Systems biology

Biological Dynamics Markup Language (BDML): an open format for representing quantitative biological dynamics data

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Abstract

Motivation: Recent progress in live-cell imaging and modeling techniques has resulted in generation of a large amount of quantitative data (from experimental measurements and computer simulations) on spatiotemporal dynamics of biological objects such as molecules, cells and organisms. Although many research groups have independently dedicated their efforts to developing software tools for visualizing and analyzing these data, these tools are often not compatible with each other because of different data formats.

Results: We developed an open unified format, Biological Dynamics Markup Language (BDML; current version: 0.2), which provides a basic framework for representing quantitative biological dynamics data for objects ranging from molecules to cells to organisms. BDML is based on Extensible Markup Language (XML). Its advantages are machine and human readability and extensibility. BDML will improve the efficiency of development and evaluation of software tools for data visualization and analysis.

Availability and implementation: A specification and a schema file for BDML are freely available online at http://ssbd.qbic.riken.jp/bdml/.
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Supplementary Information: Supplementary data are available at Bioinformatics online.

1 Introduction

With the rapid progress in live-cell imaging and modeling techniques, quantitative spatiotemporal dynamics of biological objects such as molecules, cells and organisms can be obtained from experimental measurements and computer simulations (Keller, 2013; Mogilner et al., 2006; Oates et al., 2009). Such quantitative data can provide us with new opportunities to analyze biological dynamics through various types of computational methods; these data would also provide a rich resource for understanding the mechanisms of biological systems.

A wide variety of quantitative biological dynamics data can be directly obtained from experimental measurements by using live-cell imaging and digital image processing; for example, cell division dynamics in Caenorhabditis elegans can be extracted from four-dimensional (4D) microscopic images (Bao et al., 2006; Giurumescu et al., 2012; Kyoda et al., 2013; Sarov et al., 2012). Similarly, quantitative data can be obtained for embryogenesis in Drosophila melanogaster (Keller et al., 2010; Supatto et al., 2009) and zebrafish (Keller et al., 2008) and for behavioral dynamics in adult C.elegans (Cronin et al., 2005; Yemini et al., 2013). Quantitative data can also be obtained from computer simulations, e.g. single-molecule dynamics in Escherichia coli (Arjunan and Tomita, 2010) and microtubule-dependent nuclear dynamics in C.elegans embryos (Kimura and Onami, 2005). Although most of these data are publicly available, it is often difficult to reuse them because of their intricate structure and the lack of detailed explanations of their formats.
Although various software tools have been developed independently for different types of quantitative data, they are often not compatible with each other as they tend to use different data formats. For example, dataset-specific software tools have been developed for visualization of cell division dynamics in C. elegans embryos (Boyle et al., 2006; Hamashashi et al., 2005; Kyoda et al., 2013), but they are not interchangeable and it is difficult to re-use these software tools to visualize different datasets. Similarly, separate software tools have been developed to analyze the dynamics of C. elegans and zebrafish embryos (Keller et al., 2008; Moore et al., 2013).

One of the solutions is to develop a unified format for representing quantitative biological dynamics data. Similar problems with the data formats existed in the field of systems biology, and various data formats have been developed to solve the problems. CellML is designed to represent biological models using algebraic and differential equations and associated meta-information (Hedley et al., 2001). SBML is designed for representation and exchange of biochemical network models (Hucka et al., 2003). Both CellML and SBML are based on Extensible Markup Language (XML) (http://www.w3.org/TR/2008/REC-xml-20081126/). FieldML is used to represent parameterized spatial fields such as finite element method models (Britten et al., 2013). It is based on XML and also supports HDF5, a hierarchical binary format that allows the data to be accessed more efficiently. Combined with CellML, FieldML can provide a complete vocabulary for describing models at a range of resolutions from the cellular level to the whole-organ level.

MAGE-ML (Spellman et al., 2002), MAGE-TAB (Rayner et al., 2006), MINiML (Barrett et al., 2007), mZML (Martens et al., 2011) and BioSignalML (Brooks et al., 2011) are formats for representing experimental results. MAGE-ML, MAGE-TAB and MINiML are formats for sharing microarray data; they follow the MIAME guidelines (Brazma et al., 2001). MAGE-ML and MINiML are both XML-based formats. The advantage of MAGE-ML is that it allows easy development of database applications, whereas that of MINiML is its simplicity. MAGE-TAB is a simple spreadsheet-based format for representing microarray data and associated meta-information to address the needs of experimental biologists. mZML is an open format using XML and binary formats for storage and exchange of mass spectrometry data. It allows storage of both spectral and chromatographic data as binary format data encoded into base 64 strings and includes an index to allow random access to the data. BioSignalML uses the Resource Description Framework (RDF) for encoding and storing of biomedical signals such as electrocardiograms and associated meta-information. It stores the signals as a sequence of time-varying data points in their native binary formats, e.g. HDF5.

SBRML (Dada et al., 2010) is an XML-based format for representing both experimental and simulation results. It focuses on associating systems biology data, such as microarray data, with cellular models. It also supports spreadsheet-like data and multidimensional data cubes. However, none of the formats mentioned above were designed to represent three-dimensional (3D) spatial and temporal dynamics of biological objects. Representing quantitative biological dynamics data using existing formats would be difficult and inefficient. Therefore, development of a new data format is needed.

In this study, we developed an open format for representing quantitative biological dynamics data, Biological Dynamics Markup Language (BDML). BDML can describe a wide variety of spatiotemporal dynamics of biological objects at different levels, from molecules to cells to organisms. The biological objects are represented as predefined geometric entities such as points, lines, circles, spheres, faces and combinations of the above. BDML is based on XML. The BDML format is both machine and human readable, which should enable computational biologists to efficiently develop and evaluate software tools. It is also extensible, which should enable flexible future support for new types of quantitative biological dynamics data. The current version of BDML is 0.2. We expect that the BDML framework will dramatically accelerate the analysis of quantitative biological dynamics data, which in turn will allow us to gain a better understanding of the mechanisms of biological systems.

2 Methods

2.1 Overview

BDML is based on XML, which is in turn a derivative of the Standard Generalized Markup Language (SGML). SGML is an international standard for information processing. It defines a set of markup tags to describe the document structure and other attributes. XML provides a subset of SGML markup tags and is now widely accepted by the bioinformatics community as a standard data format (Achard et al., 2001).

A specification or grammar written in XML is called a schema. A schema defines an XML document, allowing easy validation of the syntax and making the document self-contained, i.e. an XML document does not require additional files or documents to describe the data structure within the document.

Our first requirement for a unified data format was sufficient machine and human readability to allow computational biologists to accelerate software development and evaluation. The machine readability of XML with a large number of open libraries and Application Programming Interfaces (APIs) enables efficient software development and evaluation. The human readability of XML allows experimental biologists to easily access and understand the content of quantitative data. Our second requirement was flexibility and extensibility. The format needs to be flexible enough to allow future extension to accommodate new types of quantitative data. The extensibility of XML enables the BDML format to support flexible data extension. Therefore, XML was chosen as the basis for BDML.

A BDML file usually consists of six top-level elements: info, ontology, summary, contact, methods and data. The info element provides information about the BDML file, whereas the ontology, summary, contact and methods elements represent meta-information of the quantitative data. The data element contains the quantitative data obtained from either experimental measurements or computer simulations.

Info. A short description of the content of the BDML file. It includes a unique identifier for each BDML file and details of its license.

Ontology. A description of the associations between terms in BDML and those from external ontology sources.

Summary. A short summary of the quantitative biological dynamics data described in the BDML file.

Contact. Detailed information about the corresponding author of the BDML file. Contact name, affiliation and e-mail address must be included with each BDML file.

Methods. A description of the method used to obtain the quantitative data. The description should provide enough detail to allow
Data. A description of the spatiotemporal quantitative data.

The BDML data format begins with an XML declaration (Fig. 1). The next element, `<bdml>`, contains the top-level elements in the following order: `info`, `ontology`, `summary`, `contact`, `methods` and `data`. Most elements in BDML are derived from a single abstract base type, `BDBase`, which supports attaching metadata, notes and annotations to the elements. The `series` and `set` elements can be used instead of `data`. The `series` element is used when the data are too large and we want to represent a dataset in a series of data files. For example, this element can be used to divide a dataset into more than one data file, each corresponding to the data within a specific time frame. The `set` element is used when we want to treat more than one data file derived from related but separate experiments or simulations as a set. For example, this element can be used to describe a set of experimental measurements in a single published work. The `series` and `set` elements encapsulate a list of unique identifiers (see the description in the section 2.2.1).

2.2 The elements of BDML

A BDML file can contain all the quantitative data and associated meta-information in a single file. In this section, we describe each top-level element of BDML with the help of examples. To make it easier for readers to understand the BDML format, these descriptions focus on major BDML elements and omit many details. A schema and specification for BDML are available at http://ssbd.qbic.riken.jp/bdml/.

2.2.1 Info element

The `info` element describes the content of the BDML file. Each BDML file has a unique identifier `bdmlID` (Fig. 2), which is used to identify the file when it is shared or exchanged. This identifier is defined by a Universally Unique Identifier (https://tools.ietf.org/html/rfc4122), which is a standard identifier used in most software tools. It can be generated without central coordination, thus allowing the user to generate his or her own identifier without worrying that someone else will generate the same identifier. License information such as the Creative Commons licenses (http://creativecommons.org/licenses/) should be explicitly described to avoid unnecessary conflicts.

2.2.2 Ontology element

The `ontology` element associates terms in BDML with those from external ontology sources (Fig. 2). The use of ontological references ensures unambiguous interpretation of information in a BDML file. Each term in BDML can be associated with a term from different ontology sources in the `ontologyTerm` element. The elements `id` and `term` represent a unique identifier for the ontology term and the term itself, respectively. The elements `ontologyID` and `ontologyURI` represent an accession identifier and a unique identifier of the ontology source, respectively. The `ontologyRef` attribute can be used in the following elements: `datatype`, `organism` (see section 2.2.3 and Fig. 2), `objectName`, `xyzUnit`, `tUnit` and `featureUnit` (see section 2.2.6 and Fig. 3). The `ontologyRef` attribute refers to `id` defined in the `ontologyTerm` element (Figs 2 and 3). The `ontology` element is optional in the current version of BDML (0.2). Although biologists producing quantitative biological dynamics data are in the best position to annotate their data using ontological terms, most biologists are not well versed in the use of ontologies.

2.2.3 Summary element

The `summary` element provides a concise description of the quantitative data in the BDML file. The `datatype` element is used to indicate what biological process was targeted to obtain the quantitative data. A target organism should be indicated according to National Center of Biotechnology Information (NCBI) taxonomy (NCBI Resource Coordinators, 2014) (Fig. 2). The `localID` element can be used to link `bdmlID` to the internal identifier names of each author in the laboratory. The `container` element indicates whether the data are derived from an experimental measurement or computer simulation. Detailed information on a published paper or database can be included in the `summary` element.

2.2.4 Contact element

The `contact` element describes detailed information about the corresponding author of the BDML file. Contact name, e-mail address and affiliation of the corresponding author should be listed (Fig. 2).

2.2.5 Methods element

The `methods` element describes the procedure used to produce the quantitative spatiotemporal data described in the BDML file. This element is designed to enable reproduction of the quantitative data from the original sources by providing references to previous work (Waltemath et al., 2011). This element includes two hyperlinks that are defined as Uniform Resource Identifiers. The first link points to the original sources such as microscopic images (for an experimental measurement) or files of a mathematical model (for a computer simulation). The second link points to a description of the procedure (which can be a web page or file) used to obtain the quantitative spatiotemporal data from the original sources (Fig. 2). As an alternative description of such procedure, we prepared an XML-based language named Procedure for Data Processing Markup Language (PDPML) (Supplementary Section S1). A schema and specification for PDPML are available at http://ssbd.qbic.riken.jp/pdpml/.

2.2.6 Data element

The `data` element contains the quantitative spatiotemporal data (Fig. 3). It has four sub-elements: `scaleUnit`, `object`, `feature` and `component`. The scale and units of the coordinates and time are defined in `scaleUnit`. For experimental spatiotemporal datasets, spatial information is often recorded as a set of pixel coordinates measured directly from the microscopic images, whereas time is usually considered as a sequence of regular time frames. The `scaleUnit` element can be used to convert each set of pixel coordinates and time frames into the actual positions and actual time,
respectively. The scale factors for the $x$, $y$ and $z$ dimensions and time can be defined separately. The actual positions can be directly described by setting the scale factors for the $x$, $y$ and $z$ dimensions to 1.0. In the same way, the actual time or discontinuous time can be directly described when the scale factor for time is set to 1.0. If a dataset has only the $x$ and $y$ dimensions, the scale factor for the $z$ dimension should be set to zero. The units of the coordinates and time should be selected from the units predefined in the BDML schema (http://ssbd.qbic.riken.jp/bdml/).

Fig. 2. Examples of the info, ontology, summary, contact and methods elements

Fig. 3. An example of the data element

Fig. 4. An example of the measurement element. In this example, the units are in micrometers, and the scale factors for the $x$, $y$ and $z$ dimensions are 0.9, 0.9 and 1.0, respectively (see Fig. 3)
of the object's position. objectRef refers to an object defined in the object element. An object can be described by the following five types of entities: a set of points, a set of lines, a circle, a sphere, a set of faces or by a combination of the five types (Fig. 5).

Examples of representation of spatial information are given in section 3.1. The object's features can be described under the property element. The featureRef sub-element in the property element refers to a feature defined in the feature element. The numerical value of the feature can be recorded in featureVal.

### 2.2.7 Unit definitions

The units for spatial and feature information are predefined under the UnitKind element in the BDML schema (Table 1). The UnitKind element is based on the definition of the SBML schema (Hucka et al., 2003). We defined several additional units that are often used in experimental measurements and in computer simulations, such as a.u. (arbitrary unit) and micrometer. For example, fluorescence intensity in arbitrary units is used in many biological research projects and is included in the reported data (Bao et al., 2006; Keller et al., 2008; 2010; Sarov et al., 2012). We also predefined the units for temporal information under the tUnitKind element in the BDML schema; these units range from nanosecond to year (Table 2). More detailed information on the BDML schema is available online at http://ssbd.qbic.riken.jp/bdml.

### 3 Results

#### 3.1 Examples of BDML usage

We provide five detailed examples on how to describe object’s spatial information obtained from microscopic images or from computer simulation. These examples demonstrate that BDML can represent quantitative biological dynamics data from molecules to cells or organisms.

The first example is a computer simulation of single-molecule dynamics in E.coli (Fig. 6; Arjunan and Tomita, 2010), in which each molecule is represented as a point. Therefore, spatial information for a single molecule can be described by the point entity type in BDML. The coordinates of each molecule are described by the xyz element.

The second example is an experimental measurement of cell division dynamics in C.elegans embryo (Fig. 7). Kyoda et al. (2013) quantitatively extracted the dynamics of nuclear division by using differential interference contrast microscopy and image processing. Each nucleus is outlined by a set of closed polygonal chains, i.e. series of connected line segments with start point and end point joined together. The contour of a nucleus is therefore represented by the line entity type. In BDML, a closed polygonal chain is represented as a series of sequentially connected coordinates. The sequence of coordinates is described within the xyzSequence element.

The third example is a computer simulation of nuclear migration in a C.elegans embryo (Fig. 8; Kimura and Onami, 2005). The dynamics of the male pronucleus was predicted by calculating the dynamics of microtubules and their resultant forces on the pronucleus. The pronucleus is represented as a sphere and microtubules as a set of line segments. Spatial information for the pronucleus and microtubules can therefore be described using the sphere and line entity types, respectively. BDML has the flexibility to describe these objects as either one component or separate components (Fig. 8).

The fourth example is an experimental measurement of nuclear division and gene expression dynamics in a C.elegans embryo (Fig. 9; Bao et al., 2006). The dynamics of nuclear division was quantified by confocal microscopy and image processing. Each nucleus is represented as a sphere. Spatial information for the nucleus can therefore be described using the sphere entity type. Bao et al. (2006) also measured the expression dynamics of a gene encoding a GFP–histone fusion protein at single-cell resolution. BDML allows description of such a feature under the property element.

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**Table 1.** Units for spatial and feature information predefined under UnitKind. The underlined words represent additional units, which are not defined in the SBML schema. The units a.u. and p.d.u. represent arbitrary unit and procedure defined unit, respectively.

| UnitKind     | Symbol | Description |
|--------------|--------|-------------|
| ampere       | a.u.   | becquerel   |
| Celsius      | dimensionless | candel | gram |
| joule        | joule  | hertz       |
| liter        | liter  | lumen       |
| meter        | meter  | micrometer  |
| mole         | mole   | ohm          |
| p.d.u.       | radian | pascal      |
| steradian    | tesla  | sievert     |

**Table 2.** Units for temporal information predefined under tUnitKind

| UnitKind     | Symbol | Description |
|--------------|--------|-------------|
| nanosecond   |        | second      |
| minute       |        | year        |
| hour         |        |            |
| millisecond  |        |            |
| second       |        |            |
| day          |        |            |
| month        |        |            |
The final example is an experimental measurement of the behavioral dynamics of an adult *C. elegans* (Fig. 10). Cronin et al. (2005) quantitatively tracked the behavior of an individual worm, which is represented as a polygonal chain, i.e., series of connected line segments. Spatial information for the worm can therefore be described as the line entity type. In this case, the zScale element should be set to zero because the data were obtained from two-dimensional time-lapse microscopic images.

### 3.2 Software development

The BDML format allows easy development of software tools, because a large number of open libraries and APIs for XML are freely available. To demonstrate this point, we developed a visualization software tool named BDML4DViewer. It reads BDML files and produces an onscreen interactive 4D visual representation of spatial information of the objects described in these files (Fig. 11). The user can view spatial information and scroll through different time frames interactively by using a mouse and keyboard. We developed this software tool as a plugin for ImageJ, a public-domain Java-based image processing application (Schneider et al., 2012), by using JAXB (Java Architecture for XML Binding) and JOGL (Java Binding for the OpenGL) APIs. This result demonstrates the ease of developing software tools using the BDML format. All source codes and the executable JAR file of BDML4DViewer are available online at http://ssbd.qbic.riken.jp/BDML4DViewer/.

### 4 Discussion

BDML is an open XML-based format for representing quantitative biological dynamics data. Although the five entity types used to describe dynamic spatial information (a set of points, a set of lines, a circle, a sphere and a set of faces) cover most of the publicly available data, other types of spatial entities (such as a cube or cylinder) can be potentially used. BDML can easily support these types of spatial entities by extending its format using XML with reference to geometric primitives commonly used in computer graphics such as X3D (Brutzman and Daly, 2007).

BDML provides a medium for representing a wide variety of quantitative data. Nearly 300 BDML datasets are currently available online at the Systems Science of Biological Dynamics (SSBD) database (http://ssbd.qbic.riken.jp). These datasets include dynamics of molecules, cells (nuclei) and gene expression and dynamics of whole organisms such as *E. coli*, *C. elegans*, *D. melanogaster* and zebrafish. Some of these datasets were derived from experimental measurements, whereas others were produced by computer simulation. BDML enables us to represent various types and scales of biological dynamics for different species.

Taking advantage of the BDML format, we developed and released BDML4DViewer for visualizing quantitative data from the open-source libraries and APIs. We are also developing software...
tools for extracting phenotypic characteristics from the data in the BDML format. Several of these tools are already available online at http://ssbd.qbic.riken.jp/phenochar/. The development of these software tools further demonstrates the flexibility of using BDML for visualization and analysis of different types of quantitative data. In addition, we believe that the BDML format would provide new opportunities for scientists in other fields such as statistics, physics and information science and facilitate bringing new ideas and approaches to biological analysis.

Although the ontology element is optional in the current version of BDML (0.2), it can provide unambiguous definitions of the terms in the BDML file. As most biologists are not familiar with ontological terms, tools for helping them to annotate the data in ontological terms at the time of file creation would be needed to make the option compulsory. Moreover, meta-information definition can be provided in the annotation element of the BDBase element by using the RDF. These definitions enable computer programs to understand the meaning of the terms and meta-information in the BDML file. The ontological references and annotations can be attached when the data are registered in some repository databases, such as SSBD.

A limitation of the current version of BDML (0.2) is the lack of hierarchical representation of meta-information about genetic perturbations (e.g. mutants, gene editing and RNAi treatments) and chemical perturbations (e.g. drug treatments). Such information would be useful for systematic comparison and analysis of biological

Fig. 9. An example of gene expression dynamics at single-cell resolution in C.elegans embryo. Each nucleus is represented as a sphere, and total GFP signal is described in the property element. In this example, the units are in micrometers, and the scale factors for the x, y and z dimensions are defined separately in the scaleUnit as 0.9, 0.9 and 1.0, respectively.

Fig. 10. An example of behavioral dynamics of an adult C.elegans, represented as a set of line segments. In this example, the units are in micrometers and the scale factors for the x, y and z dimensions are defined separately in the scaleUnit as 4.1, 4.1 and 0, respectively.
dynamics by using more than one BDML file. Therefore, a future version of the BDML format will extend the BDML schema to support such information. As meta-information about genetic and chemical perturbations can be useful for other XML-based data formats such as MINiML (Barrett et al., 2007), mzML (Martens et al., 2011), OME (Allan et al., 2012), CellML (Hedley et al., 2001), SBML (Hucka et al., 2003) and SBRML (Dada et al., 2010), we aim to collaborate with these projects to incorporate this information in a future release.

Integration and comparative analysis of various types of quantitative data are straightforward when they are represented in the BDML format. Such integration has the potential to lead to new insights into biological mechanisms; for example, an integrated study of the dynamics of cell morphology and protein activity has explored the relationship between biophysical phenomena and biochemical signaling (Tsukada et al., 2008). Comparison of experimental measurements and computer simulations has elucidated the mechanisms of various kinds of biological dynamics (Aliee et al., 2012; Grill et al., 2001; Kimura and Onami, 2005; Kozlowski et al., 2007; Krieg et al., 2008; Pecreaux et al., 2006; Rauzi et al., 2008; Stoma et al., 2011). BDML will facilitate such comparative analysis and comparison of the data from different laboratories. We believe that the BDML format will widen the range of scientific approaches to understanding biological systems.

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