# Data-driven learning of Boolean networks and functions by optimal causation entropy principle

## Highlights

- Development of a new information-theoretic method for learning Boolean networks

- BoCSE is computationally efficient and resilient to noise

- Diagnosis of urinary diseases, and cardiac SPECT diagnosis

- Risk causality analysis of loans in default status

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## In brief

For decision-makers to scientific problems from a wide range of areas, making decisions is often reduced to Boolean function inference, meaning yes or no answers to similarly input data. We have developed an information-theoretic approach here, called Boolean optimal causation entropy, which is capable of inferring the interaction network and the underlying functions simultaneously, accurately, and efficiently. We show that this method also allows for identifying underlying essential features for a related reduced-order Boolean model.

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# Data-driven learning of Boolean networks and functions by optimal causation entropy principle

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**THE BIGGER PICTURE** From decision-makers to scientific problems from a wide range of areas, processing information and making decisions are often reduced to Boolean function inference, meaning yes or no answers to similarly input data. When these interactions occur in complex networks, solutions of the underlying functions from data become exponentially computationally intensive. We have developed an information-theoretic approach here, called Boolean optimal causation entropy, which is capable of inferring the interaction network and the underlying functions simultaneously, accurately, and efficiently. We show that this method also allows for identifying underlying essential features for a related reduced-order Boolean model.

1 2 **3** 4 5 **Development/Pre-production:** Data science output has been rolled out/validated across multiple domains/problems

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## SUMMARY

Boolean functions, and networks thereof, are useful for analysis of complex data systems, including from biological systems, bioinformatics, decision making, medical fields, and finance. However, automated learning of a Boolean networked function, from data, is a challenging task due in part to the large number of unknown structures of the network and the underlying functions. In this paper, we develop a new information theoretic methodology, called Boolean optimal causation entropy, that we show is significantly more efficient than previous approaches. Our method is computationally efficient and also resilient to noise. Furthermore, it allows for selection of features that best explains the process, described as a networked Boolean function reduced-order model. We highlight our method to the feature selection in several real-world examples: (1) diagnosis of urinary diseases, (2) cardiac single proton emission computed tomography diagnosis, (3) informative positions in the game Tic-Tac-Toe, and (4) risk causality analysis of loans in default status.

## INTRODUCTION

In this paper we consider an important problem in data science and complex systems, which is the identification of the hidden structure and dynamics of a complex system from data. Our focus is on binary (Boolean) data, which commonly appear in many application domains. For example, in quantitative biology, Boolean data often come from gene expression profiles where the observed state of a gene is classified or thresholded to either "on" (high expression level) or "off" (low to no expression level).

In such an application, it is a central problem to understand the relation between different gene expressions, and how they might impact phenotypes, such as occurrence of particular diseases. The interconnections among genes can be thought of as forming a Boolean network, via particular sets of Boolean functions that govern the dynamics of such a network. The use of Boolean networks has many applications, such as for the modeling of plant-pollinator dynamics,[1] yeast cell cycles,[2,3] pharmacology networks,[4] tuberculosis latency,[5] regulation of bacteria,[6] biochemical networks,[7] immune interactions,[8] signaling
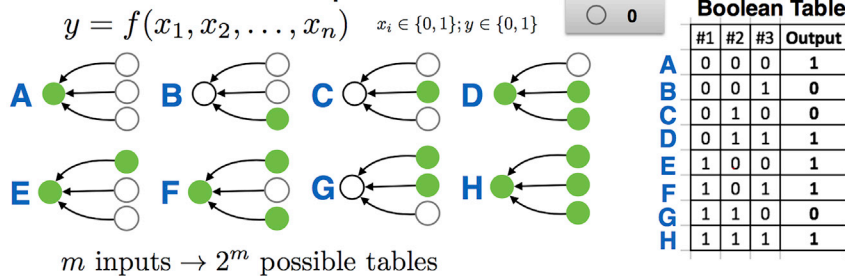
**Figure 1. A Boolean function can be uniquely identified by a truth table, called a Boolean table**

For a $k$-ary Boolean function, the table has $2^k$ rows, and $k+1$ columns. For each row, the first $k$ entries correspond to a particular input binary string (e.g., (0,1,0)), and the last entry represents the output of the function.

networks,[9] gut microbiome,[10] drug targeting,[11] drug synergies,[12] floral organ determination,[13] gene interactions,[14] and host-pathogen interactions.[15] In general, the problem of learning Boolean functions and Boolean networks from observational data in a complex system is an important problem to explain the switching relationships in these and many problems in science and engineering.

To date, many methods have been proposed to tackle the Boolean inference problem.[16–22] Notably, REVEAL (reverse engineering algorithm for inference of genetic network architectures), which was initially developed by Liang et al. in 1998[19] has been extremely popular. REVEAL blends ideas from computational causality inference with information theory, and has been successfully applied in many different contexts. However, a main limitation of REVEAL is its combinatorial nature and thus suffers from high computational complexity cost, making it effectively infeasible for larger networks. The key challenge in Boolean inference are due to two main factors: (1) the system of interest is typically large, containing hundreds, if not thousands and more, components; (2) the amount of data available is generally not sufficient for straightforward reconstruction of the joint probability distribution.

A function of the form

$$f : \mathbb{D} \to \mathbb{B}, \text{ where } \mathbb{B} = \{0,1\}, \quad \text{(Equation 1)}$$

is called a Boolean function, where $\mathbb{D} \subset \mathbb{B}^k$ and $k \in \mathbb{N}$ is the arity of the function. For an $k$-ary Boolean function, there are $2^k$ possible input patterns, the output of each is either 0 or 1. The number of distinct $k$-ary Boolean functions is $2^{2^k}$, a number that clearly becomes extremely large, extremely quickly, with respect to increasing $k$. Consider, for example, $2^{2^3} = 256$, $2^{2^5} \approx 4.295 \times 10^9$, and $2^{2^8} \approx 1.158 \times 10^{77}$ (comparable with the number of atoms in the universe, which is estimated to be between $10^{78}$ and $10^{82}$). This underlies the practical impossibility of approaching a Boolean function learning problem by brute force exhaustive search.

Each Boolean function can be represented by a truth table, called a Boolean table. The table identifies, for each input pattern, the output of the function. An example Boolean function $y = f(x_1, x_2, x_3)$ together with its corresponding Boolean table are shown in Figure 1.

A Boolean function is useful to model a system that has multiple binary inputs and a single binary output. More generally, a system can have multiple outputs, in which case multiple Boolean functions are needed, each capturing the relation between

an output variable and the set of input variables. The collection of these individual functions constitute a Boolean network. Formally, a Boolean network is characterized by a triplet of sets, denoted as $G = (V; E; F)$, where $(V; E)$ represents a graph that encodes the structure of the network: $V(G) = \{1, 2, ..., n\}$ is the set of nodes, and $E(G) \subset V \times V$ is the set of directed edges (possibly including self-loops). The functional rules of the network are encoded in $F(G) = (f_1, f_2, ..., f_n)$, which is an ordered list of Boolean functions. For each node $i$ in the network, we represent its set of directed neighbors by $\mathcal{N}_i = \{j : (i, j) \in E\}$ and the degree of node $i$ as the cardinality of $\mathcal{N}_i$, denoted as $k_i = |\mathcal{N}_i|$. Thus, $f_i : \mathbb{B}^{k_i} \to \mathbb{B}$ is a $k_i$-ary Boolean function that represents the dependence of the state of node $i$ on the state of its directed neighbors. Note that, alternatively, the dependence patterns of a Boolean network can also be represented by an adjacency matrix $A = [A_{ij}]_{n \times n}$, where:

$$A_{ij} = \begin{cases} 1, & \text{if } j \in \mathcal{N}_i; \\ 0, & \text{otherwise} \end{cases}. \quad \text{(Equation 2)}$$

Thus, the adjacency matrix $A$ encodes the structure of a Boolean network, although not the functional rules. More details on stochastic Boolean function, stochastic Boolean network, and a discussion of several forms of data that commonly appear in application problems are presented in the problem of learning a Boolean network from observational data. We show that data can either be directly represented or rearranged into a set of input-output pairs:

$$\{(\mathbf{x}(t), \mathbf{y}(t)) : t = 1, ..., T\}, \quad \text{(Equation 3)}$$

where,

$$\begin{aligned} \mathbf{x}(t) &= [x_1(t), ..., x_n(t)] \in \mathcal{B}^n = \{0,1\}^n, \text{ and,} \\ \mathbf{y}(t) &= [y_1(t), ..., y_\ell(t)] \in \mathcal{B}^\ell = \{0,1\}^\ell, \end{aligned} \quad \text{(Equation 4)}$$

are both vectors of Boolean states.

In this paper, we propose that information flow built upon causation entropy for identifying direct versus indirect influences,[23,24] using the optimal causation entropy principle (oCSE)[25] is well suited to develop a class of algorithms that furthermore enable computationally efficient and accurate reconstruction of Boolean networks and functions, despite noise and other sampling imperfections. Instead of relying on a combinatorial search, our method iteratively and greedily finds relevant causal nodes and edges and the best Boolean function that utilizes them, and thus is computationally efficient. We validate the
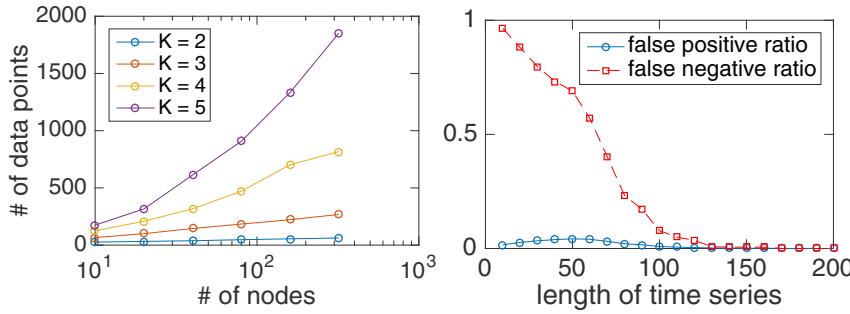
**Figure 2. Number of data points required for learning random Boolean networks with no error (left) and error ratios as a result of applying the proposed method (right)**

BoCSE, for learning random Boolean networks of fixed size $n = 50$ and degree $K = 3$. For both panels, each point on the plotted curve is the result of an average over 50 random realizations. These test networks are generated in a random process. For each node $i$, $K$ out of the remainder $n - 1$ are selected with directed links to node $I$. The Boolean function is defined by assigning randomly an output of either 0 or 1 to each input pattern, with equal probability.

effectiveness of our new approach that here we call, Boolean optimal causation entropy (BoCSE), using data from several real-world examples, including for the diagnosis of urinary diseases, cardiac single proton emission computed tomography (SPECT) diagnosis, Tic-Tac-Toe, and risk causality analysis of loans in default status.

## RESULTS

Given a set of input-output pairs $\{\mathbf{x}(t), y(t)\}$, (here $y(t)$ is a single bit), we want to find a minimal Boolean function that is sufficient in representing the data. To quantify the complexity of the Boolean function, we state the following information-theoretic criterion

$$\min_{K \subset [n]} |K|, \text{s.t.} I\left(X^{(K)}; Y\right) = \max_{K \in [n]} I\left(X^{(K)}; Y\right). \quad \text{(Equation 5)}$$

Here,

$$\begin{aligned}
[n] &= \{1, 2, \ldots, n\}, \\
K &= \{k_1, \ldots, k_\ell\} \text{ is a subset of } [n], \\
Y &= [y(1), \ldots, y(t)], \text{.and} \\
X^{(K)} &= \left[X^{(K)}\right]_{T \times \ell} \text{ where } \left[X^{(K)}\right]_{tj} = X(t)_{k_j}
\end{aligned} \quad \text{(Equation 6)}$$

The symbol $I$ denotes mutual information, that is, $I(X^{(K)}; Y)$ is the mutual information between $X^{(K)}$ and $Y$.

At a glance, solving this combinatorial problem seems to be computationally complex. In our previous work[25] we proposed an oCSE algorithm for the case of general distributions that can find $K$ efficiently, and we proved in Sun et al.[25] that it correctly infers the underlying network as it is able to distinguish direct versus indirect connections correctly. In this work we build upon these previous results to develop a fully automated framework for learning Boolean networks and functions. Basic concepts from information theory are reviewed in the discussion, and a detailed presentation of the BoCSE framework is provided in BoCSE for data-driven learning of the structure and function of Boolean networks. In this section we present examples of applications of BoCSE, the proposed Boolean learning method.

### Benchmark on random Boolean networks

We first evaluate BoCSE for learning randomly generated boolean networks. These networks are generated with two parameters, $n$ is the number of nodes, and $K$ is the in-degree of each node in the network (for example, $K = 3$ means that each node $i$ receives three inputs from other nodes, randomly chosen).

The Boolean function associated with each node $i$ is constructed by assigning randomly an output of either 0 or 1 to each input pattern, with equal probability. Figure 2 shows that the number of data points needed for correctly learning the entire Boolean network scales sublinearly as the size of the network (left panel). Although the scaling becomes worse as $K$ increases, it is still within practical reach for networks of several hundred of nodes. In the right panel of Figure 2, we show the error of learning for networks of fixed size $n = 50$. As the length of data increases (more data points), both false positive and false negative ratios decrease toward zero, confirming the validity and convergence of the method.

### Automated diagnosis of urinary diseases

As an application to aid the automation of medical diagnosis, we consider a dataset that documents the symptoms and diagnosis outcomes of 120 patients. The data are an extended version of the table used in Czerniak and Zarzycki[26] and are available at the UCI Machine Learning database via the following link under the name "Acute Inflammations": https://archive.ics.uci.edu/ml/datasets/Acute+Inflammations.

In this extended dataset, there are descriptions from a total of 120 patients, each with 6 attributes and 2 decision variables. The attributes are (1) temperature, (2) nausea, (3) lumbar pain, (4) urine pushing, (5) micturition pains, (6) burning of urethra, itch, swelling of urethra outlet. Other than temperature, which takes a value in the range of 35°C–42°C), all the other 5 attributes are recorded as a Boolean value, either "1" (symptom exists) or "0". In our analysis, we threshold the temperature data into binary values by simple thresholding: temperature equal or above 38°C are converted into "1" (fever) and those below are converted into "0" (no fever). The two decision (outcome) Boolean variables are

1. (acute) inflammation of the urinary bladder
2. nephritis of renal pelvis origin

In Table 1 we summarize the description of the attributes and decision variables.

We apply the BoCSE learning method separately to the two outcome variables. For each outcome variable, we treat each patient's attributes as one input Boolean string and the corresponding recorded outcome as a single output.

For the first outcome variable $Y_1$, that is inflammation of the urinary bladder, we found that the relevant attributes are (in terms of decreasing order of importance): (4) urine pushing, (5)

**Table 1. Attributes and outcome variables for the urinary disease data**

| attributes | description |
|---|---|
| $X_1$ | fever |
| $X_2$ | nausea |
| $X_3$ | lumbar pain |
| $X_4$ | urine pushing |
| $X_5$ | micturition pains |
| $X_6$ | burning of urethra, itch, swelling of urethra outlet |
| Outcome | |
| $Y_1$ | (acute) inflammation of urinary bladder |
| $Y_2$ | nephritis of renal pelvis origin |

Each variable is Boolean and takes a value 1 or 0 representing the presence or absence of a particular attribute/outcome.

micturition pains, and (6) burning of urethra, itch, swelling of urethra outlet. The inferred Boolean function for the relation between these attributes and the outcome are shown in the left-hand part of Table 2, and is found to accurately describe every individual data record. Interestingly, for the other outcome $Y_2$, the relevant attributes become $X_1$ and $X_3$ (in order of decreasing importance), and the inferred Boolean function, as shown in the right-hand part of Table 2, can be written using a simple "and" gate: $Y_2 = X_1 \wedge X_2$, which implies that the diagonals of nephritis of renal pelvis origin can be based on having both symptoms: fever and lumbar pain. Yet again, this relation is consistent with every single patient's record in the dataset. Note that in the inferred Boolean network, several links are undetermined and marked as N/A since the input patterns are not observed in the available data thus causing ambiguity; such ambiguity can potentially be resolved with additional data or other side information, and integrating such information into the learning process will be an interesting topic of research on its own.

Next, using the inferred attributes from the entire dataset (120 samples), we explore the dependence of the accuracy of our Boolean inference on the sample size. We do this by randomly selecting a subset of the samples, and use such "down-sampled" data instead of the full dataset for Boolean inference. For each sample size, we repeat such inference 50 times and compute the average number of false positives (attributes inferred using the down-sampled data that are not present using the full-size data) and false negatives (attributed to inference using the full dataset, which now appears using the down-sampled data). The results are shown in Figure 3. Interestingly, for this particular example our method never seems to produce false positives, and the number of false negatives decreases rapidly to zero as more samples are used in Boolean inference, which suggests the effectiveness of the method in automated diagnosis systems via relatively small sample sizes.

### Automated cardiac SPECT diagnosis

In this example, we test our Boolean learning method on an existing dataset that aims at automated image-based cardiac diagnosis. The dataset is derived from a set of images obtained by cardiac SPECT.[27] In particular, there is a total of $T = 267$ patients, each of whom is classified as either normal ($y_t = 1$) or abnormal ($y_t = 0$). The data are divided into a training set that contains $T_1 = 80$ patients and a test (validation) set of $T_2 = 187$ patients. For each patient's image set, a total of $n = 22$ binary feature patterns were created, defining $x_i(t) = 1$ if the $i$-th feature is present in the SPECT images of the $t$-th patient, and $x_i(t) = 0$ otherwise, for $i = 1, \ldots, 22$ and $t = 1, \ldots, 267$. Finally, this post-processed Boolean dataset is further divided into a training set that contains 87 out of the 267 patients' features and diagnosis, and a validation set that contains such information for the remaining 180 patients.

Focusing on this post-processed Boolean data, we are interested to see if our automated Boolean inference method is able to learn the decision rules, that is, to diagnose a patient based on a reduced set of Boolean features out of the 22 features. In this sense, our methodology can be understood as useful for reduced-order modeling in the realm of complex Boolean function inference problems. Said another way, this method describes a way to simplify decision-making problems by focusing on the most relevant factors, which are those that lead to important outcomes. As shown in Figure 4, our method is able to learn a Boolean function that achieves near 80% of decision accuracy on the validation data across a wide range of parameters. The achieved accuracy, generally using only a subset of the full set of 22 Boolean features, and without any fine-tuning of parameters or further optimization, is already comparable with the best known result on such datasets.[28]

### Tic-Tac-Toe

Tic-Tac-Toe is a classical two-player board game, which is also often played using pencil and paper. The "board" is a 3-by-3 grid with a total of 9 slots, as illustrated in Figure 5A. At the beginning of the game, the board is empty. Then, the two players take turn to mark any empty "slot" in each turn—typically one uses "X" the other uses "O". The player who is the first to have marked three consecutive horizontal, or vertical, or diagonals slots, wins the game. For instance, Figures 5B–5D is an example of the sequence of marks made by the players, where the first player (player "X") eventually wins by having marked an entire row (in this case, the top row). In general, if both players do their best at every move, the outcome would be a draw.

Our interest here is not (re)analysis strategies of this relatively simple game. For those who are interested, variants of the game actually has a connection to Ramsey theory.[29,30] Here, we are interested in testing our Boolean learning algorithm to see if it provides any useful information. To this end, we collected the complete set of possible board configurations at the end of a Tic-Tac-Toe game via the following link under the name "Tic-Tac-Toe Endgame DataSet ": https://archive.ics.uci.edu/ml/datasets/Tic-Tac-Toe+Endgame. There is a total of 958 instances. For the $t$-th instance, we use $\mathbf{x}(t) = [x_1(t), \ldots, x_9(t)]^\top$ to present the state of the $i$-th slot, ordered as follows: upper-left, upper-middle, upper-right, middle-left, center, middle-right, lower-left, lower-middle, and lower-right. Each $x_i(t)$ can either be 1 (if marked by "X"), $-1$ (if marked by ("O"), or 0 (if empty). Corresponding to each instance $t$ is the final outcome, which we denote as $y(t)$, which either equals 1 if player "X" wins or 0 if "X" does not win. Interpreting $(t)$ and $y(t)$ as samples of random variables $\boldsymbol{X}$ and $\boldsymbol{Y}$, we can ask the question of which slots in the board, statistically, are more relevant (or predicative) for the first player to win the game.

**Table 2. Inferred Boolean relations by BoCSE for the two outcome variables: $Y_1$ (left-hand part of table) and $Y_2$ (right-hand part of table)**

| $X_4$ | $X_5$ | $X_6$ | $Y_1$ | Occurrence (%) | $X_1$ | $X_3$ | $Y_2$ | Occurrence (%) |
|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 25.00 | 0 | 0 | 0 | 33.33 |
| 0 | 0 | 1 | N/A | 0 | 0 | 1 | 0 | 16.67 |
| 0 | 1 | 0 | 0 | 8.33 | 1 | 0 | 0 | 8.33 |
| 0 | 1 | 1 | N/A | 0 | 1 | | 1 | 41.67 |
| 1 | 0 | 0 | 1 | 8.33 | | | | |
| 1 | 0 | 1 | 0 | 17.50 | | | | |
| 1 | 1 | 0 | 1 | 16.67 | | | | |
| 1 | 1 | 1 | 1 | 24.17 | | | | |

Each entry in the "occurrence" column shows the fraction of observed attribute data: $(X_4, X_5, X_6)$ for the left-hand table and $(X_1, X_3)$ for the right-hand table. For each attribute pattern, the "predicted" value of outcome is shown in the $Y$ column, where "N/A" refers to cases where no such input pattern is ever seen in the empirical data.

Applying our Boolean learning algorithm, we found a list of most important slots, ordered in decreasing value of (added) relevance: $i_1 = 5$ (center), $i_2 = 1$ (upper-left), $i_3 = 9$ (lower-right), $i_4 = 3$ (upper-right), $i_5 = 7$ (lower-left), $i_6 = 8$ (lower-middle), and $i_7 = 2$ (lower-right). To quantify the relative importance of each attribute, we compute the conditional entropy $H(Y|X_{i_1\ldots i_k})$ for $k = 0, \ldots, 7$, where $H(Y|X_{i_0})$ is used to represent $H(Y)$. This shows that, as the number of attributes increases, uncertainty decreases monotonically and reaches 0 (complete predictability) when 7 attributes are used (Figure 6). In this example, the best Boolean network is not uniquely defined due to the symmetry in the problem—all corners are equivalent; however, as soon as one of them is selected as the second most important, it breaks the symmetry and leads to a unique set of subsequent variables.

## Risk causality analysis of loans in default status

Loan default prediction is an essential problem for banks and insurance companies to fiscally responsibly approve loans. However, in many cases, the borrowers fail to pay the loan as agreed, called loan default, which motivates the risk analysis problem in the banking industry, to identify those parameters that identify one borrower as trustworthy, and another borrower as representing a high risk.

We consider the open dataset from LendingClub (American peer-to-peer lending company), which can be downloaded from the LendingClub website. We considered the dataset for the year 2019 (four quarters). The dataset contains more than 500,000 entries (data points, sample size). However, we only considered the long term (the final) status of the loans. Therefore, we excluded all the loans with the status *Current* as an outcome, to have a sample size of 62,460 for our analysis. That is, all can be classified to an outcome *Paid in full*, or *Default* status. We should emphasize here that we only considered the parameters as Boolean in nature, which limits those considered to those 10 parameters that we investigate as to their influence on the outcomes.

This example gives a causality driven description of those parameters that, *combined*, can represent a high risk that the

borrower will not be able to pay his loan in full. This causality inference occurs within the Boolean framework for parameters concerning the loan long-term status. Table 3 shows the attributes and their description. In loan issuing risk analysis, the amount of the requested loan and the annual income of the borrower are important variables to consider, and they are both numeric variables. We introduce here the combined attribute, loan to income ratio, which combines both variables in the form of a Boolean variable. Our dataset has a sample size of 62,460, and the loan to income ratio range from 0.0001 to 36,000. So, we considered the median value $\mu \approx 0.2$ to be our threshold step, such that $X_9 = 0$ indicates that the loan to income ratio of the loan request is less than 0.2, and it is within the lowest 50% of all the requested loans over the period (which is, in our case, 1 year).

We then apply BoCSE, the proposed Boolean factors learning approach to the outcome variable $Y$, where we found that the relevant attributes are, in decreasing order of importance:

- $X_9$, loan to income ratio
- $X_{10}$, loan terms
- $X_3$, verification of the reported income

We expect that the probability of having the loan fully paid ($Y = 1$) will be larger than a default ($Y = 0$) in this example, for all the observed combinations of the relevant attributes. However, the challenge here is to find the combination of attributes that, together, represent a high risk if approving the loan. For example, if for some attribute combinations (binary string) $X$, the probability $Pr(Y = 1) = 0.8$, and $Pr(Y = 0) = 0.2$, we may not be satisfied by saying that the expected outcome that the borrower will pay the loan in full because $Pr(Y = 1) > Pr(Y = 0)$. Our focus here will be that there is a risk that the borrower will not pay the loan with probability $Pr(Y = 1) = 0.2$, which represents a high risk.

In Table 4, we can see the inferred Boolean function relationship between these attributes and the resulting outcomes. From application of our automated Boolean function learning method (results shown in Table 4), we summarize these interesting summary observations:

- The first four rows represent patterns where $X_3 = 0$, that describe loans in which the borrower's income was not verified. We see that this feature coincides with a significant increase in the probability that the loan will not be paid in full. The lowest value in this group of patterns is $(X_3, X_9, X_{10}) = (0, 0, 1)$, which represents an unverified income, low loan to income ratio, and a 60-month loan term, and the joint probability is then 1.9%. We conclude that low loan to income ratio combined with a long-term loan (which implies low monthly payment) reduces the risk of loan default.
- For the same pattern, but with a 36-month loan term, $(X_3, X_9, X_{10}) = (0, 0, 0)$, we see a significant increase in risk from 1.9% to 9.6%. For the pattern $(X_3, X_9) = (0, 1)$, the risk increases with the 36-month term loan, from 6.3% to 8.1%. This indicates that higher monthly payments indicate a higher risk. However, the effect of the loan term becomes neutral, meaning no effect in terms of observing only the verified income patterns ($X_3 = 1$). For these two patterns, where we have a verified income, the same
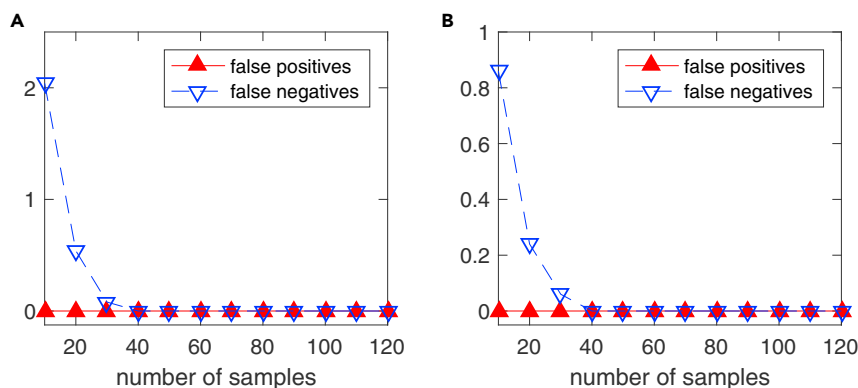
**Figure 3. Boolean inference error as a function of sample size for the urinary disease example**

Here, the "true" set of relevant attributes are taken to be the ones inferred using the full data (120 samples).

(A) Inference error as a function of sample size (from 10 to 120) for the first outcome variable, $Y_1$, where error is quantified by false positives and false negatives. The number of true attributes is 3 in this case.

(B) Similar to (A), but for $Y_2$. The number of true attributes is 2 in this case. In each plot, each data point is an average over 50 independent random down-samplings of the full dataset.

risk conclusions follow for both the 36- and 60-month term loans.

- Comparing the above two points, we conclude that, if the borrower's reported income is verified, there is no difference in the risk between different loan terms. However, if it is not verified, then going with the 60-month term loans can profoundly reduce the risk, regardless of the loan to income ratio.

- We see that the lowest risk, or the most trustworthy borrowers, are the ones with the combination $(X_3, X_9, X_{10}) = (1, 0, 1)$, which represents a verified income, low loan to income ratio, and 60-month term loan reflecting low monthly payments. The risk, in this case, is about 0.4%. Unfortunately, however, such a pattern occurs infrequently, representing fewer than 1% of the borrower customers.

- On the other hand, we see that a significant high risk associates with the combination $(X_3, X_9, X_{10}) = (0, 0, 0)$, which represents unverified income, low LTI ratio, and 36-month term loan (high monthly payments). This is particularly interesting since a low LTI may on its own may suggest a safer primary indication because it implies a high income, low loan value, or both. However, we see that, even with high income, or low requested loan amount, the combination of unverified income together with large monthly payment, $(X_3, X_{10}) = (0, 0)$, has the highest risk compared with all other combinations in the table: 9.6% and 8.1%.

## DISCUSSION

Although black box machine learning methods have become increasingly more popular due to their relative ease of implementation without deep understanding of how they work, in some applications, such as quantitative biology, where it is essential to uncover causal and relevant factors beyond functional fitting. A prototype problem of such is to learn, from noisy observational data, the structure and function of a Boolean network. The classic widely used REVEAL approach accomplishes this by performing a combinatorial search in the space of Boolean variables, and its performance relies heavily on having a relatively small network size and small maximum degree, two aspects that are in sharp contrast to typical biological systems that can be large and complex. To overcome these difficulties, here we present BoCSE as a new learning approach based on the optimi-

zation of causation entropy applying to Boolean data. This new approach relies on computing entropies of judiciously constructed subsets of variables, and does not require the combinatorial search typically used in other methods. We benchmark the effectiveness of BoCSE on random Boolean networks and further apply it in several real-world datasets, including in finding the minimal relevant diagnosis signals, quantifying the informative signs of a board game Tic-Tac-Toe, and in determining the causal signatures in loan defaults. In all examples, the BoCSE provides outcomes that are directly interpretable and relevant to the respective application scenarios.

## Basic concepts from information theory

In this section, we review some basic concepts from information theory. These concepts are rooted in information and theory,[31,32] and are heavily utilized in our computational approach for Boolean inference.

The (Shannon) *entropy* of a discrete random variable $X$ is given by
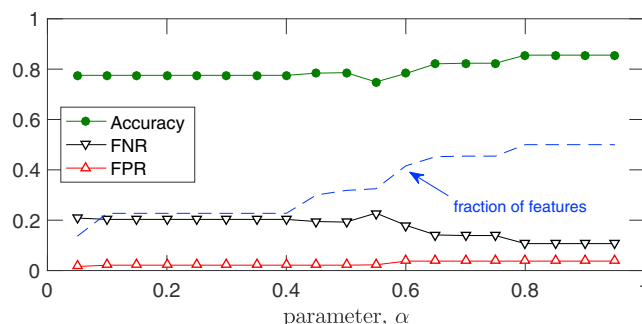


**Figure 4. Automated diagnosis of heart disease using 22 Boolean attributes derived from cardiac SPECT**

Here, we explore how the diagnosis accuracy changes as the parameter $\alpha$ (confidence control parameter, see estimation of conditional mutual information and tests of significance for details) in our Boolean inference method is varied. In particular, we apply BoCSE to the training data (80 patients) and validate the resulting Boolean functions on the validation set (187 patients). We compute the accuracy of diagnosis as the overall percentage of correct diagnoses in the validation set, as shown in the figure. In addition, we also compute and plot, for each $\alpha$, false-positive ratio (FPR) and false-negative ratio (FNR), together with the effective number of Boolean variables inferred by our method (dashed curve).
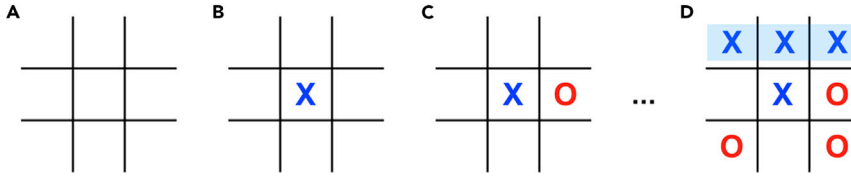
**Figure 5. Tic-Tac-Toe game**
(A) Start of the game, where the board is made up of a 3-by-3 grid.
(B–D) Example of a sequence of moves made by two players, where player "X" plays first, and eventually wins the game by filling in an entire horizontal row.

$$H(X) = - \sum_x P(x) \log P(x), \qquad \text{(Equation 7)}$$

where $P(x) = \text{Prob}(X = x)$ and the summation is over the support of $P(x)$, that is, all values of $x$ for which $P(x) > 0$. The base of the "log" function is typically chosen to be 2 so that the unit of entropy becomes "bit," although other base values can also be used depending on the application. Entropy is a measure of "uncertainty" associated with the random variable: generally the larger the entropy is the more difficult it is to "guess" the outcome of a random sample of the variable.

When two random variables $X$ and $Y$ are considered, we denote their joint distribution by $P(x,y) = \text{Prob}(X = x, Y = y)$ and conditional distributions by $P(y|x) = \text{Prob}(Y = y|X = x)$ and $P(x|y) = \text{Prob}(X = x|Y = y)$, respectively. These functions are used to define the joint entropy as well as the conditional entropies, as:

$$\text{Joint entropy}: \ H(X,Y) = - \sum_{x,y} P(x,y) \log P(x,y),$$

$$\text{Conditional entropies}:$$

$$Y \text{ given } X: \ H(Y|X) = - \sum_{x,y} P(x,y) \log P(y|x),$$

$$X \text{ given } Y: \ H(X|Y) = - \sum_{x,y} P(x,y) \log P(x|y).$$

While the joint entropy $H(X,Y)$ measures the uncertainty associated with the joint variable $(X,Y)$, the conditional entropy $H(Y|X)$ measures the uncertainty of $Y$ given knowledge about $X$ and similar interpretation holds for $H(X|Y)$. In general, $H(Y|X) \leq H(Y)$ and $H(X|Y) \leq H(X)$, with " = " if and only if $X$ and $Y$ are independent. Interestingly, the reduction of uncertainty as measured by $H(Y) - H(Y|X)$ coincides with $H(X) - H(X|Y)$, leading to a quantity called the mutual information between $X$ and $Y$, given by:

$$I(X;Y) = H(X) - H(X|Y) = H(Y) - H(Y|X). \qquad \text{(Equation 8)}$$
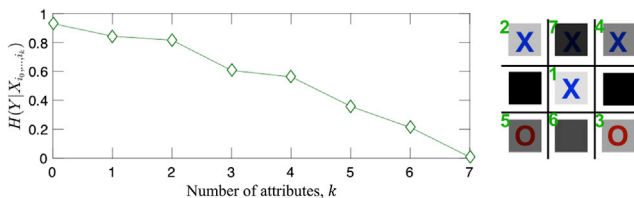


**Figure 6. Decrease of uncertainty in "predicting" the outcome of a Tic-Tac-Toe game using partial observations of the board in the final configuration**
Here, uncertainty is measured by the conditional entropy $H(Y|X_{i_1 \ldots i_k})$, and the indices $i_k$ are obtained using our Boolean inference algorithm: $i_1 = 5$ (center), $i_2 = 1$ (upper-left), $i_3 = 9$ (lower-right), $i_4 = 3$ (upper-right), $i_5 = 7$ (lower-left), $i_6 = 8$ (lower-middle), $i_7 = 2$ (lower-right), and the index $k$ in $i_k$ is shown in green numbers.

Mutual information is symmetric $I(X;Y) = I(Y;X)$, and also nonnegative: $I(X;Y) \geq 0$ with $I(X;Y) = 0$ if and only if $X$ and $Y$ are independent.

Finally, the conditional mutual information between $X$ and $Y$ given $Z$ is

$$I(X;Y|Z) = H(X|Z) - H(X|Y,Z), \qquad \text{(Equation 9)}$$

which measures the reduction of uncertainty of $X$ given $Z$ due to extra information provided by $Y$. Conditional mutual information is symmetric with respect to interchanging $X$ and $Y$, and nonnegative, equaling zero if and only if the conditional probabilities $P(x|z)$ and $P(y|z)$ are independent: $P(x|z)P(y|z) = P(x,y|z)$.

### The problem of learning a Boolean network from observational data
#### Stochastic Boolean function and stochastic Boolean network

In practice, the states and dynamics of a system are almost always subject to noise. Therefore, it is important to incorporate randomness and stochasticity into a Boolean network. To do so, we first extend the Boolean function concept from the deterministic definition to a stochastic generalization, defining a stochastic Boolean function as

$$g(x) = f(x) \oplus \xi, \qquad \text{(Equation 10)}$$

where $f$ is a (deterministic) Boolean function and $\xi$ is a Bernoulli random variable that controls the level of randomness of the function. In this model, the function contains a deterministic part, given by the Boolean function $f(x)$; the actual output of the function $g(x)$ is given by the output of $f(x)$ subject to a certain probably of being switched.

Following the notion of a stochastic Boolean function, we now define a stochastic Boolean network as a quadruple of sets, $G = (V; E; F; \mathbf{q})$, where the triplet of sets $(V; E; F)$ represents a (deterministic) Boolean network, and the vector $\mathbf{q} = [q_1, \ldots, q_n]^\top \in [0,1]^n$ represents the level of noise, each as a random variable, each with $q_i$ quantifying the probability of switching the output state at node $i$, a scalar parameter describing the Bernoulli random variable $\xi_i \sim Bernoulli(q_i)$.

#### Data from Boolean functions and Boolean networks

We start by discussing several forms of data that commonly appear in application problems. These include: (1) input-output data from a single Boolean function; (2) input-output data from a Boolean network, which can be regarded as a generalization of (1); (3) time series data from a Boolean network. In each one of these scenarios, the data can either be directly represented or rearranged into a set of input-output pairs. Recall from Equation 3:

**Table 3. Attributes for the loan issuance data**

| Attributes | description |
|---|---|
| $X_1$ | home ownership: (1) homeowner; (0) not a homeowner |
| $X_2$ | delinquency in the past 2 years: (1) delinquency occurred more than 2 times; (0) no more than 2 delinquencies occurred in the past 2 years |
| $X_3$ | verification of the reported income: (1) income verified; (0) income not verified |
| $X_4$ | history of public records: (1) there is a public record; (0) no public records |
| $X_5$ | application type: (1) individual; (0) with co-borrower |
| $X_6$ | 120 days past due date: (1) have an account ever past due date by more than 120 days; (0) never past due date by more than 120 days |
| $X_7$ | recent opened accounts in the last 12 months: (1) have opened a new account in the last 12 months; (0) no new accounts opened |
| $X_8$ | bankruptcies: (1) have declared bankruptcies; (0) never declared bankruptcies |
| $X_9$ | loan to income ratio (see caption) |
| $X_{10}$ | terms: (1) 60-month term; (0) 36-month term |

All variables are Boolean. The outcome $Y$ is a Boolean vector that takes the value 1 if the loan is fully paid, and 0 otherwise (charged off or marked as default). The loan to income ratio is the ratio $r = \dfrac{\text{the loan amount}}{\text{annual income}}$, and it is formed as a Boolean function such that $X_9 = \begin{cases} 1, r > \mu \\ 0, r \le \mu \end{cases}$, where $\mu$ is a threshold ratio that we selected to be the median value of the ratio of all the available dataset, and it was $\mu = 0.2$.

$$\{(\boldsymbol{x}(t), \boldsymbol{y}(t)) : t = 1, \ldots, T\}, \qquad \text{(Equation 11)}$$

(1) Input-output data from a single Boolean function. For a Boolean function (either deterministic or stochastic), if observations or measurements are made about its inputs and outputs, such data can be represented in the form of Equation 3, where $\boldsymbol{y}(t)$ is a scalar (i.e., $\ell = 1$). Here, each pair $(\boldsymbol{x}(t), \boldsymbol{y}(t))$ represents the observed input string of $k$ bits, encoded in $\boldsymbol{x}(t)$, and the corresponding output $\boldsymbol{y}(t)$. The ordering of the input-output pairs is arbitrary.

(2) Input-output data from a Boolean network. For a (deterministic or stochastic) Boolean network of $n$ nodes, input-output data of the network come in the form similar to that of a single Boolean function, except that each output itself is no longer a single bit, but instead multiple bits representing the state of all the nodes in the network. Thus, the dimensionality of $\boldsymbol{x}(t)$ and $\boldsymbol{y}(t)$ are both equal to $n$, that is, $\ell = n$ in the general form of Equation 3. The ordering of input-output pairs is arbitrary.

(3) Time series data from a Boolean network. For a time series observed on a Boolean network of $n$ nodes, we can represent such data using a sequence of Boolean vectors

$(\boldsymbol{x}(t))_{t=0}^{T}$, where $\boldsymbol{x}(t) = [x_1(t), \ldots, x_n(t)]^{\top} \in \mathcal{B}^n$ represents the state of the entire network at time $t$. The pair $(\boldsymbol{x}(t-1), \boldsymbol{x}(t))$ can be described as an input-output data pair from the underlying Boolean network. For this matter, time series data from a Boolean network can also be put into the input-output data form of Equation 3 with the additional constraint that

$$\boldsymbol{y}(t) = \boldsymbol{x}(t+1) \text{ for every } t = 1, \ldots, T - 1. \qquad \text{(Equation 12)}$$

Here, unlike the case of input-output data as in (1) and (2), the temporal ordering in the time series data is unique and should not be (arbitrarily) changed.

To summarize, in these three commonly encountered scenarios as we discussed above, observational data from a Boolean network can be represented as input-output pairs as in Equation 3. When the network contains only one node it is really just a Boolean function and thus each $\boldsymbol{y}(t)$ is a scalar; on the other hand, when the data come from time series then each $\boldsymbol{y}(t) = \boldsymbol{x}(t-1)$ and the temporal ordering of the data becomes fixed.

### The problem of learning the structure and function of a Boolean network

Given Boolean data in the standardized form of Equation 3, we interpret data as samples of a multivariate conditional probability distribution

$$p(\boldsymbol{y}|\boldsymbol{x}) = \text{Prob}(Y(t) = \boldsymbol{y}|X(t) = \boldsymbol{x}) \qquad \text{(Equation 13)}$$

$$= \prod_{i=1}^{k} \text{Prob}(Y_i(t) = y|_i X(t) = \boldsymbol{x}) = \prod_{i=1}^{k} p(y_i|\boldsymbol{x}), \qquad \text{(Equation 14)}$$

where $\boldsymbol{x} \in \mathcal{B}^k$ and $\boldsymbol{y} \in \mathcal{B}^{\ell}$, and thus

$$p(y_i|\boldsymbol{x}) = p(y_i|x_1, \ldots, x_n). \qquad \text{(Equation 15)}$$

The problem of reconstructing or learning the Boolean network then is, can $p(y_i|\boldsymbol{x})$ be maximally reduced to a lower-dimensional distribution. That is, does there exist a smallest (sub)set of indices,

$$S_i \subset \{1, \ldots, \ell\}, \text{ such that } p(y_i|\boldsymbol{x}) = p(y_i|\boldsymbol{x}_{S_i}). \qquad \text{(Equation 16)}$$

Once we have identified, for each $i$, this set of nodes $S_i$, they together constitute a network, where a directed link $j \to i$ corresponds to having $j \in S_i$. Furthermore, to identify such a subset of explaining variables that closely approximates this conditional equality statement represents a simplified or reduced-order presentation of the process.

### BoCSE for data-driven learning of the structure and function of Boolean networks

In this section we develop a computational framework to reconstruct both the structure and function of a Boolean network from observational data. We start with the reconstruction of a minimally sufficient Boolean function from input-output data. This method is repeated to find the neighbor set and function for each node, and as a result reconstructs the whole network.

**Table 4. Inferred Boolean relations for the outcome variable $Y$**

| $X_3$ | $X_9$ | $X_{10}$ | $Pr(Y = 0)$ | $Pr(Y = 1)$ |
|-------|-------|----------|-------------|-------------|
| 0 | 0 | 0 | 0.24836 | 0.75164 |
| 0 | 0 | 1 | 0.33667 | 0.66333 |
| 0 | 1 | 0 | 0.34837 | 0.65163 |
| 0 | 1 | 1 | 0.39923 | 0.60077 |
| 1 | 0 | 0 | 0.31724 | 0.68276 |
| 1 | 0 | 1 | 0.38599 | 0.61401 |
| 1 | 1 | 0 | 0.41463 | 0.58537 |
| 1 | 1 | 1 | 0.46288 | 0.53712 |

Given each attribute pattern, the conditional probability that value of outcome $Pr(Y = 0)$, meaning that the probability that the borrower will not fully pay the loan, is shown in the $Pr(Y = 0)$ column, and the probability that the borrower will fully pay the loan, is shown in the $Pr(Y = 1)$ column. The reader can refer to the provided code for reproducing this table. See the data and code availability.

### Reconstruction of a minimally sufficient Boolean function

Given a set of input-output pairs $\{\mathbf{x}(t), y(t)\}$, (here $y(t)$ is a single bit), we want to find a minimal Boolean function that is sufficient in representing the data. To quantify the complexity of the Boolean function, we state the following information-theoretic criterion

$$\begin{cases} \min_{K \subset [n]} |K|, \\ \text{s.t. } I\left(X^{(K)}; Y\right) = \max_{K \in [n]} I\left(X^{(K)}; Y\right). \end{cases} \quad \text{(Equation 17)}$$

Here,

$$\begin{aligned} [n] &= \{1, 2, \dots, n\}, \\ K &= \{k_1, \dots, k_\ell\} \text{ is a subset of } [n], \\ Y &= [y(1), \dots, y(t)], \text{ and} \\ X^{(K)} &= \left[X^{(K)}\right]_{T \times \ell} \text{ where } \left[X^{(K)}\right]_{tj} = X(t)_{k_j}. \end{aligned} \quad \text{(Equation 18)}$$

The symbol $I$ denotes mutual information, that is, $I(X^{(K)}; Y)$ is the mutual information between $X^{(K)}$ and $Y$.

At a glance, solving this combinatorial problem seems to be computationally complex. However, in our previous work[25] we developed an oCSE algorithm that can find $K$ efficiently, and we proved in Sun et al.[25] that it correctly infers the underlying network as it is able to distinguish direct versus indirect connections correctly. Here, we further develop the concept to also learn the associated Boolean functions on the networks, which we call BoCSE. Although various extensions of the oCSE algorithm are possible, some may even yield better results in certain scenarios. We focus here on the most basic version of our otherwise greedy search algorithm that consists of only two stages, a forward selection stage and a backward elimination stage.

- Forward selection. We initialize the solution set $K_f = \varnothing$, and, in each iteration, we choose an element $k$ that satisfies the following conditions

$$\begin{cases} \max_j I\left(X_j; Y | X^{(K_f)}\right) > 0, \\ k = \text{argmax}_j I\left(X_j; Y | X^{(K_f)}\right). \end{cases} \quad \text{(Equation 19)}$$

If such a $k$ exists, then we append it to the set $K_f$ and proceed to the next iteration; otherwise, when no such $k$ exists, the forward selection is terminated.

- Backward elimination. Start with $K_b = K_f$, in each step of backward elimination, we select an element $k$ that satisfy the following

$$k = \text{argmin}_{j \in K_b} I\left(X_j; Y | X^{(K_b / \{j\})}\right). \quad \text{(Equation 20)}$$

Such $k$ always exists since $K_b$ is a finite set. Then, if

$$I\left(X_k; Y | X^{(K_b / \{k\})}\right) = 0, \quad \text{(Equation 21)}$$

we remove $k$ from $K_b$ and repeat; otherwise, the algorithm terminates.

The result of the algorithm is a set $K_b = \{k_1, \dots, k_\ell\}$, which is an estimate of the index set of the minimal Boolean function that fits data. Finally, given such a set $K_b$, we construct the corresponding Boolean function by estimating the best output (0 or 1) for each unique input pattern available from the data. Symbolically, for each $\mathbf{x}_0 \in \mathbb{B}^\ell$, we define the set

$$\mathcal{T}_{K_b}(\mathbf{x}_0) = \left\{ t : \mathbf{x}^{(K_b)}(t) = \mathbf{x}_0 \right\}, \quad \text{(Equation 22)}$$

and define

$$g(\mathbf{x}_0) = \frac{\sum_{t \in \mathcal{T}_{K_b}(\mathbf{x}_0)} y(t)}{\left| \mathcal{T}_{K_b}(\mathbf{x}_0) \right|} \in [0, 1]. \quad \text{(Equation 23)}$$

Then, we obtain $f : \mathbb{B}^\ell \to \mathbb{B}$ using the tabular form, by defining

$$f(\mathbf{x}_0) = \lceil g(\mathbf{x}_0) \rceil \in \{0, 1\}. \quad \text{(Equation 24)}$$

If $\mathcal{T}_{K_b}(\mathbf{x}_0) = \varnothing$ for some $\mathbf{x}_0$, it means that particular input pattern is never observed in the data. Then, in the absence of additional information, the value of $f$ for such input cannot be optimally determined (the choice of either $f(\mathbf{x}_0) = 0$ or $f(\mathbf{x}_0) = 1$ makes no difference in "fitting" the data).

### Estimation of conditional mutual information and tests of significance

The proposed BoCSE learning approach requires estimating various forms of mutual information and conditional mutual information (see Equations 7–9) from data. In practice (i.e., when entropies need to be estimated from data), a threshold (either $\epsilon$ or $\eta$) needs to be determined in each step of either the forward or backward stage of the algorithm. The key is to decide, from data, whether an estimated conditional mutual information of the form $\widehat{I} = I(X; Y|Z)$ should be regarded as zero, with confidence (as opposed to positive). In particular, we need to consider

$$\begin{cases} H_0 \text{ (null hypothesis)} : \widehat{I} = I(X; Y|Z) = 0, \\ H_1 \text{ (alternative hypothesis)} : \widehat{I} = I(X; Y|Z) > 0. \end{cases} \quad \text{(Equation 25)}$$

To decide whether or not to reject $H_0$ (here equivalent as accepting $H_1$), we construct shuffled data by permuting the time ordering of the components in $X$. To be specific, suppose that

$$\sigma : \{1, \dots, T\} \to \{1, \dots, T\} \qquad \text{(Equation 26)}$$

is a random permutation function, from which we compute $I(X^\sigma; Y|X_{\widehat{S}})$ where $X^\sigma$ represents the shuffled time series $\{x_{\sigma(1)}, x_{\sigma(2)}, \dots, x_{\sigma(T)}\}$. By sampling $\sigma$ uniformly, we then obtain a cdf

$$F(x) = P(I(X^\sigma; Y|X) \le x). \qquad \text{(Equation 27)}$$

From this cdf, we can then estimate the $p$ value under $H_0$ to be $1 - F(\widehat{I})$, from which we can determine the threshold. For a given $\alpha$ level (e.g., $\alpha = 0.01$), the corresponding threshold can then be decided as

$$\begin{cases} \varepsilon = F^{-1}(1-\alpha), & \text{for forward selection;} \\ \eta = F^{-1}(1-\alpha), & \text{for backward elimination.} \end{cases} \qquad \text{(Equation 28)}$$

Throughout this paper, we set the same $\alpha = 0.05$ for both the forward and backward stage of the algorithm (unless otherwise noted), and obtain the cdf $F(x)$ by uniformly sampling by selecting 1,000 independent random permutation functions $\sigma$.

## EXPERIMENTAL PROCEDURES

### Resource availability
#### Lead contact
Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Abd AlRahman R. AlMomani (almomana@erau.edu).
#### Materials availability
This study did not generate new unique materials.
#### Data and code availability
All of the original code has been deposited at GitHub under https://github.com/almomaa/Boolean_oCSE and is publicly available.

## AUTHOR CONTRIBUTIONS

Conceptualization, J.S. and E.B.; methodology, J.S., A.A.R.A., and E.B.; software, J.S. and A.A.R.A.; validation, J.S. and A.A.R.A.; writing – original draft, J.S.; writing– review & editing, J.S., A.A.R.A., and E.B.; visualization, J.S. and A.A.R.A.; funding acquisition, E.B.

## DECLARATION OF INTERESTS

The authors declare no competing interests.

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