Mathl Comput. Modelling, Vol. 11, pp. 1189–1194, 1988
Printed in Great Britain

0895-7177/88 $3.00 + 0.00
Pergamon Press plc

MEDICAL SIMULATION AND MODELLING

ON ACTIVE LINEAR COMPARTMENTS

Marek Kimmel and Ovide Arino

Investigative Cytology Laboratory
Memorial Sloan-Kettering Cancer Center
1275 York Avenue, New York, New York 10021, USA

Department of Mathematics, The University of Pau
Avenue de l'Universite, 64000 Pau, France

Abstract. Active linear compartments are capable of transforming input substances into each other. Based on several general axioms of functioning of these compartments their mathematical description in the form of matrix convolution operators is derived. Results are prcvided, regarding relationships between two alternative modes of mathematical description of linear active compartments. Then, properties of systems of active compartments are considered, based on results from the renewal theory.

Keywords. Compartmental systems; axiomatic definition; convolution operators; renewal theory.

INTRODUCTION

In this paper, we consider a class of dynamical systems, which is a generalization of the well known compartmental systems. We call our compartments active since they have the ability, absent in the traditional formulation, of actively transforming one substance flowing through the system into another, with a global balance of substance satisfied.

Traditionally, compartmental systems are a tool used to describe the circulation of substances in the models of various biological processes: in cell biology, ecology, immunology etc. (see eg. Sandberg (1978)). Intuitively, a compartment is a black box containing a number (N) of distinct substances. Each of these substances may flow into the compartment, flow out of it, or may be stored in it. Compartments are usually grouped into compartmental systems, making it possible to model the processes of circulation of the substances involved in various parts of the object considered, as for example the circulation of radioactive tracers in various organs of an animal or human body. In the extensive literature on the subject, the dynamics of compartmental systems is usually described with the aid of systems of ordinary differential equations (Anderson (1983), Rubinow (1975), Sandberg (1978)), or systems of delay differential equations (Győri and Eller (1981)).

We propose an approach which generalizes these models in two ways: First, we add the possibility of substance transformation; thus a given substance may be changed in the compartment, partly or completely, into one or more other substances. Second, even in the special case of no substance transformation, the formalism of integral equations of renewal type that we employ provides a more general description and deeper understanding of compartmental systems than other approaches available.

We start by specifying a set of axiomatic properties which should be satisfied by an active compartment. Based only on these axioms, we then derive a representation of the operators defining a compartment in terms of convolutions by appropriately chosen impulse response functions. Further properties of these cperators are then considered. Among others, we investigate the asymptotic properties of systems of active compartments. The present communication has a preliminary character and results are provided without proof. A detailed treatment of the subject is in preparation.

DEFINITION AND MATHEMATICAL DESCRIPTION OF AN ACTIVE COMPARTMENT

We will employ cumulated flows rather than flow rates. Thus, $X_i(t)$ will be understood as the quantity of the i-th substance that flows into the compartment in the time interval $[0,t]$. Analogously, $Y_i(t)$ will be the quantity of the i-th substance that flows out of the compartment during $[0,t]$. V_i denotes the quantity of the i-th substance present at time t in the compartment. Let us remark that the use of cumulated flows makes it possible to consider equivalents of impulse flow rates ("Dirac deltas") without having to employ the formalism of the generalized functions (Schwartz distributions). The following set of axioms defines active compartments:

(a) Real functions X_i and Y_i, $i=1,\dots,N$, defined on the semiaxis of nonnegative reals (R^+), are nonnegative and nondecreasing. Real functions V_i, $i=1,\dots,N$, from R^+ into itself, are of bounded variation on the bounded subsets of R^+ (consult eg. Łojasiewicz (1973) for a definition of variation of a function). All the above functions are considered continuous from the right.

(b) Let us denote by RBV the set of N-vector functions on R^+ with the entries right continuous and of locally bounded variation; by RBV^+, the subset of RBV consisting of functions with nonnegative entries; and by ND^+, the subset of RBV^+ consisting of functions with nonnegative and nondecreasing entries. Let us define two operators

$$A: ND^+ \longrightarrow RBV^+,$$
$$B: ND^+ \longrightarrow ND^+,$$

such that

$$\mathbf{V} = A(\mathbf{X}), \ \mathbf{Y} = B(\mathbf{X}),$$

where $\mathbf{V} = \mathrm{col}(V_1,\dots,V_N)$, etc. Operator A will be called the "inflow-content operator" while B will be called the "inflow-outflow operator".

(c) The overall balance of substance is verified:

$$\sum_{i=1}^{N} X_i(t) = \sum_{i=1}^{N} Y_i(t) + \sum_{i=1}^{N} V_i(t).$$

(d) Operators A and B are additive and nonnegatively homogenous. They are also monotonous ie.:

$$A(\mathbf{X}^1) \geq A(\mathbf{X}^2),$$
$$B(\mathbf{X}^1) \geq B(\mathbf{X}^2),$$

if $\mathbf{X}^1 \geq \mathbf{X}^2$, where the inequality is defined componentwise.

(e) Let us denote by $\mathbf{W}_T(t)$ the translation of a vector function $\mathbf{W}(t)$ by T. It is assumed that both operators commute with translation:

$$A(\mathbf{X}_T) = [A(\mathbf{X})]_T, \ B(\mathbf{X}_T) = [B(\mathbf{X})]_T.$$

(f) Both operators obey a nonanticipation principle: For each $t>0$, if $\mathbf{X}^1(s) = \mathbf{X}^2(s)$, $s \leq t$, then $\mathbf{Y}^1(s) = \mathbf{Y}^2(s)$ and $\mathbf{V}^1(s) = \mathbf{V}^2(s)$, $s \leq t$; where $\mathbf{V}^i = A(\mathbf{X}^i)$ and $\mathbf{Y}^i = B(\mathbf{X}^i)$.

The description of a compartment in terms of operators A and B seems perhaps unnatural compared to the description in terms of A (inflow-contents) and another operator: C (contents-outflow) mapping $\mathbf{V}$ into $\mathbf{Y}$. However, the description we propose is more general.

Hypothesis **(e)** means that the properties of the compartment do not change with time (ie. the compartment is autonomous). Hypothesis **(f)** states that for each $t>0$, $\mathbf{V}$ and $\mathbf{Y}$ restricted to the interval $[0,t]$ depend only on the restriction of $\mathbf{X}$ to $[0, t]$.

Suppose that $\mathbf{A}(t)$ and $\mathbf{B}(t)$ are matrix functions on R^+, of locally bounded variation, and continuous from the right. The dimensions of $\mathbf{A}$ and $\mathbf{B}$ must be chosen so that the ordinary matrix product $\mathbf{AB}$ is well defined.) By a convolution of two such functions, we will understand the following matrix function $\mathbf{C}(t)$ on R^+:

$$\mathbf{C}(t) = \int_{[0,t]} d_s\mathbf{A}(s)\ [\mathbf{B}(t-s)],$$

where the integral is understood in the Lebesgue-Stieltjes sense (Łojasiewicz (1973), page 200). Convolution is symbolically denoted in the following ways:

$$\mathbf{C}(t) = (\mathbf{A}*\mathbf{B})(t) = \mathbf{A}(t) * \mathbf{B}(t).$$

Theorem 1. (i) There exist (N, N) matrix functions $\mathbf{G}$ and $\mathbf{H}$ on R^+, such that

$$\mathbf{V} \equiv A(\mathbf{X}) = (\mathbf{H}*\mathbf{X}),$$
$$\mathbf{Y} \equiv B(\mathbf{X}) = (\mathbf{G}*\mathbf{X}).$$

The entries of $\mathbf{G}(t) = [G_{ij}(t)]$ are nonnegative, nondecreasing functions on R^+ continuous from the right, while the entries of $\mathbf{H}(t) = [H_{ij}(t)]$ are nonnegative functions on R^+ of locally bounded variation, continuous from the right. The following is satisfied:

$$\sum_{i=1}^{N} G_{ij}(t) + \sum_{i=1}^{N} H_{ij}(t) = 1.$$

(ii). Conversely, for $\mathbf{G}$ and $\mathbf{H}$ such as in part **(i)**, operators A(.) and B(.) satisfy hypotheses **(a)** through **(f)**.

OPERATOR CONTENTS-OUTFLOW

Example. Let us consider an example of a "no memory" active compartment describable by differential equations (formally equivalent to a classical compartment system; see section 4): Suppose that a small portion of the j-th substance present at time t in the compartment,

- either transforms in a short time interval [t,t+u] into a portion of one (eg. the i-th) of the other substances with probability $a_{ij}u+o(u)$ [where o(u) is a quantity small compared to u, ie. o(u)/u tends to zero as u tends to zero],

- or it leaves the compartment with probability $a_{jj}u+o(u)$,

- or it remains unchanged inside the compartment with probability $1-(a_{1j}+\ldots+a_{Nj})u+o(u)$.

These assumptions define a Markov process the expected value of which may be described either in terms of a system of differential equations or equivalently in terms of the following system of integral equations:

$$V_j(t)=$$

$$\int_0^t [-\sum_{i=1}^N a_{ij}V_j(s)+\sum_{\substack{i=1\\ i\neq j}}^N a_{ji}V_i(s)]ds+X_j(t),$$

$$Y_j(t) = a_{jj}\int_0^t V_j(s)\,ds,$$

where j=1,...,N. Operator A(.) here has the form:

$$A(\mathbf{X}) = \mathbf{H} * \mathbf{X},\ \mathbf{H} = \exp(\mathbf{A}t),$$

where $\mathbf{A} = [A_{ij}]$; $A_{ij} = a_{ij}$, $i\neq j$ while $A_{ii} = -(a_{1i}+\ldots+a_{Ni})$. The above equations are consequences of the usual variation of constants formulae for ordinary differential equations, including nonzero initial conditions [since $X_j(0)>0$ implies $V_j(0)>0$]. Operator C(.), mapping compartment contents into outflows has the form:

$$C(\mathbf{V}) = \mathbf{K} * \mathbf{V},$$

where

$$\mathbf{K}(t) = t\ \mathrm{diag}(a_{11},\ldots,a_{NN}).$$

In the present example it is more straightforward to describe the compartment using the pair (A, C) of operators. However, this is not generally true. We will now state the properties that should be satisfied by C:

(g) For each t>0 there exists $K_t>0$ such that

$$\sup_{[0,t]} |C(\mathbf{V}^1)(s)-C(\mathbf{V}^2)(s)|$$

$$\leq K_t \sup_{[0,t]}|\mathbf{V}^1(s)-\mathbf{V}^2(s)|,$$

(where $|\mathbf{V}|=|V_1|+\ldots+|V_N|$), for all the $\mathbf{V}$ in the range of operator A(.) [ie. in $A(ND^+)$].

(h) Nonanticipation [analogous to **(f)**].

(i) Autonomy [analogous to **(e)**].

(j) Additivity and positive homogeneity [analogous to **(d)**].

Let us note that A and B enjoy a property analogous to **(g)** as a consequence of monotonicity and balance equation. Neither of these assumptions can be asserted for C. Moreover, since the condition **(g)** is restricted to functions **V** in the range of operator A, it does not imply that C is of the convolution type. This means that the problem of finding an operator C, in its generality, might not be well posed. From now on we will consider a restricted version of the problem: we will look for the existence of a convolution type operator C.

Theorem 2. If the determinant of matrix **H**(0) is not equal to zero: $D[\mathbf{H}(0)]\neq 0$, then operator C(.) exists and satisfies properties **(g)** through **(j)**.

The proof of this apparently simple condition requires investigation of the properties of the algebraic ring of convolutions over the space of functions of locally bounded variation. In general terms, the invertibility of the element of this ring which plays the role of the determinant of a generalized matrix, has to be characterized.

The basic question is whether or not the condition $\det[\mathbf{H}(0)]\neq 0$ is very restrictive; in other words, if a large enough class of compartments can be equivalently described both in the terms of the pairs of operators (A,B) and (A,C). Let us consider a compartment which is a description of a real biological process. As no changes of one "substance" into another can be instantaneous, it seems reasonable to assume $H_{ij}(0)=0$, $j\neq i$ as well as $G_{ij}(0)$, $j\neq i$. This implies $\det[\mathbf{H}(0)] = H_{11}(0)\ldots H_{NN}(0)$ and $H_{ii}+G_{ii}=1$, i=1,...,N. Suppose now that the determinant of **H**(0) is equal to zero. This requires $H_{jj}(0)=0$ for at least one j. But then $G_{jj}(t) = G_{jj}(0) = 1$, $t\geq 0$ and this in turn implies $H_{jj}(t)=0$, $t\geq 0$. Therefore, the case of $\det[\mathbf{H}(0)]=0$ does not seem to be of much practical importance. The form of operator C can be however very complicated (see an example further in the text). In general, it may not even be positive.

SYSTEM OF ACTIVE COMPARTMENTS

We will consider a system of M compartments linked together so that a constant fraction b_i^{mn} of the i-th substance outflow from the n-th compartment flows into the m-th compartment. We will generally assume that losses of substance can occur, so that:

$b_i^{1n}+\ldots+b_i^{Mn} \leq 1$, $i=1,\ldots,N$, $n=1,\ldots,M$.

We will also admit substances from the environment to flow into each compartment. Let us denote by V_i^m, X_i^m, Y_i^m and W_i^m, the accumulation, cumulated inflow, cumulated outflow and cumulated flow from the environment (i-th substance, m-th compartment), respectively. We have:

$$X_i^m = W_i^m + \sum_{n=1}^{M} b_i^{mn} Y_i^n.$$

Let us define column vectors:

$$\mathbf{y} = \mathrm{col}\ (Y_1^1,\ldots,Y_N^1,\ldots\ldots,Y_1^M,\ldots,Y_N^M),$$

$$\mathbf{v} = \mathrm{col}\ (V_1^1,\ldots,V_N^1,\ldots\ldots,V_1^M,\ldots,V_N^M),$$

$$\mathbf{x} = \mathrm{col}\ (X_1^1,\ldots,X_N^1,\ldots\ldots,X_1^M,\ldots,X_N^M),$$

$$\mathbf{w} = \mathrm{col}\ (W_1^1,\ldots,W_N^1,\ldots\ldots,W_1^M,\ldots,W_N^M).$$

We obtain:

$$\mathbf{x}(t) = \mathbf{w}(t) + \mathbf{b}\ \mathbf{g}(t)*\mathbf{x}(t),$$
$$\mathbf{y}(t) = \mathbf{g}(t)*\mathbf{x}(t),$$
$$\mathbf{v}(t) = \mathbf{h}(t)*\mathbf{x}(t),$$

where $t\geq 0$, and the matrices $\mathbf{b}$, $\mathbf{g}$ and $\mathbf{h}$ consist of the following blocks: $\mathbf{b} = [\mathbf{b}^{mn}]$, $\mathbf{b}^{mn} = \mathrm{diag}(b_1^{mn},\ldots,b_N^{mn})$, $\mathbf{g} = \mathrm{diag}(\mathbf{G}^1,\ldots,\mathbf{G}^M)$, $\mathbf{G}^m = [G_{ij}^m]$, $\mathbf{h} = \mathrm{diag}(\mathbf{H}^1,\ldots,\mathbf{H}^M)$, $\mathbf{H}^m = [H_{ij}^m]$. The functions G_{ij}^m and H_{ij}^m are the transition functions G_{ij} and H_{ij} of Theorem 1, for the m-th compartment. Let us note that this system of equations has unique solutions $\mathbf{x}(t)$, $\mathbf{y}(t)$ and $\mathbf{v}(t)$, defined on R^+ (actually, $\mathbf{x}$ and $\mathbf{y}$ are in ND^+ and $\mathbf{v}$ is in RBV^+).

In what follows, we will be borrowing extensively from the renewal theory, specifically from the asymptotic results for systems of renewal equations (Crump (1970)). The relevant properties are qualitatively different if the matrix of the system is of the lattice type. The abnormality of systems of renewal equations with lattice matrices is caused by the fact that all the iterates of the kernel of the integral operator have points of increase (ie. the jumps) concentrated on a lattice and thus the system resembles more a time discrete than a time continuous object. We will not consider the lattice case here.

Theorem 3. Suppose that $\mathbf{g}(t)$ is not lattice, matrix $\mathbf{b}\bar{\mathbf{g}}$ is positive with the spectral radius equal to one, $\bar{\mathbf{g}}-\mathbf{g}(t)$ is integrable on R^+, $\mathbf{h}(t)$ is directly Riemann integrable on R^+. Suppose further that $\mathrm{Var}_{t\geq 0}[\mathbf{w}(t)-\mathbf{w}_0 t]$ is finite for some constant nonzero vector $\mathbf{w}_0$ with nonnegative components, and that

$$\left(\int_{s\geq 0}\mathbf{h}(s)ds \right) \mathbf{w}_0 \qquad (\#)$$

is in the range of $\mathbf{1}-\mathbf{b}\bar{\mathbf{g}}$.

Then the functions $\mathbf{v}(t)$ tend to a finite limit as t tends to infinity.

CLASSICAL COMPARTMENTS

Suppose that a system of M compartments with a single substance is considered. A portion of a substance present in compartment m may, in a short period (t, t+s), leave it and enter compartment n ($n\neq m$) with probability $a_{nm}s+o(s)$, while it may leave the whole system with probability $a_{mm}s+o(s)$. Let us define matrix $\mathbf{A}$ with elements $A_{nm}=a_{nm}$ off its diagonal and with elements $A_{mm}=\sum_{k=1}^{M}a_{km}$ on its diagonal. Then, $\mathbf{h}(t) = \exp[\mathrm{diag}(A_{11},\ldots,A_{MM})\ t]$, $\mathbf{g}(t) = \mathbf{1}-\mathbf{h}(t)$, and matrix $\mathbf{b}$ has zeros on its diagonal and elements $a_{nm}/\sum_{k=1}^{M}a_{km}$ off its diagonal. It is easy to see that condition (#) reduces to the known requirement that $\mathrm{Rank}(\mathbf{A}|\mathbf{w}_0) = \mathrm{Rank}(\mathbf{A})$. If $\mathbf{w}(t)$ is absolutely continuous, then we can also write:

$$\dot{\mathbf{v}} = \mathbf{A}\mathbf{v} + \dot{\mathbf{w}}.$$

This last equation is equivalent to equation describing an active compartment without memory. Equivalence of this type is possible only in the "no memory" case. Condition (#) is reduced to a previously known one also in the case of the "pipe-compartmental" systems introduced by Győri and Eller (1981) (classical "ideal mixing" compartments connected by piston flow pipes of various length).

LEUKEMIC CELL DISINTEGRATION

We will now illustrate our considerations with an example based on an interesting biological process (for biological background, cf. Skierski and Doroszewski (1977) and Skierski et al. (1979)). The L1210 leukemia, transplantable by means of cell injection into DBA inbred mice, is the most convenient and well known experimental model of leukemia. In the experiments considered, radiochromium labeled L1210 cells were injected into the mouse or pumped into separate mouse organs in order to investigate how they disintegrate and/or are eliminated by active organs: lungs and liver. The kinetics of elimination was modeled in Kimmel et al. (1983) as an active compartmental system (using the terminology of this paper), with the transition functions G_{ij} estimated in specially designed experiments.

We will present a hypothetical model of one of the organs (liver). This example is only for the purpose of illustrating the relevance of the concept of general compartment; therefore no biological consequences will be discussed. We treat liver as a system of ramifying channels (blood vessels) of various length through which blood flows. Since the ramifications are numerous we are justified in considering the length (L) of the route chosen by a small portion of blood to be a random variable with cumulative distribution:

$$F(l) = \mathrm{Prob}\{L \leq l\}.$$

We assume now that two substances are carried by blood: (1) L1210 leukemia cells and (2) disintegrated fragments of L1210 cells. We also assume that both substances are transported by blood at the same rate v and that this rate is the same in all the ramifications. Exactly halfway through the liver, both substances encounter a small vesicle the surface of which consists of active cells having the ability to fractionate and (possibly) eliminate (ingestion) L1210 cells. The cell fragments carried by blood can also be eliminated by the vesicles. To be specific, let us assume that a L1210 cell entering the vesicle leaves it intact with probability p_k and leaves it as a number of cell fragments (following fractionation) with probability p_{ks} (cell is eliminated with probability $1-p_k-p_{ks}$). Each small portion of cell fragments entering the vesicle leaves it with probability p_s and is eliminated with probability $1-p_s$. Summarizing, the three following alternatives are possible:

1. Cells eliminated as "intact" cells.
2. Cells turned into fragments some or all of which are eliminated.
3. Fragments coming from a preceding organ eliminated, some or all.

If we denote $P(t)=F(tv)$, we obtain:

$$\mathbf{H}(t) = \begin{bmatrix} 1-p_kP(t)-(1-p_k)P(2t) & 0 \\ P(2t)(1-p_k)-p_{ks}P(t) & 1-p_sP(t) \end{bmatrix}$$

$$\mathbf{G}(t) = \begin{bmatrix} p_kP(t) & 0 \\ p_{ks}P(t) & p_sP(t) \end{bmatrix},$$

where 1 stands for the unit step function at zero, 1(t). We will check if operator C(.) exists for our model, by computing the determinant:

$$D(\mathbf{H})=[1-p_kP(t)-(1-p_k)P(2t)]*[1-p_sP(t)]$$

We see that $D[\mathbf{H}(0)] = [1-P(0)][1-p_sP(0)]$ and is nonzero if $P(0)<1$, which, in turn, can be safely assumed [in fact, it is not unreasonable to assume that distribution P(.) has a density, whence $P(0)=0$]. Therefore the inverse of $D(\mathbf{H})$ exists in the ring of the RBV[1] functions and is equal to

$$D(\mathbf{H})^{-1} =$$

$$\{\sum_{i\geq 0}[p_kP(t)+(1-p_k)P(2t)]^{*i}\}$$

$$*\{\sum_{i\geq 0}[p_sP(t)]^{*i}\}.$$

Now, we will find matrix $\mathbf{K}(t)$, which defines operator C(.) (the result is easy to check by direct substitution),

$$\mathbf{K} = \mathbf{G} * \sum_{i\geq 0} (1 - \mathbf{H})^{*i}.$$

As demonstrated, operator C(.) exists in this example. Its form, however, is much more complicated than those of operators A(.) and B(.) and it is not positive.

FINAL REMARKS

Ordinary differential equations of the classical compartmental system can be interpreted as describing the expected values of a time continuous finite Markov chain. It is clear that equations of active compartments can be treated as describing expectations of a semi-Markov process with finitely many states. Full exploration of this analogy exceeds the scope of the present paper. The environmental flows $\mathbf{w}(t)$ may represent substances injected into the system from outside. However, they may also model the distributed initial conditions ie. the outflows from the preceding compartment(s) which represent the history of the system ($t<0$). A detailed account of how to model the initial conditions via $\mathbf{w}(t)$ in an analogous framework of the theory of branching processes applied to cell kinetics, is provided in Kimmel (1981).

ACKNOWLEDGEMENTS

This work was supported in part by the US PHS grants CA23296 and CA28704. Marek Kimmel is a Visiting Investigator from the Institute of Automation, Silesian Technical University, Gliwice, Poland. Frank Traganos helped editing the manuscript.

REFERENCES

Anderson D.H. (1983). Compartmental Modeling and Tracer Kinetics, Lecture Notes in Biomathematics, vol. 50, Springer, Berlin.

Crump K.S. (1970). On Systems of Renewal Equations, J. Math. Anal. Appl., 30, 425.

Győri I. and J. Eller (1981). Compartmental Systems with Pipes, Math. Biosci., 53, 223.

Kimmel M. (1981). General Theory of Cell Cycle Dynamics Based on Branching Processes in Varying Environment, In: Biomathematics and Cell Kinetics (M. Rotenberg, ed.), Elsevier/North Holland Biomedical Press, Amsterdam, pp. 357-375.

Kimmel M., B. Kimmel and J. Skierski (1983). Mathematical Model of Leukemic-Cell Circulation in the Mouse, Math. Biosci., 67, 81.

Łojasiewicz ST. (1973). Wstęp do teorii funkcji rzeczywistych (Introduction to the Real Functions Theory, in Polish), Polish Scientific Publishers, Warsaw.

Rubinow S. I. (1975). Introduction to Mathematical Biology, Wiley, New York.

Sandberg I.W. (1978). On the Mathematical Foundations of Compartmental Analysis in Biology, Medicine and Ecology. Trans. IEEE, CAS-25, 273.

Skierski J. and J. Doroszewski (1977). The Role of Lungs and Liver in the Kinetics of Transplanted Lymphoid Leukemia L1210 Cells Labelled with Radiochromium Cr^{51}, Leukemia Res. 1, 309.

Skierski J., J. Doroszewski and T. Leżoń (1979). The fate of L1210 Leukemia Cells Labeled with Radiochromium Cr^{51} in the Perfused Mouse Liver, Leukemia Res. 3, 153.