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Antibiotic Resistance Genes Online (ARGO): A Database on vancomycin and β-lactam resistance genes

Joy Scaria[1], Umamaheswaran Chandramouli[2], Sanjay Kumar Verma[1*]

[1]Center for Biotechnology, Biological Sciences Group, Birla Institute of Technology & Science, Pilani-333031, India;
[2]Teledata Informatics Limited, Chennai, India;

Sanjay Kumar Verma* - Email: skverma@bits-pilani.ac.in; * Corresponding author

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Abstract:

Vancomycin and β-lactams are antibiotics that inhibit gram positive bacteria by interfering with cell wall synthesis. However, continuous use of antibiotics results in the emergence of multi-drug resistant (MDR) bacterial strains. Here, we describe ARGO, a database containing gene sequences conferring resistance to these two classes of antibiotics. It is designed as a resource to enhance research on the prevalence and spread of antibiotic resistance genes. ARGO is the first attempt to compile the resistance gene sequence data with state specific information.

Availability: ARGO is available for free at http://www.argodb.org/

Key words: antibiotic resistance, β-lactamase, vancomycin, gene, sequence

Background:

Antibiotics have become major means of treating bacterial infections since their discovery sixty years ago. Global antibiotic market is now estimated at more than US$25 billion per year. **[1]** However, the increased use of antibiotics forced the evolution of drug resistant bacterial strains at a high frequency. Resistance to every antibiotic in clinical use has been observed throughout the world and many strains exhibit resistance to multiple antibiotics. **[2]** In many cases, resistance to a new antibiotic emerges within three years from the date of FDA approval. **[3]** The antibiotic resistance genes (ARG) are rapidly spread by the mechanism of horizontal gene transfer within and across bacterial phylogeny. **[1]** Horizontal gene transfer occurs through plasmids, transposons and integrons from one species to another. For example, the first plasmid-mediated β-lactamase gene TEM-1 in a gram negative bacteria was described in the early 1960's. **[4]** Now the TEM-1 β-lactamase gene is wide spread and is found in *Pseudomonas aeruginosa*, *Haemophilus influenzae*, and *Neisseria gonorrhoeae.* **[5]** Thus, antibiotic resistance genes evolve rapidly in response to the clinical/agricultural use of antibiotics. **[1]** Therefore, it is of interest to collate different ARG sequences in the form of a database. The ARG sequences are not available in a concerted manner in GenBank (a largest repository of gene sequences). **[6]** Hence, we developed ARGO (Antibiotic Resistance Genes Online), a curated online database for storing genetic information on β-lactam and vancomycin resistance genes.

Methodology of development:

ARGO was developed and deployed using an open source software system. MySQL database version 4.0 was used to store sequence information. We used GenBank to retrieve ARG sequence data and the data was processed using a filtering algorithm. **[6]** The filtering algorithm was implemented using a set of routines written in Hypertext Preprocessor4 (PHP4). By definition, a GenBank record is considered for retrieving ARG sequence if the LOCUS LINE contains `DNA` and `BCT`. Additionally, the GENE record in the FEATURES should contain terms describing ARG (for example, `TEM` or `SHV` or `VAN`). GenBank records annotated as `cloning vector` were excluded from the dataset. We used these criteria to parse a local mirror of GenBank for the identification of ARG. The PHP enabled database is searchable by `organism name`, `country name`, `gene category` and `year of publication` of ARG. The database facilitates to retrieve results in `Text` or `Table` or `Graphical` format. Detailed sequence and literature information can be obtained from the corresponding hyperlinks. A representation of the ARGO database system and the filtering scheme is given in Figure 1.

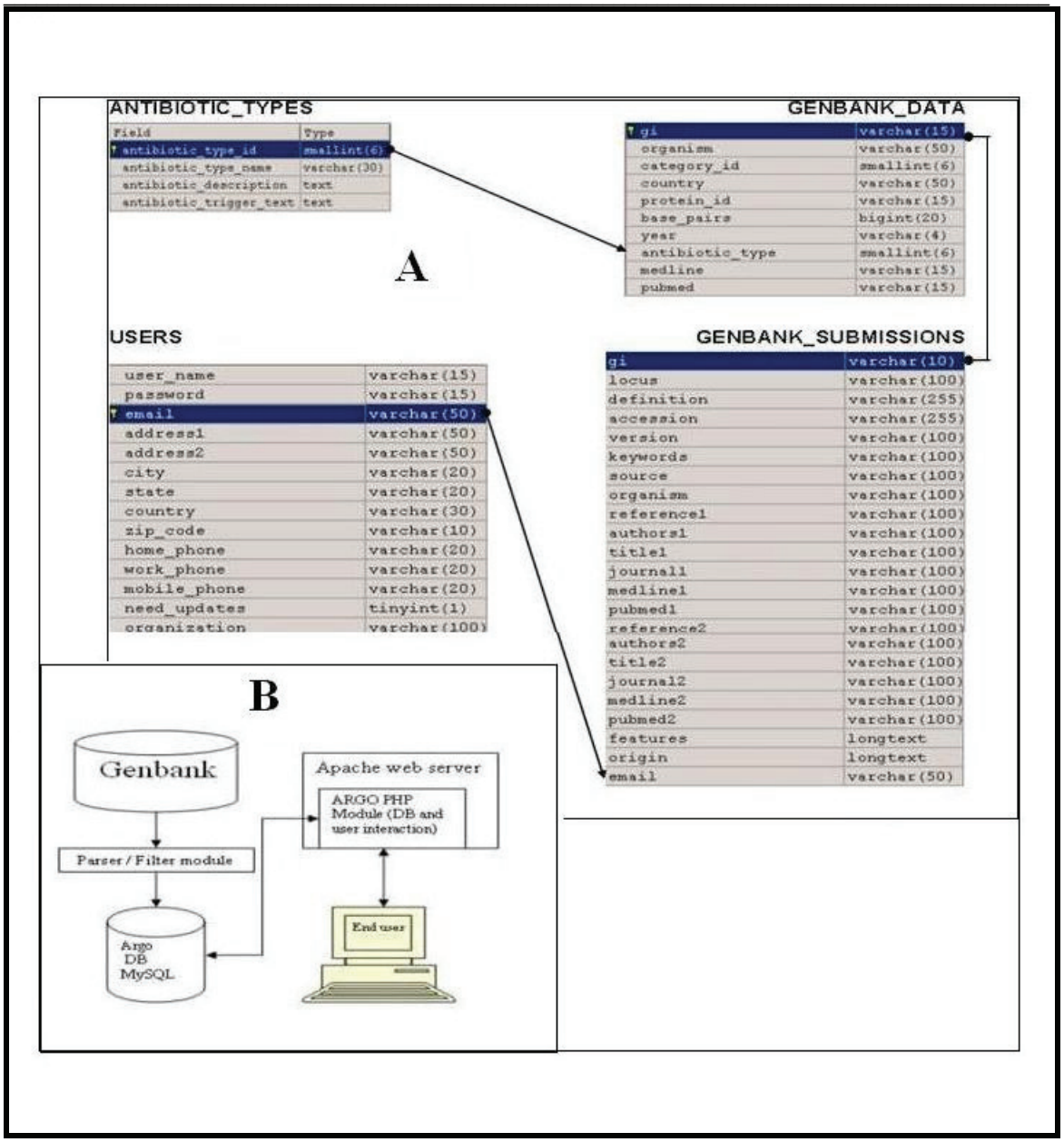

Figure 1: A representation of ARGO (A: database schema, B: database architecture). The relationships in the database are shown in the schema using connecting lines (arrow-heads indicate *many* and solid-balls indicate *one*)

Utility:

The present version of ARGO contains 555 β-lactamase and 115 Vancomycin resistance gene sequences reported from 1991 to 2004. An analysis of ARGO data suggests that a majority of these sequences were identified in samples from Europe, Asia and North America (easy sampling is possible due to the availability of advanced technologies). The global spread of ARG warrants the determination of antimicrobial susceptibility of a clinical isolate for an optimal antimicrobial treatment. **[7]** In recent years, nucleic acid based technologies like PCR (polymerase chain reaction) and molecular beacons have been commonly employed to detect drug resistance. Hence, sequence data in ARGO is of clinical importance in the diagnosis of antibiotic resistance by designing primers that are both specific and sensitive. Rapid evolution of ARG demands the continuous development of new antibiotics. **[1]** However, only one class of antibiotic was introduced in the last 40 years and this followed the development of a large number of derivatives. **[8]** Therefore, it is of interest to predict antibiotic resistance using sequence data stored in ARGO. Determination of antibiotic resistance using transposon **[9]** and protein engineering **[10]** tools are expensive and laborious. We believe that ARGO sequence data will help in the prediction of antibiotic resistance using sequence profiling and molecular modeling techniques.

Future Developments:

Work is in process to update ARGO with other classes of antibiotic resistance genes. The database is available for free at http://www.argodb.org/

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