UNIVERSIDAD NACIONAL DE COLOMBIA

On Chemical Activity

Foundations of a classificatory approach to the study of chemical combination

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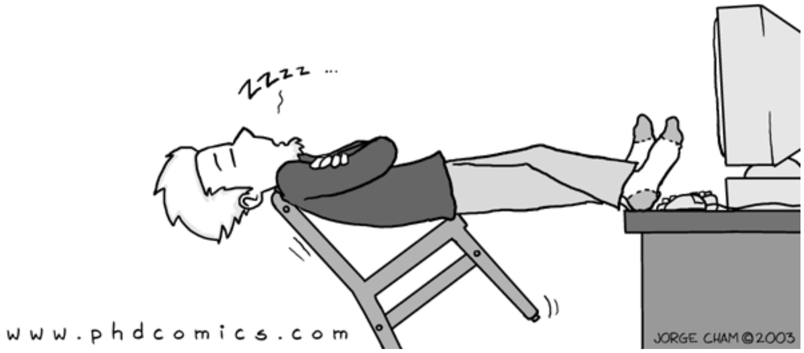

In memóriam
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Abstract

Structure and activity are central yet ambigous concepts of chemical science, being susceptible to a variety of distinct denotations. The popular (though seldom explicit) attachment of chemical structure to an atomic constitution theory that accounts for the behavior of matter as it undergoes chemical change conflicts with contemporary perspectives in the history and philosophy of chemistry and trivializes the concept of chemical activity, depriving it of any relevant theoretical dimension. Against this perspective, we define structure and activity as opposing epistemic approaches that interplay in chemical theory and are characterized by reverse ontological priorities ascribed to the concepts of property and relation. The prioritization of relations as determinants of substance properties characteristic of chemical activity theory motivates a peculiar mathematization of this epistemic approach, using the formalisms of category theory, formal concept analysis, and network analysis. The resulting mathematical formalism allows or suggests the possibility of a successful reconstruction of key chemical constructs such as acid, base, and organic function; provides the foundation of a methodology for the analylsis of similarity in chemical reaction networks; and unveils the potential of chemical activity as a fully-fleshed theory of chemical combination, complementary to structure theory and readily capable of constructing chemical knowledge by its own means.

Keywords: Mathematical Chemistry, Structure-Activity Relationships, Reaction Networks, Directed Hypergraphs, Philosophy of Chemistry, Category Theory, Formal Concept Analysis.

Resumen

Estructura y actividad son conceptos centrales y sin embargo ambiguos de la química que admiten una variedad de denotaciones distintas. La popular (aún si raramente explícita) identificación de estructura química con una teoría atómica de la constitución de la materia que da cuenta de su comportamiento durante el cambio químico entra en conflicto con perspectivas contemporáneas en la historia y la filosofía de la química. Al mismo tiempo, trivializa el concepto de actividad química, privándolo de cualquier dimensión teórica relevante. En contra de esta perspectiva definimos estructura y actividad como aproximaciones epistémicas opuestas, caracterizadas por otorgar prioridades ontológicas inversas a los conceptos de relación y propiedad, que interactúan en la teoría química. La prioridad dada a las relaciones como determinantes de las propiedades de las sustancias característica de la teoría de la actividad química motiva una matematización peculiar de esta aproximación epistémica, usando los formalismos de la teoría de categorías, el análisis formal de conceptos, y el análisis de redes. El formalismo matemático resultante permite o sugiere una reconstrucción exitosa de constructos químicos clave tales como ácido, base, y función orgánica, provee los fundamentos de una metodología para el análisis de similitud entre sustancias vistas como objetos en una red de reacciones químicas, y revela el potencial de la actividad química como una auténtica teoría de la combinación química, complementaria a la teoría estructural y perfectamente capaz de construir conocimiento químico por sus propios medios.

Palabras clave: Química Matemática, Relaciones Estructura-Actividad, Redes de Reacciones, Hipergrafos Dirigidos, Filosofía de la Química, Teoría de Categorías, Análisis Formal de Conceptos.

List of Symbols

(X, Y, R)	The dual of context (X, Y, r), page 98
A°	The interior of subset A in a topological space, page 98
$N_{in}(v)$	The in-neighborhood of vertex v in a digraph, page 54
$N_{out}(v)$	The out-neighborhood of vertex v in a digraph, page 54
α	A mapping $\alpha : A_{H_1} \to A_{H_2}$ that preserves the cardinals of heads and tails, page 66
$\bar{A}$	The closure of subset A in a topological space, page 96
β	A role model, page 66
$\bigvee$	Supremum operator in a lattice
$\bigwedge$	Infimum operator in a lattice
$\binom{n}{k}$	The binomial coefficient indexed by n and k
$\lessdot$	The cover relation in a POSET, page 79
The power set of X ., page 32	
$\simeq$,$\simeq_{\mathcal{C}}$	Equivalence relation on a category $\mathcal{C}$. If $\mathcal{C}$ =**Cat**, $\simeq$ is given by the existence of a natural transformation; else, it is given by the existence of an isomorphism. See pages 24 and 27
τ_R	The R-topology on X, page 95
$\tau_R(\mathcal{C})$	The category of R-topological spaces for all $r \in \mathcal{C}_1$ and continuous functions, page 95
τ_r	The r-topology on X, with $r : X \to Y$, page 93

$\tau_r(\mathcal{C})$	The category of r-topological spaces for all $r \in \mathcal{C}_1$ and continuous functions, page 93
ϑ	A natural transformation, page 25
ϑ_C	The component of natural transformation ϑ at object C, page 26
$\lvert A\rvert$	The cardinal of set A
1_A	The identity morphism of A, page 23
A^{ab}	The set of arcs going from vertices in V^a to vertices in V^b in a bipartite digraph, page 54
A^{ba}	The set of arcs going from vertices in V^b to vertices in V^a in a bipartite digraph, page 54
A_D	The arc set of directed graph D
A_H	The hyperarc set of directed hypergraph H, page 50
BDgraphs	A category of bipartite digraphs, page 52
$\mathcal{C}$	A category, page 23
$\mathcal{C}_0$	The collection of objects in category $\mathcal{C}$, page 23
$\mathcal{C}_1$	The collection of morphisms in category $\mathcal{C}_0$, page 23
Cat	The category of categories and functors, page 25
$\mathrm{Cod}(f)$	The codomain of morphism f, page 23
Digraphs	The category of directed graphs and adjacency preserving mappings, page 24
$\mathrm{Dom}(f)$	The domain of morphism f, page 23
d_X	The metric in metric space X
$f : A \to B$	A morphism f with $\mathrm{Dom}(f) = A$ and $\mathrm{Cod}(f) = B$, page 23
$F(f)$	The image of morphism f under functor F, page 25
f^{-1}	The inverse of morphism f, page 24
FA	The image of object A under functor F, page 25

$F_{A,B}$	The mapping $F_{A,B} : \mathrm{Hom}_{\mathcal{C}}(A, B) \to \mathrm{Hom}_{\mathcal{D}}(FA, FB)$ for functor $F : \mathcal{C} \to \mathcal{D}$, page 27
$\mathrm{Fr}A$	The boundary of subset A in a topological space, page 100
$\mathbf{Fun}(\mathcal{C}, \mathcal{D})$	The category of functors $F : \mathcal{C} \to \mathcal{D}$ and natural transformations between those functors, page 26
$g \circ f$	The composition of morphisms f and g, page 23
Graphs	The category of graphs and adjacency-preserving mappings, page 24
$\mathrm{head}(a)$	The head of hyperarc a, page 50
$\mathrm{Hom}_{\mathcal{C}}(A, B)$	The collection of morphisms in $\mathcal{C}_1$ with domain A and codomain B, page 27
HyperD	The category of directed hypergraphs and role assignments, page 65
K_a	The acid dissociation constant, page 71
$\ker r$	The kernel of binary relation r, page 32
$\mathcal{M}$	The category of metric spaces and functions $f : X \to Y$ such that $d_X(x_1, x_2) \leq d_X(x_1, x_3)$ implies $d_Y(f(x_1), f(x_2)) \leq d_Y(f(x_1), f(x_3))$, page 30
Met	The category of metric spaces and metric maps, page 24
$N(v)$	The neighborhood of v in a graph
$N_{in}(v)$	The in-neighborhood of vertex v in a directed graph, page 60
$N_{out}(v)$	The out-neighborhood of vertex v in a directed graph, page 60
Pos	The category of partially ordered sets and monotone functions, page 24
O^r, A^r	See *concepts*, page 34
r_β	The role assignment induced by role model β, page 67
$\mathbb{R}^+$	The set of positive real numbers including 0, page 41
Rel	The category of sets and binary relations, page 24
Sets	The category of sets and functions, page 24
$\mathcal{T}$	The category of dendrograms and dendrogram cuts, page 31

tail(a)	The tail of hyperarc a, page 50
Top	The category of topological spaces and continuous functions, page 24
V^a, V^b	The sets of mutually non-adjacent vertices in a bipartite digraph, page 54
V_G	The vertex set of graph G (directed or not)
V_H	The vertex set of directed hypergraph H, page 50

Contents

Introduction

> *"One of the first duties of a scientist is to determine the extent not of the acquired knowledge, for that knowledge will explain itself, but, rather, of the ignorance."*
>
> –Stanislaw Lem, His master's voice

Twentieth century witnessed the raise of QSAR methods applied to chemistry, pharmacology, and toxicological research. Significant amounts of money, manpower and computational resources are devoted nowadays to QSAR studies aimed at developing new drugs, assessing environmental problems, assisting the resolution of mixtures, predicting thermodynamic and mechanical properties of new materials, etc. (see e.g. Karelson & Lobanov (1996); Eriksson *et al.* (2003); Du *et al.* (2008); Gharagheizi (2007); Bhhatarai *et al.* (2011)). However, after the initial enthusiasm engendered by the promising results of pioneer works, a feeling of disillusionment has begun to spread among QSAR practitioners, who feel that "it has not fulfilled the expectations set for its ability to predict activity" (Johnson, 2008). In what follows, we will argue that this disillusionment is an understandable consequence of the tremendous theoretical indeterminacies that underly QSAR as it is often applied.

At its core, QSAR invokes the theoretical assumption that the structure of a substance is a determinant of its activity. This assumption (also known as the SAR principle) supports the general methodological approach followed in most QSAR studies, which consists in characterizing each element of a family of compounds with a set of structural and activity descriptors, building a statistical model that correlates the first family of descriptors with the second, and using the model to interpolate the activities of compounds of known structure but unknown activity.

Along the historical development of QSAR techniques, significant emphasis has been placed on the statistical rigor and sophistication of the correlation model (see e.g. Tropsha *et al.* (2003), Eriksson *et al.* (2003)). Unfortunately, though concern for statistical rigor is of the utmost relevance, it has been emphasized at the cost of overlooking the need of theoretical clarity. Large QSAR studies resort to sets of hundreds of structural descriptors, chosen more on statistical than theoretical grounds. On the other hand, surprisingly low attention is devoted to the choice of an often lone activity descriptor. Yet, the success of this approach is clearly contingent on the choice of descriptors, which evokes a fundamentally theoretical problem that cannot be handled by statistics: the definition of structure, activity, and the nature of the relation between them.

The core of the issue is that statistical correlation cannot be equated to causality. For instance, anyone can trace a plot between the most improbable variables (e.g. fresh lemons imported to USA from Mexico and total US highway fatality rate (Johnson, 2008)) with a high linear correlation coefficient; but it would be a huge mistake to infer from this plot that there is a causal relationship between those variables. A principle of causality can only be formulated within a scientific theory, so over-reliance on statistical tools necessarily leads to an ever increasing collection of meaningless propositions.

QSAR methods, then, require the support of clear-cut theoretical principles both before and after statistics come into play: before, in order to define the relevant variables to be introduced into the correlation model; and after, in order to make sense of their correlation. And there are huge indeterminacies regarding this indispensable theoretical background:

- There is no consensus on the definition of structure within the context of QSAR. Some authors identify it with chemistry's structural formulas, others with molecular geometry, others with critical points in the Born-Oppenheimer potential energy hyper-surface, with the ground-state wave-function of the molecule, with the shape of its electron density, etc. Furthermore, there are differences in the way different researchers interpret these objects. For instance, structural formulas are susceptible of being interpreted as a simplified image of the distribution of a molecule's atoms in space, as a compilation of neighborhood relations between the atoms that are manifested over the course of reactions, or as a particular representation of the symmetry of the molecule[1]. The ambiguity in the definition of structure is handled in QSAR at the level of descriptor selection, either by selecting structural descriptors *ad hoc* according to previous knowledge and expectations of the researcher, or by using statistical tools to choose a few structural descriptors from a large and varied pool with no influence from the modeler (Gramatica, 2008). Neither of these approaches takes us any closer to the delimitation and formalization of the concept of structure in QSAR.

- There is no clear, explicit, and widely agreed definition of the concept of activity, as evidenced by the diversity of interpretations seen in different QSAR studies. Just to mention a few, activity has been related to phase-transition constants (Karelson & Lobanov, 1996; Duchowicz *et al.* , 2008; Bhhatarai *et al.* , 2011), enzyme binding(Karelson & Lobanov, 1996), kinetics of specific chemical

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[1] Daza and Villaveces (1997) offer an analysis of the advances towards the definition of the concept of chemical structure, which though ten years old still offers a broad perspective that approaches the present state of the matter

reactions(Karelson & Lobanov, 1996), and complex toxicological and pathogenic phenomena, probably involving undetermined synergic effects (Du *et al.* , 2008). Some authors try to diminish the ambiguity by making a distinction between QSAR and QSPR: the first refers to studies that deal with the prediction of biological activity of a substance, understood as any perturbation that it induces on a living organism, and the later to studies concerned with the prediction of any other property of a compound (see e.g. Karelson and Lobanov (1996)). This distinction may help make the QSAR principle more precise within the domain of medical science, but may also move it uncomfortably close to a problematic form of chemical reductionism. On the other hand, the distinction increases the ambiguity on all other fields were QSAR (now QSPR) may be of utility, by linking the diffuse concept of structure to just about any material property one may think of. This QSPR principle feels very close to the trivial assertion that theories of matter speak of the properties of matter.

- The function linking structure and activity spaces remains unknown. Whatever this function may be, it seems that it is of notable complexity, probably involving severe discontinuity. Regarding this point, Maggiora (2006) suggests that the disappointing predictive power of QSAR models might be a consequence of the structure-activity surface not being as smooth as often assumed, an idea that Johnson (2008) retakes. They suggest that one needs only look at the evidence to find that such assumption should have never been made, as large changes in activity as a consequence of small changes in structure are customary.

This thesis is concerned with the formalization of the notion of activity. In that sense, it can be seen as part of a program that intends to strengthen the theoretical foundations of QSAR. Yet, we actually prefer to settle for a more restricted goal. Structure and activity are wide notions that appear in a broad range of disciplines that differ at many levels (phenomenological, methodological). Our focus of interest is not on the common elements that may determine transversal definitions of the concepts of structure and activity, but on the particulars of their identity within our main field of research. Thus, we aim at the specific goal of formalizing the notion of *chemical* activity; that is, we will focus on the particular meaning that we can ascribe to the term “activity”, starting from the broad context of the SAR assumption, but promptly moving into the specific context of the core principles of chemical theory. Furthermore, we will see no issue in dropping the idea of a causal relationship between structure and activity as soon as our chemical knowledge suggests the necessity. In this sense this work could be seen as part of the proper program of theoretical chemistry.

In the end, we are just taking the indeterminacies of QSAR as a starting point for theoretical digression; so though we hope to be able to contribute to that debate, this work is not about QSAR but about a core element of chemical theory that appears in its particular formulation the SAR hypothesis. By delimiting and formalizing the diffuse notion of chemical activity we expect to make a valuable contribution to the contemporary practice of chemistry.

Outline

According to the usual formulation of the SAR hypothesis in chemistry, activity refers to the behavior of substances in chemical reactions, and structure refers to the essential atomic constitution of matter that determines that behavior. In such terms, chemical activity just points to the phenomenological field of chemistry, which is already perfectly determined and merits no further theoretical digression. Chapter 1 starts considering an issue of the previous enunciation of the SAR principle: it comports a commitment to epistemological reductionism that conflicts with contemporary knowledge on the history and philosophy of chemistry. The assumption that atomism (regarded as a theory on the constitution of matter) provided a prolific ground for the development of chemical ideas is questioned through the examination of classic works in the history of chemical combination. Early theories of chemical change arose not following on the emerging program of constitutional atomism, but in open opposition to it. Seventeenth century chemists distanced themselves from corpuscularian philosophy, in face of its inability to account for chemical phenomena. Going into the nineteenth century, pioneers of structure theory still rejected the identification of chemical atoms with metaphysical entities, which did not prevent them from constructing a rich theoretical field. In the end, chemical knowledge could be and was constructed without resort to the hypothesis of an underlying particulate reality.

The existence of a theory of chemical combination independent of the program of atomic constitution questions both the sufficiency of structure theory and the triviality of the notion of chemical activity. Against the idea of a unidirectional cause-and-consequence relationship between structure and activity, we propose a picture of bidirectional interaction between epistemic perspectives. We identify chemical activity with an epistemic perspective that is founded on the conceptualization of substances as *internally related entities*; that is, as entities that cannot be abstracted from their mutual relations. This perspective leads to the configuration of a theoretical approach where substances are characterized in terms of properties determined by examination of the structure of chemical reaction networks. On the other hand, we characterize chemical structure as the opposing epistemic perspective: substances are regarded as *externally related entities*, that come into being before their mutual relations, leading to an approach where primary properties of substances are seen as determinants of their relations.

These epistemic perspectives are not disjoint alternatives, but complementary approaches that allow chemists to deal with the complex selectivity of chemical relations. The activity approach unveils patterns in the intricate network of chemical reactions, inducing properties on the internally related substances. These properties then are abstracted from the network of reactions and assigned to the isolated substances, thus constructing structural representations of the substances themselves. Then, this representations acquire an identity of their own, becoming able to infer hypothesis on unobserved chemical phenomena that modify the network of chemical reactions, thus transforming our understanding of the chemical activity of substances.

Having identified chemical activity with an epistemic approach that induces the characteristic properties of substances from the relations they establish among each other by means of chemical reactions, we aboard the problem of formulating this approach on mathematical terms. Chapter 2 considers the general problem of constructing a mathematized theory of internal relations. Taking Category Theory as the fundamental mathematical frame, we propose a model based on the idea of a *classification system*, that is, a mathematical framework where entities are characterized in terms of properties induced by classifications. A classification system is defined by a category of structured sets and binary relations, built in accordance to the relational logic of the family of entities being studied. Structure-preserving transformations with domain on a structured set determine a classification of its elements, according to a pattern of classes given by the codomain set.

Each ordered pair (u, v) in such a transformation reveals the existence of a connection between the situation of u in the relational structure of the domain set, and that of v in the relational structure of the codomain. In other words, the transformation reveals that v characterizes some aspect of the unique identity of u as an internally related entity. In consequence, we propose that elements of the codomain of a structure-preserving transformation can be regarded as properties of the elements of its domain, induced by the relational pattern unveiled by the transformation. In this way we establish a strong link between the problem of classifying a collection of entities and the problem of determining their properties in a theory of internal relations, which justifies the important role that classificatory approaches have played in the development of chemistry. Furthermore, the identification of the codomain of a structure-preserving transformation in a classification system with a set of properties characterizing the elements of its domain opens the road for systematic definition of concepts by means of the formalism of *Formal Concept Analysis*.

Equivalences of categories provide another important element of our proposal. An equivalence of categories can be understood as a transformation that relates mathematical formalisms with essentially the same logical structure. They can thus be used to induce *changes of representation*, motivating subtle shifts of perspective that may unveil properties of the subjects of study that could be hidden in the original model. Also, they provide a criterion of equivalence between classification systems, allowing us to determine the viability of different mathematical images of our field of inquiry. In this sense, we resort to equivalences of categories to compare some graph-like models of chemical reaction networks that could be used as the basis for the model of chemical activity that we present on the next Chapter.

Chapter 3 thus aboards the specific problem of building a mathematical model of chemical activity. The foundation of such model should be given by a classification system comprising suitable mathematical images of chemical reaction networks. After pointing the inadequacies of graph models of reaction networks, we choose a representation in terms of directed hypergraphs. Classifications of substances are then determined by adjacency-preserving relations between hyperdigraphs, which we call *role assignments*, that extend the concept of adjacency-preserving mapping in graph theory. Then, we propose a criterion of classification optimality based on the idea of maximizing its predictive power. Furthermore, the more restrictive demands posed on optimal role assignments operate in such a way that they allow to determine a consistent classification of chemical reactions associated with the classification of substances given by the role assignment. In this way, role assignments induce classifications that follow the recursive principle that 'similar substances react in a similar way with similar substances, to produce substances that are also similar among themselves'.

After illustrating how this formalism relates to key chemical concepts such as organic function and acidity, at the end of Chapter 3 we re-examine the matter of the relation between chemical structure and chemical activity, considering the case of structural formulas. Starting from the principle that reaction networks constitute the primary image of chemical phenomena, the demand for consistency with empirical knowledge is translated into the demand that structural formulas span an equivalent image of the reaction network, related to it by a change of representation. Unlike the original reaction network, that is determined by explicit accumulation of observed reactions, the equivalent network of structural formulas is defined by intension, in terms of generalized properties of its vertices. This procedure is permitted by the fact that structural formulas are not mere points devoid of properties other than being related, but sophisticate mathematical objects with properties of their own. This fact motivates a change in the methodology, shifting the focus of attention from the relational structure of the reaction network to the individual properties of structural formulas.

Features of chemical structures not determined by equivalence to a chemical reaction network motivate new statements regarding the reactivity of chemical substances that transcend the predictions of activity theory. Interestingly, this means that such statements are unsupported by empirical evidence. Following this line of reasoning we propose that the main value of structural formulas does not lay in their ability to offer precise predictions on the outcome of specific chemical transformations (a goal that activity theory is equally apt to accomplish), but in their potential to motivate hypotheses with high empirical content. If corroborated by experiment, these hypotheses provoke significant changes in the classifications of activity theory, thus transforming our understanding of the phenomena of chemical combination.

Chapter 4 explores the possibility of constructing conceptual characterizations of a classification system other than its associated concept lattice. The main focus of attention is a topological characterization of chemical similarity based on a method proposed by Restrepo and collaborators. By taking classes in a role assignment as a sub-base of closed sets, we induce a topological space on a classification's domain. Then, we prove that formal concepts determined by the classification are related to closed sets in this topological space, and show how its topological invariants provide a mathematical description of similarity among chemical substances.

The value of this topological representation is contingent on the structure of the associated classification. For instance, we note that classifications in mutually disjoint classes produced by standard clustering methodologies induce a relatively trivial topological image. At the end of the chapter, we point that this triviality ultimately reflects the inability of disjoint classifications to account for similarity, due to the constraints introduced by the transitivity of the equivalence relation underlying such classifications.

Along the manuscript we use several examples to illustrate the meaning of the mathematical formalism begin developed. Some were taken from the bibliography; they comprise either standard material or ideas introduced by other authors and we give the corresponding references to the original sources. Most of the examples, however, were worked by us, and present our own take on the material they comprise. These examples pursuit objectives that go beyond illustration: they test the adequacy of the model in development against its ability to formalize existing chemical knowledge, or present results that are of relevance in upcoming developments. In consequence, they should be considered as an integral part of our proposal.

Chapter 1

Structure and activity

> *"I agree with J. van Brakel that the older definition (used in the 18th and in the first half of the 19th century) of chemistry as a science of substances and their transformations is to be preferred to those of contemporary textbooks saying, for example, that chemistry is the science of transferring electrons between atoms and/or molecules, or something like that."*
>
> –Rein Vihalemm

> *"For anyone who thinks there is only one true explanation of a psychic process, this vitality of psychic contents, which necessitates two contradictory theories, is a matter for despair, especially if he is enarmoured of simple and uncomplicated truths, incapable maybe of thinking both at the same time."*
>
> –Carl Gustav Jung

When asked about the meaning of 'structure', a chemist will most likely answer in terms of structural formulas and/or mechanical or quantum-mechanical models of molecules. Chances are that he will link both to an atomic theory of matter. If further questioned on its utility, he will try to show how they can be used to predict what happens when two substances are mixed, or how DNA can be translated into a protein, or why that protein is able to catalyze the oxidation of sugar. On this hypothetical interview, the chemist is illustrating his particular interpretation of the SAR principle. His answers reveals the double identity of chemistry in the mind of its practitioners: it is seen as a science concerned with the intimate constitution of matter, and as a science concerned with transformations of substances.

According to the orthodox history, it was the discovery of the atomic constitution of matter that allowed the pioneers of chemistry to understand, predict, and control its transformations. In these terms, the SAR principle boils down to the acknowledgement that the atomic nature of matter (its structure) determines the transformations of substances that conform the field of chemical research (its activity). This statement adopts different meanings depending on what fundamental philosophical tenats accompany it. If we avoid the naive identification of a theory with an objective reality it may represent and understand constitutional atomism as a theory of matter, the above formulation of SAR turns into a commitment to epistemic reductionism: it states that the same atomic theories describing the fundamental constitution of matter offer an adequate account of chemical combination. This premise comports the following historical assumption: either the first successful chemical theories arose from the program of constitutional atomism, or at some point they were replaced by one such theory. On the first sections of this chapter we illustrate why we believe this assumption to be wrong.

Early chemical theories in the seventeenth century appeared not as a consequence of the emerging corpuscularian philosophy of the time, but in reply to its inability to account for the empirically observed transformations of matter. Seventeenth century atomism proved to offer a very poor theory of chemical change, being able at most to produce a series of increasingly *ad hoc* explanations, and even leading to conclusions that ran counter to empirical evidence (Section 1.1). Opposing the corpuscularian tradition, the French chemist Étienne François Geoffroy constructed a successful theory of metallic dissolution and displacement, while explicitly distancing his ideas form the corpuscularian program (Section 1.2). His classificatory approach emphasized the role of affinity relations among the substances as the key quality for recognizing a pattern on their seemingly capricious transformations.

If the first successful theories of chemical change were alien to the program of material constitution, we are left with the possibility of they being replaced by upcoming constitutional theories. Once more, contemporary history of science says something different. The ideas of seventeenth century chemists were neither rejected, nor forgotten. They played a central role in shaping a peculiar form of atomism that achieved remarkable success in nineteenth century chemistry and that is still deeply embedded in the contemporary practice of this discipline (Section 1.3). The distance separating this new "chemical atomism" from the ideas of corpuscularian philosophers is reflected in the fact that chemists could develop an atomic theory of matter, and still reject belief in the material reality of atoms.

This analysis provides a different insight into the nature of chemical structure and activity. The first theoretical ideas on chemical change were very explicit in their rejection of any attachment to a description of the ultimate constitution of matter, a position that was still common in the nineteenth century. On their purest form, these ideas conformed legitimate *theories of chemical activity*, devoid of any concern with the ultimate constituents of chemical substances. The recognition of the central role they played in shaping modern chemistry unveils the depth of the concept of chemical activity, helping us to overcome its current trivialization.

These considerations lead us to replace both the picture of a deterministic relationship between two attributes of matter and that of a unified theory successfully accounting for certain phenomenological field, with one of an interplay between epistemic perspectives. The main goal of chemistry is to gain knowledge on the phenomenon of chemical combination, whose fundamental theoretical image has the logical structure of a network (Section 1.4). There is something that we could call the 'activity approach' to the research of this network of chemical reactions, and something else that we could call the 'structure approach'. These two epistemic perspectives can be characterized in terms of opposing ontologies of concepts (Sections 1.5): while the structure approach attempts to unveil the individual properties of substances that determine the structure of the network of chemical reactions, the activity approach looks for patterns on the network itself that induce characteristic properties of the substances. The relationship between both approaches is bidirectional, each one relying on the other to configure its concepts and heuristics. The theoretical field of chemistry is conformed by neither of them, but by their interplay.

This chapter thus provides both the justification and the foundation for the rest of this work: the de-trivialization of chemical activity justifies the pursuit of its theoretical formalism, and the characterization of the activity approach provides the basis for the construction of its mathematical formalism.

1.1 The failure of mechanistic corpuscularism

Current programs in chemical education often present the rise of the atomic hypothesis as the turning point in the development of chemistry as a proper science. Atomism is introduced as the essential and fundamental ground over which chemical theories have been constructed. Contemporary history of chemistry, however, presents a very different picture. Atomism comes in several flavors, and not all of them have led to the development of central chemical ideas; for instance, mechanistic corpuscularism has been shown to be a particularly sterile philosophy for chemistry.

As early as 1952, Kuhn argued that, contrary to the widely accepted belief, Boylean atomism ran *counter* to fundamental chemical ideas and heuristics that arose not following his corpuscularian mechanism, but opposing it (Kuhn, 1952). Previous accounts of the influence of Boyle in the development of chemical ideas praised the role of his atomism in the development of "the 'modern' belief in the endurance of elements in their compounds" and in "the recognition of analysis and synthesis as fundamental tools of the working chemist", both now regarded as cornerstones of the chemical revolution (Kuhn, 1952, p. 13). But according to Kuhn, the innovation of Boyle's mechanistic corpuscularism was not in deriving the qualitative characteristics of natural substances from the permanent characteristics of their ultimate atomic constituents, but from the movement and arrangement of the corpuscles in his clockwork universe. Furthermore, the former was not even an innovation of the chemical revolution but the result of the steady work of the very authors whom Boyle harshly criticized. And, most important, the points where Boyle's atomism diverged from the ideas of his antagonists were *precisely those that lead to the cornerstones of chemistry.*

By reducing all qualities of stable bodies, as well as changes on those qualities, to the size, shape and motion of the atoms, he put an absolute emphasis on the configurations of the fundamental corpuscles as the primary cause of all perceptible qualities of matter. This emphasis lead him to reject the thesis of the existence of enduring elements. "Committed to deriving the secondary qualities of bodies from the relative positions and motions of their qualitatively neutral corpuscles, Boyle was bound to the conclusion that by sufficient rearrangement of positions and motions one could obtain, *not simply gold from lead, but anything from almost anything.* Boyle did not just reject the Aristotelian elements, but *the very idea of elemental substance.*" (Kuhn, 1952, pp. 21-22). Elemental substances, an indispensable part of modern theories of chemistry, were incompatible with Boyle's atomism.

Kim (2003) and Bensaude-Vincent and Simon (2008) have developed a similar thesis, showing how corpuscularism turned to be an unfertile ground for the growth of seventeenth-century theories of chemical combination. According to Kim, during this period chemistry came under the focus of natural philosophers "seeking to domesticate this rich empirical field in order to refurbish their systems of philosophical knowledge" (Kim, 2003, p. 3). Central to this enterprise was the introduction of popular philosophical perspectives on matter into the discourse of chemistry, in order to transform this discourse "to conform to chemists' analytic practice", but also to give it a "level of respectability and legitimacy" (Kim, 2003, p. 37). Boyle's corpuscularian program constitutes a notably explicit example of this phenomenon.

While corpuscularism would achieve significant success regarding the second point, functioning as "the legitimating discourse of chemical practice in the emerging public sphere of the early Enlightenment" (Kim, 2003, p. 47), it arguably failed regarding the first. Kim looks at the roots of this failure on her accounts of the history of seventeenth-century chemistry at the *Académie royale des sciences.* During this period she identifies a shift from distillation to solution methods as the preferred analytical technique, that would result in a significant transformation in French chemistry. The new emphasis in solution methods took the problem of selective dissolution and displacement of metals to the front of chemical philosophy (Kim, 2003, p. 112). In this way, in 1677 a prominent figure, Nicolas Lemery, identified this problem as "one of the most difficult to resolve well, of any in Natural Philosophy" and attempted to give a corpuscularian answer (Kim, 2003, p. 55). Lemery's discourse, however, promptly degenerated into elaborated *ad hoc* explanations that gained him "the satirical scorn of a number of chemists" (Bensaude-Vincent & Simon, 2008, p. 142). Bensaude-Vincent and Simon offer a beautiful example of the sterility of this discourse, quoting Lemery's corpuscularian account of the displacement of gold from a solution in *aqua regia* by the addition of an alkali:

> "I suppose that when the *aqua regia* acted on the gold in such a way that it dissolved the gold, the points which are responsible for the acid's strength were stuck into the particles of gold. But, because these little bodies are very hard, and consequently difficult to penetrate, the points only enter superficially, although far enough to suspend the particles of gold and to prevent them from precipitation; that is why, add as much extra gold as you will, when each of these points has taken up what it can support, it will not dissolve a grain more of it; it is also this suspension that renders the particles of gold imperceptible. But if you add some body, that thanks to its motion and figure can, by this shock, shake-up the acids enough to break them, the particles of gold, being free, will precipitate due to their own weight: this, I claim, is what the oil of tartar and the volatiles spirits of alkali do." (Bensaude-Vincent & Simon, 2008, pp. 141-142)

Lemery's discourse was promptly saturated with a multitude of different shapes and sizes that he had to attribute to the corpuscles (round, jagged, point, hooked), necessary for explaining a variety of transformations that refused to show any clear and simple harmony. This unrestrained multiplication of the entities was to strip the corpuscularian theories of chemistry of any theoretical value.

The problem of selective dissolution and displacement remained open and would go on to become a prevalent challenge for corpuscularian accounts of chemical phenomena at the *Académie*. After unsuccessfully trying to account for selectivity in acid-alkali reactions through a principalist approach, Homberg would resort to a "speculative corpuscular ontology" with no better results than Lemery's (Kim, 2003, pp. 75-79). Going into the eighteenth-century, Louis Lemery worked extensively on the matter, that by the time had acquired a "theoretical urgency" (Kim, 2003, p. 132). His lengthy speculations on the corpuscular mechanism of metallic displacement did not help chemists predict the outcome of dissolution reactions anymore than those of Homberg or his father (Kim, 2003, pp. 121-123). At this point, the corpuscularian language was more impeding than helpful in constructing an explanation of these phenomena.

1.2 The affinity table

This problem received a radically different treatment in the hands of Etienne François Geoffroy, with significantly better results (Kim, 2003, pp. 132-146). He shared the concern over the theoretical foundations of solution chemistry, but he "did not care much for the corpuscular ontology his colleagues employed for the purpose" (Kim, 2003, p. 134). He was more interested in the fact that chemical substances "offered a certain preferences in reactions" (Kim, 2003, p. 134). Abandoning all forms of corpuscular speculation, he instead devoted himself to the construction of a *Table des differents rapports observés entre differentes substances.* This Affinity Table summarized known reactions in solution chemistry, allowing easy access to a cumulus of data collected through years of chemical practice.

The structure of the table is relatively simple (see Figure 1.1). The top row comprises sixteen substances often employed in chemistry: 4 acids, 4 alkalis, sulphur, mercury, water, and several metals and semi-metals. On each column, a series of substances were listed in decreasing order of affinity towards the top substance. This organization summarized chemical experience on selective dissolution and displacement. For instance, the first column of the table was headed by acid spirits, followed by fixed alkali salt, volatile alkali salt, absorbent earth, and metallic substances. This meant that volatile alkali salt could displace metallic substances from its combinations with acid spirits, as it had a greater affinity for the later. Then, it could not displace fixed alkali salt, which had a greater affinity for acid spirits (Kim, 2003, p. 136).

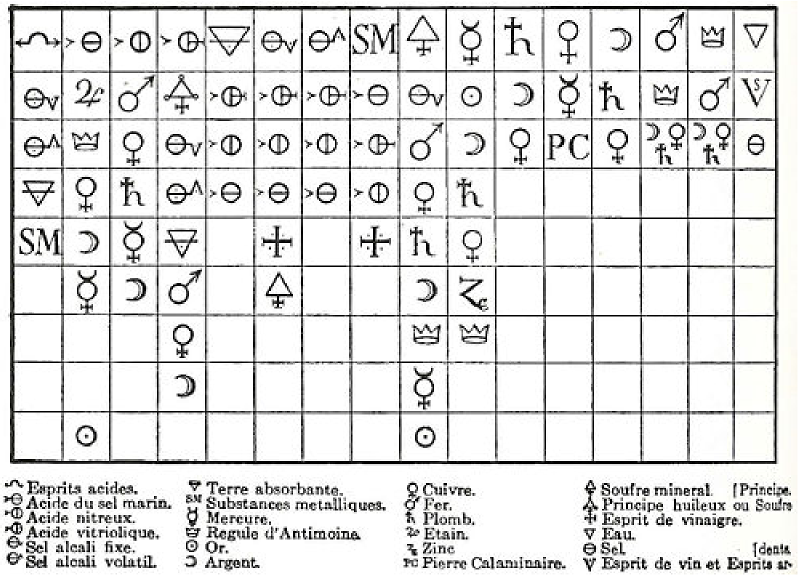

Figure 1.1: *Table des differents rapports observés entre differentes substances*, by Etienne François Geoffroy (1718).

While corpuscularian philosophers endeavored to find the causes of the selectivity of the phenomena of chemical combination in the attributes of the primary corpuscles, Geoffroy focused on characterizing that selectivity without hypothesizing on its ultimate cause. He thus "represented the order of selectivity visually in his 1718 table des rapports." (Kim, 2003, p. 113). In Geoffroy's discourse the smooth, round and small corpuscles of Lemery are replaced by simple letters designating each substance: "If among the substances [...] two were found united (A,B) and subsequently mixed with another (C), either the third substance (C) would join one of the substances (A) and shake the other (B) loose or it would not join either of the substances originally in combination (A or B). If C joined A, one could conclude with sufficient probability that C had 'more rapport of union or disposition to unite' with A than B did" (Kim, 2003, p. 135). Against the ever increasing family of attributes ascribed to the mechanical corpuscles, substances in Geoffroy's system could be characterized by a mere letter. Ultimate qualities of the individual substances were of little consequence here; all that mattered was what combined with what. If two substances shared a common affinity for a third, the affinity table reflected that feature on its classificatory structure.

Much more than corpuscularism, the affinity table provided a theory of the chemical phenomenon of metallic dissolution and displacement. The goal of such a theory would be to grant knowledge and control on the experimentally achievable combinations of metals and acids. Corpuscularian philosophers offered a theory that "relates back to a system of philosophy that could provide a set of causes and thereby claim a correspondence to nature" (Kim, 2003, p. 142), i.e they connected chemical phenomena to a metaphysical system that establishes a relation of causality between empirical facts and an underlying reality. But they failed to provide the kind of knowledge that chemists wanted: "to know what quantities of various substances should be mixed together to make successful products, which substances reacted together, and which did not"(Kim, 2003, p. 5). This was exactly what the affinity table offered.

"For Geoffroy, a theory meant a reasonable explanation of a group of chemical operations that could be applied across the boundaries of different analytical methods" (Kim, 2003, p. 142). The generality demanded on a predictive theory, that mechanistic corpuscularism accomplishes through reference to atoms as primary causes of chemical phenomena, is achieved by the affinity table by providing a systematic classification of substances that encompasses a broad family of experimental methods. Beneath this classificatory structure lied the conception of affinity, or rather of "rapport", as "mathematical ratio and relationship" between substances, a concept that "projected the affinity table as an instrument that would transform chemistry into a predictive science" (Kim, 2003, p. 444). By looking into any given column of the table, chemists were able to predict the outcome of a significant number of combinations, based on the order of relative affinities of the substances involved. Analysis of relative affinities also allowed for detailed accounts of "what went on in the mixture of several bodies" that avoided the multiplication of entities that plagued corpuscularian theories of chemical combination[1]. In this way, Geoffroy's table evidenced inconsistencies in current classifications

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[1] On this regard, see the description of the preparation of corrosive sublimate, a complex process involving a mixture of three substances with emission of a vapor, distillation, and further

of substances, allowed subtle differentiations that had not been possible previously (see e.g. (Kim, 2003, p. 141)), and provided a solid ground for predicting other reactions (Kim, 1992). Even more, it prefigured central concepts of modern chemistry, such as that of "chemical compound" (Klein, 1994), and, of course, affinity. It was, properly speaking, a powerful theory of solution chemistry, much more than the corpuscularian model.

The affinity table thus constituted a theory of chemical combination that was completely alien to the predominant atomic philosophies of the time, and that succeeded where the later failed. Affinity theories in the eighteenth century followed on the success of Geoffroy's approach, and were brought into the work of the group of The Arsenal by Lavoisier's closest collaborators, thus playing a determinant role in the chemical revolution of the seventeenth century(Kim, 2003). Against the picture of chemistry as an unavoidably atomistic science, we now face evidence of the existence of at least another theoretical approach that had a major impact on its development into an autonomous science.

But this does not mean that Geoffroy's table is embedded in a tradition that could be characterized as 'anti-atomism'. Mechanistic corpuscularism is but one of several atomic philosophies, from which it differs by other relevant characteristics that have nothing to do with its status as a particulate theory of matter. In fact, nineteenth century chemists assumed a different kind of atomism that achieved remarkable success. This peculiar "chemical atomism" was more akin to Geoffroy's perspective than to corpuscularian philosophy.

1.3 Chemical atomism

The history of chemistry in the nineteenth century opens with the publication of Dalton's atomic theory, which promptly became one of the core elements of future theoretical developments. Yet his atomic hypothesis was not universally well-received by chemistry practitioners and theoreticians. It is now acknowledged that chemists such as Berzelius, Laurent, and Ostwald were skeptical about the existence of the atoms. Furthermore, nowadays the cognitive value of Daltonian atomism has been questioned by philosophers of science such as Chalmers (2008), who argues that it only explains the laws of proportions, and Needham (2004), who concludes that it did not provide any novel explanations, since the laws of chemical combination could be interpreted without resource to Daltonian atomism .

It is worth noting, however, that Chalmers' epistemological demands on an atomic

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calcination with strong fire (Kim, 2003, pp. 137-138). By looking at the relative positions of the substances involved on this process in his affinity table, Geoffroy was able to determine the nature of the combinations involved, thus identifying all substances produced.

theory of chemistry are somewhat different from those required by Needham, and that the spirit e.g. of Laurent's rejection of atomism is very different from that of Ostwald. To understand the points of contention of the different controversies regarding atomism in the nineteenth century, it is important to realize that Daltonian atomism could be interpreted in at least two different ways: as a *metaphysical system*, or as an *epistemic perspective*. The first sense refers to the belief in an ultimate reality constituted by invisible, indivisible corpuscles that are the primary cause of chemical phenomena. Atomism in this sense was rejected by many nineteenth century chemists not as inadequate, but as irrelevant. On the other hand, atomism seen as an epistemic perspective concerns only the proposal of a discontinuous theory of matter, judged on the basis of its cognitive value. Daltonian atomism on this sense enjoyed wider acceptance.

In a way, the difference between seventeenth century corpuscularism and nineteenth century atomism lays in that the former prioritized the first sense, while the later prioritized the second. Corpuscularism was introduced in seventeenth century chemistry with the intention of including this discipline into the program of natural philosophy. It was, first and foremost, a metaphysical system, which then determined a particular epistemic approach. On the other hand, Daltonian atomism was introduced within the tradition of experimental science which, particularly in the french school, had little respect for metaphysical concerns. It was thus taken first as a discontinuous theory of matter, that could then promote the adherence to a particular metaphysical system. Adoption of the atomic metaphysics, then, was not a requirement for exploiting its theoretical power. This is particularly clear in the writings of Auguste Laurent, who saw no issue in speaking about atoms in one phrase, and disregarding them as an irrelevant hypothesis on the next[2].

Corpuscularian metaphysics configured a theory that ran counter to the developing chemical knowledge of the seventeenth century. But the problematic elements of this theory were not the defining features of an atomic system. As Bensaude-Vincent and Simon put it, "the discontinuity of matter implied by atomism fits well with the ex-

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[2] The first pages of Laurent's *Méthode de chimie* are devoted to the matter of structural formulas, with the unavoidable references to the problem of atomic weights. Then, when discussing the phenomenon of substitution, he writes: "In reply to the question, what is meant by the words: 'The chloro-ether continues an ether?' I might repeat, what I have just said, namely, that the arrangement of its atoms is the same as that of the normal ether. But *I prefer to leave hypotheses aside*, and say simply, that an ether is a body obtained by the reaction of an acid upon an alcohol, with an elimination of water, and that under certain circumstances that ether can be divided, either by regenerating the alcohol and acid which gave it birth, or by forming products which belong to the families of the alcohol and of the acid [...] *Whether or not the halides exist as such in the hyperhalides, aldehydes, and chloracids, is a matter of but little consequence.* Whatever atomic arrangement we may place to imagine, we cannot destroy the fact, that certain substances may experience chlorine substitutions without losing their fundamental properties." (Laurent, 1963 (1855), pp. 65, our italics)

planations of the phenomena of chemical combination". The issue with corpuscularism was never its character as a particulate theory of matter, but "the reduction of qualities to other parameters considered fundamental such as figure or shape and motion" (Bensaude-Vincent & Simon, 2008, pp. 139-140). It is this reduction, *which is not a necessary feature of atomic theories*, what proved once and again being unable to produce any significant chemical knowledge.

Nineteenth century chemists detached Daltonian atomism from this form of physicalist reductionism. On its most physicalist face, Dalton's hypothesis takes us back to the failure of mechanistic corpuscularism, and it is in this sense that Needham questions its cognitive value (Bernal & Daza, 2010, p. 99). But on its most chemical vein, Daltonian atomism can be formulated as the assumption that "each chemical element has least parts that are all alike and which combine in simple and characteristic ways to form the least parts of compounds" (Chalmers, 2008, p. 159). Those "least parts" are so in reference to experimental chemical methods, not to any underlying mechanical reality. This can be seen in the fact that atomic weights were relative weights, and the standard for their measure was also the atomic weight of a chemical substance: they were determined by chemical combination, so the atomic weight of any given element had to be linked to that of a potential reaction partner. More than strictly physical entities, chemical atoms were "stoichiometric atoms" (Kim, 2003, p. 445), *fundamental units of chemical combination.* On the hands of chemists such as Berzelius, Dalton's hypothesis was turned into a unique form of "chemical atomism" that played a central role in the development of chemistry in the nineteenth century (Rocke, 1984).

We see, then, how chemical atomism lays arguably closer to early affinity theories such as Geoffroy's than to previous atomic philosophies. Unlike mechanical corpuscles, chemical atoms are essentially epistemological, not metaphysical entities (see e.g. Bensaude-Vincent and Simon (2008), Chapter 11). They are determined by the same affinity relations and combination ratios that the affinity table spoke of. They were not regarded as the primary causes of chemical transformation, but as an alphabet necessary for writing chemical formulas, which conformed a language for speaking about this phenomenon. They play a *logical*, rather than an ontological role (Bensaude-Vincent & Simon, 2008, p. 191). Thanks to these differences, chemical atomism avoided both the multiplication of qualities pathological of previous atomic theories, and the absurd conclusions of Boyle's atomism: chemical atoms provided the basis for a theory of chemical combination, without requiring any quality besides their weight.

Though chemical atomism bears a high debt to seventeenth century affinity theories, it is more than a natural extension of them. Its refusal of the realist connotations of previous atomic philosophies did not make it insensible to their influence. For instance, half of the nineteenth century was spent solving the controversy surrounding the determination of atomic weights. The hypothesis of 'equal number of atoms in equal volumes of gas', reminiscent of corpuscularism, played a key role in solving this controversy (see e.g. Avogadro (1811)). Also, there is a lot more than chemical atomism to the contemporary atomic theories in chemistry: nowadays chemists seldom doubt the reality of atoms, or deny the influence of physics (a discipline whose atomic theory has developed a lot closer to the corpuscularian perspective) in shaping the atomic theory they rely on[3]. The important point here is that contemporary chemistry is linked to a tradition that tried (with significant success) to account for the transformations of matter without saying anything about its intimate constitution. *This is not just a historical but an epistemological link, and thus cannot be dismissed.*

1.4 The network structure of chemical knowledge

In the previous sections we have challenged the orthodox version of the birth of chemistry as a proper science thanks to an atomistic tradition that goes from Boyle to the Chemical Revolution, and then to Dalton. Historians have shown that there is no such tradition as it has been understood: Boylean atomism was incompatible with key chemical concepts, and Daltonian atomism had to be deprived from its most physicalist facets to be of use to chemistry. What were once thought to be major achievements of corpuscularism, were actually the fruits of the work of chemists who opposed the corpuscularian enterprise, opting instead for a very different approach.

Still, the most physicalist forms of atomism have had an influence in the development of chemistry, becoming increasingly prominent at the end of the nineteenth century and in the early twentieth century, with the appearance of the program of research on the structure of the atom. Saying that chemistry is a science concerned with atomic theories on the constitution of matter is not wrong, but incomplete. There exists another way to engage the study of the transformations of substances, which today is conjugated with the approach configured by the influences of corpuscularism, newtonianism, etc. At its core, contemporary chemistry is the fruit of the interplay between these fundamentally different epistemic approaches.

The picture of chemistry as a science standing on the verge of two opposing epistemic perspectives is not new. Schummer (2008), for instance, proposes that the coexistence of two opposing epistemic perspectives, the *form* perspective and the *stuff* perspective, is a remarkable characteristic of contemporary chemistry. Though at some point we

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[3] Then again, its influence is probably over-estimated. Late-twentieth century studies of the assimilation of quantum mechanics by the chemical community show that, to a large extent, it played a role not unlike that of mechanistic corpuscularism in the seventeenth century: it provided legitimacy to the discourse of chemists, who nonetheless kept working as they had previously, "with the comforting feeling that the most sophisticated theory in modern mathematical physics supported their actions" (Sutcliffe, 1996, p. 649).

will deviate from his proposal to present a different take on the matter, many of his ideas, particularly those regarding the logical structure of chemical knowledge, are key to developing our own picture.

According to Schummer, a material property is “reproducible behavior within certain reproducible contextual conditions” (Schummer, 1998, p. 4). Contextual conditions can be made explicit by distinguishing *contextual factors*, e.g. mechanical forces, thermodynamic factors, electromagnetic fields, or other chemical substances. Material properties can be systematically defined by reference to one of these contextual factors while standardizing the others (Schummer, 1998, p.4).

Chemistry deals with relations established among substances as they interact to undergo radical change (Schummer, 1998, p. 4). Chemical properties thus are material properties defined by reference to the *chemical factor*, i.e. with respect to *other chemical substances* they react with and transform into. In these terms, substances and reactions turn out to be the core entities of chemistry.

Chemical properties are determined by chemical reactions. From the logical point of view, the latter are “asymmetrical relations with two classes of relata: initial chemical substances before the change and different chemical substances afterwards” (Schummer, 1998, p. 9). Chemical properties, then, are intrinsically relational properties that summarize the behavior of substances when they are put together, while keeping other contextual conditions controlled. A typical chemical property would state: “under certain conditions, the combination of A and B produces C and D”. Here A-D are “stuff kinds” (Schummer, 2008), e.g. they may be either substances or classes of substances.

The key point is that chemistry emphasizes the relational nature of its entities. Chemistry does not study isolated objects: chemical properties only arise when the objects are put in relation to one another. In this way, chemical knowledge conforms a network structure within which properties are defined, substances are classified, and predictions are made (Schummer, 1998).

This take on chemical knowledge allows us to construct a clearer picture of the differentiation of two epistemic perspectives to chemistry: when chemists rejected the “reduction of qualities to other parameters”, such as shape and motion in mechanistic corpuscularism, they where rejecting an epistemic approach that intended to *explain the complexity of the vast network of chemical reactions by means of a small set of attributes of the isolated substances.* This project yielded little success in the seventeenth century because of the high *selectivity* exhibited by substances in their transformations, which forced the introduction of more and more attributes to explain a phenomenon that resisted being reduced to a simple law of interaction (Bernal & Daza, 2010). Opposing this approach, chemists endeavored to work the other way around: *exploit the complexity of this network to construct the properties of the substances.* Cornerstone chemical properties were not essential qualities of the substances that determined their behavior in chemical reactions; on the contrary, they were *derived from the behavior of* *the substance when undergoing chemical transformations.*

Let us now formulate this thesis on more formal terms.

1.5 The ontology of chemical concepts: relations and properties[4]

In the previous section we opposed the relational properties that conform the core of chemical knowledge with the primary qualities of the ultimate constituents of the world that intend to explain this knowledge on some corpuscularian philosophies. At this point, we drop the term "relational property", and instead reserve "property" to refer to qualities of the entities that are *proper* of them as individuals, and use "relation" to refer to qualities that require more than one entity to be predicated, but do not demand reference to their properties. For example, mass is a property of a body, inasmuch as we declare e.g. a body to have a mass of 100g without requiring a reference to other bodies; on the other hand, a predicate such as "sodium combines with oxygen" speaks of a relation, as it unavoidably refers to both sodium and oxygen, two different entities, but we do not need to know the properties of sodium or oxygen to state that they combine.

In this way, two opposing epistemic approaches can be formulated in terms of the ontological priority of those two basic categories: in one perspective, properties of the entities define their identity, which is then independent of their relations. The former could, in these terms, be seen as determining the later. A theory adopting this perspective would aim at deriving the relations of one object with the others from its intrinsic properties. In the other perspective, relations are prior to any property of the individual entity, which then has no existence prior to being related. The nature of the related object cannot be derived from its intrinsic properties, as in this approach there is no such thing as an isolated entity to which we could attach some fixed attributes. Relations determine the identity of the object along with all its properties, so that the work of the researcher consists in deriving the attributes of each object from emerging patterns on its relations. The first perspective ascribes to an *ontology of external relations*, while the second is linked to an *ontology of internal relations*[5](Ferrater-Mora, 2004).

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[4] The ideas introduced on this chapter have a non-incidental similarity with those introduced in Bensaude-Vincent and Simon (2008), particularly in Chapter 12: "Agency and Relations". For an account of the most notable differences between their thesis and ours see Bernal and Daza (2010), pp. 6-7.

[5] Note that our use of the word "ontology" does not point to an ultimate reality. In fact, by formulating the distinction of two approaches in the present terms, we are making sure that we keep our discourse within the space of our world representations, avoiding any claims regarding the 'real' nature of the world itself. For instance, we are avoiding the still popular distinction

The choice between each approach is taken according to their epistemic potential, which depends on the features of the phenomena being researched. To illustrate this point, let us go back to the impact of the selectivity of the phenomena of metallic substitution and displacement in the failure of seventeenth century corpuscularian models of chemistry. When strong relation selectivity is involved, a complex variety of behaviors arises that can hardly be subsumed under an unique law that describes the system through a proper set of attributes of the individual objects. If attributes of the objects are supposed to account for their relations in a reasonably simple way, but the objects display complex, varied preferences in who they relate with, external relation theories force the researcher to ascribe more and more attributes to the objects, in order to account for their different preferences. This is what happened to Nicolas Lemery when he attempted to account for selective dissolution from a corpuscularian ontology: common relations of the acids, e.g. those defined by their ability to dissolve metals, were explained by attributing the quality of being pointed to their particles. But then, to explain the preferences of some acid preparations for certain metals, additional attributes of the particles were required. Each new observation of selective interaction required an *ad hoc* mechanism and/or a new attribute of the bodies. This is what lead to the proliferation of different corpuscles that gained him the scorn of his colleagues. Adopting mechanistic corpuscularism for the study of chemical phenomena was problematic because the mixt of external relations and selective relations easily leads to a violation of Occam's razor principle. On the other hand, in this situation an ontology of internal relations naturally uses relation selectivity as a mean to describe the entities being related.

Therein lays the root of Geoffroy's success. In his system, the smooth, round, and small corpuscles of Lemery could be replaced by simple letters designating each substance. Like Lemery's corpuscles, pure substances in Geoffroy's system acted as fundamental units for a theory of chemical change; unlike Lemery's corpuscles, they are primarily devoid of qualities, they exist only as anchor points for relations. In Geofrroy's approach, qualities of the substances (or of its ultimate corpuscular constituents) need not and cannot explain the selectivity of their relations: relation selectivity determines the identity and qualities of the substances.

At the other end of the spectrum, consider e.g. the success of the coulombic approach to the study of electrostatic phenomena. Within this phenomenological domain, any

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between objective "primary qualities" of the "thing itself", and subjective "secondary qualities" that depend on the observer. For us, properties and relations are categories in the conceptual universe of our scientific theories. When marking the distinction between external relations and internal relations, we are just pointing that, in our scientific models, sometimes relations between the entities are conceived (they 'come into being') before properties of the entities themselves, while some other times we work it out in exactly the opposite way. We are dealing with epistemic, not metaphysical perspectives.

body interacts with any body, with just two opposing effects: attraction, or repulsion. There is no selectivity in the relations between the entities, which fits the external relations approach perfectly: we can abstract a property ascribed to each of the bodies by themselves (charge), conceive it as existing prior to any interaction, and formulate a simple law that allows a deductive reconstruction of all possible relations within the reach of this material context[6]. On the other hand, in this situation a theory of internal relations would tell us little more than that all bodies are alike.

The ontology of internal relations is probably attached to an older chemical tradition than the ontology of external relations. We already saw that the identification of substances with their relations played a central role in the success of the first theoretical accounts of metallic dissolution, showing that this approach was characteristic of chemistry as early as the eighteenth century[7]. The first major successes of external relations theories of chemistry came later, perhaps as late as the nineteenth century, in the form of the electro-chemical theory. This situation causes the internal relation ontology to lay closer to the fundamental core of the chemical approach, as it underlies the genesis of its most ancient concepts and heuristics. Particularly, it lays closer to the establishment of its empirical field.

As a consequence, the internal relations approach has priority over its counterpart in one sense: it provides the ultimate criterion for contrasting chemical models with empirical evidence. When their theories enter a period of crisis, chemists prioritize the unique identity given to substances by their mutual relations over the unique identity given by their intrinsic properties. This assertion is illustrated e.g. by Laurent's rejection of the most fundamental principles of the electro-chemical theory when confronted with the phenomenon of chlorine substitution (see e.g. Bensaude-Vincent and Simon (2008), p. 204, and Bernal and Daza (2010), pp. 91-94). As Berzelius showed, the dual compound formulas of electro-chemical theory could be modified to encompass the new phenomenon. Of course, this implied the use of *ad hoc* hypotheses, but such procedure is not strange to science, nor was Laurent's main criticism directed towards that point. Instead, he pointed that, under the fundamental axioms of electro-chemical theory, the formulas proposed by Berzelius implied that the corresponding compounds were bound to react in a very different way from what was observed[8]. The *ad hoc* hypothesis in-

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[6] We have not mentioned bodies of zero charge, who do not interact at all. Those bodies do not pose any problem to the external relations approach, as their lack of interaction is also entirely non-selective.

[7] This thesis has been defended on similar terms by Kim (2003) and Bensaude-Vincent and Simon (2008), who present more extensive historical evidence.

[8] Laurent is very explicit regarding his point of dissension. For instance, he tells how, upon receiving his memory on chlorine-substituted derivatives of isatine, Berzelius "endeavored to show that the chloro-derivatives of isatine, isathyde, &c, were, the one a sub-porrindinous sub-hypochlorite, the other a fluvidinous hypochlorite, and a third and acid of rubindene, &c.". In re-

troduced to save the theory actually destroyed it, as the unmodified theory was no longer able to provide an explanation for the empirical phenomena it was supposed to explain by means of the modified formula. Adopting the internal relations perspective was key in detecting and understanding the powerful consequences of this problem, and in pointing a way out of the crisis. Both Laurent's and Gerhardt's work went back to the approach set by the affinity theories of the seventeenth century, dismissing the matter of atomism and the intrinsic structure of matter as irrelevant, opting instead for a classificatory method not unlike Geoffroy's[9].

Chemist's resistance to the existence of noble gases in the late nineteenth century provides another example of the preponderance of relations over properties when threats to the foundations of chemistry appear. Though we could not speak properly of a crisis here, chemist's resistance to admit an unrelated entity was so strong that Mendeleev even felt that argon threatened the stability of his periodic system (Bensaude-Vincent, 1986). The question in debate was not whether such an entity could exist in absolute terms, but whether it could be defined within the field of chemistry: even if the mechanical and thermodynamic properties of the substance had been determined, it could not be characterized in chemical terms unless it was forced to react (Bernal & Daza, 2010, pp. 94-98).

In the end, the main goal of chemistry is to describe transforming substances. It speaks ultimately of entities in mutual relation. It is thus not by chance that its core experimental methods are synthesis and analysis, which are closer to the identification of substances with their interactions and transformations than to the explanation of those relations by reference to the intrinsic properties of the entities. When chemistry faces a theoretical crisis, prioritizing the internal relations approach ensures that the empirical phenomena that conform its field stay at the core of the controversy. This prevents the discussion from going astray, endeavoring to achieve consistency within the family of properties that characterize the individual structure of each substance, without warranting that they are also consistent with the phenomena that define the chemical context of materiality.

The previous argument, however, should not be miscontructed as a call for the absolute methodological priority of the internal relations approach. The situation we are presenting is not one of a confrontation between two epistemic alternatives, with

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ply, Laurent exclaims: "A sub-hypochlorite volatile without decomposition! A sub-hypochlorite undecomposable by sulphuric acid! A sub-hypochlorite without action upon vegetable colouring matters! [...] It is almost incredible." (Laurent, 1963 (1855), p. 63).

[9] "[Gerhardt's] main motivation was not to explain chemical combinations, but to classify the huge amount of substances that had conformed an impenetrable jungle. [...] To do it, he had to dismiss the existence of atoms, to declare the impossibility of the isolation of radicals [...] The question regarding the force that bounds atoms would probably appear to him as metaphysic and deprived of all scientific interest." (Villaveces, 1989, p. 96, my translation).

one being imposed over the other. This would underestimate the power of deductive theories of chemistry following on the external relations approach. The construction of such theories has proven to be a particularly hard enterprise; a difficulty that is partially explained by the selectivity of chemical relations, as we put it before[10]. But whenever they have appeared, they have enjoyed extraordinary success. Perhaps the earliest example of such formalism is precisely the electro-chemical theory of Berzelius: through a simple principle of dual combination of the opposites, this theory succeeded in reducing a vast variety of chemical combinations to the scale of the electro-chemical series[11].

Yet, we should also avoid the mistake of picturing chemistry as a discipline endeavoring for deductive theories, with the inductive approach of internal relation theories being used just to measure the degree of success of the former, and as a temporary replacement when they enter in crisis. Instead, we think that chemistry is at its best when both epistemic approaches *interplay* to produce a rich theoretical field.

This interplay is in broad display on chemistry's core concepts. For instance, the determination of atomic weights by exclusive reference to chemical combination lead to ambiguous results that arose huge controversy among nineteenth century chemists. The controversy was settled by Cannizzaro (1858), who brought the work of Avogadro to the front of the chemical scene. His approach was founded on two principles: first, the hypothesis of the existence of molecular elements, which arises from the stoichiometric analysis of gas phase reactions in light of the laws of proportions –the internal relations approach keeps prevalence on this part. But the experimental method he used is based on measurements of the densities of gases, a characteristic *property* of the isolated substances[12]. Furthermore, once the controversy is settled, atomic weights move from being a property of elemental substances that has to be determined by chemical combination, to being a property that *determines* the writing of formula, and thus chemist's predictions on viable combinations.

This double nature of chemical concepts is even clearer in the case of valence. Chem-

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[10] It has also been noted that such theories face important epistemological problems when dealing with radical change. See e.g. Bensaude-Vincent and Simon (2008), pp. 142-144.

[11] Note, however, that the polarities of the elements in the electro-chemical series are not of the same nature as coulombic charges. If they were, each element could be identified with a real number in such a way that their interaction would be determined by a simple algebraic law. Actually, the 'charge' of each element in the electro-chemical theory is defined *with respect to the element it may combine with.* The same element may have positive or negative charge depending on its position in the electro-chemical series relative to the element it combines with. On this light, not even the electro-chemical theory provides an example of a chemical theory strictly attached to an ontology of external relations.

[12] We previously noted the role that the hypothesis of 'equal number of atoms in equal volume of gas' played in the adoption of this empirical method. But even if we ignore this fact, it is clear that density is not a property defined by reference to chemical combination.

ical valences first appeared on Frankland's communication "On a New Series of organic bodies" (Frankland, 1963 (1852)). The main body of the text reports the synthesis of a series of organo-metallic compounds, along with their characterization through chemical analysis. Organo-metallic compounds were a novelty at the time; yet the classic status of the paper comes from a paragraph near the end, whose implications concern not just the theory of organo-metallic compounds, but the whole body of chemistry:

> "When the formulae of inorganic chemical compounds are considered, even a superficial observer is struck with the general symmetry of their construction; the compounds of nitrogen, phosphorus, antimony and arsenic especially exhibit the tendency of these elements to form compounds containing 3 or 5 equivs. of other elements an it is in these proportions that their affinities are best satisfied [...] Without offering any hypothesis regarding the cause of this symmetrical grouping off atoms, it is sufficiently evident, from the examples just given that such a tendency or law prevails, and that, no matter what the character of the uniting atoms may be, the combining power of the attracting element, if I may be allowed the term, is always satisfied by the same number of atoms. It was probably a glimpse of the operation of this law amongst the more complex organic groups, which led Laurent and Dumas to the enunciation of the theory of types; and had not those distinguished chemists extended their views beyond the point to which they were well supported by then existing facts, –had they not assumed, that the properties of an organic compound are dependent upon the position and not upon the nature of its single atoms, that theory would undoubtedly have contributed to the development of the science to a still greater extent than it has already done." (Frankland, 1963 (1852), p. 104)

Here, in the inception of the concept of valence, we find a clear instance of the internal relations approach: the extensive reports on the synthesis and analysis of a series of compounds leads to the identification of fixed proportions attached to the combinations of certain elements. But then, as experimental evidence accumulates, a principle of induction allows valences to become intrinsic and fixed attributes of the elements. Chemists move from determining valences from the chemical formulas to *using valence as a guideline for deducing the formula of new compounds, and in turn, to predict what reactions are they expected to undergo.* Atomic models such as that of Lewis furthered this shift, moving valence closer to a research program aimed at understanding the intimate structure of matter. Yet, when a compound combines in a way that resists to fit known standards, chemists surrender to the weight of the evidence of chemical relations, and declare it a substance with 'non-standard valence'. The anomaly poses a challenge to structure theory, but does not prevent chemists from exploiting the epistemic potential of the newly found valence. Analogous combinations are proposed and tested, configuring a local feature of the network of chemical reactions that determines the novel behavior, and that may eventually point to an answer to the challenge. Sooner or later the anomaly fades, and a new standard valence is included among the properties of the relevant element, thus completing another iteration of the cycle[13].

Internal and external relations ontologies offer two different epistemic perspectives, but neither is *the* chemical perspective. Perhaps Geoffroys' table could be seen as a theory of internal relations, but that is no longer the case in chemistry. The previous examples show how both perspectives are inextricably entangled in chemical theories. Disentangling them would only attain an epistemic purity of questionable value, at the price of destroying centuries-old achievements.

1.6 Structure and activity

Chemistry is the science of substances and transformations. Its experimental practice has been dominated over the centuries by synthesis and analysis. The experimentalist faces a picture of a huge family of substances that interact with complex selectivity. The selectivity of these phenomena enforces the adoption of an epistemic perspective that regards substances as fundamentally related entities, and tries to derive their properties from the relation pattern embodied in a chemical reaction network. We propose to reserve the term *chemical activity* to refer to the study of the transformations of substances following this internal relations approach

But the pursuit of its ultimate goal has connected chemistry to a research program concerned with the intimate structure of matter. After some unsuccessful attempts at its origins, chemistry has found the abstraction of an isolated entity endowed with some characteristic properties to be a useful mean to attain its objective. This abstraction is particularly strong in contemporary atomism, but such is not its only instance in the theory of chemistry. When we derive a molecular Hamiltonian from the charges and masses of the atomic constituents of a molecule, when we compute electrostatic fields and other molecular descriptors from quantum mechanical calculations, when we use graph-theoretical descriptors to characterize substances, we are attaching to an epistemic approach that characterizes our entities through their intrinsic properties, which then become determinants of their mutual interactions. Whenever we are taking this particular epistemic approach, we are talking of *chemical structure*.

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[13] It is interesting to note that IUPAC has a comprehensive rule for compounds with non-standard valences (IUPAC, 1982). This peculiar 'standard for the non-standard' illustrates the appealing paradox that arises as a consequence of the interaction between two opposing epistemic perspectives: anomalies of structure theory are quite normal and dealt with without apprehension.

Structure and activity, then, appear not as different concepts in an homogeneous theoretical field, but as opposing epistemic perspectives that interplay in our contemporary chemical theories. Neither can claim to be more fundamental than the other. In these terms, the current formulation of the SAR principle in chemistry seems too naive: chemical structure cannot claim to be a determinant of chemical activity, since there has never been anything like a 'pure' structural model that has successfully determined a 'pure' activity model.

Chapter 2

Foundations for a mathematized theory of internal relations

"Mathematicians do not study objects, but relations among objects; they are indifferent to the replacement of objects by others as long as relations do not change."

–Henri Poincaré

Within the internal relations perspective, an experiment provides information that comes in the form of a relation between empirical entities. Properties of the entities are not immediately given by the experiment. In consequence, one of the main goals of a theory of internal relations is to induce characteristic properties on each element of a delimited universe of study that are determined by its relations with the remaining elements. On this chapter we present a mathematical methodology for assessing this challenge.

From a mathematical point of view, the information accumulated through a series of such experiments can be represented as a structured set, whose elements represent the subjects of study, and whose structure embodies their relations. Different systems may exhibit different kinds of relations among their entities, which demand different mathematical representations –e.g. graph-theoretical, algebraic, or topological. In principle, this suggests that we must deal with the problem of inducing properties *ad hoc*. However, category theory offers a characterization of structured sets that transcends the frontiers between different branches of mathematics, thus allowing the formulation of a general methodology for the induction of properties on internally related entities.

A category consists of a collection of structured sets, along with a collection of structure-preserving transformations between them, known as *morphisms*. Intuitively, a structure-preserving transformation relates the elements of a structured set with those of another structured set while respecting the relevant structural features of the original set. The collection of structure preserving transformations with domain on any given set within a category provides the primary and complete characterization of that set's structure. Each of these transformations induces a classification on the domain set, which unveils common properties of its elements, determined by the particular structural features reflected in the transformation under consideration. In this way, each structure-preserving transformation allows for a characterization of the relational structure of a system of internal related entities in terms of properties of its constituents.

Section 2.1 introduces the fundamental definitions and ideas of category theory that we will rely on[1], while Section 2.2 presents a more detailed description of the mathematical methodology sketched above. Then, on Section 2.3 we show how morphism-induced classifications provide a natural link with Formal Concept Analysis[2], that allows us to go further by describing the conceptual field defined by the properties induced by a morphism.

Section 2.4 introduces the idea of equivalent categorical representations of a system of internally related entities. In principle, the system is uniquely represented by means of a set in a category that matches the logical structure of the relations among the entities being studied. However, categories are related by *functors*, i.e. structure preserving transformations between whole categories. In particular, pseudo-isomorphic functors know as *natural isomorphisms* relate categories that are identical regarding all their category-theoretical properties. This means that actually there is not a unique categorical representation of a particular system: any member of a collection of categories related by natural isomorphisms provides exactly the same information. We may then use functors to perform *changes of representation*, i.e. to transform e.g. an algebraic representation of our system of study into an equivalent topological or graph-theoretical image. The cognitive value of such changes comes from the fact that the new representation may unveil important patterns that, though present in any equivalent category, may have remained obscure in the original. Also, they provide the ultimate criterion of equivalence between different mathematical models.

Oftentimes we consider some classifications on a set of interest to be better than others –for instance, a classification in unitary classes is generally undesired, though it adequately matches the structure of pretty much any set we could think of. This preference for some specific classification(s) comports the existence of a criterion of optimality. Section 2.5 considers the matter of defining such criterion. In principle, we would expect classification optimality to be accountable in terms of the basic mathematical framework of the model we are proposing –that is, in terms of category theory. However, in our model different classifications on a given set are associated with different morphisms in its corresponding category, and we see no reason to prefer any morphism

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[1] Definitions, propositions, and examples introduced in this section were taken from Awodey (2006).

[2] Definitions and propositions presented in this section were taken from Carpineto and Romano (2004).

over the others from a strictly category-theoretical point of view. This forces us to handle the problem of classification optimization *ad hoc*. Thus, classification optimality is introduced by means of a measure function that weights the adequacy of each viable morphism according to factors that are not necessarily determined by the categorical structure of the system of study.

Last, on Section 2.6 we summarize the formalism proposed, going from its most general to its most specific elements.

All along the chapter we will use several examples to illustrate our ideas. We tried to present examples that go beyond the realm of chemistry, to emphasize the broad reach of the methodology. They link known methods of cluster analysis and network analysis, whose utility goes across the boundaries of scientific disciplines, to the category-theoretical formalism proposed. The application of the formalism to the specific case of chemical activity is left for the next chapter.

2.1 Mathematical background: category theory

The notion of a structure-preserving transformation is ubiquitous in mathematics. In group theory we have group homomorphisms, transformations that map one group in another while respecting their algebraic structure; in topology we have continuous functions, that map open sets into open sets, thus preserving the topological structure of the space; in graph theory we have adjacency-preserving mappings that preserve adjacency, and so on. If the mapping has an inverse it lets the structure of the space completely untouched; in such case we further speak of isomorphisms or homeomorphisms, transformations that define a criterion of identity between mathematical constructions. This notion that has emerged in different branches of mathematics is generalized in category theory through the definition of *morphism*.

Definition 2.1 (Category)**.** A *category* $\mathcal{C}$ consists of a collection $\mathcal{C}_0$ of *objects* and a collection $\mathcal{C}_1$ of *morphisms* such that

i) For each $f \in \mathcal{C}_1$ there exist a unique object $\mathrm{Dom}(f) \in \mathcal{C}_0$ called the *domain of* f and a unique object $\mathrm{Cod}(f) \in \mathcal{C}_0$ called the *codomain of* f. A morphism f with $\mathrm{Dom}(f) = A$ and $\mathrm{Cod}(f) = A$ is noted as $f : A \to B$.

ii) For each $A, B, C \in \mathcal{C}_0$, $f : A \to B$, and $g : B \to C$, there exists a unique morphism $g \circ f : A \to C$ in $\mathcal{C}_1$ called the *composite of* f *and* g.

iii) For each $f, g, h \in \mathcal{C}_1$, $h \circ (g \circ f) = (h \circ g) \circ f$

iv) For each $A \in \mathcal{C}_0$ there exists a morphism $1_A : A \to A$ in $\mathcal{C}_1$, called the *identity morphism of* A, such that for all $B \in \mathcal{C}_0$, $f : A \to B$, and $g : B \to A$, $f \circ 1_A = f$ and $1_A \circ g = g$.

Definition 2.2 (Isomorphism)**.** Let $\mathcal{C}$ be a category. A morphism $f : A \to B$ is an *isomorphism* if there is a $g : B \to A$ such that $f \circ g = 1_B$ and $g \circ f = 1_A$. In such case it is said that *g is the inverse of f* (from now on noted f^{-1}), and that A and B are *isomorphic*, which is noted as $A \simeq B$

Example 2.3.

i) The category **Sets** of sets and functions. Function composition and identity functions are defined in the usual way. Isomorphisms in this category are bijective functions.

ii) The category **Top** of topological spaces and continuous functions. Function composition and identities are defined as in **Sets**, which is correct because identity functions are continuous, and the composition of two continuous functions is continuous. Isomorphisms in this category are homeomorphisms.

iii) The category **Graphs** (**Digraphs**) of graphs (directed graphs) and adjacency-preserving mappings. Function composition and identities are defined as in **Sets**, which is correct since the identity mapping on the vertex set of a graph (digraph) preserves adjacency, and so does the composition of adjacency-preserving mappings. Graph-isomorphisms provide the isomorphisms of this category.

iv) The category **Met** of metric spaces and metric maps. Composition and identities are once more defined as in **Sets**. Isomorphisms in this category are isometries.

v) The category **Pos** of partially ordered sets (POSETs) and monotone functions. Isomorphisms in this category are order isomorphisms.

vi) The category **Rel** of sets and binary relations. Composition of two relations $r \subset X \times Y$ and $Y \times Z$ is defined by

$$s \circ r = \{(x, z) : \text{ there is a } y \in Y \text{ such that } (x, y) \in r \text{ and } (y, z) \in s\}, \tag{2.1}$$

and the identity on X is the identity function on X. Isomorphisms in this category are also bijective functions.

* * *

Category theory does not limit to offering a general formulation of a key concept in mathematics. It goes beyond, by intently avoiding all concepts that cannot be derived from the family of structure-preserving transformations characteristic of each object or collection of objects in a category. Though this may seem as a harsh constraint, the fact is that most concepts in many branches of mathematics can be formulated within category theory (Awodey, 2006). For instance, the category-theoretical definition of isomorphism perfectly matches the different definitions of isomorphism in algebra, topology, etc.[3]. This generality shows that the philosophy of mathematics, as seen by

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[3] Once more, we refer the reader to (Awodey, 2006) for the details.

category theory, is not unlike that of chemical activity: it does not matter what an object is 'made of', but just what it can transform into. In this way, category theory unveils the nature of formal mathematics as a discipline ascribed to an ontology of internal relations –which, of course, perfectly fits our present interest.

One of the most interesting facts of category theory is that categories conform a category themselves. Mappings from objects to objects and morphisms to morphisms known as *functors* provide the morphisms on this category.

Definition 2.4 (Functor)**.** Let $\mathcal{C}, \mathcal{D}$ be two categories. A *functor* is a mapping $F : \mathcal{C} \to \mathcal{D}$ of objects to objects and morphisms to morphisms such that:

i) $F(f : A \to B) = F(f) : F(A) \to F(B)$

ii) $F(g \circ f) = F(g) \circ F(f)$

iii) $F(1_A) = 1_{F(A)}$.

To avoid confusion, FA is used to denote the image of object A under F, and $F(f)$ is used to denote the image of morphism f under F.

Proposition 2.5. *The collection of all categories with functors as morphisms is a category.*

The category **Cat** of categories and functors thus provides a setting from comparing structures of many kinds (Awodey, 2006). Isomorphisms in **Cat** immediately stand out as particular relevant, since isomorphic categories are equivalent regarding all their category-theoretical properties. Isomorphisms in **Cat** thus allow us to move between different mathematical structures (algebraic, topological, etc.) that are ultimately equivalent, so that we can "specialize the theory" for each concrete application (Awodey, 2006, p. 125).

But presently, isomorphisms are more restrictive than required for a criterion of equivalence between categories. This is due precisely to the fact that relevant category-theoretical properties are invariant 'up to isomorphism'. Two categories, then, could be regarded as equivalent if their properties are equivalent 'up to isomorphism'. The most powerful definition of *category equivalence* is thus not given by isomorphism in **Cat**, but by a functor that, intuitively, constitutes an 'isomorphism up to isomorphism'. We now proceed to define this notion of equivalence on formal terms; but first, we require an auxiliary definition:

Definition 2.6 (Natural Transformation)**.** Let $\mathcal{C}$ and $\mathcal{D}$ be two categories. Let $F : \mathcal{C} \to \mathcal{D}$ and $G : \mathcal{C} \to \mathcal{D}$ be two functors. A *natural transformation* $\vartheta : F \to G$ is a collection $(\vartheta_C : FC \to GC)_{C \in \mathcal{C}_0}$ of morphisms in $\mathcal{D}$ such that for any $f : C \to C'$ in $\mathcal{C}$, $\vartheta_{C'} \circ F(f) = G(f) \circ \vartheta_C$. This can be expressed by means of the diagram:

$$\begin{tikzcd} FC \arrow[r, "\vartheta_C"] \arrow[d, "Ff"'] & GC \arrow[d, "Gf"] \\ FC' \arrow[r, "\vartheta_{C'}"'] & GC' \end{tikzcd}$$

In that case, it is said that ϑ_C is the *component of* ϑ *at* C.

Note that each component of ϑ transforms the image of an object under F into the image of the same object under G, while preserving consistency with the relevant morphisms. A natural transformation thus provides a way of transforming functors into functors while respecting the internal structure of the categories involved. In fact, natural transformations act as morphisms in a category whose objects are functors.

Proposition 2.7. *Let $\mathcal{C}$ and $\mathcal{D}$ be two categories. The collection of functors $F : \mathcal{C} \to \mathcal{D}$ along with natural transformations ϑ between those functors conforms a category. This category is known as* ***Fun***$(\mathcal{C}, \mathcal{D})$*, and its isomorphisms are known as* natural isomorphisms.

Proof (Sketch). For each functor F the composite transformation of natural transformations ϑ and ϕ has components

$$(\phi \circ \vartheta)_C = \phi_C \circ \vartheta_C \tag{2.2}$$

and the identity morphism 1_F has components

$$(1_F)_C = 1_{FC} : FC \to FC. \tag{2.3}$$

□

The strict criterion of equivalence of categories is isomorphism in **Cat**. According to **Definition 2.2** two categories $\mathcal{C}$ and $\mathcal{D}$ are isomorphic if there exists an invertible functor between them, that is, if there are functors $F : \mathcal{C} \to \mathcal{D}$ and $G : \mathcal{D} \to \mathcal{C}$ such that

$$\begin{aligned} G \circ F &= 1_{\mathcal{C}} \\ F \circ G &= 1_{\mathcal{D}} \end{aligned} \tag{2.4}$$

As discussed previously, we can relax this criterion and regard two categories as equivalent if their properties are identical 'up to isomorphism'. This can be expressed by demanding not that the compositions of functors above give the identity functors $1_{\mathcal{C}}$ and $1_{\mathcal{D}}$ respectively, but that they give functors that *are isomorphic to the identities*, i.e. that are related to them by natural isomorphisms in **Fun**$(\mathcal{C}, \mathcal{C})$ and **Fun**$(\mathcal{D}, \mathcal{D})$ respectively.

Definition 2.8 (Equivalence of Categories)**.** An *equivalence of categories* consists of a pair of functors

$$\begin{aligned} F &: \mathcal{C} \to \mathcal{D} \\ G &: \mathcal{D} \to \mathcal{C} \end{aligned} \tag{2.5}$$

and a pair of natural isomorphisms

$$\begin{aligned} \alpha &: 1_{\mathcal{C}} \to G \circ F \text{ in } \mathbf{Fun}(\mathcal{C}, \mathcal{C}) \\ \beta &: 1_{\mathcal{D}} \to F \circ G \text{ in } \mathbf{Fun}(\mathcal{D}, \mathcal{D}). \end{aligned} \tag{2.6}$$

In this situation, it is said that G is a *pseudo-inverse* of F, and that $\mathcal{C}$ and $\mathcal{D}$ are *equivalent*, written $\mathcal{C} \simeq \mathcal{D}$.

It is important to note that the existence of an object to object mapping between two categories is not enough to prove their equivalence, even if that mapping is invertible. This fact will be of great relevance in the next chapter, when we choose an adequate mathematical image of chemical reaction networks.

Following we introduce a proposition that is very useful for determining if two categories are equivalent, as it avoids the need of finding a pseudo-inverse. Before we do so, we require two auxiliary definitions:

Definition 2.9. Let $\mathcal{C}$ be a category and $A, B \in \mathcal{C}_0$. The set $\mathrm{Hom}_{\mathcal{C}}(A, B)$ is defined as the set of all morphisms $f : A \to B$ in $\mathcal{C}_1$.

Definition 2.10. A functor $F : \mathcal{C} \to \mathcal{D}$ is said to be:

i) *faithful* if for all $A, B \in \mathcal{C}_0$, the map

$$F_{A,B} : \mathrm{Hom}_{\mathcal{C}}(A, B) \to \mathrm{Hom}_{\mathcal{D}}(FA, FB) \tag{2.7}$$

defined by $f \to F(f)$ is injective.

ii) *full* if for all $A, B \in \mathcal{C}_0$, $F_{A,B}$ is surjective.

iii) *essentially surjective on objects* if for each $D \in \mathcal{D}$ there is some $C \in \mathcal{C}$ such that $FC \simeq D$.

Proposition 2.11. *The following conditions on a functor $F : \mathcal{C} \to \mathcal{D}$ are equivalent:*

i) F is (part of) an equivalence of categories.

ii) F is full, faithful, and essentially surjective on objects.

2.2 Categories, classifications, and properties

As we said at the beginning of this chapter, we can represent a system of internally related entities by means of a structured set. Now we will think of this set in the context of a category. Morphisms in the category say everything there is to say about that set's structure, and how it relates to the structure of other sets of the same kind. We want these morphisms to refer explicitly to the elements of the set, so that the former can be used to characterize the later.

So let us consider the case of subcategories of **Rel**, i.e. set categories where a morphism from set X to set Y is a binary relation $r \subset X \times Y$ that is structure-preserving in some appropriate sense. Each r in the category describes a structural feature of its domain, by linking the structure of this set with that of the codomain set. This characterization of the global structure of the domain can be extended into a characterization of its individual elements, by considering the specific pairs of elements that conform the relation: for any $x \in X$, the set of $y \in Y$ related to x by a $(x, y) \in r$ gives the full family of structural descriptors of x determined by this particular morphic representation. In other words, each $y \in Y$ can be regarded as a *property* characteristic of each element of X that is related to y by r.

For the sake of clarity, let us reconstruct the previous argument more formally for the particular case where r is a function $f : X \to Y$. The binary relation $\ker f$ defined by

$$\ker f = \{(x, x') \in X \times X : f(x) = f(x')\} \tag{2.8}$$

is known as the *kernel of* f. It follows immediately that $\ker f$ is an equivalence relation, so that it induces a partition of X in equivalence classes $C_y = \{x \in X : f(x) = y\}$ for each $y \in Y$. Intuitively, each C_y defines a class of elements of X that are 'equivalent as far as f can tell'. Since f is structure-preserving, the fact that it cannot tell two elements of X apart means that they are identical regarding the particular structural features captured by f. In this way, f naturally induces a classification of the elements of X according to the set's structure.

In the broadest sense, a class may be defined as a collection that can be characterized by some properties that all its elements share. Since our objects did not have any properties before the classification was constructed, they must have been endowed with some characteristic properties as the classification was build. Indeed, in the present case the class-defining property is precisely the common image under f shared by all elements of a given class C_y: an element y in Y. This is what suggests us to think of Y as the set of properties that characterize the elements of X under the morphic representation given by f. We then say that each $x \in C_y$ *has the property* y.

In conclusion, there is a correspondence between classifications on a structured set X and morphisms f with domain on X, as well as between classes in a classification on X, elements of $\mathrm{Cod}(f)$, and structurally-determined properties of the elements of

X. We thus see how, in a theory of internal relations, properties of the entities are constructed by classifying them.

The following examples show how known methods of cluster analysis can be understood in terms of categories and morphism-induced classifications.

Example 2.12 (Non-hierarchical clustering)**.** Non-hierarchical clustering aims at classifying the elements of a set according to their similarity relationships. Many clustering techniques operate on a representation of the set to be classified in terms of a metric space: as similarity between a pair of entities increases, the metric distance between the corresponding elements of the metric space decreases. The goal is to produce classes of equivalence such that elements in the same class are closer (thus more similar) to each other than to members of other classes. In formal terms, a morphism $f : X \to Y$ inducing an adequate classification on a metric space (X, d_X) should be such that for any $x_1, x_2, x_3 \in X$ if $f(x_1) = f(x_2)$ then $d_X(x_1, x_2) \leq d_X(x_1, x_3)$. This condition is fulfilled by demanding that

$$d_X(x_1, x_2) \leq d_X(x_1, x_3) \text{ implies } d_Y(f(x_1), f(x_2)) \leq d_Y(f(x_1), f(x_3)), \tag{2.9}$$

which also warrants that similarity between two classes reflects similarities between their elements. We verify that mappings satisfying this condition are morphisms between metric spaces:

i) Domain and codomain are defined as in **Sets**

ii) Composition is defined as in **Sets**. It is known that the composition of surjective functions is surjective. It remains to prove that the composition of mappings satisfying (2.9) also satisfies the same condition. Consider two such mappings, $f : X \to Y$ and $g : Y \to Z$. Let $x_1, x_2, x_3 \in X$, such that $d_X(x_1, x_2) \leq d_X(x_1, x_3)$, so that

$$d_Y(f(x_1), f(x_2)) \leq d_Y(f(x_1), f(x_3)) \tag{2.10}$$

which implies

$$d_Z(g(f(x_1)), g(f(x_2))) \leq d_Z(g(f(x_1)), g(f(x_3))) \tag{2.11}$$

or equivalently,

$$d_Z(g \circ f(x_1), g \circ f(x_2)) \leq d_Z(g \circ f(x_1), g \circ f(x_3)). \tag{2.12}$$

iii) Composition in **Sets** is associative.

iv) For any metric space X, the identity $f : X \to X$ in **Sets** trivially satisfies (2.9), so it also gives the identity in $\mathcal{M}$.

We thus see how the goal of non-hierarchical clustering can be attained by means of classifications in a category whose objects are metric spaces, with morphisms defined by surjective mappings $f : X \to Y$ satisfying (2.9). We denote this category as $\mathcal{M}$.

* * *

Example 2.13 (Dendrogram cuts)**.** Hierarchical clustering constructs representations of similarity among elements of some given data set X by means of dendrograms. A dendrogram is a particular type of binary tree, that can be defined as a rooted tree T such that each parent node has exactly two children (see Figure 2.1). The leaves of the dendrogram represent the elements of X, and the similarity between two elements is determined by the length of the longest geodesic going from either of the corresponding leaves to their nearest ancestor. A classification is represented as a 'cut' of the dendrogram, graphically illustrated in Figure 2.1 (b): the dendrogram is partitioned in a collection of disjoint subtrees, each one determining an equivalence class conformed by its leaves.

Let us see how can we define dendrogram cuts as morphisms in a category of dendrograms. First, to emphasize the special character ascribed to the leaves of the rooted tree of the dendrogram, we more strictly define a dendrogram as a pair (X, T), where X is a set and T is a rooted tree with leaf set X and such that each parent node has exactly two children. Then, for any two dendrograms $(X_1, T_1), (X_2, T_2)$, we define a dendrogram cut as a mapping $f : X_1 \to X_2$ such that

i) T_2 is a rooted subtree of T_1 with the same root node

ii) there is a mapping $f' : V_{T_1} \to V_{T_2}$ such that $f \subset f'$ and for any $v \in V_{T_1}$ $f'(v)$ is the closest ancestor of v (including v itself) that is a vertex in V_{T_2}.

Figure 2.1 (b) illustrates the link between this definition and the pictorial notion of a dendrogram cut. We are constructing a mapping from the rooted tree of the dendrogram to the subtree starting just 'above the cut', that preserves the ancenstor-descendant relationships of the dendrogram: vertices 'below the cut' are mapped by f' into their closest ancentors 'above the cut', and vertices above the cut are mapped by f' into themselves. Leaves of T_1 are necessarily mapped into leaves of T_2, so that equivalence classes are given by the kernel of f as desired.

Now we verify that dendrogram cuts defined in this way are morphisms in a category whose objects are dendrograms.

i) Domain and codomain are defined as in **Sets**

ii) Composition is defined as in **Sets**. We prove that the composition of dendrogram cuts is a dendrogram cut: let $f : X_1 \to X_2$ and $g : X_2 \to X_3$ be two dendrogram cuts, and let $v \in V_{T_1}$. Then, either $f'(v)$ is a closest ancestor of v in T_2. In turn, $g' \circ f'(v) = g'(f'(v))$ is a closest ancestor of $f'(v)$ in T_3, which by transitivity is a closest ancestor of v in T_3.

iii) Function composition in **Sets** is associative

iv) For any dendrogram (X, T), the identity $f : X \to X$ in **Sets** is a dendrogram cut, with $f' : V_T \to V_T$.

Thus, dendrograms along with dendrogram cuts conform a subcategory of **Graphs** that embodies all classifications attainable in several hierarchical clustering methodologies. We will note this category as $\mathcal{T}$.

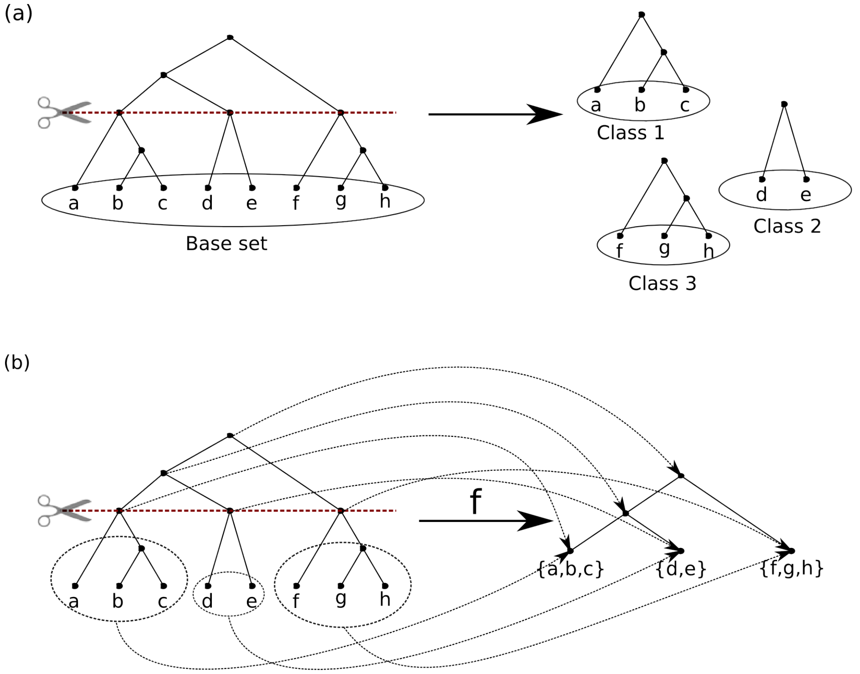

Figure 2.1: A cut of a dendrogram on the set $\{a, b, c, d, e, f, g, h\}$: (a) seen as a decomposition of the dendrogram in subtrees; (b) seen as a morphism f in the category of dendrograms $\mathcal{T}$. Leaves of $\mathrm{Cod}(f)$ are labeled with the corresponding classes in $\ker f$. Dotted arrows represent the associated mapping f'.

* * *

Example 2.14 (Regular equivalence and block modelling)**.** Block models are central tools in social network analysis. A social network may be represented as a graph whose vertex set V represents actors, and whose edge set E represents social relations between the actors. A *role assignment* is a classification of actors according to their social role. In general, a role assignment may be seen as a surjective mapping $f : V \to W$ onto a set of roles W. A role assignment is *regular* if for each $u, v \in V$, $f(u) = f(v)$ implies $f(N(u)) = f(N(v))$, where $N(u)$ is the set of neighbors of u in G. In such case, we say that u and v are *regular equivalent.* The rationale behind this definition is that actors of a given role interact with actors of the same given subset of roles.

Consensual social links between roles are summarized by means of block models. For a given graph $G = (V, E)$ and a regular role assignment f, a *block model* B is the graph with vertex set $f(V)$ such that $(f(u), (fv))$ is an edge in B if and only if $(u, v) \in E$. From this definition it is clear that f is a surjective adjacency-preserving mapping from G onto B. A regular role assignment then gives a classification of G in the category **Graphs**.

* * *

Now, we generalize the previous construction for a category where morphisms are arbitrary binary relations. The main difference is that now kernels are not necessarily equivalence relations, so that the classifications that they induce are conformed by possibly non-disjoint classes, and in consequence each element of the structured set may be characterized by more than one property.

Definition 2.15 (Kernel of a relation)**.** Let X, Y be two sets, $r \subset X \times Y$ be a binary relation, and $\mathcal{P}(X)$ be the power set of X The *kernel* of r is the binary relation defined by

$$\ker r = \{(x_1, x_2) \in X : \text{ there is a } y \in Y \text{ such that } (x_1, y) \in r \text{ and } (x_2, y) \in r\} \quad (2.13)$$

Note that whenever r is a function this definition becomes identical to (2.8), as desired. In analogy to that case, the kernel of a relation induces a classification on its domain set whose classes are given by the ‘pre-images’ of the elements of the codomain of r. In this way, the mapping $\ker r : Y \to \mathcal{P}(X)$ defined as[4]

$$\ker r(y) = \{x \in X : (x, y) \in r\} \quad (2.14)$$

provides a classification of X in possibly non-disjoint classes. Non-disjointness appears whenever there are $(x_1, y), (x_2, y) \in r$ such that $x_1 \neq x_2$, that is, whenever r is not a function. Otherwise, the mapping of the previous equation gives the partition induced by the kernel of the corresponding function. Since in the present work we will always consider subcategories of **Rel**, equation (2.14) gives the general definition of classification that we will adopt.

---

[4] We use the same notation to refer to the kernel of r and to the classificatory mapping that it induces, in order to avoid unmeasured proliferation of symbols. We think that it is possible to discern which one we are referring to by context.

Definition 2.16 (Classification)**.** Let $\mathcal{C}$ be a category where $\mathcal{C}_0$ is a collection of sets and $\mathcal{C}_1$ is a collection of left-total and surjective binary relations. Let $X, Y \in \mathcal{C}_0$ and $r \subset X \times Y \in \mathcal{C}_1$. We say that $\ker r : Y \to \mathcal{P}(X)$ defined by (2.14) is a *classification on* X, that $\ker r(y)$ is *the class induced by* y, that $x \in \ker r(y)$ *has the property* y, and that $\mathcal{C}$ is a *classification system.*

We demand the binary relation to be left-total to ensure that no elements of X are left unclassified, and to be surjective in order to avoid 'dummy' properties that are not related to any element of X.

The following examples illustrate the potential of this broader definition of classification. The first derives a well-known graph-theoretical invariant by means of a classification in a classification system. The second transcends a limitation of a role analysis methodology in social network analysis, providing an extended mathematical formalism that encompasses more sophisticated descriptions of social networks and similar systems. In both cases the key step is the construction of an extended version of the category **Graphs** by allowing morphisms to be arbitrary binary relations. This replacement of mappings by arbitrary binary relations will be a recurring theme in the present manuscript.

Example 2.17 (Vertex neighborhood)**.** Let G, H be two graphs. Recall that morphisms in **Graphs** are adjacency-preserving mappings, that is, mappings $f : V_G \to V_H$ such that $(u, v) \in E_G$ implies $(f(u), f(v)) \in E_H$. By analogy, we define an *adjacency-preserving relation* $r \in V_G \times V_H$ as a relation such that for each $(u, v) \in E_G$, there is a $(x, y) \in E_H$ such that $(u, x) \in r$ and $(v, y) \in r$. It is easy to check that the collection of graphs and of adjacency-preserving relations conform a category that has **Graphs** as a subcategory.

Now, note that E_G is an adjacency preserving relation $E_G : G \to G$ that relates each $v \in V_G$ to its neighbors. Since a vertex in a graph is completely characterized by its neighborhood, $\ker E_G$ offers a classification that is complete in the sense that it relates each vertex with a set of properties that completely determine its identity in terms of the structure of the set under consideration.

* * *

Example 2.18 (Generalized regular equivalence block modelling)**.** One issue with the block modelling technique sketched in **Example 2.14** is that it identifies each social actor with a unique role. Oftentimes this is an overly restrictive constraint, as an actor may play different roles in its social relations with different actors. For example, in a network of progeny relationships, an actor may be seen as playing the role of a son relative to its progenitor, and the role of a parent relative to its offspring.

The definition of adjacency-preserving relation of **Example 2.17** extends the concept of adjacency-preserving mapping that lays at the core of regular equivalence block modelling (see **Example 2.14**), thus allowing us to generalize this technique to overcome the limitations of unique role assignment. For instance, the binary relation given by E_G in **Example 2.17** can be seen as a generalized block model where each actor is characterized as playing a different role on each of its relations with its neighbors, but all actors play the same role when interacting with any given actor.

* * *

2.3 Concepts

Formal Concept Analysis (FCA) provides a mathematical framework for the definition of concepts. The formalism of FCA starts by considering a *context*, defined as a relation linking a set of objects with a set of attributes. Concepts are then dually defined as a pair consisting of a maximum set of objects that share a set of attributes, and of the maximum set of attributes that they share[5].

Definition 2.19 (Formal Context)**.** A *formal context* (or *context* for short) consists of a set G, a set M of *attributes*, and a binary relation $r \subset G \times M$. It is said that $x \in G$ has the attribute $y \in M$ if and only if $(x, y) \in r$.

Definition 2.20. Let (G, M, r) be a context. For any $O \subset G$ and $A \subset M$,

$$\begin{aligned} O^r &= \{y \in M : (x, y) \in r \text{ for all } x \in O\} \\ A^r &= \{x \in G : (x, y) \in r \text{ for all } y \in A\} \end{aligned} \tag{2.15}$$

In other words, O^r is the set of attributes common to all elements of O, and A^r is the subset of elements of G which have all attributes in A. For the sake of simplicity, we will note $\{x\}^r$ as x^r.

Definition 2.21 (Formal Concept)**.** Let (G, M, r) be a context. A *formal concept* (*concept* for short) in (G, M, r) is a pair (O, A), with $O \subset G$ and $A \subset M$, such that $O^r = A$ and $A^r = O$. In other words,

i) for each $x \in O$ and for each $y \in A$ we have $(x, y) \in r$

ii) for each $x \notin O$ there is a $y \in A$ such that $(x, y) \notin r$

iii) for each $a \notin A$ there is an $x \in O$ such that $(x, y) \notin r$.

For any given concept (O, A), O is known as the *extent* of the concept, and A is known as the *intent* of the concept.

---

[5] Definitions introduced in this section were taken from Carpineto and Romano (2004), but we used a different notation to avoid confusion with other concepts from the formalism introduced on previous sections.

The idea behind this definition is to make concepts ‘closed’ both regarding their intent and their extent. Indeed, the extent of a concept is a maximal subset of G characterized by the attributes in its intent, and the intent of a concept is a maximal set of attributes in M characteristic of all elements in its extent. Formally, this means that $O \subset O^{rr}$ and $A \subset A^{rr}$, and $O^{rrr} = O^r$ and $A^{rrr} = A^r$ for any $O \in G$, $A \in M$, so that the operator ^{rr} is a closure both in G and M (see e.g. Carpineto and Romano (2004), pp. 10-11 or Krötzsch (2005), pp. 20-23 for further details). A formal concept can then be constructed either by closing a subset $O \subset G$ with this operator, which produces the concept (O^{rr}, O^r), or by closing a subset $A \subset M$, producing the concept (A^r, A^{rr}).

Note that for any given subcategory $\mathcal{C}$ of **Rel** each morphism $r : X \to Y \in \mathcal{C}_1$ defines a context with $G = X$ and attribute set $M = Y$, induced by the category-theoretical identity of those sets. Concepts on this context are defined with respect to the properties induced on X by $\ker r$. Thus, we have a natural link between the category-theoretical formalism proposed and FCA, that allows us to take a further step by inducing concepts on a set of internally related entities.

Concepts in a context can be characterized in terms of partial ordered theory, thanks to the fact that they conform a lattice under set inclusion.

Proposition 2.22. *The set of all concepts on a formal context (G, M, r) together with the relation $\leq_r$ defined by*

$$(O_1, A_1) \leq_r (O_2, A_2) \text{ iff } O_1 \subset O_2 \tag{2.16}$$

is a complete lattice, called the concept lattice *of (G, M, r). The supremum (a.k.a. least upper bound) and infimum (a.k.a. greatest lower bound) of any subset of concepts are given by*

$$\begin{aligned} \bigvee_{i\in I}(O_i, A_i) &= ((\cup_{i\in I} O_i)^{rr}, \cap_{i\in I} A_i) \\ \bigwedge_{i\in I}(O_i, A_i) &= (\cap_{i\in I} O_i, (\cup_{i\in I} A_i)^{rr}) \end{aligned} \tag{2.17}$$

Example 2.23 (Concepts on natural numbers)**.** Consider a context (G, M, r) where G is the set of naturals from 1 to 10, and M comprises the attributes “composite” (c), “square” (s), “even” (e), “odd” (o), and “prime” (p), and the appropriate binary relation. Figure 2.2 shows the Hasse diagram of the corresponding concept lattice. The structure of the concept lattice unveils several generalizations that can be predicated in terms of those concepts, such as:

i) *No element of O has all attributes in A* (the infimum of the lattice is a concept with empty extent)

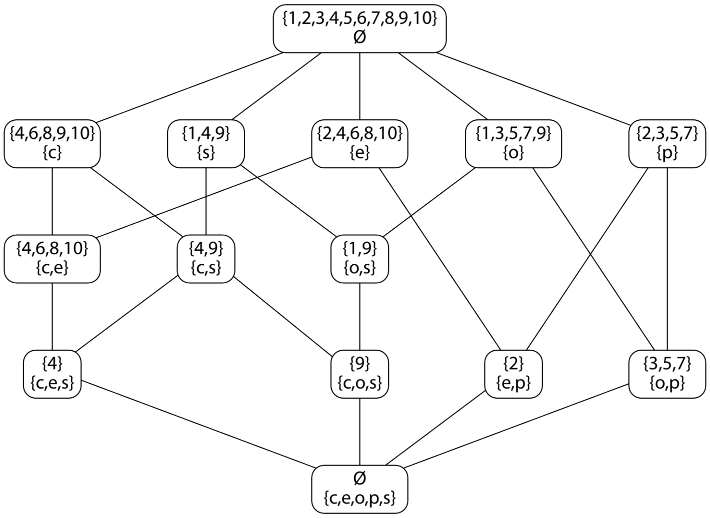

Figure 2.2: Concept lattice of the naturals from 1 to 10, with the attributes *composite* (c), *even* (e), *odd* (o), *squared* (s), and *prime* (p). Taken from http://en.wikipedia.org/w/index.php?title=Special:Search&search=semiconcept, last visit on May 17, 2011.

ii) *No element of O is both odd and even* (the infimum of the corresponding concepts is the infimum of the lattice)

iii) *Primes in O are neither square, nor composite* (the infimum of the corresponding concepts is the infimum of the lattice).

Also, note that for any given pair of subsets of attributes $A_1, A_2 \in A$, the implication $A_1 \to A_2$ holds if and only if $(A_1^r, A_1^{rr}) \leq_r (A_2^r, A_2^{rr})$; that is, if the largest concept containing A_1 as part of its intent is also described by A_2 (Carpineto & Romano, 2004). For instance, take $A_1 = \{c, o\}$ and $A_2 = \{s\}$. We have:

$$\begin{aligned} (A_1^r, A_1^{rr}) &= (\{9\}, \{c, o, s\}), \\ (A_2^r, A_2^{rr}) &= (\{1, 4, 9\}, \{s\}), \end{aligned} \tag{2.18}$$

so that $(A_1^r, A_1^{rr}) \leq_r (A_2^r, A_2^{rr})$, meaning that *in the present context* ‘odd and composite’ implies ‘squared’. In the same way we can prove that ‘even and square’ implies ‘composite’.

* * *

Example 2.24 (Network positions)**.** Consider the category of graphs and adjacency preserving relations introduced in **Example 2.17**. For any given graph G, the concept lattice of the context induced by $E_G : G \to G$ (see e.g. Figure 2.3) provides a generalization of the notion of position in network analysis.

Two vertices $u, v \in V_G$ are said to be *structural equivalent* if $N(u) = N(v)$. In that case, it is also said (mainly in the social sciences) that both vertices have the same *position* in the network. The idea is that two structural equivalent vertices share the same relations to all other vertices in the network, so their ‘position’ with respect those nodes is essentially the same. Now, note that any vertex w such that $N(u) \subset N(w)$ is related to all vertices u and v are linked to. This means that w is in a position that allows it to perform all actions that u and v may perform. For example, suppose that edges in G represent communication between the vertices they connect. This means that u may mediate communication between two vertices x and y if and only if it stands in a path going from x to y. But in that case, there is necessarily a path connecting x and y that goes through w, so it may also mediate communication between these vertices. We could then say that w is also in the same position as u and v, despite not being structural equivalent to them, or that it is in a position that *dominates* that of u and v.

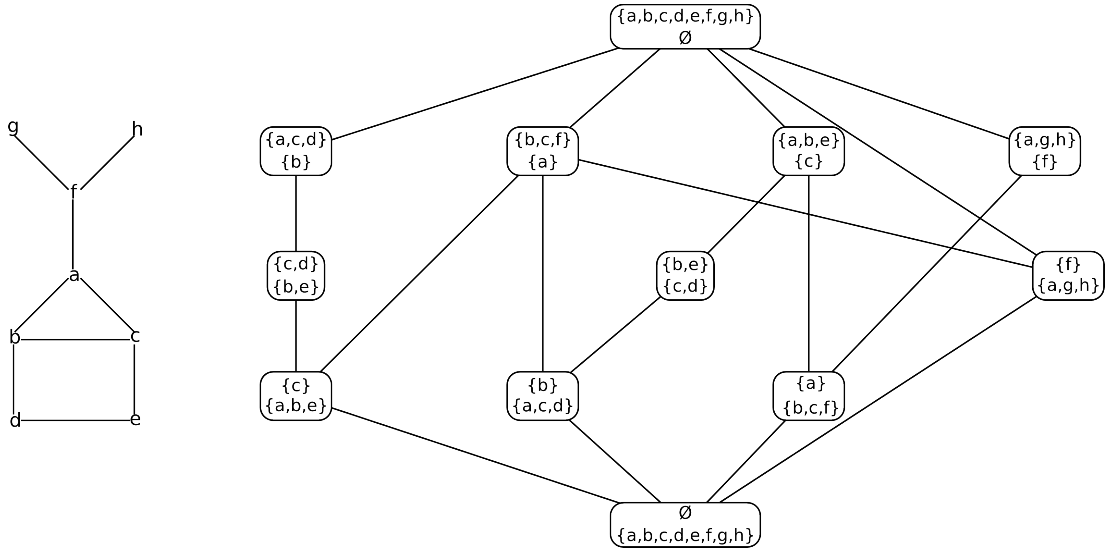

Figure 2.3: A graph (left) and the concept lattice of its positions (right).

We introduce a broader definition of position following the previous argument. The first requirement for saying that a subset of vertices are in a given position is that they are adjacent to a given subset of vertices. Thus, for a vertex subset $U \subset V_G$, we define U' as the set of vertices adjacent to all $u \in U$. In this way, we can say that all vertices in U are in the same position relative to vertices in U'. But then, any $v \notin U$ such that all vertices $w \in U'$ are adjacent to it is also in the same position as any element of U

relative to vertices in U'. Since adjacency relations are symmetric, this means that the full position is given not by U, but by U''.

Note that U'' is a closure operator analogous to ^{rr} in **Definition 2.20**, and that (U'', U') satisfies the properties of a concept introduced in **Definition 2.21**. Also, note that the relation $E_G : G \to G$ relates each $v \in V_G$ with the set of its neighbors, so that $U' = U^r$. In conclusion, a position can be defined as a concept in the context induced by $E_G : G \to G$.

Figure 2.3 depicts a graph and the concept lattice of its positions. For any given vertex v in the graph, its most specific position is given by the infimum of all concepts that include it; that is, (v^{rr}, v^r). Notice that such position is not necessarily conformed by a class of structural equivalent vertices, though it must contain one. For instance, the smallest position containing object g in Figure 2.3 is $(\{a, g, h\}, \{f\})$ –the concept of vertices related to f. Out of the three elements of its extent, only g and h are structural equivalent, and conform a full structural equivalence class. Though we cannot know this just by examining the concept extent g^{rr}, knowledge that f and g are structural equivalent is not lost: it is reflected in the fact that $(g^{rr}, g^r) = (h^{rr}, h^r)$.

Dominance relations are reflected in order relations in the concept lattice of positions. Once more, in Figure 2.3 we have $g^{rr} = \{a, g, h\}$ and $a^{rr} = \{a\}$, then $(a^{rr}, a^r) \leq (g^{rr}, g^r)$. This means that the characteristic relations of a's most specific position imply those of g's most specific position, so that the former dominates the later.

* * *

2.4 Changes of representation

Consider a system of internally related entities being represented by means of an object C in a category $\mathcal{C}$. A functor $F : \mathcal{C} \to \mathcal{D}$ in an equivalence of categories (**Definition 2.8**) maps C into an object $D \in \mathcal{D}_0$ that offers an equivalent representation of the system. In other words, everything that we may say about the structure of the system by looking into the category-theoretical properties of C can be equally said by looking into the category-theoretical properties of D.

Equivalence of categories thus introduce *changes of representation* that transform a mathematical image of a system into a new structure, while preserving all its characteristic features. Though nothing new is introduced by the change of representation, key attributes of the system that went unnoticed in $\mathcal{C}$ may stand out on its image in the codomain of $\mathcal{D}$.

Also of relevance, the lack of an equivalence of categories allow us to determine when we are *not* dealing with equivalent images of a system, raising awareness on the loss of information or introduction of artifacts involved in the transformation. The following example goes in this line, analyzing the transformation of metric spaces into dendrograms performed in many hierarchical clustering techniques. In category-theoretical terms, this transformation is carried by means of a functor $f : \mathcal{M} \to \mathcal{T}$. Here we prove that this functor cannot be an equivalence of categories, which means that transforming a metric space into a dendrogram implies loss of information on similarity.

Example 2.25 (More on hierarchical clustering)**.** On previous examples we have considered two mathematical images of similarities among elements of a set: metric spaces (**Example 2.12**) and dendrograms (**Example 2.13**). Unlike metric spaces, dendrograms can always be represented by a two-dimensional picture that can be easily read and interpreted. On light of this advantage, hierarchical clustering algorithms have been designed to transform the metric space representations of a set into a dendrogram that respects the similarities consigned in the original image.

From the perspective of classification systems and changes of representation, an algorithm of hierarchical clustering relies on a functor from a category of metric spaces into a category of dendrograms. Since elements of the dendrogram (i.e. leaves of its rooted tree) are identified with the elements of the metric space, this functor must be such that it maps metric spaces with n elements into dendrograms with n elements. Ideally, this functor should be part of an equivalence of categories, since that would mean that all similarities consigned in the original metric space are kept in the dendrogram. Is there such a functor?

Consider the category $\mathcal{M}$ of metric spaces introduced in **Example 2.12**, and the category $\mathcal{T}$ of dendrograms introduced in **Example 2.13**. In Figure 2.4 we illustrate the particular case of metric spaces and dendrograms with up to 3 elements, corresponding to the subcategories $\mathcal{M}_3$ and $\mathcal{T}_3$. Since our interest is to find an equivalence of categories $F : \mathcal{M}_3 \to \mathcal{T}_3$, we only need to consider one representative from each class of isomorphic objects on each category. In the case of $\mathcal{T}_3$ all pairs of dendrograms with the same number of elements are isomorphic, so we just pick one representative T_i from each class of dendrograms with i elements. In $\mathcal{M}_3$ we have six equivalence classes:

i) The class of metric spaces with three equidistant elements. We pick an element $M_{==}$ from this class.

ii) The class of metric spaces with three elements a, b, c, such that $d(a, c) < d(a, b) = d(b, c)$. We pick an element $M_{<=}$ from this class.

iii) The class of metric spaces with three elements a, b, c, such that $d(a, c) > d(a, b) = d(b, c)$. We pick an element $M_{>=}$ from this class.

iv) The class of metric spaces with three elements a, b, c, such that $d(a, b) < d(b, c) < d(a, c)$. We pick an element $M_{<<}$ from this class.

v The class of metric spaces with two elements, from which we pick an element M_2.

vi) The class of metric spaces with one element, from which we pick an element M_1.

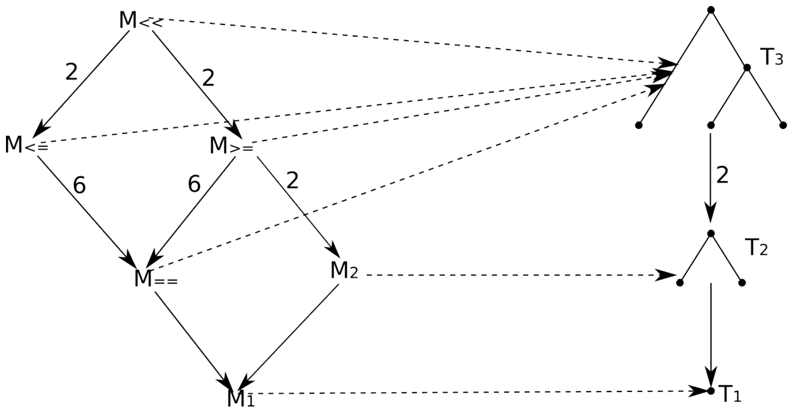

Figure 2.4: A functor $F : \mathcal{M}_3 \to \mathcal{T}_3$ such that for any metric space M, the dendrogram FM has exactly $|M|$ leaves. The diagram on the left represents $\mathcal{M}_3$, and the diagram on the right represents $\mathcal{T}_3$. We only consider one representative from each class of isomorphic objects on each category (see the text for details). Solid arrows represent morphisms in each category, arrow weights stand for the number of different morphisms with the same domain and codomain. Identity morphisms and compositions are not drawn. Dotted arrows represent the object mapping of the functor. The morphism mapping is not shown.

Since we have just one dendrogram (up to isomorphism) with 3, 2, or 1 elements, there is but one possible candidate functor (up to natural isomorphism) $F : \mathcal{M}_3 \to \mathcal{T}_3$ satisfying the restriction of mapping metric spaces with n elements into dendrograms with n elements. The object mapping of this functor is represented by the dotted arrows in Figure 2.4. This functor is not part of an equivalence of categories for two reasons:

i) since there are up to 6 morphisms between some pairs of elements in $\mathcal{M}$ but never more than 2 morphisms between any pair of elements in $\mathcal{T}$, F cannot be faithful

ii) since $M_{==}$ is not related by a morphism to M_2, the functor cannot be full. Indeed,

$$\begin{aligned} |\mathrm{Hom}_{\mathcal{M}}(M_{==}, M_2)| &= 0 \\ |\mathrm{Hom}_{\mathcal{T}}(T_3, T_2)| &= 2 \end{aligned} \tag{2.19}$$

so $F_{M_{==},M_2} : \mathrm{Hom}_{\mathcal{M}}(M_{==}, M_2) \to \mathrm{Hom}_{\mathcal{T}}(FM_3, FM_2) = \mathrm{Hom}_{\mathcal{T}}(T_3, T_2)$ cannot be surjective.

The last issue is particularly remarkable, as it points to the inadequacy of equating $M_{==}$ to T_3: by doing so we are saying that the former can also be reasonably partitioned in two classes of equivalence, which is doubtful: all elements being equidistant, clustering any two of them together while leaving a third out on its own class is very questionable, to say the least.

Though they look trivial, morphisms in $\mathcal{M}_3$ with codomain in $M_{==}$ are actually quite important. For instance, as the difference between $d(a,b)$, $d(b,c)$, and $d(a,c)$ becomes smaller $M_{<<}$ approaches $M_{==}$, so that the classification in two classes given by $h : M_{<<} \to M_2$ seems intuitively less adequate, while the one given by $f : M_{<<} \to M_{==}$ looks more attractive[6]. So, even though f may look as a trivial classification, the fact that we still have the option of choosing it above $h : M_{3<} \to M_2$ is important. By changing into a representation in terms of dendrograms we are losing this option.

In conclusion, $\mathcal{T}$ is not equivalent to $\mathcal{M}$. This means that, regardless of how much effort and care we put in the design of a hierarchical clustering algorithm, some relevant information contained in the metric space will be lost in translation.

* * *

2.5 Optimal classifications

Each morphism $f : C \to D$ in a category satisfying the conditions introduced in **Definition 2.16** provides a different classification on C. Often times scientists are interested in choosing 'the best' classification on C among all possibilities. This enterprise implies the existence of a criterion of optimality that singles a unique (up to category equivalence) morphism in the category. We may thus formulate the problem of finding an optimal classification as an optimization problem in a category $\mathcal{C}$, whose solutions are morphisms in $\mathcal{C}_1$. Let us do so in formal terms.

An optimization problem is a quadruple (I, f, m, g) where

i) I is the set of *instances* of the problem

ii) for any instance $x \in I$, $f(x)$ is the set of *feasible solutions* of the problem

iii) for any instance $x \in I$ and a feasible solution $y \in f(x)$, $m(x,y) \in \mathbb{R}^+$ is the *measure* of y

iv) g is the *goal function*, which is either min or max.

For any given instance x, the function $m(x,y)$ gives the measure of the optimality of a feasible solution y, according to the criterion introduced by the goal function. The

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[6] This intuition is formalized by the optimality criterion that will be introduced in **Example 2.26**. As we move towards the aforementioned limit, the value $m(h : M_{<<} \to M_2)$ of the measure function of equation (2.20) becomes increasingly large, showing that the corresponding classification is becoming less optimal.

objective of an optimization problem, then, is to evaluate the goal function on the measure function for some given instance of the problem.

In the case of classification optimization, the set of instances is the object set $\mathcal{C}_0$ of a classification system $\mathcal{C}$, and for any instance $C \in \mathcal{C}_0$ the set of feasible solutions is the set of morphisms in $\mathcal{C}_1$ with domain in C. The goal function is normally chosen simultaneously with the measure function, which would be the last element required for determining a classification optimization problem.

Though a classification system immediately determines the instance set and feasible solutions of a classification optimization problem, it does not naturally determine a unique measure function. This means that we may formulate multiple optimization problems on the same classification system just by introducing different measure functions. In other words, optimal classifications on a structured set are not "unique up to isomorphism". Far from considering this indeterminacy as a weakness of the method, we think that it is necessary. A category $\mathcal{C}$ taken as a mainframe for research on a system of internally related entities is constructed in accordance with the relational structure exhibited by those entities. In other words, such category is determined by general features of a given research field. On the other hand, classification optimality is heavily contingent in more specific goals set by the researcher, that may vary within the same field of inquiry. Expecting the existence of a unique legitimate criterion of classification optimality on any given category would equate to expecting the existence of a unique legitimate question to be posed on some given corner of nature.

The following examples illustrate this position. We work within the frame of non-hierarchical clustering with metric spaces, that is, within the classification system $\mathcal{M}$ of **Example 2.12**. The first example introduces a measure function that feels naturally determined by the structure of $\mathcal{M}$. But then, the second example shows that this measure function determines an optimization problem whose solutions are actually undesirable, as they do not attain the ultimate goal of clustering. In consequence, we introduce a second measure function that discards such solutions. Last, on the third example we show that regardless of which of the previous measure functions we choose, solutions of the corresponding classification problems induce trivial concept lattices. Thus, if we were looking for a classification that conforms a conceptual structure intended for logical inference, we would require a different measure of optimality.

Example 2.26. The main goal of clustering techniques is to partition a set into classes of equivalence according to similarity relationships among its elements. In **Example 2.12** we introduced a suitable category for achieving this purpose by means of metric spaces, i.e $\mathcal{M}$. In this classification system similarity between two elements is inversely proportional to their distance. Classifications are determined by morphisms that preserve order relations among distances (see equation (2.9)), so that elements of the same class are always more similar to each other than to elements of other classes. Following this same criterion, a good classification should achieve large similarity among the members of the same class, and low similarity among members of different classes. The k-medoids clustering method tries to achieve this goal by minimizing the within-cluster distance to the cluster medoid μ_y; that is, for $X \in \mathcal{M}$ and $f : X \to Y$, it minimizes the measure function

$$m(X, f) = \sum_{y \in Y} \sum_{x \in \ker f(y)} d(x, \mu_y), \tag{2.20}$$

where μ_y is the element of $\ker f(y)$ whose average distance to all remaining elements of that class is minimum.

This measure function comes quite close to the ideal of an optimality criterion that is naturally induced by the classification system. If classifications in $\mathcal{M}$ are such that elements of the same class are closer than elements of different classes, by minimizing (2.20) we are taking this condition to the extreme, asking for a classification were elements of the same class are as closely packed together as possible, and different classes are spread far away from each other.

* * *

Example 2.27. Note that any isomorphism in $\mathcal{M}$ minimizes (2.20); that is, a partition in unitary classes is optimal under this criterion. Such partition is generally undesirable in cluster analysis. The fact that it minimizes (2.20) is hardly a problem in practice, as the standard k-medoids clustering algorithm requires the number of clusters to be produced as a parameter. Yet, it is pertinent to ask what criterion of optimality are we following when discarding isomorphism-induced classifications, as it is clear that it is not the same underlying the k-medoids clustering method.

Restrepo *et al.*(2005) explain the avoidance of both the discrete partition in unitary classes and the gross partition in a single class in terms of optimization of the information contained in the classification: what we are optimizing in this case is the number of similarity and dissimilarity relations that it establishes. According to the authors, two elements belonging to the same class determines a similarity relation, and two elements belonging to different classes determines a dissimilarity relation. Thus, the authors propose

$$m(X, f) = \prod_{y \in Y} |\ker f(y)| \tag{2.21}$$

as a measure function for choosing an optimal classification on these grounds. Note how $m(X, f)$ grows with both cluster size, which is proportional to the number of similarity relations contained in the classification, and with the number of clusters, which is proportional to the number of dissimilarity relations.

* * *

Example 2.28. In **Section 2.3** we sketched how we can use FCA to define concepts on a morphism-induced classification, and then look into the concept lattice to formulate generalities and make inferences. The possibility of exploiting this tool is contingent on the structure of the concept lattice, which for the case of disjoint classifications is trivial: the concept with empty intent is the supremum of any subset of concepts, and the concept with empty extent is the infimum of any subset of concepts, all other concepts being incomparable under the partial order (see Figure 2.5). No generalities or inferences are possible, besides the assertion that all attributes are mutually exclusive. By contrast, in **Example 2.24** we showed that a non-disjoint classification induced by a general binary relation produces a concept lattice with a richer structure. Thus, disjoint classifications that are preferred in cluster analysis are highly sub-optimal when we intend to define concepts and characterize the system by means of FCA.

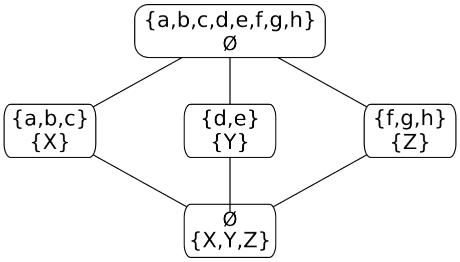

Figure 2.5: Concept lattice of a partition.

* * *

Though the criteria introduced in the previous examples are clearly different, they are not incompatible. Yet, as they aim at distinct purposes, in most situations each criteria will be associated with a different optimum. Thus, though we may combine several of these measure functions into one single classification optimization problem, it is very unlikely that its solution would be a classification with both minimum within-cluster distance, maximum information content, and inducing a complex concept lattice. Compromises are necessary, so it is important to set out priorities. Would we rather have a classification with maximum information, even if its classes are not as compact and separated as possible? How many similarity relations are we willing to sacrifice to make classes more compact? These are the kind of questions that must be solved when choosing a measure function. If data structure determines the classification system of choice, it is the awareness of the main purpose pursued on each classificatory enterprise that allows us to single one classification from all the alternatives given by the classification system.

2.6 Summarizing

Structured sets provide a mathematical image of a system of internally related entities. The collection of all subcategories of **Rel** along with their functors thus defines the broadest landscape for the mathematical formalization of the internal relations approach. In principle, each of these categories offers a mathematical representation of fundamentally different kinds of systems of study, characterized by the logical structure of the relations among its objects. Equivalent categories, however, are equivalent precisely in the sense that they share a common logical structure. In consequence, a class of equivalent categories offers a *system of models* for scientific inquiry. Functors allow us to move between these categories, looking for new yet equivalent mathematical images that may assist our intuition in different ways, revealing patterns, properties and concepts that may have gone unnoticed previously.

Once we are standing in an specific category, morphisms determine the collection of structure-preserving transformations that answer to the different patterns emerging in the relations among the relevant empirical entities. Each of these transformations induces a classification of those entities, that provides a characterization of the relational structure of the system in terms of properties of its constituents. In this way, a particular set category defines a *classification system*, i.e. a collection of viable classifications within which property and concept definition take place, thus advancing our knowledge on the nature of the entities being researched.

Though each classification within a classification system is equally legitimate and provides valuable information on the system of study, the specific purpose pursued on a given research problem leads us into preferring some classifications over others. This preference can be materialized in a measure function that links each viable classification-inducing morphism with a real number that weights its degree of optimality. We thus arrive to the formulation of a *classification problem*, i.e. an optimization problem whose goal is to find a morphism that yields an optimal classification under a criterion grounded on the particular objective pursued by the researcher.

In these terms, a mathematical model of chemical activity consists of: a set category that better suits the peculiar logical structure of chemical reaction networks, where classifications are constructed; the collection of equivalent images of that category, which offer alternative representations that may suggest new concepts and heuristics; and a collection of optimality criteria, that guide our choice of particular classifications in response to more specific goals.

Chapter 3

A network model of chemical activity

"It never occurred to anybody that a chemical analysis could contain an undisturbed object."
–Rudolf Werner Soukup

In the last chapter we proposed to use objects in set categories as the fundamental images of sets of internally related entities. We now propose a specific category designed for the characterization of chemical substances in terms of their chemical activity.

In Section 1.4 we noted that chemical knowledge on substance reactivity conforms a network of chemical reactions. It is thus natural to search candidate objects for our category among the mathematical representations used in network analysis. Graphs are the top candidates, as they are probably the most widely spread representation of networks across scientific disciplines. However, when constructing a network model, special care must be put in ensuring that node connections in the network properly match the logical structure of relations between the entities being represented. Sometimes, the relations established by edges in a graph are unable to achieve this purpose. Thus, several variations on the concept of graph, such as directed graphs, hypergraphs, and directed hypergraphs, have been proposed as representations of different kinds of networks. On Section 3.1 we argue that the peculiar relational structure of chemical reaction networks points to the inadequacy of simple graph models as a foundation for a network model of chemical activity and propose directed hypergraphs as a better suited alternative. We support this choice in an extense analysis that considers the recent impact of directed hypergraphs in the understanding of biochemical reaction networks and intently refutes the statement, sometimes found in the literature of network analysis, that hyperdigraph models of reaction networks are ultimately equivalent to a particular graph model.

In the second section of this chapter we define the category **HyperD** of directed hypergraphs which conforms the core of our model of chemical activity. We introduce adjacency preserving relations between hyperdigraphs that we call *role assignments*, and prove that they constitute the morphisms of a category whose objects are directed hypergraphs. This category defines a classification system for the characterization of substance activity. In general, classifications in **HyperD** are non-disjoint, so the question appears on how can we determine what particular property is exhibited by a substance when participating in a specific chemical reaction. To address this question, we show that role assignments are closely related to mappings that define a set of rules for assigning a unique role to each substance on each relation. We call these mappings *role models*.

After illustrating how morphisms in **HyperD** may induce well know classifications of chemical substances, on section 3.3 we consider the matter of their predictive power. We argue that the sole classificatory structure induced by a role assignment is able to make predictions on the activity of unknown substances, by means of an auxiliary hypothesis regarding the completeness of the associated concept lattice. Then, we show that the capability of a classification to make predictions depends on the size of the role assignment that induces it, which may thus be used as a criterion of optimality. In consequence, we propose to use the cardinal of role assignments as a measure function to define an optimization problem whose solutions are classifications with maximum predictive power.

Last, on section 3.4 we analyze the link between chemical activity and chemical structure by considering the case of structural formulas. We show that structural formulas can be induced by means of a change of representation into a category whose elements are sets of structural graphs. Up to this point, structural formulas are completely determined by **HyperD**, so they offer nothing more than an alternative image of the reaction network. However, since unlike vertices in a hyperdigraph structural formulas have properties of their own, an inversion of analogy allows us to generate hypotheses on the activity of chemical substances by analyzing the individual properties of their corresponding formulas. In this way, the bidirectional relation between structure and activity is made explicit: on a first moment an activity model determines an structure model, but then on a second moment the structure model becomes able to induce changes on the activity model, improving our understanding of the chemical nature of substances.

3.1 The hyperdigraph as a model of chemical reaction networks

Chemical reaction networks are becoming an important construction in systems biology, where they are used as a model for cell metabolism (see e.g. Barabási and Oltvai (2004) for a brief review on this subject). The main interest in this field is the study of global network properties that describe the organization characteristic of living beings. Several graph models of reaction networks have been proposed, which are our prime candidates for defining a category for the characterization of chemical activity:

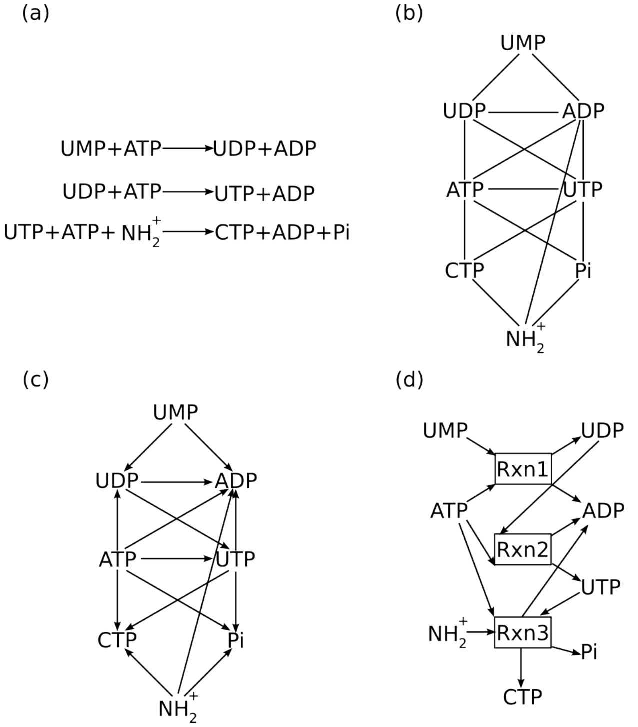

Figure 3.1: A network of three phosphorilation reactions (a) modeled as a simple substrate graph (b), as a directed substrate graph (c) and as a directed bipartite reactions-substances graph (d).

- An undirected graph, with one node for each substance, and an edge between two nodes if there is a precursor-product relation between the corresponding substances. This is known as the *substrate graph* (Figure 3.1(b)).
- A directed graph, with one node for each substance and arcs pointing from reactants to products. This is known as the *directed substrate graph* (Figure 3.1(c)).
- A bipartite digraph, where nodes of one class represent substances, nodes of the other represent chemical reactions, and arcs point from reactants to reactions and from reactions to products (Figure 3.1(d)).

With growing interest in network models of the metabolism, criticism has arisen towards these proposals. The issue pointed is that graph models are unable to capture transverse ‘and’ relations among reactants and products (Klamt *et al.* , 2009; Bernal & Daza, 2011). A chemical reaction does not take place unless all reactants are present, and cannot yield one product in the absence of the others. This means that a generic reaction, say $a + b \to c + d$, establishes a connection not from a to c or from b to d, but from a *and* b to c *and* d. The connectivity patterns of graphs suggests otherwise: notice e.g. how all graph models depicted in Figure 3.1 suggest that ADP can be obtained as the unique product of the transformation of UMP, while the reactions in Figure 3.1(a) make it clear that such transformation only happens in the presence of ATP, and inevitably yields ADP as a second product.

In light of this issue, directed hypergraphs are becoming increasingly popular as a mathematical image of chemical reaction networks (Klamt *et al.* , 2009; Bernal & Daza, 2011, and references):

Definition 3.1 (Klamt *et al.* (2009))**.** A *directed hypergraph* or *hyperdigraph* H consists of a set V_H of *vertices*, and a set A_H of ordered pairs of subsets of V_H, known as *hyperarcs*. For $a = (U, V) \in A_H$, U is know as *the tail of* a, which we note $\mathrm{tail}(a)$, and V is known as *the head of* a, which we note $\mathrm{head}(a)$.

Directed hypergraphs achieve a more faithful representation of the kind of relation established by a chemical reaction. Once more, consider a generic reaction $a + b \to c + d$, which would be represented by the hyperarc $(\{a, b\}, \{c, d\})$ (See Figure 3.2). The reactant-reactant relation between a and b is encoded by their presence in the tail of the hyperarc. In the same way, product-product relations are coded in its head. Last, regarding reactant-product relations, by coding the reaction as an ordered pair of subsets of nodes, a relation is established between the *complete* set of reactants $\{a, b\}$ and the *complete* set of products $\{c, d\}$. This offers a more accurate image of the chemical situation: all reactants must be present and consumed in order to yield all the corresponding products[1].

Some authors have pointed that hyperdigraph and bipartite digraphs models of chemical reaction networks are ultimately equivalent (see e.g. Forst *et al* (2006)). The reason behind this statement is the existence of a bijective mapping F from hyperdigraphs onto bipartite graphs: Given a hyperdigraph H with vertex set V_H and hyperarc set A_H, define the vertex set of the bipartite digraph FH as $V_D =$

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[1] It is worth noting that stoichiometry is not accounted for on this formulation. This issue has been dealt with by several authors in two ways: either define the terms of a hyperarc as *multisets* of vertices(Dittrich & di Fenizio, 2007; Centler *et al.* , 2007), so that the number of occurrences of a given vertex gives the stoichiometric coefficient of the corresponding substance; or introduce a matrix of stoichiometric coefficients, that determines a weighting on each vertex in each hyperarc(Stelling *et al.* , 2002; Klamt & Gilles, 2004). For the sake of simplicity, here we decided to let stoichiometry unaccounted for. Including stoichiometry is one of the top priorities for future iterations of the model.

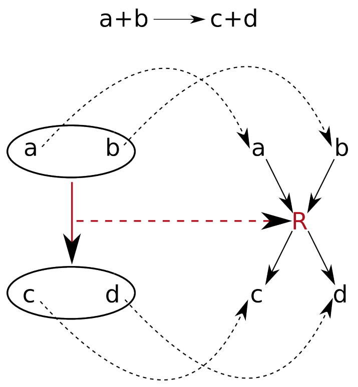

Figure 3.2: A generic reaction represented as a hyperdigraph with a single hyperarc (left) or as a bipartite digraph with one class of vertices for substances and another class for the single reaction (right). There is a bijective transformation F relating hyperdigraphs with bipartite digraphs, represented here by dotted arrows.

$V_H \cup A_H$, and for each $a \in A_H, a = (\{u, \ldots, v\}, \{x, \ldots, y\})$, introduce the subset of arcs $\{(u, a), \ldots, (v, a), (a, x), \ldots, (a, y)\}$ into FH (see Figure 3.2). This mapping can be inverted, so it defines a bijection F between hyperdigraphs and bipartite digraphs, which seems to prove the equivalence. Though so far this statement has been presented matter-of-factly and has not had much impact in the development of graph-like models of chemical reaction networks[2], if correct it would bear important consequences. While graphs have been present in chemistry for some decades and are already familiar to the community of mathematical chemists, the mathematics of directed hypergraphs necessary for their implementation in reaction network models have just started to be developed. And there would be no point in undergoing this demanding enterprise if hyperdigraphs were ultimately equivalent to a particular family of graphs. Or, more precisely, equivalence would imply that the required mathematics of hyperdigraphs have already been developed: they are the same mathematics of bipartite graphs.

This shows that the matter of equivalence between these two constructions is a key issue for the present proposal. It concerns the choice of the basic mathematical formalism to be used. If both models were equivalent, we could still rely on the standard mathematics of graphs, despite all appearences. Else, a different formalism has to be developed. We will thus take some time to dicuss in what sense can directed hypergraphs be considered equivalent to bipartite digraphs, if they can.

The first thing to note is that equivalence between two models cannot be proven by the mere existence of a bijection between their fundamental entities. We doubt anyone

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[2] For instance, Forst *et al* (2006) work all the mathematical details of an hyperdigraph model with no reference at all to bipartite digraphs beyond the brief statement that they are equivalent to hyperdigraphs.

would sustain such a thing in general. For instance, both the set of all possible bipartite digraphs and the set of all possible directed hypergraphs have the same cardinal as the set of integers and can thus be bijectively mapped into it; yet it is clear that an integer would give a very poor representation of a reaction network. It is not just because F is a bijection that we feel that it proves equivalence; there is something else that makes that particular bijection special. Indeed, there is something 'natural' in the way it maps vertices and hyperarcs of H into the vertices of FH that gives the feeling that the essential connectivity pattern of the network is being preserved. Yet, we find us at odds when attempting to define exactly what that statement means.

Things are more clear if we think in terms of category theory. Bipartite digraphs are defined as objects in a category, so "the essential connectivity pattern" of a bipartite digraph is characterized by its viable transformations. Equivalences of categories preserve those viable transformations, so the statement that bipartite digraphs and hyperdigraphs give equivalent models of reaction networks means that they span equivalent categories. This means that F just gives us one of the elements necessary to prove equivalence: an object-to-object mapping between two still undetermined categories. We still have to explicitly define the morphisms in the categories of bipartite digraphs and of hyperdigraphs, and to define two mappings connecting morphisms in each category with morphisms in the other that are pesudoinverses in **Fun** (see **Definition 2.8**, page 27). Note that the existence of such mappings depends on how we define the corresponding categories, a matter that is not solved by the sole definitions of bipartite digraph and hyperdigraph. We have to say how they can be transformed. This emphasizes the fact that the question of whether a bipartite digraph model of reaction networks is equivalent to a hyperdigraph model does not boil down to whether bipartite digraphs are equivalent to hyperdigraphs, as neither bipartite digraphs nor hyperdigraphs give a model by themselves. A model (in the internal relations perspective) comprises both its objects and their viable transformations. The question at hand cannot be solved until we define the latter.

So let us consider the matter of determining the categories involved. The rationale behind the transformation of hyperdigraphs into bipartite digraphs is that, instead of using the more complex and less known hyperdigraphs, we may rely on a representation of a reaction network as the already well-characterized and familiar directed graphs. We would thus be regarding bipartite digraphs as a subcategory of **Digraphs**, where morphisms are adjacency-preserving mappings. So we will consider the category of bipartite digraphs and adjacency preserving mappings, which we call **BDgraphs**. Regarding directed hypergraphs, we may define morphisms through a generalization of adjacency preserving mappings, i.e. mappings $f : \mathbf{V_H} \to \mathbf{V_B}$ such that for each $(\{u_1, \ldots, u_m\}, \{v_1, \ldots, v_n\}) \in \mathbf{A_H}$, $(\{f(u_1), \ldots, f(u_m)\}, \{f(v_1), \ldots, f(v_n)\}) \in \mathbf{A_B}$, thus completing the definition of the hyperdigraph category **HyperD**[3].

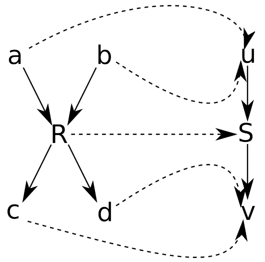

Figure 3.3: A morphism in **BDgraphs**. Solid arrows represent arcs on each graph, dotted arrows represent a morphism from the digraph on the left to the digraph on the right.

Now, consider a network of a single reaction, $a + b \to c + d$. This network would be represented by the bipartite digraph D_1 with vertex and arc sets given by

$$\begin{aligned} V_{D_1} =& \{a, b, c, d, R\} \\ A_{D_1} =& \{(a, R), (b, R), (R, c), (R, d)\} \end{aligned} \tag{3.1}$$

and by the hyperdigraph H_1 with vertex set $\{a, b, c, d\}$, and a lone hyperarc $(\{a, b\}, \{c, d\})$ (see Figure 3.2). Next, consider the bipartite digraph D_2 given by

$$\begin{aligned} V_{D_2} =& \{u, v, S\} \\ A_{D_2} =& \{(u, S), (S, v)\} \end{aligned} \tag{3.2}$$

According to the inverse object-to-object mapping F^{-1}, this digraph corresponds to the directed hypergraph H_2 with vertex set $\{u, v\}$ and a lone hyperarc $(\{u\}, \{v\})$. As shown in Figure 3.3, there is an adjacency preserving mapping $f : V_{D_1} \to V_{D_2}$ that is a morphism in **BDgraphs**. On the other hand, since the cardinalities of the terms of the only hyperarc in H_1 are greater than the cardinalities of the terms of the only hyperarc in H_2, *there is no morphism in* **HyperD** *with domain in* H_1 *and codomain in* H_2. This means that, no matter what morphism-to-morphism mapping we may propose, it cannot be such that $F(f : D_1 \to D_2) = F(f) : F(D_1) \to F(D_2)$. Thus, the object-to-object mapping F does not allow for the definition of a functor F : **HyperD** $\to$ **Digraphs**, so it cannot be part of an equivalence of those categories. In conclusion, according to our criterion we are dealing with two different models.

Though the bijective mapping F between bipartite digraphs and hyperdigraphs may be the object-to-object mapping of an equivalence of categories between **HyperD** and

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[3] It is important to note that since the terms of a hyperarc are sets, the previous condition implies that $f(u_i) \neq f(u_j)$ for $i, j = 1, \ldots, m$, and $f(v_i) \neq f(v_j)$ for $i, j = 1, \ldots, n$. In other words, the restriction of f to each of the terms of a hyperarc must be a bijective mapping.

a category of bipartite digraphs, *the latter cannot be the category* **BDgraphs** *defined above.* This shows that our take on bipartite digraphs changes at a fundamental level when we think of them as equivalent images of hyperdigraphs that thus give the same mathematical description of chemical reaction networks. Though in such case bipartite digraphs may still be defined as usual, they can no longer be transformed in the same way –i.e., they span a category whose morphisms are not the same of **BDgraphs**. These 'new' bipartite digraphs are thus embedded in a different mathematical formalism, and in that sense differ from their usual self. To determine their category we must look deeper into how chemical constraints affect the collection of viable transformations between bipartite digraphs that represent reaction networks.

So let us determine precisely what is different about the way such bipartite digraphs transform. The key change comes from our appreciation of the two vertex classes in the bipartite digraph. To show this, let us explicitly define a *bipartite digraph* as consisting of two vertex sets V^a and V^b, and two arc sets $A^{ab} \in V^a \times V^b$ and $A^{ba} \in V^b \times V^a$, so that V^a represents the substance set and V^b represents the reaction set of the network. Now, let G_1 and G_2 be two bipartite digraphs. We note that adjacency preserving mappings in **BDgraphs** that map vertices in $V^a_{G_1}$ into vertices in $V^b_{G_2}$ 'transform' substances into chemical reactions, a procedure that is not allowed by chemistry. The two vertex classes defining a bipartite digraph are incompatible, meaning that they must be transformed separately; that is, a viable transformation should map vertices in $V^a_{G_1}$ into vertices in $V^a_{G_2}$, and in the same way for $V^b_{G_i}$.

The transformation of Figure 3.3 points to another problem related to the special status of vertices in V^b. The problem with this transformation is that it does not preserve the degree of the lone vertex in $V^b_{D_1}$, which equates to changing reaction molecularity, an important chemical invariant. Morphism in **HyperD**, on the other hand, preserve this invariant by keeping the size of hyperarc heads and tails constant.Thus, just as morphisms in **HyperD** cannot add or remove vertices from an hyperarc, morphisms in the bipartite digraph category must respect the valences of the corresponding vertices.

In the end, we have found three additional restrictions that we must pose on the morphisms of a category of bipartite digraphs suitable for the study of chemical reaction networks:

i) for each $v \in V^a_1$, $f(v) \in V^a_2$ (substances transform into substances)

ii) for each $v \in V^b_1$, $f(v) \in V^b_2$ (reactions transform into reactions)

iii) let $N_{in}(v)$ and $N_{out}(v)$ be the in-neighborhood and out-neighborhood of v respectively. For each $v \in V^b_1$, $|N_{in}(v)| = |N_{in}(f(v))|$ and $|N_{out}(v)| = |N_{out}(f(v))|$ (reaction molecularity must be invariant under the transformation).

Of course, these restrictions come on top of the demand that the mappings be adjacency preserving. We denote the category of bipartite digraphs with morphism thus defined as **BipartiteD**. In the following we will prove that *there is* an equivalence of categories between **HyperD** and this new category of bipartite digraphs, devised keeping in mind the specific constraints introduced by the chemical phenomena being modeled.

First, we show that we can define a morphism-to-morphism mapping between categories **HyperD** and **BipartiteD**, that together with the standard object-to-object mapping F conforms a functor $F : \mathbf{HyperD} \to \mathbf{BipartiteD}$. Consider a morphism $f : H_1 \to H_2 \in \mathbf{HyperD}_1$, which is a vertex mapping $f : V_{H_1} \to V_{H_1}$, and the corresponding bipartite digraphs under the object-to-object mapping F, which we note FH_1 and FH_2. Note that $V^a_{FH_i} = V_{H_i}$ and $V^b_{FH_i} = A_{H_i}$. We define $F(f : H_1 \to H_2)$ as the mapping

$$\begin{aligned} F(f)(v) &= f(v) && \text{for } v \in V^a_{FH_1} \\ F(f)((U,V)) &= (f(U), f(V)) && \text{for } (U,V) \in V^b_{FH_1} \end{aligned} \tag{3.3}$$

We now prove that $F(f)$ is a morphism $F(f) : FH_1 \to FH_2 \in \mathbf{BipartiteD}_1$:

i) By construction, $Dom(F(f)) = V_{FH_1}$ and $Cod(F(f)) = V_{FH_2}$, as required.

ii) We prove that $F(f)$ is adjacency preserving for any $f \in \mathbf{HyperD}$: recall that the object-to-object mapping of F is such that arcs in FH_1 are given by

$$\begin{aligned} (u, (U,V)) &\in A^{ab}_{FH_1}, \\ ((U,V), v) &\in A^{ba}_{FH_1}, \end{aligned} \tag{3.4}$$

for each $(U,V) \in V^b_{FH_1} = A_{H_1}$, $u \in U$ and $v \in V$. Since f is adjacency preserving, we also have $(f(U), f(V)) \in A_{H_2} = V^b_{FH_2}$, which means that

$$\begin{aligned} (F(f)(u), F(f)((U,V))) &= (f(u), (f(U), f(V))) \in A^{ab}_{FH_2}, \\ (F(f)((U,V)), F(f)(v)) &= ((f(U), f(V)), f(v)) \in A^{ba}_{FH_2}, \end{aligned} \tag{3.5}$$

which together with (3.4) proves that $F(f)$ is adjacency preserving.

iii) Last, we prove that $F(f) : V_{FH_1} \to V_{FH_2}$ preserves the degrees of vertices in $V^b_{FH_1}$: by construction, for any $(U,V) \in V^b_{FH_1}$ we have $|N_{in}((U,V))| = |U|$ and $|N_{out}((U,V))| = |V|$. Furthermore, since f is a morphism in H_1, $|U| = |f(U)|$ and $|V| = |f(V)|$, and thus

$$\begin{aligned} |N_{in}(F(f)((U,V))| &= |N_{in}((f(U), f(V)))| = |N_{in}((U,V))| \\ |N_{out}(F(f)((U,V)))| &= |N_{out}((f(U), f(V)))| = |N_{out}((U,V))| \end{aligned} \tag{3.6}$$

that is, $F(f)$ preserves the degrees of elements of $V^b_{FH_1}$, so we conclude that $F(f)$ is a morphism in **BipartiteD** with domain FH_1 and codomain FH_2.

In this way, we have completed the definition of the functor $F : \mathbf{HyperD} \to \mathbf{BipartiteD}$. Now we are going to construct a functor $G : \mathbf{BipartiteD} \to \mathbf{HyperD}$. Naturally, its object-to-object mapping is the inverse of the object-to-object mapping of F. Once more, it remains to define its morphism-to-morphism mapping.

Consider a morphism $g : D_1 \to D_2$ in **BipartiteD**. We define $G(g : D_1 \to D_2)$ as

$$G(g)(v) = g(v), \quad v \in V^a_{D_1} \tag{3.7}$$

We now prove that $G(g)$ is a morphism in **HyperD**:

i) Since $V_{H_i} = V^a_{D_i}$ and $g : V_{D_1} \to V_{D_2}$, it is clear that $Dom(G(g)) = V_{GD_1}$, and $Cod(G(g)) = V_{GD_2}$, as required.

ii) We must prove that $(U, V) \in A_{GD_1}$ implies $(G(g)(U), G(g)(V)) \in A_{GD_2}$. Note that the object-to-object mapping of G transforms each $v \in V^b_{D_i}$ into an hyperarc $(N_{in}(v), N_{out}(v)) \in A_{GD_i}$, and that hyperarcs thus constructed conform the whole set A_{GD_i}. So consider any arbitrary hyperarc $(N_{in}(v), N_{out}(v)) \in A_{GD_1}$; we have that

$$(G(g)(N_{in}(v)), G(g)(N_{out}(v))) = (g(N_{in}(v)), g(N_{out}(v))). \tag{3.8}$$

Furthermore, since g is adjacency-preserving in **BipartiteD**,

$$(G(g)(N_{in}(v)), G(g)(N_{out}(v))) = (N_{in}(g(v)), N_{out}(g(v))) \in A_{GD_2}. \tag{3.9}$$

iii) It remains to prove that for any hyperarc $(N_{in}(v), N_{out}(v)) \in A_{GD_1}$, the restrictions $G(g) : N_{in}(v) \to G(g)(N_{in}(v))$ and $G(g) : N_{out}(v) \to G(g)(N_{out}(v))$ are bijective. This follows immediately from the fact that g preserves degrees of the vertices in $V^b_{D_1}$, so that $|G(g)(N_{in}(v))| = |N_{in}(g(v))| = |N_{in}(v)|$ and the same holds for N_{out}. Thus, we conclude that $G(g)$ is a morphism in **HyperD** with domain in GD_1 and codomain in GD_2.

In this way, we have completed the construction of the functor $G : \mathbf{BipartiteD} \to \mathbf{HyperD}$. Last note that for any $H \in \mathbf{HyperD}_0$, $(G \circ F)H = H$. Also, for any $f : H_1 \to H_2 \in \mathbf{HyperD}_1$ and $v \in V_{H_1}$ we have

$$G \circ F(f)(v) = G(F(f))(v) = F(f)(v) = f(v)$$

that is, $G \circ F(f) = f$, so that $G \circ F = 1_{\mathbf{HyperD}}$. We may prove in a similar way that $F \circ G = 1_{\mathbf{BipartiteD}}$. In conclusion, F and G give an equivalence of categories, so **BipartiteD** and **HyperD** are equivalent. Though this is an useful result, we must insist that it is important not to extrapolate beyond its proper meaning. The identification of objects in **BipartiteD** with objects in **Digraphs** does not preserve morphisms, so *objects in* ***BipartiteD*** *are no longer digraphs in the usual sense.*

The fact that **BDgraphs** is not equivalent to **HyperD** shows us that the existence of the object-to-object mapping F does not spare us the need of developing the mathematical formalism of directed hypergraphs in order to use them as a model of chemical reaction networks. There *is* a category of bipartite digraphs equivalent to **HyperD**, but it is as alien to **Graphs**, and thus to the standard formalism of graph theory, as **HyperD** itself. Wether we imagine our network representations as bipartite digraphs or as directed hypergraphs, it is clear that we are now working with a new model.

The issue here is that a model comprises not just its fundamental objects, but also all the methods for opperating on those objects. Mapping bipartite digraphs into hyperdigraphs is one thing, mapping the methods for operating on each construction is an entirely different thing. Graph theoretical concepts such as in-degree, out-degree, path, distance, etc. ultimately refer to the categorical structure of **Digraphs**. The existence of an invertible mapping from bipartite digraphs to hyperdigraphs is not enough to allow us to extrapolate the methods developed for operating on the former to the later –we require an equivalence of categories. The object-to-object mapping just lets us use digraphs as an image of hyperdigraphs as long as no methods are involved. We may use the same drawings that we use for representing bipartite digraphs in order to represent hyperdigraphs –but the way we read the picture must change. Or we may use the same data structures developed for bipartite digraphs in order to implement a method for operating on hyperdigraphs in an object-oriented program –but the method itself will not necessarily be shared by both the 'bipartite digraph' and 'hyperdigraph' classes, and most likely will need to be implemented from scratch.

Recent changes in chemical reaction network models used in systems biology illustrate this point. In graph models of reaction networks, key concepts from network analysis such as centrality, vulnerability and reachability are described by means of graph-theoretical invariants. The shift to a hyperdigraph model is not as simple as computing those same invariants over the new network representation. The invariants themselves have to be adapted to the new construction. Some times they can be extended to the new formalism, but the extension motivates a significant change in their interpretation. Some times they have to be re-defined, or even discarded. Also, new relevant invariants may appear. In this way, a fundamentally different description of the structure of the network is configured, changing our understanding of the underlying chemical phenomenon.

The following examples go along the lines of the previous argument. We consider two alternative accounts of vulnerability in metabolic networks: the simpler approach favored by Barabási and collaborators that uses the degree distribution as the main descriptor of network vulnerability, and the more complex approach of Elementary Flux Modes and Minimal Cut Sets proposed by Klamt and collaborators. On each case we show how the shift from a graph to a hyperdigraph model produces a significant change on the definition, meaning and values of the corresponding vulnerability descriptors that determine our knowledge on this biochemical phenomenon.

Example 3.2 (Neighborhood, degree, and vulnerability)**.** Vulnerability concerns the capability of a network of retaining its integrity upon removal of connections or nodes, the later implying the removal of all connections it is involved in. In the case of reaction networks, particularly those in the metabolism of living beings, removal of an edge from the substrate graph (see Figure 3.1(b)) is intended to represent the inhibition of a particular reaction, and removal of a vertex is intended to represent the removal of a metabolite. The later disables each reaction that involves it, which is reflected in the removal of all connections to vertices on the corresponding neighborhood.

In graph models of networks vertex degree is considered a broad index of vulnerability: removing a vertex of high degree causes a large number of links to be lost, which is expected to have a severe impact on the connectivity of the network. The degree distribution over the whole set of vertices is thus helpful in determining the vulnerability of a metabolic network (see e.g. Albert and Barabási (2002)).

We took a data set comprising 2478 substances and 1808 reactions occurring in human cell metabolism from the Reactome data base (available at www.reactome.org/download/current/homo_sapiens.sbml.gz, visited on November 2006). With this data set we built the substrate graph representation of the corresponding metabolic network, and plotted its degree distribution (see Figure 3.4). This distribution reasonably approaches the power-law distribution characteristic of *scale-free networks* (Albert & Barabási, 2002), a behavior that has been found previously on other metabolic networks (Barabási & Oltvai, 2004). Notice the high bias in degree values, with almost all vertices having low degrees, and very few vertices (known as *hubs*) having extraordinarily large degrees. This is a highly centralized structure, where connectivity of the network relies on the hubs, making it resilient to *error* but vulnerable to *attack*: error is represented by the removal of a random vertex, which is highly likely to target a vertex with low-degree, having little to no effect in the integrity of the network. On the other hand, a directed attack could target a hub, causing the removal of a large number of links, which has a dramatic effect on connectivity (Barabási & Oltvai, 2004).

The previous analysis used the substrate graph representation of the network. Changes on the underlying graph model to better reproduce the logical structure of chemical reaction networks significantly affect the final conclusion regarding vulnerability of the system. This is not because the scale-free degree distribution disappears, but because the notion of degree is transformed along with the model, altering its correct interpretation.

Consider the bipartite digraph model of Figure 3.1(d). First, note that degrees of vertices have very different meanings depending on which vertex class they belong to:

i) for each $v \in V^a$, $N(v)$ represents the set of reactions substance v is involved in

ii) for each $u \in V^b$, $N(u)$ represents the number of substances involved in reaction u.

Clearly, each degree distribution should be dealt with separately. This is easily justified in mathematical terms if we regard bipartite directed graphs as objects in **BipartiteD**, since in this category valences of each class of vertices are explicitly distinguished by morphisms. Indeed, degrees of vertices in V^a are invariant up to *isomorphism*, while those of vertices in V^b are invariant under *any arbitrary morphism*. This detail is very important, as the same does not happen in **BDigraphs**. In other words, *at this point we are regarding bipartite digraphs as directed hypergraphs.*

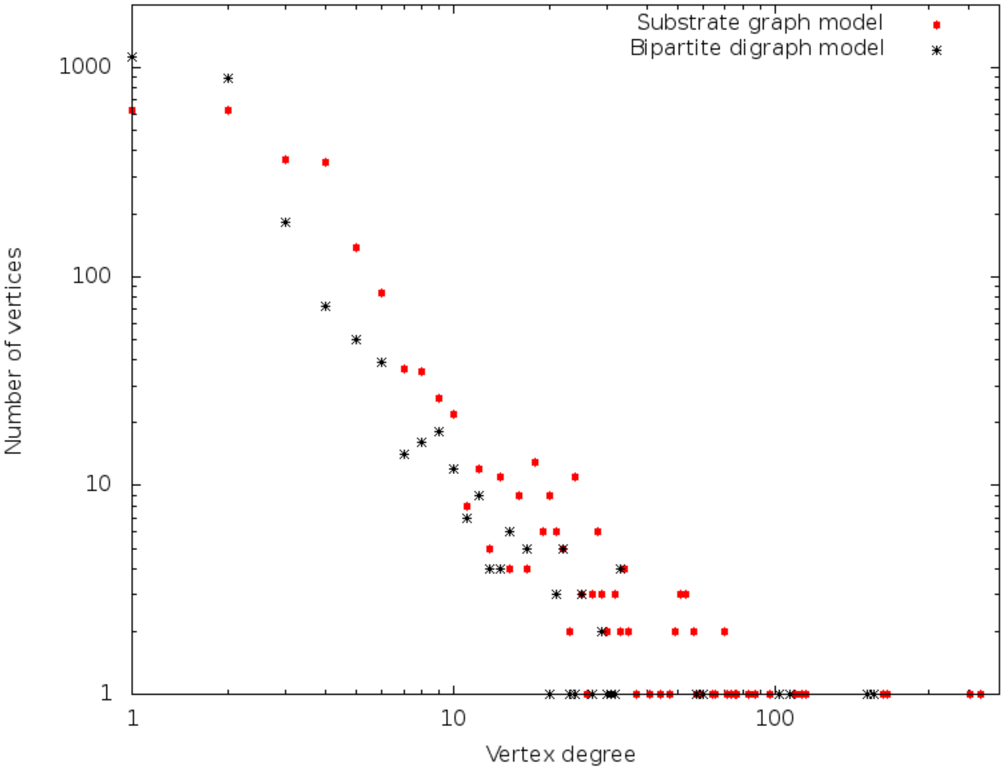

Figure 3.4: Comparison of the degree distributions of a human metabolic network when modeled as a substrate graph (points) and when modeled as a bipartite substances-reactions digraph (stars). Logarithmic scale. Data comprises 2478 substances and 1808 reactions, downloaded from http://www.reactome.org/download/current/homo_sapiens.sbml.gz. Both distributions reasonably approach a power law, but hub degrees, average degree, and number of low-degree vertices differ significantly.

Second, note that now the degrees of vertices that represent substances do not speak of the number of substances related by chemical reactions to a given substance, as happened in the substrate graph, but of the number of reactions it takes part in. This is, arguably, the correct approach: as far as vulnerability is concerned, the important point is how many relations (in this case, chemical reactions) are removed along with a given vertex, more than how many vertices where involved in those relations. It just happened that, in the case of substrate graphs, both were equivalent.

That equivalence follows on an inaccuracy of the model: approximating the higher-order relations established by chemical reactions by means of a set of binary relations between vertices. As a consequence, valences of vertices in the substrate graphs depend both on the number of reactions a substance is involved in, and on the molecularities of those reactions. Node degrees on those models are thus biased by molecularity, which leads to an overestimation of network vulnerability by a significant factor. The bipartite digraph model avoids this inaccuracy by separating the information concerned with reaction molecularity, which is now fully comprised by the valences of the elements of V^b, and the information concerned with substance reactivity, which is fully comprised by the valences of the elements of V^a.

To show this effect, in Figure 3.4 we also plotted the total distribution of the same network, now represented by a bipartite substances-reactions digraph. Note that in the bipartite digraph representation there are about twice as many low-degree nodes (non-vulnerabilities) as in the substrate graph, and the total degree of hubs (vulnerabilities) is halved. As a result, both average degree and the bias in the degree distribution decrease significantly, suggesting that the network is less vulnerable than previously thought.

Last, we note that arcs in a digraph achieve a closer representation of reaction networks, by including reaction directionality into the model. This feature also has a remarkable impact in our understanding of the vulnerability of the reaction network, as we now show.

In a directed graph $D = (V_D, A_D)$ we can distinguish two different types of neighborhoods for any given vertex: the *in-neighborhood* $N_{in}(v)$, comprising the set of vertices u such that $(u, v) \in A_D$, and the *out-neighborhood* $N_{out}(v)$, comprising the set of vertices u such that $(v, u) \in A_D$. Thus, for any $v \in V^a$, its in-degree $|N_{in}(v)|$ gives the number of reactions consuming the corresponding substance, while its out-degree $|N_{out}(v)|$ gives the number of reactions consuming the substance. These two variables have opposing effects on network vulnerability. Out-degree concerns the *demand* of a given metabolite, so that a vertex with high out-degree is indispensable for many different reactions, and thus constitutes a potential vulnerability of the system. On the other hand, in-degree concerns the *availability* of a given metabolite; a vertex with high in-degree is being produced by many different reactions, so that if one of them fails, the others may support the metabolic demand for this substance. Far from speaking of a vulnerability, high in-degree is an indicator of *robustness*. Total degree distribution adds both descriptors, and is thus unable to distinguish what may be a potential point of attack from a point of high resilience.

A better vulnerability index related to vertex degree is then given by the in-degree to out-degree ratio. In consequence, we define the *degree vulnerability index* $D(v)$ as:

$$D(v) = \begin{cases} 0 & \text{if } |N_{in}(v)| = 0, \\ 1 & \text{if } |N_{out}(v)| = 0, \\ \frac{|N_{in}(v)|}{|N_{in}(v)|+|N_{out}(v)|} & \text{in the remaining cases.} \end{cases} \tag{3.10}$$

If a substance v is not consumed by any reaction, we have $|N_{in}(v)| = 0$, and thus $D(v) = 0$: the substance is not necessary for the normal function of the metabolism, and thus represents no vulnerability for the organism. If it is consumed by some reactions, but produced by none, we have $D(v) = 1$: beyond being a potential vulnerability, this substance reveals that the system is already a failure (that is, unless the substance is provided by the growth media), as the organism cannot support the demand of this particular metabolite. In all other cases $D(v)$ grows with $N_{in}(v)$ and decreases with $N_{out}(v)$, following the idea that potential vulnerabilities are characterized by high demand and low availability.

In Figure 3.5 we present a plot of the degree distribution of the human metabolic network we have been considering so far, modeled once more by means of a bipartite digraph, but now taking into account both total valence and the degree vulnerability index. Note that for any given value of total degree, the distribution is symmetric with respect to the $D(v) = 0.5$ plane. This means that, for any given degree, there are as many vulnerable vertices as robust vertices, suggesting that the overestimation of vulnerability introduced in the substrate graph model is further multiplied by a factor of 2. For instance, the two vertices with the highest degrees in the distribution correspond to ATP and ADP. The first has a high value of $D(v)$, while the second has a low value. This is consistent with biochemical knowledge: ATP is the main energy source for cellular anabolism, so that blocking the ATP-producing reactions in cell catabolism (50 reactions here, which is nonetheless a considerable amount) would be catastrophic for the organism. ADP, on the other hand, is the main product of ATP degradation in anabolic reactions; though it can be further decomposed to produce some extra energy, it is highly available from all ATP-degrading reactions, and is unnecessary as long as ATP is available.

Furthermore, Figure 3.5 draws attention on the potential relevance of low-degree vertices when it comes to network vulnerability. For instance, there is a large number of vertices with $N(v) = 2$ and $D(v) = 0.5$, meaning that they are produced by exactly one reaction and consumed by exactly one reaction. Such substances may act as mediators in reaction cascades that ultimately lead to a central point of the network. In consequence, inhibition of their production could have a harmful impact on the organism. Whether this happens or not cannot be determined just by looking at the degree distribution: we have to consider the structure of reaction paths transversing the network. The

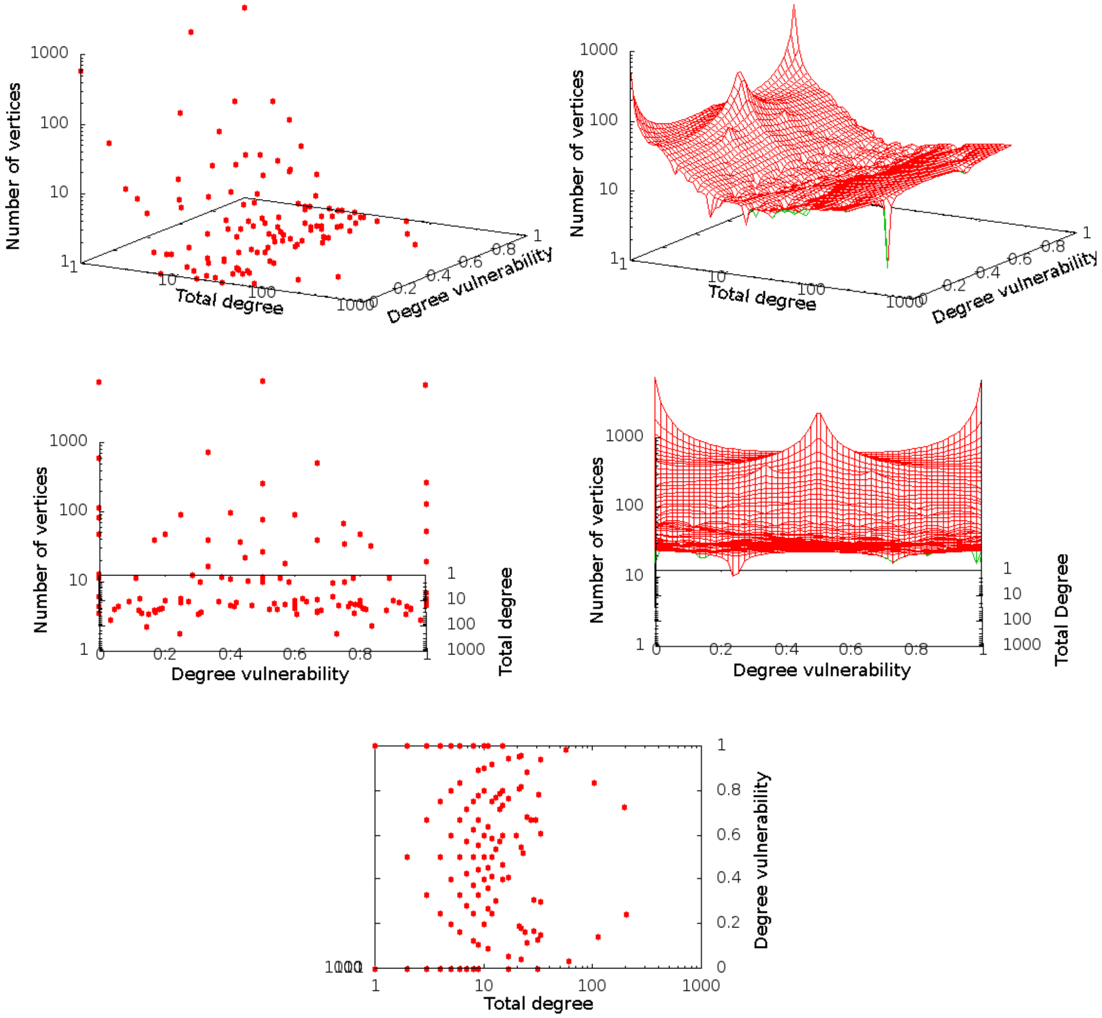

Figure 3.5: Degree × degree vulnerability distribution of a human metabolic network modeled as a bipartite substances-reactions digraph. Data comprises 2478 substances and 1808 reactions, taken from http://www.reactome.org/download/current/homo_sapiens.sbml.gz. Plots to the right show a surface fitted to the data using a 50 × 50 grid, while the others show the actual data points.

following example concerns a methodology designed to account for this aspect of network vulnerability.

* * *

Example 3.3 (Klamt and Gilles (2004))**.** The characterization of vulnerability presented on the previous example is quite incomplete. As we argue at the end, vertices with very low out-degree and average degree vulnerability can be indispensable for the connectivity of a network. An example of such situation is shown in Figure 3.6. A more thorough characterization of vulnerability then has to look at the path structure of the network, which is the ultimate responsible of signal transmission between different nodes.

In the case of reaction networks, a path is intended to represent a sequence of reactions that allow the transformation of an initial set of reactants into a final set of products. Regardless of what graph model we choose, paths are unable to achieve this goal, as for any given reaction they suppose the possibility of obtaining just one out of several reaction products from just one out of several reactants. A hyperdigraph model is the very minimum required in order to understand the path structure of a reaction network.

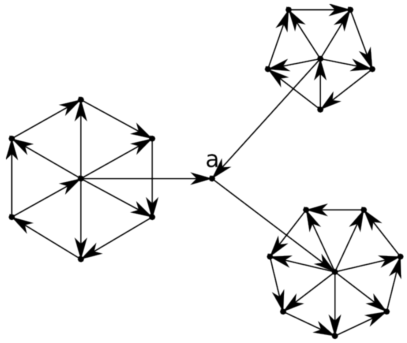

Figure 3.6: Vertex a with degree 3 and $D(a) = 1/3$ is arguably a greater vulnerability than any of the vertices with high degree and high degree vulnerability in the network. Note that, despite its low degree and degree vulnerability, a huge number of paths go through this vertex. As a consequence, it is the lone member of the graph's smallest cut set.

Vulnerability in a graph can be characterized in terms of its paths by means of cut sets. A *cut set* is a set of vertices whose removal ensures a disconnection of the graph. Clearly, this means that at least one vertex has been removed from each path connecting those parts, and that vertices in small cut sets represent remarkable vulnerabilities (see Figure 3.6). Klamt and Gilles (2004) have generalized the definition of cut set to a hyperdigraph model of chemical reaction networks. First, an Elementary flux Mode

(EM) is defined as a subset of reactions (i.e. hyperarcs in A_H) that describe a feasible and balanced flux distribution through a reaction network that is minimal with respect to utilized reactions. Minimal Cut Sets (MCS), then, are defined as minimal sets of reactions that must be blocked in order to ensure dysfunction of a target reaction. This means that no EM including the target reaction must remain viable after the removal of an MCS.

The size of MCSs involving some given reaction is an index of its importance for the integrity of the network. For instance, “if a reaction is predominately part of larger MCSs, then a malfunction of this reaction will be less crucial for the operation of the objective reaction”(Klamt & Gilles, 2004, p. 232). Thus, the inverse of the average size of all MCSs including a reaction $a \in A_H$ is an index of its vulnerability. The authors call this index the *fragility coefficient*, F_a. The minimal value of zero is achieved when the reaction is not part of any MCS, and the maximum value of 1 is achieved for essential reactions. Furthermore, the *network fragility coefficient* **F**, defined as the average of the fragility coefficient over all reactions in the network, offers a global descriptor of network vulnerability.

$$\mathbf{F} = \sum_{a \in A_H} \frac{F_a}{|A_H|} \tag{3.11}$$

The authors computed this index for the glucose metabolism network of *E. coli.* They found a value of 0.643, showing that this network has a considerable amount of vulnerabilities that remain hidden when we only look at its degree distribution.

* * *

Graphs are the most familiar, better characterized, and widely spread image of various networks. This does not mean, however, that they should be expected to offer an adequate mathematical representation of reaction networks. Through the previous examples we have shown that, when used as a model of chemical reaction networks, the inability of graphs to capture ‘and’ relations among reactants and products promotes an inaccurate appreciation of the network-theoretical identity of substances. This identity, which in network analysis is described by invariants such as vertex degree and paths, is determined in category theory by the family of morphisms that define the category of reaction networks. These morphisms constitute the key tool of our proposal of a model of chemical activity, as they are the primary inducers of classifications, and thus of properties and concepts. In consequence, though the category **Graphs** offers the advantages of an extensively characterized mathematical construction that has (indirectly) been successfully used in many different network models, we deem it an inappropriate basis for a model of chemical activity. Directed hypergraphs, on the other hand, are proving that they can offer a more faithful image of chemical reaction networks, overcoming the main limitations of graphs. In light of these considerations, we decided to use a category of hyperdigraphs as the necessary basis for defining the classification system that lays at the hearth of our model.

3.2 Role assignments and role models

Following the argument of the previous section, we decided to take directed hypergraphs as the mathematical representation of chemical reaction networks in our model. The next thing we have to do is define the morphisms of our hyperdigraph category.

On the last section we introduced the category **HyperD**, whose objects are directed hypergraphs and whose morphisms are defined as an adaptation of the concept of adjacency preserving mapping to hyperdigraphs. Now, recall that mappings always induce disjoint classifications; so restricting ourselves to a category whose morphisms are mappings would prevent us from taking advantage of the richer conceptual structures induced by general binary relations. Thus, we will instead define the morphisms of our category of hyperdigraphs as adjacency preserving relations between hyperdigraphs, which we named *role assignments*.

Definition 3.4 (Role assignment)**.** Let **H** and **B** be two hyperdigraphs. A *role assignment* is a vertex relation $r \in \mathbf{V_H} \times \mathbf{V_B}$ such that for each $(\{u_1, \ldots, u_m\}, \{v_1, \ldots, v_m\}) \in \mathbf{A_H}$, there are $(u_1, a_1), \ldots, (u_m, a_m), (v_1, b_1), \ldots, (v_n, b_n) \in r$ such that $(\{a_1, \ldots, a_m\}, \{b_1, \ldots, b_n\}) \in \mathbf{A_B}$.

Proposition 3.5. *Composition of role assignments in* **Rel** *is a role assignment.*

Proof. Let H_1, H_2, H_3 be three hyperdigraphs, and $r : V_{H_1} \to V_{H_2}$ and $s : V_{H_2} \to V_{H_3}$ be two role assignments. Since $r : V_{H_1} \to V_{H_2}$ is a role assignment, for each hyperarc $(\{u_1, \ldots, u_m\}, \{v_1, \ldots, v_n\}) \in A_{H_1}$, there are $(u_1, w_1), \ldots, (v_n, x_n) \in r$ such that $(\{w_1, \ldots, w_m\}, \{x_1, \ldots, x_n\}) \in A_{H_2}$. In the same way, since $s : V_{H_2} \to V_{H_3}$ is a role assignment, there are $(w_1, y_1), \ldots, (x_n, z_n) \in s$ such that $(\{y_1, \ldots, y_m\}, \{z_1, \ldots, z_n\}) \in A_{H_3}$. By construction, this means that $(u_1, y_1), \ldots,$
$(v_n, z_n) \in s \circ r$, so we conclude that $s \circ r$ is a role assignment with domain in V_{H_1} and codomain in V_{H_3}. □

Proposition 3.6. *The collection of directed hypergraphs and role assignments conforms a category. To avoid a proliferation of terms, from now on we will refer to this category as* **HyperD***.*

Proof. For hyperdigraphs H_1, H_2, H_3 and role assignments $r \subset V_{H_1} \times V_{H_2}$, $s \subset V_{H_2} \times V_{H_3}$, and $t \subset V_{H_2} \times V_{H_1}$:

i) $\mathrm{Dom}(r) = H_1$ and $\mathrm{Cod}(r) = H_2$

ii) composition of role assignments $s \circ r$ is defined as in **Rel**. By **Proposition 3.5**, composition of role assignments is a role assignment.

iii) composition in **Rel** is associative

iv) the identity mapping $1_{V_{H_1}} : V_{H_1} \to V_{H_1}$ is an identity in **Rel** and a role assignment, and thus an identity in **HyperD**.

□

As we saw in **Example 2.14**, regular role assignments can be seen as adjacency preserving mappings from a graph onto its corresponding block model. Then, in **Example 2.18** we showed that adjacency preserving relations between graphs generalize regular role assignments to allow for non-disjoint classifications. The previous definition further extends this approach from role analysis to networks modeled as directed hypergraphs. That is why we borrowed the name 'role assignments' to refer to morphisms in **HyperD**: given an $r : H_1 \to H_2 \in \mathbf{HyperD}_1$, each $v \in V_{H_2}$ can be interpreted as a role that any substance in $\ker r(v)$ can perform in its reactions, as long as it meets the appropriate partners. Just as regular role assignments formalize the sociological intuition that 'similar actors relate to similar actors', our generalized role assignments formalize the chemical principle of 'similar substances react with similar substances'.

Role assignments allow us to tell what roles a substance is able to play in a given reaction network. Chemists, however, are capable of more: they are not only able to determine the full set of roles that a substances is capable of playing in different chemical reactions (e.g. that of an acid, an ester, an alcohol...), but they can also tell precisely what role a substance plays in *any specific reaction*. In order to match their skill, our model should allow us to tell, for any given classification $\ker r$ with $r : H_1 \to H_2 \in \mathbf{HyperD}_1$, what role in V_{H_2} is performed by each substance in V_{H_1} *in each reaction in* A_{H_1}. This comports the identification of each hyperarc $a \in A_{H_1}$ with an hyperarc $b \in A_{H_2}$, and the introduction of a bijective mapping from a to b . Here we formalize this construction through the definition of *role model*, and show that role models and role assignments are consistent in the sense that role models induce unique role assignments.

Definition 3.7 (Role model). Let H_1 and H_2 be hyperdigraphs, and $\alpha : A_{H_1} \to A_{H_2}$, for directed hypergraphs H_1, H_2 such that $|\mathrm{tail}(a)| = |\mathrm{tail}(\alpha(a))|$ and $|\mathrm{head}(a)| = |\mathrm{head}(\alpha(a))|$ for each $a \in A_{H_1}$. Let $\mathcal{F}$ be the family of all bijections $f_a : a \to \alpha(a) \forall a \in A_{H_1}$ such that $f_\alpha(\mathrm{tail}(a)) = \mathrm{tail}(\alpha(a))$. A *role model* is a mapping $\beta : A_{H_1} \to \mathcal{F}$ such that for each $a \in A_{H_1}$, $\mathrm{Dom}(\beta(a)) = a$.

A role assignment gives us a substance classification properly by relating each role with a set of substances, that is, by telling us what substances constitute each of the substance classes. On the other hand, a role model gives us additional information, by telling us what particular role a substance performs in a given reaction, in accordance with a chosen reaction partition α. The constraints $\beta(a) : a \to \alpha(a)$ and $f_\alpha(\text{tail}(a)) = \text{tail}(\alpha(a))$ give a consistency condition, by warranting that there exists a bijective vertex-mapping for each reaction, and that it maps reactants into reactant classes and products into products classes. This condition warrants structure-preservation in the same sense demanded by a role assignment, as we prove now.

Proposition 3.8. *Let β be a role model for H_1, H_2. The relation $r_\beta = \cup_{a \in A_{H_1}} \beta(a)$ is a role assignment of H_1 onto H_2. We call this relation the* role assignment induced by *β.*

Proof. For each $a \in A_{H_1}$, $\beta(a)$ provides the subset of r_β that fulfils the defining property of a role assignment. ☐

Example 3.9 (Organic functions)**.** Recall Laurent's answer to the question of the definition of ether, that we quoted on Chapter 1: "an ether is a body obtained by the reaction of an acid upon an alcohol, with an elimination of water, and that under certain circumstances that ether can be divided, either by regenerating the alcohol and acid which gave it birth, or by forming products which belong to the families of the alcohol and of the acid". This definition, that is still important in contemporary organic chemistry, can be summarized into a set of directed hyperarcs in a hyperdigraph whose vertices are organic functions[4]:

$$\begin{gathered}\text{acid} + \text{alcohol} \to \text{ester} + \text{water} \qquad (3.12)\\ \text{ester} + \text{water} \to \text{acid} + \text{alcohol}\\ \vdots\end{gathered}$$

Any other organic function is defined on the same terms. In the end, we get a hyperdigraph O that determines the abstract chemistry of organic functions. This abstraction is linked to the 'reality' of chemical reactions by means of a relation $r : H \to O$ whose domain is the hyperdigraph representing the actual network of chemical reactions of organic compounds. Elements of this relation are determined by identifying a chemical reaction in A_H with a hyperarc in A_O, and then constructing a bijective mapping from the head and tail of the former into the head and tail of the later. For example, the reaction

$$CH_3COOH + CH_3OH \to CH_3COOCH_3 + H_2O \qquad (3.13)$$

---

[4] Laurent's ethers are now known as esters.

is identified with (3.12). Then, each term of the reaction is mapped into a unique term of (3.12):

$$\begin{aligned} CH_3COOH &\to \text{acid} \\ CH_3OH &\to \text{alcohol} \\ CH_3COOCH_3 &\to \text{ester} \\ H_2O &\to \text{water.} \end{aligned} \tag{3.14}$$

The union of all such mappings conforms the relation $r : H \to O$, so that for any $o \in O$, $\ker r(o)$ gives the class of substances associated with the corresponding organic function. In other words we have just built a role model and used it to induce a role assignment, thus showing that the classification of organic compounds in organic functions can be formalized as a role assignment.

* * *

It is important to note that role models are *consistent with* but not necessarily *equivalent to* role assignments. The later would suppose the existence of a category equivalent to **HyperD** whose morphisms are role models or are uniquely determined by role models. So far, we cannot tell that such category exists: we have proven that role models induce unique role assignments, but we have not proven that role assignments induce unique role models; much less that the implicit mappings are inverses. Though we cannot warrant that any arbitrary role assignment has an associated role model, in the following section we will see that we can prove the existence of associated role models for our preferential role assignments.

3.3 Predictive power and optimal role assignments

Given a role assignment $r : H_1 \to H_2$ and a substance $u \in V_{H_1}$, the set $r_u = \{v \in V_{H_2} : (u, v) \in r\}$ of all roles that this substance can perform in different chemical reactions completely characterizes its chemical activity under this particular morphic representation. In this way, by considering all morphisms with domain on H_1 we can express everything there is to say about the activity of substances in the corresponding reaction network. But chemists are constantly producing new compounds, so no matter how large H_1 is, it can never comprise all substances known to chemistry. This observation takes us to one of the basic demands posed on a scientific model: it has to be able to predict unobserved empirical phenomena.

In principle, any newly synthesized substance v would send us back to square one: we would have to run all possible reaction tests involving v and any $u \in V_H$ to built a new hyperdigraph $H_{1\cup\{v\}}$ with vertex set $V_H \cup \{v\}$ and hyperarc set determined by the results of the tests run, and look into morphisms with domain in this hyperdigraph to characterize the new set of substances. This is a very grim perspective: role assignments seem to lack predictive power, so we would be forced to start over after each new synthesis.

Closer examination reveals that things are not always that bad. Recall that a role assignment $r : H_1 \to H_2$ defines a formal context were concepts related to chemical activity of substances in V_H can be defined. These concepts are completely characterized by the corresponding concept lattice. Now, note that the set r_v that completely characterizes v under r is equal to v^r, the intent of the smallest concept containing v. This means that even if we introduce new substances in V_H and modify A_H in accordance to their activity, as long as the concept lattice does not change, the model remains ultimately untouched. Of course, it is impossible to determine whether this happens or not until we have run all the corresponding reactivity tests, which is exactly what we want to avoid. Thus, in order to give predictive power to a role assignment, we require a principle of induction: when V_{H_1} is sufficiently large, *we hypothesize that the concept lattice already includes all possible concepts, so it will not change any more.* In this way, the problem turns into that of positioning the new substance into the concept lattice, which can be done with fewer reaction tests: we just need to determine v^r, a problem bounded by the size of the largest concept intent in the lattice. Once we have done this, we can *predict* the results of any untested reaction involving the new substance[5].

Now that we have found a way to endow role assignments with predictive power, we want to optimize their ability to make predictions. Clearly, the smaller v^r is, the fewer reaction tests are needed in order to predict the activity of v with respect to any untested reaction. Also, the smaller r is, the smaller the expected value of v^r becomes. In consequence, we propose to use the cardinal of r as a measure of its optimality.

Definition 3.10 (Minimum role assignment)**.** Let $r : H_1 \to H_2$ be a role assignment. We say that r is *minimum* if $|r|$ is minimum over all role assignments in $\mathrm{Hom}_{\mathbf{HyperD}}(H_1, H_2)$.

In other words, while **HyperD** determines our classification system for the characterization of chemical activity, the measure function $m(r) = |r|$ determines a classification problem whose solutions are classifications with maximum predictive power.

Last, recall that though we know that a role model induces an unique role assignment (see **Proposition 3.8**), we cannot assert that each role assignment has an associated role model. However, we can prove that any *minimum* role assignment has this property.

Proposition 3.11. *Let $r : H_1 \to H_2$ be a minimum role assignment. Then there exists a role model β such that $r = r_\beta$.*

---

[5] Presently, this can only be done when we also have a role model; but we will soon see that this limitation can be easily overcome.

Proof. Since r is a role assignment, for each $a \in A_{H_1}$ there is a subset of r that is a bijective mapping from a into some $b \in A_{H_1}$ and maps heads into heads and tails into tails (**Definition 3.4**). We define each $\beta(a)$ as such a mapping. We now prove that $r_\beta = r$. As $r_\beta = \cup_{a \in A_{H_1}} \beta(a)$ and $\beta(a) \subset r$ for all $a \in A_H$, it follows that $r_\beta \subset r$. But since r is a minimum role model, this necessarily means that $r = r_\beta$, which completes the proof. □

That is, for any given optimal role assignment we can always choose a consistent role model. The existence of a role model allows us determine exactly what role any given substance plays in any given reaction. The previous result proves that we can always count with this possibility for the most relevant case of classifications with optimal predictive power.

The following example tests the adequacy of the model developed so far by using it to reconstruct some elements of chemical knowledge on acid-base behavior. First, the pertinence of our criterion of optimality is supported by the agreement between an optimal role assignment and the accepted classification of a small set of chemical substances as acids and bases. Then, the emergence of the concept of amphoteric substances is presented as an argument supporting the importance of non-disjoint classifications in chemical thought, which justifies our insistence in the use of general binary relations as classification inducers. Last, we sketch how other elements of acid-base theory can be derived from further developments built upon the basis of our model.

Example 3.12 (Acids and bases)**.** The concepts of acid and base are among the oldest constructs of chemistry. These concepts have been transformed several times during the history of chemistry, and even today different definitions coexist (e.g. the concepts of Brønsted-Lowry acid/base and of Lewis acid/base). We believe that the common element that unifies all different conceptualizations of acid and basic substances is given by a principle of complementarity: acids and bases always come in opposing pairs, each element of the pair being characterized with respect to its behavior in front of the other. The current example intends to reconstruct this broader definition of the concepts of acid and base by means of a classification in **HyperD**.

Consider a family of substances involved in acid-base reactions, represented by the hyperdigraph H_1. In general, an acid-base reaction may be defined as a reaction of the type $A + B \to A + B$. This means that we are putting the corresponding reaction network in the context of a role model, where each element of the reaction set belongs to the $A + B \to A + B$ reaction class, A being the 'acid' role and B being the 'base' role. Then, we expect the chemical classification of substances as acids and bases to be given by an optimal role assignment $r : H_1 \to H_2$, where H_2 is the hyperdigraph with a single hyperarc $(\{A, B\}, \{A, B\})$.

To test this hypothesis, we built a network of 26 substances involved in 104 acid-base reactions (see Figure 3.7). These reactions were reconstructed from the acidity constants in aqueous solution of the corresponding substances. K_a values were taken from Williams (2010) and are reported in column 3 of Table 3.1. To give a directionality to the reactions, we assumed that a reaction takes place in the direction of $K_a > 1$. For instance, for HBr we have $K_a = 1.00 \times 10^9$, corresponding to the equilibrium constant of

$$HBr + H_2O \leftrightharpoons H_3O^+ + Br^-; \tag{3.15}$$

and for NH_4^+ we have $K_a = 6.17 \times 10^{-10}$, corresponding to

$$NH_4^+ + H_2O \leftrightharpoons H_3O^+ + NH_3 \tag{3.16}$$

In the first case $K_a > 1$, so we include the reaction

$$HBr + H_2O \rightarrow H_3O^+ + Br^- \tag{3.17}$$

into the network; on the second case $K_a < 1$, so we take instead the inverse reaction:

$$H_3O^+ + NH_3 \rightarrow NH_4^+ + H_2O \tag{3.18}$$

Furthermore, by combining the last two expressions we get another reaction,

$$HBr + NH_3 \rightarrow NH_4^+ + Br^- \tag{3.19}$$

which also has an equilibrium constant $K > 1$, so it is was introduced in the network as well. We repeated this process for all substances in Table 3.1, thus generating the full network of acid-base reactions pictured in Figure 3.7.

Our purpose is to find an optimal role assignment $r : H_1 \rightarrow H_2$, where H_1 is the hyperdigraph representation of the reaction network just constructed and H_2 is the hyperdigraph with only one hyperarc $(\{A, B\}, \{A, B\})$, and to contrast the resulting classification with contemporary knowledge regarding acidity and basicity of substances in V_{H_1}. In general, the role assignment optimization problem is NP-hard, as proven by the fact that the graph homomorphism problem, which is NP-complete, is reducible to the associate role assignment decision problem. In consequence, computing an optimal role assignment even for two relatively small hyperdigraphs such as H_1 and H_2 may demand significant computation time. Fortunately, the specific instance of the role assignment optimization problem considered here allows for a simplification that achieves a significant reduction in the number of operations necessary for computing an optimal role assignment.

First, note that for any viable solution $r : H_1 \rightarrow H_2$, we can partition V_{H_1} in three sets: the set of substances that behave exclusively as acids,

$$r_A = \{v \in V_H : (v, A) \in r, (v, B) \notin r\}, \tag{3.20}$$

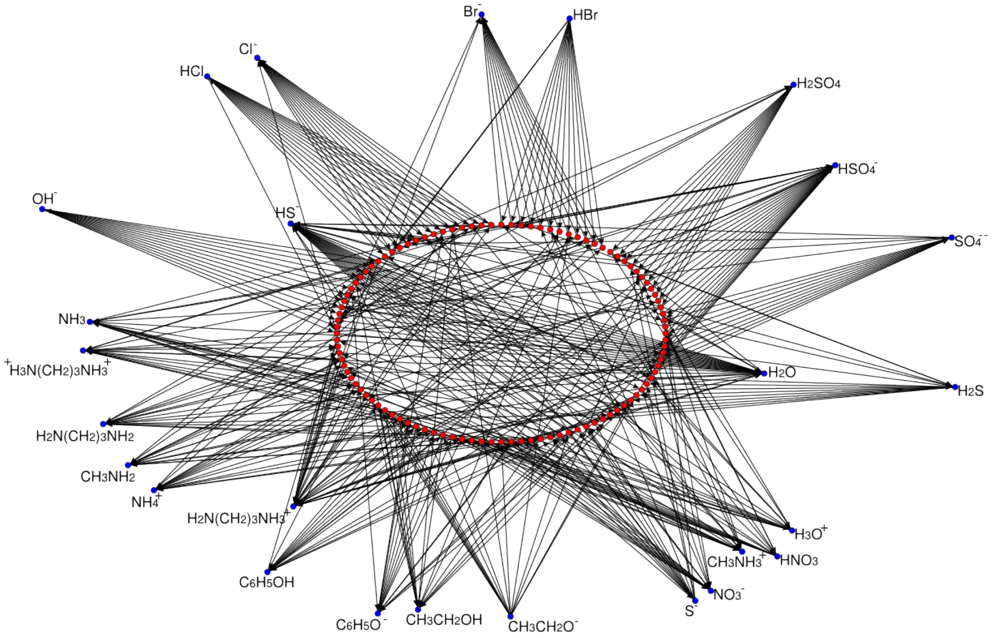

Figure 3.7: A network of acid-base reactions, depicted as a bipartite digraph. Vertices in blue represent substances (26 in total), vertices in red represent reactions (106 in total).

the set of substances that behave exclusively as bases,

$$r_B = \{v \in V_H : (v, A) \notin r, (v, B) \in r\}, \tag{3.21}$$

and the set of substances that can behave as both,

$$r_{AB} = \{v \in V_H : (v, A) \in r \text{ and } (v, B) \in r\}, \tag{3.22}$$

so that these three sets completely determine r. Clearly,

$$r_{AB} = V_{H_1} \setminus (r_A \cup r_B) \tag{3.23}$$

and the optimality parameter $|r|$ is given by

$$|r| = |r_A| + |r_B| + 2|r_{AB}|, . \tag{3.24}$$

From (3.23) and since $r_A \cap r_B = \emptyset$ we have $|r_{AB}| = |V_H| - (|r_A| + |r_B|)$, and thus

$$|r| = 2|V_{H_1}| - (|r_A| + |r_B|). \tag{3.25}$$

Equation (3.23) shows that r_A and r_B completely determine a role assignment and equation (3.25) shows that by maximizing the sum $|r_A| + |r_B|$ we find the optimum.

These two sets are the sets of vertices that can be mapped into a single role in such a way that they never appear in a hyperarc tail or head with a vertex of the same role. We could then regard the tails and heads of the hyperarcs as edges in a graph with vertex set V_H, so that $r_A \cup r_B$ induces a bipartite subgraph of that graph. The role assignment optimization problem would thus, in this particular case, turn out to be equivalent to the *maximum induced bipartite subgraph problem.* Since the minimum induced bipartite subgraph of any graph with at least one edge is the two-vertex graph with a single edge, this observation produces an interesting result:

Proposition 3.13. *In any acid-base classification there is always at least one 'pure' acid and at least one 'pure' base.*

The maximum induced bipartite subgraph problem is an NP-hard problem as well. However, a brute-force algorithm for solving it scales better than the general role assignment optimization problem: let k be the number of vertices in a maximum induced bipartite subgraph of G. In order to find such a maximum induced bipartite subgraph we would have to test at most

$$\sum_{m=k}^{|V_G|} \binom{|V_G|}{m} \tag{3.26}$$

subgraphs for bipartiteness. Each of these tests can be decided by depth-first search, so that the sum of binomial coefficients would be the dominant factor in the scaling of the algorithm. On the other hand, there are $4^{|A_H|}$ potential different role models on a given directed hypergraph[6]. This would be the amount of computations of $|r_\beta|$ required to find an optimal role assignment in the brute force approach. Since in the present case (an probably in most cases of chemical relevance) $|A_H| > |V_H|$, we have

$$4^{|A_H|} < 4^{|V_H|} = 2^{2|V_H|}; \tag{3.27}$$

and since

$$\sum_{k=o}^{n} \binom{n}{k} = 2^n, \tag{3.28}$$

whenever $V_H = V_G$ we get

$$4^{|A_H|} > \sum_{m=k}^{|V_G|} \binom{|V_G|}{m}, \tag{3.29}$$

proving that the maximum induced bipartite graph algorithm scales better. In conclusion, by formulating the acid-base role assignment optimization problem as a maximum induced bipartite subgraph problem, we now have an easy method for solving it for a reasonably small data set.

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[6] For any given reaction $a + b \to c + d$ there are 4 different ways of bijectively mapping its substances into the vertices of $A + B \to A + B$

Label	**Substance**	$\mathbf{K_a}$	**Roles**	**Acid strength** $(N_{out}(u, A))$
1	HBr	1.00×10^9	Acid	14
2	HCl	1×10^7	Acid	13
3	H_2SO_4	1.0×10^3	Acid	11
4	HNO_3	20	Acid	11
5	H_3O^+	1	Acid	9
6	HSO_4^-	1.02×10^{-2}	Acid and Base	9
7	H_2S	1.00×10^{-7}	Acid	7
8	$NH_3^+(CH_2)_3NH_3^+$	2.57×10^{-9}	Acid	6
9	NH_4^+	6.17×10^{-10}	Acid	6
10	C_6H_6OH	1.12×10^{-10}	Acid	5
11	$CH_3NH_3^+$	2.291×10^{-11}	Acid	4
12	$NH_2(CH_2)_3NH_3^+$	2.239×10^{-11}	Acid and Base	3
13	HS^-	1.202×10^{-13}	Acid and Base	2
14	H_2O	1×10^{-14}	Acid and Base	1
15	CH_3CH_2OH	2.884×10^{-16}	Acid	0
16	OH^-	–	Base	0
17	Cl^-	–	Base	0
18	Br^-	–	Base	0
19	NH_3	–	Base	0
20	S^{2-}	–	Base	0
21	NO_3^-	–	Base	0
22	$C_6H_6O^-$	–	Base	0
23	CH_3NH_2	–	Base	0
24	$NH_2(CH_2)_3NH_2$	–	Base	0
25	$CH_3CH_2O^-$	–	Base	0
26	SO_4^{2-}	–	Base	0

Table 3.1: Summary of the optimal acid-base role assignment of a network comprising 26 substances.

The fourth column of Table 3.1 summarizes the optimal role assignment computed by this method, while Figure 3.8 depicts the corresponding concept lattice. The results perfectly match the accepted chemical classification of the data set in acids and bases. The emergence of amphoteric substances is particularly remarkable. They appear not as a separate class different from those of acids and bases, but as the extent of a concept characterized by both the acid and base properties, which arguably comes closer to the way amphoteric substances have been conceptualized in chemistry. Beyond the fact that Table 3.1 shows a successful recognition of the acid and basic substances among a small collection of compounds, we want to emphasize the agreement between our approach and the logic of chemical thought: the characterization of amphoteric substances as entities with mixt behavior is made possible by the use of general binary relations as morphisms in the classification system, allowing for the existence of classifications in non-disjoint classes –a feature that we have intently included into our model.

Though this may seem as a subtle and ultimately irrelevant detail, we shall argue that it actually makes a big difference in the simplicity and cognitive value of the theory. Indeed, suppose that we had required role assignments to be adjacency preserving *mappings*, forcing us to fit the reaction network to a partition in disjoint classes of equivalence. Since we found four substances that are both acids and bases (H_2O, HS^-, $NH_2(CH2)_3NH_3^+$, and HSO_4^-) in a role assignment that minimizes the occurrence of such substances, it is clear that, had we demanded role assignments to be mappings, there would be no role assignment for this network with codomain on H_2. To get a suitable substitute for H_2, we would have to introduce at least one new vertex X in V_{H_2} to represent the class of amphoteric substances. Furthermore, since these substances react with both acids, bases, and among themselves, and also appear as accompanying products of all kinds of substances, we would need to introduce a lot of additional hyperarcs in A_{H_2} to obtain a viable fit:

$$
\begin{gathered}
(\{A,X\},\{A,B\}) \\
(\{X,B\},\{A,B\}) \\
(\{A,B\},\{A,X\}) \\
(\{A,B\},\{X,B\}) \\
(\{A,X\},\{A,X\}) \\
(\{A,X\},\{X,B\}) \\
(\{X,B\},\{A,X\}) \\
(\{X,B\},\{X,B\}) \\
(\{X,X\},\{A,B\}) \\
(\{X,X\},\{A,X\}) \\
\vdots
\end{gathered}
$$

We see how the demand for disjointness significantly increases the size of the codomain of a viable role assignment. As a result, a model that allows for restricted role multiplicity turns out to be more concise than one that plainly discards it. Even more: while the concept lattice of Figure 3.8 contains two non-trivial pairs of comparable concepts, we know that in the concept lattice of a disjoint classification any pair of non-trivial concepts are incomparable (see Figure 2.5). Thus, despite being more concise, the non-disjoint classification arguably contains more information.

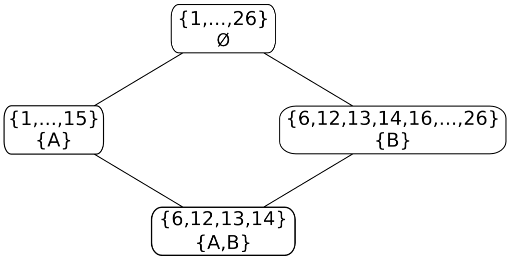

Figure 3.8: The concept lattice of an acid-base role assignment. Extents are written using the labels of Table 3.1.

Further analyses of the classification of Table 3.1 allow us to expand our knowledge on the phenomenon of acidity-basicity. For instance, note that each vertex $u \in V_{H_1}$ is completely described by its neighborhoods,

$$\begin{aligned} N_{in}(u) &= \{a \in A_{H_1} : u \in \mathit{head}(a)\}, \\ N_{out}(u) &= \{a \in A_{H_1} : u \in \mathit{tail}(a)\}. \end{aligned} \tag{3.30}$$

These sets can then be taken as the broadest descriptors of the activity of a substance. In particular, $|N_{out}(u)|$ is equal to the number of reactions where u takes part as a reactant, i.e. it gives a measure of the reactivity of u. In the same way, for any given role model β, the sets

$$\begin{aligned} N_{in}(u, v) &= \{a \in A_{H_1} : u \in \mathit{head}(a) \text{ and } \beta(a)(u) = v\} \\ N_{out}(u, v) &= \{a \in A_{H_1} : u \in \mathit{tail}(a) \text{ and } \beta(a)(u) = v\} \end{aligned} \tag{3.31}$$

describe the activity of u relative to property v. In particular, $N_{out}(u, A)$ is a descriptor of u's acid activity, and $|N_{out}(v, A)|$ measures its reactivity as an acid, that is, its *acid strength*. This central concept of chemistry can thus be attached to an invariant of the role assignment determining an acid-base classification.

Column 5 of Table 3.1 presents the values of $|N_{out}(u, A)|$ for the 26 substances in the role model induced by the optimal role assignment built. As expected, $|N_{out}(u, A)|$ is correlated with K_a, the measure of acid strength in the theory of chemical equilibrium. In the same way, $|N_{out}(v, B)|$ gives a measure of the basic strength of a substance.

The concept lattice tells us that it is possible to determine the acid-base properties of an uncharacterized substance with as few as two reaction tests –one to determine if it has the property A, and another to determine if it has the property B. The scale of acid/basic strength help us attain this minimum, as the probability that an unknown acid/base will react with the strongest acid in the network is highest. Thus, by using the strongest acid/base in the reaction tests, we optimize our chances of characterizing an unknown substance in as few steps as possible. This high probability is turned into certainty by an interesting property of the role model: for any hyperarc $a = (\{u, v\}, \{x, y\})$ we have

$$|N_{out}(u, \beta(a)(u))| + |N_{out}(v, \beta(a)(v))| \geq |N_{out}(x, \beta(a)(x))| + |N_{out}(y, \beta(a)(y))|, \quad (3.32)$$

which means that each acid-base reaction proceeds with an overall decrease of acid-basic strength, a well-known fact that naturally emerges from the role model. This fact warrants that a substance that reacts with a weaker acid/base will also react with a stronger acid/base, turning the scale of acid/base strength into a straightforward determinant of acid-base activity.

* * *

Of course, there is nothing new in the results derived in the previous example. But our point, precisely, is that there is nothing new with chemical activity: if anything, we have endeavored to show that it is one of the oldest approaches in chemical research. The novelty that we are proposing is a mathematical formulation of this approach. Having reproduced a relevant piece of chemical knowledge by means of our model raises our hopes that we are heading in a right direction.

3.4 From reaction networks to structural formulas

Structural formulas are one of the most recognizable trademarks of chemistry, and also one of the most interesting. In the historical development of chemical theory, structural formulas were primarily constructed from the examination of the network of chemical reactions and thus owed to be absolutely consistent with it. Then, at some point they gain the ability to suggest concepts, patterns, and new routes for empirical research that are not evident in the sole structure of the chemical reaction network. As Klein notes, “the manipulations of formulas on paper and the visual display of possible recombinations of signs had the suggestive power of introducing new significances, which chemists attempted to match up with experimental traces” (Klein, 2003, p. 3). In other words, structural formulas strongly inhabit that twilight zone between chemical structure and chemical activity, constituting ideal subjects for examining the matter of the relation between activity and structure theory. In this section we use the mathematical language developed thus far to discuss how structural formulas can be derived from empirically constructed reaction networks, and how they may claim independence from their absolute domain afterwards.

A reaction network is represented by a hyperdigraph $H \in \mathbf{HyperD}_0$. In turn, each substance in the network is represented by a vertex in V_H. At the moment, these vertices are devoid of any structure; they are just "anchor points for relations". But recall that H is not the unique valid representation of the network. Equivalent representations are given by

- an element of **HyperD** that is isomorphic to H,
- the image of H under an equivalence of categories[7].

Note that no demand is posed on the nature and constitution of an equivalent representation. That is, it does not matter whether it is another hyperdigraph, or a group, or a POSET; plus, it does not matter whether its elements are points, or graphs, or whatever we may please: all that matters is that it is isomorphic (up to isomorphism) to the original hyperdigraph. This observation allows us to see in what sense structural formulas are determined by reaction networks: in our model, that statement translates into the statement that there is an equivalent representation of the network whose elements are structural formulas.

Finding an equivalent representation in terms of structural formulas of a large reaction network, covering a reasonably complete fraction of empirical knowledge regarding substance reactivity, is a hard enterprise that we will not aboard here. There are some promising proposals on this regard, such as Benkö *et al.*'s toy model based on graph grammars (Benkö *et al.* , 2003) that we hope to test in future developments. Meanwhile,

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[7] Two cases are listed for the sake of clarity, but it is worth noting that actually the second includes the first: given an isomorphism $i : A \to B$ in a category $\mathcal{C}$, the functor $F : \mathcal{C} \to \mathcal{C}$ defined by

$$\begin{aligned} FA &= B \\ FB &= A \\ FX &= X \quad \text{for } X \neq A,\ X \neq B \end{aligned} \tag{3.33}$$

$$\begin{aligned} F(i) &= i^{-1} \\ F(i^{-1}) &= i \\ F(f) &= f \quad \text{for } f \neq i,\ f \neq i^{-1} \end{aligned} \tag{3.34}$$

is faithful, full, and essentially surjective, so it defines an equivalence of categories that maps A into an isomorphic object B.

we think that a restricted example using a small reaction network will be enough to show how this problem can be solved.

Example 3.14 (The structure of benzene)**.** Consider the network of chlorine substitutions on benzene. All reactions are of the type

$$\varphi - Cl_n + Cl_2 \to \varphi - Cl_{n+1} + HCl \tag{3.35}$$

where $\varphi - Cl_n$ is an n-chlorine substituted derivative of benzene. Following our general approach, this network should be represented by means of a hyperdigraph. However, since one reactant (Cl_2) and one product (HCl) are common to all reactions, we can remove them from all hyperarcs without losing information. As a result, we obtain a digraph H pictured in Figure 3.9 (a).

According to our proposal, equivalent models of this reaction network are given exclusively by images of H under an equivalence of categories. For instance, Ivanciuc *et al.* (2005) have noted that the network of chlorine-substitution reactions on benzene can be regarded as a POSET P with Hasse diagram H. The identification of H with P, however, is not a strict change of representation: since Hasse diagrams are not arbitrary digraphs but only those that correspond to the transitive interior of a POSET, we would be regarding H as an object in the category **Hasse** $\subset$ **Digraphs** of Hasse diagrams and adjacency-preserving mappings. The transformation proposed by the authors, then, would be given by a functor F : **Hasse** $\to$ **Pos** that maps Hasse diagrams into their corresponding POSETs (i.e. into their respective transitive closures). No functor satisfying this property can be an equivalence of categories: on one hand any adjacency-preserving map $f : H_1 \to H_2 \in$ **Hasse** is a monotone map $f : FH_1 \to FH_2$. Indeed, since A_{H_i} is the transitive interior of $\leq_{FH_i}$ we have $A_{H_i} \subset \leq_{FH_i}$, so that $(u, v) \in A_{H_1}$ implies $u \leq_{FH_1} v$; and since in that case $(f(u), f(v)) \in A_{H_2}$, we have $f(u) \leq_{FH_2} f(v)$. Furthermore, since FH_i is the transitive closure of H_i, monotonicity in all remaining ordered pairs is warranted by transitivity. On the other hand, not every monotone map is adjacency preserving –linear extensions provide a quick counterexample. Thus, F cannot be full.

The previous result questions the rigor of representing the benzene chlorine-substitution reaction network as a POSET. However, we can attain strict category equivalence with the digraph image of the network by considering only *cover* relations in H: for each $x, y \in P$, we say that x *covers* y (noted $x \lessdot y$) if and only if $y \leq x$ and there is no $z \neq y \in P$ such that $y \leq z \leq x$. Let $\mathcal{P}$ be the category of POSETs and mappings $f : P \to Q$ such that $x \lessdot y$ implies $f(x) \lessdot f(y)$[8]. Clearly, there is a one-to-one

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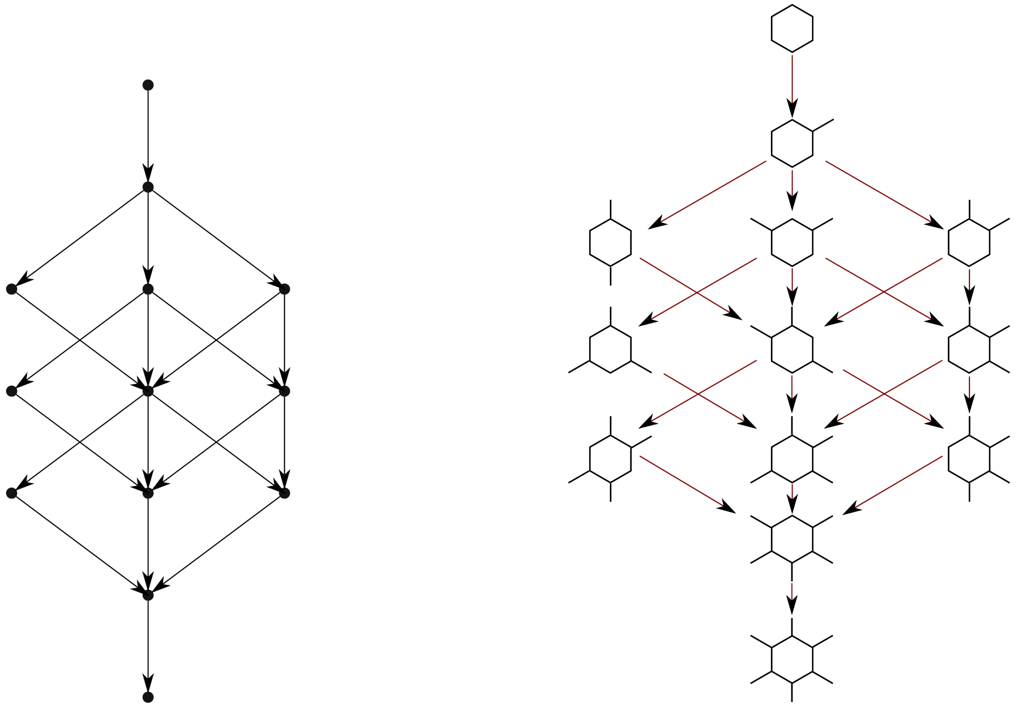
[8] Note that these mappings are analogous to monotone functions, except that the defining condition is now introduced with respect to cover rather than order relations. This means that objects in $\mathcal{P}_0$ are no longer our 'usual' POSETS, in the same sense that objects in **BipartiteD** are no longer our usual digraphs (see **Section 3.1**).



(a) (b)

Figure 3.9: (a) Network of chlorine-substitution reactions on benzene represented as a directed graph. Each dot represents a chlorine-substituted derivative, all other reactants/products were omitted (i.e. Cl_2 and HCl), arrows point from reactants to products. The upper point represents benzene, each point v below it represent an n-substituted derivative, where n is the length of the shortest path going from benzene to v. (b) Hasse diagram of the POSET of structural formulas of benzene chlorine-substituted derivatives ordered by the subgraph relation.

correspondence between cover relations in a POSET and arcs in its Hasse diagram, so $F : \mathbf{Hasse} \to \mathcal{P}$ defined by

$$\begin{cases} FH = P & \text{iff } P \text{ is the transitive closure of } H \\ F(f : H_1 \to H_2) = f \end{cases} \tag{3.36}$$

is an equivalence of categories, proving that FH is an equivalent representation of H[9].

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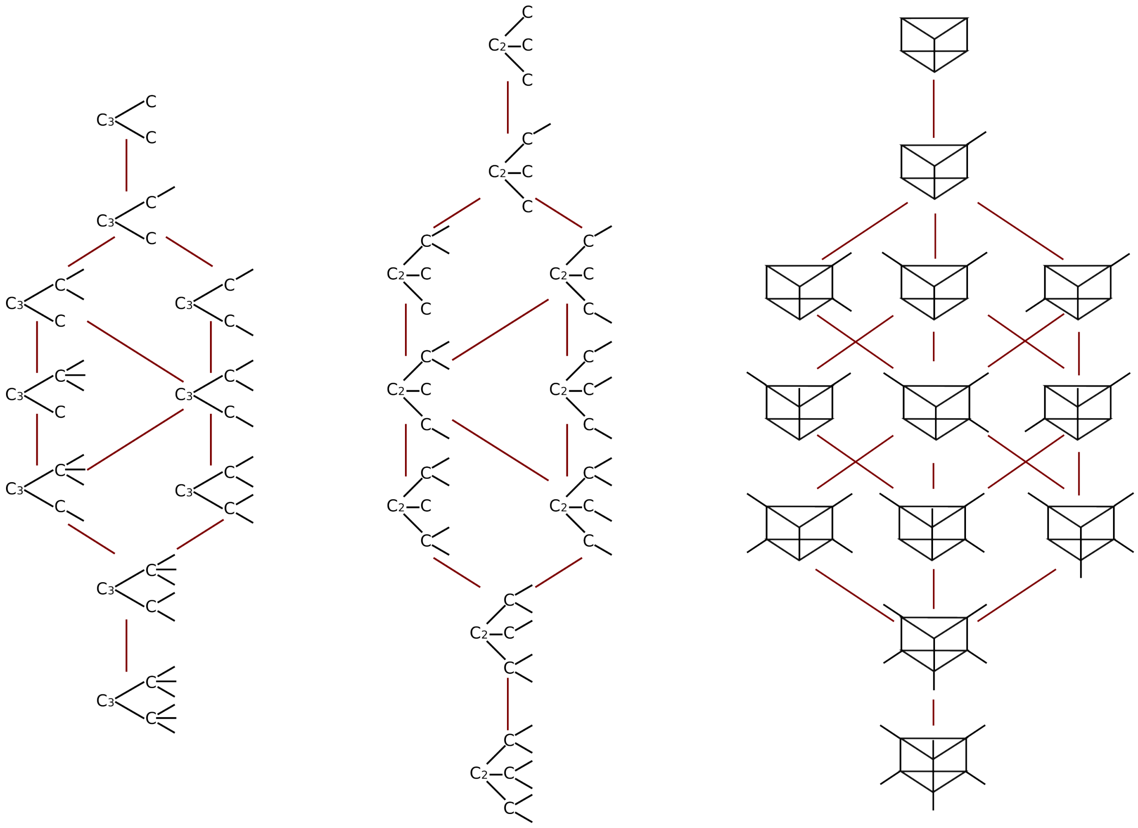
[9] Its worth noting that this transformation is consistent with the QSSAR methodology introduced by Ivanciuc *et al.* (2005), where properties of a compound are interpolated from the properties of the elements of its cover. This shows that the authors are also focusing on cover rather than order relations, so they would actually be equating the digraph of the reaction network with an object in $\mathcal{P}$.

The Hasse diagram $H \in \mathbf{Hasse}_0$ of Figure 3.9 (b) provides the primary representation of empirical knowledge on the network of chlorine-substitution reactions. The collection of morphisms with domain on H completely characterizes the structure of this Hasse diagram. In consequence, any image of H under an equivalence of categories provides an equivalent representation of the network that is consistent with the same collection of empirical facts –such is the case of $FH \in \mathcal{P}_0$. In the same way, equivalences of categories also give the consistency condition that structural formulas of chloro-benzenes must fulfil: they must span a mathematical structure that is also the image of H under an equivalence of categories, as only the existence of such functor warrants that the new model is coherent with the empirical phenomena it accounts for. Clearly, any isomorphic image of FH satisfies this condition. Such is the case of the POSET S of structural graphs of Figure 3.9 (b), also introduced by Ivanciuc *et al.* (2005). In this POSET order relations are defined as subgraph relations, i.e. $G_1 \leq G_2$ if and only if G_1 is a subgraph of G_2. For the sake of consistency, we could also define this POSET by means of cover relations, stating that $G_1 \lessdot G_2$ if G_1 is a maximum subgraph of G_2, so that $S \in \mathcal{P}_0$. From the picture of its Hasse diagram, it is clear that $S \simeq FH \simeq H$, proving that S is, indeed, an equivalent model of the reaction network being considered.

The value of the criterion of categorical equivalence as a link between activity and structure theory is demonstrated by its ability to distinguish what nineteenth century chemists considered viable structural formulas from the ones they considered inadequate. As we have just shown, the hexagonal kekulean structure determines a POSET that is equivalent to the substitution reaction network H. Furthermore, rejected candidate formulas for benzene that agree with the rules of valence such as those considered in Figures 3.10 (a) and (b) conform POSETs that are not equivalent to H. Last and most notably, Landenburg's prismane structure spans a POSET that is equivalent to H (Figure 3.10 (c)). This remarkable structure achieved significant popularity, despite its apparent deviation from the already well recieved hexagonal structure proposed by Kekulé (Rocke, 1985). While it is hard to see any similarity between the formulas themselves, the corresponding POSETs of structural graphs immediately revealed their equivalence.

Interestingly, Rocke has argued from a historical perspective that Ladenburg's prismane structure should be regarded as a "modification rather than a rejection" of Kekulé's theory, since both chemists worked close to each other in the development of their respective proposals, using the same criterion when choosing a viable structural formula: that it matched the counts of the number of known isomeric n-substituted derivatives of benzene (Rocke, 1985). From a contemporary perspective, these isomer counts are determined by the collection of paths in the chlorine-substitution reaction network, which in turn is a graph-theoretical invariant. This means that Kekulé's criterion was nothing but an invariant of that network *up to isomorphism in* **Graphs**;



(a) (b) (c)

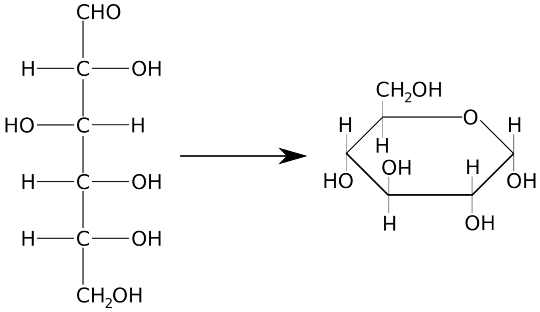
Figure 3.10: Alternatives to the hexagonal formula of benzene. (a) A failed candidate. Three carbon atoms conform a core with all but two valences saturated (labeled C_3 in the picture), that is bounded to two methyl groups (labeled C). The corresponding POSET of structural graphs ordered by the subgraph relations is not equivalent to that of Figure 3.9 (a), which is first revealed by the fact that the counts of di-substituted derivatives do not match. (b) Another failed candidate. Two carbon atoms conform a core with three free valences (labeled C_2), that are saturated by three methylene groups (labeled C). The corresponding POSET of structural graphs is isomorphic to that of (a), so this structural formula is discarded on the same grounds. (c) Ladenburg's prismane structure induces a POSET that is isomorphic to that of Figure 3.9 (a), and is thus a suitable structural formula.

so we could say, if we are allowed the anachronism, that he was ultimately demanding, just as we did here, that structural formulas conformed an object that was related to the substitution reaction network by an equivalence of categories. In this sense, the methodology we followed to derive the structure of benzene is consistent with the actual historical process that lead to the currently accepted structure.

* * *

Unlike vertices in the hyperdigraph of a reaction network, structural formulas have properties of their own. These properties allow for the definition of a category equivalent to that of reaction networks, as we showed above. This fact grants them meaning and legitimacy, so that after equivalence is proven properties of the structural graphs become the main focus of attention. At this point, an inversion in the direction of analogy occurs: structural graphs are no longer seen as determined by reaction networks but as *determinants* of reaction networks, thus gaining the ability to shape the model that gave them birth.

Example 3.15 (Organic functions revisited)**.** In contemporary chemistry, the isomerisation of glucose into the cyclic glucopiranose form,



is seen as a nucleophilic addition of an alcohol on an aldehyde, producing a hemiacetal:

$$\text{Aldehyde} + \text{Alcohol} \to \text{Hemiacetal}. \tag{3.37}$$

The acyclic form of glucose then has the aldehyde and alcohol properties, while its cyclic glucopyranose form has the hemiacetal property. But this classification is clearly impossible in **HyperD**: consider the hyperdigraph H of chemical reactions and the hyperdigraph O of organic functions introduced in **Example 3.9**. On that model glucose isomerisation is represented by a hyperarc $a \in H$, while hemiacetal formation is represented by a hyperarc $b \in O$. In turn, the family of organic functions of acyclic glucose is determined by its image under the kernel of a role assignment $r : H \to O$. Last, the role of glucose in a is determined by its image under $\beta(a)$, where β is the role model induced by r. In consequence, a role assignment that successfully reproduces the contemporary classification of glucose isomerisation as hemiacetal formation and thus characterizes cyclic glucose as a hemiacetal should be such that $\beta(a) : a \to b$. But since $|tail(a)| = 1$ and $|tail(b)| = 2$, there is no role assignment $r : H \to O$ satisfying this property.

The previous observation shows that, opposing what we said in **Example 3.9**, the modern concept of organic function (even when understood only in terms of chemical activity theory) goes beyond the reach of our current version of the activity model. The innovation identified in this example may have been promoted by the influence of structure theory: when we induce structural formulas from a reaction network through a change of representation and use them to characterize the entities, they become more than "anchor points for relations"; they acquire a rich structure, properties of their own, and thus gain an additional operability. In the present case, organic functions become attached to certain motifs in the structural graphs. Reaction classes then start to be seen as abstract operations between those motifs, so that we can define a pseudo-reaction between organic functions in the same compound. This possibility may be seen as a hypothesis generated by the structural model that is to be contrasted by experiment (see below), or it may be seen as a novel classificatory approach inspired by that model. Either way, it eventually induces a change in the activity theory that incorporates the innovation. In terms of our model, this change concerns a redefinition of the morphisms comprised in the reaction network category in order to allow for the novel classificatory structures.

* * *

The previous example illustrates how the analysis of the properties of structural formulas may suggest changes on the category of reaction networks. It is interesting to analyze this interaction between structural formulas (structure theory) and categories of reaction networks (activity theory) in epistemological terms. Reaction networks are constructed by incorporating data collected by experiment. These data are embedded in a category designed to preserve its relational structure, and knowledge on chemical activity is obtained by means of morphisms in that category. Any statement that may be produced regarding unobserved empirical phenomena within activity theory (e.g. on whether some substances react with each other or not) relies on a pattern revealed by the codomain of a structure-preserving transformation, whose domain is an empirically constructed network[10]. In this way, that pattern is supported by empirical evidence. Predictions in activity theory, thus, are inductive inferences relying on observed empirical phenomena an a suitable principle of induction.

Structural formulas are able to produce all those inductive inferences, as they span an equivalent image of the empirical reaction network. But they are also expected

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[10] On this regard, recall the connection between formal contexts and morphisms in a classification system considered on **Section 2.3**, and the possibility of producing inferences by examination of a concept lattice illustrated in **Example 2.23**.

to produce new statements that would not be possible by the sole examination of the classificatory structure induced by morphisms on the category of reaction networks. It is interesting to realize that, to do this, *one has to drop the demand for category-theoretical equivalence*. Indeed, as long as we only consider properties of structural formulas that determine an equivalent image of the original reaction network, we are constrained to work within the reach of the corresponding classification system, so we would not be able to express anything that cannot be expressed via its morphisms. To go beyond the reach of activity theory we have to consider properties of chemical structures that are not related to the underlying category of reaction networks. *But this means that novel predictions given by the analysis of structural formulas are unsupported by empirical evidence!*

To produce new statements within structure theory, the metaphor (i.e. a structural formula) has to take prevalence over its referent (i.e. a chemical reaction network). We must examine properties of structural formulas that are not category-theoretical invariants in the equivalent image of the reaction network that they conform. These properties are thus not linked to morphisms in that category, and are not grounded on the empirical evidence collected in the network. They are not supported by experiment, and thus cannot be taken as inferences of any kind. Instead, they are hypotheses pending corroboration. Furthermore, these hypotheses accomplish the popperian ideal of high empirical content: being given by generalized properties of structural graphs, they refer, in principle, to the whole family of chemical substances being researched. In this way, structural formulas constitute *systematic tools for generating hypotheses*. Their strength comes not from their ability to 'hit bulls-eye' with every single prediction, but from the large amount of hypotheses with significant empirical content that they are able to suggest. It is expected that most of these hypotheses are bound to be refuted, as high empirical content is necessarily accompanied by high refutability; but then, whenever one such hypothesis gets corroborated, it allows a big leap in the development of chemical knowledge.

It may be that this constant presence of refuted hypotheses in chemistry has promoted the mistrustful feeling that structural formulas are useless as predictive tools, being merely able to offer explanations of already known phenomena[11]; a feeling that promotes the image of chemistry as a weak an incipient science when compared e.g. to physics. This, we believe, is an unfair appreciation. Hypotheses formulation is a key element in scientific research; arguably the hardest to systematize and thus the one requiring the most creativity. Structural formulas are hypotheses-generating tools of unmatched power that assist the creativity of chemists. This feature of chemical struc-

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[11] For instance, Gay (1977) has noted that this feeling was particularly strong up to the mid-twentieth century, when even chemists overlooked the predictions of structure theory regarding the activity of noble gases, but accepted them as the natural explanation of noble gas compounds once they were synthesized.

ture theory should be considered an extraordinary theoretical strength rather than a weakness.

3.5 Summarizing

Graphs are an inadequate mathematical representation of reaction networks, as they are unable to recover the most basic characteristics of their logical structures. Directed hypergraphs properly model reactant-reactant, product-product, and reactants-products relations coded in chemical reactions, and thus constitute a suitable alternative. If hyperdigraphs conform the collection of objects of a classification system for the description of chemical activity, role assignments conform the collection of morphisms of that category. The later appear as an adaptation of the definition of adjacency-preserving relation to the case of directed hypergraphs, thus extending the criterion of structure-preservation of the standard category of graphs, **Graphs**.

The assumption that the concept lattice associated with a role assignment converges to a stable configuration as the network grows allows the use of this classificatory structure to predict unobserved phenomena. Role assignments with minimum cardinal minimize the average number of reaction tests needed to determine the position of new substances in the limit concept lattice, so they are optimal regarding their ability to predict their behavior. Furthermore, in that case the existence of an associated role model is proven, granting the possibility of determining the precise role played by each substance in each specific chemical reaction.

Last, we have sketched a formulation of the link between reaction networks and chemical structures in mathematical terms. At first, chemical structures are introduced by means of a change of representation that warrants consistency with the collection of knowledge on substance activity embodied in a reaction network. Then, properties of structural formulas that are not determined by equivalence with that reaction network suggest chemical phenomena that exceeds the reach of activity theory. However, since these predictions are not connected to empirical evidence, they cannot be taken as anything but hypotheses that have to be verified by experiment. If they happen to be corroborated, structural formulas motivate a change on the network structure of chemical knowledge, thus promoting a transformation of the activity model that engendered them. This appreciation of the structure-activity relationship significantly deviates from the orthodox picture, and grants deeper insight into these two epistemic approaches of chemistry: predictions in activity theory are better understood through the inductivist picture of laws supported on increasing accumulations of empirical facts, while those of structure theory approach the popperian ideal of a science advancing by proposing and corroborating hypotheses with large empirical content.

Chapter 4

Concept categories

"Why do you labor so hard just to keep to the pattern? I mean, is homogeneity all that terrific?"
–Goran Vlaovich

On Section 2.3 we introduced the Concept Lattice as an extension of our category-theoretical formalism of classification that exploits its affinity with Formal Concept Analysis (FCA). On this chapter we draw inspiration on this construction to propose one last element of our mathematical model of chemical classification: *Concept Categories* (which we also call *Classification Categories*) that characterize relations among concepts induced by a classification in a Classification System.

The central idea is that the concept lattice can be regarded as a particular instance of a further category-theoretical characterization of classifications in a Classification System by means of a category whose objects are morphisms in the Classification System (Section 4.1). In the particular case of Concept Lattices we deal with an algebraic description of classifications embedded in a subcategory of **Pos**. But then, different criteria of structure-preservation between morphisms in a Classification System may induce topological, geometrical, etc. descriptions of its classifications that rely on appropriate Classification Categories.

The remaining sections consider the case of one such Classification Category, inspired by the topological study of the periodic system developed by Restrepo and collaborators. First, on Section 4.2 we show that their chemotopological method can be regarded as a proposal of a Classification Category where classifications in the category $\mathcal{T}$ of dendrograms and dendrogram cuts are endowed with the structure of a topological space. Then, we show that this approach can be generalized to arbitrary Classification Systems. In this way, while Concept Lattices gives algebraic descriptions of morphisms in a Classification System $\mathcal{C}$ by associating them with a category of lattices, our generalization of the chemotopological method gives topological descriptions of the same morphisms by associating them with a category of topological spaces, which we call $\tau_R(\mathcal{C})$.

On Section 4.3 we characterize several topological invariants in $\tau_R(\mathcal{C})$. We propose that invariants such as closure, interior, and boundary are related to similarities and dissimilarities between the entities being studied, unveiled by the properties induced by a given classification. Also, we prove that closed sets can always be expressed as unions of concept extents in the corresponding classification, and that the interior of a concept extent is determined by is intent. In this way, $\tau_R(\mathcal{C})$ constructs a topological characterization of concepts induced by classifications in $\mathcal{C}$.

Along the chapter we will elaborate two chemical examples. The first deals with the topology of chemical elements published by Restrepo *et al.* On a first moment we will show how the authors resorted to topological invariants in order to describe the similarities among chemical elements, comprising and transcending the patterns found in Mendeleev's periodic table. Then, on a second moment we will show that their restricted formulation, that starts from a disjoint classification constructed by a specific clustering methodology, severely weakens the reach of their methodology and puts some of their strongest results on doubt. Last, we argue that our generalized formulation of the chemotopological method lets us avoid these issues. To illustrate this argument we contrast the status of topological invariants in the topology of the chemical elements with the corresponding invariants in the topology induced by the non-disjoint classification of substances as acids and bases introduced on the previous chapter.

4.1 Beyond the Concept Lattice

On Section 2.3 we noted that each morphism $f : A \to B$ in a Classification System determines a formal context, allowing us to link our proposal to the formalism of FCA. This link puts a vast set of theoretical tools at our disposal. Indeed, though we have just dipped into the possibilities that FCA opens, the Concept Lattice has already allowed us to generalize the notion of position in network analysis (**Example 2.24**), to define a criterion of optimality for chemical activity classifications (**Section 3.3**) and to formalize and understand the value of the concept of amphoteric substance (**Example 3.12**). However, the Concept Lattice is still, in certain way, a foreigner. Unlike classifications and properties, that were introduced using the language of objects and morphisms and thus incorporated into the logic of our category-theoretical model, concepts were just 'pasted' at one end of the formalism. We now look back into this matter, and determine the position that the Concept Lattice occupies in our proposal of a mathematized theory of internal relations.

FCA entered into our proposal through an analogy between classification-inducing morphisms and formal contexts. First, the correspondence between binary relations and formal contexts allowed us to associate each morphism in a Classification System with a unique formal context. Then, the correspondence between formal contexts and Concept Lattices allowed us to characterize the former by means of the later. Now, since in the first step we are dealing with a one-to-one correspondence, we can skip the introduction of formal contexts and go straight from a classification to a Concept Lattice. Prescinding of the mediation of formal context, we realize that we are ultimately introducing a transformation that maps each classification in a Classification System into a unique Concept Lattice.

Concept Lattices thus conform a novel mathematical description of classifications, that can be described within the logic of categories. They are complete lattices and thus POSETs, which in category theoretical terms means that they conform a subcategory of **Pos**. By using the methods of FCA, we establish a link between morphisms in a Classification System and Concept Lattices in a suitable subcategory of **Pos**. In other words, when we build Concept Lattices we are ultimately characterizing the family of classifications on a Classification System by means of a category whose objects are, naturally, *the morphisms of that system.*

This is a very powerful realization. It allows us to incorporate the tools of FCA to the core of the mathematical model that we have been developing. Most important, it motivates the exploration of other alternatives for achieving the same goal that the Concept Lattice attains. This lattice offers a particular characterization of a classification, attached to the mathematics of order; but we may explore different criteria of structure-preservation on the morphisms of a Classification System, producing multiple categories that offer varied descriptions of its classifications. This is what we call a *Classification Category.*

The next section will be devoted to the elaboration of a topological Classification Category, motivated by the work of Restrepo *et al.* (2004). We will show that their chemotopological method can be formulated as a topological Classification Category linked to the Classification System of hierarchical clustering. Then, by noticing that open sets in a topological representation of a classification in this category are related to formal concepts, we gain a clearer understanding of the limitations of Restrepo's formulation of the chemotopological method, and realize how a broader formulation allows us to transcend these limitations.

4.2 Generalized chemotopological method

In Restrepo *et al.* (2004), the authors introduced a topological description of the periodic system. Their work relies on a novel methodological approach known as the "chemotopological method"[1]. The objective of this methodology is to construct a topological description of similarity within a set of entities described by some measurable properties. It starts from a representation of the data set by means of a vector space $\mathbb{R}^n$. Each object is represented by a vector $v = (v_1, \ldots, v_n) \in \mathbb{R}^n$, where v_i is the value of the ith property of object v. Similarity regarding these properties is described by means of a metric $d : \mathbb{R}^n \times \mathbb{R}^n \to \mathbb{R}$. The set is then partitioned in classes of equivalence according to their similarities, by using a hierarchical clustering method to generate a dendrogram and then selecting a cut of the dendrogram that optimizes the parameter of Equation (2.21) (Mesa & Restrepo, 2008).

Up to this point, the chemotopological method just follows a standard approach of cluster analysis. The key innovation comes from the acknowledgement that these classes conform a basis for a topology on the data set (Restrepo *et al.* , 2004). Similarity thus becomes linked to topological neighborhood, allowing for a more sophisticate description of similarity relations contained in the classification by means of topological invariants such as boundaries and closures.

Example 4.1 (Restrepo *et al.* (2004))**.** Restrepo *et al.* applied the chemotopological method to a set of 72 chemical elements, characterized by 31 physico-chemical properties. They used the single-linkage clustering method and a dendrogram cut in clusters of up to 5 elements to obtain the following partition $\mathcal{B}$ of the element set:

$$\mathcal{B} = \left\{ \begin{array}{l} \{Sc, Sr, Mg, Ca\}, \{Ni, Cd\}, \{Y, La\}, \{Zr, Hf, Ti, V\}, \{Fe, Co, In\}, \\ \{Sn, Pb, Zn, Ga\}, \{Sb, Te, Bi, As, Se\}, \{Po, At\}, \{Cr, Mn\}, \{Ir, Pt\}, \\ \{Nb, Mo, W, Ru, Ta\}, \{Os\}, \{Rh, Au\}, \{Cu, Ag, Pd, Hg, Tl\}, \{Ba\}, \\ \{Tc, Re\}, \{B\}, \{Ge\}, \{P, S\}, \{C\}, \{Be, Al, Si\}, \{N\}, \{O\}, \{He\}, \\ \{Kr, Xe, Rn, Ne, Ar\}, \{K, Rb, Cs, Li, Na\}, \{Br, I, Cl\}, \{F\}, \{H\} \end{array} \right\} \tag{4.1}$$

Then, they constructed the topology induced by the basis set $\mathcal{B}$. Following are some of their observations:

- Robust chemical families that are strongly differentiated from all other elements, such as alkali metals, conform *perfect sets* in the topological space; that is, sets that are equal to their derived set (see Figure 4.1). In topological terms, these sets are closed sets that contain no isolated points i.e. each neighborhood of a point in the perfect set contains at least another point in the perfect set and no point satisfying this property is left out. According to the authors, this fact means that no elements other than alkali metals are such that their neighborhoods

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[1] The authors gave this name to their method in accordance to the purpose they designed it for. The name is misleading, however, as the scope of the method is not constrained to applications of chemistry. Still, in order to set up a common language, we stick to the denomination chosen by the authors.

contain elements strongly related to those of this family. At the same time, this indicates that alkali metals conform a robust group with little relationship to other elements.

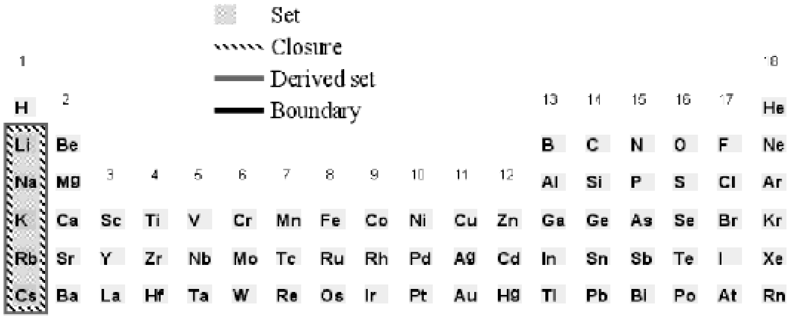

Figure 4.1: Topological properties of the alkali metals. Reproduced from Restrepo *et al* (2004).

- In contrast, elements of group 16 do not conform a perfect set in the topology. Their closure incorporates elements from the nitrogen and fluorine groups (15 and 17 respectively), but neither nitrogen nor fluorine themselves (see Figure 4.2). According to the authors, the fact that elements of these groups are adherent (in topological terms) to elements of the group 16 means that there are significant similarities in the properties of their respective elements. Then, since nitrogen and flourine are not in the closure of group 16, they do not share the similarities that other elements of their groups have with those of group 16. This difference singles out nitrogen and flourine as exceptional members of their respective families, a fact that the authors take as topological evidence of the *singularity principle* (elements of the second period behave differently from those of other periods).

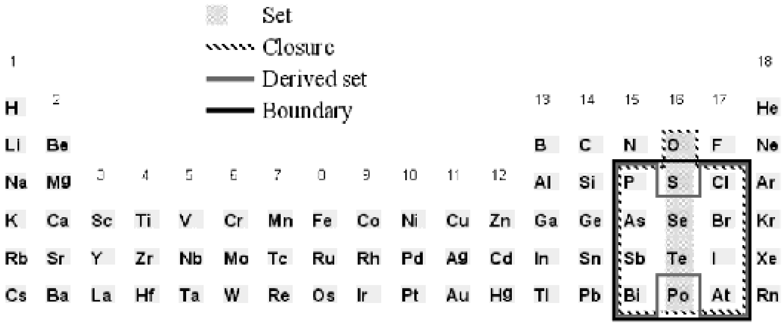

Figure 4.2: Topological properties of the group 16 elements. Reproduced from Restrepo *et al* (2004).

- The boundary of metals comprises metalloids such as *At*, *As*, *Se*, and *Sb* (see Figure 4.3). In topological terms, the boundary of a set *A* is conformed by points *x* such that each neighborhood of *x* contains points both in *A* and on its complement. It is thus very fitting that the boundary of metals comprises metalloids, as they are intuitively similar to both metals and non metals.

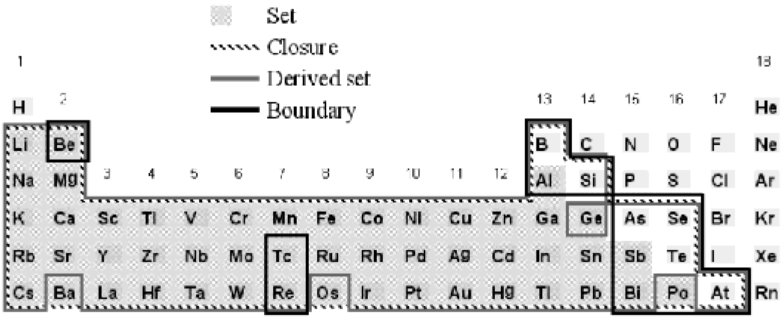

Figure 4.3: Topological properties of the metallic elements. Reproduced from Restrepo *et al* (2004).

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Consider now the chemotopological method from the point of view of our model of chemical activity. The first steps of the method follow the approach of hierarchical clustering and have already been translated to the formalism of Classification Systems: the use of a metric space representation puts us in the context of the category $\mathcal{M}$ (see **Example 2.12**); afterwards, $\mathcal{M}$ is mapped into a dendrogram in $\mathcal{T}$, a procedure that, as we showed, comports some loss of information (see **Example 2.25**); last, $\mathcal{T}$ is taken as a Classification System and a classification is induced by means of one of its morphisms. In turn, the innovative step where a topological space is introduced can be understood as the proposal of Classification Category: by transforming dendrogram cuts into topological spaces, we are characterizing $\mathcal{T}_1$ by means of a Classification Category that is a subcategory of **Top**. Objects of this category are classifications in $\mathcal{T}$, and its morphisms are continuous functions.

The first important consequence of this realization is that we are not forced to follow any of the steps of the methodology of Restrepo *et al.* that precede the appearance of a topological basis. We may completely forgo the introduction of a property vector, and start from a set of internally related entities. We are not constrained to $\mathcal{T}$, but may take any arbitrary subcategory or **Rel** as our Classification System. And, of course, we are not forced to take the problematic step that takes us from $\mathcal{M}$ to $\mathcal{T}$. In the end, we are abstracting the key innovation of the chemotopological method from the standard methodology of cluster analysis it was attached to, and embedding it into the more general formulation of Classification Systems. We summarize this generalization in the following definition.

Definition 4.2. Let $\mathcal{C}$ be a subcategory or **Rel**. For each $r : X \to Y \in \mathcal{C}_1$, the r-*topology on* X is the topology τ_r induced by the subbase $\{\ker r(y)\}_{y \in Y}$. In that case we also say that (X, τ_r) is an r-*topological space*, and define $\tau_r(\mathcal{C})$ as the category comprising the collection of r-topological spaces with $r \in \mathcal{C}_1$ as objects, and continuous functions as morphisms.

There is a close link between $\tau_r(\mathcal{C})$ and FCA, given by a correspondence between open sets in τ_r and concepts in (X, Y, r) for $r : X \to Y \in \mathcal{C}_1$.

Proposition 4.3. *Let* $\mathcal{C}$ *be a subcategory of* ***Rel*** *and* $r : X \to Y \in \mathcal{C}_1$. *A set* $O \subset X$ *is the extent of a concept in* (X, Y, r) *if and only if* $O = \bigcap_{y \in A} \ker r(y)$, *for some* $A \subset Y$.

Proof. Recall that $\ker r(y) = \{x \in X : (x, y) \in r\}$. Then, $\bigcap_{y \in A} \ker r(y)$ is the set of objects that have all properties in A –that is, A^r (see **Definition 2.20**). In consequence,

- $\to$ for a given set $O = \bigcap_{y \in A} \ker r(y)$, we have $(O, O^r) = (A^r, A^{rr})$; and since $A^{rrr} = A^r$, this pair is a concept with extent O.
- $\leftarrow$ for a given concept (O, A) in (X, Y, r), since $O = A^r$ (see **Definition 2.20**), then $O = \bigcap_{y \in A} \ker r(y)$.

□

Corolary 4.4. *The collection of concept extents in* (X, Y, r) *is a basis for* τ_r.

The connection between concepts in a formal context and basic open sets in $\tau_r(\mathcal{C})$ just proven bears some interesting consequences concerning the current status of the methodology proposed by Restrepo and collaborators. Their original formulation is constrained to $\tau_r(\mathcal{T})$, which comprises disjoint classifications exclusively. We know, from an analysis of the Concept Lattice, that concepts in a disjoint classification conform a relatively straightforward structure that under-exploits the potential of FCA (see **Example 2.28**). It is expected, given the close relation between chemotopology and FCA revealed by the previous result, that this limitation persists in Restrepo's topological characterization of the chemical elements. In fact, as we show in the following example, a deeper look reveals that the results summarized in **Example 4.1** are not as strong as they appear at first.

Example 4.5. In **Example 4.1** we saw that robust chemical families in the periodic chart are given by perfect sets in a topological space $(X, \tau_r) \in \tau_r(\mathcal{T})_0$. But it is proven that $\tau_r(\mathcal{T})$ is conformed by those topological spaces whose open sets are clopen, due to the fact that the basis used to induce τ_r is a partition of the space(Mesa & Restrepo, 2008). This means that the perfect sets of (X, τ_r) are given by unions non-unitary open sets, as we prove now.

Proposition 4.6. *Let $X \in \tau_r(\mathfrak{T})_0$. A set $A \subset X$ is perfect if and only if it is an union of non-unitary open sets.*

Proof.

→ Suppose that A is perfect, then A is closed, so it is also open, and thus an union of open sets. If any of these sets where unitary, then it would contain a single isolated point in A, so A must be an union of non-unitary open sets.

← Suppose that A is an open set that contains no unitary open sets. Then, for any $x \in A$, the smallest open set containing x is a subset of A and it contains at least another point $y \in A$, so that any neighborhood of x contains a point of A other than x. Thus, A is perfect. □

In other words, perfect sets are immediately determined by non-unitary classes in the dendrogram cut. A straightforward computation determines robust chemical families directly from the dendrogram cut, so that one may wonder what is being gained with the introduction of a topological space.

Though this observation leaves a bitter taste, the greatest issue concerns the second result outlined in **Example 4.1**. Finding that metalloids are in the boundary of metals is a valuable consequence of the model *only as long as metals themselves are a consequence of the model.* But the set of metals does not have any remarkable property in this formulation that motivates a closer examination of its topological properties. In short: it is not a concept.

Metalloids are interesting because they have both metallic properties and non-metallic properties. From the point of view of FCA, these properties should be defined by reference to the intents of a 'metal' concept and a 'non-metal' concept respectively. Neither of those makes its appearance here, as evidenced by the fact that the set of metallic elements of Figure 4.3 cannot be expressed as an union of elements of the topological basis of equation (4.1). The authors chose to analyze the topological properties of this set motivated by external knowledge that not only was not given by their model, but that even ran counter to it. In face of the absence of the concept of metallic element, metalloids being in the boundary of metals turns out to be mostly an artifact of the method.

In fact, metalloids are an impossibility under the methodology of Restrepo *et al.*! Suppose that we choose an appropriate set of properties on a family of chemical elements, define an adequate metric describing their similarity, run a suitable hierarchical clustering algorithm, cut the resulting dendrogram, and find that metallic elements *are* a concept in the resulting classification. This means that metals are a clopen set M in the corresponding topological space $X \in \tau(\mathfrak{T})$. In turn, this implies that $X \setminus M$ is also clopen and thus the extent of a concept, which would naturally be associated with non-metals. Metalloids, then, would be the elements in the boundary of metals. But as

M and $X \setminus M$ are disjoint closed sets, the boundary of metals is $\emptyset$, meaning that there would be no metalloids in the sense proposed by the authors.

* * *

Just as happens with the Concept Lattice, the chemotopological method does not work well with disjoint classifications. It's not that the method breaks down, but that there is not much to be gained from its greater degree of sophistication. On the other hand, there is plenty to be learned from the analysis of topological images of non-disjoint classifications in the broader frame of $\tau_r(\mathbf{Rel})$, as we will see in the next section.

There is one last consideration that we deem necessary before we move on. So far, we have followed the original proposal of Restrepo *et al.*(2004), and regarded classes in a classification as open sets. As proven in **Corollary 4.4**, this implies that the extents of the corresponding concepts are open sets. However, the fact that concepts are defined by means of the closure operator ^{rr} suggests that it is more natural to regard them as closed sets, as we do in the following construction.

Definition 4.7. Let $\mathcal{C}$ be a Classification System. For each $r : X \to Y \in \mathcal{C}_1$, we define the *R-topology* on X as the topology τ_R induced by the *closed sets* subbase $\{\ker r(y)\}_{y \in Y}$; that is, the smallest topology on X where each $\ker r(y)|_{y \in Y}$ is a closed set. We also say that (X, τ_R) is an *R-topological* space, and define $\tau_R(\mathcal{C})$ as the category of R-topological spaces and continuous functions.

It follows immediately from **Proposition 4.3** that concept extents in (X, Y, r) are closed sets in (X, τ_R), as desired. This motivates a closer connection between the closure operator ^{rr} induced by a morphism $r : X \to Y$ and closures in its corresponding topological representation, allowing for an easier interpretation of topological invariants in terms of the conceptual structure induced by the classification. In light of this advantage, we change our framework from $\tau_r(\mathcal{C})$ to $\tau_R(\mathcal{C})$.

This change has no effect in our appreciation of the restricted formulation of the chemotopological method proposed by Restrepo and collaborators, as r is a disjoint classification if and only if all open sets in τ_r are clopen (Mesa & Restrepo, 2008), which implies that those sets are also clopen sets in τ_R. In other words, the classifications considered by these authors are characterized by $\tau_r = \tau_R$, so they belong to both Classification Categories proposed in this section.

4.3 The topology of chemical concepts

In general, $\tau_R(\mathcal{C})$ constitutes a Classification Category that provides a topological characterization of classifications in a given Classification System $\mathcal{C}$. **Proposition 4.3** shows that this category is also closely related to concepts in the context defined by that classification–which is to be expected, given the equivalence between morphisms in a Classification System and formal contexts in FCA. Thus, just as a Concept Lattice describes an algebra of concepts in a classification, a topological space in $\tau_R(\mathcal{C})$ describes the topology of those concepts. Due to the natural emergence of formal concepts within the frame of $\tau_R(\mathcal{C})$, along with the expectation that the same thing will happen in other similar constructions, we also refer to Classification Categories as *Concept Categories.* This section explores the potential of $\tau_R(\mathcal{C})$ as a Concept Category, by means of a characterization of several topological invariants in R-topological spaces in terms of concepts in their associated contexts (X, Y, r).[2].

The following result from FCA analysis will be used repeatedly in this section:

Proposition 4.8. *Let* (X, Y, r) *be a formal context. Then, for any* $u, v \in X$*,* $u^{rr} \subset v^{rr}$ *if and only if* $v^r \subset u^r$*.*

The proof of this proposition is straightforward an sufficiently known to be omitted.

Closed sets

It is known that closed sets in the topology induced by a closed sets subbase C are intersections of unions of elements of C. Since we are dealing with finite sets, C is a finite collection of sets, so that closed sets can also be expressed as unions of intersections of elements of C, as a consequence of the distribution law

$$A \cap (B \cup C) = (A \cap B) \cup (B \cap C). \tag{4.2}$$

An R-topology is induced by the closed sets subbase $\{\ker r(y)\}_{y \in Y}$, where $r : X \to Y$. Thus, according to **Proposition 4.3**, this means that closed sets in τ_R are *unions of concepts in the corresponding classification.*

Proposition 4.9. *Let* $\mathcal{C}$ *be a Classification System, and* $r : X \to Y \in \mathcal{C}$*. A set* $K \in X$ *is a closed set in* (X, τ_R) *if and only if it is an union of concepts in* (X, Y, r)*.*

Closed sets, then, obey to a notion of closure that is related to the ^{rr} operator, but is slightly and significantly different.

Closure

The closure $\bar{A}$ of a subset A of a topological space is the smallest closed set containing A. In the case of R-topological spaces, this set can be characterized in terms of the concepts defined by the properties of the elements of A.

---

[2] In the following, when there is no place to ambiguity, we will refer to concept extents plainly as concepts.

Proposition 4.10. *Let* $\mathcal{C}$ *be a Classification System and* $A \in (X, \tau_R) \in \tau_R(\mathcal{C})$*; then* $\bar{A} = \cup_{x \in A} x^{rr}$.

Proof. x^{rr} is the smallest concept containing x. The union of those concepts over all $x \in A$ gives the smallest closed set containing A. □

Thus, $\bar{A}$ determines a minimum collection of concepts that covers A. This means that the closure of A consists of elements that are similar to members of A in that they share all their properties. In formal terms,

Proposition 4.11. *Let* $\mathcal{C}$ *be a Classification System and* $A \in (X, \tau_R) \in \tau_R(\mathcal{C})$*. For any* $u \in X$*,* $u \in \bar{A}$ *if and only if there is a* $v \in A$ *such that* $v^r \subset u^r$.

Proof.

→By **Proposition 4.10** $u \in \bar{A}$ implies $u \in v^{rr}$ for some $v \in A$. Since u^{rr} is the smallest concept containing u, this means that $u^{rr} \subset v^{rr}$, which in turn implies $v^r \subset u^r$ by **Proposition 4.8**.

← By **Proposition 4.8** $v^r \subset u^r$ implies $u^{rr} \subset v^{rr}$. Since $u \in u^{rr}$ and by **Proposition 4.10** $v^{rr} \subset \bar{A}$, then $u \in \bar{A}$. □

The closure of a set is also characterized as the set of its *adherent points*. A point x is adherent to a subset A of a topological space if all neighborhoods of x contain points of A. Intuitively, this means that any region around x intersects A, so x is 'adhered' to that set. The previous proposition let us see how points in the closure of a subset S of an R-topological space are adhered to it: for any $u \in \bar{S}$ there is a point $v \in S$ such that u is in all concepts containing v, which intuitively means that u is 'closely attached to v' in terms of their similarity with respect to the properties induced by r.

Open sets

Let $\mathcal{C}$ be a Classification System and O be an open set in $(X, \tau_R) \in \tau_R(\mathcal{C})_0$, with $r : X \to Y$. Since closed sets are unions of concepts and open sets are the complements of closed sets, by **Proposition 4.3** we can express O as

$$\begin{aligned} O &= X \setminus \left(\bigcup_{A \in \mathcal{A}} \bigcap_{y \in A} \ker r(y) \right), \\ &= \bigcap_{A \in \mathcal{A}} \left(X \setminus \bigcap_{y \in A} \ker r(y) \right), \\ &= \bigcap_{A \in \mathcal{A}} \bigcup_{y \in A} X \setminus \ker r(y), \end{aligned} \tag{4.3}$$

which, since $\{\ker r(y)\}_{y\in Y}$ is a finite collections of sets, may also be expressed as

$$O = \bigcup_{A'\in\mathcal{A}'} \bigcap_{y\in A'} X \setminus \ker r(y). \tag{4.4}$$

The inner intersection in this expression bears a strong resemblance with that of **Proposition 4.3**, that characterizes concepts in terms of $\ker r$. While a concept extent, given by $\bigcap_{y\in A'} \ker r(y)$, comprises all elements that have all properties in A', each intersection of class complements $\bigcap_{y\in A'} X \setminus \ker r(y)$ appearing in the previous equation comprises all elements that do not have any property $y \in A'$. These sets are characterized by the *dual* of (X, Y, r), that is, by the context (X, Y, R) where $R = X \times Y \setminus r$.

Proposition 4.12. *Let $\mathcal{C}$ be a Classification System, $r : X \to Y \in \mathcal{C}$, and $R = X\times Y\setminus r$. A set $O \subset X$ is the extent of a concept in (X, Y, R) if and only if*

$$O = \bigcap_{y\in A} X \setminus \ker r(y) \tag{4.5}$$

for some $A \subset Y$.

Proof. By **Proposition 4.3**, O is a concept in (X, Y, R) if and only if $O = \bigcap_{y\in A} \ker R(y)$ for some $A \subset Y$; and since by construction $\ker R(y) = X \setminus \ker r(y)$, we find $O = \bigcap_{y\in A} X \setminus \ker r(y)$. ☐

In this way, just as closed sets in τ_R are unions of concepts in (X, Y, r), characterized with respect to the properties they have, open sets in τ_R are unions of concepts in its dual context, characterized with respect to the properties they lack.

Interior

The interior A° of a set A is the largest open set that is a subset of A. Of course, this means that A° is the union of all concepts in (X, Y, R) contained in it. This observation immediately produces the following simple, yet useful result:

Proposition 4.13. *Let $\mathcal{C}$ be a Classification System. For any $A \subset (X, \tau_R) \in \tau_R(\mathcal{C})$ and $x \in X$, $x \in A^\circ$ if and only if $x^{RR} \subset A$.*

Proof. This is a direct consequence of the fact that x^{RR} is the smallest open set containing x. ☐

Furthermore, following we introduce a proposition that characterizes A° in terms of *concepts in* (X, Y, r).

Proposition 4.14. *Let $\mathcal{C}$ be a Classification System. For any $A \subset (X, \tau_R) \in \tau_R(\mathcal{C})$ and $x \in X$, $x \in A^\circ$ if and only if for any $v \notin A$, $v^r \setminus x^r \neq \emptyset$.*

Proof.

$\rightarrow$ By **Proposition 4.13** we now that $x \in A^\circ$ implies $x^{RR} \subset A$. In that case, $X \backslash x^{RR}$ is a closed set containing any $v \notin A$, which by **Proposition 4.10** means that $v^{rr} \subset X \backslash x^{RR}$. In turn, this implies $x \notin v^{rr}$ and then $x^{rr} \not\subset v^{rr}$, which by **Proposition 4.8** implies $v^r \not\subset x^r$, or equivalently, $v^r \setminus x^r \neq \emptyset$.

$\leftarrow$ Let $x \in X$ such that $v \notin A$ implies $v^r \setminus x^r \neq \emptyset$. Then $x^R \setminus v^R \neq \emptyset$, or equivalently, $x^R \not\subset v^R$, which by **Proposition 4.8** implies $v^{RR} \not\subset x^{RR}$, and then $v \notin x^{RR}$. Since v is an arbitrary element of $X \setminus A$, we conclude that $x^{RR} \subset A$, and by **Proposition 4.13** $x \in A^\circ$. □

The previous proposition shows that it is possible to distinguish any $x \in A^\circ$ from any v in its complement by a property that v has and x doesn't. We may then say that the interior of a set conforms a strong core of that set, comprising those elements that are 'separated' from its complement by significant dissimilarity in their properties. This may be easier to understand if we note that when we compute the interior of A we remove any element of A that is in the closure of its complement, and is thus 'adhered' to elements of $X \setminus A$. The interior of A then consists of all remaining points, which are not adherent to those outside of A and can be 'separated' from the rest of the space.

The interior of a concept turns out to be particularly interesting. When defining a concept, we are closing a subset of X that is described by a collection of properties that exclusively characterize its elements. Then, when computing its interior, we are separating a strong core of the concept that is further characterized by the properties that distinguish it from the rest of the space. This observation suggests a connection between the lack of those properties absent from the interior and the presence of those properties characteristic of the concept. Following we introduce a proposition that formalizes this intuition in a useful principle of inference.

Proposition 4.15. *Let $\mathcal{C}$ be a Classification System, $r : X \to Y \in \mathcal{C}_1$, and $O \in X$ be a concept extent in (X, Y, r). Then $u \in O^\circ$ if and only if for any $x \in X$, $u^R \subset x^R$ implies $O^r \subset x^r$.*

Proof.

$\rightarrow$ By **Proposition 4.13** we now that $u \in O^\circ$ implies $u^{RR} \subset O$. Now let $x \in X$, and suppose $u^R \subset x^R$, which by **Proposition 4.8** implies $x^{RR} \subset u^{RR}$, and then $x \in u^{RR}$ (**Proposition 4.10**). Since $u^{RR} \subset O$, this also implies $x \in O$. Now, O is a concept and thus a closed set, so by **Proposition 4.10** $x \in O$ implies $x^{rr} \subset O$, which by **Proposition 4.8** implies $O^r \subset x^r$. We conclude then that $u^R \subset x^R$ implies $O^r \subset x^r$.

$\leftarrow$ Let $u \in X$ such that $u^R \subset x^R$ implies $O^r \subset x^r$ for any $x \in X$. By **Proposition 4.8** $u^R \subset x^R$ means $x^{RR} \subset u^{RR}$ which is equivalent to $x \in u^{RR}$ (**Proposition 4.10**). By hypothesis, in that case $O^r \subset x^r$, which means $x^{rr} \subset O^{rr} = O$, and thus $x \in O$. Since

x is an arbitrary element of u^{RR} we conclude $u^{RR} \subset O$, which by **Proposition 4.13** implies $u \in O^\circ$. $\square$

In other words: for any $u \in O^\circ$, if x lacks all the properties that u lacks, then x has the properties O^r characteristic of the concept O.

Exterior

The exterior of a set A is the interior of its complement. Mirroring the same analysis carried on A°, we can say that $\overline{X \setminus A}$ comprises elements that are significantly dissimilar from those of A, being 'sepparable' from its adherent points.

Boundary

The boundary $\mathrm{Fr}A$ of a set A comprises the elements of X that are neither in the interior, nor in the exterior of A. Since both A° and $(X \setminus A)^\circ$ are open sets, the boundary of A is a closed set. In fact, it is proven that $\mathrm{Fr}A = \bar{A} \cap \overline{X \setminus A}$. This allows us to characterize the boundary of A in terms of the concepts whose intents comprise both properties characteristic of A and properties characteristic of its complement. To do so, we need the following result from FCA:

Proposition 4.16. *Let (X, Y, r) be a context, and $\mathcal{A} \subset \mathcal{P}(Y)$. Then,*

$$\left(\bigcup_{A \in \mathcal{A}} A \right)^r = \bigcap_{A \in \mathcal{A}} A^r. \tag{4.6}$$

Proposition 4.17. *Let $\mathcal{C}$ be a Classification System and $A \in (X, \tau_R) \in \tau_R(\mathcal{C})$. For any $v \in X$, $v \in \mathrm{Fr}A$ if and only if there are $u \in A$ and $w \in X \setminus A$ such that $u^r \cup w^r \subset v^r$.*

Proof. The boundary of A is given by

$$\mathrm{Fr}A = \bar{A} \cap \overline{X \setminus A} \tag{4.7}$$

by **Proposition 4.10** we have

$$\begin{aligned} \mathrm{Fr}A &= \bigcup_{x \in A} x^{rr} \cap \bigcup_{x \in X \setminus A} x^{rr}, \\ &= \bigcup_{u \in A} \bigcup_{w \in X \setminus A} u^{rr} \cap w^{rr}. \end{aligned} \tag{4.8}$$

Last, by **Proposition 4.16** we conclude

$$\mathrm{Fr}A = \bigcup_{u \in A} \bigcup_{w \in X \setminus A} (u^r \cup w^r)^r. \tag{4.9}$$

$\square$

The dominant theme in all previously analyzed topological invariants is *similarity* regarding the properties associated by r to the elements of its domain. Closures locate entities that are closely related to those of a given set by their common properties. Interiors single a nuclear component of a set characterized by strong similarity among its elements. On the contrary, exteriors comprise elements that are clearly separated from those of a given set by dissimilarity on their properties. Last, boundaries contain those elements that are similar to both the strong core of a set (i.e. its interior) and to its most dissimilar counterpart (i.e. its exterior).

R-topological spaces thus give a topological description of similarities among elements of a set relative to properties induced by a specific classification. As these similarities are contingent on the classification chosen, it has a heavy impact on the wealth of the information that can be provided by the corresponding R-topology. The following example illustrates this point, by comparing topological invariants on the R-topological spaces induced by two different classifications: the acid-base model of **Example 3.12**, and the classification of chemical elements of **Example 4.1**. At the same time, it exemplifies the meaning of topological invariants in $\tau_R(\mathcal{C})$ for a case of chemical relevance.

Example 4.18. Let us compute the topological invariants alluded in this section for the R-topological space associated with the acid-base model of **Example 3.12**. From now on, we well use $\mathcal{A}, \mathcal{B}$, and $\mathcal{F}$ to refer to the concepts of acid, basic, and amphoteric substance respectively, and $\mathcal{X}$ refers to the whole substance set.

The closure of a set S is given by

i) $\mathcal{A}$ if all substances in S have the acid property and at least one substance in S lacks the base property

ii) $\mathcal{B}$ if all substances in S have the base property and at least one substance in S lacks the base property

iii) $\mathcal{F}$ if all substances in S have both the base and acid properties.

iv) $\mathcal{X}$ otherwise.

In case i) all elements of S have the acid property, so any substance with that property is present in all concepts containing S, and is thus adherent to it. In consequence, the closure of S in this case is given by the concept of acid substance. In the same way, in case ii) any substance with the base property is adherent to S, so that its closures is the concept of basic substance. In case iii), on the other hand, substances in S have both the acid and base properties. Exclusively acid/basic substances are excluded from the concept of amphoteric substance that contains S; they can thus be ‘separated’ from S and are not part of its closure. In consequence, we have $\bar{S} = \mathcal{F}$. Last, in case iv) there are both exclusively acid and exclusively basic substances in S; any substance having either of these properties is adherent to the set, so that its closure extends over the whole space. In this way, the closure of a set tell us what substances are significantly similar to those of the set regarding their acid-base behavior.

Regarding interiors, we find that the interior of $\mathcal{A}$ is the set of 'pure acids', that is, it comprises substances that behave exclusively as acids. This set represents the most restricted materialization of the concept of acid: substances whose properties are fully contained in the intent of this concept. In the same way, the interior of $\mathcal{B}$ is the set of 'pure bases', which expresses a similar fact. **Proposition 4.15** gives us the (in this case somewhat trivial) inference rules "not acid then base" and "not base then acid".

The behavior of exteriors follows the opposing pattern: the exterior of any subset S of acids/bases is the set of pure bases/acids. Recall that the exterior of S is determined by the interior of the minimum concept containing $\mathcal{X} \setminus S$, and thus comprises substances that can be fully characterized by properties different from those of elements of S. In other words, compounds in the exterior of S share a significant dissimilarity in their properties with those of that subset, and can thus be 'separated' from it. The previous result, then, tells us that pure acids and pure bases are sufficiently dissimilar to be be separated from each other –a statement that agrees with our intuition. In the same way, we find that the exterior of any collection of amphoteric substances is given by the union of pure acids and pure bases. This reflects the fact that pure acids/bases are 'separated' from amphoteric substances by the lack of the base/acid property.

The boundary of acids is the set of amphoteric substances, that have both the acid property characteristic of this concept (as shown by its interior), and the base property, characteristic of its complement (as shown by its exterior). Naturally, amphoteric substances also conform the boundary of bases for an analogous reason, showing that they lay in the frontier between two completely dissimilar chemical families. We thus see how the boundary of a set gives a topological image of the notion of a chemical family whose properties put it half-way between two dissimilar families.

We have overlooked the interior of the concept of amphoteric substance in the previous analysis. At first sight, the interior of this concept presents a somewhat odd behavior. Following the idea that concept interiors materialize the hard core of the concept, we would expect the interior of $\mathcal{F}$ to be $\mathcal{F}$ itself. Yet, since elements of this set are adherent to both acids and bases, its interior happens to be empty. This result makes sense when we take other topological invariants into account. Indeed, consider the exterior of $\mathcal{A}^\circ \cup \mathcal{B}^\circ$, the union of pure acids and pure bases. We expect this exterior to comprise substances lacking both acid and base properties. As there are no such substances in the network, it is clear that the exterior of this set has to be empty. Also, by definition the exterior of this set is

$$(\mathcal{X} \setminus (\mathcal{A}^\circ \cup \mathcal{B}^\circ))^\circ = \mathcal{F}^\circ, \tag{4.10}$$

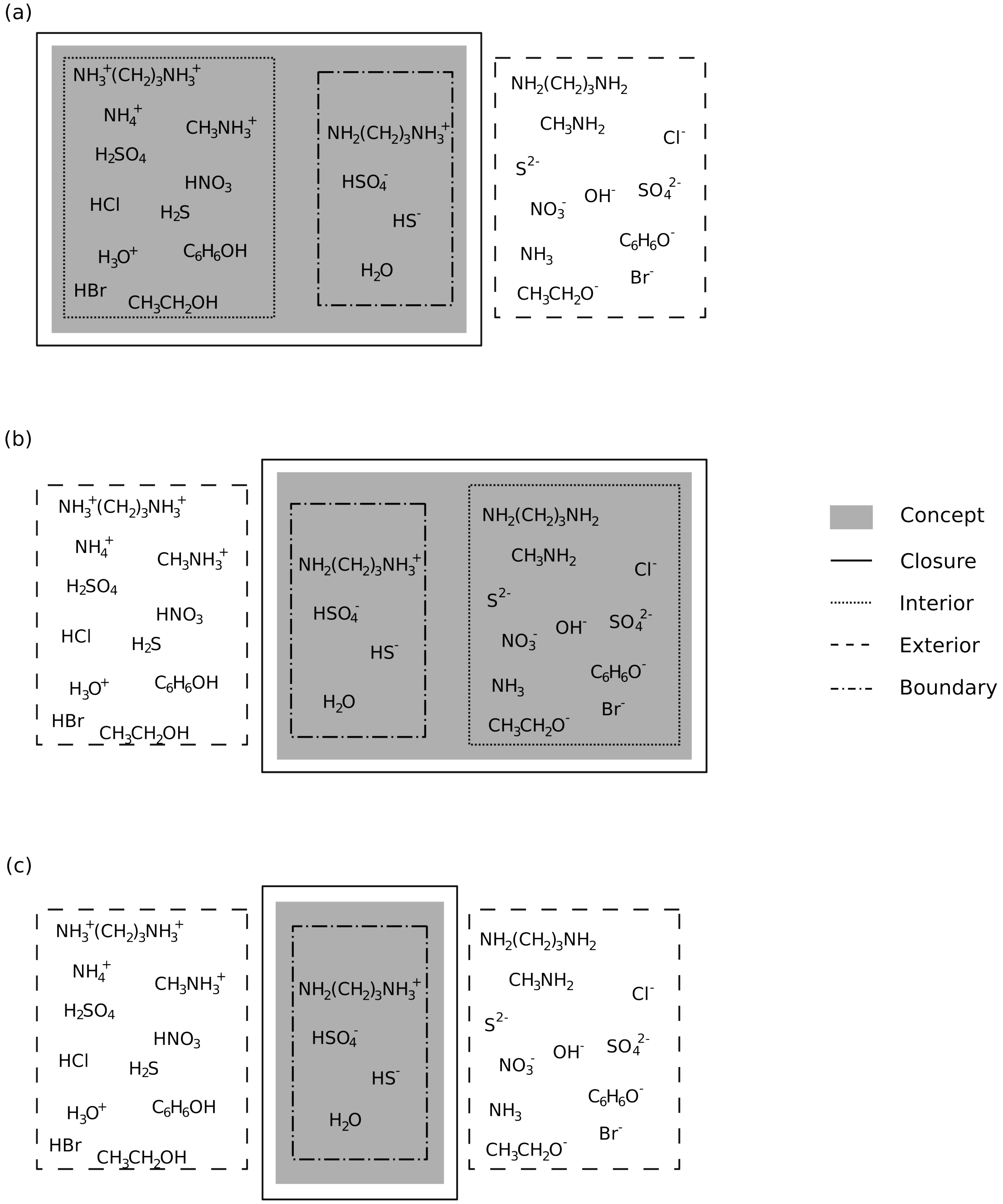

Figure 4.4: Summary of topological invariants computed on the concepts of acid (a), basic (b), and amphoteric substance (c).

that is, the interior of amphoteric substances. We thus see a first rationale for the interior of $\mathcal{F}$ to be empty. Furthermore, since $\mathcal{F}$ is the boundary of all remaining non-universal concepts in the context, our intuition tell us that the core of the concept of amphoteric substances cannot be isolated from the rest of the space –after all, we are dealing with compounds whose properties put them at the crossroads of all compounds in the network. Thus, it is actually very fitting for the interior of amphoteric substances to be empty.

Most of the previous results are summarized in Figure 4.4, where we depict the topological properties of the three concepts induced by this classification. Contrast this image with that of Figure 4.5, where we depict the topological properties of the concept of alkali metals in the context determined by the classification of equation (4.1). The concept is closed, of course, and gives the closure of any of its proper subsets. Its interior is, once more, the concept itself; its exterior is the rest of the space, and its boundary is empty. All other concepts exhibit the same behavior.

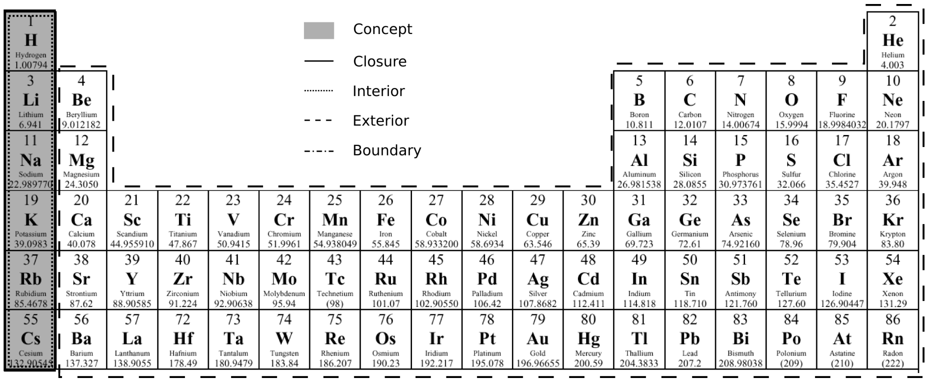

Figure 4.5: Topological properties of the concept of alkali metals in the partition of equation (4.1).

The key distinction between these two classifications boils down to the kind of morphism that induces it: in the case of the acid-base model (Figure 4.4) the classification is induced by a general binary relation, while in that of Restrepo *et al* (Figure 4.5) it is induced by a mapping. In consequence, in this second case we are dealing with a partition of the substance space. Figure 4.5 illustrates how, just as happened with their concept lattices, R-topological spaces associated with partitions have a very simple structure. Due to the disjointness of the classification, topological invariants such as closure and interior are just classes of equivalence in the classification itself, while others such as boundary are universal (i.e., they are the same for any arbitrary partition) and trivial.

* * *

4.4 The domain of similarity

In their role as determinants of properties in a theory of internal relations, classifications induce a conceptual structure on a family of internally related entities. Concept categories conformed by morphisms in a classification system advance a characterization of this structure. Chemotopology can be envisioned as an instance of a concept category $\tau_R(\mathcal{C})$, where emphasis is placed on a description of similarity. Closures identify objects that are so similar to the elements of a given set that they get ‘adhered’ to it; concept interiors conform the material core of concepts, constituted by strongly similar elements with respect to the properties characterizing their intents, that can be isolated from the rest of the space; and concept boundaries formalize the idea of a class of entities that share some similarity with two mutually dissimilar families.

Yet, the structure of topological spaces associated with disjoint classifications gives an odd feeling. It’s not that the results of the analysis of topological invariants in those spaces are counterintuitive, but that they seem to have little to say about the conceptual structure induced by the corresponding classifications –for instance, all concepts turn to be clopen sets and thus identical to their interior, which also makes all concept boundaries empty. One could suspect that this simplicity reveals the limitations of the information provided by $\tau_R(\mathcal{C})$. In a certain sense we believe that this is the issue at hand, but we would rather look at it the other way around: $\tau_R(\mathcal{C})$ has little to say about disjoint classifications because they give a poor description of the phenomenon that it characterizes; that is, they are unable to properly account for similarity.

While the kernel of an arbitrary morphism in a classification system is an arbitrary binary relation, the kernel of a mapping determining a disjoint classification is always an equivalence relation. Equivalence relations lack one of the defining qualities of similarity: intransitivity. Indeed, it is possible to move from any given object to a similar object, then to an object similar to the second and so on, eventually ending up with an object that is entirely dissimilar from the first; on the other hand, any path moving across equivalent objects always ends in an object that is equivalent to all those that precede it. Disjoint classifications are thus unable to capture this feature of similarity, and have little to gain from the topological description given by $\tau_R(\mathcal{C})$. This is particularly clear when considering concept boundaries, that relate to the intuition of objects located ‘half-way’ between two dissimilar families. As no such objects exist in a partition, all concept boundaries in its associated topological space are empty.

Cluster analysis has been used for decades to study chemical similarity by means of partitions on a metric space representing a set of chemical relevance. Classes in the resulting partition are intended to characterize families of similar substances; but actually, what is being done is exactly the opposite: those substances are not described as similar, but as equivalent. Key information, necessary for a proper account of similarity, is being lost. In consequence, to unleash the full potential of the chemotopological method as a tool for the characterization of chemical similarity we require new classification methods that produce non-disjoint classifications on a set of chemical substances. Role assignments are a suitable alternative that, we believe, is worth of being explored.

Final remarks

–"I'm not sure. I'm exceedingly ignorant."
The young man laughed and bowed. "I am honored!" he said. "I've lived here three years, but haven't yet acquired enough ignorance to be worth mentioning."
–Ursula K. LeGuin, THE LEFT HAND OF DARKNESS

The main objective of chemistry is to develop knowledge on the transformations of substances as they undergo radical change. The basic logical structure of chemical knowledge is that of a reaction network. We distinguish two epistemic perspectives in the search of chemistry's central goal: one where patterns in the relational structure of reaction networks are used to induce characteristic properties on chemical substances, and other where the intrinsic qualities of substances are taken as determinants of their position in reaction networks. The first adscribes to an ontology of internal relations, and conforms a theoretical body that we identify with chemical activity. The second adscribes to an ontology of external relations, and we identifiy it with chemical structure.

Internal relation theories follow a classificatory and inductive approach. A system of internally related entities can be represented by a structured set, i.e. by an object in a subcategory of **Rel**. Each morphism in such category determines a classification that characterizes the elements of its domain with a collection of properties given by its codomain. On these terms, activity theory deals with structure preserving transformations with domain in chemical reaction networks. It resorts to classifications in order to determine patterns that preserve the relational logic of chemical reaction networks, inducing a conceptual structure on a family of substances, that can be represented by means of a suitable concept category. Then, relaying on the hypothesis that each classification on a chemical system converges to a characteristic object in a concept category as the system grows, activity theory inductively predicts unobserved chemical phenomena involving partially-characterized substances. In turn, structure theory constructs elaborate images of chemical substances following the demand that their properties determine an equivalent representation of the classificatory logic of activity theory. Then, additional properties of these structural representations not connected to the underlying reaction network motivate powerful hypotheses that can provoke discrete changes in chemical activity classifications.

We thus see that chemistry, even on its most restricted identity, is not just about structure theory. Chemical activity classifications are not ‘mere’ classifications, fruits of an encyclopedic rather than scientific effort. Nor are they the logical consequence of the formalism of structure theory. They conform a theory on their own right, readily capable of predicting the behavior of chemical substances under unobserved conditions. Yet, this is not *the* theory of chemistry either; once more, not even on a most restricted sense. Structure and activity inhabit a cycle where models arising from one approach are permanently transforming the shape of those arising from the opposing perspective. They testify to the value of a pluralist approach where inductivism and hypothetico-deductivism, essentialism and relationism, atomism and holism, and other seemingly discordant isms co-exist in the pursuit of an unified goal.

Focusing back on chemical activity, binary relations in a classification system that are not functions are of particular relevance in the analysis of [chemical] similarity. As similarity is defined with respect to certain properties of the entities, in a theory of internal relations it is necessarily contingent on the specific classification being examined. Since the kernel of a function is always an equivalence relation, classifications induced by functions describe the entities as equivalent, rather than as similar: if they are characterized by exactly the same property they are equivalent, else they are entirely different and nothing else can be said. General binary relations give a more complex description where entities are characterized by multiple properties, allowing us to break the transitivity of equivalence relations and thus approach the specific domain of similarity. In other words, chemical similarity forces us to embrass a broader concept of classification where classes superpose with each other, as opposed to the historical focus of cluster analysis in the generation of disjoint classes.

The previous theses comprise a broad sketch of a classificatory approach to the study of chemical combination, and of its relation with a complementary, opposing perspective. Along with that general formulation, we have worked some specific details of a viable mathematical model of chemical activity. We have proposed a category of directed hypergraphs as a suitable classification system for the study of chemical change, and a category of topological spaces as an alternative concept category for the study of chemical similarity, that ressembles but is not equivalent to the category of concept lattices. These two proposals give little more than a first approach; there is still plenty of details to be worked out. For instance, just as we pointed the inadequacies of graph models of chemical reaction networks, it is not hard to see that chemistry has already exceeded the limits of the category **HyperD**. A more faitful model should introduce stoichiometric coefficients e.g. by means of a hyperarc-weighting on a vector space; try to account for chemical dynamics and reversibility; and introduce a more flexible criterion of structure-preservation that encompasses contemporary chemical classifications that cannot be induced by role assignments. On top of all that, it may be that the finiteness of the model would face major issues when dealing with chemical phenomena where definite proportion laws do not hold.

There is also a lot of work to do regarding the most fundamental elements of the model. Concept categories, for example, were introduced following on the intuition of previous developments, so their definition still lacks sufficient mathematical formality. But most notably, we have merely dipped into the sophisticated formalisms of category theory and formal concept analysis. We have yet to exploit the potential of logical inference on a formal context, and of category-theoretical constructs such as limit, initial and terminal objects, equalizer, adjoint, duality. In particular, Stone duality could help us advance the characterization of lattice and topological representations of conceptual systems. Also, chemical restrictions such as mass conservation and product uniqueness (under a fixed chemical context any set of reactants always yields the same set of products) may bear important consequences regarding the structure of chemical reaction networks that simplify the model, or unveil interesting properties under the light of category-theoretical concepts.

There is plenty of ground to cover in the development of a mathematical theory of chemical activity. We hope that the foundations that we have laid on this work will prove fruitful to this enterprise.

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