Journal of Pharmacokinetics and Pharmacodynamics (2019) 46:53–63
https://doi.org/10.1007/s10928-018-09618-z

ORIGINAL PAPER

Ordinary differential equation approximation of gamma distributed delay model

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Received: 26 October 2018 / Accepted: 31 December 2018 / Published online: 7 January 2019

Abstract
In many models of pharmacodynamic systems with delays, a delay of an input is introduced by means of the convolution with the gamma distribution. An approximation of the convolution integral of bound functions based on a system of ordinary differential equations that utilizes properties of the binomial series has been introduced. The approximation converges uniformly on every compact time interval and an estimate of the approximation error has been found $O\left(\frac{1}{N^{\nu}}\right)$ where N is the number of differential equations and ν is the shape parameter of the gamma distribution. The accuracy of approximation has been tested on a set of input functions for which the convolution is known explicitly. For tested functions, $N \geq 20$ has resulted in an accurate approximation, if $\nu \geq 1$. However, if $\nu < 1$ the error of approximation decreases slowly with increasing N, and $N > 100$ might be necessary to achieve acceptable accuracy. Finally, the approximation was applied to estimate parameters for the distributed delay model of chemotherapy-induced myelosuppression from previously published WBC count data in rats treated with 5-fluorouracil.

Keywords Binomial series · Convolution · Pharmacodynamics · Gamma distribution · Transit compartments model · Chemotherapy-induced myelosuppression

Introduction

Gamma distributed delay equations are differential equations with at least one state $y(t)$ that is delayed by the continuous distribution of delays described by the gamma probability density function $g_k^{\nu}(\tau)$ [1]:

$$\left(y * g_k^{\nu}\right)(t) = \int_{-\infty}^{t} y(\tau) g_k^{\nu}(t-\tau) d\tau \qquad (1)$$

where

$$g_k^{\nu}(\tau) = \frac{k}{\Gamma(\nu)} (k\tau)^{-1} exp(-k\tau) \qquad (2)$$

the gamma function $\Gamma(\nu)$ is the extension of the factorial $(\nu - 1)!$ defined for positive integers on the set of positive real numbers $\nu > 0$ [2]. The parameter k is referred to as a rate that defines the scale parameter $1/k$. Gamma distributed delays with the shape parameter ν being a positive integer are commonly used in pharmacodynamics to describe a signal transduction from drug-receptor complex to the effect site [3] and lifespan distribution in cell populations [4]. Gamma distributed delays with real $\nu > 0$ emerged in modeling absorption delays [5] and maturation of granulocyte precursors in the bone marrow [6].

Numerical algorithms evaluating the convolution integral (1) are computationally expensive. If $\left(y * g_k^{\nu}\right)(t)$ is a part of a differential equation, such evaluation takes place at each step size that significantly increases the computational time that for many practical applications might be prohibitively long. Expressing $\left(y * g_k^{\nu}\right)(t)$ as a solution to a system of ordinary differential equations (ODEs) that can be added to the differential equations describing $y(t)$ would not be as computationally expensive. Additionally, it will be implementable in software equipped only with ODE solvers. If ν is a positive integer, the linear chain trick allows $\left(y * g_k^{\nu}\right)(t)$ to be a solution to the transit

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10928-018-09618-z) contains supplementary material, which is available to authorized users.

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compartment model with v representing the number of transit compartments [1]. Because of this property, transit compartment model is one of the most popular ways of introducing delays in pharmacodynamic and systems pharmacology models [7]. Recently, Koch and Schropp [8] have introduced the distributed transit compartment model that can be used to approximate $(y * g_k^v)(t)$ for any real $v > 0$. In essence, for an arbitrary probability density function $g(t)$ with the cumulative distribution function $S(t)$, a given transit rate k, and a positive integer m, a grid of time points is introduced $\tau_j = j/k,\ j = 0, \ldots, m$. The jth transit compartment state $x_j(t)$ is multiplied by $S(\tau_{j-1})$ and the sum $\sum_{j=1}^{m} S(\tau_{j-1}) x_j(t)$ is used to approximate $(y * g)(t)$ as $k \to \infty$ and $m \to \infty$. They proved a convergence of such approximation and applied it to several common distributions, including the gamma distribution. An estimate of rate of convergence has not been provided.

The objective of this work is to introduce an ODE approximation of the $(y * g_k^v)(t)$ utilizing properties of the binomial series. In the following sections a proof of convergence and an estimate of the error are provided. The accuracy of approximation is tested on a set function with explicit formulas for $(y * g_k^v)(t)$. The approximation is applied to estimate parameters for the distributed delay model of chemotherapy-induced myelosuppression from previously published WBC count data in rats treated with 5-fluorouracil.

Theoretical

Typical gamma distributed delay equations consist of differential equations describing the states (including $y(t)$) for positive times $t > 0$ whereas the states values for times $t \le 0$ are subject to initial or past conditions, i.e.

$$y(t) = \varphi(t), \quad t \le 0 \tag{3}$$

where $\varphi(t)$ is a known function such that $\int_{-\infty}^{0} \varphi(\tau) g_k^v(t - \tau) d\tau$ is well defined. Then the convolution integral (1) can be written as

$$(y * g_k^v)(t) = \int_{-\infty}^{0} \varphi(\tau) g_k^v(t - \tau) d\tau + \int_{0}^{t} y(\tau) g_k^v(t - \tau) d\tau \tag{4}$$

One can expand $(t - \tau)^{-1}$ in the formula for $g_k^v(t - \tau)$ into the binomial series

$$(t - \tau)^{v-1} = t^{v-1}\left(1 - \frac{\tau}{t}\right)^{v-1} = t^{v-1} \sum_{n=0}^{\infty} (-1)^n \binom{v-1}{n} \left(\frac{\tau}{t}\right)^n \tag{5}$$

and integrate the series term-by-term to arrive at

$$\int_{0}^{t} y(\tau) g_k^v(t - \tau) d\tau = \frac{k}{\Gamma(v)} (kt)^{v-1} \sum_{n=0}^{\infty} (-1)^n \binom{v-1}{n} I_n(t) \tag{6}$$

where

$$I_n(t) = \int_{0}^{t} y(\tau) \left(\frac{\tau}{t}\right)^n \exp(-k(t - \tau)) d\tau. \tag{7}$$

Note that in case v is a positive integer (5) collapses to the binomial formula and the infinite series becomes a finite sum with $n = 0, \ldots, v - 1$. Consequently, the integral (6) can be expressed by a finite number of functions $I_n(t)$, $n = 0, \ldots, v - 1$.

Below we show that the series in (6) converges absolutely and uniformly on every interval $0 \le t \le T < \infty$ and its sum is equal to the left-hand side of (6). Further, differentiation of the integral in (7) with respect to t yields that $I_n(t)$ is a solution to the following ODE (see Appendix 1 for derivation):

$$\frac{dI_n}{dt} = y(t) - \left(k + \frac{n}{t}\right) I_n \tag{8}$$

We also show that $I_n(t)$ satisfies the following initial condition

$$I_n(0) = 0 \tag{9}$$

Consequently, the integral in (6) can be approximated on the closed interval $0 \le t \le T$ with any accuracy by the series truncated after $n = N$ terms. This implies, that $(y * g_k^v)(t)$ can be approximated on the interval $0 \le t \le T$ by solutions of $N + 1$ ODEs. In case v is a positive integer, the approximation with $N \ge v - 1$ is exact.

Special cases

For some special functions $y(t) = \varphi(t)$ that are known on the entire time interval $-\infty < t < \infty$ the convolution integral (4) can be calculated explicitly or as a solution to an ODE. Then the binomial series expansion (6) in unnecessary. Examples include Dirac delta function:

$$\int_{-\infty}^{t} \delta(\tau - t_0) g_k^v(t - \tau) d\tau = H(t - t_0) g_k^v(t - t_0) \tag{10}$$

where $H(t - t_0) = 1$, if $t > t_0$, and $H(t - t_0) = 0$, otherwise. Also

$$\int_{-\infty}^{t} H(\tau - t_0) g_k^{\nu}(t-\tau) d\tau = H(t-t_0) \int_{0}^{t-t_0} g_k^{\nu}(\tau) d\tau \tag{11}$$

The convolution integral (11) is a solution of

$$\frac{dI}{dt} = H(t-t_0) g_k^{\nu}(t-t_0) \quad \text{and} \quad I(0) = 0 \tag{12}$$

Examples (10) and (11) correspond to the convolution of the gamma pdf with a bolus input at time t_0 and a constant infusion that starts at time t_0. If the input is an infusion that starts at time t_0 and ends at time $t_1 > t_0$, then it can be considered as the difference $H(t-t_0) - H(t-t_1)$, and (11) can be applied.

Results

Convergence

The rate of convergence of the series (6) and an estimate of the truncation error are provided by the following theorem:

Theorem *Let $t, \nu, k > 0$ and $y(\tau)$ be bound for $0 \le \tau \le t$. Then the series in (6) converges absolutely and its sum satisfies Eq. (6). Moreover, for any integer $N > 0$*

$$\int_0^t y(\tau) g_k^{\nu}(t-\tau) d\tau = \frac{k}{\Gamma(\nu)} (kt)^{\nu-1} \sum_{n=0}^{N} (-1)^n \binom{\nu-1}{n} I_n(t) + R_N(t) \tag{13}$$

where

$$|R_N(t)| \le \|y\|_{L^\infty(0,t)} \frac{(kt)^{\nu} \exp(\nu^2)}{\Gamma(\nu+1) N^{\nu}} \tag{14}$$

Here $\|y\|_{L^\infty(0,t)}$ denotes the maximum value of $|y(\tau)|$ over the time interval $[0, t]$, If ν is a positive integer and $N \ge \nu - 1$, then $R_N(t) = 0$.

A proof of Theorem is provided in Appendix 2. An immediate consequence of (14) is the following remark. If $T > 0$ and $y(t)$ is bound in $0 \le t \le T$, then

$$\frac{k}{\Gamma(\nu)} (kt)^{\nu-1} \sum_{n=0}^{N} (-1)^n \binom{\nu-1}{n} I_n(t) \to \int_0^t y(\tau) g_k^{\nu}(t-\tau) d\tau \text{ as } N \to \infty \text{ uniformly in } [0, T] \tag{15}$$

The sum in (13) is the approximation of the convolution integral. An estimate of the error of approximation is shown in (14). The actual error might be substantially smaller. Its assessment is performed in the following section.

Assessment of error of approximation

Because of the uniform convergence in $[0, T]$, a natural norm for assessment of the error of approximation $R_N(t)$ is $\|\cdot\|_{L^\infty(0,T)}$. According to (11)

$$y * g_k^{\nu} = p + \sum_{n=0}^{N} a_n J_n + R_N \tag{16}$$

$$p(t) = \int_{-\infty}^{0} \varphi(\tau) g_k^{\nu}(t-\tau) d\tau = \int_{t}^{\infty} \varphi(t-\tau) g_k^{\nu}(\tau) d\tau$$

and

$$a_n = (-1)^n \binom{-1}{n} \frac{k}{\Gamma(\nu)} \text{ and } J_n(t) = (kt)^{-1} I_n(t) \tag{17}$$

According to Theorem, if ν is a positive integer and $N \ge \nu - 1$, then $R_N = 0$.

It follows from (14) that

$$\|R_N\|_{L^\infty(0,T)} \le \|y\|_{L^\infty(0,T)} \frac{(kT)^{\nu} \exp(\nu^2)}{\Gamma(\nu+1) N^{\nu}} \tag{18}$$

Note that for all $n \ge 0$

$$I_n(t) = O(t) \text{ as } t \to 0 \tag{19}$$

Hence $J_n(t)$is bound in $0 \le t \le T$. Equation (19) also implies that $I_n(t)$ satisfies the initial condition (9).

To test accuracy of the approximation (16) a family of y's for which $y * g_k^{\nu}$ is known explicitly has been selected. Assuming that $g_k^{\nu}(t) = 0$ for $t \le 0$, one can show that for any integer $n \ge 1$

$$g_k^n * g_k^{\nu} = g_k^{n+\nu} \tag{20}$$

Therefore a set of $y \in \left\{ g_k^n / \|g_k^n\|_{L^\infty(0,T)} | n \in \mathbb{Z}_+,\ k > 0 \right\}$ has been used for testing. g_k^n is known as the Erlang distribution. To be able to compare the accuracy of approximation across the test functions they were normalized by their $\|\cdot\|_{L^\infty(0,T)}$ norms. Since the mode of g_k^n is at $(n-1)/k$,

$$\|g_k^n\|_{L^\infty(0,T)} = g_k^n\left(\min\left\{T, \frac{n-1}{k}\right\}\right) \tag{21}$$

Figure 1 shows plots of $y * g_k^{\nu}$ and its approximations for selected values of T, k, ν, n, and N. Additional plots are provided in Supplementary Material. The rate of convergence is slow for $0 < \nu < 1$ and it dramatically increases when $\nu > 1$, which is consistent with the error estimate $O\left(\frac{1}{N^{\nu}}\right)$. To quantify how many terms of the approximating series (16) are required to reach a given accuracy, we introduced a parameter $N_{0.01}$, the smallest positive integer for which the relative error of approximation is less or equal 0.01:

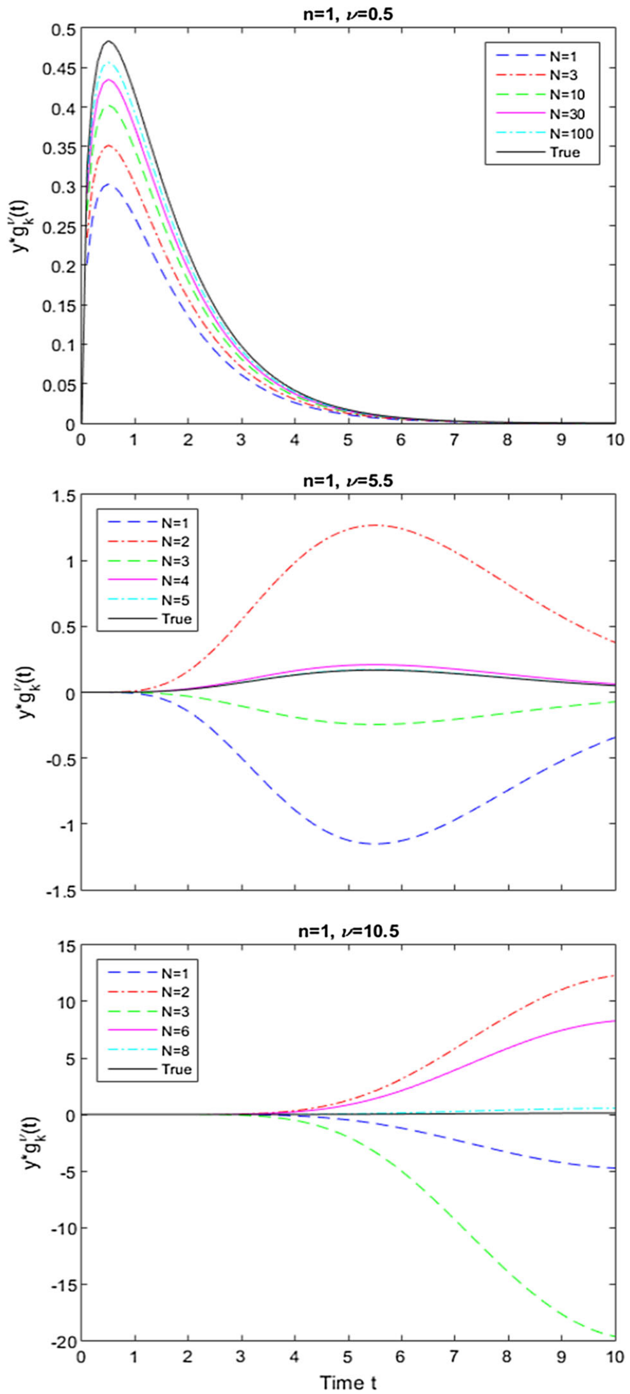

Fig. 1 Time courses of the approximations (14) for $y = g_k^n$ and $p = 0$ with increasing N corresponding to three non-integer values of $v = 0.5,\ 5.5,\ 10.5$. The time interval was $0 \le t \le 10$ and $k = 1$. The figure shows plots for $n = 1$. Additional plots for $n = 5,\ 10$ are provided in Supplementary Material Fig. S1

$$N_{0.01} = \min\left\{N > 0 \middle| \|R_N\|_{L^\infty(0,T)} / \left\|y * g_k^v\right\|_{L^\infty(0,T)} \le 0.01\right\} \tag{22}$$

Values of $N_{0.01}$ corresponding to various v and n and listed in Table 1. Generally speaking, for $v > 1$ $N = 20$ suffices to approximate $y * g_k^v$ with a relative error less than 1%. Since the error estimate provided in (14) is rather crude, a better estimate can be obtained by not completing one step of the derivation of the estimate shown in Appendix 1.

$$|R_N(t)| \le \frac{(kT)^v}{(\Gamma(v+1))} \|y\|_{L^\infty(0,t)} \sum_{n=N+1}^{\infty} \left| \binom{v}{n+1} \right| \tag{23}$$

The estimates of error given by (23) are listed in Table 1. Additional error estimates are presented in Supplementary Material Table S1. Note that if v is a positive integer, for $N \ge n + v$ the error is 0. For tested cases of $v = 0.5,\ 0.8$. The sum $\sum_{i=N_{0.01}+1}^{N_{0.01}+1000} \left| \binom{v}{i+1} \right|$ did not approximate $\sum_{i=N_{0.01}+1}^{\infty} \left| \binom{v}{i+1} \right|$ resulting in estimates of errors bigger than actual errors. Figure 2 shows the relative error $\|R_N\|_{L^\infty(0,T)} / \left\|y * g_k^v\right\|_{L^\infty(0,T)}$ versus N plots for varying v. All simulations were performed in MATLAB R2015a (MathWorks Inc.) using function *myelo* provided in Supplementary Material.

Distributed delay model of chemotherapy-induced myelosuppression

Friberg et al. introduced a semi-physiological model that accounts for the suppression of granulopoiesis by chemotherapeutic agents [9, 10]. This model is widely used to describe hematological toxicities both in animals and humans. The key model components are proliferating cells in the bone marrow and the circulating granulocytes connected by a series of transit compartments describing the maturation of granulocytes in the bone marrow. The transit compartments do not reflect stages of granulocyte development but rather are meant to quantify the duration of maturation. De Suza et al. replaced the transit compartments with a convolution integral with the gamma pdf accounting for the maturation delay [6]. The model differential equations are as follows:

$$\frac{dy}{dt} = k_p y \left(\frac{w_0}{w}\right)^{\gamma} - k_s C y - k y \tag{24}$$

$$\frac{dw}{dt} = k y * g_k^v - k_c w \tag{25}$$

The proliferating precursor cells for granulocytes y reproduce at a first-order rate k_p and convert to maturating cells in the bone marrow at a first-order rate k. The maturation process is described by the convolution integral $y * g_k^v$.The mature cells are released to the circulation and form granulocytes w which enter the extravascular tissue at a first-order rate k_c. The circulating granulocytes negatively

Table 1 Error, relative error (Rel. Err.), estimate of error (Estimate), estimate of relative error (Rel. Est.) evaluated at $N = N_{0.01}$ for approximation (16) with $y = g_k^n$ and $p = 0$ and varying n and v. Other parameters are $T = 10$ and $k = 1$. If $N_{0.01} > 1000$, the values of Error, Rel. Err., Estimate, and Rel. Est. were calculated for $N_{0.01} = 1000$

n	v	$N_{0.01}$	Error[a]	Rel. Err.[b]	Estimate[c]	Rel. Est.[d]
1	0.5	> 1000	8.62E−03	1.78E−02	1.86E−02	3.84E−02
5	0.5	> 1000	4.14E−02	4.38E−02	1.86E−02[e]	1.97E−02[f]
10	0.5	> 1000	6.10E−02	6.26E−02	1.86E−02[e]	1.91E−02[f]
1	0.8	46	4.03E−03	9.99E−03	6.20E−02	1.53E−01
5	0.8	249	9.15E−03	9.99E−03	1.28E−02	1.40E−02
10	0.8	504	9.57E−03	9.98E−03	5.91E−03[e]	6.16E−03[f]
1	5.5	6	7.36E−04	4.39E−03	4.82E+00	2.88E+01
5	5.5	11	5.48E−03	8.35E−03	7.15E−02	1.08E−01
10	5.5	18	2.36E−03	7.26E−03	3.47E−03	1.06E−02
1	10.5	10	9.66E−04	8.00E−03	2.12E+01	1.76E+02
5	10.5	15	1.04E−03	4.74E−03	1.31E−02	6.01E−02
10	10.5	20	1.52E−04	7.57E−03	2.23E−04	1.10E−02

[a]Error = $\|R_{N_{0.01}}\|_{L^\infty(0,T)}$

[b]Rel. Err. = $\|R_{N_{0.01}}\|_{L^\infty(0,T)} / \|y * g_k^v\|_{L^\infty(0,T)}$

[c]Estimate = $\frac{(kT)^v}{(\Gamma(v+1))} \sum_{i=N_{0.01}+1}^{N_{0.01}+1000} \left| \binom{v}{i+1} \right|$

[d]Rel. Est. = Estimate$/\|y * g_k^v\|_{L^\infty(0,T)}$

[e]Error > Estimate

[f]Rel. Err. > Rel. Est.

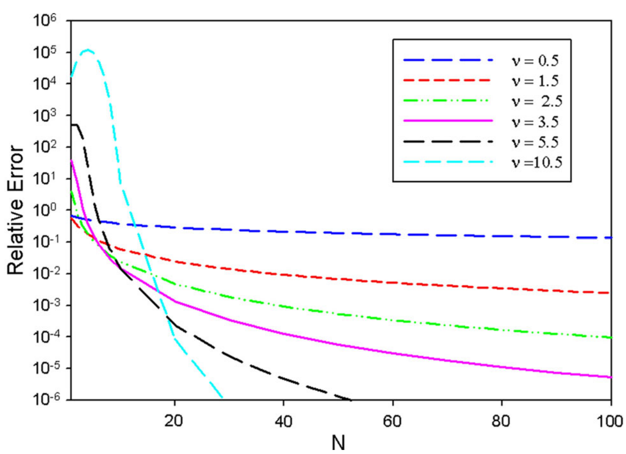

Fig. 2 Relative error for approximation (14) with $y = g_k^n$ and $p = 0$ and varying v. Other parameters are $T = 10$ and $k = 1$, and $n = 5$. The relative error was calculated as $\|R_N\|_{L^\infty(0,T)} / \|y * g_k^v\|_{L^\infty(0,T)}$

feedback on the proliferation rate of cells in the bone marrow as described by the term $(w_0/w)^\gamma$, where w_0 is the baseline count of the circulating granulocytes. The drug irreversibly removes the proliferating cells at a second-order rate k_s. The drug plasma concentration C is described by additional pharmacokinetic model. In case of IV bolus injections of 5-fluorouracil in rats, the pharmacokinetic model is the one-compartment model with the Michaelis–Menten elimination [9]:

$$\frac{dA}{dt} = -\frac{V_{max}A}{K_m + C} \tag{26}$$

where A is the amount of drug in the plasma, V_{max} and K_m are Michaelis–Menten constants, and

$$C = \frac{A}{V} \tag{27}$$

with the volume of distribution V. Both proliferating cells and circulating granulocytes are assumed to be at steady sate prior to drug administration:

$$y(t) = y_0 \text{ for } t \le 0 \tag{28}$$

and

$$w(0) = w_0 \tag{29}$$

The convolution integral was calculated according to (16) as follows

$$y * g_k^v = p + \sum_{n=0}^{N} a_n J_n \tag{30}$$

where

$$\frac{dp}{dt} = -y_0 g_k^v(t) \text{ and } p(0) = y_0 \tag{31}$$

is a differential equation defining

$$p(t) = y_0 \int_{-\infty}^{0} g_k^v(t-\tau)d\tau = y_0 \int_{t}^{\infty} g_k^v(\tau)d\tau \tag{32}$$

To ensure stability an additional assumption is made:

$$k_p = k \tag{33}$$

Then

$$y_0 = \frac{k_c}{k} w_0 \tag{34}$$

Since the parameter k_c is difficult to identify from myelosuppression WBC data, an additional assumption has been made [10]

$$k_c = k \tag{35}$$

Lastly, the mean of the gamma distribution (MTT) rather than k is used for parameter estimation

$$k = \frac{v}{MTT} \tag{36}$$

The primary model parameters are MTT, v, w_0, γ, k_s, V_{max}, K_m, and V.

Parameter estimation

The distributed delay model was applied to refit the original 5-FU plasma concentrations and WBC counts reported in [9] by Krzyzanski et al. [11]. We used the same data to test the implementation of the model by means of approximation (30). The data consist of four groups of rats that received placebo, a single injection of 5-FU 127 mg/kg on day 0, two injections of 5-FU 63 mg/kg on days 0 and 2, and three injections of 5-FU 49 mg/kg on days 0, 2, and 4. Plasma concentrations of 5-FU were measured over 2 h period after the first injection and WBC count was measured over 23 days. Data were obtained by digitizing Figs. 2 and 3 in [9]. Naïve pooled log-transformed data were used for analysis. The pharmacokinetic data were fitted by the Michealis–Menten Eqs. (26) and (27) with the constant residual error model. Subsequently, PK parameters were fixed at estimated values and WBC count data were fitted by Eqs. (24) and (25), where the convolution integral was approximated by Eq. (30) with N = 30. The constant residual error was applied. The model was implemented in NONMEM 7.4 (ICON Development Solutions) using First Order Conditional Estimation method for parameter estimation. Figure 3 shows the WBC data overlaid with model predicted WBC time courses. Parameter estimates are presented in Table 2. A NONMEM control stream for the distributed delay model is listed in Appendix 3. Additionally, the model predictions were compared with the predictions of the distributed delay model implemented in Phoenix 8.0 (Certara L.P) that were reported in [11]. As shown in Fig. 3, the WBC predictions by two implementations of the delay distributed model of chemotherapy induced myelosuppression are very close. There are differences in parameter estimates. The biggest ones concern k_s (54%) and v (34%). Given that similar differences were observed for estimates of PK parameters (V, 31%, V_{max}, 23%), these discrepancies can be attributed to different estimation methods used for by two programs, rather than inaccuracy of the approximation (30) with N = 30.

Discussion

The approximation (16) of the convolution integral $y * g_k^v$ requires evaluation of the integral $p(t)$. In the case the past function $\varphi(t)$ is constant, a differential Eq. (25) defining $p(t)$ can be added to a system of ODEs containing $y(t)$. One can extend this idea to the past function that is a solution to a system of linear ODEs with constant coefficients:

$$\frac{d}{dt}\begin{pmatrix}\varphi \\ \phi\end{pmatrix} = A\begin{pmatrix}\varphi \\ \phi\end{pmatrix} + \begin{pmatrix}\alpha \\ a\end{pmatrix}, \quad t<0 \tag{37}$$

where A is a $(1+M)\times(1+M)$ matrix,α is a number, and a is a $M\times 1$ column vector. Then

$$\frac{d}{dt}\begin{pmatrix}p \\ q\end{pmatrix} = A\begin{pmatrix}p \\ q\end{pmatrix} + \int_t^{\infty} g_k^v(\tau)d\tau\begin{pmatrix}\alpha \\ a\end{pmatrix} - g_k^v(t)\begin{pmatrix}\varphi(0) \\ \phi(0)\end{pmatrix}, \quad t>0 \tag{38}$$

This system of ODEs with adequate initial conditions can be added to the original ODE system containing $y(t)$. If $\varphi(t)$ is a real polynomial, since

$$t^n g_k^v(t) = \frac{\Gamma(v+n)}{k^n\Gamma(v)} g_k^{v+n}(t) \tag{39}$$

then $p(t)$ is a linear combination of the products $t^n\int_t^{\infty} g_k^{v+m}(\tau)d\tau$ with integers n and m less or equal to the degree of $\varphi(t)$. Note, that a real polynomial can be represented as a solution of an ODE system (25). Finally, for any $\varphi(t)$ one can consider evaluation of $p(t)$ by the quadrature, which is computationally expensive, but still faster than evaluation by the quadrature of $(y * g_k^v)(t)$.

The estimate of the rate of convergence of the approximation (16) is $O\left(\frac{1}{N^v}\right)$. This has been confirmed on a set of test functions for which $y * g_k^v$ is known exactly. Generally speaking, if $v \le 1$, the convergence is slow and it may

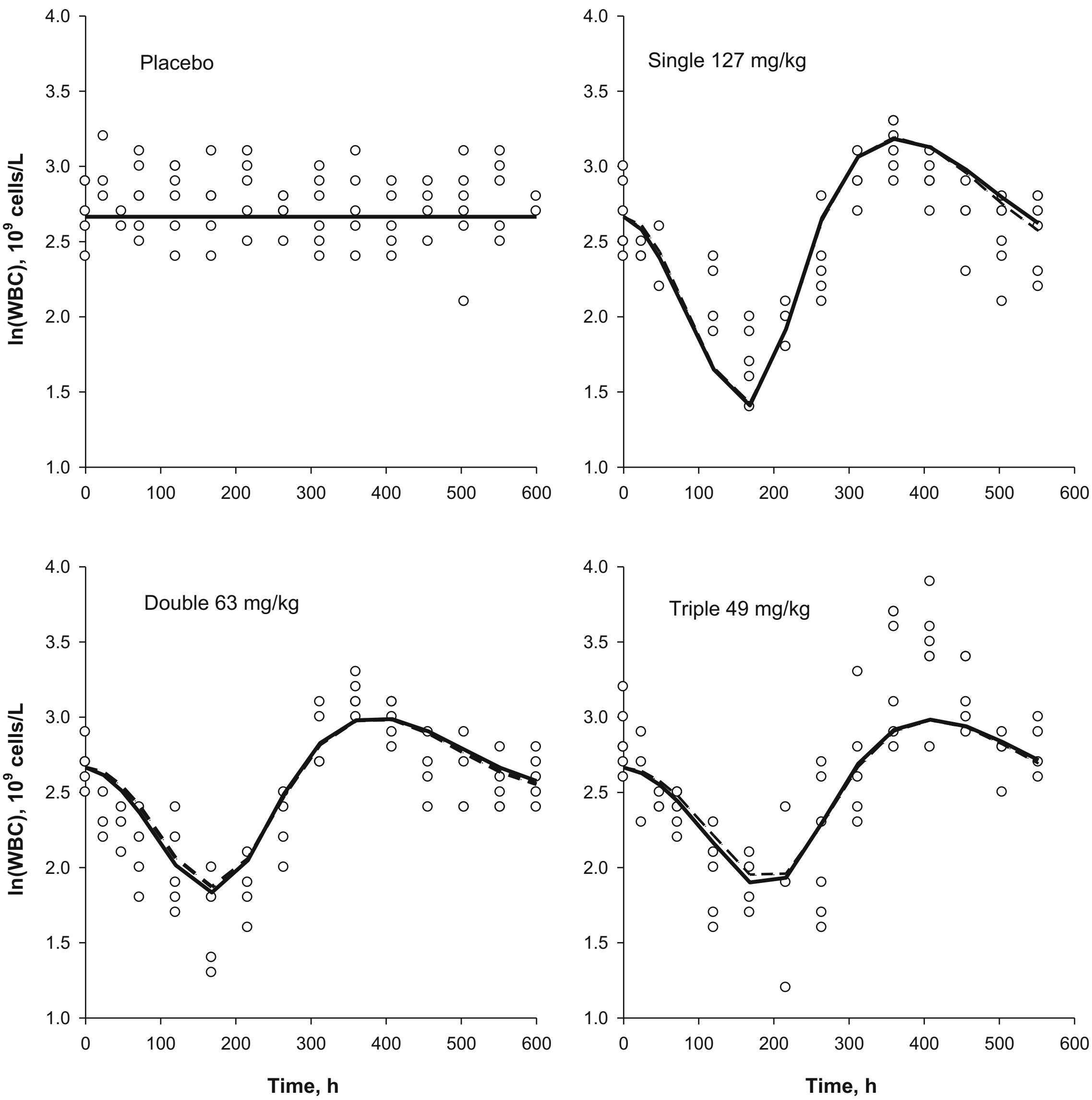

Fig. 3 Log-transformed WBC counts (symbols), model predicted log-transformed WBC versus time plots (continuous lines), and simulated log-transformed WBC versus time plots (dashed lines) for the four treatment groups. Dashed lines correspond to the distributed delay model from [11]. Parameter values used for simulations are presented in Table 2

require $N > 100$ to achieve the relative error of approximation to be of order of 1%. For $v > 1$, the convergence increases rapidly. For most of the tested functions, $N > 20$ was sufficient to achieve 1% relative error.

The distributed delay model of chemotherapy-induced myelosuppression contains three states y, w, and C, with a differential equation for C being independent of y and w The convolution of $(y * g_k^v)(t)$ accounted for the delay due to the maturation of the granulopoietic cells in the bone marrow. For a given set of model parameters, $N \geq 30$ resulted in minimal changes in the solution y obtained by the *delay*() function implemented in Phoenix 8.0 [11], implying $N = 30$ provides a good approximation. An additional differential equation was introduced to calculate p. Altogether, the ODE system approximating the model implemented in NONMEM 7.4 consisted of 35 equations. Such dimensions can be handled by most of pharmacometric software this model might be implemented in. The advantage of the ODE approximation of the convolution integral over the algorithm applied in the *delay*() function is much less numerical calculations to achieve a similar accuracy. The run time in the NONMEM implementation of the model was 24 s whereas the run time in the Phoenix implementation was 3972 s (66.2 min). This illustrates practical utility of the presented approximation.

Table 2 Parameter estimates for the distributed delay model of chemotherapy-induced myelosuppression

Parameter	Unit	Estimate (CV%)	Estimate (CV%) [11]
MTT	h	47.5 (6.8)	55.6 (6.7)
ν		0.964 (14.7)	1.46 (16.1)
w_0	10^9 cells/L	14.4 (5.3)	14.4 (4.8)
γ		0.664 (15.8)	0.507 (15.9)
k_s	L/mg/h	0.0328 (27.6)	0.0213 (28.1)
V_{max}	mg/L/h	77.2 (9.6)	100.0 (13.2)
K_m	mg/L	16.9 (16.4)	22.0 (17.2)
V	L/kg	1.35 (1.3)	1.03 (6.0)

The right column contains estimates of analogous parameters estimated for the model implemented in Phoenix 8.0 [11]

Using ODEs to approximate a convolution integral stems from the linear chain trick applied to the Erlang distributed delays. The presented approach extends this trick to the gamma distributed delays for which the properties of the binomial series are essential. It seems plausible that a similar trick would work for the Weibull distributed delays:

$$g(t) = \nu k(kt)^{\nu-1} exp\left(-(kt)^{\nu-1}\right) exp(-kt) \tag{40}$$

One can consider using the formula of Faa di Bruno [12] to expand $(k(t-z))^{\nu-1} exp\left(-(k(t-z))^{\nu-1}\right)$ into a series of binomials $t^n z^m$, as it was done here for $(t-z)^{\nu-1}$, and determine convergence of approximation.

In summary, an ODE approximation of the convolution integral with the gamma distribution utilizing properties of the binomial series has been introduced. It has been shown to converge uniformly on every compact time interval and an estimate of the approximation error has been found $O\left(\frac{1}{N^\nu}\right)$. The accuracy of approximation has been tested on a set of input functions defined by Erlang distributions for which the convolution is known explicitly. Finally, the binomial approximation has been applied to estimate parameters for the distributed delay model of chemotherapy-induced myelosuppression from previously published WBC count data in rats treated with 5-FU. A possible extension of this approach to Weibull distributed delays has been implied.

Appendix 1

Derivation of (8)

The time derivative of $I_n(t)$ defined by (7) is equal to the following:

$$\frac{dI_n}{dt}(t) = y(t) - \int_0^t y(\tau)\left(n\left(\frac{\tau}{t}\right)^{n-1}\frac{\tau}{t^2} + k\left(\frac{\tau}{t}\right)^n\right)\exp(-k(t-\tau))d\tau \tag{A1}$$

Since

$$n\left(\frac{\tau}{t}\right)^{n-1}\frac{\tau}{t^2} + k\left(\frac{\tau}{t}\right)^n = \left(\frac{n}{t} + k\right)\left(\frac{\tau}{t}\right)^n \tag{A2}$$

The integral in (A1) equals to

$$\int_0^t y(\tau)\left(n\left(\frac{\tau}{t}\right)^{n-1}\frac{\tau}{t^2} + k\left(\frac{\tau}{t}\right)^n\right)\exp(-k(t-\tau))d\tau = \left(\frac{n}{t} + k\right)I_n(\mathrm{t}) \tag{A3}$$

(A1) and (A3) imply that

$$\frac{dI_n}{dt}(t) = y(t) - \left(\frac{n}{t} + k\right)I_n(\mathrm{t}) \tag{A4}$$

and (8) follows.

Appendix 2

Proof of Theorem

We will use the following estimate. For any real $\nu > 0$ and positive integer n

$$\left|\binom{\nu-1}{n}\right| \le \frac{\exp(\nu^2)}{n^\nu} \tag{B1}$$

Proof By definition

$$\binom{v-1}{n}^2 = \prod_{j=1}^{n}\left(1-\frac{v}{j}\right)^2 \leq \left(\frac{1}{n}\sum_{j=1}^{n}\left(1-\frac{2v}{j}+\frac{v^2}{j^2}\right)\right)^n$$

Since

$$\log(n) \leq \sum_{j=1}^{n}\frac{1}{j} \text{ and } \sum_{j=1}^{n}\frac{1}{j^2} \leq 2$$

$$\frac{1}{n}\sum_{j=1}^{n}\left(1-\frac{2v}{j}+\frac{v^2}{j^2}\right) \leq 1-\frac{2v}{n}\log(n)+\frac{2v^2}{n}$$
$$= 1+\frac{1}{n}\left(2v^2-2v\log(n)\right)$$

For any real x such that $1+\frac{x}{n} \geq 0$

$$\left(1+\frac{x}{n}\right)^n \leq \exp(x)$$

Hence, since $n + 2v^2 - 2v\log(n) > 0$:

$$\left(\frac{1}{n}\sum_{j=1}^{n}\left(1-\frac{2v}{j}+\frac{v^2}{j^2}\right)\right)^n \leq \left(1+\frac{v}{n}(1+\log(n))\right)^n$$
$$\leq \exp\left(2v^2-2v\log(n)\right)$$

which completes the proof of (B1).

Proof of Theorem

Eq. (B1) implies that for $n \geq 1$ and all $0 < \tau < t$

$$\left|(-1)^n\binom{v-1}{n}y(\tau)\left(\frac{\tau}{t}\right)^n\exp(-k(t-\tau))\right|$$
$$\leq \frac{\exp(v^2)}{n^v}\|y\|_{L^\infty(0,t)}\left(\frac{\tau}{t}\right)^n$$

Since

$$\sum_{n=1}^{\infty}\frac{\exp(v)}{n^v}\int_0^t\left(\frac{\tau}{t}\right)^n d\tau = t\exp(v)\sum_{n=1}^{\infty}\frac{1}{n^v(n+1)} < \infty$$

The Lebesgue's dominated convergence theorem implies that the series in (6) converges absolutely and its sum satisfies (6). To show (14) consider an integer $N \geq 0$ and

$$|R_N(t)| \leq \frac{k}{\Gamma(v)}(kt)^{v-1}\|y\|_{L^\infty(0,t)}$$
$$\times \sum_{n=N+1}^{\infty}\left|(-1)^n\binom{v-1}{n}\right|\int_0^t\left(\frac{\tau}{t}\right)^n d\tau$$

Eq. (B1) further implies that

$$|R_N(t)| \leq \|y\|_{L^\infty(0,t)}\frac{(kt)^v}{\Gamma(v)}\exp\left(v^2\right)\sum_{n=N+1}^{\infty}\frac{1}{n^v(n+1)}$$

The sum of $(v+1)$-series can be estimated as follows

$$\sum_{n=N+1}^{\infty}\frac{1}{n^{v+1}} \leq \sum_{n=N+1}^{\infty}\int_n^{n+1}\frac{dx}{(x-1)^{v+1}} = \frac{1}{vN^v}$$

yielding (14).

Appendix 3

NONMEM control stream for the distributed delay model

```
$SIZES PC=50
$PROBLEM CIL
$INPUT ID TIME AMT RATE CMT EVID MDV DV
$DATA C:\CIL.csv IGNORE=C
$SUBROUTINES ADVAN6 TOL=6 ATOL=6
$MODEL NCOMPARTMENTS=35

$PK
V=THETA(1)+ETA(1)
VMAX=THETA(2)
KM=THETA(3)
MTT=THETA(4)
NU=THETA(5)
CIRC0=THETA(6)
GAM=THETA(7)
SLOPE=THETA(8)
KTR=NU/MTT
KPROL=KTR
KCIRC=KTR

; INITIAL CONDITIONS
A_0(2)=CIRC0
A_0(3)=CIRC0

$DES
;BASE EQUATIONS
CC=A(1)/V

DADT(1)=-VMAX*A(1)/(KM+CC)
DADT(2)=KPROL*A(2)*(CIRC0/A(3))**GAM-KTR*A(2)-SLOPE*CC*A(2)
;DADT(3)=KTR*CONV-KCIRC*A(3)
DADT(4)=KTR*EXP(-GAMLN(NU))*(KTR*(T+0.000001))**(NU-1)*EXP(-KTR*T)
DADT(5)=A(2)-KTR*A(5)

COEF=1.0
SUM=A(5)
I=1
"DO WHILE (I.LE.30)
" DADT(5+INT(I))=A(2)-(I/(0.000001+T)+KTR)*A(5+INT(I))
" COEF=-COEF*(NU-I)/I
" SUM=SUM+COEF*A(5+INT(I))
" I=I+1
"ENDDO

CONV=CIRC0*(1-A(4))+KTR*((T+0.000001)*KTR)**(NU-1)*EXP(-GAMLN(NU))*SUM

DADT(3)=KTR*CONV-KCIRC*A(3)

$ERROR

Y1=A(3)

IF(CMT==3) IPRED=LOG(Y1)
IF(CMT==3) Y=IPRED+EPS(1)

$THETA
1.35    FIX; 1: V
77.2    FIX; 2: VMAX
16.9    FIX; 3: KM
72         ; 4: MTT
3          ; 5: NU
14         ; 6: CIRC0
0.3        ; 7: GAM
0.025      ; 8: SLOPE

$OMEGA
0 FIX
$SIGMA
0.1

$ESTIMATION METHOD=1 PRINT=1 MAX=9999 SIG=3 NOABORT
$COV PRINT=E

$TABLE ID TIME IPRED DV EVID CMT NOAPPEND NOPRINT ONEHEADER
FILE=C:\CIL.tab
```

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