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# The Relationship between Stochastic and Deterministic Models for Chemical Reactions*

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The Markov chain and ordinary differential equation models for chemical reaction systems are compared. It is shown that if the volume of the reaction system is taken into account in an appropriate way in the formulation of the Markov chain model, then the o.d.e. model is the infinite volume limit of the Markov chain model. A central limit theorem is also given for the deviation of the Markov chain model from the o.d.e. model.

## I. INTRODUCTION

A number of authors have considered Markov chain models for chemical reactions (see McQuarrie[1] for a survey of work done in this area), and the question has been raised as to the relationship between these models and the classical deterministic ordinary differential equation models. Oppenheim, Shuler, and Weiss[2] have shown in certain special cases that the deterministic model is the infinite volume limit of the Markov chain models and conclude that the same must be the case for more complex systems of reactions. The present paper is a restatement of results obtained in Refs. 3–5 in terms of the chemical reaction models and proves that this conclusion is indeed correct.

## II. FORMULATION OF THE MODEL

The only difference between our formulation of the Markov chain models and earlier formulations is that we take explicitly into account the volume of the reaction system. In particular, for a reaction involving two molecules we assume that the chance of a *particular* pair of molecules reacting during a short interval of time $[t, t+\Delta t]$ is inversely proportional to the volume $V$ of the reaction system. Similarly, for a reaction involving $l$ molecules we assume that the chance of $l$ particular molecules reacting during a short interval of time is inversely proportional to $V^{l-1}$. The reason for this assumption can be seen by considering the probability of $l$ balls placed at random in $n$ boxes all ending up in the same box.

The chance of having some $l$ molecules react in a short interval of time is then inversely proportional to $V^{l-1}$ and proportional to the number of different ways of selecting the $l$ molecules.

For the simple reaction $A+B\rightarrow C$ the chance of the reaction occurring in the time interval $[t, t+\Delta t]$ is approximately $\alpha(i_1i_2/V)\Delta t\equiv V\alpha(i_1/V)(i_2/V)\Delta t$, where $i_1$ is the number of molecules of $A$ present, $i_2$ is the number of molecules of $B$, and $\alpha$ is some constant.

In general consider a system of $M$ reactants, $R_1$, $R_2, \cdots, R_M$, undergoing $N$ reversible reactions

$$\sum_{m=1}^{M} c_{nm}R_m \leftrightarrows \sum_{m=1}^{M} d_{nm}R_m, \qquad n=1, 2, \cdots, N. \quad (2.1)$$

The Markov chain model for this system may be formulated either in terms of the number of molecules of each of the reactants present at time $t$, $X^V(t)=[X_1^V(t)X_2^V(t)\cdots X_M^V(t)]$, or in terms of the number of times each of the reactions has occurred in the forward direction minus the number of times it has occurred in the reverse direction,

$$Y^V(t)=[Y_1^V(t), Y_2^V(t)\cdots Y_N^V(t)].$$

Letting $C$ denote the matrix $[(c_{nm})]$ and $D$ the matrix $[(d_{nm})]$, $X^V(t)$ and $Y^V(t)$ are related by

$$X^V(s)+[Y^V(t+s)-Y^V(s)](D-C)=X^V(t+s). \quad (2.2)$$

Let

$$c_n=\sum_{m=1}^{M} c_{nm}$$

and

$$d_n=\sum_{m=1}^{M} d_{nm}.$$

(Of course $c_{nm}$ and $d_{nm}$ are nonnegative integers.) The chance of the $n$th reaction occurring in the forward direction during the interval $[t, t+\Delta t]$ is approximately

$$\alpha_n(V^{c_n-1})^{-1}\left[\prod_{m=1}^{M}\binom{i_m}{c_{nm}}\right]\Delta t$$

$$=V\alpha_n\left[\prod_{m=1}^{M}(V^{c_{nm}})^{-1}\binom{i_m}{c_{nm}}\right]\Delta t\equiv Vf_n{}^V(\mathbf{i})\Delta t \quad (2.3)$$

and in the reverse direction

$$\beta_n(V^{d_n-1})^{-1}\left[\prod_{m=1}^{M}\binom{i_m}{d_{nm}}\right]\Delta t$$

$$=V\beta_n\left[\prod_{m=1}^{M}(V^{d_{nm}})^{-1}\binom{i_m}{d_{nm}}\right]\Delta t\equiv Vg_n{}^V(\mathbf{i})\Delta t, \quad (2.4)$$

where $\mathbf{i}=X^V(t)$.

For $\mathbf{x}=(x_1x_2\cdots x_M)$ define

$$f_n(\mathbf{x})=\alpha_n\prod_{m=1}^{M}\frac{x_m{}^{c_{nm}}}{c_{nm}!}$$

and

$$g_n(\mathbf{x})=\beta_n\prod_{m=1}^{M}\frac{x_m{}^{d_{nm}}}{d_{nm}},$$

and observe that

$$f_n{}^V(\mathbf{i})=f_n(V^{-1}\mathbf{i})+O(V^{-1})$$

and

$$g_n{}^V(\mathbf{i})=g_n(V^{-1}\mathbf{i})+O(V^{-1}).$$

If $c_{nm}$ and $d_{nm}$ are either 0 or 1 for all $n$ and $m$, then equality holds without $O(V^{-1})$.

Finally, define

$$F^V(\mathbf{i})=[F_1{}^V(\mathbf{i}),\cdots,F_m{}^V(\mathbf{i})],$$

where

$$F_m{}^V(\mathbf{i})=\sum_{n=1}^{N}(d_{nm}-c_{nm})[f_n{}^V(\mathbf{i})-g_n{}^V(\mathbf{i})]$$

and

$$F(\mathbf{x})=[F_1(\mathbf{x})\cdots F_m(\mathbf{x})],$$

where

$$F_m(\mathbf{x})=\sum_{n=1}^{N}(d_{nm}-c_{nm})[f_n(\mathbf{x})-g_n(\mathbf{x})].$$

It can be shown that

$$\frac{dE(V^{-1}X^V(t))}{dt}=E(F^V[X^V(t)])$$

$$=E(F[V^{-1}X^V(t)])+O(V^{-1}). \quad (2.5)$$

($E(\ )$ denotes the expectation of a random variable.) The system of differential equations $\dot{X}=F(X)$ is just the classical, deterministic model for our reaction system. Let $X(t,\mathbf{x}_0)$ denote the solution of the initial value problem

$$\frac{\partial X(t,\mathbf{x}_0)}{\partial t}=F(X(t,\mathbf{x}_0)), \qquad X(0,\mathbf{x}_0)=\mathbf{x}_0.$$

If

$$\lim_{V\to\infty}V^{-1}X^V(0)=\mathbf{x}_0,$$

then the theorems of Refs. 3–5 allow us to conclude that

$$\lim_{V\to\infty}P\{\sup_{s\le t}|V^{-1}X^V(s)-X(s,x_0)|>\epsilon\}=0 \quad (2.6)$$

for every $t$ and $\epsilon>0$.

We can obtain estimates on the probabilities in (2.6) in two different ways. The first is similar to the Chebychev Inequality of elementary probability and the second is similar to the Central Limit Theorem.

## III. AN INEQUALITY

Let

$$\Gamma(\mathbf{x})=\sum_{n=1}^{N}[\sum_{m=1}^{M}(d_{nm}-c_{nm})^2][f_n(\mathbf{x})+g_n(\mathbf{x})],$$

and

$$K_\epsilon=\{\mathbf{x}:\inf_{s\le t}|\mathbf{x}-X(s,\mathbf{x}_0)|\le\epsilon\};$$

i.e., $K_\epsilon$ is the set of points within a distance $\epsilon$ of the trajectory $X(s,x_0)$, $s\le t$. Define

$$\Gamma=\sup_{\mathbf{x}\in K_\epsilon}\Gamma(\mathbf{x}),$$

$$M=\sup_{\mathbf{x}_1,\mathbf{x}_2\in K_\epsilon}[|F(\mathbf{x}_1)-F(\mathbf{x}_2)|/|\mathbf{x}_1-\mathbf{x}_2|],$$

and

$$\eta=\sup_{(1/V)\mathbf{i}\in K_\epsilon}|F(V^{-1}\mathbf{i})-F^V(\mathbf{i})|.$$

Lemma (1.2) and the inequalities in Sec. 2 of Ref. 5 imply

$$P\{\sup_{s\le t}|V^{-1}X^V(s)-X(s,\mathbf{x}_0)|\ge\epsilon\}\le t\Gamma/(V\delta^2) \quad (3.1)$$

provided $\delta\equiv\epsilon e^{-Mt}-|V^{-1}X^V(0)-\mathbf{x}_0|-t\eta>0$.

It is reasonable to assume that $Y^V(0)=0$. Under this assumption define $\hat{F}^V(\mathbf{j})=[\hat{F}_1{}^V(\mathbf{j})\cdots\hat{F}_N{}^V(\mathbf{j})]$, where

$$\hat{F}_n{}^V(\mathbf{j})=f_n{}^V[X^V(0)+\mathbf{j}(D-C)]-g_n{}^V[X^V(0)+\mathbf{j}(D-C)],$$

$$\hat{F}(\mathbf{y})=[\hat{F}_1(\mathbf{y})\cdots\hat{F}_N(\mathbf{y})]$$

where

$$\hat{F}_n(\mathbf{y})=f_n[\mathbf{x}_0+\mathbf{y}(D-C)]-g_n[\mathbf{x}_0+\mathbf{y}(D-C)],$$

and

$$\hat{\Gamma}(\mathbf{y})=\sum_{n=1}^{N}\{f_n[\mathbf{x}_0+\mathbf{y}(D-C)]+g_n[\mathbf{x}_0+\mathbf{y}(D-C)]\}.$$

Let $Y(t)$ denote the solution of

$$\partial Y(t)/\partial t=\hat{F}[Y(t)],$$
$$Y(0)=0.$$

Then with $\hat{\Gamma}$, $\hat{M}$ and $\hat{\eta}$ defined in a manner similar to $\Gamma$, $M$, and $\eta$ we have

$$P\{\sup_{s\leq t} | V^{-1}Y^V(s)-Y(s) | \geq\epsilon\}\leq t\hat{\Gamma}/(V\delta^2) \quad (3.2)$$

provided $\delta\equiv\epsilon \exp(-\hat{M}t)-t\hat{\eta}>0$.

Note: If $| \mathbf{x}_0-V^{-1}X^V(0) |=O(V^{-1})$ then $\hat{\eta}=O(V^{-1})$.

## IV. A CENTRAL LIMIT THEOREM

Let

$$\gamma_{ij}(\mathbf{x})=\sum_{n=1}^{N} (d_{ni}-c_{ni})(d_{nj}-c_{nj})[f_n(\mathbf{x})+g_n(\mathbf{x})].$$

Theorem (3.5) of Ref. 5 implies the following: If

$$\lim_{V\to\infty} V^{1/2}[V^{-1}X^V(0)-\mathbf{x}_0]=0$$

then

$$\lim_{V\to\infty} P\{V^{1/2}[V^{-1}X^V(t)-X(t,\mathbf{x}_0)] \in (a_1,b_1)\times(a_2,b_2)\times\cdots\times(a_M,b_M)\}$$
$$=P\{W(t)\in(a_1,b_1)\times(a_2,b_2)\times\cdots\times(a_M,b_M)\}$$

where $W(t)$ has a multivariate normal distribution with a characteristic function $\psi(t,\boldsymbol{\theta})\equiv E(\exp\{i\boldsymbol{\theta}\cdot W(t)\})$ satisfying

$$(\partial/\partial t)\psi(t,\boldsymbol{\theta})=-\tfrac{1}{2}\sum_{j,k}\theta_j\theta_k\gamma_{jk}[X(t,\mathbf{x}_0)]\psi(t,\boldsymbol{\theta}) + \sum_{j,k}\theta_j\partial_k F_j[X(t,\mathbf{x}_0)](\partial/\partial\theta_k)\psi(t,\boldsymbol{\theta}). \quad (4.1)$$

[$\mathbf{z}\in(a_1,b_1)\times(a_2,b_2)\times\cdots\times(a_M,b_M)$ means $a_m<z_m<b_m$, $m=1,2,\cdots,M$.] Letting

$$h_{ij}(\mathbf{x})=\partial_i F_j(\mathbf{x})\equiv\partial F_j(\mathbf{x})/\partial x_i,$$

$G(\mathbf{x})$ be the matrix $((\gamma_{ij}(\mathbf{x})))$, $H(\mathbf{x})$ the matrix $((h_{ij}(\mathbf{x})))$ and $H^*(\mathbf{x})$ its adjoint, (4.1) implies $W(t)$ has mean zero and covariance matrix given by

$$\int_0^t \exp\left(\int_s^t H^*[X(u,\mathbf{x}_0)]du\right) G[X(s,\mathbf{x}_0)] \times\exp\left(\int_s^t H[X(u,\mathbf{x}_0)]du\right)ds. \quad (4.2)$$

The corresponding quantities for $Y^V$ are

$$\hat{\gamma}_{ij}(\mathbf{y})=0 \qquad i\neq j$$
$$=f_i[\mathbf{x}_0+\mathbf{y}(D-C)]+g_i[\mathbf{x}_0+\mathbf{y}(D-C)] \qquad \text{for } i=j$$

and

$$h_{ij}(\mathbf{y})=(\partial/\partial y_i)\hat{F}_j(\mathbf{y}).$$

If $| V^{-1}X^V(0)-\mathbf{x}_0 |=O(V^{-1})$ then

$$\lim_{V\to\infty} P\{V^{1/2}[V^{-1}Y^V(t)-Y(t)]\in(a_1,b_1)\times\cdots\times(a_N,b_N)\}$$
$$=P\{Z(t)\in(a_1,b_1)\times\cdots\times(a_N,b_N)\}$$

where $Z(t)$ is multivariate normal with mean zero and covariance matrix given by

$$\int_0^t \exp\left(\int_s^t \hat{H}^*[Y(u)]du\right)\hat{G}[Y(s)] \times\exp\left(\int_s^t \hat{H}[Y(u)]du\right)ds. \quad (4.3)$$

## V. EXAMPLE

Consider a single reaction $A+B\leftrightarrows C$. The $Y^V$ model is clearly the appropriate model to consider. We then have

$$f(\mathbf{x})=\alpha x_1x_2$$
$$g(\mathbf{x})=\beta x_3,$$
$$\hat{F}(y)=\alpha(x_1^0-y)(x_2^0-y)-\beta(x_3^0+y),$$
$$\hat{\Gamma}(y)=\hat{G}(y)=\alpha(x_1^0-y)(x_2^0-y)+\beta(x_3^0+y),$$

and

$$\hat{H}(y)=2\alpha y-\beta-\alpha(x_1^0+x_2^0).$$

Suppose $\alpha x_1^0x_2^0-\beta x_3^0=0$, that is $\mathbf{x}_0=(x_1^0,x_2^0,x_3^0)$ is the equilibrium value. Then $Y(t)\equiv0$ and the variance of the normal random variable $Z(t)$ is

$$\int_0^t \exp\{-(t-s)[\beta+\alpha(x_1^0+x_2^0)]\}(\alpha x_1^0x_2^0+\beta x_3^0) \times\exp\{-(t-s)[\beta+\alpha(x_1^0+x_2^0)]\}ds$$
$$=\frac{\alpha x_1^0x_2^0}{\beta+\alpha(x_1^0+x_2^0)}(1-\exp\{-2t[\beta+\alpha(x_1^0+x_2^0)]\}).$$

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