The Mass-Action-Law Based GPS Concept for Bio-Informatics

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The Mass-Action-Law Based GPS Concept for Bio-Informatics

by T.C. Chou

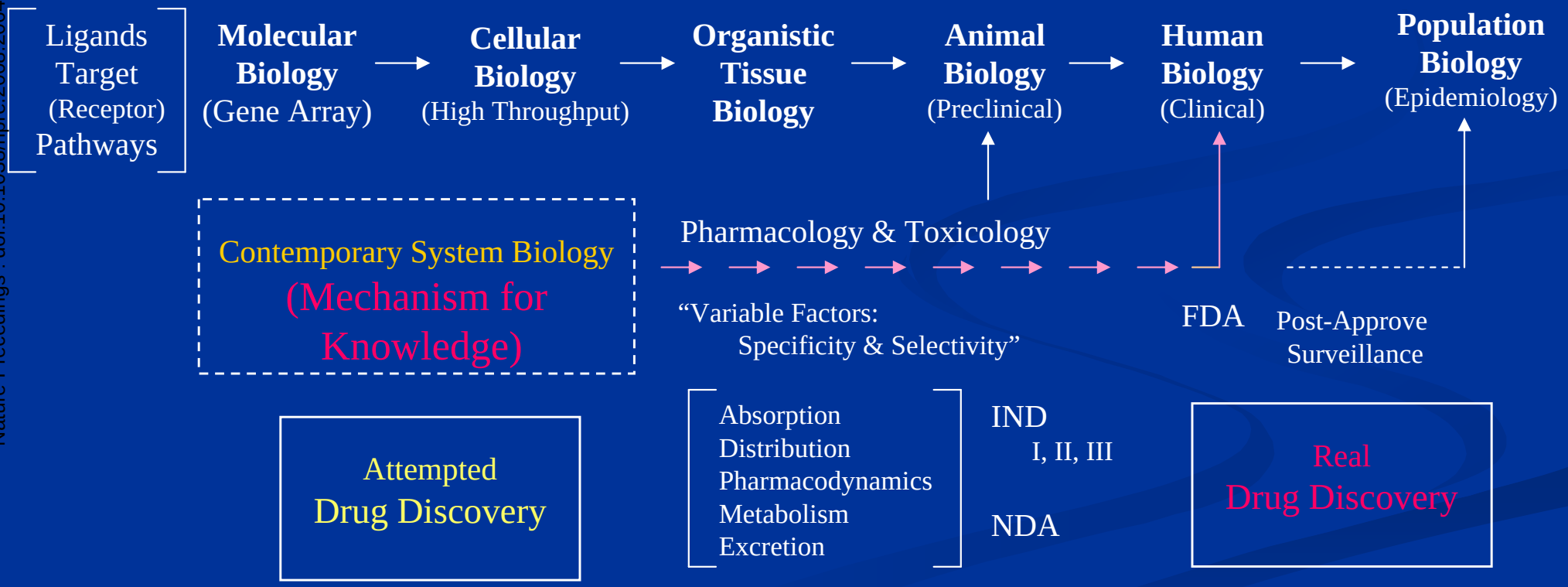
Summary

The unified theory of dose and effect, as indicated by the median-effect equation for single and multiple entities and for the first and higher order kinetic/dynamic, has been established by T.C. Chou and it is based on the physical/chemical principle of the mass-action law (*J. Theor. Biol.* 59: 253-276, 1976; *Pharmacological Rev*. 58: 621-681, 2006). Rearrangements of the median-effect equation lead to Michaelis-Menten, Hill, Scatchard, and Henderson-Hasselbalch equations. The "median" serves as the "universal reference point" and the "common link" for the relationship of all entities at all dynamic orders, and is also the "harmonic mean" of kinetic dissociation constants. Over 300 mechanism-specific equations have been derived and published using the mathematical induction-deduction process. These equations can be deduced into several general equations, including the median-mediated whole/part equation, combination index theorem, isobologram equation, and polygonogram. It is proven that "dose" and "effect" are interchangeable, thus, "substance" and "function" are interchangeable, which leads to "the-unity theory" in philosophical context. Based on the mass-action law, the fundamental conceptual claim is that "one can draw a specific cure for only two data points", if they are determined accurately. Furthermore, instead of drawing an empirical curve for data-fitting, we can now use the data points to fit the median-effect principle of the mass-action law by automated computer simulation. This small kill has far reaching consequences in biomedical sciences including small size experimentation, efficient experimental design and data interpretation, efficiency in drug discoveries, quantifying/simulating synergism in drug combinations, assessing low-dose risk of carcinogens, toxic substances or radiation, and conserving laboratory animals' lives. For the "combination index" alone, the theory has been cited in over 345 different biomedical journals, based on the Thompson-ISI Web search, indicating broad applications.

The General System Biology

(Chou, T.C. Pharmacol. Rev. 58: 621-681, 2006)

- **Based on the Physico-Chemical Principle of the Mass-Action law**
- **"Median" as the Universal "Common Link" and "Reference Point" (GPS)**
- **Approach of Efficient Pharmacodynamics**



DISCOVERY OF THERAPIES

- **Single Drug**
  - **Single Entity or Modality**

    Practical and Efficient Approach

    Median-Effect Principle of the Mass Action Law

- **Drug Combination**
  - Multiple Drugs or Modalities

    > 20 different definitions for synergy in bio-medical literature

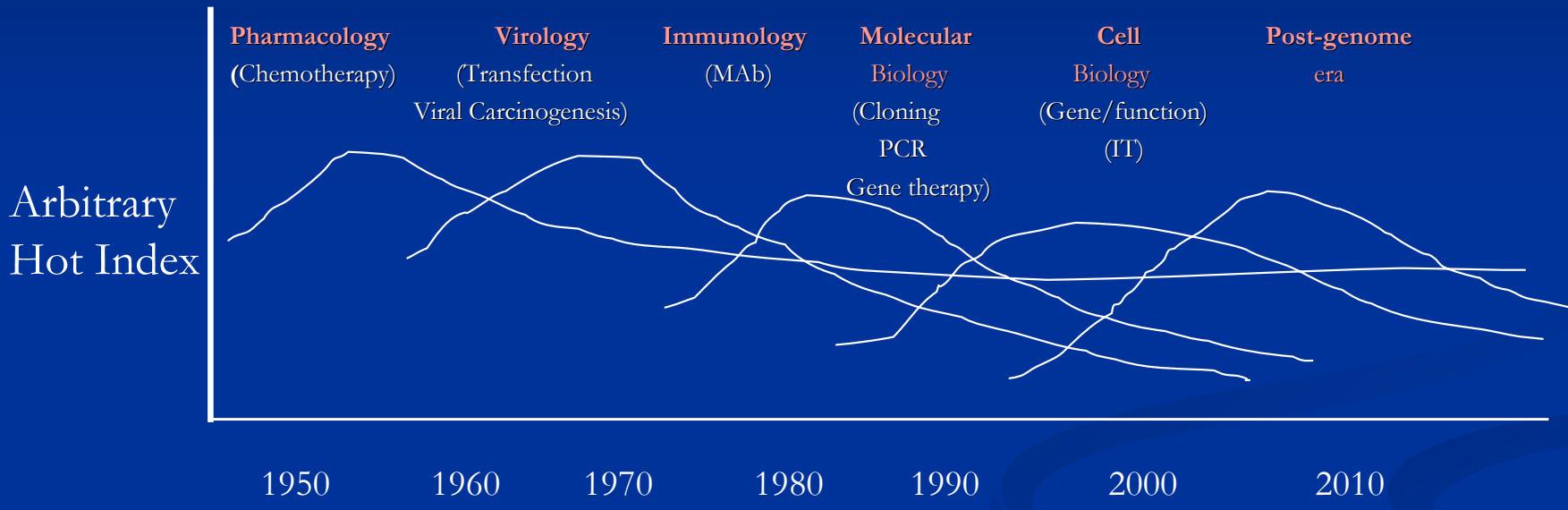
    Confusions in Synergy Claims lasted over 100 Years

    Combination Index for Synergy Definition Based on the Mass-Action Law

Changing Climates in Cancer Research

Does Anyone Know Where to Go?

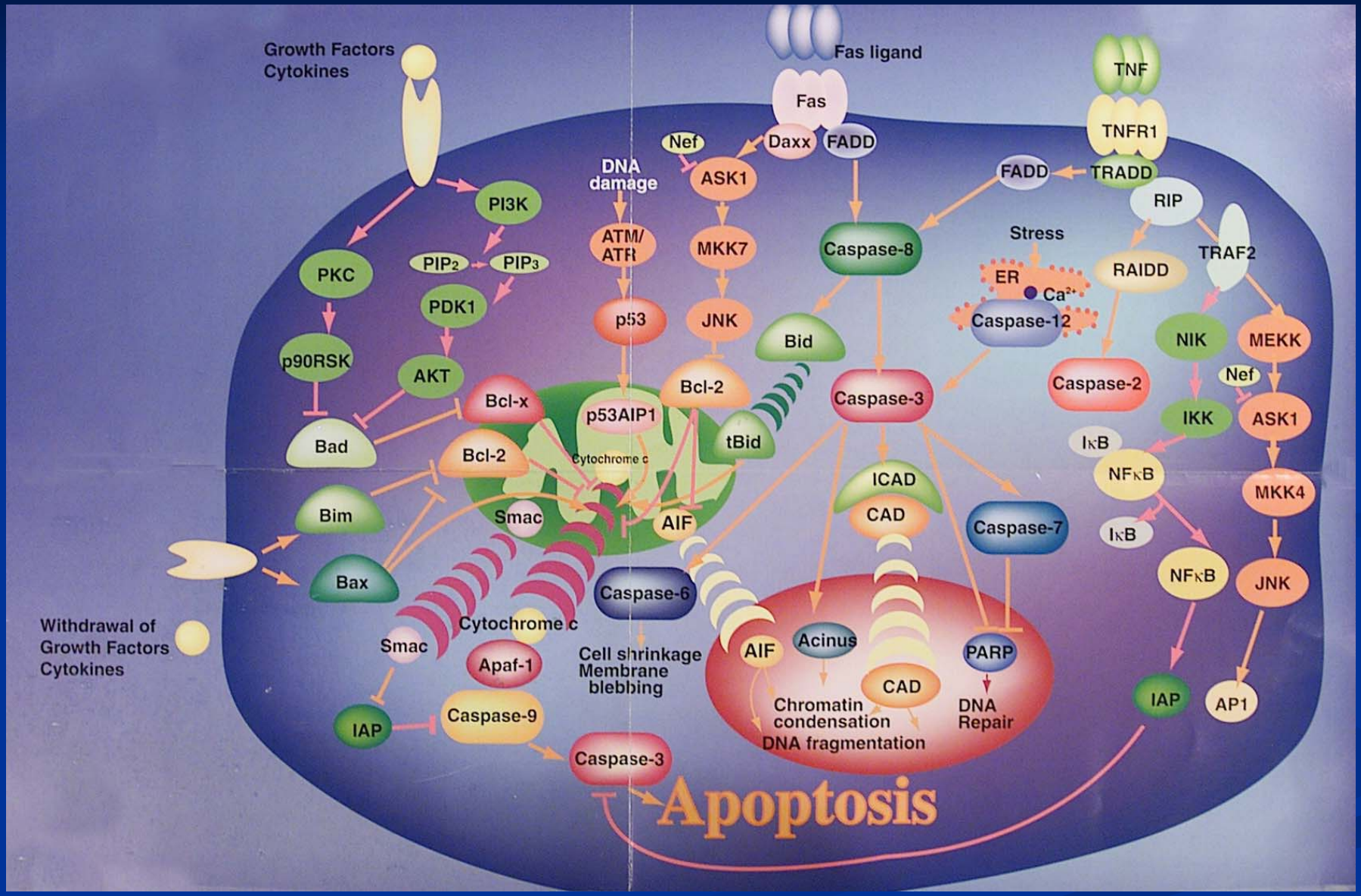
Therapy Approaches



Surgery & Radiation

Prevention

System Biology? How to Integrate These?



Myth of Semantics

What Do You Mean by "Mechanism"?

Quantum Mechanical, Chemical, Molecular,
Cellular, Pharmacological, Animal,
Clinical, Epidemiological?

Do we really understand mechanism of Aspirin?

What Do You Mean by "Target"?

Isn't It Just Receptor?

What Do You Mean by "Pathway"?

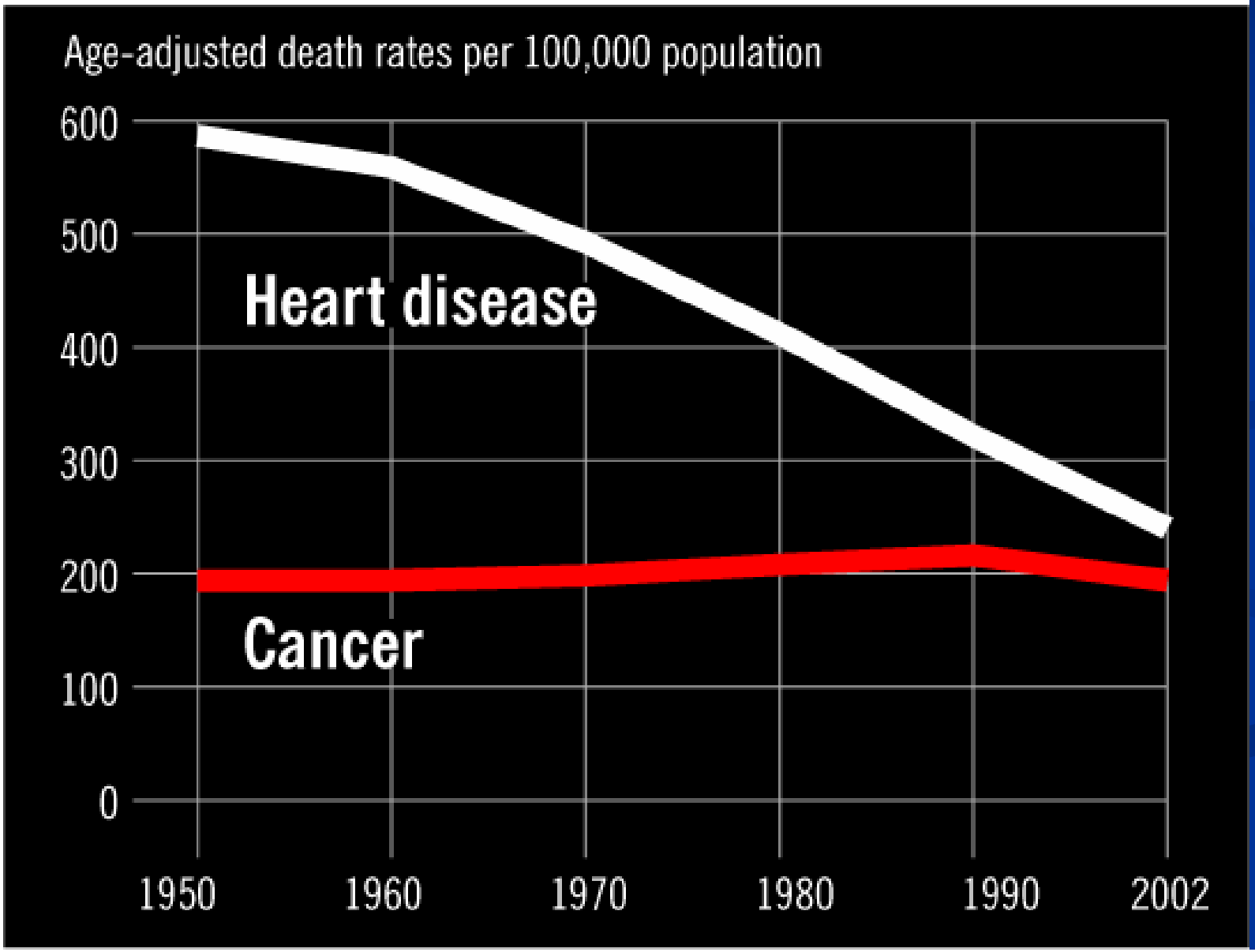
An Enzyme Reaction is a Mini-Pathway.

We Need to Understand the Kinetics/Dynamics/Mathematics
of Simple Ones First

Optimism is essential, but the percentage of Americans dying from cancer is still what it was in 1970 . . . and in 1950.

PUBLIC ENEMY NO. 1

Doctors have dramatically reduced deaths from heart disease. But cancer is as lethal as ever and may soon overtake it as the biggest killer of Americans.



FORTUNE CHART / SOURCE: CDC

DATABASES

The following terms in this article are linked online to:

Medscape DrugInfo:

http://promini.medscape.com/drugdb/search.asp

amprenavir | nelfinavir | zanamivir

Access to this interactive links box is free online.

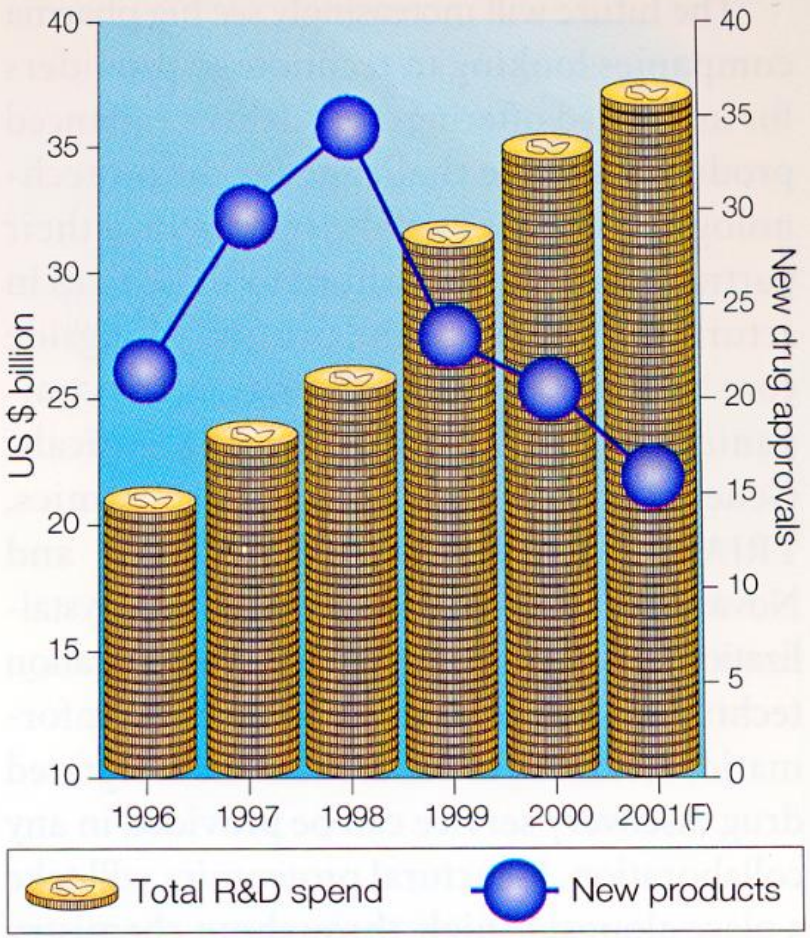


Figure 1 | **Research and development (R&D) spending versus productivity for the top 20 pharmaceutical companies.**

Basic, Fundamental Issues in Bio-Medical Research — Questions raised after spending hundred billions of dollars

1. How to Draw a Dose-Effect Curve?

[Can we draw a curve from only two data points? Yes!!]

2. What is the "Additive Effect" of Two Drugs?

[What is synergy?]

3. System Biology?

[How to integrate them?]

4. Are We on the Right Track?

[Or medical research lopsided?]

5. Is There A Unified Theory?

[Yes. There is a unified "common link" and "reference point"!]

6. What are the Roots of Skyrocketing Costs for Medical Care and Medical Research?

[Yes. There are ways to constrain or to conserve!]

A Practical R & D Proposal

T.C. Chou (a personal view)

- **To Remain Efficient and Competitive, It is Essential to Separate "Basic Research" from "Drug Discovery"**

- **To be Economical, Let Academia to Do Basic Research for "Knowledge" and Let Big Pharma focus on "Efficacy and Safety" for New Products or Pipe Line.**

- **Using the Unified Theory of Mass-Action Law to Conduct Small-Size Experimentation and Computerized Simulation to Constrain the Costs and to Conserve Animals**

"Approach" Leads to "Results" in Drug Discovery

- Based on U.S. Patent and Trademark Office Record, Researchers with 17 or More Patents since 1976 constitute 99th Percentile of Inventors.

- Chou, T.C. with Small Number of Staff and Limited Resources now has 25 U.S. Patents, since 1991.

- This Statistics Show that There Are Ways to be More Effective and Efficient in New Drug Discoveries.

Evidence of "Theory" Leads to "Efficiency"

— based on a case and statistics of T.C. Chou

- **Publication: 283 Articles**
- **Total Citation: > 11,011 Times (as of 04/03/2008)**
- **31 Papers Cited Over 100 Times, 12 of them are theoretical papers**
- **Invention: 25 U.S. Patents (> 99th percentile of Inventors)**

- **With a small number of staff and a moderate budget. It can be done.**
- **The "Theory" and "Approach" play an important Role.**

The Integration of Systems Biology

Concept Principle Philosophy

The Mighty Mass-Action Law

The Common Link

The Power of Mathematical Induction and Deduction

Deduction Lead to Discovery

The Unified Theory & GPS Concept

The Kinetics and Dynamics

◇

Connecting Entity, Time, Space, Order and Vector

The Mass-Action Law Based New Bio-Informatics

Merging the Mass-Action Law Principle with Mathematical Induction-Deduction

- The Unified Theory of Dose and Effect

(Chou T.C. J. Theor. Biol. 59: 253-276, 1976)

- The Combination Index Theorem

(Chou T.C. & Talalay P. Adv. Enz. Regul. 22: 27-55, 1984)

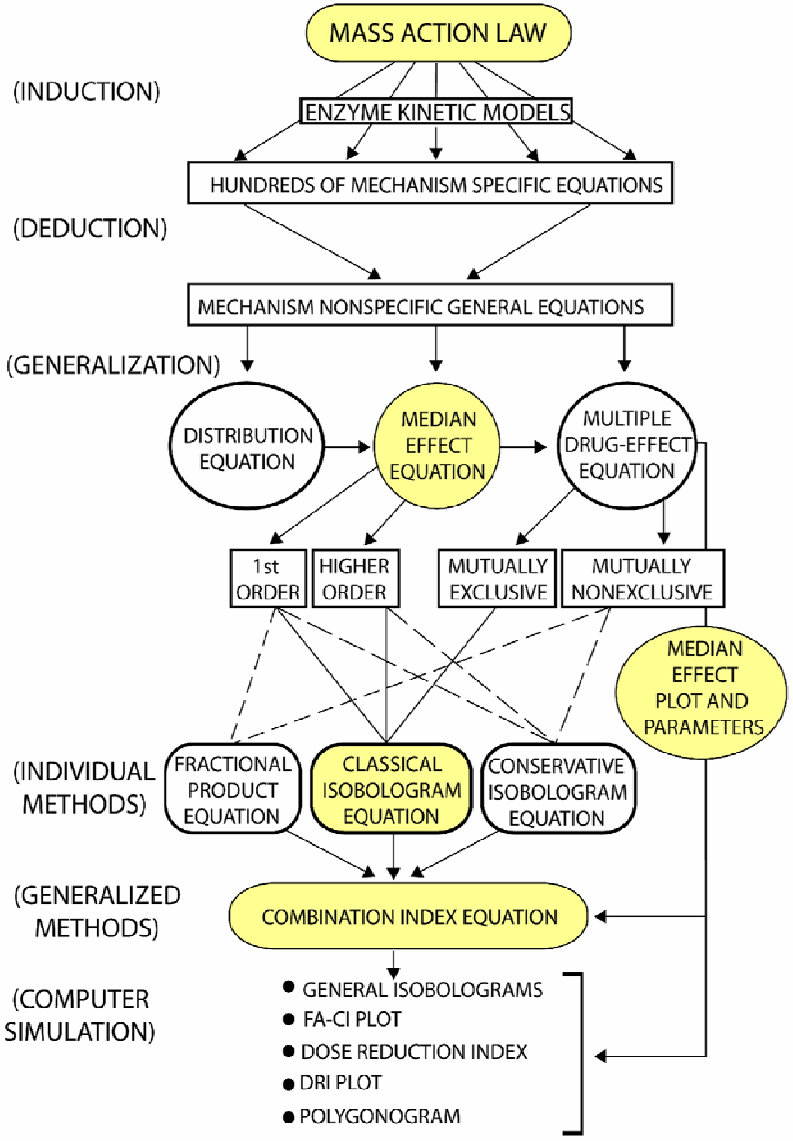
- The Integration & Consolidation and Overview

(Chou T.C. Pharmacol. Rev. 58: 621-681, 2006)

[Based on the Thompson-ISI Web of Science search, the above theory, equation, method and computer software have been cited in over **3,365 scientific papers** **in over 346 different biomedical journals**]

a

The Derivation of the Median-Effect Principle and Its Extentions to Multiple Drug Effect Equation



b

The Derivation of Multiple Drug-Effect Equations with a Flow-Chart

THE MEDIAN-EFFECT PRINCIPLE

(EFFECT) (DOSE) (EFFECT and ENZYME SPECIES)

$$\frac{fi}{fv} = \frac{I}{I_{50}} = \frac{I}{I_{50}} = \left(\frac{fi}{fv}\right)^{\frac{1}{m}}$$

$$\frac{I}{I_{50}} = \frac{1}{k_i} x \frac{Ex}{Et}$$ → DISTRIBUTION EQUATION

$$\frac{(fi)_{1.2}}{(fv)_{1.2}} \overset{X}{=} \frac{(I)_1}{(I_{50})_1} + \frac{(I)_2}{(I_{50})_2} = \frac{(f_i)_1}{(f_v)_1} + \frac{(f_i)_2}{(f_v)_2}$$

$$E_t = E + EI_1 + EI_2$$

$$\frac{(fi)_{1.2}}{(fv)_{1.2}} \overset{NX}{=} \frac{(I)_1}{(I_{50})_1} + \frac{(I)_2}{(I_{50})_2} + \frac{(I)_1 (I)_2}{(I_{50})_1 (I_{50})_2}$$

$$= \frac{(f_i)_1}{(f_v)_1} + \frac{(f_i)_2}{(f_v)_2} + \frac{(f_i)_1 (f_i)_2}{(f_v)_1 (f_v)_2}$$

$$E_t = E + EI_1 + EI_2 + EI_1 I_2$$

$$\left[\frac{(fi)_{1.2}}{(fv)_{1.2}}\right]^{\frac{1}{m}} \overset{X}{=} \frac{(I)_1}{(I_{50})_1} + \frac{(I)_2}{(I_{50})_2} = \left[\frac{(f_i)_1}{(f_v)_1}\right]^{\frac{1}{m}} + \left[\frac{(f_i)_2}{(f_v)_2}\right]^{\frac{1}{m}}$$

$$E_t = E + E(I_1)_m + E(I_2)_m$$

$$\left[\frac{(fi)_{1.2}}{(fv)_{1.2}}\right]^{\frac{1}{m}} \overset{NX}{=} \frac{(I)_1}{(I_{50})_1} + \frac{(I)_2}{(I_{50})_2} + \frac{(I)_1 (I)_2}{(f_{50})_1 (I_{50})_2}$$

$$= \left[\frac{(f_i)_1}{(f_v)_1}\right]^{\frac{1}{m}} + \left[\frac{(f_i)_2}{(f_v)_2}\right]^{\frac{1}{m}} + \left[\frac{(f_i)_1 (f_i)_2}{(f_v)_1 (f_v)_2}\right]^{\frac{1}{m}}$$

$$E_t = E + E(I_1)_m + E(I_2)_m + E(I_1)_m (I_2)_m \ *$$

DERIVATIONS

Mol. Pharm.10: 235-247, 1974

J.Theor. Biol. 39:235-276, 1976

Mol. Pharm.10: 235-247, 1974

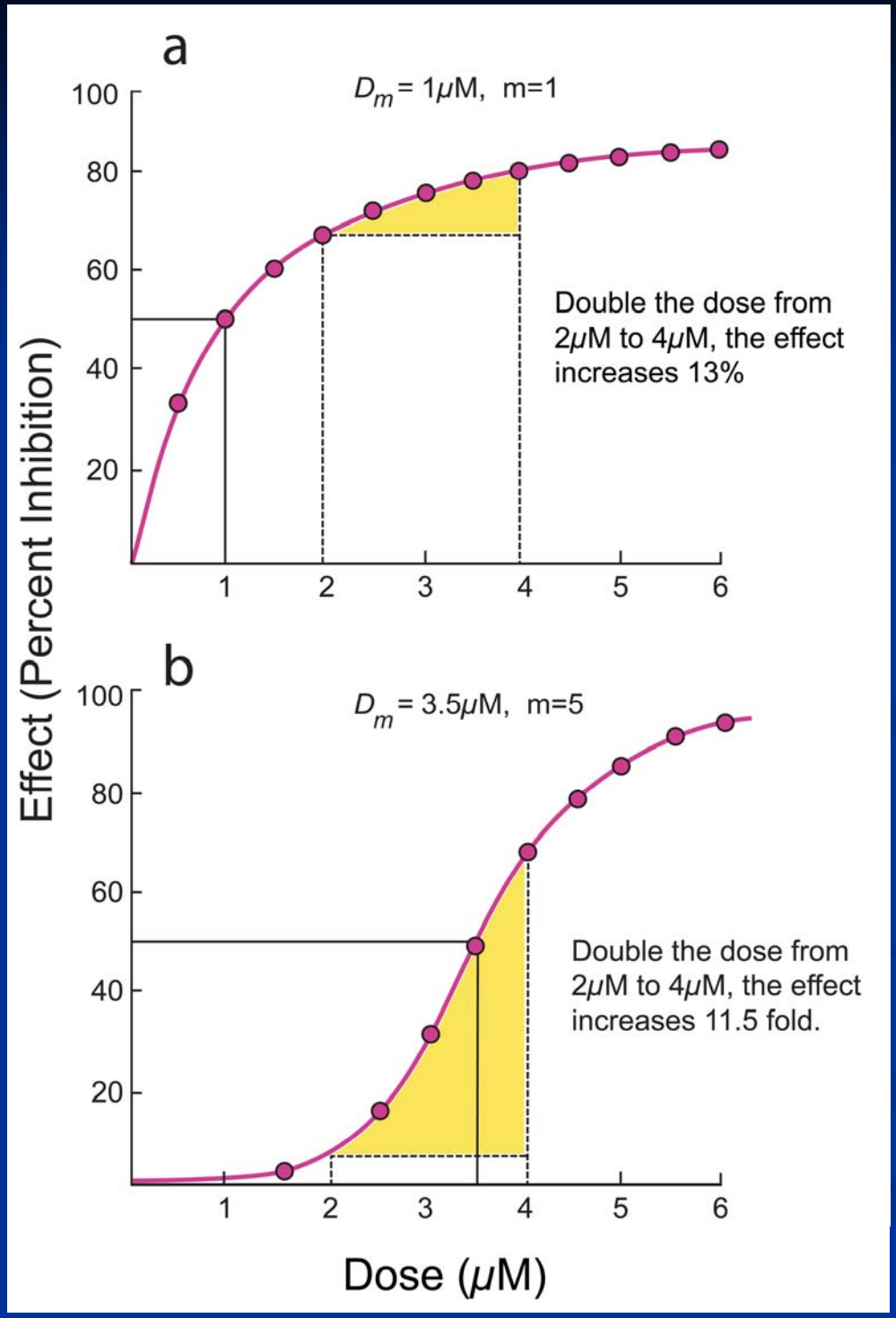
J. Biol.Chem. 252: 6438-6442, 1977

J. Biol.Chem. ibid

Eur.J. Biochem. 115:207-216, 1981

Eur.J. Biochem. ibid

* For restricted conditions



Median Effect Equation
(T.C. Chou)

HYPERBOLIC (FIRST ORDER OR MICHAELIS-MENTEN), m = 1, SIGMOIDAL (HIGHER ORDER), m>1
FOR BOTH CASES:

$$\frac{\mathbf{fa}}{\mathbf{fu}} = \left[\frac{\mathbf{D}}{\mathbf{Dm}}\right]^{m}$$

- **fa** = fraction of system affected, e.g. fractional inhibition
- **fu** = (1-fa) = fraction unaffected
- **D** = dose required to produce fa
- **Dm** = dose required to produce median effect. i.e. ED_{50}, IC_{50}
- ***m*** = sigmoidicity (shape)

The Median-Effect Plot (Chou Plot)

$$\text{Log (fa/fu)} = m \text{ Log D} - m \text{ Log Dm;} \quad (y = ax + b)$$

The Unified Theory

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

[*Chou T.C. Pharmacol. Rev. 58: 621-681, 2006*]

Henderson-Hasselbalch equation

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

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

Michaelis-Menten equation

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

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

The Median-Effect Equation

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

$$f_a/(1-f_a) = (\boldsymbol{D}/\boldsymbol{D}_m)^m$$

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

$$\log [(f_a/(1-f_a)] = m[\log(\boldsymbol{D}) - \log \boldsymbol{D}_m]$$

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

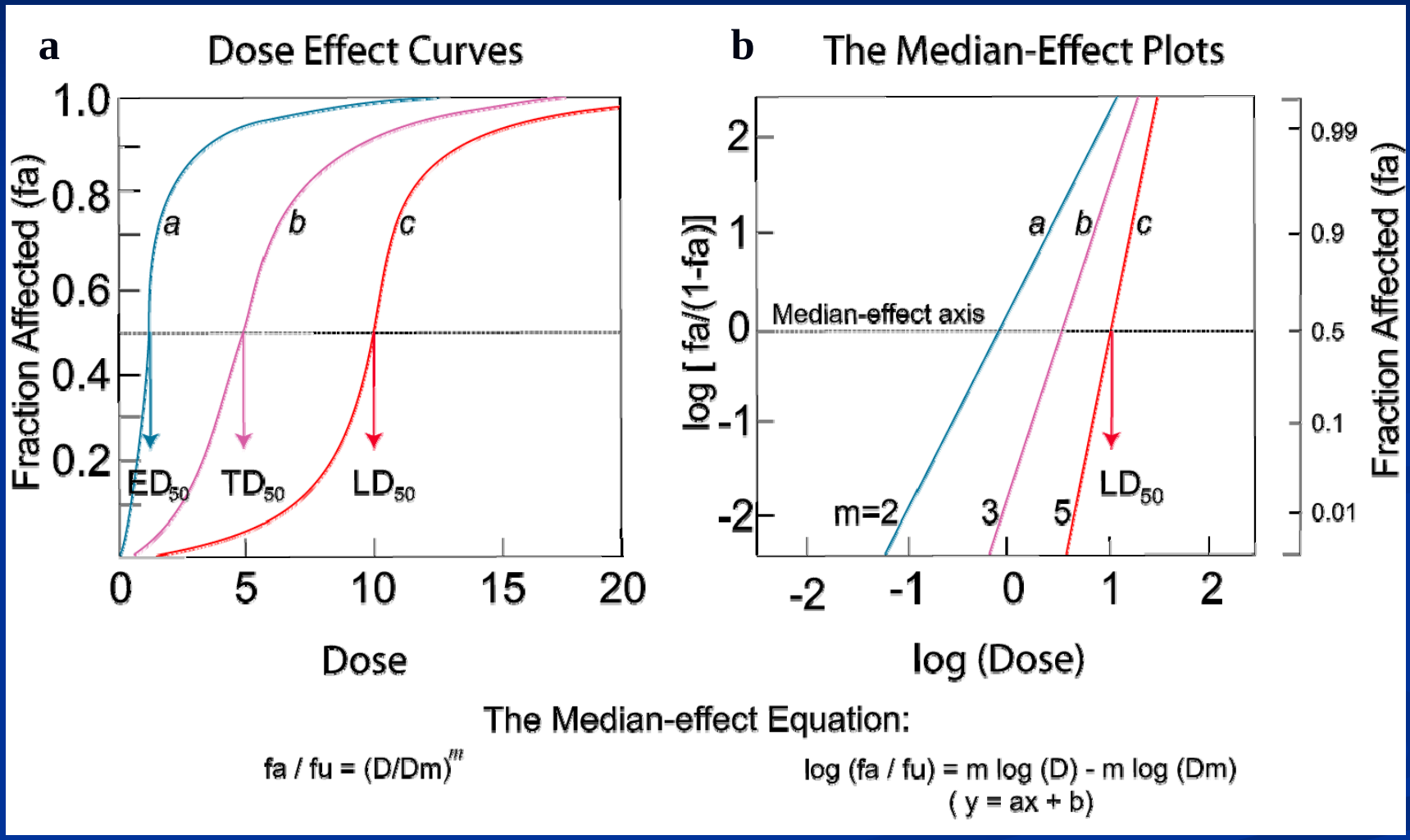
$$f_a/f_u = \boldsymbol{D}/\boldsymbol{D}_m$$

Hill equation

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

Scatchard equation

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



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

CompuSyn

For Drug Combinations

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

By Ting-Chao Chou and Nick Martin

Published and Distributed by

ComboSyn, Inc.

2006

Email: CompuSyn@gmail.com

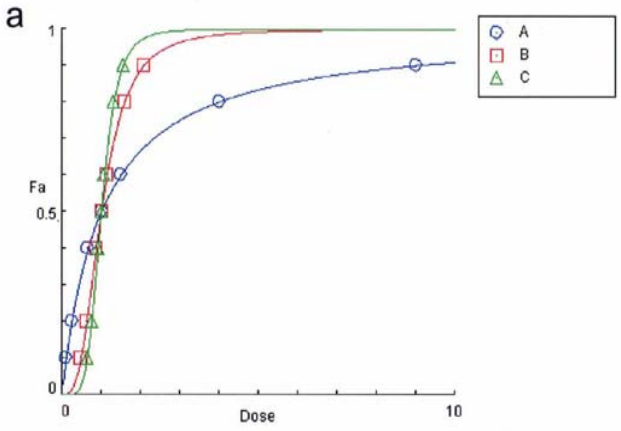
Fax: 201-857-2608

http://www.combosyn.com

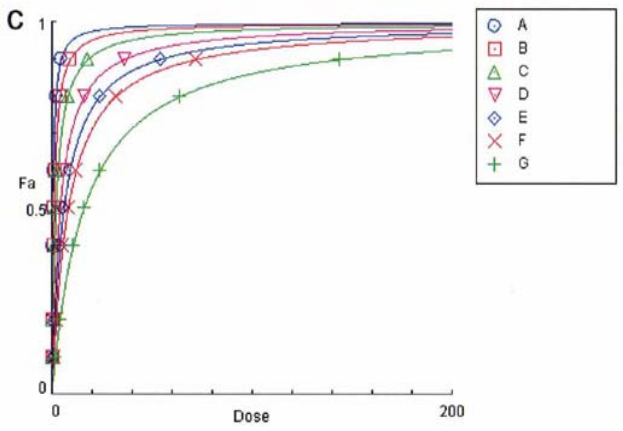
The Computer Simulation of the Median-Effect Equation

The Dose-Effect Curve:

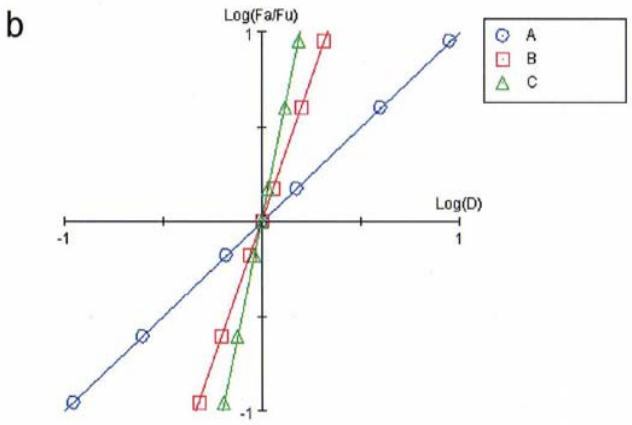
m = 1, 3, 5; D_m = 1

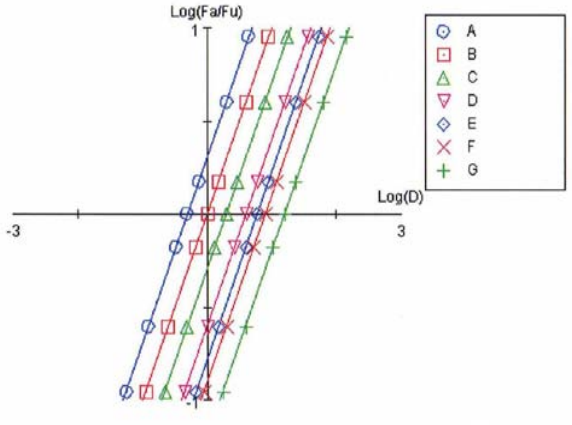


m = 1; D_m = 0.5, 1, 2, 4, 6, 8, 16



The Median-Effect Plot:





The Revelation of A Fundamental New Concept:

- **Dose-Effect Curves Follow the Median-Effect Principle of the Mass-Action Law**
- **The "GPS" Concept: The "Median" Serves As "The Universal Reference Point"**

"One can draw a specific curve with only two data points --- If they are determined accurately"

Combination of Multi-Entities

Synergism is more than Additive Effect

Antagonism is less than Additive Effect

What is "Additive Effect"?

COMBINED EFFECTS OF TWO DRUGS: D_1 AND D_2

(Chou & Talalay : Eur. J. Biochem. 115. 207-216, 1981)

CASE 1: FIRST ORDER

$$\frac{(f_a)_{1,2}}{(f_u)_{1,2}} = \frac{(f_a)_1}{(f_u)_1} + \frac{(f_a)_2}{(f_u)_2} = \frac{(D)_1}{(D_m)_1} + \frac{(D)_2}{(D_m)_2}$$

CASE 2: HIGHER ORDER

$$\left[\frac{(f_a)_{1,2}}{(f_u)_{1,2}}\right]^{1/m} = \left[\frac{(f_a)_1}{(f_u)_1}\right]^{1/m} + \left[\frac{(f_a)_2}{(f_u)_2}\right]^{1/m}$$

$$= \frac{(D)_1}{(D_m)_1} + \frac{(D)_2}{(D_m)_2}$$

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

(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 $(D)_1/(D)_2 = P/Q$

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

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

D = Dose

f_a = fraction affected

f_u = fraction unaffected

D_m = median-effect dose

m = slope, Hill-type coefficient or kinetic order

CI : Combination Index

CI = 1 (summation)

< 1 (synergism)

> 1 (antagonism)

DRI: Dose-Reduction Index

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

For ***n*** Drug Combinations:

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

General Equation for 5-Drug Combination

$$
{}^{5}(CI)_x = \frac{(D_x)_{1\text{-}5}[P/(P+Q+R+S+T)]}{(D_m)_1\left\{(fa_x)_1/[1-(fa_x)_1]\right\}^{1/m_1}} + \frac{(D_x)_{1\text{-}5}[Q/(P+Q+R+S+T)]}{(D_m)_2\left\{(fa_x)_2/[1-(fa_x)_2]\right\}^{1/m_2}}
$$

$$
+ \frac{(D_x)_{1\text{-}5}[R/(P+Q+R+S+T)]}{(D_m)_3\left\{(fa_x)_3/[1-(fa_x)_3]\right\}^{1/m_3}} + \frac{(D_x)_{1\text{-}5}[S/(P+Q+R+S+T)]}{(D_m)_4\left\{(fa_x)_4/[1-(fa_x)_4]\right\}^{1/m_4}}
$$

$$
+ \frac{(D_x)_{1\text{-}5}[T/(P+Q+R+S+T)]}{(D_m)_5\left\{(fa_x)_5/[1-(fa_x)_5]\right\}^{1/m_5}}
$$

General Equation for N-Drug Combination

$$ {}^{n}(CI)_x = \sum_{i=1}^{n} \frac{(D_x)_{1\sim n}\left\{ [D]_i \Big/ \sum_{1}^{n} [D] \right\}}{(D_m)_i \left\{ (fa_x)_i \Big/ [1-(fa_x)_i] \right\}^{\frac{1}{m_i}}} $$

${}^{n}(CI)_x$ Combination index for n drugs at x% inhibition

$(D_x)_{1\sim n}$ The sum of n drugs that exerts x% inhibition in combination

$\left\{ [D]_i \Big/ \sum_{1}^{n} [D] \right\}$ The proportionality of each of n drugs that exerts x% inhibition in combination

$(D_m)_i \left\{ (fa_x)_i \Big/ [1-(fa_x)_i] \right\}^{\frac{1}{m_i}}$ The dose of each drug alone that exerts x% inhibition.

Where D_m: The median-effect dose (Antilog of the x-intercept of the median-effect plot)

fa_x: Fractional inhibition at x% inhibition

m: The slope of the median-effect plot which depicts the shape of the dose-effect curve. m=1, >1, and <1 indicates, hyperbolic, sigmoidal, and negative sigmoidal curve, respectively.

Nature Precedings : doi:10.1038/npre.2008.2064.2 : Posted 18 Jul 2008

The Scientist
August 2007 (vol. 21, No. 8, p.15)
www.the-scientist.com

What is Synergy?

It is difficult to believe that biomedical communities are still debating how to define an "additive drug effect" for over 100 years, even for the combination of only two drugs in vitro. This is after spending a tremendous amount of effort and resources during the past decades on basic biomedical research. I believe the time has finally come to call for a consensus on "what is an additive effect" and thus, on "what is synergy," to avoid the harms of faulty synergy claims.

Without using a clear definition of synergism, it's misleading to make **claims** about synergy, whether in paper in a scientific journal, a research grant application, claiming a discovery of a new utility patent for a new drug combination, or seeking approval of a new drug combination for clinical trials and use from the FDA. Individuals have their own definition of synergism based on their preferences, purposes and agenda.

In my recent article on drug combiation,[1] I argue that there is only one definition for synergy (i.e., CI < 1), and there is only one basis to determine it, which is the mass-action law. I extend an **open invitation** to all methods that claim to determine synergism using anything other than the combination index method based on the mass-action law.

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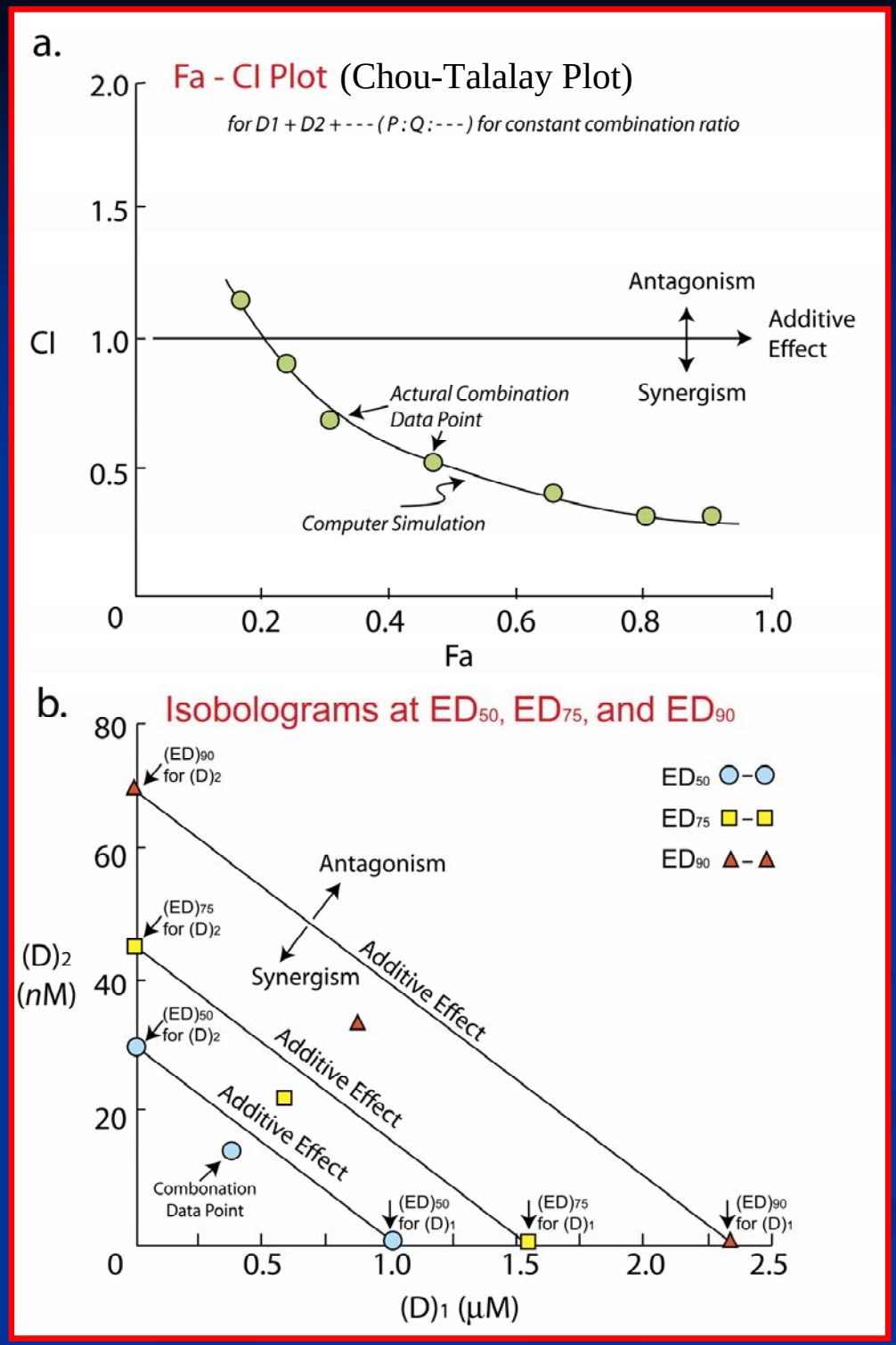
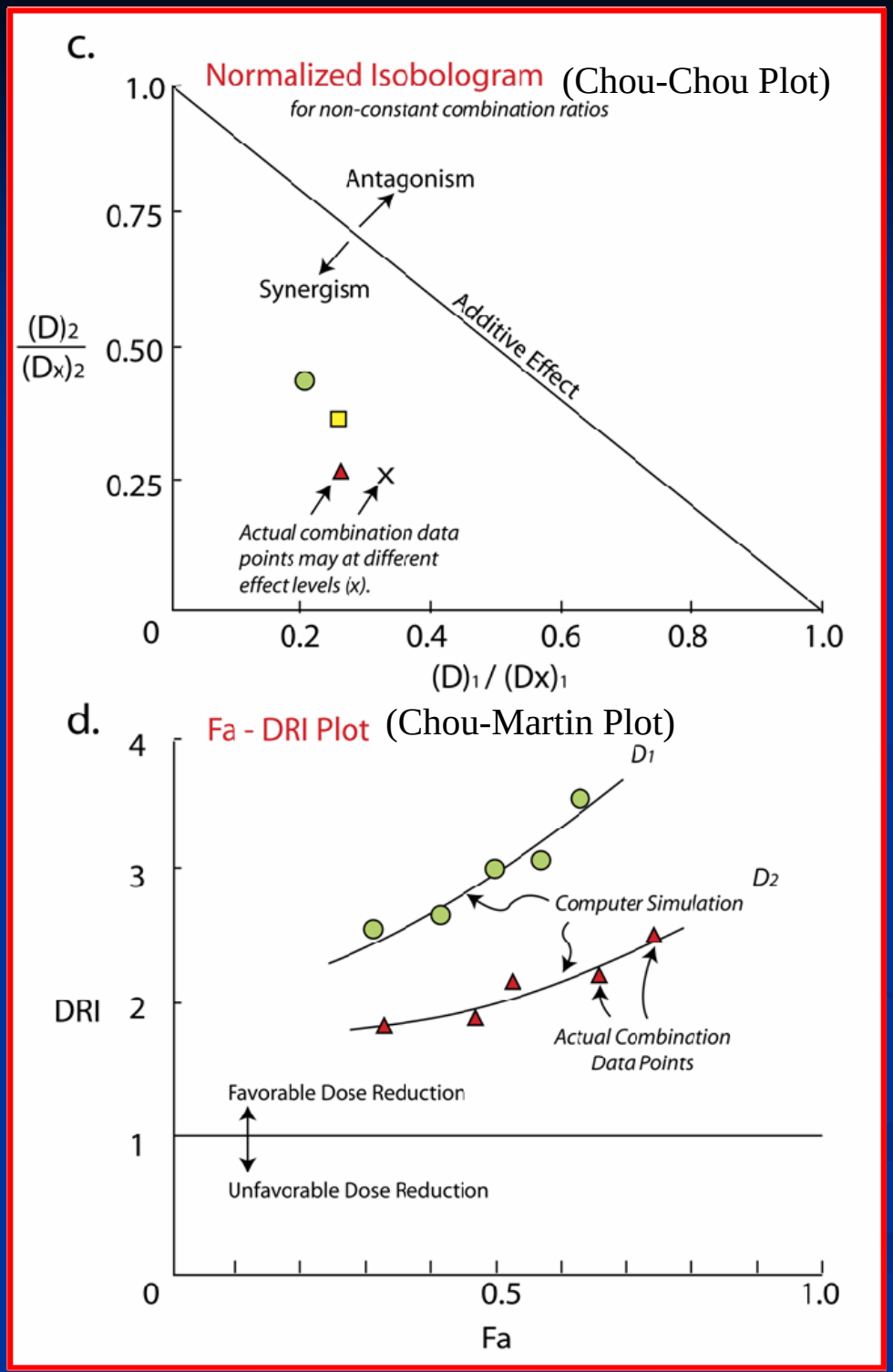
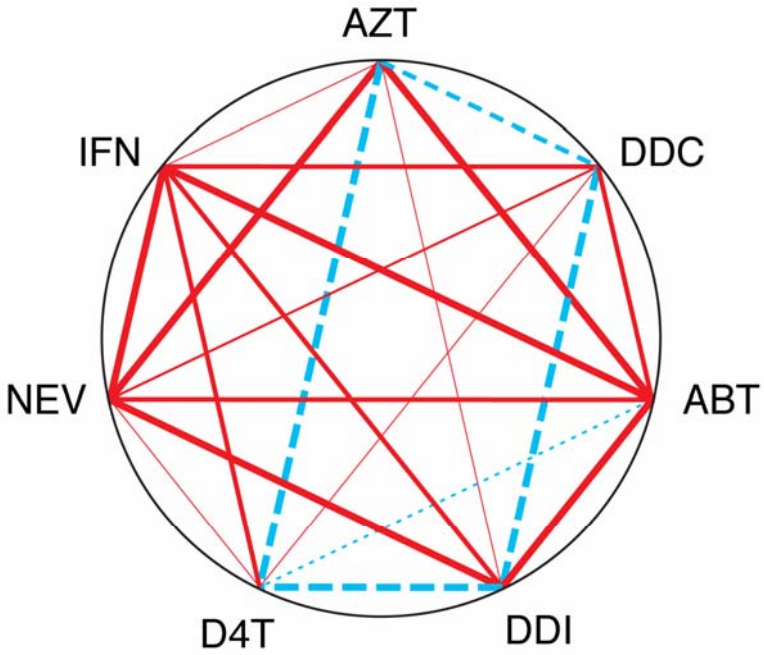
1. T.C. Chou, "Theoretical basis, experimental design, and computerized simulation of synergism and antagonism in drug combination studies," *Pharmacol Rev*, 58: 621-81, 2006

(Web link: http://pharmrev.aspetjournals.org/cgi/content/abstract/58/3/621)





Two Drug Combinations for Seven Anti-HIV Agents and the Heptagonal Polygonograms for Cocktail Selection



Synergism	———	+++
Moderate Synergism	———	++
Slight Synergism	———	+
Nearly Additive Effect	———	±
Antagonism	– – –	– – –
Moderate Antagonism	– – –	– –
Slight Antagonism	·····	–

$$\sum_{r=2}^{7} C_r^7 = 120$$

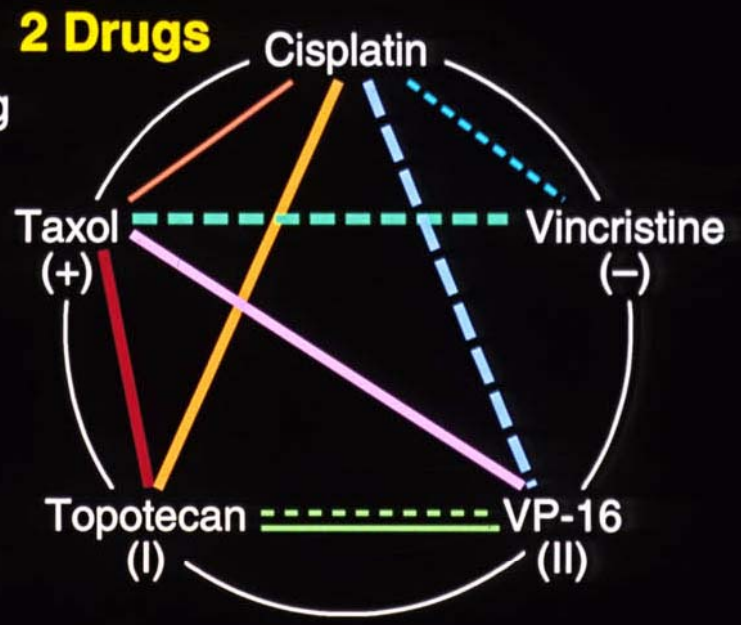
Mechanism

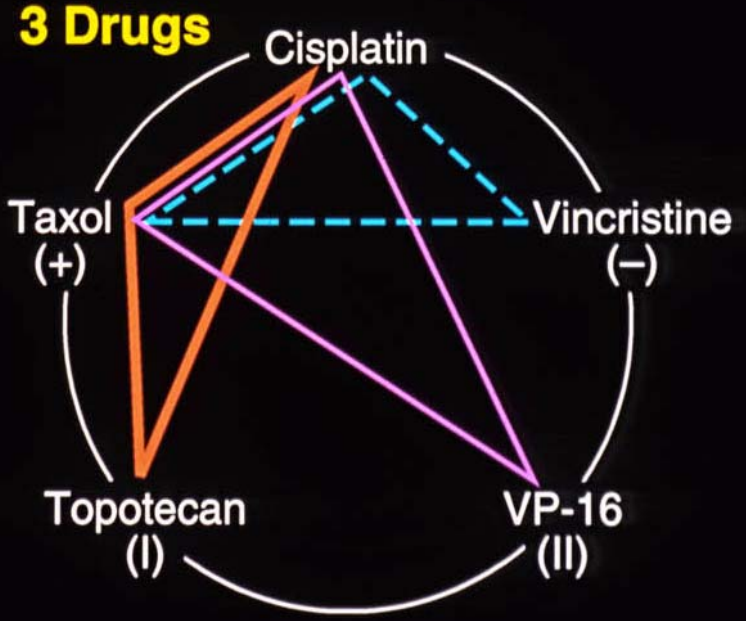
Alkylation
DNA cross-linking

Microtubule
Polymerization

DNA
Topoisomerase
Inhibition

Drug Interactions





Computerized Simulation of Synergism/Antagonism

[The Practical & Quantitative Bio-Informatics]

Primary Questions:

- Are 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
- Schedule dependency
- Selectivity of synergism
- Condition directed synergism

Toward the "Unified Biology"

—The Mass-Action Law Based Bio-Informatics

The Unified Theory: The Median-Effect Principle

[Chou. J. Theor. Biol. 39: 253-276, 1976]

The Combination Index Theorem: "Median" as the Common Link

[Chou. Pharmacol. Rev. 58: 621-681, 2006]

- **Universal:** **Regardless of Entities, Mechanisms, Modes of Action**
  [From Molecular, Cell, In vitro, In vivo to Epidemiology]
- **Dimensionless:** **Any Units (e.g., μM, μg/ml, IU, Rad…..)**
- **Simplicity:** **Effectiveness and Economy**
  [Draw a curve for Two Data Points: A "GPS" Concept]
- **Serving Humanity:** **Drug Discovery: single & multi-entities**
  Risk Assessment
  Regulatory Affairs
  Conservation of Laboratory Animals

The "Unified Theory" Based on The Mass-Action Law Reveals:

"We can draw a specific curve with only two data points,

if they are determined accurately"

- **This small skill (GPS Concept) makes fundamental conceptual claim that has far reaching consequences in bio-medical sciences**
- **These consequences include conservation of research time, effort, and resources, as well as regulatory affairs and saving animal's lives**

"Empirical Curve-Fitting" Has No Science in It, and "Over Stressing Statistics" is wasteful and inefficient

- **We need quantitative biology based on The Mass-Action Law**

The Mathematical / Philosophical Contents

— For details, see Chou T.C. Pharmacol. Rev. 58: 621-681, 2006

The Median-Effect Equation

$$f_a/f_u = (D/D_m)^m \quad \text{(Eq. 1)}$$

$$\log (f_a/f_u) = m \log(D) - m \log(D_m) \quad \text{(Eq. 2)}$$

$$D = D_m [f_a/(1-f_a)]^{1/m} \quad \text{(Eq. 3)} \qquad D \;\&\; f_a \qquad f_a = 1/[1 + (D_m/D)^m] \quad \text{(Eq. 4)}$$

Substance & Function — **Interchange**

The Combination Index Theorem

$$\frac{(f_a)_{1,2}}{(f_u)_{1,2}} = \frac{(f_a)_1}{(f_u)_1} + \frac{(f_a)_2}{(f_u)_2} = \frac{(D)_1}{(D_m)_1} + \frac{(D)_2}{(D_m)_2} \quad \text{(Eq. 5)}$$

$$\left[\frac{(f_a)_{1,2}}{(f_u)_{1,2}}\right]^{1/m} = \left[\frac{(f_a)_1}{(f_u)_1}\right]^{1/m} + \left[\frac{(f_a)_2}{(f_u)_2}\right]^{1/m} = \frac{(D)_1}{(D_m)_1} + \frac{(D)_2}{(D_m)_2} \quad \text{(Eq. 6)}$$

Kinetic Order — **Common Link**

$$^n(CI)_x = \sum_{j=1}^{n} \frac{(D)_j}{(D_x)_j} \quad \text{(Eq. 7)}$$

N = 1~ n — **Generalization**

$$CI = \frac{(D)_1}{(D_x)_1} + \frac{(D)_2}{(D_x)_2} = \frac{(D)_1}{(D_m)_1 [f_a/(1-f_a)]^{1/m_1}} + \frac{(D)_2}{(D_m)_2 [f_a/(1-f_a)]^{1/m_2}} \quad \text{(Eq. 8)}$$

Entities — **Integration**

Nature Precedings : doi:10.1038/npre.2008.2064.2 : Posted 18 Jul 2008

The Modern Science Algorithms and The Ancient Philosophy

- New Mathematical Interpretations of Ancient Philosophy

[Confucian Doctrine of the Mean (中庸); Dao's Harmony (和諧/中節); Fu-Si Ba Gua (伏羲八卦) and Chou's Wu-ji er Tai-ji (無極而太極)]

- Common Link among Theories and Philosophy

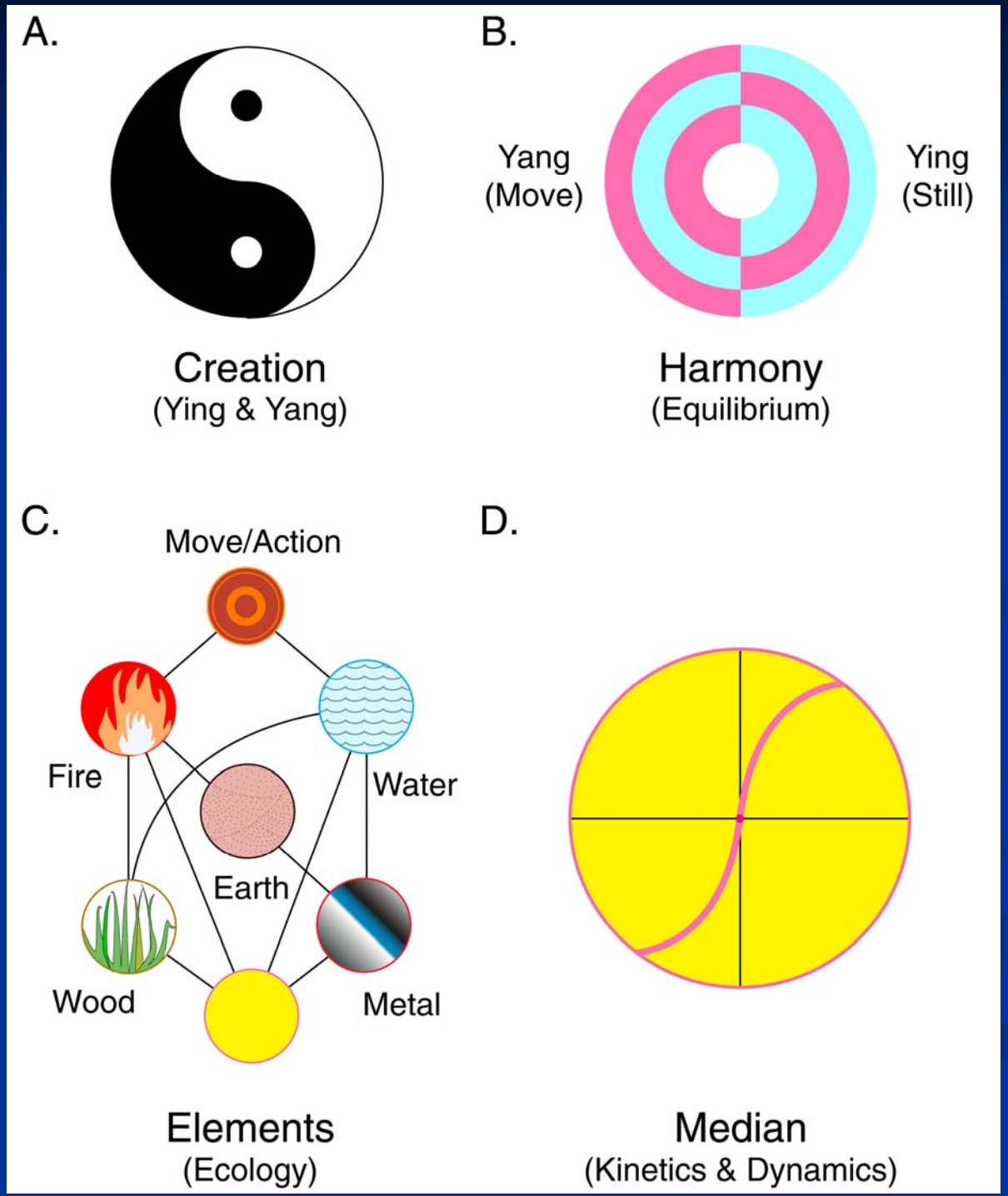
[The Median-Effect Principle of the Mass-Action Law]
(質量作用中效定理)

- Introduce the Dynamic Equilibral Philosophy for Interchangeability of "Dose and Effect"; "Material and Mind"; "Yin and Guo"; and "Knowledge and Execution"

- Complements of East and West Philosophy via Scientific Exploration

[Western Science and Eastern Principle]
(中學為體,西學為用)

Ancient Philosophy and Modern Interpretations



Pure-Noncompetitive ⟷ Harmony

Median

$$IC_{50} = \frac{2\ K_{is}\ K_{ii}}{K_{is} + K_{ii}} \quad \text{(Eq. 9)}$$

⟷ **Harmonic Mean**

Chou, T.C. Mol. Pharmacol. 10: 235-247, 1974

Rate Equation for Non-competitive Inhibition:

$$V_i = \frac{VS}{K_m [\ 1 + (I/K_{is})\ ] + S [\ 1 + (I/K_{ii})\ ]}$$

Graphics for Non-competitive Inhibition:

Rearrangement of Eq. 10 yields:

$$\frac{1}{v_i} = \underbrace{\frac{K_m}{V}\left(1 + \frac{I}{K_{is}}\right)}_{\text{(slope)}} \frac{1}{S} + \underbrace{\frac{1}{V}\left(1 + \frac{I}{K_{ii}}\right)}_{\text{(intercept)}}$$

Therefore, a plot (i.e., the Lineweaver-Burk plot) of x = 1/S *vs.* y = $1/v_i$

yields a slope of : $\frac{K_m}{V}\left(1 + \frac{I}{K_{is}}\right)$

and a y-intercept of : $\frac{1}{V}\left(1 + \frac{I}{K_{ii}}\right)$

Hence,

$$K_{is} = \frac{I}{[\,(\text{slope})_i \;/\; (\text{slope})_o\,] - 1}$$

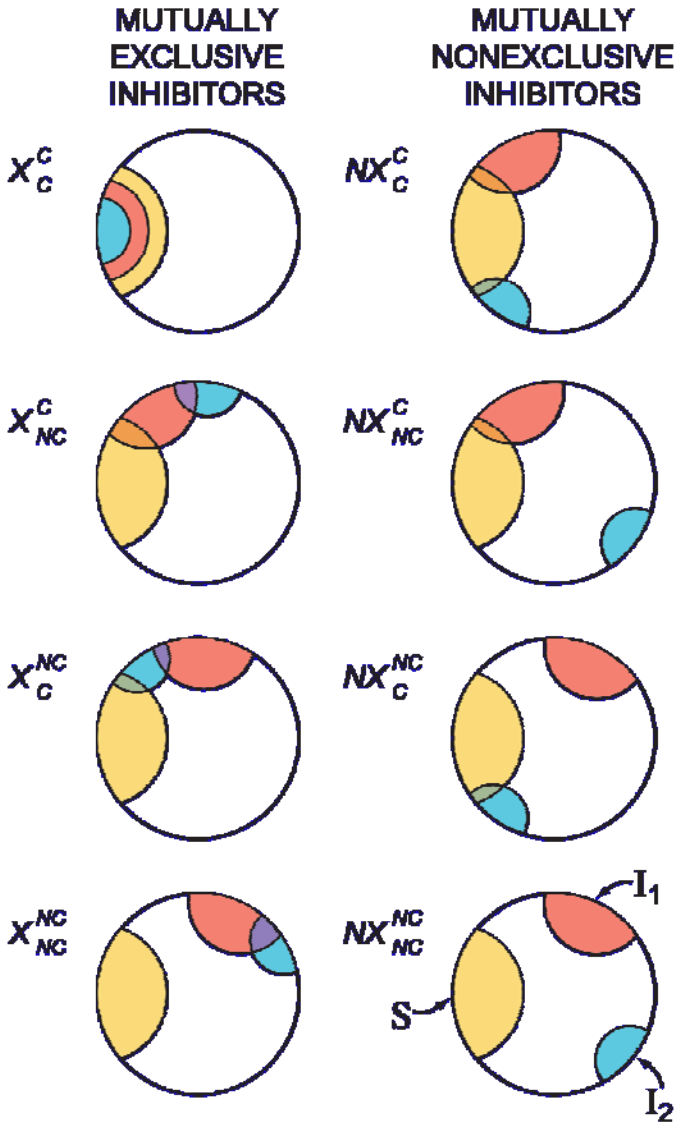
$$K_{ii} = \frac{I}{[\,(\text{y-intercept})_i \;/\; (\text{y-intercept})_o\,] - 1}$$

When the plots of the uninhibited control and the noncompetitive inhibitor intercept both on the x-axis on the same point, then $K_{is} = K_{ii}$ which leads to $IC_{50} = K_i$, and, therefore, "pure non-competition" is ensured for harmony.

Therefore, there is a physical, chemical, geometrical, mathematical and ethical link between "harmony" and "non-competitiveness", and literally, Chung-Yung is the "center of harmony"

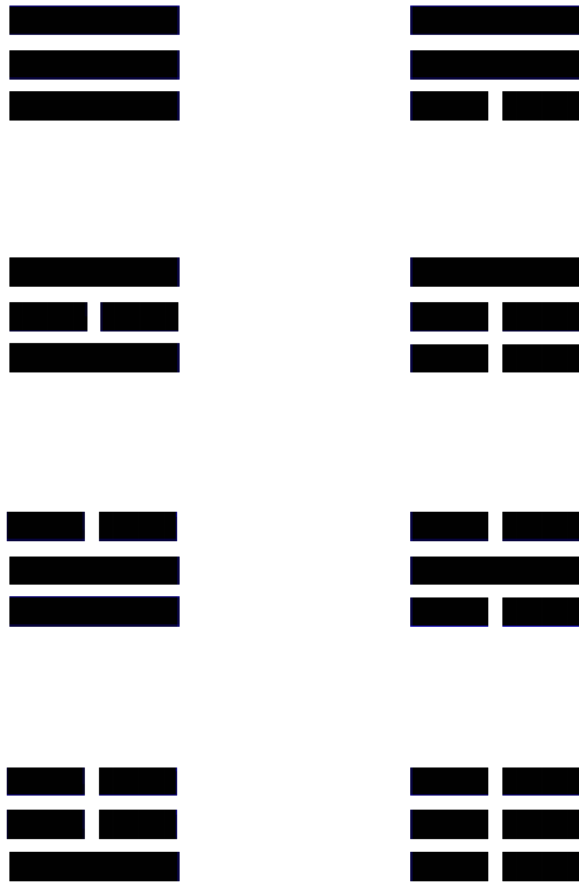
Modern Topological Analysis

(Chou, TC. Pharmacol. Rev. 58: 621-681, 2006)



The Corresponding Fu-Si Ba Gua

伏羲八卦(> 2000 BC)



Applications of MEP and Combination Index Theorem

- Simplified, Efficient, Economical Small Size Experimentation
- Non-Empirical Curve-Fitting for Dose-Effect Curves
- Calculation of K_i from IC_{50}
- Determination of Mass-Action Law Parameters
- Mass-Action Law Based Algorithms for Computer Simulation
- Definition for the Additive Effect or Definition of Synergism
- Low Dose-Risk for Carcinogens, Toxic Substances or Radiation
- Epidemiological Projection of Age-Specific Cancer or Other Disease Rates
- Conservation of Laboratory Animals
- Design of Anti-HIV Cocktail, or Combination Chemotherapy of Cancer by Using Polygonogram

Merging the Mass-Action Law with Mathematical Induction and Deduction Leads to the Unified Theory:

(Chou, T.C. *J. Theoretical Biol.* 59: 253-276, 1976)

The Median-Effect Principle (MEP)
The Median-Effect Equation (MEE)

A. The "Median" is the "Common Link" for

- The 1st order to the Higher-Order Dynamics
- The Single Entity and Multiple Entities
- Competitiveness
- Exclusivity

B. The "Median" is the "Universal Reference Point" for

- The GPS Concept for Bio-Informatics
- Drawing a Specific Curve for Only Two Data Points
- Using the Data to fit the Mass-Action Law

C. These "Common Link" and the "Reference Point" are also Revealed by the Confucian Doctrine of the Mean; Chou Dun-Yi's Wu-Ji Er Tai-Ji; Dao's Five Elements and Harmony; and Fu-Si's Ba-Gua.

Merging the Mass-Action Law with Mathematical Induction and Deduction Leads to the Multiple Drug Effect Equation:

(Chou-Talalay, *Eur. J. Biochem.* 115: 207-216, 1981)

The Combination Index Theorem
The Isobologram Equation
The Dose-Reduction Equation

- General, Efficient, Economical, Dimensionless and Mechanism Independent
- Algorithms for Computer Simulation of Synergism
- Define Synergism (CI < 1), Additive Effect (CI = 0), and Antagonism (CI > 1)
- Use Any Units: μM, ng/ml, IU, MOI, Rad, etc.
- Dose-Reduction Index
- The F_a-CI Plot (Chou-Talalay Plot); Normalized Isobologram (Chou-Chou Plot); F_a-DRI Plot (Chou-Martin Plot), and Polygonogram by Computer Automation
- "Part" and "Whole" Equation for K_i/IC_{50}

New Concept for New Biology

Are We Lopsided? How is the Peer Review Today?

--- Are New Ideas Encouraged or Suppressed?

Contrast of New and Old

1. Mass-Action Law *vs.* Empirical
2. Convergent *vs.* Divergent
3. Quantitative *vs.* Qualitative
4. Deterministic *vs.* Statistical
5. GPS *vs.* Random Walk
6. Economic *vs.* Consumptionism
7. Fundamental *vs.* Mechanistics
8. Biological System *vs.* System Biology
9. Definition *vs.* Semantics
10. Novelty *vs.* Conformationism

Issues

Draw a Dose-Effect Curve?

Philosophy?

What is Additive?

What is Synergy?

Universal Reference Point?

Efficiency?

Unified Theory?

Integration?

Algorithm?

Peers?

Thanks