runBioSimulations: an extensible web application that simulates a wide range of computational modeling frameworks, algorithms, and formats

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1 ABSTRACT

2 Comprehensive, predictive computational models
3 have significant potential for science, bioengineer-
4 ing, and medicine. One promising way to achieve
5 more predictive models is to combine submodels of
6 multiple subsystems. To capture the multiple scales
7 of biology, these submodels will likely require multi-
8 ple modeling frameworks and simulation algorithms.
9 Several community resources are already available
10 for working with many of these frameworks and
11 algorithms. However, the variety and sheer number
12 of these resources make it challenging to find and
13 use appropriate tools for each model, especially
14 for novice modelers and experimentalists. To make
15 these resources easier to use, we developed
16 runBioSimulations (<https://run.biosimulations.org>),
17 a single web application for executing a broad range
18 of models. runBioSimulations leverages community
19 resources, including BioSimulators, a new open
20 registry of simulation tools. These resources cur-
21 rently enable runBioSimulations to execute nine
22 frameworks and 44 algorithms, and they make run-
23 BioSimulations extensible to additional frameworks
24 and algorithms. runBioSimulations also provides
25 features for sharing simulations and interactively
26 visualizing their results. We anticipate that runBio-
27 Simulations will foster reproducibility, stimulate col-
28 laboration, and ultimately facilitate the creation of
29 more predictive models.

30 INTRODUCTION

31 More comprehensive and predictive models have significant
32 potential for biology, bioengineering, and medicine. For
33 example, models of entire cells could help synthetic biologists
34 design cells and help physicians personalize medicine (1, 2).
35 Due to the complexity of biology, building such models
36 will likely require collaboration among many modelers and
37 experimentalists. One promising way to harness this diverse

38 expertise is to combine multiple submodels of individual
39 subsystems, each developed by a small group of experts.

40 To capture the multiple scales relevant to biology at a
41 practical computational cost, these submodels will likely
42 require multiple modeling frameworks. For example, a model
43 of the phenotypic heterogeneity of single cells might need
44 to capture slow processes, such as transcription, precisely,
45 while fast processes, such as metabolism, could be captured
46 coarsely. Numerous frameworks and simulation algorithms
47 already exist for several scales. For example, stochastic kinetic
48 simulations can capture the cell-to-cell variability in gene
49 expression, and flux-balance analysis (FBA) can capture the
50 distribution of fluxes over metabolic networks.

51 To facilitate collaboration, several model formats have been
52 created for these frameworks and algorithms. For example, the
53 BioNetGen Language (BNGL, 3), CellML (4), NeuroML (5),
54 and the Systems Biology Markup Language (SBML, 6) can
55 capture kinetic models, and the SBML flux balance constraints
56 (SBML-fbc; 7) and qualitative modeling (SBML-qual; 8)
57 packages can capture flux balance and logical models.

58 Furthermore, numerous software tools support these for-
59 mats. For example, BioNetGen (9), NFSim (10), and Virtual
60 Cell (VCell; 11) support BNGL; BoolNet (12) and The Cell
61 Collective (13) support SBML-qual; CBMPy (14), COBRApy
62 (15), and The Cell Collective support SBML-fbc; COPASI
63 (16), JWS Online (17), StochSS (18), tellurium (19), and
64 VCell (11) support SBML; OpenCOR supports CellML (20);
65 and Open Source Brain supports NeuroML (21).

66 These resources provide experts rich silos for modeling
67 individual subsystems. However, this siloing poses obstacles
68 to composing models of multiple subsystems and scales
69 into comprehensive models. The effort required to learn the
70 unique frameworks, algorithms, formats, software tools, and
71 conventions associated with each silo also impedes collabora-
72 tion, especially for novice modelers and experimentalists.

73 To help investigators use these resources, we developed
74 runBioSimulations, an extensible REST API and graphical
75 web application for executing simulations involving a broad
76 range of frameworks, algorithms, and model formats. runBio-
77 Simulations leverages several community resources, including
78 model formats such as SBML, the Simulation Experiment
79 Description Language (SED-ML, 22), the COMBINE archive

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Figure 1. runBioSimulations is an extensible, standards-driven web application for executing models across a broad range of modeling frameworks, simulation algorithms, and model formats. runBioSimulations can execute models (a) and simulations (b) described with community resources such as COMBINE, SBML, and SED-ML with standardized simulation tools registered with BioSimulators (c). runBioSimulations produces results in HDF5 format (d). runBioSimulations also provides tools for interactively visualizing simulation results (e).

80 format (23), and BioSimulators (<https://biosimulators.org>),
81 a new open registry of standardized simulation tools. As
82 of this writing, runBioSimulations supports nine frame-
83 works, 44 algorithms, and five model formats (Table S1).
84 This includes 37 algorithms for continuous, discrete, hybrid,
85 and rule-based kinetic simulation with BNGL and SBML;
86 five algorithms for flux balance simulation with SBML-fbc;
87 and three algorithms for logical simulation with SBML-
88 qual. Importantly, the community can expand runBioSim-
89 ulations to additional frameworks, algorithms, and formats
90 by contributing additional simulation tools to BioSimula-
91 tors. runBioSimulations also provides features for visualizing
92 simulation results and debugging, managing, and sharing
93 simulations. Furthermore, the runBioSimulations API enables the
94 community to develop additional front-end applications that
95 utilize runBioSimulations' unique simulation capabilities. For
96 example, model repositories could use the API to provide
97 interactive simulations of their models.

98 By making it easier to execute a broad range of mod-
99 els, we anticipate that runBioSimulations will foster model
100 reuse, bolster collaboration, and empower peer review. In turn,
101 we anticipate this will accelerate the development of more
102 comprehensive and more predictive models.

103 Below, we describe the key features of runBioSimulations,
104 its architecture, and how it facilitates model reuse and collabor-
105 ation. In addition, we outline our future plans for runBio-
106 Simulations. The [Supplementary Data](#) summarizes the frame-
107 works, algorithms, formats, and simulation tools supported
108 by runBioSimulations; provides additional information about
109 the implementation of runBioSimulations; presents a case
110 study of using runBioSimulations to evaluate the practical
111 reusability of existing published simulations to individual
112 investigators that illustrates the utility of runBioSimulations;
113 compares runBioSimulations to other tools; and outlines how
114 the community can contribute to runBioSimulations.

115 KEY FEATURES

116 The key feature of runBioSimulations is the capability to
117 execute a broad range of simulations that involve a variety
118 of modeling frameworks, simulation algorithms, and model

119 formats from a single, simple, consistent interface. This
120 is achieved through a modular architecture that leverages
121 existing resources including model formats such as SBML,
122 SED-ML, and the COMBINE archive format to encapsulate
123 the details of each framework, algorithm, and model for-
124 mat. This architecture is implemented as a REST API. The
125 runBioSimulations graphical user interface (GUI) provides
126 investigators a user-friendly client to this powerful API.

127 The starting point to using runBioSimulations is a
128 COMBINE archive that contains one or more models in a for-
129 mat such as BNGL or SBML and describes one or more simu-
130 lations of these models in SED-ML. Users can obtain models
131 and simulations encoded in these formats from repositories
132 such as BioModels (24) or use tools such as VCell to create
133 models and simulations in these formats. Models and simu-
134 lations can be packaged into COMBINE archives using tools
135 such as CombineArchiveWeb (25).

136 The runBioSimulations GUI enables users to execute mod-
137 els and retrieve and visualize their results in three simple
138 steps. First, users use the GUI to select a COMBINE
139 archive to execute and a simulation tool to run the archive
140 (Figure 2b). Users can choose any of the standardized simu-
141 lation tools available in the BioSimulators registry and any
142 of their versions. To help investigators find tools that are
143 compatible with specific types of models and/or that sup-
144 port specific simulation algorithms, BioSimulators provides
145 detailed information about the capabilities of each simula-
146 tion tool (Figure 2a). The ability to use multiple simulators
147 has several benefits. (a) This makes it easier to reuse mod-
148 els, including older models that require legacy formats. (b)
149 This design makes the simulation logic of runBioSimula-
150 tions transparent and portable, ensuring users that they can
151 continue work initiated with runBioSimulations onto their
152 own computers using the same simulators, further lowering
153 the barrier to model reuse. (c) Because BioSimulators is an
154 open registry, this design enables the community to extend the
155 simulation capabilities of runBioSimulations.

156 Users can manage their simulations and monitor their
157 progress using a table that summarizes their simulations
158 (Figure 2g). Optionally, users can also provide an address to

Figure 2. runBioSimulations provides a single GUI for executing a broad range of models and visualizing their results. (a) Users can use BioSimulators to select tools for executing specific simulations. **(b–e)** runBioSimulations provides simple forms for executing simulations and designing visualizations of their results. runBioSimulations also provides a summary table **(g)** and structured logs **(f)** for managing and debugging simulations.

receive emails about the completion of the execution of their archives. This feature is valuable for long simulations.

Once simulations complete, users can download and visualize their results. Simulation results can be downloaded in HDF5 format. The GUI provides users a simple form (Figure 2c) for designing two-dimensional plots of model predictions (Figure 2d, e).

Users also have the option to upload Vega visualizations (26) to visualize simulation results. This enables investigators to visualize their simulation results with a broad range of charts, as well as custom, interactive, publication-quality diagrams. This also makes it easier to reuse visualizations across multiple simulation conditions by re-painting them with results of alternative simulations. Together, this combination of runBioSimulations and Vega ensures that the provenance of simulation results and visualizations of simulation results are transparent by capturing all of the information needed to reproduce each result and visualization, including the model, simulation, and simulator which generated each result and the transformations used to map each result to each diagram.

To help users debug simulations, the GUI also displays structured logs of their execution (Figure 2f). This can help direct users to errors in specific SED-ML tasks and outputs.

runBioSimulations also makes it easy for users to share simulations and their results via persistent URLs similar to file sharing services such as Google Drive. These links enable users to revisit their simulation results, share simulations with collaborators, anonymously share simulations with peer reviewers, and publish simulations by embedding links into articles. runBioSimulations is particularly well-suited to sharing computationally-expensive simulations because it enables investigators to quickly retrieve their results without having to wait for long simulations to complete.

Furthermore, developers can use runBioSimulations' REST API to build additional client applications that leverage runBioSimulations' simulation logic. For example, developers could use the API to build additional clients for executing simulations such as Jupyter notebooks or desktop applications.

METHODS

runBioSimulations is composed of a GUI for submitting simulations, managing simulations, and visualizing their results; services for executing simulations on a high-performance computing (HPC) cluster, monitoring their progress, and collecting their results; and a database for storing simulations and their results (Figure 3). More information about the design, implementation, and deployment of runBioSimulations is available in the [Supplementary Data](#).

USE CASES

Publishing simulations

We believe that runBioSimulations' standards-driven design and unique capability to execute a broad range of simulations is ideal for publishing simulations. As more tools embrace SED-ML, runBioSimulations will help authors publish simulations that other investigators can easily reuse. For example, investigators could use runBioSimulations to explore

Figure 3. Overview of the implementation (blue) and deployment (orange) of runBioSimulations. The application consists of a GUI; services for executing, monitoring, and logging simulations; and a database of simulations and their results which interact via a REST API. To support multiple simultaneous users, runBioSimulations is deployed using the cloud and HPC.

additional conditions and predictions of a model beyond those reported by its authors. Furthermore, by providing simple access to multiple simulators, runBioSimulations can help authors and model curators verify that simulation results are reproducible across simulation algorithms and simulators.

Collaboration and peer review

We believe that runBioSimulations is similarly well-suited for sharing simulations with collaborators and reviewers. By helping investigators work with different frameworks and algorithms, runBioSimulations makes it easier for investigators to contribute to multiple collaborations. In particular, runBioSimulations' simulation URLs make it easy for investigators to share simulations with collaborators, and they enable peer reviewers to access simulations anonymously.

Comparing simulation tools

Because runBioSimulations can execute the same simulations with multiple simulation tools, runBioSimulations is also well-suited to assessing the compatibility between tools. For example, investigators could compare results of the same simulations generated with multiple tools to evaluate the performance of the tools, identify inconsistencies among the tools, or detect potential errors in the tools.

Multiscale modeling education

Furthermore, we believe that runBioSimulations could be a valuable educational tool. In particular, instructors who use runBioSimulations for assignments involving multiple frameworks would only need to teach their students a single tool. Instructors could also leverage runBioSimulations' simulation results storage for assignments involving the analysis of results of computationally-expensive simulations.

DISCUSSION

In summary, runBioSimulations provides a simple GUI for executing a broad range of simulations described using community resources such as SBML and SED-ML. Importantly, the community can extend these simulation capabilities by contributing additional standardized simulation tools to the BioSimulators registry. The runBioSimulations GUI also provides users features for managing their simulations, interactively visualizing their results, and sharing their simulations through persistent URLs. In addition, developers can use runBioSimulations' API to build custom applications for executing simulations and/or analyzing simulation results. Together, we believe runBioSimulations will both help authors of in silico experiments share their simulations and help other investigators reproduce and reuse their studies. Ultimately, we believe runBioSimulations will facilitate collaboration and foster more comprehensive and more predictive models.

Additional modeling formalisms, algorithms, and formats

We invite developers to extend runBioSimulations to more simulations by contributing additional standardized simulation tools to BioSimulators. To help developers standardize their tools, BioSimulators provides a Python library for executing COMBINE archives, a test suite for validating simulation tools, several examples, and documentation.

More sophisticated data visualizations

We also aim to expand the visualization features of runBioSimulations by using Vega to support a broad range of canonical chart types, as well as custom charts, such as network maps. By capturing how charts can be painted with data, Vega would also enable users to reuse diagrams with multiple models and simulations, furthering our goals of reuse and collaboration.

Online platform for sharing entire simulation projects

Furthermore, we plan to use the runBioSimulations API to develop an online platform that will help authors create and publish entire simulation studies and provide the community a central place to discover and reuse studies. This platform will layer several additional capabilities on top of runBioSimulations. The platform will enable authors to publish models, simulations, simulation results, and data visualizations of simulation results. The platform will also help the community create and execute variants of published models and simulations to explore alternative simulation conditions, as well as help the community reuse published data visualizations to examine their results. We anticipate this platform will further bolster model reuse, composition, and collaboration.

Additional modeling and simulation tools

Finally, we aim to help the community use runBioSimulations' API to develop additional tools. For example, model repositories could use runBioSimulations to provide capabilities for executing their models, and model format developers could use runBioSimulations to implement test suites for verifying that simulators correctly support their formats.

AVAILABILITY

The application and API are freely available without registration at <https://run.biosimulations.org> along with a tutorial, examples, and documentation. The source code is openly available under the MIT license at <https://github.com/biosimulations/Biosimulations>.

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Conflict of interest statement.

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