Physiological systems are often modelled by a set of compartments. Alternatively they can be described by the diffusion-convection-reaction equations governing distributed systems. The problem considered here is that of identifying a continuously changing input of some metabolite (tracee), endogenous to the system and hence inaccessible, when a nonlinear or time-varying component is also introduced into the loss parameter, as for example through feedback mechanisms. A tracer is used to determine the steady-state impulse response under time-invariant, linear conditions. A known input of tracer is also administered when the system is driven out of steady state. The integral equations developed utilize the predetermined impulse response, the measured concentrations of both tracer and tracee (output) in some region of the system to estimate the changing loss parameter and the unknown input in a continuous fashion.

Introduction. The measurement of turnover—that is the rates of production (appearance) and utilization (disappearance) of metabolites in in vivo situations or, equivalently, the inputs into and depletion from physiological systems—is an important tool in the discovery of the finer details in the regulation of metabolism. Under steady-state conditions, it has now been accomplished under very general conditions (e.g. Stetten et al., 1951; Tait and Burstein, 1964). Under nonsteady-state conditions, fewer methods are available. For linear, time-invariant systems the input can be determined simply by deconvoluting the output with the impulse response function (e.g. Sheppard, 1962). For systems that are time-varying, nonlinear or both, the problem becomes more difficult.

* Present address: Fraser Labs for Research in Diabetes, Royal Victoria Hospital, 687 Pine Ave. W., Montreal, Quebec, Canada.
It has been solved for specific, single input–single output systems which could be modelled by one- or two-dimensional realizations (Steele, 1959; Radziuk et al., 1974, 1975; Norwich et al., 1974 and Steele et al., 1974) with a single parameter containing the non-linearity or time-dependence.

The experimental methodology involved in the measurement of these inaccessible inputs in physiological systems is based on a known external input of tracer—that is a very small or infinitesimal input of the metabolite in question which will not affect the non-linear parameter. To distinguish this tracer input from the unknown input (much larger) of the metabolite, the tracer is labelled—with a radioactive isotope or otherwise. Mathematically, since the tracer is assumed to obey the same equations as the unlabelled metabolite, it in effect linearizes the system. As a result we have two systems—the linear, time-varying tracer system and the nonlinear and/or time-varying system corresponding to the unlabelled metabolite (tracee). From the tracer system, where we know both the input and the output, we can determine the unknown time-varying parameter. This is similar to the more general case previously treated (Landahl, 1954; Hart, 1960) although the parameter treated here has no predetermined functional form. The time-varying parameter in the tracer system is numerically identical with the corresponding parameter in the tracee system which is nonlinear or time-varying. It is now determined and hence can be substituted into the tracee system equations. The only remaining unknown, time-varying variable in this system is the tracee input which can now be calculated.

In this paper the same philosophy is followed in the extension of the one- and two-dimensional (or equivalently compartment) cases to the more general $n$-dimensional case—described by $n$ simultaneous first-order ordinary differential equations—again with one parameter which can be nonlinear and/or time-varying. An identical integral equation approach will be shown to be valid in the case of dispersion by diffusion and convection where disappearance takes place throughout the system by chemical reaction or otherwise. In this case also a degree of non-linearity and time-dependence will be allowed to enter the disappearance term by means of a single parameter.

Branson (1946, 1947) was probably the first to write down an integral equation which related what he at first called the accumulation rate of metabolite in a system, $R(t)$ and the metabolizing function $F(t)$ to the amount of metabolite present at time $t$, $M(t)$:

$$M(t) = M(0)F(t) + \int_0^t R(\theta)F(t-\theta)d\theta,$$

where $M(0)$ is the amount of metabolite present at time zero. $F(t)$, from its method of measurement using a tracer impulse, is an impulse response function. It was later made to depend on $M(0)$ as well, to account for non-linearities in the system. This dependency was criticized by Hearon (1953) and Wijsman.