An Interpretation of Transit Compartment Pharmacodynamic Models As Lifespan Based Indirect Response Models

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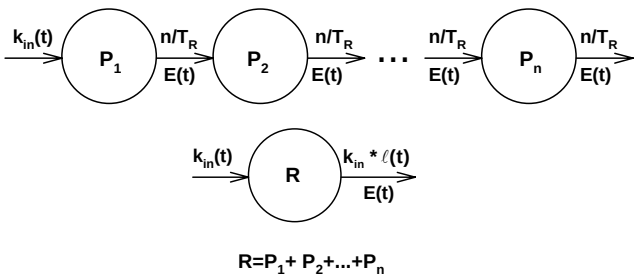
Objectives

Transit compartments (TC) models are used to describe pharmacodynamic responses that involve drug action on cells undergoing differentiation and maturation [1-3]. Such PD systems can also be described by lifespan based indirect response (LIDR) models [4]. Our objectives were to determine the lifespan distribution for which the LIDR model coincides with the TC model, to show that if the number of transit compartments n increases to infinity, then the TC model approaches the basic LIDR model with the point lifespan distribution centered at the mean lifespan TR, and to propose a new class of LIDR models for agents acting on the cell lifespan distribution.

Methods

The TC model consists of a series of compartments P_1, …, P_n connected with each other by first-order processes in a catenary manner as shown in Fig. 1. 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 TR denotes the mean cell lifespan. It is assumed that cells are produced at a time dependent zero-order rate $k_{in}(t)$, and the drug affects the transit rates between the compartments. The drug effect is described by a function E(t).

PK/PD Model



$$R = P_1 + P_2 + \ldots + P_n$$

Fig. 1. Schematic representation of TC model (upper) and basic LIDR model (lower). In both models cells are produced at a zero-order rate that can be affected by drug $k_{in}(t)$. The transfer rates between the transit compartments are first-order constants n/T_R where n is the number of compartments and T_R is the total mean transit time through all compartments. The cell elimination for the lifespan indirect response model is determined by their time dependent lifespan distribution $\ell(t,\tau)$. Drug affects both n/T_R and $\ell(t,\tau)$ via mechanism described by the effect function E(t). The sum of the transit compartments P_1, P_2, …, P_n can be described by a lifespan driven indirect response R.

TC Model

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

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

E(t) = drug effect function.
R_0 = number of cells in all compartments at steady-state

LIDR Model

$$\frac{dR}{dt} = k_{in}(t) - \int_0^\infty k_{in}(t-\tau)\ell(t-\tau,\tau)d\tau$$

$$R(0) = R_0 = k_{in0} \cdot T_R$$

k_{in0} = cell production rate at steady-state

Baseline conditions:

$$k_{in}(t) = k_{in0} \quad E(t) = 1 \quad \text{for } t \le 0$$
$$R_0 = k_{in0} \cdot T_R$$

Drug effect

Stimulation of kin_0: $k_{in}(t) = k_{in0}\left(1 + \frac{S_{max}C(t)}{SC_{50} + C(t)}\right)$, $E(t) \equiv 1$

Inhibition of kin_0: $k_{in}(t) = k_{in0}\left(1 - \frac{I_{max}C(t)}{IC_{50} + C(t)}\right)$, $E(t) \equiv 1$

Stimulation of n/T_R: $E(t) = 1 + \frac{S_{max}C(t)}{SC_{50} + C(t)}$, $k_{in}(t) \equiv k_{in0}$

Inhibition of n/T_R: $E(t) = 1 - \frac{I_{max}C(t)}{IC_{50} + C(t)}$, $k_{in}(t) \equiv k_{in0}$

S_{max} = maximal drug effect.
SC_{50} = drug plasma concentration eliciting 50% of the maximum effect.

I_{max} = maximal drug effect.
IC_{50} = drug plasma concentration eliciting 50% of the maximum effect.

Results

Solution to TC model:

$$P_i(t) = \frac{R_0}{n} + \frac{1}{(i-1)!}\left(\frac{n}{T_R}\right)^{i-1}\int_0^t\left(k_{in}(\tau) - \frac{R_0}{T_R}E(\tau)\right)\left(\int_\tau^t E(z)dz\right)^{i-1}\exp\left(-\frac{n}{T_R}\int_\tau^t E(z)dz\right)d\tau$$

Lifespan distribution for LIDR model:

$$\ell_n(t,\tau) = \left(\frac{n}{T_R}\right)^n \frac{E(t+\tau)}{(n-1)!}\left(\int_t^{t+\tau} E(z)dz\right)^{n-1}\exp\left(-\frac{n}{T_R}\int_t^{t+\tau} E(z)dz\right)$$

Stimulation of kin_0 (E(t)≡1)
Inhibition of kin_0

$$\ell_n(t,\tau) = \gamma_n(\tau) = \left(\frac{n}{T_R}\right)^n \frac{\tau^{n-1}}{(n-1)!}\exp\left(-\frac{n}{T_R}\tau\right)$$

Stimulation of n/T_R ($k_{in}(t)=k_{in0}$)
Inhibition of n/T_R

$$\ell_n(t,\tau) = \gamma_n \circ \hat{E}_t(\tau) = \gamma_n\left(\hat{E}_t(\tau)\right)\frac{d\hat{E}_t}{d\tau}(\tau)$$

where $\hat{E}_t(\tau) = \int_t^{t+\tau} E(z)z$

Convergence of TC model as $n \to \infty$: $\gamma_n(\tau) \to \delta(\tau - T_R)$ (The approximate identity)

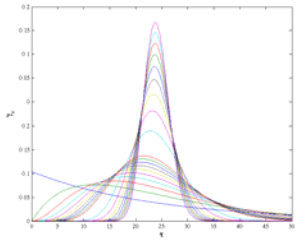


Fig. 2. Simulated profiles of the p.d.f. $\gamma_n(\tau)$ for n = 1,2,…, 10, 20,…, 100. The $T_R = 24$. Each curve has a unique peak at $\tau_n = (1-1/n)T_R$.

$$R_n(t) \to R_\infty(t)$$

$$\frac{dR_\infty}{dt} = k_{in}(t) - k_{in}(t - T_R)$$

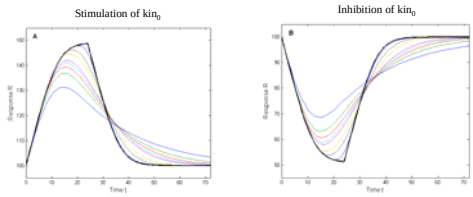


Fig. 3. Response time courses for TC models corresponding to the monoexponential pharmacokinetic function C(t) =Dose/V·exp(-k_{el}·t) for n = 1, 2, 3, 4, 5, 10, 20, 100. The bold curves represent solutions of LIDR model $R_\infty(t)$. The parameter values used for simulations were Dose = 10000, V = 3, k_{el} = 0.3, $kin_0 = R_0/T_R$, R_0 = 100, T_R = 24, $I_{max} = S_{max}$ = 1, and $IC_{50} = SC_{50}$ = 100.

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

$$\frac{dT_E}{dt} = \frac{E(t)}{E(T_E(t))} \qquad T_E(0) = -T_R$$

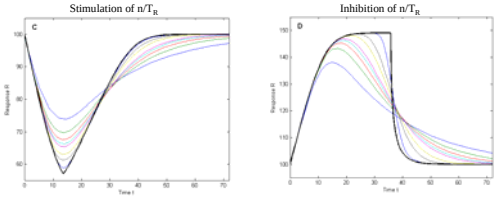


Fig. 4. Response time courses for TC models corresponding to the monoexponential pharmacokinetic function C(t) =Dose/V·exp(-k_{el}·t) for n = 1, 2, 3, 4, 5, 10, 20, 100. The bold curves represent solutions of LIDR model $R_\infty(t)$. The parameter values used for simulations were as in Fig. 3.

Table 1. Percent difference between the transit compartment response Rn and a limit lifespan based indirect response R_∞ for four models. The difference was evaluated at indicated R_∞ peak times: $|R_n(T_{peak})-R_\infty(T_{peak})|/|R_\infty(T_{peak})-R_0|\times 100$. The model parameters are as in Fig. 3

n	Stimulation of k_{in0} T_{peak} = 24	Inhibition of k_{in0} T_{peak} = 24	Stimulation of n/T_R T_{peak} = 13.7	Inhibition of n/T_R T_{peak} = 35.8
1	49.8	96.4	39.8	60.0
2	39.5	80.3	29.7	55.9
3	35.5	64.3	26.7	53.9
4	31.4	52.2	21.1	51.8
5	29.3	36.1	18.7	49.8
10	23.2	32.1	14.1	47.8
20	17.0	26.5	9.4	43.7
100	6.8	16.1	4.6	35.5

Conclusions

- TC models can be considered as LIDR models with the gamma lifespan distribution.
- If the number of compartments increases and the mean lifespan is constant, then the TC models approach a basic LIDR model with a point lifespan distribution.
- TC models with the number of TCs between 5 and 20 provide a good approximation of the basic LIDR model.

References

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Acknowledgment

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