

## NONCOMPARTMENTAL ANALYSIS

### Deficiencies of compartmental analysis:

1. Lack of meaningful physiological basis for derived parameters.
2. Lack of rigorous criteria to determine # of compartments necessary to describe disposition.
3. Lack of ability to elucidate organ specific elimination.
4. Inability to relate derived parameters to quantifiable physiological parameters.
5. Inability to predict impact of pathophysiology.
6. Inability to provide insight into mechanism of drug-drug and drug-nutrient interactions.
7. Highly sensitive to sampling frequency.

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## GENERAL PRINCIPLES OF STATISTICAL MOMENTS

**MOMENT:** A mathematical description of a discrete distribution.

### STATISTICAL MOMENTS:

- Utilized in chemical engineering to describe flow data
- First applied to biological systems by Perl and Samuel in 1969 to describe the kinetics of cholesterol

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## Examples of Statistical Moment Usage

	<u>In statistics</u>	<u>In physics</u>
$M_0$	<b>N</b>	weight
$M_1$	$\bar{X} = \frac{\sum X_i}{N}$ (mean)	Center of mass
$M_2$	$\sigma^2 = \frac{\sum (X_i - \bar{X})^2}{N}$ (variance)	Moment of inertia
$M_3$	$\gamma_1 = \frac{\sum (X_i - \bar{X})^3}{(\sigma^2)^{3/2} N}$ (skewness)	
$M_4$	$\gamma_2 = \frac{\sum (X_i - \bar{X})^4}{(\sigma^2)^2 N}$ (kurtosis)	

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In statistics, the mean is a measure of a sample mean and is actually an *estimate* of the true population mean. In pharmacokinetics, we can calculate the moment of the theoretical probability density function (i.e., the solution of a differential equation describing the plasma concentration time data), or we can calculate moments from measured plasma concentration-time data. These curves are referred to as *sample moments* and are estimates of the true curves.

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Assume a theoretical relationship of  $C(t)$  as a function of time. The *non-normalized* moments,  $S_r$ , about the origin are calculated as:

$$S_r = \int_0^{\infty} t^r C(t) dt \quad (r = 0, 1, 2, \dots, m)$$

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Non-normalized moments

Kinetic parameter

$$S_0 = \int_0^{\infty} C(t) dt$$

**AUC**  
Area under the curve

$$S_1 = \int_0^{\infty} tC(t) dt$$

**AUMC**  
Area under the moment curve

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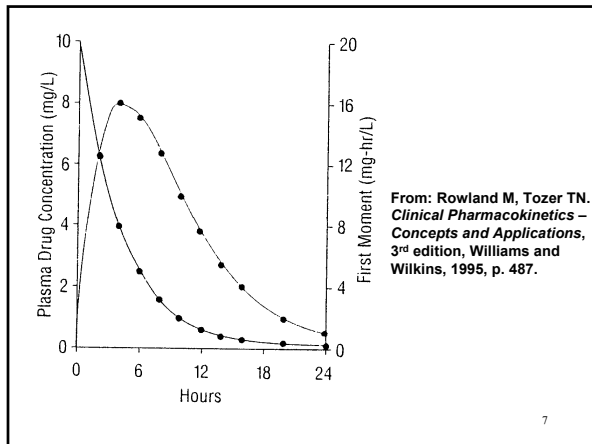
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**Normalized moments**                      **Kinetic parameter**

**First moment:**

$$\frac{S_1}{S_0} = \frac{\int_0^{\infty} tC(t)dt}{\int_0^{\infty} C(t)dt} = \frac{AUMC}{AUC}$$

**MRT**  
Mean residence time

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**AREA DETERMINATION**

**A. Integration of Specific Function**

- Must elucidate the specific function
- Influenced by the quality of the fit

$$AUC = \sum \frac{C_i}{\lambda_i} \quad \text{example: } AUC = \frac{C_1}{\lambda_1} + \frac{C_2}{\lambda_2}$$

$$AUMC = \sum \frac{C_i}{\lambda_i^2} \quad \text{example: } AUMC = \frac{C_1}{\lambda_1^2} + \frac{C_2}{\lambda_2^2}$$


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**B. Numerical Integration**

- 1. Linear trapezoidal
- 2. Log trapezoidal

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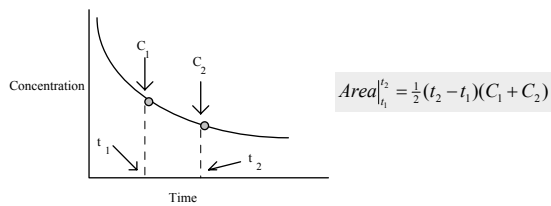
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**B. Numerical Integration**

- 1. Linear trapezoidal



$$Area_{t_0}^{t_n} = \frac{1}{2}(C_1 + C_2)(t_2 - t_1) + \frac{1}{2}(C_2 + C_3)(t_3 - t_2) + \dots + \frac{1}{2}(C_{n-1} + C_n)(t_n - t_{n-1})$$

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**B. Numerical Integration**

- 1. Linear trapezoidal

**Advantages:** Simple (can calculate by hand)

**Disadvantages:**

- Assumes straight line btwn data points
- If curve is steep, error may be large
- Under or over estimate depends on whether curve is ascending or descending

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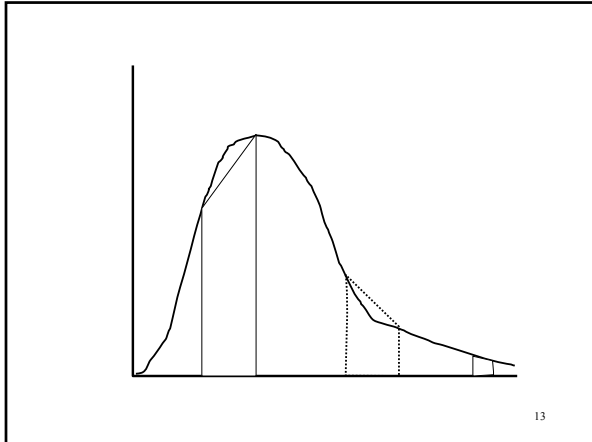
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**B. Numerical Integration**

1. Linear trapezoidal
2. Log trapezoidal

$$Area \Big|_{t_1}^{t_2} = \frac{(C_1 - C_2)(t_2 - t_1)}{\ln C_1 - \ln C_2}$$

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**B. Numerical Integration**

1. Linear trapezoidal
2. Log trapezoidal

$$Area \Big|_{t_1}^{t_2} = \frac{(C_1 - C_2)(t_2 - t_1)}{\ln C_1 - \ln C_2}$$

<p><b>Advantages:</b></p> <ul style="list-style-type: none"> <li>•Hand calculator</li> <li>•Very accurate for mono-exponential</li> <li>•Very accurate in late time points where interval btwn points is substantially increased</li> </ul>	<p><b>Disadvantages:</b></p> <ul style="list-style-type: none"> <li>•Limited application</li> <li>•May produce large errors on an ascending curve, near the peak, or steeply declining polyexponential curve</li> </ul>
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**B. Numerical Integration**

1. Linear trapezoidal
2. Log trapezoidal
3. Extrapolation to infinity

$$AUC|_{t_n}^{\infty} = \int_{t_n}^{\infty} C dt = \frac{C_n}{\lambda_z} \quad \text{Assumes log-linear decline}$$

$$AUMC|_{t_n}^{\infty} = \frac{C_n}{\lambda_z^2} + \left( t_n \times \frac{C_n}{\lambda_z} \right)$$

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$$AUC|_0^{\infty} = AUC|_0^{t_n} + \frac{C_n}{\lambda_z}$$

$$AUMC|_0^{\infty} = AUMC|_0^{t_n} + \frac{C_n}{\lambda_z^2} + \left( t_n \times \frac{C_n}{\lambda_z} \right)$$

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<u>Time (hr)</u>	<u>AUC Determination</u>		<u>AUMC Determination</u>	
	<u>C (mg/L)</u>	<u>Area (mg-hr/L)</u>	<u>C x t (mg/L)(hr)</u>	<u>Area (mg-hr<sup>2</sup>/L)</u>
0	2.55	-	0	-
1	2.00	2.275	2.00	1.00
3	1.13	3.13	3.39	5.39
5	0.70	1.83	3.50	6.89
7	0.43	1.13	3.01	6.51
10	0.20	0.945	2.00	7.52
18	0.025	0.900	0.45	9.80
		<u>Total 10.21</u>		<u>37.11</u>

$$AUC|_0^{t_{18}} = 10.21 \text{ mg} \cdot \text{hr} / \text{L}$$

$$AUMC|_0^{t_{18}} = 37.11 \text{ mg} \cdot \text{hr}^2 / \text{L}$$

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$$AUC_0^\infty = AUC_0^{t_{18}} + \frac{C_{18}}{\lambda_z}$$

$$AUC_0^\infty = 10.21 \text{ mg} \cdot \text{hr} / \text{L} + \frac{0.025 \text{ mg} / \text{L}}{0.26 \text{ hr}^{-1}}$$

$$AUC_0^\infty = 10.31 \text{ mg} \cdot \text{hr} / \text{L}$$

$$AUMC_0^\infty = AUMC_0^{t_{18}} + \frac{t_{18} C_{18}}{\lambda_z} + \frac{C_{18}}{\lambda_z^2}$$

$$AUMC_0^\infty = 37.11 \text{ mg} \cdot \text{hr}^2 / \text{L} + \frac{0.45 \text{ mg} \cdot \text{hr} / \text{L}}{0.26 \text{ hr}^{-1}} + \frac{0.025 \text{ mg} / \text{L}}{(0.26 \text{ hr}^{-1})^2}$$

$$AUMC_0^\infty = 39.21 \text{ mg} \cdot \text{hr}^2 / \text{L}$$

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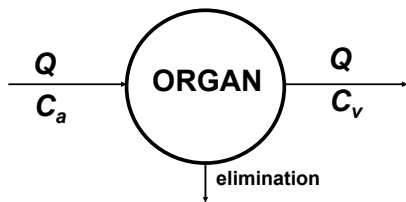
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### CLEARANCE CONCEPTS



If  $C_v < C_a$ , then it is a clearing organ

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$$\text{Rate In} = QC_a$$

$$\text{Rate Out} = QC_v$$

$$\begin{aligned} \text{Rate of elimination} &= QC_a - QC_v \\ &= Q(C_a - C_v) \end{aligned}$$

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**Extraction Ratio:**

Ratio of the rate of xenobiotic elimination and the rate at which xenobiotic enters the organ.

$$E = \frac{\text{Rate of Elimination}}{\text{Rate of Entry}}$$
$$E = \frac{Q(C_a - C_v)}{QC_a} = \frac{C_a - C_v}{C_a}$$

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$$CL = QE = \frac{Q(C_a - C_v)}{C_a}$$

**Clearance:**

The volume of blood from which all of the drug would appear to be removed per unit time.

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**Relationship between CL & Q**

Since  $CL = QE$ , if  $E \sim 1$ :  
 $CL \rightarrow Q$

Perfusion rate-limited clearance

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## Total Clearance

**Total (systemic) Clearance:**

$$CL_T = \frac{dX/dt}{C} = \frac{\text{Elimination rate}}{\text{concentration in blood}}$$

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## Total Clearance

**Total (systemic) Clearance:**

$$CL_T = \frac{dX/dt}{C} = \frac{\text{Elimination rate}}{\text{concentration in blood}}$$

Integrating from  $0 \rightarrow \infty$ ,

$$CL_T = \frac{\int_0^{\infty} \frac{dX}{dt} dt}{\int_0^{\infty} C dt}, \text{ where } \int_0^{\infty} \frac{dX}{dt} dt = \text{total amt eliminated (Div)}$$

$$\text{and } \int_0^{\infty} C dt = AUC$$

$$\text{Therefore } CL_T = \frac{D_{iv}}{AUC|_0^{\infty}}$$

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## Additivity of clearance

**Rate of elimination = Rate of Renal Excretion +  
Rate of Hepatic Metabolism**

**Dividing removal rate by incoming concentration:**

$$\frac{\text{Rate of Elimination}}{C_a} = \frac{\text{Rate of Renal Excretion}}{C_a} + \frac{\text{Rate of Hepatic Metabolism}}{C_a}$$

**Total Clearance = Renal Clearance + Hepatic Clearance**

$$CL_T = CL_R + CL_H$$

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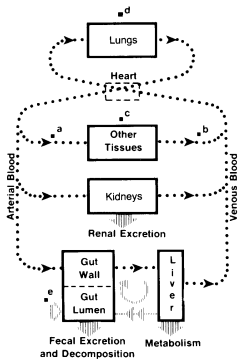
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**Exception: sig. pulmonary elimination**



From: Rowland M, Tozer TN. *Clinical Pharmacokinetics – Concepts and Applications*, 3<sup>rd</sup> edition, Williams and Wilkins, 1995, p. 12.

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$$f_R = \frac{X_u^\infty}{D_{iv}}, \quad CL_R = CL_T \times f_R$$

100 mg drug administered to a volunteer resulted in 10 mg excreted in urine unchanged:

$$f_R = \frac{X_u^\infty}{D_{iv}} = \frac{10 \text{ mg}}{100 \text{ mg}} = 0.1$$

$$CL_R = CL_T \times f_R = \frac{D_{iv}}{AUC} \times f_R$$

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**Application of Clearance Concepts**

*Prediction of the effect of pathophysiological changes*

A new antibiotic has just been introduced onto the market. Currently, there are no studies examining the effect of renal disease on the pharmacokinetics of this compound. Is dosage adjustment necessary for this drug when used in pts with renal failure? How can we gain some insight into this question? A study in normal volunteers was recently published and the following data was included (mean):

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### Application of Clearance Concepts

*Prediction of the effect of pathophysiological changes*

**$CL_T = 1.2 \text{ L/hr}$     $Div = 500 \text{ mg}$   
Amount in urine unchanged = 63 mg**

$$f_R = \frac{X_u^\infty}{D_{iv}} = \frac{63 \text{ mg}}{500 \text{ mg}} = 0.126$$

$$CL_R = CL_T \times f_R \\ = 1.2 \text{ L/hr} \times 0.126 = 0.15 \text{ L/hr}$$

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### *Mechanisms of altered elimination*

Verapamil has been shown to elevate serum digoxin concentrations in patients receiving both drugs concurrently. A study by Pedersen et al (*Clin Pharmacol Ther* 30:311-316, 1981.) examined this interaction with the following results.:

<u>Treatment</u>	$CL_T$	$CL_R$	$CL_{NR}$
Digoxin	3.28	2.18	1.10
Dig + verapamil	2.17	1.73	0.44

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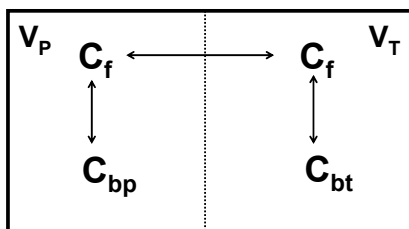
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### STEADY-STATE VOLUME OF DISTRIBUTION



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$f_{up} = \frac{C_f}{C_P}$        $f_{ut} = \frac{C_f}{C_T}$

$C_P = C_f + C_{bp}$        $C_T = C_f + C_{bt}$

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**At steady-state:**

$$V_{SS} = \frac{A_{SS}}{C_{PSS}}$$

$$A_{SS} = C_{PSS}V_P + C_{TSS}V_T \text{ or } V_{SS} = V_P + \left(\frac{C_{TSS}}{C_{PSS}}\right)V_T$$

**Substitute:**

$$C_{TSS} = \frac{C_f}{f_{ut}} \quad \text{and} \quad C_{PSS} = \frac{C_f}{f_{up}}$$

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$$V_{SS} = V_P + \left(\frac{C_f f_{up}}{C_f f_{ut}}\right)V_T$$

**Simplifying:**

$$V_{SS} = V_P + \left(\frac{f_{up}}{f_{ut}}\right)V_T$$

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Using blood concentrations:

$$V_{SS} = V_B + \left( \frac{f_{ub}}{f_{ut}} \right) V_T$$

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Calculation via moment analysis:

$$V_{SS} = \frac{D_{iv} AUMC}{AUC^2}$$

Assumptions:

- Linear disposition
- Administered and eliminated via sampling site
- Instantaneous input

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If administration via a short term infusion:

$$V_{SS} = \frac{K_0 T (AUMC)}{AUC^2} - \frac{K_0 T^2}{2 AUC}$$

$K_0$  = infusion rate  
 $T$  = infusion duration

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**MEAN RESIDENCE/TRANSIT TIME**

Administration of a small dose may represent a large number of molecules:

**Dose = 1 mg    MW = 300 daltons**

# of molecules =  $(10^{-3} \text{ g}/300) \times (6.023 \times 10^{23})$

**$\sim 2 \times 10^{18}$  molecules**

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Instantaneous administration of the entire dose will result in xenobiotic molecules spending various amounts of time in the body. Evaluation of the time various molecules spend in the body (*residence time*) can be characterized in the same manner as any statistical distribution.

***Mean residence time:*** The average time the molecules of a given dose spend in the body.

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A conceptual understanding can be gained from the following example: Assume a child received 20 dimes for his birthday and immediately places them in his piggy bank. Over the next month, he periodically removes 1 or more dimes from the piggy bank to purchase candy. Specifically, 3 days after placing the coins in his bank he removes 5 dimes, on day 10 he removes 4 dimes, on day 21 he removes 6 dimes and on day 30 he removes 5 dimes. At the 30th day after placing the coins in his bank, all of the coins have been removed. Hence, the *elimination* of the deposited dimes is complete. The *MRT* of the dimes in the piggy bank is simply the sum of the times that coins spend in the bank divided by the number of dimes placed in the bank.

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$$MRT = \frac{3+3+3+3+10+10+10+10+21+21+21+21+21+30+30+30+30}{20}$$

$$MRT = \frac{(3 \times 5) + (10 \times 4) + (21 \times 6) + (30 \times 5)}{20}$$

$$MRT = 16.55 \text{ days}$$

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**MRT can be determined for any given number of drug molecules ( $A_i$ ) that spend a given amount of time ( $t_i$ ) in the body:**

$$MRT = \frac{\sum_{i=1}^n A_i t_i}{A_{total}}$$

where  $n$  = total number of residence times

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**The mean rate of drug leaving the body relative to the total amount eliminated can be expressed in terms of concentration:**

$$MRT = \frac{\int_0^{\infty} tC(t)dt}{\int_0^{\infty} C(t)dt}$$

$$MRT = \frac{AUMC}{AUC}$$

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$$MRT = \frac{AUMC}{AUC}$$

This is not a *definition* of MRT, rather it is a means of calculating MRT when CL is constant.

$$\frac{AUMC_{po}}{AUC_{po}} \neq MRT$$

When calculated in this fashion, it is often said that MRT is a function of the route of administration. However, MRT is independent of the route.

**Meant Transit Time (MTT):** The average time for xenobiotic molecules to leave a kinetic system after administration.

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Since an iv bolus assumes instantaneous input:

$$\frac{AUMC_{iv}}{AUC_{iv}} = MRT = MTT_{iv}$$

$$\frac{AUMC_{po}}{AUC_{po}} = MTT_{po}$$

$$MTT_{po} = MTT_{iv} + MAT = MRT + MAT$$

MAT – mean absorption time

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$$MRT = \frac{V_{ss}}{CL}$$

If drug declines via monoexponential decline:

$$MRT = \frac{AUMC}{AUC} = \frac{C_0/\lambda^2}{C_0/\lambda} = \frac{1}{\lambda}$$

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**SYSTEMIC AVAILABILITY**

$$F = \frac{AUC_{po} \times D_{iv}}{AUC_{iv} \times D_{po}}$$

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