MATCH
Communications in Mathematical and in Computer Chemistry

MATCH Commun. Math. Comput. Chem. **77** (2017) 213-232

ISSN 0340 - 6253

Maximum Common Subgraph Isomorphism Algorithms

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(Received June 26, 2016)

Abstract

Maximum common subgraph (MCS) isomorphism algorithms play an important role in chemoinformatics by providing an effective mechanism for the alignment of pairs of chemical structures. This article discusses the various types of MCS that can be identified when two graphs are compared and reviews some of the algorithms that are available for this purpose, focusing on those that are, or may be, applicable to the matching of chemical graphs.

1. Introduction

A common requirement in chemoinformatics is the ability to align pairs of molecules to identify the degree of structural overlap that they have in common, for applications such as identifying chemical reaction sites [1], bioactivity prediction of compounds [2], and exploring structure-activity relationships [3] *inter alia*. The molecules in chemoinformatics systems are normally represented as graphs and the degree of overlap can hence be identified by means of techniques from graph theory, specifically by the use of maximum common subgraph (MCS) isomorphism algorithms.

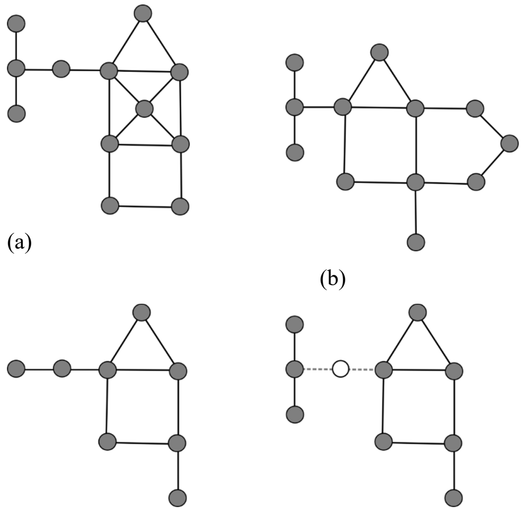
MCS algorithms are used not only in chemoinformatics but also in other disciplines (such as malware detection, protein function prediction and pattern recognition *inter alia* [4-6]) with the result that many different MCS algorithms have been reported in the literature. Our interest in this topic has been in the context of aligning 2D molecules [7], where one seeks to maximise the overlap of atoms and bonds, but the procedures to be described here are also applicable in many cases to the alignment of pairs of 3D molecules [8].

This paper discusses a range of algorithms for detecting the MCS between pairs of graphs, and hence provides an update to previous reviews of MCS algorithms that have been used in chemoinformatics [9, 10]. The paper is structured as follows. The next section introduces basic graph notions, and describes different types of MCS that can be identified when two graphs are compared. There is then a description of cliques, modular products and graph colouring, three concepts that underlie many important MCS algorithms. The fourth section focuses on the use of clique-detection algorithms, and this is followed by descriptions of several non-clique methods.

2. Basic definitions

We begin our description of MCS algorithms with basic definitions and concepts in graph theory [11]. A graph, G, is defined as $G = (V, E)$, where V and E represent the *vertices* (or nodes) and *edges*, respectively. An edge connects two adjacent vertices; thus, if two vertices v_1 and v_2 are adjacent then $(v_1, v_2) \in E(G)$. $E(G)$ and $V(G)$ represent the edge and vertex sets in a graph, respectively. The chemical graphs considered here are *labelled* and *weighted*, in that both the vertices and edges have descriptors attached to them *viz* the atom and bond types, respectively. A *line graph* is a graph that can be derived from the edges of an input graph by making an edge in a graph G a vertex in its line graph $L(G)$, so that two vertices are connected in $L(G)$ if they share a common vertex in G.

Two graphs G_1 and G_2 are *isomorphic* if there is a one-to-one mapping of vertex sets $V_1 \rightarrow V_2$, and a one-to-one mapping of edges $E_1 \rightarrow E_2$. A *subgraph* of graph G is a graph G' such that $G' \in G$, thus possessing a smaller set of the vertices and edges of the parent graph. An *induced subgraph* is a subgraph G' of a graph G where all edges connecting the used vertices V' in G' are also present in G. An *edge-induced subgraph* by contrast is a set of edges taken from the parent graph, in which vertices connected to the edges are included. A subgraph is a *common subgraph* of graphs G_1 and G_2 if it is isomorphic to the subgraphs G'_1 and G'_2 of G_1 and G_2 respectively. A *vertex cover* C is a subset of vertices such that for all edges $(u,v) \in E$, $u \in C$ or $v \in C$. It is thus a set of vertices that "includes" all the edges in the graph, in that for each edge in the graph G there is at least one vertex in the cover which is adjacent to said edge. A related concept is that of an *independent set*, which is a set of vertices in which no vertex is adjacent to another in the set. For a given graph, the vertices which are not part of a vertex cover form an independent set, and *vice versa*.



(a) (b) (c) (d) (e)

Figure 1. (a) and (b) represent the graphs G_1 and G_2. (c), (d) and (e) are respectively the MCIS, the cMCES and the dMCES for G_1 and G_2 (the white node in (e) is a feature from G_1, and has been included for ease of understanding but is not part of the dMCES).

The *Maximum Common Induced Subgraph* (MCIS), as shown in Figure 1c above, is the largest (in terms of the number of vertices) induced subgraph common to G_1 and G_2, whereas the *Maximum Common Edge Subgraph* (MCES) is the largest (in terms of the number of edges) induced subgraph common to G_1 and G_2. There are two types of MCES: the *connected MCES* (cMCES) and the *disconnected MCES* (dMCES), as shown in Figures 1d and 1e respectively. A cMCES is one in which each constituent vertex is connected by at least one path in the graph, i.e., the MCES consists of a single, connected subgraph; in a dMCES, conversely, this condition does not hold and the MCES can hence contain two or more subgraphs.

3. Cliques, modular products and colouring

A *clique* is a set of vertices in a graph such that each vertex is connected to each and every other vertex, with a maximal clique in a graph being one that is not contained within another, larger clique and with the *maximum clique* being the maximal clique with the greatest number of vertices. Levi [12] and Barrow and Burstall [13] appear to have been the first to realise that algorithms for the detection of maximum cliques could be used to identify the MCIS (and thus the MCES) by using the *modular product* of the two line graphs describing G_1 and G_2. As will be seen in Section 4, the modular product forms the basis for several important MCS algorithms that are based on clique detection.

The modular product of two graphs, sometimes referred to as a compatibility graph, is a graph with the vertex set $V_1 \times V_2$ of graphs G_1 and G_2 respectively. If the edge set of G_1 is $E(G_1)$, where an edge is a pair of vertices (e.g. (u_i,u_j)), and analogously for G_2, $E(G_2)$ and (v_i,v_j), then an edge between two vertices exists in the modular product where

$$(u_i,u_j) \in E(G_1) \text{ and } (v_i,v_j) \in E(G_2) \text{ or,}$$

$$(u_i,u_j) \notin E(G_1) \text{ and } (v_i,v_j) \notin E(G_2).$$

The maximum clique(s) in the modular product then correspond to the MCIS between the two graphs [14]. In weighted and labelled graphs, an additional condition applies such that only vertices of the same label are matched, and likewise for the edges, i.e:

$$w(u_i,u_j) = w(v_i,v_j),$$

where $w()$ denotes the vertex and edge labels for a pair of vertices comprising an edge.

The module product is described in Figure 2, where it will be observed that edges exist between vertices of the modular product when an edge exists for G_1 for a given pair of vertices, and an edge also exists for G_2. Vertices A and B in G_2 and X and Y in G_1 show this, since an edge exists between both A and B in G_2, and X and Y in G_1, thus giving rise to an edge between vertices 1 and 5. An edge also exists between vertices 1 and 12, since no edge exists between the corresponding G_2 vertices A and D, and neither is there an edge between X and Z in G_1. No edge, however, exists between vertices 1 and 6, for whilst there exists an edge between A and B in G_2, vertex X is not joined to vertex Z in G_1. Four cliques (and two unique MCISs) are highlighted in the figure, e.g., the clique (4,8,12) corresponds to the MCIS involving vertices (B,C,D) in G_1, and (X,Y,Z) in G_2.

The procedures described above find the MCIS, as is the case with many published MCS algorithms. However, the MCES better describes the notion of chemical similarity, and finding the MCES is computationally simpler than finding the MCIS. This is because in the former case, one must take into account both vertex and edge labels, rather than just vertex labels as in the MCIS, with the result that the modular product will contain fewer vertices and edges. The problem of identifying the MCIS can be converted to that of identifying the MCES using a theorem due to Whitney [15] (as discussed by by Raymond *et al*. [9] and by Nicholson

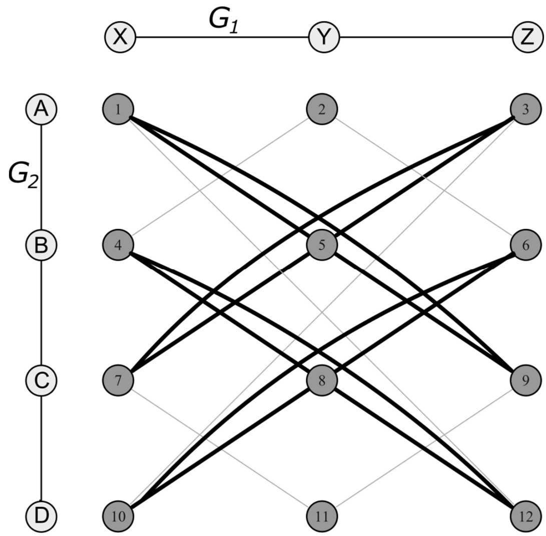


Figure 2. Modular product of two graphs G_1 and G_2, where G_1 is a linear connection of three vertices (X, Y and Z) and G_2 a linear connection of four vertices (A, B, C and D). Edges in bold are part of the four cliques that exist, whereas edges in light grey are not part of these cliques. The numbers have been assigned to each node of the modular product for referencing purposes.

et al. [16]), who showed that it is possible to reconstruct a graph from its respective line graph, and *vice versa*. By analogy, it is thus possible to construct the MCES from the MCIS by constructing a modular product from the line graphs instead of the original graphs. In this case, a vertex in the modular product will now represent an edge match between the two original graphs, instead of a vertex match. It should be noted that there is one exception to Whitney's theorem. This is the so-called Δ-Y exchange where two different graphs lead to isomorphic edge-graphs and hence to erroneous results for the MCES when translating back from line graphs to the original graphs: however, such results are easy to identify and prune, hence ensuring the identification of the correct MCES [17-19].

It will be clear from the above that the modular product graph constructed from two molecular graphs can be large, and more importantly, have a high edge density. The latter is a direct result of the sparseness in degree of chemical graphs, and leads to a more time-consuming search process for clique detection algorithms. The time requirements can be substantially reduced by simplifying the modular product, but this needs to be done without removing chemical meaning and without reducing the size of the MCS that is identified. To this end, Kawabata [20] introduced what he referred to as the *topologically-constrained dMCS* (tdMCS) (a concept that has parallels in several older publications [21-23]). Although the conventional dMCS is suitable for mapping multiple disconnected fragments between two molecules, no constraints on the distance between the fragments are considered, which can yield alignments that are unlikely (or even nonsensical) in some cases. The tdMCS has the attractive property of producing a dMCS that can involve more realistic alignments, and is faster to calculate than a conventional dMCS.

The tdMCS is based on the topological distance $T(a,b)$ between two atoms (or edges) a and b, i.e., the minimum path distance between two features in a graph. The tdMCS is the dMCS resulting from the application of the following constraint when constructing edges in the modular product graph for two graphs A and B:

$$|T_A(a_i, b_i) - T_B(a_j, b_j)| \leq \theta \text{ for } 1 \leq i < j \leq |m|.$$

Here, θ represents a threshold on the maximum allowed difference in distance between two pairs of vertices (or edges), and $|m|$ represents the number of vertices in the modular product graph. Any edge in the modular product that violates this constraint is deleted, and the resulting maximal clique(s) correspond to tdMCSs. Kawabata found that the tdMCIS yielded better agreements with alignments of superimposed ligands in ligand-protein structures than did the dMCIS [20]. Related work has been reported by Klinger and Austin [22] and by Raymond *et al.* [24]. Klinger and Austin described a neural network algorithm to identify two types of MCS that were referred to as "bond types" (which was similar to a dMCIS) and "topological distances" (which was a tdMCIS with θ=0), while Raymond *et al.* introduced a complex set of heuristics that sought to identify an MCS equivalent or near in size to the dMCS, whilst significantly reducing the required search time by deleting both vertices and edges from the modular product graph.

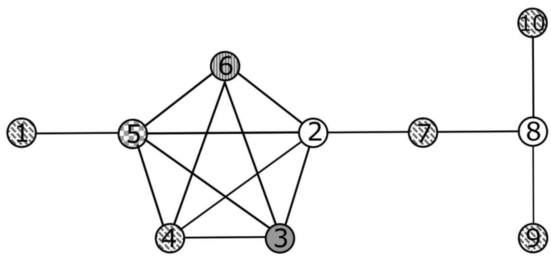


Figure 3. Example of a coloured graph that contains a clique, with vertices {2, 3, 4, 5, 6}). The chromatic number here is 5.

A further important component of many clique-based MCS algorithms is the concept of *graph colouring*, an NP-complete problem that originally arose from the need to colour the countries on a map so that no neighbouring countries would be the same colour. Mathematically, graph colouring (of vertices) can be represented as a function $c(v)$ for a given vertex v, such that $c(v_1) \Leftrightarrow c(v_2)$ when $(v_1,v_2) \in E(G)$. As with maps, each vertex must have a colour that is different from its neighbours' colours, and the smallest number of unique colours in a graph is denoted by its *chromatic number* (which is sometimes written as $\chi(G)$ for a graph G) [11]. The use of graph colouring for clique detection is exemplified in Figure 3, where all the vertices in a clique have different colours. Thus, a clique can be easily detected by showing that all of the neighbours of a given node possess different colours, a fact that forms the basis for several clique detection algorithms.

4. Algorithms based on clique detection

Having introduced the relationship between maximum cliques and MCSs, we now describe a range of algorithms that are based on cliques, with others being discussed in earlier reviews by Gardiner *et al.* [25] and by Pardalos and Rebennack [26].

In its simplest form, a backtracking clique detection algorithm involves traversing a search tree based on the following recursive definition [9]:

$$\omega(G) = \max\{1 + \omega(N_G(v)),\ \omega(G\backslash v)\}.$$

Here, $\omega(G)$ is the maximum clique of graph G (which is usually the modular product in this context), $N_G(v)$ is the set of vertices adjacent to vertex v in G, and $G\backslash v$ is graph G with vertex v deleted. A pseudocode version of this basic algorithm is shown in Figure 4 (an efficient, non-recursive version of this algorithm is described by Carraghan and Pardalos [27]). Here, the vertices in G are processed in ascending order of degree, where v_1 has the smallest degree in G, v_2 has the smallest degree in $G\backslash v_1$, and v_k is the vertex of smallest degree in $G\backslash\{v_1,\ldots,v_{k-1}\}$.

4.1 Bron-Kerbosch

The Bron-Kerbosch algorithm [28], which is shown in its simplest, recursive form in Figure 5, has been widely used in chemical and life science applications since an early comparison of several algorithms by Brint and Willett [29]; indeed, over one-third of the 735 citations in the *Web of Science Core Collection* database to Bron and Kerbosch's 1973 article come from chemical or life science journals (with the *Journal of Chemical Information and Modeling* being the second-largest single source of citations). It will be realised that their algorithm is very similar to the basic procedure shown in Figure 4 in that it recurses through neighbourhoods of selected vertices in the graph. There are, however, two major differences that have caused it to be widely used. First, it keeps track of previously-used vertices (represented as X in the figure), hence substantially increasing performance by the avoidance of futile backtracking; second, it reports all of the maximal cliques that are found, and not just a single maximum clique. A modification of the algorithm by the same authors, and more formally defined by Cazals and Karande [30], involves the selection of a pivot vertex from $P \cup X$ and consideration for clique exploration only those vertices that are not adjacent to this pivot vertex.

Koch [17] developed three extensions to the Bron-Kerbosch algorithm, all of which relied on removing redundant cliques that did not contribute to finding the MCS when using the modular (or edge) product of two graphs. These extensions were based on the concept of a *c-edge*, something that is described most readily if we consider the modular product of a graph with itself. In this case, the c-edges are the edges in the product where the edges (e_1,f_1) and (e_2,f_2) possess a common vertex, where (e_1,e_2) is an edge in G_1 and (f_1,f_2) is an edge in G_2. In this case for clique detection, G_1 is isomorphic to G_2. A clique is spanned by a connected graph of c-edges, so Koch applied the modified Bron-Kerbosch algorithm to find these

Data: vertex set G (of modular product), current clique C, max clique $\omega(G)$

Result: Maximum Clique $\omega(G)$

Function FindCliques(G)**:**

    While *G is not empty* **do**

        select v from G;

        $C = C \cup v$;

        FindCliques($N_G(v)$) ;

        If $|C| > |\omega(G)|$ **then**

            $\omega(G) = C$

        end

        $G = G \backslash v$;

    end

Figure 4. A simple backtracking maximum clique-detection algorithm

Data: vertices in clique R, current vertex set (of modular product graph) P, previously-processed vertices X

Result: Maximal Cliques C

Function BK(R,P,X)**:**

  If *P is empty and X is empty* **then**

    add R to C ; // A maximal clique has been found

  end

  else

    for *vertex $v \in P$* **do**

      BK($R \cup v$, $P \cap N_G(v)$, $X \cap N_G(v)$) ;

      $P = P \cup v$;

      $X = X \cup v$;

    end

  end

Figure 5. The Bron-Kerbosch algorithm.

connected c-edges, and then translated the set to the relevant vertices in the parent graph to yield the maximum clique in G. The maximum clique of the c-edges, a *c-clique*, corresponds to the cMCES between the two graphs, and Koch found that this simple modification was significantly faster than the standard Bron-Kerbosch algorithm. This algorithm, despite the above description, can be applied to non-isomorphic graphs and thus yields the maximal c-cliques between the two graphs.

A further development of this basic approach is described by van Berlo *et al*. [31], who extended the Bron-Kerbosch algorithm and Koch's c-edge approach to find the maximal clique corresponding to the cMCIS and cMCES. This is achieved using several heuristics that were applied to improve search times. For example, the algorithm orders vertices in the search tree based on their "centrality" (an average of the shortest path lengths to every other node in the modular product), where those that are most central are selected first. Another heuristic is the application of 68 atom-types that are used to label the atoms in the two molecules that are being compared. An initial MCS is found by matching based on these atom types and the resulting mapping is then used to seed the search for the actual MCS, in which the atomic symbol is used as the label.

4.2 TOPSIM

TOPSIM [18] is an MCES-finding algorithm that relies on finding the maximum clique in a reduced compatibility graph of the line graphs of two weighted graphs, where a reduced compatibility graph is constructed where vertices are made only for matching atom and bond labels. A node in the modular product here is labelled as (e, e') where e is an edge from G_1 and e' is an edge from G_2 with the same edge label, and the vertices on the edge both have the same labels as in e. Edges between these vertices are constructed in the same way as with the modular product, and, like the modular product, the maximum clique corresponds to the MCES. A branch-and-bound algorithm was employed for clique detection in TOPSIM. Starting from the root, the depth-first algorithm explores each node of the tree (which represents a vertex in the reduced modular product). The next node chosen in the tree is considered legal if it is connected to every other node in the clique identified so far (or if no clique has been found, the first node is selected by default). Once all possible vertices in a path have been explored, the algorithm backtracks, deleting vertices and exploring different paths in the same branch (or perhaps exploring a different branch of the tree), with the largest clique found being returned upon exhaustion of the entire search tree. The lower bound of the algorithm is the maximum clique determined from a pruned version of the reduced modular product (the pruning will not be discussed, though it aimed to preserve edges which had identical neighbouring edges in both graphs) while the upper bound is the maximum possible clique size.

4.3 Babel

Babel [32] described an early colouring algorithm for finding the maximum weighted clique of a graph. The algorithm starts initially with a random vertex, and then starts assigning colours such that neighbours do not possess the same colour. The next vertex chosen in the graph is the one with the greatest number of colours already assigned to its neighbours, in effect colouring vertices in a localised order of degree. The maximal cliques are found using a branch-and-bound algorithm in which the upper and lower bounds are the largest assigned colour for a vertex and the weight of the heaviest clique found over the course of the algorithm, respectively. The basic concept underlying the algorithm is that if a vertex is in a clique then the number of colours assigned to its neighbours must be equal to, or greater than the number of colours in the greatest clique found thus far: if this is not the case then that vertex is eliminated from the graph being studied.

4.4 RASCAL

Raymond *et al*. developed the algorithm RASCAL (for RApid Similarity CALculation) for graph-based similarity searching in chemical databases, as well as for chemical MCES detection [19, 24]. RASCAL relies on an initial screening process to significantly boost the speed of searching, eliminating a large fraction of the molecules in a database so that the computationally demanding graph search is only performed when a pair of molecules are similar enough to suggest that an MCS calculation is warranted. The screening stage prefaces a branch-and-bound algorithm for finding cliques in the modular product of two line graphs, with the condition that upon finding the MCES via the clique, the degree sequences of the vertices of the relevant subgraphs are compared to ensure that a Δ-Y exchange has not occurred. The graph colouring used in RASCAL is referred to as node partitioning. Here, vertices in the modular product are initially grouped into colours or "partitions" based on whether they can actually be neighbours with each other. Given all the vertex pairs (v_i, v_j) in a modular product, those with the same v_i are grouped in the same partition, so that a graph G_1 with n vertices would initially have n partitions. During each iteration of the clique search, vertices remaining in the search tree can be re-assigned into other partitions based on whether they are not neighbours to the existing vertices in a partition. This acts as a fast method of shrinking the chromatic number, which also serves as an upper bound, as against re-colouring the graph after each iteration. RASCAL utilises three different methods for calculating the upper bound, based on the size of the candidate set of vertices to add to the clique, and the calculated upper bound is the minimum of these three values at each stage during the search. RASCAL also employs two pruning heuristics that attempt to remove neighbouring vertices to a clique that could not possibly extend the clique, and to remove symmetric vertices.

Barker et *al*. [21] used RASCAL to find the MCS in reduced graphs as a similarity measure. Notably, the MCIS and MCES were used, and two types of reduced graph were made. The first type were "topologically-connected" graphs, where only vertices connected immediately to each other were joined by edges in the reduced graph (in other words, a standard reduced graph). The other was "fully connected," where all vertices in the reduced graph were connected, and each edge was assigned a weight based on the shortest path length from one node to the other in the topologically-connected graph (essentially, a tdMCS with θ=0). A similar reduced-graph study by Takahashi *et al*. [23] allowed for overlapping features in the reduced graph, and edges in the fully-connected reduced graphs could have multiple weights (representing multiple paths from one feature to another, instead of simply the shortest path).

4.5 Iterated local search

The iterated local search procedure of Grosso *et al*. [33] used neighbourhood rules to obtain a maximal clique, with three fundamental aspects: movement operators; node penalisation; and restart rules. The first operator is an "add" move, which augments the current clique with an immediate neighbouring node not present in the clique. The other operator is a "swap" move, which adds a node not adjacent to exactly one other node in the clique, and then removing its neighbours in the clique, yielding an equal-sized clique to the previous one but transformed to a different location in the given graph. Vertex penalties are assigned to a vertex whenever it has already been featured in a clique computed from a previous iteration, where the penalty is equivalent to the number of cliques it had featured in. Finally, the restart rules return a clique to a smaller former state. The simpler restart rule reverts the clique to a selected vertex in the entire graph, and its immediate neighbours, while a more complex rule involves only performing such a restart if the move is guaranteed to remove a minimum fixed number of vertices. It must be emphasised that this algorithm is non-deterministic, with most stages relying on random selection to some degree: that said, and despite the fact that it is a maximal (rather than maximum) clique algorithm, it was generally found to identify a maximum clique in practice.

A modification of this algorithm has been used by Englert and Kovács [34] at ChemAxon to give what is claimed to be the fastest inexact method for finding the dMCES between two molecules. Their procedure seeks the maximum clique in the modular product of two graphs using the algorithm of Grosso *et al*. [33], with several heuristics to improve the time performance and to optimise the MCS that is returned upon completion of the clique search. Two of these heuristics are applied to bias the search space. The first involves the calculation of a “connectivity score” which represents the number of c-edges in a candidate node during clique expansion. Vertices with a higher connectivity score are selected, thus biasing the search towards the detection of less fragmented MCSs. The second is a similarity measure that is based on the Morgan algorithm and that calculates the maximum radius (in topological distance) at which two vertices have identical circular environments. During clique expansion, vertices are selected in the modular product with the highest weighted sum of the scores from these two heuristics. In addition, the “labelled projection” upper bound for the largest possible size of the dMCES described previously by Raymond *et al*. [19] is used as an early termination criterion, with additional heuristics being employed to modify the MCS post-clique search so as to improve the quality of the final mapping.

4.6 MaxCliqueSeq

The MaxCliqueSeq algorithm of Depolli *et al*. [35] is exact but involves an approximate colouring method, albeit one that was found to be more robust in practice than that described by Babel [32]. Starting from an initial colour, this colour is assigned to the highest-degree vertex, instead of a randomly chosen one as is the case with the Babel algorithm. The neighbours of this coloured vertex are then removed from a set dictating the vertices to colour. Once this set becomes empty, it is refilled with uncoloured vertices, and the colour is incremented to the next colour. The next vertex chosen for colouring is the first available in the set, and the process is then repeated until all vertices are coloured. In addition to the use of this approximate colouring algorithm, MaxCliqueSeq orders the vertices in descending order of degree prior to searching for cliques. The actual algorithm is a depth-first backtracking algorithm, which relies on successive removal of non-neighbours and identically-coloured neighbours to the current clique set. A pruning condition is used to control the search:

$$|U| + |C| \leq |C_{max}|$$

where $|U|$ is the size of the working set of vertices to explore, $|C|$ is the size of the current clique, and $|C_{max}|$ the size of the largest clique found thus far. Whenever this condition is breached, the algorithm stops exploring that particular branch of the search tree. The speed of the algorithm can be enhanced significantly by distributing the branch-and-bound search tree across multiple cores as parallel processes, the resulting speed-ups being particularly large when the algorithm is applied to the comparison of protein structures containing very many amino acid residues.

5. Other types of algorithm

While clique detection lies at the heart of many MCS algorithms, other approaches have been described and some of these are reviewed in this section.

5.1 Subgraph enumeration algorithms

A conceptually simple approach to the detection of the cMCS involves enumerating all connected subgraphs common to the two graphs that are being compared and then returning the largest such subgraph. Perhaps the earliest use of this approach was described by Armitage and Lynch in a study of techniques for the automatic indexing of the substructural changes occurring in chemical reactions [36]. The algorithm commences by enumerating all connected two-atom substructures in the two molecules that are being compared. Those substructures that do not match (in terms of their atom and bond types) are discarded, and the remaining substructures are then extended by one atom, and the atom and bond type filters applied again. This extension-and-comparison process is continued until no common subgraphs exist, at which point the common subgraph(s) from the previous iteration represent the MCS(s). An important part of this algorithm (and of related ones adopting an analogous approach) is the use of a fast canonicalisation procedure to ensure that identical subgraphs can be identified as rapidly as possible.

Varkony *et al*. [37] extended the above algorithm by introducing multiple "similarity definitions," enabling users to produce MCSs which ignored atom and bond types, topology-type matching (i.e., ring atoms could not map to chain atoms) and even to take into account the attachment points of a substructure in a molecule. An important feature of the algorithm, and one that distinguishes it from those described thus far, was that it was specifically designed to allow the comparison of not just two but multiple molecules, with the smallest molecule under consideration being taken as the starting point for the enumeration. The extension of this algorithm to 3D chemical graphs is described by Crandell and Smith [38].

The algorithm described by Takahashi *et al*. [39] is very similar to that of Varkony *et al*. but used a faster method for identifying subgraph isomorphism, specifically the set reduction technique first described by Sussenguth [40] and used for many years in chemical substructure searching algorithms (though it has now been largely supplanted for that purpose by the algorithm due to Ullmann that is briefly described in the next section). A recent example of the enumeration approach is the fMCS algorithm of Dalke and Hastings [41]. Like its precessors, fMCS first deletes all atoms and bonds that are not in common between the molecules being compared, yielding fragments. The largest fragment from each molecule is taken, and the smallest of these largest fragments is tested for subgraph isomorphism in the other molecule(s), and then extended. If this fails to yield the cMCS, the method then starts with single bond fragments instead, which are enumerated from the input graphs.

Finally in this section we describe the MultiMCS algorithm of Hariharan *et al*. [42], which is again designed so that it can handle more than two graphs at a time. This is based on exhaustive enumeration, but differs from the other algorithms above in that it involves the enumeration of all of the maximal common substructures for pairs of molecules, instead of all of the substructures for a single molecule. One of the molecules is selected and this is then matched in turn against each of the remaining molecules in turn, with the overall MCS then being the intersection of all of resulting sets of maximal common substuctures. An analogous strategy for handling multiple molecules based on the Bron-Kerbosch algorithm was described by Brint and Willett [29] and subsequently by Martin *et al*. [43]; Hariharan *et al*. instead developed a novel divide-and-conquer strategy that provides substantial speedups when detecting all of the maximal common substructures for a given molecule-pair.

5.2 McGregor's algorithm

The MCS algorithm described by McGregor [44] employs a simple backtracking search but reduces the number of backtrack instances necessary by inspecting the set of possible solutions remaining at some point in the depth-first search and determining whether it is necessary to extend the current solution. This is effected using a modification of the subgraph isomorphism algorithm that was first described by Ullmann [45] and that now forms the basis for most operational 2D and 3D chemical substructure searching systems [46]. The Ullmann algorithm is based on a match matrix that initially encodes all possible equivalences between the vertices comprising the two graphs that are to be compared, and this matrix is progressively refined as definite vertex-to-vertex mismatches are identified during the exploration of the search tree. When used for MCES detection in labelled and weighted graphs, the match matrix encodes corresponding edges, rather than vertices. An ordering scheme is used to modify the order of edges explored given the currently found common subgraph, so as to maximise the number of corresponding edges between the two graphs as soon as possible.

Although first described over three decades ago, the McGregor algorithm is of continuing interest since it is an important component of the Small Molecule Subgraph Detector (SMSD) Toolkit described by Rahman *et al*. [47]. This contains three different MCS algorithms: one based on the implementation of the Bron-Kerbosch algorithm as provided in the Chemical Development Kit [48]; one based on the algorithm of Cazals and Karande [30]; and the third a subgraph isomorphism procedure that has been modified to enable it identify approximate MCSs [47]. The choice of algorithm in a particular case is based on the complexity of the two molecules that are to be compared, and the McGregor algorithm is used in SMSD to check whether it is possible to further extend the MCSs identified by the second and third of these three procedures.

5.3 *consR*

The approximate MCES algorithm described by Zhu *et al*. [49] uses an approach termed *anchor selection and expansion*, which generates a match matrix between two large graphs. The anchors here are vertices in the two graphs that possess a high similarity and comparatively large degrees between the two graphs. Anchors are then expanded to match neighbouring vertices that are highly similar, giving a list of possible candidate matches. The most similar pair of vertices is registered in the match matrix, and any other candidate matches assigned provided that neither of the vertices in the pair have been previously assigned. These assigned vertices become anchors themselves for which neighbourhood expansion is then repeated, until the whole graph has been analysed. A refinement of this procedure uses minimal vertex covers; however, the identification of these is another NP-complete problem so the authors used randomly-determined minimal vertex covers with the result that their algorithm is non-deterministic in operation.

5.4 kCombu

The final algorithm to be described here is Kawabata's kCombu algorithm, which circumvents the potentially costly requirement of constructing and searching the modular product graph that is used in clique-detection MCS algorithms [20]. In the context of generating the MCIS, pairs of vertices – one vertex in one graph and one vertex in the other – are ranked based on a heuristic score. This score consists of three distances (so that the lower the overall score, the better matched the two vertices are): a distance representing the difference in the number of neighbours between two vertices; an extended-connectivity value based on the Morgan algorithm; and a topological distance similar to the tdMCS constraint described earlier.

A fixed number K of correspondences are generated (where the first element is one of the top K pairs), and for each extension of each correspondence, the next best-scoring pair is added, this process continuing until all (matchable) atoms have been used. The fact that multiple correspondences are produced, means that up to K MCISs can be obtained (though in practice several of these MCS results can be isomorphic).

6. Conclusions

In this paper we have briefly summarised the principal characteristics of several algorithms for MCS detection. It will be clear that MCS detection is a problem of continuing interest to a range of academic disciplines, not least chemoinformatics, and we must emphasise that our review has been necessarily selective given the vast literature associated with the subject.

In this concluding section, the reader might be expecting us to recommend some sort of "best buy" algorithm from amongst those that have been described, but we do not believe that this is possible for at least four reasons. First, as noted in Sections 2 and 3, there are several different types of MCS (even if one does not differentiate between MCIS and MCES), with many of the algorithms being restricted to the detection of the cMCS. Second, applications in chemoinformatics may require not only the maximum common subgraph but also some or all of the maximal ones, this requirement precluding the use of those algorithms that identify only the former. Third, algorithmic efficiency can be crucially dependent on the size (in terms of the numbers of vertices and edges) of the graphs that are to be compared, on their complexities (with highly symmetric graphs often proving problematic), and on the degree of inter-graph similarity (where, e.g., back-tracking algorithms can be very slow if there are many small common subgraphs present). Finally, and perhaps most importantly, only a few papers report comparative experiments where two or more algorithms are applied to the same set of molecules to ascertain their effectiveness, i.e., whether they do in fact find the true MCS(s), and their efficiency, i.e., the time taken to achieve this. Even when such comparisons are conducted, e.g. in the papers describing MultiMCS [42] and SMSD [47], it is normal for only a few algorithms to be involved: it is hence to be hoped that more extensive comparisons can be carried out in the future.

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