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NEW DEVELOPMENTS IN USING STOCHASTIC RECIPE FOR MULTI-COMPARTMENT MODEL: INTER-COMPARTMENT TRAVELING ROUTE, RESIDENCE TIME, AND EXPONENTIAL CONVOLUTION EXPANSION

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Abstract. Drug residence time in "compartmentalized" human body system had been studied from both deterministic and Markovian perspectives. However, probability and probability density functions for a drug molecule to be (1) in any compartment of study interest, (2) with any defined inter-compartment traveling route, and (3) with/without specified residence times in its visited compartments, has not been systemically reported. In Markovian view of compartmental system, mathematical solutions for the probability or probability density functions, for a drug molecule with any defined inter- compartment traveling routes in the system and/or with specified residence times in any visited compartments, are provided. Matrix convolution is defined and thus employed to facilitate methodology development. Laplace transformations are used to facilitate convolution operations in linear systems. This paper shows that the drug time-concentration function can be decomposed into the summation of a series of component functions, which is named as convolution expansion. The studied probability or probability density functions can be potentially engaged with physiological or pharmacological significances and thus be used to describe a broad range of drug exposure-response relationships.

1. **Introduction.** To explore drug absorption, distribution, metabolism, and elimination of drug administered into human body, two types of mathematical formulations have been used to describe the dynamic processes. Pharmacokinetics and Pharmacodynamics, which falls into the category of deterministic compartmental models, are conventionally used. In contrast, continuous-time Markovian models with finite number of states, categorized as stochastic models, have also been investigated as another approach [1, 3, 7, 9, 10, 13, 14, 15]. The theoretical frameworks have been well established and outlined for Markovian models [11, 12]. Noteworthy, if the retention time density function cannot be described by a single exponential function, the stochastic compartmental system will be labeled as "non-Markovian" or "semi-Markovian." However, these systems can be expanded to or approximated

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by virtual ordinary Markovian models with more compartments or states using appropriate transformation rules [12].

Although originated independently from different scientific fields, the deterministic and stochastic formulations are mathematically equivalent in their final expressions to describe pharmacokinetic-pharmacodynamic processes such as drug concentration profile against time. However, stochastic models prompt to the exploration of the probability and probability density functions of drug residence times and number of visits to other "states," equivalent to "compartments" in the language of pharmacokinetics, before exiting to the system exterior [9, 18, 19, 20, 21]. In this paper, the quantity of residence time is defined as the time or the cumulative time for a drug molecule to reside in a chosen compartment during its single or multiple visits before exiting to other compartments or the system exterior. The drug residence time in compartment of pharmacological significance is of great importance in predicting drug efficacy and safety, and can be studied with physiologically based pharmacokinetic models. A full physiologically based pharmacokinetic model attempts to describe all aspects of a drug's absorption, distribution and elimination in terms of organ or regional blood flows, plasma and tissue binding constants, fluid volumes and pH's, and passive or active transport capacities, and enzyme affinities, etc. The area under drug concentration-time curve (AUC) in the target organ, either determined experimentally or inferred from physiologically based pharmacokinetic models, has been considered as a superior drug exposure measure to predict drug responses. However, AUC cannot tell the fraction of drug that has visited the target organ with residence time bigger than the minimally required incubation time to allow the drug to exert therapeutic or toxic effect.

Methods capable of deriving probability functions for a drug molecule with certain visits to other compartments and the probability density functions (PDF's) associated with the corresponding residence times can potentially enhance the performances and capabilities of physiologically based pharmacokinetic models. The residence time or cumulative residence time for a drug molecule in an interested organ or drug target site, once understood, can potentially provide us with a better measure of drug exposure that highly correlates with drug efficacy and safety. As known in cancer research, the incubation time of cancer cells with anti-cancer agents such as paclitaxel and doxorubicin determines their potency of cytotoxicity [6, 22]. As known in anti-infectious disease research, the duration of viral or bacterial exposure to minimally effective drug concentration dictates whether or not the treatment is successful. As generally known in immunology, number of visits of an antigen or immunogen to lymphoid organs or B cells may be a better causal metric for the extent of immune responses. Consequently, PDF's and probability functions associated with residence times and defined inter-compartment traveling routes can be further adopted to explain pharmacological efficacy and safety in many cases held in the fields of anti-caner and anti-infectious disease research.

The residence time for a drug molecule to reside in the whole body with one or multiple elimination compartment or compartments has been researched [5, 11, 12, 19, 20]. For compartmental models, Yu and Wehrly presented the method of using saddlepoint approximation to approximate the densities for the residence time using the moment generating function (MGF) for a two-compartment model [21]. To a certain degree of complexity for pharmacokinetist and clinicians, this approach can be extended to multi-compartment (> 2) models using cofactor rule [11]. For circulatory models, research efforts have been focused on the drug residence time

in the whole system or human body. In comparison to the approaches used in compartmental models, Laguerre series approximation has been used to construct the residence-time density by Smith et al. [18], given that the first four moments of the cycle time can be made available by taking advantage of the Laplace-Stieltjes transforms of residence time and cycle time. However, probability and probability density functions for a drug molecule, with a joint numbers of visits to multiple compartments, a specified inter-compartment traveling route, a joint cumulative residence times in different compartments, and the specified residence times in conjunction to the number of visits or specified traveling route etc in a multi-compartment (> 2) system, have not been reported.

This paper will adopt stochastic Markovian view of pharmacokinetic system and provide new approaches to capture the PDF's of residence time and probability functions as discussed. The proposed methodologies will render exact mathematical expressions for probability functions and PDF's, which is different from conventional approximation forms such as saddlepoint approximation. They can also be flexibly used to address any arbitrary probability functions and PDF's of study interest. The newly developed methodologies, compared with published works, are capable of addressing (1) probability functions for a drug molecule to travel along any defined inter- compartment route or (2) the PDF's for a drug molecule to sojourn in a single or any series of compartments with specific residence times during any interested inter-compartment traveling route or any routes.

2. **Notations and theoretical frameworks for stochastic Markovian models.** The theoretical frameworks for stochastic Markovian models and the associated notations are outlined as follows for an n-compartment model.

1. $P_{ij}(t)$, with $i, j = 1, \ldots, n$, denotes the probability for a random drug molecule to start from compartment i and end in compartment j after an elapsed time t. Noteworthy, uppercase P indicates probability function and lowercase p indicates probability density function.
2. $X_{ij}(t)$ represents the amount of drug molecules that start from compartment i and end in compartment j after an elapsed time t.
3. $C_{ij}(t)$ denotes concentration of drug molecules that start from compartment i and end in compartment j after an elapsed time t.
4. $E[X(t)]$ and $E[C(t)]$ be matrices of expected values of $X(t)$ and $C(t)$.
5. K_{ij}, for $i = 1, \ldots, n$, $j = 0, \ldots, n$, $i \neq j$, be a probability intensity coefficient defined by Prob(a given unit in i transfers to j in $(t, t + \Delta t)|P(t)) = K_{ij}\Delta t + o(\Delta t)$. It is quantitatively equivalent to the transfer rate constant as defined in deterministic compartment models and will be referred as transition coefficient in this paper. Here 0 represents the system exterior.
6. $K_{ii} = -\sum_{j=1, j\neq i}^{n} K_{ij}$. K_{ii} be a probability intensity coefficient defined by Prob(a given unit in i transfers back to i in $(t, t + \Delta t)|P(t)) = K_{ii}\Delta t + o(\Delta t)$.
7. $P(t) = [P_{ij}(t)]$, $X(t) = [X_{ij}(t)]$, $K = [K_{ij}]$, and $C(t) = [C_{ij}(t)]$ be matrices of probabilities, amounts, transfer rates, and concentrations, respectively.
8. The definition of convolution is given by $f(t) * g(t) = \int_0^t f(tt)g(t - tt)dtt$. $\overbrace{f(t) * \cdots * f(t)}^{nf(t)\text{s}}$ will be abbreviated as $f(t)^{*n}$ and n will be originally named as the convolution power of order n by this paper.
9. Matrix convolution, originally defined by this paper, will be referring to convolution product of two matrices. That is, if $A(t)$ and $B(t)$ are matrix valued

functions, then

$$(A(t) * B(t))_{ij} = \sum_{k=1}^{n} \int_0^t A_{ik}(tt) B_{kj}(t - tt) dtt.$$

In other words, Matrix convolution is performed by switching the multiplication operations to convolution operations in each element of the outcome matrix resulted from conventional matrix multiplication.

10. Throughout this paper, operator "$*$" between two functions/matrices will be used to indicate operation of convolution and operator "." or space between two functions/matrices will be used to indicate operation of normal multiplication.
11. For a two-compartment model, $P_{11}^{V_n}(t)$ will indicate the probability for a drug molecule to be in the compartment one with n times of visit to compartment two, given it is initiated at compartment one and after an elapsed time t; For a multi (> 2)-compartment model, $P_{ij}^{n}(t)$ will indicate the probability for a drug molecule to be in the compartment j with n times of inter-compartment transitions, given it is initiated at compartment i and after an elapsed time t. The physical meaning of "one inter-compartment transition" can be viewed as a drug molecule travels from one compartment to a different compartment once.
12. Throughout this paper, the pharmacokinetic translation of "a drug molecule is initiated from compartment i" is that the drug is administered with a bolus dose to compartment i.

Conventionally, the matrix of probabilities assumes the form as described by (1) [11].

$$P(t) = \exp(Kt) = \sum_{i=1}^{\infty} \frac{1}{i!} K^i t^i. \tag{1}$$

Provided the eigenvalues of K ($\lambda_l, l = 1, \ldots, n$) are distinct and real, each element of matrix $P(t)$ can be described by (2) [11].

$$P_{ij}(t) = \sum_{l=1}^{n} A_{ijl} \exp(\lambda_l t). \tag{2}$$

Here A_{ijk} indicates a specific constant ($k = 1, \ldots, n$ and n is the total number of distinct eigenvalues of K). Noteworthy, if the eigenvalues of K are complex, the methodology developed in this paper still applies. The expected drug concentration can be calculated by (3).

$$E[C(t)] = C(0)P(t). \tag{3}$$

The significance of the above equation can be intuitively interpreted as follows. If drug is initiated at compartment i with initial concentration $C(0)$, the drug concentration function against time t for compartment j, where j represents any arbitrary compartment, is $C(0)P_{ij}(t)$. $C(0)P_{ij}(t)$ is mathematically equivalent to the concentration function obtained via solving conventional deterministic differential equations for pharmacokinetic compartment models.

3. **Overview of methodology development.** The methodology development takes the following three major steps. Initially, methodologies will be developed for a two-compartment system. The conventional two-compartment pharmacokinetic model, along with its two complementary models as originally defined by this paper,

will be introduced. The probability function against time t, for a drug molecule to be in the central compartment after exactly n times accomplished visits to the peripheral compartment, will be derived. The PDF against time t, for a drug molecule in the central compartment that has not only visited the peripheral compartment exactly n times but also stayed for a cumulative residence time T, will be derived. Furthermore, all of the derivations and theoretical developments will be extended to general models with > 2 compartments using matrix convolution.

4. Methods and results for two-compartment model.

4.1. The two-compartment model.

The two-compartment model used for demonstration is depicted by Figure 1A, with compartment one representing the central compartment and compartment two representing the peripheral compartment. Unless specifically mentioned, it is assumed that drug is originally administered to the central compartment throughout the paper. Although compartmental models are commonly understood, it is deemed necessary to present it again to illustrate the construction of its two complementary models. For convenience, this paper will use $P(t)$ to denote the probability function matrix for the original model as depicted by Figure 1A; $P^{(1)}(t)$ for the first complementary model by Figure 1B; $P^{(2)}(t)$ for the second complementary model by Figure 1C. In principle, the first complementary model is constructed in a way that guarantees all drug molecules in the peripheral compartment will never go to the central compartment. The second complementary model is constructed in a way that guarantees all drug molecules in the central compartment will never visit the peripheral compartment. With such changes,$P_{11}^{(1)}(t)$ or $P_{22}^{(2)}(t)$, compared to $P_{11}(t)$ or $P_{22}(t)$, only represents the probability for a drug molecule that has never traveled out from compartment one or two by excluding those probabilities for it to have visited the other compartment but returned to compartment one or two, after an elapsed time t. $P_{12}^{(1)}(t)$ represents the probability for a drug molecule that has traveled from compartment one to two only for the first time, after an elapsed time t. For models with > 2 compartments, the complementary models to the original model will be constructed with similar underlying principles (Fig 2) and one example for its usage can be found in Appendix A.

4.2. Probability function for number of visits in a two-compartment model.

The probability for a drug molecule to be in the central compartment with n times of accomplished visits to the peripheral compartment, given drug is initiated at the central compartment and after an elapsed time t, can be calculated by (4). Its derivations can be found in Appendix B.

$$P_{11}^{V_n}(t) = K_{12}^n K_{21}^n (P_{11}^{(1)}(t) * P_{22}^{(2)}(t))^{*n} * P_{11}^{(1)}(t). \tag{4}$$

Here operator "$*$" represents convolution. Superscript $*n$ is the convolution power of order n. $P_{11}^{(1)}(t)$ and $P_{22}^{2}(t)$ are the corresponding elements of probability function matrices $P^{(1)}(t)$ and $P^{2}(t)$ as defined in the previous section, respectively.

Given drug is initiated at the central compartment and after an elapsed time t, the probability for a drug molecule in the central compartment is the summation of the probabilities for it to be in the central compartment and with exactly i $(i = 0, 1, \ldots, \infty)$ times of accomplished visits to the peripheral compartment. The

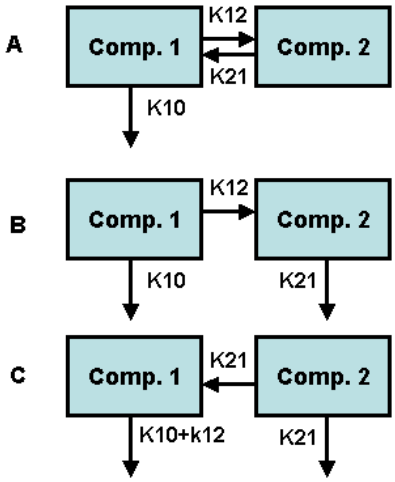

FIGURE 1. The two-compartment model. Compartment one represents the central compartment and compartment two the peripheral compartment. A. The original model. B. Complementary model one. C. Complementary model two. Specification of dosing compartment is not indicated because in a Markovian system, the probability function $P_{ij}(t)$ spontaneously assumes drug is given is compartment i. Note that, the first complementary model is constructed in a way that guarantees all drug molecules in the compartment two will never go to the compartment one. The second complementary model is constructed in a way that guarantees all drug molecules in compartment one will never visit compartment two. With such requirements, the transition coefficient of K21 for both complementary models, originally indicating the transition rate from compartment two to compartment one, have been switched to a transition coefficient indicating the transition rate from compartment two to system exterior.

above statement and its brief proof can be mathematically expressed by (5). Further details can be found in Appendix C.

$$\begin{aligned} P_{11}(t) &= L^{-1}\left(\frac{K_{21}+s}{K_{10}(K_{21}+s)+s(K_{21}+K_{12}+s)}\right) \\ &= L^{-1}(L(\sum_{i=1}^{\infty} P_{11}^{V_i}(t))) = \sum_{i=1}^{\infty} P_{11}^{V_i}(t). \end{aligned} \tag{5}$$

4.3. **PDF for residence time in two-compartment model.** The PDF for a drug molecule to be in the central compartment after an elapsed time t, with 1) n accomplished visits to and 2) a cumulative residence time T in the peripheral

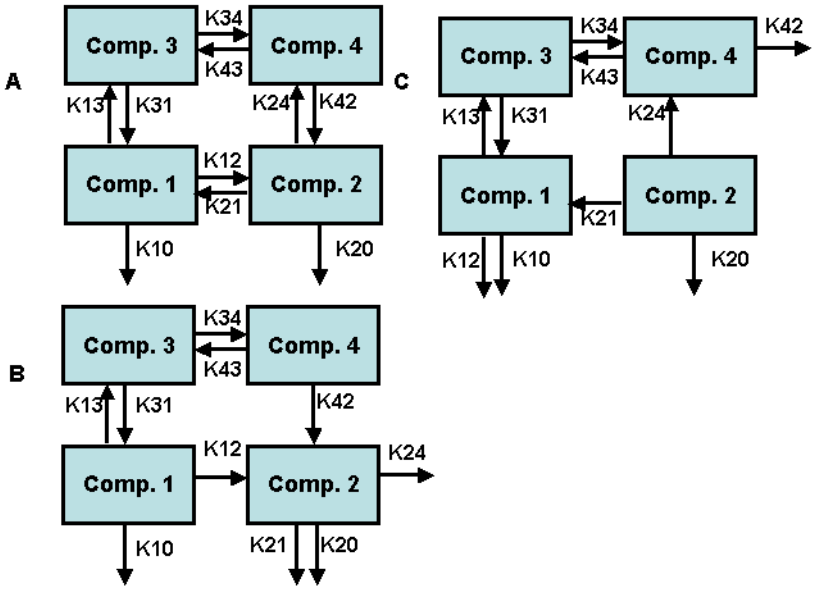

FIGURE 2. The four-compartment model. Compartment one represents the central compartment and compartment two the interested compartment. A. The original model. B. Complementary model one. C. Complementary model two. Note that, the first complementary model is constructed in a way that guarantees all drug molecules going to compartment two for the first time will never go back to the rest of compartments. The second complementary model is constructed in a way that guarantees all drug molecules starting from compartment two will never travel back to compartment two. The use of complementary models is to simplify the overall matrix convolution maneuvers with details illustrated in Appendix A.

compartment can be generalized by (6).

$$P_{11}^{V_n,T=\sum_{i=1}^{n} X_i}(t,T) = (P_{22}^{(2)}(T))^{*n} K_{12}^{n} K_{21}^{n} (P_{11}^{(1)}(t-T))^{*(n+1)}. \tag{6}$$

Here x_i represents the drug residence or retention time in the peripheral compartment during its ith visit. Following immediately from (6), the PDF, for a drug molecule to be in the central compartment and with a cumulative residence time of T in the peripheral compartment during its visits, can be calculated by (7).

$$p_{tt}(t,T) = \sum_{n=1}^{\infty} p_{11}^{V_n,T=\sum_{i=1}^{n} x_i}(t,T). \tag{7}$$

Its derivations can be found in Appendix D.

5. Methods and results for general multi-compartment model.

5.1. Extension to multi-compartment models.

The probability and probability density functions associated with the number of visits to and residence time in another compartment can be easily extended to > 2 compartment models by taking advantages of matrix operations. For convenience, > 2 compartment model will be referred to as multi-compartment model throughout this paper and one of such model is illustrated by Figure 2A. Basically, all of the findings for two-compartment model can be mapped to ones for multi-compartment model with simple modifications. Firstly, the number of visits to the peripheral compartment in two-compartment model will be viewed as number of inter-compartment transitions in multi-compartment system. Secondly, the convolution operation between two functions in two-compartment model will be viewed as convolution operation between two probability function matrices in multi-compartment model. The multi-compartment counterpart to (4), which becomes the probability matrix for a drug molecule that has traveled from compartment k to compartment j (k, $j = 1, \ldots, n$, with n as the number of total compartments) with i inter-compartment transitions after an elapsed time t, is shown by (8)

$$P^i(t) = (R(t) \cdot K')^{*i} * R(t), \tag{8}$$

where,

$$K' = \begin{bmatrix} K_{11} & \ldots & K_{1n} \\ \vdots & \ddots & \vdots \\ K_{n1} & \ldots & K_{nn} \end{bmatrix} - \mathrm{Diag}(K_{11}, \ldots, K_{nn}) = \begin{bmatrix} 0 & \ldots & K_{1n} \\ \vdots & \ddots & \vdots \\ K_{n1} & \ldots & 0 \end{bmatrix},$$

and

$$R(t) = \begin{bmatrix} P'_{11}(t) & \ldots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \ldots & P'_{nn}(t) \end{bmatrix}$$

with $P'_{ii}(t) = \exp\left(-(\sum_{j=1, j\neq i}^{j=n} K_{ij})t\right)$.

Here, i represents i times of inter-compartment transitions. The proof for (8) can be simply handled by mathematical induction and is left out by this paper. The physical interpretation for the elements of $P^i(t)$ is rather simple. That is, if a drug molecule is administered in compartment k, its probabilities in all compartments (from 1 to n), after i inter-compartment transitions and after an elapsed time t, are represented by the kth row vector of $P^i(t)$. Following immediately, the general probability function matrix can calculated by (9)

$$P(t) = \sum_{i=1}^{\infty} P^i(t) = \sum_{i=1}^{\infty} (R(t) \cdot K')^{*i} * R(t). \tag{9}$$

By definition, $P^k_{ij}(t)$ is the element of function matrix $P^k(t)$ in its ith row and jth column with k representing k times of inter-compartment transitions. It gives the probability of a drug molecule that is initiated from the compartment i and destined to the compartment j after an elapsed time t and with exactly k inter-compartment transitions in all of its possible traveling routes.

5.2. **Probability function for joint numbers of visits.** The joint probability for a drug molecule, which has visited > 1 compartments of "study interest" with specified number of visits in each of them, can also be conveniently addressed by matrix convolution operations. In a general multi-compartment model and given drug is initiated at compartment one, the probability function for a drug molecule in compartment one, which has visited compartment two $n2$ times and compartment three $n3$ times after an elapsed time t, can be calculated by (10).

$$P_{11}^{\text{conditions given above}}(t) = \sum K_{1i}K_{ij}\dots K_{kl}\cdot P'_{11}(t)*P'_{ii}(t)*\cdots*P'_{kk}(t)*P'_{11}(t). \quad (10)$$

In (10), $\sum K_{1i}K_{ij}\dots K_{kl}$ corresponds to all possible inter-compartment traveling routes for the drug to initiate from and return to compartment 1 (i.e., $\sum$ (route of $1 \to i \to j \to \cdots \to k \to 1$)) in condition with "2" appearing in the subscripts of these transition coefficients for $2.n2$ times and 3 appearing for $2.n3$ times. Note that, for any arbitrary traveling route, say $1 \to i \to j \to k \to 1$, its corresponding transitions coefficients must be $K_{1i}.K_{ij}.K_{jk}.K_{kl}$ and its corresponding convolution operations must be $P'_{11}(t) * P'_{ii}(t) * P'_{jj}(t) * P'_{kk}(t) * P'_{11}(t)$. The same procedures can be followed to obtain any arbitrary joint probability functions.

5.3. **PDF's for joint residence times in multi-compartment model.** The joint PDF for a drug molecule that has visited > 1 compartments of "study interest", with both a specified number of visit to and a corresponding cumulative residence time in each of them, can also be conveniently addressed by convolution operations. In a general n-compartment ($n > 2$) model and given drug is initiated at compartment one, the PDF for a drug molecule in compartment one, which has visited compartment two exactly $n2$ times with a cumulative residence time $T2$ and compartment three exactly $n3$ times with a cumulative residence time $T3$, can be calculated by (11).

$$\begin{aligned} P_{11}^{\text{conditions given above}}&(t, T2, T3) \\ &= \sum K_{1i}K_{ij}\dots K_{kl}P'_{11}(t-T2-T3)^{*2} * P'_{ii}(t-T2-T3) * \cdots \\ &\quad * P'_{kk}(t-T2-T3).P'_{22}(T2)^{*n2}.P'_{33}(T3)^{*n3}. \end{aligned} \quad (11)$$

In (11), $\sum K_{1i}K_{ij}\dots K_{kl}$ corresponds to all possible inter-compartment traveling routes for a drug molecule to be both initiated from and destined to compartment one in condition with "2" appearing in the subscripts of transition coefficients for $2.n2$ times and 3 appearing for $2.n3$ times. For more general cases, the arbitrarily chosen compartments "two" and "three" in the above example can be replaced by any number of compartments of study interest and the same procedures should be followed to obtain the corresponding joint PDF.

6. **Exponential convolution expansion of probability functions in a linear system.** As illustrated by (9), the probability function for a drug molecule in any compartment can be decomposed to a series of components representing the probabilities for the drug molecule that has made i (an integer ranging from 0 to positive infinity) times of inter-compartment transitions in its traveling route. This type of decomposition will be named as convolution expansion and is illustrated by (12)

$$P(t) = \sum_{i=0}^{\infty} P^i(t). \quad (12)$$

Here, $P^i(t) = (R(t)K')^{*i}R(t)$ as defined in (8). Further derivations can show that each element of the n-by-n matrix $P^n(t)$, after performing convolution operations, is a function expressed as $P^n_{ij}(t) = f(P'_{11}(t), \ldots, P'_{nn}(t), t)$, where $P'_{ii}(t0$ is the same as defined in (8).

In a linear system, each element of $P(t)$ can also be expressed by $P_{ij}(t) = g(P'_{11}(t), \ldots, P'_{nn}(t), t)$, where "$g$" indicates a function. With further derivation, the probability for a drug molecule to be in compartment s, after an elapsed time t and given it is initiated in compartment k, can be calculated by (13)

$$P_{ks}(t) = \sum_{i=1}^{\infty} A_i P'_{ii}(t) = \sum_{i=1}^{\infty} A_i e^{-(\sum_{j=1, j\neq i}^{j=n} K_{ij})t}, \tag{13}$$

where $A_i = \sum_{j=1}^{\infty} a_{ij} t^{j-1}$ (a polynomial function of time) and all a_{ij}'s are constants. The expansion form shown by (13) will be named as Exponential Convolution Expansion. The following example will demonstrate how it works. In a three-compartment model with 1) all compartments are mutually communicative, 2) compartment one as the only compartment of drug elimination, and 3) pharmacokinetic parameters of K12 = 0.5, K13 = 1, K10 = 2.1, K21 = 5, K23 = 2, K31 = 0.8, and K32 = 0.1, the probability for a drug molecule to start from and end in compartment one after an elapsed time t can be described by the tri-exponential (14)

$$P_{11}(t) = 0.13e^{-7.62t} + 0.75e^{-3.38t} + 0.12e^{-0.50}. \tag{14}$$

It is important to note that (14) is obtained by solving the conventional pharmacokinetic differential equation system after proper translation into probabilistic formulas. That is

$$\begin{aligned} d(P_{11}(t))/dt &= -(K_{12} + K_{13})P_{11}(t) + K_{21}P_{12}(t) + K_{31}P_{13}(t) \\ d(P_{12}(t))/dt &= -(K_{21} + K_{23})P_{12}(t) + K_{12}P_{11}(t) + K_{32}P_{13}(t) \\ d(P_{13}(t))/dt &= -(K_{31} + K_{32})P_{13}(t) + K_{13}P_{11}(t) + K_{23}P_{12}(t). \end{aligned}$$

Alternatively, based on (13) that describes Exponential Convolution Expansion, $P_{11}(t)$ can be expanded as the summation of probabilities for a drug molecule with i accomplished inter-compartment transitions ($i = 0, 1, 2, \ldots, +\infty$). The exponential convolution expansion form of $P_{11}(t)$, given i ranging from 0 to 7 and omits the rest, is described by (15)

$$\begin{aligned} P_{11}(t) \approx &(0.95 - 0.53t + 0.0062t^2 + 0.00045t^3)e^{-3.6t} \\ &+ (0.067 - 0.049t + 0.048t^2)e^{-7t} + (-0.025 + 0.051t + 0.010t^2)e^{-0.9t}. \end{aligned} \tag{15}$$

Note that $3.6 = K12 + K13 + K10$, $7 = K21 + K23$, and $0.9 = K32 + K31$ for the magnitudes of the exponential powers in (15). This pattern will always be the case regardless the upper limit values that i assumes, which is demonstrated by (8)). Values of $P_{11}(t)$, calculated by (14) and (15), are plotted against time simultaneously in Figure 3. It graphically demonstrates that exponential convolution expansion perfectly approximates the exact solution. Noteworthy, the PDF for any specified cumulative residence time T in the compartment of "study interest" can also be decomposed into a series of PDF's associated with defined numbers of inter-compartment transitions. This type of expansion has been left out by this paper.

The probabilities associated with numbers of inter-compartment transition are not a monotone function of transition number. That is, elements of $P^n(t)$ are not

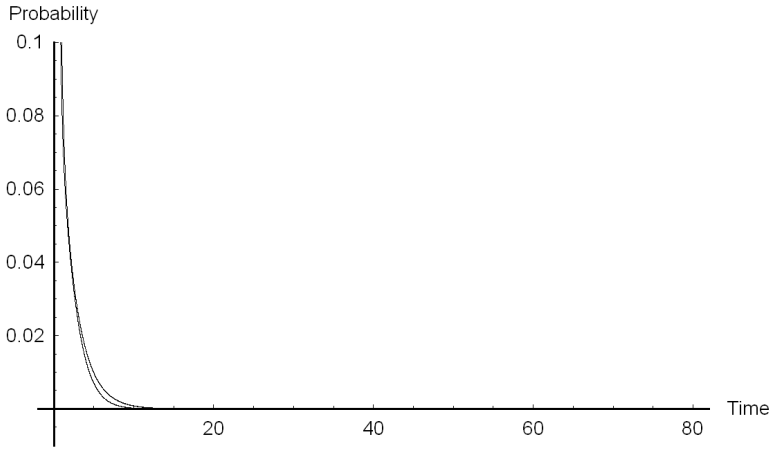

FIGURE 3. Exponential convolution expansion of probability function. Given a drug molecule is administered in compartment one in a three-compartment model, the probability function against time for it to be in compartment one is approximated by exponential convolution expansion. The line on the top and the line on the bottom represent the true probability function and the approximated probability function, respectively.

monotone increasing or decreasing function of n. For example, the probabilities for a drug molecule with 3 and 5 inter-compartment transitions are less than the probabilities for a drug molecule with 4 and 6 transitions in a three-compartmental model, respectively, as shown by Figure 4A. However, for a two-compartment model, the probability for a drug molecule to be in compartment one with bigger number of visits to compartment two is always less, as shown by Figure 5.

The PDF's associated with numbers of inter-compartment transitions are not a monotone function of transition number as well. As shown by Figure 6, the magnitude of densities for a drug molecule to be in compartment one, with defined numbers of visits to and a cumulative residence time T in compartment two, does not monotonely decrease with increasing number of visits. Corresponding to the chosen set of transition coefficients, the density initially increases with increasing number of visits up to the seven and then decreases with increasing number of visits.

7. **Discussion.** The derived methods in this paper provide new approaches to calculate probability and probability density functions for a drug molecule with arbitrary requirements in its residence time and inter-compartment traveling route in a multi-compartment system. In practice, the probability function and the drug concentration can be easily converted to each other. For example, the probability for a drug molecule, to be in the central compartment after an elapsed time t, equals the ratio of drug amount in the central compartment at time t to the total dose administered to the central compartment at time 0 ($C(t).Vd/\text{Dose}$, with Vd as the apparent volume of distribution). It is felt that the number of drug molecules are usually quite large and therefore little concern is given to use pharmacokinetic equations to describe stochastic behavior.

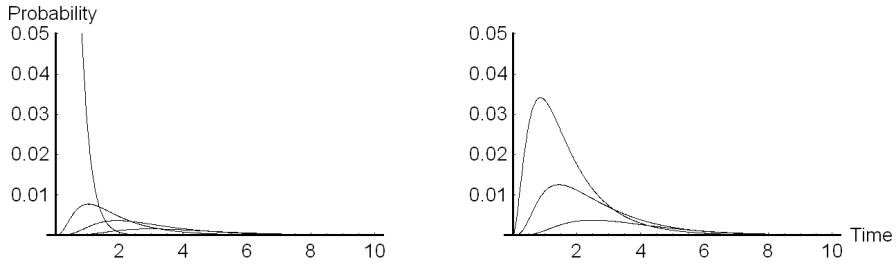

FIGURE 4. Probability function for number of transitions in a three- compartment model. Given a drug molecule is initiated in compartment one in a three-compartment model, the probability functions for it to be in compartment one with specified numbers of inter-compartment transitions in its traveling route are plotted simultaneously. A. Corresponding to unit time 1, the plotted curves from top to bottom represent probability functions for a drug molecule with 0, 3, 5, and 7 inter-compartment transitions in its traveling route, respectively. B. Corresponding to unit time 2, the plotted curves from top to bottom represent probability functions for a drug molecule with 2, 4 and 6 inter-compartment transitions in its traveling route, respectively.

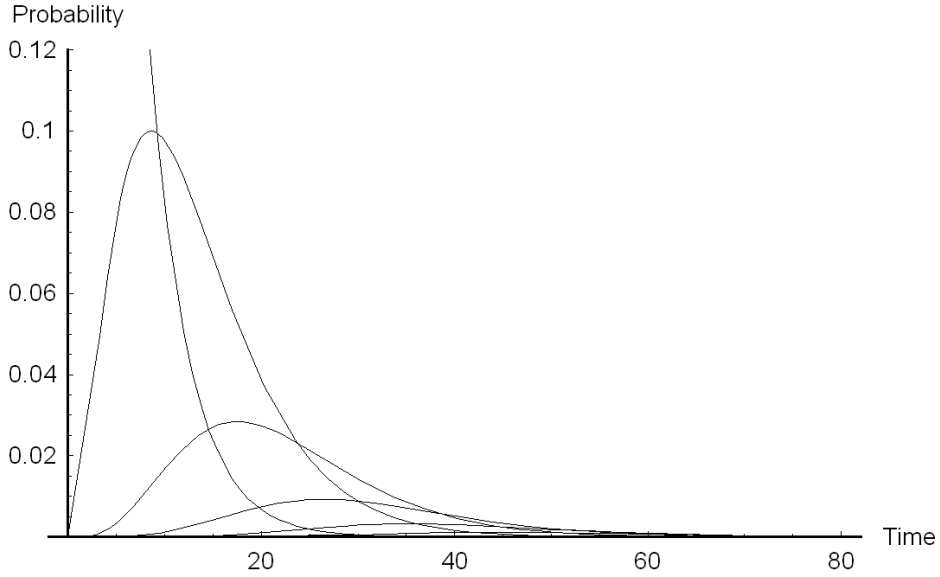

FIGURE 5. Probability function for number of visits (transitions) in a two- compartment model. Given a drug molecule is initiated in compartment one in a two-compartment model, the probability functions against time for it to be in compartment one with specified numbers of visits to compartment two are plotted simultaneously. Corresponding to unit time 10, plotted curves from top to bottom represent probability functions for a drug molecule with 0, 1, 2, 3, 4, and 5 visits to compartment two.

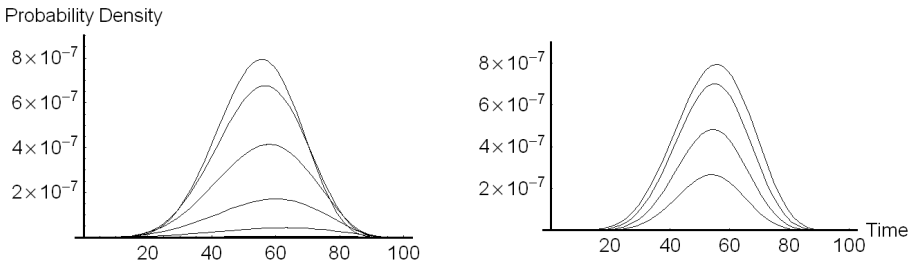

FIGURE 6. PDF for cumulative residence time. Given a drug molecule is initiated in compartment one in a two-compartment model, the probability densities for it to be in compartment one with specified number of visits to and a common cumulative residence time T ($T = 50$ time units) in compartment two are plotted simultaneously. Curves in the left panel, from bottom to top, represent the density functions for a drug molecule with 1, 2, 3, 4, 5, 6, and 7 accomplished visits to compartment two, respectively; Curves in the right panel, from top to bottom, represent the density functions for a drug molecule with 7, 8, 9, and 10 accomplished visits to compartment two, respectively.

Compared with using saddlepoint approximation, using convolution expansion to capture the residence time distribution gains flexibility and convenience. Saddlepoint approximations have been the conventional tool for approximating the density or tail probability using the cumulant generating function (CGF). It has been shown to yield good accuracy when estimating very small tail probabilities or densities because its error rate is directly proportional to the magnitude of the density or distribution function. However, when being used to approximate the probability density function for cumulative residence time, saddlepoint approximation is computationally intensive. It involves a broad spectrum of procedures such as producing the cumulant generating function, solving partial differential equations, obtaining determinants of the covariance matrix composed of the second derivatives of CGF [21]. In semi-Markovian cases, Cofactor rule needs to be engaged to extrapolate this approximation approach from a two-compartment model to a general multi-compartment model. In comparison, the convolution expansion approach, as shown by this paper, can be conveniently carried out to describe the residence time distribution in any interested compartment, either by one visit or cumulatively by many visits, jointly or not jointly studied with residence time distributions in other compartments, and with or without any specified traveling route. Convolution calculation is the main computational requirement to implement this approximation method. Finally, the convolution expansion of probability or density functions, as summations of probability or density functions associated with all possible traveling routes, are engaged with physical meanings and their calculations can be facilitated with corresponding Laplace Transformations, a technique that culminated in works of Benet & Turi [2] and Nakashima & Benet [16] to solve pharmacokinetic differential equations.

Convolution expansion of probability and probability density functions is a unique and powerful methodological extension to conventional approximation algorithms

used in pharmacokinetics-pharmacodynamics. In situations when the number of compartments in a linear system is too big to allow obtaining closed form solutions, the exponential convolution expansion technique can be exploited and significantly reduce the computation time by providing an "approximated" closed form solution, as manifested by equation (9). In addition, convolution expansion is not a type of expansion similar to Taylor Series. It features itself in the following manners. Firstly, it does not have the problem of error propagation associated with the conventional numerical approximation methods. Error propagation can happen when numerically solving differential equations and can pose a problem when the dependent variable corresponds to a independent variable that is far from its origin, or numerically calculate a drug concentration corresponding to a large time. Secondly, both its approximation accuracy and precision are controlled by "convolutionally" expanding the probability or drug concentration profile function up to a component associated with a sufficiently high number of inter-compartment transitions. Thirdly, approximation based on convolution expansion can be used to predict probabilities and densities corresponding to a time beyond the study range, where approximations based on Taylor Series Expansion will fail.

The probability functions for a drug molecule with certain accomplished visits to other compartments also provide more flexible options to address a broad range of pharmacodynamic patterns (Fig 4-5). It can potentially become the alternatives to the conventionally used pharmacodynamic models, such as effect-compartment model proposed by Sheiner et al. [17] and indirect-response models proposed by Dayneka et al. [4] and Krzyzanski & Jusko [8], to model drug efficacy and safety endpoints. For example, when the peak drug concentration precedes the maximum effects, the effects-vs-concentration loop becomes counterclockwise and a hysteresis pattern of drug action is identified. Such delayed effect-concentration relationship has been conventionally described by the effect-compartment model or by the indirect-response model when the effect delay can not be addressed by a linear system. Alternatively, it can be modeled by associating the extent of drug efficacy or toxicity positively to the number of drug visits to the physiologically relevant compartment, or empirically to the peripheral compartment. That is because the probability function for a drug molecule with higher number of visits to other compartment/compartments usually has longer delays for its peak value. With this alternative, non-linearity assumptions for transfer rates associated with the effect compartment for over-delayed effects can be avoided. When peak drug concentration precedes the maximum effects, the effect-vs-concentration loop becomes clockwise and a proteresis pattern of drug action is identified. Proteresis is rare in pharmacodynamics and it is sometimes explained by the development of drug tolerance due to down regulation or reduction of drug affinity or accumulation of antagonist metabolite. Nevertheless, drug tolerance can be modeled with a positive relationship to the number of drug visits to the physiologically relevant compartment, or empirically to the peripheral compartment. The same concept can be used to model drug safety endpoints. Noteworthy, the PDF's for drug residence times also assume a broad range of dynamic patterns against time and can also be exploited to model various hysteresis and proteresis patterns, depending on the understanding of pharmacological actions.

In summary, this paper originally defined matrix convolution and used it to capture probability and probability density functions for a drug molecule with any defined inter-compartment traveling route and number of visits to other compartment,

in or not in conjunction with residence times in physiologically related compartments. It also originally identified that the conventional pharmacokinetic formula to describe drug concentration can be de- composed by Convolution Expansion. The in-depth translation of stochastic concepts and further development of those concepts can feed into various pharmacokinetic and pharmacodynamic needs and opens up a new territory for pharmacokinetists and modeling and simulation experts to explore. Their potential usages can be very rewarding.

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Appendix A. **Usage of complementary models to calculate specific probability and probability density functions.** In practice, the calculation of any interested probability functions can be greatly simplified by taking advantage of probability matrices inferred from the two complementary models. One example is shown by Figure 2 where compartment one is chosen as the drug-dosing compartment and compartment two as the interested peripheral compartment. For instance, it is assumed that the probabilities for a drug molecule to be in compartments one and four at time t who has visited compartment two exactly n times during travel is of research interest. Based on the first complementary model (Figure 2B), the probability for a drug molecule, who starts from compartment one and ends in compartment one or four after an elapsed time t without paying any visit to compartment two, is $P_{11}^{(1)}(t)$ or $P_{14}^{(1)}(t)$, respectively. Based on the second complementary model (Figure 2C), the probability for a drug molecule, who starts from compartment two and ends in compartment two after an elapsed time t without paying any visit to compartment one or four, is $P_{22}^{(2)}(t)$. In a system with constant transition coefficients and given drug is initiated in compartment one, the probabilities for it to be in compartments one and four with n visits to compartment two during travel can be calculated by (A1)

$$\begin{aligned}&(P_{11}^{n \text{ visits to comp.2}}(t), P_{14}^{n \text{ visits to comp.2}}(t))\\ &= (P_{11}^{(1)}(t), P_{14}^{(1)}(t)) * \begin{bmatrix} K_{12}K_{21} & K_{12}K_{24} \\ K_{42}K_{21} & K_{42}K_{24} \end{bmatrix}^{n} * (P_{22}^{(2)}(t))^{*n} \begin{bmatrix} P_{11}^{(1)}(t) & P_{14}^{(1)}(t) \\ P_{41}^{(1)}(t) & P_{44}^{(1)}(t) \end{bmatrix}^{*n}\\ &= (P_{11}^{(1)}(t), P_{14}^{(1)}(t)) * (AP_{22}^{(2)}(t)P)^{*n},\end{aligned} \tag{A1}$$

where, $A = \begin{bmatrix} K_{12}K_{21} & K_{12}K_{24} \\ K_{42}K_{21} & K_{42}K_{24} \end{bmatrix}$, $P = \begin{bmatrix} P_{11}^{(1)}(t) & P_{14}^{(1)}(t) \\ P_{41}^{(1)}(t) & P_{44}^{(1)}(t) \end{bmatrix}$, and the calculated probabilities are in a row vector. If the PDF of a drug molecule in compartments one and four that not only has paid n visits to compartment two but also had sojourned with a cumulative residence time T is in need, the above expression can be simply modified to (A2).

$$\begin{aligned}&(P_{11}^{n \text{ visits to comp.2 with residence time } T}(t,T), P_{14}^{n \text{ visits to comp.2 with residence time } T}(t,T))\\ &\qquad = P_{22}^{(2)}(T)^{*n} . ((P_{11}^{(1)}(t-T), P_{14}^{(1)}(t-T))A^{n}) * P(t-T)^{*n}.\end{aligned} \tag{A2}$$

Noteworthy, (A1) is originated from (8). (A2) is derived from (A1) by following rules as discussed in Appendix E.

Appendix B. **Probability function for number of visits in two-compartment model.** Given drug is initiated in compartment one, $X_{11}^{V_i}(t)$ and $P_{11}^{V_i}(t)$ are used to denote the amount and probability, respectively, for drug molecules at compartment one that have visited the compartment of "study interest" exactly i times after an elapsed time t. The compartment of "study interest" is compartment two or the peripheral compartment in this case. At time t, the fraction of the total administered drug amount or the probability for a drug molecule in compartment one (the central compartment in terminology of Pharmacokinetics), that has visited the compartment two (the peripheral compartment) exactly once, will be researched first. Between time t and time $t+\Delta t$, the amount of drug (ΔAMT) that is traveling to compartment two for the first time can be described by (A3).

$$\Delta\text{AMT} = \text{Dose}P_{11}^{(1)}(t)K_{12}\Delta t. \tag{A3}$$

It is assumed that the drug molecule is initiated from compartment two. Based on the second complementary model, the probability function, for this drug molecule to be residing in compartment one without revisiting compartment two, is denoted by $P_{21}^{(2)}(t)$. $X_{11}^{V_1}(t)$ can be calculated by (A4).

$$\begin{aligned} X_{11}^{V_1}(t) &= \text{Dose}P_{11}^{V_1}(t) = \int_0^t d\text{AMT}P_{21}^{(2)}(t) = \int_0^t \text{Dose } P_{11}^{(1)}(tt)K_{12}P_{21}^{(2)}(t-tt)dtt \\ &= \text{Dose}K_{12}P_{11}^{(1)}(t) * P_{21}^{(2)}(t). \end{aligned} \tag{A4}$$

Here, operator $*$ indicates operation of convolution. Further derivation on (A4) leads to (A5).

$$X_{11}^{V_t}(t) = \text{Dose}K_{12}K_{21}P_{11}^{(1)}(t) * P_{22}^{(2)}(t) * P_{11}^{(1)}(t). \tag{A5}$$

It means, the probability of a drug molecule in central compartment that has traveled to compartment two exactly once, given drug is initiated in compartment one and after an elapsed time t, can be shown by (A6).

$$P_{11}^{V_1}(t) = K_{12}P_{11}^{(1)}(t) * P_{21}^{(2)}(t) = K_{12}K_{21}P_{11}^{(1)}(t) * P_{22}^{(2)}(t) * P_{11}^{(1)}(t). \tag{A6}$$

The probability for a drug molecule, who is currently at the central compartment and has visited compartment two exactly twice given the same condition as for (A6), can be further derived as shown by (A7).

$$\begin{aligned} P_{11}^{V_2}(t) &= K_{12}P_{11}^{V_1}(t) * P_{21}^{(2)}(t) = K_{12}(K_{12}P_{11}^{(1)}(t)P_{21}^{(2)}(t)) * P_{21}^{(2)}(t) \\ &= K_{12}^2P_{11}^{(1)}(t) * P_{21}^{(2)}(t) * P_{21}^{(2)}(t) \\ &= K_{12}^2K_{21}^2\left(P_{11}^{(1)}(t) * P_{22}^{(2)}(t)\right)^{*2} * P_{11}^{(1)}(t) \end{aligned} \tag{A7}$$

Here superscript $*2$ is the convolution power of order 2. In view of the patterns as revealed by (A6) and (A7) and by principle of mathematical induction, $P_{11}^{V_n}(t)$can be calculated by (A8).

$$\begin{aligned} P_{11}^{V_n}(t) &= K_{12}P_{11}^{V_{n-1}}(t) * P_{21}^{(2)}(t) = K_{12}(K_{12}P_{11}^{(1)}(t) * P_{21}^{(2)}(t)) * P_{21}^{(2)}(t) \\ &= K_{12}^nP_{11}^{(1)}(t) * \left(P_{21}^{(2)}(t)\right)^{*n} \\ &= K_{12}^nK_{21}^n\left(P_{11}^{(1)}(t) * P_{22}^{(2)}(t)\right)^{*n} * P_{11}^{(1)}(t) \end{aligned} \tag{A8}$$

Appendix C. **Proof of decomposition of probability function in two compartment model.**

Proof. In the case of a two-compartment linear model as depicted by Figure 1A, Laplace transform of $P_{11}^{V_n}(t)$ yields (A9).

$$L(P_{11}^{V_n}(t)) = \frac{K_{12}^n K_{21}^n}{(K_{10}+K_{12}+s)^{n+1}(K_{21}+s)^n}. \tag{A9}$$

Summing up all of the Laplace transforms of $L(P_{11}^{V_i}(t))$'s $(i = 0, 1, \ldots, \infty)$ yields results as shown by (A10).

$$\begin{aligned}\sum_{i=1}^{\infty} L(P_{11}^{V_i}(t)) &= \sum_{i=0}^{\infty} \frac{K_{12}^i K_{21}^i}{(K_{10}+K_{12}+s)^{i+1}(K_{21}+s)^i} \\ &= \frac{1}{(K_{10}+K_{12}+s)} \sum_{i=0}^{\infty} \left(\frac{K_{12}K_{21}}{(K_{10}+K_{12}+s)(K_{21}+s)} \right)^i \\ &\overset{a\leq 1}{=} \frac{1}{(K_{10}+K_{12}+s)} \left(\frac{1}{1-\frac{K_{12}K_{21}}{(K_{10}+K_{12}+s)(K_{21}+s)}} \right) \\ &= \frac{K_{21}+s}{K_{10}(K_{12}+s)+s(K_{12+}K_{21}+s)}.\end{aligned} \tag{A10}$$

In derivations shown in (A10), $a = \frac{K_{12}K_{21}}{(K_{10}+K_{12}+s)(K_{21}+s)}$. The results above verify that the $\sum_{i=1}^{\infty} L(P_{11}^{V_i}(t))$ is exactly the Laplace transform of the drug concentration in the central compartment normalized by its initial value, as obtained by solving deterministic differential equations shown in most pharmacokinetic textbooks. It means, the probability for a drug molecule in the central compartment at time t, given drug is initiated at the central compartment, is the summation of the probabilities for it to have exactly i times of accomplished visits to the peripheral compartment $(i = 0, 1, \ldots, \infty)$. This statement can be mathematically expressed by (A11).

$$\begin{aligned}P_{11}(t) &= L^{-1}\left(\frac{K_{21}+s}{K_{10}(K_{12}+s)+s(K_{12+}K_{21}+s)} \right) = L^{-1}\left(L\left(\sum_{i=1}^{\infty} (P_{11}^{V_i}(t)) \right) \right) \\ &= \sum_{i=1}^{\infty} P_{11}^{V_i}(t).\end{aligned} \tag{A11}$$

In general, the probability function against time for a drug molecule to be in any chosen compartment can be decomposed into the summation of a series of probabilities for that drug molecule to be with defined numbers of visits to other compartments. □

Appendix D. **PDF for residence time in two-compartment model.** Given a drug molecule is initiated in the central compartment, the probability function for it to be in the central compartment after an elapsed time t with exactly one accomplished visit to and a residence time of $> T$ in the peripheral compartment

can be addressed by (A12).

$$P_{11}^{V_1}(t,T) = \int_0^T \int_0^{t-TT} P_{11}^{(1)}(tt)K_{12}dttP_{22}^{(2)}(TT)K_{21}dTTP_{11}^{(2)}(t-TT-tt) \quad \text{(A12)}$$

$$= \int_0^T \left[\int_0^{t-TT} P_{11}^{(1)}(tt)K_{12}P_{22}^{(2)}(TT)K_{21}P_{11}^{(2)}(t-TT-tt)dtt\right] dTT$$

$$= \int_0^T K_{12}K_{21}P_{22}^{(2)}(TT)\left[\int_0^{t-TT} P_{11}^{(1)}(tt)P_{11}^{(2)}(t-TT-tt)dtt\right] dTT$$

$$= \int_0^T K_{12}K_{21}P_{22}^{(2)}(TT)\left[P_{11}^{(1)}(t-TT) * P_{11}^{(2)}(t-TT)\right] dTT$$

The corresponding PDF with regard to T is derived by (A13).

$$p_{11}^{V_1}(t,T) = \frac{dP_{11}^{V_1}(t,T)}{dT} = K_{12}K_{21}P_{22}^{(2)}(T)(P_{11}^{(1)}(t-T) * P_{11}^{(2)}(t-T)) \quad \text{(A13)}$$

$$\overset{P_{11}^{(1)}(t-T)=P_{11}^{2}(t-T)}{=} K_{12}K_{21}P_{22}^{(2)}(T)(P_{11}^{(1)}(t-T))^{*2}.$$

Notice that in the above equation, uppercase P is used to represent probability function. Lowercase p is used to represent PDF. $P_{11}^{V_1}(t,T)$ indicates the probability for a drug molecule, which starts from compartment one and return to compartment one with a residence time of $< T$ during its only visit in compartment two, after an elapsed time t. With simple algebraic manipulation, the PDF for a drug molecule to be in the central compartment after an elapsed time t, with two accomplished visits to the peripheral compartment and a residence time of x and y during the first and second visit respectively, can be derived as shown by (A14).

$$P_{11}^{V_2}(t,x,y) = K_{12}^2K_{21}^2P_{11}^{(1)}(t-x-y)^{*3}P_{22}^{(2)}(x)P_{22}^{(2)}(y). \quad \text{(A14)}$$

With constraint of $T = x + y$, (A14) becomes (A15).

$$P_{11}^{V_2}(t,T=x+y) = \int_0^T K_{12}^2K_{21}^2P_{11}^{(1)}(t-T)^{*3}P_{22}^{(2)}(x)P_{22}^{(2)}(T-x)dx \quad \text{(A15)}$$

$$= \int_{x=0}^{x=t} P_{22}^{(2)}(x)P_{22}^{(2)}(T-x)dxK_{12}^2K_{21}^2P_{11}^{(1)}(t-T)^{*3} \quad \text{(A16)}$$

$$= P_{22}^{(2)}(T) * P_{22}^{(2)}(T)K_{12}^2K_{21}^2P_{11}^{(1)}(t-T)^{*3}. \quad \text{(A17)}$$

Given a drug molecule is initiated in the central compartment, (A15) is the PDF for it to be in the central compartment after an elapsed time t, with two accomplished visits to and a cumulative residence time T in the peripheral compartment. In view of patterns as revealed by (A14) and (A15) and by principle of mathematical induction, the PDF for a drug molecule to be in the central compartment after an elapsed time t, with n accomplished visits to and with a cumulative residence time T in the peripheral compartment can be generalized by (A18).

$$P_{11}^{V_n,T=\sum_{i=1}^{n}x_i}(t,T) = \left(P_{22}^{(2)}(T)\right)^{*n}K_{12}^nK_{21}^nP_{11}^{(1)}(t-T)^{*(n+1)}. \quad \text{(A18)}$$

Appendix E. **Linkage between probability and probability density functions.** For each element in the n-by-n probability matrix given by (8), it can be decomposed to be a function of $P'_{ii}(t)$'s ($i = 1, \ldots, n$, as defined in (8)) and transition coefficients (the elements of matrix K). By definition, $P_{ij}^k(t)$ is the probability function describing the probability for a drug molecule to travel from compartment

i to compartment j with k times of inter-compartment transitions after an elapsed time t. As a rule of thumb, converting the probability function for a drug molecule, with any defined traveling route or routes, to its corresponding PDF for a drug molecule with not only the same inter-compartment traveling route or routes but also a combination of defined residence times in its visited compartments (e.g., denoted by $P_{ij}^{\#\text{ of transitions},T2\text{ in comp.2},T3\text{ in comp.3}}$), can be conveniently carried out by performing the following four conversion steps. For instance, it is assumed that $P'_{ij}(t)$'s $(i = x, y, \ldots)$ correspond to the compartments of "study interest" (e.g., compartments two and three in (11)); $P'_{jj}(t)$'s $(j = v, w, \ldots)$ correspond to the rest of compartments (e.g., compartments other than two and three in (11)). For illustration purpose, the case represented by (10) and (11) will be used as an example.

Step 1: collect all $P'_{jj}(t)$'s in (10) and keep their sequential order of convolution operations.

Step 2: for each $P'_{ii}(t)$, collect all of its terms in (10) and group them into one "new" component with convolution power of order k; k is the number of $P'_{ii}(t)$ collected (i.e., $P'_{22}(T2)^{*n2}$ and $P'_{33}(T3)^{*n3}$ in (11)).

Step 3: use ordinary product operations as denoted by "." (1) between any pair of the "new" components (i.e., $P'_{22}(t)^{*n2}$ and $P'_{33}(t)^{*n3}$) and (2) between any of these "new" components and collected $P'_{jj}(t)$'s,.

Step 4: substitute time "t" in the "new" components with the specified cumulative residence times (i.e., $P'_{22}(t)^{*n2}$ to $P'_{22}(T2)^{*n2}$ and $P'_{33}(t)^{*n3}$ to $P'_{33}(T3)^{*n3}$); substitute time "t" in the $P'_{jj}(t)$'s with "$t-T$". T is the sum of cumulative residence times in all of the compartments of "study interest" (e.g., $T = T2+T3$ in (11)).

A four-compartment model, as shown by Figure 2A, can be used for illustration. For instance, the PDF for a drug molecule in compartment one that has visited compartment two and three exactly once with cumulative residence times of $T2$ and $T3$ respectively after an elapsed time t, given drug is administered at compartment one and has made three inter-compartment transitions can be calculated by

$$p_{11}^{3,T2\text{ in comp }2,T3\text{ in comp }3}(t, T2, T3) = (K_{12}K_{23}K_{31}+ K_{13}K_{32}K_{21})P'_{11}(t - T2 - T3)^{*2}P'_{22}(T2)P'_{33}(T3).$$

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