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Referat (sammandrag)

The random effects in tracer kinetics and cell cycle kinetics are usually described by the particle residence time. An analytical framework is developed, and the importance of the residence time independence is emphasized.

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INTRODUCTION

The flow of particles through a system of tanks and pipes is
analyzed in the theory of <u>flow systems</u>. See for instance [1].
Although the very nature of the particle propagation is sto-
chastic, the systems are usually considered to be determinis-
tic, the reason being that the variation around the mean va-
lues 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 equa-
tions 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 ana-
lyzed 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, τ, 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 $[y(0),\ldots,y(n),\ldots]$ belongs to a multinomial distribution. See [3]. The mean and the covariance functions are given by

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

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

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

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

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

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

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

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

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

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

Proof: Theorem 1 gives

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

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

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

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

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

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

□

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 μ_i by

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

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

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

where K_i is usually of the order of 1. Thus the coefficient
of variation, μ_i, tends to zero as $1/\sqrt{N}$, and it is required
that $N > 10\ 000$ for μ_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 re-
presented 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,

$$p = [p(0),\ldots,p(n)]^T$$
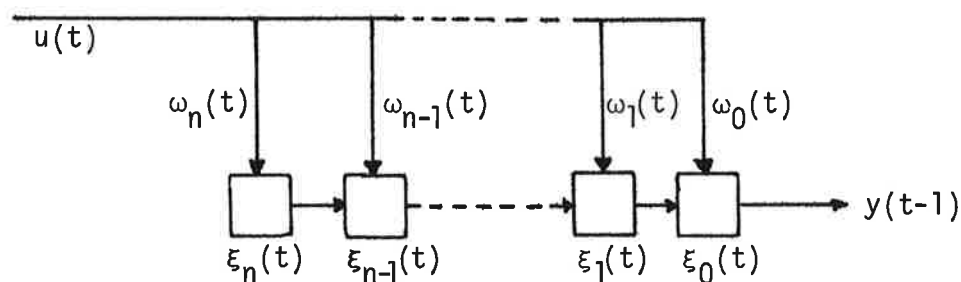
Fig. 1 - Internal model of a stochastic flow system.

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

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

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

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

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 ξ can then be evaluated with respect to the joint probability of the statistics of u and ω. 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 η, 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. ξ 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

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

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

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

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

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

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

$$e^T A = e^T, \qquad e_i = 1 \qquad i = 0,\ldots,n \qquad (26)$$

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

and

$$e^T f = \bar{t} \qquad (28)$$

$$e^T R = 0 \qquad (29)$$

$$e^T x(t) = M \qquad \text{all } t \qquad (30)$$

Equations (26) and (29) also give that

$$e^T P(t) e = e^T P(0) e \qquad \text{all } t \qquad (31)$$

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

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

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

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

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

$$Var\ \omega(t) = R\bigl(u(t)\bigr)^2$$

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 simula-
tions like Monte Carlo simulations, [10, 11], and the coeffi-
cient 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 non-
linear 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 par-
ticles entering the system during the interval (t,t+dt), and
let y(t)dt be the number of particles leaving the system dur-
ing the same interval. The residence time, τ, 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

$$Ey(t) = \int_0^t p(t-s)u(s)ds \qquad (35)$$

$$Cov[y(t_1),y(t_2)] = \int_0^{\min(t_1,t_2)} [p(t_1-s)\delta(t_1-t_2) -$$

$$- p(t_1-s)p(t_2-s)]u(s)ds \qquad (36)$$

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

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

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

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

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 _almost_ 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 pro-
cess, was then characterized by the mean value function and
the covariance function and by stochastic difference or diffe-
rential equations with additive noise. The statistical assump-
tions on the residence time were found to be important.

A few years ago attempts were made to use differential equa-
tions 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 resi-
dence time distribution may depend on the number of particles
in the system.

The simplest process in queuing and renewal theory, the Pois-
son process, has been used in this connection. Another popu-
lar 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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