



# LUND UNIVERSITY

## Random Effects in Biomedical Flow Systems

Hagander, Per

1977

*Document Version:*

Publisher's PDF, also known as Version of record

[Link to publication](#)

*Citation for published version (APA):*

Hagander, P. (1977). *Random Effects in Biomedical Flow Systems*. (Technical Reports TFRT-7113). Department of Automatic Control, Lund Institute of Technology (LTH).

*Total number of authors:*

1

### General rights

Unless other specific re-use rights are stated the following general rights apply:

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

Read more about Creative commons licenses: <https://creativecommons.org/licenses/>

### Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

LUND UNIVERSITY

PO Box 117  
221 00 Lund  
+46 46-222 00 00

RANDOM EFFECTS IN BIOMEDICAL FLOW SYSTEMS

PER HAGANDER

Department of Automatic Control  
Lund Institute of Technology  
March 1977

Dokumentutgivare  
Lund Institute of Technology  
Handläggare Dept of Automatic Control  
P 0 Hagander  
Författare  
P 0 Hagander

Dokumentnamn  
REPORT  
Utgivningsdatum  
March 1977

Dokumentbeteckning  
LUTFD2/(TFRT-7113)/1-021/(  
Ärendebeteckning  
06T6

10T4

Dokumenttitel och undertitel  
38T0  
RANDOM EFFECTS IN BIOMEDICAL FLOW SYSTEMS

## Referat (sammandrag)

26T0

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.

PER HAGANDER

## Referat skrivet av

Author

## Förslag till ytterligare nyckelord

Flow systems, Analytical solution, Input dependent noise variance.

## Klassifikationssystem och -klass(er)

50T0

## Indextermer (angs källa)

52T0

## Omfång

56 pages

## Övriga bibliografiska uppgifter

56T2

Se även  
Englisch

Department of Automatic Control  
Lund Institute of Technology  
March 1977

ISSN  
60T4

ISBN  
60T6

## Dokumentet kan erhållas från

Department of Automatic Control  
Lund Institute of Technology  
P O Box 725, S-220 07 LUND 7, Sweden

Mottagarens uppgifter  
62T4

Pris  
66T0

SIS-  
DB 1

DOKUMENTDATA A Dän 10 SIS 62 10 12

Dokumentutgivare  
Lund Institute of Technology  
Handläggare Dept of Automatic Control  
R Hagander  
Författare  
R Hagander

Dokumentnamn  
REPORT  
Utgivningsdatum  
March 1977

Dokumentbeteckning  
LUTFD2/(TFRT-7113)/1-021/(1977)  
Ärendebeteckning  
LUTFD2

Dokumenttitel och undertitel

Random effects in biomedical flow systems

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.

Referat skrivet av

Author

Förslag till ytterligare nyckelord

Flow systems, Analytical solution, Input dependent noise variance.

Klassifikationssystem och -klass(er)

Indextermer (ange källa)

Omfång  
21 pages

Övriga bibliografiska uppgifter

Språk  
English

Sekretessuppgifter

ISSN

ISBN

Dokumentet kan erhållas från

Department of Automatic Control  
Lund Institute of Technology  
P O Box 725, S-220 07 LUND 7, Sweden

Mottagarens uppgifter

Pris

## 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  $T = \{0, 1, \dots\}$ . Its distribution is called  $p(t)$ , i.e.

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

$$E y(i) = u(0)p(i)$$

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

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

$$E y(i) = u(0)p(i) + u(1)p(i-1) + \dots + u(i)p(0)$$

$$\begin{aligned} \text{Cov}[y(i), y(j)] &= u(0)[p(i)\delta_{ij} - p(i)p(j)] + \dots + \\ &\quad + u(i)[p(0)\delta_{ij} - p(0)p(j-i)] \quad i \leq j \end{aligned}$$

□

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 *a 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

$$E y(i) = \sum_{k=0}^i p(i-k)m_u(k) \quad (6)$$

$$\begin{aligned} \text{Cov}[y(i), y(j)] &= \sum_{k=0}^i p(i-k) [\delta_{ij} - p(j-k)] m_u(k) + \\ &+ \sum_{k=0}^i \sum_{\ell=0}^j p(i-k) p(j-\ell) r_u(k, \ell) \end{aligned} \quad (7)$$

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:

$$E\xi = E_{\eta}(E[\xi | \eta]) \quad (8)$$

$$\begin{aligned} \text{Cov}(\xi_1, \xi_2) &= \text{Cov}_{\eta}(E[\xi_1 | \eta], E[\xi_2 | \eta]) + \\ &+ E_{\eta}(\text{cov}[\xi_1, \xi_2 | \eta]) \end{aligned} \quad (9)$$

□

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

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

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

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

where  $K_i$  is usually of the order of 1. Thus the coefficient of variation,  $\mu_i$ , 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  $p$ ,

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



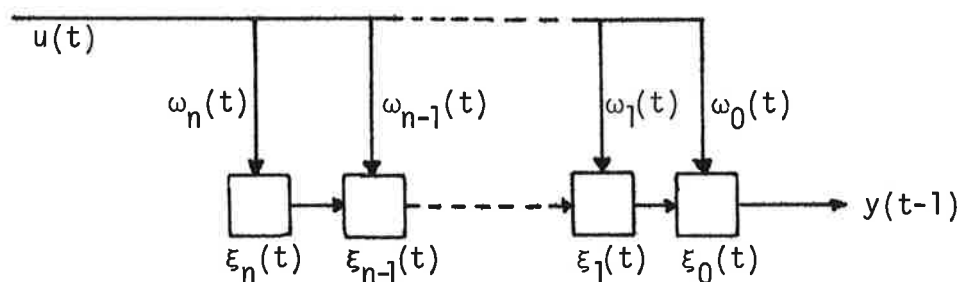


Fig. 1 - Internal model of a stochastic flow system.

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

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

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

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

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

The system can be described by the stochastic difference equation

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

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

$$\xi_i(0) = 0 \quad i = 0, \dots, n$$

or using vector notation and the shift matrix  $N$ :

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

where

$$N = \begin{bmatrix} 0 & 1 & 0 \\ & \ddots & \ddots \\ 0 & & 0 \end{bmatrix} \quad (11)$$

Define

$$x(t) = E\xi(t) \quad (12)$$

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

and also

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

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

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

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

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

$$y(t-1) = C\xi(t) = \xi_0(t) \quad (17)$$

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:

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

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  $\text{Var } y(t)$  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

$$x(t+1) = Nx(t) + pm_u(t) \quad (18)$$

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

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  $p(i) \rightarrow 0$  as  $i \rightarrow \infty$  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

$$x(t) = Nx(t) + px_0(t) = (N+pc)x(t) = Ax(t) \quad (20)$$

$$\begin{aligned} P(t+1) &= NP(t)N^T + NP(t)C^T p^T + pCP(t)N^T + pCP(t)C^T p^T + \\ &\quad + Rx_0(t) = AP(t)A^T + Rx_0 \end{aligned} \quad (21)$$

where

$$A = N + pc \quad (22)$$

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

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

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

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

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

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

$$A f = f, \quad f_i = \sum_{j=i}^n p_j \quad i = 0, \dots, n \quad (27)$$

and

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

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

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

Equations (26) and (29) also give that

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

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

From the conditions  $\sum p(i) = 1$  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  $i + 1 = kj$ ,  $j = 1, \dots$ . 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,  $k = 1$

$$x(t) \rightarrow f \frac{M}{t}, \quad t \rightarrow \infty \quad (32)$$

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

where  $S$  is the unique solution to

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

If  $k > 1$ , (32) and (33) hold as  $t = sk$ ,  $s \rightarrow \infty$ . 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

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

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

where  $R$  was defined in (15). In this case the coefficient of variation does not vanish as  $u(t) \rightarrow \infty$ . 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

$$E y(t) = \int_0^t p(t-s) u(s) ds \quad (35)$$

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

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  $\text{Cov}(\xi(t; s_1), \xi(t; s_2)) = P(t; s_1, s_2)$ .

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

$$\left\{ \begin{aligned} \frac{\partial}{\partial t} x(t; s) &= \frac{\partial}{\partial s} x(t; s) + p(s) u(t), \quad s \geq 0 \\ \lim_{s \rightarrow \infty} x(t; s) &= 0, \quad x(0; s) = 0 \end{aligned} \right. \quad (37)$$

$$\left\{ \begin{aligned} \frac{\partial}{\partial t} P(t; s_1, s_2) &= \frac{\partial}{\partial s_1} \frac{\partial}{\partial s_2} P(t; s_1, s_2) + R(s_1, s_2) u(t) \\ \lim_{s_1 \text{ or } s_2 \rightarrow \infty} P(t; s_1, s_2) &= 0 \\ P(0; s_1, s_2) &= 0 \end{aligned} \right. \quad (38)$$

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

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



The solution of (37) and (38) is

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

$$\begin{aligned} P(t;s_1,s_2) &= \int_0^t R(t+s_1-q, t+s_2-q)u(q) dq = \\ &= \int_0^t p(t+s_1-q)\delta(s_1-s_2)u(q) dq - \\ &\quad - \int_0^t p(s_1+t-q)p(s_2+t-q)u(q) dq \end{aligned} \quad (40)$$

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  $^{24}\text{Na}$  tracer experiment,  $T_{1/2} = 15\text{h}$ , for a flow of 1 ml/s with the radioactivity of  $10^{-4} \mu\text{Ci/ml}$  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).

## ACKNOWLEDGEMENTS

The author wants to thank Prof. K.J. Åström, Lund, for constant encouragement and help, and Prof. J.F. Gross, Tucson, for the introduction to the interesting field of cell cycle kinetics. The work was partly supported by fellowships from the Swedish Natural Science Research Council and the Sweden-America Foundation.

## 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 Simula-  
tion 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 Uncertain-  
ties in Rateconstants III, Math Biosci 19 343-353 (1974).
- [7] Tsokos J O, Tsokos C P: Statistical Modelling of Pharmaco-  
kinetic 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 Experi-  
ments 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).