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Exploration of bimodal kinetics in marker digesta outflows using compartmental models

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ABSTRACT

A deterministic compartmental model is developed for examining the dynamics of digesta marker outflows in animals, focussing on models which will simulate bimodal kinetics with two peaks in the time course of marker outflow.

First, to establish the background to the subsequent modelling of bimodal flow, we examine the compartmental scheme which gives rise mechanistically to the gamma function, and derive or describe various useful properties. This is illustrated by varying two key parameters of the gamma function, n (the number of compartments), and k (the rate constant for compartment emptying).

Next, a more articulated compartmental scheme is constructed, and by progressive parameter changes, it is shown how bimodal faecal marker outflow can be achieved.

Last, progressive simplification is applied to this scheme to arrive at what is (hopefully) the simplest compartmental scheme which can be used to simulate bimodal kinetics. This may be used mechanistically to describe the role of digesta flow in animals which exhibit such characteristics.

1. Introduction

Digesta marker fluxes in animal faeces have been used as a tool for studying aspects of animal nutrition and growth for many years (e.g. Thornley and France, 2007, pp. 547–553). In many ruminants, after a pulse dose of marker, output marker flux can be described by a simple linear compartment model of the type that gives rise to gamma-function behaviour (Thornley and France, 2007, pp. 818 – 822). Here the rate of appearance of marker plotted against time variable, t, exhibits one maximum, whose height and position in time can be varied by the two parameters defining the gamma function: the number of compartments and the rate constant between the compartments. However, some ruminants exhibit kinetics which are not easily fitted by a single-maximum gamma function, and may require a more articulated representation. Here we use a series of three linked compartments to generate a range of kinetic responses varying from a single maximum to bimodal with two maxima.

Compartment models have long been used to study digestion in ruminating animals (e.g. Blaxter et al., 1956; France et al., 1985; Pond et al., 1988) and non-ruminants such as fish, horses and swine (e.g. Boyce et al., 2000; Rosenfeld et al., 2006; Wilfart et al., 2007). They continue to be used to study different aspects of the processes involved. Adeleye et al., (2016, Fig. 2) give some results that cannot be accommodated using traditional approaches, although they do not comment on this. Several authors describe data which could possibly be better fit and understood using equations based on the methodology presented in the current paper: e.g. Matsuda et al., (2015, Figs. 1 and 2), Hammond et al., (2014, Fig. 1), Schwarm et al., (2009, Fig. 1), Sanaka et al., (2005, Fig. 2), Wyse et al., (2001, Fig. 6), and Sakaguchi et al., (1987, Fig. 1a, who also say “No equation could be fitted to the time-course changes for the excretion of Co, …). In 1983, Cork and Warner (1983, p. 43), when examining passage through the gut of the koala, suggested that “this caused the particulate marker to distribute in two pools situated in parallel producing a marker excretion curve different from that reported in any other mammals.”

The objective of the work presented here is pedagogic: to construct a transparent flexible mechanistic compartment model of the digestive tract which can be easily extended and can be used to simulate various forms of marker outflow kinetics, including bimodal time responses.

2. Modelling

First we describe the linear compartment model that gives rise to the gamma function in some detail, because this provides the essentials for understanding the subsequent bimodal analysis.

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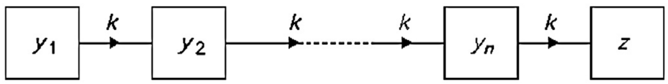

Fig. 1. Compartmental scheme with n compartments with outflows, labelled y_1, y_2, ..., y_n, with a final compartment, z. A single rate constant, k (h^{-1}), applying to all compartments giving rise to the gamma function, $\gamma(t, n, k)$, as the outflow rate from the n^{th} compartment, ky_n [Eq. (3)]. At time $t = 0$ h, $y_1 = 1$ (mg marker, say) and y_i, $i > 1 = 0$, $z = 0$.

2.1. Gamma function and gamma distribution

Fig. 1 shows a scheme which generates the gamma function. Following Thornley and France (2007, pp. 818–822), the differential equations for Fig. 1 are

$$\frac{dy_1}{dt} = -ky_1, \quad \frac{dy_2}{dt} = ky_1 - ky_2, ..., \frac{dy_n}{dt} = ky_{n-1} - ky_n, \quad \frac{dz}{dt} = ky_n, \tag{1}$$

with at $t = 0$ h: $y_1 = 1, \quad y_2 = y_3 = ... = y_n = z = 0$.

Time t (h) is the independent variable. Eq. (1) have two parameters, n, the number of compartments, and the rate constant k (h^{-1}).

Solving Eq. (1) sequentially, therefore gives

$$y_1 = e^{-kt}, \quad y_2 = kte^{-kt}, \quad y_3 = \frac{(kt)^2}{2!}e^{-kt}, \quad ..., \quad y_n = \frac{k^{n-1}t^{n-1}}{(n-1)!}e^{-kt}. \tag{2}$$

The gamma function, $\gamma(t, n, k)$, can be identified with the outflow rate, O_n, from the nth compartment, i.e., $k \times y_n$ of the above Eq. (2) to give:

$$\gamma(t, n, k) = O_n = ky_n = \frac{k^n t^{n-1}}{(n-1)!}e^{-kt}. \tag{3}$$

The dimensions of $\gamma(t, n, k)$ are time^{-1} or in our case h^{-1}. This is normalized so that

$$\int_0^\infty O_n dt = \int_0^\infty \gamma(t, n, k) dt = \int_0^\infty \frac{k^n t^{n-1}}{(n-1)!}e^{-kt} dt = 1. \tag{4}$$

The incomplete gamma function, $\Gamma(t, n, k)$, is obtained by stopping the integration at time, t:

$$\Gamma(t, n, k) = \int_0^t O_n dt = \int_0^t \gamma(t, n, k) dt = \int_0^t \frac{k^n t^{n-1}}{(n-1)!}e^{-kt} dt. \tag{5}$$

The gamma function $\gamma(t, n, k)$ [Eq. (3)] has mean t, $\langle t \rangle$ (h), mean t squared, $\langle t^2 \rangle$ (h^2), variance of t, σ^2 (h^2), standard deviation t_{sd} (h), mode t_{max} (h, time t where γ is a maximum), value of γ at time $t = t_{max}$ (h^{-1}) (the mode) and coefficient of variation (CV) given by

$$< t > = \frac{n}{k}, \quad < t^2 > = \frac{n(n+1)}{k^2}, \quad \sigma^2 = < t^2 > - < t >^2 = \frac{n}{k^2},$$
$$t_{sd} = \sigma = \frac{n^{\frac{1}{2}}}{k},$$
$$t_{max} = \frac{n-1}{k}, \quad \gamma(t_{max}, n, k) = \frac{k(n-1)^{n-1}}{(n-1)!}e^{-(n-1)},$$
$$\text{and CV} = \frac{t_{sd}}{< t >} = \frac{1}{\sqrt{n}}. \tag{6}$$

Fig. 2 illustrates some of the principal properties of linear compartments models (as in Fig. 1) in relation to the gamma function, $\gamma(t, n, k)$ (Eq. (3)). Increasing n makes for increasing spikiness

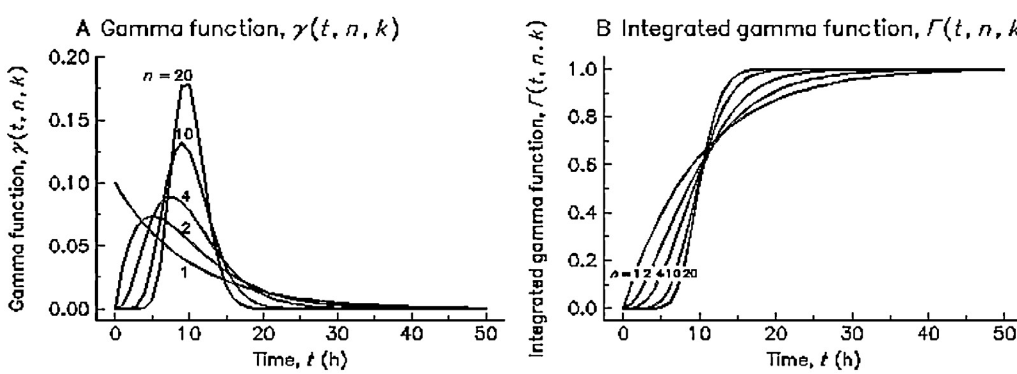

Fig. 2. Time plots of A the gamma function $\gamma(t, n, k)$ [Eq. (3)], and B the integrated (incomplete) gamma function $\Gamma(t, n, k)$ of Eq. (5). The simulations have been performed for increasing values of n, the number of compartments (Fig. 1). The rate constant k (Fig. 1) is simultaneously increased so that the mean value $\langle t \rangle$ [Eq. (6)] remains constant at $n/k = 10$ h.

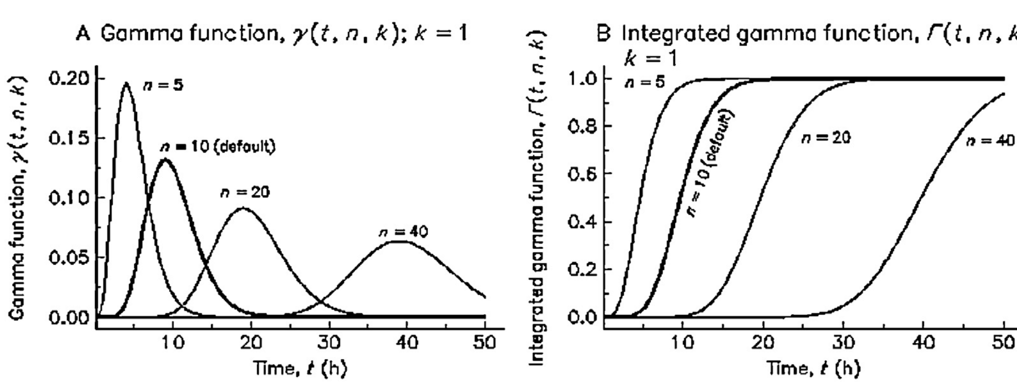

Fig. 3. Time plots of A the gamma function $\gamma(t, n, k)$ of Eq. (3), and B the integrated gamma function $\Gamma(t, n, k)$ of Eq. (5). The simulations have been performed for increasing values of n (the number of compartments (Fig. 1) with rate constant k (Fig. 1) constant at $k = 1$ h^{-1}, so that the mean value $\langle t \rangle = n/k$ [Eq. (6)] increases to $n/k = n$ h.