

The Robot Scientist Platform

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1 Overview

The aim of the *Robot Scientist* project is to construct a physical implementation of a scientific active learning system (see Figure 1). The system will construct an initial set of hypotheses and then repeat the following cycle: (1) devise experiments to select between competing hypotheses, (2) direct a robot to physically perform these experiments, (3) automatically analyse the experimental results, and (4) revise its hypothesis set in the light of the experimental results. This cycle is then repeated until only one hypothesis remains. The Robot Scientist project is investigating scientific active learning by applying it to the problem of functional genomics to automatically produce useful knowledge about genes of unknown function [1].

The *Robot Scientist Platform* is a system for conducting microbiology assays with minimal human intervention. The platform consists of a laboratory robot (Figure 2), a plate reader (Figure 3) and a dedicated personal computer to control them. The robot automates the task of liquid handling and can conduct assays by pipetting and mixing liquids on microtitre plates (Figure 6). The microtitre plates can be measured using the adjacent plate reader using a variety of protocols. Results are returned to the laboratory information system (LIMS) on the dedicated PC or a networked computer.

The platform's main use to date has been yeast growth experiments on knockout strains. By automating a large portion of the laboratory procedure, the task of conducting assays has been made considerably less laborious and less error-prone. A key feature of the platform is its very high-level interface. For instance, for a yeast growth assay, it is sufficient to specify the liquids (growth media, organism strain etc.) and volumes and growth time to obtain an estimate of the number of cells. From an abstract perspective, the robot scientist platform can be seen as an *oracle* that can be queried about the observable behaviour of microorganisms. Once the protocol has been finalised, the number of different assays that can be performed is essentially limitless. It is for this express reason that it was built with the objective of connecting it to an intelligent algorithm capable of choosing future assays based on previous assay outcomes.

This report gives an overview of the platform's components and its architecture. It also illustrates how assays can be sent to the platform and how results are returned.

2 Architecture of the Robot Scientist Platform

The main components of the platform are shown in Figure 4.

2.1 The Hardware

Robot. The robot is a Beckman Coulter Biomek 2000 Workstation, a liquid handling robotic workstation¹. The robot has a work surface consisting of 12 cells. Each cell can hold either a microtitre plate (Figure 6), reservoirs for liquids, tips for pipetting, or tools for pipetting and gripping.

Plate-Reader. The reader is a Wallac Victor2 plate reader². The reader's counting modes cover all the main non-radioactive counting technologies, including TR-luminometry and photometry. It also has shaking and temperature control features.

Server. The server is an IBM PC running Windows NT4. It hosts the robot and reader's software. The server can host the platform's high level interface or it may be operated remotely over the internet.

The robot and reader are adjacent so that the robot is able to transfer microtitre plates from its worksurface to the reader.

2.2 The Software

The Oracle

The high-level interface to the robot scientist platform is called the *Oracle*. The oracle takes as input a query and returns a response; the query corresponds to an assay and the response is the assay's outcome which is established by conducting the assay.

Queries to the oracle are specified as clauses in the Prolog logic programming language and the results are also returned as Prolog clauses (see Example 1). The Prolog specification of an assay is compiled into a sequence of steps to be performed by the robot and plate reader. These instructions are queued to be executed by the robot.

After the assay, results are collected and stored in laboratory information system (LIMS). Since microbiological assays are susceptible to random error, a number of assay replicates are performed and statistical analysis can determine the most likely outcome.

Example 1 *Is the yeast strain with gene YHR137W deleted viable on minimal medium? There should be 730 μ L medium and 20 μ L inoculum and 8 replicates. This query is presented to the oracle as:*

```
expt(expt49,           % experiment ID
     plate3,          % plate ID
     [                % list of liquids
       minimal-media:730, % medium and volume
       'YHR137W':20      % strain and volume
     ],
     8).              % repetitions
```

¹See <http://www.beckman.com>.

²See <http://lifesciences.perkinelmer.com>.

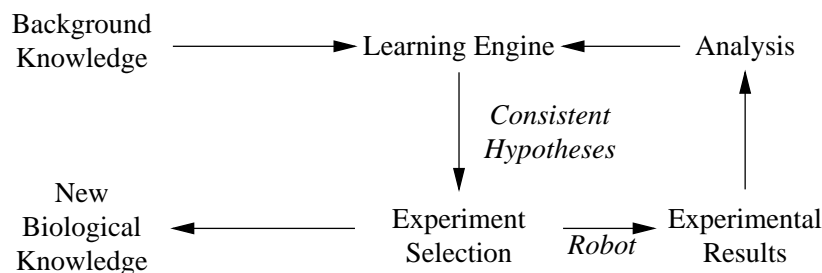


Figure 1: An overview of the Robot Scientist.

The first two parameters are labels to identify the assays. This is followed by a list of liquids and their respective volumes. The final parameter denotes the number of replicates.

The outcome is a set of 8 readings:

```

outcome([
    % list of liquids
    minimal-media:730,
    'YHR137W':20
]),
[
    % list of readings
    0.09,0.07,0.11,0.08,
    0.09,0.11,0.08,0.08
]).
  
```

When there are results for a sterile control (medium with no inoculum) statistical analysis can ascertain whether these readings correspond to viable or non viable. This answers the questions whether or not the gene significantly affects growth. The resulting statement from the oracle is either of the following:

```

grows([minimal-media:730,'YHR137W':20],yes).
grows([minimal-media:730,'YHR137W':20],no).
  
```

Software Architecture

The software consists of the following components:

The Oracle. The interface to the platform. The oracle consists of the compiler and the laboratory information management system (LIMS).

The Compiler. The Robot Scientist Compiler takes high level descriptions of experiments and compiles them into instructions for execution on the robot. The robot instructions are transferred to the Job-Server.

The FTP-Server. Connects the server to the oracle. It accepts robot-instruction files from the oracle and returns result files.

The Job-Server. This component maintains a queue of robot-instruction files from the oracle. When the robot is ready it transmits the next batch of instructions to the robot's on-board controller.

LIMS. The Laboratory Information Management System (LIMS) maintains a database of assays and their

outcomes. The database can be queried and reports may be generated. It also allows statistical analysis of the results.

Details of the operation of these components can be found in the User Guide [2].

3 Programmed Experimental Procedure

The experimental protocol currently being used by the robot is Figure 5. For yeast growth experiments, technician support is required to prepare inocula, growth media and metabolites, and to transfer microtitre plates to an incubator. Apart from these steps, the experimental procedure can be fully automated.

1. for each microtitre plate:
 - (a) prepare growth media in all wells.
 - (b) add inoculum.
 - (c) mix all wells.
2. allow to incubate.
3. for each microtitre plate:
 - (a) mix all wells.
 - (b) transfer a small amount of each well to a plate.
 - (c) move the plate to the plate reader.
 - (d) measure absorbance for each well.

Figure 5: The Robot Scientist platform's experimental procedure.

4 Conclusion

The Robot Scientist Platform is a robotic system that automates microbiological assays. The aim has not been to build a completely automated system, but one where human intervention is minimal. The interface to the platform is very high-level and is suited to a system that can intelligently use the outcomes of previous assays to select future assays. Such an assay-selecting system could be a human expert or a machine-learning algorithm.

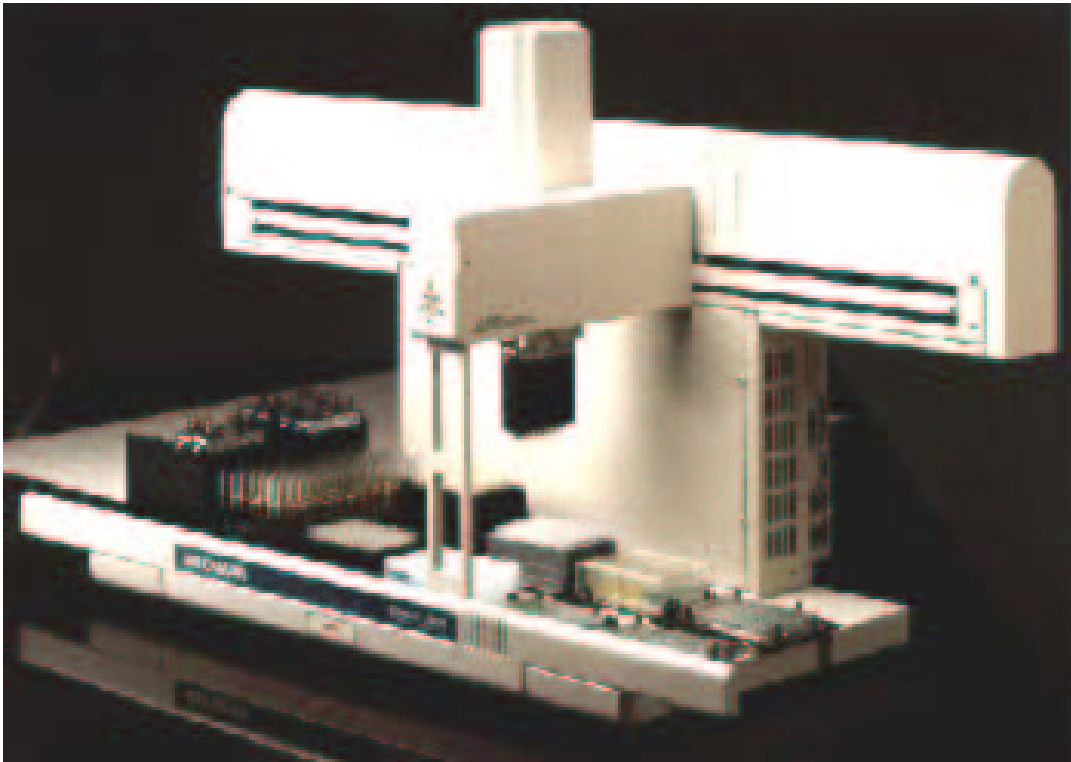


Figure 2: The Biomek 2000 liquid-handling robot.



Figure 3: The Victor2 plate reader.

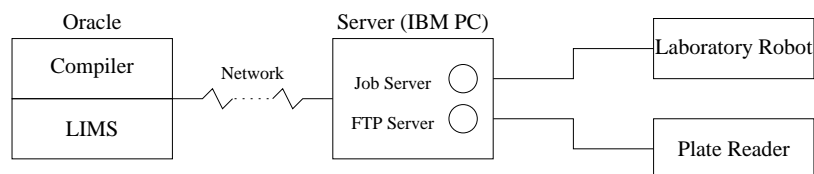


Figure 4: Architecture of the Robot Scientist Platform.

Acknowledgements

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References

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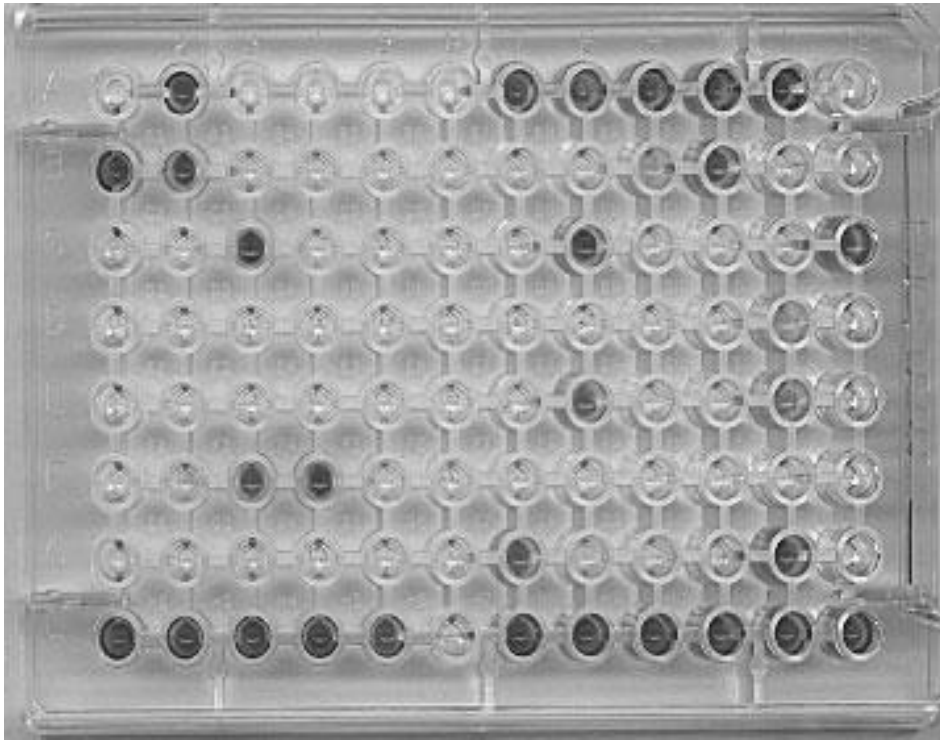


Figure 6: A 96-well microtitre plate on which assays are conducted.