A Coordination Model for Enhancing Research on Rare Diseases

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The Problem

What a rare disease is.

In Europe a disease is considered *rare* if it affects no more than 5 individuals out of 10,000 people.

There exist in between 6,000 and 8,000 rare diseases which may affect 30 million of European Union citizens.

Medical products for prevention, diagnosis or treatment of this kind of disorders are called *orphan drugs*.

Research and development (R&D) of such drugs can have great costs.

Incentives to production.

In 2000 in Europe, the *Regulation on Orphan Medicinal Products* (following the *Orphan Drug Act* of 1983 in the United States) provided fee reductions and 10 years monopoly on the production of an orphan drug.

Our question.

How to enhance the research on rare diseases?

A Possible Solution: Coordination

The R&D assignment problem.

A set of companies allow a decision-maker to *coordinate* their R&D processes on a set of diseases (common and rare).

Formally, the setting is given by:

- a set $F = \{f_1, \ldots, f_n\}$ of n companies;
- a set $D = \{d_1, \ldots, d_m\}$ of m diseases;
- the maximum budget b_i of the firm i, $i = 1, \ldots, n$;
- the cost k_j and the profit g_j of the R&D on disease j, $j = 1, \ldots, m$;
- a preference profile $\succ_i$ for company i, $i = 1, \ldots, n$, on the set of diseases;
- a preference profile $\sqsupset_j$ for disease j, $j = 1, \ldots, m$, on the set of companies.

The Multiple Knapsack Problem (MKP)

- Integer linear programming problem introduced by Martello and Toth (1980).
- Given a set of objects and a set of knapsack, it consists in assigning the objects to the knapsacks (an object to only one knapsack) without violating capacity constraints and maximizing the total value of the selected items.
- We consider the MTM algorithm (Martello and Toth, 1980) to solve the problem.

The Multiple Knapsack Problem (MKP)

Given a set $M = \{1, \dots, m\}$ of items and a set $N = \{1, \dots, n\}$ of knapsacks, with $n \leq m$, let be

- p_j the *value* of item $j \in M$;
- w_j the *weight* of item $j \in M$;
- a_i the *capacity* of knapsack $i \in N$.

Let us assume:

(1) w_j, p_j, and a_i are positive integer numbers;

(2) $w_j \leq \max_{i \in N}\{a_i\}$, $j \in M$;

(3) $a_i \geq \min_{j \in M}\{w_j\}$, $i \in N$;

(4) $\sum_{j=1}^{m} w_j > a_i$, $i \in N$.

The Multiple Knapsack Problem (MKP)

The *0-1 multiple knapsack problem* (*MKP*) [6] consists in assigning the objects to the knapsacks (an object to only one knapsack) without violating capacity constraints and maximizing the total value of the selected items. Formally,

$$
\begin{array}{lll}
\text{maximize} & z = & \sum_{i=1}^{n} \sum_{j=1}^{m} p_j x_{ij} \\
\text{subject to} & & \sum_{j=1}^{m} w_j x_{ij} \leq a_i \\
 & & \sum_{i=1}^{n} x_{ij} \leq 1 \\
 & & x_{ij} \in \{0,1\} \quad i \in N, \; j \in M
\end{array}
$$

where

$$
x_{ij} = \begin{cases} 1 & \text{if item } j \text{ is assigned to knapsack } i \\ 0 & \text{otherwise} \end{cases}
$$

The College Admission Problem (CAP)

- Matching problem introduced by Gale and Shapley (1962).

- Given a set of colleges and a set of students, it consists in matching students to colleges taking into account their preferences to each other and without exceeding the quota of students each college can admit.

- We consider the algorithm proposed by Gale and Shapley (1962) to solve the problem.

The College Admission Problem (CAP)

Given C the set of colleges and S the set of students, a *matching* μ is a function from the set $C \cup S$ into the set of unordered families of elements of $C \cup S$ such that

1. $|\mu(s)| = 1$ for every $s \in S$ and $\mu(s) = s$ if $\mu(s) \notin C$;
2. $|\mu(c)| = q_c$ for every $c \in C$ and if $|\mu(c) \cap S| = r < q_c$ then $\mu(c)$ contains $q_c - r$ copies of c;
3. $\mu(s) = c$ if and only if s is in $\mu(c)$.

An assignment of applicants to colleges is called stable if it does not occur that there are two applicants s and t who are assigned to colleges A and B, respectively, although t prefers A to B and A prefers t to s.

A stable assignment is called optimal if every applicant is at least as well off under it as under any other stable assignment.

R&D Models

The MKP Model.

- Knapsacks are the firms: $N = F$
- Capacities are their budgets: $a = b$
- Objects are the diseases: $M = D$
- Values are their profits: $p = g$
- Weights are their costs: $w = k$

In this model, preferences are fixed: firms are only interested in monetary profits, diseases in being studied.

The CAP Model.

- Colleges are the firms: $C = F$
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Objective parameters (budgets, profits and costs) are not explicitely taken into account.

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Toy-Model

Basing on realistic data (see DiMasi *et al.* 2003, Gites *et al.* 2010, Grabowski 2005, Love 2003), we built the following model:

- $n = 2$ companies, f_I and f_{II} and $m = 6$ diseases, $d_1, \ldots, d_6$, among which d_1 to d_4 are common, d_5 and d_6 are rare;
- the budgets of the companies are $b = (1650, 2900)$;
- the costs k_j and the profits g_j of the diseases are:

$$\begin{array}{rcccccccc} k = & (& 950 & 1050 & 950 & 900 & 450 & 650 &) \\ g = & (& 55000 & 80000 & 10000 & 40000 & 300 & 800 &) \end{array}$$

- the preference profiles for the firms and the ones for the diseases are:

$$\begin{array}{llll} f_I: & d_2 \succ_I d_1 \succ_I d_4 & f_{II}: & d_2 \succ_{II} d_1 \succ_{II} d_4 \succ_{II} d_6 \succ_{II} d_3 \succ_{II} d_5 \\ d_1: & f_{II} \sqsupset_1 f_I & d_4: & f_{II} \sqsupset_4 f_I \\ d_2: & f_I \sqsupset_2 f_{II} & d_5: & f_I \sqsupset_5 f_{II} \\ d_3: & f_{II} & d_6: & f_{II} \sqsupset_6 f_I \end{array}$$

- Without coordination: $f_1 \longleftrightarrow d_2,\ f_{II} \longleftrightarrow d_2, d_1, d_4$

The MKP Solution

Branching Tree.

$U = 185800; L = 185300$

$$x = \begin{pmatrix} 0 & 1 & 0 & 0 & 1 & 0 \\ 1 & 0 & 1 & 1 & 0 & 0 \end{pmatrix}$$

$2 \longrightarrow f_I$

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MKP solution.

$f_I \longleftrightarrow d_1, d_6$

$f_{II} \longleftrightarrow d_2, d_3, d_4$

The CAP Solution

Gale-Shapley Algorithm.

1. d_2 and d_5 "visit" f_I, which could accept both of them but is not interested in d_5, then it chooses to accept only d_2;
   d_1, d_3, d_4 and d_6 "visit" f_{II}, which could accept no more than 3 of them and accepts d_1, d_4 and d_6 according to its preferences.

   At the end of the first step, the assignment is given by $(0,1,0,0,0,0)$ for f_I and $(1,0,0,1,0,1)$ for f_{II}.

2. d_3 "visits" f_I, which could accept one more disease but is not interested in d_3, so it decides not to accept it;
   d_5 "visits" f_{II}, which could accept no more diseases and decide not to change its current assignment because it prefers it to any other containing d_5 (which is its less preferred disease).

   At the end of the second step, the assignment is given by $(0,1,0,0,0,0)$ for f_I and $(1,0,0,1,0,1)$ for f_{II} and the algorithm stops (each non-assigned disease has "visited" all the firms).

CAP solution.

$f_I \longleftrightarrow d_2$

$f_{II} \longleftrightarrow d_1, d_4, d_6$

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CAP solution.

$f_I \longleftrightarrow d_2$

$f_{II} \longleftrightarrow d_1, d_4, d_6$

Solutions to the Toy-Model

Solutions.

Without coordination:	$f_I \longleftrightarrow d_2$	$f_{II} \longleftrightarrow d_2, d_1, d_4$
MKP solution:	$f_I \longleftrightarrow d_1, d_6$	$f_{II} \longleftrightarrow d_2, d_3, d_4$
CAP solution:	$f_I \longleftrightarrow d_2$	$f_{II} \longleftrightarrow d_1, d_4, d_6$

Discussion.

- Both the MKP and CAP solutions are more efficient.
- In particular, the MKP solution is the most efficient one, but gives "too much power" to the decision maker.
- The CAP solution "suffers" from the constraint given by the preferences and can provide non-feasible solutions.
- Both the solutions allows recovering one of the two rare diseases (d_6).

Concluding Remarks

- A greedy variation of CAP based on *marriage problems* has been implemented to recover the objective parameters.
- MKP is rooted in the idea of efficiency, but does not take into account preferences.
- CAP is strongly oriented into preferences, but can be inefficient.
- The greedy variation is in the middle, but also suffers from inefficiency.

- A collaboration with Ospedale Giannina Gaslini of Genova has recently started.

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