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Designing an Optimal Medicine Cocktail Is NP-Hard

Luc Longpré and Vladik Kreinovich

Abstract In many cases, a combination of different drugs – known as a medicine cocktail – is more effective against a disease than each individual drug. It is desirable to find the most effective cocktail. This problem can be naturally formulated as a problem of maximizing a quadratic expression under the condition that all the unknowns (concentrations of different medicines) are non-negative. At first glance, it may seem that this problem is feasible – since a similar economic problem of finding the optimal investment portfolio is known to be feasible. However, it turns out that the cocktail problem is different: it is NP-hard.

1 Formulation of the Problem

Need to find an optimal medicine cocktail. Nowadays, many people regularly take several different medicines. The ubiquity of this phenomenon shows that such combination is often more effective than taking a single medicine. However, sometimes, such combinations often lead to problems, since some medicines are incompatible, and this makes the resulting cocktail less effective. It is therefore desirable to find an optimal medical cocktail, a cocktail that is the most effective against the disease; see, e.g., [6].

Let us describe this problem in precise terms. Let us denote the number of appropriate medicines by n . To describe a cocktail, we need to describe the amounts $x_1 \geq 0, \dots, x_n \geq 0$ of all these medicines in the cocktail. The effectiveness E of a cocktail depends on these amounts: $E = E(x_1, \dots, x_n)$.

The amount of each medicine is usually reasonably small, so quadratic terms are much smaller than linear ones, cubic terms are much smaller than quadratic ones,

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etc. Thus, we can get a good approximation to the cocktail's effectiveness if we expand the dependence $E(x_1, \dots, x_n)$ in Taylor series and only retain the first few terms in this expansion.

The simplest case is when we consider only linear terms, i.e., when we consider a linear approximating expression

$$e_0 + e_1 \cdot x_1 + \dots + e_n \cdot x_n.$$

However, under this approximation, we do not get a realistic solution to our problem: the maximum is attained when for each i , the amount x_i is equal either to 0 (when the coefficient e_i is negative) or to infinity (when $e_i > 0$). So, to get a realistic description of the problem, we need to also consider quadratic terms in the Taylor expansion. In this case, we face a problem of maximizing the corresponding quadratic expression

$$e_0 + e_1 \cdot x_1 + \dots + e_n \cdot x_n + e_{11} \cdot x_1^2 + e_{12} \cdot x_1 \cdot x_2 + \dots + e_{1n} \cdot x_1 \cdot x_n + \dots + e_{nn} \cdot x_n^2 \quad (1)$$

under the constraints $x_i \geq 0$.

At first glance, it may seem that this problem is feasible. If we ignore the constraints $x_i \geq 0$, then maximizing a quadratic function is easy: we simply equate all n partial derivatives of the quadratic expression to 0. A derivative of a quadratic function is linear, so we get a system of n linear equations with n unknowns – and there exist efficient algorithms for solving such systems.

At first glance, it may seem that the presence of constraints should not lead to a drastic change in computational complexity. For example, in economics, a problem of optimal (least risky) portfolio of investments – pioneered by a Nobelist Harry Max Markowitz – reduced to minimizing a quadratic expression for risk under a linear constraint, and for this problem, feasible algorithms are well known; see, e.g., [1, 4].

What we show in this paper. In this paper, we show that this first impression is wrong, and that, in general – in contrast to the Markowitz optimal portfolio problem – the problem of finding the optimal medicine cocktail is NP-hard; see, e.g., [2, 3, 5].

Comments.

- Of course, we can feasibly solve the cocktail problem for small n . Indeed, once we know the set Z of all the variables x_i that are equal to 0, we can equate the derivatives with respect to remaining variables to 0 and solve the resulting system of equations. Thus, we can solve the cocktail problem by repeating this procedure for all 2^n sets $Z \subseteq \{1, \dots, n\}$, and selecting the solution with the largest effectiveness. This works for small n , but for reasonable-size n , the number of linear systems that we need to solve grows exponentially and becomes unfeasible very fast.

- The solution to a system of linear equation is a rational function of all the coefficients – indeed, it can be described, by Cramer’s Rule, as a ratio of two polynomials. Thus, if all the coefficients are rational, the values at which the maximum is attained are also rational, and thus, the largest value of the quadratic expression – if it is finite – is also a rational number.

2 Main Result

Proposition. *The following problem is NP-hard:*

- *Given: a quadratic expression (1) with rational coefficients e_i and e_{ij} , and a rational number r .*
- *Task: check whether the supremum of the expression (1) is smaller than r .*

Comment. This implies that computing the optimal values x_i – for which the expression (1) attains its maximum – is also NP-hard: if we knew these maximizing values, we would be able to compute the largest value of the expression (1) and thus, compare this value with the given threshold r .

Proof.

1°. By definition, a problem is NP-hard if every problem from the class NP can be reduced to this problem. Thus, if a known NP-hard problem can be reduced to our problem, then, by transitivity of reduction, we will be able to deduce every problem from the class NP to our problem – and hence, we will prove that our problem is also NP-hard.

2°. As a known NP-hard problem, let us consider the *subset sum* problem, where we are given positive integers s_1, \dots, s_m, S , and we need to find a subset of s_i ’s that add up to S , i.e., equivalently, to find the values $z_1, \dots, z_m \in \{0, 1\}$ for which

$$\sum_{i=1}^m z_i \cdot s_i = S,$$

where $z_i = 1$ if we select the i -th number and $z_i = 0$ if we don’t.

Let us show how each instance of the subset sum problem can be reduced to an appropriate instance of our problem. For this purpose, we consider the problem of maximizing the following quadratic expression with unknowns $x_1, \dots, x_m, x_{m+1}, \dots, x_{2m}$:

$$1 - \left(\sum_{i=1}^m x_i \cdot s_i - S \right)^2 - \sum_{i=1}^m x_i \cdot x_{m+i} - \sum_{i=1}^m (x_i + x_{m+i} - 1)^2. \quad (2)$$

Let us show that maximum of this function over all $x_i \geq 0$ is equal to 1 if and only if the original instance of the subset sum problem has a solution.

3°. Let us first prove that the maximum of the expression (2) is always smaller than or equal to 1.

Indeed, the above expression (2) is obtained by subtracting, from 1, a sum of non-negative terms. Thus, the value of this expression is always smaller than or equal to 1. Hence, the maximum of this expression is also smaller than or equal to 1.

4°. Let us prove that if the maximum of the expression (2) is equal to 1, then this maximum is attained for some values x_i .

Indeed, if for some i from 1 to m , the value x_i is greater than 2, then we would have $x_i + x_{m+i} - 1 \geq 1$, thus $(x_i + x_{m+i} - 1)^2 \geq 1$, and the expression (2) is smaller than or equal to 0. Thus, the values greater than 0 – that contribute to the maximum – are attained only for $x_i \leq 2$.

Similarly, we can conclude that to find the maximum, it is sufficient to only consider the values $x_{m+i} \leq 2$. So, to find the maximum, it is sufficient to limit ourselves to the box $[0, 2]^{2m}$. This box is a bounded closed set, thus a compact set. The expression (2) is a continuous function, and it is known that for every continuous function on a compact set, its maximum is attained at some point.

5°. Now, we can prove that if the maximum of the expression (2) is equal to 1, then the original instance of the subset sum problem has a solution.

If the maximum of the expression (2) is equal to 1, then, according to Part 4 of this proof, there exists values x_i for which this expression is equal to 1. Since the expression (2) is obtained by subtracting non-negative terms from 1, the fact that the value of this expression is equal to 1 means that all subtracted terms are 0s. In particular, this means that $x_i + x_{m+i} - 1 = 0$, i.e., that $x_{m+i} = 1 - x_i$. The fact that the product $x_i \cdot x_{m+i} = x_i \cdot (1 - x_i)$ is equal to 0 means that either $x_i = 0$ or $1 - x_i = 0$, i.e., that each x_i is equal either to 0 or to 1. In this case, the fact that

$$\sum_{i=1}^m x_i \cdot s_i - S = 0$$

means that the values x_1, \dots, x_m provide the solution to the original instance of the subset sum problem.

6°. To complete the proof of the proposition, it is sufficient to prove that if the original instance of the subset sum problem has a solution z_i , then the maximum of the expression (2) is equal to 1.

Indeed, the value of the expression (2) is equal to 1 when we take, for all i from 1 to m , $x_i = z_i$ and $x_{m+i} = 1 - z_i$.

The proposition is proven.

Comment. If the original instance of the subset sum problem does not have a solution, then the maximum of the expression (1) is not only smaller than 1, it is actually smaller than $1 - \delta$ for some $\delta > 0$. Let us find such δ .

Indeed, suppose that, for some $\delta > 0$, the expression (2) is larger than $1 - \delta$. This means, in particular, that each of the terms subtracted from 1 in this expression is bounded by δ . In particular, it means that $(x_i + x_{m+1} - 1)^2 \leq \delta$, i.e., that $|x_i + x_{m+1} - 1| \leq \sqrt{\delta}$, i.e., that

$$1 - x_i - \sqrt{\delta} \leq x_{m+1} \leq 1 - x_i + \sqrt{\delta}.$$

We also have $x_i \cdot x_{m+1} \leq \delta$. Let us consider two possible cases: $x_i \leq 1/2$ and $x_i \geq 1/2$. Let us take $\delta \leq 1/36$, then $\sqrt{\delta} \leq 1/6$. For $x_i \leq 1/2$, from $1 - x_i - \sqrt{\delta} \leq x_{m+1}$ and $\sqrt{\delta} \leq 1/6$, we conclude that

$$1/3 = 1 - 1/2 - 1/6 \leq 1 - x_i - \sqrt{\delta},$$

so $1/3 \leq x_{m+1}$ and thus, $1/3 \cdot x_i \leq x_i \cdot x_{m+1} \leq \delta$, hence $x_i \leq 3\delta$.

Similarly, if $x_i \geq 1/2$, then we get $1 - x_i \leq 3\delta$. In both cases, if we denote by z_i the integer closest to x_i – which is equal to 0 or 1 – we get $|x_i - z_i| \leq 3\delta$.

We also have

$$\left(\sum_{i=1}^m x_i \cdot s_i - S \right)^2 \leq \delta,$$

hence

$$\left| \sum_{i=1}^m x_i \cdot s_i - S \right| \leq \sqrt{\delta}.$$

From $|x_i - z_i| \leq 3\delta$, we conclude that

$$\left| \left(\sum_{i=1}^m x_i \cdot s_i - S \right) - \left(\sum_{i=1}^m z_i \cdot s_i - S \right) \right| \leq \sum_{i=1}^m s_i \cdot 3\delta,$$

so

$$\left| \sum_{i=1}^m z_i \cdot s_i - S \right| \leq \sqrt{\delta} + \sum_{i=1}^m s_i \cdot 3\delta.$$

If we use δ for which

$$\sqrt{\delta} + \sum_{i=1}^m s_i \cdot 3\delta < 1,$$

then we conclude that the absolute value of the integer

$$\sum_{i=1}^m z_i \cdot s_i - S$$

is smaller than 1, so this integer is equal to 0 – i.e., we have a solution to the original instance of the subset sum problem.

Since $\sqrt{\delta} \leq 1/6$, the inequality

$$\sqrt{\delta} + \sum_{i=1}^m s_i \cdot 3\delta < 1$$

will be guaranteed if

$$\frac{1}{6} + \sum_{i=1}^m s_i \cdot 3\delta < 1,$$

i.e., if

$$\sum_{i=1}^m s_i \cdot 3\delta < \frac{5}{6}$$

or, equivalently, if

$$\delta \leq \frac{5}{18 \cdot \sum_{i=1}^m s_i}.$$

For such δ , if the maximum of the expression (2) is greater than or equal to $1 - \delta$, then the original instance of the subset sum problem has a solution. Thus, if the original instance does not have a solution, then the maximum of expression (2) must be smaller than $1 - \delta$.

Discussion. So how come the optimal portfolio problem is feasible? The answer is that in the portfolio problem, the quadratic form is minus covariance matrix and is, thus, negative definite, so the maximized expression is concave, and concave optimization problems are feasible. In the cocktail problem, we can have a generic quadratic expression which is not necessarily negative definite.

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