The BioRECIPE Representation Format

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1 INTRODUCTION

The BioRECIPE (Biological system Representation for Evaluation, Curation, Interoperability, Preserving, and Execution) representation format was introduced¹ to facilitate seamless human-machine interaction while creating, verifying, evaluating, curating, and expanding executable models of intra- and intercellular signaling. This format allows a human user to easily preview and modify any model component, while it is at the same time readable by machines and can be processed by a suite of model development and analysis tools. The BioRECIPE format is a (directed) graph-based tabular format, that is, it is most suitable for representing influences and executable network models that have a directed graph as their underlying structure (example in Figure 1A) although it can also be used for representing undirected network models. Here, we provide details and demonstrate the utility of the BioRECIPE representation format for:

- event-based interaction lists
- element-based executable models.

When creating interaction lists or models in the BioRECIPE format, information and data can be obtained from different sources, and input into BioRECIPE tables or spreadsheets automatically or manually (Figure 1B). Interaction lists and models written in the BioRECIPE format are convenient for different types of analysis and use (Figure 1C), either with automated tools, or manually, when human input is needed.

¹ Additional details on how to create files in the BioRECIPE format, examples, and links to related code can be found in BioRECIPE’s documentation: https://melody-biorecipe.readthedocs.io

Figure 1. (A) Signaling network that can be represented in the BioRECIPE format, (B) Multiple types of information are compatible with BioRECIPE format, (C) Models and interaction lists represented in the BioRECIPE format have a wide variety of uses. *ER-endoplasmic reticulum, NLP-natural language processing, DL-deep learning, LLM-large language model.
2 Interaction Lists

In the BioRECIPE format, interactions can be represented using the event-based interaction list format, that is, a format in which each individual interaction (biological event) is represented separately, and interaction participants are represented as arguments of the event. In the tabular form, each interaction is assigned one row and the column headers match interaction attribute names. An example biological interaction, represented as a directed signed edge between two nodes, including node, edge, context, and provenance attributes is illustrated in the figure below (subscripts: s – source node, t – target node, e – edge).

As illustrated in Figure 2, the BioRECIPE representation of an interaction includes four types of attributes:

- element (node) basic attributes
- interaction (edge) basic attributes
- interaction context attributes
- interaction provenance attributes

![Figure 2. An example interaction in the BioRECIPE interaction list format (subscripts: s - source node, t - target node, e - edge).](image)

Table 1 provides details for each attribute, including attribute name used in the BioRECIPE spreadsheet, a symbol used in detailed definitions in Section 2, a brief description of the attribute, allowed values, and a few examples. In the following, we provide formal definitions of the components of an interaction, and the attributes of these components. We also include additional details about attributes and examples of their values.

2.1 Element (node)

**Definition 1.** An element (node), \( v = v(a^v) \), is defined by its name, type, and unique identifier (ID), and these attributes are written as a vector \( a^v = (a^{\text{name}}, a^{\text{type}}, a^{\text{database}}, a^{\text{ID}}) \). These are required element attributes in the BioRECIPE format.

The attribute \( a^{\text{name}} \) is an element name, usually following the standard nomenclature used by biologists and in the literature (e.g., acronym ERK1 is used instead of a longer name “extracellular signal-regulated kinase 1”). The attribute \( a^{\text{type}} \) represents element type, usually genes, RNAs, proteins, chemicals, or biological processes. Biological entity names often have multiple synonyms (e.g., ERK1 may also be referred to as MAPK3), and therefore, unique identifiers (IDs) are used, which are stored in attribute \( a^{\text{ID}} \). These IDs can be obtained from standard databases such as UniProt, PubChem, or the Gene Ontology.
Databases (GO). The unique ID attribute is often written as two attributes, the name of the database from which the ID is retrieved, $a_{\text{database}}$, and the ID, $a_{\text{ID}}$. In addition to the required attributes, we include an optional ID attribute, $a_{\text{HGNCsymbol}}$, the gene symbol from the HGNC database, as this is recognized by experts, in contrast to e.g., numbers used by UniProt, and therefore, it can assist in human-driven curation.

The node attribute vector $a_e$ may also include other attributes that help describe the element. For example, attributes $a_{\text{compartment}}$ and $a_{\text{compartmentID}}$ hold information about the cellular compartment, where the element is found, and the compartment ID, respectively. We use the GO database to obtain these compartment IDs. A subtype attribute, $a_{\text{subtype}}$, may be used to indicate additional type of an element, such as $a_{\text{subtype}} = \text{receptor}$ for an element with $a_{\text{type}} = \text{protein}$. An element usually represents a biomolecular species, a chemical, or a biological process.

### 2.2 Interaction (edge)

**Definition 2.** A directed signed interaction (directed edge) $e = e(v_s, v_t, a^e)$ is defined with its source element $v_s$, target element $v_t$, and vector of attributes $a^e$. The interaction attribute vector always includes at least the sign $a_{\text{sign}}$ and connection type $a_{\text{connectiontype}}$ attributes: $a^e = (a_{\text{sign}}, a_{\text{connectiontype}})$. The direction of an interaction is implicitly defined with source and target nodes, and therefore, not explicitly listed among its attributes.

The $a_{\text{sign}}$ attribute indicates the sign (also referred to as polarity) of the influences, and it can take two values, $a_{\text{sign}} = \text{positive}$ (e.g., activation) or $a_{\text{sign}} = \text{negative}$ (e.g., inhibition). Sometimes, only the information about indirect influences on pathways is known, and therefore, the attribute $a_{\text{connectiontype}}$ is used to indicate whether the interaction $e$ is a direct physical interaction ($a_{\text{connectiontype}} = \text{direct}$) or an indirect influence from the source node to the target node ($a_{\text{connectiontype}} = \text{indirect}$). Since the interaction definition allows for indirect interactions, it is possible that source and target node are not in the same compartment, and this is the reason we assign the compartment attribute to nodes and not to the interaction.

The list of other attributes is not necessarily fixed; the components in it may vary, dependent on the goals of the analysis. A more specific information about the biological mechanism and the molecular site of an interaction can be included in the $a_{\text{mechanism}}$ and the $a_{\text{site}}$ attributes, respectively. We note here that, occasionally, $a_{\text{sign}}$ is not explicitly stated in statements about influences that describe mechanisms (e.g., A phosphorylates B). In such cases, it would be up to the user to either fill in this information from other sources or accept a default attribute assignment. For example, the default assignment could be positive for phosphorylation, although this may not always be the case, and would require curation.

The interaction attribute vector can also include the $a_{\text{cellline}}$, $a_{\text{celltype}}$, $a_{\text{tissueType}}$, $a_{\text{organism}}$ attributes, which hold the context information about the cell line, cell type, tissue type, and organism where the interaction is observed, respectively.

Finally, provenance attributes can be used. The $a_{\text{score}}$ attribute can include either a summary score for confidence, or a quantifier of available evidence for the interaction. The $a_{\text{source}}$ attribute indicates whether source of evidence is literature, expert knowledge, databases, or data. The $a_{\text{statements}}$ attribute stores the statements, parts of sentences or sentences where the interaction is mentioned. The $a_{\text{paperID}}$ attribute holds IDs of the papers (e.g., PMCID) with sentences mentioning the interaction. Whenever the information about the non-essential attributes is not available, these attributes are assigned an empty value.

### 3 DIRECTED GRAPHS

To describe model representation with the BioRECIPE format, we start with the model topology.

**Definition 3.** Model structure (static). Models that have a directed graph, $G(V, E)$, as their underlying structure, include a set of nodes $V = \{v_1, v_2, ..., v_N\}$, where each node $v_i = v(a_i^e) (l = 1, ..., N)$ is one model element, and a set of directed edges $E = \{e_1, e_2, ..., e_M\}$, where
an edge \( e_j = \{v_{sj}, v_{tj}, a^e_j\}, (v_{sj}, v_{tj} \in V, j = 1, \ldots, M) \) indicates a directed interaction between elements \( v_{sj} \) and \( v_{tj} \), in which source node \( v_{sj} \) influences target node \( v_{tj} \). Vectors \( a^e_j \) and \( a^a_j \) include node and edge attributes, respectively.

We note here that the BioRECIPE representation format can also be used for undirected graphs - in that case, the distinction between source and target nodes will not be relevant. Undirected graphs and directed graphs (i.e., static structure of executable models) can be represented in the BioRECIPE format as lists of interactions (edges), following the descriptions in Section 2.

### Table 1. An illustration of the interaction list in the BioRECIPE format, with all the attributes (current version supports one source node and one target node in each interaction).

<table>
<thead>
<tr>
<th>Elements (nodes, ( v ))</th>
<th>Interaction (edge, ( e ))</th>
<th>Metadata</th>
<th>Context</th>
<th>Provenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulator (source node, ( v_s ))</td>
<td>Regulated (target node, ( v_t ))</td>
<td>Influence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regulator (Hierarchical Symbol, ( H ))</td>
<td>Regulated (Hierarchical Symbol, ( H ))</td>
<td>Regulation Type (Gene, Pathway)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regulator (Compartment ID, ( C ))</td>
<td>Regulated (Compartment ID, ( C ))</td>
<td>Regulation Context (Compartment)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regulator (Compartment, ( C ))</td>
<td>Regulated (Compartment, ( C ))</td>
<td>Regulation ID (Compartment)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tissue Type (( t ))</td>
<td>Cell Type (( c ))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Source (statements)</td>
<td>Statement (#(of 2))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paper ID(s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. The list of interaction attributes, using the formal notation for attributes, brief description of each attribute, examples values for each attribute. For more details on how to form attribute values, see [1]. *-required attribute
4 EXECUTABLE MODELS

The BioRECIPE format supports representation of the static graph structure of models, as well as attributes necessary to study the dynamics, often through simulations. We refer to the models that can be simulated as executable models and represent them in the BioRECIPE format using the element-based approach.

In the BioRECIPE format, each element in a model is assigned a row in the model table/spreadsheet. Different from event-based representation of interactions, in the element-based representation all interactions in which a given element participates as a regulated element (i.e., a target node of interaction edges) are combined within a row in the table dedicated to this particular element. In the model representation, the attributes are organized into three groups:

- **Element**:  
  - basic element attributes  
  - context attributes
- **Regulation**:  
  - basic regulation attributes  
  - provenance attributes
- **Simulation parameters**:  
  - (update) rule attributes  
  - value attributes  
  - timing attributes

The basic element attributes, and context attributes are inherited from the interactions in which the element participates as a regulated element and are referred to as Element attributes in the model representation format. The basic regulation attributes and provenance attributes are formed by combining corresponding attributes from the individual interactions in which the element participates as a regulated element into an ordered list. These attributes are referred to as Regulation attributes, and their value lists are assembled following the same order as for the Regulation attributes.

We note here that it may occasionally happen (especially if the model assembly process is automated) that the context varies across the interactions where the element is a regulated element. In such cases it is left to the modelers to utilize the context attributes in a manner that best suits their goals. For example, the modeler may either consolidate context attribute values from different interactions and decide to use the one that is most suitable for each attribute, or create a list of values for each attribute, following the same order as for the Regulation attributes.

The BioRECIPE format supports several different model representation schemes (Table 3), ranging from less detailed to more detailed, including either previously described “static” attributes only, or some or all of the “dynamic” attributes. These dynamics related attributes are necessary for simulation and the analysis of dynamic behavior; they are referred to as Simulation parameters, and are used to determine element update rules, and element value and timing parameters for the simulation of executable models. Depending on which attributes are used, we distinguish between the following model representation formats:

- **STATIC** – only required basic Regulation attributes  
  - simple – only required basic Element attributes  
  - detailed – all Element attributes and provenance Regulation attributes
- **DYNAMIC** – all basic Regulation attributes  
  - scenario-independent – all rule attributes and only Variable value attribute in Simulation parameters  
    - simple – only required basic Element attributes  
    - detailed – all Element attributes and provenance Regulation attributes  
  - scenario-dependent – all Simulation parameters attributes  
    - simple – only required basic Element attributes  
    - detailed – all Element attributes and provenance Regulation attributes
4.1 Model definitions

In this section, we provide definitions that are relevant for representing executable models, as well as definitions and details for model specific attributes.

**Definition 4.** An input node is a node that is not a target node of any edge in the model, and an output node is a node that is not a source node of any edge in the model. In the graph, input and output nodes are “hanging” from the rest of the model.

**Definition 5.** We define a path in a model as $n > 1$ connected edges: $p(v_{s_p}, v_{t_p}, \alpha^{\text{sign}}_p) = (e(v_{k_1} = v_{s_p}, v_{k_2}, a^{e}_{k_1}), e(v_{k_2}, v_{k_3}, a^{e}_{k_2}), \ldots, e(v_{k_n}, v_{k_{n+1}} = v_{t_p}, a^{e}_{k_n}))$. The direction of the path is implicitly defined with the source node $v_{s_p}$ and target node $v_{t_p}$. The regulation sign $\alpha^{\text{sign}}_p$ is considered positive when the number of negative signs in the set $\{a^{\text{sign}}_{k_1}, a^{\text{sign}}_{k_2}, \ldots, a^{\text{sign}}_{k_n}\}$ is even, and negative when this number is odd. Cycles and feedback loops may be defined in cases where the path source is also the path target, i.e., $p(v_{s_p}, v_{s_p}, \alpha^{\text{sign}}_p)$.

For example, in Figure 3, on the path from source node $v_6$ to target node $v_{13}$, the number of negative regulations is odd, due to only one negative regulation from node $v_8$ to $v_9$, and so the sign of this overall path is negative.

![Figure 3. Toy example of a directed signaling network where the sign of the overall path is negative.](image-url)
Definition 6. An element-based executable model is a triple $\mathcal{M} = \langle G, \mathcal{X}, \mathcal{F} \rangle$, where $G(V, E)$ is a static network structure of the model (see Definition 3), $\mathcal{X} = \{x_1, x_2, \ldots, x_N\}$ is a set of $N$ state variables corresponding to nodes in $V = \{v_1, v_2, \ldots, v_N\}$, and $\mathcal{F} = \{f_1, f_2, \ldots, f_N\}$ is a set of $N$ regulatory (update) functions such that each element $v_i \in V$ has a corresponding function $f_i \in \mathcal{F}$.

In element-based modeling, the function and element types are usually decided based on the knowledge or the information available about the modeled system and its components. In other words, the element-based modeling approach can represent indirect influences between elements, and it can model systems where the knowledge about element interaction mechanisms is incomplete. An example of element-based model is a discrete model, where each element state variable is assigned a discrete set of values. Boolean models [2-4] are a subset of discrete models, where elements can have only two values, 0 (also referred to as OFF or False) and 1 (also referred to as ON or True).

Definition 7. When element update functions $f_i \in \mathcal{F}$ have different mathematical form across elements $v_i \in V$ within the same model, for example, logical, discrete, or continuous functions, we refer to these models as hybrid element-based executable models.

In hybrid element-based models, individual elements within the same model can have very different update functions. The set or interval of possible values assigned to each model element can also vary. Using such hybrid collection of element update rules within a single model enables model simulation and studies of cell dynamics, state transitions, and feedback loops, while utilizing the available information, in the absence of complete knowledge of interaction mechanisms. These hybrid element-based models enable integration of both prior knowledge and data, and the analysis of hybrid networks (systems involving protein-protein interactions, gene regulations, and/or metabolic pathways).

Definition 8. A source node $v_j$ of an edge in graph $G(V, E)$ that has $v_i$ as a target node is called a regulator of $v_i$. In other words, for each element $v_i$, any element $v_j$ that influences the state of $v_i$ such that the function $f_i$ is sensitive to the value of $x_j$ is called a regulator of $v_i$.

Definition 9. For each element $v_i$, an influence set, denoted as $V_i^{\text{influence}} \subseteq V$, consists of all regulators of $v_i$. The state variables that correspond to the elements in $V_i^{\text{influence}}$ form set $\mathcal{X}_i^{\text{influence}}$.

Definition 10. Any element $v_j \in V_i^{\text{influence}}$, for which the edge $e(v_j, v_i, a^e)$ has a positive sign, $a^e_{\text{sign}} = \text{positive}$, belongs to the positive regulator list for element $v_i$, denoted as $v_j \in V_i^{\text{influence,+}} \subseteq V_i^{\text{influence}}$, represented with attribute $a^{\text{posreglist}}$. Any element $v_j \in V_i^{\text{influence}}$, for which the edge $e(v_j, v_i, a^e)$ has a negative sign, $a^e_{\text{sign}} = \text{negative}$, belongs to the negative regulator list for element $v_i$, denoted as $v_j \in V_i^{\text{influence,-}} \subseteq V_i^{\text{influence}}$, represented with attribute $a^{\text{negreglist}}$.

Definition 11. For each element $v_i \in V$, its state variable $x_i \in \mathcal{X}$ can take any value from a set or an interval of values $X_i$. The state variable $x_i$ is represented with attribute $a^{\text{variable type}}$, and is assigned either the amount or activity value type of $v_i$, represented with attribute $a^{\text{value type}}$.

Definition 12. The state variables $x_i$ that correspond to elements in $V_i^{\text{influence,+}}$ form set $\mathcal{X}_i^{\text{influence,+}} \subseteq \mathcal{X}_i^{\text{influence}}$, and are used for creating a positive regulation rule for $v_i$, represented with attribute $a^{\text{posregrule}}$. The state variables $x_i$ that correspond to elements in $V_i^{\text{influence,-}}$ form set $\mathcal{X}_i^{\text{influence,-}} \subseteq \mathcal{X}_i^{\text{influence}}$, and are used for creating a negative regulation rule for $v_i$, represented with attribute $a^{\text{negregrule}}$. 
**Definition 13.** When $X_i$ is a set of discrete values, $|X_i|$ is referred to as the number of levels of $v_i$, represented with attribute $a^{\text{levels}}$.

**Definition 14.** An array of $k$ state values $X_i^0, X_i^t_1, X_i^t_2, \ldots, X_i^t_{k-1}$ that are assigned to $v_i$ at $t_0, t_1, t_2, \ldots, t_{k-1}$ time steps during simulation, where $t_0$ is the initial time step, and $t_0 < t_1 < t_2 < \cdots < t_{k-1}$, is called state list and is represented with attribute $a^{\text{state list}}$. Multiple state lists are allowed within the BioRECIPE table, in consecutive columns, named "State list #" where #=$0,1,2,\ldots$.

**Definition 15.** When the state variable $x_i$ has a constant 0 value throughout the entire simulation, this is referred to as a constant OFF state, and represented with attribute $a^{\text{const OFF}}$.

**Definition 16.** When the state variable $x_i$ has a constant nonzero value (e.g., the highest value from $X_i$) throughout the entire simulation, this is referred to as a constant ON state, and represented with attribute $a^{\text{const ON}}$.

**Definition 17.** The next state of element $v_i$, denoted as $x_i^\ast$, is computed using the element update rule $f_i$ and current states of all elements in its influence set, that is, current values of all variables in $X_i^{\text{influence}}: x_i^\ast = f_i(X_i^{\text{influence}})$.

5 Translators and Compatibility

The BioRECIPE documentation is also available as ReadtheDocs pages [1], where further details are provided on how to create interaction lists and executable models in this format, as well as links to examples and available translators to and from other representation formats and various tool inputs and outputs.

The BioRECIPE format is compatible with several common representation formats (e.g., SBML) used by the systems and computational biology community that are created mainly for machine use.

The BioRECIPE format is also compatible with the output of several machine readers (TRIPS [5] and REACH [6]), as well as with the INDRA output [7]. Through the model translation, BioRECIPE is compatible with a number of tools and databases that are used to analyze or store models (e.g., CellCollective [8], NDEx [9], BioModels [10], many of the simulators available in the BioSimulators [11] and CoLoMoTo [12] repositories).

Finally, BioRECIPE is also compatible with a suite of tools within the Dynamic System Explanation (DySE) framework [13]. For model simulation and analysis, the DiSH simulator [14] and PIANO [15] accept files in BioRECIPE format. Several tools that curate, verify, and extend models, such as FLUTE [16], VIOLIN [17], CLARINET [18], ACCORDION [19], FIDDLE [20], and MINUET [21], all use BioRECIPE format and output their results in a BioRECIPE-compatible format.

6 Conclusion

The BioRECIPE representation format is a valuable tool for the field of systems and computational biology by promoting model curation using both human and machine curators. The complexity of cellular signaling pathways and their components necessitate modeling methods that can account for a multitude of details. To compensate, the BioRECIPE representation format allows for many element and interaction attributes to be included, as well as attributes for simulation. The BioRECIPE format is compatible with multiple tools for model curation, information extraction, and existing formats for systems biology. This interoperability ensures that researchers can seamlessly integrate BioRECIPE into their existing workflows. Future directions include additional functionality to translate between existing formats (such as SBOL [22]), or integration of the BioRECIPE representation format as input to model curation and storage platforms (such as CellCollective [8] or NDEx [9]). These platforms play a crucial role in managing and
disseminating computational models, and closer integration with BioRECIPE could streamline the process of model sharing and collaboration within the scientific community. In conclusion, the BioRECIPE representation format offers a leap forward in the field of systems biology. Its ability to support comprehensive model curation makes it a valuable resource for researchers and practitioners in the biological sciences.

7 Acknowledgments

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8 References


