

FDA PUBLIC MEETING PROMOTING EFFECTIVE DRUG DEVELOPMENT PROGRAMS: OPPORTUNITIES AND PRIORITIES FOR FDA'S OFFICE OF NEW DRUGS

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**Mass-Action Law Pharmacodynamics (MAL-PD) for Quantitative Biomedical
R&D, and Efficient Drug-Evaluation Guidance: Computerized Data Analysis of
Single Drug and Drug Combinations** in Vitro, in Animals and in Clinical Trials

Place: Food and Drug Administration
White Oak Campus, 10903 New Hampshire Ave. Silver Spring, MD 20993

Date: November 7, 2019

Times Cited: 3,213 (2,306 Citations in 941 Journals) [11.5.2019 Citation Results]

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The Mass-Action Law PD/BD Theory, Equations, Algorithms and Computer Simulation

Chou TC. Pharmacol. Rev.
58: 621-681, 2006.
Eqs. 7-9; 16,19,20; and 21-23.

I. Median-Effect Equation [MEE] & Plot (Chou, 1976) [1st Law of MAL] {Doctrine of the Median}

$$\frac{f_a}{f_u} = \left(\frac{D}{D_m} \right)^m \quad D = D_m \left(\frac{f_a}{1 - f_a} \right)^{\frac{1}{m}} \quad f_a = \frac{1}{1 + \left(\frac{D_m}{D} \right)^m}$$

D & E Interchangeability
D-E Curves Linearization
D_m as Universal Reference Point
and Dynamic Common Link.

II. Combination Index Equation [CIE] & Plot (Chou-Talalay, 1984)

$$\begin{aligned} CI &= \frac{(D_{\text{comb}})_1}{(D_{\text{alone}})_1} + \frac{(D_{\text{comb}})_2}{(D_{\text{alone}})_2} = \frac{(D)_1}{(D_x)_1} + \frac{(D)_2}{(D_x)_2}, \quad \text{Ratio: } \frac{(D)_1}{(D)_2} = \frac{P}{Q} \\ &= \frac{(D)_{1,2} [P/(P+Q)]}{(D_m)_1 [f_a/(1-f_a)]^{1/m_1}} + \frac{(D)_{1,2} [Q/(P+Q)]}{(D_m)_2 [f_a/(1-f_a)]^{1/m_2}} \end{aligned}$$

CI = 1 indicates additive effect
< 1 indicates synergism
> 1 indicates antagonism

Dynamic Interaction
Dynamic Integration
Synergy Quantification

III. Dose-Reduction Index [DRI] & Plot (Chou-Chou, 1988)

$$(DRI)_1 = \frac{(D_{\text{alone}})_1}{(D_{\text{comb}})_1} = \frac{(D_x)_1}{(D)_1} = \frac{(D_m)_1 [f_a/(1-f_a)]^{1/m_1}}{(D)_1}, \quad (DRI)_2 = \dots$$

DRI = 1 No dose reduction
> 1 Favorable dose reduction
< 1 Not favorable dose reduction

Retaining Efficacy &
Decreasing Toxicity
Therapeutic Advantage

The Unified PD/BD Theory of The Mass-Action Law

Derivation of Major Biochemical and Biophysical Equations from the Median-Effect Equation

[Chou T.C. Pharmacol. Rev. 58: 621-681, 2006; Fig. 4]

Henderson-Hasselbalch equation

$$\log [H^+] = \log K_a + \log \frac{[HA]}{[A^-]}$$

$$\text{pH} = \text{p}K_a + \log \frac{[A^-]}{[HA]}$$

Michaelis-Menten equation

(Lineweaver-Burk Plot)

$$v/V_{\max} = [1 + (K_m/S)]^{-1}$$

$$\frac{f_a}{f_u} = \left(\frac{D}{D_m} \right)^m$$

The Median-Effect Equation

Chou, J. Theor. Biol. 59: 253-276, 1976

$$f_a / (1 - f_a) = (D/D_m)^m$$

$$f_a = [1 + (D_m/D)^m]^{-1}$$

$$\log [(f_a / (1 - f_a))] = m [\log(D) - \log D_m]$$

$$\log [(f_a)^{-1} - 1]^{-1} = m \log(D) - m \log D_m$$

$$f_a / f_u = D / D_m$$

The Unified Median-

Effect Equation of MAL:

“Derived” (Proven) from the Mass-Action Law.

[The four major Equations in *Biochemistry and Biophysics* Are the *Special Cases* of the Unified PD/BD/BI Theory]. [If ME Eq. were wrong, then textbooks would need to be revised]

**“Doctrine of the Median”
for Bio-dynamics (BD):**

Dm: Half Affected

Km: Half Saturated

Ka: Half Ionized

K: Half Occupied

Kd: Half Bound, Half Free

Hill equation

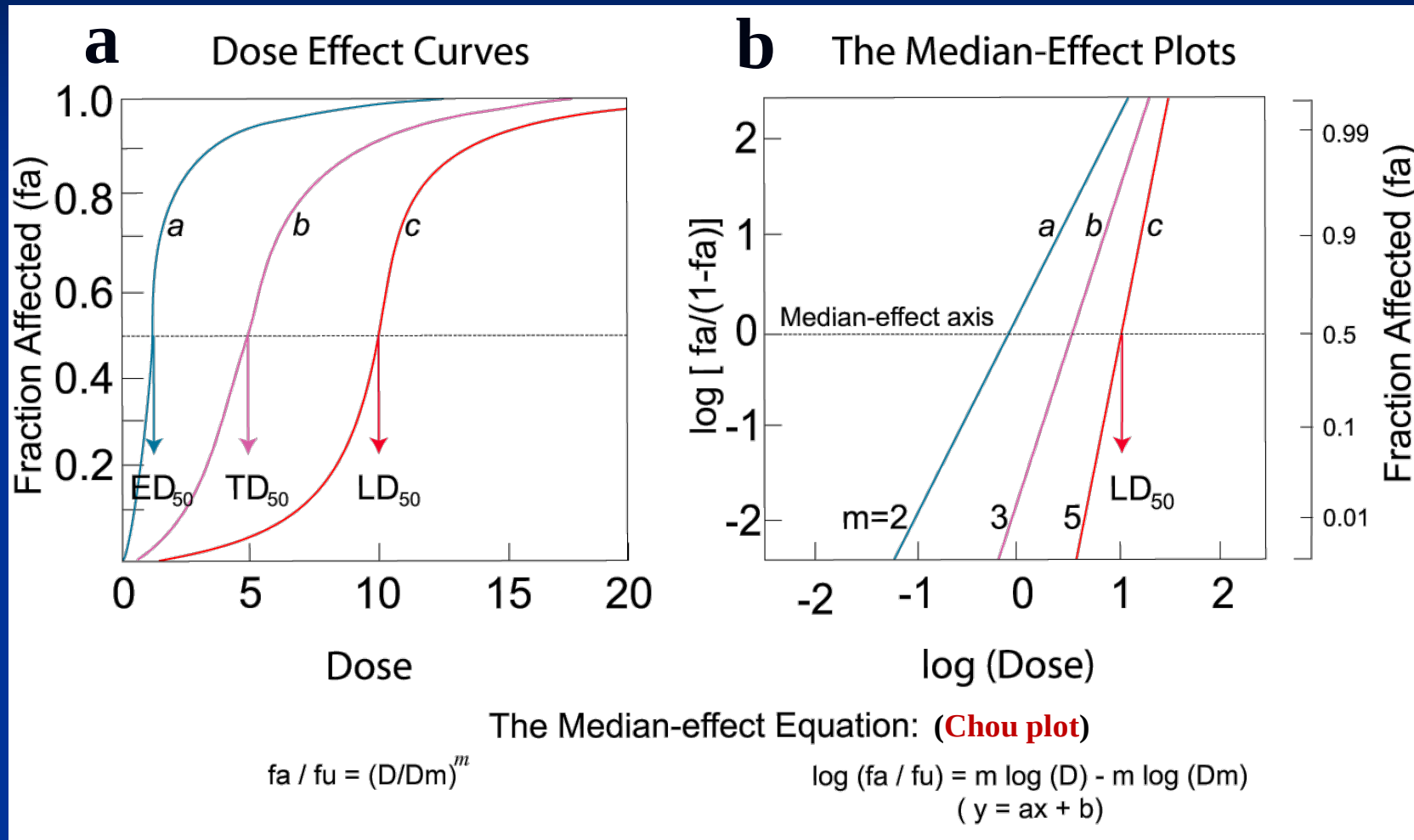
$$\log [v / (V_{\max} - v)] = n \log(S) - \log(K)$$

Scatchard equation

$$\frac{[L]_b}{[L]_f} = \frac{n[M]_t}{K_d} - \frac{[L]_b}{K_d}$$

“Linearization” of Dose-Effect Curves

[X-Intercept for Potency; Slope for Dynamic Order (Sigmoidicity of Shape)]

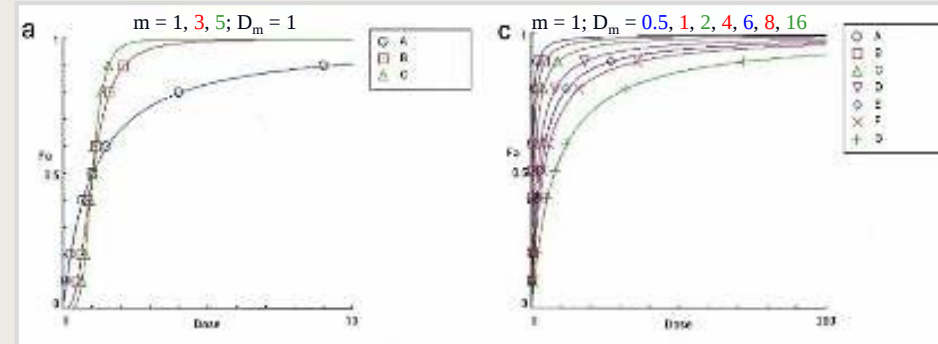


[Chou T.C. J. Theor. Biol. 59: 253-276, 1976]

The Computer Simulation of the Median-Effect Equation

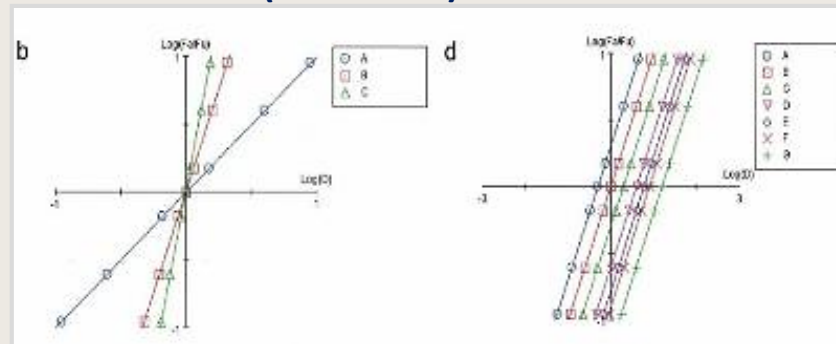
The Dose-Effect Curves: with different “shape” and “potency”

Linearize All Dose-Effect Curves of Different Shapes and Different Potencies with a Minimum of Only Two Data Points.



The Most Important Bio-Dynamic Findings of MAL-MEE ! Using the Reverse Logics.

The Median-Effect Plot: (Chou Plot): The “Linearization” Principle



Source: Chou TC.
Pharmacol. Rev. 58:
621-681, 2006. Fig. 11.
Chou TC. *Integr. Biol.* 3:
548-559, 2011. Fig. 1.

“ The Two-Data Point Theory” :
A New Paradigm that
Defies The Centuries-Old Common Held Belief!”

With MAL-PD, “Only Two Data Points” are required to simulate A Dose-Effect Curve !

- Dose-Effect Curves Follow the Median-Effect Principle of the Mass-Action Law: The “Median” Serves as “The Universal Reference Point and Link as The Largest Common Denominator for Simplifying the Complex Biological Systems”.
- “One can draw a specific dose-effect curve with a *theoretical minimum* of “only two data points” - [The 3rd Point is dose zero, and the 4th point the Median-Effect Dose (Dm). Any 2-data points on a line represent the same line or the same Dose-Effect Curve!] {The Two Data Points Minimum Theory}. This the Basis for the “Digital Bio-Dynamics” and for the Efficient, Effective “Econo-Green” Biomedical Research & Development and Regulations. [Chou TC. *Integr. Biol.* 3: 548-559, 2011]

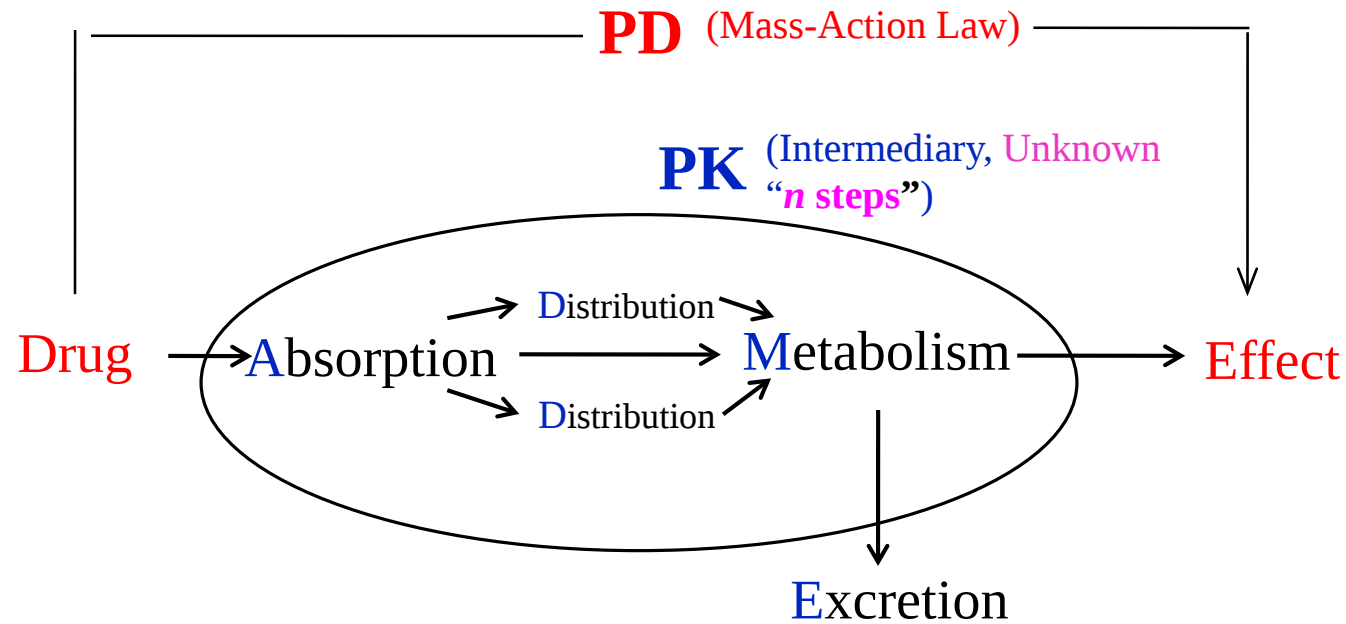
The Nature's Mass-Action Law Is The “Model” of “PD”

PD Is The Fundamental “Dose” and “Effect” Mathematical Relationship.

[PK is Empirical Observational Science that Has *No “Model”*].

[PK is Just the Intermediary *n*-Steps (ADME) within the PD Domain].

[PK Is An Endless Sink of Research Resources]. **[“PD” Determines of Drug Efficacy & Toxicity; But “PK” Does Not].**



Let's Work Together for **Innovation/Modernization** and Set The Basic **Conceptual Priority** !

Chou, TC. Comments to FDA
& NIH/ASPET/AACR, 2017-19
PD Science, LLC (USA)

Source: Chou TC.
Am J Cancer Res. 1:
925-954, 2011. Fig. 7

“PD” Should Have Higher Priority than “PK” in
Drug Evaluations and Regulations !

PD to Avoid Wasting Time, Effort, and Resources.

PD trims the R&D Attrition Rate by “Optimized PD Practice”

We, the Biomedical
Communities, FDA, NIH
and USPTO need to
**Define “What Is MAL-
PD”?** & **“What is
Synergy”?** to avoid
confusion, Inefficiency
and waste of resources.

Why Emphasis on Pharmacodynamics (PD) Over Pharmacokinetics (PK)

[Presented at Drug Development Summit, Zurich, Switzerland, by Chou TC 6.08.2011; *Am J Cancer Res* 1(7): 925-954, 2011, Table 2]

Items	PD	PK
Mode of action	<i>What drug does to the body</i>	<i>What body does to the drug</i>
Characteristics	Mainly vary dose (fixed time) Single Unified Theory of Mass-Action Law	Mainly vary time (fixed dose) Observational Multi-Factorial Mix
Principle	The median-effect principle of the mass-action law	Empirical phenomenal /observations
Rigorousness	<i>Explicitly derived equations</i>	<i>Empirically perceived formula</i>
Applications	Physico/chemical quantitative parameters in Vitro & in Vivo	Probabilistic empiric parameters in Vivo Only
Parameters & Constants [<i>Defined PD</i> <i>And Empirical PK</i>]	$D_m, m, r, CI, DRI, IC_{50}, K_m, K_i, K_a$ and K_d Competitiveness, Exclusivity, Synergism, Antagonism [Mass-action parameters for potency, shape, dynamic order, and interaction indices]	$t_{1/2}, C_{max}, CI, AUC, V_{dis}$ Absorption, Distribution, Metabolism, Excretion [Measurement of Parameters without direct physico- chemical bearing]
Determining Efficacy	Yes	No
Determining Toxicity	Yes	No
Determinant for	<i>What it takes to be a good drug</i>	<i>Help proper use of a drug</i>

Algorithm for Computerized Simulation of Synergism, Additivism and Antagonism of the Effect of Multiple Drugs

The Median Effect Equation

- (1) $f_a/f_u = (D/D_m)^m$
- (2) $\text{Log}(f_a/f_u) = m\text{log}(D) - m\text{log}(D_m)$
- (3) $f_a = 1/[1+(D_m/D)^m]$
- (4) $D_x = D_m[f_a/(1-f_a)]^{1/m}$

D = Dose

f_a = Fraction affected

f_u = Fraction unaffected

D_m = Median-effect dose

m = Slope, Hill-type coefficient or kinetic/dynamic order

The Combination Index Equation

$$(5) CI = \frac{(D)_1}{(D_x)_1} + \frac{(D)_2}{(D_x)_2} = \frac{1}{(DRI)_1} + \frac{1}{(DRI)_2}$$

$$(D_x)_{1,2} = (D)_1 + (D)_2$$

$$\text{and } (D)_1/(D)_2 = P/Q$$

$$(D)_1 = (D_x)_{1,2} \times P/(P+Q)$$

$$(D)_2 = (D_x)_{1,2} \times Q/(P+Q)$$

CI : Combination Index

$CI = 1$ (additive effect)

< 1 (synergism)

> 1 (antagonism)

DRI: Dose-Reduction Index

$$(DRI)_1 = \frac{(D_x)_1}{(D)_1}, \quad (DRI)_2 = \frac{(D_x)_2}{(D)_2}$$

System Analysis with General Applications:
This unified algorithm is *Independent* to drug ratio, drug units, mode of actions, and “mechanism of actions”.

It is *valid* for n drugs or entities for combination interactions in vitro and in vivo.

General Theory for General Bio-Interactions Dynamics

[Chou. Pharmacol Rev 58: 621-681, 1984. Fig. 7]

For n Drug Combinations:

$$CI = \sum_{j=1}^n \frac{(D)_j}{(D_x)_j}$$

A “Constant-Ratio” Econo-Green Experimental Design Showing the Outlay of Two Drugs for Drug Combination Analysis *in Vitro*

[Using Only 16 Data Points, $(3 \times 5 + 1 = 16)$ in duplicates or triplicates]*

Simple and Efficient
Constant-Ratio
Diagonal Combo Design
(Recommended)

		Drug 1					
		0	0.25X (ED ₅₀) ₁	0.5X (ED ₅₀) ₁	(ED ₅₀) ₁	2X (ED ₅₀) ₁	4X (ED ₅₀) ₁
Drug 2	0	Control (f _a) ₀	(f _a) ₁	(f _a) ₁	(f _a) ₁	(f _a) ₁	(f _a) ₁
	0.25X (ED ₅₀) ₂	(f _a) ₂	(f _a) _{1,2}				
	0.5X (ED ₅₀) ₂	(f _a) ₂		(f _a) _{1,2}			
	(ED ₅₀) ₂	(f _a) ₂	-----		(f _a) _{1,2}		
	2X (ED ₅₀) ₂	(f _a) ₂				(f _a) _{1,2}	
	4X (ED ₅₀) ₂	(f _a) ₂					(f _a) _{1,2}

[The “Non-Constant Ratio Design” can also be used for quantitative Synergy determination. But No automatic computerized simulation can be done]

Chou TC.
Pharmacol. Rev. 56:
621-681, 2006. Table 5.

*For animal or clinical trials, the practical minimum is 10 data points $(3 \times 3 + 1 = 10)$, by removing the lowest and highest doses in this scheme. Each Dose has 4-6 or more animals or patients, depending on the measurement need, in vivo with 1.3-1.5 fold serial dose dilutions instead of 2-fold dilutions in vitro.

[The Recommended Practical Minimum Number of Data Points for Two Drug Combinations In Vitro, In Animals and In Clinical Trials need: 16, 10, and 10 Dose-Points, respectively]

CompuSyn

For PD/BD/BI of “Single Drug” or “Drug Combinations”

[An “One Second” Automated Data Analysis Based on The Mass-Action Law]

A Computer Program for Quantitation of
Synergism and Antagonism in Drug Combinations,
and the Determination of IC_{50} , ED_{50} and LD_{50} Values.

By Ting-Chao Chou (MSKCC)
and Nick Martin (MIT)

The Quantitative,
Derived, Proven
PD Software.

Published by ComboSyn, Inc.

©Copyright 2004, Offered for Free Download as A Donation to the Biomedical Communities upon
Registration: Since 8/1/2012

[As of 11.5.2019: 35,806 Downloads by Bio-Medical Scientists from 129 Countries or Territories]

<http://www.combosyn.com> – PD Science, LLC (USA)

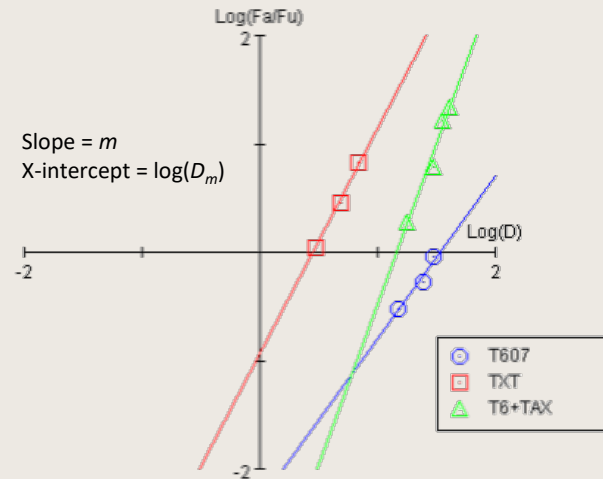
Graphic Dynamic Transformations by Mass-Action Law Algorithms

“Drug Combination Study *In Animals* Using Only 10 Data Points”

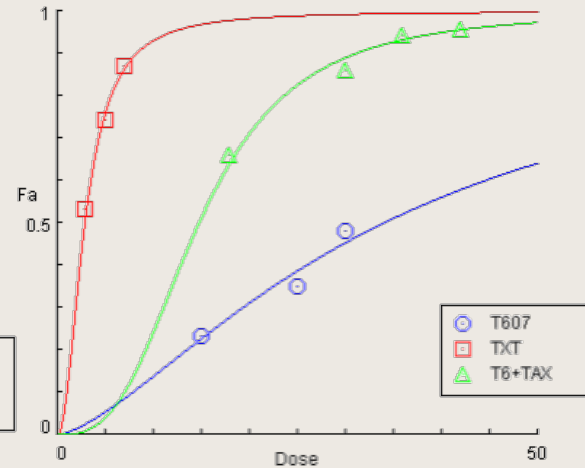
Anti-HCT-116 Tumor Xenograft in Nude Mice: T-607:Taxotere & Combinations (5:1), Day 35 Data. (Each dose point, $n=6$ mice/dose).

Fu J, Zhang N, Chou JH, Dong H, Lin SF, Ulrich-Merzenich G, & Chou TC. *Synergy 3: 15-30, 2016. (Figs.4 & 5)*

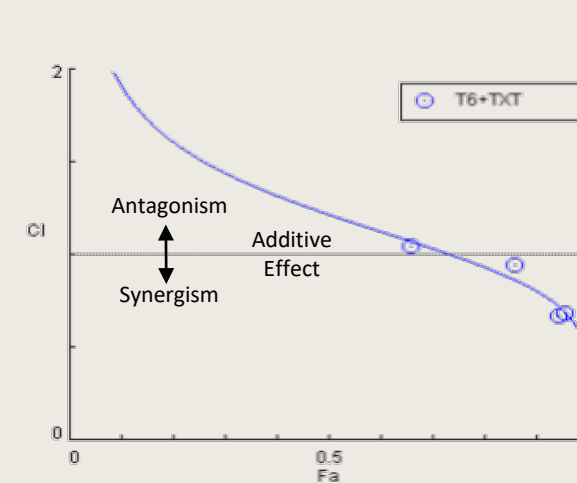
A. Median-Effect Plot (Chou Plot)



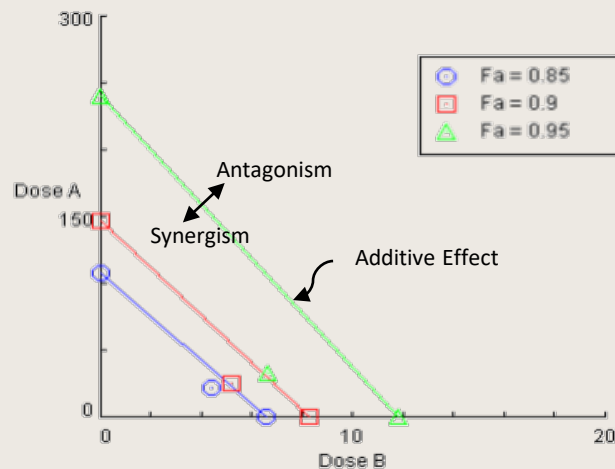
B. Dose-Effect Curve (Simulated)



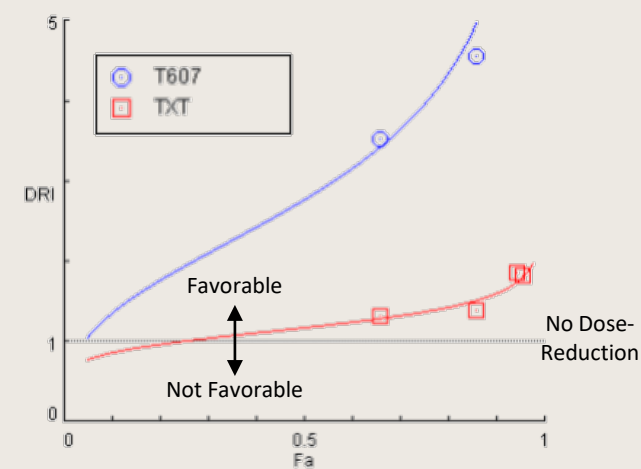
C. Fa-CI Plot (Chou-Talalay Plot)



D. Isobolograms (Classic Isobol)



E. Fa-DRI Plot (Chou-Martin Plot)



MAL New Informatics:

We Cannot Use Over 3 or 4 Data Points in Animals or in Humans! It Would be *too Toxic* or *too Ineffective*. This Problem is Now Solved with the *Minimum 2-Data Points Theory of MAL-PD/BD*. [see slide #6 above]

All five Diagnostic Graphs are based on the “**Same**” **10 Dose-Data Points** in **Graph “A”** or **“B”** (3+3+4) by automated computerized simulation of 5 graphs in a second.

Comparison of Two-Drug Combinations for Anti-Cancer Agents Using “Econo-Green” Small Size Experimental Design

[Chou TC, Am J Cancer Res 1(7): 925-954, 2011, Table 6]

[Chou TC, Integrative Biol. 3: 548-559, 2011, Table 1]

Efficient,
Cost-Effective.
Fewer
Doses/Data
Point.
Computer-
Simulated
Quantitative/
Indexed
Conclusions.

No Reason to
Waste Time,
Efforts and
Resources in
Animal Studies and
in Clinical Trials
When Quantitative,
Efficient, Effective
Method Is
Available.

	In Vitro	In Animal	In Clinic (Phase I)
Time & Effort	2 weeks	2 months	>1 year
Non-wage Cost	\$200 [cells and chemicals]	\$3,000 [nude mice]	Expensive Trials [\$ Multi- millions, Vary]
Sample Size	> 2 x 10 ⁶ [cells]	> 65 [nude mice] [Chou-Talalay method]	> 36 [vary based on accuracy of end-point determination] [Chou-Talalay method]
“Practical” Minimum of Data Points (Econo-Green Approach)	16* (5+5+5+1)	10 (3+3+3+1)	10 (3+3+3+1)
Quantitative “ Synergy ” Determination	Very Easy [But frequently not done properly in the past]	Not Difficult [Rarely properly done in the past]	Difficult Use Surrogate Markers, Fractional Doses and Scanning

“Design”

Dictates
Analytic Method
and *Precludes*
Possible
Conclusions.

“If use only *single*
dose of any drug
in drug
combination, it is
not possible to
determine
“Synergy”, no
matter how
accurate is your
assay, or how long
time you spent for
your project!”

*Practical increase of data points in vitro due to simplicity, low cost, and no ethical, legal restrictions.

Tales of Two Anti-HIV Clinical Trials

AZT + 3TC

AZT + INF_α

Authors	J.J. Eron et al. (9 authors + Northern Am. HIV Working Party)	D. Mildvan et al. (21 authors)
Publication	<u>N. Engl. J. Med.</u> 333: 1662-1669, 1995	<u>Antiviral Therapy</u> 1(2): 77-88, 1996
Journal Impact Factor	28.5	3.1
Number of Patients	366 [<u>Problems with Design & Analysis</u>]	36
Surrogate Marker	CD ₄ ⁺ , HIV-RNA	P24 Antigen, CD ₄ ⁺
Treatment Design	Fractionated Repeated Doses AZT <u>Single Dose</u> , 3TC 2 Doses	Fractionated Repeated Doses Both Drugs have 3 Doses. Used Only 10 Data Points
What They Have Proved	<u>“Combination Effect is Greater than Each Drug Alone”</u> <u>Statistics Not Possible to Claim Synergism</u> A+B > A, A+B > B (p<0.001). Axiom Does Not Need A Proof !	<u>“Quantitative Determination of Synergism”</u> Using Combination Index Method Simulation (CI < 1 determined synergism) Used Chou-Talalay CI Method. Adv. Enz. Regul. 22: 27-55, 1984

Conclusion: Synergy is Not determined by *p* values but rather by the CI values
 Synergy is Not a Statistical Issue but rather a Mass-Action Law Issue
 [Chou T.C. *Integrative Biol.* 3: 548-559, 2011. p.557 and Chou TC. *Synergy* 1: 3-21, 2014. Table 4]

It Is *Not Possible* to Quantify Synergy with a Single Dose of *Any Drug* !

AZT+INFN Is A Life Example for Econo-Green, Efficient, Computerized Clinical Protocol Design, Using the Chou-Talalay CI Method.

PD Needs Two (or More) Doses, for both “Potency” and “Shape”. **Single Dose Generates A Potency Point, but No Shape.**

The PD-Doctrine Challenges *All* Clinical Trials for Protocol-Designs Using “Only Single Dose”.

Trends of Drug Combination Methods for Synergy Determination, 1900 to October, 2019*

Method, and Reference Source		Thomson Reuters Web of Science Citation Database					Total Citations Since Publication	Average Citations per year
		Trend of Citation						
		2015	2016	2017	2018	2019*		
A. Chou, TC & Talalay, P		309	311	329	325	256	4,929	141.5
Adv. Eng. Regul. 1984; 22:27-55	[MEE & CI Theory]							
B. Chou, TC		265	302	319	300	276	2,359	183.9
Pharmacol. Rev. 2006;58: 621-681	[MEE, CI Review]							
C. Chou TC		242	293	323	340	351	1,989	225.3
Cancer Res. 2010; 70: 440-446	[CI Perspectives]							
D. Berenbaum, MC		40	51	40	43	31	1,123	37.6
Pharmacol. Rev. 1989; 41: 93-141								
E. Bliss, CI		68	105	88	99	70	1,105	13.8
Ann. Appl. Biol. 1939; 26: 585-615								
F. Greco, WR et al		73	78	75	63	50	931	39.1
Pharamacol. Rev. 1995; 47: 331-385								
G. Steel GG & Peckham MJ		18	18	22	11	14	765	19.2
Int. J. Radiant. Oncol. BioPhys. 1979; 5: 85-91								
H. Tallarida, RJ		46	31	36	24	21	488	7.5
J. Pharmacol. Exp. Ther. 2001; 298: 865-872								
I. Elion GB, Singer S & Hitchings GH		7	3	7	4	1	472	26.5
J. Biol. Chem. 1954; 208: 477-488								
J. Prichard, MN & Shipman C Jr		27	35	30	15	9	450	15.6
Antiviral Res. 1990; 14: 181-205								
K. Webb J.L.		7	7	11	11	6	315 [#]	5.6
Acad. Press. 1963; 1: 66-79, 488-512								
L. Loewe, S		2	0	2	2	0	126	2.0
Pharmacol. Rev. 1957; 9: 237-242								

*Based on Thomson Reuters Web of Science [all database](#), as of [October 21, 2019](#). (Citation numbers are higher in Google Scholar Citations).

[#]Based on Google Scholar Citations, as of October 21, 2019.

The Combination Index (CI) equation is actually “mathematically derived” from system analysis of the mass-action law (MAL), and its algorithm is exactly for general “quantitative determination” of synergy. This set the CI method apart from *all* others Methods.

This Table Is Updated from Zhang N. et al. Synergy 6: 97-104, 2016. [Table 2](#).

MAL-PD Based Computerized CI Simulation of Synergism/Antagonism by CompuSyn [The Practical , Efficient, Econo-Green & Quantitative Bio-Informatics]

Refs. Chou TC.

[Pharmacol. Rev.](#) 58: 621-681, 2006. pp.638-643.

[Cancer Res.](#) 70:440-446, 2010. p.444

[Integr. Biol.](#) 3: 548-559, 2011, p. 558.

[Synergy](#) 1: 3-21, 2014. (Q&A).

[Synergy](#) 3: 15-30, 2016.

Fu J. et al (CompuSyn Report : pp.21-26).

Primary Questions:

- Is there any synergism?
- How much synergism?
- Synergism at what dose levels?
- Synergism at what effect levels?
- What the exhibited isobologram looks like?
- How many folds dose reduction for each drug as results of synergism?

Other Questions:

- Optimal combination ratio (1:1; 3:1; 1:3 which better?)
- Schedule dependency (Simultaneous, A follows B, B follows A)
- Selectivity of synergism (Target vs Host)
- Condition directed synergism (Temperature, Pressure, pH, Oxygen Tension ..)

These Questions Are Answered by Combination Index Equation and CompuSyn software.

Among *all* ten Drug Synergy Determination Methods, “Only CI Method is Quantitative”.

Combination Therapy Is the Mostly Widely Used Treatment for the Most Dreadful Diseases Such As Cancer and AIDS. It is extremely Important to “Quantify Synergy”.



Thanks