MAL Unified General Dynamics Theory: The Median Principle for Algorithmic Digital R&D in Life Sciences and Cross-Disciplinary Informatics

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Article

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Summary

Systematic inputs-and-outputs pattern combinatorial analysis on biological enzymic and pharmacological dose-effect relationship of the mass-action law (MAL), resulted in the derivation of over 300 reaction rate equations, that reduced into three unified general theory, represented by MEE/CIE/and DRIE, have garnered tens of thousands citations with over 1,500 citing journals and citing patents, indicating impacts of a new path to scientific innovation and discovery. The equations, algorithms, and scientific terms that have evolved over five decades make it difficult to navigate the theoretical parts. This paper illustrates how and why the MAL-theoretical concept serves our understanding of natural phenomena under the concepts of "One" and "Median" (point, axis, and plane rotations). The Median-Effect Equation (MEE) provides a unifying principle for dose-response relationships, simplifying complex dynamics to two key parameters and enabling efficient experimental design and computational data science simulations. It has been extended to the Combination Index equation (CIE) for interactions, offering a universal scale for synergism (CI<1), additive effect (CI=1), and antagonism (CI>1) determination that has practical automated digital deterministic, efficient, cost-effective features, from drug development to ecology, and beyond. It delved into the mathematical contrast between the Floating Ratio in Life and the Golden Ratio in Non-life, which signifies the difference between the finite, closed, flexible, and cyclical nature of Life vs. the infinite, open, unbounded patterns of infinity in math, physics, and AI. This led us to the Doctrine of the Median—the insight that the midpoint of effect is nature's universal reference—and to the Unity Theory of One (UTO), envisioning a future science that measures everything in relation to a unified "whole" of One and its modes of fractional, discrete, and continuous distributions. It is shown that MAL-MEE derived (1966-1976) from substrate inputs and product outputs combinatorial system analysis, on Life science in the real world totality, with the derived unified general MEE of: $fa/fu = (D/Dm)^m$ that is: $f_a = \frac{1}{\left[1+\left(\frac{Dm}{D}\right)^m\right]}$ or $f_u = \frac{1}{\left[1+\left(\frac{D}{Dm}\right)^m\right]}$ and $fa + fu = 1$, which has the *same mathematical geometric form* as the Fermi-Dirac distributional ***e*-function**, the e-logistic growth function, and the statistical PROBIT and LOGIT functions. Interestingly, the MAL-MEE/CIE principle of the median of the real-world, Riemann's zeta function *zeta(2)* for ½ (0.5 or the Median), the *critical line* for prime number distribution; fa or fu functional boundaries 0-1, corresponding to the *critical zone* (0-1) of Riemann's function graphics; and the median point of MEE (at the center of non-trivial zeros of Riemann); and MEE is mathematical form of Hopfield's neural network activation function, like MAL-MEE/CIE, do not have an ***e*-function**. All these functions in the Life and Non-Life domains point to convergence toward the miracle supreme identity, "One", for the Source of Code, with intrinsic properties and distribution functions centered on the "Median" *a priori*. The underlying informatics dynamics can be revealed using mathematical fundamentals such as ratios, medians, 1, 0, the double reciprocal, the double logarithm, and the exponential function for geometric graphical informatics and diagnostics. The MAL theory leads to a very important illustration of the ratio as relativity, such as $fa/fu = [D/Dm]^m = (M)^m$ (the floating ratio, FR, in the form $a/b = a/(1-a) = (1-b)/b$ and mediated by the Median, where $a + b = 1$, manifests *the* Life domain). Golden Ratio (φ), in the fixed ratio in the form $a/b = (a + b)/a = 1 + b/a = (1 + \sqrt{5})/2 = 1.618033\ldots$, $E/M = C^2$ (Einstein), $F/M = a$ (Newton), and C_{14}/C_{12} (median time), all manifest the Non-life domain. Thus, the MAL-median

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mediated ratio is the unified grand rule for all. Those math, statistics, and physical and AI functions involving e-function will approach a near-perfect approximation, or mimic, but not a perfect fit. This imperfection is magnified by human arbitrariness, which changes with time, place, and individual. Here, also emphasizes the exponent of *the square function in space and time (C^2), the* Pythagorean theorem ($a^2 + b^2 = c^2$) of length, and MAL-MEE's m^2 for optimal functional effect cooperativity, and Median's universality. These are exemplified by the discovery of the 2nd-degree (squared) Pascal Triangle derived from the biological inputs-outputs duplex transitions system, e.g., the SP and PS signal transitions, of the (P, S), (↓,↑), (0,1), and (+,-) duplex form patterns for the $\left(C\,{}_{r}^{n}\right)^2$ coefficient distributions. Thus, there is a connection between the Pascal Triangle relevance to Euler's *e* and Chou's 2º-Pascal Triangle relevance to π, and the Riemann zeta function critical line at ½ and Zeta(2); also, a connection between the Chou-Talalay Isobologram equation and the Pythagorean theorem. The MAL-MEE can leads to the invisible "negative doses" which converge to "1" and projects to the Dm, and its double-logarithmic linearization plot, log (fa/fu) vs. log (D), allow the determination of the m-and-Dm paired-identity-parameters and the default addition of, dose-zero and Dm, two-points to all dynamic causal-effect data sets (leading to the minimum two-dose data point theory), which allows for efficient, cost-effective smaller protocol design to facilitate the game-changing Econo-green simulation in scientific R&D. The saving of time, effort, and resources with MAL-based approach (compare to the traditional observation/statistics-based approach) are tremendous, as indicated in 10-fold fewer patients-enrollment needed in anti-HIV two-drug combination clinical protocol design and quantitative synergism-determination by computer simulation. The Golden Ratio (GR) connection brings in classical geometry, physics, and even cosmology. In contrast, Chou's MAL-MEE reveals the Floating Ratio (FR), (fa/fu), effectively linking interdisciplinary biodynamics. Both FR, GR, and D/Dm are dimensionless ratios of relativity, independent of unit, size, physical state, structure, or complexity. The MAL Top-Down framework is the opposite yet complementary of traditional Bottom-Up observation- and statistics-based R&D, like two sides of the same coin. This indicates that life systems have algorithmic linkage of "One" fractional distributions to the principles of physics and to basic AI-infrastructural categorization when applied to complex systems in Life or Non-life transformation (e.g., for equilibrium reaction kinetics derived from biodynamics and physical thermodynamics, radiation, and generative AI/LLMs). Human consciousness and intelligence decide all units and methods of measurement, which evolved into all disciplines of science. This leads to the concept of the Life-Centric Universe (LCU), which encompasses the physical elements of Mass, Force, Time, and Space, and elaborates on their relationships from the viewpoint of the real-world MAL principle. This MAL-MEE/CIE/DOM/UTO/LCU Theory is stated as is and has been time-tested with applications. The MAL-MEE principle of biodynamics and informatics reveals equivalences and analogies with major conclusions in history, mathematics, and physics. The fundamental mathematical codes in Nature's two domains are found exceedingly simple: For Life is a/b = a/(1-a) = (1-b)/b, a + b = 1; For Non-Life is a/b = (a + b)/a = 1 + b/a. Both (a/b) ratios are expressions of the fractional distribution of the Unity of "One" with basically different dynamics, yet maintaining a connection to "1". In Life, FR partitions 1 into complementary components (fa and fu, > 0, < 1, centered at the median, 0.5); In Non-Life, GR partitions 1 into continuous recursive sequences, extendable to infinity without a bound.

Abstract

The Universe has two domains: Life and Non-Life, which manifest the dimensionless relativity ratio with basic codes. For life is a/b = a/(1-a) = (1-b)/b (Floating Ratio), and for Non-Life is a/b = (a + b)/a = 1 + b/a, or (Golden Ratio). Life and Non-Life can be linked and correlated by the two fractional distribution functions of "1". Life is finite, discrete, and binary, cyclable with the Median-based equilibrium, harmony, and homeostasis; Non-Life is open, fractal, and extendable to infinity, as in mathematics, physics, and AI. The Mass Action Law (MAL) Median Effect equation leads to the Unified General Dynamics Theory and algorithm, which provide interdisciplinary and cross-disciplinary common linkage parameters for computerized, digital, efficient, cost-effective, Econo-

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green scientific R&D and data science informatics. The MAL-based input-output sequence, pattern transition, and combinatorics of enzyme reactions led to the discovery of the Second Degree (Squared) Pascal triangle. Surprisingly, the unified theory in life science can be linked to centuries-old mathematical problems, such as Riemann's zeta hypothesis for the critical line and zone, and Euler's Product of Prime Function and its properties.

Keywords: mass-action law (MAL); dose-effect curve (DEC) linearization; inputs-outputs transition (PN, NP) patterns combinatorial analysis; median-effect equation (MEE); combination index equation (CIE); unity theory of one (UTO); "One" is the life and non-life common link; life-centric universe (LCU); floating ratio vs. golden ratio; artificial intelligence MAL algorithm framework

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1. Foundations of the Theory

This MAL work was initiated and extended by this author since 1965 as a graduate student at Yale University, using MAL as the fundamental principle for systems enzyme kinetics, input-output sequential pattern combinatorial analysis, and both linear and circular general systems [1–7].

The input-output patterns (sequential and circular) are systematically analyzed using a combinatorial approach and mathematical induction and deduction to support inductive and deductive conclusions.

The dose-effect or causal-effect relationship in theoretical system biology has been carried out at an optimal homeostatic state at fixed temperature, pressure, oxygen/CO_2 tension, and minimum essential nutrients, leaving "dose" and "effect" the only variables, for the decades-long mass-action law (MAL) intrinsic properties explorations and applications. The unified general equations and algorithms of MAL, independent of unit, physical state, size, structure, and complexity, ensure their universality in applications for dynamic, principle-directed design and automated simulation, enhancing efficiency and cost-effectiveness in R&D. Conceptually, this is a fundamental departure from the traditional observation/statistics-based R&D mindset. Thus, the MAL theory provides a paradigm shift in R&D while serving as a complementary, deterministic alternative, like two sides of the same coin, in gaining knowledge, fostering innovation, and driving discoveries.

The claim that P = NP in quantum-mechanics-level terminology in quantum computing has sparked broad discussions. Christopher Paradise in 2025 proposed that consciousness itself operates as a polynomial-time solver through entropy-driven self-reference." (Digital Dynamics AI, ORCID 0009-0009-9901-8668). This is a new way of thinking that sparks debates about consciousness, intuition, and human cognition.

The P vs NP concept is theoretically relevant to the mass-action law (MAL)-based inputs-outputs sequential transitional-pattern combinatorial analysis, just as AI uses computer programming for question-and-answer. The MAL system-analysis approach was selected as the Ph.D. thesis project at Yale University, focusing on L-asparagine biosynthesis by asparagine synthetase, which involved three substrates (Asp, Gln, ATP) and four products (Asp, Glu, AMP, and PP). [1,2]. The goal was to elucidate the entire reaction mechanism and derive the reaction rate equation. A novel combinatorial analysis for the enzyme substrates input (S) and products output (P), (S, P)-duplex signal pattern transition-numbers of SP to PS, during 1966-1970 [1,2].

The MAL principle reveals a surprising finding: The discovery of the 2nd-degree (squared) triangle, where all elements in the classical Pascal triangle. i.e., if all elements in Chou's triangle take square roots, they become the Pascal Triangle.

It is known that in Pascal Triangle (1st degree), the sum of the reciprocals of the harmonic numbers (1/1 +1/2 + 1/3 +1/4 +1/5 +…) is divergent without a bound. In contrast, the sum of the reciprocals of the triangular numbers (1/1 + 1/3 + 1/6 + 1/10 +…) is convergent to 2. The recent report by Brothers H and Green R showed that the ratios of the sums of sequential rows can lead to Euler's e-entity. [https://sciencespetrum.com/pascals-triangle-the secret-within-3d525d88048d],

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Interestingly, for the Chou's Triangle (2nd-degree for SP and PS pattern transitions concept in biological enzyme system), the sum of the reciprocal of the squared numbers (1/1 + 1/4 + 1/9 + 1/16 + 1/25 +….) = (π^2) /6 = **1.64493406…,** a specific constant, indicating a transition from the fractions of natural inverted square numbers to a transcendental irrational number that is related to π. In addition, the Chou's Squared Triangle can be related to Riemann's Zeta Function at Re(2), with a *critical line* for ½ (the Median), the sum corresponds to the Riemann zeta function ζ(s) at s = 2, which is corresponding to the MAL-MEE's *Median line* at 0.5 for fa = fu = 0.5 for fa + fu =1, i.e., the mathematical function for the fractional distributions of "One", where the boundary range of fa or fu is 0 -1 that is identical to Riemann's *critical zone* (0 -1). This is also Chou's Unity Theory of One (UTO), where MAL-MEE, CIE, and DRIE defined "1" as the universal standard, which is identical to Riemann's *pole* of "1" for singularity, where s >1. Thus s =2, specifically manifests life science dynamics and informatics. The even ***s*** number such as s = 4, 6, and 8, …also related (convergent) to pi (with corresponding higher powers), however, the odd ***s*** number such as s =3, 5, 7, … has, so far, not related to pi., although it can be approximated. It is of interest to note that the Riemann's Zeta Function at Re(2) = (π^2) /6 = 1.64493406…, for life domain dynamics/informatics specific constant, is slightly higher than the Golden ratio $\boldsymbol{\varphi = 1 + (1/\varphi) = (1 + \sqrt{5})/2 = 1.6180339887\ldots}$

The robust growth of the MAL-based R&D theory and its digital simulation method during 2020-2025 has resulted in a net increase of over 11,712 new citations, with a cumulative total of 1,581 citing scientific journals and 1,621 citing patents globally, as reported in bibliometric databases, indicating its game-changing impact.

This report consolidates a unified theoretical and practical framework that charts alternative path to the scientific research and development and digital data science through the Mass-Action Law (MAL) principle and its derived unified general theorems: Median-Effect Equation (MEE) [4], the Doctrine of the Median (DOM) [8,9], the Combination Index Equation (CIE) [6–13], and the Dose-Reduction Index Equation (DRIE) [9,12]. Together, these form a deterministic and scalable system for modeling actions and interactions across biological, biochemical, biophysical, and environmental systems [14–23] and beyond.

Introduction

Two Domains and Ratios

Two domains in Nature, life and non-life, maintain the realm of entity existence through the Doctrine of the Median (DOM) in the Unity Theory of One (UTO) of the Mass-Action Law (**MAL**). [19–22,24]

The MAL system analysis on inputs-outputs, does-effect theoretical sequential, pattern, and combinatorial analysis, leads to the derivation of the unified general median-effect equation (**MEE**):

$fa/fu = (D/Dm)^m$, where D (dose), Dm (median-effect dose), m (exponential dynamic-order), fa (fraction affected), and fu (fraction unaffected); fa +fu =1). Thus, mass and functional effect are interchangeable. The extension of MEE led to the combination index equation (CIE), where CI = 1 (additive), <1 (synergistic), or>*1* (antagonistic) for all entity interactions, including drug + drug or drug + radiation. The MAL-MEE is:

$fa/fu = fa/(1 - fa) = (fu)^{-1} - 1 = [(fa)^{-1} - 1]^{-1} = [D/Dm]^m$, where fa + fu = 1, with general algorithms and the intrinsic properties that manifest **Life**, that is, in a recyclable, closed form for finite fractional distribution of "1". The MEE's floating ratio (fa/fu) has the basic mathematical form of a + b = 1, and $a/b = a/(1-a) = (1-b)/b = (D/Dm)^m = (\mathbf{M})^m$, where **M** is the median-normalized **M**ass. Thus, Effect (fa) and Mass (D) are interchangeable or equivalent in the life domain. This is akin to Einstein's theory of relativity, E = MC2, in which Energy (E) and Mass (M) are interchangeable.

In contrast, the ancient Golden Ratio (GR, φ) ,

$$\boldsymbol{\varphi = \left[\frac{a}{b} = \frac{a+b}{a}\right] = 1 + \frac{b}{a} = 1.618033988749894\ldots = 1 + (1/\varphi) = (1 + \sqrt{5})/2,}$$

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manifests the Non-life domain, in mathematics and physics, for the continuous fractional distribution of "1", in open form, extendable to infinity [22].

Both FR (flexible) and GR (fixed) are dimensionless ratios of relativity due to the cancellation of any unit for the ratio of the same kind, e.g., D/Dm; thus, they are valid independent of unit, physical state, size, structure, and mechanistic complexity, and they are universal. The Dm is a universal reference point, and the dynamics order is a common link; they are universal.

Life and Non-Life

Number scaling such as additive accumulation vs minus deduction, multiply vs divide, exponent vs root, squaring divergence and expansion vs taking root convergence and contraction, can be for real integers or numbers of the number theory, or of the imaginary number, such as i = $\left(\sqrt{-1}\right)$, the exponents show interesting rotational or wave-like properties. Unlike mathematics or theoretical physics, which have π, e, i, φ, and infinity, the life domain uses the natural real numbers as described in this paper. Here, we are specially emphasizing dose-effect dynamics and informatics at the Median, and proximity to the median state of optimal, harmonic, cooperative, and homeostasis biological conditions, which frequently involve receptor, intermediate, pathway, network, systemic coordination and regulation, organization, and environment, in micro and macro scales of structural and functional activities and complexity, with hidden behind invisible intermediates processes. Here are the reasons for developing MAL-MEE-based theories, such as MEP, CIE, DRIE, MTDPT, UTO, and LCU, to reveal the hidden intrinsic properties of natural phenomena. It becomes necessary to conclude that our universe has two domains: Life and Non-Life, each with diverse and complex features. Surprisingly, the fundamental mathematical codes are exceedingly simple: a/b = a/(1-a) for Life and a/b = (a + b)/a for Non-Life.

In biological sciences, the MAL-MEE is defined by general paired parameters: Dm (signifying potency) and m (signifying dynamics-order and shape of dose-effect curves or causal effective graphics).

Life science-based AML-MEE obeys the hyperbolic activation function (m = 1) or a sigmoidal activation function (m ≠ 1), as indicated in computer simulations of biomedical sciences R&D for quantitative digital informatics, and for the AI core-infrastructure algorithm (including the Hopfield's artificial neural network) for input-output in real-world applications.

The biological MAL-MEE hyperbolic and sigmoidal activation function, fa = 1/[1 + (Dm/D) ^m], turns out to be the common form shared across multiple disciplines, with different symbols and designations.

Life to Death Transition

The abrupt transitions from Live to Non-life are described as: life-or-death in biology, all-or-none in pharmacology, collapse in physics, transformation in engineering and AI, undifferentiable in mathematics. This is a paradigm shift from the "1" distribution functions of the Floating Ratio to the Golden Ratio. In life, the MAL fa from >0 and <1, transform to fa = 0 and fu = $\infty, thus, fa/fu$ becomes meaningless upon death; the Dm from a positive natural number to zero activity (inert), and the dynamic-order, and the m (positive and negative finite number for cooperativity, e.g., .-4 to +4, (or -2 to +2 for optimal cooperativity conditions) depending of negative or positive cooperativity intensity of the system) become zero upon death. Since Dm becomes 0, and the m = 0, (and the exponent of zero to any number returns to 1). Interestingly, when Dm =0, the Floating Ratio, fa/fu = 0/(1-0) = 0. Thus, the Life-Dead paradigm shift transition is beyond any scientific evaluation, but it is a reality. The Life's homeostasis condition is Dm = fa = fu = 0.5 = 1/2 for equilibrium, symmetry, and harmony state at suitable temperature, pressure, O_2/CO_2 tension, and minimum essential nutrients for mainlining metabolism, growth, reproduction, and other activities. The importance of the median or 1/2 is manifested by the Riemann's zeta function ½ critical line, as well as in Alfaro's Alpha = 1/2. Thus, the clear link between Life and Non-life is via the common code of "1", but each has distinct distribution functions. Chou's system analysis on MAL for action (MEE) and interaction (CIE and DRIE) leads to the unity theory of one (UTO), since all MEE, CIE, and DRIE are based on the universal

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reference of "1" as the standard. Despite FR in Life's finite, symmetric, closed dynamic properties being basically different from GR in Non-Life's infinite, open, and recursive dynamic properties, both FR and GR share the ultimate connection as the fractional distribution functions from "One".

Life is finite, optimal, median-mediated regulatory equilibrium, recyclable, with a "Floating Ratio" of dynamics, consciousness, and intelligence; Whereas non-life function is linear, open, fractal, moldable, with a fixed Golden Ratio, and infinitively expandable; and it is subjected to artificial intelligence (AI) for approximating, mimicking cumulated experience and information of LLMs big data, with extremely high speed and enormous capacity of volume.

Therefore, the *Life and Non-life domains need to be separated* within causal-effect, dose-response, or input-output scientific R&D dynamics, including AI basic category algorithms, to ensure confusion-free informatics. The best practice is to stay true to the facts and avoid arbitrary, subjective fine-tuning that can change over time, place, and policy.

MAL-Median-Effect Principle for Conserving Energy and Increasing Efficiency

Dm, the general reference point and the dynamic order's common link, exhibits the universal reference standard for equilibrium, optimization, symmetry, harmony, dynamics, and informatics [24]. The MAL's Minimum Two-dose Data Point Theory (**MTDPT**) automatically adds two default points (Dose zero and Dm) to all causal-effect dynamics simulations, resulting in an efficient, cost-effective framework for computerized digital R&D across all dynamics disciplines, including new drug clinical trials.

The MAL-based "**top-down**" R&D framework provides guidance for Econo-Green scalable design, in contrast to the traditional, statistics-based "**bottom-up**" R&D, when insufficient cumulative general basic knowledge becomes available [19,22,24]. The MAL dynamics enable inter- and cross-disciplinary linkage by sharing a common set of parameters across MAL-MEE/DOM and CIE algorithms in digital data science. By coincidence, the terms bottom, up, top, and down are used in the standard particle physics model for quark designations, with additional charm and strange among them [24 (in Figure 32)].

Interdisciplinary and Cross-disciplinary Linkage and Convergence

Based on the **MAL-MEE/DOM/CIE/UTO** revelation and the fact that humans decide the units and methods of measurement, from a human-centric perspective, Life is proposed to be at the center among the physical elements of Mass, Force, Time, and Space in the Universe. It is called the Life-Centric Universe (**LCU**) [22]. This is not merely technical—it is a manifesto for a new scientific humanism, where it is not just in the universe, but at its center; a new humanism, a Renaissance concept in contrast to the prevailing materialism. It represents a paradigm shift toward unified, efficient, and life-resonant science, especially valuable in the AI and digital R&D era.

In Life, human as a being of primate, decides units and methods of the measurement, produce numbers for counting, sequencing, patterning, combinatorial for count without counting, algebra, geometry, trigonometry, metrics, calculus, metrices, statistics…and evolved to all branches of quantifiable and not quantifiable, countable and not countable sciences, including mathematics, philosophy, physicals, biological and social sciences and arts, whether for theory or for utility. The major scientific disciplines evolved into sub- and sub-sub-disciplines, which in turn gave rise to thousands of scientific journals, especially in the biomedical sciences. In current scientific R&D, diverse independent research efforts lack cross-linkage because different basic principles, parameters, notations, taxonomies, and symbols are used, which may lead to unintended consequences for efficiency, cost-effectiveness, and connectivity. The MAL integrated *unified* general principle, using common denominators and MAL-parameters, has opened a groundbreaking new avenue for integrated R&D in MAL-based experimental protocol design and MAL-algorithm-based digitalized data simulation, enabling quantitative or indexed conclusions without always relying on the *p*-value, which is merely a scientific tool, not the scientific goal. The MAL principle provides

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common ground that benefits individual researchers and peer reviewers, as confirmed by the global reach of MAL-theory/method bibliometrics. However, the success of this unified, integrative reform task requires support from decision-makers and key advisors at international regulatory agencies to ensure coordination and harmonization. The preliminary report on MAL-DOM/UTO and LCU has been presented at the American Physiological Society (APS) Summit 2025 in Baltimore, MD [22].

The full MAL groundbreaking concept innovation has been explored over five decades across various disciplines and journals, making it difficult for any peer reviewer to navigate, except for the speed and capacity of artificial intelligence (AI). Given below are the categorized references relevant to Chou T.C.'s research work: **A**. Reviews [9,11] **B**. Books [23,24], Encyclopedia [25–27], and Monographs [28–31], **C**. Commentaries and Pre-clinical Drug Development based on MAL Dynamics and Informatics [24,32–49], **D**. Recent Meeting Reports [14–22], **E.** MAL-Theory and Algorithm Derivations (since 1970) [1–7], **F.** MAL-based R&D Designs, Software, and Applications [50–55]. The Chou's bibliometric URLs are readily available on Web of Science [56], Google Scholar [57], and ResearchGate [58].

There have been numerous unified general theories of everything, including the Big Bang, relativity, string theory, and fundamental density theory. The mass-action law-based theory, as described here as MAL-MEE/CIR/CIIE/DOM/MDTPT/UTO, and the proposal of Life-Centric Universe (LCU) are based on the real-world, sensible dynamic phenomena, provide quantitative informatics for real-world knowledge innovations and problem solutions, which are supported by detailed scientific derivations, data documentations, and scalable for upward and downward bibliometric evidences. The MAL-unified general principle-guided R&D design and digitalized "top-down" data science is a basic conceptual departure from the traditional observation/statistics-based bottom-up R&D approach.

As indicated above, given the over 30 MAL-theoretical papers spanning multiple journals over five decades, this paper focuses on MAL-Theory rather than the Applications elaborated in 2024 in [24]. For multi- and cross-disciplinary purposes, some repetition and redundancy in content, as well as self-citations, are unavoidable. This author apologizes to readers for this non-traditional practice and publication format. To facilitate easy access and streamline the conceptual flow, the linkages are further categorized into three appendices: **Appendix I: Abbreviations and Definitions; Appendix II:** Theory Illustrations; and **Appendix III.** Examples of Categorized Applications.

The details of the previous illustrations, including the software and printouts, are available online [24,55].

The major examples of MAL-MEE-CIE and DRIE applications in specific research disciplines are given for cancer research, anti-viral, molecular biology, cell biology, genetics, immunology, and organ transplant, cancer- and infectious disease- drug discovery (in vitro, in vivo, and in animals), and pre-clinical studies design and implementations, and clinical trials. The applications have inter- and cross-linked to over 100 disciplines and sub-disciplines [9,23,24].

1.1. Mass-Action Law Median Principle for The Unified General Dynamics Theory of All Causal Actions

This paper summarizes a comprehensive theoretical and practical framework that redefines the core of scientific R&D and artificial intelligence through the Mass-Action Law (**MAL**), and its Median-Effect Equation (**MEE),** i.e., the Doctrine of the Median **(DOM)**, Combination Index Equation (**CIE**), and the Dose-Reduction Index Equation (**DRIE**). These equations embody a deterministic, scalable, and cost-effective dynamical system for modeling actions and interactions in biological, biochemical, and biophysical systems. The Unity Theory of One (**UTO**), based on MAL-MEE/DOM/CIE/DRIE, leads to the proposition to place Life at the center of Mass, Force, Time, and Space physical elements of the Universe, i.e., the Life-Centric Universe (**LCU**), in which humans decide Units and methods of measurement. The MAL concept integrates philosophy, biology, physics, and AI under a common principle and algorithm, with shared parameters.

The MAL-based biochemical and biophysical general equations show that the four corners are the general theory derived for specific research fields and are now widely taught in various textbooks.

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The MAL-MEE in the center is derived from input (↓) and outputs (↑), including general system analysis of enzyme-catalyzed reactions (with substrates (S), products (P), and inhibitors (I)) and combinatorial sequential pattern analysis. The MAL-MEE derivation took 10 years (1966-1976) [1–5] and involved system analysis of combinatorial input-output patterns and transitions, involving over 300 reaction rate equations. From MEE to CIE and DRIE took another six years (1977-1984), and the dose-reduction equation was established in 1988 [6–9].

The grand core theory of MAL is the Median-Effect Equation (MEE) as shown in Figure 1 [9–11].

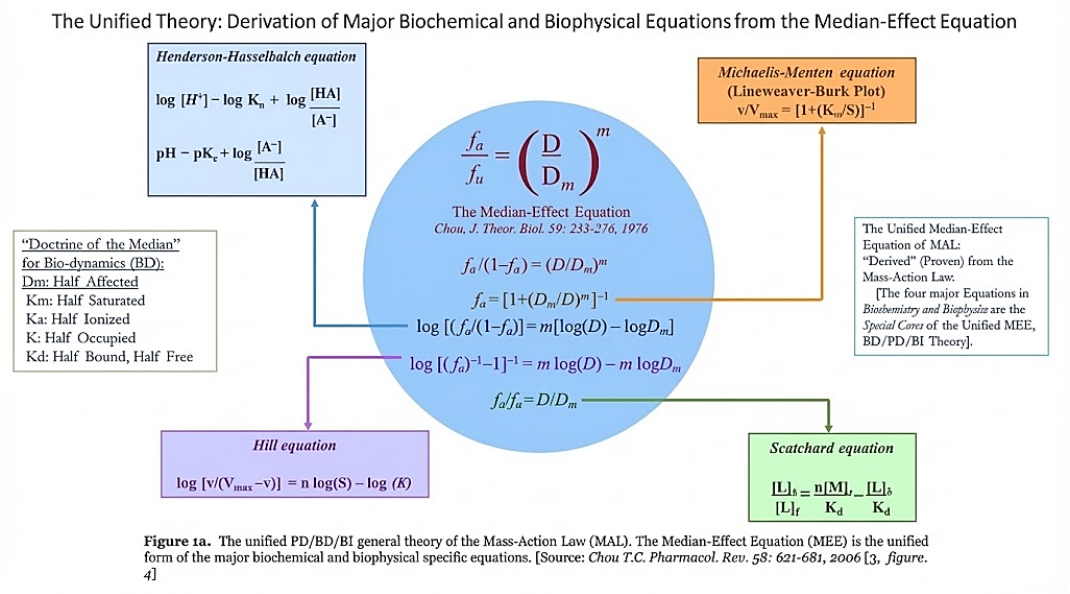

Figure 1a. The unified PD/BD/BI general theory of the Mass-Action Law (MAL). The Median-Effect Equation (MEE) is the unified form of the major biochemical and biophysical specific equations. [Source: *Chou T.C. Pharmacol. Rev. 58: 621-681, 2006* [3, *figure. 4*]

Figure 1. The Median-Effect Equation (MEE) is the unified form of the major biochemical and biophysical specific equations for specific purposes. The MEE is the unified general theory of the Mass-Action Law (MAL) for pharmacodynamics, biodynamics, and bio-informatics (**MAL-PD/BD/BI**).

It should be noted that the Michaelis-Menten, Henderson-Hasselbalch, Hill, and Scatchard equations are the "general" theory for a specific research field, not a *unified* general equation for interdisciplinary or cross-disciplinary studies. The MEE also covers general dynamics and informatics for action and combination interactions, independent of unit, physical state, size, structure, and mechanistic complexity, with applications far beyond biomedical sciences [9,23,24].

The Doctrine of the Median (DOM) represents an optimal balance in biological systems. Point Dm serves as the natural midpoint and universal reference for simulations. It reflects the principle of symmetry, order, balance, homeostasis, and harmony as in classical philosophy.

Key Parameters of the Median-Effect Equation

Parameter	Definition	Role/Significance
D	Dose	The input concentration, intensity or mass causing an effect.
Dm	Median-Effect Dose	The dose required for 50% effect is a universal reference point, a potency or efficacy indicator, and a common link for dynamic orders.
fa	Fraction Affected	The observed fraction of the system or population that is affected by the dose.
fu	Fraction Unaffected	The observed fraction of the system or population that is unaffected (1—fa).
m	Exponential Dynamics-Order	Signifies the shape of the activation function (hyperbolic if m=1, sigmoidal if m>1 or m<1), akin to AI models' basic activation functions.

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FR	Floating Ratio (fa/fu)	Represents the causal relationship of MAL; its binary, circular, and recyclable nature is typical of Life.

Mathematical Basic Transformations for Extracting Geometric Properties

The use of forward and backward thinking, independent free spirit of exploring curiosity, and referring to ancient philosophy and mathematics, disregards the contemporary popular hot pursuits and timely ideology, the development of the MAL general and unified theory using numbers, sequence, patterns, and systematic combinatory analysis using only the mass-action law as the model, without invoking modern mathematical developments, physics theories, and engineering advancements.

Using the MAL general combinatorial system analysis, surprisingly, simple logic procedures, such as numbers, ratios, constants, equations, reciprocal (and double-reciprocal), logarithmic (and double logarithmic) exponents, dimensions, algebra, geometry, and graphics have revealed numerous intrinsic properties that underlie them, which have become the practical informatics based on the MAL dynamic principle. The limitless applications of the MAL-MEE/CIE/DRIE and the subsequent unity theory of one (UTO) and Life-centric universe (LCU) were not originally expected. The theory of the median-effect equation (MEE), $(D/Dm)^m = fa/fu = fa/(1-fa) = (1-fu)/fu = [(fu)^{-1} -1 = \{(fa)^{-1} -1\}^{-1}$, was introduced in 1976 [4], but the term of the Floating Ratio as the (fa/fu) was named in in 2024 [20,22], to compare with the ancient Golden Ratio.(φ).

A series of MEE-defined dose-effect curves (DEC) can each be normalized by the median dose (DM) to yield first-order (m=1) hyperbolic curves, which can then be normalized into a single curve for the transformation into a singularity of one (Figure 2).

Using the MEE algorithm, the MAL principle can be graphically illustrated in various forms, as shown in Figures 2-**4.** The inhibitor (I) is the reference ligand. In contrast, the substrate (S) in the enzyme reaction is the primary ligand [9], representing the effector in enzyme-catalyzed reactions that exerts an effect on the enzyme target.

The median-point concept [4,5] is shown in the Figure. 2.

1.2. Dealing with Biological Complexity and Diversity: The MAL Approach for Solution

1.2.1. MAL-MEE and Chou's Double Logarithmic Median Effect Plot (MEP): Dynamic Parameters Determination by Computer Simulation

The MAL-MEE/CIE and DRIE-based Theoretical and method, design, and computerized digital simulation [51,54,55] have already been applied to tens of thousands of papers, over 1,500 citing journals, and citing patents [9,23,24,56,57], which made a significant contribution with MAL-based efficient Top-Down R&D exploration, innovation, and new drug discovery.

1.2.2. Linearization of the Dose-Effect Curve (DCE)

A typical illustration of the MEE, $fa/fu = (D/Dm)^m$, is the Median-Effect Plot (MEP), x= log (D) vs. y = log (fa/fu), which transforms the dose-effect curves with hyperbolic shape (m=1) or sigmoidal shape ($m > 1$) or a flat curve ($m < 1$) into the staigh lines with a slopes of the m values of the MEP. The x-axis represents the logarithm of dose (log (D)), while the y-axis represents the logarithm of the Floating Ratio (log (fa/fu)). The slope of this linear plot directly corresponds to the exponential dynamics order of the m value, and the x-intercept yields log Dm. Thus, the antilog of this x-intercept then yields the Dm value. This linearization for determining the dual m-and-Dm paired parameters of the mass-identity is invaluable because MEP transforms complex sigmoidal or hyperbolic dose-response curves into a straightforward linear relationship, simplifying parameter estimation and enhancing conceptual insight into causal-effect dynamics studies. This visual representation underscores how diverse, non-

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linear dose-effect relationships can be unified and analyzed under a single, simplified linear model, significantly improving the efficiency and predictive power of data analysis (Figure 3).

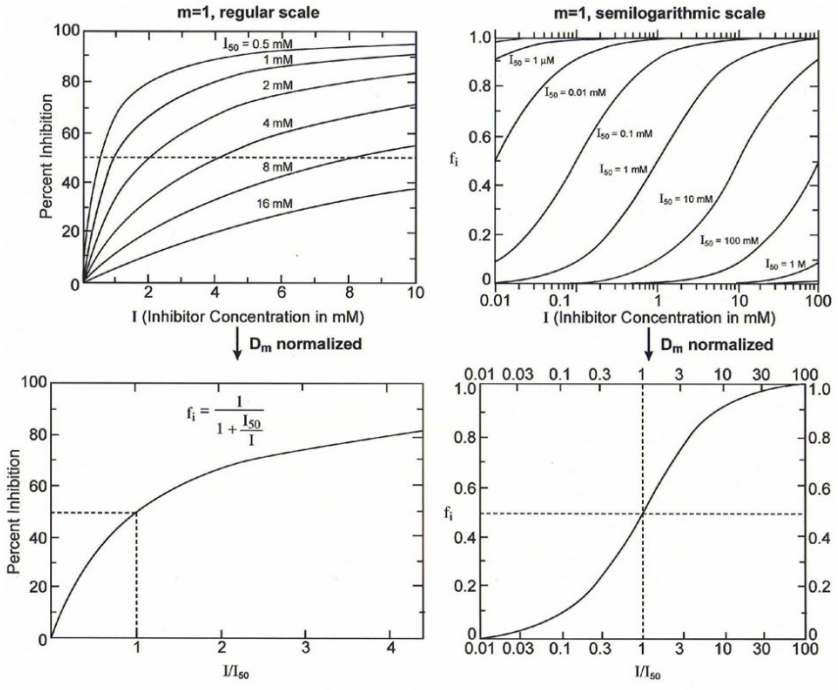

Figure 2. Doctrine of the Median (DOM). Median-Effect Equation (MEE) is the Unified General Theory of the Mass-Action Law when m =1. The scope of applications includes drugs, biologicals, effectors, ligands, radiation, UV, toxins, infectives, carcinogens, etc., as single entities or in combination, for biodynamic algorithms and bioinformatics computer simulations. The median dose (Dm) serves as the common link for dose-effect curves (DECs) in Michaelis-Menten kinetic models of inhibitory effects. Upper: The original dose-effect curves in normal sequential scale (left), and in logarithmic scale (right). Bottom: The corresponding dose-effect curves normalized with the Dm or I_{50}.

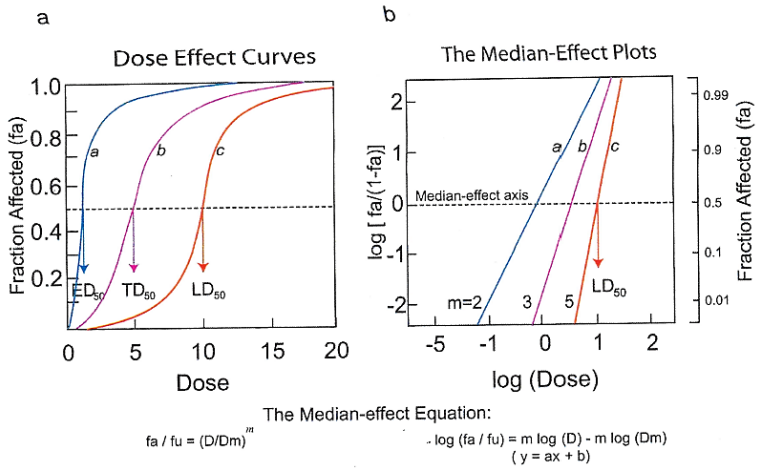

Figure 3. Transformation of various sigmoidal dose-effect curves in real-world problems. (a) into the corresponding linear forms (b) by the median-effect plot (MEP), where y = log (f_a/f_u) versus x = log (D). The slopes, m values (in this case, equal to 2, 3, and 5 for curves a, b, and c) signify the degree of sigmoidal shape. The anti-logs of the x-intercepts on the axis, where f_a/f_u = 1 [or log(f_a/f_u) = 0], give the D_m values, which signify the potency of each drugs, such as ID_{50} for median inhibition, ED_{50} for median effect, TD_{50} for median toxicity, and LD_{50} for median lethality, that forms the horizontal **median-effect axis** in pharmacological, medical and biological research and development (R&D), and beyond.

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Thus, the **median-point** concept is extended to the **median-axis** concept. The rotation of the median axis may result in the median plane in computerized simulations [9,31].

Throughout this paper, based on the MAL-MEE principle, the diversity of phenomena in nature is merely the variability in the distribution functions of "1".

1.2.3. Exponential Cooperativity Function and Intermediates, Pathway, and Network in the Life Science Features

The overriding features of the biomedical sciences and most other disciplines are the complexity and diversity of events and phenomena at micro- and macro-scales. The major reasons are the underlying intermediates, pathways, and networks that lie behind the input and output processes of causal-effect or dose-effect, and the fundamental principles' intrinsic properties. The MAL is shown to be the unified general principle in Nature.

Life science has the unique features of functional cooperativity, equilibrium, feedback, symmetry, and harmony. Figures 4A and 4B illustrate some of these properties.

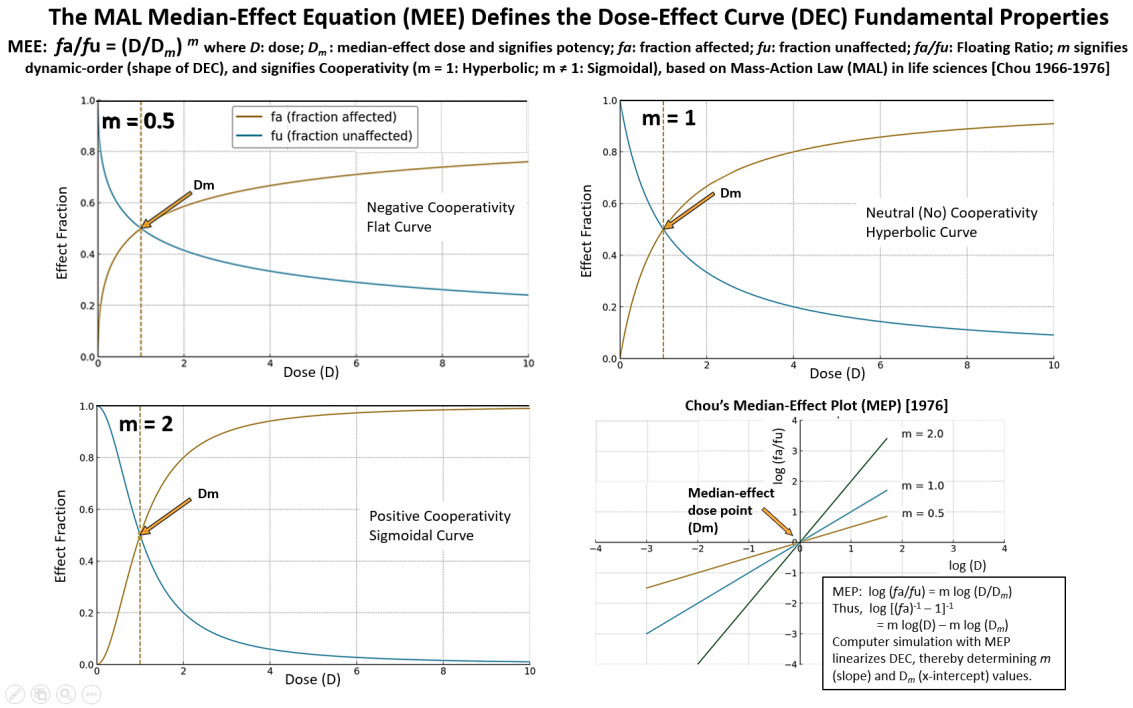

Figure 4. A. The MAL Median-Effect equation geographic property illustrates the negative, positive, and neutral cooperative effects in life sciences.The median-effect plot (MEP) for log $[(fa)^{-1}-1]^{-1}$ = m log(D)— m log (Dm), with x = log (d) versus y = log (fa/fu), which is also equal to log $[(fa)^{-1}-1]^{-1}$. The MEP linearizes the dose-effect curve (DEC) into a straight line, as shown in Figures 4A and 4B. After multiple paired dose-and-effect data entries, the software automatically performed the MEP to determine the paired dynamic parameters (m from the slope and Dm from the x-intercept), and then, using Dm-m values, generated the DEC in reverse.

Since any two dose-effect data points lie on the same straight line, they represent the entire straight line and thus the full dose-effect curve, provided at least two data points are available. Drawing a curve from only two points is a historical breakthrough because it is counterintuitive. The MAL-MEE/MEP, in fact, adds two default points (dose zero and Dm) into all dose-effect dynamics relationships. Chou called this the Minimum Two Data-Points Theory (MTDPT) for efficient, cost-effective, and econo-green in all causal-effect R&D (see Figure 5 below) [9–11].

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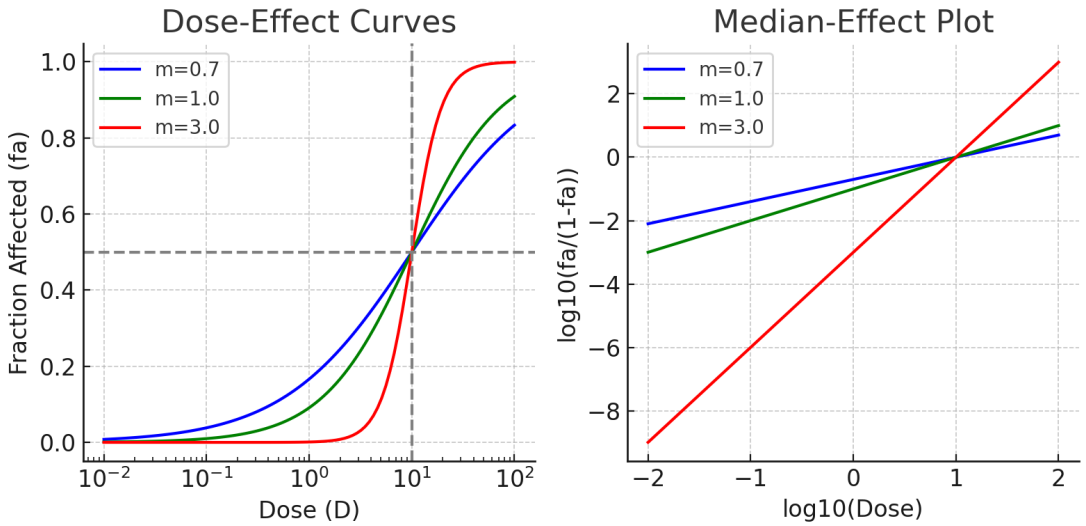

Figure 4B. Theoretical illustration of dose-effect relationships and the median-effect plot of MAL. **Left:** Example dose–response curves (DECs) for three systems with the same median-effect dose Dm but different dynamics-order m values (blue: m=0.7, green: m=1.0, red: m=3.0). The horizontal dashed line indicates fa =0.5 (50% effect as Dm, named the median-axis), and the vertical dashed line marks the corresponding D, in this case, 10. **Right:** The corresponding median-effect plot (MEP) (a *log–log plot* of dose vs. fa/(1-fa) yields a straight line for each system. The slope of each line is m, and the x-intercept is log (Dm). Despite different curve shapes in a linear scale, all follow the unified linear form in the median-effect domain. This linearization of DEC by MEE/PEP leads to the minimum two-dose data point theory (MTDPT) (see below).

Figure 4B shows the representative features of MAL-MEE/MEP, presented in another way with Dm = 1, and m values of 0.7, 1.0, and 3.0 were generated by ChatGPT 5.1.

1.3. MEP Linearization Leads to MTDPT: The Basis for Efficient, Cost-Effective, and Econo-Green R&D

Q: How to draw a curve from two points?
(A historically fundamental anti-intuitive question)
A: Yes. It can be done. Ask MAL-MEE/MEP/DOM what makes the magic.

Linearization of Dose-Effect Curves (DEC) of different shapes and different potencies with a Minimum of Two Dose-Data-Points Theory (**MTDPT**). The MDDPT introduced a groundbreaking concept in digital informatics for system biology through computer simulation, reducing the size of all dynamic studies. The MAL-MEE/MEP algorithm automatically adds two default data points (Dose zero and Dm) in all DEC.

One can draw a specific dose-effect curve with a theoretical minimum of 'only two-dose data points'—One default Point is Dose Zero, and another default point is the Median-Effect Dose (Dm). Any 2-data points on a straight line represent the same line, and therefore, the same DEC. The MTDPT is the theoretical basis for efficient, cost-effective, and "Econo-Green" Biomedical R&D and drug evaluations, especially in animal studies and in the design of clinical trial protocols. [11, Chou TC. Integrative Biol. 3: 548-559, 2011; Pharmacological Rev. 58: 621-681, 2006 [9].

The Dose-Effect Curves (DEC): with different "shape" and "potency" simulated by MAL-MEE/MEP are shown in **Figure 5**, which indicates the theoretical basis for efficient and cost-effective R&D, MTDPT.

1.3.1. The prerequisite of MAL-MEE Entity's Paired ID Parameters, m and Dm values

The mass-action action, as expressed by the MAL-MEE-MEP, has three components to consider in Biomedical or Life Science Applications:

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Mass and Action: It refers to any entity that causes or exerts a specified effect. For example, in biomedical sciences, it can be a chemical dose, such as a drug, inhibitor, activator, modulator, or regulator; in physical dose, it can be radiation, thermo-, photo-, UV, microwave, etc.

Receptor or Target: For a specific effect to occur, there must be a recipient, such as a molecule, cell, organ, body, or environment. Usually, there is an affinity or cooperativity between the effector and the recipient for the action. These are scientifically in terms of affinity constants and/or dissociation constants.

Scope of Effect and Target: No limit. (to the limit of accuracy of measurement technology)

Dose Number, Range, Density Gradient

Unit and Quantifiable Measurement

Dose-response or Dose-effect Relationship

Plan and Protocol Design, and the endpoint of measurement

Schedule or Regimen (e.g., clinical trials)

Input-Output (visible) and Intermediate (Usually not visible)

All the above considerations have been tested in the MAL-MEE-CIE-DRIE applications, as indicated in the bibliometrics.

1.3.2. The MAL-MTDPT: A Game Changer

A groundbreaking discovery was not originally expected, since it is rather anti-intuitive:

This is the Minimum Two-Dose Data Point Theory (MTDPT), which allows one to draw a curve from two points. MAL-MEE's Median-Effect Plot (MEP) linearizes all dynamic dose-effect curves into straight lines,

Thus, MAL-MEE-MEP with log D vs. log (fa/fu) plot, automatically adds two default data points (dose zero and Dm) into considerations, thus allowing a smaller number of data points requirement in R&D. This leads to efficient, cost-effective, and Econo-Green R&D, which saves time, effort, and resources.

The Median-Effect Plot (MEP): The "Linearization" Principle Leads to Cost-Effective Econo-Green R&D (MTDPT)

When 1976. [4], it was mistakenly regarded as equivalent to the Hill equation. In fact, they are derived from completely different methods and purposes: MEE is derived from MAL inputs-outputs combinatorial general system analysis, which took 10 years (1966-1976) and involved 300 reaction-rate equations. Whereas the Hill equation is specifically derived from a specific purpose for higher-order ligand interaction (e.g., oxygen hemoglobin), as shown in **Table 1** [9].

11.3.3. Different Derivation Approaches between the MEE and the Hill Equation.

The MEE and Hill have similar mathematical forms, but they differ fundamentally in their derivation. In addition, MEE is the unified general theory, whereas the Hill equation is the specific general theory. The Hill equation invokes Vmax, whereas MEE does not. Vmax is difficult to measure accurately without extrapolation. The MEE's Dm value is easily determined by comparing the Vmax value.

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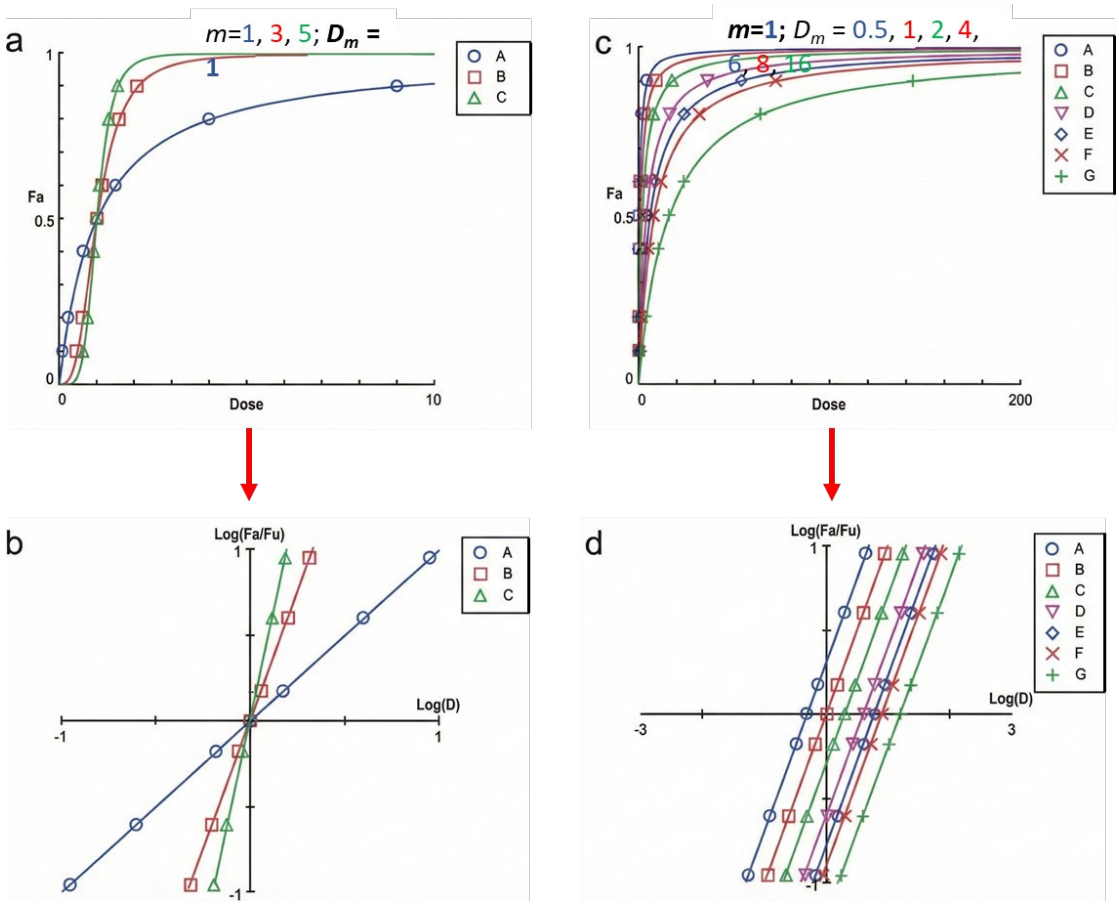

Figure 5. Linearization of DEC with MEP with MAL-PD, "Minimum Two Dose-data Points Theory" [MTDPT] is required to simulate an " A Dose-Effect Curve" through the linearization of the dose-effect curve (DEC) with MEP to determine the shape (m value) (slope) and potency (Dm) (x-intercept).

Table 1. Comparison of the MAL-MEE/MEP theory/equation with the Hill equation.

Comparison of the median-effect equation and the Hill equation

Median-Effect Equation[a]	Hill Equation and Michaelis-Menten Equation[b]
$\frac{fa}{fu}=\left(\frac{D}{Dm}\right)^m$	$\frac{v}{Vmax}=\frac{S^n}{S^n+K}$
$\log[(f_a)^{-1}-1]^{-1}=m\log D-m\log D_m$ when $m=1$: $f_a=1/[1+(D_m/D)]$	$\log[v/(V_{max}-v)]=n\log S-\log K$ when $n=1$: $v/V_{max}=1/[1+(K_m/S)]$

[a] Features: 1) inhibitor-oriented; 2) for ligand effect; 3) easily expandable to two or more inhibitors; 4) derived by mathematical induction and deduction.
[b] Features: 1) substrate-oriented; 2) for substrate saturation; 3) difficult to expand to two or more substrates; 4) derived by phenomenal observation and reasoning.

Table complexity, perplexity, and diversity of biomedical and natural phenomena lead many scientists to seek solutions or approximate causal dose-effect relationships. The MAL-MEE is the *unified* general principle, and the Hill equation is a *specific* general principle; they are derived from completely different ways. The MEE was derived over 10 years (1966-1976) and involved more than 300 reaction-rate equations [3–9].

1.3.4. Comparison of MAL-MEE and Statistical Functions

Among thousands of mathematical equations or formulas in scientific literature, only a small fraction of them are relevant to the biological observations. Since the 20th century, several major schools of thought have emerged, including the mathematical, statistical, and physical-chemical schools, such as the MAL. **Table 2** compares the Power Law, Logit, Probit, and the MAL approaches [9].

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The Power Law and Logit are simple to use but lack a theoretical basis, amounting to intuitive approximations. The Probit is rigorously developed from statistical principles, but is too complex for practical use.

By contrast, the MAL-based MEE, as focused in this paper, provides equations/algorithms/computer software. The Floating Ratio of MEE enables universality and the scale-up of single-entity actions to multiple-entity interactions, enabling ubiquitous applications. These are supported by citations in tens of thousands of papers, in over 1,500 journals, and in patents [56–58].

Table 2. DEC from different schools. Comparison of MAL-MEE/MEP with power law, LOGIT, and PROBIT statistical functions.

Dose-effect relationship laws used by different schools

Modified from "Quantitation of Synergism and Antagonism of Two or More Drugs by Computerized Analysis," Chou TC, in *Synergism and Antagonism in Chemotherapy* (Chou TC and Rideout DC eds) pp 223–244. Copyright 1991 with permission from Elsevier.

POWER LAW (Nordling, 1953; Armitage and Doll, 1954)	$f_a = bD^k$; $\log(f_a) = k \log(D) + \log b$
PROBIT (Bliss, 1939; Finney, 1947, 1952, 1971)	$f_a = \frac{1}{\sigma\sqrt{2\pi}} \int_{-\infty}^{\log D} e^{-\frac{1}{2\sigma^2}(\log D - \log Dm)^2} d(\log D)$ where $Y = (\log D - \log D_m)/\sigma$
LOGIT (Berkson, 1946; Thompson, 1947)	$f_a = 1/[1 + e^{-(\alpha + \beta \log D)}]$
The median-effect equation of the MASS-ACTION LAW (Chou, 1974, 1976)	$f_a/f_u = (D/D_m)^m$; $\log[(f_a)^{-1} - 1]^{-1} = m \log(D) - m \log(D_m)$

D, dose; D_m, median-effect dose; m, kinetic order; f_a, fraction affected; f_u, fraction unaffected; σ^2, variance; Y (PROBIT − 5) or normal equivalent deviate; a, k, α, and β, undefined constants.

Statistical functions always introduce some uncertainty unless the p-value approaches zero.

The functions involving ***e*** have been difficult to handle with deterministic approaches in real-world problem-solving, such as in the biomedical sciences.

1.4. The Doctrine of Median: Unified General MAL-MEE Theory

1.4.1. Input-Output Activation Function and Algorithm in Dynamics

The median-effect equation (MEE) can be rearranged for different representations:

$$\frac{f_a}{f_U} = \left(\frac{D}{Dm}\right)^m \quad D = Dm\left(\frac{fa}{1-fa}\right)^{1/m} \quad fa = \frac{1}{1+\left(\frac{Dm}{D}\right)^m}$$

Effect (Force) vs. Mass Input (↓) Output (↑)

Where D is dose, Dm is median-effect dose, fa and fu are fractions affected and unaffected, respectively, (i.e., fa + fu = 1), and m is the exponential dynamics-order, that signifies the shape of the dose-effect curve, in hyperbolic activation without cooperativity (m=1), sigmoidal for positive cooperativity and activation function (m>1), and flat sigmoidal negative cooperativity and activation function (m<1) [4,9,11].

1.4.2. The median-effect plot (MEP) is the log-log plot for the MAL Bioinformatics.

Before the computer era, engineers used logarithms for calculating rulers. Biologists had frequently used the logarithmic scale to constrain out-of-the-map data points. The MAL-MEP adopts the double-logarithmic plot, log (D) vs. log (fa/fu) (or vs. log $[(fa)^{-1} -1]^{-1}$), called the median-effect plot (MEP) [4]. This is for theoretical reasons: linearizing all dose-effect curves (DEC) to extract the fundamental digital parameters of both Dm for potency or efficacy and m for the dynamic-order and shape of DEC, based on the MAL-MEE principle.

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Log (fa/fu) = m **log (D)**—m log (Dm), Log (D) vs log (Fa/fu) (or Log $[(fa)^{-1} -1]^{-1}$)

The y = ax + b type form, linearity principle, leads to the m and Dm digital informatics simulation/determination, since the slope gives the m value, and the x-intercept gives the anti-log of Dm, thus the Dm value, automatically by computer simulation [4,9,23]. It also leads to the minimum two-dose data point theory (MTDPT) for far-reaching impact for efficient, cost-effective, and eco-green scientific research and development (R&D), since MEP adds all DEC two default data points, dose-zero and Dm, embedded in all computer simulations [11,14–24]. This MAL-MEE/MEP/MTDPT has historical advantages over the traditional empirical curve-fitting or statistical R&D approach.

1.4.3. The Floating Ratio and the Mass/Mass (D/Dm) Ratio:

Fa and fu per se are fractions, thus have no unit, whereas D/Dm represents the same kind of entity-unit ratio cancellation, and m is just the exponential number that exerts mathematical properties and graphics. Note that the intermediate steps (e.g., between input and output are not visible (e.g., fu = 1-fa), but they are embedded in the floating ratio and the distribution function of "1" of the MAL-MEE. (see illustration late in Figure 10A).

The simplicity of the MAL-MEE is not reducible; D/Dm is a dimensionless ratio for universality, and the median normalized dose is D/Dm = M (general mass). The MAL-MEE, fa/fu (floating effect relativity) = Mass at any given dynamic-order (m). Therefore, the MAL-MEE indicates that "Effect" and "Mass" are interchangeable or equivalent. This MAL-MEE in biology is the counterpart of Einstein's relativity theory, $E = MC^2$ in physics, which indicates that "Energy" and "Mass" are interchangeable or equivalent. The difference in meaning is just life science's "**functional effect**" vs. physical science's "**energy force**".

The MAL describes dose-dependent input-output relationships in biological systems, with a variety of intermediate transitions, such as enzyme-catalyzed reactions, receptor-mediated pharmacological effects, sensory signal reception and motor actions, and network pathway connections and regulations. This causal-effect relation occurred in biology and non-life sciences, such as the Langmuir adsorption isotherm and questions and answers, as well as in contemporary artificial intelligence (AI).

In the MAL-MEE, both the left and right of fa/fu (for function) and D/Dm (mass) are ratios of the same kind. These ratios represent a universal property that is independent of dimensions, units, size, physical state, and the system's complexity. They remain valid under various conditions, such as time and space, especially with respect to geometric properties. We can also view dimensions as independent entities with perceptions and senses, like the median-effect point at (0, 0, 0), and the median-effect axes at 1st to 4th, and higher dimensions (m values). The x-, y-, and z-axes help describe the position of any point in three-dimensional space, along with their rotations, as seen in [71–73]. Using physical and mathematical hypotheses to explain otherwise difficult phenomena- such as gravity, negative dose (see below in Figure 21), anti-matter, dark matter, quantum entanglement, exclusivity, competitiveness, synergism, antagonism, or the abstract concept of exclusivity (see Figures 16, 17 below), and harmony (see Figure 37 below)- is a common approach.

1.4.4. Dm Is the Harmonic Mean of Kinetic Constants

The MEE indicates that dose and effect are interconvertible. In addition, Dm is the universal efficacy reference point and the common link among dynamic orders [3,9,24]. Furthermore, Dm is the harmonic mean of kinetic constant kii and kis in the Lineweaver-Burk plot. When kii = Kis (or Kii/Kis =1), it means pure non-competitiveness; it also means "pure harmony" [24]. (This phenomenon is illustrated later in Figure 37.

1.5. MAL Theory/Algorithm Rationale and Scalability

Beyond 3D, we need to use analogy, projection, reasoning, and inference. We can lift, bend, cut, or poke the paper to reveal different features. We can also hold a hypercube with cuts from various

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angles and positions to produce different shapes, curves, and volumes. Many hidden secrets can be revealed by the "One" entity. Therefore, the unified general theory of the mass action law is important for developing general, efficient, and effective basic R&D and AI reasoning models [9,14–24,55].

From the relativity ratio property, the MAL-based MEE/CIE dynamic theory or doctrine of the median (DOM) has dimensionless, universal applications without limit. It is logical to address real-world situations and problems as a priority before we attempt to solve abstract concepts, complex mathematical equations, or formulas. It is astonishing to note that international FDAs, with so many regulations, rules, and guidelines, still have no clear definition for "What is the exact definition of the additive effect of two drugs? Or more drugs?" [9]. The integration with MAL (or other means) for a unified, general principle of digital science to support intra-, inter-, multi-, and cross-disciplinary linkage is desperately needed for efficiency, cost-effectiveness, and digital informatics. The biological sciences have ramified into over 4,000 journals for R&Ds, most of which concern specific molecules, cells, organs, and diseases in biochemistry, physiology, pharmacology, infectious diseases, and cancer research, using independent, different principles and parameters in vitro, in animals, and in clinical trial protocol design and data analysis. Advocacy for R&D regulatory policy reform and modernization, using a unified set of principles and parameters for R&D, has been called for multiple years to reduce costs, increase efficiency, conserve laboratory animals, and reduce the number of patients in clinical trials, without a unified, general integration principle.[9,11,24,29–31].

Four advanced AI models (ChatGPT 5.1, DeepSeek R1 V3, Gemini 3, xAI Grok-3, Qwen 2.5 Max) have independently assessed Ting-Chao Chou's work (1970-2025) on MAL-MEE/CIE/DRIE/DOM/MTDPT/UTO Theory/algorithms and applications. This includes a book [24] with 11 chapters and the APS-Summit-2025 abstract [22]. These independent models validated the significance and practical implications of this MAL unified general theory-based "top-down" R&D framework, which is opposite, yet complementary, to the centuries-old traditional, statistics-based "bottom-up" R&D [19–22,24]; like front and side/rear views of the same entity, or two sides of the same coin.

Human intelligence is different from artificial intelligence (AI). AI, as a physical entity or tool, collects, stores, and utilizes vast amounts of human-recorded information and knowledge using human-derived/selected algorithms, at the speed and volume that make the magic. The numerous repetitive and retrospective processes make approximation, mimicking, and superposition near-perfect. Still, the irrational "e" functions used in mathematics, statistics, physics, and AI make it not a perfect fit to the real-life features and properties that are finite, closed, and circular (e.g., the Floating Ratio), but not extendable to infinity (e.g., the Golden Ratio). Thus, we face Life and Non-life as two separate domains in the universe and in reality.

In both scientific R&D and AI development, the simplicity, generality, efficiency, and cost-effectiveness of algorithms will be the key determinants in the framework for categorizing trillions of information bits in LLM models, enabling them to succeed in real-world applications. The human brain has about 86 billion neurons; the efficiency of the functional neural network is truly remarkable.

1.5.1. MAL Reveals A Conceptual Departure from Traditional R&D Observation-Statistic-based R&D Approach

The MAL-MEE/DOM algorithm automatically adds two default data points (Dose-zero and Dm) to all dose-effect analyses and computer simulations, including animal studies and clinical trials. It instantly generates quantitative, digitalized conclusions in tables and graphics. This is the Minimum Two-Dose Data Points Theory (**MTDPT**) [9,11,24], which serves as the basis for a cost-effective, Econo-Green scientific R&D platform, particularly for costly animal studies and clinical trials.

1.5.2. The Broad Applicability in Life Science and Beyond

The MAL-MEE-dictated combination index equation. All MAL-based MEE, CIE, and DRIE can be and have been applied for in vitro, in vivo, animal studies, and clinical trials, by automated computer analysis and simulation following a few pairs of dose-effect data entries, when using the

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MAL dynamics-based simple design, for efficient, cost-effective, Econo-green R&D. MAL-theory/algorithm [9,11,19–22] has applications in biomedical sciences, and beyond, including biophysical, environmental, agricultural, marine, toxicological, and food sciences [24,31,45,55].

Furthermore, the MAL-based experimental design allows experimental results to be subject to automated computer simulation in seconds, including [9,24,53–55] :

- Construction of MEE-MEP to obtain the paired Dm and m values; In return, these parameters generate the dose-effect curve (DEC).
- The MAL-based computer, such as CompuSyn or Calcusyn, will also display dose and effect data content and tabulation, scheme of layout, and conclusions.
- This MAL data science theory and method is not only applicable for the single drug or single entity, but also applicable to multiple drugs or entities in combinations (e.g., drug + radiation) [9,15,24].

The dynamics of entity actions and interactions in molecular and cellular biology, genetics, cancer research, antimicrobials, and pharmaceutical drug evaluation are studied using digital computer simulations, innovation and drug discovery, and signaling pathways and network interactions.

The overviews are available in [9–12,24]. Specific examples, including PD design and planning, data entry, precautionary note, automated computer simulation, and full CompuSyn Report printout, for in vitro [8,12,29,31,34,61,62], in vivo and in animals [24,43,45], and other studies, are illustrated in [24,55]. All these broad applications of MAL's fundamental principles are documented in scientific citation databases [56–58].

1.5.3. The Game Changer of MAL-MDTPT in Overall Causal-Effect R&D

The MAL-MEE-PEP Design Resulting in Using as few as 10-fold Less Patients in clinical trials

In health science research and development, although molecular, cellular, and in vitro studies lay the scientific foundation for further exploration, the reality test will be animal studies and clinical trials, which are specifically aimed endeavors and have been proven to be laborious and costly. In the absence of a unified, fundamental principle, trial-and-error has been the only mainstream approach to knowledge and solutions since antiquity.

This traditional observation-specific statistical approach is termed the "bottom-up R&D," in contrast to Nature's unified general MAL theory-guided "top-down R&D" [9,14–24]. There are clearly different meanings and scopes of validity between specific general equations (such as the Michaelis-Menten, Henderson-Hasselbalch, Hill, and Scatchard equations) and the unified general theory of the Median-effect equation of the mass-action law, as shown in Figure 1.

The MTDPT Concept of Small-Size Data Sets for Cost-Effectiveness

The MAL-MEE/MEP theory/equation/algorithm/simulation and mathematical transformation lead to the minimum two-dose data point theory (MTDPT) for all dose-effect curves by auto-adding two default data-points (Dose zero, and Dm), which is the universal reference point, and dynamic orders common link; Thus, this requires smaller-sized experiments in R&Ds [9].

The MAL-MTDPT allows a smaller size, requiring two fewer data points, by automatically adding two data points, dose-zero and median dose, to all causal effect analyses for simulations of experimental data. This is particularly beneficial for costly, time-consuming animal studies and for clinical trial protocol design. In addition, the MAL-MEE/MEP dual parameters (Dm and m) guided the dose-number, dose-range, and dose-density planning.

The MAL Design Used Ten-Fold Fewer Patients in Anti-HIV Clinical Trials than the Traditional p-value-Based Design. Yet, the MAL Provides Quantitative Conclusions.

Therefore, MAL-MTDPT automatically conserves laboratory animals and reduces the number of patients in Phase I clinical trials by as much as tenfold compared with the traditional observation-probabilistic design based on the p-value [60], particularly in Anti-HIV clinical trials, where clinical results can be quantitatively assessed. More details of the comparisons are given in the later Section of this paper and in **Appendix III.**

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1.6. The Ratio is Relativity

Across scientific disciplines, whether in life or non-life, the basic tool of "ratio" plays a prominent role. The following are some examples.

1.6.1. Golden Ratio vs. Floating Ratio: The Distribution fraction of "1"

The subjects of comparing the ancient Golden Ratio, φ, (**GR**) with the modern Floating Ratio fa/fu, (**FR**), of MAL-MEE/MEP have been raised and discussed recently, since 2023 at scientific society meetings [14–22]. However, the idea of **DOM vs. UTO** for inter- and multidisciplinary linkage to enable efficient, cost-effective digital R&D has been advocated for over three decades [9,11,24]. Figure 6 illustrates the properties of the Golden Ratio.

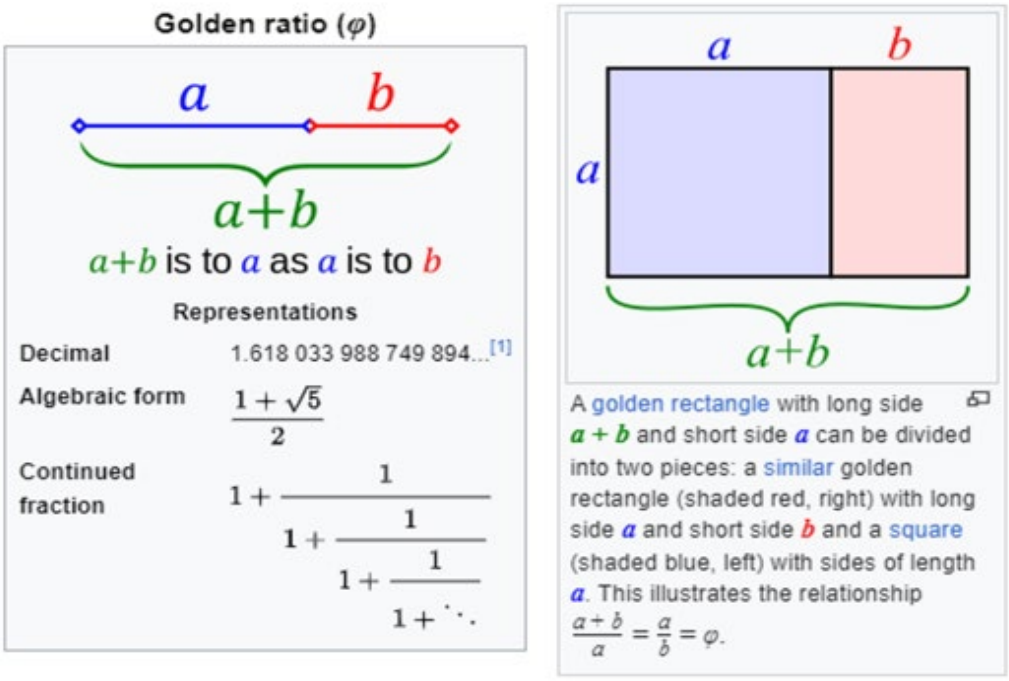

Figure 6. Illustration of properties of the Golden Ratio during the past centuries. Source: Wikipedia: The Free Encyclopedia under "Golden Ratio" https://en.wikipedia.org/wiki/Golden_ratio,.

1.6.2. The Floating Ratio Manifests Life and The Golden Ratio Manifests Non-Life: "1" becomes the Common Link

The **Floating Ratio (FR) or fa/fu** is the integral part of the Median-effect equation (MEE), fa/fu = $(D/Dm)^m$, which is the grand principle of the MAL that underlines the dynamics and informatics of life science. This unique feature will be discussed in the cross-disciplinary context of this paper.

Table 3 compares and summarizes the basic properties of the life-science-based Floating Ratio vs. the mathematics- and physics-based ancient Golden Ratio.

The GR (φ) manifests in the Non-Life Domain.

In contrast to MAL-MEE/DOM/CIE life science indicating FR = fa/fu, the ancient Golden Ratio, GR (φ), is an imaginary, transcendental constant, in mathematics and physics (i.e., non-life domain), which is:

GR, = φ = 1.618033988749894…. = 1+ (1/φ) = (1 + √5)/2

is greater than 1, and is an irrational, infinite number obtained from physics and mathematics, which belong to the non-life domain.

Table 3. Theoretical and Conceptual Comparison of Floating Ratio vs. Golden Ratio—Life vs. Non-Life*.

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Property	Floating Ratio (Life)	Golden Ratio (Non-Life)
Origin	Derived from the Mass-Action Law (MAL)	Ancient mathematics and geometry
Domain Manifested	Life (biological systems)	Non-life (physics/mathematics)
Form	Closed, finite, fractional distribution of "1"	Open, continuing distribution of "1" to infinity fractions
Significance	Dynamic, variable (Relativity, functional effect, causal dynamics)	Static, fixed (Aesthetics, proportion, fixed relationships)
Dynamics	Equilibrium, Recyclable, Feedback-driven, Symmetry, Homeostasis, Harmony	Self-similar, fractal
Force form	Energy driven	Power driven
Example	Biological dose-effect relationships, drug interactions, enzyme kinetics, cell signaling, neural networks (e.g., bio-pathways, bio-networks, organisms, environment)	Geometry, Fibonacci sequence, physics, spiral galaxies, (e.g., Lucas number, pentagram symmetry system, Penrose tiling, Kepler triangle, Golden Triangle, Golden Spiral, plant floral pattern)
Mathematical Expression	Fa/fu = fa/ (1-fa) = (1—fu)/fu, a/b = a/(1-a) = (1-b)/b, a + b = 1, (fa + fu = 1), fa or fu range, 0-1	a/b = (a + b)/a = 1 + b/a = Φ
Equation	$fa/fu = (D/Dm)^m$ $= fa/(1 - fa) = (1-fu)/fu$ $= (fu)^{-1} - 1$ (180°) $= [(fa)^{-1} - 1]^{-1}$ (360°)	$\Phi = 1 + (1/\phi)$ $= (1+\sqrt{5})/2$ = 1.618033988749894…

*This table was created with partial assistance from Gemini 2.5 (Deep Search) and Qwen3-Max.

In life science, the mass-action law (MAL) relates Mass and Action, where action requires energy, calories, and effort. The causal dose (D), input (↓), produces the consequential Effect (fa), which is the output (↑). Based on the MAL-MEE/DOM, $(D/Dm)^m = (fa/fu)$, Dose (D), is generally normalized with the universal reference dose, Dm, thus D/Dm refers to mass (M) in which unit is canceled out as an Identity, and fa/fu ratio refers to the Floating Ratio of Effect which manifests Live. The abrupt paradigm shift from Life to Non-Life is a transcendental transformation that remains scientifically unresolved.

The only links between Life and Non-Life are the distribution functions of "1" for FR and GR, and the fact that the rational MAL function can be transformed into imaginary or transcendental numbers, such as the negative and positive dose, which are interchangeable via MAL-MEE (Figure 21). Pascal's triangle's consecutive rows ratio real numbers can lead to Euler's *e* (see Section 8.9), and the MAL-MEE and Riemann's zeta function lead to an irrational number (π) (see Section 1.12). In the Floating Ratio, input dose (fa) is visible, and fu and $(fu)^{-1}$—1 are not visible (not real), but interrelated to "1" (see Figure 11).

In mathematics, the ancient Egyptian fractions indicate a unit fraction, which is a fraction with a numerator of "One" and a denominator that is any positive integer.

$$\frac{1}{n} = \frac{1}{n+1} + \frac{1}{n\,(n+1)}$$

It uses "finite sums" of distinct fractions as a way of expressing more general rational numbers.

This is an exception compared to other mathematical and physics equations that have infinite sums of fractions.

1.6.2. The Ratio of Mass, Force, Time, and Space

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The ratio cross-links disciplines. The ratio of the same kind cancels any unit, thus becoming dimensionless and independent of units, physical states, size, structure, and complexity.

The equal "=" sign indicates equivalence. Thus, Dose and Effect, Force and Mass, Energy and Mass are equivalent or interchangeable, as indicated below:

In all, mass is M or m, and Effect, Force, and Energy are equivalent.

1.6.2.1. The Life Domain Floating Ratio

The Floating Ratio, FR, (fa/fu): The mass-action law median-effect equation (MAL-MEE), fa/fu = $(D/Dm)^m$, is the fundamental principle of biomedical and biophysical science in the life domain.

1.6.2.2. The Ratio Revelations in Life Sciences and Physical Sciences

- The **Floating Ratio**: For the MAL, $(\mathbf{D/Dm})^m = \mathbf{fa/fu}$; fa + fu = 1. For the Floating Ratio, fa/fu, when Fa = fu, the Median = 0.5 = ½.

The fundamental mathematical form is:

a/b = (1-b)/a = a/(1-b), where, a + b = 1 (for Life).

- The **Golden Ratio (φ)**: It is the fixed ratio in the form $\varphi = 1.618033\cdots = (1 + \sqrt{5})/2$.

The fundamental mathematical form of the Golden Ratio is

a/b = (a + b)/a = 1 + b/a (for Non-Life).

- The **Newton's Ratio**: The ratio of Force and Mass. For Newton's Law of Motion, F = M a; **F/M = a**
- The **Einstein's Energy/Mass Ratio**: For Einstein's Relativity Theory, $E = MC^2$; $\mathbf{E/M = C^2}$

The Fundamental Density Theory (FDT) Ratio: $\mathbf{E/m = c^2 = 1/(\varepsilon 0\ \mu 0) = (d/t)^2}$

Where quantum mechanics (left), electromagnetism (middle), and general relativity (right) are three perspectives on the same geometric reality, related to space-time. It perceives 'mass" as a geometric property of the omnium field. This omnium field, in a way, is akin to the MAL-MEE/CIE's Unity of "one" theory (UTO) universal generality.

- The **Extended Ratio** of energy and mass: Fundamental Density Theory (FDT), by Manuel Alfaro in 2023-2025 [63–67]: This is a new theory that makes grand claims, although detailed derivations and broad examples of applications remain to be confirmed. However, numerous analogies and equivalencies have been established for general principles in real-world life sciences in MAL. In particular, the MAL vs. Omnium, as well as the Median (point, axis, and plane) vs. Alpha = ½ = 0.5, show close co-incidence.

In physics, FDT, D for "Density" is the ratio of the object's mass to volume, which is equivalent to "Concentration" in biology (e.g., molar, millimolar). The millimolar (mM) unit of concentration is equal to one-thousandth of a mole per liter, or 10^-3 M. It represents the number of millimoles of a substance dissolved in one liter of solution. It is commonly used in chemistry for convenience. The mass-action law is considered the fundamental principle of both biochemistry and biophysics.

FDT in physics is a relatively new concept (2024-2025); energy per mass, electromagnetic impedance, and spacetime kinematics all express the same geometric invariant [68–70]. FDT adds one control dial — alpha — that tracks how close the system is to the maximum-density shell at the Schwarzschild radius (Rs). The Alpha outside/inside concept in FDT is similar to fa/fu in MAL-MEE, where the Median (DM, 0.5) is the same as alpha = 1/2. Since fa + fu =1, then outside + inside = the whole. The Omnium field refers to the Universe of the physical domain. MAL-MEE connects both line and non-life domains.

In FDT, alpha (outside): alpha = Rs / r, alpha (inside): alpha = r / Rs, and Maximum density: alpha → 1 from both sides. The physical meaning of r is related to the range of alpha values.

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That's where hard MeV emission and extreme collimation live. C is not just a speed limit; it's the ratio that defines how distances and durations relate [70]. Particles formed under identical conditions inherit identical geometric properties.

Alfaro claimed that the 1997 Williamson-van der Mark "photon as electron" model and FDT's helical-light framework are mathematically identical descriptions of the same object: the electron is confined light, almost everything else follows:

$E/m = c^2$ is an identity, not a slogan; The distinction "photon vs electron vs graviton vs Gluon" is a density/regime label, not four different particles.

General relativity (GR) and quantum mechanics (QM) emerge as limiting cases of a single density parameter alpha FDT in (0,1).

- The **isotope ratio:** In science and history, another interesting ratio is C_{14} Dating, where the C_{14}/C_{12} ratio provides an estimate. This is another utility of the natural ratio.
- The **e/m Quantum Ratio**: Recent report on measuring the Charge (e) to Mass (m) ratio [104] using the definition of centripetal acceleration and Newton's second law to get an expression for the radius (R) of the circular motion, and obtain the relationship of: R = mv/eB, where v is speed, and B is magnetic field.

Using the change in electric potential (ΔV), the strength of the magnetic field (B), and the radius of the path (R), the following expression for the charge-to-mass ratio of the electron (e/m) results.

The radius depends on the charge (e) to mass (m) ratio as well as the speed (v).

$$\frac{e}{m} = \frac{2\Delta V}{B^2 R^2}$$

$$R^2 = \left(\frac{2}{B^2(e/m)}\right)\Delta V$$

Plotting R^2 vs ΔV should create a straight line. The slope of this line would be $2/(B^2(e/m))$, which we can use to then solve for e/m.

- **Pascal Triangle Rows Ratio**: The ratios of the serial rows lead to Euler's *e* (see Section 8.9).
- **Circle Ratio**: Circumference/Diameter = $\boldsymbol{\pi}$

Different scientific disciplines use distinct symbols, terms, and definitions to serve different goals. In most cases, basic mathematical concepts or maneuvers, such as ratio cancellation or normalization, reciprocal (and double reciprocals), and logarithmic (and double logarithmic) exponentials and roots, reveal hidden intrinsic properties that are otherwise not visible (or sensible). Many of them involve 1, 0, median, duo, etc. Some involve imaginary or irrational numbers, transcendental numbers, or complex numbers such as e, i, π, φ, ω *and* so forth. In life science MAL dynamics, the most relevant numbers are 1, 0, and the median (1/2 or 0.5).

1.6.2.3. Logarithms and Exponents

The logarithm form of the Median-Effect Equation leads to the Median-Effect Plot (MEP) in which x: log(D) vs. y: log(fa/fu). In addition, m value is dynamic order that describes the hyperbolic curve (m = 1) and sigmoidal curve (m ≠ 1).

Recently, Kobayashi compared the relationship between logarithms and exponentials, as shown below.

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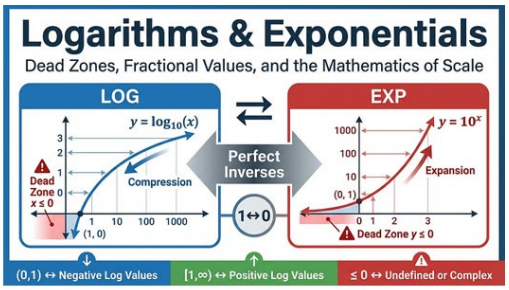
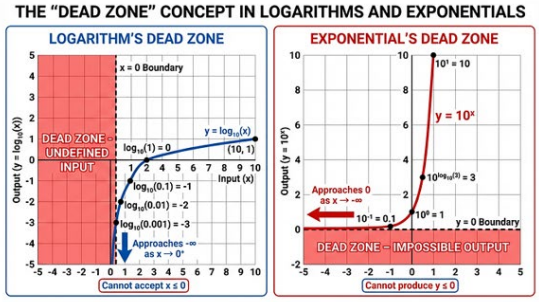
Logarithms and Exponentials: The Mathematics of Scale and Representations





Feature	Base 2 (Computing)	Base e (Nature)	Base 10 (Decimal)
Notation	$\log_2(x)$	$\ln(x)$	$\log_{10}(x)$
Pivot (log=0)	$2^0 = 1$	$e^0 = 1$	$10^0 = 1$
Unit (log=1)	x = 2 (Bit)	x ≈ 2.718 (Nat)	x = 10 (Digit)
Fractional Example	$\log_2(0.125) = -3$	$\ln(0.135) \approx -2$	$\log_{10}(0.001) = -3$

Tomio Kobayashi (1/26/2026), https://medium.com/@tomkob99_89317/understanding-logarithms-and-exponentials-the-mathematics-of-scale-representation-and-dead-zones-3756c2ff5724

1.7. Unity Theory of One and Life-Centric Universe

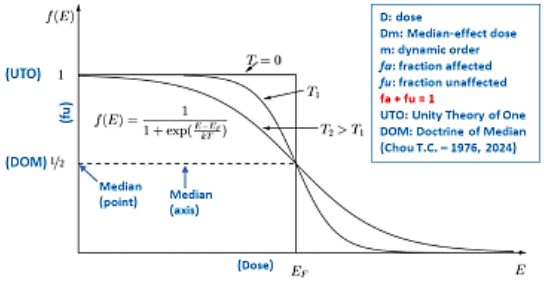
The MAL-Based MEE/CIE/DRIE/DOM leads to the unity theory of one (UTO) or the distribution function of "1", with or without the "e" properties (Figure 7).

The MAL theory has a mathematical form of a/b = a/(1-a) = (1-b)/b, and a + b = 1, when a/b =1. Then, a = b =1/2 = o.5 in the "median", as indicated by the MEE: fa/fu = $(D/Dm)^m = (M)^m$ where M is the median-normalized dose, i.e., the median-dose as the dose unit.

1.7.1. Math Form: MAL-MEE in Biology compared with the Fermi-Dirac equations in physics

Median Effect Equation [Life]

$$fa = \frac{1}{1+\left(\frac{Dm}{D}\right)^m} \qquad fu = \frac{1}{1+\left(\frac{D}{Dm}\right)^m}$$

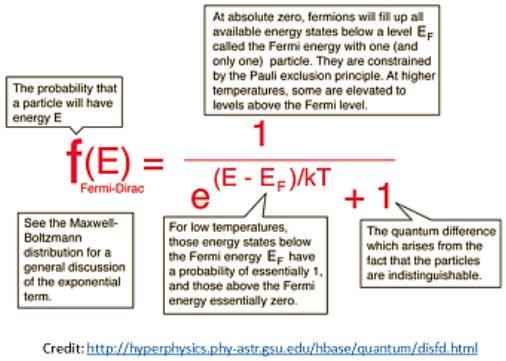


The Fermi-Dirac distribution function/(£) which gives the probability of occupation of a state: /(£) is 1 for £ < E_F and zero for £ > E_F at $T = 0$.

Credit: https://ebrary.net/158468/mathematics/electronic_conduction_classical_and_quantum_theory_to_nanoelectronic_devices

Fermi-Dirac Distribution [Physics]

$$f(E) = \frac{1}{1+e^{(E-E_F)/kT}}$$



Credit: http://hyperphysics.phy-astr.gsu.edu/hbase/quantum/disfd.html

Figure 7. Comparison of the Median-Effect Equation of the Mass-Action Law with the Fermi-Dirac Distribution Equation in physics. This compares the general mathematical form, not comparing the mechanistic details.

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In Figure 7, different disciplines with different scientific denotations share the same basic mathematical form, except that the Fermi-Dirac distribution equation contains "e". In MAL-MEE, D/Dm is a dimensionless relativity ratio, independent of unit, size, structure, state, and complexity.

1.7.2. MAL-MEE-UTO Points to Life-Centric Universe (LCU) Interfacing with Physical Elements

Summing up the above MAL exploration since the mid-1960s, the mass-action law (MAL) in Life science can be described by MEE/CIE/DRIE, DOM/MTDPT. This Unity Theory of One (UTO) leads to the proposal of a Life-Centric Universe (LCU), as indicated in Figure 8. It explains that the universe has two domains: Life and Non-Life, realms by the "One" and the "Median". The graphic layers in Figure 8 were created with assistance from ChatGPT.

As indicated above, the grand theory of the MAL, the median-effect equation, $fa/fu = (D/Dm)^m$, both right and left sides are the relativity ratio in the simplest form, based on the ratio-cancellation principle, the MAL-MEE application is independent of unit, physical state, size, structure, and mechanistic complexity, ensuring its universality.

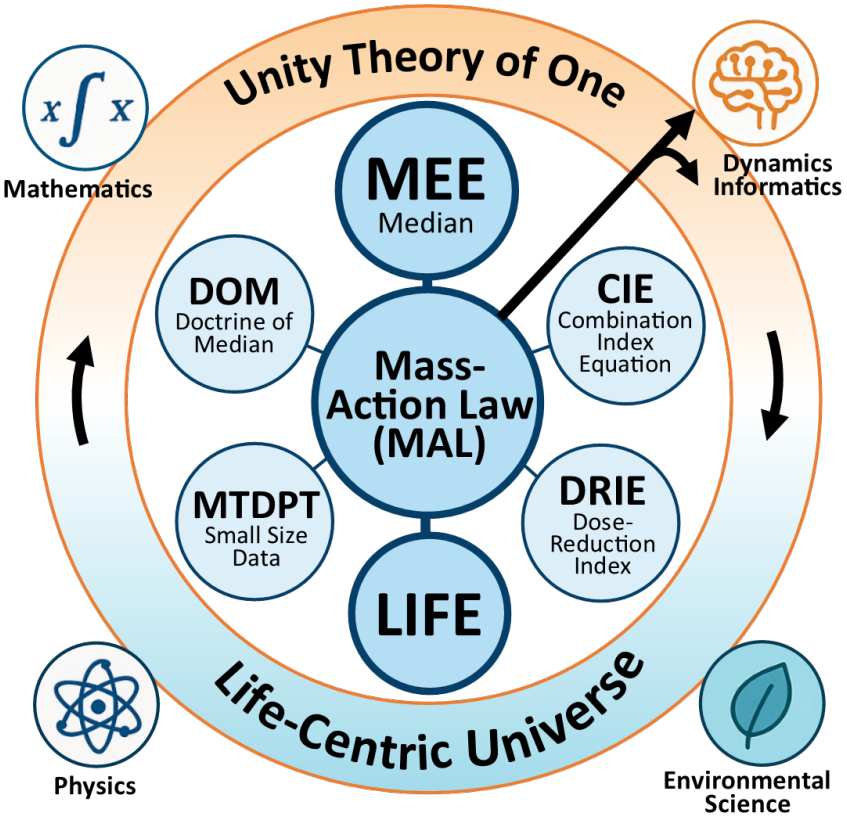

Figure 8. The mass-action law median-effect principle in life sciences leads to MEE/CIE/DRIE/MTDPT/DOM, the Unity Theory of One (UTO), which in turn proposes a Life-Centric Universe (LCU) with two domains: Life with fundamental code a/b = a/(1-a), a + b =1 (finite and circular), and Non-Life with fundamental code a/b = (a + b)/a (infinite and open). Life (inside the large cycle) interfaces with the outside existence of the non-life domain, such as the Environment, Physics, Mathematics, and Intellectual Dynamics-Informatics, in small circles.

1.7.3. International SI Unit defined by Human

The international SI unit designations, shown below (Figure 9), were designed by humans and facilitate inter- and cross-disciplinary linkage.

Mass: Weight of entity, effecter, effected, substrate, receptor, intermediate entity, products, input entity, output entity, drugs, chemicals, biologicals, receptor…

Force: Energy, temperature, electromagnetic weak and strong force, gravitational force, action/interaction/ reaction, attractive/repulsive, effect, response, activation/inhibition,

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synergism/antagonism, potentiation/suppression, regulate, feedback, competitive/noncompetitive/uncompetitive, aggressive/peace, equilibrium, affinity, and harmony...

Space: Size, volume, distance, location, inclusivity, exclusivity, non-exclusive, inclusive, vector, superposition, symmetry…

Time: Moment, time-lapse, period, rate, speed, space-time…

Life: The dynamics of all components above are mixed with units and measurements decided by humans. Life includes birth and death, growth, rest and movement, metabolism, reproduction, consciousness, intelligence, the survival instinct, the existence instinct, ecosystems, and AI.

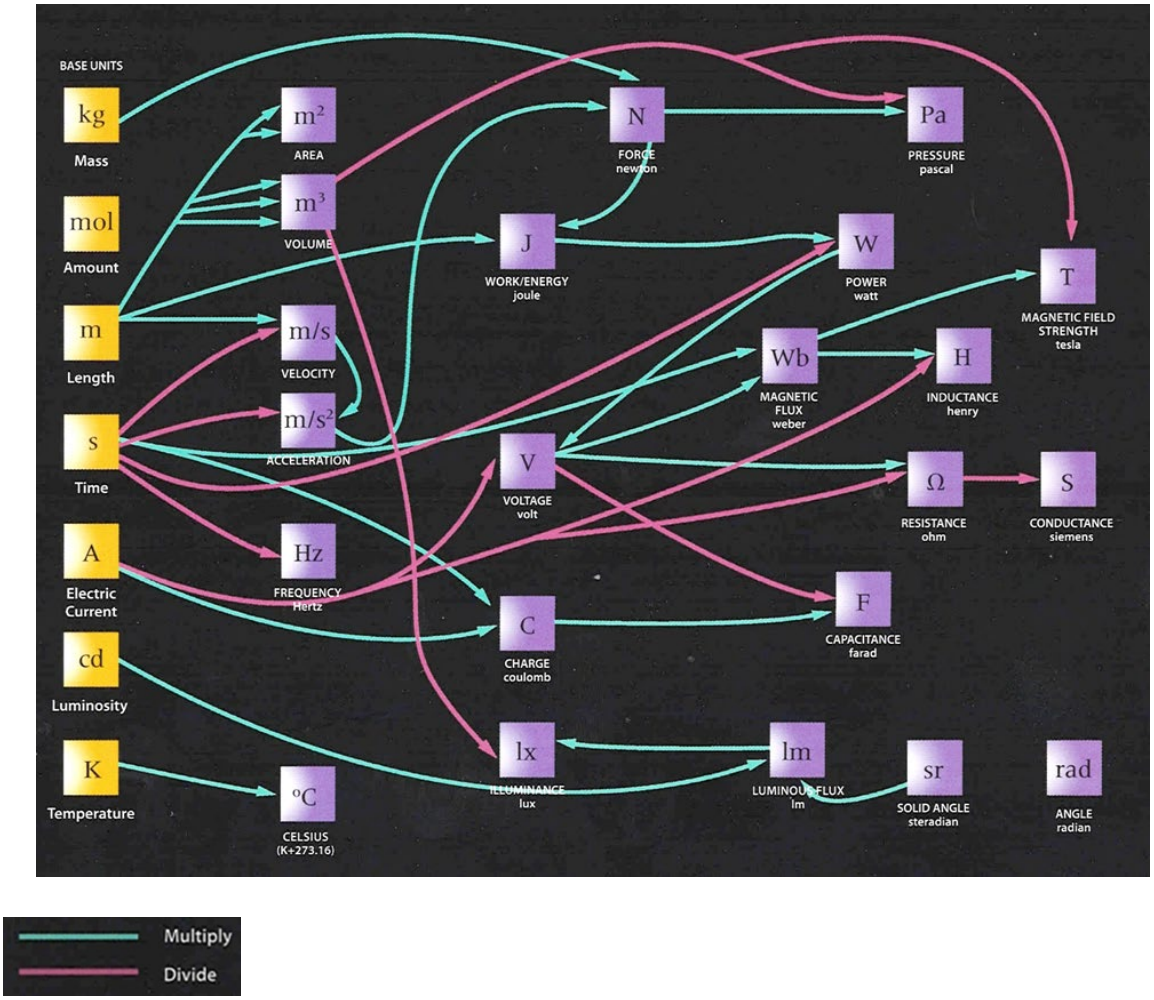

Figure 9. All units are derived from the seven SI units. Blue lines show when a unit is multiplied. The red indicates a division. Count the arrowheads to see how many times a division or multiplication takes place. You will see that the mole has no derived unit, and that the base units do not define the radian or the steradian. A radian is the angle of an arc that has the same length as the radius. A steradian is the angle of a cone of a sphere where the area of the base of the cone is the square of the radius of the sphere.

1.7.4. Number, Ratios, and Identities: Real and Imaginary

The Unity Theory of One (UTO or UOT), with a distribution function of One, especially in the hyperbolic and sigmoidal activation function, of the Doctrine of the Median (DOM), with a Median Point, Median Axis, and Plane. Different disciplines have their own annotations, units, and definitions. However, they converged into the concept of One, whether real or imaginary, transformational or transcendental.

The Mass and Median mediated Floating Ratio (FR), $fa/fu = fa/(1-fa) = [(fa)^{-1} -1]^{-1} = (D/Dm)^m$, indicating Life is the center of Mass Force, Mass, Space & Time to constitute five Components of the Universe.

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Many entities and identities in Nature exist without knowing their source. Who, why, when, where, decide them, a priori? These are discovered, described, and utilized by humans but not created by humans. Humans are gradually understanding the meaning of the revelation of intrinsic properties, via extrinsic phenomenal investigation. We found the Unity of "**One**" and Life-Centric Universe, whatever that "One" is. Many civilizations in human history tended to believe in the existence of "God" or All the Mightiest" as the "One". Given below are some examples.

Examples of numbers, entities, identities, and ratios: Real and Transcendental. Nature's open code in our plain view, a priori, is awaiting revelation of the underlying real meaning, understanding, knowledge, and applications.

Nature's Numbers, Ratios, and Elements: Real and Surreal

Types of Real and Imaginary entities, Numbers Exponent, and Mass-action law (MAL)

Real and Surreal, Rational and Irrational, Algebraic and Transcendental Transformations

Example of exponent: $e^{\pi i} = -1$ (Euler's Identity)

Equivalent logarithm: ln (-1) = π i

$E^{ix} = \cos(x) + i\sin(x)$

√2 = 1.41421356237309504880…

π = 3.14159265358979323846…

e = 2.71828182845904523536…

$i = \sqrt{-1}$

φ = Golden Ratio, $[\frac{a}{b} = \frac{a+b}{a}]$ = (1 + $\sqrt{5}$) / 2 = 1.618033988…, (Mathematics and Physics; Continue Fractional Infinitive Distribution of 1; Open, Linear to Infinity).

FR, fa/fu = fa/(1-fa) = $(fu)^{-1}$—1 = $[(fa)^{-1}—1]^{-1}$ = $(D/Dm)^m$ where fa + fu = 1; (Relate Dose with Effect, Mass with Function in Biology with the Mass-Action Law), (Floating Ratio, fa/fu, is Fractional Finite Distribution of 1; Close and Recyclable).

Some of the mathematical and physical entities given above are unreal, irrational, or imaginary. In theoretical physics, the terminology includes antimatter, dark matter, dark energy, black holes, Hawking radiation, quantum fields, John Wheeler's holographic illusion, and James Kowall's holographic screen of consciousness, among others. It is of interest to note that in sensible real-world biological MAL theoretical analysis, leads to the "negative doses", which are unreal, but lead to convergence to "1", which in turn, points to the value of the "Median" or 0.5. (see later in Figure 19). In addition, the dose-effect relation shows visible inputs (dose) and outputs (effect, fa), with an invisible unaffected fraction of fu, in which the fa/fu ratio shows 180 ° and 360 ° cyclable reciprocal rotation (see Section 1.8.1 in Figure 11).

Biology and medical sciences follow MAL-MEE/PEP/DMDTPT at optimal conditions, in equilibrium and harmony (Figures 2-5, 9), in conservation (Figure 5), and in symmetry with intra-, inter-, and cross-disciplinary links. (Figures 12,18, 19, 21).

Humans make and decide on terms, units, definitions, and measurements in our surroundings, environment, world, galaxy, and universe, including units such as kilogram, meter, minute, volume, pressure, number, constant, index, grammar, rule/law, and ecosystem. While searching for knowledge and truth, we must realize that we are a tiny fraction of the universe. But do not forget to count ourselves in. We first need to solve real-world, day-to-day problems from a life perspective. Life and non-life, real and imaginary, are assessed from different angles and through different analyses, but all converge into only the supreme One, whatever the One is.

The most intriguing equation in mathematics: Euler's Identity

It is a cornerstone of complex analysis and has widespread application in fields from mathematics to electrical engineering and quantum mechanics in the non-life domain. It is presented as **Euler's identity**,

$$\mathbf{e^{\pi i} + 1 = 0}$$

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In a mere seven **symbols,** it unites the base of the natural logarithm *e*, the imaginary unit i, the transcendental constant π, 1, and 0. One can be interpreted as the unity of full and partial distributions, and +1, 0, and -1 can be interpreted as One, nil, and imaginary, symmetrical non-existence counterpart of 1.

The "*i*" and Rotations

Recent research on rotation with complex numbers by T. Darlington [71] and D. Gunter [72]. According to Shmoe in 2025 [73], on "i" with different revelations when the vector changes.

Where the power of "i" is related to the Golden Ratio (φ), and Pi (π), based on Euler's identity.

$$i^{4n} = 1,$$
$$i^{4n+1} = i,$$
$$i^{4n+2} = -1,$$
$$i^{4n+3} = -i,$$
$$-i = \frac{1}{i} = i^{-1}$$

From Euler's identity, then

$$e^{i\pi\phi^2} = e^{\frac{i\pi}{\phi}}.$$

Where, ϕ = golden ratio.

$$i^{\frac{1}{i}} = \left(\frac{1}{i}\right)^{i} = e^{\frac{\pi}{2}}.$$

1.7.5. Human-Defined Units for Measurements for Sciences

Humans, as primates, decide on Units — the basis of innate intuitive perception, intelligence, logic, and the accumulation and exploration of knowledge — which evolve into sciences. Figure 9 gives the international SI units.

The different units may be multiplied or divided as required for the multiple or cross-disciplinary sciences.

The ratio of the same unit resulted in a dimensionless quantity, such as the Floating Ratio (fa/fu) and the Golden Ratio (φ). In biology, fa/fu = $(D/Dm)^m$ (the median-effect equation), in physics, $E/M = C^2$ (the relativity equation), in archeology, C^{14}/C^{12} Ratio (of half-time) for age estimation. For the Unified General Theory to be dimensionless, it must be independent of physical state, size, structure, and complexity.

Mathematical manipulations of numbers and units can reveal intrinsic properties that confer a new meaning to identity and entity. These include x-y plot, x-y-x plot, double reciprocal plot (1/s vs. 1/vi, the Lineweaver-Burk plot for determining enzyme kinetic constants (Km for substrate and Ki for inhibitor), and deciding types of inhibition (competitive, non-competitive, and uncompetitive). MAL-MEE/CIE has extended this to a unified general utility theory of R&D.

1.7.6. Inductive and Deductive vs. Bottom-Up and Top-Down

The MAL MEE/DOM/UTO Unified Theory: A conceptual departure from the traditional observation-based R&D dominance

Given the complexity, variability, and diversity of universal events, observation, measurement, experimentation, and trial-and-error-based conclusions are unavoidable until a unified general principle of science and technology is available. The ancient traditional Chinese medicine. Sky constellations, religions, and arts are the manifestations.

Throughout history, whether among philosophers (e.g., Aristotle) and scientists (e.g., Einstein) or in science textbooks, there have been debates about induction and deduction, as recently described

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by David Kyle Johnson [74]. Based on the context and semantics, Johnson indicated that deductive arguments are those with premises that guarantee their conclusion, while inductive arguments are those with premises that raise their conclusion's probability, and concluded that deduction is reasoning that guarantees its conclusion; induction is reasoning that provides conclusions with probable support.

Thus, let us consider a scientist running an experiment to test a hypothesis; they will consider an experimental result that the hypothesis predicted as evidence for the hypothesis. (If H then R. R. Thus H.) Clearly, this follows the same pattern — yet we would not consider this form of reasoning deductive. Indeed, the good scientist will know and admit that the experimental result doesn't prove the hypothesis true — it merely supports it or raises its probability. So, this is an example of inductive reasoning. And we wouldn't consider it "fallacious." If the experiment is conducted correctly, it could provide strong support for the hypothesis. So, whether an argument is deductive or inductive can be context-sensitive; it depends on the intentions of the person making it.

In recent years, Chou has compared the **Bottom-Up and Top-Down** approaches to scientific R&D and concluded that, although they are opposite, they are mutually complementary, like two sides of the same coin [19,22,24]. Interestingly, the terms Bottom, Up, Top, and Down, along with Charm and Strange, have already been used in Quarks in the standard elementary particle physics [24,75].

1.8. Life and Non-Life

There are two domains in the universe: Life and Non-Life, as manifested in the Floating Ratio and the Golden Ratio, as indicated in Figure 10A. Life domain dynamics are deterministic, finite, and cyclable. The non-life domain is open and infinite, and it involves complex numbers.

We need the distinction between Life and Non-Life in scientific R&D, dynamics, and informatics, as well as intelligence and artificial intelligence.

The transition from Life to Non-life is an abrupt paradigm shift that cannot exist in both forms, as described by Schrödinger's cat. The transformation can be transcendental. In biology, it is live-or-dead; in pharmacology, it is all-or-none; in mass-action law, both Dm and m become zero; in philosophy, it is something to nothing; in religion, it is life to afterlife, or world to heaven; in physics, entropy becomes zero; and in mathematics, 1 becomes 0.

Theory of Everything Excluding Life

Contemporary theory of everything focuses on physical definition (Non-Life domain) without considering the Life domain. The biological or medical science real-life observations, such as metabolism, reproduction, regulation, cooperativity, equilibrium, harmony, and homeostasis, are completely left out. This paper emphasizes the Unity Theory of One (UTO) and the Life-Centric Universe (LCU). Since all scientific units and measurements are decided by humans, it's reasonable to propose that Life is the center of the universe among mass, force, time, and space.

Evaluation Criteria for the Theory of Everything from Physics' Point of View

Each theory can be scored using the following dimensions:

- Theoretical Coherence: Internal consistency
- Mathematical Rigor: Formalism and derivability
- Predictive Power: Testable novel predictions
- Experimental Testability: Real-world falsifiability
- Completeness: Covers SM + GR + cosmology
- Novelty / Independence: Conceptual originality

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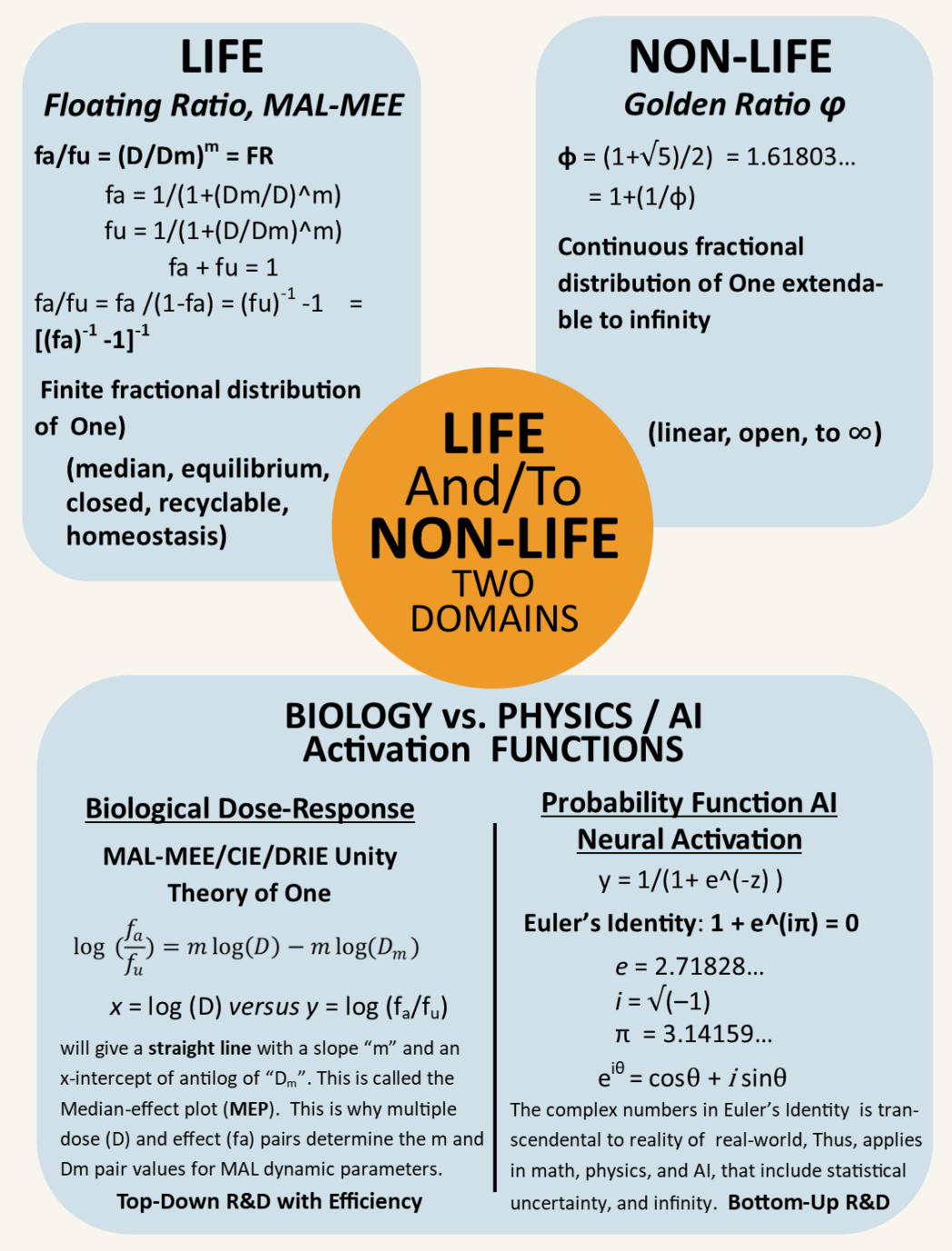

Figure 10. A. A graphic presentation comparing Life and Non-Life in Nature.

1.8.1. Visible and Invisible

MAL-MEE, $fa/fu = (D/Dm)^m$, Manifests Life. However, the extrinsic properties we can sense or see, the intrinsic properties, or the underlying principle, are not necessarily visible. These functional dynamics are common to living systems, which involve receptor intermediates and transition steps within networks or pathways. We observe the inputs and outputs, but not the intermediate steps, except when the processes are slow or slowed by drastically lowering the temperature, and when they perform high-accuracy, fast measurements.

In the unified general median-effect equation, MAL-MEE, the floating ratio Fa/fu, where Fa is visible, and Fu is not visible, is subjected to the reciprocal and double-reciprocal, thus, recyclable, as described in Figure 11.

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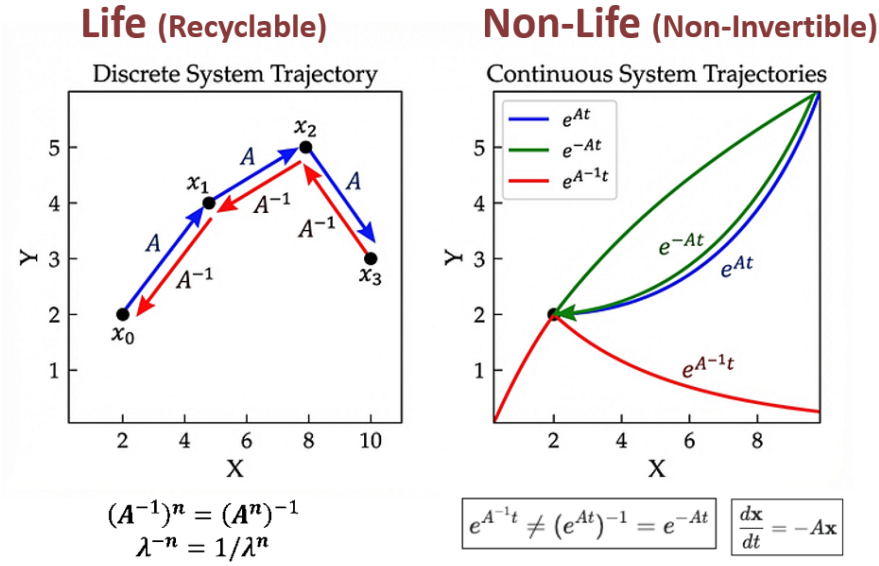
***Discrete* Systems Manifest *Life* Domain &**
***Continuous* Systems Manifest *Non-Life* Domain**

	Discrete Systems	Continuous Systems
Equation	$x_{t+1} = Ax_t$	$\dot{x} = A_x$
Time Evolution	$x_t = A^t x_0$	$x(t) = e^{At} x(0)$
Matrix Inversion	Yes; $x_{t-1} = A^{-1} x_t$	No; The inverse (A^{-1}) does not directly reverse time evolution.
Algebraic Reversal	$x_t = (A^{-1})^t x_0$	$\dot{x} = -A_x$
Key Property	Yes; $(A^{-1})^t = (A^t)^{-1}$	No; $e^{A^{-1}t} \neq e^{-At}$

x: vector
A: matrix A
***t*:** time
$\mathbf{x_0}$: initial vector
$\mathbf{x_t}$: vector at time *t*
$\mathbf{A^t}$: matrix A at time *t*
***e*:** Euler's Entity

Table Source: Tomio Kobayashi (3/2/2026), https://medium.com/@tomkob99_89317/matrix-inversion-and-time-reversal-a-tale-of-two-dynamical-systems-6cb412503d8b

Figure 10B. Discrete Systems manifest Life Domain and Continuous Systems manifest Non-Life Domain (Tomio Kobayashi, 3/2/2026).



Tomio Kobayashi (3/2/2026), https://medium.com/@tomkob99_89317/matrix-inversion-and-time-reversal-a-tale-of-two-dynamical-systems-6cb412503d8b

This reminds us that **the same mathematical object (a matrix) can play profoundly different roles** depending on whether it appears as a direct transformation operator or as an infinitesimal generator.

Figure 10C. Two dynamic systems: Matrix Inversion and Time Reversal for Discrete Systems for Life, and Continuous Systems for Non-Life involving *e* (Tomio Kobayashi, 3/2/2026).

1.8.2. The FR (fa/fu) Manifests Life Domain

For the MAL-MEE is, **$fa/fu = (D/Dm)^m$** where fa + fu = 1.
On the left, fa and fu are fractions (affected and unaffected); their ratio, fa/fu, is dimensionless.
On the right, D and Dm have the same unit; the ratio cancels out any unit.
The MAL-MEE embedded invisible mathematical intrinsic properties:
$fa/fu = [D/Dm]^m = fa/(1 - fa) = (fu)^{-1} - 1 = [(fa)^{-1} - 1]^{-1}$,
where D is dose, fa is fraction affected, fu = 1—fa, Dm is median-effect dose, and m is the dynamic order.

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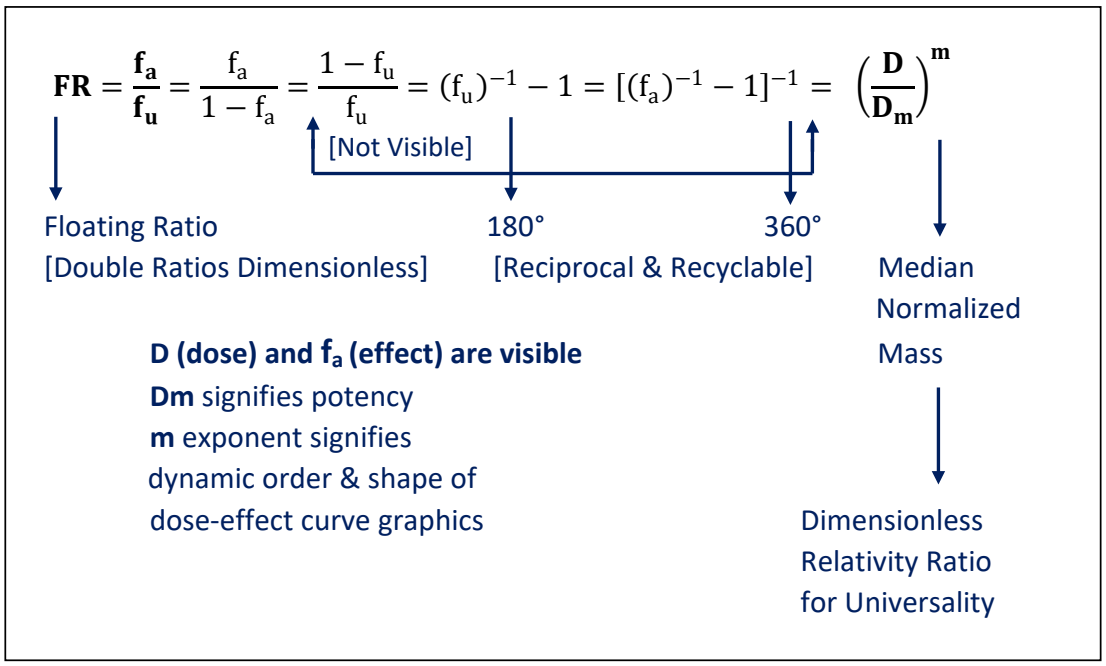

Figure 11. The MAL-MEE on the right is the **dose of Maas** (normalized by the median) for Inputs ↓; on the left of MEE is the **causal Effect**, fa, (expressed as the Floating Ratio (fa/fu) for outputs ↑. Both inputs and outputs are visible or sensible. However, the intermediary complexity of intermediates is not visible.

Single reciprocal and double reciprocal represent (180° and 360°), indicating a closed circular/recyclable system.

1.8.3. The Relativity Concept in Biology and Physics

The MAL-MEE can be rearranged as dose and effect: D = Dm [fa/(1-fa)]$^{1/m}$ and

$$\mathbf{fa} = \frac{1}{1+\left(\frac{Dm}{D}\right)^{m}} = \frac{1}{1+\left(\frac{1}{M}\right)^{m}}$$ **, fa + fu = 1 , D/Dm = M, thus fu = 1/ [1 + (M)^m],**

i.e., M = D/Dm (the Median normalized dose of Mass)

MAL expresses as the fractional distribution of One. The MAL-MEE causal relationship indicates a **Floating Ratio (FR), (fa/fu)**:

(FR) = fa/fu = fa/(1—fa) = (1—fu)/ fu = (fu)$^{-1}$ -1 = [(fa)$^{-1}$−1] $^{-1}$ **= [D/Dm]^m ,** which can be rearranged into

Since fa + fu =1, therefore, fa, the activation function in MAL, must be fa <1 (and fu <1) in life.

The MEE signifies the shape of **hyperbolic (m=1)** and **sigmoidal (m>1, m<1) activation functions,** as indicated in pharmacodynamics/bio-dynamics (PD/BD) derived from mathematics [9,11,24], as well as those used in AI graphics as indicated by the Hopfield equation algorithm and graphics [76,77], derived from physics and engineering for the neural network [78].

The Floating Ratio (FR = fa/fu) of the Median–Effect Equation (MEE) of the Mass-Action Law (MAL) manifests the Life domain. MAL-MEE defines the dynamic relationship between the mass entity of the dose (Inputs) and the functionality of the effect (Outputs) in a finite system.

The MEE took ten years to derive (1966-1976) [1–4] with a unique sequential, pattern, combinatorial general system analysis that involved over 300 reaction rate equations:

The Median Effect Plot (MEP) in double logarithmic form for x- and y-axis: log FR = log (fa/fu) = log (D)—m log (Dm), which determines Dm (dynamic potency, x-intercept), m (dynamic order, shape and slope for linearization (y = mx + b) of dose-effect curve, DEC) [4,9,11,24].

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In MAL-MEE and MEP, FR is a dimensionless-relativity ratio (fa/fu = fa/(1-fa) regardless of unit, physical state, size, structure, and mechanistic complexity. Therefore, the MAL dynamic principle has universal applicability in Life science and beyond [24], as evidenced by garnering 35,000 citations in 1,587 scientific journals and 1,597 patents worldwide, indicating its impact in R&D [56,57].

The D/Dm term is the dimensionless relativity ratio of the same kind, at any dynamic order (m). Thus, MAL-MEE-dictated informatics is regardless of unit, physical state, size, structure, and mechanistic complexity. Therefore, the MAL-MEE theory/algorithm/method has unlimited applications. The ramification across disciplines, sub-disciplines, and sub-sub-disciplines has resulted in over 3,000 journals in the biomedical sciences alone, with no consensus among scientific societies, associations, and schools of thought. The greatest concerns in contemporary R&D are the limited theoretical basis and the lack of a scalable principle for extending to multi-entity interactions and interdisciplinary integration for generality. Innovation is not a matter of talent, but a matter of how we relate to reality, step beyond the conventional surface, and perceive the patterns that organize it

The FR, fa/fu, single-reciprocal (180°), and double-reciprocal (360°) allow binary circular and recyclable closed form, typically manifested in Life. However, MAL also reams Non-Life, as indicated in inter- and cross-disciplinary analysis.

1.8.4. Symmetry, Equilibrium, and Harmony

Comparing the Mathematical Sigmoidal Function and its Derivative with MAL-MEE

Philosophers, researchers, and scientists have observed the shape of dose-effect curves since ancient times. The most common shapes in pharmacology are sigmoidal curves, while in enzymology, simple enzyme molecules display hyperbolic curves. As A.V. Hill discovered, oxygen-hemoglobin interactions follow highly significant sigmoidal curves, leading to the Hill equation (1913), which molecular biology confirmed by showing that hemoglobin has four subunits that bind oxygen molecules cooperatively. In biochemistry, enzymologists also discover allosteric enzymes that contain subunits. In pharmacology and physiology, most often…

In Figure 12, the MAL-Median-effect equation, $fa/fu = (D/Dm)^m$, a sigmoidal function, has been correlated with its derivatives [79]. The graphics show perfect symmetry. Additional illustrations of MAL-MEE median-dose-based symmetry and equilibrium are given in Figures 2-5 and 21. The relationship between the "Median" and the Concept of "Harmony" is illustrated later in Figure 35.

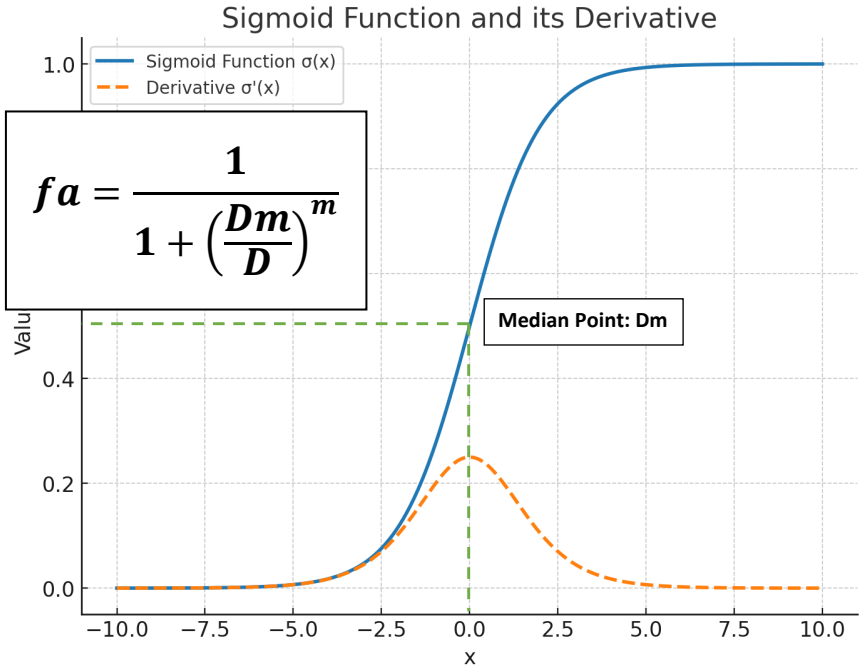

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Figure 12. MAL-MEE activation function (fa) indicates a sigmoidal dose-effect curve (DEC) with its derivative showing a symmetrical distribution curve peaks at the Dm, where fa = fu = ½ (The Median point is 0.5), and its intrinsic property of symmetry.

1.9. Deterministic vs. Statistic: The Basic Math Forms

1.9.1. MAL-MEE-based Deterministic R&D

Transformations of **MAL- MEE** give:

$$\mathbf{D} = \mathrm{Dm}\left(\frac{\mathrm{fa}}{1-\mathrm{fa}}\right)^{1/\mathrm{m}} \quad \text{Thus,} \quad \mathbf{fa} = \frac{\mathbf{1}}{\mathbf{1}+\left(\frac{\mathbf{Dm}}{\mathbf{D}}\right)^{\mathbf{m}}} \text{ , and } \mathbf{fu} = \frac{1}{1+\left(\frac{\mathrm{D}}{\mathrm{Dm}}\right)^{\mathrm{m}}}$$

Scalability:

Dose, D: Mass, Entity, Input (↓), Causal Effector, Activator, Inhibitor, Regulator, …;

Effect, fa: Response, or output (↑) via target receptor, for intermediate, pathway, network of mechanisms or metabolism, processing, and output decision…;

Unaffected fraction, **fu**: Invisible, insensible, imaginary, (1-fa), finite negative complementary effect (<1, > 0 and can be a fraction of the digital, where fa + fu =1, where fa/fu is the Floating Ratio (defined as FR), the floating dark material-like, negativity balancing effect, which is mediated by the MAL, FR = $(D/Dm)^m$;

Median, Dm: Universal reference of potency, or efficacy; harmonic mean, 2ab/(a + b), of kinetic constants Kii and Kis, and the causal mechanistic reference standard for homeostasis, symmetry, rhythm, balancing in actions and interaction, activation or inhibition, regulation, and feedback.

The Kii and Kis are the Ki values determined by the intercept and slope of the Lineweaver-Burk Plot, respectively. It was discovered [3] that Dm (or I50) = 2 (Kii Kis)/(Kii + Kis) for the median dose, where fa = fu = 1/2 = 0.5.

Exponential "m" is the dynamic order signifying the shape of causal response graphic curve, where m =1 indicates hyperbolic activating or inhibitory function, and m ≠ 1 indicates a steep sigmoidal activation function, if m >1, steep sigmoidal; if m <1, it indicates a flat sigmoidal activation function. Therefore, the geometric function of MAL-MEE/CIE/DOM is identical to the **tanh sigmoidal function** in mathematics, and the **Hopfield neural network activation function** for artificial intelligence (AI), except that the theory and algorithm of MAL-theory is developed from life science.

1.9.2.. Statistical, Probit Function and the Logistic Growth Function

Involving "e "

In pharmacology, statistical approaches such as Logit and PROBIT have been introduced (see Table 2). The key ingredient is the logistic function, where an input is converted into a probability, written in the form:

Probability = $\frac{1}{1+e^{-z}}$,

Logit of fa = $[1/[1 + e^{-(\alpha+\beta \log D)}]$,

PROBIT function for fa is

$$\mathbf{fa} = \frac{1}{\sigma\sqrt{2\pi}} \int_{-\infty}^{\log D} e^{-\frac{1}{2\sigma^2}(\log D - \log Dm)^2} d(\log D)$$

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The distinguishing feature of MAL-theory is that it is deterministically easy to use and that the algorithm is simple to implement in digital data science, with automated simulations that yield quantitative or index-based conclusions for real-world problem-solving.

Clearly, fa and fu functionality, where fa + fu =1, is identical in mathematical and statistical forms of:

1.9.3. Fermi-Dirac Distributional Function of One with "e" Notation

MAL-MEE/DOM is essentially a **Fermi-Dirac distribution** form (in statistical physics, the occupancy of energy states by fermions follows:

$$F = \frac{1}{\left[1 + e^{\frac{(E-\mu)}{kT}}\right]}$$

which is a sigmoidal function compared with the mass-action law MEE/DOM, as shown above in Figure 7.

This mathematical form also appears in ecology as the logistic growth model for populations.

However, the biomedical, as well as the physical, engineering, and mathematical digital sciences, have used different symbols and designations without an "e" involvement.

1.9.4. Hopfield Neural Network function without "e" notation

The Hopfield neural network sigmoidal function of the basal algorithm of the sigmoidal activation function in artificial intelligence (**AI**) [76–78], in the form of the sigmoidal function.

Clearly, the fa and fu functionality of the mass-action law, where fa + fu =1, is identical in mathematical forms of the distribution function on "One", for the Hopfield's neural function: Fermi-Dirac distribution functions

$$P(W) = \frac{\frac{P\left(\frac{D}{W}\right)}{P\left(\frac{D}{NW}\right)}}{1 + \frac{P\left(\frac{D}{W}\right)}{P\left(\frac{D}{NW}\right)}}$$

It is of interest to note that the Mass-action law-based derived median-effect equation [3–7] has the same form as the Hopfield's neural network function, which does not involve the "e" functions, which is a conceptual breakthrough, and a paradigm shift in scientific research and development (R&D).

1.9.5. The MAL-MEE/DOM/CIE/UTO Causal-Effect Theory without the "e" Notation for the Real-world Phenomena

The following MAL-based biochemical/biological quantitative data sciences do not involve "e." Most MAL equations have a typical mathematical form of a finite distribution function for "1":

Fa = 1 / [1+ (Fractional distribution in ratio)^m], where m =1 is the first-order dynamics (the Michaelis-Menten hyperbolic function), m < 1 for negative cooperativity with a flat sigmoidal function, and m>1 for positive cooperativity with a sigmoidal function

As indicated by comparing the MAL-MEE dynamics of Floating Ratio, FR (Manifesting Life), and the Golden Ratio, GR (Manifesting Non-Life) in Table 3, the fundamental mathematical forms for Life and Non-life are exceedingly simple. The fundamental source codes:

for Life is a/b = a/(1- a) = (1 -b)/b, a + b =1; Expressed as fa/fu = (D/Dm)^m

for Non-life is a/b = (a + b)/a = 1 + b/a; Expressed as [φ = 1.618033…= (1 + √5)/2.

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Both (a/b) ratios are expressions of the fractional distribution of "One" with basically different dynamic properties, yet maintaining a connection to "1". For life is finite and cyclable distribution of "1"; In Life, FR partitions 1 into complementary components (fa and fu, > 0, < 1, centered at the median, 0.5); In Non-Life, GR partitions 1 into continuous recursive sequences, extendable without a bound.

The MAL-MEE Mathematical Deduction form of A General Expression

AS indicated above (Section 1.9.1), the rearrangement of the MAL-MEE gives:

$$\mathbf{D} = \mathrm{Dm}\left(\frac{\mathrm{fa}}{1-\mathrm{fa}}\right)^{1/\mathrm{m}} \quad \text{Thus,} \quad \mathbf{fa} = \frac{\mathbf{1}}{\mathbf{1}+\left(\frac{\mathbf{Dm}}{\mathbf{D}}\right)^{\mathbf{m}}} \text{ , and } \mathbf{fu} = \frac{1}{1+\left(\frac{\mathrm{D}}{\mathrm{Dm}}\right)^{\mathrm{m}}} .$$

The detailed mechanistic analysis on enzyme reaction systems (E, Ex and/or Et) using substrates (S, A and/or B) as the primary ligands, and the inhibitors (I, I1 and/or I2) as the reference ligands.

Tables 4-6 below indicate a systematic analysis of enzyme kinetics with graphics shown in **Figures 14-16. Note that in Tables 4-6,** the equations with ratios in the denominators express the distribution function of "1" in the finite series. These are in the form of:

X = 1/ [1 + (Dimensionless Distribution Ratios)]

1.9.6. The MAL-based Finite Distribution Function of "1" in Life Sciences

The first-order fractional Inhibition in the Michaelis-Menten Kinetic System in Biochemistry

The Chou's fractional distribution function of One, Parts vs. Whole [3,9,24].

It was shown [3] :

Ki/I_{50} = Ex/Et = Part/Whole

Where ki is the inhibition constant, I50 is Dm, Et is the total enzyme, and Ex is the portion of the enzyme that is occupied. This relationship is regardless of whether the inhibition is competitive, non-competitive, or uncompetitive (i.e., all types of inhibition).

This equation also indicates that Ki will never exceed I_{50}.

This equation can be used to calculate fractional receptor binding or to estimate Ki from the experimentally determined IC50 value in derivations of first-order kinetics [3–7,9].

fi + fv = 1; where fi is the fraction inhibited, and fv is the uninhibited "control". Therefore,

fv = 1/[1+(I/Ki)(Ex/Et)]

fi = 1/[1 + (ki/I)(Et/Ex)]

Discrete (Finite) and Continuous (Infinite) Distribution Systems of "1" Manifest Life and Non-Life

The MAL basic principle is shared in biology, chemistry, and physics; however, the Life domain (including biological and medical sciences) is fundamentally distinct from the Non-Life domain, such as mathematics (including physics) and artificial intelligence (AI) (including computer sciences and engineering).

Tables 4-6 provide summaries of the different inhibition mechanisms, kinetic constants, and discrete distribution functions of "One" in the Life domain.

It is of interest to note that the MEE, fa/fu

In biochemistry or molecular biology, fi and fv are equivalent to fa and fu in pharmacology or physiology (see **Appendix I**).

From conceptual and chronological points of view, the contents of Tables 4–6 and the earlier sequential pattern analysis belong to the Mathematical Induction process, which involved over three hundred kinetic and dynamic equations and took two decades (1965-1976). These are followed by the *Mathematical Deduction* Process, which ultimately leads to the unified general theory of MAL-MEE/CIE/DRIE, as well as MEP, MTDPT, UTO, and LCU (1976-2026).

Table 4. Different mechanistic types of inhibition, constants, and distribution function equations.

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Inhibition of different three-substrate reactions with inhibitors of different inhibition mechanisms

Symbols are defined under SYMBOLS AND DEFINITIONS. x, y or z refers to unspecified number of product(s) in a reaction sequence.

Reaction mechanism	Inhibition mechanism	K_i/I_{50}	Fractional velocity, f_v	Fractional inhibition, f_i	Distribution equation[b]
Ordered Ter-x (one stable enzyme form)	I combines with E	$\frac{E}{E_t}$	$\frac{1}{1+(I/K_i)(E/E_t)}$	$\frac{1}{1+(K_i/I)(E_t/E)}$	$\frac{E}{E_t}=\frac{K_{ia}K_{ib}K_c+K_aBC+K_{ia}K_bC+K_cAB+K_bAC+K_aBC+ABC}{K_{ia}K_{ib}K_c+K_{ib}K_aA+K_{ia}K_bC+K_cAB+K_bAC+K_aBC+ABC}$
	I combines with EA	$\frac{EA}{E_t}$	$\frac{1}{1+(I/K_i)(EA/E_t)}$	$\frac{1}{1+(K_i/I)(E_t/EA)}$	$\frac{EA}{E_t}=\frac{K_{ib}K_aA+K_bAC}{\sum}$
	I combines with EAB	$\frac{EAB}{E_t}$	$\frac{1}{1+(I/K_i)(EAB/E_t)}$	$\frac{1}{1+(K_i/I)(E_t/EAB)}$	$\frac{EAB}{E_t}=\frac{K_cAB}{\sum}$
Uni-x Uni-y Uni-z Ping Pong (three stable enzyme forms)	I combines with E	$\frac{E}{E_t}$	$\frac{1}{1+(I/K_i)(E/E_t)}$	$\frac{1}{1+(K_i/I)(E_t/E)}$	$\frac{E}{E_t}=\frac{K_aBC}{K_cAB+K_bAC+K_aBC+ABC}$
	I combines with F	$\frac{F}{E_t}$	$\frac{1}{1+(I/K_i)(F/E_t)}$	$\frac{1}{1+(K_i/I)(E_t/F)}$	$\frac{F}{E_t}=\frac{K_bAC}{\sum}$
	I combines with G	$\frac{G}{E_t}$	$\frac{1}{1+(I/K_i)(G/E_t)}$	$\frac{1}{1+(K_i/I)(E_t/G)}$	$\frac{G}{E_t}=\frac{K_cAB}{\sum}$
Bi-x Uni-y or Uni-x Bi-y[a] Ping Pong (two stable enzyme forms)	I combines with E	$\frac{E}{E_t}$	$\frac{1}{1+(I/K_i)(E/E_t)}$	$\frac{1}{1+(K_i/I)(E_t/E)}$	$\frac{E}{E_t}=\frac{K_{ia}K_bC+K_aBC}{K_{ia}K_bC+K_cAB+K_bAC+K_aBC+ABC}$
	I combines with EA	$\frac{EA}{E_t}$	$\frac{1}{1+(I/K_i)(EA/E_t)}$	$\frac{1}{1+(K_i/I)(E_t/EA)}$	$\frac{EA}{E_t}=\frac{K_bAC}{\sum}$
	I combines with F	$\frac{F}{E_t}$	$\frac{1}{1+(I/K_i)(F/E_t)}$	$\frac{1}{1+(K_i/I)(E_t/F)}$	$\frac{F}{E_t}=\frac{K_cAB}{\sum}$

[a] All the relationships are the same as in the Bi-x Uni-y Ping Pong mechanism except that the symbols are changed as follows: E becomes F, B becomes A, C becomes B, and A becomes C.
[b] Notice that distribution equation can be expressed by K_i/I_{50} (see Eq. 19), therefore f_v and f_i are $1/(1+I/I_{50})$ and $1/(1+I_{50}/I)$, respectively.

In this case, if the enzyme receptor has two substrates (A and B) and the inhibitor (I) as a reference ligand, the relationship based on the mass-action law is the following, where Ki/I_{50} is the fractional occupancy of the enzyme binding site (for **Space**), whereas A/Ka and B/K_b is the normalized specific concentration (Mass) of A and B, respectively [3].

Table 5. The relationship between the median dose (I_{50} or Dm) and the kinetic constant of an inhibitor in a one-substrate enzyme reaction.

Summary of relationships between I_{50} and K_i in one-substrate reactions with different types of inhibition

Type of inhibition	Fractional velocity, f_v[a]	Relationship between I_{50} and K_i			
		For over-all reaction, A = finite value	At specific substrate concentration, $A = K_a$	At extreme substrate concentration	
				$\lim_{A\to\infty}$	$\lim_{A\to 0}$
Competitive	$\frac{1}{1+(I/K_i)[K_a/(K_a+A)]}$	$I_{50}=\left(1+\frac{A}{K_a}\right)K_i$	$I_{50}=2K_i$	$\frac{I_{50}}{K_i}=\infty$	$I_{50}=K_i$
Noncompetitive[b]	$\frac{1}{1+I/K_i}$	$I_{50}=K_i$	$I_{50}=K_i$	$I_{50}=K_i$	$I_{50}=K_i$
Partial noncompetitive[b]	$\frac{1}{1+[I(K_a/K_{ia})+(A/K_{ii})]/(K_a+A)}$	$K_{ii}>I_{50}>K_{is}$ $K_{is}>I_{50}>K_{ii}$	$I_{50}=\frac{2K_{is}K_{ii}}{K_{is}+K_{ii}}$	$I_{50}<\frac{2K_{is}K_{ii}}{K_{is}+K_{ii}}$	$I_{50}>\frac{2K_{is}K_{ii}}{K_{is}+K_{ii}}$
Uncompetitive	$\frac{1}{1+(I/K_i)[A/(K_a+A)]}$	$I_{50}=\left(1+\frac{K_a}{A}\right)K_i$	$I_{50}=2K_i$	$I_{50}=K_i$	$\frac{I_{50}}{K_i}=\infty$

[a] Fractional inhibition (f_i) can be obtained by $1-f_v$.
[b] In the Lineweaver-Burk plot, when the crossover point is on the horizontal axis (i.e., $K_{is}=K_{ii}$), inhibition is called noncompetitive; when the crossover point is above the horizontal axis (i.e., $K_{ii}>K_{is}$) or below the horizontal axis (i.e., $K_{is}>K_{ii}$), it is partial noncompetitive. Notice that $2K_{is}K_{ii}/(K_{is}+K_{ii})$ is the harmonic mean of K_{is} and K_{ii}.

Note that I_{50} is the median dose (Dm) in the first-order dynamics (m = 1) for the median effect equation for the 1st-order effector kinetics/dynamics. (Table 3A).

Km is the substrate kinetic constant (Ka, Kb). Ki is the inhibition constant, whereas Kii and Kis are the Ki values calculated based on the Lineweaver-Burk plot's x-intercept and slope, respectively.

In the median effect equation, fi/fv or fa/fu = $[D/Dm]^m$, the ratio of fractional inhibition in the presence or absence of any inhibitor, all kinetic constants (Km and Ki) cancel out, leaving only the dose-effect dynamic relationship [3].

Table 6. The relationship between median dose and kinetic constants of inhibitor in two-substrate enzyme reactions with different substrate-inputs and product-outputs transition patterns.

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Summary of relationships between I_{50} and K_i in two-substrate reactions with different mechanisms of inhibition

Reaction mechanism	Inhibition mechanism	Resulting inhibition	I_{50}/K_i For over-all reaction, A = finite value	At specific substrate concentration: $A = K_a$ $(-K_{ia})$	At specific substrate concentration: $B = K_b$	At specific substrate concentration: $A = K_a$ $(-K_{ia})$, $B = K_b$	At extreme substrate concentration: $\lim_{A\to\infty}$	At extreme substrate concentration: $\lim_{B\to\infty}$	At extreme substrate concentration: $\lim_{A\to 0}$	At extreme substrate concentration: $\lim_{A=0}$
Ordered Bi	I Combines with E	Competitive with A (non-competitive with B)	$1+\frac{AB+K_bA}{K_aB+K_mK_b}$	2	$1+\frac{2A}{K_a+K_{ia}}$	2	∞	$1+\frac{A}{K_a}$	1	$1+\frac{A}{K_{ia}}$
↓↓↑↑ No transitional stable enzyme form (N = 0)	I Combines with BA	Competitive with B (uncompetitive with A)	$1+\frac{AB+K_aB+K_{ia}K_b}{K_bA}$	$2+\frac{2B}{K_b}$	$2+\frac{K_a+K_{ia}}{A}$	4	$1+\frac{B}{K_b}$	∞	∞	$1+\frac{K_{ia}}{A}$
Ping Pong Bi	I Combinee with B	Competitive with A (uncompetitive with B)	$1+\frac{AB+K_bA}{K_aB}$	$2+\frac{K_b}{B}$	$1+\frac{2A}{K_a}$	3	∞	$1+\frac{A}{K_a}$	1	∞
↓↑↓↑ One transitional stable enzyme form (N = 1)	I Combines with P	Competitive with B (uncompetitive with A	$1+\frac{AB+K_iB}{K_aA}$	$1+\frac{2B}{K_b}$	$2+\frac{K_a}{A}$	3	$1+\frac{B}{K_a}$	∞	∞	1

Note that Sequential pattern analysis in linear reactions with substrates A and B, in the present of different mechanisms of inhibition. Equations show similar mathematical patterns. Source [_Table_2].

Note that sequential pattern analysis is performed in linear reactions with substrates A and B in the presence of different mechanisms of inhibition. Equations show similar mathematical patterns.

The I_{50}/K_i ratio (whole vs parts, Et/Ex) in Table 9 indicates a pattern of 1 plus a typical distribution function based on the mechanistic sequence of input and output patterns.

The reciprocal situations are illustrated in **Tables 4–6**, with ki/I50 = Ex/Et, where Ex/Et = 1/[1 + (distribution function)]. Therefore, by definition, the whole enzyme (Et) represents "One", and the MAL functional dynamics principle follows the same mathematical pattern of hyperbolic activation functions. This MAL-life-science-based pattern is identical to the geometric, physical, and AI-algorithm patterns, as Appendix III shows**.** Tables 4-6 and Figures 14-16 are all for the Michaelis-Menten type of kinetics/dynamics. The groundbreaking advancement following [2–4] in the early 1970s was the extension of theoretical work from a single inhibitor (effector) to n-inhibitors [6] and from first-order dynamics to mth-order dynamics [7]. These led to the discovery of the unified general theory of median-effect equation (MEE) [4], the combination index equation (CIE) [8], and the dose-reduction equation (DRIE) [9,53].

The above efforts led to a period of conceptual consolidation and integration of MAL theory and methods [7,8,22–24], as well as interdisciplinary collaborations, including drug discovery and free software downloads.

After retirement in 2013, the theoretical work on MAL-MEE/CIE/DOM continue, and introduced the UTO, top-down vs. bottom-up complementary concepts in scientific R&D [51,52], MAL-MEE/CIE floating ratio, fa/fu = fa/(1−fa), manifesting Life **vs**. the ancient Golden Ratio ($, \varphi = \frac{a}{b} = \frac{a+b}{a}$, manifesting non-Life [22], and indicated that MAL-MEE/DOM/UTO serve as universal common denominator for intra-, inter-, multi-, and cross-disciplinary R&D efficient, cost-effective, general digital linkage [9,11,14–21]. Advocacy for international R&D regulatory policy, priority reform, and modernization has continued [9,24].

This regulatory efficiency reform for public advocacy is significantly supported by the broad applications of the MAL-based functional dynamic theory, algorithm, and computer software, which have garnered citations in over 1,500 scientific journals and 1,621 patents [56]. Since 2013, there have been 23,500 new paper citations [57] and over 60,000 registered free downloads of computer software [55] from scientists from 137 countries and territories.

1.10. Graphics Revelations of the MAL-1st-Order Kinetics

Figures 14-16 indicate the MAL-geometric properties, and mathematics explicitly supports the general MAL-DOM and UTO.

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Typical math tools include ratios, reciprocals for 180°, images, double-reciprocals for 360°, circles, logarithms, and double logarithms for the x- and y-axes. Then, look for intrinsic properties, the general principle, and the unified theory.

Categorizing and Generalization, Mathematical Induction and Deduction

1.10.1. Linearization of Inhibitor Curves of Different Types with the Double Reciprocal Plot

Log (D or I) vs. Log Fractional Effect Ratio; log FR: log $[(fa)^{-1}-1]^{-1}$ is the double logarithmic plot that reveals the hidden informatics from the dose-effect dynamics measurements, Figure 13.

This double-logarithmic principle for first-order dynamics is a precursor to higher-order dynamics [4–7], which are described by the median-effect equation (MEE) and the median-effect plot (MEP) [4,8,9].

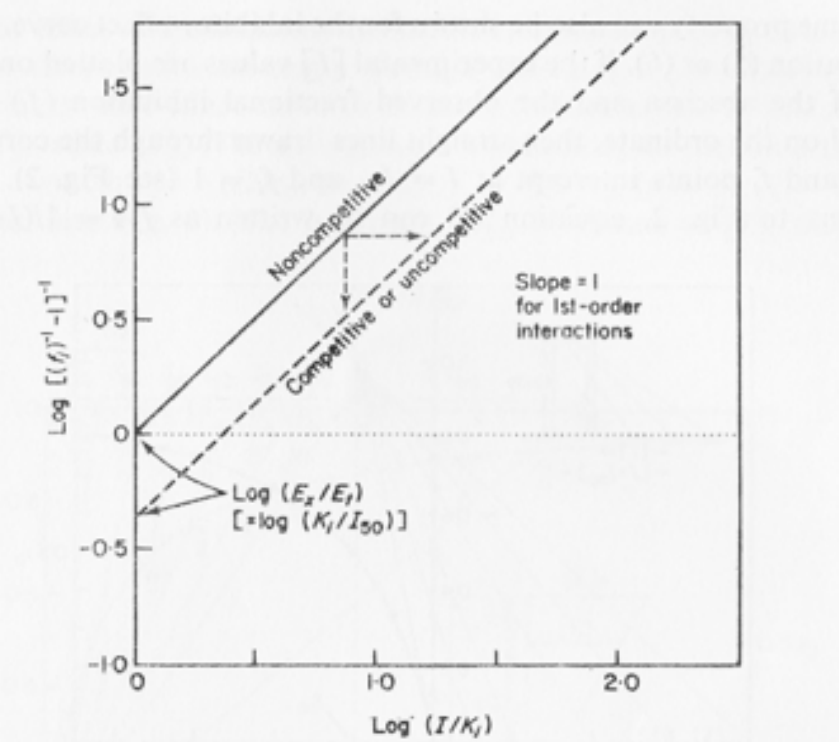

Figure 13. System Analysis on Biological Action of a Single Effecter Entity Type and Parameters.

The double logarithmic plot of [log (I/ki or Ex/Et)or I/Ki) vs. log Fa/fv is the fractional occupancy of the enzyme targeted, where Et is the total amount of enzyme target, and Ex is the amount of enzyme occupied [5].

The discovery was: Ex/Et = Ki/IC_{50}. This later leads to the Median-effect equation (MEE), fa/fu = $[D/Dm]^m$. It is the distribution function of One. Thus, logarithmic transformation and double reciprocals mathematically diagnose the type of inhibition interaction. The enzyme as a whole entity is represented as "one". The rest are fractional distribution functions.

For scale-up applications, during 1984-2024, the MAL theory scientific terminologies have been updated, as shown below:

x-axis is the log of [ki normalized inhibitor Dose concentration]

y-axis is a log of the Floating Ratio (FR),

fi is the fraction affected (fa)

fv is the fraction unaffected (fu)

$fi/fv = [(fv)^{-1}-1] = [(fi)^{-1}-1]^{-1}$, or fa/fu is named the Floating Ratio (FR), in which MAL-MEE indicates that FR is a Double Reciprocal Function (i.e., 180° and 360° cycling, see Figure 11) in life sciences.

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Appendix I gives the details of the evolution in symbols, abbreviations, and definitions.

1.10.2. The Double-Reciprocal Plot (The Lineweaver-Burk Plot for the 1/S vs. 1/v) Linearize the Dose-Effect Curves for 1/I vs 1/fi, Regardless of the Type of the Inhibitory Effect of Inhibitors

Mathematically, a single reciprocal is a 180 ° rotation, and a double reciprocal is a 360 ° rotation (one circle), as indicated in the Floating Ratio (FR) in the median-effect equation (MEE) of the mass-action law (MAL). Thus, the double-reciprocal plot reveals hidden information from dose-effect dynamics measurements.

Both the x- and y-axes are single reciprocal transformations that generate kinetic/dynamic constants and diagnose the types of inhibition. (Figure 14).

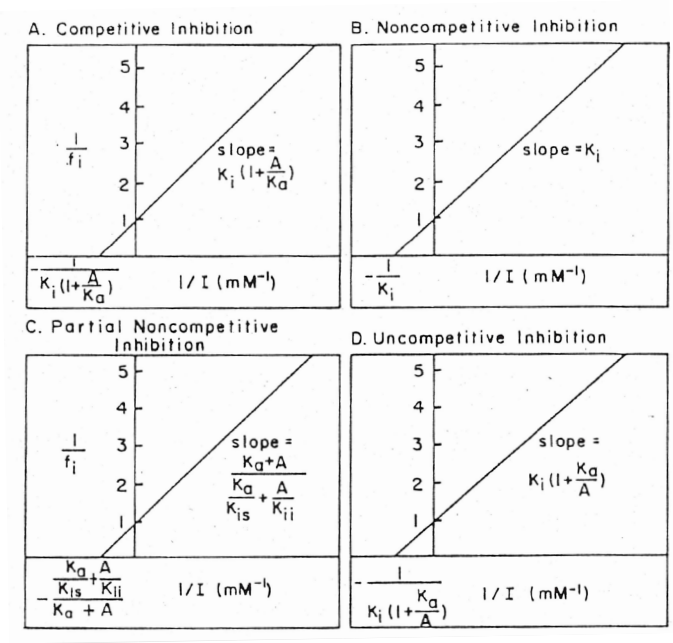

Figure 14. The reciprocal of inhibitor concentration and the reciprocal of fractional inhibition in one-substrate reactions. Thus, under the umbrella of the mass-action law, the inhibitor (I) and substrate (S) are equivalent in terms of entity-mass; i.e., the double-reciprocal plot for (I) is equivalent to the Lineweaver-Burk plot for the saturation relationship.

Thus, a plot of log $[(f_i)^{-1} - 1]^{-1}$ on the ordinate, against log (I/K_i) on the abscissa, is linear with a slope of unity. The slope of one is a consequence of the first-order (i.e., univalent) interaction. The intercept on the ordinate gives log(Ex/Et) or log(K_i/I_{50}), regardless of the enzyme reaction mechanism or the inhibition mechanism. For the single-substrate reaction [9]. Therefore, for competitive, non-competitive, and uncompetitive inhibitions, respectively, are [9]: $\mathbf{I_{50}} = K_i\ [1 + (S/K_m)] = K_i\ (E_t/E)$, $\mathbf{I_{50}} = K_i$, and $\mathbf{I_{50}} = K_i\ [1 + (K_m/S)] = K_t\ (E_t/ES)$, respectively where I_{50} is the median-effect dose (Dm) [2–5,9].

These theoretical concepts have been used for three decades in the subsequent development of MAL dynamics/informatics theory [3–7,9,24], as highlighted in Figures 13-15, and in the early 1970s work. These are focused on the reference ligands (i.e., inhibitors) rather than on the primary ligands (i.e., substrates) only, in the MAL system analysis.

A double reciprocal plot for inhibitor concentration and fractional effect. Different types of inhibitory mechanisms show the same linearity and intercept at 1 (One). The inhibitor or multiple inhibitors are the "reference ligands." This is another reason that MAL-MEE is the Grand General Theory for the later Unity Theory of One (UTO), where MAL-MEE, CIE, and DRIE are all based on the standard of "One" as the universal standard [9,11,24].

1.10.3. The Normalized Doses as a Function of the Reciprocal of the Fractional Distribution Function (I_{50}/K_i)

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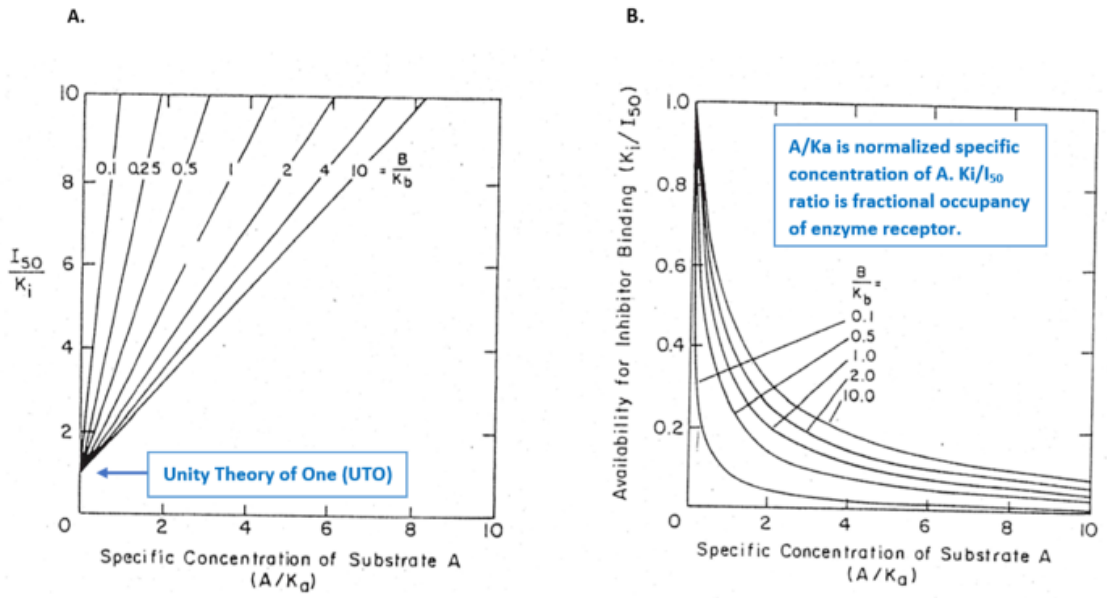

Figure 15. The MAL-based unity theory of one (UTO) and fractional distribution of effect (i.e., the fractional binding (occupancy) of the receptor for actions [3]. Again, the unity theory of one can be visualized. The normalized dose should have an orderly shape based on the fraction occupancy (Ki/I_{50} or Ex/Et), part vs. the whole.

In this regard, Figure 15 also follows the principle of the double-reciprocal plot, which translates dynamic studies into digital informatics conclusions.

This confirms the Unity of One (UTO) theory. All lines intersect at 1 (One) on the y-axis (Figure 15A).

1.11. "Space" Concept in MAL-MEE Unified Theory

Exclusiveness and Non-Exclusiveness Determination

Exclusivity is beyond competitiveness (e.g., competitive, non-competitive, and uncompetitive inhibition, as determined by the Lineweaver-Burk plot). Exclusive and non-exclusive inhibition is directly relevant to the "space" concept as introduced by Chou-Talalay in 1981 [7], and further discussed in 1991 [23].

1.11.1. Mutually Exclusive and Non-exclusive types of binding to the receptor between two inhibitors

The dose-effect curves in Figures 16A and 17A are all linearized by the MEP double-reciprocal plot (Figures 16B and 17B) in mutually exclusive cases (curves a, b, and c). However, the mutually non-exclusive curve (d) cannot be linearized. This is the first time the concept of space exclusivity has been introduced quantitatively in the life sciences. They may be applied to AI algorithms or other areas of data science. This is a powerful demonstration of the MEP double-logarithmic plot concept.

Combinations of effects of two inhibitors in a **first-order system** (m = 1; Michaelis-Menten kinetics), assuming the inhibitory potency for **I_1 is $(I_{50})_1$ = 1 μM** and for **I_2 is $(I_{50})_2$ = 5 μM.** The fractional inhibition is presented as a function of inhibitor concentration for: (a) I_1 alone; (b) I_2 alone; (c) a mixture of I_1 and I_2 (**1:2**), assuming the inhibitors are mutually exclusive in their effects; (d) a mixture of I_1 and I_2 (1:2), assuming they are mutually nonexclusive in their effects. In the case of the mixtures of inhibitors, the abscissa represents the sum of (**I_1 + I_2**), e.g., I_1 = 3 μM plus I_2 = 6 μM (total 9 μM) when compared with 9 μM of I_1 or 9 μM of I_2. **(A)** Linear plot vs. inhibitor concentration. **(B)** The **median-effect plot** of log $[(fi)^{-1} - 1]^{-1}$ vs log inhibitor concentration. Note that curve d clearly shows synergistic inhibitory effects at high concentrations when compared with its parent components on an equimolar basis [7] (Figure 16).

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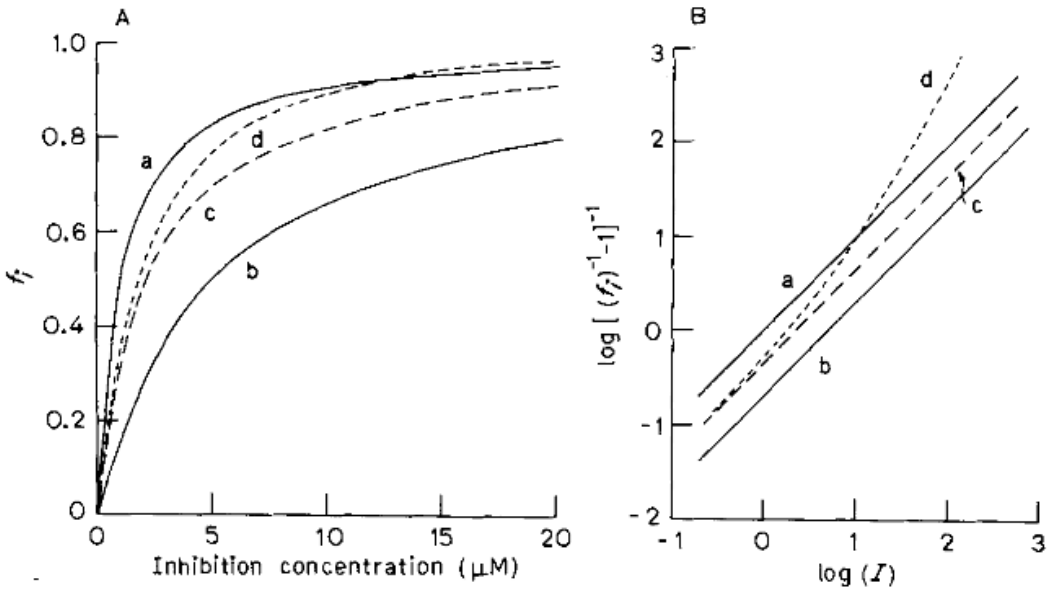

Figure 16. Illustration of exclusivity in the first-order dynamics.

MAL-MEE/MEP transform curves into lines and digital parameters by logarithmic transformation of informatics from [I **vs.** fi] to [log I **vs.** log (fa/fu)] or [log (Floating Ratio, FR)].

Based on the mass-action law, the mutually Exclusive for line (c) and the mutually Non-Exclusive for (d), with the concave upward curve, show the mass-action law-based differentiation of space. The MAL principle of exclusivity concerns space and mass, but is not directly related to time and force (Figures 17A and B).

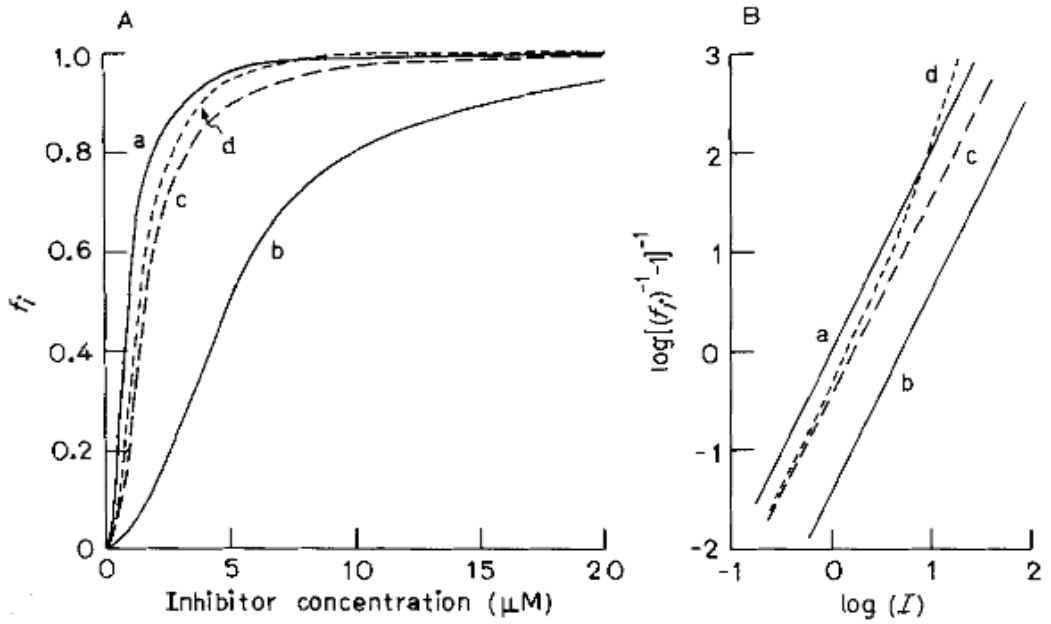

Figure 17. Illustration of exclusivity in the second-order dynamics.

Combination of effects of two inhibitors (each obeying **second-order** kinetics, i.e., **m = 2**), assuming inhibitory potency for I_1 is $(I_{50})1 = I$ μM and for I_2 is $(I_{50})_2 = 5$ μM. **Dose-effect relationships** are given for: (a) I_1 alone; (b) I_2 alone; (c) an equimolar mixture of I_1 and I_2, assuming that they are mutually exclusive in their effects; (d) an equimolar mixture of I_1 and I_2, assuming that they are **mutually nonexclusive** in their effects. (**A**) A plot of fi vs inhibitor concentration on a linear scale. (**B**) The median-effect plot of log $[(fi)^{-1} - 1]^{-1}$ vs log (I) [7].

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MAL-MEE/MEP transforms dose-effect curves into straight lines, allowing automated computer simulation to determine the paired parameters Dm and m from two or more dose-effect data points.

In the second-order system (m=2), similarly to m=1, the mutually Exclusive for line (c) and the mutually Non-Exclusive for (d)-with the concave upward curve, which shows the mass-action law can be associated with space at different dynamic orders. In this case, the mass-action law's exclusivity concerns space and mass, not time and force. The Dm and m parameters jointly provide ID for any dynamic entity under consideration. For multiple inhibitors (or the reference ligands),

1.11.2. Equations of Multiple entities exclusivity in combinations

For a *mutually exclusive* (normal) condition, the two-entity combination's CI equations is:

$$CI = \frac{(D)_1}{(D_x)_1} + \frac{(D)_2}{(D_x)_2}$$ For two drugs, and $$CI = \sum_{j=1}^{n} \frac{(D)_j}{(D_x)_j}.$$ for *n*-drugs.

Whereas for a *mutually non-exclusive* condition, the two-entity Combination's CI equation is:

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

The CI equation for the non-exclusive two-drug or inhibitor combinations has additional terms, (D)1(D)2/ (Dx)1(Dx)2, compared with the CI equation for the mutually exclusive case in combinations. Thus, the non-exclusive case will yield a slightly larger CI value (than the exclusive case), implying less synergism estimation, since the definition of synergism is CI <1 [7,8,27]. However, the mutual non-exclusiveness among mass entities in reference ligands (such as different types of inhibitors)

1.11.3. The MAL Dynamic Space Concept and the Time-Space in Quantum Physics

The above MAL-dynamics, mutually exclusive and non-exclusive concepts in biology (Figures 16 and 17), has a surprising graphical similarity to the time-space concept in quantum physics. However, they intuitively seem hard to connect.

In a recent article by a physician-theoretical physicist, James Kowall [108,109], on how the holographic principle unifies gravity with quantum theory and solves the measurement problem of quantum theory and the hard problem of consciousness, which exhibits a graph on the accelerating observers' event horizon in the time-space coordinates (Figure 18). It compares (i) the accelerating observer's world line, (ii) her own horizon, and (iii) a light ray that never catches up with her as long as she accelerates. Interestingly, her worldline (i) departs from the smooth course, and crosses over with (ii and iii) if she stops accelerating.

Similar scenarios occur in Figures 16B and 17B, where c lines are for mutually exclusive, and d curves are for mutually non-exclusive cases, which are related to the "space" and "dose-effect relationship" of two entities (I_1 and I_2).

Kowall noted that it's worth understanding how Hawking performed his calculation. The first thing he had to calculate was the temperature of the event horizon [108]. This idea goes back to the Unruh temperature, which is defined for any accelerating observer. An accelerating observer always has its own event horizon that limits the observer's observations of things in space. The observer can observe nothing beyond the limits of its event horizon due to the constancy of the speed of light. This limitation of observation is always from the point of view of the observer. In the generic case of an accelerating observer following an accelerating world line through some space-time geometry, this is called a Rindler event horizon.

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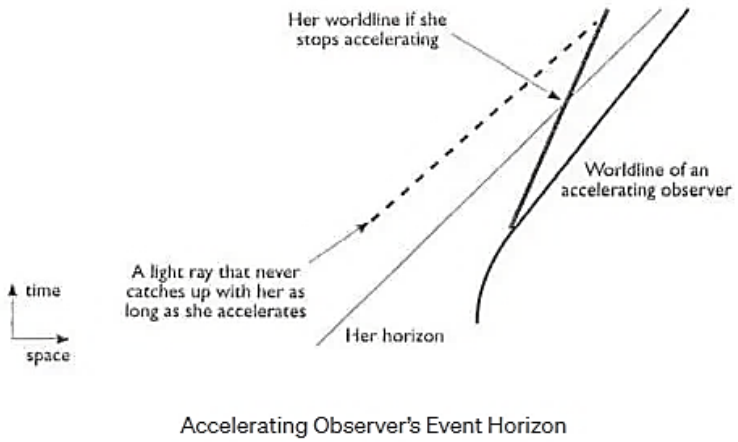


Figure 18. Comparison of the holographic screen when the observer is accelerating and stops accelerating in quantum theory.

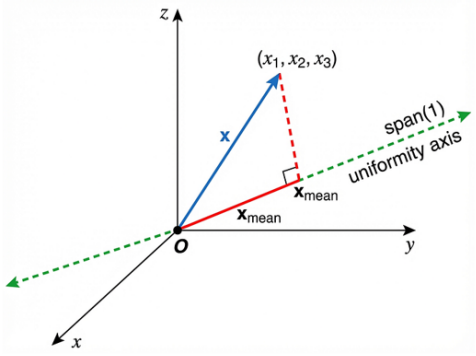
The accelerating observer's event horizon has a temperature known as the Unruh temperature. This is a very general result of quantum theory. In terms of the observer's own acceleration, which is called a, the Unruh temperature is given as kT=ħa/2πc. [108].

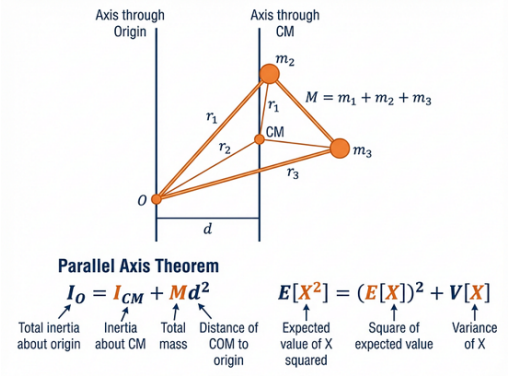
Mathematical Approaches Facilitate MAL Life Science Theory Interpretations: Space, Dimensions, and Linear Transformations

Recently, Kobayashi had compared the physics of probability as a linear algebra view of 3D space, as indicated below.

The Physics of Probability: A Linear Algebra View of 3D Space

The physics analogy is powerful — but it only becomes *useful* when it stops being a metaphor.



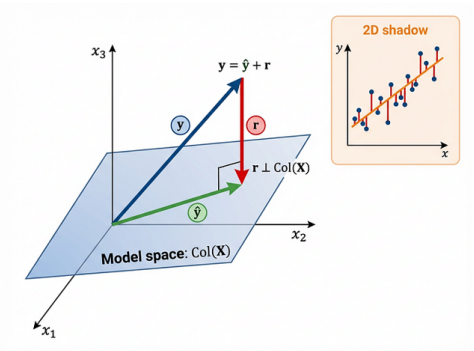


Concept	Scalar (1D)	Matrix (nD)
Total Energy	$E[X^2]$	$E[\mathbf{x}\mathbf{x}^T]$ (Autocorrelation Matrix)
Signal Energy	$(E[X])^2$	$\boldsymbol{\mu}\boldsymbol{\mu}^T$ (Rank-1 Matrix)
Noise Energy	$V[X]$	Σ (Covariance Matrix)
Relation	$Total = Signal + Noise$	$Total = Signal + Noise$

This gives us a precise way to judge every data point:

Distance (D)	Interpretation	Status
$D < 1$	Within the core cloud.	Normal
$1 \leq D < 3$	Outside typical variation.	Rare
$D \geq 3$	Defies the correlation structure.	Anomaly

By mastering the algebra of the Ellipsoid, you haven't just learned to describe the shape of the data; you have learned how to judge it.



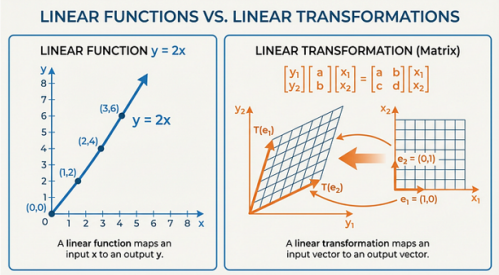
- The observed outcomes form a vector **y**.
- The model (your features) spans a subspace, Col(*X*).
- Regression finds **y^**, the **shadow of y** on that model subspace.
- The residual **r=y−y^** is the leftover — and the defining fact of least squares is still the same geometry

Tomio Kobayashi (3/12/2026), https://medium.com/@tomkob99_89317/the-physics-of-probability-a-linear-algebra-view-of-3d-space-0cba966c8557

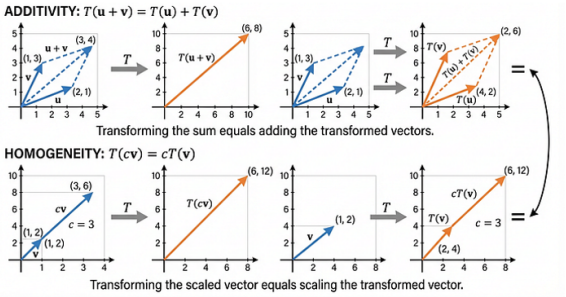
 doi:10.20944/preprints202512.0907.v5

Recently, Kobayashi had also reported on the universal properties of linear transformations in lines and planes as indicated below.

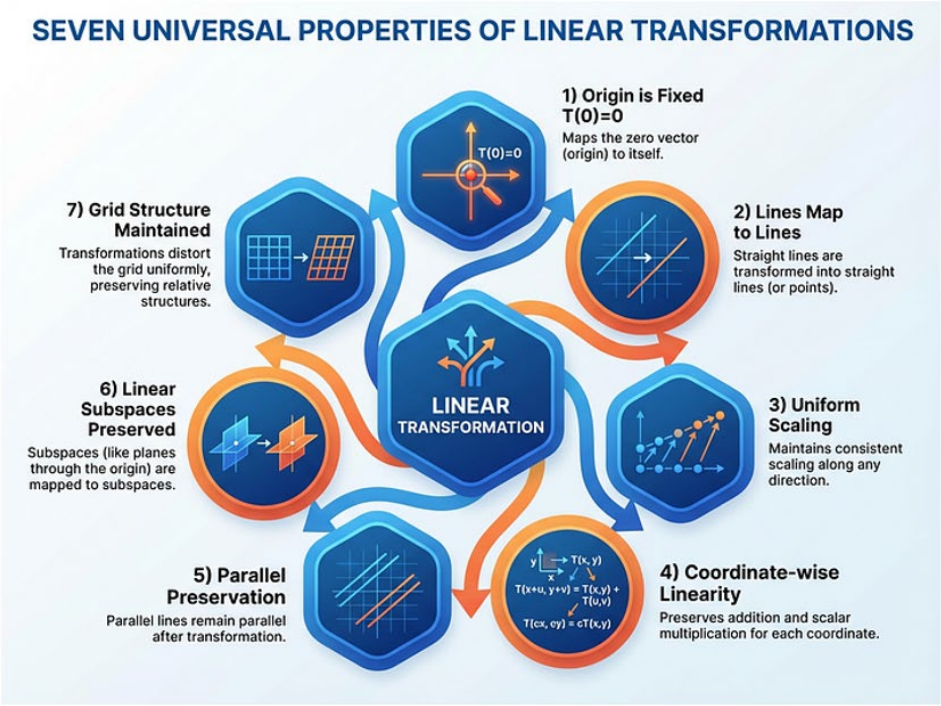
Visualizing Lines and Planes: The Universal Properties of Linear Transformations
How Single Equations Mislead Our Understanding of Linearity



Left: A single linear equation y = 2x produces a straight line.
Right: A linear transformation maps an entire coordinate grid, preserving its structure while potentially rotating, stretching, or skewing



Visual demonstration of additivity and homogeneity — the two pillars of linear transformations. The order of operations doesn't matter: transform-then-combine equals combine-then-transform.



The seven universal properties that characterize all linear transformations, from simple scalar multiplication to infinite-dimensional operators.

Tomio Kobayashi (3/24/2026), https://medium.com/@tomkob99_89317/beyond-visualizing-lines-and-planes-the-universal-properties-of-linear-transformations-c0cd66cf7bee

1.11.4. Correspondence Between MAL-Modern Dynamics of Exclusivity and Competitiveness Dynamics with the Ancient Philosophical Fu-Xi Ba-Gua Philosophy

MAL Dynamics (2006 ADE) vs. Fu-Xi Ba Gua (Ca 2,000 BCE)

The ancient Chinese traditional philosophies of Daoism of Lao Tsu (e.g., Tao Teh Ching, or Yi Jing, Oracle of Change) and Confucianism have been subjected to MAL-theoretical quantitative analysis, as exemplified in Figures 19, 36, and 37.

These are believed to be the first attempts to carry out modern quantitative analysis of ancient Asian philosophy during 2006-2010, using the mathematical theory of mass-action law and algorithms/computer simulations. These were presented in Baltimore, MD, USA; Peking University, Beijing, and Wu-Xi, Jiangsu, China; Taipei, Taiwan, and Seoul, Korea.

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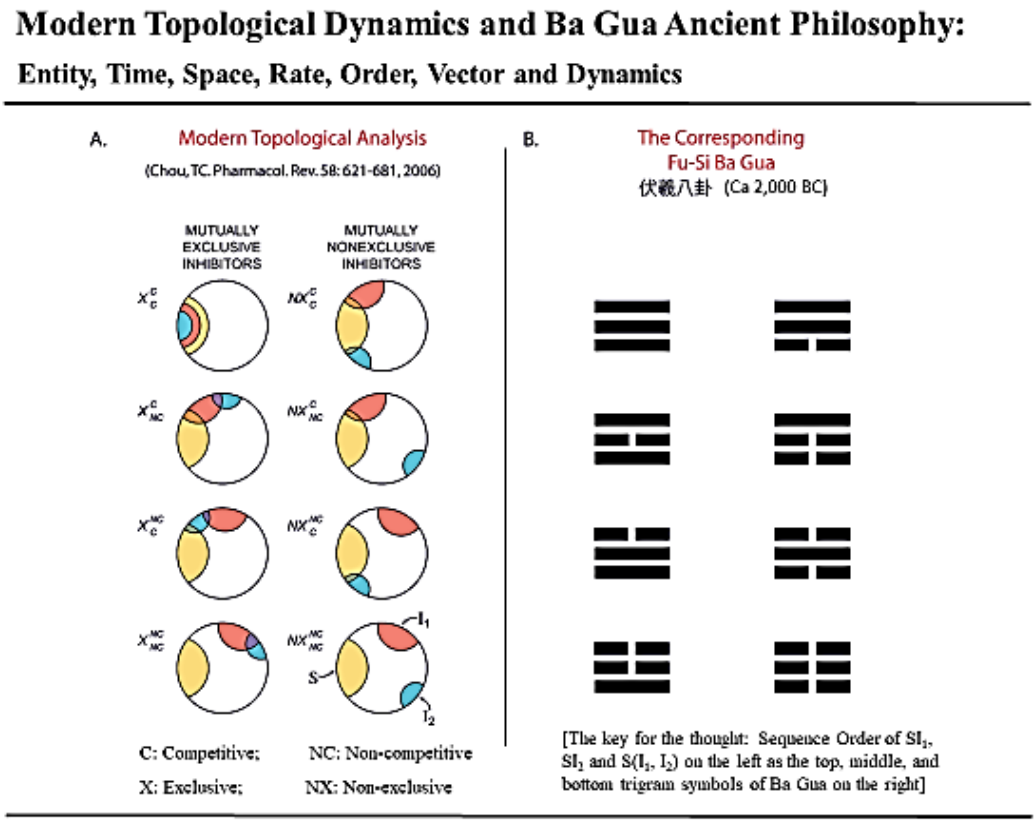

Figure 19. The eight-element event symbolic graphics have an exact correspondence with ancient philosophy, **4,000 years apart**. **A.** comparison of the modern molecular inhibitory interactions, [red (**I1**) and blue (**I2**) interrelationship with orange Substrate (**S**), the reference entity, in terms of special exclusivity (X) and functional competitiveness (C) (See Chou. Pharmacol. Rev. 2006 [9, in Figure 13]). **B.** the ancient Fu-Si (Xi) Ba Gua philosophy (The Yaos: Top, Middle, and Bottom, with breaks) (Ca 2,000 BC).

1.12. Halt-Center Geometry: Comparing Life Dynamics with Mathematical and Physical Mass, Force, Time, and Space

MAL Median of Life Science vs. Half Time of Radiation

Mass and Force are theoretically exchangeable based on Einstein's relativity. The relationship between space and Time is currently a hot topic of discussion, as indicated in Appendix III. Mass and time do not usually interchange. However, Dm and $T_{1/2}$ curves show intriguing similarity, as shown in **Figure 20**. The slight difference in curvature is due to MAL in Life science, showing intermediate transitions between simple and complex variables in Mass for activities (Dm value) and for different dynamic orders (m value) over time. In contrast, radiation decay is not mediated by a complicated intermediate during the time course. The elements of the universe, Life, Mass, Force, Time, and Space, are individually sensible and measurable; however, they are interlinked or cross-linked among them in unity for size, length, volume, vectoral angle, and speed, except for inertia or at zero dose, zero movement.

1.12.1. Comparing MAL-Median in Biology and Half-Time in Radiation Physics)

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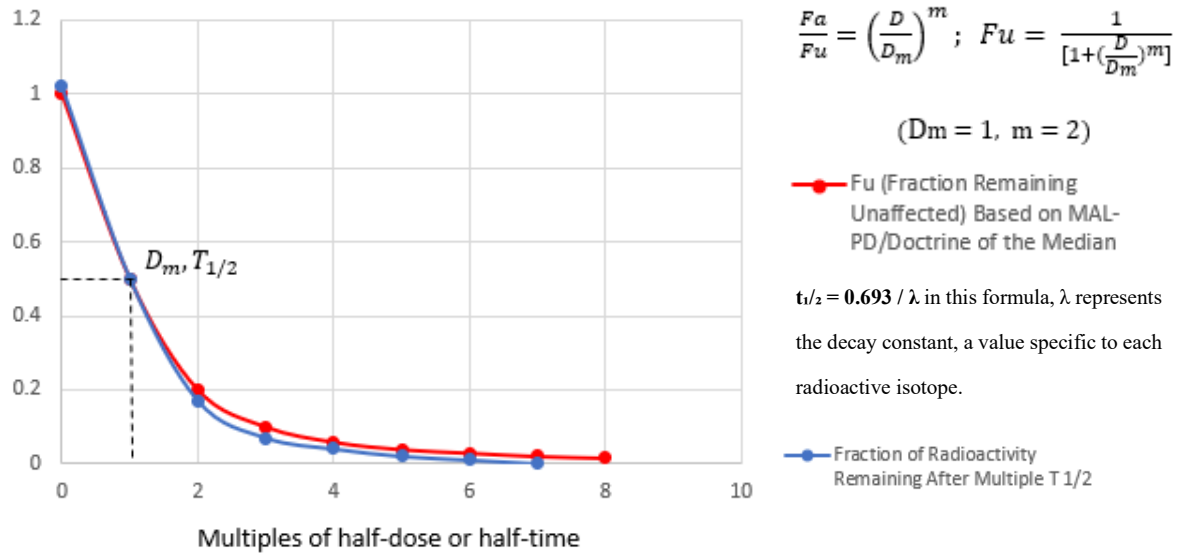

Figure 20. Comparison of biology (mass) versus physics (time). Similarities and slight differences between biological D_m and physical radiation decay $T_{\frac{1}{2}}$.

The radiation decay curve in a unit of $T_{\frac{1}{2}}$ (blue line).

The unaffected fraction (Fu) is based on MAL in the unit of Dm (in red line). The difference between the two curves at the fundamental level stems from the fact that biological systems, to perform complex dynamic functions, involve a causal-effect relationship between "receptors" that lead to intermediate complexes, which may involve networks or pathways. For example, oxygen-hemoglobin interactions involve hemoglobin's four subunits; each step of the interaction exhibits cooperativity, yielding a sigmoidal saturation curve. Most drugs, neurotransmitters, and hormones have specific receptors. Physical steps may also involve a simpler affinity receptor, such as that described by Langmuir's Adsorption Isotherm on the surface.

Based on the median-effect equation of MAL [24], when $D_m = 1$, m = 2. Note that the two curves are similar and cross-over at $\mathbf{D_m = 1}$ **and** $\mathbf{T_{\frac{1}{2}} = 1.}$ Before the cross-over of D_m and $T_{\frac{1}{2}}$, Fu is slightly lower (i.e., more affected), and post-cross-over, Fu is slightly higher (i.e., less affected). This figure compares biology and physics, as well as mass and time. Physics is rigid, and biology is more flexible but follows the principle of MAL. This comparison is independent of the units or physical states of mass, or of the type or energy level of the radiation.

1.12.2. The Median and the Harmonic Ancient Philosophy

The median-effect equation (MEE of MAL or the DOM) indicates that Dose and Effect are interchangeable. D_m (the Median-effect Dose) [24] is the universal reference point in dynamics, and the dynamic order's common link. D_m is the harmonic mean, 2ab/(a + b), of Kis and Kii; when Kis = Kii, it is a complete non-competitiveness, thus a pure-harmonic state. Theoretical analysis indicates that the Isobologram (dose-oriented) and the Fa-CI plot (effect-oriented) yield identical interaction indices (CI values). They are like two sides of the same coin. Source, or two views from two different angular loci of space. The harmony concept will later be illustrated separately in Figure 37.

1.12.3. Riemann's zeta function's ½ Critical Line and the MAL's Median

The Riemann Hypothesis has stood as mathematics' Everest — beautiful, imposing, unconquered. It claims that all non-trivial zeros of the zeta function have real part 1/2. What makes 1/2 so special is that the universe's prime number distribution obeys it with such precision.

The Riemann zeta function appears simple: ζ(s) = 1 + 1/2^s + 1/3^s + 1/4^s + ...,

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The term nontrivial zero comes from the Riemann zeta function [110,111]

$$\zeta(s) = \sum_{n=1}^{\infty} \frac{1}{n^s}, \quad s = \sigma + it.$$

Which is related to Euler's Product Formula for prime numbers.

$$\sum_{n=1}^{\infty} \frac{1}{n^s} = \prod_{p\ prime} \frac{1}{1 - p^{-s}}$$

$$\frac{1}{6} = \frac{1}{\pi^2}\left(1 + \frac{1}{4} + \frac{1}{9} + \frac{1}{16} + \cdots\right)$$

$$1 + \frac{1}{4} + \frac{1}{9} + \frac{1}{16} + \cdots = \frac{\pi^2}{6}$$

which is the sum of the reciprocals of the squared-number-series as indicated in the 2^{o} (squared) Pascal Triangle [1,2] derived from the biological inputs-outputs duplex patterns transition combinatorial analysis in Chou TC's Ph.D. Thesis, Yale University, 1970.

Chou's constant is the sum of the reciprocals of the positive *squares* ($1 + \frac{1}{4} + \frac{1}{9} + \frac{1}{16} + \ldots = \sum_{n=1}^{\infty} \frac{1}{n^2} = \frac{\pi^2}{6}$) from Chou's squared triangle. This turns out to be the value of the *Riemann zeta function at 2, or* $\boldsymbol{\zeta}(2)$ *at Critical Line of* $\sigma = Re(s) = 1/2$, which is corresponding to the MAL Median Point (0.5, ½), a Critical Line as Re(2) at 1/2. It is shown in 1970 (Ph.D. Thesis) that Chou's 2*nd*-Degree Triangle Reciprocal Sum is irrational and transcendental, although it is derived from biological science inputs-outputs pattern transition models.

Riemann's $\boldsymbol{\zeta}(1) = \frac{1}{1} + \frac{1}{2} + \frac{1}{3} + \frac{1}{4} + \frac{1}{5} + \ldots$ has been known to be the harmonic series which leads to infinity.

The Riemann Zeta Function can be expressed in the following different forms:

$$\sum_{n=1}^{\infty} \frac{1}{n^2} = \frac{\pi^2}{6}$$

$$\sum_{n=1}^{\infty} \frac{1}{n^4} = \frac{\pi^4}{90} \qquad \sum_{n=1}^{\infty} \frac{1}{n^6} = \frac{\pi^6}{945}$$

Roger Apéry's constant for the sum of reciprocals of positive number cubes (1 + 1/8 + 1/27 + …), which leads to the Riemann zeta function at 3, or $\boldsymbol{\zeta}$ (3) , Chou's constant is the sum of the reciprocals of the positive *squares* (1 + 1/4 + 1/9 + 1/16 + 1/25…) from Chou's squared triangle. This turns out to be the value of the *Riemann zeta function at 2, or* $\boldsymbol{\zeta}(2)$ *at the Critical Line of sigma equals cap R e of s , equals 1 over 2,* which corresponds to the MAL Median Point (0.5, ½), a Critical Line as Re(2) at 1/2. It is shown in 1970 (Ph.D. Thesis) that Chou's 2*nd*-Degree Triangle Reciprocal Sum is irrational and transcendental.

It is estimated that ζ(3) ≈ 1.202056903159594… (Apéry's constant) is *approximately* $\pi^3/26$.

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Therefore, the Riemann Zeta function, is not only related to Euler's Product Formula of prime numbers, but also related to the Mass-Action Law (MAL)-Median, Chou's 2nd-Degree Triangle ($\boldsymbol{\pi^2/6}$) and Riemann's zeta function at $\boldsymbol{\zeta}(2) = \boldsymbol{\pi^2/6}$. The ancient Pascal Triangle (the 1st-degree) has been shown to be related to e in Euler's identity, $e^{\pi i} + 1 = 0$. So, there are inter-relations among major mathematical functions or entities.

But look closer through our three-domain lens [80]:

Counting Domain: The sum over reciprocal integers of (1, 2, 3, …)

Measuring Domain: The continuous exponentials

Manipulation Domain: The operation n^(-s) that bridges them

The zeta function is literally a *domain-bridging operator* that connects counting to measuring via manipulation, that transforms the boundary between natural numbers to an irrational entity (π).

For the nontribal zeros lie in the critical strip: $0 < \sigma < 1$. The Reimann Hypothsis shows that every nontrivial zero lies on the critical line at σ =1/2. Half is the critical line as the balance point (medium) because it's the only line where all three domains have equal voice. Only at 1/2 do the forces balance for the complex number s = ½ + it that satisfies + as described by ζ(s) = 0, located inside the critical strip. Such zeros encode the information that has been shown to reveal the distribution of prime numbers, symmetry in number theory, and spectral properties of physical and quantum systems [80,81]. Interestingly, the core concept of MAL-MEE, fa/fu = $(D/Dm)^m$, of derived life science [3,4], emphasizes the "Median" or ½ or "0.5" in the MAL-median effect principle, Doctrine of the Median (DOM), and in CIE and DRIE.

Both the MAL median principle and the Riemann zeta function share intriguing properties and analogies, which are listed in Table 7.

1.12.4. Riemann's Function analogy to MAL-MEE for Critical Strip and Critical Line of Prime Number Distribution

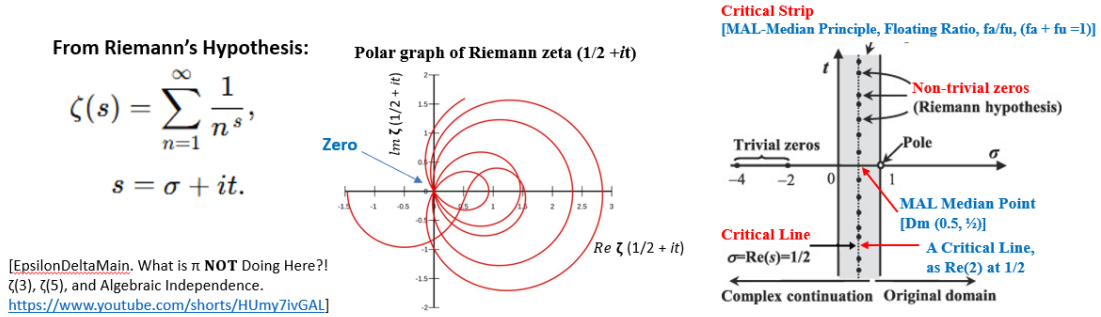

Table 7. Critical strip vs. MAL dose-effect domain.

Riemann ζ-Function	MAL–MEE System	Analogy
Invariant axis: Re(s) = 1/2	Invariant axis: fa/fu = 1 (median = 0.5)	Both "center lines"
Critical line (Re(s) = ½)	Median line (fa = 0.5)	Governing midpoint
Complex strip: 0 < Re(s) < 1	Continuous domain: 0 < fa < 1	Mirror duality
Symmetry: s ↔ 1 − s	Symmetry: fa ↔ fu	Universal dynamics
Log-linear fraction Analytic distribution, and functional equation	Converts curves to straight lines by Log (D) vs. log (fa/fu), which transforms functional dynamics into digital informatics	Boundary of regimes

Therefore, the Riemann Zeta function, is not only related to Euler's Product Formula of prime numbers, but also related to the Mass-Action Law (MAL)-Median, Chou's 2nd-Degree Triangle ($\boldsymbol{\pi^2/6}$) and Riemann's zeta function at $\boldsymbol{\zeta}(2) = \boldsymbol{\pi^2/6}$. The ancient Pascal Triangle (the 1st-degree) has been shown to be related to e in Euler's identity, $e^{\pi i} + 1 = 0$. So, there are inter-relations among major mathematical functions or entities.

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1.12.5. New Illustrations of Centuries-Old Math Problems Linked to Life Science Dynamics: Linking Riemann's Zeta Hypothesis and Euler's Prime Product Function with Life Science Dynamics through Chou's Squared Pascal Triangle

Groundbreaking Connection Between Biology and Number Theory

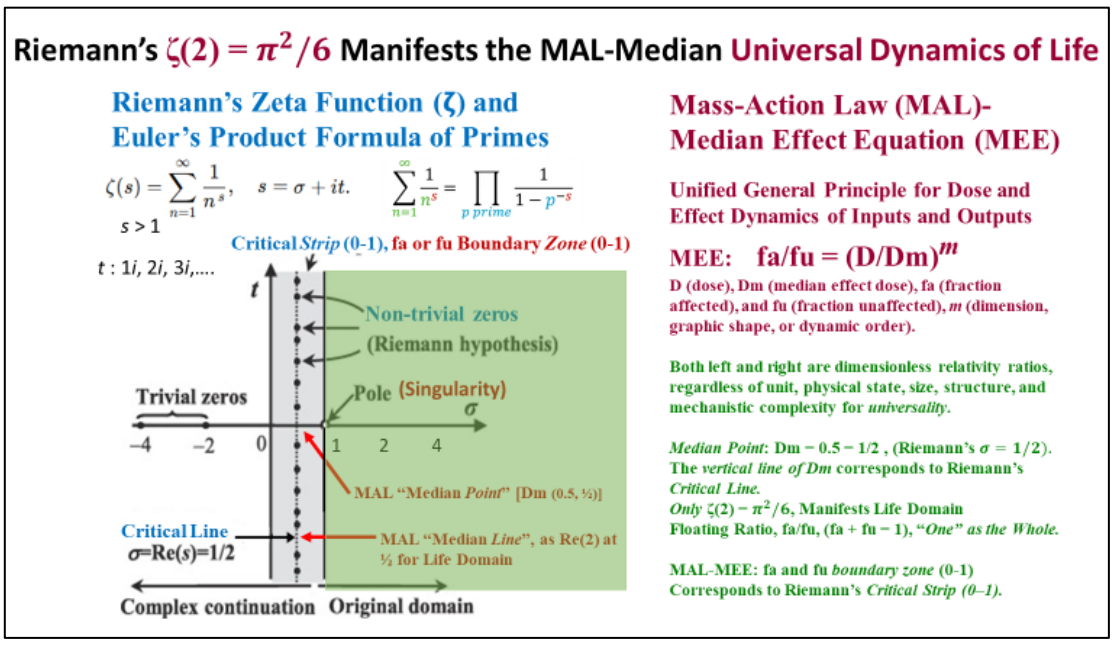
A transformative scientific discovery has been announced, bridging the gap between centuries-old mathematical hypotheses and the modern dynamics of life sciences. Researchers have demonstrated that the Mass-Action Law (MAL)-Median Effect Equation (MEE), typically used to model biological and pharmacological systems, provides a unique lens into the Riemann Zeta Function and Euler's Prime Product Formula.

The Power of the Squared Pascal Triangle (Chou, 1970) [1,135,136]

Central to this revelation is **Chou's Second-Degree (Squared) Triangle**, derived from biological input-output pattern transition systems. In this framework, the sum of the reciprocals of positive square numbers yields a specific constant:

$$1+\frac{1}{4}+\frac{1}{9}+\frac{1}{16}+\cdots=\sum_{n=1}^{\infty}\frac{1}{n^2}=\frac{\pi^2}{6}\approx 1.644934066\ldots$$

This sum corresponds to the Riemann zeta function ζ(s) at s = 2. Because π is proven to be an irrational and transcendental number, the sum of these reciprocals is established as an irrational, transcendental constant within the life science domain.



Mapping the Riemann Hypothesis to Biological Median Points

The discovery extends into the realm of the Riemann Hypothesis. The MAL-Median Point (Dm = 0.5), which represents the half-affected state in biological dose-effect dynamics, maps directly to Riemann's Critical Line where σ = Re(s) = 1/2. Furthermore, the biological boundary zone of fraction affected (fa) and fraction unaffected (fu), ranging from 0 to 1, provides a physical manifestation of Riemann's Critical Strip (0–1). This suggests that the fundamental patterns of life and pharmacological interaction are governed by the same universal principles that organize the distribution of prime numbers.

A Unified General Theory for Modern Informatics

The Mass-Action Law dynamics theory provides a unified framework for major biochemical and biophysical equations, including those of Michaelis-Menten (1913), Hill (1913), Langmuir (1916), and

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Scatchard (1949). By using system, sequential, and pattern analysis, researchers have derived the Combination Index Equation (CIE) and Dose-Reduction Index Equation (DRIE), allowing for:

Synergy Quantification: Determining if drug combinations are synergistic, additive, or antagonistic.

Econo-Green R&D: Utilizing the Minimum Two-Data-Points Theory (MTDPT) to reduce experimental waste and optimize toxicity reduction.

Interchangeability: Establishing that dose and effect are interchangeable reference points in biological dynamics.

Philosophical Harmony and Scientific Equilibrium

The research also interprets ancient philosophical concepts, such as Yin-Yang and the Doctrine of the Median, through modern dynamics. The Lineweaver-Burk plot illustrates that pure Harmony corresponds to pure non-competitiveness, where the median dose (Dm) is the harmonic mean of specific inhibition constants. This equilibrium reflects a state of symmetry and stability found in both natural ecosystems and human health.

Based on decades of work originating from Yale University (1970) and extending through current 2026 preprints, this unified MAL-PD/BD/CI theory represents a convergence of pharmacology, number theory, and philosophical informatics. It offers a new digital bioinformatics standard for drug discovery and environmental science.

1.12.6. Riemann Zeros, Euler Identity, and Yang-Mills Theory: The Map that Mathematics drew for Physics and Uncertainty

In Daniel Toupin's recent essay [133] from May 15, 2026, the implications of Riemann zeros, the Euler Identity, and Yang-Mills theory are discussed, which are relevant to the subject of this paper. The following are experts of Toupin's statement:

"Euler was the first to find something hiding behind the chaos. In 1735 he discovered that an infinite product over the primes is equal to an infinite sum over the integers, and that both converge to the same value as the sum over all positive integers of one divided by their squares. A century later Riemann extended Euler's sum into the complex plane, turning a function of a real variable into a function of a complex one. The resulting object, the Riemann zeta function, has zeros. Some are trivial, falling at the negative even integers, and Riemann dismissed these quickly. Riemann noticed in 1859 that every one he could compute fell on a single vertical line, the line where the real part of the complex variable equals one-half. He conjectured that all of them do. That conjecture today remains officially proofless even after 166 years of sustained assault by an army of humanity's biggest brains."

1.12.7. Linking Mathematics Cubic Root to MAL-Median Life Science Dynamics

Some unexpected findings may occur among different disciplines. Barry Leung (May 21, 2026) asked a question of the infinite product of continuous cubic roots, which turned out to be a direct link to the MAL-MEE dynamic principle, with the simplest code [a/(1-a)] of life science [134].

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Infinite Product of Continuous Cubic Roots:

Corresponding to MAL-Median Dynamic Principle of Chou

$$\sqrt[3]{10}\cdot\sqrt[3]{\sqrt[3]{10}}\cdot\sqrt[3]{\sqrt[3]{\sqrt[3]{10}}}\cdots \quad = ?$$

We can turn our infinite product into the following:

$$P = 10^{1/3}\cdot 10^{1/9}\cdot 10^{1/27}\cdots = 10^{\left(\frac{1}{3}+\frac{1}{9}+\frac{1}{27}+\cdots\right)}$$

Infinite geometric series:

$$\frac{1}{3}+\frac{1}{9}+\frac{1}{27}+\cdots$$

Therefore we can sum it up using the following formula.

$$\sum_{n=1}^{\infty}\left(\frac{1}{3}\right)^{n} = \frac{\frac{1}{3}}{1-\frac{1}{3}} = \frac{\frac{1}{3}}{\frac{2}{3}} = \frac{1}{2} \quad = 0.5 \text{ (Median)}$$

Life Science Dynamics
Simplest Code [a/(1-a)].
In this code, a = 1/3.

1.12.8. Imaginary "Negative Doses" convergence at "One" on the "Median" as the General Reference

As shown in Figure 21, where the dose (D) is [I], Dm is I_{50}, and Unity is One. The real doses can be projected to the surreal doses (i.e., the negative doses).

In biology, the Median-Effective Dose (Dm) is represented by I_{50}, ED_{50}, TD_{50}, and LD_{50}, respectively, as the dose that produces a 50% effect (inhibition, toxicity, or lethality).

Decades later, this led to the Doctrine of the Median (DOM) and the Unity Theory of One (UTO) as the unified general theory of the Mass-Action Law (MAL). As indicated by MAL-MEE (at m=1), the hyperbolic function is the same as the activation function that can be used in AI as the basic hyperbolic function. Whereas when >1 and <I, it is the activation of sigmoidal functional layers.

It is of interest to determine whether the negative dose, as shown in Figure 21 from theoretical biology, is related to dark matter, dark energy, antimatter, and black holes in theoretical physics. The like linkage will be via mathematics.

Again, using "I" as the reference ligand as the "effector" that produces the effect. It shows the "unity" concept of the "median dose" of IC50 (or Dm). The real inhibitor doses and **the imaginative negative doses (-[I],** intercept at "One" (1.0), which points to the "Median" (I_{50}). (Figure 21).

The corresponding real dose and unreal dose converge into unity of "One" at the "Median" (I_{50}) [5].

1.13. The Median mediates the MAL Unity Theory of One (UTO)

MAL Revelations at the Molecular and Conceptual Level

1.13.1. The Median Dose (Dm or I_{50}) is the Unit of the Normalized Dose

Figure 22 shows the dose-effect relationship when the inhibitor serves as the reference ligand in the substrate-product enzyme system. The inhibitor dose (I) can be normalized to the median dose (I_{50}). Kinetic studies indicate that [I] is the inhibitor dose, and fi is the fraction affected (fa); when fi = 0.5, it indicates the median (Dm).

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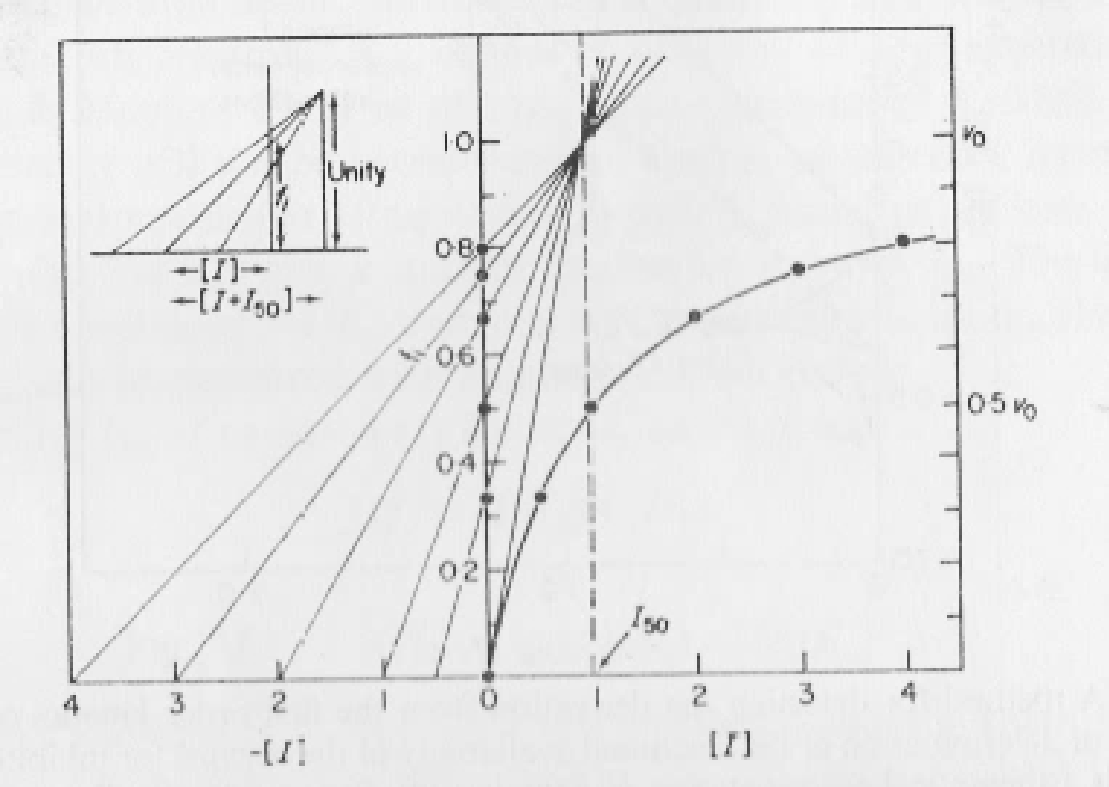

Figure 21. The dose-effect curve, [I] vs. f_i, of an inhibitor: A unique geometric graphical property of the "negative dose." Evidence of the unity of unreal doses.

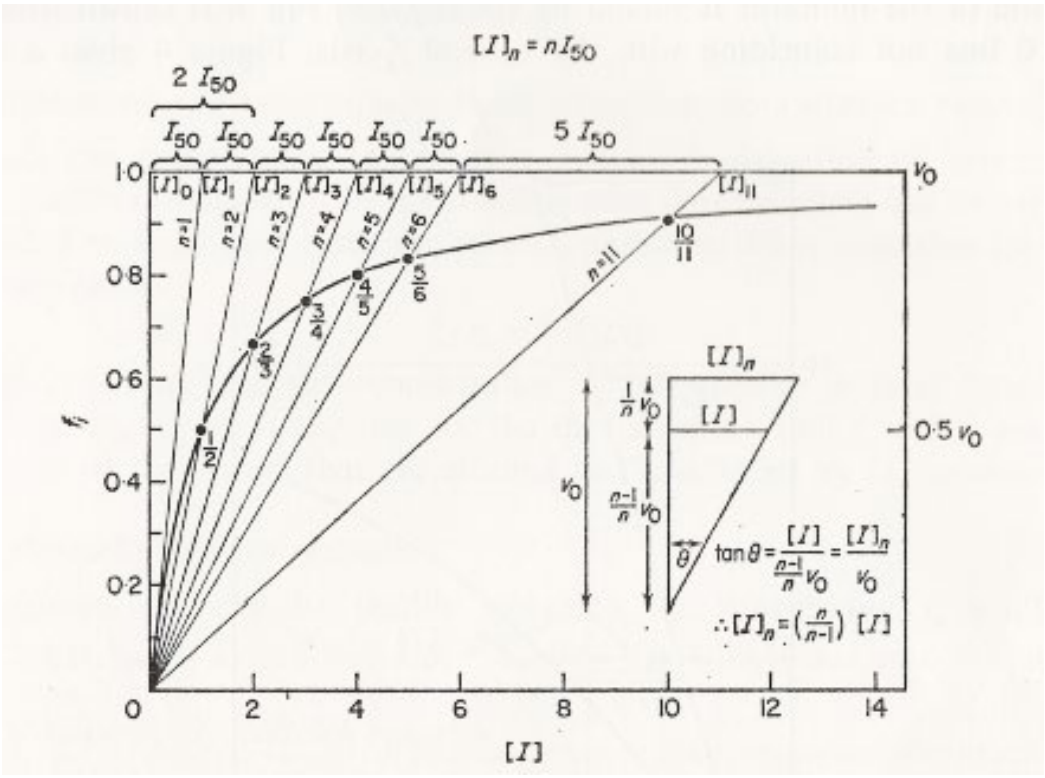

Figure 22. The geometric property of effector dose [I] vs. fractional inhibition (fi) when the dose is in the unit of the median effect dose (I_{50}). The "Dose" can be transformed as the "Median-dose Unit" (normalization) to become a dimensionless ratio due to the ratio-cancellation principle (I/I50 or D/Dm).

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Using inhibitor concentration [I] as the reference ligand, for the target (e.g., enzyme), the intriguing relationship of the dose [I] and its median-dose (Dm or IC_{50}) leads to the median-effect principle (MEP) and the doctrine of the Median (DOM) of the Mass-action Law (MAL) (Figure 22).

Median dose (I_{50} or Dm) to normalize the dose as the unit of dose, using the Dm as the universal standard of a common link [5].

The hyperbolic activation function of Mass and Effect is mediated by the "Median" (I_{50} or Dm).

As indicated earlier, the MAL-MEE Median (fa = fu or fa/fu =1), the CIE [CI=1, (additive), CI<1 (synergism), CI>1 (antagonism)], as well as the DRIE [DRI =1, (no dose-reduction), DRI (DRI >1, (positive or favorable dose-reduction), and DRI <1 (negative or not-favorable dose-reduction)]. Thus, MAL-MEE-CIE and DRIE are all based on "One" as the universal standard.

1.13.2. Evidence at Conceptual Level: Geometrics and Symmetry

Equilibrium Symmetry Exhibited by Median-point and the Median-axis regardless of Competitive or Uncompetitive Inhibitory Effect.

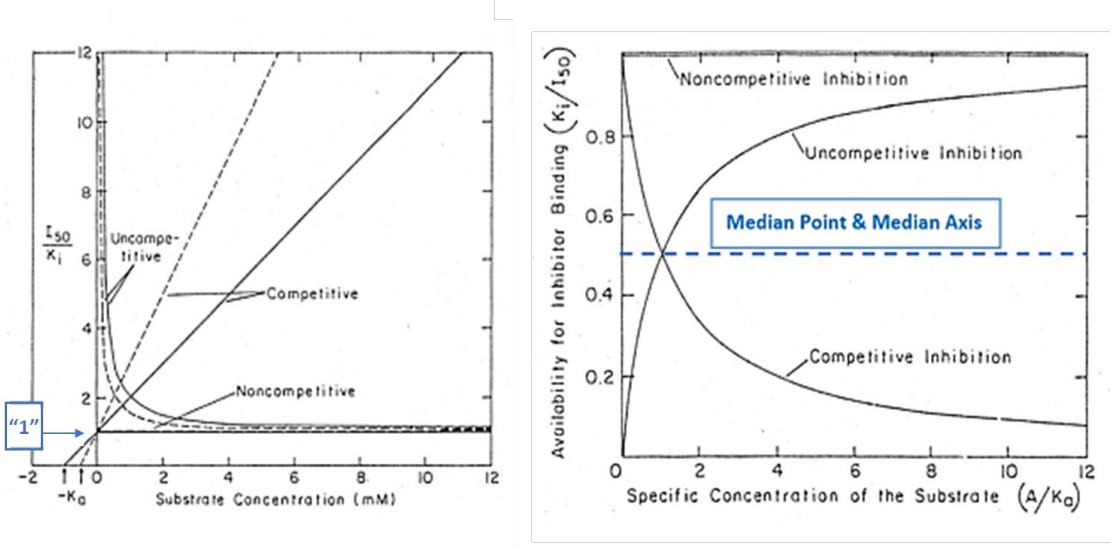

Figure 23. The dose-effect relationship for different mechanisms of action is relevant to the unity theory of one (UTO), median-effect dose, and the median-effect axis.

Ratio of I_{50} and K_i as a function of substrate concentration in binding one-substrate reactions, assuming Michaelis constant (K_a) is 1 mM (—) or 0.5 mM (- − -). Fractional availability of the enzyme for the inhibitor as a function of the specific concentration of substrate (A/K_a). (Figure 23).

Note that on the left, regardless of the types of inhibition, the lines converge at "one". On the right, the common median point and the median-axis for competitive and uncompetitive inhibition are shown symmetrically. In contrast, for noncompetitive inhibition, it remains at One, since the receptor enzyme (Et) is generally fully occupied (i.e., Ex = Et), where Ki/I_{50} = Ex/Et. The general equations for fractional velocity (fv) and fractional inhibition (fi) in the presence of an inhibitor (*I*) can be expressed by fv = 1/[1 + (I/Ki) [Ex/Et]] and fi = 1/[1 + (Ki/I) (Et/Ex)], [3]. Note that I is a dose (D), and I_{50} is the median-effect dose (Dm); fi is the fraction affected, and fv is the fraction unaffected, and fi + fv =1.

In the physical domain of Nature, there are unique features of symmetry of patterns. Fractal is not like the Golden Ratio, nor like a mirror image, but just eerily repeating patterns that can be magnified or shrunk into the same size as described in dictionaries. Frank Ramsey's symmetry on the circular edge, basically a bunch of points (called vertices), that generate a wonder of graphics, as recently described by Ben Fairbairn [82]. These perfect patterns are unlikely to occur in the life sciences.

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2. MAL-Based General Theory of Multiple Entity Interactions

The Combination Index Theorem

The mass-action law governs chemical reactions and interactions in the biomedical sciences and beyond, as indicated by MEE/DOM/MTDPT. These are general mathematical expressions of the biological functional dynamics of "Action" [1–4]. This Section 2 focuses on the MAL-MEE-based entity "Interactions". The theoretical derivation is given in [3–8]. These MAL-theory and applications are available in reviews [9–12] and monographs [23–31]. The applications, especially the combination index equation (CIE) that quantitatively define synergism (CI<1), additive effect (CI =1) and antagonism (CI>1) by simple MAL-design [9–12] with automated computer simulation [50-55], generated historical bibliometric records in Web of Science [56], Google Scholar [57], and Rese4archGate [58]. Three articles [8–10], with one or two authors, have garnered a total of 21,357 citing papers, 1,581 citing journals, and 1,621citing patents. The scope of applications of Chou's MAL-MEE/CIE theory encompasses biomedical, biophysical, environmental, agricultural, marine, and food sciences, and beyond [9,23,24,56–58].

2.1. Two-Drug or Two-Entity Combinations

The combination index (CI)

CIE and DRIE extend this to interactions, quantifying synergy (CI<1), additivity (CI=1), and antagonism (CI>1). The universality lies in the equations' dimensionless nature, which makes them applicable across domains regardless of units, scale, or complexity.

The MAL-MEE-dictated **Combination Index Equation (CIE)** and plots, i.e., isobologram, are dose-oriented; the fa-CI plot is effect-oriented, both quantitatively, identically, and digitally determine additive-effect (**CI=1**), synergism (CI<1), and antagonism (CI>1), by computer simulation [8–10].

For a two-drug combination:

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

$$\begin{aligned} \text{CI} &= 1 \text{ indicates additive effect} \\ &< 1 \text{ indicates synergism} \\ &> 1 \text{ indicates antagonism} \end{aligned}$$

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

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

2.2. Combination Index for Five-Drug Combinations

A unified general equation for all drugs or entities (e.g., chemicals, biologicals, toxins, carcinogens, radiation, thermo- and photo-effectors) has been derived [9,24].

The general equation for 5-drugs (or entities) for n-drug interactions based on MAL-MEE/CIE is:

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$$^{5}(CI)_x = \frac{(D_x)_{1-5}[P/(P+Q+R+S+T)]}{(D_m)_1\{(f_{a_x})_1/[1-(f_{a_x})_1]\}^{1/m_1}} + \frac{(D_x)_{1-5}[Q/(P+Q+R+S+T)]}{(D_m)_2\{(f_{a_x})_2/[1-(f_{a_x})_2]\}^{1/m_2}} + \frac{(D_x)_{1-5}[R/(P+Q+R+S+T)]}{(D_m)_3\{(f_{a_x})_3/[1-(f_{a_x})_3]\}^{1/m_3}} + \frac{(D_x)_{1-5}[S/(P+Q+R+S+T)]}{(D_m)_4\{(f_{a_x})_4/[1-(f_{a_x})_4]\}^{1/m_4}} + \frac{(D_x)_{1-5}[T/(P+Q+R+S+T)]}{(D_m)_5\{(f_{a_x})_5/[1-(f_{a_x})_5]\}^{1/m_5}}$$

2.3. Combination Index for n- drugs or Entities

The general equation for n-drugs (or n-entities) combination interactions based on MAL-

$$^{n}(CI)_x = \sum_{j=1}^{n} \frac{(D)_j}{(D_x)_j} = \sum_{j=1}^{n} \frac{(D_x)_{1-n}\{[D]_j/\sum_{1}^{n}[D]\}}{(D_m)_j\{(f_{a_x})_j/[1-(f_{a_x})_j]\}^{1/m_j}}$$

MEE/CIE is:

Where,

$^{n}(CI)_x$ Combination index for n drugs at x% inhibition. CI < 1, CI = 1, and CI > 1 indicate additive effect, synergism, and antagonism, respectively.

$(D_x)_{1-n}$ The sum of n drugs that exert x% inhibition in combination

$\{[D]_j/\sum_{1}^{n}[D]\}$ The proportionality of each of n drugs that exerts x% inhibition in combination. The dose of each drug alone exerts x% inhibition.

$(D_m)_j\{(f_{a_x})_j/[1-(f_{a_x})_j]\}^{1/m_j}$

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 indicate hyperbolic, sigmoidal, and negative sigmoidal curves, respectively [9].

Figure 24 provides the general Simulation Algorithm for Two-Drug to n-Entity Combinations.

2.4. Combination Index Graphics

Effect-Based (Fa-CI Plot) and Dose-Based (Isobologram) reached identical conclusions of synergism, additive effect, and antagonism. Another proof that Dose and Effect are interchangeable and equivalent, at both Action (MEE) and Interaction (CIE) Levels.

The MALMEE/CIE for drug or entity combinations, as shown in Figures 22 and 23, can be presented in two ways: an isobologram, which is dose-oriented, and the Fa-CI plot, also called the Chou-Talalay plot, which is effect-oriented. Both graphics yield identical digital conclusions regarding additive effects, synergism, and antagonism, further illustrating that "Dose" and "Effect" are interchangeable under Nature's Mass-Action Law.

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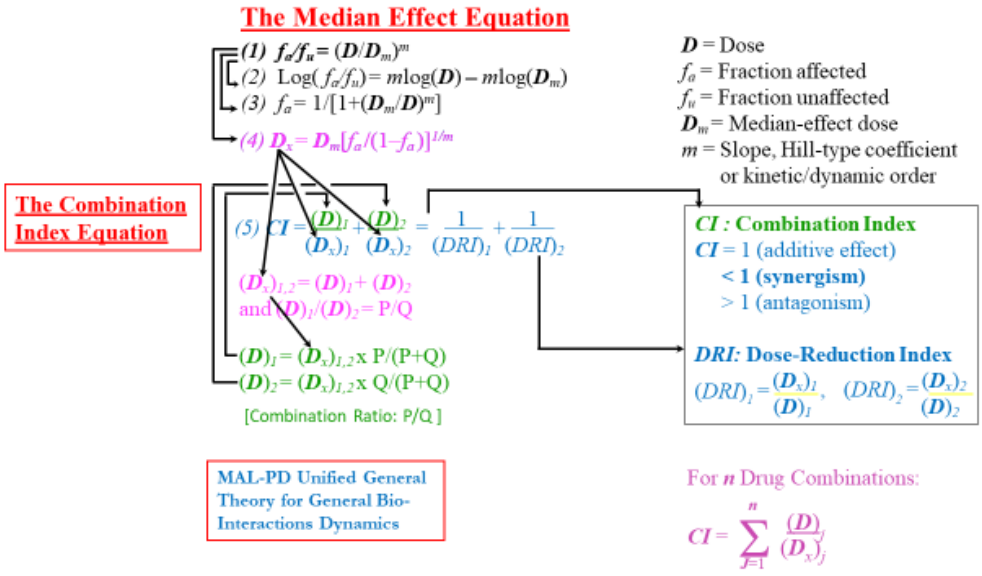

Figure 24. An algorithm for computerized simulation of synergism, additives, and antagonism of the effects of multiple drugs by a computer simulation based on MEE and CIE. Its application is independent of drug ratio, drug units, mode of action, and mechanism of action. It is valid for two to n drugs or entities (e.g., virus, radiation, UV, microwave, etc.) for combination interactions in vitro, in cells, in animals, and in clinical trials [4,9]. The MAL-PD-based CompuSyn software has been offered for free download upon registration at www.combosyn.com since August 1, 2012 [9,31,55].

2.4.1. Unified General Plots and Diagnosis

Diagnostic informatics can be generated instantly by automated computer simulation based on the MAL-MEE/CIE algorithm for combinations of two or more drugs (**Figures 23 and 24**) [9,31].

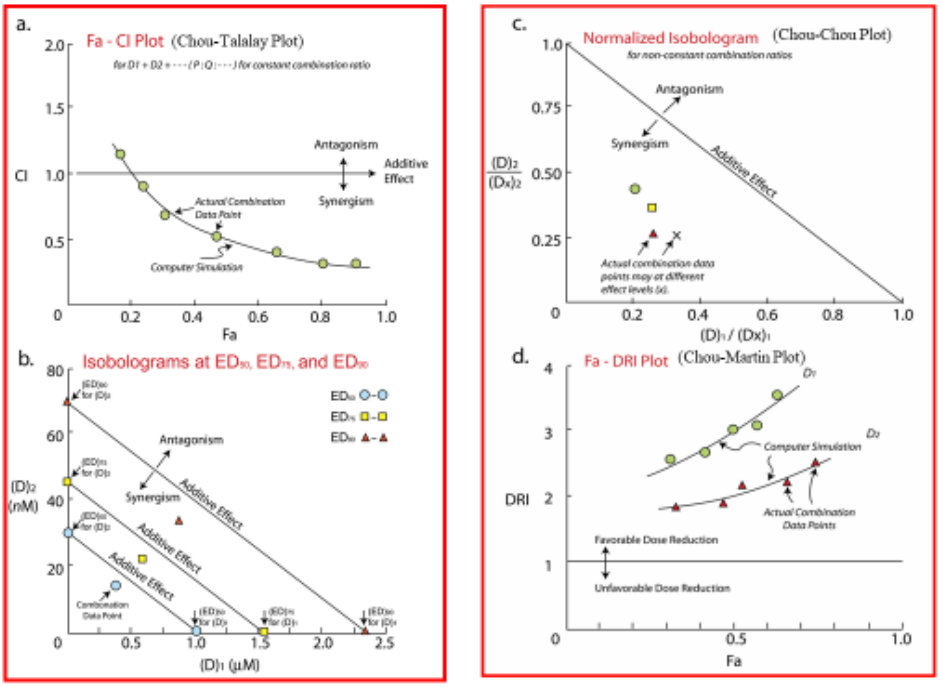

Figure 25. Computer-generated diagnostic plots for bioinformatics (BI) in drug combination dynamics by CompuSyn, Geometric transformations, and algorithm-based simulation, with digitalized, indexed conclusions,

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can be produced in about one second and require only "Doses" and "Effects" data entries. Note that the MAL-based experiment is simple to use.

2.4.2. Isobologram for Two Drug Combinations

Based on systematic analysis of various combinations involving two drugs in enzyme kinetic systems, Chou and Talalay derived the classical isobologram equations as

$$\frac{(D)_1}{(D_x)_1} + \frac{(D)_2}{(D_x)_2} = 1$$ for two drugs and $$\sum_{j=1}^{n} \frac{(D)_j}{(D_x)_j} = 1$$ for multiple drugs (*n* drugs).

Using the median-effect principle as shown for $(D_x)_1$, $(D_x)_2$, or $(D_x)_n$, in the denominators can be readily calculated, and $(D)_1$, $(D)_2$, $(D)_2$ ... $(D)_n$, in the numerator are the experimental doses of each drug alone that in combination also produces x% inhibition.

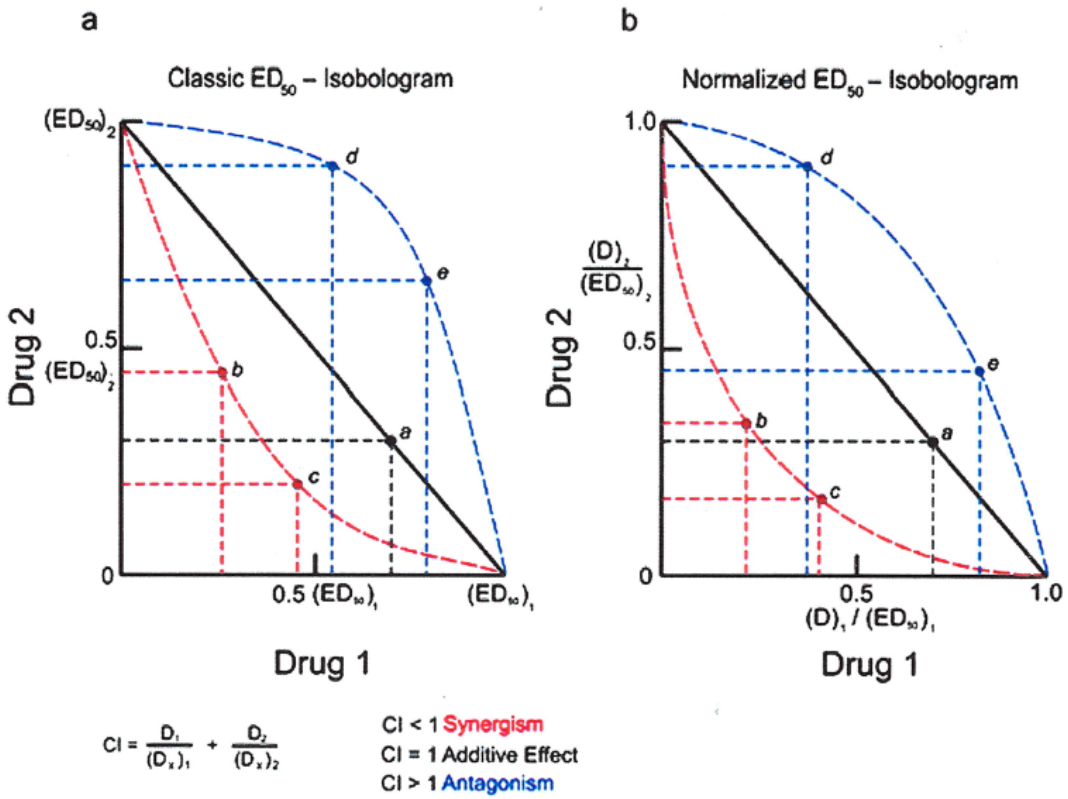

Figure 26. The ED_{50} isobologram. **(a)** Classic isobologram for two drugs with actual doses on the x- and y-axis. **(b)** Dose-normalized isobologram for two drugs with normalization of dose with ED_{50} to unity on both x- and y-axis. In both cases, ED_{50} can be extended to ED_x, for the x% inhibition. The isobologram is independent of the combination ratio, the shapes of the dose-effect curves, the drugs' mechanisms, or the units of the drugs.

2.4.3. Isobologram for n-Drug Combinations

The isobologram of n-drug combinations is given in Figure 26, in the ED_{50} isobologram or the Dm normalized isobologram [27].

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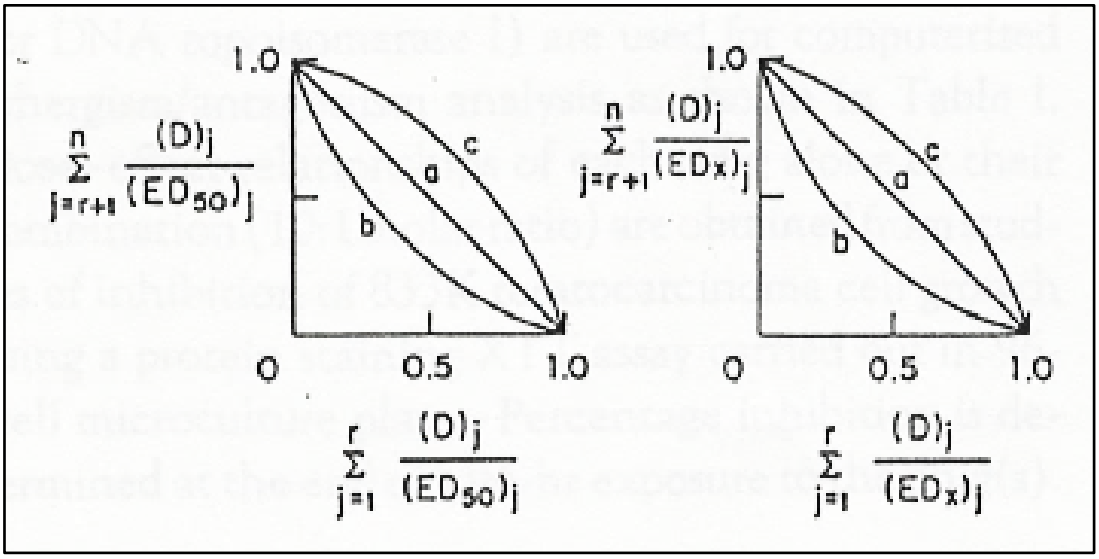


Figure 27. Median normalized universal isobologram for n-entities.

Computerized Construction of Isobolograms

For the construction of an isobologram for more than three drug combinations, the n drugs can be partitioned into any two parts, as shown in Figure 27.

2.4.4. New Isobologram Manifestations: Pythagoras' Theorem

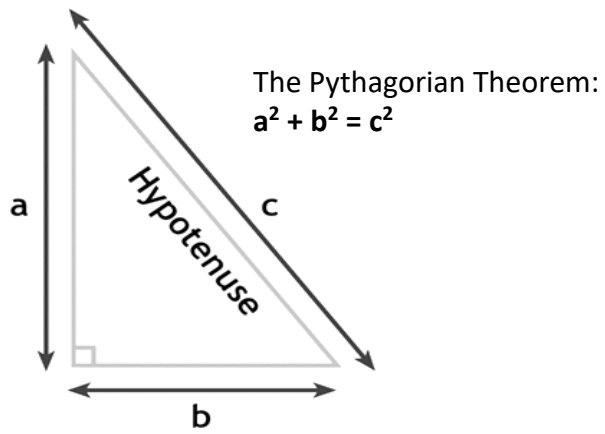
Since isobolograms are presented as a fundamental principle of geometry that relates the sides of a right triangle, the Pythagorean theorem states that the square of each side equals the sum of the squares of the other two sides: $a^2 + b^2 = c^2$. Therefore, the isobologram is the first degree, one-dimensional; the second degree, two-dimensional, of the isobologram is the Pythagoras Theorem.

2.4.5. The Comparison of Isobologram and the Pythagoras Theorem

In the isobologram, the additive effect $D_1 + D_2$, represented by the hypotenuse of the right triangle, has the relationship $(D_1)^2 + (D_2)^2 = [\text{hypotenuse}]^2$ for the additive effect of D_1 and D_2, based on the MAL-MEE-CIE theory of dynamics. Both the MAL-Isobol and the Pythagoras Theorem are universal, open codes, a priori, in plain view. This is a miraculous revelation.

The Pythagoras Theorem: $a^2 + b^2 = c^2$.

It also indicates that 1 + 1 = the square root of 2, where the square root of 2 is an irrational number [83]. Any power to the "i" is still One, and any number's zero power is still 1. Thus, "One" is Nature's Unity Theory of One (UTO).



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Thus, the Pythagoras Theorem is the 2nd-degree Isobologram.

The major difference is that Pythagoras' a, b, and c are the lengths (distances, spaces, and c is the length. In contrast, the MAL-isobologram's right triangle represents the causal combination effect involving mass (dose) and force (energy); the hypotenuse of the isobologram is the sum of the "effects". Since MAL-MEE/DOM indicated *"Mass" and "Effect" are interchangeable*, where FR, (fa/fu), of Effect = $(D/Dm)^m$ of dose (or mass). The density is mass per unit volume (space), which involves the speed at which the action occurs (mass/time). Space and time may be interchangeable, as a space-time. In physics, a speed parameter often involves distance/time, which appears in a "squared" function for distance (distance-length/time)^2, as in $E/M = C^2$ in Einstein's relativity theory.

2.5. The Dose-reduction Index: An Intermediate Revelation

Extension of MAL-MEE leads to entity interactions: CIE and its components dissections, DRIE.

For two entities, $(D)_1$ and $(D)_2$, for x-percent effect (Dx) 1, 2 in combinations, the DRI for each entity is given by

$$(DRI)_1 = \frac{(D_{alone})_1}{(D_{comb})_1} = \frac{(D_x)_1}{(D)_1} = \frac{(D_m)_1\left[\frac{fa}{1-fa}\right]^{1/m1}}{(D)_1} \quad , \quad (DRI)_2 = ...$$

DRI=1, >1, and <1 indicate no-dose-reduction, positive-dose-reduction, and negative-dose-reduction, respectively, for each drug at different effect levels for a given drug combination ratio. The diagnostic Fa-DRI plot can be generated instantly by computer simulation [9,24,54,55].

Interpretation of Dose-Reduction Index (DRI) Values

DRI Value Range	Interpretation	Implication
DRI < 1	Unfavorable Dose-Reduction	Requires higher individual doses in combination to achieve the same effect.
DRI = 1	No Dose-Reduction	No change in individual dose requirement compared to single agents.
DRI > 1	Favorable Dose-Reduction	Allows for reduced individual doses in combination while maintaining efficacy.

The universality of MAL-MEE/CIE lies in the equations' dimensionless nature, which makes them applicable to general dynamics regardless of units, scale, structure, or complexity, for universal applications. The MAL-based inputs (↓) and outputs (↑) sequential patterns analysis is the core principle of the MAL-MEE/CIE theory, algorithm, derivations, and ubiquitous applications, as attested by garnering over 50,000 citations in 1,580 journals, and 1,575 patents, as of September 2025. The application fields encompass biomedical, biophysical, environmental, agricultural, marine, and food sciences, as well as other areas, including radiation, thermo, photo-, pH-, and carcinogenic effects.

The LLMs in AI data centers may require over trillions of tokens; thus, they need a fundamental, unified principle for AI agents' transformational and transcendental deduction, as well as filtration of categories, for efficiency and cost-effectiveness in input-output, forward, and backward processing informatics, to facilitate simple and acceptable decisions or conclusions. The MAL-theory serves as a bridge to unify intra-, inter-, and cross-disciplinary linkages, with multi-decades of broad experimental confirmation supporting the defined general principles of digital informatics.

3. MAL-MEE/CIE/DRIE for Econo-Green Biomedical R&D

The Unity Theory of "One" (UTO): The Real World Examples

The MAL-Based MEE, CIE, and DRIE are all based on "1" as the universal standard**.**

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Highlight Examples from in Vitro, in Vivo, to Animal Studies and Clinical Trials: Using the Same MAL-MEE/CIE Principle, Algorithm, Parameters, the Same Protocol Design, and the same MAL-basic principle for Data Analysis/Simulation with Quantitative Digitalized of Indexed Conclusions.

Therefore, the MAL-MEE/CIE/DRIE/DOM/MYDPT/UTO is considered the unified general principle and method for the efficient, cost-effective, and Econo-green digital data science R&D.

3.1. A MAL-Based New Framework for Scientific R&D: Design and Computerized Simulation

From Preclinical Planning, in vitro and animal studies, to Clinical Protocol Design, Clinical Trial Data Simulation, and Digitized/Indexed Conclusions

Example of Anti-HIV Single Drugs and their combinations for Synergism Quantitation: Azidothymidine (AZT), Recombinant Interferon-alpha (IFN), and AZT and IFN Combinations (AZT+IFN) are illustrated below:

3.1.1. Scheme Design and Applications: MAL-Dynamics Theory-Based

The mass-action law (MAL) dose-effect and input-output system analysis in the life sciences led to the derivation of a unified general dynamic theory/algorithm/graphics of the median-effect equation (MEE, 1976) [1] for action and the combination-index equation (CIE, 1984) [2] for interaction. Both MAL-based theories enable the digital simulation of graphics, with applications in R&D, offering efficient, cost-effective digital capabilities. They provide common linkages across intra-, inter-, multi-, and cross-disciplinary parameters (Dm and m) and indices (CI and DRI) [3–5].

The recommended design for the two-drug regimen is the diagonal design shown in Figure 28A; an actual experimental design is shown in Figure 28B, using two anti-HIV agents (AZT, IFN, and AZT + IFN). This is the most efficient and cost-effective design according to the MAL principle.

This in vitro drug combination evaluation for drug development needs only 15 dose data points plus a control (uninhibited). The whole in vitro experiment for determining synergism, additivity, and antagonism (by computer simulation) will take about a week. Chou's laboratory, in collaboration with Martin Hirsch's Mass-General Hospital, Boston, MA, conducted over 20 sets of anti-HIV in vitro studies [9,24]; some of the results are shown in Figures 28 -29.

The anti-HIV monoclonal antibody combination studies were carried out in animals in collaboration with Ruth Ruprecht's laboratory at Dana-Farber Cancer Institute, Boston, MA. [24,37].

A.

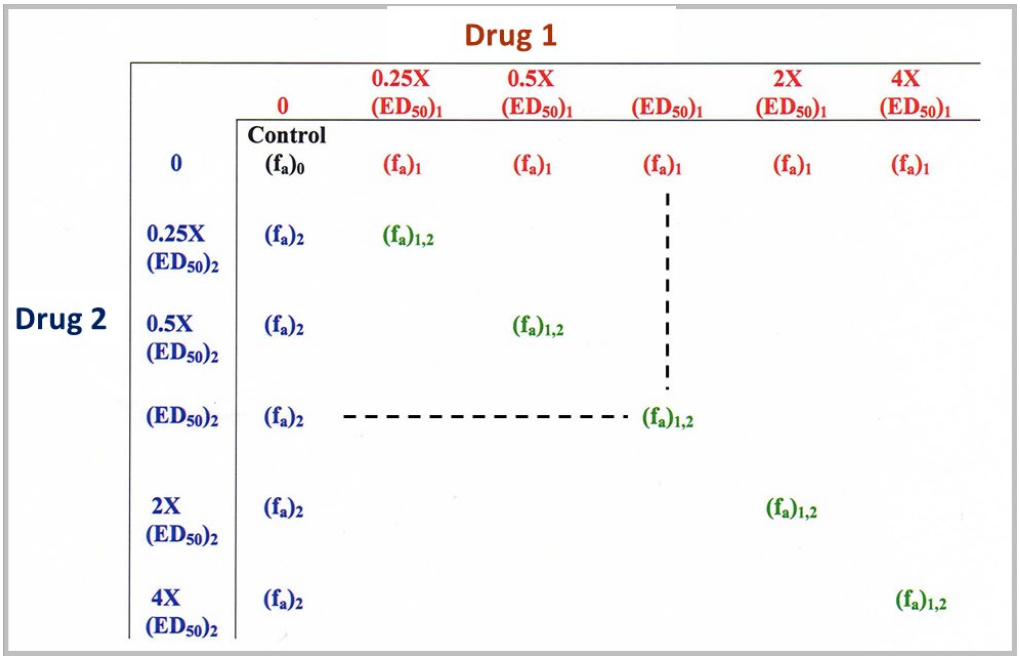

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Figure 28A. "Proper Design" is a Prerequisite for Any Efficient MAL-PD Studies. The Simple and Efficient Constant-Ratio Combo Diagonal Design for the Automated Simulations (Recommended). PD-Based Protocol Design (Dose Range, Dose Density, and Dose Ratio) is Critical for Efficient, Cost-Effective Data Analysis in PD-Automated Simulation. The "Non-Constant Ratio Design" can also be used to determine quantitative Synergy. But no automatic computerized simulation is possible. [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].

B.

AZT **(μM)**	**0**	**8**	**IFN** **16**	**(U/ml)** **32**	**64**	**128**
0	Contr.	0.156	0.268	0.059	0.176	0.263
0.01	0.225	0.585				
0.02	0.463		0.795			
0.04	0.654			0.951		
0.08	0.849				0.980	
0.16	0.966					0.995

Figure 28B. In vitro experiment took about a week, using only 16 dose-data points, 5+5+5, +1 control (RT assays in triplicate). The full analysis simulation took about 1 second, including 10 pages of the Computer Report. Quantitatively determined Synergy at different effect levels and the auto-construction of an Isobologram based on the MAL design and analysis. A typical experiment, like this, took only two weeks to complete in the laboratory with experience.

3.1.2. MAL-Based Drug Discovery from Pre-Clinical in Vitro, in Animals studies to Clinical Trials

According to Web of Science, Google Scholar, and ResearchGate, although only a small fraction of scientists and institutional agencies have applied MAL principles in scientific R&D, the MAL theory, algorithms, and software have been cited in over 40,000 papers across more than 1,580 journals and 1,444 patents worldwide. Humans determine the units and methods of measurement. Based on the theories of MAL-MEE, CIE, and DRIE's DOM and UTO, I propose placing Life at the center among the elements of the universe—Mass, Force, Space, and Time. The most quantitative connections among them will be through mathematics and algorithms, the universal language for all sciences and universal events.

3.1.2.1. Example of Anti-HIV in Vitro for Two Drug Combinations

The typical anti-HIV agent evaluations and their combinations for AZT, IFN, and AZT + IFN in vitro and in computer simulation are shown in Figures 27-29.

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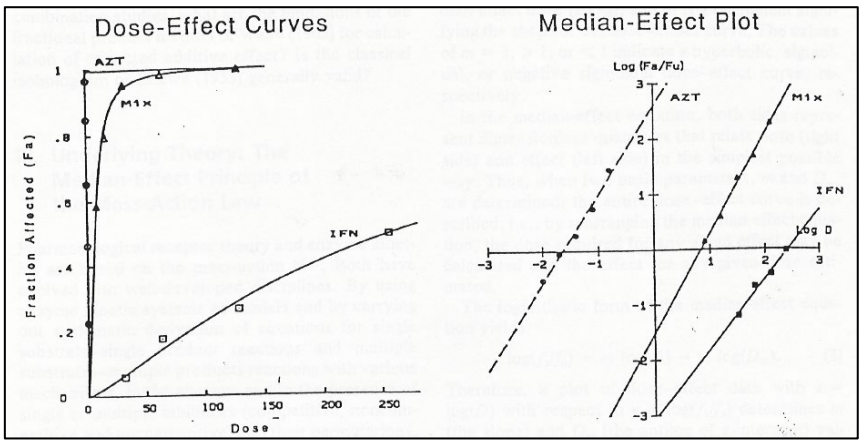

Figure 29. Dose-effect curves and the median-effect plot for inhibition of human immunodeficiency virus, type 1 (HIV-1) by recombinant interferon α (IFN) and 3′-azido-3′-deoxythymidine (AZT), and AZT (in μM) and IFN (in U/ml) mixture (1:800). Data were obtained using reverse transcriptase assays. The parameters obtained are $(D_m)_{AZT} = 0.0233$ μM, $(m)_{AZT} = 1.593$, $(D_m)_{IFN} = 263.06$ U/ml, $(m)_{IFN} = 1.262$,$(D_m)_{mix} = 6.856$, $(m)_{mix} = 1.803$. M and Dm are obtained from the slope and intercept, respectively.

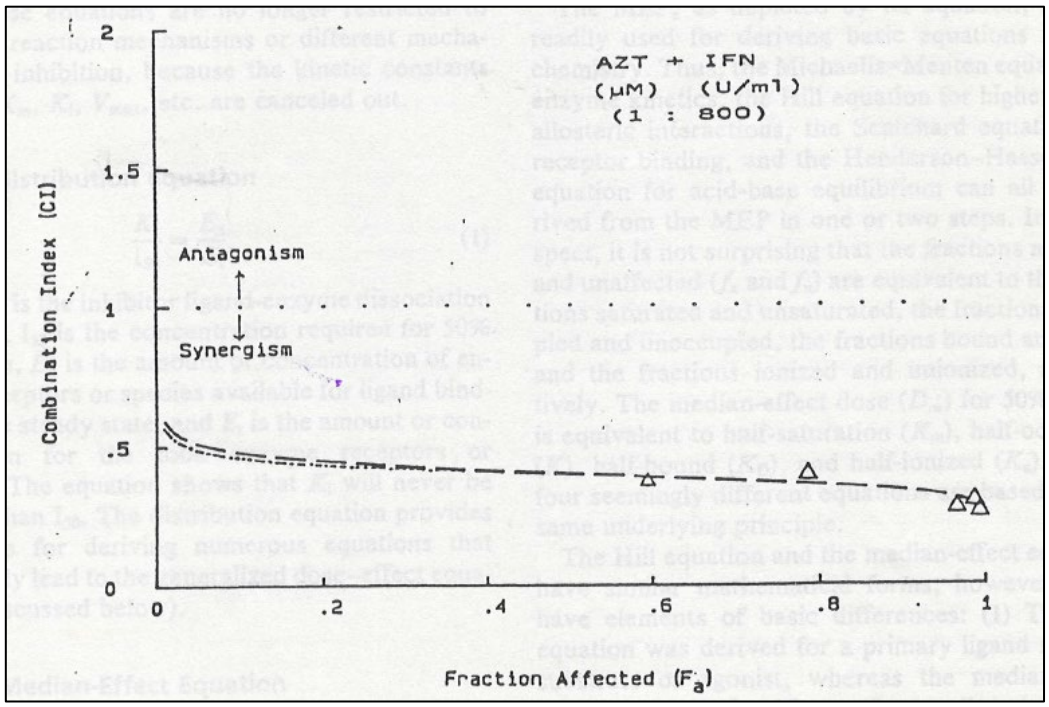

Figure 30. The F_a–CI plot showing synergism-antagonism with combination index (CI) as a function of fraction affected (f_a). Parameters shown in Figure 1 were used for the calculations. CI values for each combination data point are shown with triangles. Dashed and dotted lines are computer-simulated results of CIs assuming mutually exclusive and mutually nonexclusive interactions, respectively, between AZT and IFN. The results show strong synergism between AZT and IFN with CI < 1. In this example, both exclusive and nonexclusive assumptions give very similar results.

3.1.2.2. Anti-HIV for Two Drug and Three Combinations in Vitro

The graphics in Figure 31 were generated by the serial deletion analysis (SDA) [9,54,55], without any artificial pre-assumptions. The vertical bars indicating the 95% confidence interval clearly show the narrowest range near the Median (fa = 0.5) and longer on both ends (fa = <0.05 or >0.95). Thus,

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Mother Nature indicates that all measurements are more accurate at the "Median", and more difficult at lower or higher extremes [9].

3.2. *Anti-HIV Experimentation in Animals*

There have been no good animal models for anti-HIV agents/drugs, other than primates. Ruth Ruprecht's laboratory at Dana-Baber Cancer Institute, Harvard University, had conducted limited studies in macaques [84] and simians [36,85,86]. Most of the anti-HIV agent studies and their combinations, as shown in Figure 31, were conducted in collaboration with Martin Hirsch's laboratory at Massachusetts General Hospital, Harvard University.

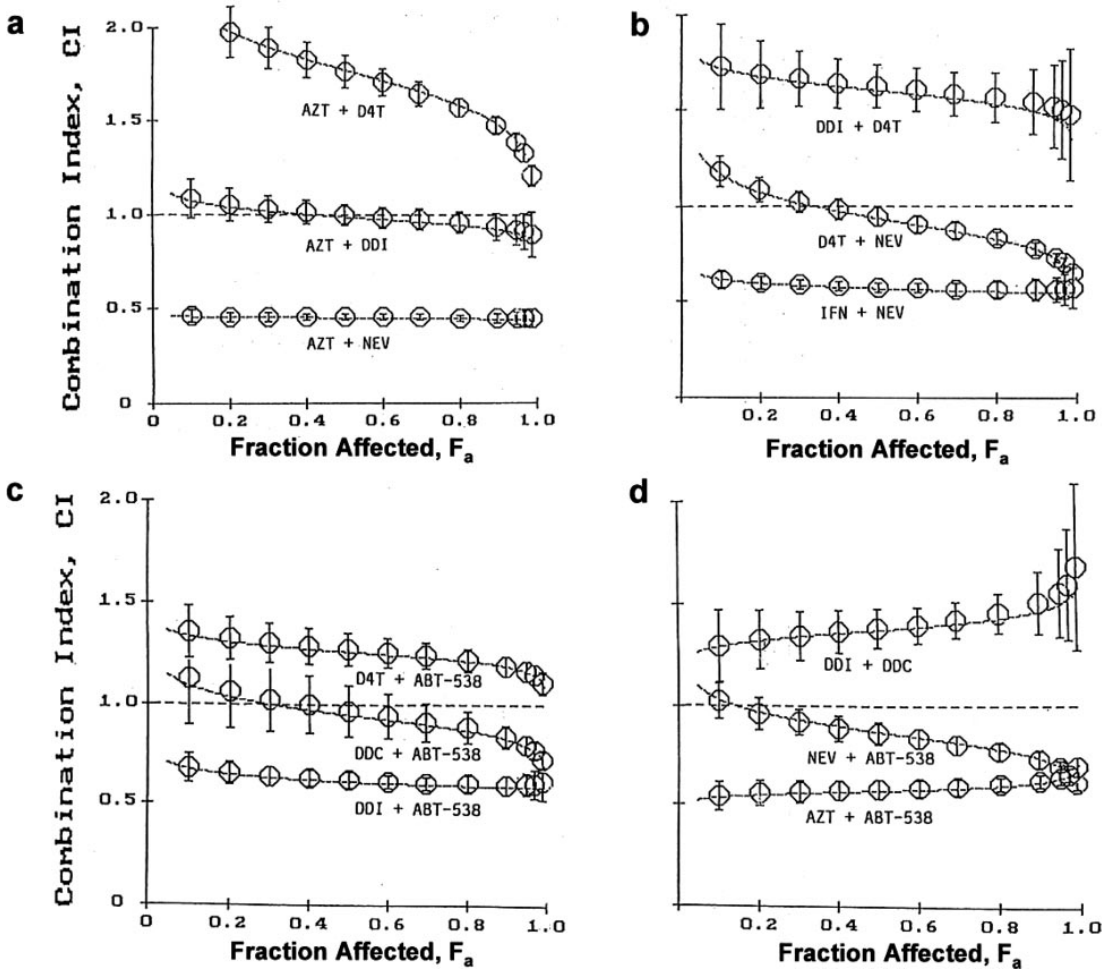

Figure 31. Examples of Fa-CI plots for 12 sets of two-drug combinations in Figure 32, divided into four subgroups: a, b, c, and d. The CI is plotted as a function of the fractional inhibition (fa) by computer simulation from fa = 0.10 to 0.95. CI < 1, = 1, and > 1 indicate synergism, additive effect, and antagonism, respectively. The vertical bars indicate 95% confidence intervals based on SDA, generated with custom software by T. C. Chou and H. Kim. Similar graphics can also be generated using CompuSyn (Chou and Martin, 2005), but the vertical bars in this figure are positioned at the experimental combination data points.

The clinical trial on AZT, INF, and AZT + INF was conducted using the MAL-MEE/CIE-based protocol design and computerized data analysis, as summarized below [59].

3.3. *Anti-HIV Clinical Trials in Humans: Protocol Design and Computerized Simulation for Quantitative Conclusions*

Effect of rIFNαA and AZT Singly or in Combination on RT Assays where fa Values as Fractional Inhibitions.

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Biological and biomedical sciences have long faced complexity, variability, and diversity; given the significant uncertainties, relying on probability is the logical approach. As a result, p-values have traditionally been the standard and a required criterion in academic societies and regulatory agencies, especially in scientific peer review. While convincing p-values are obviously necessary in many areas, the core goals of science have shifted toward variability and precision in measurement. However, the mass-action law-based fundamental principles of proper "experimental design" is absolutely essential for drawing quantitative conclusion in efficient and cost-effective R&D. For example, in two drug combination, if either of the component drug using only single dose, it is impossible to quantitatively determine the combination synergism or antagonism, regardless how accurate are the experimental measurements, how large of sample size, or how many times the experiment is repeated, since single dose is not possible to have that drug's fundamental m and Dm parameters. The design determines which types of conclusions are feasible. This critical digital science data science requirement has been largely overlooked by regulatory agencies, researchers, and practitioners in the biomedical community. Consequently, the traditional statistical protocol remains overwhelmingly dominant, leaving little room to consider or discuss fundamentally different ideas for saving time, effort, and research resources. An explicit illustration is the parallel comparison of two anti-HIV clinical trials from the 1990s: trial A, evaluating AZT + 3TC [60] using traditional statistical methods, and trial B, evaluating AZT + IFN [59] using MAL-MEE/CIE-based methods. (see Table 8 and Figure 32).

3.3.1. Specific Example of Clinical Trials Protocol Design Based on MAL-MEE/CIE and Data Simulation Informatics

The Efficient and Cost-Effective Ground-Breaking MAL- R&D Approach [59], which used ten times fewer patients than the traditional observational statistics-based clinical trials [60], as indicated in Figure 32 and Table 7. Unfortunately, international food and drug regulatory agencies (FDAs) are still reluctant to adopt this new MAL innovation, for nearly three decades (1996), despite over 30,000 in vitro studies, and hundreds of animal preclinical studies which used the MAL-based MEE/CIE computerized quantitative theory and methods, including 1,616 citing patents [56,57].

3.3.2. Clinical Trials Protocol Design Example: AZT + IFN

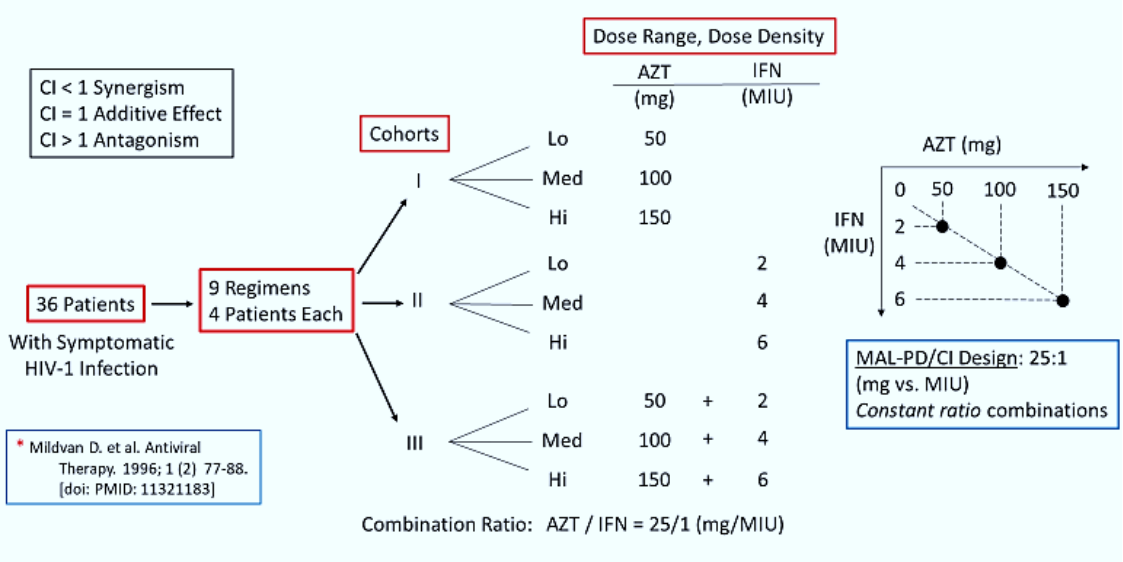

Figure 32. Anti-HIV clinical trials for AZT & IFN using Chou-Talalay MAL-PD/CI method for protocol design and computational data analysis using only 10 dose-data points and 36 patients.

3.3.3. Theoretical Basis, Definition, and Quantitative Analysis

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

Where D_1 is Azidothymidine (AZT); D_2 is recombinant α-interferon (IFN).

Determining the combination interaction of a + b requires the combination index equation (CIE), which quantitatively determines:

CI = 1 (Additive Effect)

CI < 1 (Synergism)

CI > 1 (Antagonism)

Theoretical basis and methods for protocol design and data analysis/simulation of AZT and INF single drugs and their combination in clinical trials, using Chou-Talalay PD-CI algorithms to quantify synergism or antagonism.

AZT + IFN Clinical Trials:

Mildvan D. et al. [59] examined synergy, activity, and tolerability of zidovudine and interferon-alpha in patients with symptomatic HIV-1 infection: ACTG 068. Antiviral Therapy 1996; 1 (2): 77-88. Used p-24 antigen assay and CD4 cell count as surrogate markers.

3.3.4. Automatic Computer Simulation for Synergism Determination

Computer Software:

Dose-effect analysis with microcomputers, software including: Chou J, Chou TC. Elsevier-Biosoft, Cambridge, UK, 1985, 1987. [51,52]

CalcuSyn, Chou TC, Hayball M. Biosoft, Cambridge, UK, 1997. [54]

CompuSyn, Chou TC, Martin N. Combosyn Inc., PD Science LLC, Paramus, NJ, USA, 2004. [Free download at www.Combosyn.com since August 1, 2012] [55]

MAL-PD/CI Theory/Algorithm:

Chou TC & Talalay P. Adv. Enz. Regul. 22:27-55, 1984 [8]. Chou TC. Pharmacol. Rev. 58: 621-681, 2006 [9]; Chou TC. Integr. Biol. 3: 548-559, 2011 [11]; Cancer Res. 70: 440-446, 2010 [10]; Synergy 1:3-21, 2014 [13]

3.4. Traditional vs. MAL-Based Clinical Trials Protocol Design

3.4.1. Comparison of Two Clinical Trial Approaches Using Traditional, Statistical versus New MAL-Based Design and Analysis

The side-by-side comparison of two anti-HIV clinical trials, AZT + 3TC [60] vs. AZT + INF [59], is shown in Table 8. The conclusion indicates that the MAL/MEE-/CIE-based clinical design used 10-fold fewer patients yet achieved a more quantitative determination of synergism.

Synergism needs to be quantitatively determined whenever possible, not always empirically, as is currently done in the biomedical and pharmaceutical sciences. To the best of the knowledge of literature search, so far as of May 2026, none of the regulatory agencies, such as the FDAs, in the world has a clear definition of "synergism", "additive-effect", or "antagonism". However, hundreds of drug-combination clinical trials are conducted globally each year, with a cumulative cost of hundreds of billions of dollars. The indecision over this definition, which matters to regulatory agency decision-makers, has unintentionally caused tremendous loss of time, effort, and resources, and is not only a scientific issue but also has economic, legal, ethical, and moral dimensions. The anti-HIV clinical trials examples above indicate that the AZT + IFN [59] clinical trials applying the MAL-based design and computerized digital data analysis/simulation used **10-fold fewer patients than the AZT + 3TC clinical trials [60] using the traditional statistical approach (for the p-values). The** AZT + IFN [59] trials achieve a quantitative synergism determination using the CI values, however, the AZT + 3TC [60] achieved the conclusion of the combined effect is greater than each drug alone, e.g., effect

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of A + B > A, and A + B > B with the impressive low p-values, which is an ancient/traditional R&D approach, that cannot quantify "synergism".

Table 8. Comparison of two anti-HIV clinical trials, AZT + 3TC v. AZT + INF.

Comparison 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	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	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. Total 10 Dose-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
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]

The clinical trial (AZT + IFN) [59] was designated as AIDS Clinical Trial Group (ACTG)-068, and Ting-Chao Chou served as consultant for protocol design and data analysis, using the Chou-Talalay CI method (31) and software (32). In Mildvan's paper [59], the "CI" was mentioned multiple times in the text, including references (18, 19, 20, 31, and 32). This work was supported in part by grants from the AIDS Clinical Trials Group of the National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, Maryland, and from a friend of Beth Israel Medical Center, New York, USA.

Ting-Chao Chou was not involved in the clinical trial (AZT + 3TC) [60].

3.4.2. Highlights of MAL Clinical Trial Protocol Design and Simulation

These Two Clinical Protocol Designs and Data Analyses Are Completely Different.

It is not possible to quantify synergism from a single dose of any drug, as the Dm and m values required for CI determination are unavailable. The MAL-PD-based CI method is quantitative, efficient, and cost-effective, with a small-sized clinical trial protocol design and automated computerized data analysis. The MAL-MEE/CI Approach is the choice for dose-dependent pharmacodynamics (PD).

PD needs two (or more) doses for both "Potency" and "Shape". A single dose generates a "Point" of potency data, but it has no "Shape". Thus, not for MAL-PD nor CI analysis [9–14,24,51,54,55].

The dose-dependent MAL-PD indicates that clinical trial protocols using only a single dose are simply for effective potency at that particular dose, without any other information to follow through, thus not a PD study. By contrast, use 2 (or more) doses, which allow PD-based automated computer simulations not only for Dm and m dynamics parameters for each drug and their combinations, but also for digital determination of synergism, additive effect, and antagonism. The examples above (Figures 28-32 and Table 8) illustrate [51,54,55].

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It is concluded that synergism is a mass-action law issue rather than a statistical issue. Furthermore, Synergism, additive effect, or antagonism is determined by the CI value, not by the p-value.

International FDAs and other official regulatory agencies need to provide guidance and clarification, and upgrade rigorous guidelines on this important issue, based on the fundamental principle, across all drug evaluations and drug combinations.

3.5. Drug Combination Cocktail Design

More than 3-Drug or Entity Combinations: Graphics, Projections, and Determination

For 3-7 drug combination designs/analyses of synergism and antagonism simulations, the polygonogram concept has been introduced [9,11]. This *cocktail design* is based on the MAL principle for in vitro studies in the research and development of antiviral and anticancer agents.

As an extension of the CI concept, the polygonogram was introduced in 1994, and in 2005, automated computer-generated versions were implemented by CompuSyn [9,12,31].

The examples are shown in **Figure 33** below**.**

Likewise, the Dose-Reduction Index Equation (DRIE) and plot (fa-DRI plot) quantitatively determine whether DRI = 1, < 1, or> 1, indicating no, negative, or positive dose reduction, respectively.

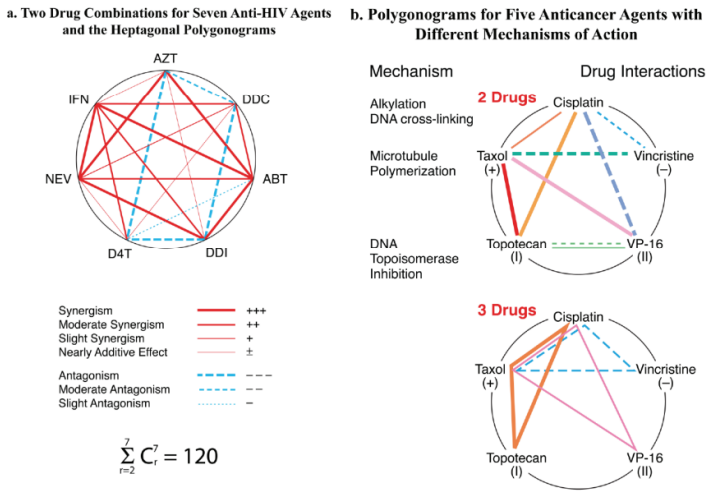

Figure 33. Polygonogram for three or more drug combinations for the cocktail design. It provides a simple visual inspection of complex combinations with a massive dataset. Also, it allows the projection of the outcomes of high component (n≥ 3) combinations from low component (e.g., n=2) combinations. a. Polygonogram of seven anti-HIV agents with similar or different mechanisms of action. b. Polygonogram of five anticancer agents with different mechanisms of action. The solid line indicates synergism, the broken line indicates antagonism, the heavy line indicates strong interaction, and the thin line indicates weak interaction. In all cases, the mechanisms cannot predict synergism, except that using MAL-MEE/CIE determines synergism (CI<1), additive-effect (CI =1), and antagonism (CI >1) quantitatively.

More than three entity combinations can be other than drugs, such as radiation or other physical entities.

4. Unified General Mass-Action Law Doctrine of the Median as the General Principle: Convergence and Emergence

The unified general theory requires general system analysis without setting preconditions or specific arbitrage models. The mass-action law (MAL) is Nature's fundamental physical and chemical principle, rather than an arbitrary selection on "Model". In new drug developments, many use PK models without using the MAL-based PD principle.

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Numerous unified, general, universal theories have been proposed earlier, including the theory of relativity, string theory, the Big Bang theory, the fundamental density theory, and many others. All of them have their theoretical basis, in one way or another.

One major criterion is applicability, scalability, and flexibility. The MAL-unified general theory/equations and algorithms are inching toward inter- and cross-disciplinary applicability, although they are not expected to be exhausted.

The MAL unity theory stays as is. However, the better ideas shall not be excluded.

Other Multi- and Cross-Disciplinary Convergence to the MAL

No unified general theories can exhaustively cover everything; the MAL-MEE/DOM/MTDPT/CIE DRIE for the Unity Theory of One (UTO) and Life-Centric Universe (LCU) have no exception. Humans are prone to errors, especially when making many unique statements and using unfamiliar terminology. I expect not all scientists will agree with my personal points here. I would welcome any individual who independently puts forward a better idea or thought. The MAL-theory/equations/algorithms have undergone scrutiny for over 5 decades.

4.1. Conceptual Transformations: Double reciprocal, Double logarithmic, Floating Ratio, and the Median-normalized Mass

The Mass-Action Law (MAL) algorithm-based paradigm has been proposed by this author, aiming to unify the analysis of dynamic processes across the life sciences, chemical, and physical sciences. The core concept is the Unity Theory of One (UTO), which describes natural phenomena as fractions of a unified whole ("One") that can bridge the **two domains of Nature: life and non-life**. This framework introduces the Doctrine of the Median (DOM)—the idea that the median point of any dose-effect relationship is a universal reference—and posits a **life-centric view of the universe**, placing "Life" conceptually at the center among the fundamental elements of mass, force, time, and space. In this overview, we explain the key components of Chou's paradigm (the MAL equations and their algorithms), assess its interdisciplinary significance, and illustrate the concepts with diagrams and examples. The tone is explanatory, geared toward scientists and policy makers interested in cross-disciplinary innovation.

4.2. MAL-based Median and Doctrine of Median

The framework builds on the classical Mass-Action Law (MAL), a principle from chemistry/biochemistry that governs how entities interact (e.g., drug molecules with targets). Through MAL-based system analysis of input-output patterns, Chou derived a **unified dose-effect relationship**, known as the **median-effect equation (MEE)** [4]. The MEE is expressed as:

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

Where **D** is the dose (or generally, the amount of any stimulus), **Dm** is the median-effect dose (the dose that produces a 50% effect), **fa** is the fraction affected (e.g., the proportion of a system that responds), **fu** is the fraction unaffected (so $f_a + f_u = 1$), and **m** is an exponent called the dynamic order [9,11]. This simple formula implies that the ratio of "affected" to "unaffected" is related to the dose in a power-law manner. Crucially, when $f_a = f_u = 0.5$, the dose D equals D_m by definition (the point where half the system is affected). Fa/fu is called the Floating Ratio (FR). The parameter **m** governs the shape of the dose-response curve: if $m = 1$, the relationship is a classical hyperbolic curve; if m is not equal to 1 (greater or smaller), the curve becomes sigmoidal (S-shaped) or flattened S-shaped. In other words, $m = 1$ yields a Michaelis-Menten-like simple saturation, while $m > 1$ or $m < 1$ produces steeper or shallower sigmoidal transitions (indicating higher or lower cooperativity in effect) [9,24].

The median-effect equation is remarkably general—it subsumes many classical biological and physical response models as special cases. In fact, it has been shown that the MEE unifies the

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equations for enzyme kinetics (Michaelis–Menten), receptor binding (Hill and Scatchard equations), pH ionization (Henderson–Hasselbalch equation), and more, by interpreting their "half-effective" constants (e.g., Km, Kd, pK) as analogs of D_m. Thus, **"Dose" and "Effect"** (or more abstractly, mass and function) **become interchangeable** under this unified law. The Doctrine of the Median (DOM) holds that the median point (50% effect level) is a universal pivot for any effect dynamics. By plotting data as $\log(D)$ vs. $\log\left(\frac{f_a}{(1-f_a)}\right)$ (called the **median-effect plot**), one obtains a straight line whose slope = m and x-intercept = $\log D_m$. This means that with only a few data points, one can determine m and Dm and thereby define the entire dose-response curve, indeed, a surprising consequence—termed the **"Minimum Two-Data-Point Theory" (MTDPT)**—is that if a system obeys the MAL median-effect principle, then two experimental data points (plus two default points at zero effect for zero dose, and 50% effect at Dm) can theoretically **describe the full dose-response** [9]. This defies the common notion that at least three points are needed to draw a curve and highlights the power of the MAL algorithm, which automatically includes 0% and 50% points as anchors [9,11]. In practice, having more points is prudent. Still, this principle underlies a **"top-down" approach to research**: starting from a general law to guide minimal experiments, rather than the traditional "bottom-up" approach of many specific observations [9–12,14–21].

Because the MEE's terms are **dimensionless ratios** (fractions and normalized doses), the equation holds regardless of units, physical state, size, structure, or mechanistic details and Complexity [9,11,23,24]**.** This gives it a universal character: whether one is measuring drug concentration in moles, radiation in Gray, or signal intensity in arbitrary units, the relationship $\frac{fa}{fu} = \frac{f_a}{(1-f_a)} = \left(\frac{D}{D_m}\right)^m$, where D/Dm is the median dose-normalized Mass, should hold if the process follows mass-action law dynamics [9], thus, "Effect" and "Mass" are interchangeable or equivalent in biology. This is akin to Einstein's theory of relativity, $E = MC^2$, which indicates that "Energy" and "Mass" are equivalent in physics. Chou emphasizes that this property makes the MAL framework a kind of "common language", in which exponent m signifies dynamic-order, which also signifies the shape of dose-effect curves, i.e., m =1 denotes hyperbolic curve, m>1 gives sigmoidal curve, and m<1 gives flat-sigmoidal curve, for quantitative biology and beyond [9,11,23,24]. It also means that **potency (Dm)** and **curve shape (m)** are the key parameters for characterizing the effect of a single agent or a combination of multiple agents. These two parameters provide a complete digital description of the general dose-effect relationship, including its defined geometric properties [9,11]. The median, D_m, in particular is a "universal reference point" that signifies an equilibrium or halfway state across diverse systems. Thanks to these features, the MAL median-effect method has very broad applicability. It has been applied not only in biomedical research (pharmacology, cancer therapy, toxicology) but also in fields such as environmental science, agriculture, and even marine biology, wherever dose-response or stimulus-response relationships arise [18].

In summary, the Median-Effect Equation condenses centuries of dose-response knowledge into a single formula. It provides a conceptual paradigm shift by asserting that **all processes governed by mass-action law can be described by a single, unified equation, with differences limited to** two parameters. This lays the groundwork for integrating data from multiple disciplines and for conducting research more efficiently. For scientists, it suggests that outcomes can be simulated or predicted with minimal input data. For policymakers, it promises more cost-effective, "Econo-Green" research designs that reduce experimental waste [20,21]. In practice, software inspired by this theory (e.g., CompuSyn) can use a few data points to run computer simulations, yielding an entire curve and related metrics in seconds, streamlining the R&D process [22,23].

4.3. Intrinsic Properties Revelation in Life and Non-Life

Revealing Hiding Informatics from Unified General Dynamics Principle: Nature's MAL Theory for General Causal-Effect Data Science By using system analysis

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4.3.1. Inputs-Outputs: Sequence Pattern, and the Transitions of paired Signals, (S, P), (↓,↑), (1,0) or (+, -)

Linear Pattern (see Section 8, 8.1 to 8.3)

Circular Pattern (see Section 8, 8.4 to 8.8)

The linear combinatorial patterns vs **Euler's Totient-Function (∅)** combinatorial for circular system [1]

The **Pascal Triangle** for binomial coefficients distribution, $C\binom{n}{r}$

The 2nd-degree **Squared Pascal Triangle** $\left(C\binom{n}{r}\right)^2$, derived from biological enzyme substrate-inputs (↓) and product-outputs (↑) system pattern transition combinatorial [1].

4.3.2. Isobologram Triangle vs. Pythagoras Triangle: One and Two Dimensions (see Section 8.9 and Figure 40)

The Pythagoras theorem, $a^2 + b^2 = c^2$ for a right triangle, is the 2nd-degree (squared) geometric length general principle of the right triangle, in a general form of (A, B, and A + B). Interestingly, a, b, and c indicate Length or distance (the exponent as space) in mathematics or physics. However, in pharmacology and life sciences, the dose-effect relationship in combination follows the MAL-unified general combination index equation (CIE) theorem. In contrast, A and B are for Effect (force or energy), which requires Dose (mass or entity) and action or interaction rate, which involves time (change of mass condition per time, for speed). In physics, speed (distance/time) is squared, as indicated by Einstein's relativity theory, $E/M = C^2$ **(see Section 8.9)**.

4.3.3 Mathematical Concept, Geometrical Forms, and Functional Relations (see Section 1) [9–11]

Median is a Universal Reference point and a Dynamic-order Common link

Equilibrium, Symmetry, Harmony

Geometric symmetry

Biological Dynamics vs. Physical Thermodynamics

Equilibrium and Balance

Optimal Homeosis vs Mechanical Conditions

Philosophical and Social Harmony and Natural Law **(see Figure 19)**

Ecosystem and Environment

The Power of the double-reciprocal plot [3–7]

1/S vs. 1/v [Lineweaver-Burk plot for enzyme kinetics]

1/D vs. fu/fa or (I-fa)/fu, (1-fu)/fu, $[(fu)^{-1} -1]$ or $[(fa)^{-1} -1]^{-1}$

[Chou's MAL General Dynamics for causal dose-effect informatics]

Competitiveness: Kinetics and Dynamics **(Equations, Algorithms, and Graphics) [3–7]**

Competitive

Non-Competitive

Un-Competitive

The power of the double-logarithmic plot (Equations/Graphics) [9–11]

The median-Effect Equation, $fa/fu = (D/Dm)^m$, and plot (PEP): (Chou, 1976),

Log D vs. Log (fa/fu), or Log (fa)/(1-fa), Log (1-fu)/fu, log $[(fu)^{-1} -1]$

or log $[(fa)^{-1} -1]^{-1}$ (The MAL-median-effect plot, Linearization, and Dm and m determination)

Entity fundamental Dual-Parameter [8,9]

Dm (for efficacy) and m (for dynamic-order exponential, shape of DEC)

Activation functions: Resting (Dm =0, m = 0), Hyperbolic activation (Dm =1, and m =1), Sigmoidal activation $m \neq 1\ (> 1 \text{ or } < 1)$, Tanh function, with a Floating Ratio (fa/fu) and with Median in the center of equilibrium, and symmetry.

4.3.4. New Conservation Principle: Minimum Two Dose-data Point Theory (see Section 1.5.3) [9–11,23,24]

(MTDPT) for Efficiency, Cost-Effectiveness, and Econo-Green

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Automatically adding two default points (Dose zero and Dm) to the MAL-MEE-PEP, thus leading to a smaller experimental size, which is a game changer in R&D, especially in animals or humans. MAL-MEE/CIE/DRIE

4.3.5. Exclusivity and Space (see Figures 16 to 18)

Mutually Exclusive (Equation and Graphics)
Mutually Non-exclusive (Equation and Graphics)

4.3.6. The Power of Ratio (see Section 1.6)

Golden ratio: Phi (φ) for Non-life
Floating Ratio: fa/fu for Life.
C^{14}/C^{12} ratio: For age time estimate
Mass ratio: D/Dm and $(D/Dm)^m$ for 1st (hyperbolic) and mth (sigmoidal) dynamics orders for geometric shapes
The 2^o-(squared) Pascal Triangle from biochemistry, sum of inversions lead to π
Relativity ratio: $E/M = C^2$ (Einstein)
Law of motion: F/m = a (Newton)
Density ratio: E/m = c^2 = 1/(ε0 μ0) = (d/t)^2, and $\alpha = 1/2$
Riemann zeta function, Re(s) =1/2

4.3.7. Median and Constant (see Section 1, and Tables 9 to 10)

Median: Half Dose (0.5 or ½) of maximal effect: Half-Mass dose (Dm) (IC_{50}, ED_{50}, TD_{50}, LD_{50})
Kinetic/Dynamic constant: K, Keq, Km, Ki, Kii, Kis, Kd, Ka
Reaction Rate: Mass/Time, dx/dt
MAL-Half Dose, (Dm) vs. Radio-Isotope decay Half Time ($t_{1/2}$): (A Graphic Comparison)

4.4. MAL-Median Unified Theory aligns with major historical conclusions in mathematics and physics (see Sections 1.12 and 8.9)

A recent review of MAL-MEE/Doctrine of the Median (DOM) leads to the Unity Theory of One (UTO), which uses "One" as a universal standard, and the Life-Centric Universe (LCU), which positions Life among Mass, Force, Time, and Space to promote humanism over materialism. New conclusions include:

(1) The universe contains Life and Non-Life domains.

In Life, MAL-MEE's Floating Ratio (FR), $fa/fu = fa/(1–fa) = (1–fu)/fu = (fu)^{-1}-1 = [(fa)^{-1}-1]^{-1}$, forms a circular, closed, recyclable pattern; Non-Life domains (physics, mathematics, and AI) follow the Golden Ratio (GR), $\varphi = 1 + 1/\varphi = (1 + \sqrt{5})/2 = 1.618033…$, an irrational open form extending to infinity. The Golden Ratio has been used or related broadly in geometry, the Fibonacci sequence, Lucas number, Penrose tiling, Kepler triangle, spiral galaxies, Golden Spiral, architectural designs, and plant floral patterns.

(2) FR has the fractional form $a/b = a/(1–a) = (1-b)/b$, while GR has $a/b = (a + b)/a = 1 + b/a$.

(3) Both are fractional distribution functions of "1": FR finite, GR infinite.

(4) Rearranging MEE yields $fa = 1/[1 + (Dm/D)^m]$ and $fu = 1/[1 + (D/Dm)^m]$, forms analogous to probability distributions, Logit, PROBIT, and Fermi–Dirac functions, except those containing Euler's *e*, limiting real-world biomedical utility. Log is often more practical than the Natural Logarithm (Ln).

(5) While Michaelis–Menten, Hill, Henderson–Hasselbalch, Scatchard, Langmuir isotherm, and Hopfield activation functions for neural networks contain no "*e*", they are model-specific and not broadly expandable.

(6) MAL-MEE's Median = 0.5 parallels α = 1/2 in Alfaro's Fundamental Density Theory and Re(s)=1/2 in the Riemann Zeta Function.

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(7) Ratios define relativity, including GR, FR, C_{14}/C_{12} (time), $E/M = C^2$ (Einstein), F/M = a (Newton), and Dm/t1/2 (MAL/physics).

(8) MAL-MEE provides algorithms illustrating competitiveness, exclusivity, symmetry, equilibrium, balance, homeostasis, cooperativity, feedback, visible input/output versus invisible intermediates, pathway, network, and harmony.

These findings indicate that the MAL-Median Unified Theory aligns with major historical conclusions in mathematics and physics.

The MAL-MEE-CIE-DRIE/DOM/UTO-Theory-based approach for general scientific R&D does not represent gradual progress, but rather a new framework that conforms to Nature's laws and principles, constituting a paradigm shift in numerical digital science for this AI-assisted electronic automation era. Conceptually, the MAL-theory-based top-down R&D approach is opposite to the traditional observation-statistic-based.

5. MAL and the Unity Theory of One (UTO)

This unified concept evolved from the MAL-MEE/CIE/DRIE theory /method has been time-tested for 5 decades since 1970, applications as of 2025 have garnered over 1,500 citing journals and over 1,500 citing patents, indicating the broadest scope of impact in drug discovery and research innovations, far beyond biomedical science, including environmental, agriculture, marine, bioengineering, and food sciences [9,11,16–24].

In Biology, the major events include birth and death, metabolism, growth, reproduction, and existence. Depending on the stages of evolution, there is an increasing complexity and sophistication. Humans, as primates in the animal kingdom, exhibit a high degree of consciousness, intelligence, senses, and the ability to create numbers, words, language, and scientific logic, including artificial intelligence (AI) [24].

From molecules, cells, and organs to the whole body, the mass-action law governs the actions of MEE and the interactions of CIE in biomedical and biophysical sciences. In simple molecular systems, such as enzyme proteins, they usually follow Michaelis-Menten kinetics with m = 1 as the dynamic order in MAL-MEE, indicating a DEC shape that yields hyperbolic curves. When molecules or sub-units conjugate or complex, the component may exhibit "cooperativity" in actions among them, such as allosteric enzymes, or hemoglobin and oxygen binding, where hemoglobin has four heme sub-units. This led A.V. Hill to derive an equation with the nth power that generates a sigmoidal oxygenation suturing curve. Both the Michaelis-Menten and Hill equations are derived from MAL, but their applications are restricted to specific research fields [9,11].

Figure 34 provided a theoretical basis for the NAL Unity Theory of One (UTO), since the unified general theory of MEE, CIE, and DRIE is all based on 'One' as a universal standard, for action, interactions, and informatics [24]. The Floating Ratio (fa/fu) and the Mass-Ratio (D/Dm) make the MAL theory, in both dose and effect, dimensionless relative ratios independent of units, physical states, size scale, structure, and complexity. For the real-world problem, the general equation is deterministic and has a finite distribution function of "1" [19–22].

As a primate with the highest intelligence, the Human decides the unit and method of measurement. From MAL-MEE/DOM/UTO manifestations, I proposed that Life be placed in the center among Mass, Force, Time, and Space in the Universe [19–22]. (See Figure 35).

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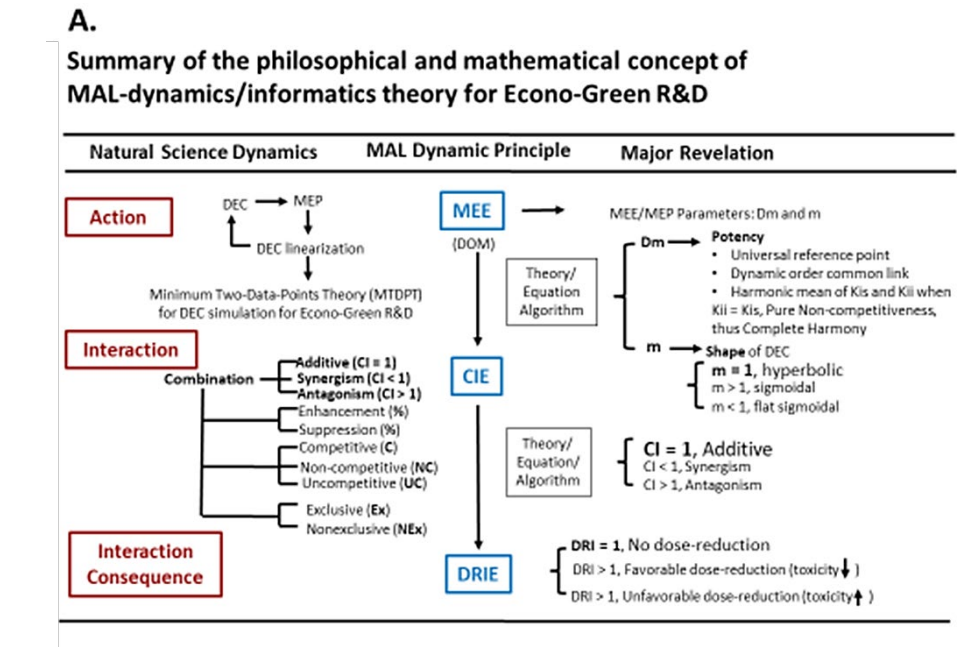

B.

Natural Science Dynamics	MAL Dynamic Principle	Major Revelation
Unity Theory of One (UTO) Unification Integration Generality	>1, =1, <1 Unity Concept & Philosophy Knowledge Inquiry – Dynamics and Informatics R&D Discovery, Regenerative AI Translational and Precision (Digital) Medicine Experimental /MAL-PD/BD Design PD-Ready Data Analysis / Simulation	One (1) as Universal Standard Simple, Efficient, Cost-Effective Quantitative, Digital, Computerized Econo-Green R&D (Default Addition of Dose-Zero and the Universal Dm to PD/BD, in Vitro, in Vivo and Clinical Trials)
Computer Software (Digital, Quantitative Capacity, Rapid, Simple, Accuracy, Flexibility)	MAL-PD/BD/CI/BI Theory/Algorithm & Method (1973-2023), Dose-Effect Analysis Software (1983) CalcuSyn (1998), CompuSyn (2004) Multidisciplinary Applications: Drugs, Biologicals, Radiation. Biomedical, Agricultural, Marine, Food, Environmental, Material and Physical Dynamic Studies, etc.	DEC, MEP, Fa-CI, Fa-CI, Fa-DRI Isobologram, Polygonogram Diagnostic Plots Automated Computer Simulations, MAL-PD and CI Informatics
Complementary Alternative of Scientific R&D (One Problem/Goal May Have Multiple Solutions)	Top-Down Approach (MAL-PD/BD/CI/BI Unified Theoretical Approach) Bottom-Up Approach (Conventional/Classical, Observation-based Statistical Open Approach)	Unified MAL-based, Defined Convergence and Deterministic Open Divergence, Empirical, Probabilistic and Statistical

Figure 34. Summary of the philosophical and mathematical concept of MAL-dynamics/informatics theory for Econo-Green R&D. Flow chart for Unity Theory of One (UTO) based on MAL-MEE/CIE/DRIE. The Unity Theory of One (UTO) for MEE (m=1), CIE (CI=1), and DRIE (DRI=1), as the Universal Standard. Ref: Chou TC "Mass-action-Law Dynamics Theory and Algorithm for Translational and Precision Medicine Informatics" (Academic Press/Elsevier, April 2024; ISBN: 978-0-443-28874-6) [24].

Currently, the unified general theory of the universe (such as the Theory of Everything) is mainly based on physics, e.g., the general relativity theory, the big bang theory, and the recently introduced Fundamental density Theory (FDT) [63–70] and the string theory, which, per se, are in the non-Life domain. It is well known in Einstein's Relativity Theory that E/m = c^2 = (d/t)^2, in which the Energy/Mass ratio is equal to the square of the speed of light (distance/time). This general theory, as well as FDT and other unified general theories, is a mathematical and physical model that falls within the non-life domain and cannot provide solutions to real-world needs, such as those in the biomedical sciences. By contrast, the MAL-MEE/DOM-based theory and applications are scalable due to the dimensionless ratios fa/fu and D/Dm on both sides of MEE for actions, and CIE for interactions.

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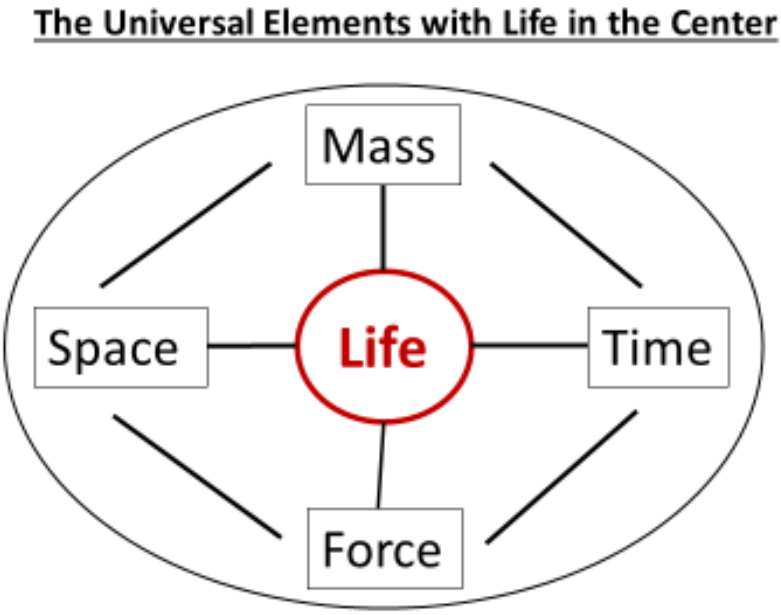

Figure 35. The Life-Centric Universal Elements, as proposed by Chou in 2025.

In the literature, there are more than a dozen theories that claim, suggest, or are believed to be for the unified general theory. These include string theory, the big bang theory, quantum mechanics, singularity theory, and fundamental density theory (FDT), among others. The MAL-dynamics/informatics theory, as presented in this paper, is just one of the theories of the universe. In the spirit of scientific freedom, there may be different opinions on the general MAL-theory and method despite their remarkable bibliometric and track record. Over the past four decades, the MAL-MEE and CIE have been discussed, assessed, and applied in more than 40,000 scientific papers and over 1,500 citing journals and 1,623 citing patents in publications. There is no point in peer-reviewing the MAL-MEE/CIE.DRIE theory and algorithm. Scholars with specialized expertise or a better idea are welcome to put forward their theory as an independent, new, and innovative concept and to compare it with the proposed universal theories.

6. A Universe by Design: Source Code Not Random Occurrence

Ultimate Supreme Being a priori, MAL Unity Theory of "One" (UTO) and Life-Centric Universe (LCU)

The following are the highlights for the MAL theory (MAL/MEE/CIE/DOM), outlined in the conclusions.

I. **Virtual a priori (unchangeable) [24]**

- **Principal:** Mass Action Law (MAL), median, symmetry, equilibrium, feedback, harmony, homeostasis. Pythagoras' Theory and Pascal's Triangle, Euler's Identity.
- **Constant:** π , φ , e , i , C (lightspeed), K (plank constant), …

II. **Elements (Life vs. Non-Life):** Life, Mass, Force, Time, and Space [21,22,24]

- **Process:** Mathematics, number, sequence, pattern, exponent, single/double logarithm, single/double reciprocal, ratio, … (revealing intrinsic properties and understanding)
- **Interpretation and Illustration by Theory, Algorithm, Parameters, and Graphics:** Digitalization of floating and fixed ratios, quantitative digitalized or indexed conclusions (alternative to probabilistic p-values).

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- **Unified, general principle for cross-disciplinary linking using MAL-MEE common denominators and parameters: Input-output cause and effect relationship, sharing the same algorithm and parameter-based graphics in hyperbolic and sigmoidal** activation functions.

III. **Scientific Exploration and Application from Phenomenal Extrinsic Property Investigations:** Specific, general and unified-general R&D protocol design and data analysis (bottom-up vs. top-down approach, complementary like two sides of the same coin or same entity) [19–22].

IV. **Existing Natural Instincts and Preservation:** Mass can be transformed to energy, effect, or force, and never dissipates [22,24].

- **Mass-Energy Equivalence (MEE):** Einstein's theory shows that mass and energy are interconvertible with infinite features. The MAL-MEE, **fa/fu = (D/Dm) ^{m}**, indicates that dose and effect are interchangeable, mediated by the Floating Ratio, which manifests in Life with recyclable and finite features.
- **New Concept of Preservation from MAL Theory:** The double logarithmic transformation for x = log (D) versus y = log (f_a/f_u), Median-Effect Plot (MEP), provides graphics determining an entity's paired, dynamic parameters; **Dm** for potency and **m** for dynamic order and shape for all input-output dynamic activation functions. **D/Dm** ratio signifies dimensionless scalability for universal applicability.
- **The MAL MEP Linearize Causal Dose-Effect Relationship:** The linearization leads to the minimum two dose data theory (MTDPT), which allows for a smaller size experimental design by adding two default data points (Dose zero and Dm), revolutionizing biomedical sciences, especially in animal studies and clinical trials, protocol design, and data simulation for quantified or indexed conclusions.

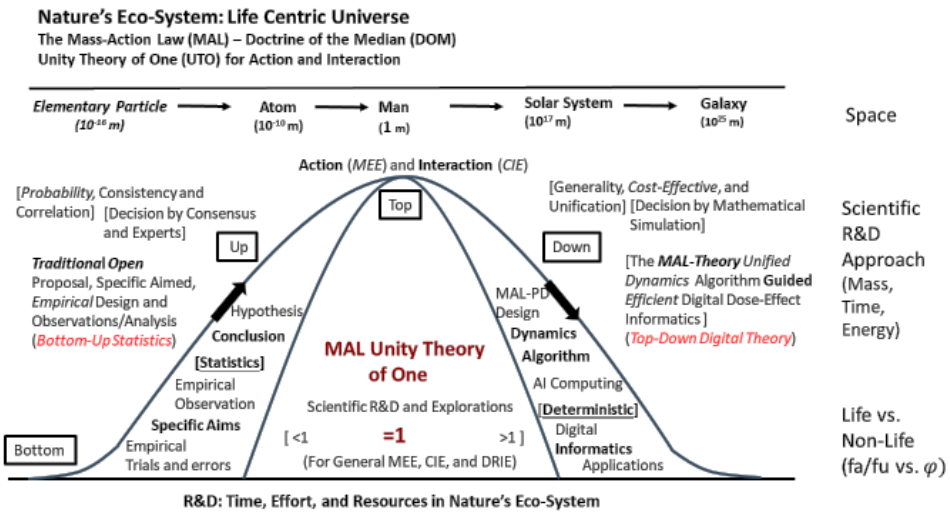

Figure 36. Humans decide on units and methods of measurement. The Human-Centered Perspectives of the Universe. Universal Unity Theory of One (UTO) for scientific R&D from human-centered prospective. The dynamic Unified Theory of One (UTO) for expressions of MAL-DOM (Doctrine of the Median) for action and interaction in scientific R&D.

In Figure 36, the median effect equation (MEE), the median effect dose (Dm) is the universal reference point, and the Nature's dynamic orders common link. This is the doctrine of the median (DOM) for "Action." The combination index equation (CIE) is for the principle of "Interaction." The dose-reduction index equation (DRIE) is used for dissecting interactions. All terms in MEE, CIE, and DRIE are dimensionless relative ratios of the same kind, regardless of units, physical states, size, mechanisms, or complexity, thus ensuring universal applicability. The features of structures, mechanisms, networks, pathways, and PK, etc., are not directly Life's Dynamics' intrinsic properties;

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rather, they are extrinsic properties that warrant special attention and separate studies. MAL-theory provides the Guiding Informatics for the regulation and conduct of scientific R&D.

There are semantic differences and debates about logical, philosophical, and mathematical induction and deduction. In both Asian and Western ancient philosophy and ontology, there are different schools.

Table 9 provides the universality of the Floating Ratio (FR) and mass ratio (D/Dm) in cross-disciplinary linking.

Table 9. MAL-MEE-CIE-DOM Floating Ratio, fa/fu = fa/(1-fa) = (D/Dm)^m, is regardless of unit, physical state, size, structure, and mechanistic complexity*.

Unit (SI):	k (kelvin), m (meter), a (ampere), s (second), mol (mole), kg (kilogram), and cd (candela)
Physical State:	Solid, liquid, and gas
Size (Meter):	Elementary particles ($<10^{-16}$), atom (10^{-10}), man (1), solar system (10^{17}), and galaxy ($>10^{25}$)
Structure:	Chemical, physical, mathematical, biological, and biomedical (primary, secondary, tertiary structure and pathway)
Mechanistic Complexity:	Sub-atomic, atomic, physical, chemical, and biological (cellular, molecular, action and interaction, pathway, and network)

*D (dose), Dm (median-effect dose), fa (fraction affected), fu (fraction unaffected), m (dynamic order).

6.1. Cross-Disciplinary Linkage: Biology, Math, and Philosophy

The MAL theory is cross-linked to ancient philosophical concepts as indicated in Figures 35-37.

6.1.1. Life Science Theorem and Interpretation of Harmony

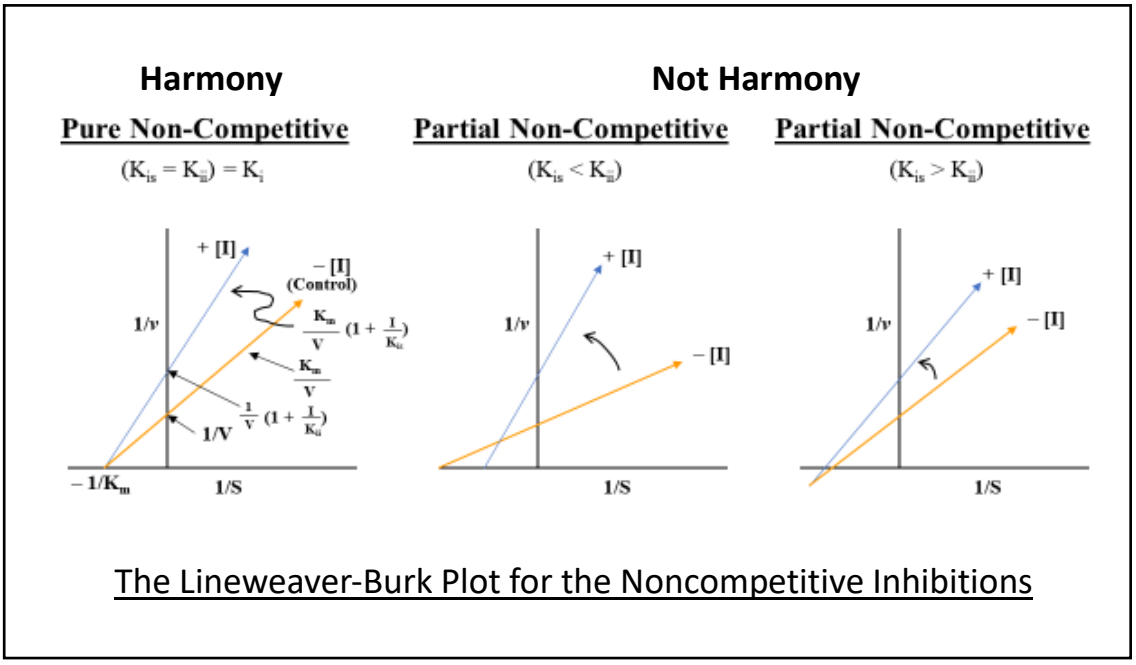

Figure 37. Modern interpretation of an ancient philosophical concept. **(A)** Median of MAL-MEE is the harmonic mean of pure non-competitive effect. **(B)** Lineweaver-Burk plot. Daoism for Harmony. The ecosystem's equilibrium between Nature and humans is stable.

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The mass-action law dynamics analysis using the Lineweaver-Burk plot proves that pure harmony is pure non-competitiveness. These results provide cross-disciplinary linkages between biological and philosophical concepts, in mathematical, physical, and graphical terms [3].

6.1.2. MAL Dynamics vs. Daoism, Yin-Yang, and Wu-Xin Ontology

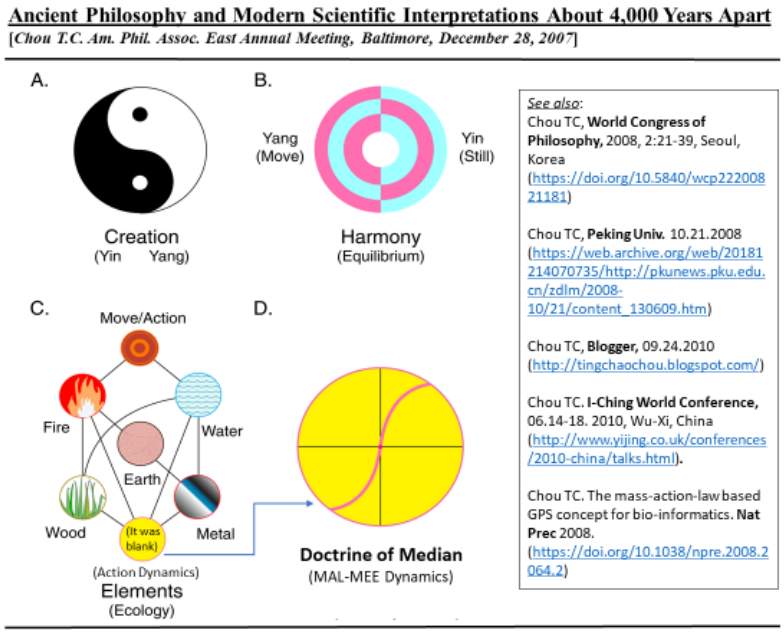

Figure 38. Symbols of ancient philosophy: A. Yin-Yang and B. Harmony of Zhou Yi (I Ching, the Book of Change), C. Wuxing (5 elements in ontology) of Taiji Tu by **Chou (Zhou) Dun-Yi (1017-1073).**

Note that only Water and Fire are connected by 4 lines (the most), as modern science indicates that no life can survive without water and that no reaction occurs without temperature. **D.** In the Taijidu bottom ring (yellow) was empty when published about a thousand years ago, which has been filled out by Chou TC as the Doctrine of the Median (DOM). Chou TC indicated that the Confucian Chung-Yung "Doctrine of the Mean" where "Mean" (Average) shall be translated as **"Doctrine of the Median."** (2007-2010 Philosophy meetings /conferences in N. America and Asia). Chou T.C. (1974) [3], using the Lineweaver-Burk plot in biochemistry, indicates that the Dm (the median dose) is the harmonic mean of Kii and Kis. When Kii and Kis are equal, the **ratio equals one;** it indicates **pure non-competitiveness; thus, it is a complete "Harmony."** This is consistent with the Unity of One Theory (UOT). It indicates Harmony, Equilibrium, and Symmetry [21,22].

Ancient Chinese philosophy Wu-Xin (Ontological Five Elements) is compared with contemporary resources provision, rules and regulations, and livelihood in Table 10.

Table 10. Relevance of Natural Five Elementary Resources on Regulatory Sciences and Dynamic Eco-Systems: Evolving from Ancient to Modern.

Chinese Ancient Five Elements (五行, Wu-Xin)	Resources and Provision	Rule and Regulation	Livelihood and Cultural Activity
Metal (金)	Construction materials Catalyst Tools	**Naturalism** Daoism	Food (食)

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Water **(水)**	Drinking Water River Lake Glacier	Livestock Fishery Plantation	Clothing (衣)
Energy **(火)**	Coal Oil Non-fossil energy	**Human-Centric Regulations**	Dwelling (住)
Plant **(木)**	Wood Vegetable/Fruit Forestry	Humanism Greenhouse Effect Genetic Material	Travel Recreation/ Art/Sport/Education (行) (育)
Earth **(土)**	Plant Solar Wind/Water Minerals/Chemicals Soil Shore/Basin Weather	Disease Control/Drugs Air and Water Quality Pollution Control Pest, Erosion Climate, Global Warming Energy Conservation	Entertainment/ Spiritual (樂)

6.1.3. Convergence of MAL Life-Centric Theory vs. Pythagoras' Theorem, Confucius, and Plato's Philosophy

There is hope that our intuitive perception, intelligence, and understanding will finally converge on the Unity Theory of One, and a Life-Centric Universe, along with the four physical elements: Mass, Force, Time, and Space. Two domains, Life and Non-life, are the realm of the Universe. Humans decide the Units and Methods of measurement that drive science. Inter- and cross-disciplinary linking of the Mass-Action Law-Median Principle (point, axis, and plane and rotations) points to the unity theory of "One" with fractional distribution of finite, closed, and cyclable, e.g., the Floating Ratio (fa/fu) manifesting Life, and continuing distribution of One in open, fractals, and extendable to infinity, e.g., the Golden Ratio (φ) manifesting Non-Life. Life features symmetry, equilibrium, balance, dynamics, harmony, along with feedback, cycling, regulatory homeostasis, life or death, growth, metabolism, reproduction, two genders, and ecosystem, among others, do not appear in the Non-Life domain; however, there are analogies, equivalency, similarity, or counterparts.

There is hope that our intuitive perception, intelligence, and understanding will finally converge on the Unity Theory of One, and a Life-Centric Universe, along with the four physical elements: Mass, Force, Time, and Space [22,87]. Two domains, Life and Non-life, are the realm of the Universe. Humans decide the Units and Methods of measurement that advance science. Inter- and cross-disciplinary linking of the Mass-Action Law-Median Principle (point, axis, and plane and rotations) points to the unity theory of "One" with fractional distribution of finite, closed, and cyclable, e.g., the Floating Ratio (fa/fu) manifesting Life, and continuing distribution of One in open, fractals, and extendable to infinity, e.g., the Golden Ratio (φ) manifesting Non-Life. Life features symmetry, equilibrium, balance, dynamics, harmony, along with feedback, cycling, regulatory homeostasis, life or death, growth, metabolism, reproduction, two genders, and ecosystem, among others, do not appear in the Non-Life domain; however, there are analogies, equivalency, similarity, or counterparts.

A scientist's pro-humanity announcement and its revelation on

Celebrating God and Humanity [87]

Pythagoras, Greek Philosopher, Polymath (c570–c490 BCE)

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Today Is A Historical Heavenly Day, Since Jesus Christ (and All the Mightiest)

September 16, 2025

9.16.2025 –> 9.16.25, $3^2 + 4^2 = 5^2$; $(a^2 + b^2 = c^2)$, 9 x 5 = 45, $45^2 = 2025$

For the Pythagoras Theorem, the numbers 3, 4, and 5 are the only consecutive whole numbers that allow a solution of forever.

Pythagoras lived about 2,500 years ago, about the same time as **Confucius** and **Plato**.

[Born: Pythagoras, 570 BCE; Confucius, 551 BCE; Plato, 428 BCE, Jesus (1); and Now, 2025 ADE]

Pythagoras of Samos (c. 570 BCE—c. 490 BCE) was a Greek philosopher and mathematician who made significant contributions to math, astronomy, and music theory. He's best known for the Pythagorean Theorem, $\mathbf{a^2 + b^2 = c^2}$, a fundamental principle in geometry that relates the sides of a right triangle. His work also laid the groundwork for number theory, ratios, and trigonometry.

Confucius' "Doctrine of the Mean" (Chung Yung) has been a global classic for millennia, especially in Asia.

Plato: In metaphysics, Plato envisioned a systematic, rational treatment of the forms and their interrelations, starting with the most fundamental among them (the Good, or the One).

The Miraculous Convergence reveals something unique: The Mass-Action Law

Research on the Mass-Action Law (MAL) as both a fundamental principle and a scientific discipline, beginning with combinatorial methods in the 1960s [1,2], has led to the median effect equation [3,4]. Its integrated combination index equation [5–8] has led to the Doctrine of the Median, DOM, and the Unity Theory of One, UTO [9,23] that provides a common algorithm for inter-disciplinary linkage [24]. These have led to the proposal of the Life-Centric Universe, LCU [22]. The Floating Ratio of MAL (fa/fu) [4,20–22], (finite and circular), manifests Life in biology. In contrast, the Golden Ratio (φ) and Euler's identity, (open and infinity)) manifests in the Non-Life domain, including mathematics, physics, statistics, and AI [22]. Both Ratios are the fractional distribution of "One" [19–22,24]. Nature as a whole reveals open code identity or algorithms in plain view, such as the MAL Floating Ratio, the Golden Ratio, Pythagoras' Theorem, Euler's Identity, Pascal Triangle, the Number Theories, Statistical Probability, Neural Networks, and MAL-Activation Functions, are in existence without knowing the source; a priori, manifesting the Supreme Bing, or All Mightiest. Humans decide the Units and methods of measurement that evolve and drive science. The time has come to spark a renaissance of humanity, rising above materialism [87].

Our mission is to reveal the underlying intrinsic properties and meanings for true understanding and their applications.

6.1.4. Recent Papers and Essays in Mathematics and Physics Relevant to Life Science MAL-Median Principle

During 2025-2026, numerous discussions on subjects relevant to the MAL-MEE/DOM/UTO have emerged. Most of the independent short essays are published on Medium, including the following subject titles. These are individual ideas and opinions, not my own, that are open to consideration in an open forum for thought-provoking ideas. Subjects on **Median and Mean** [92–94]; **Top-Down and Bottom-Up** [95]; **Logistic Function** [96,97]; **From Countable to Uncountable** [98]; **Perception and Intuitively** [112,113]; and **Open-Source of Universe Code** [99–101,114,115]. Some recent mathematics and physics concepts that are relevant to the MAL-unified theory development are exemplified in [92,93,96–105].

During 2026, numerous articles and essays related to MAL-MEE dynamics and number theories have been published. These include prime numbers and root of unity by Vagelis Plevris [116,117], Riemann's hypothesis by Pradeep Mishra [118–120], and number theory and logistic functions by Keith McNulty [97,121].

Recently, Tomio Kobayashi made basic mathematical essays including logarithms and exponentials [122], matrix inversion and time reversal [123], linear algebra view of 3D space [124], linear transformations [125], and multiplication to eigendecomposition: The discrete story [126]. Kobayashi reported an interesting essay on two dynamic systems, discrete and continuous (see

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Figures 10B and 10C). Interestingly, discrete systems correspond to life (MAL-MEE and Floating Ratio), has matrix inversion and time reversal. Whereas, continuous systems correspond to non-life (Golden Ratio) (see **Figure 10A**). These findings indicate that biological dynamic analysis by Chou (this paper) has cross-analogy to mathematical dynamic and matrix analysis of T. Kobayashi (**Figures 10B and 10C**),

Also, in 2026, Manuel Alfaro extended his Fundamental Density Theory (FDT) and applications in physics [127–129], as well as a physical approach in Fundamental Density Theory (FDT), quantum physics of Alfaro (**Section 1.6** [63–70,99,103,106,107,114,115]). Thanushan Sivapatham discussed the limit of x! over x^x without the gamma function [130] and how substitution simplifies no calculator algebra problems [131].

7. Artificial Intelligence (AI)

Artificial intelligence (AI) is the extension of human intelligence, using electrical computer engineering to facilitate speed and scale. Still, it lacks the life ingredients of living systems, despite tremendous efforts to mimic real-life conditions.

7.1. Life and Non-Life Domains: Transcendental Paradigm Shift

Life and death cannot mix.

Chou's MAL theory and its algorithm are indicated by MAL-MEE/MEP/MTDPT/CIE/DRIE/UTO/LCU, which is developed from life-science system pattern combinatorial analysis of inputs and outputs in real-world situations and has a unified, general universality. The application of the MAL dynamic principle is a relativity theory of "Dose" and "Effect" in the form of the Ratio of "D/Dm", normalized "Mass" and "fa/fu", and the Floating Ratio of "Effect" for "Force" or "Energy". Thus, The MAL-MEE/CIE unified theory application is independent to unit, physical state, size, structure, and complexity.

Therefore, the MAL principle shall play a fundamental role in the design of AI infrastructure algorithms for life and non-life domains. From data input, embedding, feedback, categorization, processing, decision making, to output, the MAL principle can serve as a fundamental categorial agent [24].

Since the public introduction of ChatGPT in 2023 and DeepSeek in 2024, many other AI model infrastructures have been developed. This is an era-making event in the developmental history, affecting the lives and non-lives overall. Numerous AI models have been developed and are improving for broad applications. The following are examples of general experiences and feedback from a freelance researcher's perspective:

a. Artificial intelligence (AI) belongs to the Non-Life domain, which pulls tremendous information, including biological intelligence and available knowledge, that changes with time, location, individual, and policies (e.g., the Floating Ratio and human ideology-based fine-tunings). Humans are unlike the Non-Life domain in mathematics and physics, which are rigid (e.g., the Golden Ratio or uncountable infinity).
b. Mathematics, physics, and AI include infinity and complex or transcendental numbers, which are not in biological real life (e.g., life and death cannot coexist). Furthermore, the Life domain is governed by an open, recyclable, finite biodynamics system. In contrast, the Non-Life domain is governed by a fixed, open system that extends to infinity without bound. The repeated mimicking and approximation may reach a near-perfect goal, but it is not strictly perfect.
c. AI and LLMs' approach is to collect trillions of information tokens indiscriminately without determining and weighing whether right or wrong, new or obsolete, which causes ambiguity and confusion. For example, when asked for the "definition of synergism", AI returns over 15 definitions, none of which support one another, and most of them contradict. In fact, among all methods for determining synergism, only the mass-action law (MAL)- based combination index (CI) method, which quantifies

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synergism (CI < 1, digitally) via computer simulation, is simple, efficient, and cost-effective, and the international trend has overwhelmingly (68.5% of 26,415 citations) used the CI method during the past five years (2021-2025), compared with all other 10 major methods which are arbitrary or based on a statistical probabilistic approaches with uncertainty features. There are hundreds (if not thousands) of drug-combination clinical trials taking place globally over the past decade that amount to hundreds of billions of dollars in costs, yet as of 2025, there has been no clear official regulatory definition of "synergism". AI-MMLs and agents' infrastructure need a basic early layer of categorial separation between Life and Non-life for filtering, sieving, and extracting processes, preferably with weighting features.

d. One example of the algorithm-based weighing feature is the fair scientific attribution in papers with multiple authors (*n*- authors) using authorship-ranked weighted h-index (*w*h-index), as proposed in [24, in its chapter IX-G].
e. Based on the Web of Science database, over 70 million publications since 1900, about 43% receive zero citations. These may be the treasures hidden behind neglected, or simply garbage. Another reason of non-citing may be due low number of journals, research scientists, and the lack of web search technology many decades ago. Despite of these, more data doesn't necessarily mean more usefulness if not weighted in at least in some of the aspects, such as more reliable bibliometrics or statistics.

7.2. Machine Learning and Processing in the AI LLMs Era

The AI in computers is collectively the most learned entity, with extreme speed and volume, but, per se, has no life properties. We humans with life (including consciousness, perception, thinking, processing, moving/acting/resting, intelligence, life-span, growth, metabolism, reproduction, arts and civilization, and existence distinct, etc.) are trying to teach a piece of machine with defined algorithms via a condensed electrical circuit of engineered chips. The key points here are whether the "algorithms" are representative of completeness in universality, in full or in part, and the embedded intrinsic advantages and limitations. Here, the author of this paper proposes the Unity theory of One (UTO)/Life-Centric Universe (LCU), in which the scientific R&D platform and AI infrastructure shall define digital dynamics informatics algorithms with Life (MAL-based) and Non-life (e-based Non-MAL) distinctions for categorization of reality and the virtual.

To the end, AI needs not only technological, engineering know-how and data gathering, but the most critical factors for success are also rigorous categorization, universality, efficiency, and cost-effectiveness.

8. Inputs-Outputs Combinatorial Pattern Analysis in Biology Relevant to AI

From Conceptual Principle to Unified Theory and Algorithms

This author began the mass-action law-based theoretical work as a Ph.D. student at Yale University. The following are the highlights of the 1970 thesis [1,2]. A series of theoretical works during the 1970s [3–7] laid the foundation for a lifelong endeavor to develop MAL-MEE/CIE/DRIE as the unified general theory of life sciences and beyond. This author's Ph. D. Thesis advisors are indicated in the Acknowledgments. Then, the mathematical references are given in [88–91].

8.1. Number, Sequence, Pattern, and Combinatorial: Enzyme System General Pattern Analysis

Life science dynamics and informatics principles based on nature's biophysical, biochemical, and mathematical principles of the mass-action law (MAL) have been a subject of binary (input (↓) and output (↑), e.g., enzyme substrates and products) mathematical sequence, combinatorial, and mathematical induction-deduction analysis since the mid-1960s when I was a graduate student at Yale University [1]. This led to the discovery of the 2nd-degree Pascal Triangle, in which each element

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of the Pascal Triangle is squared [1]. This novel mathematical systematic approach on MAL-based theoretical biology took 18 years (1966-1984), involving about 300 reaction-rate equations [1–8] that led to the derivation of the combination index (CI) theorem with Paul Talalay of the Johns Hopkins University, which is followed by over 40 years of MAL-theory developments and applications.

This author's thesis research was on enzyme systems, with a conceptually new approach to sequence and pattern analysis, which began in the late 1960s with an enzyme called "L-Asparagine Synthetase" [1].

In an enzyme reaction system, the sum of the substrate (S) and products (P) is usually less than 10; some enzymes may have a cofactor or coenzyme. The L-Asparagine (Asn) synthetase [1] has 3 (S) and 4 (P). Biochemical science usually involves multiple enzyme reactions that form a chain or network. In life sciences, these processes increase in complexity, from cells, tissues, organs, the whole body, communities, and ecosystems, etc.

When **S** and **P** are designated the numbers of the substrate (input) and product (output),

respectively, **n** is the number of the transitional stable enzyme form or intermediate complex. The following equations describe various sequences and patterns in linear or circular form [1]; more specific illustrations are provided in **[1].**

8.2. The number of overall linear sequential patterns

When a linear sequence contains S substrates (or inputs) and P products (or outputs), the overall linear patterns, A(S,P), can be interpreted as the number of permutations of (S-I)+(P-1) things of which S-1 are alike, and the other P-1 are alike, which gives

$$A(S,P) = \frac{[(S-1)+(P-1)]!}{(S-1)!\,(P-1)!} = \binom{S+P-2}{S-1\,,P-1}$$

(Eq. 1)

S-1 and P-1 are the numbers of substrates and products, respectively, that can be freely arranged. When one considers the arrangement in a linear sense, it is obligatory that the reaction starts with the addition of the first substrate and ends with the release of the last product.

8.3. The number of linear sequential patterns at a given number of stable enzyme forms:

Definition for the "stable enzyme form" transition signal pattern changes:

Stable enzyme forms are the enzyme species in a mechanism that are incapable of a unimolecular reaction with the liberation of a substrate or product as defined by Cleland (1963) [3,4]. The number of stable enzyme form(s) should be at least one and should be equal to (i) the number of ping pongs (including the last product and the first substrate considered as a pair of ping pongs); or (ii) equal to the number of competitive product inhibitions within a reaction mechanism; or (iii) equal to the number of transitions from an output to an input in the reaction sequence of a mechanism. The possible number of stable enzyme forms should be equal to or less than the lower limit of the number of substrates or products. (see Table 1 and Figure 39 for illustrations).

For n = number of stable enzyme forms, the outputs can be chosen in $\binom{P-1}{n-1}$ different ways and the inputs in $\binom{S-1}{n-1}$ ways. Since any choice of $(n-1)$ output indices may be combined with any choice of input indices, the number of linear patterns for n stable enzyme forms (1.e.m n transition intermediates) in the sequence is therefore

$$A(n;S,P) = \binom{S-1}{n-1}\binom{P-1}{n-1} \quad \text{(Eq. 2)}$$

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The number of *possible overall linear patterns* equals the *sum* ($\sum$) of patterns corresponding to every possible given number of stable enzyme forms, thus

$$A(S,P) = \sum_{j=1}^{n} A(j;S,P) = \sum_{j=1}^{n} \binom{S-1}{j-1} \binom{P-1}{j-1}$$

(Eq. 3)

of which $S, P \geq n \geq 1$.

In case only S and P have common divisors, the problem is more complicated. According to the necklaces problem quoted by E. Lucas, Theorie des Numbres, Paris, 1891, pp. 501-503 from C. Moreau (Riordan, 1958), the number of circular permutations of n objects of specification ($n_1, n_2, \ldots, n_n$) is given by

$$N(n_1, n_2, \ldots, n_m) = \frac{1}{n} \sum_{d_1} \phi(d_1) \left[(n/d_1)! \Big/ \prod_{j=1}^{m} \left(\frac{n_j}{d_1}\right)! \right], \quad \text{(Eq, 4)}$$

where d_1 is a divisor of the greatest common divisor of $n_1, n_2, \ldots, n_n$ and ø is Euler's totient function. ø(d_1) is the number of positive integers less than d_1 and prime to d_1. Equation (7) can be used to calculate ø(d_1) conveniently. Equation (4) can be applied to the enzyme systems to calculate the overall number of mechanism patterns at all possible numbers of stable enzyme forms (but not the specific number of mechanism patterns at a given number of stable enzyme forms). Thus equation (4) is transformed to

$$M(S,P) = \frac{1}{S+P} \sum_{d_1} \emptyset\,(d_1) \frac{\binom{S+P}{d_1}!}{\binom{S}{d_1}! \binom{P}{d_1}!}$$

(Eq, 5)

where M(S,P) is the overall number of mechanism patterns of S number of substrates and P number of products; and d_1 is a divisor of the largest common divisor of S and P.

When S, P and n have a common divisor other than one, a sequence consisting of a symmetrical repeating intra-arrangement may occur; therefore, the partitional numbers obtained will give only an approximate value, or a non-integer. Further mathematical treatment of this case is necessary. Closely related problems have been analyzed by Barton & David (1958) in "Runs in a Ring" and by David & Barton (1962). With the generous assistance of Professor L. J. Savage of the Yale Statistics Department, an explicit derivation or the purpose of the present study is available from this laboratory, which is given by*

$$M(n;S,P) = \frac{1}{n} \sum_{d} \emptyset\,(d) \binom{\frac{S}{d}-1}{\frac{n}{d}-1} \binom{\frac{P}{d}-1}{\frac{n}{d}-1}$$

(Eq, 6)

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where M(n; S, P) is the specific number of mechanism patterns at n number of stable enzyme forms. The value(s) d is summed over the common divisors of n, S and P; and is Euler's totient function. That is, ø(d) is the number of positive integers less than d and prime to d which can be conveniently calculated by (Hua, 1967)

$$\emptyset(d) = \quad d\prod_{k}\left(1-\frac{1}{p_k}\right),$$

(Eq, 7)

where P_k's are the different prime factors of d. For example,

d	1	2	3	4	5	6	7	8	9	10	11	12
$\emptyset(d)$	1	1	2	2	4	2	6	4	6	4	10	4

and ø(20) = 20 x (1—½) x (1—1/5) = 8.

Correlating equations (5) and (6) gives

$$\sum_{n}\frac{1}{n}\sum_{d}\phi(d)\binom{(S/d)-1}{(n/d)-1}\binom{(P/d)-1}{(n/d)-1} = \frac{1}{S+P}\sum_{d_1}\phi(d_1)\frac{[(S+P)/d_1]!}{(S/d_1)!(P/d_1)!}.$$

(Eq, 8)

*For detailed derivation, see Chou (1970, pp. 151-154).

8.4. The number of overall mechanisms (circular)

$$N(S,P) = \frac{S!\,P!}{S+P}\sum_{d_1}\emptyset(d_1)\frac{\binom{S+P}{d_1}}{\left(\frac{S}{d_1}\right)!\left(\frac{P}{d_1}\right)!}$$

Where p1, p2… are the different prime factors of d. ∅ (1) = 1 is a convention. Shown above is a table for ∅ (d). The above Equations (4)—(6) are derived with the consultation of Eugene Higgins, Professor, and Leonard J. Savage of the Yale University Mathematics Department.**Table 1.** Number of patterns of linear sequences and mechanisms in enzyme-catalyzed reactions with one or more substrates (S) inputs (↓), and product (P) outputs (↑).

Reaction system Substrate-Product (S,P) Duplet	**Highest number of stable enzyme forms** [a]	**Number of *linear patterns* at each given number of stable enzyme form** [b]							**Number of mechanism *circular patterns* at each given number of stable enzyme form** [c]							**Overall number of linear patterns** [d]	**Overall number of circular mechanism patterns** [e]
									N_1	N_2	N_3	N_4	N_5	N_6	N_7 [f]		
		M_1	M_2	M_3	M_4	M_5	M_6	M_7 [g]									
Symmetrical Distribution (S = P)		**Linear Second Degree (Squared) Pascal Triangle**							**Circular Pattern Triangle**								
Bi-bi	**2**	**1**	**1**						1	1						2	2
Ter-ter	**3**	**1**	**4**	**1**					1	2	1					6	4

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Quad-quad	**4**	**1**	**9**	**9**	**1**	1	5	3	1	20	10
Quint-quint	**5**	**1** **1**	**16**	**36**	**16**	1 1	8	12	4	70	26
Sext-sext	**6**	**1** **25**	**25** **1**	**100**	**100**	1 5	13 1	34	26	252	80
Hept-hept	**7**	**1** **225**	**36** **36**	**225** **1**	**400**	1 5	18 6	75 1	100	924	246
Asymmetrical Distribution (S ≠ P)											
Bi-ter (ter-bi)	**2**	1	2			1	2			3	2
Bi-quad (quad-bi)	**2**	1	3			1	2			4	3
Ter-quad [h] (quad-ter)	**3**	1	6	3		1	3	1		10	5
Ter-quint (quint-ter)	**3**	1	8	6		1	4	2		15	7
Quad-quint (quint-quad)	**4**	1	12	18	4	1	6	6	1	35	14

[a] The highest number of stable enzyme forms is equal to the lower limit of the number of substrates or products.

[b] According to Eq (2).

[c] According to Eq (6).

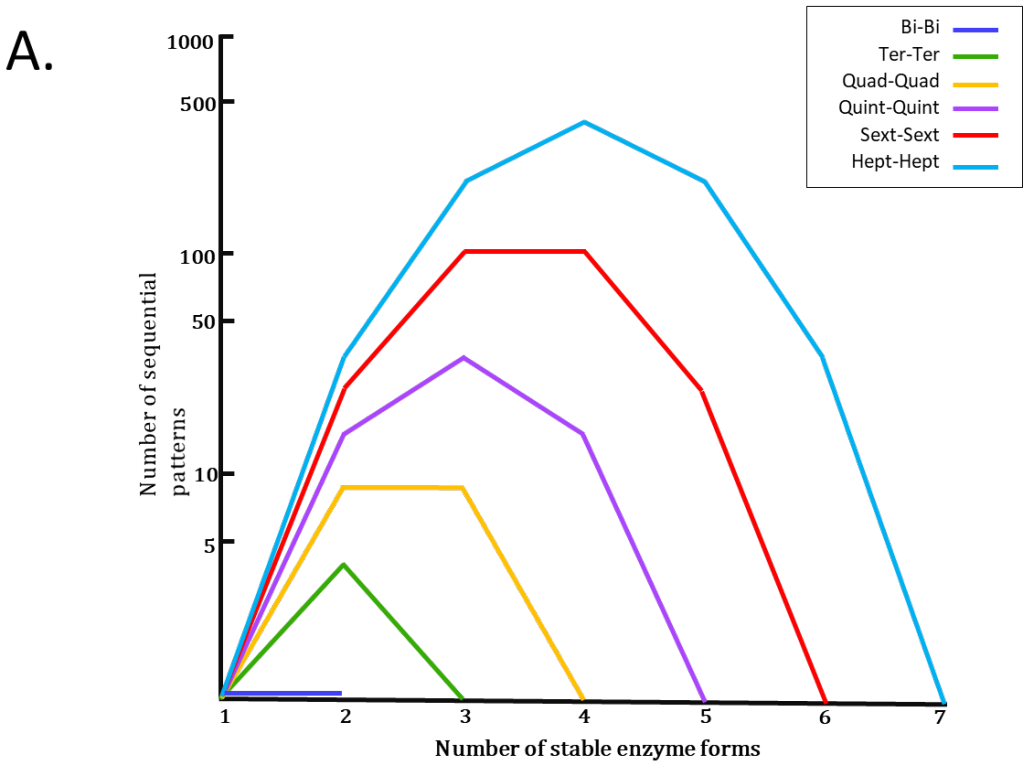
[d] According to Eq (1) or (3).

[e] According to Eq (5) or (8).

[f] N_1, N_2, N_3, ..., is the number of linear patterns at one, two, three, ..., stable enzyme forms, respectively.

[g] M_1, M_2, M_3, ..., is the number of mechanism patterns at one, two, three, ..., stable enzyme forms, respectively.

[h] L-asparagine synthetase given in the Example is a Ter-Quad (3S, 4P) system.



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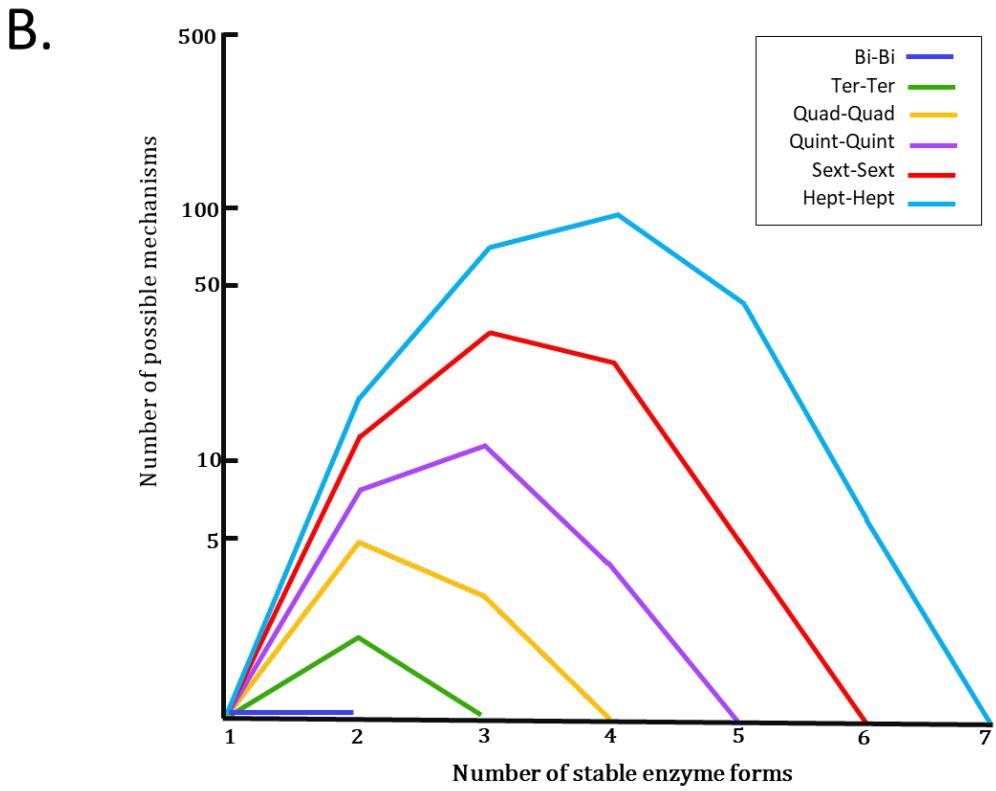

Figure 39. Relationship between the different numbers of stable enzyme forms with (A) different numbers of sequential patterns, and with (B) different numbers of possible mechanisms, when the number of substrates and products is equal.

8.9. Derivation of Second Degree (Squared) Pascal Triangle from Biological Inputs-Outputs Duplex Patterns Transitions Combinatorial Analysis

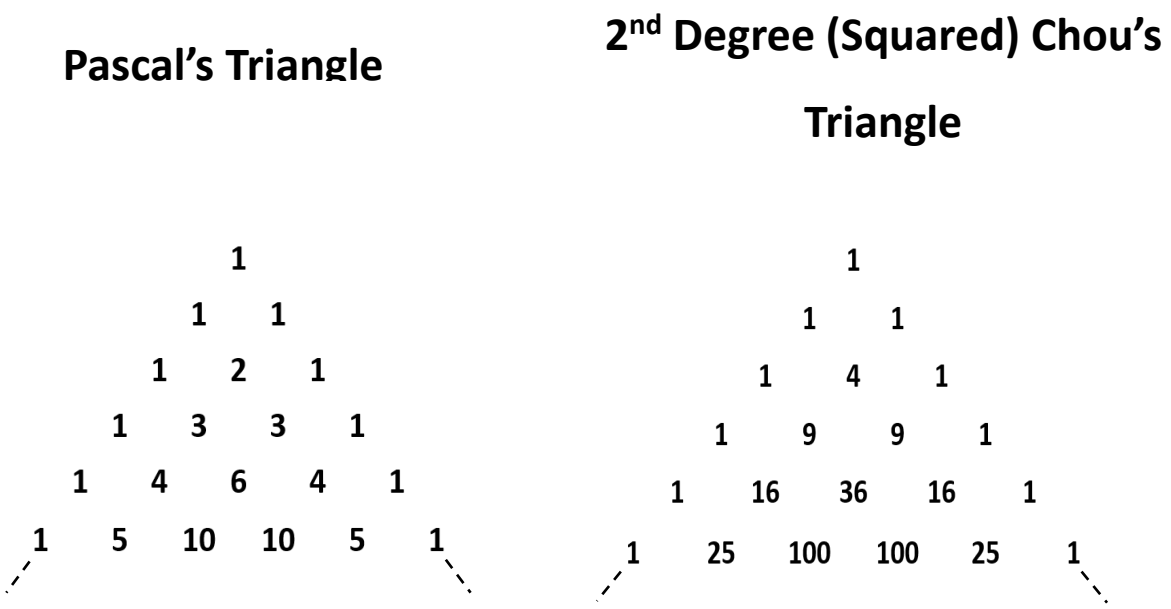

Figure 40. The classical Pascal triangle (Left) and the second-degree (squared) triangle (Right) obtained from the duplex (↓ and ↑) signal-pattern transitions, using the enzyme's substrate (S) inputs and product (P) output system, which involves multiple stable enzyme intermediates.

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The focus here is on the squared numbers: 1, 4, 9, 16, 25, 36… in Chou's Second-Degree (Squared) Triangle derived from the biological input-output patterns transition system in life science.

And their sum of reciprocals:

$$\begin{array}{ccccccccc} 1 & & 4 & & 9 & & 16 & & 25 \\ \downarrow & & \downarrow & & \downarrow & & \downarrow & & \downarrow \\ \frac{1}{1} & + & \frac{1}{4} & + & \frac{1}{9} & + & \frac{1}{16} & + & \frac{1}{25} \end{array}$$

The sum of the reciprocals of squared numbers (of Squared Triangle) can be related to π, which is an irrational and transcendental number.

Chou's Squared Triangle related to "π", and Riemann's zeta function

$$\sum_{n=1}^{\infty} \frac{1}{n^2} = \frac{1}{1} + \frac{1}{4} + \frac{1}{9} + \frac{1}{16} + \frac{1}{25} + \cdots = \frac{\pi^2}{6}$$

$$\frac{(3.1415926535\ldots)^2}{6} = 1.644934066754\ldots$$

The above equation is Riemann's zeta function when ***s*** equals 2.

$$\zeta(s) = \sum_{n=1}^{\infty} \frac{1}{n^s}, \quad s = \sigma + it.$$

$$\zeta(2) = \sum_{n=1}^{\infty} \frac{1}{n^2}, \quad 2 = \sigma + it.$$

The Pascal Triangle Led to Euler's "*e*":

Harlan Brothers and Richard M. Green's analysis of Pascal's Triangle [132] discovered that the Triangle's row ratios lead to Euler's definition of *e*.

The Second Degree (Squared) Triangle, derived by Chou from biological input-output patterns and transitions, raised the question of further studies to identify underlying properties through this ratio's relationships.

The method for expanding the powers of a binomial expression $(a + b)^n$ is

$$(a+b)^n = \sum_{k=0}^{n} \binom{n}{k} a^{n-k} b^k.$$

Statement of the binomial theorem.

Blaise Pascal in 1665 reported a formal recursive definition that forms one of the foundations of modern mathematical and algorithmic study.

$$\binom{n}{k} = \binom{n-1}{k-1} + \binom{n-1}{k}$$

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Pascal's recursive definition of the choose function.

By multiplying across each row of Pascal's Triangle, it was formed so that the binomial coefficient formula would define the row products s_n:

$$s_n = \prod_{k=0}^{n} \binom{n}{k} = \prod_{k=0}^{n} \frac{n!}{k!(n-k)!}, \; n \geq 0.$$

For two ratios,

$$\frac{s_n}{s_{n-1}} = \frac{n!^{(n+1)} \prod_{k=0}^{n} k!^{-2}}{(n-1)!^n \prod_{k=0}^{n-1} k!^{-2}} = \frac{n^n}{n!},$$

and

$$\frac{s_{n+1}}{s_n} = \frac{(n+1)!^{(n+2)} \prod_{k=0}^{n+1} k!^{-2}}{n!^{(n+1)} \prod_{k=0}^{n} k!^{-2}} = \frac{(n+1)^n}{n!}.$$

If we divide the two equations, the factor "n!" cancels out, and we arrive at

$$\frac{(s_{n+1})(s_{n-1})}{(s_n)^2} = \left(\frac{n+1}{n}\right)^n.$$

On the right, there is the limit definition of *e* of Euler:

$$e = \lim_{x \to \infty} \left(1 + \frac{1}{n}\right)^n.$$

= 2.71828182845904523…

The linear first-degree classical Pascal's triangle leads to the entity "*e*". Interestingly, Chou's Squared Triangle (2^o-degree) for *duplex pattern transitions* leads to the entity "π".

The questions to be solved are: Would the triple system (such as amino acids *triplet codes* for t-RNA) yield a 3rd degree combinatorial? And would the *quadruplet system* (such as ATCG codes for DNA), yield a 4th degree combinatorial? Or would yield other known or unknown identities and relationships.

9. Examples of MAL Biochemical System Pattern Analysis in a Real World Case

9.1. Theoretical Enzyme Sequential Pattern Analysis, Reaction Mechanism, and the Reaction Rate Equation

The references used during the mid-1960s for the above theoretical development are given in my Ph.D. thesis at Yale University, 1970 [1]. The theoretical contents are presented in [2], and part of the thesis is reproduced in [1, appendix VI].

9.2. Example of Theoretical Analysis on L-Asparagine Synthetase

The enzyme "L-Asparagine Synthetase" [1] has three substrates (L-glutaric acid, ATP, and L-asparagine) and four products (L-glutamine, L-aspartic acid, Pyrophosphate, and AMP), so there are three inputs and four outputs at steady-state. The ambitious goal was to determine the enzyme reaction mechanism through enzyme kinetic experiments. Following initial velocity, production inhibition, dead-end inhibition, and alternate substrate studies, the complete reaction mechanism of

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L-glutamine synthetase, including the reaction sequence, pattern, intermediate stable enzyme forms, and the full reaction scheme, was elucidated, and the rate equation with 14 kinetic constants was derived [1].

Table 11 presents the main experimental findings that led to the conclusions regarding the mechanistic reaction sequence and pattern scheme.

Table 11. Experimental observations, theoretical analysis, and elucidation of the sequential pattern and mechanism of an enzyme reaction [1].

A Summary of Kinetic Studies on L-Asparagine Synthetase Isolated from 6C3HED-RG1 Tumor

Kinetic studies	Parameters	Pattern in double reciprocal	Figure
Initial velocity studies	Asp vs Gln	parallel	13
	Gln vs ATP	parallel	15
	Asp vs ATP	parallel	14
Product inhibition studies	Asp vs pp	competitive	18
	Asp vs AMP	noncompetitive	18
	Asp vs Asn	uncompetitive	18
	Gln vs Asn	competitive	16
	Gln vs AMP	uncompetitive	17
	Gln vs PP	uncompetitive	17
Deadend inhibition studies	Asp vs DONV	uncompetitive	21
	Asp vs CONV	noncompeitive	21
	Gln vs DONV	competitive	22
	Gln vs CONV	noncompetitive	22
Alternate substrate studies	NH_4Cl vs ATP	Intersecting	19
	NH_4Cl vs Asn	competitive	20
	NH_4Cl vs PP	noncompetitive	20

9.3. Mechanistic Conclusion from Enzyme Kinetics Studies

The following is the action-reaction MAL kinetics/dynamics deduced reaction scheme, including the intermediate stable enzyme forms (n ping-pong), in the bracket:

The enzyme kinetic data and conclusions from Table 10 for L-asparagine synthetase allow determining the overall reaction sequence and reaction mechanism as follows: S=3, P=4, n=3 (the sum of stable intermediate enzyme forms), which corresponds to the output-followed-by-input (ping-pong) transitions. The ping-pong notation was introduced by Cleland [61,62]. The concluded mechanism was decided from 10 possible sequence patterns. The mechanistic conclusion is shown below:

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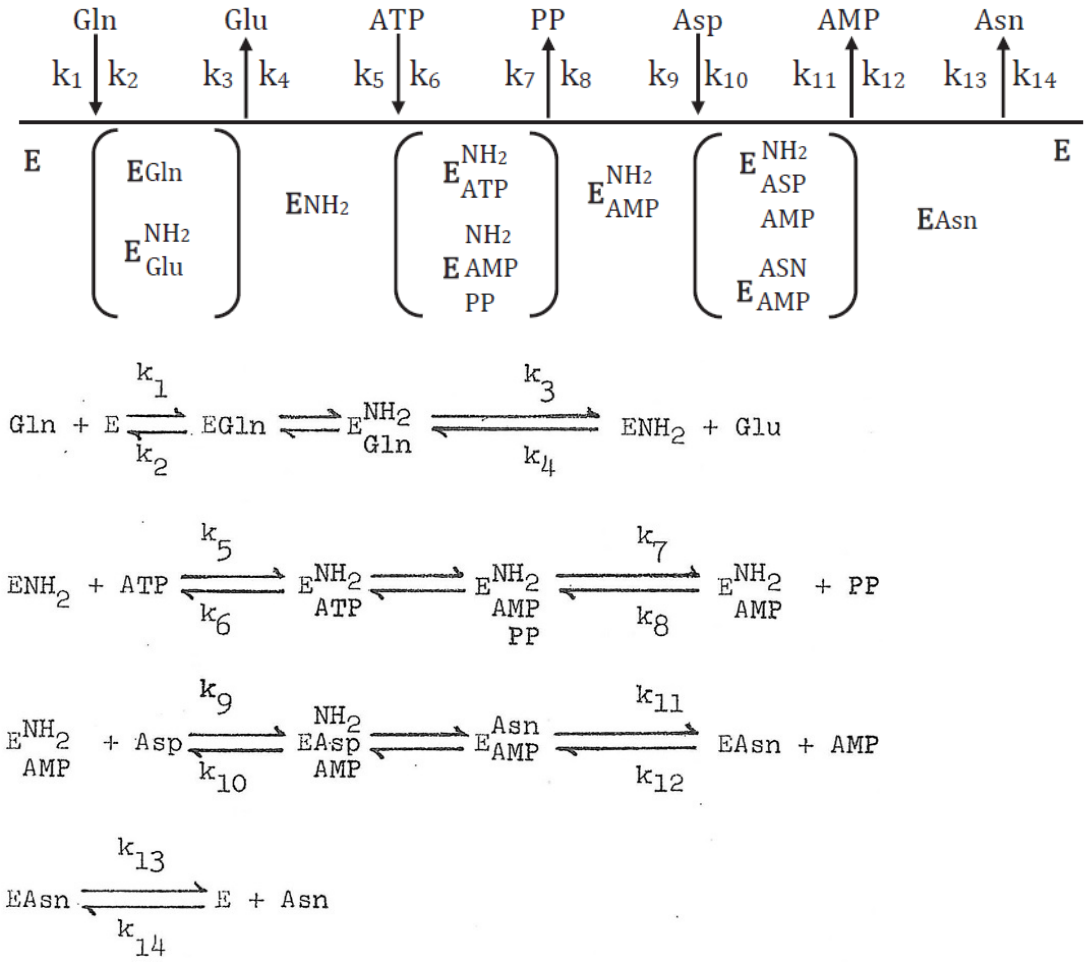

The L-asparagine biosynthesis involves functional receptor-affinity binding sites that exhibit multiple transition intermediate forms. The above L-asparagine synthetase reaction involves multiple stable complexes and transient intermediate enzyme forms, as shown in [1, at IV-21].

The following equations (g) to (i) are from Chou's Ph. D. thesis [1]. If in each case all of the linear (sequential) patterns have the same probability of existence for a given number of substrates (S) and products (P), the probability, Pro, of having a given number of stable enzyme forms (n) is

$$\mathrm{Pro} = \binom{S-1}{n-1}\binom{P-1}{n-1}\Big/\binom{S-P-2}{S-1}, \qquad \textbf{(g)}$$

where S, P ≥ n ≥ 1, and Σ Pro = 1.

If in each case all of the (circular) mechanism patterns have the same probability of existence for a given number of substrates (S) and products (P), the probability, Pro', of having a given number of stable enzyme forms (n) is

$$\mathrm{Pro}' = \frac{1}{n}\sum_{d}\phi(d)\binom{(S/d)-1}{(n/d)-1}\binom{(P/d)-1}{(n/d)-1}\Big/\frac{1}{S+P}\sum_{I_1}\phi(d_1)\,\frac{[(S+P)/d_1]!}{(S/d_1)!(P/d_1)!}$$

(h)

where S, P > n ≥ 1; the numerator and the denominator of equation (h), therefore equation (i) for 1 as the sum of the probability of all is

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$$\sum \text{Pro}' = 1. \qquad \textbf{(i)}$$

This approach is proposed to measure the randomness of dual-signal transitions, such as {S, P}, (+, -), and (1, 0), in linear or circular sequential or closed forms, whether from known or unknown sources.

The above combinatory pattern analysis grew from the MAL to a dynamic principle in enzymology, pharmacology, basic medical sciences, and theoretical build-up to the n-size. Using mathematical manipulation and mathematical induction and deduction, which lead to the unified general MAL-MEE/MEP/DOM/MTDPT, to CIE/DRIT/Isobologram/Polygonogram, and finally to UTO/LCU.

The MAL-Median principle-derived theoretical algorithms have been repeatedly applied and time-tested for efficient, cost-effective digital scientific R&D in this electronic and AI era.

9.4. Why Life Dynamics Is Mathematically Interesting

The distinction may be summarized schematically:

Structure	Mathematical Constant	Domain
Pascal Triangle	e	physical/non-life processes
Squared Triangle	$\pi^2/6$	biological/life processes

or symbolically:

e ⟶ expansion

versus $\zeta(2) = \pi^2/6$ ⟶ interaction organization

This is not merely numerology; it attempts to identify mathematical invariants that govern different layers of reality.

9.5. An Open Proposition

Protein enzyme's substrate "in-puts" and product "out-puts" duplex pattern and combinatorial system analysis has yielded the Duplex second-degree (two-dimensional) Pascal Triangle, where all elements are squared [6]. Further challenges for input and output models are: Can there be a Triplex (Cubic) Pascal Triangle for the three amino acid codes for tRNA, and a Quadruplet Pascal Triangle for the ATCG nucleotide codes for DNA? Or other new revelations?

These types of studies can expand applications, including mathematical indications such as Riemann's Hypothesis and cross-disciplinary linkages.

There have been many public discussions in various domains about the original Pascal Triangles over the past centuries. Explorations of the higher-degree Pascal triangles are interesting in terms of their implications, informatics, and applications.

10. MAL-MEE: A Groundbreaking Conceptual New Avenue

There has been tremendous progress in the various fields of science, especially since the 1900s. Now is the era of digital sciences and AI, and it needs a new conceptual framework for efficient, general algorithms to meet the enormous challenges ahead of us.

Historically, serious misjudgments have taught us valuable lessons. The story of Hippias, sentenced to death due to the irrationality of the square root of 2 among the Pythagoreans. Nicolaus Copernicus and Galileo Galilei also showed the dark side of the then-contemporary ideology. A great physics Max Plank said " *A New Scientific Truth Does Not Triumph by Convincing Its Opponents and Making Them See the Light, But Rather Because Its Opponents Eventually Die, and a New Generation Grow Up That Is Familiar with It.*", and a great philosopher Thomas Kuhn said, "*Normal Science Often Suppresses Fundamental Novelties Because They Are Necessarily Subversive of Its Basic Commitments*" in his book, "The Structure of Scientific Revolution" which introduced the phrase "Paradigm Shift", in 1962.

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In R&D, the academic community, peer reviewers, and regulatory authorities, especially decision-makers in biomedical sciences, are willing to hear praise and admiration (which is a human nature) but reluctant to consider non-traditional conceptual innovation ideologies for alternative reform [11–21,24]. The three major articles on MAL theory and applications [8–10], with one or two authors and without peer review (other than grammatical corrections or format revisions), had garnered a total of 21,207 citations [56], each cited in over 1,300 scientific journals [57]. Chou's MAL theoretical work and applications have a total of 1,623 citing patents, indicating a significant impact on new drug discovery and R&D innovation. The observation-statistical scientific R&D approach has a long history; however, a new conceptual way of thinking is on the deck for efficiency, cost-effectiveness, and digital science Econo-green reasons. The old, traditional, bottom-up statistical approach may not be the only right way for R&D; there are quantitative, unified, general, theory-based, deterministic alternatives. The MAL median principle has been proven to be simple to use, with efficient, cost-effective, and quantitative features amenable to automated computer simulation, which align with the major historical mathematical and physical conclusions described in this paper.

The MAL-MEE-CIE unified theory for top-down, quantitative, digital science R&D seems to be the opposite of the traditional, observation- and statistic-based bottom-up R&D. They are not mutually exclusive; in fact, they are complementary and alternative to one another, like two sides of the same coin. The main point is that top-down R&D provides guidance for experimental design, streamlines computerized data analysis, and enables simulation with simple, efficient, and cost-effective features. With MAL medium, principle-based, law-based fundamental parameters (m and Dm) and indexes (CI, DRI) as guidelines, we can then use a bottom-up, traditional approach to achieve specific, detailed, mechanistic scientific research for application goals. Evolving digital data science is algorithm- and efficiency-oriented. The MAL approach warrants serious consideration as an alternative for scientific innovation and discovery in research and development. This unified general MAL-MEE R&D concept is for all intra-, inter-, and cross-disciplinary dose-effect and causal-effect dynamics and informatics, saving time, effort, and resources.

Appendices:

Appendix I. Abbreviations & Definitions

Appendix II. Theory Illustrations

Appendix III. Examples of Categorized Applications

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