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Covid-19 meets game theory: a proposed experiment

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Abstract

Researchers around the globe are searching for a "combo-drug" against Covid-19 by trying to combine various existing drugs. Given a set of such drugs, various algorithms (based, for example, on artificial intelligence) are used to identify the efficacy of different shares of the constituent drugs in the combo-drug. Namely, the relative weight of each drug in a "cooperative" scheme of therapy is sought-after. In the current note we propose to identify these weights using the theory of cooperative games, and in particular the Shapley value, one of the fundamental solution concepts of such games. We derive the weight of each drug by its (normalized) average marginal contribution over all possible "coalitions" of drugs it is used with, where a drug's marginal contribution to a coalition is defined as the increase in the coalition's probability to act against a virus should the drug become its "member". Hence we endow each drug with a consistent measure of significance (which is due to the consistency that Shapley value is associated with). At a theoretical level, we build the cooperative game, and compute the Shapley values, within a milestone model in drug combination theory, the Bliss independence model. At a practical level, the predictions of our game-theoretic model can be tested by using in-vitro experiments, namely experiments that are conducted in test tubes.

Keywords: Covid-19; combo-drug; Bliss independence; coalition; cooperative game; Shapley value

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1 Introduction

Covid-19 has impacted the lives of humans at unprecedented levels. As a result, the scientific community is devoting more and more of its resources trying to fight the virus. Can game theory contribute to this? The purpose of this short note is to suggest an area where the input of game theory, and in particular, cooperative game theory, could be of importance. The area is related to the design of optimal combinations of drugs that may jointly fight Covid-19.

In order to develop a therapy against Covid-19, a number of scientists have proposed the creation of a combo-drug that will be composed of various existing drugs at certain shares. Indicative examples of such attempts include Ianevski et al. (2020); Abdula et al. (2020); Hung et al. (2020), etc.¹ Some of the trials of the created drugs take place via in-vitro experiments. Namely, the researchers isolate a virus, place it in a controlled environment (a test tube) and then apply various drugs/treatments to it. Various algorithms are used to determine the optimal combination of drugs and the optimal share of each drug in the combination. For example, Abdula et al. (2020) use artificial intelligence methods to search within a 12 drug/dose parameter space and locate the optimal combination(s) against the coronavirus disease.

In other words, when trying to identify an optimal combination of drugs that act "cooperatively", the researchers essentially try to find the relative significance of each drug in the "cooperative" scheme. But this is reminiscent of a similar problem economists face when they want to identify the payoff of a player, and also his *significance*, in a given cooperative environment. Such environments are often analyzed via cooperative games, namely games in which agents form coalitions and allocate the resulting payoffs among themselves. A fundamental solution to the said problem is the *Shapley value* (Shapley 1953), which associates each player with the average of his marginal contributions to all possible coalitions he might join. The marginal contribution of a player to a coalition is the difference between the payoff of the coalition when the player is a member of it and its payoff when that player is not a member. Averaging all such contributions of a player certainly provides a proper measure of his significance in a cooperative scheme.

If we call a "combination of drugs" as a "coalition of drugs" and identify the payoff of each "coalition", then we essentially have a cooperative game in which we can define and compute the Shapley value of each player-drug. Then each drug's weight or significance in a combo-drug (which can be identified as the grand coalition) can be given by the drug's normalized Shapley value.²

Is the above of importance and should we be interested in it? The answer seems to be yes, at least theoretically, as the proposed index of "significance" of a drug takes into account all its co-effects relatively to all possible groups of the other drugs. Hence it is a proper measure of how important the drug is in a "cooperative" scheme of therapy. Of course this is not enough, because we are mainly interested in the practical implications of any proposal. To this issue we will return later on.

One key issue is to identify a theoretical framework in which we can base our cooperative game. To this end we adopt a reference model in the theory of drugs combination, the Bliss independence model (Bliss 1939). This model, which is very popular in the area, assumes that the effect of two or more drugs when used in combination has a simple additive structure (hence any further interactions among the drugs are assumed away). The model has a probabilistic basis: the joint effect of two or more drugs against a virus is modelled as the probability of at least one drug acting against it (Baeder et al. 2016). This probability is the joint *inhibition rate* of these

¹The number of such examples is large and we not plan to list them all here.

²The normalized Shapley value of a player is his Shapley value divided by the sum of the Shapley values of all players so as to have a share.

drugs, namely their ability to fight the disease when used together.

Using the above framework, we first posit the existence of a set of, say, n drugs, which are the agents of our game. We define the worth of any coalition of drugs, i.e., any subset of the set of n drugs, by its inhibition rate, following the logic of the Bliss model. Given this, we then compute the marginal contribution of each drug to all possible coalitions and derive its Shapley value and also its share in the (theoretical) combo-drug. The predicted shares turn out to be simple functions of the individual inhibition rates of the drugs, which provide the basis for an easy design of the combo-drug.

Our approach could have testable implications. The efficacy of a combo-drug designed via our theoretical method can be tested by the scientific community using in-vitro methods, namely experiments in test tubes. The set of all drugs to be used (or, in our terminology, the grand coalition) is to be decided, of course, by experts in the area who might be interested in performing such experiments. For example, independently of the current project, Said (2020) has suggested a set of drugs consisting of remdesivir, chloroquine and camostat mesylate;³ Abdula et al. (2020) focused, as we said earlier, on a set of twelve drugs, etc. Perhaps our theoretical design could provide an additional input on how to think about the interrelations among these (or other) drugs.

In what follows, in section 2 we first present the Bliss independence model. Then we derive the associated cooperative game and compute the Shapley values and the shares of the drugs in a theoretical combo-drug. The last section concludes.

2 The Bliss independence model and Shapley value

As a reference case, we first present the Bliss independence model for the two-drug case (Zhao et al. 2014; Demidenko and Miller 2019). Let drugs 1 and 2 inhibit a disease at some rates: when drug i is used alone at dose a_i , it inhibits the disease by $x_i = x_i(a_i)$, $i = 1, 2$. We set $x_i(a_i) \in [0, 1]$ and express the inhibition rate as a probability. The independence assumption states that the combined inhibition from the joint use of the two drugs is given by the probability that at least one drugs inhibits it. This is given by

$$x_1 + x_2 - x_1x_2 \quad (1)$$

If we instead had three drugs, namely 1, 2 and 3, their combined inhibition rate would be given by

$$x_1 + x_2 + x_3 - x_1x_2 - x_1x_3 - x_2x_3 + x_1x_2x_3, \quad (2)$$

which again gives the probability that at least one drug acts against the disease.

The generalization to the case of any number, n , of drugs is straightforward. Let $N = \{1, 2, \dots, n\}$ denote the set of drugs. Extending expressions (1) and (2) gives us an inhibition rate

$$\sum_{j \in N} x_j - \sum_{\substack{j, k \in N \\ j < k}} x_j x_k + \sum_{\substack{j, k, m \in N \\ j < k < m}} x_j x_k x_m - \dots + (-1)^{s+1} \prod_{j \in N} x_j \quad (3)$$

All the above allow us to define a cooperative game as follows. Take a set of drugs N and fix some initial levels of doses, say equal doses which means equal weights initially. Consider the corresponding individual inhibition rates $\{x_1, x_2, \dots, x_n\}$. From now on these rates are fixed. Let

³We refer the reader to <https://www.researchgate.net/post/Remdesivir-Chloroquine-and-Camostat-Mesylate-Combination-A-Potential-anti-SARS-CoV-2-Treatment>.

$S \subseteq N$ be a "coalition" of drugs. In accordance to the above, the worth of S , which we denote by $v(S)$, is

$$v(S) = \sum_{j \in S} x_j - \sum_{\substack{j, k \in S \\ j < k}} x_j x_k + \sum_{\substack{j, k, m \in S \\ j < k < m}} x_j x_k x_m - \dots + (-1)^{s+1} \prod_{j \in S} x_j \quad (4)$$

Expression (4) is the *characteristic function* of S , which is a function that specifies the worth or payoff of S . Hence, we identify the worth of a coalition by the inhibition rate produced by the action of all of its members. The worth of the grand coalition in particular, i.e., $v(N)$, is given by (3); finally we use the standard convention $v(\emptyset) = 0$. All these result in a cooperative game which we denote by (N, v) , i.e., an entity consisting of the set of all agents, and the characteristic function of each coalition.

Recall next that the Shapley value allocation (Shapley 1953) is the unique allocation of $v(N)$ that satisfies the axioms of efficiency (all of $v(N)$ is used), symmetry (similar players are rewarded similarly), null player (a player who contributes nothing to every coalition that he joins, gets no reward) and additivity (the sum of the rewards of a player in two different games equals his reward in the game that results by adding the characteristic functions of the two games). The Shapley value allocation gives each player the average of his marginal contributions to all possible coalitions he joins, where by marginal contribution of i to a coalition we define the difference between what the coalition achieves with i and without i in it.

The marginal contribution of $i \in S$ to coalition S is given algebraically by $v(S) - v(S \setminus \{i\})$, where $S \setminus \{i\}$ denotes coalition S without i in it. Denoting the Shapley value of i by $\phi_i(v)$, it can be computed via the formula

$$\phi_i(v) = \sum_{S: i \in S} \frac{(s-1)!(n-s)!}{n!} (v(S) - v(S \setminus \{i\})) \quad (5)$$

Then we propose that the *share (or weight)* of drug i in a theoretical combo-drug consisting of the n drugs in N is its normalized Shapley value

$$\psi_i(v) = \frac{\phi_i(v)}{\sum_{j \in N} \phi_j(v)} \quad (6)$$

We will compute all the above for our game. Using (4) and simple calculations we first get that

$$v(S) - v(S \setminus \{i\}) = x_i - x_i \sum_{\substack{j \in S \\ j \neq i}} x_j + x_i \sum_{\substack{j, k \in S \\ j < k, j, k \neq i}} x_j x_k - \dots + (-1)^{s+1} \prod_{j \in S} x_j \quad (7)$$

Using (5) and (7), the Shapley value of i then is

$$\phi_i(v) = \sum_{S: i \in S} \frac{(s-1)!(n-s)!}{n!} \left(x_i - x_i \sum_{\substack{j \in S \\ j \neq i}} x_j + x_i \sum_{\substack{j, k \in S \\ j < k, j, k \neq i}} x_j x_k - \dots + (-1)^{s+1} \prod_{j \in S} x_j \right) \quad (8)$$

Usually the number of combined drugs is small. So let's give explicitly the Shapley values for the cases of two, three and four constituent drugs. Consider the case $n = 2$. The marginal

contributions of drug 1 to the two coalitions that it joins are $v(N) - v(\{2\}) = x_1 - x_1x_2$; and $v(\{1\}) - v(\emptyset) = x_1$. Likewise, the marginal contributions of drug 2 are $v(N) - v(\{1\}) = x_2 - x_1x_2$ and $v(\{2\}) - v(\emptyset) = x_2$. Hence the Shapley values are as in Table 1.

Table 1: $n = 2$

<i>Agent</i>	<i>Shapley value</i>
1	$x_1 - \frac{x_1x_2}{2}$
2	$x_2 - \frac{x_1x_2}{2}$

The predicted share (weight) of each constituent drug is its normalized Shapley value. By (6) the two shares are

$$\psi_1(v) = \frac{x_1 - x_1x_2/2}{x_1 + x_2 - x_1x_2}, \quad \psi_2(v) = \frac{x_2 - x_1x_2/2}{x_1 + x_2 - x_1x_2}$$

Consider now the case $n = 3$. Take, say, drug 1. The marginal contribution of 1 to coalition of 2 and 3 is $x_1 - x_1x_2 - x_1x_3 + x_1x_2x_3$; the marginal contribution of 1 when it enters in a coalition with drug 2 is $x_1 - x_1x_2$; and with 3, $x_1 - x_1x_3$; finally the marginal contribution of 1 in a singleton situation is $x_1 - 0 = x_1$. In the same way we may find all marginal contributions of 2 and 3. Using all these, we end up with the Shapley values in Table 2.

Table 2: $n = 3$

<i>Agent</i>	<i>Shapley value</i>
1	$x_1 - \frac{x_1x_2 + x_1x_3}{2} + \frac{x_1x_2x_3}{3}$
2	$x_2 - \frac{x_2x_1 + x_2x_3}{2} + \frac{x_1x_2x_3}{3}$
3	$x_3 - \frac{x_3x_1 + x_3x_2}{2} + \frac{x_1x_2x_3}{3}$

The predicted shares are again given by the normalized Shapley values, which are presented in the Appendix.

Finally the Shapley values for the case of $n = 4$ are presented in Table 3. All relevant derivations are relegated to the Appendix (notice that all Shapley values, for all n , are positive numbers as $0 \leq x_i \leq 1$).

From the tables we can readily see that the Shapley value of a drug decreases as n increases.

Summing up, the following can be easily shown.

Table 3: $n = 4$

<i>Agent</i>	<i>Shapley value</i>
1	$x_1 - \frac{x_1(x_2 + x_3 + x_4)}{2} + \frac{x_1(x_2x_3 + x_2x_4 + x_3x_4)}{3} - \frac{x_1x_2x_3x_4}{4}$
2	$x_2 - \frac{x_2(x_1 + x_3 + x_4)}{2} + \frac{x_2(x_1x_3 + x_1x_4 + x_3x_4)}{3} - \frac{x_1x_2x_3x_4}{4}$
3	$x_3 - \frac{x_3(x_1 + x_2 + x_4)}{2} + \frac{x_3(x_1x_2 + x_1x_4 + x_2x_4)}{3} - \frac{x_1x_2x_3x_4}{4}$
4	$x_4 - \frac{x_4(x_1 + x_2 + x_3)}{2} + \frac{x_4(x_1x_2 + x_1x_3 + x_2x_3)}{3} - \frac{x_1x_2x_3x_4}{4}$

Proposition 2 *The Shapley value of i in a game with n drugs is given by*

$$\phi_i(v) = x_i - \sum_{\substack{j \in N \\ j \neq i}} x_i x_j / 2 + \sum_{\substack{j, k \in N \\ j < k; j, k \neq i}} x_i x_j x_k / 3 - \dots + (-1)^{n+1} \prod_{j \in N} x_j / n \quad (9)$$

As before, the share of i in a theoretical combo-drug consisting of n drugs will be given by its normalized Shapley value in (9).

3 Conclusions

In this paper we have suggested the use of the tools of cooperative game theory in the design of combo-drugs against viruses like Covid-19. We provided a consistent measure of the significance of each drug in a combo-drug using the Shapley value concept. The relevant theoretical derivations were conducted within a milestone model of drugs combination theory, the Bliss independence model.

The current paper has only suggested the method. What is now needed is experts running in-vitro experiments using their set of drugs and the Shapley value-predicted shares. This will measure the efficacy of the suggested procedure.

Appendix

Shares of drugs when $n = 3$

The shares are given by the following formulas:

$$\psi_1(v) = \frac{x_1 - x_1x_2/2 - x_1x_3/2 + x_1x_2x_3/3}{\sum_{j \in N} x_j - x_1x_2 - x_1x_3 - x_2x_3 + \prod_{j \in N} x_j}$$

$$\psi_2(v) = \frac{x_2 - x_2x_1/2 - x_2x_3/2 + x_1x_2x_3/3}{\sum_{j \in N} x_j - x_1x_2 - x_1x_3 - x_2x_3 + \prod_{j \in N} x_j}$$

$$\psi_3(v) = \frac{x_3 - x_3x_1/2 - x_3x_2/2 + x_1x_2x_3/3}{\sum_{j \in N} x_j - x_1x_2 - x_1x_3 - x_2x_3 + \prod_{j \in N} x_j}$$

Determining the Shapley value allocation when $n = 4$

We focus on one agent, say agent 1. The marginal contribution of 1 to the grand coalition is

$$x_1 - x_1(x_2 + x_3 + x_4) + x_1(x_2x_3 + x_2x_4 + x_3x_4) - x_1x_2x_3x_4$$

The marginal contributions of 1 when it joins with 2, or with 3, or with 4 are respectively

$$x_1 - x_1x_2, \quad x_1 - x_1x_3, \quad x_1 - x_1x_4$$

The marginal contributions of 1 when it joins coalitions $\{2, 3\}$, $\{2, 4\}$ and $\{3, 4\}$ are respectively

$$x_1 - x_1x_2 - x_1x_3 + x_1x_2x_3$$

$$x_1 - x_1x_2 - x_1x_4 + x_1x_2x_4$$

$$x_1 - x_1x_3 - x_1x_4 + x_1x_3x_4$$

Using the above contributions, plus the contribution of 1 when it joins the trivial coalition of the empty set, and repeating the same exercise for all agents, gives us the Shapley values of Table 3.

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