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Bioaccumulation models with time lags: Dynamics and stability criteria

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Abstract

Simple bioaccumulation models predict a monotonic increase in concentration with time until an equilibrium concentration is reached. However, unconsidered dynamics including deterministic oscillations occur if realistic time lags are incorporated. Stability criteria are provided for difference and differential forms of the simplest model. These criteria provide the means of identifying systems expected to exhibit monotonically damped, exponentially damped, or diverging oscillations in toxicant concentration. These unconsidered dynamics can render invalid the assumption of a single equilibrium concentration used in estimation of bioconcentration factors.

Keywords: Bioaccumulation; Stability; Time lag; Toxicology

1. Introduction

Most descriptions of contaminant bioaccumulation begin with or build upon a one-compartment model with first-order uptake and elimination kinetics, e.g., Spacie and Hamelink (1985), Connell (1989), and Barron et al. (1990). The model may be implemented as a rate constant- or clearance constant-based model depending on its intended use and the training of the researcher (Barron et al., 1990). Units differ depending on whether changes in mass or concentration are modeled. Traditional description of the model starts with the differential equation for the change in concentration with time,

$$\frac{dC}{dt} = k_u C_s - k_e C \quad (1)$$

where C = concentration in the organism (mass · mass^{-1}), C_s = concentration in the source (mass · mass^{-1}), k_e = elimination rate constant (time^{-1}), and k_u = uptake rate constant (time^{-1}, volume · mass^{-1} · time^{-1}, or volume · volume^{-1} · time^{-1} depending on the model formulation).

Integration of Eq. 1 results in the familiar monoexponential model.

$$C_t = C_s[k_u/k_e][1 - e^{-k_e t}] \quad (2)$$

This model predicts a monotonic increase in concentration until a steady state equilibrium concentration is reached ($dC/dt = 0$). Concentration

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approaches an equilibrium concentration that is maintained indefinitely if the associated assumptions remain satisfied. Cornerstone concepts in ecotoxicology such as the bioconcentration factor ($BCF = C_{ss}/C_s$) are based on this assumption of a single steady state concentration (C_{ss}), albeit one subject to stochasticity. More complex models are also presumed to monotonically approach unique equilibrium points.

This model, the most frequently used for bioaccumulation in ecotoxicology (Barron et al., 1990), is based on several assumptions: (1) there is a source of constant concentration (C_s) subject to uptake as described by first-order reaction kinetics, (2) there is instantaneous mixing in one homogeneous compartment, (3) the probability of elimination for any molecule or atom is independent of its residence time in that compartment, and (4) elimination from the compartment conforms to first-order kinetics.

It is self-evident that these assumptions may be invoked for their simplicity, not their realism. Often, models describe mathematical compartments with only vague linkage to physical compartments or mechanisms. Rate constants, composite statistics reflecting many simultaneous processes, are apparent first-order constants (Gibaldi and Perrier, 1982). Although many of these shortcomings can be alleviated by building a more complicated model, statistical difficulties in developing even a three-compartment model (Myhill, 1967; Matis and Tolley, 1980; Whicker and Schultz, 1982) are considerable. Hence, the present widespread reliance on this parsimonious approach and reluctant acceptance of associated assumptions.

Although mathematically expedient, assumptions of instantaneous mixing in a single compartment and elimination independent of residence time can be dubious (Matis and Tolley, 1980; Matis et al., 1983). Greenblatt and Shader (1985) state that the assumption of instantaneous mixing is universally inaccurate in the context of oral drug administration. Gibaldi and Perrier (1982) and Matis et al. (1983) argue that the assumption of instantaneous mixing in pharmacokinetic studies is rarely justified and leads to estimation errors for basic constants, e.g., the apparent volume of distribution and passage rate. Violations in these assumptions can create a delay between a molecule or atom's entry into a compartment and its availability for removal from that compartment. For example, Atkins (1969) described elimination involving linked exponential compartments for orally administered tetracycline with a time lag model.

Time lags can be generated by many mechanisms such as noninstantaneous passage through a series of cryptic compartments (Atkins, 1969). Although tractable models capable of accommodating time lags have been developed, they and their associated dynamics are unjustifiably ignored in ecotoxicology. Wise (1979 models tracer elimination with such a time delay using a realistic 'drift' compartment in which passage of an atom or molecule is described as the random walk of a Brownian particle. Wise (1979) argues that curve fitting under the assumption of exponential compartments is frequently done without consideration of alternative models. Consequently, the favored status of the monoexponential model is based on its frequency of use in the literature, not its confirmed superiority to other models. Similarly, gamma compartment models provide parsimonious descriptions of tracer elimination with the monoexponential model being a special case (Matis et al., 1983). (A monoexponential model is a gamma model with the scale parameter, $\lambda = 1$.) Recently, Matis et al. (1991) described a gamma model for mercury bioaccumulation in fish.

More potential mechanisms for the generation of time lags can be identified if the system of interest moves from a predominantly pharmacokinetic context as described above to an ecological context. For example, externally cued lags can become important. Time scales for these lags can vary from those associated with tidal (e.g., Watkins and Simkiss, 1988; Wilcock et al., 1993), diurnal (e.g., activity cycles or photoperiod; e.g., Bowling et al., 1983), or annual rhythms (e.g., Kolehmainen, 1972; Scott et al., 1986). Delays associated with detoxification enzyme induction, saturation kinetics, or seasonal changes in titers (e.g., Chambers and Yarbrough, 1979; Neff, 1985; Walker, 1987; Gibaldi, 1991), or delays associated

with acclimation (e.g., Oladimeji et al., 1982) could also contribute to lags.

Omission of such time lags in this foundation model and the general lack of acceptance of alternative models has drawn attention away from a potentially important model quality, equilibrium stability. As will be shown, the models described above may not always predict a gradual increase in concentration until a single equilibrium concentration is reached. We will illustrate that the addition of realistic time lags to the simple bioaccumulation model can alter its dynamics. The deterministic oscillations in concentrations demonstrated herein have widespread implications in ecotoxicology. Specifically, it is our intent to provide the stability criteria for the simplest bioaccumulation model and illustrate their potential importance in bioaccumulation modeling. Our arguments against considering only the traditionally anticipated behavior of simple bioaccumulation models are based on those developed in population biology during the early 1970s (e.g., May, 1973a,b; May et al., 1974).

2. Methods

2.1. Stability criteria for the differential equation

Eq. 1 is modified to Eq. 3 to describe a continuous bioaccumulation model with a time lag (T).

$$\frac{dC(t)}{dt} = k_u C_s - k_e C(t-T) \tag{3}$$

The methods such as those outlined in May et al. (1974) for establishing stability regions of differential population growth models can then be applied directly to bioaccumulation. Eq. 3 can be written in the form of eq. 27 in May et al. (1974),

$$\frac{dC(t)}{dt} = [g(C(t-T))]C(t) \tag{4}$$

where g is some function of $C(t-T)$. It follows that

$$\frac{dC(t)}{dt} = \left[\frac{k_u C_s}{C(t)} - \frac{k_e C(t-T)}{C(t)}\right] C(t) \tag{5}$$

The equilibrium concentration, C^*, can be evaluated by setting $g(C^*) = 0$.

$$C^* = \frac{k_u C_s}{k_e} \tag{6}$$

A β analogous to that used by May et al. (1974) can be defined,

$$\beta = -\left[C\frac{dg}{dC}\right]^* = \frac{1}{T_R} = k_e \tag{7}$$

The T_R is the characteristic return time in the population models of May et al. (1974). In bioaccumulation models, it is referred to as the mean lifetime, mean retention time, or turnover rate for the toxicant in the compartment (Whicker and Schultz, 1982; Matis et al., 1991).

The stability of the equilibrium depends on the relationship between k_e and T. The stability criteria tabulated by May et al. (1974) are directly applicable to Eq. 3. If $0 < k_e T < e^{-1}$, the model predicts a monotonic damping as the concentration approaches equilibrium (Fig. 1A). This is consistent with our present understanding of the dynamics of the simple bioaccumulation model.

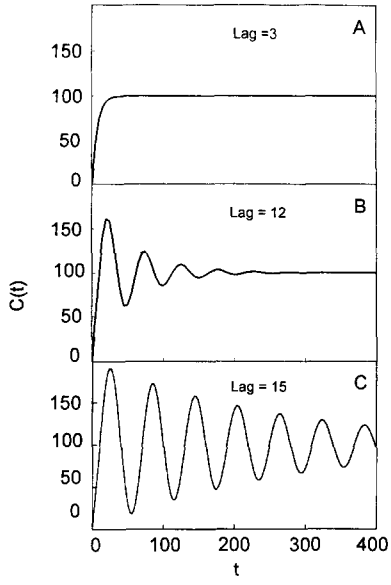

Fig. 1. Dynamics of the differential form of the single compartment model with $k_e = 0.10$. (A: $k_e T$ in region of monotonically damped oscillations, and B and C: $k_e T$ in region of exponentially damped oscillations).

However, if $e^{-1} < k_e T < \pi/2$, the concentration will approach equilibrium through a series of exponentially damped oscillations (Fig. 1B and C). Unstable conditions with diverging oscillations result if $k_e T > \pi/2$. If a clearance rate-based model is used, simple substitution of constants (Eq. 8) is used to define these stability criteria in the appropriate terms.

$$k_e = \mathrm{Cl}/V_d \quad (8)$$

where V_d = apparent volume of distribution (volume), Cl = clearance (volume · time^{-1}).

2.2. Stability criteria for the difference equation

If changes in concentrations occur in distinct pulses, a time step (τ) analogous to population generation time (nonoverlapping generations) is defined and a difference equation employed.

$$C_{t+\tau} = C_t + k_u C_s - k_e C_t \quad (9)$$

Following May et al. (1974), stability criteria for the difference model can also be generated. Stability criteria in terms of k_e are the following for the difference equation: monotonic damping to a stable equilibrium if $\tau < k_e^{-1}$; exponentially damped oscillations to a stable equilibrium if $0.5\tau < k_e^{-1} < \tau$; and diverging oscillations (unstable equilibrium) if $k_e^{-1} < 0.5\tau$.

3. Results

Diagrams of stability regions can be generated from the criteria provided above, e.g., Fig. 2 for the differential form of the monoexponential model. Using hours as the units of time, biologically reasonable k_e values and time lags generate heretofore unsuspected dynamics. For example, time lags associated with daily or tidally cued processes (i.e., in the range of 4 to 12 h) combined with k_e values estimated for some common drugs (Vožeh et al., 1989), organic contaminants (e.g., 1,4-dichlorobenzene, Könemann and van Leeuwen, 1980; benzo(a)pyrene, Leversee et al., 1982; p-nitroanisole, Foster and Crosby, 1986; Cyanophos or chlorothion, De Bruijn and Hermens, 1991), radiological contaminants (e.g., tissue water tritium, Blaylock and Frank, 1979; Rodgers, 1986; or ^{60}Co, table 14 in Whicker and Schultz, 1982), or metals (e.g., fast component for Cd in crayfish blood, Lyon et al., 1984) fall outside the region of monotonic damping to a single equilibrium concentration.

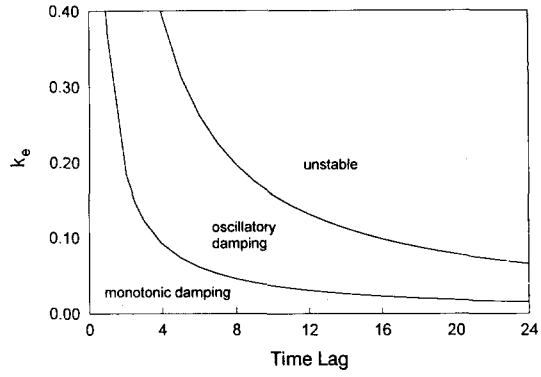

Fig. 2. Stability regions for the differential form of the single compartment model.

Following methods outlined by population biologists two decades ago (e.g., May et al., 1974), the simplest and most commonly used models for bioaccumulation are shown to be capable of exhibiting previously unsuspected dynamics. Contrary to the common assumption of a single equilibrium concentration, stable or unstable oscillations are predicted in a model involving realistic time lags and biologically reasonable constants. Stability criteria are defined for this simple model. These unexpected behaviors are also possible in more complicated models.

4. Discussion

The potential for bioaccumulation dynamics other than a monotonic increase to a single equilibrium concentration has significant implications in several areas of ecotoxicology. First, many modeling efforts are based on the assumption of a single equilibrium concentration. These efforts include such diverse applications as ecosystem fate models (e.g., Clark et al., 1988), food chain transfer models (e.g., Thomann, 1981), and bioaccumulation models advocated for establishing en-

vironmental quality criteria (e.g., Di Toro et al., 1991). Often discussion of the nonlinear relationship between concentration and toxic response assumes one equilibrium concentration. Second, a mechanism with deterministic underpinnings can be added to the potential factors generating variation in toxicant concentrations for populations of individuals assumed to be at equilibrium (e.g., Pinder and Smith, 1975; Giesy and Wiener, 1977; Lobel et al., 1991). Finally, if one assumes a correlation between duration of exposure with animal age (or size), an additional mechanism for the age- or size-dependent variation in animal body concentrations can be stated. Under certain conditions, younger animals have a higher probability of widely varying (oscillating) body concentrations than older animals.

Whether the oscillations described here for the time lag models occur in the laboratory or field remains untested. The predominant ecotoxicological methods (experimental designs with an accumulation phase leading to practical equilibrium concentrations followed by a subsequent elimination phase) do not lend themselves to detection of these oscillations. Within the theoretical context outlined above, there is no obvious reason to dismiss this possibility without serious testing. The stability criteria given above can be used to select toxicant-organism pairs with which to rigorously test this hypothesis of oscillatory behavior under certain conditions.

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