Update of KDBI: Kinetic Data of Bio-molecular Interaction database

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ABSTRACT

Knowledge of the kinetics of biomolecular interactions is important for facilitating the study of cellular processes and underlying molecular events, and is essential for quantitative study and simulation of biological systems. Kinetic Data of Bio-molecular Interaction database (KDBI) has been developed to provide information about experimentally determined kinetic data of protein–protein, protein–nucleic acid, protein–ligand, nucleic acid–ligand binding or reaction events described in the literature. To accommodate increasing demand for studying and simulating biological systems, numerous improvements and updates have been made to KDBI, including new ways to access data by pathway and molecule names, data file in System Biology Markup Language format, more efficient search engine, access to published parameter sets of simulation models of 63 pathways, and 2.3-fold increase of data (19 263 entries of 10 532 distinctive biomolecular binding and 11 954 interaction events, involving 2635 proteins/protein complexes, 847 nucleic acids, 1603 small molecules and 45 multi-step processes). KDBI is publically available at http://bidd.nus.edu.sg/group/kdbi/kdbi.asp.

INTRODUCTION

Biomolecular interactions, via individual and network actions, play fundamental roles in biological, disease and therapeutic processes (1–4). Extensive experimental and computational studies have significantly advanced our understanding of the characteristics, organization, evolution and complexity of biomolecular interaction networks in biological systems (5–8), and enabled the generation of genome-scale protein–protein interactions and the development prediction tools (6,7,9–12).

Many databases have been developed for providing information about biomolecular interactions [e.g. MIPS (13), DIP (14), BIND (15), Biocyc (16), MINT (17), Biomodels (18), STRING (19) and IntAct (20)], and biological networks and pathways [KEGG (21), BioGRID (22), NetworKIN (23), STITCH (24), DOMINE (25), CellCircuits (26), Reactome (27) and enzyme reactions (28)].

In view that quantitative as well as mechanistic understanding of biomolecular interactions is important for exploration and engineering of biological networks and for the development of novel therapeutics to combat diseases (29,30), kinetic data of biomolecular interactions have been provided in some databases. For instance, BRENDA (31) and SABIO-RK (32) provide kinetic constants of enzymatic activities, DOQCS contains kinetic parameters of simulation models of cellular signaling derived from experimental and other sources (33). To complement these databases for providing the kinetic data not yet covered by other databases, we have developed the Kinetic Data of Bio-molecular Interactions database [KDBI; (34)] to provide experimentally measured kinetic data for protein–protein, protein–nucleic acid and protein–small molecule interactions aimed at facilitating mechanistic investigation, quantitative study and simulation of cellular processes and events (31–33,35–39). Kinetic data in KDBI have been manually collected from literatures, a substantial percentage of which are not yet available in other databases (e.g. some protein–protein interactions in thrombin, translation initiation, DNA repair, and ion transport pathways, and individual protein–nucleic acid interactions).

In the updated KDBI, apart from 2.3-fold increase of experimental kinetic data, we added four new features. The first is the access of KDBI entries via the list of nucleic acid and pathway names. The second is the inclusion of literature-reported kinetic parameter sets of 63 pathway

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Figure 1. Experimental kinetic data page showing protein–protein interaction. This page provides kinetic data and reaction equation (while available) as well as the name of participating molecules and description of event.

simulation models (35–44) for facilitating the applications, assessments and further development of these pathway models. The third is the facility for collectively accessing the available kinetic data of multi-step processes (e.g. metabolism and pathway segments) collected in KDBI. The fourth is the availability of SBML (45) files for all records of the kinetic parameter sets of pathway simulation models for facilitating the use of the relevant data in such software tools as Celldesigner (46), Copasi (47), cPath (48), PaVESy (49) and SBMLeditor (50).

EXPERIMENTAL KINETIC DATA AND ACCESS

Additional sets of the experimentally determined kinetic data of biomolecular interactions were collected from published literatures. Compared to the last version of KDBI, the number of entries in the updated KDBI is increased by 2.3-fold to 19 263, which include 2635 protein–protein, 1711 protein–nucleic acid, 11 873 protein–small molecule and 1995 nucleic acid–small molecule interactions. Each entry provides detailed description about binding or reaction event, participating molecules, binding or reaction equation, kinetic data and related references. As shown in Figures 1–3, kinetic data for protein–protein, small molecule–nucleic acid and protein–small molecule interactions are provided in terms of one or a combination of kinetic quantities as given in the literature of a particular event. These quantities include association/dissociation rate constant, on/off rate constant, first/second/third/...order rate constant, catalytic rate constant, equilibrium association/dissociation constant, inhibition constant, and binding affinity constant, IC50, etc. and experimental conditions (pH value and temperature).

These data can be accessed via input of names of molecules and bio-events (association, dissociation, complex formation, electron transfer, inhibition, etc.), and via selection of pathway and protein name from the pathway list and protein list fields in KDBI webpage. The kinetic data of an event are searchable by several methods. One method is via the name of participating molecules (protein, nucleic acid, small peptide, ligand or ion) or pathway involved in an event. In some events described in the literature, a participating entity is an unidentified molecule located in the membrane of a cell or on the surface of a virus. In these entries, only the name of the cell or virus is given. An entry can also be searched through a Swiss-Prot AC number for a protein or the CAS number for a small molecule ligand. Moreover, keyword-based text search is also supported. To facilitate convenient access of relevant data, partial lists of proteins and nucleic acid are provided. Searches involving combination of these methods or selection fields are also supported.

PARAMETER SETS OF PATHWAY SIMULATION MODELS

As part of the efforts for facilitating the understanding and quantitative analysis of complex biological processes and network responses, mathematical simulation models of various pathways have been developed and extensively used for studying and quantitative understanding of signaling dynamics (35–39), signal-specific sensing (40) and discrimination (44), feedback regulations and cross-talks (42,43), and receptor cross-activation (41) and internalization (42). These mathematical models typically use ordinary differential equations (ODEs) to describe the temporal dynamic behavior of molecular species in the pathway. The kinetic rate constants of protein–protein,

Figure 2. Experimental kinetic data page showing small molecule–nucleic acid interaction. This page provides kinetic data and reaction equation (while available) as well as the name of participating molecules and description of event.

Figure 3. Experimental kinetic data page showing protein–small molecule interaction. This page provides kinetic data and reaction equation (while available) as well as the name of participating molecules and description of event.

protein–small molecule, protein–nucleic acid and other interactions (e.g. binding association rate K_f, binding dissociation rate K_b, reaction rate K, reaction turnover rate K_{cat}, Michaelis–Menten constant K_m) are needed to establish these ODEs, which have been primarily generated by combinations of experimental data, computed theoretical values and empirically fitted values computational (39–44). To facilitate further applications, developments and assessments of the published pathway models, we collected and included in KDBI the parameter sets of 63 published ODE-based models, which can be accessed from the pathway list in the 'Pathway Simulation Parameters'

field in KDBI webpage. Moreover, we added kinetic data type to every entry to clearly distinguish its original source (experimental or simulation model). In particular, for the kinetic data of a simulation model that have been obtained from other publications, cross-reference to the original source is provided. A typical search result is shown in Figure 4.

KINETIC DATA FOR MULTI-STEP PROCESSES

Some published studies provide information about the experimental kinetic data for multiple components of

Figure 4. Pathway parameter set page. This page provides kinetic data and reaction equation (while available) as well as the name of participating molecules and description of event.

Figure 5. Multi-process kinetic data page. This page provides kinetic data and reaction equation (while available) as well as the name of participating molecules and description of event.

multi-step processes (51–53). Examples of these processes include RNA binding activity to translation initiation factors eIF4G, 70-kDa heat shock protein polymerization, control of platelet function by cyclic AMP, GroEL interaction with conformational states of horse cytochrome c, intermolecular catalysis by hairpin ribozymes, antisense RNA interaction with its complimentary RNA and nucleotide binding to actin. To facilitate the development of pathway simulation models based on these building blocks, we provided direct access to the collection of the kinetic data for each of these processes, which can be accessed via a separate search field 'Multi-step processes' in KDBI webpage. A typical search result is shown in Figure 5.

KINETIC DATA FILES IN THE SYSTEMS BIOLOGY MARKUP LANGUAGE FORMAT

Systems Biology Markup Language (SBML) has been developed as a free, open and XML-based format for

representing biochemical reaction networks, and it is a software-independent language for describing models common to computational biology research, including cell signaling pathways, metabolic pathways, gene regulation and others (54). Many pathway simulation and analysis software tools have built-in SBML compatibility features to allow the input, manipulation, simulation and analysis of different pathway models and parameters (45,54–58). To facilitate the input of the pathway parameter sets into these software tools, we created the SBML file for the parameter sets of all 63 pathway simulation models included in KDBI, which can be downloaded via the link provided on the top of the page that displays the relevant kinetic data. SBML file for the user-selected kinetic data can be dynamically generated and exported by clicking the selected entries and then the SBML file export button.

REMARKS

The updated version of KDBI is intended to be a more useful resource for convenient access of available biomolecular kinetic data to complement other biomolecular interaction and pathway databases in facilitating quantitative studies of biomolecular interactions and networks. New technologies have been developed in employing surface plasmon resonance technology for deriving real-time dynamics and kinetic data (59), and in using protein microarrays (60) and solution NMR spectroscopy (61) for monitoring and characterizing biomolecular interactions. Moreover, new experimental designs of the well-established technologies such as isothermal titration calorimetry allow the measurement and estimate of previously inaccessible kinetic parameters (62). Resources for collecting and accessing the increasing amount of kinetic data can better serve the need for mechanistic investigation, quantitative study and simulation of biological processes and events.

FUNDING

Conflict of interest statement. None declared.

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