Inducing Explanatory Process Models from Biological Time Series

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Abstract

We address the task of inducing explanatory models from observations and knowledge about candidate biological processes, using the illustrative problem of modeling photosynthesis regulation. We cast both models and background knowledge in terms of processes that interact to account for behavior. We also describe IPM, an algorithm for inducing quantitative process models from such input, and we demonstrate its use on the photosynthesis domain. In closing, we consider the generality of our approach, discuss related research on biological modeling, and suggest directions for future work.

1. Introduction and Background

Biomedical science aims to understand the mechanisms by which organisms survive, grow, and reproduce. Like other scientific fields, it collects observations, identifies recurring phenomena, and attempts to explain these phenomena using existing knowledge. However, this endeavor is a complex one, and biologists would benefit from additional tools to assist them in constructing and evaluating their models.

The success of machine learning and data mining in commercial domains has led to increased interest in using similar methods to discover biological knowledge. However, the best-developed techniques are designed to operate on large data sets and in the absence of background knowledge. Despite rhetoric the contrary,[1] biology remains a data-sparse field, but it has considerable knowledge available to constrain the search for models.

Another drawback of standard induction methods is that they construct descriptive models. These can make accurate predictions on new test cases, which may be sufficient for commercial applications, but biologists typically desire *explanatory* models of behavior. An explanation of some phenomenon is cast in terms of other knowledge, such as structures or processes that are familiar to domain experts.

[1] For example, microarray technology produces many numbers but very few samples, whereas most induction methods assume many of the latter.

Finally, traditional induction techniques produce models that are expressed in notations developed by computer scientists, few of which biologists find comprehensible. Even work on inducing causal models, which sometimes have an explanatory flavor, focuses on abstract formalisms that make little contact with concepts from biomedical science. Notations that incorporate domain concepts more directly would presumably be easier to understand and provide additional constraints on model induction.

In this paper, we describe an approach to inducing biological models that responds to each of these issues. Our models are cast as sets of interacting processes that explain rather than describe the data, and we report a method that constructs such models from background knowledge stated as generic processes, which serve both to constrain search through the model space and make contact with familiar concepts. We illustrate this approach on a problem of central interest to biologists – the regulation of photosynthesis – for which there is limited data but some knowledge. However, the approach is a general one that should apply to other biomedical problems, which we discuss in closing along with related research and our plans for future work.

2. The Regulation of Photosynthesis

Photosynthesis is a complex combination of reactions that are catalyzed by a system of protein complexes, most of which are bound into the thylakoid membrane of the chloroplasts of higher plants. These include 'light' reactions, which operate only in the light and use absorbed energy to produce a variety of biochemical species, which are in turn used by the remainder of the cell as energy. In contrast, 'dark' reactions do not require light but use energy produced by the light reactions to combine CO_2 molecules into sugars, which are then used to produce cellular energy and other products or stored for later utilization.

One side effect of the normal photosynthetic reaction is the creation of 'reactive oxygen species' (ROS), which can be very damaging to cellular components, especially those in the photosynthetic apparatus. Cells appear to have systems that aim to minimize creation of ROS, that 'clean up' or

neutralize ROS, and for repairing damage. For these and other reasons, the complex network of mechanisms for energy production, storage, and utilization in cells includes many regulatory controls.

Although the biochemical reactions involved in photosynthesis, and the general shape of its regulation, are fairly well understood, the details of regulatory signals and mechanisms remain obscure. Biologists know about a variety of abstract regulatory mechanisms that could affect photosynthetic activity, such as signal transduction and transcription, but they are uncertain about which ones are responsible and the detailed forms in which they occur. For instance, the protein produced during translation is known to degrade, but it remains unclear whether this takes place at a constant rate or whether it is regulated.

To further elucidate the details of photosynthesis regulation, Labiosa et al. (2003) carried out an experiment with Cyanobacteria, a unicellular organism, under simulated naturalistic conditions. In particular, they constructed a cyclostat which replicated the light variations that occur with the 24-hour day-night cycle.[2] Samples of the organism were collected at nine distinct times throughout the day-night cycle, then analyzed using cDNA microarray technology to measure mRNA levels for 3000 genes in each sample.

Inspection revealed that the 17 genes whose expression levels were most highly correlated with light intensity had each been implicated in photosynthesis previously, which makes biological sense. However, the shape of their curves was somewhat unexpected. Expression levels were low at night, increased rapidly when the sun rose, and decreased again after sunset, but they also exhibited a substantial drop around noon. An adequate model of these genes' regulation should account for all of these regularities in at least qualitative terms, and preferably in quantitative ones as well. In addition, it should be consistent with existing knowledge about photosynthesis and other biological mechanisms.

3. Process Models of Biological Systems

Before we can assist biologists in constructing models of gene regulation, we must select some formalism in which to represent candidate models. Because biology does not have a tradition, like physics and chemistry, of formal notations, most work along these lines has borrowed frameworks from other fields, yet only some of these formalisms characterize the behavior of dynamical systems that change over time. These include Boolean networks (e.g., Shmulevich et al., 2002), dynamic Bayesian networks (e.g., Ong et al., 2002), differential equations (e.g., Tomita et al., 1999), and Petri networks (e.g., Peleg et al., 2002; Matsuno et al., 2002). But despite their representational power, these frameworks make limited contact with established biological concepts.

The problem is that biologists' papers and talks repeatedly make informal reference to *processes* that operate within living organisms. Research in artificial intelligence has produced formalisms that cast models as sets of interacting processes to explain dynamical behavior, with Forbus' (1984) qualitative process theory being a notable example. This offers a notation for biological mechanisms, but it focuses on qualitative simulations that predict only the directions in which continuous variables change over time.

Table 1. A process model for photosynthetic regulation.

model Photo_Reg;
variables $light, mRNA, protein, ROS, redox, transcr\_rate$;
observables $light, mRNA$;
process photosynthesis;
  equations $d[redox, t, 1] = 1.50 * light * protein$;
    $d[ros, t, 1] = 1.00 * light * protein$;
process photo_translation;
  equations $d[protein, t, 1] = 0.20 * mRNA$;
process protein_degradation_ros;
  conditions $protein > 0, ROS > 0$;
  equations $d[protein, t, 1] = -0.05 * ROS$;
    $d[ROS, t, 1] = -0.05 * ROS$;
process mRNA_transcription;
  equations $d[mRNA, t, 1] = transcr\_rate$;
process regulate_light;
  equations $transcr\_rate = 0.80 * light$;
process regulate_redox;
  conditions $redox > 0$;
  equations $transcr\_rate = -2.00 * redox$;
    $d[redox, t, 1] = -1.00 * redox$;
process mRNA_degradation;
  equations $d[mRNA, t, 1] = -0.20 * mRNA$;

Instead, we have explored a hybrid representation that embeds numeric equations within the qualitative structures provided by Forbus' approach. A model consists of a set of biological processes, each of which describes the quantitative relations among two or more variables that are cast as one or more algebraic or differential equations. Each process may also include arithmetic conditions on quantitative variables that specify when it is active. Such a quantitative process model must refer to some measurable variables, but it may also include unobservable, theoretical terms.

For example, Table 1 shows one possible model of the expression phenomena described earlier. This specifies six quantitative variables – light intensity, the concentrations of mRNA, photosynthetic protein, and reactive oxygen species (ROS), energy in the system (redox), and the rate of mRNA transcription. Only two of these variables – light and mRNA – are directly observable, with the remainder being theoretical terms that are biologically plausible.

The model incorporates seven distinct processes. Photosynthesis combines light with proteins to produce energy or redox, but it also increases ROS as a side effect. The photo_translation process increases the concentration of photosynthetic proteins, with the increase depending on the concentration of mRNA. However, another process, protein_degradation_ros, leads to a reduction in both protein and ROS concentration. A fourth process,

[2]This device was built, and the study run, in the Carnegie Institute of Washington's Department of Plant Biology.

mRNA_transcription, increases the mRNA concentration by an amount controlled by the variable transcr_rate, which is in turn influenced by two other processes. The first, regulate_light, states that the rate is directly proportional to light, whereas the other process, regulate_redox, states that it is inversely proportional to redox, which is itself reduced. A final process, mRNA_degradation, claims the mRNA concentration decreases by a fixed proportion every time step.

Like any model, this example makes important simplifying assumptions. For instance, it refers to a single, aggregate measure of mRNA rather than to the amounts for individual genes, and does the same for protein and transcr_rate. Photosynthesis is treated as a single process, rather than as the complex set of activities that we know it involves, and the processes of transcription, degradation, and transcription regulation are abstracted in a similar way. Also, the component processes are all plausible biologically, but some are more so than others. For instance, we know that transcription is regulated and that both protein and mRNA can degrade, but not the details of these activities.

Nevertheless, given such a quantitative process model, we can simulate it to make predictions about how variables will change over time. This involves compiling the process notation into a set of linked algebraic and differential equations, giving them initial values for some variables, and invoking numerical approximation techniques to calculate values for trajectories. One complication is that the conditions on processes may lead different sets of equations to apply during different intervals. Also, if multiple processes influence the same variable, we assume their effects are additive. Otherwise, the simulation process is straightforward. However, finding a model that can generate the observed trajectory is another story, and the model in Table 1 provides a poor fit to the Labiosa et al. data. We would like a computational method that combines knowledge and data to search the space of models, to which we now turn.

4. Encoding Background Knowledge

A key characteristic of the model just described is that it moves beyond a simple description of observations to *explain* them in terms of other, more basic, structures or processes. The explanatory referents are typically unobservable in the current situation, but they make contact with known, familiar mechanisms. The automated construction of such explanatory models requires that we represent the background knowledge to which they refer.

To this end, we utilize the notion of *generic processes*. These are similar in spirit to the specific processes that appear in a model, in that they incorporate equations and activation conditions, but they do not commit to particular variables or parameter values. Table 2 presents seven generic processes for the domain of plant biochemistry, most of which have direct analogs in Table 1.

Note that each generic process includes a set of generic variables, along with type information that constrains the specific variables against which they can match. Each structure also includes the names of parameters that appear in conditions or equations, along with upper and lower bounds on their values. For instance, the generic process consuming_regulation involves one variable, R, that must be a rate, and another, C, that must be a concentration (such as redox or ROS), and it refers to two parameters, one of which (pi) must fall between zero and one.

Table 2. Seven generic processes for gene regulation.

process photosynthesis;
  variables $L\{light\}, P\{protein\}, R\{redox\}, S\{ROS\}$;
  parameters $alpha$ $[0, 1], beta$ $[0, 1]$;
  equations $d[R, t, 1] = alpha * L * P$;
  $d[S, t, 1] = beta * L * P$;
process controlled_degradation;
  variables $D\{degradable\}, E\{degrader\}$;
  parameters $delta$ $[0, 1]$;
  conditions $D > 0, E > 0$;
  equations $d[D, t, 1] = -1 * delta * E$;
  $d[E, t, 1] = -1 * delta * E$;
process automatic_degradation;
  variables $C\{concentration\}$;
  parameters $gamma$ $[0, 1]$;
  conditions $C > 0$;
  equations $d[C, t, 1] = -1 * gamma * C$;
process translation;
  variables $P\{protein\}, M\{mRNA\}$;
  parameters rho $[0, 10]$;
  equations $d[P, t, 1] = rho * M$;
process transcription;
  variables $M\{mRNA\}, R\{rate\}$;
  equations $d[M, t, 1] = R$;
process unconsuming_regulation;
  variables $R\{rate\}, S\{signal\}$;
  parameters mu $[-1, 1]$;
  equations $R = mu * S$;
process consuming_regulation;
  variables $R\{rate\}, C\{concentration\}$;
  parameters nu $[-1, 1], pi$ $[0, 1]$;
  equations $R = nu * C$;
  $d[C, t, 1] = -1 * pi * C$;

Some generic processes are more specific than others. For example, those for photosynthesis, transcription, and translation effectively refer to specific variables, and are generic only in not committing to parameter values. Others, like those for degradation and regulation, refer to classes of variables and can be instantiated in different ways. This lets us encode uncertainty about which variables are actually involved in these processes, but still supports the constrained search for specific models.

5. Inducing Dynamic Biological Models

Taken together, time-series data about gene expressions and generic biological processes provide us with the raw material to construct regulatory models. This task is an instance of what we have called *inductive process modeling* (Langley et al., 2003). The goal of process model induction is to generate a specific process model, like the one in Table 1, that makes reference to known generic processes and that fits

the trajectories of observed variables. The resulting model is explanatory, rather than purely descriptive, because it refers to unobserved variables and processes. Moreover, it should be understandable to domain scientists because it is cast in terms of familiar concepts, much as in Falkenhainer and Forbus' (1991) work on compositional modeling.

In our current problem, the data concern the expression levels of photosynthetic genes over time, along with the associated light intensities. The background knowledge includes plausible forms for processes like photosynthesis, transcription, translation, and degradation, like those in Table 2, including type constraints on their variables and bounds on their parameters. The target is a model like that in Table 1, which contains variants of these generic processes that commit to specific variables and their parameter values. Ideally, this specific model should generate trajectories that match the training data and make accurate predictions about future values.

We have implemented an algorithm, IPM, that addresses this task. Its inputs include a set of observable and optional unobservable variables to be included in the model, the types for these variables, a set of generic processes from which to construct candidate models, and a time series of observed values to which models should be fit. As output, the system produces a set of parameterized models ranked their by mean squared error on the training data.

IPM decomposes the task of inductive process modeling into two subproblems, with the first involving a constrained exhaustive search through the space of model structures. To this end, the system finds all ways to instantiate the generic processes with known specific variables that are consistent with the type constraints. Some 14 instantiated processes are generated in this manner from the background knowledge about photosynthesis and gene regulation presented earlier. IPM then composes these instantiated components in all possible ways that involve at least L and no more than U processes, that include all observed variables, and that form a single connected graph. For the run below, we used $L = 4$ and $U = 10$, which produced 158 model structures.

Each such candidate specifies the model's variables and their causal relationships, but it does not include the values for parameters. Thus, IPM's second stage carries out a search through the parameter space defined by each model structure. The system first selects a random set of values that fall within the parameter ranges specified in the generic processes, then carries out gradient descent using the Levenberg-Marquardt method until it converges to a local optimum. Next, IPM generates several new candidates by making random jumps for the values of each parameter. If one or more jumps produces lower error, it selects the best such point and continues using the Levenberg-Marquadt method; otherwise, the system repeatedly increases the jump size and generates new candidates. However, if no no improvement occurs after 20 iterations, it restarts the entire process from a new random initial point. We have found this parameter-estimation method to produce reasonable matches to time series from various domains.

Table 3. Model for photosynthetic regulation induced by IPM.

model Photo_Reg;
variables $light, mRNA, protein, ROS, redox, transcr\_rate$;
observables $light, mRNA$;
process photosynthesis;
  equations $d[redox, t, 1] = 3.623 * light * protein$;
            $d[ROS, t, 1] = 1.340 * light * protein$;
process photo_translation;
  equations $d[protein, t, 1] = 0.048 * mRNA$;
process mRNA_transcription;
  equations $d[mRNA, t, 1] = transcr\_rate$;
process consuming_regulation_1;
  equations $transcr\_rate = -12.720 * redox$;
            $d[redox, t, 1] = -1 * 5.309 * redox$;
process controlled_degradation_1;
  conditions $protein > 0, ROS > 0$;
  equations $d[protein, t, 1] = -1 * 0.102 * ROS$;
            $d[ROS, t, 1] = -1 * 0.102 * ROS$;
process automatic_degradation_1;
  conditions $mRNA > 0$;
  equations $d[mNRNA, t, 1] = -1 * 0.816 * mRNA$;

Recall that the example model in Table 1 includes a number of unobserved variables, some of which occur in the left-hand sides of differential equations. This means that, in addition to finding values for the parameters in each process, IPM must also infer the initial values for each such variable. To this end, the system simply treats these as additional terms that must be fit by the parameter estimation module. Elsewhere (Langley et al., 2003) we have evaluated this capability on synthetic data, and also shown that one can use a similar approach to induce the thresholds that appear in conditions on processes.

To demonstrate that IPM can produce reasonable models of the processes that govern photosynthesis regulation, we provided it with the background knowledge from Table 2 and time-series data from the cyclostat study. However, because we had only nine samples, we did not attempt to construct a model that predicted separate expression levels for each of the 17 genes. Instead, we averaged the results for these genes at each time step and use the resulting means as the training set for model induction. We also told the system that candidate models should include the observable variables light and mRNA, along with the optional unobservable variables protein, ROS, redox, and transcr_rate.

The top-ranked process model that IPM generated from these data, shown in Table 3, has similarities to and differences from the model presented earlier in Table 1. The new model includes processes for photosynthesis, translation, and transcription, but this is hardly surprising, since their variable types were so constrained as to demand their incorporation. More interesting was the inclusion of controlled degradation of photosynthetic proteins by ROS, automatic degradation of mRNA, and controlled regulation of transcription rate. The model claims that light affects mRNA transcription, but only indirectly through its influence on redox, rather than through a direct causal link.

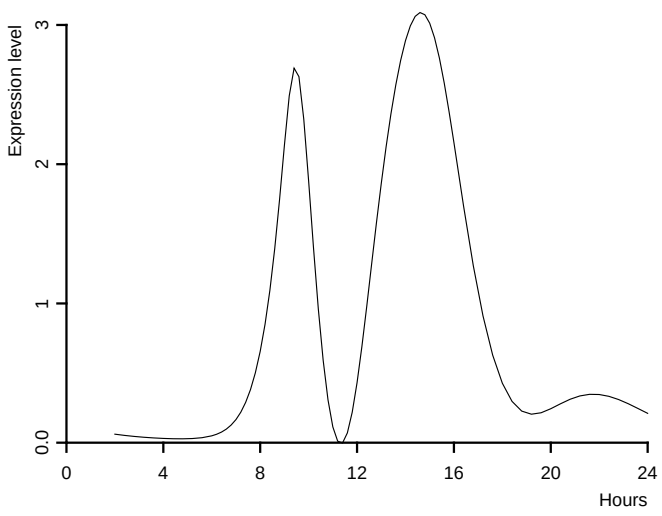

Figure 1. Average expression for 17 genes related to photosynthesis over a 24-hour period, as predicted by the best induced model. The dependent variable is the ratio of mRNA in each sample to the mRNA in a mixture of all the samples.

Figure 1 shows the trajectories that this model predicts over a 24-hour period. We have not reported the average expression levels from the cyclostat experiment because our biologist collaborators have not yet published them, but the quantitative fit is quite good, with a mean squared error of 0.000289. The qualitative match is also good, in that the model reproduces the general M shape that was observed in the study. Equally important, it makes biological sense in that it includes plausible processes for photosynthesis, translation, transcription, regulation, and degradation.

However, we should note that data obtained from microarrays are typically very noisy, and with only nine samples, we should not be confident that the model is correct. Our main goal has been to demonstrate that inductive process modeling can construct a model for phenomena of scientific interest that is consistent with biological knowledge and matches the data. We should also note that IPM cannot produce models that fit arbitrary curves even in cases where they contain more parameters than the number of observations. The constraints imposed by generic processes, including ranges on parameters and functional forms, should produce relatively low variance even on the small data sets that predominate in biological studies.

6. Generality, Limits, and Related Work

Although we have focused here on inducing models of gene regulation, the paradigm of inductive process modeling is quite general. Elsewhere (Langley et al., 2003) we have demonstrated that the approach can infer process models of ecosystem behavior, and the basic approach is applicable to any biological domain in which one can identify generic processes with plausible functional forms and for which quantitative data are available. Here we have emphasized dynamical models and time series, but our methods can handle algebraic models and static data equally well.

One biomedical area that seems a likely candidate is physiology, where there have already been efforts to manually develop quantitative models of behavior using the formalism of differential equations. Another promising topic involves the spread of infectious diseases, for which there already exist numerical models that incorporate ideas from population dynamics. Both fields have considerable knowledge about component processes and functional forms, but data are expensive to collect and the model space is large.

Although our initial results in modeling gene regulation have been encouraging, it is clear that more work still lies ahead. One obvious direction for future research would develop analogous process models for other facets of photosynthesis, such as energy storage and utilization. This would require the creation of generic processes for these mechanisms and their use in modeling the expression levels of these genes. We should also carry out studies with synthetic data, averaged over different training sets, to better understand how our methods scale to settings with different noise levels, more generic processes, and more complex target models.

More important, we must extend our framework to support larger-scale models of biological systems. A promising response would utilize hierarchical models that describe the organism in terms of subsystems and that are based on background knowledge about generic subsystems in addition to generic processes. Also, we should adapt our approach to reflect the qualitative nature of many biological models and the fact that biomedical scientists often care only about qualitative fits. In response, we plan to explore methods that induce semi-quantitative process models (e.g., Kay et al., 2000), which can specify ranges on parameters rather than precise values. Such a revised system might direct search based on models' abilities to account for qualitative relations (e.g., one measurement being higher than another) rather than mean squared error.

Our approach to biological discovery has close connections with other recent efforts. For example, Bay et al. (2003) present an approach to inducing linear causal models of gene regulation from expression data and background knowledge stated as an initial model. Both Zupan et al. (2001) and Bryant et al. (2001) report systems that infer qualitative genetic networks from biological knowledge and the results of auxotrophic growth experiments, while Mahidadia and Compton (2001) report a similar system that revises qualitative causal models based on experimental results in neuroendocrinology. Ong et al. (2002) describe yet another technique that uses knowledge about promoters to constrain induction of dynamical models for Tryptophan metabolic regulation. However, all have assumed abstract representations that make limited contact with biological concepts like translation, transcription, and degradation.

Another line of research that is closer in its technical details has addressed the induction of quantitative models of dynamical systems. For example, Koza et al. (2001) used genetic methods to infer the structure and parameters of a metabolic model from time-series data about concentra-

tions. Bradley et al. (1999) describe a different approach to finding differential equation models that draws on knowledge about the behaviors produced by alternative classes of equations. The most similar research comes from Todorovski (2003), whose LAGRAMGE system utilizes domain-specific knowledge, some cast as processes, to guide search for differential equation models. However, his work has focused on environmental domains rather than biomedical ones, such as the one we have addressed here.

7. Concluding Remarks

In this paper, we have described an approach to representing, utilizing, and inducing causal biological models. This paradigm – inductive process modeling – supports the construction of explanatory rather than descriptive models, casts these models in terms of familiar biological processes, and takes advantage of background knowledge to constrain search and produce plausible accounts even when there are few samples. We reported a specific system, IPM, that carries out a two-stage search through a space of model structures and their parameters, and we illustrated its operation on background knowledge and time-series data related to the regulation of photosynthesis.

The system produced a model that reproduced both the qualitative shape and the quantitative details of the expression data, while incorporating processes that made biological sense. The small number of samples make this result unreliable, but, we maintain, more plausible than ones found without the benefit of background knowledge. We argued that our approach is a general one that has applications to other biomedical domains like physiology and epidemiology, but we also identified limitations that should be addressed in future research. Finally, we noted its connections to other work on computational scientific discovery that uses background knowledge to produce interpretable causal models.

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