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## INTRODUCTION

The flow of particles through a system of tanks and pipes is analyzed in the theory of flow systems. See for instance [1]. Although the very nature of the particle propagation is stochastic, the systems are usually considered to be deterministic, the reason being that the variation around the mean values can be neglected, when the number of particles is large.

Tracer kinetics is included in the framework, and cell cycle kinetics is another application of increasing importance, e.g. [ 2 ]. The systems are usually defined by the particle residence time, and Monte Carlo simulations are often used to analyze the dynamic behaviour, [10], [11]. For systems with negligible variation around the means analytical results are derived in e.g. [12] concerning the residence time statistics in simple compartment systems.

The random effects are investigated in this paper, and equations for the mean and covariance functions are derived using external and internal descriptions of the system. Analytic tools are thus obtained, which for instance facilitates parameter fitting to limited biological data. The results were originally developed to evaluate Monte Carlo simulations of cell cycle kinetics.

For the sake of simplicity only the discrete time case is analyzed in detail. The corresponding continuous time results are inferred by analogy.

## BASIC ASSUMPTIONS

The time a particle spends in a flow system, the residence time, is considered to be a stochastic variable, $\tau$, taking its values from the set $T = \{0,1,...\}$. Its distribution is called $p(t)$, i.e.

distribution. This means that y(i) is binomially distributed, and the random variable [y(0),...,y(n),...] belongs to a multinomial distribution. See [3]. The mean and the covariance functions are given by

$$Ey(i) = u(0)p(i)$$

$$Cov[y(i),y(j)] = u(0)[p(i)\delta_{ij} - p(i)p(j)]$$

Similarly, for a general input sequence u, the random variable [y(0),...,y(n),...] is the sum of independent random variables that have a multinomial distribution. The mean and the covariance formulas are obtained by adding independent variables:

$$Ey(i) = u(0)p(i) + u(1)p(i-1) + \ldots + u(i)p(0)$$

$$Cov[y(i),y(j)] = u(0)[p(i)\delta_{ij} - p(i)p(j)] + \ldots +$$

$$+ u(i)[p(0)\delta_{ij} - p(0)p(j-i)] \quad i \leq j$$

□

It may also happen that the input sequence u is a stochastic process, and that it is interesting to regard the mean and the covariance with respect to the joint probability of the statistics introduced by the flow system and the à priori statistics of u.

Corollary 1: Let the sequence u be a stochastic process with the mean value function $m_u(k)$ and the covariance function $r_u(k,\ell)$. Then

$$Ey(i) = \sum_{k=0}^{i} p(i-k)m_u(k) \tag{6}$$

$$\mathrm{Cov}[y(i),y(j)] = \sum_{k=0}^{i} p(i-k)[\delta_{ij} - p(j-k)]m_u(k) +$$

$$+ \sum_{k=0}^{i}\sum_{\ell=0}^{j} p(i-k)p(j-\ell)r_u(k,\ell) \qquad (7)$$

Proof: Theorem 1 gives

$$E[y(i)\,|\,(u(k))] = \sum_{k=0}^{i} p(i-k)u(k)$$

$$\mathrm{Cov}[y(i),y(j)\,|\,(u(k))] = \sum_{k=0}^{\min(i,j)} p(i-k)[\delta_{ij} - p(j-k)]u(k)$$

and the formulas (6)-(7) follow immediately from an application of the basic formulas for conditional mean and covariance:

$$E\xi = E_\eta(E[\xi\,|\,\eta]) \qquad (8)$$

$$\mathrm{Cov}(\xi_1,\xi_2) = \mathrm{Cov}_\eta(E[\xi_1\,|\,\eta],E[\xi_2\,|\,\eta]) +$$

$$+ E_\eta(\mathrm{cov}[\xi_1,\xi_2\,|\,\eta] \qquad (9)$$

□

When regarding y in the Theorem 1 as the sum of a deterministic component and some additive zero mean noise, the noise has some interesting properties. It is correlated in time as described by (5), and its covariance is a linear function of the input sequence. The correlation is strong and important, and it makes for instance the (external) stochastic analysis of flow systems with recirculation quite complicated. Analysis based on the internal description will, however, be simpler.

Before starting with the internal approach it is appropriate to illustrate how many particles are required in order to neglect the random fluctuations.

Example: Consider a constant input sequence $u(i) = N$, $i \geq 0$. Theorem 1 gives the coefficient of variation $\mu_i$ by

$$\mu_i = \sqrt{\text{Var } y(i)}/Ey(i) = \sqrt{N \sum_{k=0}^{i} \left(p(i-k) - p^2(i-k)\right)} \Big/ \left(N \sum_{k=0}^{i} p(i-k)\right) =$$

$$= K_i/\sqrt{N}$$

$$K_i = \sqrt{\sum_{k=0}^{i} p(k) - \sum_{k=0}^{i} p^2(k)} \Big/ \sum_{k=0}^{i} p(k)$$

where $K_i$ is usually of the order of 1. Thus the coefficient of variation, $\mu_i$, tends to zero as $1/\sqrt{N}$, and it is required that $N > 10\ 000$ for $\mu_i$ to be less than 1%.

□

INTERNAL DESCRIPTION

Assume that there exists a number n such that $p(i) = 0$ for all i larger than n, i.e. there exists a maximal residence time. The system introduced can then be represented by a delay line consisting of n boxes. All the particles in one box are forwarded to the next box at each time point. An incoming particle has the probability p(i) to enter the box number i with i time steps to go before it leaves the delay line. This is illustrated in Fig. 1.

Let the probabilities form the vector p,

$$p = [p(0),\ldots,p(n)]^T$$

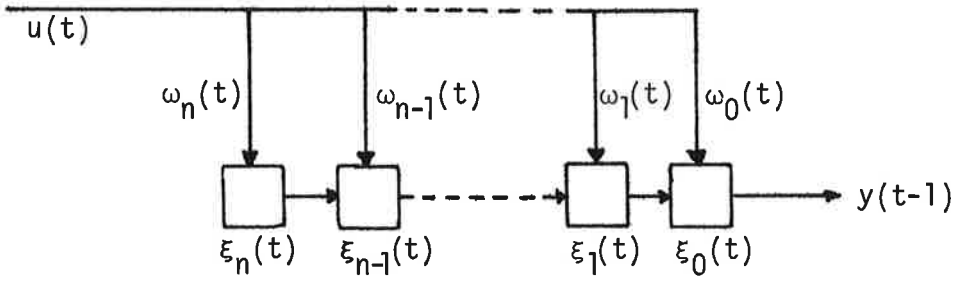


Fig. 1 - Internal model of a stochastic flow system.

and let the number of particles in box i at time t be $\xi_i(t)$, forming the vector function

$$\xi(t) = [\xi_0(t),\ldots,\xi_n(t)]^T$$

The number of particles added to box i from the input at time t is denoted by $\omega_i(t)$,

$$\omega(t) = [\omega_0(t),\ldots,\omega_n(t)]^T$$

$$\sum_{i=0}^{n} \omega_i(t) = u(t)$$

The system can be described by the stochastic difference equation

$$\xi_i(t+1) = \xi_{i+1}(t) + \omega_i(t) \qquad i = 0,\ldots,n-1$$

$$\xi_n(t+1) = \omega_n(t)$$

$$\xi_i(0) = 0 \qquad i = 0,\ldots,n$$

or using vector notation and the shift matrix N:

$$\begin{cases} \xi(t+1) = N\xi(t) + \omega(t) \\ \xi(0) = 0 \end{cases} \tag{10}$$

where

$$N = \begin{bmatrix} 0 & 1 & & 0 \\ & \ddots & \ddots & \\ & & \ddots & 1 \\ 0 & & & 0 \end{bmatrix} \tag{11}$$

Define

$$x(t) = E\xi(t) \tag{12}$$

$$P(t) = \text{Var } \xi(t) \tag{13}$$

and also

$$R = \text{diag}\{p(i)\} - pp^T \tag{14}$$

It is now straightforward to derive recursions for x and P.

Theorem 2: The mean and the covariance functions x and P obey the difference equations

$$\begin{cases} x(t+1) = Nx(t) + pu(t) \\ x(0) = 0 \end{cases} \tag{15}$$

$$\begin{cases} P(t+1) = NP(t)N^T + Ru(t) \\ P(0) = 0 \end{cases} \tag{16}$$

The number of particles at the outlet, y(t), is obtained from $\xi(t)$ by

$$y(t-1) = C\xi(t) = \xi_0(t) \tag{17}$$

and $\xi(t)$ is a sum of stochastic variables with different multinomial distributions.

Proof: Since the residence times for the different particles are independent, $\omega(t)$ belongs to a multinomial distribution:

$$P\left(\omega(t) = [k_0,\ldots,k_n]^T\right) = u(t)! \prod_{i=0}^{n} \frac{[p(i)]^{k_i}}{k_i!}$$

where

$$\sum_{i=0}^{n} k_i = u(t)$$

The mean and the variance of $\omega(t)$ are

$$\begin{cases} E\omega(t) = pu(t) \\ \text{Var } \omega(t) = R\, u(t) \end{cases}$$

with R defined by (14). Thus from (10)

$$x(t+1) = E[N\xi(t) + \omega(t)] = NE\xi(t) + pu(t)$$

and since $\xi(t)$ and $\omega(t)$ are independent

$$P(t+1) = \text{Var}[N\xi(t) + \omega(t)] = N \text{ var } \xi(t) N^T + R\, u(t)$$

which proves (15) and (16). Equation (10) also gives that

$$\xi(t) = \sum_{s=0}^{t-1} N^{t-s-1} \omega(s)$$

so that $\xi(t)$ is a sum of variables with different multinomial distributions.

□

It is straightforward to see that Theorem 2 gives the same expression for Ey(t) and Var y(t) as Theorem 1. As in Corollary 1, u might be a stochastic process. The mean and the covariance of $\xi$ can then be evaluated with respect to the joint probability of the statistics of u and $\omega$. If u is uncorrelated in time, then

$$x(t+1) = Nx(t) + pm_u(t) \tag{18}$$

$$P(t+1) = NP(t)N^T + Rm_u(t) + pp^T r_u(t,t) \tag{19}$$

A time correlation in u is often represented by an internal model, with state $\eta$, driven by an uncorrelated process. The variance matrix for the joint state $\begin{bmatrix}\xi\\ \eta\end{bmatrix}$ should, of course, then be updated.

The restriction made for internal models, that $p(i) = 0$, $i>n$, is most often valid. However, the analysis is true also without the restriction. Some requirement on how fast $p(i) \to 0$ as $i \to \infty$ has to be added instead for the statistical moments to exist. $\xi$ will be an infinite dimensional vector.

An interesting example of the use of the internal description is a recirculated flow system.

Example: Let $u(t) = y(t-1) = \xi_0(t)$. Then

$$x(t) = Nx(t) + px_0(t) = (N+pC)x(t) = Ax(t) \tag{20}$$

$$P(t+1) = NP(t)N^T + NP(t)C^Tp^T + pCP(t)N^T + pCP(t)C^Tp^T +$$

$$+ Rx_0(t) = AP(t)A^T + Rx_0 \tag{21}$$

where

$$A = N + pC \tag{22}$$

$$R = \text{diag}\,(p(i)) - pp^T \tag{23}$$

Since $\Sigma p(i) = 1$, A has one eigenvalue, $\lambda = 1$. Denote the corresponding left and right eigenvectors by e and f respectively. Introduce also

$$M = \sum_{i=0}^{n} x_i(0) \tag{24}$$

$$\bar{t} = \sum_{i=0}^{n} (i+1)p(i) \tag{25}$$

M is the total number of particles, and $\bar{t}$ is their mean transit time around the loop. Then

$$e^TA = e^T, \qquad e_i = 1 \qquad i = 0,\ldots,n \tag{26}$$

$$Af = f, \qquad f_i = \sum_{j=i}^{n} p_j \qquad i = 0,\ldots,n \tag{27}$$

and

$$e^Tf = \bar{t} \tag{28}$$

$$e^TR = 0 \tag{29}$$

$$e^Tx(t) = M \qquad \text{all } t \tag{30}$$

Equations (26) and (29) also give that

$$e^TP(t)e = e^TP(0)e \quad \text{all } t \tag{31}$$

Equations (30) and (31) mean that the total number of particles is always kept the same.

From the conditions $\Sigma p(i) = 1$ and $p(i) \geq 0$ it follows that no eigenvalue of A is outside the unit circle. It also follows that the eigenvalues with $|\lambda| = 1$ have multiplicity one, and

the corresponding modes are not controllable from R, so x(t) and P(t) are bounded. $\lambda = 1$ is essentially the only eigenvalue on the unit circle. Let k be the largest integer such that $p(i) \neq 0$ only for $i + 1 = kj$, $j = 1,...$ Then A has k eigenvalues on the unit circle given by $\lambda^k = 1$. x(t) is asymptotically periodic with the period k. For the most common case, $k = 1$

$$x(t) \to f \frac{M}{\bar{t}}, \quad t \to \infty \tag{32}$$

$$P(t) \to P_\infty = S \frac{M}{\bar{t}} + ff^T \frac{e^T P(0) e}{M/\bar{t}}, \quad t \to \infty \tag{33}$$

where S is the unique solution to

$$\begin{cases} S = ASA^T + R \\ e^T S = 0 \end{cases} \tag{34}$$

If $k > 1$, (32) and (33) hold as $t = sk$, $s \to \infty$. The coefficient of variation of y(t) is thus asymptotically proportional to $1/\sqrt{M}$.

## MODIFICATION OF THE BASIC INDEPENDENCE ASSUMPTION

The fundamental probabilistic assumption of the present analysis is that the residence times of the different particles are independent and equally distributed. This can be modified giving two extremes. It can be assumed that the particles are distributed to the boxes so that

$$\omega(t) = pu(t)$$

without any statistical variation. This is, of course, only possible when u(t) is very large. The other extreme is that

all the incoming particles at time t fall into the same box. Which box they enter is governed by the distribution p. Then

$$E\omega(t) = pu(t)$$

$$\text{Var } \omega(t) = R\big(u(t)\big)^2$$

where R was defined in (15). In this case the coefficient of variation does not vanish as $u(t) \to \infty$. An intermediate case is when groups of particles fall into the same box.

The assumption in this paper seems to be the most natural one, at least as an approximation to the continuous time behaviour. The grouping is, however, a common technique in event simulations like Monte Carlo simulations, [10, 11], and the coefficient of variation may be considerable in such cases.

Of course, the model is too simple to handle the situations when the residence time depends on the number of particles in the boxes, which is often the case in queuing systems. From the nonstochastic case it is straightforward to see how nonlinear the behaviour will be with such an assumption.

## CONTINUOUS TIME

In order to obtain the continuous time analogy of the external description in Theorem 1 define $u(t)dt$ as the number of particles entering the system during the interval $(t,t+dt)$, and let $y(t)dt$ be the number of particles leaving the system during the same interval. The residence time, $\tau$, is a continuous stochastic variable with density p, i.e.

$$p(t) \geq 0$$

$$\int_0^\infty p(t)dt = 1$$

Provided p and u fulfil some regularity conditions the mean and the covariance are obtained by

$$Ey(t) = \int_0^t p(t-s)u(s)ds \tag{35}$$

$$\begin{aligned} Cov[y(t_1),y(t_2)] = \int_0^{\min(t_1,t_2)} & [p(t_1-s)\delta(t_1-t_2) - \\ & - p(t_1-s)p(t_2-s)]u(s)ds \end{aligned} \tag{36}$$

For the internal description define the number of particles in the system at time t, that will leave the system during the interval (t+s,t+s+ds) to be $\xi(t;s)ds$, so that $y(t) = \xi(t;0)$. Denote also $E\xi(t;s) = x(t;s)$ and $Cov(\xi(t;s_1),\xi(t;s_2)) = P(t;s_1,s_2)$.

Then the equations corresponding to (15) and (16) become

$$\begin{cases} \frac{\partial}{\partial t} x(t;s) = \frac{\partial}{\partial s} x(t;s) + p(s)u(t), \quad s \geq 0 \\ \lim_{s\to\infty} x(t;s) = 0, \quad x(0;s) = 0 \end{cases} \tag{37}$$

$$\begin{cases} \frac{\partial}{\partial t} P(t;s_1,s_2) = \frac{\partial}{\partial s_1}\frac{\partial}{\partial s_2} P(t;s_1,s_2) + R(s_1,s_2)u(t) \\ \lim_{s_1 \text{ or } s_2\to\infty} P(t;s_1,s_2) = 0 \\ P(0;s_1,s_2) = 0 \end{cases} \tag{38}$$

$$R(s_1,s_2) = p(s_1)\delta(s_1-s_2) - p(s_1)p(s_2)$$

Equation (37) is an internal description of (15) along the same ideas as in [4].

The solution of (37) and (38) is

$$x(t;s) = \int_0^t p(t+s-q)u(q)dq \qquad s \geq 0,\ t \geq 0 \qquad (39)$$

$$P(t;s_1,s_2) = \int_0^t R(t+s_1-q,t+s_2-q)u(q)dq =$$

$$= \int_0^t p(t+s_1-q)\delta(s_1-s_2)u(q)dq -$$

$$- \int_0^t p(s_1+t-q)p(s_2+t-q)u(q)dq \qquad (40)$$

which should be compared with the mean and variance functions of $y(t) = \xi(t;0)$ from eqs. (35) and (36).

Note that $y(t)$ can be separated into the mean value $x(t;0)$ plus <u>almost</u> white noise with incremental variance $r$

$$r(t) = \int_0^t p(t-s)u(s)ds$$

A constant infusion $^{24}Na$ tracer experiment, $T_{1/2}$ = 15h, for a flow of 1 ml/s with the radioactivity of $10^{-4}$ μCi/ml would give $x(t;0) \approx 10^{12}$ atoms/s and $r(t) \approx 10^{12}$ atoms/s. The random fluctuations in the system are thus negligible for most tracer experiments.

## CONCLUSIONS

The particle propagation in a flow system was defined by a single stochastic variable, the residence time. The number of particles at the outlet, considered as a stochastic process, was then characterized by the mean value function and the covariance function and by stochastic difference or differential equations with additive noise. The statistical assumptions on the residence time were found to be important.

A few years ago attempts were made to use differential equations with stochastic processes as parameters or stochastic weighting functions, e.g. [5, 6, 7]. The approach with the residence time as a stochastic variable has some connections with these techniques, but the real relation is with queuing theory. Queuing theory is, however, more general. The residence time distribution may depend on the number of particles in the system.

The simplest process in queuing and renewal theory, the Poisson process, has been used in this connection. Another popular assumption in both process industry and biology [8, 9] is the gamma distributed residence time.

In many applications Monte Carlo simulations have been used to analyze the behaviour of a system defined by residence time distributions, also when the probabilistic assumptions are quite simple [10, 11]. The analytical tools derived in this paper facilitates for instance parameter sensitivity studies or curve fitting (identification).

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REFERENCES

[1] Åström K J: Flow Systems, in Ho Y-C, Mitter S K (eds), Directions in Large Scale Systems, Plenum Press, New York 1976.

[2] Aroesty J, Lincoln T, Shapro N, Boccia G: Tumor Growth and Chemotherapy: Mathematical Methods, Computer Simulation and Experimental Foundations, Math Biosci 17 243--300 (1973).

[3] Cramér H: Mathematical Methods in Statistics, Princeton 1946.

[4] Balakrishnan A V: Identification and Stochastic Control of Nondynamic Systems. In Eykhoff (ed): Identification and System Parameter Estimation, Proc. of the 3rd IFAC Symposium, 12-15 June, 1973, North-Holland 1973.

[5] Adomian G: Linear Stochastic Operators, Review of Modern Physics 35 185-207 (1963).

[6] Soong T T, Dowdee J W: Pharmacokinetics with Uncertainties in Rateconstants III, Math Biosci 19 343-353 (1974).

[7] Tsokos J O, Tsokos C P: Statistical Modelling of Pharmacokinetic Systems, Journal of Dynamical Systems, Measurement and Control 98 37-43 (1976).

[8] Naor P, Shinnar R, Katz S: Indeterminacy in the Estimation of Flow Rate and Transport Functions from Tracer Experiments in Closed Circulations. Int J Engng Sci 10 1153-1174 (1972).

[9] Jansson B, Révész L: Analysis of the Growth of Tumor Cell Populations, Math Biosci 19 131-154 (1974).

[10] Wilson R L, Gehan E A: A Digital Simulation of Cell Kinetics with Application to L-1210 Cells. Comp Prog in Biomed 1 65-73 (1970).

[11] Mauer A M, Evert C G, Lampkin B C, McWilliams N B: Cell-kinetics in Human Acute Lymphoblastic Leukemia; Computer Simulation with Discrete Modelling Techniques, Blood 41 141-154 (1973).

[12] Rescigno A: On Transfer Times in Tracer Experiments. J Theor Biol 39 9-27 (1973).