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

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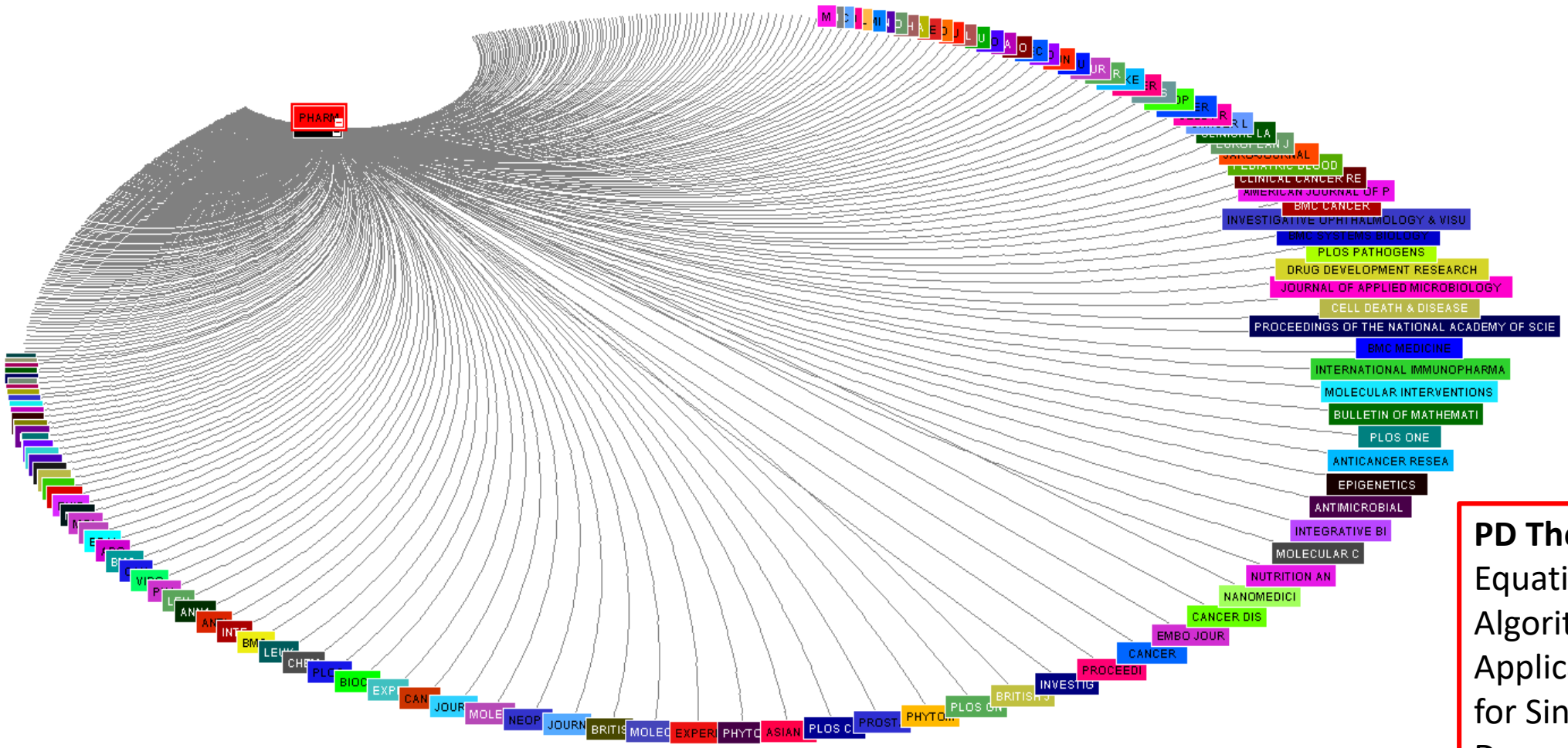
Mass-Action Law Pharmacodynamics (MAL-PD) for Quantitative Biomedical R&D, and Efficient Drug-Evaluation Guidance: Computerized Data Analysis of Single Drug and Drug Combinations in Vitro, in Animals and in Clinical Trials

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

Date: November 7, 2019

"Theoretical Basis, Experimental Design, and Computerized Simulation of Synergism and Antagonism in Drug Combination Studies"



CHOU TC, Pharmacological Reviews 58: 621-681, 2006

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

PD Theory: Equations, Algorithms & Applications for Single Drug and Drug-Combinations

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}

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

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

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

$$CI = \frac{(D_{comb})_1}{(D_{alone})_1} + \frac{(D_{comb})_2}{(D_{alone})_2} = \frac{(D)_1}{(D_x)_1} + \frac{(D)_2}{(D_x)_2}, \qquad \text{Ratio: } \frac{(D)_1}{(D)_2} = \frac{P}{Q}$$

$$= \frac{(D)_{1,2}[\,P/(P+Q)\,]}{(D_m)_1[\,f_a/(1-f_a)\,]^{1/m_1}} + \frac{(D)_{1,2}[\,Q/(P+Q)\,]}{(D_m)_2[\,f_a/(1-f_a)\,]^{1/m_2}}$$

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

Dynamic Interaction
Dynamic Integration
Synergy Quantification

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

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

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

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

$$pH = pK_a + \log \frac{[A^-]}{[HA]}$$

"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

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

The Median-Effect Equation
Chou, J. Theor. Biol. 59: 253-276, 1976

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

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

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

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

$$f_a/f_u = D/D_m$$

Michaelis-Menten equation
(Lineweaver-Burk Plot)
$v/V_{max} = [1+(K_m/S)]^{-1}$

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]

Hill equation

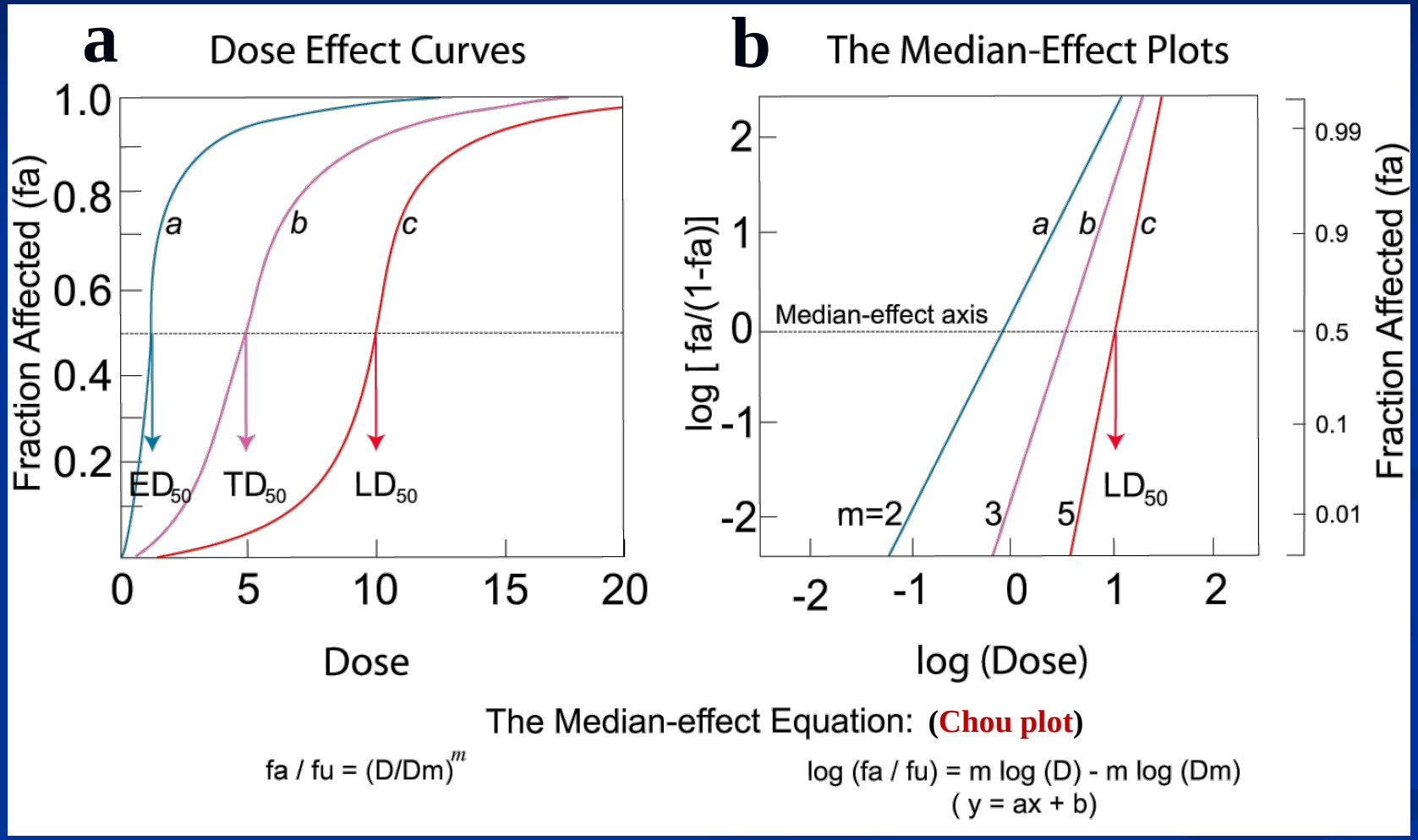
$$\log [v/(V_{max}-v)] = n \log(S) - \log (K)$$

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)]



The Median-effect Equation: **(Chou plot)**

$fa / fu = (D/Dm)^m$

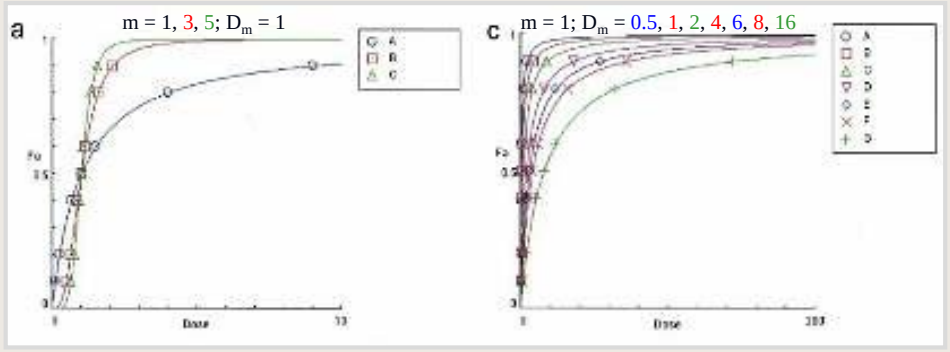
$\log (fa / fu) = m \log (D) - m \log (Dm)$

(y = ax + b)

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

The Computer Simulation of the Median-Effect Equation

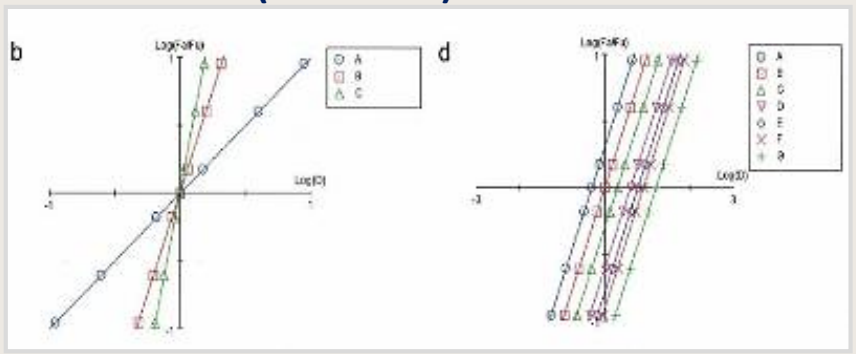
The Dose-Effect Curves: *with different "shape" and "potency"*



***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"

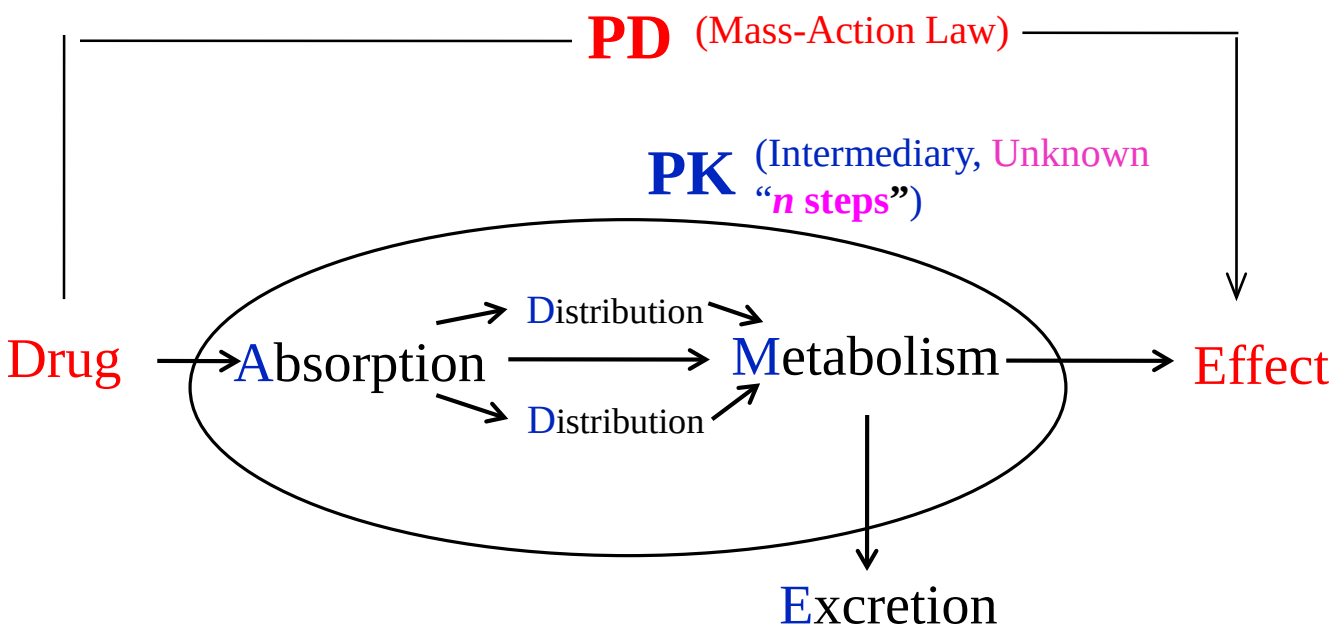
PD Is The Fundamental "Dose" and "Effect" Mathematical Relationship.

[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)

"**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.

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

Why Emphasis on Pharmcodynamics (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	***What drug does to the body***	***What body does to the drug***
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	**Explicitly derived equations**	**Empirically perceived formula**
Applications	Physico/chemical quantitative parameters in Vitro & in Vivo	Probabilistic empiric parameters in Vivo Only
Parameters & Constants [*Defined* PD And *Empirical* PK]	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]	$\mathbf{t_{½}}$, C_{max}, Cl, 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	***What it takes to be a good drug***	***Help proper use of a drug***

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) $\text{Log}(f_a/f_u) = m\log(D) - m\log(D_m)$

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

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

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

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

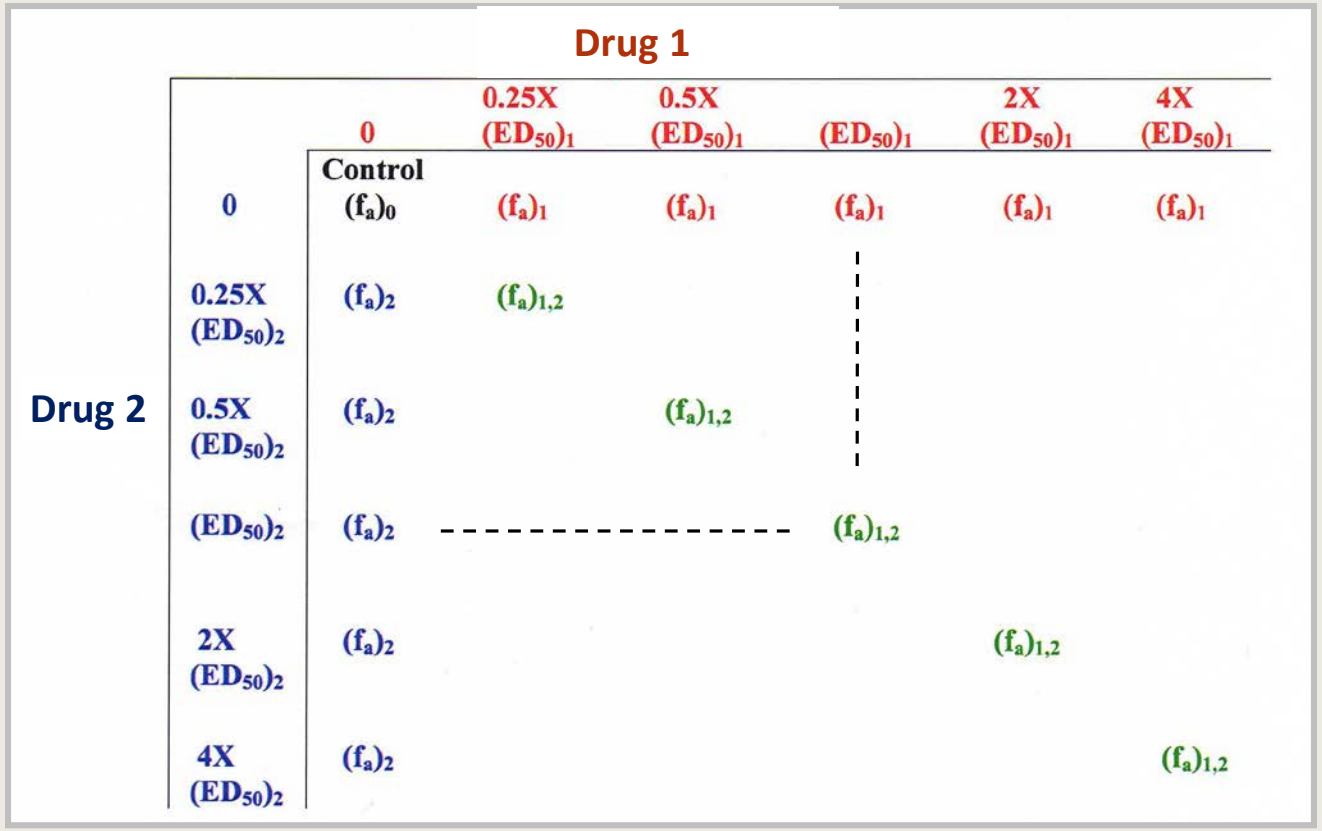
For ***n*** Drug Combinations:

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

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

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

[Using Only 16 Data Points, (3X5 +1 = 16) in duplicates or triplicates]*



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

[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 (3X3 +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.***

[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)

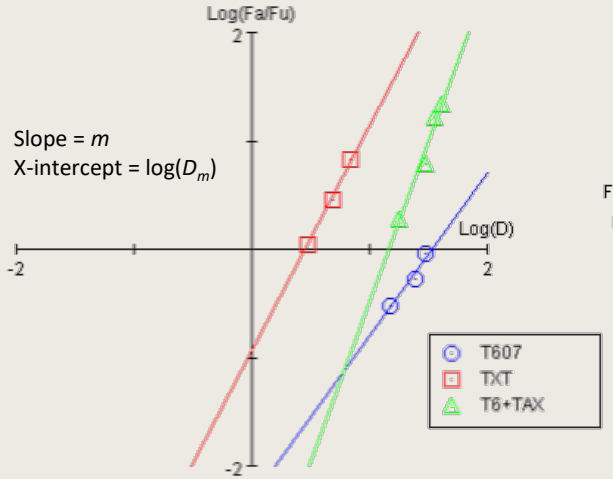
Graphic Dynamic Transformations by Mass-Action Law Algorithms

"Drug Combination Study *In Animals* Using Only *10 Data Points*"

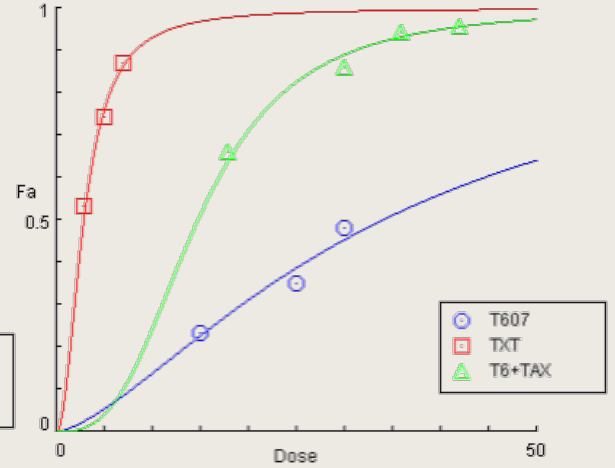
Anti-HCT-116 Tumor Xenograft in Nude Mice: T-607:Taxotere & Combinations (5:1), Day 35 Data. (Each dose point, n=6 mice/dose).

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

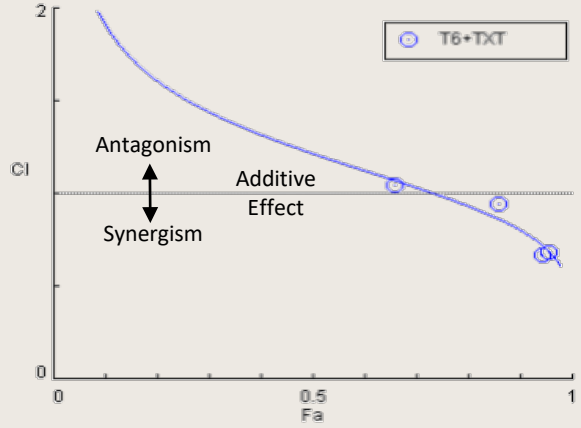
A. Median-Effect Plot (Chou Plot)



B. Dose-Effect Curve (Simulated)

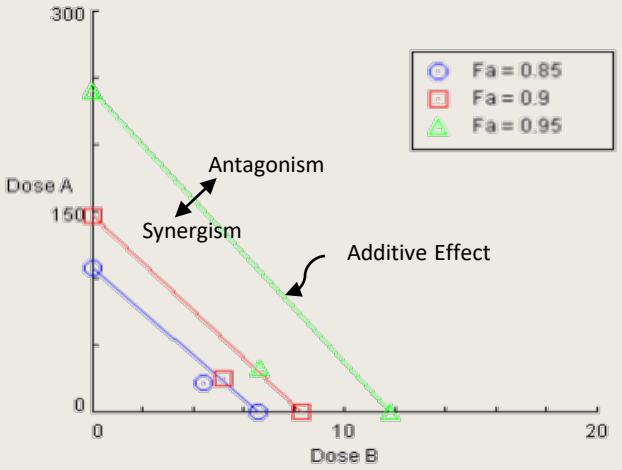


C. Fa-CI Plot (Chou-Talalay Plot)

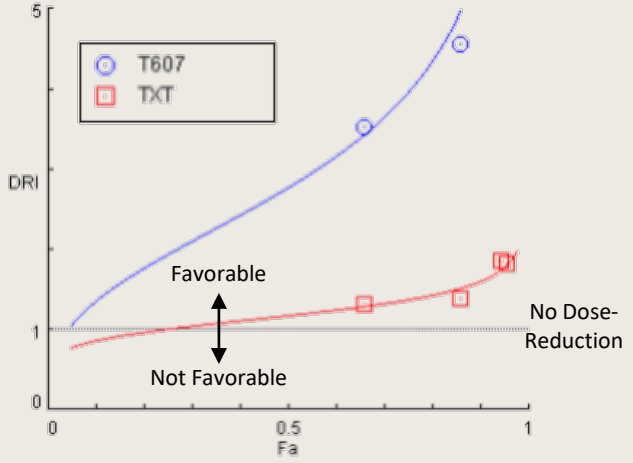


MAL New Informatics:
We Cannot Use *Over* 3 or 4 Data Points in Animals or in Humans! It Would be *too Toxic or too Ineffective.* This Problem is Now Solved with the *Minimum 2-Data Points Theory of MAL-PD/BD.* *[see slide #6 above]*

D. Isobolograms (Classic Isobol)



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



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

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

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

	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	N. Engl. J. Med. 333: 1662-1669, 1995	Antiviral Therapy 1(2): 77-88, 1996
Journal Impact Factor	**28.5**	**3.1**
Number of Patients	**366** [Problems with *Design & Analysis*]	**36**
Surrogate Marker	CD_4^+ , HIV-RNA	P24 Antigen, CD_4^+
Treatment Design	Fractionated Repeated Doses AZT *Single Dose*, 3TC 2 Doses	Fractionated Repeated Doses Both Drugs have 3 Doses. **Used Only 10 Data Points**
What They Have Proved	"Combination Effect is Greater than Each Drug Alone" Statistics Not Possible to Claim Synergism A+B > A, A+B > B ($p<0.001$). Axiom Does Not Need A Proof !	"Quantitative Determination of Synergism" Using Combination Index Method Simulation (CI < 1 determined synergism) Used Chou-Talalay CI Method. Adv. Enz. Regul. 22: 27-55, 1984

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

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

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]

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

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

*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.

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?

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".

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 ..)

Thanks