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Lifespan based indirect response models

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Abstract

In the field of hematology, several mechanism-based pharmacokinetic-pharmacodynamic models have been developed to understand the dynamics of several blood cell populations under different clinical conditions while accounting for the essential underlying principles of pharmacology, physiology and pathology. In general, a population of blood cells is basically controlled by two processes: the cell production and cell loss. The assumption that each cell exits the population when its lifespan expires implies that the cell loss rate is equal to the cell production rate delayed by the lifespan and justifies the use of delayed differential equations for compartmental modeling. This review is focused on lifespan models based on delayed differential equations and presents the structure and properties of the basic lifespan indirect response (LIDR) models for drugs affecting cell production or cell lifespan distribution. The LIDR models for drugs affecting the precursor cell production or decreasing the precursor cell population are also presented and their properties are discussed. The interpretation of transit compartment models as LIDR models is reviewed as the basis for introducing a new LIDR for drugs affecting the cell lifespan distribution. Finally, the applications and limitations of the LIDR models are discussed.

Keywords

Cell lifespan; Delay differential equations; Indirect response models; Cell populations

Introduction

Over the last years, the field of pharmacokinetic and pharmacodynamic (PK/PD) modeling has clearly moved from using empirical functions to describe and summarize the data to the utilization of mechanism-based models [1]. Mechanism-based PKPD modeling quantifies and predicts drug disposition and dynamics on the basis of the essential underlying principles of pharmacology, physiology and pathology [2]. In the field of hematology, several mechanism-based PK/PD models have been developed to understand the dynamics of different blood cell populations under different clinical conditions [3–11]. In general, a population of blood cells is basically controlled by two processes: the cell production and cell loss [4]. Under homeostatic conditions, the proliferation, differentiation or maturation of stem cells and/or precursor cells originates new cells, which remain in the circulation for a certain period of time, which depends on the elimination processes such as the tissue uptake, the maturation to other cell type, the random destruction or the cell senescence. In addition, several diseases and pharmacological agents exhibit an indirect mechanism of action by

inhibiting or stimulating the production or elimination of certain blood cells or the feedback mechanisms intended to control the cell homeostasis.

The long time delays in drug response observed in hematological systems becomes an additional complexity to take into account in developing mechanism-based PKPD models to quantify the dynamics of erythropoiesis, granulopoiesis, or thrombopoiesis. The long time delays in drug response might be related to the duration of the physiological processes or the time the pharmacological effects becomes evident or both. For instance, as the production rate of neutrophils is controlled by the duration of the differentiation and maturation of stem cells and progenitor cells, respectively, drugs affecting directly the proliferation of stem cells will exhibit an effect on neutrophil counts in the circulation with a delay of 4–5 days, which is equivalent to the duration of the differentiation and maturation processes [12]. Similarly, the time to achieve hemoglobin concentrations at steady state following the treatment with erythropoiesis stimulating agents in anemic patients with chronic kidney diseases depends on the lifespan of red blood cells, which is approximately 2–3 months [13]. These two examples illustrate the importance of accounting for the long duration of the physiological processes involved in both the production and elimination of cells in order to adequately characterize the time course of drug response. Another important cause of long time delays in drug response is due to the pharmacological effects that exhibit a slow signal transduction process. A prolonged delay between activation of glucocorticosteroid receptor and pharmacodynamic response can be observed in the time courses of pharmacological effects of corticosteroids [14]. The parasympathomimetic effect of scopolamine and atropine on heart rate variability causes a delayed response attributed to a signal transduction [15]. Pharmacodynamic models based on a cascade of transit compartments have been proposed to describe a delay due to the signal transduction [16]. However, this review will not discuss this mechanism, but rather will be focused on lifespan models, and their different mathematical formulations, as they have been extensively used to deal with the complexities of hematological systems generated by long time delays in drug response, among other applications.

Numerous mathematical models of hematopoietic regulation have been developed [3, 17] and each major hematopoietic line including erythropoiesis [18], granulopoiesis [19], and thrombopoiesis [20] has been modeled. A compartmental approach has been commonly used where the number of compartments can vary from one to many. The regulatory role of hematopoietic growth factors was expressed by parameters describing their effects on the proliferation, differentiation and maturation of progenitor and precursor cells at various stages. These multi-compartmental models are of physiological nature where different inputs to the same model can account for a variety of changes of the normal steady-state. The lifespan based approach assumes that cells are eliminated from the population not by a first-order process but due to a natural senescence [4]. A fundamental assumption is that every cell in the population is assigned a unique lifespan, T . This assumption makes the lifespan a random variable defined on a given cell population. If the age of a cell reaches its lifespan, then the cell has to leave the population. The most natural example is cell senescence, where the cell death determines its lifespan as the duration of aging process. However, other mechanisms of cell loss can be interpreted as expiration of the lifespan. If cell loss is lifespan based, then cells of the same age will leave the population at the same time. In the most simplistic case, all cells will have the same lifespan. However, a more realistic assumption would be that the lifespan is continuously distributed and characterized by a probability density function (p.d.f.) $f(t, \tau)$, that can change in time or be time variant [21]. The time variant p.d.f. for lifespan distribution can be interpreted using an infinitesimally small time interval $\Delta \tau$ as follows:

$$\ell(t, \tau)\Delta\tau = \text{probability of finding a cell of the lifespan } \tau \leq T \leq \tau + \Delta\tau \text{ at time } t. \quad (1)$$

If the cell lifespan distribution does not change with time (time invariant distribution), then the p.d.f. depends only on the lifespan variable $\ell(t, \tau) \equiv \ell(\tau)$. The time invariant lifespan distribution is expected if a cell population is at steady-state. On the other hand, if cell survival is affected by a change in environment, disease progression, toxic or therapeutic drug effect, or any time-dependent process, one might expect a time variant [22, 23] p.d.f.

The cell turnover in a population is determined by two processes: production and loss. If the production rate $K_{\text{in}}(t)$ and loss rate $K_{\text{out}}(t)$ are functions of time, then the change in the cell number N is determined by the mass balance equation 2 (Fig. 1):

$$\frac{dN}{dt} = K_{\text{in}}(t) - K_{\text{out}}(t) \quad (2)$$

The assumption that each cell exits the population when its lifespan expires allows one to determine $K_{\text{out}}(t)$ if the lifespan distribution is known. It can be shown that [22, 24]

$$K_{\text{out}}(t) = \int_0^{\infty} K_{\text{in}}(t-z)\ell(t-z, z)dz \quad (3)$$

The integral in Eq. 3 can be written as the convolution $K_{\text{in}} * \ell(t)$ and Eq. 2 can be simplified to the following equation describing the change in the cell number if the cell loss is determined by the lifespan distribution:

$$\frac{dN}{dt} = K_{\text{in}}(t) - K_{\text{in}} * \ell(t) \quad (4)$$

Equation 4 has been introduced before for models applying the lifespan concept to describe kinetics of cell populations [22, 24]. Equation 4 is not complete without specifying an initial condition. Therefore it is assumed that any perturbation of the cell population occurred for positive times $t > 0$, and prior to that the system was at steady-state defined by a constant production rate $k_{\text{in}0}$, time invariant lifespan distribution $\ell(\tau)$, and a constant number of cells N_0 . The steady-state assumption and Eq. 4 imply the baseline relationship:

$$N_0 = k_{\text{in}0}T_R \quad (5)$$

where T_R is the mean cell lifespan at steady-state:

$$T_R = \int_0^{\infty} z\ell(z)dz \quad (6)$$

An interpretation of the cell age as the time that elapsed from its birth can be generalized to the time that passed since its entry to the population. The mitotic creation of a new cell can be replaced by its attaining some morphological or other properties that are characteristic for the population. Analogously, the cell death can be generalized to a loss of such properties. In this setting, the cell lifespan can be defined as the time between its entry to and exit from the

population and, therefore, lifespan model can be used to model the cell differentiation and cell maturation besides the cell senescence.

Basic LIDR models for agents affecting cell production

The basic lifespan based models assume that all cells have the same lifespan T_R . Mathematically, this implies that $\ell(t, \tau)$ is a point distribution centered at T_R :

$$\ell(t, \tau) = \delta(\tau - T_R) \quad (7)$$

where $\delta(z)$ is the Dirac delta function. For this p.d.f. the convolution integral in Eq. 3 becomes a delay operator and Eq. 4 simplifies to

$$\frac{dN}{dt} = K_{in}(t) - K_{in}(t - T_R) \quad (8)$$

Equation 8 states that for a population with the same cell lifespan T_R , the elimination rate is equal to the production rate delayed by T_R .

According to the concept of an indirect response, a drug can stimulate or inhibit the production of the response by means of the Hill function [25] where the Hill coefficient is set to 1 in the following:

$$K_{in}(t) = k_{in} \left(1 \pm \frac{E_{max} C(t)}{EC_{50} + C(t)} \right) \quad (9)$$

where '+' is for stimulation and '-' for inhibition. Here k_{in} is the zero-order production rate in the absence of the drug, $C(t)$ denotes the drug concentration at the site of action, E_{max} is the maximum drug effect (efficacy) and EC_{50} stands for drug concentration eliciting 50% of maximum drug effect (potency). It is assumed that for negative times $t < 0$, $C(t) = C_b$, where the C_b is the endogenous (baseline) drug concentration at the effect site, which in some cases might be equal to 0. Since measurable cell response might not be an absolute cell count N , but rather cell concentration (e.g. in blood), another variable R is used to denote the response. Equation 8 with $K_{in}(t)$ described by Eq. 9 constitutes the basic lifespan based indirect response (LIDR) models [4]:

$$\frac{dR}{dt} = k_{in} \left(1 + \frac{S_{max} C(t)}{SC_{50} + C(t)} \right) - k_{in} \left(1 + \frac{S_{max} C(t - T_R)}{SC_{50} + C(t - T_R)} \right) \quad (10)$$

where E_{max} and EC_{50} were replaced by S_{max} and SC_{50} to reflect that the effect is stimulatory. Similarly,

$$\frac{dR}{dt} = k_{in} \left(1 + \frac{I_{max} C(t)}{IC_{50} + C(t)} \right) - k_{in} \left(1 + \frac{I_{max} C(t - T_R)}{IC_{50} + C(t - T_R)} \right) \quad (11)$$

where E_{max} and EC_{50} were replaced by $0 < I_{max} < 1$ and IC_{50} to reflect that the effect is inhibitory. The mechanism by which the drug affects the response production k_{in} is identical with IDR Models I and III [25]. The baseline Eq. 5 becomes

$$R_0 = k_{in0} T_R = k_{in} T_R \left(1 \pm \frac{E_{max} C_b}{EC_{50} + C_b} \right) \quad (12)$$

Simulated time courses of responses corresponding to the monoexponential $C(t)$

$$C(t) = C_b + \frac{Dose}{V} \exp(-k_{el}t) \quad (13)$$

are shown in Fig. 2. Many features of the response versus time curve can be derived from the following equation obtained by integration of Eq. 8 over time

$$R(t) = \int_{t-T_R}^t K_{in}(z) dz \quad (14)$$

Equation 14 provides an interpretation of the response as a partial area under $K_{in}(t)$ versus time curve over the time interval bound by $t - T_R$ and t . A partial solution to Eq. 14 is shown in Table 1. The most visible characteristics of the response curve is the peak (a local maximum or minimum) described by the peak value R_{peak} and the peak time t_{peak} . It can be shown, that for concentrations $C(t)$ decreasing with time, the occurrence of the peak coincides with T_R [4]. The R_{peak} calculated from Eq. 14 is presented in Table 1. This property implies that the t_{peak} does not change with increasing doses of the drug, which is a distinct feature from basic indirect response (IDR) models where the t_{peak} changes with dose [26]. Assuming that at each time $t > 0$, $C(t)$ approaches infinity as drug dose becomes very large, the limiting value for $R(t)$ can be calculated as shown in Table 1. This large dose approximation provides useful relationships between the initial slope S_I and maximal response R_{max} are identical with analogous equations derived for IDR models [26]. These relationships can serve as source for initial estimate of model parameters k_{in} and E_{max} , if response data following large doses are available.

The area between the response curve and the baseline (AUCE) provides a measure of the total net effect [27]. Subtraction of the baseline response R_0 from both sides of Eq. 14 and integration from 0 to infinity over time results in [4]:

$$AUCE = k_{in} T_R \int_0^\infty \left(\frac{E_{max} C(z)}{EC_{50} + C(z)} - \frac{E_{max} C_b}{EC_{50} + C_b} \right) dz \quad (15)$$

For drugs exhibiting monoexponential kinetics Eq. 13 the integral in Eq. 15 can be calculated explicitly (see Table 1). Equation 15 is identical with AUCE values calculated for basic IDR models if $C_b = 0$ [27]. Consequently, the net pharmacological effect is proportional to E_{max} and logarithmically increases with the dose.

Basic LIDR models for agents affecting cell lifespan distribution

The basic LIDR models for drugs affecting cell elimination are fundamentally different from IDR models. For the latter the drug effect is described by the product of the response elimination rate constant k_{out} and the Hill function. Since the elimination rate for basic LIDR is determined by the mean lifespan T_R , one can postulate to describe the drug effect as the product $T_R H(t)$ where $H(t)$ is a function that relates $C(t)$ to the effect (e.g. the Hill function in Eq. 9). This will result in a time variant p.d.f. for lifespan distribution:

$$\ell(t, \tau) = \delta(\tau - H(t)T_R) \quad (16)$$

In this situation, the elimination rate will be determined from Eq. 3. Although plausible, such an approach leads to difficult mathematical problems in calculation of the convolution integral Eq. 3 that has been solved recently [22]. An alternative approach has been presented where the lifespan distributions that are combinations of a finite number of the Dirac delta functions multiplied by time dependent coefficients $\alpha_i(t)$ [5]:

$$\ell(t, \tau) = \alpha_1(t)\delta(\tau - T_1) + \dots + \alpha_K(t)\delta(\tau - T_K) \quad (17)$$

where

$$\alpha_1(t) + \dots + \alpha_K(t) = 1 \text{ and } \alpha_i(t) \geq 0, \quad i=1, \dots, K. \quad (18)$$

The time dependent coefficients can be considered as weights determining the contribution of each point distribution to the overall distribution. A basic postulate is that the drug does not affect the location of points $T_1, \dots, T_K$ on the lifespan axis, but rather impacts the weights $\alpha_1(t), \dots, \alpha_K(t)$, and consequently temporally changes the lifespan distribution. Following the formalism of Eq. 16, the drug effect on the lifespan distribution can be described as

$$\alpha_1(H(t))\delta(\tau - T_1) + \dots + \alpha_K(H(t))\delta(\tau - T_K) \quad (19)$$

Contrary to Eq. 16, the convolution integral in Eq. 3 can be easily calculated for the lifespan distribution described by Eq. 17 yielding

$$K_{\text{out}}(t) = K_{\text{in}}(t - T_1)\alpha_1(H(t - T_1)) + \dots + K_{\text{in}}(t - T_K)\alpha_K(H(t - T_K)) \quad (20)$$

Notice that if $K = 1$, then according to Eq. 18, $\alpha_1(t) \equiv 1$ is a constant function and no drug effect can be exercised. The simplest non-trivial lifespan distribution that, in the absence of drug, is centered about T_R and upon drug effect a second mode T_D temporally contributes to the lifespan distribution. The drug effect is manifested by changing the weights between two point distributions $\delta(\tau - T_R)$ and $\delta(\tau - T_D)$, where T_D is the lifespan of a cell exposed to the drug that can be longer or shorter than the lifespan of a cell in the absence of drug. The Hill function is used to describe the effect as shown in Eq. 19:

$$\ell(t, \tau) = \left(1 - \frac{E_{\text{max}}C(t)}{EC_{50} + C(t)}\right)\delta(\tau - T_R) + \frac{E_{\text{max}}C(t)}{EC_{50} + C(t)}\delta(\tau - T_D) \quad (21)$$

where $E_{\text{max}} = 1$. In the absence of drug ($C(t) \equiv 0$), the p.d.f. in Eq. 21 reduces to $\delta(\tau - T_R)$. Equation 6 allows one to determine the effect of drug on the mean lifespan of the cell population $ML_R(t)$ that depends on time due to the drug action on the lifespan distribution:

$$ML_R(t) = T_R + \frac{E_{\text{max}}C(t)}{EC_{50} + C(t)}(T_D - T_R) \quad (22)$$

According to Eqs. 2 and 20, the equation describing cell counts in the population with a constant production rate $K_{\text{in}}(t) \equiv k_{\text{in}}$ is as follows

$$\frac{dR}{dt} = k_{\text{in}} - k_{\text{in}} \left(1 - \frac{E_{\text{max}}C(t - T_R)}{EC_{50} + C(t - T_R)}\right) - k_{\text{in}} \frac{E_{\text{max}}C(t - T_D)}{EC_{50} + C(t - T_D)} \quad (23)$$

Since the steady-state cell production rate $k_{\text{in}0} = k_{\text{in}}$, the baseline condition for Eq. 23 is

$$R_0 = k_{in}T_R + \frac{k_{in}E_{max}C_b}{EC_{50} + C_b}(T_D - T_R) \quad (24)$$

Schematic diagrams for the LIDR models described by Eq. 23 are shown in Fig. 3.

Since the drug effect increases the contribution of $\delta(\tau - T_D)$ into the cell lifespan distribution, if $T_D > T_R$, then the drug effect transiently increases the apparent cell mean lifespan, whereas, if $T_D < T_R$, the mean lifespan transiently decreases and returns to T_R after $C(t)$ becomes C_b . The increase in the apparent mean lifespan results in accumulation of cells in the circulation, which then is followed by a return to the number of cells at the baseline as the apparent mean lifespan goes back to the baseline mean lifespan. Such a time course is characteristic for the IDR Model II where drug inhibits response removal [25].

Similarly, the transient decrease in the apparent mean lifespan accelerates depletion of cells in the circulation and a decrease in the cell count can be observed as the cell lifespan return to its baseline value. This is a characteristic pattern for the IDR Model IV where drug stimulates the response removal [25]. In that respect, the case $T_D > T_R$ is analogous to IDR Model II, and the case $T_D < T_R$ to IDR Model IV. These and other important properties of the R versus t curve can be deduced from the partial solution for $R(t)$ shown in Tables 2 and 3 [5].

Similarly to basic LIDR models, this relationship provides a geometrical interpretation of the difference between $R(t)$ and R_0 as the area below the Hill function that extends from $t - T_D$ to $t - T_R$ with an appropriate correction for the sign. This implies that for strictly decreasing concentrations $C(t)$, the response has a unique peak at time t_{peak} listed in Tables 2 and 3. The peak responses can be also obtained by evaluating $R(t_{peak})$ (see Tables 2, 3). Equation 23 implies the existence of a lag time t_{lag} for the response curve (see Tables 2, 3). The lag time is always the minimum of T_R and T_D , whereas the peak time is equal the largest of T_R and T_D . Consequently, both the peak and the lag time are dose independent, which is a distinct feature from basic IDR Models II and IV where the t_{peak} changes with dose [26]. For large doses, the responses will approach a limiting curve that can be characterized by explicit equations shown in Tables 2 and 3 [5]. Consequently, for large doses, the slope of the onset part of the response curve S_I and the maximal response R_{peak} can also be explicitly calculated (see Tables 2, 3). The initial slope for large doses is identical with S_I for the basic LIDR models and, in the absence of the endogenous drug ($C_b = 0$), it is determined by the product of E_{max} and k_{in} . Similarly to the basic LIDR models, the peak response value for large doses is determined by k_{in} , E_{max} , T_R and T_D . Both S_I and R_{peak} values for large dose responses can be used to obtain initial estimates of k_{in} and E_{max} . Integration of both sides of the equation describing $R(t)$ allows one to calculate AUCE [5]:

$$AUCE = k_{in}|T_D - T_R| \int_0^\infty \left(\frac{E_{max}C(z)}{EC_{50} + C(z)} - \frac{E_{max}C_b}{EC_{50} + C_b} \right) dz \quad (25)$$

The absolute value notation has been used to avoid differentiation between T_D and T_R . In particular, for monoexponential drug concentrations described by Eq. 13, an explicit solution of Eq. 25 can be derived (see Tables 2, 3).

Basic LIDR models with a precursor pool

If there is a precursor pool for the cell population M , then Eq. 4 applies to describe the number of cells

$$\frac{dM}{dt} = K_{in}(t) - K_{in} * \ell_M(t) \quad (26)$$

Here $K_{in}(t)$ denotes the precursor cell production rate and $\ell_M(\tau)$ is the p.d.f. for precursor cell lifespan distribution. If precursor cells M become mature cells N , then loss rate for precursor cells coincides with the production rate for mature cells. Consequently,

$$\frac{dN}{dt} = k_{in} * \ell_M(t) - k_{in} * \ell_M * \ell_N(t) \quad (27)$$

$\ell_N(\tau)$ is the p.d.f. for the lifespan distribution for mature cells. The baseline conditions for the precursor M_0 and mature cells N_0 become:

$$M_0 = k_{in0} T_M \text{ and } N_0 = k_{in0} T_N \quad (28)$$

where T_M and T_N denote the means of the lifespan distributions for M and N , respectively. If all precursor cells have the same lifespan T_p , then for drugs that inhibit or stimulate the production of the precursor cells Eq. 26 becomes the basic LIDR model

$$\frac{dP}{dt} = k_{in} \left(1 \pm \frac{E_{max} C(t)}{EC_{50} + C(t)} \right) - k_{in} \left(1 + \frac{E_{max} C(t - T_p)}{EC_{50} + C(t - T_p)} \right) \quad (29)$$

where P is the cell response in the precursor pool derived from M by the same transformation as R is derived from N (e.g. $P = M/V$ and $R = N/V$). Consequently, Eq. 27 is

$$\frac{dR}{dt} = k_{in} \left(1 \pm \frac{E_{max} C(t - T_p)}{EC_{50} + C(t - T_p)} \right) - k_{in} \left(1 + \frac{E_{max} C(t - T_p - T_R)}{EC_{50} + C(t - T_p - T_R)} \right) \quad (30)$$

The baseline conditions for Eqs. 29 and 30 are

$$P_0 = k_{in} T_p \left(1 \pm \frac{E_{max} C_b}{EC_{50} + C_b} \right) \text{ and } R_0 = k_{in} T_R \left(1 \pm \frac{E_{max} C_b}{EC_{50} + C_b} \right) \quad (31)$$

It is important to emphasize that Eq. 30 can be solved without solving Eq. 29, since the variable P is not present in any term of the right-hand side of Eq. 30.

Simulated time courses of responses $R(t)$ corresponding to the monoexponential $C(t)$ for several doses are shown in Fig. 4. Equation 30 implies that there is a lag time in the response curve and it is equal to T_p . The response curve $R(t)$ is identical with a response curve for a basic LIDR delayed by time T_p . As for the basic LIDR models, for concentrations $C(t)$ decreasing with time, the occurrence of the peak coincides with $T_p + T_R$, and the is shown in Table 4. The limiting value for $R(t)$ corresponding to large doses, initial slope S_I defined as the derivative of R at time $t = T_p$ and maximal response are also presented in Table 4.

LIDR models for agents with toxic effects on cell populations

LIDR models for agents with toxic effects on cell populations is illustrated with the cytotoxic effect of anticancer agents, however these models can be generalized to other types of toxicities. The LIDR model for the cytotoxic effect of anticancer agents (see Fig. 5) consists of a blood compartment R and two precursor compartments (P and M). As for other

models, the hematologic effect R can represent any natural cells including platelet, leukocyte or neutrophil, or red blood cells counts. These cells are released to the circulation from the bone marrow in the last stage of their development. The cells that are sensitive to toxic effects of an anticancer agent are progenitor cells in their mitotic phases, which form the pool P . The cells in P are produced at the zero-order rate k_{in} from the stem cells. There are two loss processes from the mitotic compartment P : killing by the anticancer agent and the conversion (or maturation) to another cell type M after survival in the compartment P . The surviving cells live for the duration of T_p . The killing rate at time t is proportional to the cell number in the pool P , following the control function, $f(C)$ which is nonnegative and increases with the plasma concentration, C , of the anticancer drug. If the cytotoxic process is dose proportional (linear), then $f(C)$ takes the form

$$f(C)=kC \quad (32)$$

where k denotes the killing rate constant. If the killing process is saturable (nonlinear), $f(C)$ can be described by the Hill function

$$f(C)=\frac{K_{\max}C}{KC_{50}+C} \quad (33)$$

where $K_{\max}$ is the maximum rate of the killing, and KC_{50} denotes the drug concentration eliciting 50% of $K_{\max}$. In the absence of the toxic agent the removal rate of the mitotic cells is equal to the production rate delayed by T_p . However, when M cells are killed a correction of the conversion rate by a surviving fraction $SF(t)$ is necessary. The fraction of the precursor cells that survived the cytotoxic effect of anticancer agent and is converted to the maturing cells is [6]:

$$SF(t)=\exp\left(-\int_{t-T_p}^t f(C(z))dz\right) \quad (34)$$

and the equation describing the change of cell number in the compartment P is

$$\frac{dP}{dt}=k_{in}-k_{in}SF(t)-f(C(t))P \quad (35)$$

Each mature cell remains for time T_M in the maturation compartment and then is released to the circulation pool R . The maturation rate is equal to the production rate but delayed by the time T_M (see Eq. 8):

$$\frac{dM}{dt}=k_{in}SF(t)-k_{in}SF(t-T_M) \quad (36)$$

Since each cell that matures is released to the circulation, the production rate for the circulation pool must be equal to the maturation rate for the pool M . The mature cells stay in the circulation for time T_R after which they are removed by transit to peripheral tissues or senescence:

$$\frac{dR}{dt}=k_{in}SF(t-T_M)-k_{in}SF(t-T_M-T_R) \quad (37)$$

If there is no drug ($C(t) \equiv 0$), then the cell populations in all compartments remain constant and equal to their baseline levels P_0 , M_0 , and R_0 .

$$P_0 = k_{in} T_P, M_0 = k_{in} T_M, \text{ and } R_0 = k_{in} T_R \quad (38)$$

Typical time course of the response patterns are shown in Fig. 5 where solutions of Eq. 37 corresponding to monoexponential pharmacokinetics of the drug are plotted. Equation 37 implies that there is a lag time in the response curve and it is equal to T_M .

If the kinetic function is decreasing or biphasic, i.e. there exists exactly one concentration peak at time t_{max} , then one can show that there exists the lowest point R_{nadir} for the response function which occurs at the time t_{nadir} . The durations of characteristic phases of the response time profile are determined by combination of time constants T_P , T_M , T_R , and T_f , a time after which $f(C)$ is negligible (i.e. $f(C(t)) \approx 0$ for $t > T_f$) [6]. The approximate value of $R_{nadir} = R(t_{nadir})$ is

$$R_{nadir} \approx R_0 \exp(-AUC_f) \quad (39)$$

where AUC_f is the total area under $f(C)$ versus t curve. If the killing process is linear (see Eq. 32), then AUC_f is proportional to AUC and Eq. 39 becomes

$$R_{nadir} \approx R_0 \exp(-kAUC) \quad (40)$$

Thus, the total exposure to the toxic agent AUC is a major pharmacokinetic factor controlling hematologic toxicity for linear toxic effects.

Assuming that at each time $t > 0$, $C(t)$ approaches infinity as dose of drug becomes very large, $R(t)$, R_{nadir} , and S_I approach limiting values shown in Table 5 where the linear killing was assumed. This limiting function for $R(t)$ is nothing else but the survival curve delayed by time T_M for the cells in the circulation pool and can be derived if the production rate for this compartment is shut down. In the case of the saturable killing process Eq. 33, the function $f(C(t))$ approaches K_{max} as the dose becomes large, and similar relationships can be derived.

LIDR models versus transit compartments models

Transit compartments (TC) models are used to describe pharmacodynamic responses that involve drug action on hematopoietic cells undergoing differentiation and maturation. A TC model consists of a series of compartments representing various stages of cell development that are meant to reflect the time course of the cell population count in tissues such as bone marrow and blood [12]. These compartments are connected via first-order cell transfer rates and represent the maturation process from progenitor cells in bone marrow to peripheral cells in blood. The reciprocal of each rate constant is the mean transit time of a cell, which is interpreted as an average age of cells in the compartment. Therefore, a sequence of the age compartments may also account for a cell development process starting from their production (birth) and ending with elimination (death or transfer to another tissue) [7]. Such a sequence of compartments is necessary to account for a delay between exposure of progenitor cells to a therapeutic/ toxic agent and its effect which is typically determined from the blood cells count (maturation) or the time dependent change in the age of a particular cell type (senescence). A sequence of age compartments is the bone structure of more complex pharmacodynamic models of drugs affecting hematopoietic cell populations such as neutrophils [8, 28, 29], red blood cells [13, 30–32], and platelets [7, 9]. In these

models drug stimulated or inhibited the production of cell precursors or the transfer rate between the age compartments. Mathematically, the TC model consists of a series of compartments $P_1, \dots, P_n$ connected with each other by first-order processes in a catenary manner as shown in Fig. 6. A compartment P_i represents a subset of cells of a mean age $i \cdot T_R/n$, since the mean transit time through each compartment is T_R/n , if T_R denotes the mean cell lifespan. We assume that cells are produced at a time dependent zero-order rate $K_{in}(t)$ (see Eq. 9), and the drug affects the transit rates between the compartments. The drug effect is described by the E_{max} model

$$E(t) = 1 + \frac{S_{max}C(t)}{SC_{50} + C(t)} \quad (\text{stimulation of } n/T_R) \quad (41)$$

and

$$E(t) = 1 - \frac{I_{max}C(t)}{IC_{50} + C(t)} \quad (\text{inhibition of } n/T_R) \quad (42)$$

Then transit compartments model is described by the following system of differential equations:

$$\frac{dP_1}{dt} = k_{in}(t) - \frac{n}{T_R} E(t) P_1, \quad P_1(0) = \frac{R_0}{n} \quad (43)$$

$$\frac{dP_i}{dt} = \frac{n}{T_R} E(t) (P_{i-1} - P_i), \quad P_i(0) = \frac{R_0}{n}, \quad i=2, \dots, n \quad (44)$$

where R_0 is the total number of cells in all compartments. It is additionally assumed that drug was administered at time $t = 0$, and prior to that the system was at steady state:

$$k_{in}(t) = k_{in}, \quad \text{and } E(1), \quad \text{for } t \leq 0 \quad (45)$$

Consequently, the initial conditions can be determined from the baseline equation:

$$R_0 = k_{in} T_R \quad (46)$$

A pharmacodynamic response R_n that consists of the total cell count:

$$R_n = P_1 + \dots + P_n \quad (47)$$

Note that if $R_n = P_n$, then the response as a signal transduction variable is distinctly different from a lifespan driven response. As the number of transit compartments increases to infinity and the mean lifespan T_R is constant, the total cell count approaches a response R_∞ that represents a cell population with a point distributed lifespan T_R and the drug effect is described by the following equation [33]:

$$\frac{dR_\infty}{dt} = k_{in}(t) - k_{in}(T_E(t)) \frac{E(t)}{E(T_E(t))} \quad (48)$$

with the initial condition

$$R_{\infty}(0)=k_{in}T_R \quad (49)$$

where the variable T_E is a solution to the following differential equation:

$$\frac{dT_E}{dt} = \frac{E(t)}{E(T_E(t))} \quad (50)$$

with the initial condition

$$T_E(0)=-T_R \quad (51)$$

In particular, when the drug affects only k_{in} , $E(t) \equiv I$, then the solution to Eqs. 48–51 is

$$T_E(t)=t-T_R \quad (52)$$

In this case Eq. 48 simplifies to the basic LIDR model Eq.(8). The signature profiles for $R(t)$ corresponding to the monoexponential pharmacokinetic function are shown in Fig. 6. Equations 48–51 constitute a definition of another basic LIDR model with a drug effect on the lifespan distribution (LIDRE) which differs in the mechanism of action of the drug effect on the lifespan distribution from the LIDR model described by Eq. 23. The properties of the LIDRE models are subjects for future analysis. Simulations show that if n is less than 5, then approximations of R_{∞} by R_n are not satisfactory [33]. Increasing n leads to a gradual improvement but there is no outstanding number that can be considered as a mark. In practice, this implies that a transit compartments model with n between 5 and 20 provides a relative good approximation of the LIDR model. A modest improvement of this approximation can be observed if the number of the transit compartments exceeds 20.

Results of comparisons of performance of mechanistic cell lifespan models and semi-mechanistic transit compartments using population approach have been published elsewhere [34–36]. The comparison performed with an experimental dataset from multiple dose administrations of an erythropoietin mimetic to cynomolgus monkeys [35] and chemotherapy induced neutropenia [36] concluded that both models were able to adequately describe the time course of RBCs.

Application of LIDR models

The lifespan models have been used to characterize the effects of haematopoietic growth factors on the proliferation of precursor cells, which mature to become circulating blood cells before the tissue uptake them or die due to the senescence or random destruction. In the case of erythropoiesis stimulating agents (ESA), the lifespan models have been used to simultaneously describe the dynamics of reticulocytes, mature red blood cells and hemoglobin following rHu-EPO administration to rats [37], monkeys [38], sheep [21–23], and healthy volunteers [39, 40]; or the peptidic erythropoiesis receptor agonist [41] or erythropoietin mimetibody construct CNTO 528 [10] administration to healthy subjects. Following the administration of rHu-EPO, the time course of hemoglobin in adult anemic patient with chronic renal failure [42] and newborns [43] has been also described using the lifespan models. Interestingly, in all these models the drugs were assumed to have the same mechanism of action, which was described by the stimulatory function of the precursor cell production rate driven by the free concentration. Consequently, the lifespan models presented here could be useful to explore the role of erythropoietin stimulating agents half-life in the stimulation of the production rate of erythropoietic precursor cells and/or the

prolongation of the reticulocytes lifespan, which would be helpful to differentiate across the several compounds available to treat patients.

Similar applications have been reported to analyze the clinical response affecting the neutrophils and platelets following the administration of colony stimulating factors [4, 11] or thrombopoiesis receptor agonists [44], respectively. Lifespan models can be also used in dealing with preclinical information and using them as the basis for the interspecies PK/PD extrapolation, which will allow the optimization of first in human studies as recently has been demonstrated for rHuEPO [45] and other ESA [1]. In addition, the lifespan models are also able to deal with drug effects that alter the lifespan distribution of cell populations and, as a consequence, it might be useful to analyze the increase in lifespan of cells due to the entry of younger cells in the circulation, the inhibition of the apoptosis, and/ or the prolongation of mature cell survival [5, 46]. Besides these research applications, the models have been used to advance the development of ESA by assisting in the dose (or regimen) selection and/or predicting the outcome of for future studies in other populations.

LIDR models for toxic effects on cell populations were adopted to describe hematological toxicities of chemotherapeutic agents in animals and humans. Carboplatin induced anemia in rats was modeled by a LIDR model accounting for up-regulation of endogenous erythropoietin levels [47]. Cytotoxic effect of paclitaxel on neutrophils in rats was analyzed by the multiple-pool LIDR model [48]. A similar pharmacodynamic model was used for population analysis of time courses of neutropenia in cancer patients [36, 49].

Limitations

Due to the fact that delay differential equations (DDE) are needed for lifespan-based PD models, their software implementation is not straightforward. Available software for PK/PD data analysis is not equipped with DDE solvers, but has robust ODE solvers. Therefore, the method of steps, a numerical technique available to transform any system of DDEs to a system of ODEs by a step-wise procedure, needs to be applied if lifespan models are used for data analysis employing ODE software [50]. The biggest limitation of this method is that, in general, the number of ODEs depends on the ratio of the smallest delay time to the overall time range of the data to be solved. If the number of ODEs generated by the method of steps exceeds the maximum number allowed by software, then the method of steps cannot be applied. However, this limitation does not apply for a DDE system, if the software supports the DDE solver (e.g. MATLAB or S-ADAPT [51]).

Another important limitation in using the method of the steps and the ODE solver to analyze DDEs is due to the minimization algorithm and the lifespan parameter discontinuity. While this limitation might not be relevant in using geometric algorithms to get convergence, the algorithms based on the gradients of the first and second derivative are not the optimal methods to find the actual value of the lifespan parameter due to the discontinuity in the underlying mathematical function. Recently, the method of steps, in its general form, was successfully implemented in NONMEM V software and applied to three different lifespan-based PD models for dealing with hematological drug effects [52]. In this particular software, the first order conditional estimation method with a log-transformation at both sides was the most stable method yielding the lowest number of minimization failures as well as the lowest imprecision and bias on the parameter estimates. A more recent evaluation in NONMEM 7 conducted by the authors, suggested that the new ADVAN 13 is twice as fast as ADVAN 9 in estimating the lifespan model parameters.

Lifespan-based PD models exhibit a compartmental structure and preserve the law of mass balance. However, caution should be exercised when additional processes are added into the model structure. Each elimination process violates the basic assumption that the cell removal

is determined by the cell lifespan and an additional correction to the lifespan driven cell removal rate is necessary to account for an extra cell loss. An example is the survival fraction SF derived for the LIDR models for agents with toxic effects on cell populations Eq. 34, where such a factor accounts for cells that survived the killing due to exposure to a cytotoxic agent. Derivation of the equation for SF is presented in [6]. At present there are no general guidelines how to correct the lifespan driven removal rate for an arbitrary loss process.

A distinct feature of the multiple pool LIDR models is an accumulation of the lifespans for the subsequent compartments resulting in delays that are sums of the lifespans of the preceding compartments. This results in a redundancy of the model differential equations, since the observable response R might not require all the precursor compartments to be completely defined as mentioned earlier in this chapter. For example, Eq. 30 alone suffices to describe the response R in the LIDR model with a precursor. The differential equation for the precursor P is redundant, since this variable is not present in Eq. 30. One can omit Eq. 29 when coding the model equations. On the other hand, when selecting model parameters one needs to keep in mind that some of the lifespans of these precursors might not be separately resolved and can be identified only as a sum. This situation is demonstrated in a LIDR model describing the effect of rHuEPO on reticulocyte counts, where only the sum of the BFU cell and normoblast lifespans could be estimated [5].

Presented here LIDR models operate under the assumption that the cell lifespan distribution is centered at one or two points. This assumption is unrealistic but justified by the principle of parsimony. Indeed, more realistic lifespan distributions have been studied [24], but continuous probability functions require at least two parameters to be described. These are notoriously difficult to be resolved from typical cell count based pharmacodynamic data. Of particular importance is the gamma function with an integer number value of its shape parameter n . It can be shown, that a LIDR model with the gamma lifespan distribution is equivalent to a transit compartments model with n compartments interpreted as ageing or maturing pools [33]. The identifiability of the multi-parameter lifespan distribution would be possible if, in addition to PK/PD data, analysis included data containing information about cell lifespans such as survival curves or cell cohort time courses [7]. More theoretical work on such experimental designs is necessary to establish optimal conditions for utilization of the cell survival measurements in conjunction with PK/PD data.

Applications of the lifespan concept to describe cell kinetics need further theoretical development to account for processes not included into the scope of presented models. Of importance are accumulation of cells in organs or extravascular tissues followed by redistribution to the circulation which is the common sampling site for the hematopoietic cell count measurements. Spleen acts as a storage compartment for RBCs and platelets [53]. Lymphocytes are known to traffic across endothelial venules and circulate between blood and lymphoid tissues [54]. Half of the human blood neutrophils temporarily marginate along the vessels walls [53]. Such processes violate the fundamental assumption for lifespan driven elimination that cell exiting the population cannot re-enter (be “born”) again. Also theoretically challenging remain adaptation of the lifespan concept to the cell populations with an input of cells of unknown age (e.g. during blood transfusions).

Virtually no research has been done on identifiability and estimability of LIDR model parameters [52]. In contrast, IDR models are relatively well studied with that respect [55, 56]. However, despite structural similarity with IDR models, LIDR models exhibit differences warranting separate analysis. The results available for IDR models addressing the impact of sampling designs, intra- and inter-subject variability, sparseness of data, and

other factors, on the bias and precision of parameter estimates, cannot be directly translated to LIDR models without validation that is a subject for future studies.

Prospectus

The concepts presented here were applied to describe effects of therapeutic agents on hematopoietic cell populations of myeloid lineage. In principle other cell populations (e.g. lymphocytes) or organisms (e.g. viruses, bacteria, parasites) that undergo transitions between stages of development may fall into a category of lifespan-driven processes. Drugs affecting these populations are natural candidates for lifespan based pharmacodynamic models. As the delayed differential equations handling in available software for PKPD modeling becomes more user friendly, it can be expected a growing number of LIDR models in future applications of the PK/PD modeling of cellular responses.

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Fig. 1.
Schematic diagram representing the cell turnover process. The cell population size is a net effect of the production $K_{in}(t)$ and loss $K_{out}(t)$

Fig. 2.

Schematic diagrams for LIDR models and signature response versus time profiles. The *solid box* represents a drug inhibition of the cell production rate k_{in} and an *open one* represents a drug stimulation. The *solid lines* are responses to a single dose input whereas the *dotted lines* are the limiting values of the response for dose approaching infinity. The simulated response curves were generated for the monoexponential kinetic function Eq. 13 with $k_{el} = 0.3$, $V = 1$, $C_b = 10$, and *Dose* as indicated in the plots. The PD parameters were set as follows $R_0 = 100$, $T_R = 48$, $E_{max} = 1$, $EC_{50} = 100$, and k_{in} were calculated from the baseline Eq. 12

Fig. 3.

Schematic diagrams and signature response versus time profiles for basic LIDR models for agents affecting cell lifespan distribution. The *solid box* represents an inhibition of the cell elimination rate that takes place if $T_D > T_R$, and an open one represents a stimulation if $T_D < T_R$. The *solid lines* are responses to a single dose input whereas the *dotted lines* are the limiting values of the response for dose approaching infinity. The simulated response curves were generated for the monoexponential kinetic function Eq. 13 with $k_{el} = 0.3$, $V = 1$, $C_b = 10$, and *Dose* as indicated in the plots. The PD parameters were set as follows $R_0 = 100$, $T_R = 48$, $E_{max} = 1$, $EC_{50} = 100$, and k_{in} were calculated from the baseline Eq. 24. For the inhibitory model $T_D = 72$, and for the stimulatory one $T_D = 24$.

Fig. 4.

Schematic diagrams and signature response versus time profiles for basic LIDR models with a precursor pool. The *open box* represents a stimulation and the *solid box* an inhibition of the precursor cell production. The *solid lines* are responses to a single dose input whereas the *dotted lines* are the limiting values of the response for dose approaching infinity. The simulated response curves were generated for the monoexponential kinetic function Eq. 13 with $k_{el} = 0.3$, $V = 1$, $C_b = 10$, and *Dose* as indicated in the plots. The PD parameters were set as follows $R_0 = 100$, $T_R = 48$, $T_P = 24$, $E_{max} = 1$, $EC_{50} = 100$, and k_{in} were calculated from the baseline Eq. 31

Fig. 5.

A schematic diagram and signature response versus time profiles for the LIDR model for agents with toxic effects on cell populations. A linear killing function $f(C)$ Eq. 32 was used for simulations. The *solid lines* are responses to a single dose input whereas the *dotted lines* are the limiting values of the response for dose approaching infinity. The simulated response curves were generated for the monoexponential kinetic function Eq. 13 with $k_{el} = 0.1$, $V = 1$, $C_b = 0$, and *Dose* as indicated in the plots. The PD parameters were set as follows $R_0 = 100$, $T_R = 20$, $T_P = 100$, $T_M = 50$, $k = 0.001$, and k_{in} were calculated from the baseline Eq. 38

Fig. 6.

Transit compartments model approaches LIDR model as the number of compartments increases to infinity. Schematic representation of the transit compartments model (*upper*) and response time courses for transit compartments models with an increasing number of compartments (*middle* and *lower*). The sum R_n of the transit compartments constitutes the pharmacodynamic response described by the TC model represented by *thin lines* whereas the *thick lines* are the LIDR model predictions based on Eqs. 48–51. The parameter values used for simulations were, $k_{in} = R_0/T_R$, $R_0 = 100$, $T_R = 24$, $I_{max} = S_{max} = 1$, and $IC_{50} = SC_{50} = 100$, $Dose = 10,000$, and $n = 1, 2, 3, 4, 5, 10, 20, 100$

Table 1

Properties of the responses for basic LIDR models for agents affecting cell production: values of the response at time t , $R(t)$, peak time t_{peak} , peak response R_{peak} , initial slope S_I , and area under the effect curve AUCE

Variable	Relationship for arbitrary $C(t)$	Relationship for $Dose \rightarrow \infty$
$R(t)$	$k_{in} T_R \pm k_{in} E_{max} \int_{t-T_R}^t \frac{C(z) dz}{EC_{50} + C(z)}$	$R_0 \pm k_{in} \frac{E_{max} EC_{50}}{EC_{50} + C_b} t, 0 < t < T_R$ $k_{in} T_R (1 \pm E_{max}), t = T_R$
t_{peak}	T_R	T_R
R_{peak}	$k_{in} T_R \pm k_{in} E_{max} \int_0^{T_R} \frac{C(z) dz}{EC_{50} + C(z)}$	$k_{in} T_R (1 \pm E_{max})$
S_I	$k_{in} \left(\mp \frac{E_{max} C_b}{EC_{50} + C_b} \pm \frac{E_{max} C(0+)}{EC_{50} + C(0+)} \right)$	$\pm k_{in} \frac{E_{max} EC_{50}}{EC_{50} + C_b}$
AUCE	$\frac{k_{in} T_R E_{max} EC_{50}}{(EC_{50} + C_b) k_{el}} \ln \left(1 + \frac{Dose/V}{EC_{50} + C_b} \right)$	∞

The relationships for $R(t)$ and S_I are independent of the pharmacokinetic function. However, the equations for t_{peak} and R_{peak} hold for a decreasing $C(t)$, and AUCE equation is valid for the monoexponential pharmacokinetic profile as described by Eq. 13. For the relationships in the third column, it is additionally assumed that $C(t)$ approaches infinity as $Dose$ becomes large. The “+” corresponds to the stimulation of k_{in} whereas “-” to the inhibition

Table 2

Properties of the responses for basic LIDR models for agents affecting cell lifespan distribution with $T_D > T_R$

Variable	Relationship for arbitrary $C(t)$	Relationship for $Dose \rightarrow \infty$
t_{lag}	T_R	T_R
$R(t)$	$k_{in}T_R \pm k_{in}E_{max} \int_{t-T_D}^{t-T_R} \frac{C(z)dz}{EC_{50}+C(z)}$	$R_0, 0 < t < T_R$ $R_0 + \frac{k_{in}E_{max}EC_{50}}{EC_{50}+C_b}(t-T_R), T_R \leq t < T_D$ $k_{in}T_R + k_{in}E_{max}(T_D - T_R), t \geq T_D$
t_{peak}	T_D	T_D
R_{peak}	$k_{in}T_R + k_{in}E_{max} \int_0^{T_D-T_R} \frac{C(z)dz}{EC_{50}+C(z)}$	$k_{in}T_R + k_{in}E_{max}(T_D - T_R)$
S_I	$k_{in} \left(\frac{E_{max}C(0+)}{EC_{50}+C(0+)} - \frac{E_{max}C_b}{EC_{50}+C_b} \right)$	$k_{in} \frac{E_{max}EC_{50}}{EC_{50}+C_b}$
AUCE	$\frac{k_{in} T_D-T_R E_{max}EC_{50}}{(EC_{50}+C_b)k_{el}} \ln \left(1 + \frac{Dose/V}{EC_{50}+C_b} \right)$	∞

The initial slope S_I was evaluated at $t = T_R$. The relationships for $R(t)$ and S_I are independent of the pharmacokinetic function. However, the equations for t_{peak} and R_{peak} hold for a decreasing $C(t)$, and AUCE equation is valid for the monoexponential pharmacokinetic profile as described by Eq. 13. For the relationships in the third column, it is additionally assumed that $C(t)$ approaches infinity as $Dose$ becomes large

Table 3Properties of the responses for basic LIDR models for agents affecting cell lifespan distribution with $T_D < T_R$

Variable	Relationship for arbitrary $C(t)$	Relationship for $Dose \rightarrow \infty$
t_{lag}	T_D	T_D
$R(t)$	$k_{in} T_R \pm k_{in} E_{max} \int_{t-T_D}^{t-T_R} \frac{C(z) dz}{EC_{50} + C(z)}$	$R_0, 0 < t < T_D$ $R_0 - \frac{k_{in} E_{max} EC_{50}}{EC_{50} + C_b} (t - T_D), T_D \leq t < T_R$ $k_{in} T_R - k_{in} E_{max} (T_R - T_D), t \geq T_R$
t_{peak}	T_R	T_R
R_{peak}	$k_{in} T_R - k_{in} E_{max} \int_0^{T_R - T_D} \frac{C(z) dz}{EC_{50} + C(z)}$	$k_{in} T_R - k_{in} E_{max} (T_R - T_D)$
S_I	$k_{in} \left(\frac{E_{max} C_b}{EC_{50} + C_b} - \frac{E_{max} C(0+)}{EC_{50} + C(0+)} \right)$	$-k_{in} \frac{E_{max} EC_{50}}{EC_{50} + C_b}$
AUCE	$\frac{k_{in} T_D - T_R E_{max} EC_{50}}{(EC_{50} + C_b) k_{el}} \ln \left(1 + \frac{Dose/V}{EC_{50} + C_b} \right)$	∞

The initial slope S_I was evaluated at $t = T_D +$

The relationships for $R(t)$ and S_I are independent of the pharmacokinetic function. However, the equations for t_{peak} and R_{peak} hold for a decreasing $C(t)$, and AUCE equation is valid for the monoexponential pharmacokinetic profile as described by Eq. 13. For the relationships in the third column, it is additionally assumed that $C(t)$ approaches infinity as $Dose$ becomes large

Table 4

Properties of the responses for basic LIDR models with a precursor pool

Variable	Relationship for arbitrary $C(t)$	Relationship for $Dose \rightarrow \infty$
t_{lag}	T_P	T_P
$R(t)$	$k_{in} T_R \pm k_{in} E_{max} \int_{t-T_P-T_R}^{t-T_P} \frac{C(z) dz}{EC_{50} + C(z)}$	$R_0, 0 < t < T_P$ $R_0 \pm k_{in} \frac{E_{max} EC_{50}}{EC_{50} + C_b} (t - T_P), T_P < t < T_P + T_R$ $k_{in} T_R (1 \pm E_{max}), T_P + T_R < t$
t_{peak}	$T_P + T_R$	$T_P + T_R$
R_{peak}	$k_{in} T_R \pm k_{in} E_{max} \int_0^{T_R} \frac{C(z) dz}{EC_{50} + C(z)}$	$k_{in} T_R (1 \pm E_{max})$
S_I	$k_{in} \left(\pm \frac{E_{max} C(0+)}{EC_{50} + C(0+)} \mp \frac{E_{max} C_b}{EC_{50} + C_b} \right)$	$\pm k_{in} \frac{E_{max} EC_{50}}{EC_{50} + C_b}$

The initial slope S_I was evaluated at $t = T_P +$. The relationships for $R(t)$ and S_I are independent of the pharmacokinetic function. However, the equations for t_{peak} and R_{peak} hold for a decreasing $C(t)$. For the relationships in the third column, it is additionally assumed that $C(t)$ approaches infinity as $Dose$ becomes large. The “+” corresponds to the stimulation of k_{in} whereas “-” to the inhibition

Table 5

Properties of the responses for basic LIDR models for cytotoxic agents

Variable	Relationship for arbitrary $C(t)$	Relationship for $Dose \rightarrow \infty$
t_{lag}	T_M	T_M
$R(t)$	$k_{in} \int_{t-T_M-T_R}^{t-T_M} S F(z) dz$	$R_0, 0 \leq t < T_M$ $k_{in}(T_M - t) + R_0, T_M \leq t < T_M + T_R$ $0, t \geq T_M + T_R$
R_{nadir}^a	$R_0 \exp(-kAUC)$	0
S_I	0	$-k_{in}$

The initial slope S_I was evaluated at $t = T_M^+$. The relationships for $R(t)$ and S_I are independent of the pharmacokinetic function. However, the equations for t_{peak} and R_{peak} hold for a decreasing $C(t)$ and a linear kinetic function $f(C)$. For the relationships in the third column, it is additionally assumed that $C(t)$ approaches infinity as $Dose$ becomes large

^aEquation for R_{nadir} is approximate and holds true only if $T_R \ll T_P$