

Autonomous Models as agents for advancing scientific knowledge

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Abstract

Simulation experiments are extensively used to study the operation of a system by abstracting the complexities (Glutzer et al. 2013). Experiments conducted using the computational models are especially useful in advancing scientific knowledge (Teran-Somohano et al. 2015). However, the current studies in these areas fail to effectively articulate all aspects of the scientific discovery process. There is still a huge gap in the ability of simulation experiments to acquire results and analyze them to predict and discover model behavior. The experiment life-cycle include tasks like identifying, prioritizing, formulating questions, and conjecturing mechanisms, defining or generating experiments designed to answer questions, drawing inferences, and evaluating results within an incremental and iterative discovery cycle (Bunge 1998). In this report, we aim to show that Model-Driven Engineering strategies coupled with cognitive computing tools aid scientists in advancing scientific knowledge. This include tasks like identifying, prioritizing, formulating questions, and conjecturing mechanisms, defining or generating experiments designed to answer questions, drawing inferences, and evaluating results within an incremental and iterative discovery cycle (Bunge 1998). We also discuss a solution of Our aim is to use entropy-based information gain theory to reduce the uncertainty in the system and identify the relevance of the events. This information based approach helps in determining events that better characterize the model behavior (Fan et al. 2011) and will be used as a reward for adapting experiment parameters to strongly prove the validity of mechanism in the system.

Introduction

Computation is viewed as a powerful formal framework and exploratory apparatus for the conduct of science (Honavar, Hill, and Yelick 2016). The claim is supported by the observation that computation, mathematics, and science are often used ubiquitously for augmenting scientific knowledge by answering . By experimenting on models, we can anticipate behavior and flaws that would otherwise be difficult to discover in the actual system or may prove to be cost ineffective. Determination of such characteristics about the

system manually requires substantial human effort, and may still miss distinctions in content and learning. Since explicit characterization in this manner is infeasible, approaches that do not require exhaustive experimentation need to be considered (Murphy 2011). In supporting computational discovery, reliable models are necessary but not sufficient in addressing complex research problems (Kleijnen et al. 2005) as proper design and management of experiments are critical to instill confidence in the use of computer simulations (Ewald and Uhrmacher 2014). Scientific experiments are defined with a set of goals and have a purpose to answer certain questions. Its strength lies in analyzing the real effects of alternative conditions and courses of action using what if hypotheses (under certain assumptions), on a model representing the fundamental behavior of the system. The use of simulation models for scientific experiments and model discovery has been well established (Teran-Somohano et al. 2015). In order to produce improved experimentation practices and support computational discovery, the dependencies among goals, hypotheses, and experiments needs to be considered for evaluation of computer simulation studies (Yilmaz, Chakladar, and Doud 2016). The principles of Model-Driven Engineering (MDE) aid the transformation process and to facilitate the search within the operational level of hypotheses and the tactical level of experiments.

Computational models as abstract representation is widely used to solve research queries effectively (Glutzer et al. 2013). These tools are useful in conducting simulation experiments and addressing questions about the simulation model. Yet, these tools are only useful to capture few aspects of the entire scientific process and fail to include the efficient execution, analysis and management of the complete process under study, for e.g., estimation of necessary replications (Robinson 2005) or assessing the statistical significance of the results (Lee and Arditi 2006). There is a huge gap between the ability to collect, store and process the data and the ability to make effective use of the data to advance discovery (Honavar, Hill, and Yelick 2016).

Despite successful automation, the simulation experiment management and data analysis requires considerable human intervention. Cognitive tools are required to bridge the gap between the data acquisition and data analysis for developing abstractions to address research questions. This calls for intensive research study focused on development, anal-

ysis, integration and simulation of information processing abstractions of natural processes, aided with formal methods and tools for their analyses and simulation (Honavar, Hill, and Yelick 2016). It also requires the abstract representation of the different aspects of the scientific process, the development of computational artifacts (representations, processes, protocols, workflows, software) that represent the understanding of the system behavior, and the integration of the resulting cognitive tools into collaborative human-machine systems and infrastructure to advance science.

We propose to address some of the above challenges by defining a framework for hypothesis testing that is simulation platform independent by using the principles of Model-Driven Software Development. The proposed solution provides a domain specific language for hypothesis specification and automated model checking to evaluate these hypotheses using a statistical model checker. Our aim is to show in extensive computational experiments that the integration of learning method in simulation experiments can lead to higher accuracy in prediction of system behavior with significantly fewer experiments than a random learner, in many cases with perfect accuracy without exhaustive experimentation. By incorporating the results of model checking into learning networks, better experiments can be developed at a faster rate to increase knowledge gain. Bayesian networks can be used to characterize the statistical dependencies between the system variables. The probabilistic representation of the simulation system can be used for generating an explanatory inference of the system which is easier to understand and make the decision making process quicker. We discuss the entropy-based information gain theory for evaluating and revising experiments by selecting attributes that provide maximum information about the output. This serves as a run-time cognitive model that is used in determining events that better characterize the model behavior and will be used as a reward for adapting experiment parameters to strongly prove the validity of mechanism in the system.

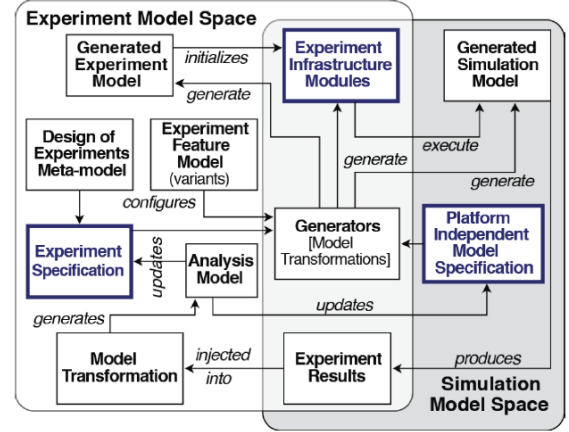
Methodology

In the context of scientific discovery, simulation experiments are viewed as an incremental and iterative process. This calls for explicit models of hypotheses, experiments, and models, along with traceability among them to support the computational discovery process. In this section, we overview the various components of the adaptive experimentation process that assist in augmenting scientific knowledge about the system.

DSL for Experiment and Hypothesis Modeling

Experiments are performed with specific goals and definite questions in mind. These questions and goals are formulated in the form of hypotheses that drive the experimentation process with the help of models. For generating experiment specifications from research questions and hypotheses, the DOE methodology in simulation experiment design (Sanchez, Sánchez, and Wan 2014), could provide a structured basis for automation. The DOE metamodel defines the

vocabulary and grammar. i.e., the abstract syntax for building the experiment domain model. To support the instantiation of the experiment specifications conforming to the DOE metamodel, a suitable Domain Specific Language is needed. In recent years, the efforts to support simulation reproducibility have inspired the use of DSLs as means to express model specifications (Darden 2001). The experiment model defined by the DSL needs to be configured with constraints. The constraints defined in the specification guides the cognitive learning process.



Simulation Model Space

The aim of searching the model space is to evaluate questions of interest to generate a model mechanism. Model-driven engineering principles and feature-oriented analysis (Meinicke et al. 2016) provide a basis for generative modeling. This generative architecture is also used to derive templates for generating the transition of mechanisms from the hypothesis space to the implementation space. A text-model transformation takes place that generate code templates to replicate the phenomenon represented by the hypotheses. Template-based modeling provides a path for using prior knowledge or specific experimental outcome.

Experiment Model Space

The experiment space is used to construct an experiment based on user input and research question being evaluated. The experiment generated is effective in explaining the current hypothesis being examined and discriminating competing hypothesis by efficiently covering the parameter space of the system. The experiment is used for executing the simulation model based on the design points of the experiment. The results of the experiments are used to test the outcome of the hypothesized model mechanism(s) to the expected behavior in the system.

Formal Verification

Formal methods of software verification are traditionally used to prove that algorithms are correct, in the sense that they exhibit the mechanisms that are necessary to output the correct value(s). Based on this observation, the connection can be made that, if formal verification can be done autonomously, without the intervention of human analysts, it

could be used to verify mechanistic hypotheses on simulation models at a faster rate. Applying formal methods to hypothesis evaluation would allow not only for evaluating the correctness of a mechanism when it conflicts with the evidence from prior experimentation, but for exploration of new hypotheses that increase information gain as well. Probabilistic model checking is a means of verifying mechanistic hypotheses autonomously from recorded experiment executions. The aim of this is to take some of the guesswork out of experimentation in a systematic way that reduces time spent on designing experiments, and reducing costs of reagents on experiments that give less information. Hypotheses can be defined in terms of specification patterns, which is a high-level language abstraction to describe well-defined temporal logic that can be checked against the produced verification model. The results of the probabilistic model checking can be translated as visual representation of the body of domain knowledge, and can guide a scientist to the next step of experimentation.

Analysis Model

The scientific discovery process is constituted by a series of feedback. Self-regulating the learning environment to emerge with a definitive behavior is problematic (Hofer, Yu, and Pintrich 1998). The inefficiency in learning occurs due to absence of proper definition of the goals and the failure in utilizing the prior knowledge as feedback for solving the problem at hand (DeJong and Mooney 1986). After specifying the question of interest and goal of study, we analyze the results from the experiments and probabilistic model checking to explain the rationale for the system's decision.

The system's decision can be represented as a statistical analysis of the data. These numbers were helpful because their compactness, relative to the full data set, and their clarity supported understanding, comparisons, and decision making. Summary statistics appealed to the rational thinkers who were attracted to the objective nature of data comparisons that avoided human subjectivity (Darden 2001). Bayesian networks (Pearl 2014) are a compact graphical representation of joint probability distributions. They can also be viewed as providing a causal model of a domain (Pearl 2003).

Models as Cognitive Agents

In order to answer complex scientific questions, it is important to synthesize data from observational and experimental studies to draw valid conclusions (Honavar, Hill, and Yelick 2016). While causal discovery from observational and experimental data is an active topic of research (Bareinboim et al. 2013), a great deal of work is needed to characterize the precise conditions under which findings of the studies can be incorporated, and to develop cognitive tools for integrating such findings under appropriate conditions. The aggregation of experimental results and adaptation of experiments to answer a research phenomenon, is critical to support automation of the scientific process. Towards this end, we propose an active learning agent that supports adaptive tuning of the experiment management system to be more effective in uncovering the underlying structure.

The agent evaluates the experiment results and if the results are unsatisfactory, an appropriate experiment is designed using the feedback from the earlier observed data and user defined parameters. This is used to run a new set of simulation and the formal verification methods are used to explain the mechanistic hypothesis. The outcome is represented graphically to aid the learning process.

Information theory based on entropy function is widely used to study nonlinear problems and complex system (Fan et al. 2011). The entropy function is a nonlinear transformation of parameters under study and is commonly used in information theory as a measure the uncertainty (Shannon 1948). The entropy-based approach is likely to be very useful to study the nonlinear relationship between evidences and mechanistic hypotheses, and to interpret their interactions in the simulation system. Our aim would be to reduce the uncertainty in the system and identify the relevance of the events. This information based approach helps in determining events that better characterize the model behavior and will be used as a reward for adapting experiment parameters to strongly prove the validity of mechanism in the system.

In this report, we elaborate the implementation of this approach which can be used to select the attribute or experiment parameter which helps in defining uncertainty in the model. This attribute can be used for designing experiments by emphasizing on the selected attribute and distinguishing mechanisms from competing mechanisms in the model.

Experiment

In order to test the validity of our framework and the practical utility of the approach, we used our project to demonstrate the ISHC model. The DSL we developed is abstract and free of any technical terms. The DSL covers all relevant concepts of the domain with language elements. All schematically-implementable code fragments of the reference implementation are covered by constructs of the DSL. The reference ISHC model is an instance of the DSL. The DSL for simulation experiment model is developed by mapping the experiment ontology metamodel.

Model

Model consists of a specification about the models name, the mechanisms, the events and the factor parameters. Mechanisms consist of the processes which is assumed to take place in the simulation system. Events define the path for tracing the functions that evaluate the events that form a part of the evidences. Parameters are the inputs to the model and their properties, which have an impact in determining the response/output of the simulation run.

```

model ISHC{

  mechanism M1 = inflammatoryAgent + Kupffercells
  [inflammatoryAgent > inflammatoryThreshold] -> Cytokines

  mechanism M2 = inflammatoryAgent + Kupffercells [noOfCytokine
  > cytokineThreshold] -> Cytokines

  event inflammation = 'void
  ishc.model.KupfferCell.handleInflammation()'

  parameter LPS = Solute with properties {tag: LPS, bindable: true,
  bolusRatio:1.0 , pExitMedia: 0.1 , pExitCell: 1.0 , bindProb : 0.25 ,
  bindCycles : 1 , numProps : 8 , membraneCrossing: true, bileRatio :
  0.5 , core2Rim : 0.50 , metProbStart : 0.3 , metProbFinish : 0.3 ,
  metabolites: 'LPS-Metabolite_A', inflammatory : true , pDegrade :
  0.0}

  parameter forwardBias = DISCRETE with values {0.5}

}

```

Goal

Goals define what the purpose of the experiment is. It also gives an idea about the specific field of concern and the context under which the study is performed.

```

goal
{
  object of study : 'Immune system influence on hepatic cytochrome
P450 regulation'

  purpose : 'Explain / characterize'

  focus : 'the reason for changes in downstream drug metabolism
and hepatotoxicity'

  view point : 'based on the response of hepatic cytochrome P450-
regulating mechanisms'

  context : 'when health and/or therapeutic interventions change.'
}

```

Hypotheses Hypotheses consists of relational hypotheses, mechanistic hypotheses and expected regularities. Mechanistic hypotheses deal with the effect of changes in the mechanism of the model. Relational hypotheses deal with the impact of changes in inputs or outputs. In order to represent behavioral changes in the model, we focus on mechanistic hypotheses for the study. Expected regularities are the temporal properties that are to be verified in the experimental run. It is stated in terms of state of factors and their properties.

The coherence model describes the explanatory coherence relation [Thagard 1989] between the hypothesis and the evidence. The evidence can have an activation weight which indicates its reliability. This is used to establish the weightage of the link between the evidence and hypothesis in the coherence network. We identified the explanatory coherence concept that would be relevant in our framework and would help in discovering the model mechanisms.

```

hypotheses
{
  mechanistic hypotheses
  {
    H3 : M1 occurs before M2
  }

  evidence
  {
    E1 : inflammation occurs after inflammatoryAgent > inflammatoryAgentThreshold
    activation weight : 0.5
    E2 : inflammation is absent after cytokine < cytokineThreshold
    activation weight : 0.5
  }

  coherence model
  {
    EXPLAIN (H1)(E1)
    EXPLAIN (H1 H2)(E1)
    ANALOGOUS (H1)(H2)
    DATA (Experiment1)(E1 E2)
  }
}

```

Experiment The ontology for the experiment section encompasses the structural elements of an experiment which includes the experiments design and performance measure. Based on the models parameters and their levels, the hypotheses and goal of the experiment, a design is created that is used in subsequent steps of the experiment life-cycle.

The experimental design is defined by the dependent variables, the control variables, the independent variables and their levels, constraints and values which in turn are mappings of the variables provided by the user. Based on this design, one can define what is known as a design matrix, which specifies the actual experimental runs, that is, the combination of factor levels.

```

experiment Experiment1
{
  design
  {
    designType FULLFACTORIAL

    variables
    {
      independent variables
      {
        LPS are at levels : LOW where LOW is in the range 1.0 to 1.0
        TOL are at levels : LOW where LOW is in the range 1.0 to 1.0
        DZ are at levels : LOW where LOW is in the range 1.0 to 1.0
      }

      dependent variables
      {
        cytokines : type SIMPLE
      }
    }
  }
}

```

Performance Measure An experiment consists of performance measure parameters which defines the criteria for successful experimental run. Basing on this measure we can decide whether additional iterations are required for satisfying the experiments objective. It is defined in terms of the expected value of the response or output of the experiment and its standard deviation.

performance measure is

```
{  
    cytokines= 500 +-10  
}
```

In the above example, the expected value of the cytokines after successful experiment execution is 500 with a standard deviation of 10.

Code Generation

We used the Xtend code generation process for mapping the DSL to platform. A set of templates were derived from the reference implementation and used for the transformation step.

```
class DOEGenerator implements IGenerator {  
    override void doGenerate(Resource resource, IFileSystemAccess  
    fsa) {  
        fsa.generateFile('ishc.properties',  
        toISHCProperties(resource.allContents  
            .filter(typeof(ModelSection)).head))  
        fsa.generateFile('delivery.properties',  
        toDeliveryProperties(resource.allContents  
            .filter(typeof(ModelSection)).head ,  
            resource.allContents.filter(typeof(Experiment)).head))  
        fsa.generateFile("KupfferCell.java",  
        toKupfferCell(resource.allContents  
            .filter(typeof(ModelSection)).head))  
        fsa.generateFile("Hepatocyte.java",  
        toHepatocyte(resource.allContents  
            .filter(typeof(ModelSection)).head))  
    }  
}
```

Generated Artifacts

The experiment specification is used for code generation by the template engine. The experiment specification defined using the DSL and the generated artifacts were used to run the ISHC simulation model in MASON to get the results.

delivery.properties

```
dose.0.solute.0.tag = LPS  
dose.0.solute.0.bindable = true  
dose.0.solute.0.pExitMedia = 0.1  
dose.0.solute.0.pExitCell = 1.0  
dose.0.solute.0.numProps = 3  
dose.0.solute.0.property.0.key = membraneCrossing  
dose.0.solute.0.property.0.type = boolean  
dose.0.solute.0.property.0.val = true  
dose.0.solute.0.property.5.key = metabolites  
dose.0.solute.0.property.5.type = map  
dose.0.solute.0.property.5.val = Metabolite_A  
=> <0.0,1.0>  
dose.0.solute.0.property.6.key = inflammatory  
dose.0.solute.0.property.6.type = real  
dose.0.solute.0.property.6.val = true  
dose.0.solute.0.property.7.key = pDegrade  
dose.0.solute.0.property.7.type = real  
dose.0.solute.0.property.7.val = 0.0
```

Code generated in
response to :

parameter LPS = Solute with
properties {tag: LPS,
bindable: true , pExitMedia:
0.1 , pExitCell: 1.0 ,
bindProb : 0.25 , numProps:
3 , membraneCrossing:
metabolites: 'LPS-
Metabolite_A',
inflammatory : true ,
pDegrade : 0.0}

LPS are at levels : 0 , 1.0

KupfferCell.java

```
public void handleInflammation()  
{  
    int numInflammatoryStimuli = 0;  
    int numCytokines = 0;  
    for(Object o : solutes)  
    {  
        Solute s = (Solute) o;  
        if(s.hasProperty("inflammatory") &&  
        ((Boolean)s.getProperty("inflammatory")))  
        {  
            numInflammatoryStimuli++;  
        }  
        if(s.type.equals("Cytokine"))  
        {  
            numCytokines++;  
        }  
        if(s.type.equals("inflammatoryAgent"))  
        {  
            if("inflammatoryAgent" > "inflammatorythreshold")  
            numCytokines++;  
        }  
        if(s.type.equals("inflammatoryAgent") {  
            if("noOfCytokine" > "cytokineThreshold")  
            numCytokines++;  
        }  
    }  
    if(numCytokines >= parent.cytokineThreshold)  
    {  
        return;  
    }  
}
```

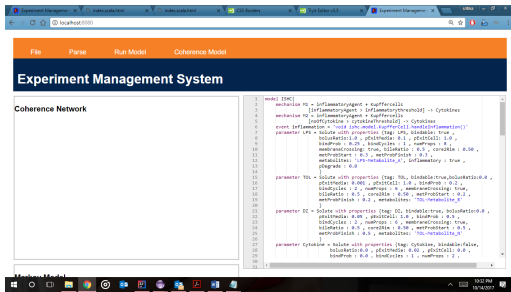
Code generated in response to the mechanism:

mechanism M1 =
inflammatoryAgent + Kupffercells
[inflammatoryAgent >
inflammatorythreshold] ->
Cytokines

mechanism M2 =
inflammatoryAgent + Kupffercells
[noOfCytokine >
cytokineThreshold] -> Cytokines

Application

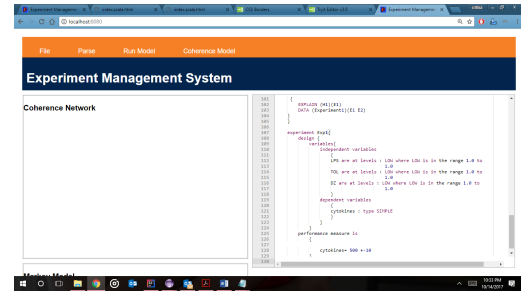
We developed an application to demonstrate our framework and its functionalities. The experiment specification defined using the DSL and the generated artifacts were used to run the ISHC simulation model (Petersen, Ropella, and Hunt 2014) in MASON to get the results. The figures below illustrate various functions supported by the application.



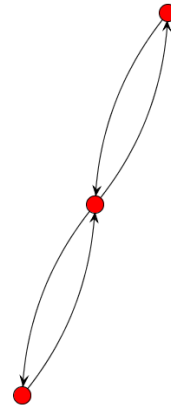
The web interface is shown above. The experiment management system shows an online DSL editor, coherence network and the Markov model. It supports functionalities like opening a reference model implemented using the DSL grammar, editing it and saving changes. The online editor also supports syntax highlighting.

When the user selects to Parse the input, the following operations are executed:

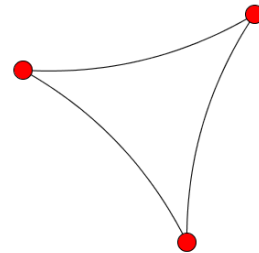
- The mechanistic hypothesis is translated and a model with the defined mechanism is generated.
- The parameters defined in the model section is used to generate the default values of the model parameters.
- The levels and values of independent variables in the experiment section are used to generate a full-factorial design. This is used to run the simulation model.
- The evidences are translated into LTL properties which is used in the model verification process.



When the user selects Run Model, the generated design matrix is used to run the simulation model which incorporates the user defined mechanisms. The results from the run are then analyzed and a Discrete Time Markov Chain(DTMC) model is constructed by carefully inspecting the results and recording the changes that trigger a transition in the output variables. This generated DTMC model is shown to the user. This is used for model verification using the PRISM interface.



When the user selects Coherence Model, the initial explanatory coherence network is generated based on the user definition in the DSL.



Bayesian Network

Bayesian networks are used to characterize the statistical dependencies between the system variables. The probabilistic

representation of the simulation system can be used for generating inference of the system which is easier to understand and make the decision making process quicker.

ID3

Our aim would be to reduce the uncertainty in the system and identify the relevance of the events. This information based approach helps in determining events that better characterize the model behavior and will be used as a reward for adapting experiment parameters to strongly prove the validity of mechanism in the system.

The ID3 algorithm iterates through every unused attribute of the dataset and calculates the entropy and information gain of that attribute.

```
37 //The following function calculates the entropy from the given data
38 private static double computeEntropy (int[] data, int c) {
39     double totalDataCnt = 0;
40     int count = 0;
41     double Entropy = 0;
42     for (int i = 0; i < 2; i++) {
43         if (data[i] == c) {
44             count++;
45             totalDataCnt += data[i];
46         }
47     }
48     if (totalDataCnt == 0 || count == 1)
49         return 0;
50     if ((count-1) / totalDataCnt > 0) {
51         for (int i = 0; i < 2; i++) {
52             if (data[i] != c) {
53                 Entropy += (-1) * (data[i] / totalDataCnt) * (Math.Log10(data[i] / totalDataCnt)) / Math.Log10(2);
54             }
55         }
56     }
57     else {
58         if (data[0] != 0 || data[1] != 0) {
59             Entropy = -data[0] / totalDataCnt * Math.Log10(data[0] / totalDataCnt) - data[1] / totalDataCnt * Math.Log10(data[1] / totalDataCnt);
60         }
61     }
62     return Entropy;
63 }
64
65
66
67
```

It then selects the attribute which has the smallest entropy (or largest information gain) value.

```
9 // The following function calculates the information gain
10 public static double computeGain (int colIndex, TreeInst datasets, TreeInst resultRows, int c) {
11     Arraylist<int[]> dataCount = getResultCounts(colIndex, datasets, resultRows);
12     int[] resultCount = getResultCounts(colIndex, datasets, resultRows);
13     double totalResultCount = 0;
14     double[] totalDataCnt = new double[2];
15     double Entropy = 0;
16     double gain = computeEntropy(resultCount, c);
17     for (int i = 0; i < 2; i++) {
18         totalResultCount += resultCount[i];
19         for (int j = 0; j < 2; j++) {
20             totalDataCnt[j] += dataCount.get(i)[j];
21         }
22     }
23     for (int i = 0; i < 2; i++) {
24         Entropy += (-1) * (totalDataCnt[i] / totalResultCount) * computeEntropy(dataCount.get(i), c);
25     }
26     gain = Entropy - g;
27     return gain;
28 }
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```

The dataset is then split by the selected attribute to produce subsets of the data. The algorithm continues to recursively on each subset, considering only attributes never selected before.

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design which can provide a better rationale for system's decision and discriminate competing hypotheses.

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