Beyond Heuristic DENDRAL

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I. INTRODUCTION

Theory formation in science embodies many elements of creativity
which make it both an interesting and challenging task for
artificial intelligence research. One of the goals of the
Heuristic DENDRAL project has long been the study of processes
underlying theory formation. This paper presents the first steps
we have taken to achieve that goal, in a program called
Meta-DENDRAL.

The Heuristic DENDRAL project has concentrated its efforts on the
inductive analysis of empirical data for the formation of
explanatory hypotheses. This is the type of inference task that
calls for the use of a scientific theory by a performance
program, but not for the formation of that theory. When we
started on Heuristic DENDRAL we did not have the insight,
understanding, and daring to tackle ab initio the problem of
theory formation. But now we feel the time is ripe for us to

turn our attention to the problem of theory formation. Our understanding and our technical tools have matured along with the Heuristic DENDRAL program to the point where we now see clear ways to proceed.

As always, the proper choice of task environment is crucial, but for us the choice was absolutely clear. The theory formation task most accessible to us is the task of forming mass spectral theory because the Heuristic DENDRAL performance program uses such a theory to elucidate molecular structures of organic chemical molecules. Hence, the notion of building a level of programs "meta" to the DENDRAL performance program.

The theory of mass spectrometry contains numerous statements about the fragmentation patterns of chemical molecules upon electron impact in a mass spectrometer. Because this is a new science, the theory is still expanding rapidly. In other words, there exists a possibility that a theory formation program could discover genuine extensions of the theory.

The Heuristic DENDRAL system already contains an excellent mass spectral theory. We, therefore, have a clear idea of what a "correct answer" is like. DENDRAL's theory is represented in at least two different forms at present, so that we have a fair idea of the issues involved in representing mass spectral theory for a program. A theory language of notations, data structures, and

primitive concepts (with which we are intimately familiar because we developed it) is available. People who are expert in mass spectral theory are members of the DENDRAL research team. Many programs for manipulating mass spectral data have already been developed and are ready to be exploited as Meta-DENDRAL tools.

The goal of the Meta-DENDRAL program is to infer the theory that the performance program (Heuristic DENDRAL) needs in order to solve problems of mass spectral analysis. The following table attempts to sketch some differences between the programs at the performance level and the meta-level.

	Heuristic DENDRAL	Meta-DENDRAL
Input	The mass spectrum of a molecule whose structure is not known (except, of course, in our test cases).	A large number of recorded mass spectra and the associated (known) molecular structures.
Output	A molecular structure inferred from the data.	A set of cleavage and rearrangement rules constituting a subset of the theory of mass spectrometry.
Example	Uses alpha-carbon fragmentation theory rules in planning and in validation.	Discovers (and validates) alpha-carbon fragmentation rules in a space of possible patterns of cleavage. Uses set of primitive concepts but does not invent new primitives.

In our view, the continuity evident in this table reflects a continuity in the processes of inductive explanation in science. Moves toward meta-levels of scientific inference are moves toward encompassing broader data bases and constructing more general rules for describing regularities in the data.

Beyond this level of Meta-DENDRAL there are still higher levels. Not all theory formation is as simple as the program described here assumes it is. For example, the representation of chemical molecules and the list of basic mass spectral processes are both fixed for this program, yet these are concepts which a higher level program should be expected to discover. Also, there is no postulation of new theoretical entities in this program.

But, again, higher levels of theory formation certainly do include this process.

The task of theory formation certainly can be and has been discussed out of the context of any particular theory. However, writing a computer program to perform the general task is more difficult than working within the context of one particular scientific discipline. While it is not clear how science proceeds in general, it may be possible to describe in detail how the scientists in one particular discipline perform their work. From there, it is not a large step to writing the computer program. Thus this paper attacks the general problems of theory formation by discussing the problems of designing a computer program to formulate a theory in a specific branch of science.

The general strategy of Meta-DENDRAL is to reason from data to plausible generalizations and then to integrate the generalizations into a unified theory. The input to the Meta-DENDRAL system is a set of structure-mass spectrum pairs. It receives essentially the same data as a chemist might choose when he attempts to elucidate the processes underlying the mass spectrometric behavior of a class of molecules. When the pioneers of the field turn their attention to a class of chemical compounds whose mass spectrometric behavior is not well understood, they must collect mass spectra for a number of the compounds and look for generalizations in the data. The

generalizations have to be tested against new data and against
the established theory. If new data provide counterexamples, the
generalizations are changed. If the generalizations are not
compatible with the old theory either the old theory or the
generalizations are changed, depending on the seriousness of the
discrepancy, the nature of the statements involved, the
scientist's commitment to the old theory, and so on.

This paper is organized by the three main subproblems around
which the program is also organized. The first is to explain
each individual spectrum, given the molecular structure
associated with it. That is, determine the processes (or
alternative sets of processes) which account for the experimental
data. The second subproblem is to generalize the results from
each spectrum to all spectra. In other words, find the common
processes and sets of processes which can explain several
spectra. The last is to integrate the generalizations into the
existing theory in such a way that the theory is consistent and
economical. Within each of the three main sections, the
subsections indicate further subproblems which the program must
solve.

II. FIRST SUBPROBLEM: EXPLAINING EACH SPECTRUM

The so-called "method of hypothesis" in science is sometimes

proposed as the essence of scientific work. Restating it, in a deliberately imprecise way, the method is roughly to formulate a hypothesis to account for some of the observed data and make successively finer adjustments to it as more observations are made. Very little is said about the details of a scientist's intellectual processes as he goes through the method. Thinking of hypotheses, for example, is an unsystematic and mysterious task which must be elucidated before the method can be programmed. That is the task we have designated as the first subproblem.

The program starts with individual spectrum- structure pairs as separate from one another. It constructs alternative explanations for each spectrum and then considers the spectra all together. An explanation, for the program, as for the chemist, is a plausible account of the mass spectrometric mechanisms which produced the peaks in the spectrum. The explanation is something like a story of the molecule's adventures in the mass spectrometer: certain data points appear as a result of cleavage, others appear as a result of more complex processes. At this stage of development of the theory, the chemist's story does not account for every data point because of the complexities of the instrument and the vast amount of missing information about mass spectrometry.

A. REPRESENTATION

The well-known problem of choosing a representation for the statements of a scientific theory and the objects mentioned by the theory is common to all sciences. In computer science it is recognized as a crucial problem for the efficient solution (or for any solution) to every problem. Improper choices of representation can forestall the solution for both humans and machines. At this stage there are no computer programs which successfully choose the representation of objects in a problem domain. Therefore we, the designers of the Meta-DENDRAL system, have chosen representations with which we have some experience and for which programmed subroutines have already been written in the Heuristic DENDRAL performance system.

It was natural to use these representations since the meta-program itself will not only interface with the Heuristic DENDRAL performance program, but is built up from the LISP functions of the performance program. Except for some supervisory routines, all of the routines used for solving the first subproblem (reasoning from data to plausible individual explanations) had already been written for use in predicting mass spectra. For example, the routine to break a bond is used in both the meta-program and the predictor phase of the Heuristic DENDRAL system. These common features will be described in more detail below.

Specifically, for this program, the input data are chemical
structures paired with their experimental mass spectra:
((Structure-1 . Spectrum-1) ... (Structure-n . Spectrum-n)).
The representation of chemical structures is just the DENDRAL
representation used in the Heuristic DENDRAL system. It has been
described in detail elsewhere <1,2,4,7>: essentially it is a
linear string which uniquely encodes the graph structure of the
molecule. The mass spectra, also, are represented in the same
way as for the Heuristic DENDRAL performance system. Each
spectrum is a LISP list of dotted x-y pairs, where the x-points
are masses of fragments and the y-points are the relative
abundances of fragments of those masses.

Internally, a molecular structure is stored as a list of named
atoms in the structure (e.g., C1, O2, C3) and the connections
among the atoms. By putting the connections of the atoms on
their property lists (along with other properties such as the
type of atom (carbon, oxygen, etc.) and the number of hydrogens),
manipulating chemical structures in LISP becomes a matter of
changing values on property lists. This representation has been
used in the mass spectrum predictor, for which the functions for
manipulating structures were also developed.

The representation of the statements in the program's mass
spectrometry theory is also the one used in the predictor phase
of the Heuristic DENDRAL system. It is discussed in detail in

Section IV of this paper.

B. SEARCH

It is not clear what a scientist does when he "casts about" for a
good hypothesis. Intuition, genius, insight, creativity and
other faculties have been invoked to explain how a scientist
arrives at the hypothesis which he later rejects or comes to
believe or modifies in light of new observations. From an
information processing point of view it makes sense to view the
hypothesis formation problem as a problem of searching a space of
possible hypotheses for the most plausible ones. This
presupposes a generator of the search space which, admittedly,
remains undiscovered for most scientific problems.

In the Heuristic DENDRAL performance system the "legal move
generator" is the DENDRAL algorithm for constructing a complete
and irredundant set of molecular models from any specified
collection of chemical atoms. Each complete molecular structure
is the terminus of some branch in the tree generated by the
program. Intermediate nodes in the tree represent structures
partially determined but with some chemical atoms as yet
unallocated to the emerging structure. The primitive concepts of
this generator are chemical atoms and bonds of molecules (or
nodes and edges of graphs) and valence of atoms (number of
allowable edges emanating from any node).

The problem of finding sets of mass spectrometric processes to explain each spectrum is also conceived as a heuristic search problem. As such, the structure of the computer program is easily described. In broad terms, the program contains (1) a generator of the search space, (2) heuristics for pruning the tree, and (3) evaluation criteria for guiding the search. Except for problems inherent in the task, then, the problems of such a program are reasonably well understood. These three main components of the heuristic search program are considered one at a time in the immediate discussion.

1. GENERATOR

Writing a computer program which solves a scientific reasoning problem is facilitated by seeing the problem as one of heuristic search. This is as true of the meta-program which reasons from collections of data to generalizations as for the performance system which reasons from one set of data to an explanation. For this reason we have called the process of induction "a process of efficient selection from the domain of all possible structures."[17]

For this part of the Meta-DENDRAL system, the generator is a procedure for systematically breaking apart chemical molecules to represent all possible processes occurring in a mass

spectrometer. In addition to single cleavages, the generator must be capable of producing all possible pairs of cleavages, all possible triples, and so forth. And, for each cleavage or set of cleavages it must be able to reproduce the result of atoms or groups of atoms migrating from one fragment to another. For example, after the single break labeled (a) in Figure 1 below, subsequent cleavage (b) may also occur. The result of (a) + (b) is the simple fragment CH3.

$$
\text{CH3} \quad \overset{\displaystyle }{\underset{(b)}{\Big\}}} \quad \overset{\displaystyle \overset{O}{\overset{\|}{C}}}{\vphantom{x}} \quad \overset{\displaystyle }{\underset{(a)}{\Big\}}} \quad \text{CH2} \; - \; \text{CH2} \; - \; \text{CH3}
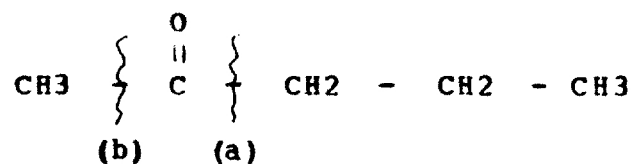$$

FIGURE 1

Or, for the same molecule cleavage (c) may be followed by migration of one hydrogen atom from the gamma position (marked with an asterisk) to the oxygen, as shown in Figure 2:
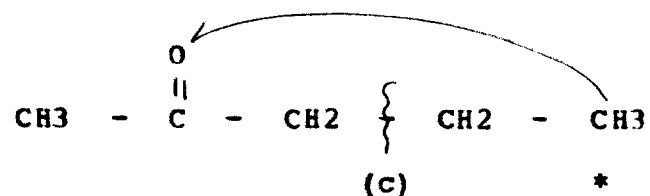

$$
\text{CH3} \; - \; \overset{O}{\overset{\|}{C}} \; - \; \text{CH2} \; \underset{(c)}{\Big\}} \; \text{CH2} \; - \; \underset{*}{\text{CH3}}
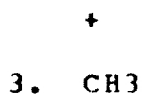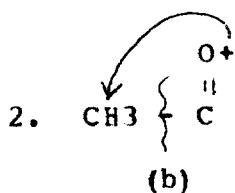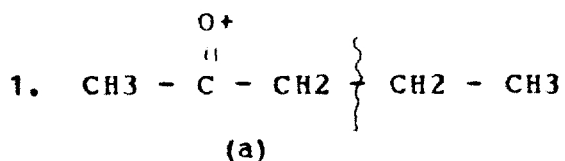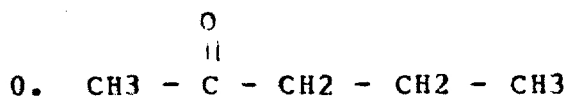$$

FIGURE 2

The resulting fragment, then, contains three carbon atoms, six

hydrogens and an oxygen (C3H6O). Since no such fragment results from simple cleavage or any combination of simple cleavages, it is necessary to postulate cleavage plus hydrogen migration as the origin of the mass spectral peak corresponding to this fragment and peaks corresponding to similar fragments for the mass spectra of other molecules. Historically, this double process was postulated for just these reasons and was subsequently confirmed experimentally.

The generator of the search space will postulate these processes as possible explanations of the mass spectral peaks at masses 15 (CH3) and 58 (C3H6O) for this particular molecule. But it will also postulate the simple cleavage (b) in Figure 1 as the explanation of the peak at mass 15. And for the peak at mass 58 from the process in Figure 2 it will postulate the alternative migration of a hydrogen atom from the position labeled beta. From the generator's point of view these processes are at least as good as the more or less accurate processes shown in Figures 1 and 2.

Another device is used by mass spectroscopists to explain their preference for the double cleavage (a) + (b) over the simple cleavage (b) for describing the mechanism resulting in the peak at mass 15 (CH3) for the molecule shown. Mass spectroscopists often appeal to the localization of the positive charge in the charged molecule to explain why one peak appears in a spectrum

but another does not. It is known that only the charged

fragments are recorded by the mass spectrometer. In this

particular case (Figure 1) the positive charge initially resides

on the C=O group of the molecule. For this reason, the simple

cleavage (b) will produce a peak corresponding to the fragment

C_4H_7O, the right-hand fragment resulting from that break. But

since there is no positive charge on the CH_3 fragment after (b)

above, the peak at mass 15 in the spectrum could not have

resulted from this process. Because of the particular stability

of carbon monoxide, however, the experts are willing to postulate

that cleavage (a) is followed by loss of the uncharged C=O piece

from cleavage (b), thus leaving a positive charge on the only

other atom in the original fragment. The generator program must

also manipulate charges then. It does this particular piece of

reasoning in several steps, as shown in the steps of Figure 3,

not just by the double process described above.

```
                          O
                          ||
      0.   CH3 - C - CH2 - CH2 - CH3
```

```
                          O+                      Place the plus
                          ||                      charge on the O
      1.   CH3 - C - CH2 ⌠ CH2 - CH3              of C=O.*
                         ⌡
                    (a)                           Make cleavage (a)
                                                  leaving left-hand
                                                  side.
```

```
                    ⌐───→
                    │      O+                      Migrate the charge
                    ↓ ⌠    ||                      from C=O to CH2.
      2.   CH3 ⌡    C
                 (b)
```

```
           +                                       Final result,
      3.   CH3                                      mass=15, after
                                                   cleavage (b).
```

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*The correct notation from a chemist's point of view is O+.
instead of O+ -- the dot representing a free electron on the
oxygen. The Meta-DENDRAL program ignores this subtlety,
although the Heuristic DENDRAL program gets this straight.

FIGURE 3

The primitive mechanisms of the generator are charge
localization, cleavage, and group migration (where a group can be
a positive charge, a single atom, or a set of connected atoms).
The generator is a procedure for producing all possible charged
fragments, not just all possible fragments, in other words.
Putting these mechanisms together in all possible ways leads to
an extremely large space of possible explanations for the peaks
in the mass spectrum of a molecule. The pruning heuristics
discussed in the next section alleviate that problem somewhat;
for the moment let us turn to the actual design of the generator.

There are clearly several alternative ways of putting the three
primitive mechanisms together into a generator of charged
fragments. For example, chemists consider the initial
localization of the charge before the possibilities for simple
cleavage. But an alternative is to consider the possibility of
cleavages first and then ask about the location of the positive
charge. The generator actually programmed allows for changing
the canons of generation to experiment with these alternatives,
but only the set of canons described below has actually been used
thus far.

At the first level of branching in the tree all possible single
cleavages are performed on the original molecular structure
resulting in all possible primary fragments. At the next level,
the positive charge is assigned to all possible atoms in the

fragments. (Switching these two steps gives the same results and is closer to the conceptualization used by the chemist; it results in a less efficient program, however.) Starting with level 3 the procedure for generating successive levels is recursive: For each charged fragment at level n (n > 2) produce the charged fragments resulting from (i) cleavage of each bond in the fragment and (ii) migration of each group from its origin to each other atom in the fragment, where 'group' currently means 'positive charge or hydrogen atom'.

In general a group can be any radical in the fragment, and the generator can handle the general case. Limiting group migrations is done by having the program consult a list of items it will consider as candidates for group migrations. That list now contains only '+' and 'H', which reflects both the designers' and the chemists' preference for simple migrations. The generation tree is schematized in Figure 4.

level 0   O

0.   Initial molecular structure

level 1   O   O ... O

1.   Fragments resulting from simple cleavag

level 2   O   O ... O   ...

2.   Charged primary fragments

level 3   O   O...O   □   □ ... □

3.   Secondary fragments charged primary fra ments with (i) succ sive cleavage (circ (ii) successive gro migration (square)

level 4   O   O...O   □   □...□ ... O   O...O

4.   Tertiary fragments secondary fragments with (i) successive cleavage (circle) (ii) successive gro migration (square)
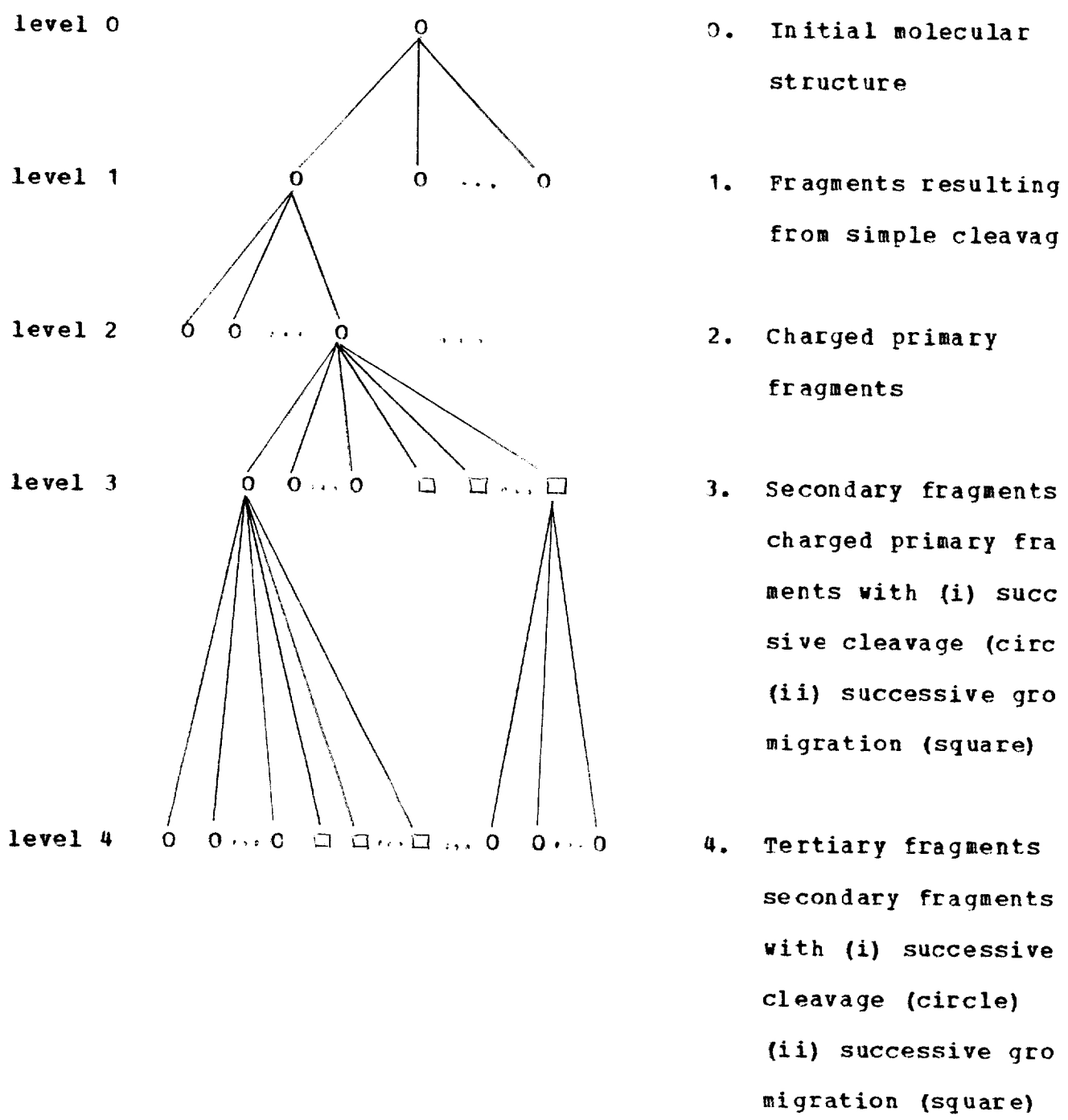
FIGURE 4

It is desirable to avoid the possibility of successive levels of
some branch in this tree containing all the same atoms and
differing only in the migration of atoms or of the charge. In
this case duplications would result and the tree would be
infinite. Thus the generating algorithm applies the group
migration mechanism only to nodes in the tree which resulted from
cleavage.* The generating process terminates when there are no
more bonds to break in a fragment.

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*In principle it is desirable to allow fragments resulting from
n group migrations and only a single cleavage. Thus the
algorithm is constructed to allow up to n group migrations after
a cleavage. Currently n=1, so the procedure works as described
in Figure 4.

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2. PRUNING HEURISTICS

The size of the search tree may become quite large, for there are
many combinations of mechanisms to consider. For example, if
only bond cleavages are considered, the number of possible
explanations for data points in the spectrum of a molecule is the
number of ways of breaking combinations of the bonds in the
molecule. The number of combinations of b bonds in a molecule

is $2**b - 1$. This number represents a lower bound on the size
of the search space, since secondary processes such as group
migrations will be considered in conjunction with bond cleavages.
As with any large search tree, then, pruning heuristics are
essential for reducing the search.

Three simple pruning techniques are currently used by the
program. (1) Since the result of breaking a pair of bonds (or n
bonds) is independent of the order in which the bonds are broken,
allow only one occurrence of each bond set; (2) Since mass
spectrometric processes tend to follow favorable pathways, prune
any branch in the tree which is no longer favorable, as evidenced
by failure of a fragment's mass to appear in the mass spectrum;
(3) Limit the number of allowable group migrations after each
cleavage.

The first pruning technique is hardly a heuristic, in the sense
of a risky technique, but its pruning effectiveness should be
obvious. Duplications of nodes in the search space are
unnecessary in this case and can be avoided by removing a bond
from consideration after all possible results of breaking it have
been explored. The second technique does carry an element of
risk, because mass spectrometry theory includes no guarantee that
every fragment in a decomposition pathway will produce a peak in
the mass spectrum. In fact, the pruning can only be done after a
complete cycle of cleavage plus migration because these processes

occur together in the mass spectrometer -- without the appearance
of the intermediate fragments. The third technique also is truly
heuristic since there are no theoretical reasons why group
migrations might not occur in complex and exotic patterns between
cleavages. It has been mentioned earlier that the current limit
is one group migration after any cleavage. Migrations of two and
three hydrogens are known in mass spectrometry, so these will not
now be found by the program. Also, limiting allowable migrations
to hydrogen atoms and the plus charge is somewhat risky since
there are known cases of migration of larger groups, such as
methyl $(CH3)$. The bias of mass spectroscopists toward simple
mechanisms, however, leads us to believe that they would place
little faith in exotic mechanisms as explanations of mass
spectral peaks, at least not without other corroborating
evidence.

3. EVALUATION

The search tree can be pruned effectively using the techniques
just mentioned, with a substantial but not breath-taking
reduction in search. Evaluation of alternative mechanisms is
still necessary, either during generation or after it is
completed, in order to distinguish the highly attractive
explanatory mechanisms from those which are merely possible.
Evaluation routines applied during generation can also be used to

limit search it threshold values can be established with
confidence. This has not been done because of our lack of
experience with the program so far. But even when the mechanisms
are evaluated individually during generation, the program must be
prepared to evaluate sets of alternative mechanisms later to find
consistent and simple explanations. Evaluation of individual
mechanisms and of sets of mechanisms will be considered
separately in the following discussion, although it is clear even
to the designers that these evaluation criteria are not
independent.

We would be very happy to have the program rediscover just those
explanatory mechanisms which expert mass spectroscopists have
postulated, and even happier if the program postulated a set
which mass spectroscopists accepted as a viable alternative to
their own. So far, however, our evaluation criteria have not
been strong enough to pick out mechanisms which experts think are
plausible, while giving a low ranking to the others.

Without building in the biases of experts toward their current
theory it is difficult to evaluate mechanisms at all. The
concept of cleavage adjacent to the C=O (alpha-cleavage) in
molecules like that of Figure 1 is well-established in the mass
spectrometry literature. Without putting in criteria relating
score to distance from non-carbon atoms, it is difficult to
discover the attractiveness of alpha-cleavage. The criteria

must, it seems, be independent of any particular theory; they must be criteria for evaluating the worth of generalizations in any theoretical domain.

The program's evaluation routine presently contains only one a priori principle. In an attempt to measure the simplicity of the statements describing mechanisms, the program counts the number of primitive mechanisms necessary to explain a peak. Thus when there are alternative explanations of the same data point, the program chooses the simplest one, that is, the one with the fewest steps. Simple cleavage is preferred to cleavage plus migration plus cleavage, for example.

It is not desirable to use this ranking principle for pruning during generation, however, because there are cases where fragments can only come from complex pathways. For example, a simple mechanism and a complex mechanism may both explain the same peak, but a daughter peak can only be derived from the fragment along the more complex branch of the tree. The reason for this is simple: although different fragments may have the same mass (and thus explain the same peak), daughters of those fragments will not always have identical masses. So, the program must save the complex pathways as long as they may lead to fragments whose mass is not the same as the mass of fragments arrived at by a simple pathway.

The result of the generation process as described so far, with pruning and evaluation, is a set of candidate mass spectrometric processes for each structure which provides alternative explanations for data points in the associated mass spectrum. For instance, the program breaks the molecular structure shown in Figure 6 at individual bonds or pairs of bonds to give the following information (atoms in the structure are numbered from left to right):

MASS EXPLAINED	PROCESS
103	cleavage: C2-C1
	cleavage: C6-C7
89	cleavage: s3-C2
	cleavage: C5-C6
75	cleavage: C4-C5
61	cleavage: S3-C4
60	cleavage: C4-C5 & C2-C1
57	cleavage: C4-S3
46	cleavage: S3-C4 & C2-C1
43	cleavage: C5-C4
42	cleavage: C42-C7 & C4-S3
29	cleavage: C2-S3
28	cleavage: C5-C6 & C4-S3

CH3 - CH2 - SH - CH2 - CH2 - CH2 - CH3

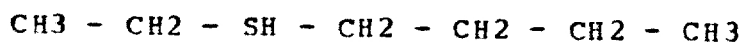FIGURE 5

In this example, the program used no migrations or charge localization information, for purposes of simplicity. The program explored all simple cleavages and found peaks corresponding to every resulting fragment but two.* For each of the successful fragments, the program broke each of the remaining bonds. From all the secondary breaks considered, the resulting fragments corresponded to only four additional peaks in the spectrum. So these four branches of the search tree were each expanded by one more simple cleavage. None of the tertiary fragments were found in the spectrum so the program terminated. It explained 11 data points in this way, the unfragmented molecule accounted for another one, and the program left 24 data points unexplained. Eight of these are explainable by hydrogen migration in conjunction with one or two cleavages, so just this additional capability adds substantial power to the program.

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*The CH3 fragment was produced twice but there was no peak at mass 15 in the spectrum.

III. SECOND SUBPROBLEM: GENERALIZING TO ALL STRUCTURES

The method of hypothesis, mentioned earlier as a vague description of scientific work, suggests that a plausible hypothesis can be successively modified in light of new experience to bring a scientist closer and closer to satisfactory

explanations of data. Apart from the problem of formulating a
starting hypothesis discussed above and the problem of
terminating the procedure, it is not at all clear how the
adjustments are to be made nor how to select the new experiences
so as to make the procedure relatively efficient, or at least
workable. These are well-known problems in the methodology of
science. In other terms, the problem of successive modifications
can be viewed as a problem of generalizing a hypothesis from one
set of observations to a larger set.

The Meta-DENDRAL system does not yet contain a programmed
procedure which solves this second main subproblem. The design
of the procedure will be described only briefly in this section
for this reason. The task is to generalize the explanations for
each of the molecules into a consistent and simple set of
explanations for the whole set of molecules.

The input to this phase of the program is the set of explanatory
mechanisms for each of the molecules in the original class. The
output is one set of mechanisms which can explain every peak
explained by the individual sets of explanations. If the program
is successful, the output set of explanations will be a unified
"theory" of the mass spectrometric behavior of all the molecules
in the class. In operational terms, this means, at least, that
the final set of explanations will be smaller than the union of
all the individual sets of explanations.

A. REPRESENTATION

Perhaps the most pressing problem is to represent the candidate
explanations in such a way that they can be compared and unified,
without building in concepts which would beg the theory-formation
question. The bonds in each molecule are now named only by the
arbitrary numbering of atoms, the C1-C2 bond, for example. This
is a convenient representation, for bonds in a single molecule
but does not allow comparisons of bonds between molecules. What
does the C1-C2 bond in one molecule have in common with the C2-C3
bond in another?

An attractive representation of a bond is a description of its
environment: the types of atoms it links; the number of
hydrogens, oxygens, nitrogens and so forth on each of the linked
atoms; the types of bonds emanating from the linked atoms
(single, double, triple); and so on for successive atoms and
bonds away from the bond in question. This is attractive because
it is easy to give the program just the right information for
efficient comparisons. But this is the danger, too, for omitting
"superfluous" information gives the program much too great a head
start on the problem. It might discover what we want it to
discover--the old principles-- but it would never discover
anything new.

The most neutral representation for bonds we have found which
still allows comparison is the pair of graph structures of the
pieces of the molecule joined by the bond. Breaks (a) and (b) of
Figure 1, then become:

$$CH3 - \overset{\overset{\textstyle O}{\|}}{C} \{ CH2 - CH2 - CH3$$

<div align="center">(a)</div>

$$CH3 \} \overset{\overset{\textstyle O}{\|}}{C}$$

<div align="center">(b)</div>
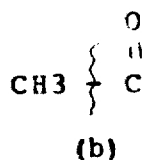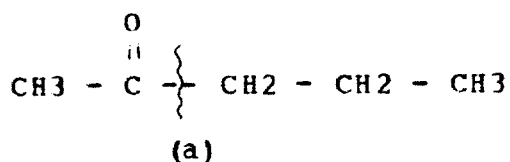
Group migrations present a difficult problem. The most
attractive representation now seems to be representing each
migration as "before and after" graph structure pairs.

Graphs carry all the information about bonds and migrations;
their main drawback is that they carry too much information. The
program which looks for common features in subgraphs must be able
to limit the amount of information it considers relevant. Some
heuristics will be necessary--to limit the size of the
environment that will be considered, for example. Again, at this
point, there is a danger of telling the program too much about

what we want it to discover, or do not want it to discover.

B. SEARCH

As in any learning problem there will need to be considerable
readjustment of the learned generalizations as new data are
considered. It should also be expected that learning rates will
be highly dependent upon the order of presentation of the data.

It is anticipated that the program will search for
generalizations in roughly the same way as our mass
spectroscopist friends say they do. The program will first
choose one member from the class of compounds which is judged to
be "typical", but "simple". By that, a chemist means a structure
which is not so small as to present an inaccurate picture of the
bond environments, and not so large and highly substituted as to
bring in too many special problems. The program should allow
these working definitions to be easily changed.

The fragmentation and migration patterns already observed for
this typical member of the class will then be postulated to be
typical for all members of the class. The rest of the program
must look at patterns for additional molecules and adjust the
initial hypothesis accordingly.

Again it should be noted that this design is certainly not the
only alternative. It happens to be the one which appears most
promising, in part because of its closeness to the procedure
acually used by experts. Thus, it is the design we are now
actively considering.

IV. THIRD SUBPROBLEM: INTEGRATING NEW STATEMENTS INTO EXISTING
THEORY

Supposing the method of hypothesis to work, the scientist's
problem does not necessarily end with the satisfactory
formulaticn of a general statement explaining all the observed
data. If he is working in a discipline for which there is no
existing theory, he might stop here. But it is rare to be out of
any theoretical context. Typically, the hypotheses are
formulated as extensions of some existing theory.

In the course of formulating and modifying hypotheses, the
existing theory usually serves as a guide for pursuing some
hypotheses and not others. However, for reasons of simplicity
the Meta-DENDRAL system currently ignores the existing theory
until the end of its chain of reasoning. We are assuming here

that the classes of problems given to the system--the data to be explained--cannot be solved using the existing theory and that they do not conflict with the theory. These simplifying assumptions mean that the theory formulated by the program can be built up stepwise, class by class. New statements which are formulated are assumed to be consistent with the theory. Then the main problem remaining is to fit the new statements in with the old ones in an econcnical way.

One of the reasons we have rewritten the DENDRAL system's mass spectrum predictor was to separate the mass spectrometry theory from the LISP functions it drives. Making changes to the theory, then, does not require reprogramming, in the usual sense. Consequently, writing a program which updates the theory no longer seems to be an insurmountable task.

The problems of integrating new statements into the old theory are independent of the source of those statements. In order to study these problems we have written a program which (a) accepts new rules from human chemists and (b) updates the theory table of the program. The program for doing (a), called the dialog program, is not central to this paper, thus this section will focus on the work to accomplish (b), updating the theory. The dialog program represents one way of obtaining new chemical information to enter into the system. The automated data-analysis and theory-formation program incorporated in

Meta-DENDRAL represents another approach. The reason for discussing the former is that it serves as a simulation of the latter. Thus the problems of putting new chemical information into the system can be discussed from the standpoint of the dialog program, with which we have more experience.

A. REPRESENTATION

The mass spectral theory is represented in the program as a table of situation-action rules (S-A rules), patterned after Waterman's table of heuristics for good poker play.*

---

*D.A. Waterman, "Generalization Learning Techniques for Automating the Learning of Heuristics". Artificial Intelligence, 1:121 (1970).

Situations are predicates which are either true or false of a particular molecule or molecular fragment. (This is equivalent to Waterman's representation of situations as state vectors, but seems more economical for this program, because of the large number of terms which would have to be included in the state vector.) Actions are sequences of primitive mass spectral processes constituting rewrite rules for transforming one structural fragment into another. In this system, an action can also be another S-A rule, allowing nesting of rules in a manner quite natural to the current textbook descriptions of mass spectral theory.

The chemist interacting with the dialog program in time-sharing
has already been given the explanation of primitive concepts
known to the system which is given in Appendix A. For example,
the chemist is told that he can use the functions BREAKBOND and
ADDH, and is given some explanation of them. Mostly, the names
of the LISP functions which are available suggest the effects of
the function to the chemist.

All new rules must be expressed in terms of these concepts. This
is a reasonable constraint in the dialog phase of this program
because we have been willing to add new primitives whenever a
chemist found some rule he could not express otherwise. For
example, the concept of n-cleavage was added as a primitive to
allow expression of a gamma-cleavage rule (NCLEAVAGE (QUOTE
GAMMA)). This constraint also insures that the output from the
dialog phase and the output of the automatic generalization
program will contain the same terms.

As an additional means of maintaining parallelism between the
dialog program and the automatic generalization program, the
dialog program writes S-A rules on the basis of information
obtained from the chemist, but does not allow him to write his
own rules. The dialog program prompts the chemist for the
information it needs in order to write the rules, and allows no
opportunity for him to deviate from its prompting format. For
each S-A rule, accompanying LISP code is written from the

information supplied by the chemist to define new situations and new actions, unless the chemist has merely put together old situations and old actions in new ways.

B. INTEGRATION

The output from the dialog phase is the same as the anticipated output from the generalization program: a set of S-A rules with accompanying definitions of situations and actions. The only expected difference is that the chemist can assign names to situations and actions during the dialog which are meaningful to him, whereas the generalization program must create its own symbols.

Inserting a new rule into the theory table requires an initial scan of the theory to find out whether the new rule describes (1) an entirely new situation, (2) a situation which subsumes an existing one, or (3) a situation which can be subsumed under an existing one. For cases (2) and (3), where there is some overlap between the new rule and some existing one (assuming for the moment there is only one), the actions of the rules must also be considered in deciding where in the table the new rule must go. After deciding where the rule must be inserted, the program adds the definitions of the new situation name and action name to the system.

Case (1), in which the situation of the new rule does not overlap with any exisiting situation, makes the insertion of new rules a simple matter of appending them to the theory table. The names of the situation and action are then given to the system with definitions, and the updating is completed.

Cases (2) and (3) are much more general and common, for there will often be some overlap between new situations and existing ones. The program must decide whether the overlap is interesting or substantial enough to warrant the extra work of reshuffling all the rules in order to insert the new one. It may decide that the situation is essentially a new one, in spite of some pieces of the situation appearing elsewhere. In this case it treats the rules as a case (1) rule and merely appends it to the table. This saving in processing at update time carries a corresponding cost in duplication of some parts of the rule. But the results of executing the rules will be the same in either case, with very little difference in execution time.

It is desirable to have the program nest rules some of the time, however, for reasons of conceptual clarity. If a new and an old rule describe exactly the same situation, for example, it inflates the theory needlessly to separate them as (i) S --> A1, and (ii) S --> A2. What we want is one rule of the form S --> A1&A2. Duplication of situations represents an extreme case of overlap which is also easy for the program to handle, once it

recognizes the duplication. It merely puts the second action
into the action list of the old situation. Care is necessary, of
course, to maintain independence of the actions so that they can
be executed in any order with the same result.

Work on updating the theory has progressed this far. New rules
can be added if the overlap with situations of existing rules
either is null or the program decides it is insignificant. Or, a
new rule can be added if the new situation is a duplicate of an
old one. For the other cases, the general forms of (2) and (3),
there is both the difficulty of finding the appropriate place to
insert the non-overlapping pieces of the situation and the
non-overlapping pieces of the action, and the the difficulty of
deciding which of several rules should be updated to incorporate
the new one.

V. CONCLUSION

The Meta-DENDRAL program described here is a vehicle for studying
problems of theory formation in science. It is built upon the
concepts and programmed routines already available in the
Heuristic DENDRAL performance program, which uses a scientific
theory to explain analytical data in organic chemistry. The
Meta-DENDRAL system goes beyond the performance program, however,

in attempting to formulate the theory which the performance
program will use.

The Meta-DENDRAL program works much like a chemist who is
extending his theory of mass spectrometry by looking at
collections of experimental results. The data, for both the
chemist and program, are mass spectra and the associated
molecular structures. By selecting some "typical" examples,
first-order general hypctheses about the whole collection of data
can be proposed. Then, by subsequent adjustments, the
generalizations are modified tc explain all the data. The new
generalizations are then integrated into the existing corpus of
theoretical statements in ways dictated by considerations of
simplicity and personal preference.

The first version of the Meta-program, which is described here,
suggests that the design is workable. But it accentuates the
arbitrariness of our design decisions and raises the questions of
what alternative designs would look like and how good they would
be. It also raises a number of issues important to understanding
scientific methodclogy in general. The design question is
certainly one such issue. Others are questions concerning the
criteria of acceptable generalizations, criteria of good
scientific theories, and criteria for deciding on a set of
primitive concepts for a theory. None of these general issues
will be resolved satisfactorily in the context of this program.

Yet none can be resolved for this program without saying
something about the general solutions.

APPENDIX A.

PRIMITIVE CONCEPTS OF MASS SPECTROMETRY

KNOWN TO THE DENDRAL PROGRAM

This list is taken from an outline given to chemists who define
new mass spectrometry rules for the system. The functions at the
front of the list are most primitive, those at the end are more
complex, and in fact are built out of the simpler ones. The
starred functions perform "housekeeping" on electrons and charge,
without the chemist having to handle these details explicitly.

To the chemist this list serves as a reminder of the names and
associated syntax of the "building blocks" available to him for
defining new rules. To the present reader it is meant to
illustrate the concepts already programmed into the system.

FUNCTION	ARGUMENTS	DESCRIPTION

HOUSEKEEPING FUNCTIONS:

ADDCHARGE	atm	Assign a positive charge to atm.
ADDDOT	atm	Assign a free electron to atm.
IONIZE	atm	Assign a dot and a charge to atm.
PAIRELECTRONS	list;nolist	Look among the atoms of LIST for adjac< atoms with free electrons. Pair up th< electrons to make an explicit bond unl< the pair is named in NOLIST.
REMOVECHARGE	atm	Take away the positive charge from atm
REMOVEDOT	atm	Remove the dot (if present) from atm

FUNCTIONS FOR MANIPULATING STRUCTURE WITHOUT HOUSEKEEPING:

```
ADDH               atm              Put a hydrogen on atm.
CHANGEBOND         atm1;atm2;n      Add n (pos. or neg.) to the order of th
                                    atm1-atm2 bond.
JOINATOM           oldatm;atm;bond;atomtype;nodenum;
                                    Bring atm into the structure -- attach
                                    to oldatm with bond order BOND.  Give a
                                    the atom type and node number specified
REMOVEBOND         atm1;atm2        Remove the bond between atm1 and atm2.
REMOVEH            atm              Take a hydrogen off atm.
```

STRUCTURAL MANIPULATION FUNCTIONS WITH HOUSEKEEPING:

```
BREAKBOND      *   atm1;atm2        Replace the atm1-atm2 bond with a
                                    pair of electrons.
                                    Try to pair any other free electron
                                    with one of the new free electrons.
BREAKRING      *   atm1;atm2        Do the same as BREAKBOND when it is
                                    certain that the atm1-atm2 bond is in
                                    a ring.
ELIMINATEH     *   atm              Eliminate a hydrogen from atm, leaving
                                    a free electron.
LOSEALPHARAD   *   atm              Lose the largest radical alpha to atm.
LOSENEXTRAD    *   atm              Lose the largest radical adjacent to at
MAKERING       * atm1;atm2;bond     Join atm1 & atm2 with bond to form a ri
MIGRATEH       *   atm1;atm2        Move a hydrogen from atm1 to atm2, leav
                                    a free electron on atm1 (unless atm1 =
                                    ANYATOM, in which case the H comes from
NCLEAVAGE      *   n,pct            Break the nth bonds away from
                                    the heteroatoms in the molecule
                                    and assign intensity=pct*oldint/100.
                                    If n is 0 or (quote adjacent), the
                                    adjacent bonds are broken, 1=(quote alp
                                    2=(quote beta), 3=(quote gamma).
NEWBOND        *   atm1;atm2        Replace adjacent free electrons on atm1
                                    with an explicit bond.
```

FUNCTIONS FOR CARRYING OUT COMPLEX REARRANGEMENTS:

```
AMINERR        *   atmlst           Migrate an H to node 2; Change bond bet
                                    nodes 1 & 2 (+1); Break bond between 2-
COELIM         *   atmlst           Breakbond between 3 & 2.
CO2ELIM        *   lst              Breakbond between 4 & 3.
ELIM           *   lst              Remove an H from node 1; breakbond betw
ELIM1          *   lst              Eliminate an H from node 2.
MRRFGT         *   lst              Change bond between nodes 1 & 2 (-1);
                                    Migrate an H from node 6 to node 2;
                                    Change bond between nodes 1 & 4 (+1);
                                    Break bond between nodes 4 & 5.
```

FUNCTIONS FOR HIGHER-LEVEL MASS SPECTROMETRIC PROCESSES:

ALLCLEAVAGES   *   nil   Break each bond in the molecule (MOLAT
                                   and return a list of masses of fragmen
                                   each consed to intensities calculated
                                   MSTHEORY. (This is the default functi
                                   to be called when no functional groups
                                   be identified.)

LOSENEXTRAD   *   atm   Lose the largest radical next to atm.

MAJORALPHACLEAVAGE * nil   Consider all bonds alpha to the first
                                   in ATMLST and break the one which lose
                                   largest radical.

MCLAFFERTY   *   nil   Find which McLafferty Rearrangements
                                   will occur (single, dbl, two dbl)
                                   and do them.

MINORALPHACLEAVAGES * nil   Consider all bonds alpha to the first
                                   heteroatom in ATMLST and break each on
                                   except the major.

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