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A COMPUTER PROGRAM FOR FITTING TRACER KINETIC AND OTHER DIFFERENTIAL EQUATIONS TO DATA[1]

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Abstract. A computer program is available for fitting any linear or nonlinear ordinary differential equations to data, and for estimating transfer rates and/or compartment sizes from time-series tracer data in a compartmental system. The program is easy to use because compartment problems are specified simply in terms of the geometry of the components and transfers between them. The program generates confidence limits for the estimates, a feature that can be used to examine in advance the effectiveness of proposed tracer experiments.

Key words: Productivity; tracer kinetics; mineral cycling; radiotracers; quasilinearization; ecosystem; food web; biomathematics; computer programs; differential equations; energy budget.

In the course of studies on aquatic productivity in the Canadian International Biological Program, we have prepared a computer program for interpreting tracer experiments that may be of use to others. It may be obtained, accompanied by a detailed write-up, from the Librarian, Institute of Resource Ecology, University of British Columbia.

Although the program is especially designed for tracer kinetics, it may be used to fit diverse differential equations to data. Coefficients of the differential equations are found which generate a solution, usually through time, that comes closest to experimental observations in a least squares sense. The program may be used for a variety of ordinary differential equations, linear or nonlinear, which are specified in a FORTRAN subroutine supplied by the user. For example, bacterial Michaelis-Menton parameters may be estimated from population transients in a chemostat, or the logistic parameters of a fisheries population may be estimated from the time course of catch following intensification or diminution of fishing effort.

When the program is used for tracer problems, the objective is to measure the rate of material transfer between components of a system, based upon the appearance and disappearance of tracer in various components. Conover and Francis (1973) have surveyed the complications that arise when tracers are used to measure transfers of materials in a food chain. An example from our own research will illustrate some of the complications.

Carbon-14 glucose is placed into lake sediment in order to trace the rate at which animals are con-suming detrital bacteria (Marten 1976). The tracer passes from glucose into bacteria and from there into grazers. Figure 1 shows the hypothetical time-course of tracer activity in glucose, bacteria, and grazers of different sizes.

The experiment is interpreted most easily if the accumulation of tracer in the grazers is simply linear through time. This happens if, (1) the amount of tracer in the grazer's food is constant throughout the experiment and (2) the grazers are not losing any tracer. In fact, the tracer increases in bacteria during the 1st h, as they accumulate it from the glucose pool, with the result that grazers receive much less tracer during the first 15 min than they do during a similar interval 1 h later. If the experiment were to continue beyond the 6 h shown in Fig. 1, the tracer would decline in the bacteria as tracer in the glucose pool becomes exhausted and bacteria lose tracer through respiration.

Furthermore, the grazers themselves are continually losing tracer through excretion and respiration. As a result, their tracer activity levels off, more quickly in animals with a rapid turnover, such as ciliates, than in others with a slower turnover, such as amphipods. Eventually, after the tracer declines in bacteria, it will decline in grazers as well.

Using tracer accumulation after a few hours to calculate the total quantity of carbon that has passed into grazers is therefore far from straightforward. If grazers are acquiring and losing tracer by several different pathways, the situation becomes overwhelmingly complex.

Assume that the tracer experiment spans a short enough period that the transfer rates to be measured do not change appreciably during the course of the experiment. The time course of tracer activity in various components can be described realistically by the system of differential equations:

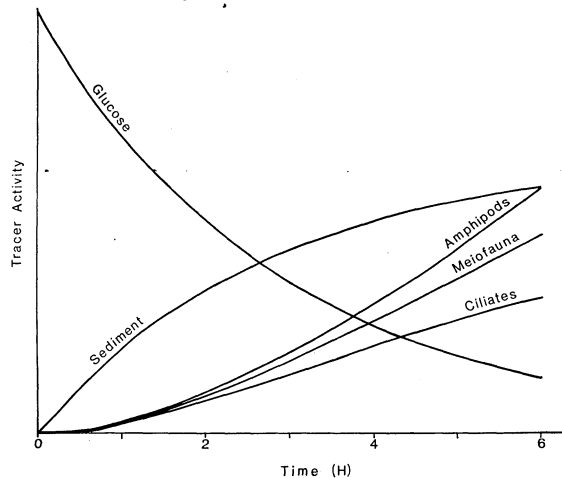$$dx_i/dt = \Sigma_j(r_{ij}x_j/w_j) - \Sigma_j(r_{ij}x_i/w_i) \qquad (1)$$

Fig. 1. Time course of tracer activity in hypothetical glucose, bacteria ("sediment"), and bacterial grazers (amphipods, meiofauna, ciliates). The glucose pool turns over every 3 h, but the bacteria take several weeks to turn over. Bacteria receive only half of the carbon lost by the glucose pool because the other half is mineralized immediately to carbon dioxide. Ciliates turn over their carbon about once a day, whereas amphipods turn over about once a month, with meiofauna having an intermediate rate of turnover. Tracer activities in the grazers are shown on amplified scales.

where x_i is the total tracer activity in the ith component, r_{ij} is the transfer rate of traced material (e.g., carbon) from the ith to jth component, and w_i is the amount of traced material (i.e., biomass) in the ith component.

These equations describe only the kinetics of the tracer and assert nothing about ecological factors underlying the transfers. The equations are intended only for measurement purposes. The x_i are observations at discrete points in time, and the r_{ij} and w_i are parameters some of which are to be estimated. Robinow and Winzer (1971) and Conover and Francis (1973) have derived explicit solutions of Eq. (1) for estimating transfers in the case of two or three components. However, when there are more than three components, the estimation problem is intractable to explicit solution.

Sheppard (1962) suggested fitting Eq. (1) to tracer kinetic data by searching for settings on an analog computer that made its time solution for Eq. (1) come closest to observed data. Patten and Witkamp (1967) followed this procedure with experimental data, but this approach has difficulty finding the best fit when there are more than two or three transfers to be estimated and consequently many possible combinations of transfer rates to be considered. It is even difficult to ascertain whether there is a single best fit, or whether, as with the data of Patten and Witkamp and other tracer data

in the ecological literature, a number of very different estimates will produce a perfect fit to the observations. This happens when the observations do not contain enough information about the transfers.

Only numerical methods offer a practical solution to complex problems in tracer kinetics. Davis and Ottaway (1972) examined a variety of numerical search procedures for fitting Eq. (1) to data, but we found that their most effective procedure was prohibitively expensive even for simple tracer experiments in ecology. Fortunately, the quasilinearization method of Bellman and Kalaba (1965) has proved effective. Leary and Skog (1972) have given a layman's description of the quasilinearization method and illustrated its application to some ecological equations. The computer program described below is based on computational procedures outlined by Lee (1968).

The program is designed to be easy to use. When the program is used for tracer kinetics, the worker need not concern himself with differential equations, specifying his tracer problem instead in terms of the geometry of the components and connections between them.

Because a tracer gives the best information about transfers in the vicinity of its introduction, more information may be obtained by introducing the tracer to several different components in separate experiments. The program finds the single set of estimates which best fits all experiments. There is an option between two least squares criteria: one based simply upon deviations between observed and expected values, and the other based upon the same deviations in proportion to observed values.

If some parameters (i.e., transfer rates or component biomasses) are known in advance, they may be fixed in order to utilize available information to estimate the remaining parameters with greater precision. This feature may also be used when the observations contain sufficient information to estimate turnover rates (i.e., transfer rates per unit of donor biomass), but not enough to resolve transfer rates and component biomasses. The biomasses are set to unity, and estimates for "transfer rates" printed by the program become in actuality estimates for turnover rates.

If the rates of change in some of the compartment biomasses are known, equality constraints may be placed on the transfer rates, thereby reducing the number of independent parameters to be estimated. This may occur, for example, when change in a compartment's biomass is measured directly or when a compartment is known to experience no change in biomass due to steady state conditions. This feature can be critical when tracer observations do not pro-

vide sufficient information for independent estimates of all transfers.

The program also allows for observations that are the sum of two or more components, a complication arising when two components cannot be physically separated for tracer counting. We encountered this situation in sediment samples containing both microscopic algae and bacteria.

The program uses an iterative procedure, and experience has shown that convergence occurs rapidly unless initial guesses of parameters are in error by more than several orders of magnitude. Computation time is simply proportional to the number of components and number of parameters to be estimated and does not increase exponentially out of bounds for complex problems, as is common with other methods. Problems within the bounds of feasible ecological experiments can be solved at reasonable cost.

Once parameters are estimated, the program generates confidence limits for the estimates. Heineken et al. (1967) have given equations for first-order approximations to the variances of quasilinearization estimates, but our computer program uses instead the Monte Carlo method. Variances alone may not be useful because the distribution of estimates is markedly nonnormal.

To implement the Monte Carlo method, we evaluate the variance of the measurements from the deviation of observations about the best fitting solution. Then artificial random observations having that variance are generated by means of a random-number generator and used to obtain new parameter estimates. This process is repeated to give a distribution of hypothetical estimates.

This feature may also be used before an experiment to generate confidence limits for estimates at specified levels of hypothetical observational errors. One may examine various sampling regimes in advance to ascertain whether they contain sufficient information to estimate the unknown parameters uniquely and with desired precision.

The program may be illustrated with real data for the situation given in Fig. 1. Samples of glucose, sediment, amphipods, and meiofauna were taken one-half h and 6 h after introduction of the glucose tracer (Marten 1975). Turnover rates were estimated as shown in Table 1, and the solution converged within five iterations. The program was applied to hypothetical tracer observations from a more complex food web containing 10 components and 27 transfers, and the solution converged within 15 iterations.

TABLE 1. Successive iterations in estimating turnover rates per hour, with iteration zero as the initial guess

Iteration	From glucose to bacteria	From bacteria to amphipods	From bacteria to meiofauna
0	1.20	3.00×10^{-4}	50.0×10^{-4}
1	2.17	$-.154 \times 10^{-4}$	-1.72×10^{-4}
2	2.94	$.605 \times 10^{-4}$	1.44×10^{-4}
3	3.21	$.605 \times 10^{-4}$	$.903 \times 10^{-4}$
4	3.32	$.605 \times 10^{-4}$	$.967 \times 10^{-4}$
5	3.37	$.605 \times 10^{-4}$	$.957 \times 10^{-4}$
6	3.38	$.605 \times 10^{-4}$	$.958 \times 10^{-4}$

Measurement errors in this experiment were between 10% and 20%. A general study of errors for turnover estimates in this situation, using the Monte Carlo method, has shown that estimation errors are of about the same magnitude as measurement errors (up to about 25%). Above that level, estimation errors become much larger than measurement errors.

The distribution of the estimates is distinctly nonnormal, particularly when observational errors are large. This is because the estimates for some replicates can be totally wrong, even though there is a reasonable fit. Considering the large errors normally present in real ecological experiments, it is essential to have several replicate experiments which agree before estimates of transfers can be accepted with confidence.

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