Alternative formulations and moment estimates for the chemical Langevin equation

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Dissertation for transfer to DPhil student status

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Abstract

The chemical Langevin equation (CLE) is a multivariable Itô stochastic differential equation that describes the time evolution of molecular counts of reacting chemical species (Gillespie, 2000). It lies between the deterministic ordinary differential equation (ODE) model and the discrete probabilistic chemical master equation model in that it is continuous and probabilistic.

Suppose n chemical species react through m reaction channels, and the $n \times m$ stoichiometry matrix is denoted by S. Gillespie formulated the CLE with m independent standard Brownian motions. In the first half of this report we show that the same distribution of variables is given by an alternative formulation of the CLE which uses only $m - \dim(\operatorname{Ker} S) = n - \dim(\operatorname{Ker} S^T)$ Brownian motions, and this is minimal. However, this formulation is computationally too expensive for numerical simulation. We present a computationally tractable formulation which omits one independent Brownian motion for each pair of reversible reactions. If $\widetilde{m}$ is the number of pairs of reversible reactions, then in Gillespie's formulation there would be $2\widetilde{m}$ Brownian motions for the reversible reactions, while in our formulation there would only be $\widetilde{m}$.

In the second half of the report we discuss why all attempts to calculate the moments of the Itô process given by the CLE have so far been unsuccessful: we will give the ODEs that the first two moments satisfy and observe that to integrate them, information from higher moments is required. We propose an approximative computation which is based on the linearisation of the CLE. For such linear stochastic differential equations the ODEs for the moments can be integrated numerically. Accurate estimates of the first two moments are derived in two examples which support the validity of this new method.

Contents

1 Introduction

Mathematical modelling has become an indispensable tool for modern systems biology (Murray, 2003; Szallasi, Stelling, and Periwal, 2006). Simple qualitative descriptions are proving increasingly insufficient for understanding the intricate dynamical properties of microbiological phenomena. As a result, quantitative mathematical models are now routinely used in order to describe and analyse protein interactions (Cornish-Bowden, 2004), metabolic pathways (Heinrich and Schuster, 1996; Fell, 1997), the regulation of gene expression (Bower and Bolouri, 2004), and other biochemical processes.

Activities and the observed behaviour of cells mostly reflect ongoing intracellular biochemical processes. Therefore understanding the behaviour of microbes, or the subcellular basis of physiological processes of complex multicellular organisms is impossible without understanding the underlying biochemistry.

Throughout this report we will assume that we are given a fixed set of interacting molecular species, an exhaustive list of reactions with the corresponding *reaction propensities* (or *reaction intensities*) that may occur using and producing some of these species like in this example:

$$k_1\mathcal{S}_1 + \cdots + k_\alpha\mathcal{S}_\alpha \xrightarrow{k} \ell_1\mathcal{P}_1 + \cdots + \ell_\beta\mathcal{P}_\beta. \tag{1.0.1}$$

(Here $k_1, \ldots, k_\alpha, \ell_1, \ldots, \ell_\beta \in \mathbb{N}$. In this example $k \in]0, \infty[$ is just a *reaction rate constant* and we will give an explanation of it shortly. The set of species found on the left-hand side do not need to be disjoint from those on the right-hand side.) We want to understand the dynamics of how the concentrations (or counts) of molecules change in the closed system from their initial values as the listed reactions take place with their given intensities.

We will use the convention that in our models $n \geq 1$ chemical species $\{S_1, \ldots, S_n\}$ react through $m \geq 1$ reaction channels $\{R_1, \ldots, R_m\}$. All state vectors will be written as column vectors. To get a row vector from such a column vector, we will use the transposition symbol ^{T}. The state of the system at time t is described by either the vector of copy numbers of the molecular species, $X(t) = (X_1(t), \ldots, X_n(t))^T$ (or just $X_t = (X_{1,t}, \ldots, X_{n,t})^T$), or the vector of concentrations, $c(t) = (c_1(t), \ldots, c_n(t))^T$ (or $c_t = (c_{1,t}, \ldots, c_{n,t})^T$). X_t and c_t uniquely determine one another. The change in molecular counts corresponding to the different reaction channels is represented by the *stoichiometry matrix* $S \in \mathbb{Z}^{n\times m}$: a single firing of the jth reaction channel changes the count of the ith species by S_{ij}. The *propensity* (or *intensity*) function is denoted by $a(X) = (a_1(X), \ldots, a_m(X))^T$. Its interpretation is that in state X the probability of a single firing of reaction channel j in an infinitesimal time interval of length h is $a_j(X)h$. This can also be given as a function of concentrations, $\tilde{a}(c) = (\tilde{a}_1(c), \ldots, \tilde{a}_m(c))^T = a(X)$. The $m \times m$ diagonal matrix created from the coordinates of $a(X)$ will be denoted by $A(X) = \mathrm{diag}(a(X))$.

We will use the dot notation to select a column or a row of a matrix: for matrix S, $S_{\cdot j}$ is the n-dimensional column vector given by the entries of the jth column, whereas $S_{i\cdot}$ is the m-dimensional row vector given by the entries of the ith row.

Note that left nullvectors of S correspond to conservation laws in the reaction system, that is, to preserved linear combinations of different species' counts. Right nullvectors correspond to sequences of firings of reaction channels such that if starting in state X all reactions occur the number of times that is given by such a right nullvector, then the chemical system will eventually return to the original molecular counts X.

1.1 Frameworks for the mathematical modelling of biochemical reaction dynamics

Traditionally, mathematical modelling of reaction dynamics in chemistry and chemical engineering has relied on multivariable *ordinary differential equations* (ODEs). In a closed, well-stirred solution of fixed volume and constant temperature different chemical species can be modelled as continuous entities residing in the same spatial location. Then the system behaves as if the mass of reactants flowed through chemical reactions to be turned into mass of reaction products. The amount of these superposed entities and the changes thereof can be quantified by a vector of changing concentrations, each coordinate corresponding to one species. The ODEs used for these models are *autonomous*, that is, the rate of change of concentrations is a function of the current concentration, but not of the time variable.

The most widely used model of reaction kinetics is the *law of mass action* (Heinrich and Schuster, 1996). This law assumes that the intensity with which a reaction occurs is proportional to the concentrations of participating molecular species raised to the power of their respective molecularity. In full generality, if the the concentration of species $\mathcal{S}_i$ is denoted by $[\mathcal{S}_i]$, then the term corresponding to reaction (1.0.1) is

$$\tilde{a}(c) = k \prod_{i=1}^{\alpha} [\mathcal{S}_i]^{k_i}.$$

This term appears on the right-hand side of each ODE corresponding to a species which is involved in this reaction either as a reactant or a product: reactant $\mathcal{S}_i$ would have $-k_i\tilde{a}(c)$, whereas product $\mathcal{P}_j$ would have $+\ell_j\tilde{a}(c)$ in its describing ODE. It is often argued that in any chemical reaction at most two molecules react at a given time, that is, reactions are at most second-order (or can be replaced by successive second-order reactions). (Wilkinson, 2006)

In biochemistry, for modelling intracellular reactions one can look at cells as containers in which reactions occur in the cytoplasm as in any other solvent. This naturally leads to the transfer of the ODE framework to biochemical modelling.

One drawback of this framework is that by assuming well-stirredness the spatial structure of a cell is ignored. In reality there are molecules confined to certain locations (e.g. transmembrane proteins), and in eukaryotic cells, there is a complex internal membrane structure which hinders the free diffusion of solved molecules (Alberts *et al.*, 2002).

If we suppose that spatial structure does not play a role in the modelled processes, which we will do throughout this report, then another concern stems from the low copy number of molecules in a cell and how this affects the validity of ODE models (Wolkenhauer *et al.*, 2004). Certain proteins are present in a cell with copy numbers in the order of magnitude of hundreds or only dozens. Particular genes are usually present in even lower numbers. There has been a report (Brenner and Tomizawa, 1991) of an average level of only 3–11 unbound RNA II regulatory molecules of the ColE1 system present in a single *Escherichia coli* cell (7 nM concentration).* For such chemical species the assumption that their concentrations change continuously is clearly inaccurate. Moreover, any departure from the assumed, only hypothetical uniform spatial distribution of molecules will change which reactions occur and in what order. This causes divergence from the average relative intensities among different reaction channels, leading to fluctuations around the average overall concentrations of species. This inherent fluctuation in concentrations is called *intrinsic* (or *internal*) *noise*, to distinguish

*With an estimated cell volume of $0.6\text{–}2.7 \times 10^{-15}$ ℓ, 0.6–2.8 nM concentration corresponds to one molecule per cell. (Arkin *et al.*, 1998; Brenner and Tomizawa, 1991; Hayot and Jayaprakash, 2004; Santillán and Mackey, 2004; Wilkinson, 2006)

it from fluctuations caused by environmental changes and interference with other intracellular processes, collectively called *extrinsic* (or *external*) *noise* (Gillespie, 2000; Paulsson and Ehrenberg, 2001; van Kampen, 1992).

There is experimental evidence to show that stochastic fluctuations are a prevalent phenomenon in living cells. Elowitz and colleagues (Elowitz *et al.*, 2002) expressed cyan and yellow alleles of green fluorescent protein (gfp) controlled by identical promoters in *Escherichia coli* cells. Through microscopy imaging they compared the relative fluorescent levels of these two proteins in various experiments. They showed that at strong constitutive expression of both proteins both the relative difference between their fluorescence intensities and the overall cell-cell variation were low. On the other hand, in wild-type (*lacI*$^+$) *E. coli* strains, where the artificial lac-repressible promoters are repressed, the gfp expression fell to 3–6%, and both intrinsic and extrinsic noise rose approximately fivefold. (They defined the measure of noise as standard deviation divided by the mean.) With the addition of saturating amounts of the *lac* repressor inactivating isopropyl β-D-thiogalactopyranoside (IPTG), both internal and external noise and levels of fluorescent proteins returned to the levels observed in the first experiment. This and further experiments with different levels of added IPTG, and lac repressor expressed from plasmids or by the synthetic oscillatory network, the Repressilator (Elowitz and Leibler, 2000), prove that noise increase in the wild-type strain is directly correlated to higher repressor concentration.

The golden standard in stochastic chemical reaction network modelling is the *chemical master equation* (CME), pioneered in the 1960s (McQuarrie, 1967) and 1970s (Gillespie, 1976, 1977), and from a physical model that uses colliding spheres to represent interacting molecules, rigorously derived in the early 1990s (Gillespie, 1992). As its starting assumptions are very general (and are assumed in almost every analogous modelling framework, e.g. in the ODE framework);

- the chemically reacting system is gas-phase[†], in a container of constant volume,
- it is well stirred, that is, it is spatially homogeneous with random fluctuations; the position of a randomly selected molecule is a uniformly distributed random variable,
- it is in thermal equilibrium, that is, at a constant absolute temperature; the velocity of a randomly selected molecule follows the Maxwell–Boltzmann distribution with a fixed temperature;

the result is widely applicable (as widely, say, as the ODE framework).

Given an initial state $X(t_0) = X_0$ of the state variable $X = (X_1, \ldots, X_n)^T \in \mathbb{N}^n$, and using the standard o notation for an unspecified one-variable real-valued function for which $\lim_{h\to 0} o(h)/h = 0$, a well-known argument from the theory of Poisson processes yields

$$\begin{aligned}\mathrm{P}(X, t+h \mid X_0, t_0) = \mathrm{P}(X, t \mid X_0, t_0) \left(1 - \sum_{j=1}^{m} a_j(X)h + o(h)\right) \\ + \sum_{j=1}^{m} \mathrm{P}(X - S_{\cdot j}, t \mid X_0, t_0)\big(a_j(X - S_{\cdot j})h + o(h)\big) + o(h)\end{aligned}$$

(Feller, 1957; Karlin, 1966). This says that the event that the system is in X some infinitesimal time h after time t is the disjoint union of two kinds of events. One is that the system was in

[†]It is generally accepted that without this assumption the results would still hold with new rate coefficients.

X at t and then no reaction occurred in the interval up to $t + h$ (plus an event with a small probability that the state left X and then returned again). The other is that the system was in another state at t, but jumped into state X by a single firing of a reaction channel (plus an event with a small probability that this transition took more than one jump, and there is a further event with a small probability that the state jumped to X from a state which is not of the form $X - S_{\cdot j}$). Simple algebraic rearrangement and passage to the limit $h \to 0$ gives the *chemical master equation*:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{P}(X, t \mid X_0, t_0) = -\sum_{j=1}^{m} \mathrm{P}(X, t \mid X_0, t_0) a_j(X) + \sum_{j=1}^{m} \mathrm{P}(X - S_{\cdot j}, t \mid X_0, t_0) a_j(X - S_{\cdot j}).$$

This CME is a *forward equation* that describes the distribution of a continuous time, discrete space Markov process. It is a system of ODEs where variables are probabilities. For each X there is an equation which gives the time evolution of the probability that at time t there are X_i S_i molecules present in the system for all i, given their initial values (or their initial probability distributions) at time $t_0 \leq t$. This system of ODEs is linear, but unfortunately it may be infinite: this typically occurs if one assumes an unlimited source of basic molecules, an influx of metabolites, or, for example, the constitutive expression of a gene. In such cases there is no upper bound for some of the individual X_i values. Even if all variables are upper bounded, due to the large number of equations, the numerical solution of the CME is computationally very challenging.

The two papers by Gillespie (1976, 1977) considered sampling from this distribution instead of solving the CME. Gillespie's method, the *Stochastic Simulation Algorithm* (SSA) is easy to implement, and has become a very popular computational tool. To simulate the evolution of a chemical system from an initial state over a fixed time interval, in each step one draws a random waiting time until the next reaction and which reaction will occur is also chosen randomly. Then one updates the state according to how this reaction changes molecular counts, and starts over again. This repeated draw of reactions ends once the cumulative sum of waiting times surpasses the time horizon of the simulation.

The underlying assumption is that at time t the time until the first firing of any reaction channel R_j is an exponential random variable with rate $a_j(X(t))$, independent from the other waiting times. Once the smallest waiting time is passed, the corresponding reaction occurs instantaneously. As this changes the molecular counts, the intensities have to be updated, and the waiting times resampled. In practice, one samples from an exponential distribution with parameter $\sum_{j=1}^{m} a_j(X(t))$ to get the waiting time τ, and then draws independently a random variable which tells them which reaction occurs: reaction R_k occurs with probability $a_k(X(t)) / \sum_{j=1}^{m} a_j(X(t))$. If R_k is drawn indeed as above, then the new state is $X(t + \tau) = X(t) + S_{\cdot k}$.

Many studies which rely on stochastic biochemical models do not go any further than generating many realisations of the Markov process by the SSA (or by some improved descendant of it), and analysing the empirical distribution of molecular counts (Barkai and Leibler, 2000; Gonze, Halloy, and Goldbeter, 2002). The bottleneck in applications of this method is the computational cost of repeated pathwise simulations. There is a palpable shortage of methodologies to mathematically analyse the discrete space Markov process describing the time evolution of chemical processes. The problem with finite samples from simulations is that they can never be evidence that the distribution is wholly explored and no rare events (maybe with substantial negative effects on the living biochemical system) evade our attention. Another challenge, which also arises in the ODE framework but is even more pronounced here, is inference that is robust to parameter uncertainty.

Ball, Kurtz, Popovic, and Rempala (2006) pioneered an asymptotic analysis of approximations to the reaction system dynamics. They formulated equations, which basically described the SSA, and carried out rigorous model reduction through admittedly somewhat *ad hoc* scaling. This scaling is used to balance the discrepancies in the population counts of interacting molecular species and the different time scales in which different reactions take place. Due to the very technical, mathematically advanced nature of these methodological developments, the impact of the paper is very limited outside a specialist community. More work is needed to develop this approach into an accessible methodology for the wider system biologist community.

There is an intermediate regime between the deterministic, continuous ODE regime and the stochastic, discrete Markov process regime (which includes the equivalent CME, the SSA, and Kurtz's and co-workers' equations with Poisson processes). This is a stochastic but continuous modelling framework with stochastic differential equations (SDEs), the so-called *chemical Langevin equation* (CLE) (Gillespie, 2000). This regime corresponds to a physical system with not too low but not too high molecular copy numbers. Mathematically it can also be seen as a diffusion approximation to the discrete Markov model.

1.2 Gillespie's chemical Langevin equation

Gillespie (2000) set out to approximate the distribution of the discrete Markov process of molecular counts by making two simplifying assumptions. His argument went like this.

If at time t the chemical system is in state $X(t)$, and the random variable $K_j(X, h)$ is the number of times reaction R_j occurs in a time interval of length h if the system is released from state X, then after h time has passed, the system will be in state

$$X(t+h) = X(t) + \sum_{j=1}^{m} K_j(X(t), h) S_{\cdot j}. \tag{1.2.1}$$

Now assume *Condition 1* holds: h is small enough that the change in the state during $[t, t+h]$ will be so small that none of the propensity functions a_j changes substantially,

$$a_j(X(s)) \approx a_j(X(t)), \quad \text{for all } s \in [t, t+h].$$

In any reaction typically no molecular count changes by more than two. Hence this condition can be satisfied if the expected number of firings of a reaction channel is much smaller than the population of the least populous species. This requirement can always be met if all molecular populations are sufficiently large. The assumption that the propensities remain approximately constant in the time interval implies that the random variables $K_1(X(t), h), \ldots, K_m(X(t), h)$ are independent, and $K_j(X(t), h)$ is Poisson distributed with parameter $a_j(X(t))h$ for all j.

Then he stipulated *Condition 2*: h is large enough that the expected number of firings for each reaction channel R_j, namely

$$\mathrm{E}\big(K_j(X(t), h)\big) = a_j(X(t))h,$$

is much larger than 1. This obviously runs counter to Condition 1. In cases where the two cannot be met simultaneously, Gillespie's approximation will fail. But large molecular populations help to satisfy this condition, just as with the previous one. In this case the Poisson random variable $K_j(X(t), h)$ is well approximated by a random variable from the normal distribution with matching mean and variance,

$$\mathcal{N}\big(a_j(X(t))h,\ a_j(X(t))h\big).$$

(Here we use the standard notation $\mathcal{N}(\mu, \sigma^2)$ for a normal distribution with mean μ and variance σ^2.) Thus the independent, discrete Poisson random variables are replaced by the same number of independent but continuous normal random variables. It is well known that this distribution is a transformed standard normal distribution:

$$\mathcal{N}\big(a_j(X(t))h,\ a_j(X(t))h\big)\ \sim\ a_j(X(t))h + \sqrt{a_j(X(t))h}\,\mathcal{N}(0,1).$$

Substituting these approximations, (1.2.1) takes the form

$$X(t+h) = X(t) + \sum_{j=1}^{m} a_j(X(t))h\, S_{\cdot j} + \sum_{j=1}^{m} \sqrt{a_j(X(t))h}\, S_{\cdot j} N_j \tag{1.2.2}$$

with independent standard normal random variables $N_1, \ldots, N_m$. Here we keep t fixed and ignore the dependence of N_j on t. One should now recall the notion of *Brownian motion*, or *Wiener process*, which is an almost surely continuous, real-valued, one-dimensional stochastic process starting from zero, with independent increments following normal distribution: for $0 \le t_0 \le t_1$, $B(t_1) - B(t_0) \sim \sqrt{t_1 - t_0}\,\mathcal{N}(0,1)$. Then clearly (1.2.2) is nothing else but an n-variable Itô stochastic differential equation (Øksendal, 2007)

$$\mathrm{d}X(t) = \sum_{j=1}^{m} a_j(X(t))\, S_{\cdot j}\, \mathrm{d}t + \sum_{j=1}^{m} \sqrt{a_j(X(t))}\, S_{\cdot j}\, \mathrm{d}B_j(t),$$

which we call the *chemical Langevin equation*.

We have seen that in Gillespie's derivation two approximative steps facilitated by two assumptions lead to an Itô SDE model.

1.3 Alternative formulations of the chemical Langevin equation: model reduction, alternative physical interpretations

Now that the background is sketched, in the forthcoming two sections a quick overview of the main contents of this report is given.

Through a second-order Taylor series expansion of the propensity functions a_j, the CME can be used to derive ODEs giving the first and second moments of the state variable, $\mathrm{E}(X_t)$ and $\mathrm{E}(X_t X_t^T)$ (van Kampen, 1992; Tomioka, Kimura, Kobayashi, and Aihara, 2004). The approximation is in fact exact when the law of mass action dynamics is assumed and all reactions are at most second-order. (That is, at most two molecules interact in any reaction channel.) Kevin Burrage proposed that this should impose a constraint on the CLE: Gillespie's derivation of the CLE can be correct only insofar as the first two moments of its solution match those of the CME (personal communication).

This requirement gives that the simplest way for an n-variable stochastic differential equation

$$\mathrm{d}X_t = f(X_t)\,\mathrm{d}t + g(X_t)\,\mathrm{d}B_t$$

to be a valid chemical Langevin equation is to have

$$f(x) = Sa(x),$$

exactly as in Gillespie's CLE, and (recall the notation $A(x) = \mathrm{diag}(a(x))$)

$$g(x)g(x)^T = SA(x)S^T. \tag{1.3.1}$$

In fact equality is not required pointwise, only in L_1 for each t. Konstantinos Zygalakis observed that Gillespie's diffusion term satisfies this condition (personal communication). However, with this approach there are infinitely many parameterisations of the CLE, infinitely many functions g for which (1.3.1) holds.

If we pick some g^1 and g^2 which both satisfy (1.3.1), then the corresponding Itô diffusions must have identical first and second moments because they are both equal to those derived from the CME. In fact, a simple argument proves that not only the first two moments, but the full finite-dimensional distributions of these Itô diffusion processes will be identical. Therefore different g solutions to (1.3.1) will give equally valid CLEs (in the weak sense probabilistically), and Gillespie's CLE is just one possible parameterisation.

One can ask the question what the minimum size solution is to the square root problem (1.3.1). The g with the minimum number of columns gives a CLE with the minimum number of independent Brownian motions. One finds that this number is $n - \dim(\mathrm{Ker}\, S^T)$. This is equal to $m - \dim(\mathrm{Ker}\, S)$, always less than or equal to m, the value given by Gillespie's argument. Theoretically this is minimal: we give two different constructions for g and also prove that it cannot be further improved. The physical interpretation of this result is intriguing: it is enough to use this many independent noise variables to describe the moments of the Itô diffusion process that matches the first two moments of the solution to the CME.

Another question is the practical use of this minimality result. For instance, is the minimum size construction able to speed up a pathwise numerical simulation scheme for the CLE? The minimal construction needs an eigendecomposition of $SA(X)S^T$ for each time step, which is computationally very costly. Following ideas of Tomioka *et al.* (2004) there is a construction with as many Brownian motions as lines given by the directions of the stoichiometry vectors (the columns of the stoichiometry matrix). The computations only require taking the square root of scalars and matrix multiplication. The most obvious application of this formulation is that it requires one independent Brownian motion for a pair of reversible reactions, which may be considered as a more natural description than one Brownian motion for each reaction channel. It is still an open question if there are smaller but computationally equally expensive or just slightly more expensive formulations.

The computationally fastest formulation will depend on the cost of random number generation versus the cost of floating point operations, as well as the size and structure of the stoichiometry matrix. Burrage, Mélykúti, and Zygalakis (2009) will present computational benchmarking of the different constructions alongside the theory that is also presented in this work. The three examples used for the benchmarking will also be discussed here to demonstrate these reduction techniques. The authors are not aware of other studies in this direction. To their knowledge this is the first time alternative forms of the CLE are proposed.

1.4 Moment estimation: the moment closure problem and estimation based on linearisation

It has been mentioned that the first two moments of the chemical Langevin equation are approximately equal to those of the chemical master equation, or the equivalent SSA. The approximation is actually exact when the law of mass action dynamics is assumed and all reactions R_j are at most second-order. As it has already been pointed out, most studies infer these via sampling from the distribution. This is achieved by repeated simulations with the SSA. In the second half of this report we investigate the moments of the state variables in the chemical Langevin equation. This calculation is lesser-known than the derivation of moments for the CME and therefore it will be discussed in detail (Lemma 2.0.1). To get the moments of

the CME one can multiply each equation with a fixed monomial of the state vector coordinates and sum these for all states. It is not difficult to see that this will give an ODE for the time evolution of any given moment.

We will arrive at this observation through the application of Itô's formula. Either way, one can see that the time derivative of a state variable mean is a function of the means of propensity functions. Except for the simplest case when all reactions are at most first-order (each reaction R_j has at most a single molecule as its reactant), the propensities (under the law of mass action) are at least second-order polynomials of the state variables. Let us assume for simplicity that the reactions are at most second-order, in which case there will be polynomials of degree two. Their mean is not an information that can be read out from this equation. For that one needs the ODE for the time evolution of the second moments, which will be dependent on third (for at most second-order reactions) or higher moments (in the general case). This goes on *ad infinitum*; to specify the ODE of any moment the knowledge of higher moments is needed. How to close this open lattice of interdependent problems, or generally, that of any nonlinear stochastic system is called the *moment closure problem* and its solution is unknown. Only approximations are available, especially for one-variable problems.

The author proposes the approximation of the CLE by its linearisation driven by the observation that for linear SDEs the describing ODEs of the moments are self-contained and thus can be numerically integrated. We expect this approximation to be valid in steady states of the deterministic ODE model of the chemical system. To assess the validity of this approach we compare the prediction based on this linearisation to moments of the empirical distributions from simulations of the SSA, the CLE and the linearised CLE in two examples. We find that the linearisation technique gives a good estimate of the first two moments in our examples at a fraction of the computational cost of stochastic simulations.

This report will be concluded by outlining the proposed direction of future research.

2 Alternative formulations of the chemical Langevin equation: model reduction, alternative physical interpretations

In order to motivate the investigations of this section, we revise well-known facts about the CME, which we treat as our reference stochastic model. The time evolution of the first moment of the state variable of the CME is given by the ordinary differential equation

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{E}\big(X_t\big) = S\mathrm{E}\big(a(X_t)\big), \tag{2.0.1}$$

whereas the time evolution of the second moment is well approximated by

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{E}\big(X_t X_t^T\big) = \mathrm{E}\big(h(X_t)X_t^T\big) + \mathrm{E}\big(X_t h(X_t)^T\big) + \mathrm{E}\big(B(X_t)\big), \tag{2.0.2}$$

where $h(x) = Sa(x)$, and the diffusion matrix $B(x)$ is defined as

$$B(x) = S\,\mathrm{diag}(a(x))S^T$$

(van Kampen, 1992; Tomioka *et al.*, 2004). It has already been mentioned in the Introduction that this approximation is based on a second-order truncation of the Taylor expansion of the propensity function. Under the law of mass action when all reactions are at most second-order the approximation is actually exact.

The main goal of Section 2 is to explore the different possibilities of how the stochastic process solution of the CME can be approximated by a multi-dimensional Itô diffusion process given by a stochastic differential equation. We aim for a weak approximation, in other words, a diffusion process of which the distribution at each time instance approximates that of the distribution given by the CME. In particular, we design the diffusion process such that its first two moments match those of the solution to the CME.

Formally, we seek $f:\ [0,\infty[^n \to \mathbb{R}^n$ and $g:\ [0,\infty[^n \to \mathbb{R}^{n\times d}$ such that the solution to

$$\mathrm{d}X_t = f(X_t)\,\mathrm{d}t + g(X_t)\,\mathrm{d}B_t, \tag{2.0.3}$$

with d-dimensional standard Brownian motion B, has its first two moments given in (2.0.1), (2.0.2). This problem has been touched upon, for instance, by Wilkinson (2006) but has not been explored in depth.

Notice that satisfying (2.0.1) is trivial. One takes the expectation on both sides of (2.0.3) to get

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{E}\big(X_t\big) = \mathrm{E}\big(f(X_t)\big).$$

Comparing this to (2.0.1) gives f:

$$f(x) = Sa(x).$$

Although this solution is not unique, this is the simplest choice (not only for matching the first moments but also for the second moments as we will see shortly). We now need to calculate the second moment for X_t from (2.0.3) and in order to do this it is enough to calculate $\mathrm{E}(X_{i,t}X_{k,t})$ for $i,k \in \{1,\dots,n\}$. For the ease of notation we will often drop the time variable t from X_t in the following calculations.

Lemma 2.0.1. *For equation* (2.0.3)*,*

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{E}\big(X_{i,t}X_{k,t}\big) = \mathrm{E}\big(f_i(X_t)X_{k,t}\big) + \mathrm{E}\big(X_{i,t}f_k(X_t)\big) + \sum_{j=1}^{d}\mathrm{E}\big(g_{ij}(X_t)g_{kj}(X_t)\big). \tag{2.0.4}$$

Proof. We apply the multi-dimensional Itô's formula. This claims that when substituting time t and a diffusion process X_t into a function $u(t,x):\ \mathbb{R}\times\mathbb{R}^n \to \mathbb{R}$, then

$$\mathrm{d}u(t,X_t) = \frac{\mathrm{d}u(t,X_t)}{\mathrm{d}t} + \sum_{i=1}^{n}\frac{\partial u(t,X_t)}{\partial x_i}\,\mathrm{d}X_{i,t} + \frac{1}{2}\sum_{i,j=1}^{n}\frac{\partial^2 u(t,X_t)}{\partial x_i \partial x_j}\,\mathrm{d}X_{i,t}\,\mathrm{d}X_{j,t}$$

holds, where the rules for computing $\mathrm{d}X_{i,t}\,\mathrm{d}X_{j,t}$ are $\mathrm{d}t\,\mathrm{d}t = \mathrm{d}t\,\mathrm{d}B_{j,t} = \mathrm{d}B_{j,t}\,\mathrm{d}t = 0$, $\mathrm{d}B_{j,t}\,\mathrm{d}B_{j',t} = \delta_{jj'}\,\mathrm{d}t$ (Kronecker delta). (One can find more details about Itô's formula in numerous standard textbooks, e.g. Øksendal (2007).) Let us apply the formula with $u(t,x) = x_i x_k$.

$$\begin{aligned}
\mathrm{d}(X_iX_k) &= 0 + (X_k\,\mathrm{d}X_i + X_i\,\mathrm{d}X_k) + \frac{1}{2}\,(\mathrm{d}X_i\,\mathrm{d}X_k + \mathrm{d}X_k\,\mathrm{d}X_i)\\
&= (X_k\,\mathrm{d}X_i + X_i\,\mathrm{d}X_k)\\
&\quad + \frac{1}{2}\,2\left(f_i(X)\,\mathrm{d}t + \sum_{j=1}^{d} g_{ij}(X)\,\mathrm{d}B_{j,t}\right)\left(f_k(X)\,\mathrm{d}t + \sum_{j'=1}^{d} g_{kj'}(X)\,\mathrm{d}B_{j',t}\right)\\
&= (X_k\,\mathrm{d}X_i + X_i\,\mathrm{d}X_k) + \sum_{j=1}^{d}\sum_{j'=1}^{d} g_{ij}(X)g_{kj'}(X)\,\mathrm{d}B_{j,t}\,\mathrm{d}B_{j',t}
\end{aligned}$$

$$= \left(X_k f_i(X)\,\mathrm{d}t + X_k \sum_{j=1}^{d} g_{ij}(X)\,\mathrm{d}B_{j,t} + X_i f_k(X)\,\mathrm{d}t + X_i \sum_{j=1}^{d} g_{kj}(X)\,\mathrm{d}B_{j,t} \right) + \sum_{j=1}^{d} g_{ij}(X) g_{kj}(X)\,\mathrm{d}t.$$

Taking the expectation on both sides yields

$$\mathrm{dE}\big(X_i X_k\big) = \mathrm{E}\big(X_k f_i(X)\big)\,\mathrm{d}t + \mathrm{E}\big(X_i f_k(X)\big)\,\mathrm{d}t + \sum_{j=1}^{d} \mathrm{E}\big(g_{ij}(X) g_{kj}(X)\big)\,\mathrm{d}t,$$

which is just another form of (2.0.4). □

If one compares (2.0.4) with (2.0.2), it is seen that enforcing

$$\sum_{j=1}^{d} g_{ij}(x) g_{kj}(x) = B_{ik}(x)$$

for all i and k is the most natural choice in order that the second moments match, which is just (1.3.1),

$$g(x)g(x)^T = S\,\mathrm{diag}(a(x))S^T.$$

Corollary 2.0.2. *Any $g : \mathbb{R}^n \to \mathbb{R}^{n\times d}$ for which* (1.3.1) *holds will give a chemical Langevin equation*

$$\mathrm{d}X_t = Sa(X_t)\,\mathrm{d}t + g(X_t)\,\mathrm{d}B_t \tag{2.0.5}$$

(B is d-dimensional standard Brownian motion) of which for every t the solution X_t has its first two moments evolving exactly as what the approximation gave for the chemical master equation, (2.0.1) *and* (2.0.2)*.*

Before exploring the set of solutions g, first note this insight.

Lemma 2.0.3. *Different solutions g in Corollary 2.0.2 all give chemical Langevin equations which have the same finite-dimensional distributions. (In different terminology: which coincide in law.)*

This means that although Corollary 2.0.2 allows for different gs to result in CLEs of which only the first two moments are the same, in fact, all their moments will be identical.

Proof. This can be easily derived by applying Theorem 8.4.3 of Øksendal (2007), but we give a direct proof. We will, however, assume previous knowledge of a standard tool, the Kolmogorov forward equation (Øksendal, 2007). For the solution g of (2.0.5), the probability distribution function $p_t(X_0, X)$ of a transition from X_0 to X in a time interval of length t evolves according to the partial differential equation

$$\frac{\mathrm{d}p_t(X_0, X)}{\mathrm{d}t} = -\sum_{i=1}^{n} \frac{\partial\big(p_t(X_0, X)(Sa(X))_i\big)}{\partial X_i} + \frac{1}{2}\sum_{i,k=1}^{n} \frac{\partial^2\big(p_t(X_0, X)(g(X)g(X)^T)_{ik}\big)}{\partial X_i \partial X_k}.$$

$p_t(X_0, X)$ evolves identically for all solutions g to (2.0.5), because $p_0(X_0, X) = \delta_{X_0}(X)$ (the Dirac delta function at X_0) does not depend on g, and the parameters in the Kolmogorov forward equation $Sa(X)$ and $g(X)g(X)^T = B(X)$ are identical for any g. □

2.1 Gillespie's original solution

Construction 1. *Using the physical and probabilistic assumptions discussed in Section 1.2, in his seminal paper Gillespie (2000) derived that g is of the form*

$$g(X) = S \operatorname{diag}(\sqrt{a_1(X)}, \ldots, \sqrt{a_m(X)}).$$

This is trivially a special case of (1.3.1) with $d = m$. Here every independent Brownian motion corresponds to one reaction channel. Hence the physical interpretation of this model is quite clear. Every variable is forced by as many Brownian motions as there are reaction channels which change its count.

Gillespie himself mentioned (Gillespie, 2000) that this is not the only possible formulation, and other formulations with differing numbers of Brownian motions are conceivable. He referred to his former work (Gillespie, 1996), where equations were laid down which if satisfied by both a g^1 and a g^2 then the two Langevin equations with either g^1 or g^2 would have increments with identical distributions. This is analogous to our Lemma 2.0.3.

2.2 The minimal solution

In this part we are exploring different natural choices for the formulation of the CLE and hence for the choice of d. A natural question is what is the minimum number of Brownian motions in the CLE (2.0.5), or equivalently, what is the minimum d for which the factorisation of

$$B(X) = SA(X)S^T$$

in (1.3.1) is possible.

As $B(X)$ is a symmetric square matrix for all X, it can be diagonalised by a change of basis with an orthonormal matrix $U(X)$ of which the columns are eigenvectors of $B(X)$:

$$B(X) = U(X)D(X)U(X)^T. \tag{2.2.1}$$

Let us partition the eigenvectors based on whether they belong to zero eigenvalue ($U_0(X)$) or some nonzero eigenvalue ($U_1(X)$) and arrange them such that $U(X) = [U_1(X)\ U_0(X)]$. Then there are $n - \dim(\operatorname{Ker} B(X))$ nonzero eigenvalues, so $D(X)$ is of the form

$$D(X) = \begin{bmatrix} D_1(X) & 0 \\ 0 & 0 \end{bmatrix}$$

with a diagonal $D_1(X) \in \mathbb{R}^{(n-\dim(\operatorname{Ker} B(X)))\times(n-\dim(\operatorname{Ker} B(X)))}$.

The construction for $g(X)$ is then

$$g(X) = U(X)D(X)^{1/2} = [U_1(X)D_1(X)^{1/2} \quad 0],$$

or simply $g(X) = U_1(X)D_1(X)^{1/2} \in \mathbb{R}^{n\times(n-\dim(\operatorname{Ker} B(X)))}$. Indeed,

$$g(X)g(X)^T = U(X)D(X)^{1/2}D(X)^{1/2}U(X)^T = B(X).$$

This formulation shows that $n-\dim(\operatorname{Ker} B(X))$ Brownian motions are enough to define (2.0.5).

This factorisation is minimal indeed, since the rank of $g(X)$ cannot be less than the rank of $B(X) = g(X)g(X)^T$, that is, $n - \dim(\operatorname{Ker} B(X))$.

In order to avoid digression the proofs of the next two lemmas are found in the Appendix.

Lemma 2.2.1. *For every strictly positive X (it is enough that for all X and each reaction channel j, $a_j(X) > 0$ holds),* $\dim(\operatorname{Ker} B(X))$ *is equal to the number of linearly independent conservation laws of the reaction network,* $\dim(\operatorname{Ker} S^T)$*. In fact, a vector $y \in \mathbb{R}^n \setminus \{0\}$ is a (right) nullvector of $B(X)$ if and only if it is a left nullvector of the stoichiometry matrix S.*

The following lemma explains when and by how much this construction decreases the number of Brownian motions compared to the m of Gillespie's construction.

Lemma 2.2.2. $n - \dim(\operatorname{Ker} S^T) = m - \dim(\operatorname{Ker} S)$.

We summarise the results of this section.

Construction 2. *The previously described*

$$g(X) = U_1(X)D_1(X)^{1/2}$$

gives a chemical Langevin equation (2.0.5) *with* $n-\dim(\operatorname{Ker} S^T) = m-\dim(\operatorname{Ker} S)$ *independent standard Brownian motions. Any CLE requires at least this many Brownian motions.*

Note that Gillespie (2000) (Appendix B) and Wilkinson (2006) (p 189) are both inaccurate when claiming that generally the number of Brownian motions d must be no less than n. We will return to the problem of state space reduction where we prove that there is an equivalent formulation of the CLE with $n - \dim(\operatorname{Ker} S^T)$ states, and as we see here, $n - \dim(\operatorname{Ker} S^T)$ Brownian motions (Section 2.4).

The minimum number of Brownian motions needed is interesting for efficient numerical simulation. Notice that the solution in Construction 2 is not satisfactory since U_1 is dependent on X. Hence in a numerical simulation scheme for each time step a new diagonalisation of $B(X)$ is required, which is computationally expensive.

As a first improvement, we propose another approach which results in a g of the same size, but potentially decreases the requirement for repeated computation at the cost of increased initial, one-off computation. A substantially different construction will be presented in the next section (Construction 4).

Let $W = [W_1\ W_0] \in \mathbb{R}^{n\times n}$ be an orthogonal matrix such that the columns of $W_0 \in \mathbb{R}^{n\times\dim(\operatorname{Ker} S^T)}$ form an orthonormal basis in the left nullspace of S, $\operatorname{Ker} S^T$, and the columns of $W_1 \in \mathbb{R}^{n\times(n-\dim(\operatorname{Ker} S^T))}$ are an othonormal basis in the orthogonal complement, $\operatorname{Im} S$. Let us define the *square root* $\bar{M} = \sqrt{M}$ of a square matrix $M \in \mathbb{R}^{k\times k}$ as any square matrix $\bar{M} \in \mathbb{R}^{k\times k}$ such that $\bar{M}\bar{M}^T = M$, if such an $\bar{M}$ exists.

Construction 3.

$$g(X) = W_1\sqrt{W_1^T S A(X) S^T W_1}$$

gives a chemical Langevin equation (2.0.5) *with* $n-\dim(\operatorname{Ker} S^T) = m-\dim(\operatorname{Ker} S)$ *independent standard Brownian motions.*

Proof. We verify that $\hat{g}(X) = W\sqrt{W^T S A(X) S^T W}$ is a valid diffusion term (it satisfies (1.3.1)) and that the stated g is equivalent to $\hat{g}$. Note that $W^T S A(X) S^T W$ and $W_1^T S A(X) S^T W_1$ are symmetric positive semidefinite matrices, therefore their square root can be taken the way it was done with $B(X)$ earlier in this section.

$$\hat{g}(X)\hat{g}(X)^T = WW^T S A(X) S^T WW^T = S A(X) S^T$$

since W is orthogonal, so (1.3.1) is satisfied. Also,

$$W^T S A(X) S^T W = \begin{bmatrix} W_1^T S \\ 0 \end{bmatrix} A(X) \begin{bmatrix} S^T W_1 & 0 \end{bmatrix}$$
$$= \begin{bmatrix} W_1^T S A(X) S^T W_1 & 0 \\ 0 & 0 \end{bmatrix}$$

shows that it is enough to use the top left block with $W_1^T S A(X) S^T W_1$: on the right the last $\dim(\operatorname{Ker} S^T)$ Brownian motions, on the left the columns of W_0 would be multiplied by zeros. □

This is an improvement over Construction 2 in that here the square root of a state-dependent $(n - \dim(\operatorname{Ker} S^T)) \times (n - \dim(\operatorname{Ker} S^T))$ matrix is taken instead of an $n \times n$ matrix.

2.3 A general, state-independent, *'small'* (as opposed to minimal) solution

In the previous section a practical constraint for numerical simulations was discussed. Constructions which require in each time step an eigendecomposition of a state-dependent matrix are computationally too costly. In the following we develop a construction in which to compute $g(X)$ only matrix products and taking the square root of a state-dependent diagonal matrix are required. This construction will give a CLE which generally may need more than $n - \dim(\operatorname{Ker} S^T) = m - \dim(\operatorname{Ker} S)$ independent standard Brownian motions, but certainly not more than m.

For a positive integer k, let I_k denote the $k \times k$ identity matrix. We say two nonzero vectors $y_1, y_2 \in \mathbb{R}^n \setminus \{0\}$ represent the same *direction*, if there is a $\lambda \in \mathbb{R} \setminus \{0\}$ such that $y_1 = \lambda y_2$.

Construction 4. *Let s be the number of different directions given by the columns of S. There exist matrices $J \in \mathbb{R}^{m \times s}$ and $V \in \mathbb{R}^{s \times m}$ such that $VA(X)V^T \in \mathbb{R}^{s \times s}$ is diagonal with only nonnegative entries and*

$$g(X) = SJ\sqrt{VA(X)V^T} \tag{2.3.1}$$

gives a chemical Langevin equation (2.0.5) *with s independent standard Brownian motions, $m - \dim(\operatorname{Ker} S) \leq s \leq m$.*

Proof. Let us permute the columns of $S \in \mathbb{R}^{n \times m}$ such that we have $S = [S_1 \ S_2]$, where $S_1 \in \mathbb{R}^{n \times s}$ has one representative column vector for each direction given by the columns of S. Then the columns that are left (S_2) are each a constant multiple of one column in S_1. One has to permute the entries of $A(X)$ accordingly.

Let

$$S_2 = [S_1 v^{(1)} \ \dots \ S_1 v^{(m-s)}],$$

where for all i, $v^{(i)} \in \mathbb{R}^s$ has one nonzero entry.

Introducing $M = [v^{(1)} \ \dots \ v^{(m-s)}] \in \mathbb{R}^{s \times (m-s)}$, the definitions are

$$J = \begin{bmatrix} I_s \\ 0 \end{bmatrix} \in \mathbb{R}^{m \times s},$$
$$V = \begin{bmatrix} I_s & M \end{bmatrix} \in \mathbb{R}^{s \times m}.$$

First, partitioning $A(X)$ according to the sizes of blocks of V,

$$\begin{aligned} VA(X)V^T &= \begin{bmatrix} I_s & M \end{bmatrix} \begin{bmatrix} A_1(X) & 0 \\ 0 & A_2(X) \end{bmatrix} \begin{bmatrix} I_s \\ M^T \end{bmatrix} \\ &= A_1(X) + MA_2(X)M^T \\ &= A_1(X) + \sum_{j=1}^{m-s} (A_2(X))_{jj} v^{(j)} v^{(j)^T}, \end{aligned}$$

where the last step follows from

$$(MA_2(X)M^T)_{ik} = \sum_{j=1}^{m-s} (v^{(j)})_i (A_2(X))_{jj} (v^{(j)})_k^T.$$

Since $v^{(j)}$ have only one nonzero entry for all j, $\sum_{j=1}^{m-s} (A_2(X))_{jj} v^{(j)} v^{(j)^T}$ is diagonal with only nonnegative entries, and consequently $VA(X)V^T$ too.

Secondly,

$$SJV = [S_1 \ S_2] \begin{bmatrix} I_s & M \\ 0 & 0 \end{bmatrix} = [S_1 \quad S_1 M] = [S_1 \ S_2] = S.$$

Hence $\sqrt{VA(X)V^T}$ exists trivially, and

$$\begin{aligned} g(X)g(X)^T &= SJ\sqrt{VA(X)V^T} \left(SJ\sqrt{VA(X)V^T} \right)^T \\ &= SJVA(X)V^T J^T S^T = SA(X)S^T \end{aligned}$$

so (1.3.1) is satisfied. The actual form of g is

$$\begin{aligned} g(X) &= [S_1 \ S_2] \begin{bmatrix} \sqrt{A_1(X) + MA_2(X)M^T} \\ 0 \end{bmatrix} \\ &= S_1 \sqrt{A_1(X) + MA_2(X)M^T} = S_1 \sqrt{A_1(X) + \sum_{j=1}^{m-s} (A_2(X))_{jj} v^{(j)} v^{(j)^T}}. \end{aligned}$$

□

Corollary 2.3.1. *There is a formulation of the chemical Langevin equation* (2.0.5) *which is constructed from Gillespie's original CLE by omitting one independent Brownian motion for each pair of reversible reactions and assigning to the retained Brownian motion either respective stoichiometry vector multiplied by the square root of the sum of the two propensities and which is computationally inexpensive to numerically simulate. If $\tilde{m}$ is the number of pairs of reversible reactions, then in Gillespie's formulation there would be $2\tilde{m}$ Brownian motions for the reversible reactions, while in this formulation there would only be $\tilde{m}$.*

In fact, the result is slightly more general than what Corollary 2.3.1 claims. Consider chemical systems with reactions

$$\left.\begin{array}{rcl} A + B & \longrightarrow & C \\ 2C & \longrightarrow & 2A + 2B \end{array}\right\}, \qquad \text{or} \qquad \left.\begin{array}{rcl} A & \xrightarrow{k_1} & B \\ 2A & \xrightarrow{k_2} & 2B \end{array}\right\}.$$

In both cases one independent Brownian motion can be spared. Note that the reactions in these examples are at most bimolecular.

2.4 State space reduction

Another form of model reduction we have not discussed yet is the reduction of the number of variables. The conservation laws describe linear dependencies between the counts of molecular species. This can be used to express certain variables as functions of others. Having $\dim(\operatorname{Ker} S^T)$ linearly independent conservation laws it is possible to reduce the number of variables from n to $n - \dim(\operatorname{Ker} S^T)$.

To this end we specify an invertible matrix $T \in \mathbb{R}^{n\times n}$ such that TS will take over the role of S. (For aesthetic reasons one may prefer $T \in \mathbb{Z}^{n\times n}$.)

T is just a change of basis of the state space. To see this, multiply the CLE (2.0.5) with T from the left to get an equation in a new variable $Z = TX$:

$$\mathrm{d}(TX_t) = TSa(T^{-1}TX_t)\,\mathrm{d}t + Tg(T^{-1}TX_t)\,\mathrm{d}B_t,$$

or, by letting $\circ$ denote the composition of functions, and $\cdot$ multiplication (a special composition), we have

$$\mathrm{d}Z_t = (T \cdot S \cdot a \circ T^{-1})(Z_t)\,\mathrm{d}t + (T \cdot g \circ T^{-1})(Z_t)\,\mathrm{d}B_t.$$

We define T such that the last $\dim(\operatorname{Ker} S^T)$ coordinates of the new state variable Z are the conservation laws, which do not change at all.

We give T for Construction 1 first. Let us order the columns of $S \in \mathbb{R}^{n\times m}$ such that we have $S = [S_b\ S_c]$, where the columns of $S_b \in \mathbb{R}^{n\times(m-\dim(\operatorname{Ker} S))}$ form a basis for $\operatorname{Im} S$, and $S_c \in \mathbb{R}^{n\times\dim(\operatorname{Ker} S)}$ is the collection of the rest of the column vectors. These are linearly dependent on columns of S_b. Then, similarly to Construction 4, there are vectors

$$w^{(1)}, \ldots, w^{(\dim(\operatorname{Ker} S))} \in \mathbb{R}^{m-\dim(\operatorname{Ker} S)},$$

and a matrix

$$N = [w^{(1)}\ \ldots\ w^{(\dim(\operatorname{Ker} S))}] \in \mathbb{R}^{(m-\dim(\operatorname{Ker} S))\times\dim(\operatorname{Ker} S)}$$

such that $S_c = S_b N$.

Let us define $S_b^\perp \in \mathbb{R}^{n\times\dim(\operatorname{Ker} S^T)}$ such that its columns form a basis of the orthogonal complement space of $\operatorname{Im} S$, and let

$$T = \begin{bmatrix} (S_b^T S_b)^{-1} S_b^T \\ (S_b^\perp)^T \end{bmatrix}.$$

(To get an integer-valued T, one may put an appropriate diagonal matrix $D_0 \in \mathbb{Z}^{(n-\dim(\operatorname{Ker} S^T))\times(n-\dim(\operatorname{Ker} S^T))}$ in front of $(S_b^T S_b)^{-1} S_b^T$, and choose $S_b^\perp \in \mathbb{Z}^{n\times\dim(\operatorname{Ker} S^T)}$.)

Hence

$$\begin{aligned} TS &= \begin{bmatrix} (S_b^T S_b)^{-1} S_b^T \\ (S_b^\perp)^T \end{bmatrix} [S_b\ S_c] \\ &= \begin{bmatrix} I_{m-\dim(\operatorname{Ker} S)} & (S_b^T S_b)^{-1} S_b^T S_c \\ 0 & 0 \end{bmatrix} \\ &= \begin{bmatrix} I_{m-\dim(\operatorname{Ker} S)} & N \\ 0 & 0 \end{bmatrix}. \end{aligned}$$

Therefore in no CLE formulation will the last $\dim(\operatorname{Ker} S^T)$ variables be affected by the drift term $TSa(X)$. Since in Constructions 1 and 4 the first factor in $g(X)$ is S, the last $\dim(\operatorname{Ker} S^T)$

rows of the diffusion term $Tg(X)$ will vanish too. Consequently, the last $\dim(\operatorname{Ker} S^T)$ variables of Z are constant, and can be omitted from a numerical simulation.

The same argument holds for Construction 3, using W_1 and W_0 instead of S_b and $S_b^\perp$, respectively, in T. In the case of Construction 2, the state space reduction must precede the reduction of Brownian motions. This method is actually very similar to Construction 3. For Construction 4 a finer partitioning of matrices S, J, V is proposed. The detailed calculations are in the Appendix. These considerations prove the following result.

Theorem 2.4.1. *For Constructions 1–4 a state space transformation is possible which reduces the number of variables from n to $n - \dim(\operatorname{Ker} S^T) = m - \dim(\operatorname{Ker} S)$ without changing the number of independent Brownian motions.*

We illustrate the reduction of the number of independent Brownian motions in the CLE in three examples. In order to focus on the application of our main results we will not carry out the fairly well-known state space reduction in any example.

2.5 Example 1: A cyclical reaction system

Consider the following ring of $m = 3$ reactions with $n = 3$ species, $(A_1, A_2, A_3)^T$:

$$\begin{array}{ccc} A_1 & \xrightarrow{k_1} & A_2 \\ {\scriptstyle k_3}\,\nwarrow & & \swarrow\,{\scriptstyle k_2} \\ & A_3 & \end{array}$$

The indexing of reactions R_j follows that of rate constants k_j. This specifies the order of columns in the stoichiometry matrix,

$$S = \begin{bmatrix} -1 & 0 & 1 \\ 1 & -1 & 0 \\ 0 & 1 & -1 \end{bmatrix}.$$

This has rank 2. The propensity function is just

$$a(X) = \begin{pmatrix} k_1 X_1 \\ k_2 X_2 \\ k_3 X_3 \end{pmatrix}.$$

Gillespie's diffusion term (Construction 1) from this is

$$g^1(X) = \begin{bmatrix} -\sqrt{k_1 X_1} & 0 & \sqrt{k_3 X_3} \\ \sqrt{k_1 X_1} & -\sqrt{k_2 X_2} & 0 \\ 0 & \sqrt{k_2 X_2} & -\sqrt{k_3 X_3} \end{bmatrix}.$$

As there are no parallel stoichiometry vectors, Construction 4 cannot reduce the number of Brownian motions.

Constructions 2 and 3 can be computed analytically for such a small example. In Construction 2 finding the eigenvalues of the rank 2, 3×3 matrix requires the solution of a cubic equation (roots of the characteristic polynomial). But we know that one eigenvalue is zero and this reduces the problem to quadratic. This gives $D(X)$. Finding the eigenvectors is done by solving a linear equation for each nonzero eigenvalue, and then the vectors need to be normalised to create $U_1(X)$.

The calculations giving Construction 3 can be coded up in step-by-step instructions. The orthogonal matrix W can be chosen as

$$W = [W_1\ W_0] = \left[\begin{array}{cc|c} -1/\sqrt{2} & -1/\sqrt{6} & 1/\sqrt{3} \\ 1/\sqrt{2} & -1/\sqrt{6} & 1/\sqrt{3} \\ 0 & 2/\sqrt{6} & 1/\sqrt{3} \end{array}\right].$$

This is computed only once, therefore its computational cost is almost irrelevant. Then one needs

$$W_1^T SA(X)S^T W_1 = \left[\begin{array}{cc} 2a_1(X) + \frac{1}{2}a_2(X) + \frac{1}{2}a_3(X) & -\frac{\sqrt{3}}{2}a_2(X) + \frac{\sqrt{3}}{2}a_3(X) \\ -\frac{\sqrt{3}}{2}a_2(X) + \frac{\sqrt{3}}{2}a_3(X) & \frac{3}{2}a_2(X) + \frac{3}{2}a_3(X) \end{array}\right].$$

To take the square root of this or, in general, of a matrix

$$\left[\begin{array}{cc} M_{11} & M_{12} \\ M_{12} & M_{22} \end{array}\right] \in \mathbb{R}^{2\times 2},$$

one can compute the two eigenvalues as the roots of the characteristic polynomial, which is quadratic. These are

$$\lambda_{1,2} = \frac{M_{11} + M_{22} \pm \sqrt{(M_{11} - M_{22})^2 + 4M_{12}^2}}{2}.$$

The corresponding normalised eigenvectors are

$$v_1 = \frac{1}{\sqrt{(\lambda_1 - M_{22})^2 M_{12}^{-2} + 1}} \left(\begin{array}{c} (\lambda_1 - M_{22})M_{12}^{-1} \\ 1 \end{array}\right),$$

$$v_2 = \frac{1}{\sqrt{(\lambda_2 - M_{22})^2 M_{12}^{-2} + 1}} \left(\begin{array}{c} (\lambda_2 - M_{22})M_{12}^{-1} \\ 1 \end{array}\right).$$

Thus

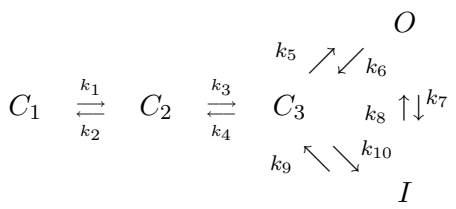
$$g^3(X) = W_1 \left[\sqrt{\lambda_1(X)}v_1(X) \quad \sqrt{\lambda_2(X)}v_2(X)\right]$$

is the product of a 3×2 and a 2×2 matrix, and requires 2 Brownian motions.

Which construction requires the least computation time hinges on how the cost of these computations compares to the cost of generating time increments of Brownian motions (that is, normal random variables). This question is beyond the scope of this work.

2.6 Example 2: Markov model for a K^+ channel

We model the transformations of human ether a-go-go related gene (HERG) encoded K^+ channels between three closed states (C_1, C_2, C_3), one open state (O) and one inactivation state (I) as $n = 5$ chemical species $(C_1, C_2, C_3, O, I)^T$ reacting through $m = 10$ reactions:



(For details see Brennan *et al.* (2009) and references therein.) Thus the stoichiometry matrix is

$$S = \begin{bmatrix} -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & -1 & -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & -1 & 1 & 0 & 0 & 1 & -1 \\ 0 & 0 & 0 & 0 & 1 & -1 & -1 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & -1 & 1 \end{bmatrix},$$

and the propensity function is

$$a(X) = \begin{pmatrix} k_1 X_1 \\ k_2 X_2 \\ k_3 X_2 \\ k_4 X_3 \\ k_5 X_3 \\ k_6 X_4 \\ k_7 X_4 \\ k_8 X_5 \\ k_9 X_5 \\ k_{10} X_3 \end{pmatrix}.$$

The Gillespie formulation (Construction 1) from this is

$$g^1(X) = S\sqrt{\operatorname{diag}(a(X))}.$$

The rank of the stoichiometry matrix S is 4, which allows for a CLE specification with 4 Brownian motions. Thus our minimal solutions g^2 and g^3 from Constructions 2 and 3, respectively, are of the form

$$g^2(X) = U_1(X) D_1(X)^{1/2},$$
$$g^3(X) = W_1 \sqrt{W_1^T S A(X) S^T W_1},$$

where $U_1(X), W_1$ are 5×4, $D_1(X)$ and $\sqrt{W_1^T S A(X) S^T W_1}$ are 4×4 matrices, respectively. With the exception of W_1, we could only compute either of these matrices analytically if we solved a quartic equation. To avoid this extremely laborious task one resorts to standard numerical computations which we do not present here.

On the other hand, Construction 4 gives a simple closed form diffusion term. Indeed, this is a classical example where the number of Brownian motions can be decreased by half, to 5:

$$g^4(X) = \begin{bmatrix} -1 & 0 & 0 & 0 & 0 \\ 1 & -1 & 0 & 0 & 0 \\ 0 & 1 & -1 & 0 & 1 \\ 0 & 0 & 1 & -1 & 0 \\ 0 & 0 & 0 & 1 & -1 \end{bmatrix} \operatorname{diag} \begin{pmatrix} \sqrt{a_1(X) + a_2(X)} \\ \sqrt{a_3(X) + a_4(X)} \\ \sqrt{a_5(X) + a_6(X)} \\ \sqrt{a_7(X) + a_8(X)} \\ \sqrt{a_9(X) + a_{10}(X)} \end{pmatrix}.$$

2.7 Example 3: The Goldbeter–Koshland switch

This example studied by Goldbeter and Koshland (1981) is a system of covalent modifications facilitated by two converter enzymes, E_1 and E_2. A typical example is a phosphorylation–

dephosphorylation system. It consists of the following $m = 6$ reactions:

$$\begin{aligned} S + E_1 &\underset{k_2}{\overset{k_1}{\rightleftarrows}} C_1 \xrightarrow{k_3} P + E_1, \\ P + E_2 &\underset{k_5}{\overset{k_4}{\rightleftarrows}} C_2 \xrightarrow{k_6} S + E_2, \end{aligned}$$

with $n = 6$ chemical species, $(S, E_1, C_1, P, E_2, C_2)^T$. The corresponding stoichiometry matrix is

$$S = \begin{bmatrix} -1 & 1 & 0 & 0 & 0 & 1 \\ -1 & 1 & 1 & 0 & 0 & 0 \\ 1 & -1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & 1 & 0 \\ 0 & 0 & 0 & -1 & 1 & 1 \\ 0 & 0 & 0 & 1 & -1 & -1 \end{bmatrix},$$

while the propensity function $a(X)$ is given by

$$a(X) = \begin{pmatrix} k_1 X_1 X_2 \\ k_2 X_3 \\ k_3 X_3 \\ k_4 X_4 X_5 \\ k_5 X_6 \\ k_6 X_6 \end{pmatrix}.$$

The Gillespie formulation (Construction 1) from this is

$$g^1(X) = S\sqrt{\operatorname{diag}(a(X))}.$$

However, the rank of the stoichiometry matrix S is 3, which implies that we only need 3 Brownian motions in the CLE. As with the K^+ channel, this can only be practically computed through numerical computations.

The closed form diffusion term from Construction 4 requires 4 Brownian motions. Removing the stoichiometry vectors corresponding to reactions 2 and 5, we have

$$g^4(X) = \begin{bmatrix} -\sqrt{a_1(X) + a_2(X)} & 0 & 0 & \sqrt{a_6(X)} \\ -\sqrt{a_1(X) + a_2(X)} & \sqrt{a_3(X)} & 0 & 0 \\ \sqrt{a_1(X) + a_2(X)} & -\sqrt{a_3(X)} & 0 & 0 \\ 0 & \sqrt{a_3(X)} & -\sqrt{a_4(X) + a_5(X)} & 0 \\ 0 & 0 & -\sqrt{a_4(X) + a_5(X)} & \sqrt{a_6(X)} \\ 0 & 0 & \sqrt{a_4(X) + a_5(X)} & -\sqrt{a_6(X)} \end{bmatrix}.$$

These examples demonstrated cases in which the stoichiometry matrix is rank deficient and a reduction in the number of Brownian motions is possible. In Example 1 there were no parallel stoichiometry vectors, thus Construction 4 could not be deployed. In Examples 2 and 3 some Brownian motions could be spared for reversible reactions. These were also cases in which Constructions 2 and 3 could reduce the system size even further.

3 Estimating the fluctuations of a biochemical reaction system around a strictly positive steady state by the linearisation of the chemical Langevin equation

3.1 Mean and variance

Let us revisit the discussion of the CLE mean and second moment at the beginning of Section 2. We called an n-variable Itô stochastic differential equation the chemical Langevin equation if it is the form

$$\mathrm{d}X_t = Sa(X_t)\,\mathrm{d}t + g(X_t)\,\mathrm{d}B_t, \tag{2.0.5}$$

with a $g:\ [0,\infty[^n \to \mathbb{R}^{n\times d}$ that satisfies

$$g(x)g(x)^T = S\,\mathrm{diag}(a(x))S^T. \tag{1.3.1}$$

Theorem 3.1.1. *In the chemical Langevin equation, the mean $\hat{X}_t = \mathrm{E}(X_t)$ satisfies the ordinary differential equation*

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{E}\big(X_t\big) = S\mathrm{E}\big(a(X_t)\big), \tag{2.0.1}$$

whereas the covariance $P_t = \mathrm{E}\big(\big(X_t - \hat{X}_t\big)\big(X_t - \hat{X}_t\big)^T\big)$ satisfies

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{d}t}P_t = {} & S\Big(\mathrm{E}\big(a(X_t)X_t^T\big) - \mathrm{E}\big(a(X_t)\big)\mathrm{E}(X_t)^T\Big) + \Big(\mathrm{E}\big(X_t\,a(X_t)^T\big) - \mathrm{E}(X_t)\mathrm{E}\big(a(X_t)\big)^T\Big)S^T \\ & + \sum_{j=1}^{m}\mathrm{E}\big(a_j(X_t)\big)S_{\cdot j}(S_{\cdot j})^T.\end{aligned} \tag{3.1.1}$$

Proof. We have proved the equation for the mean in the introduction of Section 2. For the covariance matrix $P_t = \mathrm{E}(X_tX_t^T) - \hat{X}_t\hat{X}_t^T$, we compute the infinitesimal increments of these two terms separately. Lemma 2.0.1 gave the equation for the second moment,

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{E}\big(X_tX_t^T\big) = S\mathrm{E}\big(a(X_t)X_t^T\big) + \mathrm{E}\big(X_ta(X_t)^T\big)S^T + \sum_{j=1}^{m}\mathrm{E}\big(a_j(X_t)\big)S_{\cdot j}(S_{\cdot j})^T. \tag{2.0.4}$$

More generally, the same calculation with Itô's formula gives that for n-dimensional Itô processes X and Y,

$$\mathrm{d}(X_tY_t^T) = (\mathrm{d}X_t)Y_t^T + X_t\,\mathrm{d}Y_t^T + \mathrm{d}X_t\,\mathrm{d}Y_t^T. \tag{3.1.2}$$

If we apply this to $\mathrm{d}(\hat{X}_t\hat{X}_t^T)$, we get

$$\begin{aligned}\mathrm{d}(\hat{X}_t\hat{X}_t^T) &= (\mathrm{d}\hat{X}_t)\hat{X}_t^T + \hat{X}_t\,\mathrm{d}\hat{X}_t^T + \mathrm{d}\hat{X}_t\,\mathrm{d}\hat{X}_t^T \\ &= S\mathrm{E}\big(a(X_t)\big)\hat{X}_t^T\,\mathrm{d}t + \hat{X}_t\mathrm{E}\big(a(X_t)^T\big)S^T\,\mathrm{d}t,\end{aligned}$$

by (2.0.1). The third term vanishes. These two equations give

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{d}t}P_t = {} & S\Big(\mathrm{E}\big(a(X_t)X_t^T\big) - \mathrm{E}\big(a(X_t)\big)\hat{X}_t^T\Big) + \Big(\mathrm{E}\big(X_ta(X_t)^T\big) - \hat{X}_t\mathrm{E}\big(a(X_t)^T\big)\Big)S^T \\ & + \sum_{j=1}^{m}\mathrm{E}\big(a_j(X_t)\big)S_{\cdot j}(S_{\cdot j})^T.\end{aligned}$$

and the proof is complete. □

Let us examine what this result tells us. For every t, P_t is a symmetric matrix. Its entries together with the entries of $\hat{X}_t$ form an $n + \frac{n(n+1)}{2}$-dimensional ODE. Given the initial conditions for the mean and covariance, one wishes to numerically integrate this ODE.

We now make two already familiar assumptions. First, that the kinetics follow the law of mass action. Secondly, that reactions are at most second-order. This means that for all j, $a_j(X_t)$ is either a constant (if reaction R_j is zeroth-order), or its form is $c_j X_{i,t}$ or $c_j X_{i,t} X_{k,t}$ for some constant $c_j > 0$ (for first-order or second-order reactions, respectively). If $i = k$ in a second-order reaction, then we will approximate the propensity $a_j(X_t) = c_j X_{i,t}(X_{i,t} - 1)$ with $c_j X_{i,t}^2$.

A zeroth-order reaction (a reaction of the form $\varnothing \to \dots$) means the consecutive production of molecules. For instance, if the number of genes from which a protein is expressed is fixed, and all constituents of the molecular machinery involved are present in a constant concentration, then the modelling assumption of consecutive expression is reasonable.

If no reactions are second-order, then the ODE (2.0.1) can be integrated separately from (3.1.1). In this case equation (3.1.1) is basically the *fluctuation-dissipation theorem* (Paulsson, 2004, 2005) and it also can be integrated numerically.

However, if there is at least one second-order reaction, then this (quadratic) nonlinearity will render the integration impossible. To see this note that the right-hand side of (2.0.1) can be computed if one knows P_t. If $a_j(X_t) = c_j X_{i,t} X_{k,t}$, then $\mathrm{E}\big(a_j(X_t)\big) = c_j(\hat{X}_{i,t}\hat{X}_{k,t} + P_{ik,t})$. But the right-hand side of (3.1.1) cannot be determined: $\mathrm{E}\big(a(X_t)X_t^T\big)$ will have third-order moments of the coordinates of X_t.

In fact, to compute any moments the knowledge of higher moments is required, which leads to an infinite lattice of dependent tasks. It is not known how this problem can be solved. There are only approximative methods, in which higher-order moments are estimated with nonlinear functions of lower-order moments. (See, for instance, Singh and Hespanha (2006a).) Often this function is just the product of lower moments. This may arise when the random variable is assumed to be approximately following a certain known distribution, and the higher-order moments of this distribution can be expressed from lower-order ones (Singh and Hespanha, 2006b). How the infinite problem can best be turned into a finite one by some approximation is generally called the *moment closure problem.*

3.2 Linearisation

Since one cannot integrate the ODE (3.1.1) in the general nonlinear case, we approximate the system equation (2.0.5) with its linearisation. In this linear case the equations for the mean and covariance will be self-contained, and will allow integration. Partly because fluctuations are most important in states where there is no deterministic drift, and partly because of the relative mathematical simplicity of linearisation in a steady state compared to other states, we will initially linearise only around steady states. But first let us see the definition.

We call $X^* \in \mathbb{R}^n$ a *steady state* of the CLE, if $Sa(X^*) = 0$. If there is no zeroth-order reaction in the model, then we can get a steady state by setting 'enough' X_i to zero (that is, by ensuring that all reaction channels are switched off). However, here we are interested in the system behaviour in a steady state where all reaction channels are active. From now on we require that for all $j \in \{1, \dots, m\}$, $a_j(X^*) > 0$. Let us consider what this restriction means. An inactive reaction channel has no effect on the system dynamics in the steady state, consequently it could be excluded from the model. However, in a perturbed state it may be switched on, so if the gradient of such an a_j is small, then the linearisation with the assumption of strict positivity may still be rather accurate.

For a differentiable function $f\colon \mathbb{R}^n \to \mathbb{R}$ the derivative of f in $x \in \mathbb{R}^n$ is an n-dimensional row vector (the *gradient* vector), which we denote by the nabla symbol:

$$f'(x) = \nabla f(x) = \left(\frac{\partial}{\partial x_1} f(x), \dots, \frac{\partial}{\partial x_n} f(x) \right).$$

The derivative of the differentiable $g = (g_1, \dots, g_n)^T : \mathbb{R}^n \to \mathbb{R}^n$ in $x \in \mathbb{R}^n$ is an $n \times n$ matrix, the *Jacobian*: for all $i, k \in \{1, \dots, n\}$,

$$\big(g'(x)\big)_{ik} = \big(\mathrm{D}g(x)\big)_{ik} = \frac{\partial}{\partial x_k} g_i(x).$$

We expect that the linearisation of (2.0.3) with respect to the state space is

$$\mathrm{d}\tilde{X}_t = f(X^*)\,\mathrm{d}t + f'(X^*)\big(\tilde{X}_t - X^*\big)\,\mathrm{d}t + g(X^*)\,\mathrm{d}B_t + g'(X^*)\big(\tilde{X}_t - X^*\big)\,\mathrm{d}B_t \tag{3.2.1}$$

now with a new stochastic process $\tilde{X}$. Let us drop the tilde, keeping in mind that this new X is an approximation of the original one. Here $f(X^*) = 0$ by the definition of a steady state. However, (3.2.1) is incorrect (even dimensions do not match) as long as we do not explain how we mean the differentiation of g.

For simplicity, let us only consider Gillespie's original construction:

$$\mathrm{d}X_t = Sa(X_t)\,\mathrm{d}t + \sum_{j=1}^{m} \sqrt{a_j(X_t)}\, S_{\cdot j}\,\mathrm{d}B_{j,t}. \tag{3.2.2}$$

From this form it is clear that we can linearise the $\mathbb{R}^n \to \mathbb{R}^n$ functions $x \mapsto \big(a_j(x)\big)^{1/2} S_{\cdot j}$ ($j \in \{1, \dots, m\}$) independently. Their differentiation is straightforward, then we multiply by $X - X^*$, and by $\mathrm{d}B_{j,t}$.

Proposition 3.2.1. *The linearisation of Gillespie's CLE in a steady state $X^* \in \mathbb{R}^n$ where for all $j \in \{1, \dots, m\}$, $a_j(X^*) > 0$ is*

$$\mathrm{d}X_t = F\big(X_t - X^*\big)\,\mathrm{d}t + G\,\mathrm{d}B_t + \sum_{j=1}^{m} G_j\big(X_t - X^*\big)\,\mathrm{d}B_{j,t}, \tag{3.2.3}$$

where

$$\begin{aligned} F &= S\,\mathrm{D}a(X^*) \in \mathbb{R}^{n\times n}, \\ G &= \Big[\sqrt{a_1(X^*)}\, S_{\cdot 1} \quad \dots \quad \sqrt{a_m(X^*)}\, S_{\cdot m}\Big] \in \mathbb{R}^{n\times m}, \\ G_j &= \frac{1}{2\sqrt{a_j(X^*)}}\, S_{\cdot j}\, \nabla a_j(X^*) \in \mathbb{R}^{n\times n}, \quad \text{for all } j \in \{1, \dots, m\}. \end{aligned}$$

3.3 Displacement mean and variance

Let us define the *displacement* of the state as the difference between the state and the steady state: $x_t := X_t - X^*$. In this section we derive the ordinary differential equations governing the time evolution of the mean

$$\hat{x}_t = \mathrm{E}(x_t)$$

and the covariance

$$P_t := \mathrm{E}\big((x_t - \hat{x}_t)\,(x_t - \hat{x}_t)^T\big)$$

of the displacement for the linearised model (3.2.3) of Proposition 3.2.1.

Theorem 3.3.1. *In a steady state $X^* \in \mathbb{R}^n$ of the linearised chemical Langevin equation in which for all $j \in \{1, \ldots, m\}$, $a_j(X^*) > 0$, the mean displacement $\hat{x}_t = \mathrm{E}(X_t - X^*)$ satisfies the ordinary differential equation*

$$\frac{\mathrm{d}}{\mathrm{d}t}\hat{x}_t = F\hat{x}_t, \tag{3.3.1}$$

whereas the covariance $P_t = \mathrm{E}\big(\big(x_t - \hat{x}_t\big)\big(x_t - \hat{x}_t\big)^T\big)$ satisfies

$$\frac{\mathrm{d}}{\mathrm{d}t}P_t = FP_t + P_tF^T + \sum_{j=1}^{m}(G_{\cdot j} + G_j\hat{x}_t)(G_{\cdot j} + G_j\hat{x}_t)^T + \sum_{j=1}^{m} G_jP_tG_j^T. \tag{3.3.2}$$

Proof. The proof closely follows that of Theorem 3.1.1 and is to be found in the Appendix. □

One should appreciate that through linearisation we could derive an equation for the covariance matrix that can be integrated without further obstacles. This covariance matrix is informative, but has its weaknesses.

First, as with any linearisation, we can only expect it to be reliable if the state remains in a small neighbourhood of the steady state X^* around which we linearise.

We suspect that this linearisation method will give incorrect estimates in certain situations where nonlinearity plays an important role. This can be expected, for instance, in bistable systems, where in equilibrium internal noise causes occasional jumps between neighbourhoods of two steady states (which corresponds to a bimodal probability mass distribution). A well-known example is the lysogeny-to-lysis switching of λ phage (Arkin, Ross, and McAdams, 1998; Hasty, Pradines, Dolnik, and Collins, 2000).

Secondly, this first requirement cannot be enforced. To see this, note that there are two different notions of steady state we must deal with. One is what we defined as a steady state: $X^* \in \mathbb{R}^n$ for which $Sa(X^*) = 0$. This can be found numerically. More relevant here is the steady state of the ODE (2.0.1). If the CLE is in its equilibrium distribution (let us assume it has one and it is unique), then the mean of this distribution $\widehat{X^{\mathrm{eq}}} \in \mathbb{R}^n$ is a steady state of (2.0.1): $0 = \frac{\mathrm{d}}{\mathrm{d}t}\widehat{X^{\mathrm{eq}}} = S\mathrm{E}\big(a(\widehat{X^{\mathrm{eq}}})\big)$.

This is a general phenomenon with nonlinear stochastic differential equations. Taking the expectation of (2.0.3), we get an ODE describing the time evolution of the mean of the process,

$$\mathrm{dE}(X_t) = \mathrm{E}\big(f(X_t)\big)\,\mathrm{d}t.$$

Even if at time t we know $\mathrm{E}(X_t)$ (at $t = 0$ from the initial condition), hence $f\big(\mathrm{E}(X_t)\big)$, we could integrate further only if we knew $\mathrm{E}\big(f(X_t)\big)$. For a nonlinear f these two are not equal in general and one usually cannot know much about their difference.

3.4 Iterated linearisation

It was discussed after Theorem 3.1.1 that in the CLE, if one stipulates law of mass action kinetics and at most second-order reactions, the previously presented difficulty becomes more benign. Consider the jth propensity function. The problematic term on the right-hand side of (2.0.1) can be expressed as

$$\mathrm{E}\big(a_j(X_t)\big) = a_j\big(\hat{X}_t\big) + \Big(\mathrm{E}\big(a_j(X_t)\big) - a_j\big(\hat{X}_t\big)\Big).$$

For zeroth and first-order reactions $\mathrm{E}\big(a_j(X_t)\big) = a_j\big(\hat{X}_t\big)$. For second-order reactions, when $a_j(X_t) = c_j X_{i,t} X_{k,t}$, the term in brackets is just

$$\mathrm{E}\big(a_j(X_t)\big) - a_j\big(\hat{X}_t\big) = c_j P_{ik,t}.$$

Therefore we could compute the time evolution of the mean approximately if we had an estimate for the covariance matrix. For simplicity, let us investigate the system in stationary distribution only. It is natural to use the linearisation around the steady state, for which we can compute the covariance, and use this to update the steady state in the hope that this will be closer to the true mean. This procedure of linearisation, followed by the computation of the covariance for the linear approximation, and updating of the point of linearisation based on this covariance can be repeated indefinitely. Algorithm 1 is just this method which aims to estimate the mean of the equilibrium distribution.

As we will linearise in points other than steady states, we need to extend the scope of (3.2.3) slightly. The linearisation in a point $\tilde{X} \in \mathbb{R}^n$ is

$$\mathrm{d}X_t = f(\tilde{X})\,\mathrm{d}t + F\big(X_t - \tilde{X}\big)\,\mathrm{d}t + G\,\mathrm{d}B_t + \sum_{j=1}^{m} G_j\big(X_t - \tilde{X}\big)\,\mathrm{d}B_{j,t}. \tag{3.4.1}$$

Repeating the calculation in Theorem 3.3.1 with $x_t := X_t - \tilde{X}$, (3.3.1) becomes

$$\frac{\mathrm{d}}{\mathrm{d}t}\hat{x}_t = f\big(\tilde{X}\big) + F\hat{x}_t, \tag{3.4.2}$$

but the ODE for the covariance remains (3.3.2). F^{-1} may not exist, hence computing $\hat{x} = \hat{X} - \tilde{X}$ as $\hat{x} := -F^{-1}f\big(\tilde{X}\big)$ may be impossible, but in equilibrium $\hat{x}$ is just zero, therefore (3.1.1) will be well approximated by

$$FP + PF^T + \sum_{j=1}^{m} G_{\cdot j} G_{\cdot j}^T + \sum_{j=1}^{m} G_j P G_j^T = 0. \tag{3.4.3}$$

We will use this form in our algorithm.

In order to illustrate the use of the linearisation technique and to assess its accuracy we will present two examples. The iterated linearisation method has also been applied to some simple problems. Experience shows that in these examples it converges and the convergence is very quick (some 5–7 steps are enough to reach a fixed point). However, it has so far remained unclear how much this iteration improved the estimate of the mean in comparison with our simple linearisation method. We have pursued to find a general sufficient condition for convergence of the iteration method and to understand its connection with previously proposed solutions to the moment closure problem. Establishing such a connection would give an interpretation of the fixed point. Further scrutiny is required to achieve these goals.

Before discussing our two examples, first a technical point needs to be addressed.

3.5 Transforming the chemical Langevin equation between counts and concentrations formulations

Although the CLE model was developed to describe changes in molecular counts (Gillespie, 2000), it is often beneficial to track changes in molecular concentrations. In our second example reaction volume will change while the reactions take place, and we will only talk about the

Algorithm 1 Iterated linearisation

$i := 0$; fix $\varepsilon > 0$
$\hat{X}^{(0)} := X^*$, for which $f(X^*) = 0$ (steady state)
while $i = 0$ or $|\hat{X}^{(i)} - \hat{X}^{(i-1)}| > \varepsilon$ **do**
  linearise around $\hat{X}^{(i)}$
  solve (3.4.3) for P symmetric, and call its solution $P^{(i+1)}$
  for all j **do**
    if R_j is second-order **then**
      let r, s be the indices of the reactants in reaction R_j
      $\tilde{a}_j(X) := c_j\Big(X_r X_s + \big(P^{(i+1)}\big)_{rs}\Big)$
    else if R_j is first-order **then**
      let r be the index of the reactant in reaction R_j
      $\tilde{a}_j(X) := c_j X_r$
    else if R_j is zeroth-order **then**
      $\tilde{a}_j(X) := c_j$
    end if
  end for
  solve $S\tilde{a}(X) = 0$, and call its solution $\hat{X}^{(i+1)}$
  $i := i + 1$
end while
Output: $\hat{X}^{(i)}$

steady state of concentrations, and not counts, which must increase to keep up with the volume growth.

Let v_t denote the volume of the solution in which the reaction system is found (e.g. the cytoplasm) at time t. This may be constant, or may change deterministically (and smoothly).

With N_A denoting the *Avogadro constant*, the relationship between counts $X_t \in \mathbb{R}^n$ and concentrations $c_t \in \mathbb{R}^n$ is

$$X_t = N_A v_t c_t. \tag{3.5.1}$$

(The units we use are litres for volume, and mol/ℓ for concentrations.) If one assumes varying volume, then it follows that the propensities should be modelled as a function of concentrations and not counts: in a solution with expanding volume and constant molecular counts the collisions of molecules would become rarer and therefore reactions would slow down. However, this phenomenon is captured directly by using concentrations.

Let Gillespie's original CLE, (3.2.2), be our starting point. If we assume that there are at most bimolecular reactions, then it is enough to consider zeroth, first and second-order reactions. The propensity of a zeroth-order reaction is just a constant: the number of molecules produced in a unit of time. For first-order reactions, the propensity is proportional to the number of reactant molecules already present. However, for second-order reactions in changing volume, propensity is not just simply proportional to the product of the two molecular counts, because it has to vary inversely with volume: if we assume for a moment that the molecular count of one reactant species is fixed, then the number of collisions between the two different species (and consequently the number of reactions) is proportional to the *concentration* of the other species. Hence the reaction rate coefficient can be formulated as a constant divided by the volume, and (for aesthetic reasons) by the Avogadro constant. Bearing this in mind, let

us consider just three representative entries of a, for some $i, k \in \{1, \ldots, n\}$

$$a(X_t) = \begin{pmatrix} k_0 \\ k_1 X_{i,t} \\ \frac{k_2}{N_A v_t} X_{i,t} X_{k,t} \end{pmatrix}.$$

Applying the product rule (3.1.2) to (3.5.1) we have

$$\mathrm{d}X_t = N_A(\mathrm{d}v_t)c_t + N_A v_t \,\mathrm{d}c_t + 0. \tag{3.5.2}$$

The last term vanishes because of the computation rules from the proof of Lemma 2.0.1. (Recall that we assumed v_t is deterministic.) Now modify a so that it becomes a function of concentrations,

$$\tilde{a}(c_t) := a(X_t) = \begin{pmatrix} k_0 \\ k_1 \, N_A v_t \, c_{i,t} \\ \frac{k_2}{N_A v_t} (N_A v_t)^2 \, c_{i,t} c_{k,t} \end{pmatrix} = N_A v_t \begin{pmatrix} \frac{k_0}{N_A v_t} \\ k_1 c_{i,t} \\ k_2 \, c_{i,t} c_{k,t} \end{pmatrix}.$$

Furthermore let

$$\hat{a}(c_t) := \begin{pmatrix} \frac{k_0}{N_A v_t} \\ k_1 c_{i,t} \\ k_2 \, c_{i,t} c_{k,t} \end{pmatrix}.$$

We substitute these into the CLE (3.2.2) and have

$$N_A v_t \,\mathrm{d}c_t = N_A v_t \, S\hat{a}(c_t) \,\mathrm{d}t - N_A c_t \,\mathrm{d}v_t + \sum_{j=1}^{m} \sqrt{N_A v_t} \sqrt{\hat{a}_j(c_t)} \, S_{\cdot j} \,\mathrm{d}B_{j,t},$$

or after dividing by $N_A v_t$

$$\mathrm{d}c_t = S\hat{a}(c_t) \,\mathrm{d}t - c_t \frac{\mathrm{d}v_t}{v_t} + \sum_{j=1}^{m} \frac{1}{\sqrt{N_A v_t}} \sqrt{\hat{a}_j(c_t)} \, S_{\cdot j} \,\mathrm{d}B_{j,t}. \tag{3.5.3}$$

This is the CLE for concentrations.

Now let us calculate what the transformation is in the other direction. If we start with

$$\mathrm{d}c_t = Sb(c_t) \,\mathrm{d}t - c_t \frac{\mathrm{d}v_t}{v_t} + \sum_{j=1}^{m} \frac{1}{\sqrt{N_A v_t}} \sqrt{b_j(c_t)} \, S_{\cdot j} \,\mathrm{d}B_{j,t},$$

for some b of typical entries

$$b(c_t) = \begin{pmatrix} \frac{k_0}{N_A v_t} \\ k_1 c_{i,t} \\ k_2 c_{i,t} c_{k,t} \end{pmatrix}.$$

Recall that any zeroth-order reaction is the production of a given number of molecules of some molecular species in a unit of time. Therefore its contribution to the change in concentration is inversely proportional to the volume. Hence the division in the first entry of $b(c_t)$. Substituting $\mathrm{d}c_t$ from (3.5.2) and introducing

$$\tilde{b}(X_t) := b(c_t) = \begin{pmatrix} \frac{k_0}{N_A v_t} \\ k_1 \frac{1}{N_A v_t} X_{i,t} \\ k_2 \frac{1}{(N_A v_t)^2} X_{i,t} X_{k,t} \end{pmatrix} = \frac{1}{N_A v_t} \begin{pmatrix} k_0 \\ k_1 X_{i,t} \\ k_2 \frac{1}{N_A v_t} \, X_{i,t} X_{k,t} \end{pmatrix}$$

and

$$\hat{b}(X_t) := \begin{pmatrix} k_0 \\ k_1 X_{i,t} \\ k_2 \frac{1}{N_A v_t} X_{i,t} X_{k,t} \end{pmatrix}$$

we have

$$\frac{1}{N_A v_t} \mathrm{d}X_t = \frac{1}{N_A v_t} S \hat{b}(X_t)\, \mathrm{d}t + \sum_{j=1}^{m} \frac{1}{\sqrt{N_A v_t}} \left(\frac{1}{\sqrt{N_A v_t}} \sqrt{\hat{b}_j(X_t)} \right) S_{\cdot j}\, \mathrm{d}B_{j,t}.$$

We just multiply both sides with $N_A v_t$ to finish this calculation,

$$\mathrm{d}X_t = S \hat{b}(X_t)\, \mathrm{d}t + \sum_{j=1}^{m} \sqrt{\hat{b}_j(X_t)}\, S_{\cdot j}\, \mathrm{d}B_{j,t}.$$

3.6 Example 4: Protein dimerisation

The goal of the following two sections is to compare the estimate of the covariance matrix P_t of the displacement from steady state by the linearisation technique (Section 3.3) to computer-simulated data. The chemical systems will be simulated with the exact Stochastic Simulation Algorithm (Gillespie, 1976, 1977), which we also compare to simulations of the approximative CLE and the linearised CLE systems by a fixed step-size semi-implicit Euler scheme (Kloeden and Platen, 1992).

In a paper by Hayot and Jayaprakash (2004) protein production, dimerisation, and decay are modelled in the most straightforward way by

$$\begin{aligned} \varnothing &\xrightarrow{k_3} P \\ P &\xrightarrow{k} \varnothing \\ 2P &\underset{k_2}{\overset{k_1}{\rightleftharpoons}} P_2 \end{aligned}$$

In addition to $N_A = 6 \times 10^{23}$ mol^{-1}, we will use slightly adjusted parameter values $k = 0.0007$ s^{-1}, $k_1 = 0.03 \times 10^9$ ℓ(mol s)$^{-1}$, $k_2 = 0.5$ s^{-1}, $k_3 = 0.07 \times 10^{-9}$ mol(ℓs)$^{-1}$, and a fixed volume of $v := v_t = 10^{-15}/3$ ℓ to ensure that the steady state is exactly $X_1^* = 20$ for the protein monomer and $X_2^* = 120$ for the dimer. Note that these rate coefficients correspond to b of the previous section, and we convert them to $\hat{b}$,

$$\begin{aligned} \hat{k} &= k, & \hat{k}_2 &= k_2, \\ \hat{k}_1 &= \frac{k_1}{N_A v}, & \hat{k}_3 &= N_A v\, k_3, \end{aligned}$$

to write the CLE in the usual counts formulation,

$$\begin{aligned} \mathrm{d}X_{1,t} &= -\hat{k} X_{1,t}\, \mathrm{d}t - 2\hat{k}_1 X_{1,t}^2\, \mathrm{d}t + 2\hat{k}_2 X_{2,t}\, \mathrm{d}t + \hat{k}_3\, \mathrm{d}t \\ &\quad - \sqrt{\hat{k} X_{1,t}}\, \mathrm{d}B_{0,t} - 2\sqrt{\hat{k}_1 X_{1,t}^2}\, \mathrm{d}B_{1,t} + 2\sqrt{\hat{k}_2 X_{2,t}}\, \mathrm{d}B_{2,t} + \sqrt{\hat{k}_3}\, \mathrm{d}B_{3,t}, \\ \mathrm{d}X_{2,t} &= \hat{k}_1 X_{1,t}^2\, \mathrm{d}t - \hat{k}_2 X_{2,t}\, \mathrm{d}t + \sqrt{\hat{k}_1 X_{1,t}^2}\, \mathrm{d}B_{1,t} - \sqrt{\hat{k}_2 X_{2,t}}\, \mathrm{d}B_{2,t}. \end{aligned}$$

(Note that reaction indexing starts at zero.) By Proposition 3.2.1, the linearised CLE is

$$\mathrm{d}X_t = F\big(X_t - X^*\big)\,\mathrm{d}t + G\,\mathrm{d}B_t + \sum_{j=0}^{3} G_j\big(X_t - X^*\big)\,\mathrm{d}B_{j,t}$$

with matrices

$$F = S\,\mathrm{D}a(X^*) = \begin{bmatrix} -1 & -2 & 2 & 1 \\ 0 & 1 & -1 & 0 \end{bmatrix} \begin{bmatrix} \hat{k} & 0 \\ 2\hat{k}_1 X_1^* & 0 \\ 0 & \hat{k}_2 \\ 0 & 0 \end{bmatrix} = \begin{bmatrix} -\hat{k} - 4\hat{k}_1 X_1^* & 2\hat{k}_2 \\ 2\hat{k}_1 X_1^* & -\hat{k}_2 \end{bmatrix},$$

$$G = \begin{bmatrix} -\sqrt{\hat{k} X_1^*} & -2\sqrt{\hat{k}_1 (X_1^*)^2} & 2\sqrt{\hat{k}_2 X_2^*} & \sqrt{\hat{k}_3} \\ 0 & \sqrt{\hat{k}_1 (X_1^*)^2} & -\sqrt{\hat{k}_2 X_2^*} & 0 \end{bmatrix},$$

$$G_0 = \frac{1}{2\sqrt{a_0(X^*)}}\, S_{\cdot 0}\, \nabla a_0(X^*) = \begin{bmatrix} -\frac{\sqrt{\hat{k}}}{2\sqrt{X_1^*}} & 0 \\ 0 & 0 \end{bmatrix},$$

$$G_1 = \frac{1}{2\sqrt{a_1(X^*)}}\, S_{\cdot 1}\, \nabla a_1(X^*) = \begin{bmatrix} -2\sqrt{\hat{k}_1} & 0 \\ \sqrt{\hat{k}_1} & 0 \end{bmatrix},$$

$$G_2 = \frac{1}{2\sqrt{a_2(X^*)}}\, S_{\cdot 2}\, \nabla a_2(X^*) = \begin{bmatrix} 0 & \frac{\sqrt{\hat{k}_2}}{\sqrt{X_2^*}} \\ 0 & -\frac{\sqrt{\hat{k}_2}}{2\sqrt{X_2^*}} \end{bmatrix},$$

$$G_3 = \frac{1}{2\sqrt{a_3(X^*)}}\, S_{\cdot 3}\, \nabla a_3(X^*) = \begin{bmatrix} 0 & 0 \\ 0 & 0 \end{bmatrix}.$$

Everything is ready to write up the differential equation (3.3.2) for P_t. The following tables and graphs present statistics (means, variances, cross-correlations) for the protein monomer and dimer counts from the SSA, the CLE and the linearised CLE simulations, (5000 simulations in each case, each simulation recorded at various time points; the CLE and the linearised CLE simulations used 0.001 s time steps.) and compare these to the estimate from (3.3.2) (solved by numerical integration). In each simulation the initial state was chosen to be the steady state $(X_1(0), X_2(0)) = (20, 120)$, consequently the initial covariance matrix was zero.

Mean	X_1				X_2			
Time (s)	SSA	CLE	lin.CLE	$\hat{X}_{1,t}$	SSA	CLE	lin.CLE	$\hat{X}_{2,t}$
0.01	20.0	20.0	20.0	20	120.0	120.0	120.0	120
0.1	19.9	20.0	20.0	20	120.0	120.0	120.0	120
1	19.5	19.8	20.1	20	120.2	120.1	120.0	120
10	19.7	19.5	20.0	20	120.2	120.3	120.0	120
100	19.6	19.7	20.0	20	120.2	120.1	120.0	120

Variance	X_1				X_2			
Time (s)	SSA	CLE	lin.CLE	$(P_t)_{11}$	SSA	CLE	lin.CLE	$(P_t)_{22}$
0.01	7.1	1.0	1.0	4.3	1.8	0.3	0.3	1.1
0.1	17.9	5.2	5.2	18.0	4.5	1.3	1.3	4.5
1	19.3	18.6	18.6	19.7	4.8	4.6	4.6	4.9
10	19.7	18.4	19.4	19.7	5.0	4.6	4.9	5.0
100	19.2	19.5	19.4	19.7	5.3	4.9	4.9	5.6

Cross-correlation

Time (s)	SSA	CLE	lin.CLE	$(P_t)_{12}$
0.01	-3.5	-0.5	-0.5	-2.1
0.1	-9.0	-2.6	-2.6	-9.0
1	-9.6	-9.3	-9.3	-9.8
10	-9.8	-9.2	-9.7	-9.8
100	-9.4	-9.7	-9.7	-9.8

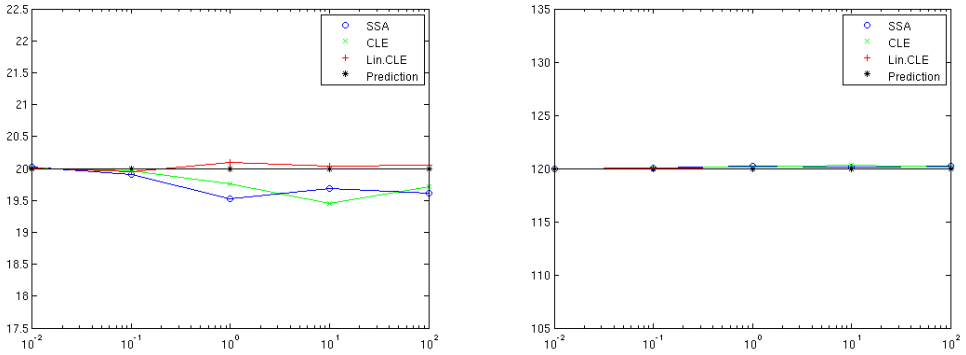


Figure 1: Comparison of the means of X_1 (left) and X_2 (right) from the different simulations with their estimates ($\hat{X}_{1,t}$ and $\hat{X}_{2,t}$, respectively).

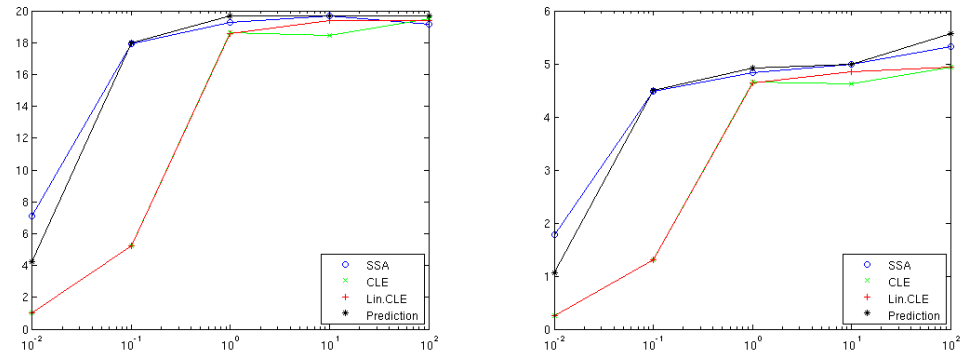


Figure 2: Comparison of the variances of X_1 (left) and X_2 (right) from the different simulations with their estimates ($(P_t)_{11}$ and $(P_t)_{22}$, respectively).

The simulation data demonstrates that the estimation method is very accurate. The only discrepancy is that at 0.01 s and 0.1 s the CLE and linearised CLE simulations show much smaller covariance values as either our estimate or the SSA simulation. We repeated these simulations with shorter step sizes (down to 0.000001 s) but this further decreased the covariances. The good correspondence between the SSA simulations and the estimates based on the linearised CLE suggests that this problem may be rooted in numerical issues in the CLE simulations, that is, the semi-implicit scheme may prevent the emergence of greater fluctuations on this time scale. Simulations longer than 100 s were impractical due to the computation cost of the SSA, but pose no problems to the estimation method. In fact, the latter becomes

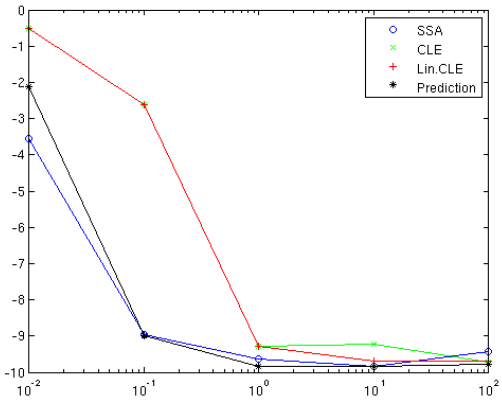


Figure 3: Comparison of the covariance of X_1 and X_2 from the different simulations with their estimates ($(P_t)_{12}$).

the most powerful tool to learn about the system behaviour. It predicts that ultimately P_t converges to its own steady state

$$P^* = \begin{bmatrix} 20.52 & -0.195 \\ -0.195 & 120.9 \end{bmatrix}.$$

That is, fluctuations in the protein dimer increase and become ever less anticorrelated to the fluctuations of the monomer. The apparent reason for this is that on a longer time scale protein production and decay blunt the anticorrelation between the fluctuations of monomer and dimer counts.

3.7 Example 5: The ColE1 bacterial plasmid replication control system

In a model of plasmid replication control studied by various groups (see Bremer and Lin-Chao (1986), Ehrenberg (1996), Paulsson and Ehrenberg (1998), Paulsson and Ehrenberg (2001), Lestas, Vinnicombe, and Bishop (2005) and references therein) RNA molecules are transcribed from plasmids and act as a negative feedback signal by inhibiting the plasmid replication process with a certain probability. We propose the following model in which plasmids P generate RNA I molecules R_1, which decay at a certain rate. Attempts of plasmid replication are either blocked by an RNA I molecule binding to the complementary single-stranded RNA II molecule which is being transcribed from the plasmid or not, but in either case the replication primer precursor RNA II will soon pair up with one RNA I, and will effectively remove it from the system.

$$\begin{aligned} P &\xrightarrow{k_1} P + R_1 \\ R_1 &\xrightarrow{k_2} \varnothing \\ P &\xrightarrow{k_3(X_{R_1})} P - R_1 \\ P &\xrightarrow{k_4(X_{R_1})} 2P - R_1 \end{aligned}$$

We are interested in the change of plasmid and RNA I counts in a single cell over one complete cell cycle in which cell volume doubles with exponential growth $v(t) = v(0)\,2^{t/T}$

($t \in [0, T]$). Keeping to experimentally measured values as much as we can, we set parameter and initial values such that the steady state of concentrations corresponds to a doubling of plasmid count from 10 to 20, and RNA I count from 400 to 800 during the cell cycle. Our parameters are as follows.

Length of cell cycle: $T = 50$ min.

Initial intracellular volume: $v_0 = 10^{-15}$ ℓ.

Dilution rate: $k_d = \frac{\log 2}{T} = 0.000231\ldots$ s^{-1}.

Avogadro number: $N_A = 6 \times 10^{23}$ mol^{-1}.

RNA I transcription frequency: $k_1 = 0.1$ s^{-1}.

RNA I degradation rate: $k_2 = 0.002$ $\mathrm{s}^{-1} - k_d = 0.00176\ldots$ s^{-1}.

RNA II transcription frequency: $k_{II} = k_1 - (k_2 + k_d)\,\frac{c^*_{R_1}}{c^*_P} = 0.02$ s^{-1}. This is set such that the stipulated ratio between the two steady state concentrations is achieved ($c^*_{R_1}/c^*_P = 40$).

Rate of failed plasmid replication attempts: $k_3(X_{R_1}) = k_{II} - k_4(X_{R_1})$. This is the rate coefficient of replication attempts (that is, RNA II transcriptions) minus the successful attempts.

Plasmid replication rate: $k_4(X_{R_1}) = k_{II} Q_0 \varrho$. This is the rate coefficient of RNA II transcription multiplied by the probabilities that replication priming is not inhibited by RNA I:RNA II complex formation and that a mature primer eventually initiates plasmid replication.

The probability that replication priming by RNA II is not inhibited by RNA I This is where one makes a distinction between two cases. Following Ehrenberg (1996) and Paulsson and Ehrenberg (1998), we let

$$Q_0^{\mathrm{hyp}} = \frac{1}{1 + \frac{X_{R_1,t}}{K_I^{\mathrm{hyp}} v_t}} = \frac{1}{1 + \frac{N_A c_{R_1,t}}{K_I^{\mathrm{hyp}}}}$$

in the hyperbolic case, and

$$Q_0^{\mathrm{exp}} = \exp\left(-\frac{X_{R_1,t}}{K_I^{\mathrm{exp}} v_t}\right) = \exp\left(-\frac{N_A c_{R_1,t}}{K_I^{\mathrm{exp}}}\right)$$

in the exponential case.

The probability that a mature primer initiates plasmid replication: $\varrho = 0.5$.

Inhibition constant for RNA I:RNA II complex formation This is set such that if the initial value is the steady state ($(c_P(0), c_{R_1}(0)) = (c^*_P, c^*_{R_1})$), then exactly one replication occurs per plasmid until the end of the cell cycle thus providing an exact duplication of the plasmid population. In other words, we choose it such that it guarantees a constant plasmid concentration: $k_4\big(c^*_{R_1}\big) = k_d$ gives

$$K_I^{\mathrm{hyp}} = \frac{N_A\, c^{*,\mathrm{hyp}}_{R_1}}{\frac{k_{II}\,\varrho}{k_d} - 1},$$

and

$$K_I^{\exp} = -\frac{N_A\, c_{R_1}^{*,\exp}}{\log \frac{k_d}{k_{II}\,\varrho}}.$$

The system equations for molecular counts are

$$\begin{aligned}
\mathrm{d}X_{P,t} &= k_4\big(X_{R_1,t}\big)X_{P,t}\,\mathrm{d}t + \sqrt{k_4\big(X_{R_1,t}\big)X_{P,t}}\,\mathrm{d}B_{4,t},\\
\mathrm{d}X_{R_1,t} &= k_1 X_{P,t}\,\mathrm{d}t - k_2 X_{R_1,t}\,\mathrm{d}t - \Big(k_3\big(X_{R_1,t}\big) + k_4\big(X_{R_1,t}\big)\Big)X_{P,t}\,\mathrm{d}t\\
&\quad + \sqrt{k_1 X_{P,t}}\,\mathrm{d}B_{1,t} - \sqrt{k_2 X_{R_1,t}}\,\mathrm{d}B_{2,t}\\
&\quad - \sqrt{k_3\big(X_{R_1,t}\big)X_{P,t}}\,\mathrm{d}B_{3,t} - \sqrt{k_4\big(X_{R_1,t}\big)X_{P,t}}\,\mathrm{d}B_{4,t}.
\end{aligned}$$

In this example steady state only makes sense for concentrations therefore we will transform the CLE into concentrations formulation. We have already derived how to do this (see (3.5.3) in Section 3.5). Note that we have a fairly simple situation since all reactions are first-order. This was achieved by hiding the nonlinearities of interactions and their volume dependencies into the k_3 and k_4 coefficients.

$$\begin{aligned}
\mathrm{d}c_{P,t} &= k_4\big(c_{R_1,t}\big)c_{P,t}\,\mathrm{d}t - k_d c_{P,t}\,\mathrm{d}t + \frac{1}{\sqrt{N_A v_t}}\sqrt{k_4\big(c_{R_1,t}\big)c_{P,t}}\,\mathrm{d}B_{4,t},\\
\mathrm{d}c_{R_1,t} &= k_1 c_{P,t}\,\mathrm{d}t - k_2 c_{R_1,t}\,\mathrm{d}t - \Big(k_3\big(c_{R_1,t}\big) + k_4\big(c_{R_1,t}\big)\Big)c_{P,t}\,\mathrm{d}t - k_d c_{R_1,t}\,\mathrm{d}t\\
&\quad + \frac{1}{\sqrt{N_A v_t}}\sqrt{k_1 c_{P,t}}\,\mathrm{d}B_{1,t} - \frac{1}{\sqrt{N_A v_t}}\sqrt{k_2 c_{R_1,t}}\,\mathrm{d}B_{2,t}\\
&\quad - \frac{1}{\sqrt{N_A v_t}}\sqrt{k_3\big(c_{R_1,t}\big)c_{P,t}}\,\mathrm{d}B_{3,t} - \frac{1}{\sqrt{N_A v_t}}\sqrt{k_4\big(c_{R_1,t}\big)c_{P,t}}\,\mathrm{d}B_{4,t}.
\end{aligned}$$

We can now proceed to the differential equation (3.3.2) for P_t. Due to the changing volume, this time the matrices involved will be time-dependent. This does not matter though, as the linearisation was done with respect to space.

$$F = \begin{bmatrix} 0 & k_4'(c_{R_1}^*)c_P^* \\ k_1 - k_{II} & -k_2 - k_d \end{bmatrix},$$

$$G_t = \begin{bmatrix} 0 & 0 & 0 & \frac{1}{\sqrt{N_A v_t}}\sqrt{k_4(c_{R_1}^*)c_P^*} \\ \frac{1}{\sqrt{N_A v_t}}\sqrt{k_1 c_P^*} & -\frac{1}{\sqrt{N_A v_t}}\sqrt{k_2 c_{R_1}^*} & -\frac{1}{\sqrt{N_A v_t}}\sqrt{k_3(c_{R_1}^*)c_P^*} & -\frac{1}{\sqrt{N_A v_t}}\sqrt{k_4(c_{R_1}^*)c_P^*} \end{bmatrix},$$

$$G_{1,t} = \begin{bmatrix} 0 & 0 \\ \frac{\sqrt{k_1}}{2\sqrt{N_A v_t}\sqrt{c_P^*}} & 0 \end{bmatrix},$$

$$G_{2,t} = \begin{bmatrix} 0 & 0 \\ 0 & -\frac{\sqrt{k_2}}{2\sqrt{N_A v_t}\sqrt{c_{R_1}^*}} \end{bmatrix},$$

$$G_{3,t} = \begin{bmatrix} 0 & 0 \\ -\frac{\sqrt{k_3(c_{R_1}^*)}}{2\sqrt{N_A v_t}\sqrt{c_P^*}} & -\frac{k_3'(c_{R_1}^*)c_P^*}{2\sqrt{N_A v_t}\sqrt{k_3(c_{R_1}^*)c_P^*}} \end{bmatrix},$$

$$G_{4,t} = \begin{bmatrix} \frac{\sqrt{k_4(c_{R_1}^*)}}{2\sqrt{N_A v_t}\sqrt{c_P^*}} & \frac{k_4'(c_{R_1}^*)c_P^*}{2\sqrt{N_A v_t}\sqrt{k_4(c_{R_1}^*)c_P^*}} \\ -\frac{\sqrt{k_4(c_{R_1}^*)}}{2\sqrt{N_A v_t}\sqrt{c_P^*}} & -\frac{k_4'(c_{R_1}^*)c_P^*}{2\sqrt{N_A v_t}\sqrt{k_4(c_{R_1}^*)c_P^*}} \end{bmatrix}.$$

Note that for the purpose of simulation both forms of the CLE are equally valid. The transformation was only necessary for the linearisation.

A comparison similar to that of the previous section can be carried out. The initial state is again the steady state with probability 1 (hence the initial covariance is zero). In each block the first three columns show statistics from 5000 simulations in each case, the fourth column is the prediction. Here we are only interested in statistics at one time instance, the end of the cell cycle. For clarity, concentrations are converted to counts.

Mean	X_P				X_{R_1}			
Case	SSA	CLE	lin.CLE	$\hat{X}_{P,T}$	SSA	CLE	lin.CLE	$\hat{X}_{R_1,T}$
hyperbolic	19.97	19.94	20.01	20	799.2	797.7	799.1	800
exponential	20.24	20.27	20.02	20	808.8	807.8	800.0	800

Variance	X_P				X_{R_1}			
Case	SSA	CLE	lin.CLE	$(P_T)_{11}$	SSA	CLE	lin.CLE	$(P_T)_{22}$
hyperbolic	12.17	11.99	11.73	11.95	17222	16941	16939	17065
exponential	4.92	4.87	4.72	4.86	6764	6464	6571	6709

Cross-correlation

Case	SSA	CLE	lin.CLE	$(P_T)_{12}$
hyperbolic	419.3	413.2	408.6	413.2
exponential	136.9	131.8	132.0	134.7

The only unsolicited finding is that the average plasmid count in the exponential case is above 20.2 in the nonlinear simulations (SSA, CLE). This is apparently caused by a difference between the steady state of the ordinary differential equation and the mean of the state in the stochastic models (SSA, CLE) which is fundamentally a consequence of the nonlinearity of chemical reaction models.

The linearisation method proposed to estimate steady state fluctuations of molecular counts proved reliable and accurate in our two examples. It cut computation time from hours needed for the intensive simulations to less than a second. In both examples we had $n = 2$ state variables, which led to ordinary differential equations in five variables. In the general n-dimensional case one would have an $n + \frac{n(n+1)}{2}$-dimensional ordinary differential equation to solve.

Assuming that one has a matrix differential equation solver, our method is easy to implement numerically and it only requires calculations that can be automated. There is no obstacle to applying the method in a system with many more variables. (However we note that in our examples we used direct calculations to derive ordinary differential equations in five scalar variables.) These are major advantages over van Kampen's linear noise approximation (van Kampen, 1992) that was used by Hayot and Jayaprakash (2004) who pointed out that with increasing number of reactants and reactions van Kampen's analytical results are 'typically difficult to obtain' and 'cumbersome to analyse'.

4 Direction of future research

Today there is no general stochastic theory of reaction networks that would allow algorithmical analysis. Any idea that has a chance of making progress in this direction is well worth studying.

Both for the analysis and design of intracellular reaction systems it is fundamentally important to understand how the biochemical workings of microbes achieve robust behaviour under a wide range of (external and internal) circumstances. In this report we have briefly discussed why stochastic models are better suited to biochemistry than ODE models, which were originally developed for the chemistry of solutions of volume much greater than a cell. In addition to developing system size reduction techniques and consequent computational improvements, we showed that Gillespie's chemical Langevin equation gives the same first two moments as the widely accepted chemical master equation. This, in conjunction with the fact that in experiments typically only the means and the correlations among the concentrations of reactant species are measured, supports the use of the CLE as a substitute for the CME.

In the second half of the report we studied the covariance properties of concentrations. The linearisation method pointed out that around a positive steady state of the underlying ODE noise affects the concentrations both additively and multiplicatively even in a first-order approximation to the CLE.

This brings us to our research question how the robustness of biochemical systems, their reliability and capability to avoid break-down caused by internal or external noise could be assessed. We think that we have identified a gap between the theory of stochastic processes for biochemical reactions and the theory of Lyapunov and storage functions from dynamical systems and control theory, and our main aim is to establish a connection here. We envisage an approach based on stochastic Lyapunov functions (Kushner, 1967).

The observation that the CLE is inherently loaded with an additive noise term implies that even in equilibrium distribution the state will have a sustained nonzero covariance. Hence convergence to a single state in the state space cannot be expected. Instead, such a Lyapunov function would inform us about how likely it is that the system escapes the safe region of its activity—this is what simulations cannot practically assess. Initially our focus will be the appropriate specialisation of stochastic safety verification methods (Prajna, Jadbabaie, and Pappas, 2004, 2007) to the chemical Langevin equation. Constructing the barrier certificates that lie at the heart of this method can be most easily done by the *sum of squares* (SOS) technique (Parrilo, 2000), and for practical implementation the corresponding SOSTOOLS algorithm package can be used (Prajna *et al.*, 2002). This line of enquiry would extend and generalise work by El Samad and Khammash (2004) and El-Samad *et al.* (2006) in that it would be based on the CLE formulation instead of certain less rigorous stochastic models.

Another research question we are interested in is estimating the time it takes for biochemical reaction systems to reach the proximity of their equilibrium distribution from a perturbed state. This assessment would broaden our understanding of the performance of these systems: it is not only the reliability to avoid break-downs that matters in a living organism, but also the speed with which a system can return to normal behaviour. The mathematical challenges to develop such results for specific examples in the CLE (or the CME) setting would be substantial due to the multivariable, nonlinear nature of these systems. The only result we are aware of about the expected time to reach equilibrium in a chemical system considers a single-variable system (Vellela and Qian, 2007). However, the author has experience in deriving estimates for the time that discrete time Markov chains (especially Markov chain Monte Carlo methods) on combinatorial structures require to reach equilibrium distribution (Mélykúti, 2006) and wishes to explore whether similar methods can be applied in this setting.

Acknowledgements

The author wishes to acknowledge financial support from the EPSRC through the Life Sciences Interface Doctoral Training Centre, University of Oxford. His work was enormously helped by discussions with his supervisors, Dr. Antonis Papachristodoulou and Prof. Alison Etheridge, for which he is most grateful.

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Appendix

Proof of Lemma 2.2.1

Proof. Let us denote the factor in Gillespie's factorisation by

$$\sigma(X) = S\,\mathrm{diag}(\sqrt{a_1(X)}, \ldots, \sqrt{a_m(X)}).$$

First we prove that the nullvectors of $B(X)$ are the same as the left nullvectors of $\sigma(X)$.

If $y \in \mathbb{R}^n \setminus \{0\}$ is a nullvector of $B(X)$, then $0 = B(X)y = \sigma(X)\sigma(X)^T y$, hence $0 = y^T\sigma(X)\sigma(X)^T y = \|\sigma(X)^T y\|^2 = \|y^T\sigma(X)\|^2$, so $y^T\sigma(X) = 0$, and y is a left nullvector to $\sigma(X)$.

In the other direction, if $y^T\sigma(X) = 0$, then $0 = (y^T\sigma(X))(\sigma(X)^T y) = y^T(\sigma(X)\sigma(X)^T y)$, so $y \perp \sigma(X)\sigma(X)^T y$. But then y is contained in $(\mathrm{Im}(\sigma(X)\sigma(X)^T))^\perp = \mathrm{Ker}\left((\sigma(X)\sigma(X)^T)^T\right) = \mathrm{Ker}(\sigma(X)\sigma(X)^T)$. Hence $B(X)y = \sigma(X)\sigma(X)^T y = 0$.

We only need to prove that the left nullvectors of $\sigma(X)$ and S are the same. But this is obvious, since $\sqrt{a_1(X)}, \ldots, \sqrt{a_m(X)}$ are all positive by assumption. □

Proof of Lemma 2.2.2

Proof. The column rank of $S \in \mathbb{R}^{n\times m}$ is just $\dim(\mathrm{Im}\, S)$. It is well known that

$$\dim(\mathrm{Im}\, S) + \dim(\mathrm{Ker}\, S) = m.$$

The row rank of S is the column rank of S^T, or $\dim(\mathrm{Im}\, S^T)$. Similarly,

$$\dim(\mathrm{Im}\, S^T) + \dim(\mathrm{Ker}\, S^T) = n.$$

It is also well known that the column and row ranks are always equal. Therefore

$$m - \dim(\mathrm{Ker}\, S) = \mathrm{rank}\, S = n - \dim(\mathrm{Ker}\, S^T).$$

□

State space reduction for Construction 4

For Construction 4 a finer partitioning of the matrices is proposed. Let us order the columns of $S \in \mathbb{R}^{n\times m}$ such that we have $S = [S_1\ S_2\ S_3\ S_4]$, where the columns of $S_1 \in \mathbb{R}^{n\times(m-\dim(\mathrm{Ker}\, S))}$ form a basis for $\mathrm{Im}\, S$; S_3 is the collection of the column vectors which are constant multiples of any single column of S_1; the columns of S_2 represent all the directions specified by columns of S that are distinct to directions of the columns of S_1 (columns of S_2 are linearly dependent on columns of S_1, they are a linear combination of more than one); and finally S_4 is the collection of the column vectors which are constant multiples of any single column of S_3. Let the sizes of these matrices define r_2, r_3 and r_4: $S_2 \in \mathbb{R}^{n\times r_2}$, $S_3 \in \mathbb{R}^{n\times r_3}$, $S_4 \in \mathbb{R}^{n\times r_4}$. Obviously, $m - \dim(\mathrm{Ker}\, S) + r_2 = s$, and $r_2 + r_3 + r_4 = \dim(\mathrm{Ker}\, S)$. The entries of $A(X)$ are permuted accordingly, and then $A(X)$ is partitioned to blocks.

This uniquely specifies the matrices

$$\begin{aligned} N &\in \mathbb{R}^{(m-\dim(\mathrm{Ker}\, S))\times r_2}, \\ M_3 &= [v^{(1)}\ \ldots\ v^{(r_3)}] \in \mathbb{R}^{(m-\dim(\mathrm{Ker}\, S))\times r_3}, \\ M_4 &= [w^{(1)}\ \ldots\ w^{(r_4)}] \in \mathbb{R}^{r_2\times r_4}, \end{aligned}$$

such that $S_2 = S_1 N$, $S_3 = S_1 M_3$, $S_4 = S_2 M_4$, and all $v^{(i)}$ and $w^{(k)}$ have only one nonzero entry each. Then let

$$J = \begin{bmatrix} I_{m-\dim(\operatorname{Ker} S)} & 0 \\ 0 & I_{r_2} \\ 0 & 0 \\ 0 & 0 \end{bmatrix} \in \mathbb{R}^{m \times s},$$

$$V = \begin{bmatrix} I_{m-\dim(\operatorname{Ker} S)} & 0 & M_3 & 0 \\ 0 & I_{r_2} & 0 & M_4 \end{bmatrix} \in \mathbb{R}^{s \times m},$$

J having first r_3 then r_4 rows of zeros.

The construction is again (2.3.1). For the sake of notational clarity, let

$$C_1(X) = A_1(X) + \sum_{j=1}^{r_3} (A_3(X))_{jj} v^{(j)} v^{(j)T} \in \mathbb{R}^{(m-\dim(\operatorname{Ker} S)) \times (m-\dim(\operatorname{Ker} S))},$$

$$C_2(X) = A_2(X) + \sum_{j=1}^{r_4} (A_4(X))_{jj} w^{(j)} w^{(j)T} \in \mathbb{R}^{r_2 \times r_2}.$$

Then

$$VA(X)V^T = \begin{bmatrix} C_1(X) & 0 \\ 0 & C_2(X) \end{bmatrix}$$

is diagonal. $SJV = S$ and (1.3.1) hold. Defining T with S_1 in the role of S_b,

$$g(X) = S_1 \begin{bmatrix} \sqrt{C_1(X)} & N\sqrt{C_2(X)} \end{bmatrix},$$

$$Tg(X) = \begin{bmatrix} \sqrt{C_1(X)} & N\sqrt{C_2(X)} \\ 0 & 0 \end{bmatrix},$$

of which the nonzero blocks together are in $\mathbb{R}^{(m-\dim(\operatorname{Ker} S)) \times s}$, as required.

Proof of Theorem 3.3.1

Proof. We will follow the calculation for Theorem 3.1.1. Since $\mathrm{d}X^* = 0$, (3.2.3) becomes

$$\mathrm{d}x_t = Fx_t\,\mathrm{d}t + G\,\mathrm{d}B_t + \sum_{j=1}^{m} G_j x_t\,\mathrm{d}B_{j,t}. \tag{A.1}$$

Taking expectation on both sides one arrives at

$$\mathrm{d}\hat{x}_t = F\hat{x}_t\,\mathrm{d}t. \tag{A.2}$$

This proves the first claim.

For the covariance matrix $P_t = \mathrm{E}(x_t x_t^T) - \hat{x}_t \hat{x}_t^T$, we will apply (3.1.2) to $\mathrm{d}(x_t x_t^T)$ and $\mathrm{d}(\hat{x}_t \hat{x}_t^T)$, and then substitute the right-hand sides of (A.1) and (A.2), respectively.

$$\begin{aligned}\mathrm{d}(x_t x_t^T) &= Fx_t x_t^T\,\mathrm{d}t + (G\,\mathrm{d}B_t)x_t^T + \sum_j (G_j x_t\,\mathrm{d}B_{j,t})x_t^T \\ &\quad + x_t x_t^T F^T\,\mathrm{d}t + x_t(G\,\mathrm{d}B_t)^T + x_t \sum_j (G_j x_t\,\mathrm{d}B_{j,t})^T \\ &\quad + \left(Fx_t\,\mathrm{d}t + G\,\mathrm{d}B_t + \sum_j G_j x_t\,\mathrm{d}B_{j,t}\right)\left(x_t^T F^T\,\mathrm{d}t + (G\,\mathrm{d}B_t)^T + \sum_j (G_j x_t\,\mathrm{d}B_{j,t})^T\right),\end{aligned}$$

by substituting (A.1). Then by the computation rules from the proof of Lemma 2.0.1

$$\begin{aligned}\mathrm{d}(x_t x_t^T) &= Fx_t x_t^T\,\mathrm{d}t + (G\,\mathrm{d}B_t)x_t^T + \sum_j (G_j x_t\,\mathrm{d}B_{j,t})x_t^T \\ &\quad + x_t x_t^T F^T\,\mathrm{d}t + x_t(G\,\mathrm{d}B_t)^T + x_t\sum_j (G_j x_t\,\mathrm{d}B_{j,t})^T \\ &\quad + \left(\sum_j G_{\cdot j}(G_{\cdot j})^T + \sum_j G_{\cdot j}x_t^T G_j^T + \sum_j G_j x_t (G_{\cdot j})^T + \sum_j G_j x_t x_t^T G_j^T\right)\mathrm{d}t.\end{aligned}$$

After taking expectations one gets

$$\begin{aligned}\mathrm{d}\mathrm{E}(x_t x_t^T) &= F\mathrm{E}(x_t x_t^T)\,\mathrm{d}t + \mathrm{E}(x_t x_t^T)F^T\,\mathrm{d}t + \left(\sum_j G_{\cdot j}(G_{\cdot j})^T + \right. \\ &\quad \left. + \sum_j G_{\cdot j}\hat{x}_t^T G_j^T + \sum_j G_j\hat{x}_t(G_{\cdot j})^T + \sum_j G_j\mathrm{E}(x_t x_t^T)G_j^T\right)\mathrm{d}t.\end{aligned}$$

Formula (3.1.2) for the differential of a product can be used to compute $\mathrm{d}(\hat{x}_t\hat{x}_t^T)$ too:

$$\begin{aligned}\mathrm{d}(\hat{x}_t\hat{x}_t^T) &= (\mathrm{d}\hat{x}_t)\hat{x}_t^T + \hat{x}_t\,\mathrm{d}\hat{x}_t^T + \mathrm{d}\hat{x}_t\,\mathrm{d}\hat{x}_t^T \\ &= F\hat{x}_t\hat{x}_t^T\,\mathrm{d}t + \hat{x}_t\hat{x}_t^T F^T\,\mathrm{d}t\end{aligned}$$

by (A.2). The third term vanishes. $\mathrm{d}P_t$ is given by the difference of the last two equations.

$$\begin{aligned}\mathrm{d}P_t &= (FP_t + P_tF^T)\,\mathrm{d}t + \sum_j (G_{\cdot j} + G_j\hat{x}_t)(G_{\cdot j} + G_j\hat{x}_t)^T\,\mathrm{d}t \\ &\quad - \sum_j G_j\hat{x}_t(G_j\hat{x}_t)^T\,\mathrm{d}t + \sum_j G_j\mathrm{E}(x_t x_t^T)G_j^T\,\mathrm{d}t \\ &= \left(FP_t + P_tF^T + \sum_j (G_{\cdot j} + G_j\hat{x}_t)(G_{\cdot j} + G_j\hat{x}_t)^T + \sum_j G_j P_t G_j^T\right)\mathrm{d}t,\end{aligned}$$

and this completes the proof. □