

Systems biology

WEbcoli: an interactive and asynchronous web application for *in silico* design and analysis of genome-scale *E.coli* modelTae-Sung Jung^{1,2}, Hock Chuan Yeo², Satty G. Reddy², Wan-Sup Cho¹
and Dong-Yup Lee^{2,3,*}¹Department of Information Industrial Engineering, CBITRC, Chungbuk National University, Cheongju Chungbuk 361-763, Korea, ²Bioprocessing Technology Institute, Agency for Science, Technology and Research (A*STAR), 20 Biopolis Way, #06-01, Centros, Singapore 138668 and ³Department of Chemical and Biomolecular Engineering, National University of Singapore, 4 Engineering Drive 4, Singapore 117576

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ABSTRACT**Summary:** WEbcoli is a *WEB* application for *in silico* designing, analyzing and engineering *Escherichia coli* metabolism. It is devised and implemented using advanced web technologies, thereby leading to enhanced usability and dynamic web accessibility. As a main feature, the WEbcoli system provides a user-friendly rich web interface, allowing users to virtually design and synthesize mutant strains derived from the genome-scale wild-type *E.coli* model and to customize pathways of interest through a graph editor. In addition, constraints-based flux analysis can be conducted for quantifying metabolic fluxes and characterizing the physiological and metabolic states under various genetic and/or environmental conditions.**Availability:** WEbcoli is freely accessible at <http://webcoli.org>.**Contact:** cheld@nus.edu.sg**1 INTRODUCTION**

As one of best characterized bacterium, *Escherichia coli* has been the workhorse and model organism for biochemical, genetic and metabolic engineering researches. Spurred by the availability of its genome-scale *in silico* model (Reed *et al.*, 2003), research on this microbe has been further advanced within the context of systems biology and biotechnology (Lee *et al.*, 2005; Price *et al.*, 2004). A multitude of such applications demonstrating the predictive power of the model were recently reviewed by Feist and Palsson (2008); their growing scope ranges from fundamental understanding of the microbe to metabolic engineering for strain improvement.

Currently, several software tools are available for facilitating the quantitative flux analysis of the *E.coli* model. They include FluxAnalyzer (Klamt *et al.*, 2003), COBRA Toolbox (Becker *et al.*, 2007), both running under the MATLAB environment, and a standalone tool, MetaFluxNet (Lee *et al.*, 2003). None of them, however, adopted a web-based approach which can have several advantages over standalone tools in terms of accessibility, platform independency, software update and computational capability potential (Lee *et al.*, 2009). Thus, exploiting advanced web-technologies to enhance the response speed and richness of the

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**Fig. 1.** Three-tier architecture of the WEbcoli system. Several software technologies and libraries are used to implement the configured layers including data, logic and presentation.

interface, we developed an integrated environment, WEbcoli, for designing and analyzing genome-scale *E.coli* metabolic model online.

2 SYSTEM OVERVIEW

The WEbcoli system is designed and implemented on the basis of three-tier (presentation, business and data layers) client-server architecture (Fig. 1). It is hosted on Apache's Jakarta Tomcat application server where MySQL is used for storing and managing model data and in-house KEGG (<http://www.genome.jp/kegg/>) database. Open source libraries, JUNG (<http://jung.sourceforge.net/>) and libSBML (Benjamin *et al.*, 2008), are used for graph layout and pathway visualization and for SBML-formatted data manipulation, respectively, while commercial optimization engine, ILOG CPLEX (<http://www.ilog.com/products/cplex/>), is embedded

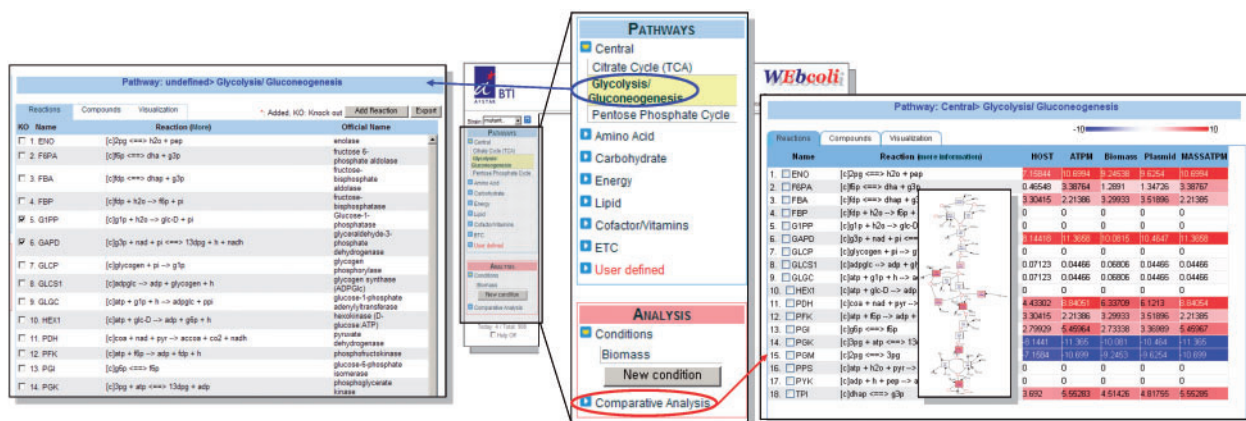


Fig. 2. Screen shot of the WEbcoli interface for representing (left) and analyzing (right) virtual *E.coli* system over the web.

for solving constraints-based optimization problems to determine flux distributions. In addition, the combined use of state-of-the-art Java technologies, including Ajax, Java Web Start and Java Servlet allows improved responsiveness and rich user experience through both client- and server-side executions over the web.

3 FUNCTIONAL FEATURES

WEbcoli is interfaced to provide an integrated modeling and analysis environment. Users can login to the WEbcoli system after creating a user account or taste basic features as a guest user. A walk-through user manual detailing the functional capacity and steps involved in designing and analyzing this virtual *E.coli* system is available at <http://webcoli.org>. The system is mainly comprised of three functional features: (i) comprehensive representation; (ii) virtual design and modeling; and (iii) *in silico* analysis of metabolic pathways in *E.coli* as depicted in Figure 2.

3.1 Representation of metabolic pathways in *E.coli*

The WEbcoli system compiled metabolic reaction dataset from the publicly available genome-scale model iJR904 (Reed *et al.*, 2003). The stoichiometrically balanced metabolic reactions are classified according to functional categories, including the central metabolism, energy, redox and transport pathways. Thus, users can intuitively access the pathway information through multiple tabs, such as reactions, compounds and visualized pathway diagram, thereby improving the users understanding of the cellular metabolism in *E.coli* before concomitant metabolic design and engineering. Moreover, each pathway diagram can be visually edited using a web-client application, the WEbcoli graph editor, which is launched with Java Web Start independent of the web browser. Pathways can also be exported in SBML format (Hucka *et al.*, 2003) in order to facilitate the communication with other systems biology tools.

3.2 Design and synthesis of *E.coli* system

The *E.coli* system can be virtually engineered and designed through modification of template wild-type strain. Mutational changes of relevant genes can be made by deleting or adding associated metabolic reactions, thus mimicking mutant strains under consideration. As one of unique features, WEbcoli allows users to

submit a wide range of queries for searching reactions available in other organisms from in-house KEGG database, so that a novel route toward desirable metabolite production can be potentially identified and synthetically designed. The engineered mutant strain can be then saved for further analysis to explore its physiological and metabolic behaviors under different genetic conditions. In this sense, WEbcoli can be considered as one of tangible synthetic biology applications for engineering *E.coli* system (Leonard *et al.*, 2008).

3.3 Flux analysis and visualization of metabolic pathways in *E.coli*

On the basis of experimentally determined measurements and selected cellular objective, metabolic fluxes can be quantified by resorting to flux balance analysis (Price *et al.*, 2004). Resulting flux distributions under environmentally and/or genetically changed conditions can be saved and compared side by side in a table and differences are highlighted using a selectable color code. Alternatively, flux changes can be visualized in a graphical pathway interface, providing an intuitive understanding of metabolic behavior. This feature enables the users to not only characterize the global context of the metabolic system in *E.coli*, but also design various metabolic engineering strategies.

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