y\}}}.$$  

The correlation is a dimensionless number between $-1$ and $+1$, with the value $+1$ implying that $X$ and $Y$ are perfectly correlated (as would be the case if $Y = X$), the value $-1$ implying that $X$ and $Y$ are perfectly anti-correlated (as would be the case if $Y = -X$), and the value 0 implying that $X$ and $Y$ are uncorrelated. It follows from Eqs. (25) that

$$\text{corr}\{X_i(t), X_j(t)\} = \text{corr}\{Z_i(t), Z_j(t)\} \equiv \frac{\kappa_{ij}(t)}{\sqrt{\kappa_i(t) \kappa_j(t)}}. \quad (26)$$
As shown in Appendix 10.2 – see Eqs. (47) and (48) – the normality of $X_i(t)$ and $Z_i(t)$ allows us to interpret the square of the correlation (26) as the fraction of the variance in either species population that can be “explained by” the random fluctuations in the other.

But the fact that correlation (26) is independent of $\Omega$ carries a rather surprising conclusion: The correlation between the populations (or concentrations) of any two species in the LNA is exactly the same as it is in the full thermodynamic limit where the RRE applies. Therefore, as we back off from the full thermodynamic limit, the only initial indicator of the finiteness of the system will be the normal fluctuations of the individual species about their RRE means with the variances given in Eqs. (23) and (24). The off-diagonal elements of the solution to Eq. (21) describe “connections” between the concentrations/populations that are present in the same degree as in the RRE. But that correlation information is arguably useful, because it is not clear how it could be obtained directly from the RRE.

To make practical use of the LNA, we need two things: First, we need a general purpose computer program to solve the RRE (12) for a given chemical system. It could be argued that if it is at all feasible to obtain a numerical estimate of the RRE solution $\hat{Z}(t)$ for a given biochemical network, that should always be done as a first step toward understanding that network; i.e., a general purpose RRE solver ought to be a part of any biochemical analysis toolkit.

Second, we need a general purpose computer program to solve the differential equations (21) for the $\kappa_{ij}(t)$, making use of the solution to the RRE (12). Notice that Eqs. (21) are not as complicated as they might at first appear: Although they are coupled, they are linear. And the fact that the concentration propensity functions $\tilde{a}_m(z)$ are usually either linear or quadratic in the components of $z$ means that the quantities $f_{mj}(t)$ in Eq. (21), which are defined in Eq. (16), will usually be either constant or linear in a single component of $z$.

Finally, we note that if the system is stable, which means that the solution of the RRE (12) has a well defined, time-independent asymptotic limit,
\[ \hat{Z}(t \to \infty) = \hat{Z}(\infty), \]  

(27)

and if we are interested only in the equilibrium behavior of the system, then the above tasks simplify considerably: The asymptotic solution to the RRE can be most efficiently found by solving the set of purely algebraic equations obtained by setting the left side of Eq. (12) to zero:

\[ \sum_{m=1}^{M} \nu_m \tilde{a}_m (\hat{Z}(\infty)) = 0. \]  

(28)

Similarly, the \( \kappa_{ij}(\infty) \) can be found by solving the set of purely algebraic equations obtained by setting the left side of Eq. (21) to zero:

\[ \sum_{k=1}^{N} \left( \sum_{m=1}^{M} V_{im} f_{mk}(\infty) \right) \kappa_{kj}(\infty) + \sum_{k=1}^{N} \left( \sum_{m=1}^{M} V_{jm} f_{mk}(\infty) \right) \kappa_{ki}(\infty) \]

\[ + \sum_{m=1}^{M} V_{im} V_{jm} \tilde{a}_m (\hat{Z}(\infty)) = 0 \quad (i, j = 1, \ldots, N). \]  

(29)

So at equilibrium, the earliest indication of finite-system effects will be normal fluctuations in the concentration of species \( S_i \) with standard deviation \( \sqrt{\kappa_{ii}(\infty)} / \Omega \) about its steady state value \( \hat{Z}_i(\infty) \).

6. Numerical examples

We conclude by presenting three numerical examples to illustrate our thesis that, for practical purposes, the LNA will always give a good description of any real-world chemical system that is “sufficiently large”, but not necessarily if the system is “too small”. In these examples, the specific reaction probability rate constant \( c_m \) is defined so that \( c_m dt \) gives the probability that a randomly chosen set of \( R_m \) reactant molecules will react accordingly in the next \( dt \). For real-world chemical reactions, \( c_m \) will be independent of the system volume \( \Omega \) if \( R_m \) is unimolecular, inversely proportional to \( \Omega \) if \( R_m \) is bimolecular, and directly proportional to \( \Omega \) if \( R_m \) is a zeroth order reaction [6]. Our computations for these examples were performed using a general purpose LNA.
solver that was coded in C++ as a custom driver, built on top of the StochKit2 stochastic simulation software framework [22]. For the ODE solver, the code uses CVODE from the SUNDIALS numerical software suite [23].

Example 1. Our first example is the so-called decay-dimerization reaction set,

\[
\begin{align*}
S_1 & \xrightarrow{c_1} \emptyset \\
2S_1 & \xrightleftharpoons[k_2 \Omega^{-1}]{c_3} S_2 \\
S_2 & \xrightarrow{c_3} S_3
\end{align*}
\]

in which an unstable monomer \( S_1 \) can dimerize to an unstable dimer \( S_2 \), which in turn can convert to a stable form \( S_3 \). The state-change vectors for these four reactions are

\[
\nu_1 = (-1,0,0) \\
\nu_2 = (-2,1,0) \\
\nu_3 = (2,-1,0) \\
\nu_4 = (0,-1,1)
\]

The corresponding propensity functions are

\[
\begin{align*}
a_1(x) &= c_1 x_1 \\
a_2(x) &= k_2 \Omega^{-1} \frac{1}{2} x_1 (x_1 - 1) \\
a_3(x) &= c_3 x_2 \\
a_4(x) &= c_4 x_2
\end{align*}
\]

The \( \Omega \)-independent functions defined in Eq. (8) are therefore

\[
\begin{align*}
\tilde{a}_1(z) &= c_1 z_1 \\
\tilde{a}_2(z) &= k_2 \frac{1}{2} z_1^2 \\
\tilde{a}_3(z) &= c_3 z_2 \\
\tilde{a}_4(z) &= c_4 z_2
\end{align*}
\]

For the rate constant values, we will take

\[
c_1 = 1, \quad k_2 = 2, \quad c_3 = 0.5, \quad c_4 = 0.04,
\]

and for the initial conditions,
\[ X_1(0) = 5 \cdot \Omega, \quad X_2(0) = X_3(0) = 0. \quad (31e) \]

By taking the initial molecular populations of all species proportional to \( \Omega \), the system can be made to approach the thermodynamic limit simply by letting \( \Omega \to \infty \).

Figure 1. Decay-dimerization model in Eqs. (30) and (31) for \( \Omega = 1 \): (a) Mean and mean \( \pm \) one-standard deviation of the concentration of species \( S_2 \) computed from \( 10^5 \) SSA simulations (solid and dashed curves) and from the LNA (dotted curves). The gray step-curve shows a typical SSA trajectory. (b) Histogram of the species \( S_2 \) concentration at \( t = 5 \), as calculated from \( 10^5 \) SSA simulations (gray histogram), and from the LNA’s normal distribution (solid curve). The LNA is evidently not accurate for this “small” system.
In Fig. 1, we show results for this reaction set with $\Omega=1$, which by Eq. (31e) implies a “small” system with only 5 initial $S_1$ molecules. Figure 1a shows the mean $S_2$ concentration $\langle Z_2(t) \rangle$ and the corresponding one-standard deviation envelope $\langle Z_2(t) \rangle \pm \text{stdev} \{Z_2(t)\}$ as a function of $t$, computed in two different ways: The solid-and-dashed curves were obtained by averaging over $10^5$ SSA runs; the dotted curves are the LNA’s prediction, $\hat{Z}_2(t) \pm \sqrt{\Omega^{-1} \kappa_{22}(t)}$. The step function curve in Fig. 1a shows a typical SSA trajectory for $Z_2(t)$. Note that concentration trajectories will always be confined to discrete values for a finite system, and in this $\Omega=1$ case the concentration trajectory numerically coincides with the population trajectory. In Fig. 1b, the gray histogram shows the statistical distribution of $Z_2(t)$ at time $t=5$ as computed from the same $10^5$ SSA runs. And the solid curve shows the pdf of the LNA’s prediction for this histogram, $Z_2(5) \sim \mathcal{N}(\hat{Z}_2(5), \Omega^{-1} \kappa_{22}(5))$. We see from Figs. 1a and 1b that, for this “small” system, the LNA predictions, although not wildly incorrect, differ noticeably from the exact SSA results. Even more revealing of the inaccuracy of the LNA in this case is the fact that the SSA trajectory in Fig. 1a is far from being a continuous (but not differentiable) curve, as the CLE and its approximating LNA both imply.
Figure 2. As in Fig. 1, but with $\Omega = 200$: In (a) the LNA curves are covered by the SSA curves, and the single SSA trajectory has a more continuous appearance. In (b) the SSA histogram is accurately described by the LNA distribution. The LNA does quite well for this “large” system.

In Fig. 2, we repeat the foregoing analysis with $\Omega = 200$, which gives us an initially “large” system with 1000 $S_2$ molecules. We see in Fig. 2a that the LNA’s prediction for the one-standard deviation envelope for $Z_2(t)$ shows no discernable disagreement with the one-standard deviation envelope predicted by the $10^5$ SSA runs. Note that the axes in Figs. 2a are identical to the axes in Fig. 1a. The single SSA trajectory for $Z_2(t)$ in Fig. 2a (jagged curve) is evidently much closer to being continuous (but not differentiable), as implied by the CLE and the LNA. In Fig. 2b, the
$S_2$ concentration histogram for $Z_2(5)$ computed from $10^5$ SSA runs is seen to be accurately duplicated by the pdf of the LNA’s prediction, $Z_2(5) \sim N(\hat{Z}_2(5), \Omega^{-1} \kappa_{22}(5))$, which is the solid curve. The LNA for this “large” system clearly works quite well.

![Figure 3](image_url)

**Figure 3.** Correlations in the decay-dimerization model: (a) Plots of $\phi_{ij}$ in Eq. (32), the fraction of the variance in the population of species $S_i$ that is “explained by” the fluctuations in species $S_j$, and vice-versa. (b) Plots of $F_i$ in Eq. (33), the fraction of the variance in species $S_i$ that is explained by the fluctuation in the other two species.

In Fig. 3a we show plots of the squared correlation estimates
\[
\phi_{ij}(t) \equiv \frac{\kappa_{ij}^2(t)}{\kappa_{ii}(t)\kappa_{jj}(t)} \quad (ij = 12, 13, 23)
\] (32)

predicted by the LNA. These are independent of \(\Omega\). As discussed in connection with Eq. (26), \(\phi_{ij}\) can be interpreted as the fraction of the variance in species \(S_i\) that is associated with the fluctuations in species \(S_j\), and vice-versa. In Fig. 3b, we show plots of the three curves

\[
\begin{align*}
F_1(t) &\equiv \phi_{12}(t) + \phi_{13}(t) \\
F_2(t) &\equiv \phi_{12}(t) + \phi_{23}(t) \\
F_3(t) &\equiv \phi_{13}(t) + \phi_{23}(t)
\end{align*}
\] (33)

The forgoing interpretation of \(\phi_{ij}\) implies that \(F_i\) is the fraction of the variance in species \(S_i\) that is associated with the fluctuations in the other two species. Happily for this interpretation, all three of the \(F_i\) curves stay below 1; however the import of these curves is not entirely clear to us.

**Example 2.** Our second example is the well-known Schlögl reaction set,

\[
\begin{array}{c}
2S_1 \xrightarrow{k_1\Omega^{-1}} 3S_1 \\
\varnothing \xrightarrow{k_2\Omega} S_1 \\
\end{array}
\] (34)

The state-change vectors for these single-species reactions are

\[\nu_1 = 1, \; \nu_2 = -1, \; \nu_3 = 1, \; \nu_4 = -1,\] (35a)

and the propensity functions are

\[
\begin{align*}
a_1(x_i) &\equiv k_1\Omega^{-1}\frac{1}{2}x_i(x_i - 1) \\
a_2(x_i) &\equiv k_2\Omega^{-2}\frac{1}{6}x_i(x_i - 1)(x_i - 2) \\
a_3(x_i) &\equiv k_3\Omega \\
a_4(x_i) &\equiv c_4x_i
\end{align*}
\] (35b)

The volume dependence assumed here for the trimolecular rate constant \(c_2\) is what arises from any physically reasonable approximation of a set of unimolecular and
bimolecular reactions by a single trimolecular reaction. The $\Omega$-independent functions defined in Eq. (8) are

$$
\begin{align*}
\tilde{a}_1(z_1) &= k_1 \frac{1}{2} z_1^2 \\
\tilde{a}_2(z_1) &= k_2 \frac{1}{6} z_1^3 \\
\tilde{a}_3(z_1) &= k_3 \\
\tilde{a}_4(z_1) &= c_4 z_1 
\end{align*}
$$

(35c)

We take for the parameter values,

$$
k_1 = 0.03, \ k_2 = 0.0001, \ k_3 = 200, \ c_4 = 3.5,
$$

(35d)

and for the initial condition,

$$
X_1(0) = 280 \cdot \Omega.
$$

(35e)

Figure 4. Schlögl model in Eqs. (34) and (35) for $\Omega = 1$: (a) Mean and mean ± one-standard deviation of the concentration of species $S_1$ computed from $10^5$ SSA
simulations (solid and dashed curves) and from the LNA (dotted curves). The jagged gray curve shows typical SSA trajectory. (b) Histogram of the species $S_1$ concentration at $t = 10$, as calculated from $10^5$ SSA simulations (gray histogram) and from the LNA’s normal distribution (solid curve). The LNA is inaccurate for this “small” bi-stable system over this long a time frame.

Figure 4 shows numerical results for $\Omega = 1$. In Fig. 4a, the LNA’s predictions for the one-standard deviation envelope of $Z_1(t)$ (again shown by the dotted curves) is compared with SSA’s predictions (again shown by the solid and dashed curves) over the time interval $0 \leq t \leq 10$. The SSA results here were again obtained from $10^5$ simulation runs, and the trajectory of a randomly chosen one of those SSA runs is shown as the jagged gray curve. We see that, despite the fairly large number of $S_1$ molecules here (note that the population in this case is numerically equal to the concentration), the LNA performs poorly. The reason why becomes clear when we look at the corresponding predictions in Fig. 4b for the distribution of the $S_1$ concentration at time $t = 10$: The system is bi-modal, with one stable state at $z_1 = 82$ and the other at $z_2 = 563$. Since the initial $S_1$ concentration of $z_1 = 280$ is above the separating barrier state, which happens to be at $z_b = 248$, the deterministic RRE trajectory goes to the upper stable state. But some of the SSA trajectories (about 22% in this case) wind up in the lower stable state. So the LNA’s prediction for the $Z_1(10)$ distribution, namely the single peak described by the solid curve, differs markedly from the SSA’s double-peak prediction, shown by the gray histogram. The message here is that, over this time span, the system is not close enough to the thermodynamic limit for the LNA to accurately describe its behavior.
**Figure 5.** As in Fig. 4, but with \( \Omega = 100 \): Moving closer to the thermodynamic limit allows the LNA to give a much more accurate approximation over this time frame. But over much longer time frames, the performance of the LNA would again deteriorate for this bi-stable system.

But if we increase the system volume to \( \Omega = 100 \), the situation changes dramatically, as shown in Fig. 5: In Fig. 5a, the one-standard deviation envelope predicted by the LNA for practical purposes is identical to that predicted by the SSA over the same time interval \( 0 \leq t \leq 10 \). And in Fig. 5b, the \( Z_{1}(10) \) distribution predicted by the LNA (solid curve) is practically indistinguishable from that predicted by the SSA (gray histogram). At this hundred-fold larger system, it is extremely unlikely (though not absolutely impossible) for an SSA trajectory that starts at \( z_1 = 280 \) to visit the lower stable state before time \( t = 10 \). But of course, if the run time here were taken to be much
larger than 10, the gray SSA histogram would again become bimodal. The message here is that if a bistable system is sufficiently close to the thermodynamic limit, its behavior over a sufficiently restricted time span will be very well described by the LNA.

Example 3. Our final example is the famous Brusselator reaction set,

$$\begin{align*}
\emptyset & \xrightarrow{k_1 \Omega} S_1 \\
S_1 & \xrightarrow{c_2} S_2 \\
2S_1 + S_2 & \xrightarrow{k_3 \Omega^2} 3S_1 \\
S_1 & \xrightarrow{c_4} \emptyset
\end{align*}$$

(36)

The state-change vectors for these four reactions are

$$\begin{align*}
\nu_1 &= (1, 0) \\
\nu_2 &= (-1, 1) \\
\nu_3 &= (1, -1) \\
\nu_4 &= (-1, 0)
\end{align*}$$

(37a)

and the corresponding propensity functions are

$$\begin{align*}
a_1(x) &= k_1 \Omega x_1 \\
a_2(x) &= c_2 x_1 \\
a_3(x) &= k_3 \Omega^2 \frac{1}{2} x_1 (x_1 - 1) x_2 \\
a_4(x) &= c_4 x_1
\end{align*}$$

(37b)

The $\Omega$-independent functions defined in Eq. (8) are therefore

$$\begin{align*}
\tilde{a}_1(z) &= k_1 \\
\tilde{a}_2(z) &= c_2 z_1 \\
\tilde{a}_3(z) &= k_3 \frac{1}{2} z_1 z_2^2 \\
\tilde{a}_4(z) &= c_4 z_1
\end{align*}$$

(37c)

We take values for the rate constants which put the Brusselator in a limit-cycle regime:

$$k_1 = 5000, \ c_2 = 50, \ k_3 = 5 \times 10^{-5}, \ c_4 = 5.$$  (38a)

For the initial condition, we take

$$X_1(0) = 1001 \cdot \Omega, \ X_2(0) = 2002 \cdot \Omega,$$  (38b)
which is slightly off of the equilibrium point.

Figure 6. Brusselator model in Eqs. (36) - (38) for $\Omega = 1$: Mean and mean ± one-standard deviation of the concentration of species $S_1$ as computed from $10^5$ SSA simulations (solid and dashed curves) and from the LNA (dotted curves). The jagged gray curve is a typical SSA trajectory for species $S_1$; it shows, since $\Omega = 1$, that although the $S_1$ population sometimes rises to over 6000, for much of the time it is well under 200. The inaccuracy of the LNA for this “small” limit-cycle system over this time frame is mainly due to the cumulative effects of the fluctuations in the phase of the oscillator.

Figure 6 shows for the case $\Omega = 1$ the one-standard deviation envelope for $Z_1(t)$ over the time interval $0 \leq t \leq 4$ as predicted by the LNA (dotted curves) and the SSA (solid/dashed curves), the latter again being computed from $10^5$ runs. The gray jagged
curve is the $Z_1(t)$ trajectory of a typical one of those SSA runs. The performance of the LNA in this case is obviously not good. Although the RRE trajectory $\hat{Z}_1(t)$ (the heavy dotted curve) gives a reasonable representation of the behavior of the single-run SSA trajectory, except for an overall shift in phase, the LNA’s estimate of the standard deviation about $\hat{Z}_1(t)$ (lightly dotted curve) is extremely poor: The upper one-standard deviation envelope predicted by the LNA in the last oscillation peaks at about $9 \times 10^5$, and that peak value would become even larger if the run had contained more oscillations.

**Figure 7.** Same as Fig. 6, but with $\Omega = 10^5$: Moving closer to the thermodynamic limit allows the LNA to give a much more accurate approximation over the same time frame. But over longer time frames, the performance of the LNA would again deteriorate for this limit-cycle oscillator.
Figure 7 shows the results obtained if these calculations are repeated with the volume increased to $\Omega = 10^5$. Here the SSA prediction consists of only one simulated trajectory, because the SSA trajectories at this high molecular population level take a very long time to compute and the trajectories were found to be practically indistinguishable from each other over this span of time. We see that at least up to time $t = 4$, the SSA trajectory is well predicted by the LNA’s very tight one-standard deviation envelope. However, we can see evidence of a gradually increasing instability in the LNA’s one-standard deviation envelope at the peaks of the last two oscillations. If this plot had been extended to many more oscillations, these overestimates would eventually become as wildly inaccurate as the LNA estimates in Fig. 6. But all this does make our point: If the oscillating system is sufficiently large, the LNA will accurately describe its behavior over a sufficiently restricted time span.

This picture is consistent with recent work applying the LNA to chemical oscillators by Boland, et al. [24], and Scott, et al. [25]. They separated the fluctuations into components normal and tangential to the limit cycle trajectory by adopting a rotating coordinate frame in the plane of the Brusselator’s limit cycle, obtained from the RRE. One obtains an LNA variance for the normal component that is accurate for moderate molecular populations. But as discussed in Sec. 1, the tangential fluctuations, which are essentially fluctuations in the phase of the limit cycle oscillations, grow unboundedly. This unbounded growth in the phase fluctuations is responsible for the unruly behavior shown in Fig. 6 of the standard LNA for moderate population sizes.

7. Summary

In the full thermodynamic limit, where the system volume $\Omega$ and the molecular populations $X(t)$ are infinitely large but the molecular concentrations $Z(t) \equiv X(t)/\Omega$ are finite, a well-stirred chemically reacting system will evolve according to the traditional deterministic RRE (10). If the system is not too far from the thermodynamic limit, its evolution will be accurately described by the CLE (9), although for oscillators and multi-stable state systems the CLE description will be valid only over restricted time spans.
The LNA in Eqs. (11) and (17) has heretofore been regarded as an approximate solution of the CME. We have argued in this paper that it would be better to view the LNA as an approximate solution of the CLE. In that role, the LNA describes the initial departure of the CLE from the RRE as we back away from the thermodynamic limit to a large but finite system. The quantitative import of the LNA is that this initial departure from the deterministic RRE solution $\hat{Z}(t)$ consists of normal fluctuations in $Z(t)$ about $\hat{Z}(t)$ with $\text{var}\{Z_i(t)\} = \Omega^{-1} \kappa_{ii}(t)$, where $\kappa_{ij}(t)$ is the solution of the ordinary differential equation set (21) subject to the initial condition (22).

For $i \neq j$, $\Omega^{-1} \kappa_{ij}(t)$ gives the covariance of the molecular concentrations of species $S_i$ and $S_j$. The square of the corresponding correlation, in Eq. (26), can be interpreted as the fraction of the variance in either species that is in some sense “explained by” the fluctuations in the other species. Since that fraction turns out to be independent of $\Omega$, the pairwise correlations between species concentrations in the stochastic regime carry over unchanged to the full thermodynamic limit, where the variances and covariances vanish; i.e., the correlations predicted by the stochastic LNA are in some sense also present in the deterministic RRE.

If a chemical system is “sufficiently large” the LNA will give an accurate approximation to the system’s “true” behavior as predicted by the CME and the SSA, and will usually do so with much less computational effort. Unfortunately, what is meant by “sufficiently large” is not easily quantifiable in a general way. The only reliable way we know to make that determination is to compare post-facto the predictions of the LNA with those of the CME or the SSA, and then make the judgment call of whether or not the agreement is good enough. It has been our experience that when the LNA is not a good approximation, the CLE usually isn’t either. Nevertheless, we believe that viewing the LNA as an approximate solution of the CLE instead of the CME provides a better perspective of the practical uses and limitations of the LNA, affords a much easier way of deriving the LNA, and invites a much simpler way of solving the LNA.
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9. References


Appendices

10.1 Solving the LNA

Writing the LNA (17) in its component form

\[ \xi_i(t + dt) = \xi_i(t) + \sum_{k=1}^{N} \left( \sum_{m=1}^{M} v_{im} f_{mk}(t) \right) \xi_k(t) dt \]

\[ + \sum_{m=1}^{M} v_{im} \sqrt{\hat{a}_m(\hat{Z}(t))} N_m(t) \sqrt{dt} \quad (i = 1, \ldots, N), \quad (39) \]

we will first prove that the \( \xi_i(t) \) defined by this equation are all normal random variables. The key to doing that is a result in random variable theory which states that if \( Y_1 \) and \( Y_2 \) are two normal random variables, and \( c_1 \) and \( c_2 \) are two sure (non-random) variables, then \( c_1 Y_1 + c_2 Y_2 \) is a normal random variable. Note that this is true even if \( Y_1 \)
and \( Y_2 \) are statistically dependent. Therefore, since \( \xi_i(t_0) = 0 = \mathcal{N}(0,0) \) and \( N_m(t_0) = \mathcal{N}(0,1) \), we may conclude from the \( t = t_0 \) version of Eq. (39) that \( \xi_i(t_0 + dt) \) is a normal random variable – because the coefficients of both \( \xi_k(t) \) and \( N_m(t) \) on the right side of Eq. (39) are sure variables. The same reasoning applied to the \( t = t_0 + dt_0 \) version of Eq. (39) then establishes that \( \xi_i(t_0 + 2dt) \) is a normal random variable. By induction, we conclude that \( \xi_i(t) \) is normal for all \( t > t_0 \). [It should be noted that the foregoing logic cannot be applied to the LNA’s precursor equation (14), because in that equation the coefficient of \( N_m(t) \) on the right side is not a sure variable; or from a different point of view, that cannot be done because the product of a normal random variable with practically any other random variable will not be normal. Nor can we in those other cases invoke the central limit theorem to infer normality for the sum of “infinitely many terms”, because those terms are not statistically independent.] The \( N \) normal random variables \( \xi_1(t), \ldots, \xi_N(t) \) will usually not be statistically independent; however, being normal, they will be completely specified by their \( N \) means and their \( N(N - 1)/2 \) covariances.

To prove that the normal random variables \( \xi_i(t) \) have zero mean, we first take the average of Eq. (39):

\[
\langle \xi_i(t + dt) \rangle = \langle \xi_i(t) \rangle + \sum_{k=1}^{N} \left( \sum_{m=1}^{M} V_{im} f_{mk}(t) \right) \langle \xi_k(t) \rangle dt
\]

\[
+ \sum_{m=1}^{M} \sqrt{\alpha_m}(\hat{Z}(t)) \langle N_m(t) \rangle \sqrt{dt} \quad (i = 1, \ldots, N).
\]

Since \( \langle N_m(t) \rangle = 0 \), this reduces to the set of coupled ordinary differential equations

\[
\frac{d \langle \xi_i(t) \rangle}{dt} = \sum_{k=1}^{N} \left( \sum_{m=1}^{M} V_{im} f_{mk}(t) \right) \langle \xi_k(t) \rangle \quad (i = 1, \ldots, N).
\]

Equation (18) implies the initial condition \( \langle \xi_i(t_0) \rangle = 0 \) for all \( i \). But \( \langle \xi_i(t) \rangle \equiv 0 \) is a solution of Eqs. (40) which satisfies that initial condition; hence, for all \( t \geq t_0 \),
\[ \langle \xi_i(t) \rangle = 0 \quad (i = 1, \ldots, N). \]  

(41)

To derive a formula for the time-derivative of \( \kappa_{ij}(t) \equiv \langle \xi_i(t) \xi_j(t) \rangle \), we multiply Eq. (39) by itself with \( i \) replaced by \( j \). Retaining only terms up to first order in \( dt \), that gives

\[
\begin{align*}
\xi_i(t + dt) \xi_j(t + dt) & \doteq \xi_i(t) \xi_j(t) \\
& + \sum_{k=1}^{N} \left( \sum_{m=1}^{M} v_{im} f_{mk}(t) \right) \xi_k(t)\xi_j(t) dt \\
& + \sum_{m=1}^{M} v_{im} \sqrt{\bar{a}_m} \left( \hat{Z}(t) \right) N_m(t) \xi_j(t) \sqrt{dt} \\
& + \sum_{m=1}^{M} v_{im} \sqrt{\bar{a}_m} \left( \hat{Z}(t) \right) N_m(t) \xi_i(t) \sqrt{dt} \\
& + \sum_{m=1}^{M} v_{im} \sqrt{\bar{a}_m} \left( \hat{Z}(t) \right) N_m(t) \cdot \sum_{l=1}^{M} v_{jl} \sqrt{\bar{a}_l} \left( \hat{Z}(t) \right) N_l(t) \times dt.
\end{align*}
\]

Averaging this equation, using

\[
\langle N_m(t) \xi_i(t) \rangle = \langle N_m(t) \rangle \langle \xi_i(t) \rangle = 0,
\]

and

\[
\langle N_m(t) N_l(t) \rangle = \begin{cases} 
1, & \text{if } l = m \\
0, & \text{if } l \neq m,
\end{cases}
\]

we get

\[
\begin{align*}
\langle \xi_i(t + dt) \xi_j(t + dt) \rangle & \doteq \langle \xi_i(t) \xi_j(t) \rangle \\
& + \sum_{k=1}^{N} \left( \sum_{m=1}^{M} v_{im} f_{mk}(t) \right) \langle \xi_k(t) \xi_j(t) \rangle dt \\
& + \sum_{k=1}^{N} \left( \sum_{m=1}^{M} v_{jm} f_{mk}(t) \right) \langle \xi_k(t) \xi_j(t) \rangle dt \\
& + \sum_{m=1}^{M} v_{im} v_{jm} \sqrt{\bar{a}_m} \left( \hat{Z}(t) \right) dt.
\end{align*}
\]

(42)

Transposing the first term on the right side, dividing through by \( dt \), and finally taking the limit \( dt \to 0 \), we obtain Eq. (21).
10.2 Significance of the correlation of two normal random variables

It can be proved (see for instance Sec. III of [26], but earlier references unknown to us may exist) that if \( N_1 \) and \( N_2 \) are two statistically independent normal random variables with means 0 and variances 1, then the two random variables \( X_1 \) and \( X_2 \) defined by

\[
X_1 = \mu_1 + \sigma_1 N_1, \quad (43a)
\]

\[
X_2 = \mu_2 + \left( \frac{c_{12}}{\sigma_1} \right) N_1 + \sqrt{\frac{\sigma_2^2}{\sigma_1^2}} - \frac{c_{12}}{\sigma_1^2} N_2, \quad (43b)
\]

will be normal with respective means \( \mu_1 \) and \( \mu_2 \), variances \( \sigma_1^2 \) and \( \sigma_2^2 \), and covariance \( c_{12} \). Equations (43) thus provide a compact representation of any two arbitrarily correlated normal random variables \( X_1 \) and \( X_2 \) in terms of their means, variances and covariance. If we solve Eq. (43a) for \( N_1 \) and then substitute the result into Eq. (43b), we get

\[
X_2 = \frac{c_{12}}{\sigma_1^2} X_1 + \sqrt{\frac{\sigma_2^2}{\sigma_1^2}} - \frac{c_{12}}{\sigma_1^2} N_2 + \left( \mu_2 - \frac{\mu_1 c_{12}}{\sigma_1^2} \right). \quad (44)
\]

This equation shows that the randomness in \( X_2 \) can be thought of as arising from two statistically independent sources, namely \( X_1 = \mathcal{N}(\mu_1, \sigma_1^2) \) and \( N_2 = \mathcal{N}(0,1) \). A measure of the randomness in any random variable is its variance. Since for any two statistically independent random variables \( Y \) and \( Z \), and any sure variables \( a \), \( b \) and \( c \), we have \( \text{var}\{aY + bZ + c\} = a^2 \text{var}\{Y\} + b^2 \text{var}\{Z\} \), it follows from Eq. (44) that

\[
\text{var}\{X_2\} = \left( \frac{c_{12}}{\sigma_1^2} \right)^2 \text{var}\{X_1\} + \left( \sigma_2^2 - \frac{c_{12}^2}{\sigma_1^2} \right) \text{var}\{N_2\}. \quad (45)
\]

This formula evidently quantifies the “contributions” to the variance of \( X_2 \) from the two statistically independent sources \( X_1 \) and \( N_2 \). In particular, we see that the contribution to \( \text{var}\{X_2\} \) coming from the noise in \( X_1 \) is
The quantity in parentheses on the right side of Eq. (46) is by definition the correlation of \( X_1 \) and \( X_2 \), \( \text{corr}\{X_1, X_2\} \). Equation (46) thus shows that the square of \( \text{corr}\{X_1, X_2\} \) gives the fraction of the variance of the normal random variable \( X_2 \) that “is explained by” the fluctuations in the normal random variable \( X_1 \). The awkward terminology here owes to the fact that, since \( \text{corr}\{X_1, X_2\} \equiv \text{corr}\{X_2, X_1\} \), then the fraction of \( \text{var}\{X_2\} \) that is explained by the fluctuations in \( X_1 \) will be equal to the fraction of \( \text{var}\{X_1\} \) that is explained by the fluctuations in \( X_2 \). That suggests that it might not be reasonable to think of the fluctuations in either species as causing the fluctuations in the other species. In any case, this is the phrasing that is usually used in connection with the notion of “total variance”, of which the result just obtained can be viewed as an example.

We have seen in the main text that if a chemical system is sufficiently close to the thermodynamic limit, then the molecular populations \( X_1(t) \) and \( X_2(t) \) of any two species will be normal random variables with means \( \mu_i(t) = \hat{X}_i(t) \), variances \( \sigma_i^2(t) = \kappa_i(t) \) \( (i = 1,2) \), and covariance \( c_{12}(t) = \kappa_{12}(t) \), where \( \hat{X}(t) \) is the solution of the RRE \((10b)\), and the \( \kappa_{ij}(t) \) are the solution of Eq. (21). Recalling Eq. (26), the above results therefore imply that

\[
\frac{\kappa_{12}^2(t)}{\kappa_{11}(t)\kappa_{22}(t)} = \left\{ \begin{array}{l}
\text{the fraction of } \text{var}\{X_2(t)\} \text{ that is} \\
\text{explained by the fluctuations in } X_1(t) \end{array} \right\}. 
\]  
(47)

This in turn implies that

\[
F_i \equiv \sum_{j \neq i}^{N} \frac{\kappa_{ij}^2(t)}{\kappa_{ii}(t)\kappa_{jj}(t)} = \left\{ \begin{array}{l}
\text{the fraction of } \text{var}\{X_i(t)\} \text{ that is explained} \\
\text{by the fluctuations in the other } N-1 \text{ species} \end{array} \right\}. 
\]  
(48)
Logical consistency requires that $F_i \leq 1$, with $1 - F_i$ being the fraction of $\text{var}\{X_2(t)\}$ that is not explained by the fluctuations in the other species. That residual fraction $1 - F_i$ presumably must be attributed to fluctuations intrinsic to species $S_i$ itself.