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SynBioLGDB: a resource for experimentally validated logic gates in synthetic biology

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Synthetic biologists have developed DNA/molecular modules that perform genetic logic operations in living cells to track key moments in a cell's life or change the fate of a cell. Increasing evidence has also revealed that diverse genetic logic gates capable of generating a Boolean function play critically important roles in synthetic biology. Basic genetic logic gates have been designed to combine biological science with digital logic. SynBioLGDB (http://bioinformatics.ac.cn/synbiolgdb/) aims to provide the synthetic biology community with a useful resource for efficient browsing and visualization of genetic logic gates. The current version of SynBioLGDB documents more than 189 genetic logic gates with experimental evidence involving 80 AND gates and 16 NOR gates, etc. in three species (Human, *Escherichia coli* and *Bacillus clausii*). SynBioLGDB provides a user-friendly interface through which conveniently to query and browse detailed information about these genetic logic gates. SynBioLGDB will enable more comprehensive understanding of the connection of genetic logic gates to execute complex cellular functions in living cells.

Synthetic biologists seek to introduce concepts from electronic engineering into cell biology, by treating DNA/molecular elements as components in a circuit, and applying rational engineering principles to the design of biological systems[1–3]. The emerging field of synthetic biology integrates multiple digital inputs into a digital output, with the construction of diverse genetic logic gates, including those that perform AND and NOT functions[4]. The ultimate goal of synthetic biology is to connect biological logic gates together to execute complex biological tasks as in electrical circuits[5–8]. This could make it possible to decipher complex living systems and produce reliable behaviour in organisms through diverse genetic circuit modules. Genetic logic gate devices communicate with each other through changes in gene expression and activity[9,10]. For example, when a sensor is stimulated, this may lead to the activation of a promoter, which then acts as the input to a circuit[11–13]. Genetic logic gates are therefore at the core of the mechanism of synthetic biology, incorporating electronic engineering in cell biology, where biomolecular logic gates are necessary for generating genetic logic systems[14,15].

Because genetic logic gates are the basic building biobricks of electronic circuits we developed a synthetic biology database of experimentally validated logic gates (SynBioLGDB, http://bioinformatics.ac.cn/synbiolgdb/) to facilitate related research. This database is aimed at gathering a comprehensive collection of experimentally validated logic gates by manually curating the literature (Figure 1). The current version of SynBioLGDB documents more than 180 logic gates across three species (Human, *Escherichia coli* and *Bacillus clausii*). SynBioLGDB therefore provides a global view of genetic logic gates in synthetic biology. Researchers can follow these genetic logic gates to explore how the input and output of genes, proteins and promoters are organized. The whole data set can be easily queried and downloaded from the website. In addition, SynBioLGDB allows researchers to submit new logic gates.

Results

Content of the database. In the current version, SynBioLGDB documents 80 AND gates, 8 Buffer gates, 7 Combinatorial gates, 10 NAND gates, 16 NOR gates, 28 NOT gates, 17 OR gates, 7 XOR gates and 16 other gates (Figure 2) across three species (Human, *Escherichia coli* and *Bacillus clausii*)[16]. Each entry contains detailed information on a logic gate in the 'Detail' page, including gate category, input gene/protein/promoter symbols, output gene/protein/promoter symbols, species, validated method, PubMed Identifier (PMID) and

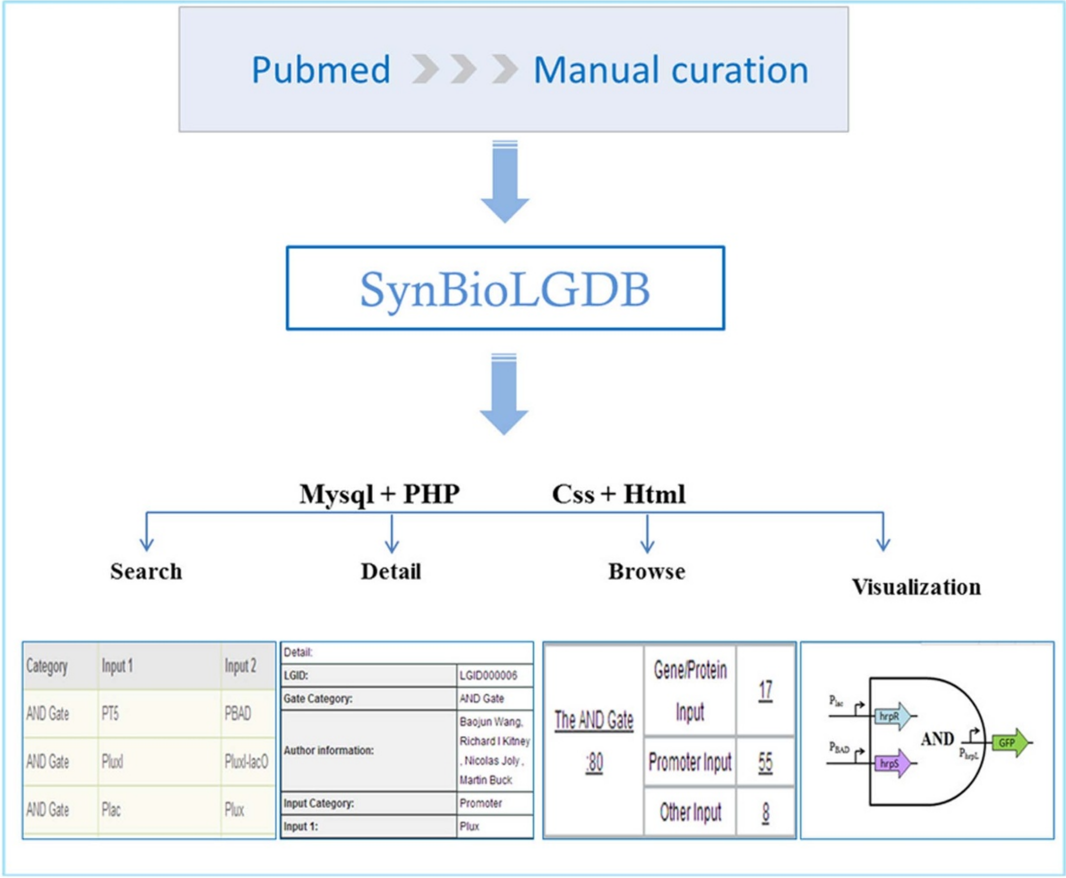

Figure 1 | Overview of the SynBioLGDB database.

detailed description. SynBioLGDB also provides three options on the 'Help' page, with instructions for using the database. These include 'Tutorial' (procedure and illustrations of the database), 'Statistics' (detailed statistical tables) and 'Error Report'. In the 'Download & API' page, users can download all logic gate data in Microsoft Excel and TXT format by selecting 'SynBioLGDB all data', or access the application programming interface (API) using scripts. In the 'Submit' page, SynBioLGDB invites users to submit novel logic gates.

Data querying, searching, browsing and visualizing. SynBioLGDB provides a user-friendly interface for convenient data retrieval. Users can search each logic gate by three Paths (Figure 3): 'By keyword' (search by any key information with support for fuzzy search); 'By gene/protein/promoter' (select specific gene/protein/promoter symbols based on the input category with multiple selection supported); and 'By gate category' (select the gate category of interest). Brief details of the search results are presented as a table in the 'Result' page, while more detailed descriptions, such as the

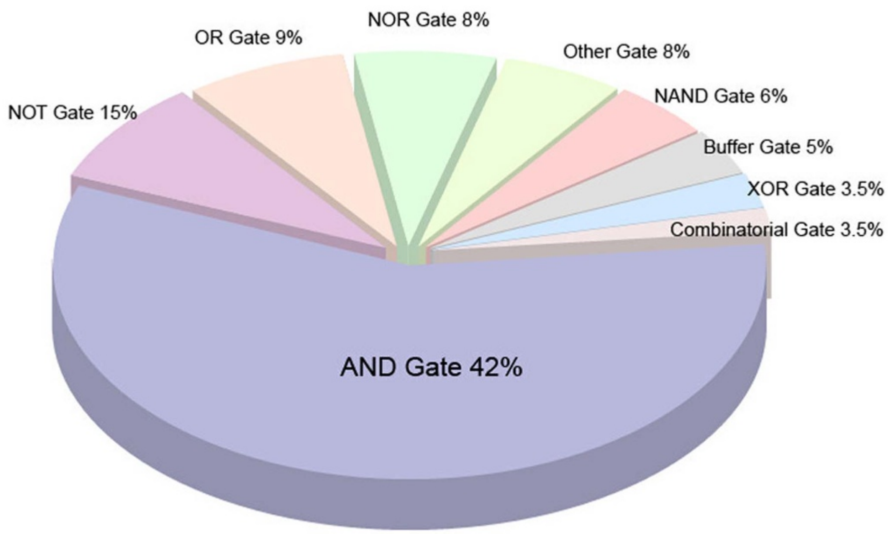

Figure 2 | Pie chart of the logic gate categories in the SynBioLGDB database.

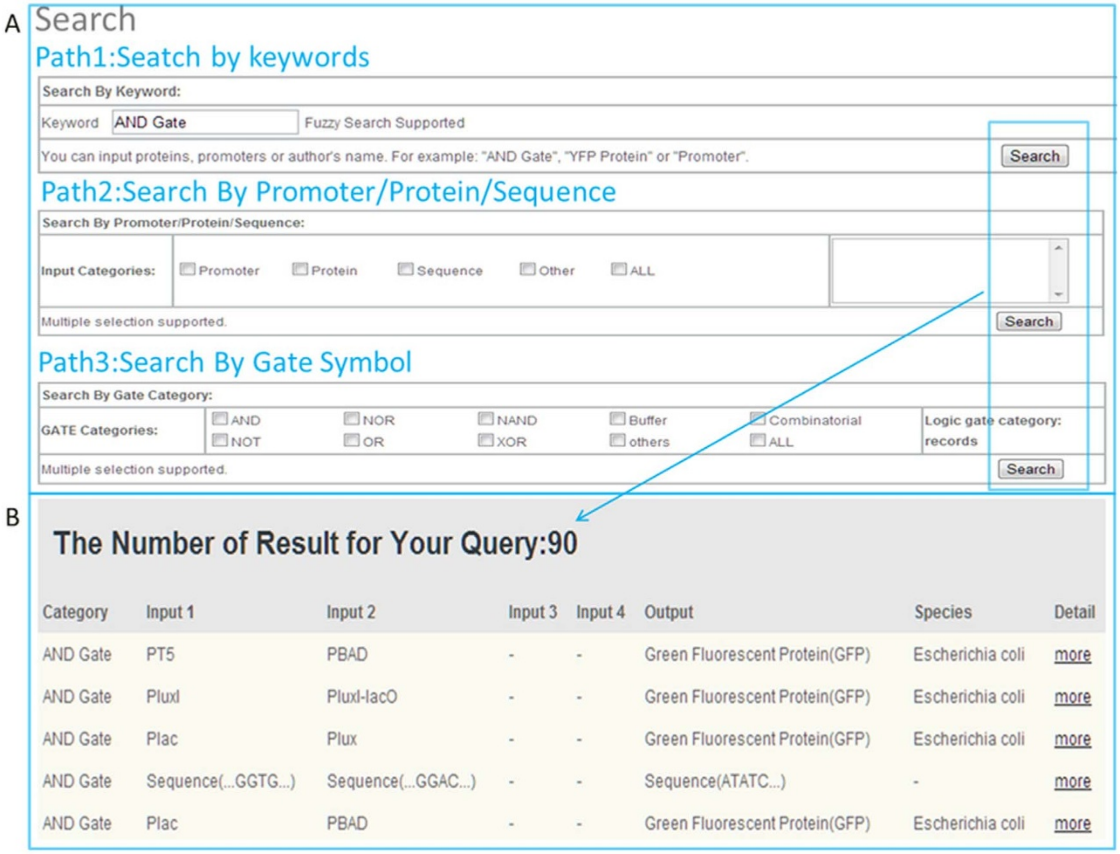

Figure 3 | Flowchart for the Search page. (A) Screenshot of the three searching interfaces to retrieve SynBioLGDB; (B) Results of a representative entry.

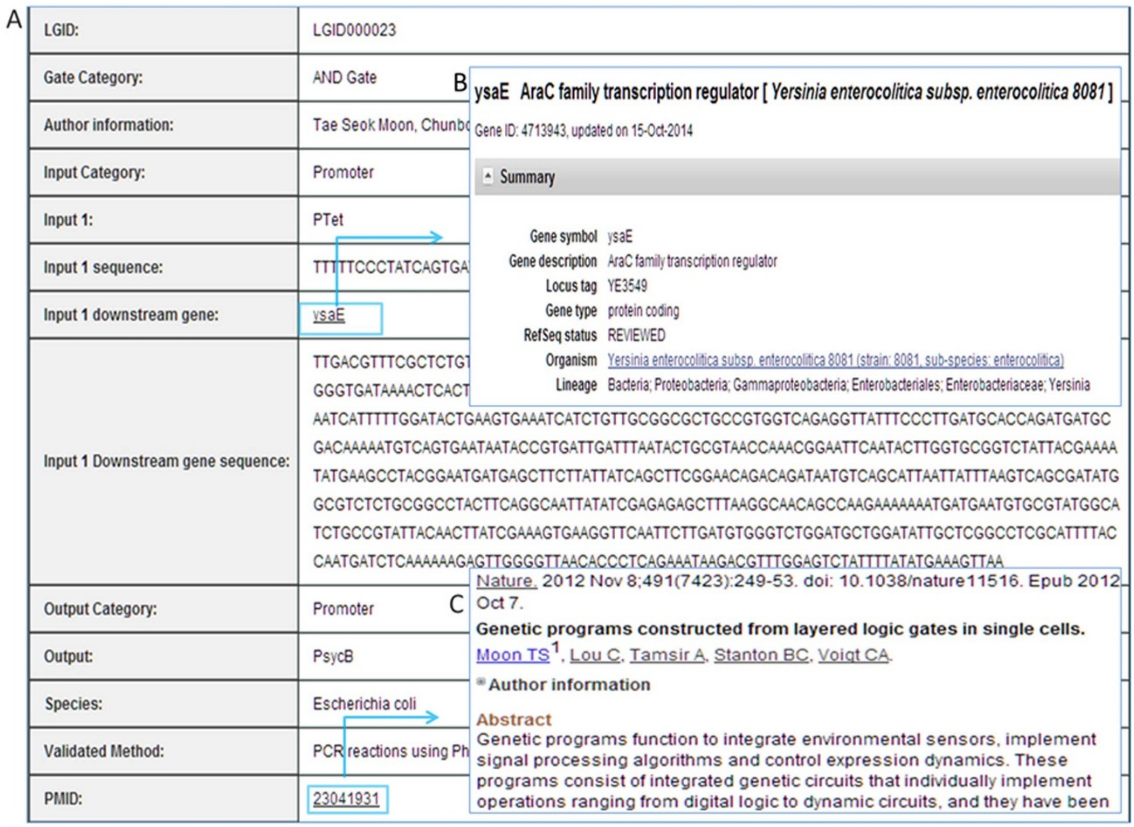

Figure 4 | Representative screenshots of the Detail page. (A) Detailed information on an entry of interest. (B) NCBI information on downstream gene. (C) PubMed references.

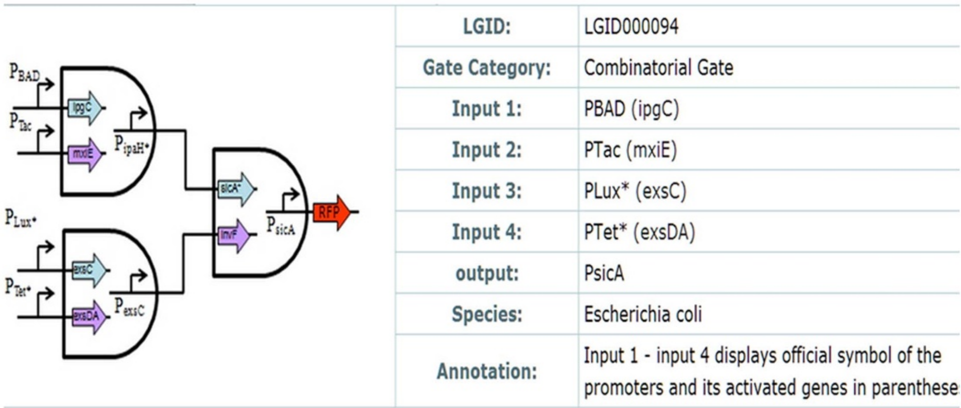

Figure 5 | **Representative screenshot of the 'Visualization' page.**

PMID and description of the reference, are displayed in the 'Detail' page, reached by selecting 'more'. When selecting the specific logic gate in the 'Detail' page (Figure 4), the summary page presents more associated information about the logic gate, such as gate category, input categories, input gene/protein/promoter symbols, input gene/protein/promoter sequence, input promoter downstream gene symbol, input promoter downstream gene sequence, output category, species, validated method, PMID and detailed description.

The 'Browse page' provides a comprehensive overview of the logic gate. Each entry is classified by logic gate category and input type (including gene/protein, promoter and other input). More detailed information is provided by selecting the number of the logic gate category and input type. To help users to visualize the logic gate, SynBioLGDB also visualizes the logic gate in the 'Visualization' page (Figure 5). The example in Figure 5 shows that designed a 4-input AND gate (input promoter: PTet*, PBAD, Ptac and Plux*) with the output promoter PsicA from experimental evidence[17].

Discussion

Synthetic biologists have deciphered genetic logic operations in living cells that may track key moments in a cell's life or change the fate of a cell, and diverse genetic logic gates integrating biological DNA/molecular inputs and output have been constructed[16,18]. However, comprehensive understanding of the mutual relationship between biological logic operations in living cells for the execution of complex biological tasks via electrical circuits remains elusive[14]. Thus, genetic logic gates are essential basic operational tools for building biologically based digital devices to simulate cell signalling. Consequently, the present authors systematically collected experimentally verified genetic logic gates and established the first database centred on the relationship between biological logic operations incorporating biological DNA/molecular inputs and outputs. SynBioLGDB will be of particular interest to the life sciences community, and facilitates the application of rational engineering principles to the design of biological systems based on genetic logic gates, thereby combining electronic engineering with cell biology. Finally, the present authors will continue to collate reference data and update SynBioLGDB.

Methods

Data sources. In order to collect and compile comprehensive logic gate data, all data in SynBioLGDB were collated manually from more than 32,000 papers archived in the PubMed database prior to October 2014 by searching on the keyword, such as ' logic or gate or device or circuit and synthetic biology'. All the papers searched were downloaded and prepared systematically for data curation by manual reading. Input, output, species information, category of logic gate and the validation method were extracted and compiled by manual reading. Finaly, SynBioLGDB integrated information on more than eight types of logic gates, including: AND, Buffer, Combinatorial, NAND, NOR, NOT, OR and XOR gates, etc[14].

Implementation. The SynBioLGDB database is implemented in HTML and PHP languages on the MySQL server. The interface component consists of a website designed and implemented in HTML/CSS in a Microsoft Windows environment. It has been tested in the Google Chrome, Firefox and Internet Explorer web browsers.

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Author contributions

W.D., L.X., L.K.N. and C.L.Q. conceived and designed the experiments. W.L.Q., H.Y., Q.K., W.D., L.H.Y., Z.T., L.C.H., Z.C.R., J.N.N., B.X.M., W.C.L., W.H., T.P.W. and L.J.P. performed the experiments. W.D., W.L.Q. and Q.K. wrote the paper.

Additional information

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