THE JOURNAL OF
PHYSICAL CHEMISTRY

# Fast variables elimination in stochastic kinetics

M. Frankowicz, M. Moreau, P. P. Szczesny, J. Toth, and L. Vicente

*J. Phys. Chem.*, **1993**, 97 (9), 1891-1895• DOI: 10.1021/j100111a029 • Publication Date (Web): 01 May 2002

J. Phys. Chem. 1993, 97, 1891-1895

# Fast Variables Elimination in Stochastic Kinetics

**M. Frankowicz,**[*,†] **M. Moreau,**[‡] **P. P. Szczęsny,**[†] **J. Tóth,**[§] **and L. Vicente**[⊥]

*Faculty of Chemistry, Jagellonian University, Cracow, Poland; Physique Théorique des Liquides, UPMC, Paris, France; Institute of Mathematics and Computer Science, Gödöllő, Hungary; and Faculty of Chemistry, UNAM, Mexico*

*Received: June 22, 1992; In Final Form: November 24, 1992*

The elimination of fast variables from the master equation of a complex chemical system is studied. Numerical treatments of full chemical schemes are compared with the results given by the master equation of reduced chemical schemes, and to a simple approximation of the full master equation based on a quasistationary assumption. It is found that although both methods give correct values of the deterministic concentrations, they do not permit the precise estimation of the variances. It is also shown that the systematic projection technique developed by other authors, when available, yields accurate values for the variance; in case this procedure cannot be used practically, useful bounds can nevertheless be obtained from the simple methods studied here.

## 1. Introduction

The problem of time evolution of a chemical system can be treated starting from two opposite levels of description; while "formal kinetics" investigates macroscopic kinetic equations which should correspond to the stoichiometry, microscopic theories deal with elementary reaction acts and try to find expressions for the reaction rates from the atomic and molecular properties. The reaction mechanisms deduced from stoichiometry are usually not unique; only recently, with development of new experimental techniques, one has been able to propose realistic mechanisms for a large class of chemical reactions. One found that even stoichiometrically simple reactions consist of many elementary steps involving various transient compounds, radicals etc. The mathematical description of such "full" schemes involving systems of coupled nonlinear differential equations is very difficult and usually only numerical analysis is possible (this analysis is not always reliable because of the instability of numerical procedures of solutions of nonlinear differential equations). Because of the above difficulties, much work has been done to find some models which would be sufficiently simple to allow for a detailed mathematical analysis (e.g., by means of the bifurcation theory) but also could display such features as spatial or temporal oscillations, excitability, multistability or chaotic behavior. Among such models one may quote the Brusselator, Oregonator, the Schlögl model, and the Rössler model (for a review, see ref 1). These models are often regarded as simplified versions of realistic multistage schemes reduced by suitable approximations in a deterministic description. The most currently used approximation is elimination of fast variables using quasistationary hypothesis; the outline of the method is shortly summarized in section 2. Section 3 is devoted to the problem of elimination of fast variables in the presence of internal fluctuations in the master equation formalism. In particular, an approximation based on a quasistationary approximation of the full master equation is proposed. Section 4 presents an example of the application of our method to the cubic autocatalator model, and the Ogg's model of decomposition of $N_2O_5$ is analyzed in section 5. Section 6 contains discussion of numerical results and comparison of our approach with the projector procedure used by Janssen. Conclusions are presented in section 7.

## 2. Deterministic Reduction

Let us consider formal kinetic equations involving two species X, Y, the concentrations of which are $x,y$:

$$dx/dt = f(x,y)$$

$$dy/dt = (1/\epsilon)g(x,y) \tag{1}$$

Here $f$ and $g$ are given functions, and $\epsilon$ is a small parameter. Then $y$ evolves much more rapidly than $x$ toward a quasistationary value $y_0(x)$ such that $g$ vanishes, and the system

$$dx/dt = f(x,y_0(x))$$

$$g(x,y_0(x)) = 0 \tag{2}$$

gives an approximate solution of (1). This method, which is sketched here in its simplest form, is usually used in chemistry[2] or in biochemistry to treat models of enzymatic reactions.[3] Its mathematical foundations and more detailed formulations have been given by Tikhonov.[4]

It has to be stressed that the applicability of the method depends on the chemical considerations and experimental results; in particular one has to choose properly the small parameters. One should also remark that the rate functions in kinetic equations derived from the full schemes are polynomials, while in the reduced schemes they are often rational fractions and they reduce to polynomials only if some terms are neglected, which is often not justified from the chemical point of view.

## 3. Stochastic Approach

In studying the fluctuations in chemical systems one applies usually simplified models (like the Schlögl model or Brusselator), arguing that these models are justified from chemical point of view because they may be obtained by the reduction of some real schemes (in particular it concerns trimolecular steps which are presented as condensed sequences of bimolecular steps[5,6]). One performs the direct stochastization of reduced deterministic schemes. Practically all analytical results as well as Monte Carlo or molecular dynamics simulations are limited to such models. There are only few works dealing with more realistic schemes.[7-9]

On the other hand, one may start from the full stochastic description and then proceed with reduction: this should in principle be a correct, although heavy, procedure.

It will be shown that in general these two paths to obtain a reduced stochastic model do not "commute" and that reduced

---

[†] Jagellonian University.

[‡] UPMC.

[§] Institute of Mathematics and Computer Science.

[⊥] UNAM.

0022-3654/93/2097-1891$04.00/0

chemical schemes are often unable to describe concentration fluctuations. Thus one should only use some approximations deduced from the complete description.

There were already some attempts to perform stochastic reduction starting from stochastic differential equation[10] according to the stochastic center manifold theory. It was done for small noise by Knobloch and Wiesenfeld[11] and by Schoner and Haken[12] (also taking as a reference deterministic solutions). A more general approach was proposed by Arnold and Boxler.[13]

Recently, Sulpice et al.[14] applied a stochastic version of the normal form theory to study a continuous approximation of the master equation in the neighborhood of a Hopf bifurcation, and in more complex cases. However the method cannot be handled easily, and it gives no practical response to the question of approximating a complex system by a simpler one which would, at least qualitatively, reproduce the behavior of the system in a large range of parameters.

An alternative approach is to start from a multivariate master equation.[1] We consider the formal case of two species X,Y reacting according to the mechanism

$$\alpha\mathrm{X} + \beta\mathrm{Y} \xrightarrow{k_1} \mathrm{P}_1$$

$$\gamma\mathrm{X} + \delta\mathrm{Y} \xrightarrow{k_2} \mathrm{P}_2 \qquad (3)$$

where $\alpha$, $\beta$, $\gamma$, and $\delta$ are stoichiometric coefficients, and $\mathrm{P}_1$ and $\mathrm{P}_2$ the products. The number of molecules X changes by $a$ ($c$) in the first (second) reaction, and the number of Y changes by $b$ ($d$); $a$, $b$, ..., may differ from $\alpha$, $\beta$, ..., if X or Y appears among the products.

The probability $P(X,Y,t)$ of having $X$ and $Y$ molecules of the respective species at time $t$ obeys the master equation

$$\partial P(X,Y,t)/\partial t = f(X-a,Y-b)\ P(X-a,Y-b,t) - f(X,Y)\ P(X,Y,t) + g(X-c,Y-d)\ P(X-c,Y-d,t) - g(X,Y)P(X,Y,t) \qquad (4)$$

where $f$ and $g$ are the transition rates of the first and second reaction. Following van Kampen[16] and Janssen,[15] we introduce the operators $E_x^m$ and $E_y^n$ (where $m$ and $n$ are positive or negative integers) which respectively change $X$ into $X + m$ and $Y$ into $Y + n$; for instance $E_x^m$ changes a function $\Phi(x)$ into $\Phi(X+m)$. Then (4) can be written in the condensed form

$$\partial P(X,Y,t)/\partial t = (E_x^{-a}E_y^{-b} - I)fP + (E_x^{-c}E_y^{-d} - I)gP \qquad (5)$$

If one reation in the scheme (3) is much faster than the other one, an approximate solution of (5) can be investigated. Following the general theory of van Kampen,[16] Janssen[15] has developed a projection technique that permits in particular cases to obtain an approximate master equation explicitly. However, the procedure is complex, rather heavy, and cannot be applied in all cases. The results of Janssen, when available, will be used for numerical treatment. However, we will now study less systematic but far simpler method, which applies when one of the variables evolves much more rapidly than the other ones. This situation is expected to hold—but not necessarily—if some of the rate constants are much larger than the other ones; furthermore it is not obvious, as it will be shown later, which variables are fast and which are slow: the conclusion should be deduced from the analysis of the macroscopic equations or from simulations. Let us suppose, for instance, that $Y$ is much faster than $X$. Then the present method is based on the intuitive assumption that its conditional probability for a given value of X tends rapidly toward a quasistationary distribution (a similar assumption is currently done for open systems when the concentrations of some chemical species are kept constant).

On this purpose we first obtain an equation for the reduced probability:

$$\bar{P}(X,t) = \sum_Y P(X,Y,t)$$

Summing eq 4 over $Y$ gives

$$\partial\bar{P}(X,t)/\partial t = \langle f(X-a,Y)|X-a\rangle\bar{P}(X-a,t) - \langle f(X,Y)|X\rangle\bar{P}(X,t) + \langle g(X-c,Y)|X-c\rangle\bar{P}(X-c,t) - \langle g(X,Y)|X\rangle\bar{P}(X,t) = (E_x^{-a} - I)\langle f|X\rangle\bar{P} + (E_x^{-c} - I)\langle g|X\rangle\bar{P} \qquad (6)$$

where

$$\langle f|X\rangle = \sum_Y f(X,Y)\ P(Y|X)$$

$$P(Y|X) = P(X,Y)/\bar{P}(X)$$

are respectively the conditional average of $f$ and the conditional probability of $Y$ when $X$ is given. Obviously, (6) is not a closed equation. We introduce now the main assumption which implies that $P(Y|X)$ approximately satisfies the one-dimensional master equation obtained when $X$ is kept constant. Although no complete justification of this assumption can be given, it is supported by the physical interpretation of the conditional probability, which is the probability distribution of $Y$ when $X$ is known; since $X$ is practically constant on the time scale of fast variations of $Y$, we apply the master equation to $Y$ only, as is currently done[1] when some chemical species are kept constant. Using the mathematical definition of conditional probabilities, it can be seen that the assumption implies that $P(Y|X)$ is a sharply peaked function of $Y$ but changes only slowly with $X$, which is intuitively necessary in order to separate the motions of $X$ and $Y$. It is clear that the method can be valid only if the fluctuations of the fast variable are not too large. Then we have

$$\partial P(Y|X)/\partial t = (E_y^{-b} - I)fP(Y|X) + (E_y^{-d} - I)gP(Y|X) \qquad (7)$$

which allows us to calculate the conditional averages $\langle f|X\rangle$ and $\langle g|X\rangle$ and to close eq 6.

## 4. Cubic Autocatalator Model

Let us first consider the model reaction scheme:

$$\mathrm{A} + \mathrm{X} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{Y}$$

$$\mathrm{X} + \mathrm{Y} \xrightarrow{k_2} 3\mathrm{X} \qquad (8)$$

$$\mathrm{X} \xrightarrow{k_3} \mathrm{C}$$

The above scheme was investigated in detail from the deterministic point of view by Cook et al.[17] If $k_{-1}$ and $k_2$ are very large in comparison with $k_1$ and $k_3$, the concentration $y$ of Y is a fast variable, and its elimination yields

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \frac{k_1k_2ax^2}{k_{-1} + k_2x} - k_3x \qquad (9)$$

When $k_{-1} \gg k_2x$, this kinetics corresponds approximately to the scheme

$$\mathrm{A} + 2\mathrm{X} \xrightarrow{k} 3\mathrm{X}$$

$$\mathrm{X} \xrightarrow{k_3} \mathrm{C} \qquad (10)$$

with $k = k_1k_2/k_{-1}$, whereas if $k_{-1} \ll k_2x$, it corresponds to the scheme

$$\mathrm{A} + \mathrm{X} \xrightarrow{k_1} 2\mathrm{X}$$

$$\mathrm{X} \xrightarrow{k_3} \mathrm{C} \tag{11}$$

The full master equation for $P(X,Y,t)$ reads

$$\partial P/\partial t = k_1(E_xE_y^{-1} - I)AXP + k_{-1}(E_x^{-1}E_y - I)YP + k_2(E_x^{-2}E_y - I)XYP + k_3(E_x - I)XP \tag{12}$$

and the reduced master equation for $\bar{P}(X,t) = \sum_Y P(X,Y,t)$ is

$$\partial \bar{P}/\partial t = k_1(E_x - I)AX\bar{P} + k_{-1}(E_x^{-1} - I)\langle Y|X\rangle\bar{P} + k_2(E_x^{-2} - I)X\langle Y|X\rangle\bar{P} + k_3(E_x - I)X\bar{P} \tag{13}$$

The procedure is completed by assuming that $P' = P(Y|X)$ satisfies

$$\partial P'/\partial t = k_1(E_y^{-1} - I)AXP' + k_{-1}(E_y - I)YP' + k_2(E_y - I)XYP' \tag{14}$$

which yields

$$\langle Y|X\rangle = \frac{k_1AX}{k_{-1} + k_2X} \tag{15}$$

(13) with (15) is closed and yields for the average $\langle X\rangle$ and the variance $\langle \delta X^2\rangle$

$$\frac{\mathrm{d}}{\mathrm{d}t}\langle X\rangle = k_1k_2A\left\langle\frac{X^2}{k_{-1} + k_2X}\right\rangle - k_3\langle X\rangle \tag{16}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}\langle \delta X^2\rangle = 2\left[k_1k_2A\left(\left\langle\frac{X^3}{k_{-1} + k_2X}\right\rangle - \langle X\rangle\left\langle\frac{X^2}{k_{-1} + k_2X}\right\rangle\right) - k_3\right]\langle \delta X^2\rangle + (2k_1A + k_3)\langle X\rangle + 3k_1k_2A\left\langle\frac{X^2}{k_{-1} + k_2X}\right\rangle \tag{17}$$

These equations can be treated by the classical expansions in powers of the inverse volume $\Omega^{-1}$ by writing[16]

$$\langle X\rangle = \Omega x, \quad X = \Omega x + \Omega^{1/2}\xi \tag{18}$$

The first-order term gives the deterministic equation for $x$. The following order gives a closed equation for $\langle \xi^2\rangle$. In the case when $k_2x \gg k_{-1}$ we get for the original variable $X$

$$\frac{\mathrm{d}}{\mathrm{d}t}\langle X\rangle = (k_1A - k_3)\langle X\rangle$$

$$\frac{\mathrm{d}}{\mathrm{d}t}\langle \delta X^2\rangle = 2(k_1A - k_3)\langle \delta X^2\rangle + (5k_1A + k_3)\langle X\rangle \tag{19}$$

which (for $k_1A \neq k_3$) gives an exponential time behavior for $\langle X\rangle$ and $\langle \delta X^2\rangle$:

$$\langle X\rangle = \langle X(0)\rangle \exp(-\lambda t)$$

$$\langle \delta X^2\rangle = \langle \delta X^2(0)\rangle \exp(-2\lambda t) + \langle X(0)\rangle\nu(\exp(-\lambda t) - \exp(-2\lambda t)) \tag{20}$$

with $\lambda = k_3 - k_1A$ and $\nu = 1 + 6k_1A/(k_3 - k_1A)$. If $k_3 < k_1A$, the system is explosive and the fluctuations diverge (so that (18) does not hold); for $k_3 > k_1A$, both $\langle X\rangle$ and $\langle \delta X^2\rangle$ decrease exponentially. For $k_3 \gg k_1A$ the system becomes quasi-Poissonian ($\langle X\rangle \simeq \langle \delta X^2\rangle$), but the assumption $k_3x \gg k_{-1}$ is no longer valid when $\langle X\rangle$ becomes very small. In any case the fluctuations do not obey the kinetics of the reduced reaction scheme (11), although the concentration does.

## 5. Decomposition of $N_2O_5$

As a more realistic example, we will now consider the decomposition of $N_2O_5$. It can take different forms depending on the conditions, the simplest one obeying the overall equation

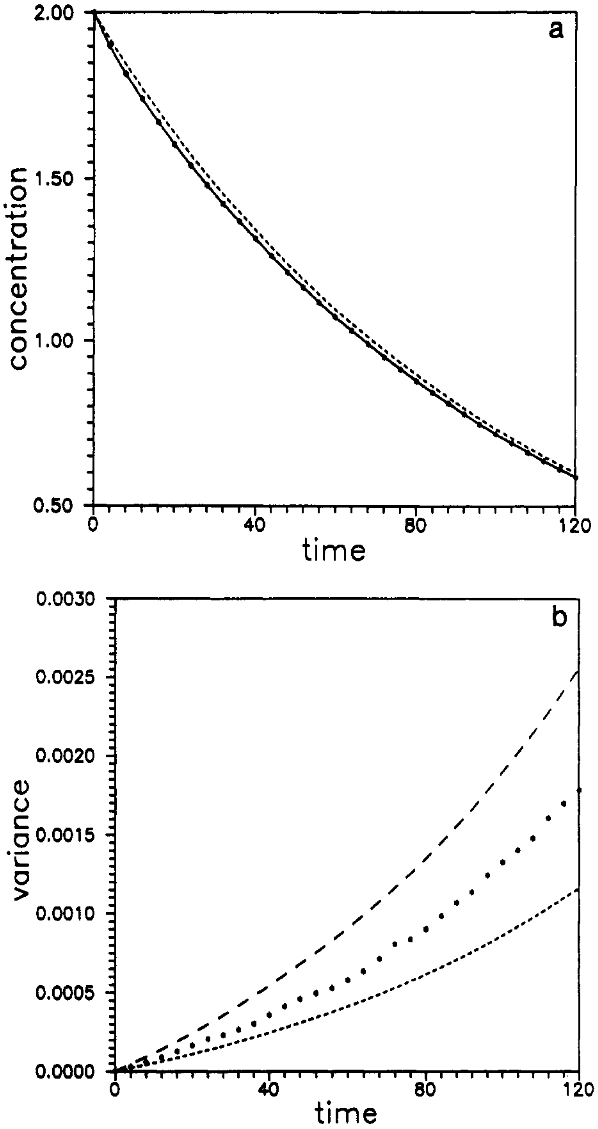

**Figure 1.** Cubic autocatalator model. $k_1 = 0.002$, $k_{-1} = 0.0001$, $k_2 = 0.1$, $k_3 = 0.0012$. Initial numbers of particles: $A(0) = 1000$, $X(0) = 2000$, $Y(0) = C(0) = 0$. Results of simulations: averaged over $10^4$ runs. (a) Time evolution of the mean concentration of X. Solid line denotes deterministic model (full scheme), broken line is the reduced model. Asterisks denote results of stochastic simulations for the full scheme. (b) Time evolution of the variance of $X$. Long dashes correspond to the proposed method (eq 20), short dashes to the reduced model (11), asterisks to stochastic simulations of the full model.

$$2\mathrm{N_2O_5} \rightarrow 4\mathrm{NO_2} + \mathrm{O_2} \tag{21}$$

However it is found experimentally that the kinetics is of first order, the concentration $[N_2O_5]$ of $N_2O_5$ obeying

$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathrm{N_2O_5}] = -k[\mathrm{N_2O_5}] \tag{22}$$

The following detailed mechanism was proposed by Ogg[18] in 1947:

$$\mathrm{N_2O_5} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \mathrm{NO_2} + \mathrm{NO_3}$$

$$\mathrm{NO_2} + \mathrm{NO_3} \xrightarrow{k_2} \mathrm{NO_2} + \mathrm{NO} + \mathrm{O_2}$$

$$\mathrm{NO_3} + \mathrm{NO} \xrightarrow{k_3} 2\mathrm{NO_2} \tag{23}$$

where the second and fourth reactions are much faster than the

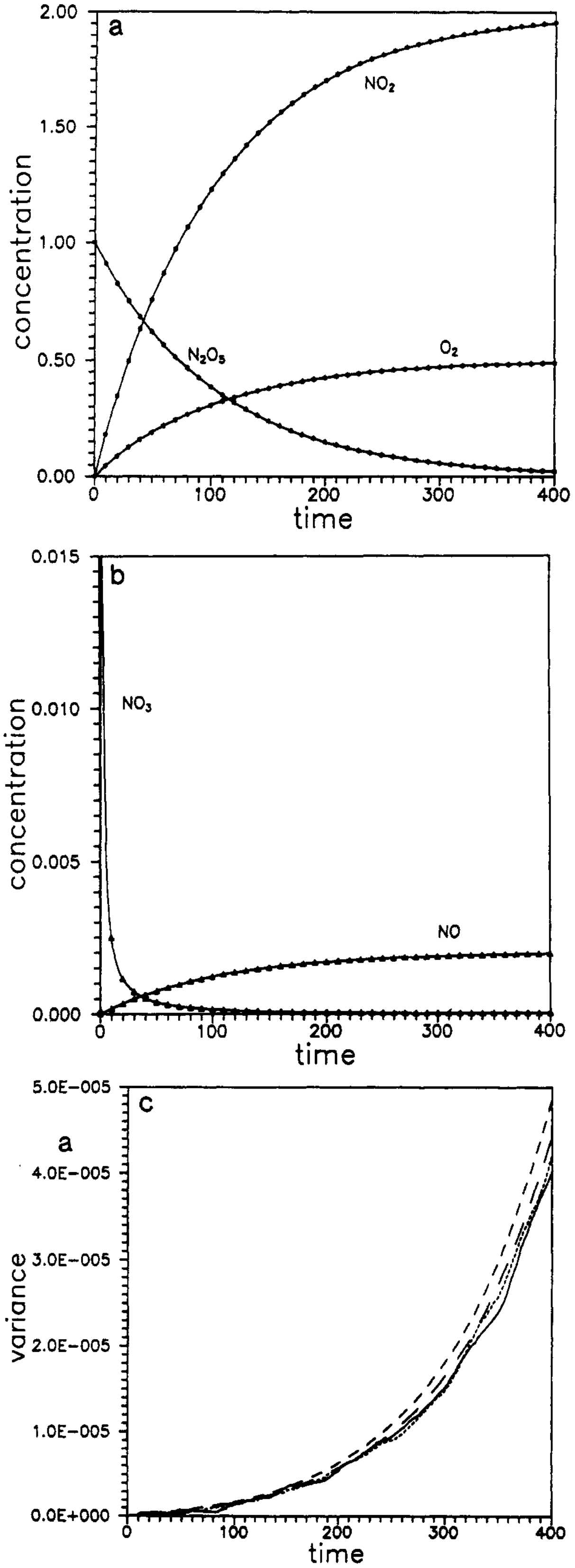

**Figure 2.** Decomposition of $N_2O_5$. $k_1 = 0.01$, $k_{-1} = 1$, $k_2 = 10$, $k_3 = 10000$. Initial numbers of particles: $N_2O_5(0) = 100\,000$, other species are initially absent. Results of simulations: averaged over $10^3$ runs. (a) Time evolution of the mean concentrations of $N_2O_5$, $NO_2$, and $O_2$ (full scheme). Solid line, deterministic model; asterisks, results of stochastic simulations. (b) Time evolution of the mean concentrations of $NO_3$ and NO (full scheme). Full line, deterministic model; triangles, results of stochastic simulations. (c) Time evolution of the variance of the number of particles of $N_2O_5$. Solid line, reduced scheme (eq 22); dotted line, full model; short dashes, our method; long dashes, Janssen's method (eq 25).

others. Assuming that $NO_3$ and NO are fast variables and performing their macroscopic elimination, it is found that $N_2O_5$ does obey the kinetics of eq 22 with

$$k = \frac{2k_1k_2}{k_{-1} + 2k_2} \tag{24}$$

Stochastic elimination of two variables (NO and $NO_3$) by the method of quasi-stationary conditional probability can be easily done; it leads to the following equations for the mean and the variance of the number of molecules of $N_2O_5$ (denoted $X_1$):

$$\frac{d}{dt}\langle X_1\rangle = -k\langle X_1\rangle$$

$$\frac{d}{dt}\langle \delta X_1^2\rangle = -2k\langle \delta X_1^2\rangle + k\nu\langle X_1\rangle \tag{25}$$

where $k$ is given by (25) and $\nu = 1 + k_{-1}/k_2$. For the stochastic version of the reduced model (21), $\nu = 1$. Janssen's method[15] gives $\nu = 1 + (k_{-1}/(k_{-1} + 2k_2))^2$.

## 6. Numerical Simulations and Discussion

A series of stochastic simulations was performed for both models discussed above, and the results were compared with those given by the proposed approximation. The Monte Carlo algorithm based on Gillespie's method[19] was used (this kind of algorithm was used in modeling some realistic chemical schemes[7,8]). The initial number of particles was of the order of $10^5$, and the results were averaged over $10^3$ runs. Simulations of full reaction schemes (8) and (23) gave good agreement for the evolution of mean values, which in our approximation is given by the deterministic rate law (Figures 1a and 2a,b), but the variance was systematically overestimated (Figures 1b and 2c). The discrepancies in the case of the decomposition of $N_2O_5$ may be partially due to the fact that NO is not a fast variable on the same scale as $NO_3$, as shown in Figure 2a,b. However, the main reason of the overestimation is certainly the fact that the method described in section 3 leads to a Poisson distribution of the fast variables, whereas the actual distribution of these variables does not reach this quasi-equilibrium situation and presumably has a smaller variance. On the contrary, it can be seen that the stochastic versions of reduced schemes (11) and (21) underestimate the value of the variance, since reduced schemes neglect sources of fluctuations related to fast variables (which are replaced by their quasistationary values).

## 7. Conclusions

In conclusion, the elimination of fast variables in stochastic kinetics is a complex procedure which should be thoroughly studied before using a reduced chemical scheme for the sophisticated theoretical applications which are currently treated in the literature. As a full stochastic analysis is very difficult, it is important to have some approximate methods which would give some estimations about the true stochastic behavior of the system. The systematic approaches developed by some authors[14,15] lead to correct approximations, but they are rather heavy and can only be applied in special cases. It seems that no simple and general method gives reliable quantitative approximations for the variance. However, the stochastization of the reduced deterministic scheme leads in general to the underestimation of the fluctuations, whereas the method of quasistationary conditional probabilities overestimates them; thus both approaches may be used at least qualitatively to determine upper and lower bounds for internal fluctuations of the full scheme.

**Acknowledgment.** J.T. has been partly supported by the National Scientific Research Fund, Hungary, under Grant 3268. M.F. and P.S. have been supported by the Grant WCH-11/91.

## References and Notes

(1) Nicolis, G.; Prigogine, I. *Self-Organization in Non-Equilibrium Systems*; Wiley: New York, 1977. Haken, H. *Synergetics. An Introduction*; Springer: Berlin, 1978.

(2) Rovinsky, A. B.; Zhabotinsky, A. M. *J. Phys. Chem.* **1984**, *88*, 6081. Bar-Eli, K. *J. Phys. Chem.* **1985**, *89*, 2855.

(3) Klonowski, W. *Biophys. Chem.* **1983**, *18*, 73.

(4) Tikhonov, A. N.; Vasilyeva, A. B.; Sveshnikov, A. G. *Differential Equations* (in Russian); Nauka: Moscow, 1985.

(5) Tyson, J. J. *J. Chem. Phys.* **1973**, *58*, 3919.

(6) Merkin, J. H.; Scott, S. K. *Dynam. Stability Syst.* **1988**, *2*, 223.

(7) Mauricio, F.; Velasco, S. *J. Stat. Phys.* **1986**, *43*, 521.

(8) Peeters, P.; Baras, F.; Nicolis, G. *J. Chem. Phys.* **1990**, *93*, 7321.

(9) Sagues, F.; Sancho, J. M. *J. Chem. Phys.* **1988**, *89*, 3793. Sagues, F.; Ramirez-Piscina, L.; Sancho, J. M. *J. Chem. Phys.* **1990**, *92*, 4786.

(10) Gardiner, C. W. *Handbook of Stochastic Methods*; Springer: Berlin, 1985.

(11) Knobloch, E.; Wiesenfeld, K. A. *J. Stat. Phys.* **1983**, *33*, 611.

(12) Schoner, G.; Haken, H. *Z. Phys. B* **1986**, *63*, 493; **1987**, *68*, 89.

(13) Arnold, L.; Boxler, P. *Synergetics, order and chaos*; Velerde, M. G., Ed.; World Scientific: London, 1988; p 671.

(14) Sulpice, E.; Lemarchand, A.; Lemarchand, H. *Phys. Lett. A* **1991**, *158*, 43. Sulpice, E. Ph.D. Thesis; Univ. P. and M. Curie, Paris: 1991.

(15) Janssen, J. A. M. *J. Stat. Phys.* **1989**, *57*, 157, 171, 187.

(16) van Kampen, N. G. *Stochastic Processes in Physics and Chemistry*; North-Holland: Amsterdam, 1981.

(17) Cook, G. B.; Gray, P.; Knapp, D. G.; Scott, S. K. *J. Phys. Chem.* **1989**, *93*, 2749.

(18) Ogg, R. A. *J. Chem. Phys.* **1947**, *15*, 337, 613.

(19) Gillespie, D. T. *J. Comput. Phys.* **1976**, *22*, 403.