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COMPUTER-AIDED DECISION MAKING IN PHARMACEUTICAL RESEARCH

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ABSTRACT

A description of a computer-aided decision making methodology, called the Analytic Hierarchy Process (AHP), is presented. The method was developed by Thomas Saaty over three decades ago to handle a variety of business-oriented decision making activities. The AHP is a flexible methodology that allows both subjective and objective data to be considered in a decision process. Moreover, it is intuitive and relatively easy to understand the way in which decisions are made. Although many business-related applications have been carried out over the years, very few science-based applications currently exist. In addition to a description of the basic methodology an example from drug-discovery research, namely biological target selection, will be presented as an illustration of how the AHP methodology can be applied in pharmaceutical research. A brief mention of other possible applications will also be provided.

INTRODUCTION

Decision making methodologies have been applied in a broad range of situations for many years. Most applications to date have been in business-related activities. This is necessitated by the number and complexity of the issues that bear upon many business decisions. Significant advances in computer software and hardware have also played a major role by providing the "computer power" necessary to treat decision problems more realistically. In pharmaceutical research, especially in large pharmaceutical companies where many projects are going on simultaneously, many of the same types of decision problems exist. However, in contrast to other business areas, decision theoretic approaches are essentially non-existent. One of the

reasons for this may be the perceived difficulty of properly formulating research-based decision problems, which involve both *quantitative* and *qualitative* variables. Moreover, the reasoning behind decision-theoretic methodologies and the results obtained from them are often non-intuitive and difficult to understand.

In the seventies Thomas Saaty developed a decision-theoretic methodology, called the *Analytic Hierarchy Process*, that is relatively simple conceptually and thus, may be more suitable to research-based decision problems. Details of his methodology were described in his first book (1). The AHP represents a fundamental approach that is based upon pairwise comparisons, is designed to cope with both the *rational* and *intuitive* aspects of a decision problem, and is capable of selecting the best alternatives with respect to a number of competing criteria. Import-antly, the AHP allows for inconsistencies in judge-ments and affords a means for improving consistency. Table 1 provides a brief listing of the some the types of decision problems that the AHP has been applied to. A number of books by Saaty and others (2,3,4,5) describe numerous types of applications with examples. More recently Saaty has generalised his theory to deal with dependence and feedback (6). Interestingly, very few applications in chemical and biological research have appeared.

Table 1. A sample of the breadth of AHP applications.

Architectural Design	Technological Choices
Conflict Resolution	Marketing Strategies
Performance Evaluations	Pricing Strategies
Student Admissions	Environmental Decisions
I/O Analysis	Cost-Benefit Analysis
Economic Forecasting	Transportation Systems
Oil Prospecting	Musical Compositions
Selection of Bridge Type	Movie Criticism

The AHP, as its name implies, deals with decision problems that can be structured hierarchically. Figure 1 depicts a simple three-level hierarchy. As is seen from the figure, the 'Goal' is evaluated with respect to the three 'Criteria' that each subsume the entire set of 'Alternatives.' The relative importance or ranking of each criterion to the decision goal is determined from pairwise comparisons among the criteria. Pairwise comparisons are based upon *relative* measurements that characterise the 'dominance' of one criterion with respect to another. As it is used here, 'dominance' is taken as a generic term that characterises the

dominance, importance, desirability, likelihood, or whatever term is appropriate, of one criterion over another.

Many of the criteria dealt with in type of decision problems illustrated in this work are *intangible* and hence, their relative measurements are largely subjective.

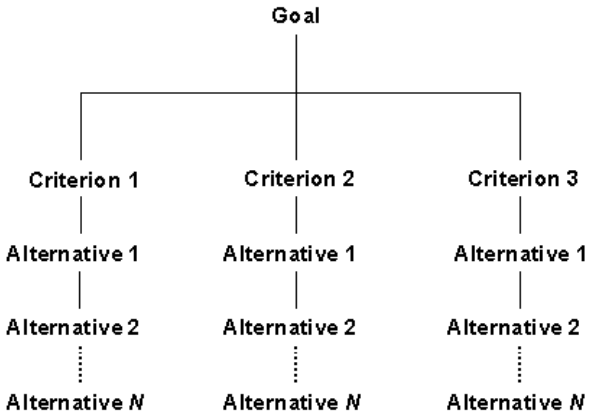

Figure 1. Example of a simple hierarchy consisting of a goal, three subordinate criteria relevant to the goal, and the *N* alternatives with respect to each of the criteria.

For example, in selecting a target for drug discovery in a large pharmaceutical company (*vide infra*), how important is 'Unmet Medical Need' compared to the company's 'Intellectual Property' with respect to the target?

While this may seem a bit like comparing 'apples' to 'oranges', it is something that humans do, subjectively, all of the time. Psychologists have studied such comparative assessments for many years and have determined that humans can only effectively handle about nine levels or gradations in making subjective, comparative assessments (7), as summarised in Table 2.

Table 2. The Fundamental Scale (7).

Intensity of Importance	Definition	Explanation
1	Equal Importance	Two activities contribute equally to the objective
2	Weak	
3	Moderate Importance	Experience and judgement slightly favour one activity over another

In addition, a *reciprocal relationship* exists such that if, for example, bioactivity is deemed to be twice as important a criterion as, say, solubility, then solubility must be only half as important as bioactivity. All of the pairwise comparisons among the criteria are elements of the pairwise comparison matrix or simply the *comparison matrix* (see *e.g.* Eq. (1)). The values of the components of the *principal eigenvector* of the comparison matrix are all positive and correspond, with suitable normalisation, to the relative ranking of the criteria, which sum to

unity. Thus, the relative ranking is a linear order that is generated from a set of pairwise comparisons.

The decision 'Alternatives,' on the other hand, are ranked with respect to each criterion using an absolute measurement scale appropriate to that criterion. For example, 'very high,' 'high,' 'medium,' 'low,' and 'very low' represent a possible scale, which could be given values 4, 3, 2, 1, 0, respectively. As has been noted by many cognitive psychologists this is well within the range of nine levels that humans can effectively discriminate (1,2,3). The final decision is achieved by weighting the result obtained for a given alternative by the relative ranking of the corresponding criterion and then summing over the three criteria. Each alternative is then placed in an ordered list with respect to its overall "score". Importantly, computing the score for a new alternative can be carried out independently of all other previously scored alternatives, which is a significant benefit when large numbers of alternatives are being considered as illustrated by the example described in this work. In many applications, alternatives are treated in an analogous fashion to criteria (*vide supra*), that is the alternatives are directly compared to each other and not to an absolute scale, but such comparisons are inappropriate in most of the types of research applications of AHP considered here. This is because in an absolute scale each alternative is evaluated separately. Adding a new alternative does not influence the values associated with any of the alternatives considered previously, and does not change their rankings relative to on another. However, the new alternative can, depending upon its value, be inserted anywhere in the previously ranked list of alternatives. This is quite advantageous in many of the types of situations in pharmaceutical research where computer-aided decision making may play a role.

The basic methodology will be presented in the METHODOLOGY section, followed in the RESULTS AND DISCUSSION section by an example based on selecting a "biological target" for drug discovery. The final section - CONCLUSIONS AND FUTURE WORK - provides a summary of the material and draws several conclusions regarding the applicability of the AHP approach to decision making in pharmaceutical research. All of the work presented here was carried out with the software product *EXPERTCHOICE2000*™ (8).

METHODOLOGY

As has been noted above, pairwise comparison is a key element of AHP methodology. A comparison matrix, **A,** is used to determine the relative dominance, order, importance, priority,

likelihood, etc. among a set of n criteria $\{C_1, C_2, ..., C_n\}$. Each element of **A,** $a_{i,j}$, is obtained by comparing criteria according to an appropriate scale: $a_{i,j}$ corresponds to how much the i-th criterion is 'favoured' over the j-th criterion. Because of the reciprocal property of these comparative judgements $a_{i,j}=1/a_{j,i}$ so, for example if $a_{i,j}=3$, then $a_{j,i}={}^1/_3$. The comparison matrix is a positive, reciprocal matrix and is as shown in eigenvalue form in Eq. (1)

$$\begin{bmatrix} 1 & a_{1,2} & \dots & a_{1,x} \\ a_{1,2}^{-1} & 1 & \dots & a_{2,x} \\ \vdots & \vdots & \ddots & \vdots \\ a_{1,x}^{-1} & a_{2,x}^{-1} & \dots & 1 \end{bmatrix} * \begin{bmatrix} w_1 \\ w_2 \\ \vdots \\ w_x \end{bmatrix} = \lambda_{max} * \begin{bmatrix} w_1 \\ w_2 \\ \vdots \\ w_x \end{bmatrix} \quad (1)$$

where λ_{max} is the principal eigenvalue, $[w_1, w_2, ..., w_n]^T$ the principal eigenvector, and 'T' represents the transpose. Because **A** is a *positive*, *reciprocal matrix* the components of its principal eigenvector are all positive (1,2,4,6) and in this work are normalised in either of two ways:

$$\overline{w}_i = \frac{w_i}{\sum_{j=1}^{n} w_j} \Rightarrow \sum_{j=1}^{n} \overline{w}_j = 1 \quad (2a)$$

or

$$\hat{w}_i = \frac{w_i}{\max(w_1, w_2, ..., w_n)} \Rightarrow \text{where } \hat{w}_i = 1 \text{ if } w_i = \max(w_1, w_2, ..., w_n) \quad (2b)$$

The normalised weights correspond to the relative dominance, importance, priority, likelihood, etc. of each criterion.

An important issue with respect to the comparison matrix is its *reciprocal consistency*, which involves the reciprocal relationship: if $a_{i,j}>1$, then $a_{j,i}<1$. In words, if i-th criterion dominates the j-th criterion, then the j-th criterion cannot also dominate the i-th criterion. This type of consistency is simple to enforce. A more complex form of consistency is *transitive consistency*, namely that $a_{i,j} \cdot a_{j,k}=a_{i,k}$. Again in words, if the i-th criterion dominates the j-th criterion by a factor of, say three, and the j-th criterion dominates the k-th criterion by a factor of, say one-half, then for transitive consistency the i-th criterion must dominate the k-th criterion by a factor of $3 \cdot {}^1/_2 = {}^3/_2$. Transitive consistency is the most difficult to achieve in practice but can be approached by a careful analysis of the comparative judgements made. As will be seen below, the inconsistency index, I, provides a useful measure of transitive consistency.

Taking the unnormalised components of the principal eigenvector form an 'adjusted' comparison matrix, **A′**, using their ratios. Thus each element of **A′** is in this case given by $a'_{ij}=w_i/w_j$. A little algebra shows that the principal eigenvector of the 'adjusted' comparison matrix is identical to that of the original comparison matrix and that the eigenvalue is equal to the number of criteria n, as shown in Eq. (3).

$$\begin{bmatrix} \frac{w_1}{w_1} & \frac{w_2}{w_2} & \cdots & \frac{w_1}{w_n} \\ \frac{w_2}{w_1} & \frac{w_2}{w_2} & \cdots & \frac{w_2}{w_n} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{w_n}{w_1} & \frac{w_n}{w_2} & \cdots & \frac{w_n}{w_n} \end{bmatrix} * \begin{bmatrix} w_1 \\ w_2 \\ \vdots \\ w_n \end{bmatrix} = n * \begin{bmatrix} w_1 \\ w_2 \\ \vdots \\ w_n \end{bmatrix} \tag{3}$$

It can be shown (2,6) that $\lambda_{max} \geq n$, so that as $\mathbf{A} \rightarrow \mathbf{A}'$, that is as **A** becomes more transitive consistent, $\lambda_{max} \rightarrow n$. Thus, one measure of consistency is

$$\mathrm{I} = \frac{\lambda_{\max} - n}{n-1} \text{ , where I } \geq 0 \tag{4}$$

which is somewhat reminiscent in form to sample variance.

Consider the set of alternatives $\{A_1, A_2, ..., A_n\}$ and the matrix **R** of alternatives ranked with respect to each of the n criteria $C_1, C_2, ..., C_n$:

$$\mathrm{R} = \begin{bmatrix} A_1(C_1) & A_1(C_2) & \cdots & A_1(C_n) \\ A_2(C_1) & A_2(C_2) & \cdots & A_2(C_n) \\ \vdots & \vdots & \ddots & \vdots \\ A_m(C_1) & A_m(C_2) & \cdots & A_m(C_n) \end{bmatrix} \tag{5}$$

Ranking the alternatives with respect to the overall goal is obtained by weighting a given alternative by each criterion, *i.e.*, $w(C_k)$, and summing the result, which gives a linear form for the i-th alternative

$$A_i(G) = \sum_{k=1}^{n} w(C_k) \cdot A_i(C_k), \; i = 1, 2, ..., m \tag{6}$$

Alternatively, Eq. (6) can be written in matrix form:

$$\begin{bmatrix} A_1(C_1) & A_1(C_2) & \cdots & A_1(C_n) \\ A_2(C_1) & A_2(C_2) & \cdots & A_2(C_n) \\ \vdots & \vdots & \ddots & \vdots \\ A_m(C_1) & A_m(C_2) & \cdots & A_m(C_n) \end{bmatrix} * \begin{bmatrix} w(C_1) \\ w(C_2) \\ \vdots \\ w(C_n) \end{bmatrix} = \begin{bmatrix} A_1(G) \\ A_2(G) \\ \vdots \\ A_m(G) \end{bmatrix} \tag{7}$$

In the more general case of a multi-level hierarchy with numerous, 'nested' criteria, a multi-linear form results rather than the linear form given in Eq. (6) (2,6). The APPENDIX should be consulted for more details.

RESULTS AND DISCUSSION

Pharmaceutical research spans a wide range of activities from the initial selection of an appropriate drug target, to the identification and optimisation of a set of lead compounds, to studies of drug absorption, distribution, metabolism, excretion, and toxicity, usually called ADMET, to the various clinical phases. In principle, the AHP can be applied throughout this process, although such applications are extremely rare and are non-existent in drug discovery. The following provides a concrete example of how the AHP can be applied in drug discovery to target selection. As is seen in Figure 2, numerous decision subcriteria are grouped under the two main classes of decision criteria, namely 'Business Issues' and Scientific Issues.

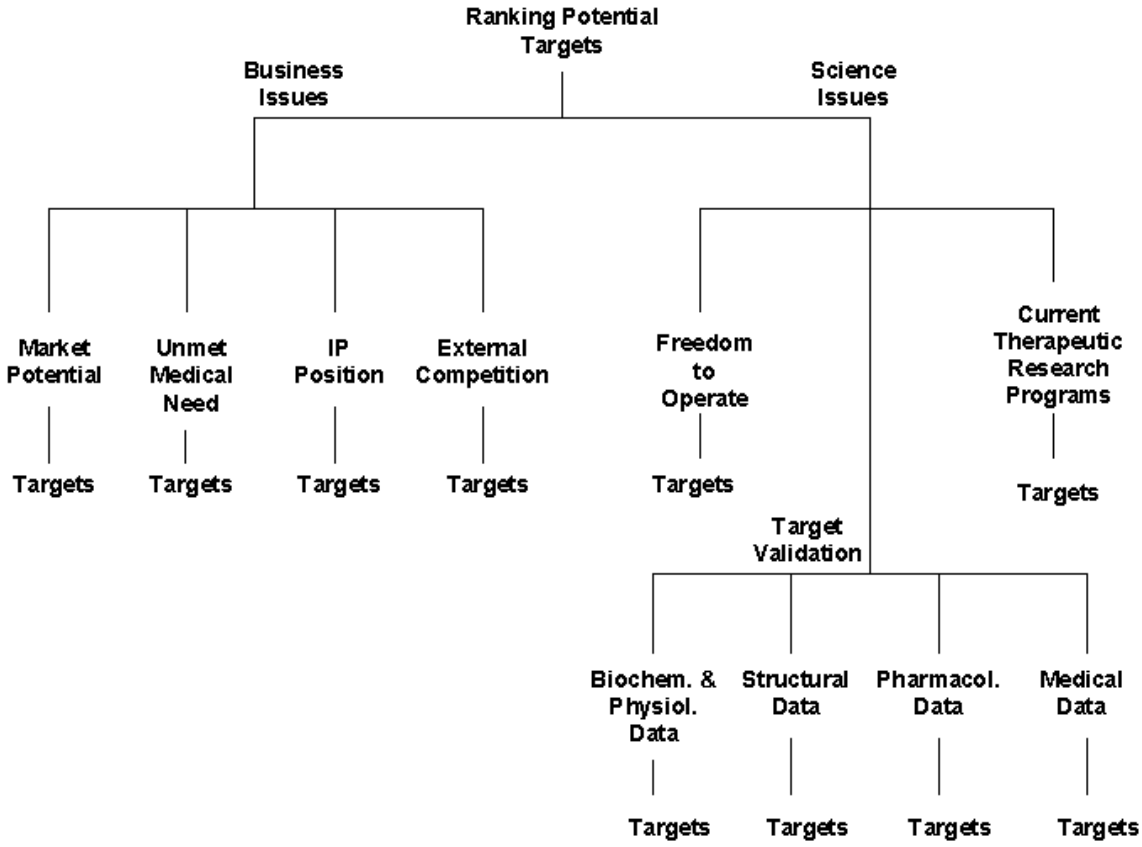

Figure 2. Hierarchy for ranking the suitability of biological targets (*e.g.*, enzymes, receptors,...). Note that "Targets" refers to the total set of targets considered, nine in the case examined in this work.

Business Issues are concerned with four major factors, Market Potential, Unmet Medical Need, Intellectual Property Position, and External Competition. As is clear from Figure 2 Scientific

Issues, namely Freedom to Operate, Target Validation, and Current Therapeutic Research Programs, have a more complex hierarchy in that Target Validation is further ramified into four subordinate decision criteria, namely Biochemical & Physiological Data, Structural Data, Pharmacological Data, and Medical Data. Importantly, the relative contribution of each of the criteria used to rank the possible targets (*i.e.*, alternatives) with respect to all of the business and scientific criteria, can easily be modified to assess their effect on the relative rankings at the various levels of the hierarchy. This is a type a sensitivity analysis that plays a crucial role in the decision process as will be seen in the sequel. It is also important to stress that this is only one possible view of the relevant business and scientific issues. In fact, the AHP is quite flexible and is well suited to assessing a large number 'what if' scenarios over many different sets of criteria and subcriteria.

First, consider comparative evaluation of the four criteria under Business Issues. Table 3 shows the relative importance attributed to each of the pairs of criteria making up the comparison matrix. The inconsistency index for this matrix is **I**=0.00, that is the comparative ratings of the criteria associated with Business Issues are internally consistent.

Table 3. Comparing Business Criteria.

	Market Potential	Unmet Medical Need	IP Position	External Competition	Priority Ranking
Market Potential	1	3/2	1	2/1	0.269
Unmet Medical Need	2/3	1	1/2	1/2	0.155
IP Position	1	2/1	1	1	0.288
External Competition	1/2	2/1	1	1	0.288

The priority rankings given in the last column of the table are the normalised components of the principal eigenvector, which indicate that IP Position and External Competition are most important followed closely by Market Potential, all three being significantly more important than Unmet Medical Need. As will be seen in the sequel, the comparative values can be easily adjusted and the impact of the adjustments on the overall rankings can be easily assessed. It is important to recognise that the methodology has tremendous flexibility and that both the criteria and their comparative values are subject to modification.

Analogously to Business Issues, the following comparative values make up the comparison matrix for Scientific Issues as shown in Table 4. Unlike for Business Issues, the comparative

ratings for the three criteria under Science Issues have an inconsistency index of **I**=0.10, which is near the upper bound of "acceptable" values for this index.

Table 4. Comparing Science Criteria.

	Freedom to Operate	Target Validation	Current Therapeutic Research	Priority Ranking
Freedom to Operate	1	3/2	1/2	0.221
Target Validation	2/3	1	2/1	0.460
Current Therapeutic Research	2/1	1/2	1	0.319

From the table it is clear that Target Validation is the most important criterion followed by Current Therapeutic Research and Freedom to Operate. Target Validation is obviously important as unvalidated targets would be less desirable than validated ones. However, consideration of the nature of the validation is also important. Thus, Target Validation is further ramified in an effort to address the relative importance of the different categories of validation, which will be discussed further below (see also Table 5). Current Therapeutic Research assesses how on-going research projects may impact the choice of new targets. This manifests itself in basically two ways, competition from on-going projects and an improved experience and knowledge base due to research that has been carried out in the area. In contrast to the case of Target Validation these two competing factors will not be explicitly considered, although to do so is quite simple, requiring only an addition level to the hierarchy subsumed under the Current Therapeutic Research category. Freedom to Operate is related to IP Position. IP Position focuses primarily on the patent status of bioactive compounds related to the target and whether there is sufficient room in chemistry space to discover and develop new compounds for the target. Freedom to Operate, on the other hand, focuses more on the patent status of the target itself as well as the related technologies needed to effectively carry out drug discovery research on the target.

A comparison of the criteria relevant to Target Validation are presented in Table 5.

Table 5. Comparing Target Validation Criteria.

	Biochem. & Physiol. Data	Structural Data	Pharmacol. Data	Medical Data	Priority Ranking
Biochem. & Physiol. Data	1	3/1	2/1	3/1	0.463
Structural Data	1/3	1	1	1	0.172
Pharmacol. Data	1/2	1	1	3/2	0.210
Medical Data	1/3	1	2/3	1	0.154

As was the case for Business Issues, the inconsistency index has a value of **I**=0.01, that is the comparative ratings are essentially fully consistent.

From the Priority Ranking column in the table it is clear that Biochemical & Physiological Data is the single most important decision criterion with respect to Target Validation, more than twice as important as any of the other criteria. As noted several times above, the results given in this table represent only one set of comparative judgements. In addition, other criteria may be added or some of the present criteria could be modified or eliminated. These are issues that must be dealt with by the decision makers who possess appropriate domain knowledge.

Global priorities for all of the criteria are given in Table 6**.** The mathematical expressions for computation of the global priorities are given in the Appendix. Note that these are in general multilinear rather than linear forms. Interestingly, Current Therapeutic Research is significantly more important than any of the other criteria. This is due to the complex chain of weightings from the different levels of the hierarchy, as shown in the Appendix.

Table 6. Global Priorities.

Criterion	Priority Rating
Current Therapeutic Research	0.213
Freedom to Operate	0.147
Biochem. & Physiol. Data	0.142
IP Position	0.096
External Competition	0.096
Market Potential	0.090
Pharmacological Data	0.064
Structural Data	0.053
Unmet Medical Need	0.052
Medical Data	0.047

To determine the overall target rankings it is necessary first to develop a *rating scale* for each of the targets with respect to each of the global priorities. Table 7 illustrates such rating scales for three of the criteria: Unmet Medical Need, External Competition, and Biochemical and Physiological Data. Typically, a rating scale assigns a numerical priority ranking to each object being ranked (targets in the present case) with respect to each of the relevant criteria. A qualitative description is associated with each priority ranking score. For example, under Unmet Medical Need the priority ranking of 1.00 is associated with the descriptive phrase “Very Large,” while the score of 0.25 is associated with “Small”. The use of such descriptive language to characterise how a given target is ranked with respect to a specific criterion facilitates the type

of qualitative reasoning that is essential in many decision making processes and is particularly useful here. Note that the largest priority value is one and that the priority values do not sum to unity. This is called the "Ideal" normalisation and is used in all of the rating scales in this study.

It is important to note that both the description and priority score should be relevant to the criterion being considered.

Table 7. Examples of Rating Scales.

Unmet Medical Need			External Competition			Biochem. & Physiol. Data	
Description	Priority		Description	Priority		Description	Priority
Very Large	1.00		None	1.00		Significant	1.00
Large	0.75		Weak	0.75		Reasonable	0.75
Moderate	0.50		Moderate	0.50		Small	0.50
Small	0.25		Strong	0.25		Very Little	0.25
Very Small	0.01		Very Strong	0.01			

Take for example the case of External Competition where the ordering of descriptions seems to be reversed from the typical ordering seen in Unmet Medical Need or in Biochemical and Physiological Data. In External Competition the description "None" corresponds to a priority value of 1.00, which is quite sensible here since the most desirable case would be one in which external competition is non-existent.

To determine the overall rankings for a specific target, each of the ten global priorities given in Table 6 is multiplied by its corresponding priority score for that target and the products are summed. The results for all nine targets are summarised in Table 8 (see next page), which shows the rank ordering of the targets and the ratings for each criterion. Target #2 is seen to be the highest ranked target and Target #9 the lowest ranked target - note that the ranking is again based upon the Ideal scale. The *relative ratings* (on the unit scale) of the five best targets is given in Table 9. These results have an overall inconsistency index of **I** = 0.02, which is quite good. From the table it is clear that the resulting rankings are reasonably close numerically, which begs the question of exactly how sensitive the final results are to the various choices of the scales and comparative judgements used in the decision model.

ExpertChoice2000™ provides a useful facility for exploring the sensitivity of the decision model to the choice of scales, comparative judgements among criteria, and the presence or absence of specific criteria. Several examples that illustrate the effect of modifying the relative weighting of various criteria on the overall goal of the decision process are provided in Figures 3-5.

Both plots in Figure 3 are concerned with the effect of modifying the four Target Validation variables-Biochemical & Physiological Data, Structural Data, Pharmacological Data, and Medical Data (see Table 5 for the weights and additional details).

Table 8. Rank ordering of the targets and the ratings for each criterion

Ideal Mode			**Ratings**									
Alternatives	Total		Market Potential	Unmet Medical Need	IP Position	External Competit.	Freedom to Operate	Biochem. & Physiol. Data	Structural Data	Pharmacol. Data	Medical Data	Current Therapeut. Research Programs
Target #2	0.741		Moderate	Moderate	Strong	None	Weak	Reasonable	Very Little	Reasonable	Small	Strong
Target #1	0.734		Large	Small	Moderate	Weak	Moderate	Significant	Small	Reasonable	Reasonable	Strong
Target #3	0.725		Very Large	Small	Strong	Strong	Moderate	Reasonable	Small	Significant	Significant	Strong
Target #4	0.685		Small	Large	Very Strong	Moderate	Weak	Significant	Reasonable	Small	Small	Modest
Target #5	0.665		Very Small	Very Large	Strong	Very Strong	Strong	Significant	Significant	Reasonable	Reasonable	Strong
Target #8	0.582		Moderate	Moderate	Very Weak	Moderate	Weak	Reasonable	Small	Reasonable	Small	Modest
Target #7	0.465		Large	Small	Weak	Weak	Weak	Small	Small	Very Little	Very Little	Weak
Target #6	0.431		Moderate	Small	Moderate	Weak	Very Strong	Reasonable	Reasonable	Small	Very Little	Weak
Target #9	0.385		Moderate	Moderate	Very Strong	Strong	Weak	Small	Very Little	Very Little	Very Little	None

Table 9. Relative ratings of five best targets.

Target Rankings	Relative Ratings
Target #2	0.211
Target #1	0.206
Target #3	0.203
Target #4	0.196
Target #5	0.184

In the upper panel the heights of the unfilled vertical bars correspond to the respective weights used in the current study, namely, 0.463, 0.172, 0.210, and 0.154, for the four variables (see the left-hand ordinate). The colored lines correspond to the normalised ratings of Targets #1–#5 with respect to each of the same four variables (see the right-hand ordinate). Ratings with a large spread of values, such as those associated with Structural Data, tend to be more sensitive than those with a small spread of values, such as Biochemical & Physiological Data, to changes in the relative weightings. The OVERALL values denote the target ratings with respect to Target Validation only.

Comparing the upper and lower panels of the figure clearly shows that by increasing the weight for Structural Data, the most sensitive variable, from 0.17 to 0.48 not only increases the general spread of the ratings values but, more importantly, causes a change in the order of target rankings. Changing the weighting of a less sensitive variable such as Biochemical & Physiological Data has a much smaller overall effect and does not change the ranking order.

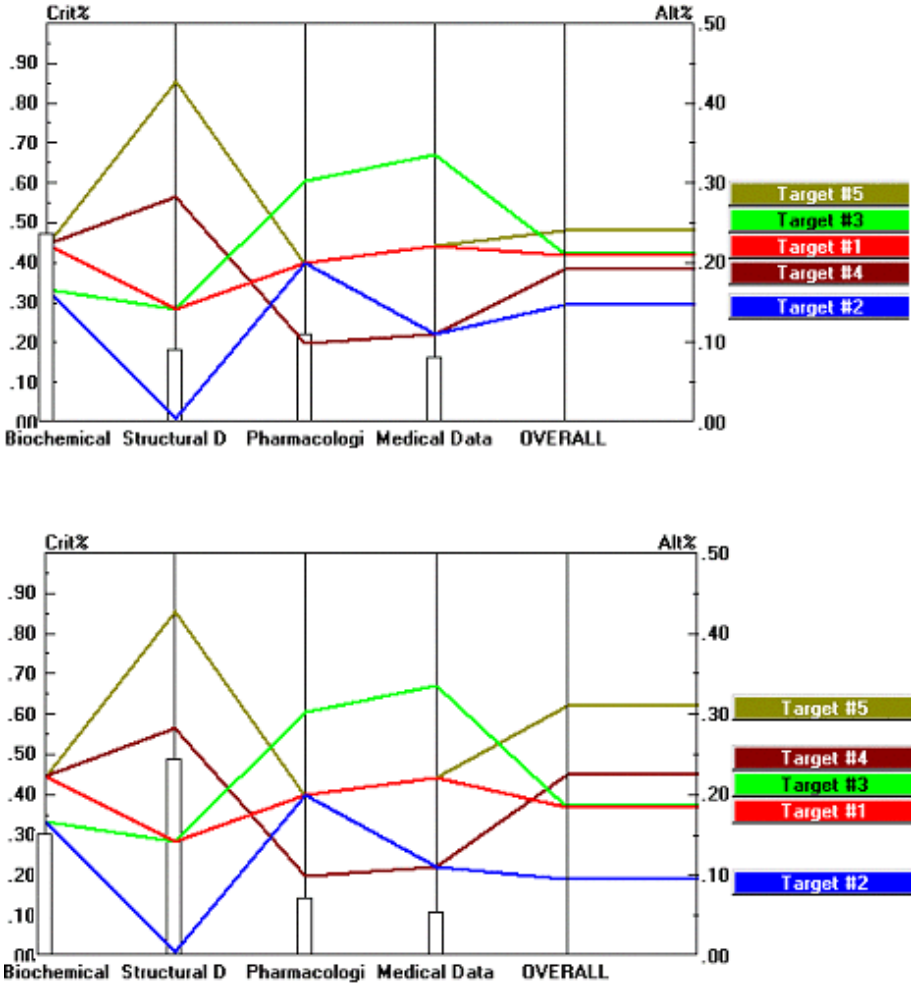

Figure 3. Sensitivity plots from *EXPERTCHOICE2000*™ showing the effect of changing the weighting of Target Validation variables - Biochemical & Physiological Data, Structural Data, Pharmacological Data, and Medical Data - on the overall target rankings. Consult the text for further details.

The upper panel in Figure 4 illustrates the sensitivity of the target rankings to changing the weightings of the four criteria associated with Business Issues - Market Potential, Unmet Medical Need, IP Position, and External Competition (see Tables 3 and 4 for additional details).

As was the case in Figure 3, the coloured lines indicate the relative ratings of the targets with respect to each of the business criteria (upper panel) and science criteria (lower panel), and the unfilled bars indicate their relative weights. Because it has the largest ratings spread, External Competition will have the largest effect on the overall target ratings with respect to Business

Issues, while Freedom to Operate will have a similar, but relatively smaller effect, on the over target ratings with respect to Science Issues.

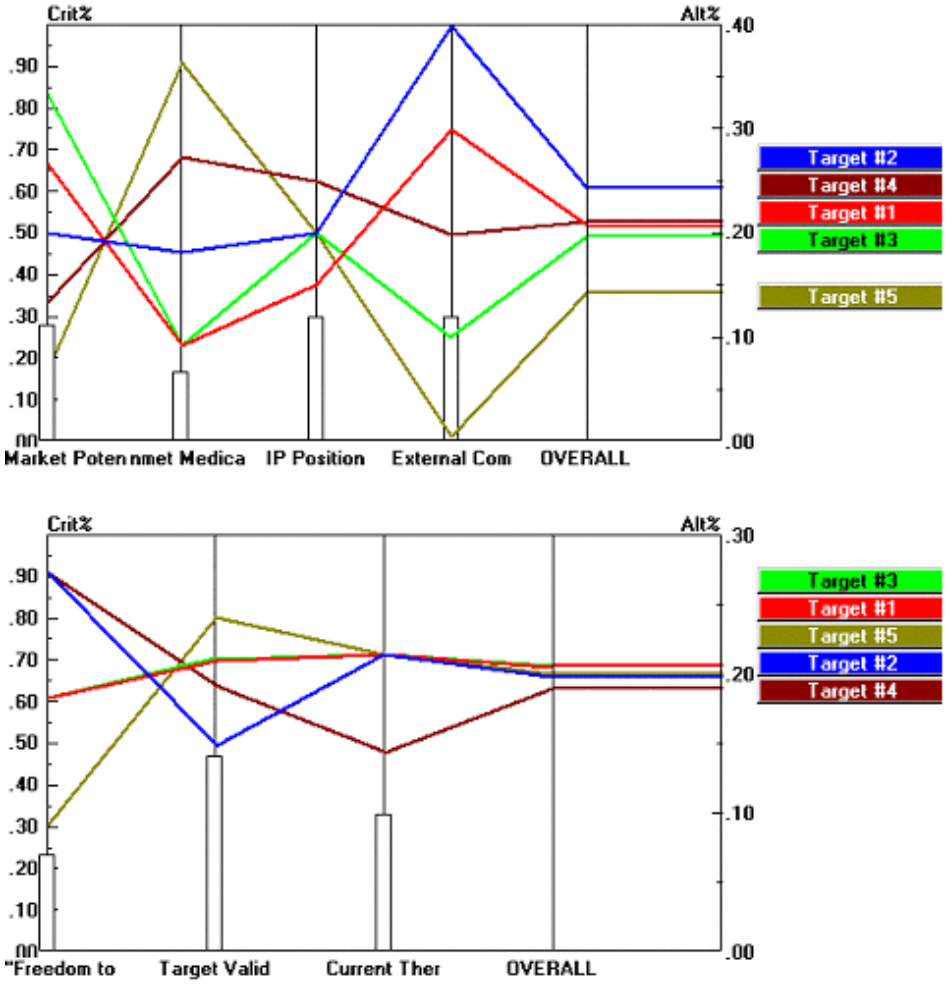

Figure 4. Sensitivity plots from *EXPERTCHOICE2000*™ illustrating the sensitivity of the four business-related issues (upper panel) and the three science-related issues (lower panel). Consult the text for further details

In the upper panel of the Figure 5 the unfilled vertical bars show the original weightings for Business Issues and Science Issues, 0.33 and 0.66, respectively. The coloured lines in the figure correspond to the values that the different targets have with respect to Business Issues and Science Issues. These values are appropriately modified by the weights for Business Issues and Science Issues and then combined to yield the OVERALL scores, which in this case are the final ratings and thus rankings of the different targets. The target rankings shown in colour correspond to the values given in Table 9. The lower panel of the figure shows the effect of modifying the weights so that Business and Science Issues are now of equal importance. As is seen in the figure, target rankings are unchanged although Target #1 is now ranked somewhat higher and Target #5 somewhat lower.

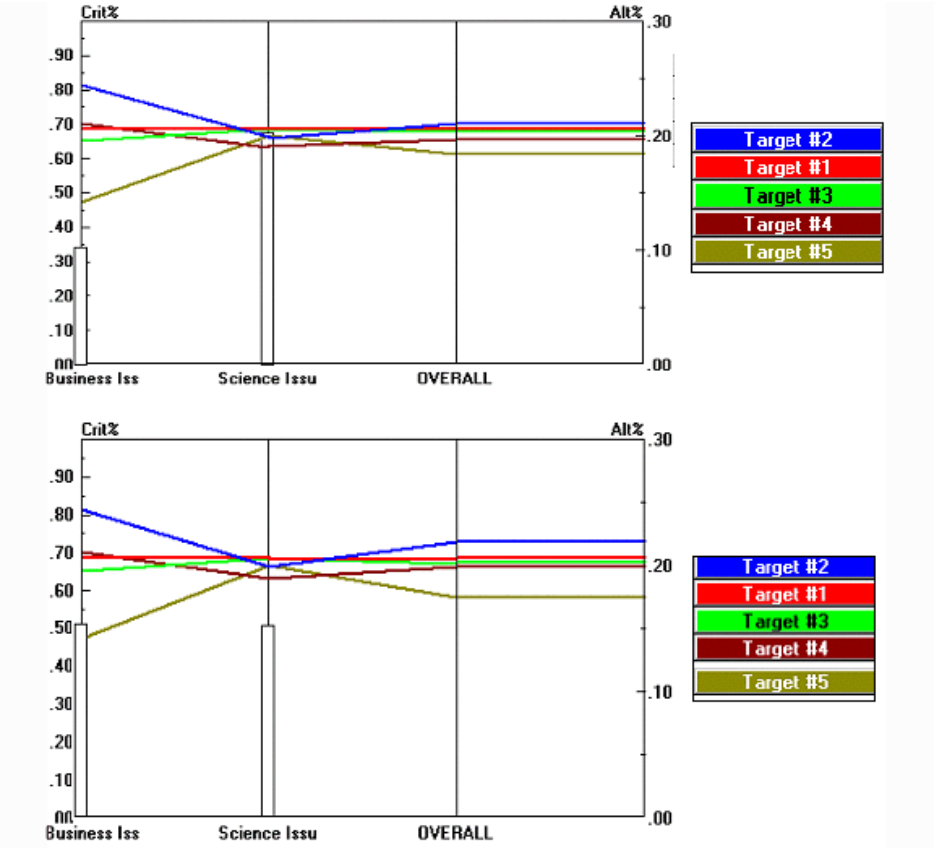

Figure 5. Sensitivity plot from *EXPERTCHOICE2000*™ showing the effect of changing the weighting of Business Issues with respect to Science Issues on the overall target rankings. Consult the text for further details.

The relative rankings of the other targets remain largely unchanged. To change the order of the rankings requires a significant distortion of the Business Issues to Science Issues ratio. Thus, the rankings are largely stable to perturbations of these weightings. This is not, however, the case with respect to other criteria, as was seen above, but this is not surprising given the narrower ratings spreads.

CONCLUSIONS AND FUTURE WORK

As research environments become more and more complex the need for computer-aided decision making methods will gain in importance. As seen in the present work, the AHP is a flexible decision-making tool that is capable of dealing with the types of subjective and objective data that are typically associated with many scientific decisions. Importantly, sensitivity analysis provides an appropriate means for assessing the robustness of a given decision model. It is also important to note that the usefulness and applicability of each decision model depends heavily on the domain knowledge of the decision makers. In fact, the results

afforded by any decision model built without appropriate domain knowledge are at best likely to be misleading and at worst likely to be entirely meaningless.

Although the example given above deals only with biological target selection, it contains many of the features found in other scientific decision processes, examples of which include: (1) assessing "molecular quality," (2) evaluating molecular docking software, (3) assessing biological promiscuity, and (4) assessing drug candidate status. An interesting possible application of the AHP methodology may be in assessing the performance of scientific research personnel. While such an application has not to my knowledge been carried out to date, many such assessments have been carried out in a number of business areas.

REFERENCES AND NOTES

[1] Saaty, T. L. (1980). *The Analytic Hierarchy Process.* McGraw-Hill, New York.

[2] Saaty, T. L. (1994). *Fundamentals of Decision Making and Priority Theory.* RWS Publications, Pittsburgh, PA.

[3] Saaty, T. L. & Vargas, L. G. (1994). *Decision Making in Economic, Political, Social, and Technological Environments.* RWS Publications, Pittsburgh, PA.

[4] Saaty, R. W. & Vargas, L. G. (Eds.) (1987). The Analytic Hierarch Process—Theoretical Developments and Some Applications. *Mathematical Modelling* **9**:161-395.

[5] Lootsma, F. A. (1999). *Multi-Criteria Decision Making Via Ratio and Difference Judgement.* Kluwer Academic Publishers, Dordrecht, The Netherlands.

[6] Saaty, T. L. (1996). *The Analytic Network Process—Decision Making with Dependence and Feedback.* RWS Publications, Pittsburgh, PA.

[7] See Table 3.1 in reference (2).

[8] *EXPERTCHOICE2000*, Expert Choice, Inc., Pittsburgh, PA, (2000).

APPENDIX

As noted by Saaty (1-4, 6), the hierarchical, weighted summations carried out in the AHP are not linear forms but are rather more complex mathematical objects called *multilinear forms*. This is illustrated by considering the hierarchy in Figure 2, which is shown again in Figure A1, where all of the explicitly designated decision criteria have been symbolically represented for mathematical convenience. Multilinear forms are constructed from the nested, weighted summations of linear forms such as those given in Eq. (6). This illustrated in Eq. (A1) for A_k (G), the value for the k-th alternative with respect to the overall goal in the hierarchy depicted in Figure A1,

$$A_k(G) = w(C_1)\sum_{i=1}^{4} w(C_i^1)\cdot A_k(C_i^1)$$
$$w(C_2)\left\{w(C_1^2)\cdot A_1(C_1^2) + w(C_2^2)\sum_{i=1}^{4} w(C_i^{22})\cdot A_k(C_i^{22}) + w(C_3^2)\cdot A_k(C_3^2)\right\} \tag{A1}$$

Expanding Eq. (A1) yields

$$\begin{aligned} A_k(G) = {} & w(C_1)\cdot w(C_1^1)\cdot A_k(C_1^1) + w(C_1)\cdot w(C_2^1)\cdot A_k(C_2^1) \\ & + w(C_1)\cdot w(C_3^1)\cdot A_k(C_3^1) + w(C_1)\cdot w(C_4^1)\cdot A_k(C_4^1) \\ & + w(C_2)w(C_1^2)\cdot A_1(C_1^2) \\ & + w(C_2)\cdot w(C_2^2)w(C_1^{22})\cdot A_k(C_1^{22}) + w(C_2)\cdot w(C_2^2)w(C_2^{22})\cdot A_k(C_2^{22}) \\ & + w(C_2)\cdot(C_2)\cdot w(C_2^2)w(C_3^{22})\cdot A_k(C_3^{22}) + w(C_2)\cdot w(C_2^2)w(C_4^{22})\cdot A_k(C_4^{22}) \\ & + w(C_2)w(C_3^2)\cdot A_k(C_3^2) \end{aligned} \tag{A2}$$

The multilinearity comes from the product weight terms terms such as $w(C_2)\cdot w(C_2^2)w(C_1^{22})$. Considering all of the A_k (G) terms, where k=1,2,...,n, yields n equations similar to Eq. (A2), which can be rearranged into the matrix equation shown in Eq. (A3) below

$$\begin{bmatrix} A_1(C_1^1) & A_1(C_2^1) & \cdots & A_1(C_1^{22}) & \cdots & A_1(C_3^2) \\ A_2(C_1^1) & A_2(C_2^1) & \cdots & A_2(C_1^{22}) & \cdots & A_2(C_3^2) \\ \vdots & \vdots & & \vdots & & \vdots \\ A_n(C_1^1) & A_n(C_2^1) & \cdots & A_n(C_1^{22}) & \cdots & A_n(C_3^2) \end{bmatrix} * \begin{bmatrix} w(C_1) * w(C_1^1) \\ w(C_1) * w(C_2^1) \\ \vdots \\ w(C_2) * w(C_2^2) * w(C_1^{22}) \\ \vdots \\ w(C_2) * w(C_3^2) \end{bmatrix} = \begin{bmatrix} A_1(G) \\ A_2(G) \\ \vdots \\ A_n(G) \end{bmatrix} \tag{A3}$$

This is identical in form to Eq. (7) except that the terms in the "weight vector" are multilinear rather than linear.

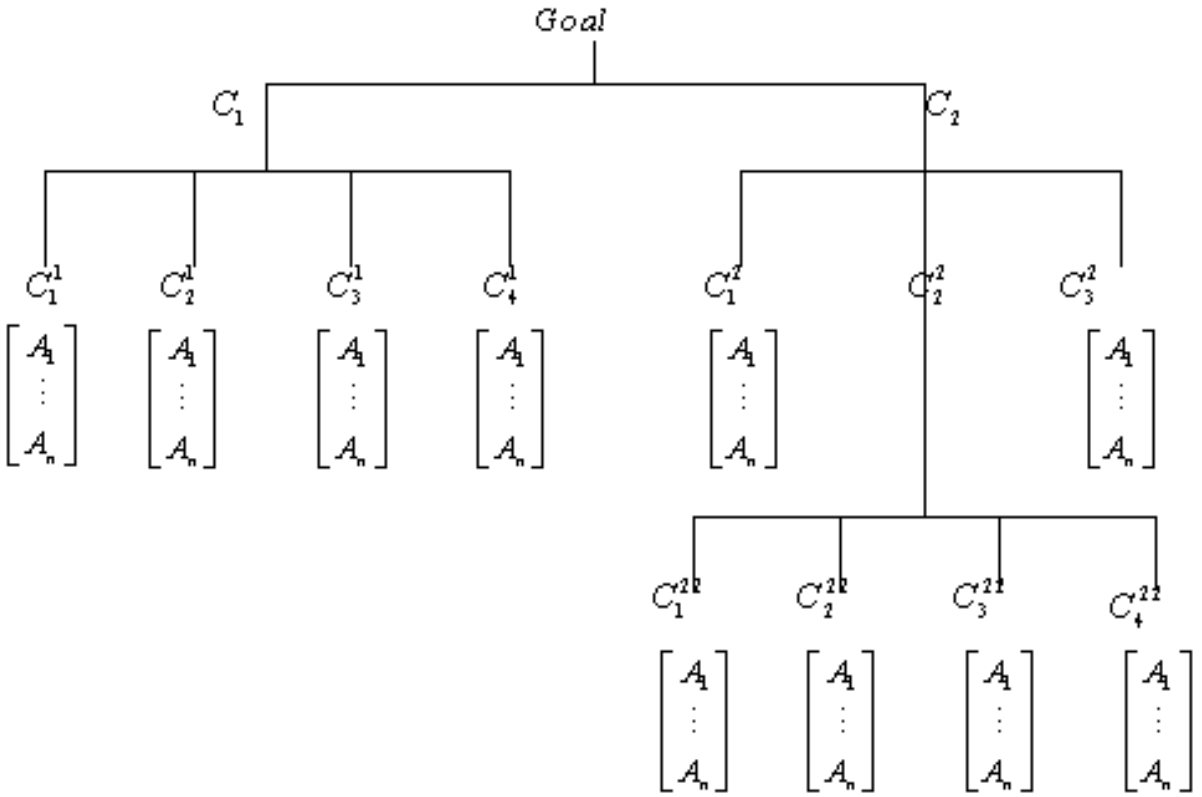

Figure A1. Target-assessment hierarchy identical to Figure 2 except that the designations have been replaced by mathematical symbols.