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Chemical Organization Theory: A Structural Framework for Analyzing Reaction Networks

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Abstract

Chemical Organization Theory (COT) provides a structural and algebraic framework for analyzing reaction-based systems independently of kinetic assumptions. By identifying closed and self-maintaining sets of species, called organizations, the theory characterizes all structurally admissible persistent configurations of a reaction network. This review synthesizes the mathematical foundations of COT, including closure operators, stoichiometric feasibility, and lattice structures, together with their algorithmic and dynamical interpretations. We examine how organizational structure constrains long-term behavior in reaction-based dynamical systems, including ordinary differential equations, stochastic processes, and spatial reaction–diffusion models. Computational

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methods for enumerating organizations and distributed organizations are reviewed, alongside extensions to discrete and stochastic settings. Applications spanning atmospheric chemistry, virus dynamics, gene regulation, cell cycle models, and data-driven reaction systems illustrate the breadth and versatility of the framework. Relations to chemical reaction network theory, autocatalytic set theory, and constraint-based approaches are clarified to position COT within the broader landscape of mathematical reaction network analysis. We conclude by highlighting open problems related to transient dynamics, structural transitions, computational scalability, and evolutionary processes, and by emphasizing COT as a unifying structural abstraction for persistence and qualitative behavior in complex reaction systems.

1 Introduction

Reaction–based systems provide a unifying modeling paradigm for a wide range of phenomena in chemistry, biology, ecology, and beyond. They are commonly represented as networks of interacting species whose dynamics are governed by reaction rules and stoichiometric constraints. Depending on the modeling assumptions, such systems may be described by ordinary differential equations (ODEs), stochastic processes, or spatially extended reaction–diffusion partial differential equations (PDEs). Despite their diversity, these models share a common structural core given by the underlying reaction network.

A central challenge in the analysis of reaction–based systems is to understand their qualitative long–term behavior independently of specific kinetic parameters. In many applications, precise rate constants are unknown, poorly constrained, or subject to substantial uncertainty. This has motivated the development of structural analysis frameworks that focus on network properties rather than detailed dynamics.

Chemical Organization Theory (COT) was introduced to address this challenge by providing a purely structural characterization of persistent species configurations in reaction networks. Originally developed by Dittrich and Speroni di Fenizio [1], COT identifies subsets of species, called *organizations*, that are both closed under the reaction rules and self–maintaining with respect to stoichiometry. These sets represent all structurally admissible candidates for long–term persistence, independent of kinetic assumptions.

Over the past two decades, different strands of research have expanded COT from its algebraic foundations to stochastic, spatial, and algorithmic perspectives, as well as to applications in chemistry, systems biology, and unconventional computing. However, these developments are distributed across distinct communities, and no unified synthesis currently exists that integrates the mathematical, dynamical, and computational aspects of COT. This review addresses this gap by consolidating these perspectives and by highlighting COT as a structural abstraction for reasoning about long-term behavior in reaction-based systems.

In particular, since its introduction, Chemical Organization Theory has developed into a mathematically rich framework with connections to lattice theory, convex geometry, and dynamical systems. Organizations form partially ordered structures that reflect the hierarchy of persistent subsystems within a reaction network. Under suitable consistency assumptions, these structures give rise to complete lattices, enabling systematic comparison and classification of reaction systems.

Beyond its static formulation, COT has been linked to the long–term behavior of dynamical systems. For reaction–based ordinary differential equations, organizations have been shown to constrain the possible limit sets and attractors of the system, establishing a rigorous connection between structural admissibility and dynamical persistence. Subsequent extensions have generalized these results to stochastic and spatially distributed models, demonstrating that organizational structures remain meaningful across different modeling paradigms.

The algorithmic computability of organizations has played a crucial role in the practical applicability of COT. Various computational approaches have been developed, including constraint–based methods and linear programming formulations, enabling the analysis of large reaction networks. These methods have facilitated applications ranging from atmospheric chemistry to systems biology and comparative model analysis.

Chemical Organization Theory has also inspired methodological extensions that go beyond analysis. In particular, it has been proposed as a foundation for chemical programming and unconventional computing, where computation is interpreted as controlled transitions between organizations. Furthermore, recent work has connected COT to formal verification and probabilistic model checking, opening new perspectives on correctness and reliability of reaction–based models.

The scope of COT applications has expanded significantly over the years. It has been applied to biological systems such as virus infection models, gene regulatory networks, and cell cycle dynamics, as well as to atmospheric and geochemical reaction networks. More recently, data–driven and large–scale model collections have been analyzed using organizational principles, highlighting the scalability and robustness of the approach.

This review provides a comprehensive and coherent overview of Chemical Organization Theory, focusing on its mathematical foundations, algorithmic aspects, dynamical interpretations, and applications. Rather than presenting isolated results, we emphasize the unifying structural ideas that connect these developments. Relations to other established frameworks, including chemical reaction network theory, autocatalytic set theory, and constraint–based approaches, are discussed to clarify the distinctive role of COT.

Scope and Perspective. The perspective taken in this review is structural rather than kinetic. We focus on closure, self-maintenance, organizational lattices, and their dynamical interpretations across deterministic, stochastic, and spatially distributed models. Implementation details, rate laws, and domain-specific kinetic analyses are not treated in depth, as COT is deliberately formulated independently of such assumptions. Instead, our aim is to clarify COT as a unifying abstraction layer for analyzing persistence and qualitative behavior in reaction-based systems. To this end, we synthesize developments that originate from mathematical foundations, algorithmic computation, and applications in chemistry, systems biology, and unconventional computing. Accordingly, the structure of this review reflects these complementary perspectives.

The review is organized as follows. Section 2 introduces the basic concepts and mathematical foundations of Chemical Organization Theory.

Section 3 examines connections to dynamical systems and persistence results. Section 4 reviews algorithmic methods for computing organizations, followed by formal verification approaches in Section 5 and stochastic and spatial generalizations in Section 6. Applications across different domains are presented in Section 7. Section 8 discusses chemical programming and computing. In Section 9, we relate COT to other theoretical frameworks. Finally, Section 10 discusses open problems and Section 11 provides concluding remarks.

2 Mathematical foundations of chemical organization theory

Chemical Organization Theory rests on a small number of algebraic and stoichiometric concepts that characterize structurally admissible species sets in reaction networks. The goal of this section is to introduce these concepts in a mathematically precise form, thereby providing the foundation for the dynamical, algorithmic, and application-oriented developments discussed in later sections. In particular, we formalize the notions of reaction systems, closure, self–maintenance, and organizations, which collectively define the structural core of COT independently of kinetic assumptions.

Chemical Organization Theory (COT) provides a structural and mathematical framework for the analysis of reaction networks whose qualitative composition may change over time. The theory was introduced to overcome a fundamental limitation of classical dynamical systems theory, which typically assumes a fixed set of components and therefore cannot adequately represent systems that produce or eliminate components during their evolution. This situation is characteristic of biochemical, ecological, and other constructive dynamical systems [1,2].

2.1 Reaction systems and algebraic chemistry

The starting point of Chemical Organization Theory is a *reaction system*, defined independently of any specific kinetic laws. A reaction system is given by a finite or countable set of molecular species M and a set of reaction rules R, where each reaction is represented as a transformation between multisets of species. Formally, this structure is called an *algebraic chemistry* $\langle M, R\rangle$, where reactions are relations $R \subseteq \mathcal{P}_M(M) \times \mathcal{P}_M(M)$, with $\mathcal{P}_M(M)$ denoting the set of all multisets over M [1].

This abstraction deliberately neglects kinetic details and focuses exclusively on the stoichiometric structure of the network. Input and output processes, such as inflow, degradation, or dilution, are incorporated by reactions of the form $\emptyset \to a$ or $a \to \emptyset$, allowing the framework to represent open systems.

2.2 Closure and closed sets

A central structural notion in COT is that of *closure*. A set of species $C \subseteq M$ is called closed if no reaction whose reactants are entirely contained in C produces a species outside of C.

For any subset $S \subseteq M$, the *closure* $G_{\mathrm{CL}}(S)$ is defined formally as:

$$G_{\mathrm{CL}}(S) = \bigcap \{C \subseteq M \mid S \subseteq C \text{ and } C \text{ is closed}\} \tag{1}$$

This is the smallest closed set containing S. Equivalently, $G_{\mathrm{CL}}(S)$ can be constructed iteratively by starting with S and repeatedly adding all products of reactions whose reactants are contained in the growing set, until no new species are added [1].

The family of closed sets forms a lattice under suitably defined union and intersection operations, reflecting the hierarchical organization of reachable species combinations. Closure captures the idea of structural completeness: once a closed set is reached, no qualitatively new species can emerge solely from internal reactions.

2.3 Self-maintenance and stoichiometric feasibility

Closure alone does not guarantee persistence. Chemical Organization Theory therefore introduces the notion of *self-maintenance*, which formalizes whether a set of species can sustain itself against internal consumption and external losses.

A set of species $C \subseteq M$ is called *self-maintaining* if there exists a non-negative reaction flux vector v such that all reactions active within C occur with positive flux and the resulting net production rates of all species in C are non-negative. This condition is expressed in terms of the stoichiometric matrix S by

$$(S \cdot v)_i \geq 0 \tag{2}$$

for all indices i belonging to species in C. It corresponds to a feasibility problem in linear algebra [1].

Self-maintenance generalizes earlier concepts of autocatalytic sets [3,4], but does not require that every species be produced catalytically. Instead, it allows compensation between reactions at the level of net fluxes, making the concept applicable to a broader class of systems.

2.4 Organizations and consistent reaction systems

An *organization* is defined as a set of species that is both closed and self-maintaining. Organizations represent structurally stable configurations that can persist over long time scales in a reaction vessel. Sets that fail to satisfy either property necessarily undergo qualitative change through species appearance or extinction [1].

A particularly important class of reaction systems are *consistent reaction systems*, for which the operations of closure and self-maintenance interact in a well-behaved manner. In such systems, every set of species generates a unique largest organization, and the set of all organizations forms a lattice under induced union and intersection operations. This lattice structure provides a global, order-theoretic view of the system's organizational landscape.

2.5 Example: HIV infection dynamics model (Wodarz–Nowak)

As an illustrative example for deriving a reaction network from an ODE model and preparing the ground for organization-based structural analysis, we consider the HIV–immune system dynamics model by Wodarz and Nowak. The model has been discussed in the context of Chemical Organization Theory in [1] (see also [5]).

ODE model The system comprises four species

$$\mathcal{S} = \{x, y, w, z\},$$

representing uninfected target cells x, infected cells y, CTL precursors w, and CTL effectors z. The dynamics is given by the ODE system [1,6]:

$$\dot{x} = \lambda - dx - \beta xy, \tag{3}$$

$$\dot{y} = \beta xy - ay - pyz, \tag{4}$$

$$\dot{w} = cxyw - cqyw - bw, \tag{5}$$

$$\dot{z} = cqyw - hz. \tag{6}$$

Here, λ denotes the inflow of healthy target cells; d, a, h are decay rates; β models infection; p models CTL-mediated killing of infected cells; and the terms involving c, q, b describe proliferation and differentiation processes within the immune response component [1,5].

Reaction rules and reaction network Following the standard interpretation used in Chemical Organization Theory, each term of the ODE system is represented by a reaction rule (typically under mass-action semantics), yielding a reaction network $(\mathcal{S}, \mathcal{R})$ [1]. Since each species has a decay term, we include outflow reactions $x \to \emptyset$, $y \to \emptyset$, $w \to \emptyset$, and $z \to \emptyset$. Moreover, λ implies an inflow reaction $\emptyset \to x$. The interaction terms correspond to the following reaction rules: infection βxy becomes $x + y \to 2y$; CTL killing pyz becomes $y + z \to z$ (catalytic in z); precursor proliferation $cxyw$ becomes $x + y + w \to x + y + 2w$; and differentiation $cqyw$ becomes $y + w \to y + z$. Altogether, the derived reaction set is [1,5]:

$$\begin{aligned} \mathcal{R} = \{\ &\emptyset \to x,\ x \to \emptyset,\ y \to \emptyset,\ w \to \emptyset,\ z \to \emptyset,\ x + y \to 2y,\ y + z \to z, \\ &\qquad x + y + w \to x + y + 2w, y + w \to y + z\ \}. \end{aligned}$$

This reaction network is the structural object on which closure and self-maintenance are defined in COT and serves as the input for computing organizations and their hierarchical relations [1].

Organizational scaffold (Hasse diagram). For the reaction network derived from the HIV immune-response model, the set of organizations forms a small chain. Concretely, one obtains exactly three organizations, $\{x\} \subset \{x, y\} \subset \{x, y, w, z\}$, where the smallest organization $\{x\}$ corresponds to the virus-free regime (only uninfected CD4$^+$ T cells present). The intermediate organization $\{x, y\}$ represents an infection state in which CTL precursors/effectors are absent, corresponding to immune-system failure, while the largest organization $\{x, y, w, z\}$ represents the regime in which virus is present but controlled by an active immune response [1].

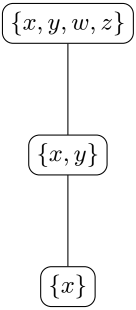

Figure 1. Hasse diagram of the organizations for the HIV immune-response model (Wodarz–Nowak), after transforming the ODE system into a reaction network. The three organizations form a chain $\{x\} \subset \{x, y\} \subset \{x, y, w, z\}$.

2.6 Relation to dynamics

Although Chemical Organization Theory is defined independently of kinetics, it establishes a fundamental connection to dynamical systems. For a wide class of ordinary differential equation models consistent with the reaction network, every stationary state corresponds to an organization, and the qualitative evolution of the system can be interpreted as a movement between organizations [1].

This separation between structural analysis and dynamics allows COT to serve as a unifying framework for studying persistence, functional modules, and qualitative transitions in complex reaction networks, independent of specific rate laws. This is described and exemplified in Section 3.

The mathematical concepts introduced above characterize organizations as structurally admissible species sets, defined independently of any kinetic assumptions. While this perspective is purely structural, it naturally raises the question of how organizational structure relates to the dynamical behavior of reaction-based systems. In particular, one may ask whether organizations correspond to long-term dynamical regimes, such as attractors, invariant sets, or persistent subsystems. We address these questions in the next section.

3 Dynamical systems and persistence results

Chemical Organization Theory (COT) was originally conceived as a structural framework independent of kinetic assumptions. Nevertheless, a central motivation of the theory has always been its relation to the long–term behavior of reaction–based dynamical systems. Over the past two decades, this relation has been clarified for increasingly general classes of dynamical systems, ranging from ordinary differential equations to spatially distributed models.

3.1 Organizations and long–term behavior of ODE systems

The first rigorous link between organizations and dynamical behavior was established for reaction–based ordinary differential equation (ODE) systems. In this setting, concentrations evolve continuously in time while the underlying reaction network determines which reactions may occur.

A foundational result was obtained by Peter and Dittrich [7], who introduced the concept of a *limit set abstraction.* Instead of focusing on attractors, which may be difficult to characterize and may not be unique, the limit set abstraction captures the sets of species that occur with strictly positive concentration in the asymptotic regime. It was shown that all elements of the limit set abstraction are closed and that every bounded limit set contains at least one self–maintaining subset, hence an organization.

As a consequence, any attractor of a reaction–based ODE system that does not intersect the boundary of the concentration space is necessarily contained within a single organization. This result provides a mathematically robust justification for the role of organizations as structural descriptors of persistent behavior, independent of specific kinetic parameters or rate laws.

Simulation–induced structural transitions. We now consider a simulation example adapted from the transition analysis of the HIV infection model by Wodarz and Nowak. The example illustrates how transient perturbations can induce structural transitions that temporarily leave the space of organizations, while the long–term dynamics return to a stable organizational configuration.

The system is initialized in the organization $\{x, y\}$, corresponding to an established infection without active immune response. At a prescribed time point, the immune precursor species w is externally induced. This perturbation drives the system into the species set $\{x, y, w\}$, which does not constitute an organization, as it is not self–maintaining.

As a consequence of the reaction structure, the presence of w induces the production of immune effector species z, and the system automatically enters the structurally admissible organization $\{x, y, w, z\}$. This transition is not externally enforced but emerges from the intrinsic network dynamics. Subsequently, immune–related species w and z are not dynamically persistent for the chosen parameter regime and decay over time.

The numerical simulation shown in Figure 2 demonstrates that the system eventually returns to the organization $\{x, y\}$. A schematic structural interpretation of this trajectory in terms of organizational transitions is provided in Figure 3. From the perspective of Chemical Organization Theory, the trajectory thus forms a closed transition loop: starting from an organization, leaving the organizational lattice via a non–organizational state, entering a larger organization, and finally converging back to the

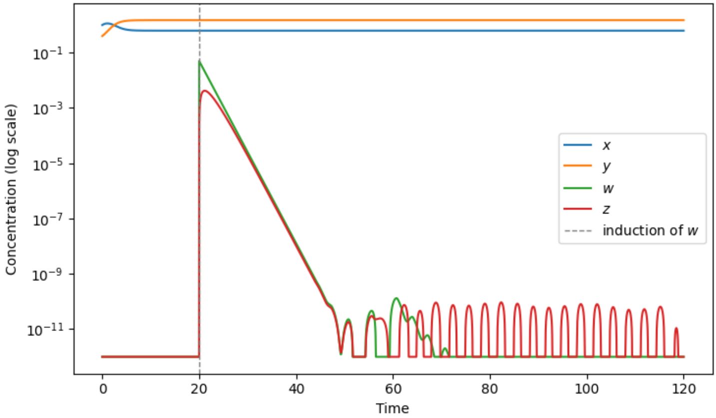

Figure 2. Numerical simulation of the HIV infection model by Wodarz and Nowak illustrating simulation–induced structural transitions. The system is initialized in the organization $\{x, y\}$. At time $t = 20$ (vertical dashed line), the immune precursor species w is externally induced, driving the system into the non–organizational species set $\{x, y, w\}$. As a consequence of the reaction structure, immune effector species z are activated and the system enters the structurally admissible organization $\{x, y, w, z\}$. For the chosen parameter regime, immune–related species w and z are not dynamically persistent and decay over time, leading the system to converge back to the organization $\{x, y\}$. All concentrations are shown on a logarithmic scale.

original organization. The example highlights that organizations characterize structural admissibility, while transient dynamics may traverse non–organizational states and larger organizations before asymptotic stabilization.

3.2 Structural notions of persistence

Classical notions of persistence in dynamical systems vary widely across disciplines and model classes, including permanence, uniform persistence, and coexistence. These concepts are typically defined with respect to particular solutions or classes of trajectories and often depend on detailed properties of the vector field.

A complementary, purely structural notion of persistence was intro-

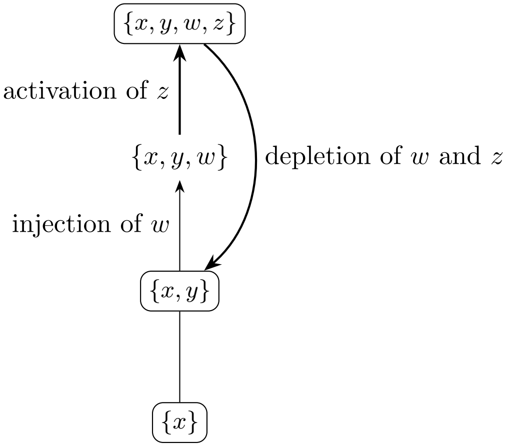

Figure 3. Structural interpretation of the simulated HIV infection dynamics. The system starts in the organization $\{x, y\}$. External induction of w drives the system into the non–organizational set $\{x, y, w\}$, from which the reaction structure enforces a transition to the organization $\{x, y, w, z\}$. For the chosen parameter regime, immune–related species w and z are not dynamically persistent and decay over time, leading the system to converge back to the organization $\{x, y\}$. All concentrations are shown on a logarithmic scale.

duced in [8, 9]. There, persistence is defined at the level of subsets of species rather than individual trajectories. A species set is called potentially persistent if there exists at least one solution of the underlying reaction–based dynamical system for which all species in the set remain present in the long term.

The main result establishes that all potentially persistent species sets form a lattice and can be characterized solely from the reaction network. To capture spatial or compartmental effects, the notion of *distributed organizations* was introduced as a generalization of classical organizations. For a broad class of reaction–based dynamical systems, including reaction–diffusion systems, every persistent species set is shown to be a distributed organization, and conversely, every distributed organization is structurally admissible as a persistent configuration.

3.3 Distributed organizations and persistence in reaction–diffusion systems

Many systems of interest exhibit spatial structure and are more adequately described by partial differential equations. In particular, reaction–diffusion systems (RDS) arise naturally in chemical, biological, and ecological modeling. Chemical Organization Theory was originally developed for well–mixed reaction systems described by ordinary differential equations. In this setting, organizations capture structurally admissible sets of species that are closed under the reaction network and self–maintaining. When spatial effects such as diffusion, advection or boundary conditions are taken into account, this classical notion is no longer sufficient, as species concentrations may vary across space and local reaction activity can differ significantly between regions.

To address this limitation, the concept of distributed organizations was introduced as a spatial generalization of classical organizations [10]. Rather than being defined by a single global species set, a distributed organization characterizes structurally admissible configurations that may be spatially heterogeneous, while remaining consistent with the underlying reaction network. This extension preserves the core intuition of Chemical Organization Theory but allows for spatially resolved reaction–diffusion systems with inhomogeneous boundary conditions and transport processes.

The introduction of distributed organizations is accompanied by a compatible refinement of persistence concepts [10]. Classical notions of persistence typically distinguish between weak, uniform, or strong persistence, often formulated independently of the reaction network structure. In contrast, the extended framework establishes a direct link between structural admissibility and dynamical persistence. In particular, the persistence concept is refined such that it applies to spatially extended systems and admits spatially varying concentration profiles, while remaining compatible with the organizational framework.

A central result of this generalized theory is that every persistent set of species arising along a solution of a reaction–diffusion system forms a distributed organization [10]. This statement unifies structural and dynamical perspectives by showing that long–term persistence in spatially extended systems is necessarily constrained by the organizational structure of the underlying reaction network. As a consequence, distributed organizations provide a natural structural counterpart to persistence in reaction–diffusion systems, extending the classical correspondence between organizations and persistence beyond well–mixed dynamics.

This result demonstrates that Chemical Organization Theory can be consistently extended to spatially distributed systems without losing its foundational structural character. It further establishes distributed organizations as a key conceptual tool for analyzing long–term behavior in reaction–diffusion models, bridging the gap between structural network properties and emergent spatial dynamics.

In the example model of HIV infection dynamics by Wodarz and Nowak discussed above, the generalization from classical organizations to distributed organizations does not give rise to any additional species subsets. However, examples of distributed organizations can be found in many other models [10–12]. This indicates that not all operational modes provided by the reaction network in these cases can be dynamically realized by well–mixed systems, but instead require more complex settings, such as systems with an explicit spatial dimension.

4 Algorithmic aspects of chemical organization theory

While Chemical Organization Theory (COT) is formulated independently of kinetic laws, its practical applicability depends crucially on the availability of algorithms that compute organizations and related structures from a given reaction network. Since the number of possible species subsets grows exponentially with network size, naïve enumeration is infeasible even for moderately sized systems. Algorithmic developments therefore play a central role in establishing COT as an operational analysis framework.

4.1 Computing organizations in reaction networks

The first systematic algorithmic treatment of COT was presented by Centler et al. [13], who introduced several methods to compute the hierarchy of chemical organizations of a reaction network. Their work translates the abstract definitions of closure and self-maintenance into concrete computational procedures.

A reaction network with species set M and reactions R induces a stoichiometric matrix $S \in \mathbb{R}^{|M|\times|R|}$. The key algorithmic challenge consists in identifying all subsets $O \subseteq M$ that are closed and self-maintaining. Centler et al. showed that testing self-maintenance can be formulated as a linear programming feasibility problem: for a candidate set O, one must determine whether there exists a non-negative flux vector v such that $Sv \geq 0$, subject to the constraint that only reactions supported by O are active [13].

4.2 Constructive and flux-based algorithms

Two complementary exhaustive algorithms were introduced. The *constructive approach* builds the hierarchy of organizations bottom-up. It first enumerates all semi-organizations, i.e. closed and semi-self-maintaining sets, and subsequently filters those that satisfy the full self-maintenance condition by solving a linear program for each candidate. This approach operates primarily on species sets and exploits the lattice structure induced by closure [13].

In contrast, the *flux-based approach* starts from the space of feasible self-maintaining fluxes. By computing extreme rays of the associated convex cone, the algorithm derives elementary organizations and combines them to obtain all reactive organizations. This method shifts the computational focus from species subsets to reaction subsets and is closely related to techniques from metabolic pathway analysis, such as the computation of elementary modes [14].

Neither approach dominates the other in terms of runtime performance. As demonstrated by extensive benchmarks, the efficiency depends sensitively on network structure, such as the presence of cycles or the number of extreme rays of the flux cone [13]. To address large-scale networks, a heuristic variant was proposed that samples candidate organizations via random walks and subsequently reconstructs the organization hierarchy from this reduced set.

4.3 From organizations to distributed organizations

More recent algorithmic developments extend classical COT to spatially or temporally distributed systems. Peter et al. [15] introduced algorithms for computing *distributed organizations* (DOs), which generalize organizations by allowing self-maintenance through compartmentalization.

A central conceptual shift in this work is the transition from species-based structures to reaction-based ones. The authors introduce elementary reaction closures (ERCs) as minimal reaction sets that are activated together, and sets of organizational reactions (SORs) as reaction-level counterparts of organizations. It is shown that the set of all SORs of a reaction network forms a lattice, analogous to the lattice of organizations [15].

4.4 Optimization-based algorithms and complexity

The computation of SORs and DOs is formulated as a mixed-integer linear programming (MILP) problem. Binary decision variables encode whether a reaction is active, while continuous variables represent reaction fluxes. The objective typically maximizes the number of active reactions, subject to stoichiometric self-maintenance and closure constraints derived from ERCs [15].

This formulation allows the systematic computation of all SORs by iteratively adding integer cuts that exclude previously found solutions. Although MILP problems are NP-hard in general, the approach benefits from the strong structural constraints imposed by reaction closures and self-maintenance. Empirical evaluations on models from the BioModels database demonstrate that the method is applicable to a wide range of biologically relevant systems [15].

4.5 Algorithmic perspective

Taken together, these algorithmic contributions establish Chemical Organization Theory as a computationally tractable framework. They show that organizations, distributed organizations, and their associated lattices can be computed without specifying kinetic parameters. This separation of structural analysis from dynamics is one of the distinctive features of COT and provides the foundation for its application to large and heterogeneous reaction networks.

5 Formal verification and model checking

Chemical Organization Theory has also been connected to formal verification techniques, in particular probabilistic model checking. This line of work aims at combining the structural decomposition provided by organizations with quantitative guarantees on system behavior.

Kaleta et al. [16] proposed an approach in which organizations are used to guide the formal analysis of reaction networks. Reaction systems are interpreted as state–transition systems, and organizational properties are exploited to reduce the complexity of the verification task. In particular, organizations serve as abstractions of stable or persistent regions of the state space, allowing the detection of inconsistencies and unreachable behaviors.

A complementary perspective was developed by Mu et al. [17], who combined Chemical Organization Theory with probabilistic model checking of continuous–time Markov chains. There, organizations are identified automatically and used to define a coarse–grained model in which transitions between organizations are analyzed using temporal logic. Quantitative properties such as transition probabilities or expected residence times can be verified without enumerating the full state space of the underlying stochastic system.

These approaches demonstrate that COT can be integrated into formal verification pipelines, providing a principled way to reason about correctness, consistency, and quantitative properties of complex reaction networks.

6 Stochastic and discrete extensions of chemical organization theory

Classical Chemical Organization Theory is formulated on the basis of continuous reaction–based dynamical systems, typically described by ordinary differential equations. This setting implicitly assumes large particle numbers and neglects intrinsic stochastic effects arising from molecular discreteness. However, many biochemical and cellular processes operate in regimes where particle numbers are small and stochastic fluctuations significantly influence long–term behavior. This has motivated several extensions of COT that explicitly address discrete and stochastic dynamics.

6.1 Particle effects and discrete chemical organizations

The influence of finite particle numbers on the qualitative behavior of reaction networks was systematically investigated by Kreyssig et al. [18]. They introduced *Discrete Chemical Organization Theory* (DOT), which extends the classical notions of closure and self–maintenance to reaction systems with discrete molecule counts and stochastic dynamics.

In DOT, the dynamics of a reaction network are represented by a Markov chain on a finite or countable state space. Discrete organizations are defined via topological properties of the corresponding transition graph and capture sets of species that can persist due to so–called particle effects. Importantly, every continuous organization is also a discrete organization, while additional *purely discrete organizations* may emerge that have no counterpart in the deterministic setting.

These results demonstrate that stochasticity and discreteness do not invalidate the organizational perspective, but rather enrich it by revealing additional structurally stable configurations that are masked by continuous approximations.

6.2 Organization–based coarse–graining of stochastic dynamics

A complementary line of work interprets organizations as macroscopic states of stochastic reaction systems. Mu et al. [19] proposed a coarse–graining approach in which the continuous–time Markov chain underlying a stochastic reaction network is projected onto an organization–level description.

In this framework, organizations correspond to metastable regions or communication classes of the Markov chain, and transitions between organizations represent rare stochastic events. The resulting reduced models preserve essential qualitative properties of the full stochastic dynamics while dramatically reducing state space complexity. This perspective establishes organizations as natural candidates for state abstraction in stochastic biochemical models.

6.3 Multiscale and hybrid modeling perspectives

The robustness of organizational structures across modeling paradigms was further investigated by Henze et al. [20]. They studied reaction networks across multiple levels of description, including particle–based stochastic simulations, continuous deterministic models, and probabilistic model checking frameworks.

Their results show that organizations act as structural invariants that can be consistently identified across these different formalisms. This multiscale perspective suggests that organizations provide a unifying semantic layer, linking microscopic stochastic dynamics to macroscopic qualitative behavior. In particular, organization–oriented coarse–graining enables the systematic comparison of models that differ substantially in their dynamical assumptions.

6.4 Conceptual implications

Taken together, these stochastic and discrete extensions demonstrate that Chemical Organization Theory is not restricted to deterministic dynamics. Organizations persist as meaningful structural entities under stochastic fluctuations, finite particle numbers, and across multiple modeling paradigms. This robustness supports the interpretation of organizations as fundamental building blocks for understanding persistence and qualitative behavior in reaction–based systems.

Moreover, these results provide a conceptual bridge between COT and stochastic process theory, opening connections to Markov chains, probabilistic model checking, and multiscale modeling. They also reinforce the role of organizations as a natural abstraction layer for analyzing complex systems beyond the limits of deterministic approximations.

7 Applications of chemical organization theory

Chemical Organization Theory (COT) has been applied to a broad range of reaction–based systems, demonstrating its usefulness as a structural analysis tool independent of kinetic parameters. Rather than focusing on the quantitative prediction of trajectories, applications of COT typically aim at identifying persistent subsystems, hierarchical organization, and structural constraints on admissible system behavior. The following examples illustrate how these concepts have been employed across different scientific domains.

7.1 Atmospheric and geochemical reaction networks

One of the earliest non–biological applications of COT was the analysis of atmospheric photochemical reaction networks. Centler and Dittrich [21] applied the theory to a detailed model of the Martian atmosphere, consisting of more than one hundred reactions. Using only stoichiometric information, the reaction network was decomposed into a hierarchy of organizations representing all potential steady–state species compositions.

A key result of this study was the identification of a small number of large organizations corresponding to chemically plausible atmospheric states, contrasted with a combinatorial explosion of small organizations arising from non–interacting species. The organizational hierarchy provided insight into the stability of CO_2 in the Martian atmosphere and revealed how recycling pathways emerge as structurally self–maintaining subsystems. This work demonstrated that COT can uncover chemically meaningful structures in large reaction networks without relying on detailed kinetics or numerical simulation.

7.2 Virus dynamics and infection models

COT has been successfully applied to the analysis of virus infection models, where large uncertainties in kinetic parameters often limit the reliability of quantitative simulations. Matsumaru et al. [5] investigated models of HIV infection using organization theory to identify persistent reaction subnetworks corresponding to viable infection states.

More recently, structural analyses of influenza A and SARS-CoV-2 models have been conducted using COT [12, 22]. In these studies, collections of independently developed models were compared based on their organizational structure rather than their dynamic output. The resulting organization lattices revealed substantial structural differences between models that would otherwise appear similar when judged solely by their simulated time series.

These applications highlight one of the central strengths of COT: models can be classified, compared, and evaluated based on their reaction network structure alone. Interventions such as drug actions or immune responses can be interpreted as structural perturbations that induce transitions between organizations, providing an abstract yet informative perspective on control strategies.

7.3 Phenotype prediction and regulatory effects

Chemical Organization Theory has also been applied to predict phenotypic outcomes of regulatory reaction networks. Kaleta et al. [23] studied gene regulatory systems and demonstrated that organizational structure constrains the set of admissible phenotypes independently of kinetic parameters.

In this framework, phenotypes correspond to organizations or sets of organizations that are structurally reachable under regulatory constraints. Perturbations such as gene knockouts or regulatory interventions can be interpreted as structural modifications of the reaction network, leading to predictable changes in the organizational landscape.

These results illustrate how COT can support qualitative phenotype prediction and robustness analysis in regulatory networks, complementing quantitative simulation–based approaches.

7.4 Large–scale comparative studies of biological models

The scalability of Chemical Organization Theory has been demonstrated in large comparative studies of biological models. In [11], COT was applied to a collection of 414 cell cycle models obtained from the BioModels database. Despite substantial heterogeneity in model size, structure, and intended biological scope, all models could be analyzed within a unified organizational framework.

By computing the lattices of organizations and distributed organizations, models were compared according to the complexity and structure of their persistent subsystems. This analysis revealed recurring organizational patterns associated with cell cycle checkpoints and oscillatory behavior, providing a structural explanation for qualitative similarities across otherwise disparate models. The study illustrates how COT can serve as a meta–analysis tool for model repositories, supporting model selection, validation, and comparison.

7.5 Data–driven and empirical studies

Recent work has demonstrated that Chemical Organization Theory can also be applied to empirically grounded models derived from experimental or observational data. Ruth et al. [24] analyzed data–driven reaction networks and used organizational structure to identify hierarchical subsystems and persistent interaction patterns.

By integrating empirical data into the construction of reaction networks, COT provides a qualitative analysis layer that is robust against noise and parameter uncertainty. These studies indicate that organizational analysis is not restricted to hand–crafted models but can be applied to data–informed systems, bridging theoretical and empirical modeling.

7.6 Beyond biological systems

Although many applications of COT are rooted in chemistry and biology, the theory is not restricted to these domains. Dittrich and Winter [25] demonstrated that the core concepts of closure and self–maintenance can be applied to abstract reaction systems modeling political decision processes. Even in this highly simplified setting, the resulting organizations captured persistent configurations of interacting entities and revealed structural constraints on system evolution.

Such examples emphasize that Chemical Organization Theory constitutes a general framework for the analysis of constructive dynamical systems. Its applicability is determined by the presence of reaction–like interactions and stoichiometric constraints rather than by the physical nature of the modeled entities.

8 Chemical programming and chemical computing

Beyond its use as an analytical framework for reaction networks, Chemical Organization Theory has also been proposed as a conceptual foundation for chemical programming and chemical computing. In this context, the central idea is not to analyze existing systems, but to design reaction networks whose qualitative behavior realizes computational tasks.

8.1 Chemical computation as organizational dynamics

Chemical computing interprets computation as the evolution of a reaction system toward stable or metastable configurations. Early work in this area explored how biochemical reaction networks can be exploited as unconventional computing substrates, emphasizing robustness, parallelism, and adaptivity. However, the intrinsic complexity of such systems makes it difficult to predict or control their macroscopic behavior based solely on reaction rules.

Chemical Organization Theory addresses this problem by introducing an intermediate, purely structural level of description. Organizations represent closed and self–maintaining subsets of species and can be interpreted as qualitative system states. Computation is then associated with transitions between organizations, rather than with individual reaction events or concentration values [26].

This perspective decouples computation from kinetic parameters and provides a symbolic abstraction that remains valid across a wide range of dynamical regimes. In particular, organizations are robust against perturbations of rate constants and initial conditions, making them attractive carriers of computational semantics.

8.2 Organization–oriented chemical programming

The use of COT as a design principle for chemical programs was developed in a series of studies by Matsumaru and colleagues. In organization–oriented chemical programming, desired computational outcomes are specified at the level of organizations, and reaction networks are constructed such that these organizations emerge as structurally stable configurations.

A paradigmatic example is the encoding of combinatorial problems into reaction networks whose organizations correspond to valid solutions. In [27], maximal independent sets of a graph are represented by organizations of a chemically programmed reaction system. The organizational structure of the network provides a direct mapping between the solution space of the problem and the lattice of organizations.

This approach emphasizes a top–down design methodology: instead of programming individual reactions, one programs the organizational landscape of the system. Chemical Organization Theory thus serves as a bridge between the microscopic specification of reaction rules and the macroscopic behavior of the resulting system.

8.3 Relation to organic and unconventional computing

Organization–oriented chemical programming is closely related to broader research directions in organic computing and artificial chemistries. While classical chemical computing often focuses on transient dynamics or specific reaction pathways, the organizational approach highlights structural persistence and qualitative behavior.

By abstracting from kinetics and embedding computation in the lattice of organizations, Chemical Organization Theory provides a principled framework for reasoning about correctness, robustness, and failure modes of chemical programs. Although practical realizations remain challenging, these studies demonstrate that COT is not only a tool for analyzing natural systems, but also a conceptual basis for the systematic design of reaction–based computational systems.

9 Relation to other frameworks

Chemical Organization Theory (COT) is part of a broader landscape of theoretical frameworks developed to analyze structure, stability, and long–term behavior of reaction–based systems. While these approaches share overlapping motivations, they differ significantly in their underlying assumptions, mathematical tools, and intended scope. This section clarifies the relation of COT to several prominent frameworks.

9.1 Chemical reaction network theory

Chemical Reaction Network Theory (CRNT) provides a rigorous mathematical framework for analyzing the existence, multiplicity, and stability of equilibria in reaction networks [28]. CRNT focuses primarily on properties of mass–action kinetic systems, such as complex balancing, deficiency, and persistence of positive steady states.

In contrast, Chemical Organization Theory abstracts from specific rate laws and focuses on structural properties of reaction networks. Organizations characterize all structurally admissible long–term species sets, including configurations in which only subsets of species persist. While CRNT addresses quantitative properties of equilibria, COT provides a qualitative classification of possible system compositions. The two approaches are therefore complementary rather than competing.

9.2 Autocatalytic sets and RAF theory

Autocatalytic sets, and in particular the RAF (Reflexively Autocatalytic and Food–generated) framework, have been developed to study the emergence of self–sustaining reaction networks, especially in the context of origin–of–life research [29].

RAF theory identifies subsets of reactions that are collectively autocatalytic and can be generated from a predefined food set. Chemical Organization Theory generalizes this perspective by removing the requirement of explicit catalysis and food sets. Organizations are defined purely by closure and self–maintenance and thus apply to a wider class of reaction systems. Every RAF induces an organization, but not every organization corresponds to an RAF, reflecting the broader scope of COT.

9.3 Flux balance and constraint–based approaches

Constraint–based modeling techniques, such as Flux Balance Analysis (FBA), analyze metabolic networks by identifying feasible steady–state flux distributions subject to stoichiometric and capacity constraints [30]. These approaches are powerful tools for quantitative prediction under specific optimization assumptions.

Chemical Organization Theory differs fundamentally in that it does not assume optimality criteria or fixed objective functions. Instead, it identifies all structurally feasible persistent species sets, independent of flux magnitudes. COT can thus be seen as complementary to constraint–based approaches, providing a qualitative layer that characterizes the space of admissible solutions before quantitative optimization is applied.

Table 1. Comparison of theoretical frameworks related to reaction-based systems.

Framework	**Primary Focus**	**Key Assumptions**	**Output**	**Relation to COT**
Chemical Reaction Network Theory (CRNT)	Mass–action kinetics	Mass–action, non-negativity	Steady states	Complementary perspective
RAF Theory	Autocatalytic networks	Catalysis, food set	RAF sets	Subset of COT
Constraint-Based Models (FBA)	Flux distributions	Steady-state + optimization	Optimal fluxes	Orthogonal to COT
Elementary Modes	Minimal pathways	Flux balance	Pathways	Reaction-level vs species-level
Artificial Chemistries	Computation	Rule-based	State transitions	COT gives semantic abstraction

9.4 Elementary modes and pathway analysis

Elementary modes and extreme pathways decompose reaction networks into minimal sets of reactions that can operate at steady state [14]. These methods focus on reaction–level structure and flux distributions.

In contrast, Chemical Organization Theory operates at the level of species sets and their self–maintenance. While elementary modes characterize how reactions can be combined, organizations characterize which species can persist. The two approaches address different but compatible aspects of network structure and can be combined to gain deeper insight into system behavior.

9.5 Artificial chemistries and unconventional computing

Artificial chemistries and chemical computing frameworks explore how reaction–like systems can be used to model computation, self–assembly, and emergent behavior [1]. These approaches often emphasize rule dynamics, simulation, or implementation aspects.

Chemical Organization Theory provides a unifying structural abstraction for such systems, identifying stable configurations and admissible transitions independent of implementation details. In this sense, COT can serve as a semantic backbone for artificial chemistries, linking microscopic rules to macroscopic qualitative behavior.

9.6 Summary

Taken together, Chemical Organization Theory occupies a distinct position among frameworks for reaction network analysis. Its defining feature is the identification of structurally admissible persistent configurations independent of kinetics, optimization, or specific modeling formalisms. This makes COT particularly suitable as a unifying abstraction layer that complements kinetic, stochastic, and computational approaches.

While conceptually distinct, certain parallels can be drawn between Chemical Organization Theory and recent approaches in representation learning, where structural patterns are inferred from complex data. Such methods address different problem domains but similarly emphasize latent structure and compositional organization [31].

10 Discussion and open problems

Chemical Organization Theory has matured into a comprehensive framework for the structural analysis of reaction–based systems. As demonstrated in the preceding sections, it provides a unifying language for studying persistence, hierarchy, and qualitative behavior across deterministic, stochastic, and spatially distributed models. At the same time, several conceptual and mathematical challenges remain, which define promising directions for future research.

10.1 Structural versus kinetic descriptions

A central feature of Chemical Organization Theory is its deliberate independence from kinetic assumptions. While this abstraction enables generality and robustness, it also raises fundamental questions about the precise relationship between structural predictions and kinetic realizability.

Although organizations characterize all admissible long–term species sets, not every organization is necessarily realized for a given choice of rate laws or parameters. A systematic characterization of kinetic conditions that select among multiple structurally admissible organizations remains an open problem. Bridging this gap would further clarify the role of COT as a predictive tool in concrete modeling scenarios.

10.2 Transient dynamics and structural transitions

Most results in Chemical Organization Theory focus on asymptotic behavior, such as persistence or extinction of species. However, many systems of interest exhibit rich transient dynamics that cannot be fully captured by terminal organizations alone.

Recent conceptual developments suggest that transient behavior can be described in terms of admissible transitions between species subsets, constrained by stoichiometry and self–maintenance. Developing a systematic theory of such *structural transitions* would extend the organizational perspective from static end states to dynamic pathways. Key open questions include the classification of admissible transitions, their minimal length, and their relation to classical bifurcation theory.

10.3 Scalability and complexity

While significant progress has been made in algorithmic computation of organizations and related structures, scalability remains a practical challenge. Large reaction networks may exhibit a combinatorial explosion in the number of organizations or organizational reactions.

Identifying structural features that guarantee tractable organizational landscapes, as well as developing approximation and sampling techniques, is an important direction for future work. Connections to constraint–based analysis, convex geometry, and lattice theory may provide valuable insights in this regard.

10.4 Integration with data and model uncertainty

The application of Chemical Organization Theory to data–driven and empirical models highlights its robustness against parameter uncertainty. Nevertheless, the construction of reaction networks from experimental data introduces structural uncertainty that is rarely addressed explicitly.

Open questions include how organizational predictions depend on network inference errors and how uncertainty at the data level propagates to the organizational level. Developing probabilistic or ensemble–based variants of COT may help to quantify confidence in structural conclusions derived from incomplete or noisy data.

10.5 Evolutionary dynamics and product inhibition

Beyond persistence and stability, Chemical Organization Theory offers a natural perspective on evolutionary dynamics. Recent stochastic models of molecular evolution indicate that product inhibition, while reducing replication efficiency, can increase the rate of evolutionary adaptation by promoting diversity and exploration of fitness landscapes [32].

From an organizational viewpoint, product inhibition reshapes the organizational landscape by stabilizing multiple coexisting subsystems and modulating transitions between them. This suggests that evolutionary processes can be interpreted as organization–level dynamics, where structural constraints influence not only survival but also evolvability.

Understanding how organizational structure interacts with mutation, selection, and inhibition mechanisms remains largely unexplored. Addressing these questions may provide new insights into prebiotic evolution, viral dynamics, and the emergence of complex adaptive systems.

10.6 Structural organization in complex technical systems

Beyond chemical and biochemical reaction networks, the notion of structural organization also appears implicitly in the analysis of complex technical systems composed of interacting subsystems. Such systems are often characterized by modular architectures, resource flows, and operational modes whose long–term behavior depends on the persistence and interaction of individual components. Although these models are not formulated within Chemical Organization Theory, they exhibit structural patterns that resonate with organizational reasoning.

An illustrative example is provided by recent performance analyses of autonomous multi–purpose supply container systems, where energy, water, climate control, and irrigation modules are jointly modeled and evaluated under varying operational conditions [33]. The analysis identifies feasible and infeasible operating regimes based on structural constraints and subsystem interactions, rather than on fine–tuned dynamical trajectories. From an organizational perspective, such regimes can be interpreted as structurally admissible configurations of interacting subsystems, analogous to organizations in reaction networks.

Related structural considerations arise in the modeling of integrated solar–powered water and energy systems, where long–term feasibility and robustness depend on the persistent interaction of production, storage, and consumption processes [34]. While these systems operate in a different physical domain, their analysis similarly emphasizes admissible configurations and sustained operational modes, highlighting conceptual parallels to organizational and persistence–based reasoning.

These examples suggest that the core ideas underlying Chemical Organization Theory—structural admissibility, persistence, and the separation of structure from detailed dynamics—may extend beyond chemical systems and provide a useful abstraction layer for analyzing complex technical and socio–technical systems. A systematic transfer of organizational concepts to such domains, however, remains an open research direction.

10.7 Toward a unified structural theory

Taken together, these open problems point toward a broader vision in which Chemical Organization Theory serves as a foundation for a unified structural theory of reaction–based systems. Such a theory would integrate persistence, stochasticity, spatial structure, transient dynamics, and evolution within a common stoichiometric framework.

Progress in this direction requires close interaction between mathematical theory, algorithmic development, and applications. The results reviewed here suggest that organizations constitute a robust and versatile abstraction layer, capable of linking diverse modeling paradigms and scientific domains. Related structural perspectives have also been discussed in more exploratory interdisciplinary contexts, for example in recent work on systems–level approaches to neurology [35], although such directions lie outside the scope of the present review.

Table 2. Summary of open problems in Chemical Organization Theory

Problem	**Key Question**	**Difficulty**	**Impact**
Structural vs kinetic	Which organizations are realized?	Medium	High
Transient dynamics	How do transitions occur?	High	High
Scalability	Can we handle 1000+ species?	Medium	Critical
Data uncertainty	How do errors propagate?	Medium	Medium
Evolutionary dynamics	How does structure shape evolution?	High	High

11 Conclusion

Chemical Organization Theory has emerged as a unifying structural framework for analyzing reaction–based systems across chemistry, biology, and beyond. By focusing on closure and self–maintenance, COT identifies all structurally admissible persistent species configurations independently of kinetic parameters, optimization principles, or specific modeling formalisms.

This review has shown how organizations provide a robust abstraction layer connecting mathematical concepts (lattice theory, convex geometry), algorithmic methods (linear programming, MILP), and dynamical systems theory across deterministic, stochastic, and spatially extended models. This robustness distinguishes COT from approaches that rely on particular kinetic assumptions or equilibrium concepts, positioning it as a complementary framework alongside chemical reaction network theory, constraint–based analysis, and autocatalytic set theory.

Applications demonstrate both theoretical depth and practical utility. COT has been successfully applied to atmospheric chemistry, virus dynamics, gene regulatory networks, cell cycle models, and large–scale biological model collections (over 400 models analyzed). These applications highlight the framework's scalability and its ability to extract structural insights from complex, parameter-uncertain systems.

Several open problems remain critical for advancing the framework. Transient dynamics and structural transitions would connect organizations to kinetic pathways, addressing the gap between structural admissibility and dynamic realizability. Scalability challenges must be overcome to handle genome-scale networks. Understanding how organizational structure shapes evolutionary adaptation represents a longer-term theoretical frontier with transformative potential for prebiotic evolution and synthetic biology.

Chemical Organization Theory provides a coherent structural framework that bridges diverse modeling paradigms. By separating structural admissibility from kinetic details, it offers a unique vantage point on persistence in complex systems. As reaction networks grow in scale and complexity—from systems biology to synthetic chemistry to computational design—COT's emphasis on qualitative persistence and structural reasoning positions it as an essential tool for mathematics, systems biology, and the theory of complex dynamical systems.

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