1 Capturing scientific knowledge in computable form

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24 **Availability:** Biofactoid server at <https://biofactoid.org>

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28 **ABSTRACT**

29 Technological advances in computing provide major opportunities to complement human
30 reasoning and to dramatically speed up science - but only if structured knowledge is
31 available to enable efficient communication between humans and computers. Traditionally,
32 biological knowledge is captured in publications and knowledge bases. Knowledge in papers
33 is not directly in a computable, structured form; curated structured knowledge bases are
34 limited by manual curation processes. To accelerate knowledge capture and communication
35 and keep pace with the rapid growth of scientific reports, we developed the Biofactoid
36 (biofactoid.org) software suite. Biofactoid accelerates the transfer of knowledge from the
37 minds of authors into computable, widely shared, structured knowledge and can be used as
38 part of the standard publication process. Biofactoid is a web-based system for scientists to
39 compose a structured representation of networks of interactions between genes, their
40 products, and chemical compounds, represented using the expressive power of a formal
41 ontology (BioPAX). The resulting knowledge items are shared via public information
42 resources and can be discovered and analyzed in the context of all existing computable
43 knowledge. We envision adoption of software technology for knowledge capture by scientists
44 and publishers as part of an ecosystem of tools, in which scientific reasoning is supported by
45 efficient knowledge computation.

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48 **INTRODUCTION**

49 Biological pathways organize sets of molecular interactions and reactions that
50 underlie cellular processes and are used for experimental design, interpretation of genomics
51 data (Khatri et al., 2012), understanding of disease mechanisms (Chinen et al., 2016; Santos
52 et al., 2014), and identification of therapeutic targets (Mack et al., 2014). To manage,
53 visualize and interpret the large amount of available pathway information, researchers
54 require computational tools such as pathway information resources, structured data
55 representation standards, and analysis software (Demir et al., 2010; Franz et al., 2016;
56 Jassal et al., 2020; Pratt et al., 2015; Rodchenkov et al., 2020; Shannon et al., 2003). These
57 computational tools are capable of accessing increasing amounts of pathway and interaction
58 data (Bader et al., 2006) collected through centralized (Gene Ontology Consortium, 2015;
59 Jassal et al., 2020) or crowdsourced curation efforts (Slenter et al., 2018). Nevertheless,
60 these existing efforts are not able to achieve wide coverage over the rapidly growing
61 scientific corpus (over 1.3 million new PubMed articles/year) (Bornmann and Mutz, 2015;
62 Cordero et al., 2016), arguing for the development of scalable and sustainable approaches
63 to complement existing approaches to knowledge acquisition (Attwood et al., 2015; Imker,
64 2018).

65 For reasons of efficiency and accuracy, structured knowledge of biomedical
66 discoveries could be provided directly by the original authors of research reports, rather than
67 captured indirectly by subsequent reading of the reports by knowledge base teams. By
68 analogy, the molecular 3D structures submitted directly by authors to the Protein DataBank
69 (PDB) (Berman et al., 2000) have become a key resource among structural biologists, so
70 much so that publication in major journals is contingent on data deposition. Similar
71 requirements and community practice have also led to direct submission of DNA sequence
72 and transcriptomics information to public databases as core components of the biological
73 research information infrastructure. In contrast, there are few efforts and little technology to

74 support direct submission by authors of biological pathway information and related
75 knowledge in computable form.

76 Here we describe Biofactoid (biofactoid.org), a web-based software system that
77 empowers authors to capture and share structured human- and machine-readable
78 summaries of molecular-level interactions described in their publications. Without such a
79 curation support tool, authors would have to spend unnecessary time figuring out the
80 computational form of their knowledge for incorporation into a computation-enabled
81 knowledge base. To overcome this and other significant barriers to computable knowledge
82 acquisition and sharing, Biofactoid was developed to ease pathway curation and to rapidly
83 generate expressive, structured representations with minimal user training. Structured
84 knowledge newly acquired in this way becomes part of the global pool of pathway
85 knowledge and can be shared in resources such as Pathway Commons (Rodchenkov et al.,
86 2020), Network Data Exchange (NDEX) (Pratt et al., 2015), and STRING (Szklarczyk et al.,
87 2017), to enhance information discovery and analysis. Biofactoid can be used by authors
88 and publishers to share structured information from existing and new research articles, in
89 voluntary or required mode. The development of Biofactoid and related computational tools
90 helps support human-computer communication and inference algorithms in an ecosystem in
91 which scientific reasoning is increasingly assisted by broad and deep knowledge
92 computation tools.

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95 RESULTS

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97 Data sharing workflow

98 Biofactoid enables molecular-level detail of biological processes reported in
99 peer-reviewed publications to be shared in a structured format accessible to humans and
100 computers. Interactions (including binding, post-translational modification, and
101 transcription/translation) involving molecules of various types (proteins, nucleic acids, genes,
102 or chemicals, e.g., metabolites and drug compounds) can be represented. Users begin by
103 entering the article title, or identifier (e.g. PubMed identifier or Digital Object Identifier, DOI).
104 Article metadata (authors, abstract & journal issue) is automatically imported if available.
105 Next, users draw a network of biological entities and interactions using the Biofactoid
106 curation tool, which is akin to graphical illustration software (e.g. Microsoft Powerpoint,
107 Adobe Illustrator), with the added ability to embed structured information (such as database
108 links and molecule types) about the network components and interaction types. The major
109 features of the Biofactoid curation tool are as follows:

110 **1. Molecular entities.** Genes, gene products or chemicals are created in the network
111 using an “add entity” tool, which creates a node (circle shape) that the user labels (Figure
112 1A). Biofactoid automatically maps the label to an external database record, NCBI Gene for
113 genes and their products, and ChEBI for small molecules (Brown et al., 2015; Hastings et
114 al., 2016). This mapping represents the top hit of a search based on the similarity between a
115 node label and a database record’s list of synonyms; for genes, organisms are given priority
116 based upon the organism of genes previously added to the network. Users can update the
117 mapping by selecting another organism (e.g. human p53 or mouse p53) or product type (i.e.,
118 RNA or protein). Alternatively, users may assign an alternate and distinct database entry
119 from an annotated list of options.

120 **2. Interactions.** A “draw interaction” tool lets users link two nodes by clicking or
121 tapping and dragging (Figure 1B). Biofactoid uses common visual representations in
122 biological process diagrams (a normal arrow indicates stimulation or activation, a ‘T-bar’
123 arrow head indicates inhibition or repression, and an undirected line indicates any other
124 interaction) and generally follows an Activity Flow representation paradigm (Le Novère et al.,
125 2009). The relationship type can be refined by selecting from a list that currently includes
126 binding, transcription/translation, or common forms of post-translational modifications, with
127 more detailed interaction types following the BioPAX ontology (Demir et al., 2010) to be
128 added in a future release.

129 **3. Complexes.** Molecular complexes can be created by dragging gene or chemical
130 nodes together (Figure 1B). Those nodes are then enclosed by a box that represents the
131 complex, which can be named.

132 **4. Automatic saving and co-editing.** Pathway representations in Biofactoid are
133 automatically saved as changes are made and a live-sync capability enables multiple
134 authors to collaboratively edit the same pathway, analogous to Google Docs.

135 Once complete, the pathway data is validated by pressing a ‘Submit’ button. At this
136 point, the user may address any potential quality issues (e.g. unlabelled nodes, empty
137 document) and then can confirm submission. Upon submission, Biofactoid makes the shared
138 pathway visible and explorable on the Biofactoid website, posts a graphical abstract to social
139 media (e.g. Twitter: @biofactoid), and makes the pathway data available in standard formats
140 (e.g. BioPAX) to be integrated in public, searchable databases, such as Pathway Commons
141 (Rodchenkov et al., 2020), NDEX (Pratt et al., 2015) and Reactome (Jassal et al., 2020).
142 Biofactoid information thus becomes part of a growing corpus of widely available pathway
143 information in computable form, enhancing both human and computational discovery
144 processes.

146 **Data exploration workflow**

147 All user-submitted pathways are made immediately available as graphical abstracts
148 on the Biofactoid homepage which researchers, or journal editors tracking a submission,
149 may freely browse. Each pathway is linked to its associated author and article information
150 and its structured data in the Biofactoid ‘Explorer’ app (Figure 1C). Articles with related
151 content (e.g. molecules and interactions from the Biofactoid pathway) are shown to help the
152 user explore similar knowledge in the literature. This information is accessed via a
153 customized search process from pathway and interaction databases and biomedical
154 literature using natural language processing (NLP) tools and databases (e.g. REACH,
155 INDRA) (Gyori et al., 2017; Valenzuela-Escárcega et al., 2018), with results ranked by
156 similarity to text associated with the query pathway, using a deep-learning based method
157 (Giorgi et al., 2020). A future release will link Biofactoid data to similar pathways, accessed
158 from pathway knowledge bases.

160 **DISCUSSION**

161 Biofactoid has focused on the capture of published pathway information to augment
162 discovery, attribution and communication of scientific knowledge. In developing our strategy,
163 we have considered how technology can best be used to aid authors; the result is a generic
164 approach that can be extended towards the acquisition of other types of biological
165 knowledge in computable form. A convenient time to capture knowledge is during

publication, as this represents a period when authors provide other types of data for deposition (e.g. sequence data) and is a time when they are most keenly aware of the information used in their report. Thus, Biofactoid will ideally be part of the publication process, but also possibly as part of more general crowdsourcing efforts, such as curating and sharing all published knowledge about SARS-CoV-2 (Ostaszewski et al., 2020). To be successful, Biofactoid development has focused on exploring key elements of efficiency, incentives, added value for researchers and better technology for human-computer communication. The computable knowledge capture model proposed here includes formal knowledge representation using ontologies, easy to use curation support software that links molecules to corresponding database identifiers (grounding or normalization) and a connection with the publication process and author attribution. This model expands on prior work defining digital abstracts and building pathway data crowdsourcing efforts and software (Bharadwaj et al., 2017; Ceol et al., 2008; Liechti et al., 2017; Pratt et al., 2015; Seringhaus and Gerstein, 2007; Slenter et al., 2018; Todorov et al., 2019; Waagmeester et al., 2020). Future development will include expanding the model to capture increasing amounts of literature-described pathway information, such as additional relationship types, context and direct vs. indirect interactions, prioritized by frequency of occurrence in publications.

To improve the efficiency and utility of Biofactoid, we are developing natural language processing (NLP) technology to assist in the Biofactoid workflow and enable the representation of pathways in textual form (Giorgi et al., 2019; Giorgi and Bader, 2020, 2018; Valenzuela-Escárcega et al., 2018). As images and text are the main modes of communication with humans, the system will permit graphical or textual entry of pathway information and automated conversion between these two forms. Automated NLP processing of a manuscript will extract phrases describing pathways (Gyori et al., 2017), which will then be suggested to the author who can choose to include them in their pathway. Further development of NLP methods for the reliable extraction of pathway information from the entire full-text corpus of publications, followed by new tools for curation and quality control, will help get the community closer to the goal of full coverage of current pathway knowledge in computable form. This would significantly increase the benefit to the research community from using powerful methods for network and pathway searches, logical inference of information propagation through pathways, and machine learning for the elucidation of essential cell biological processes, which benefit from increased coverage of network data to find important relationships. We are also improving the search and exploration functions of the system, ensuring Biofactoid information is well connected to other useful knowledge, and that these connections to related information are browsable starting from a Biofactoid entry of interest. In the future, we envision that an author will signal their interests in specific molecules, relationships and context by entering information they publish about these in Biofactoid, which will then act as a custom query that regularly alerts authors to new information (e.g. from publications) related to their interests, including interacting molecules, phenotypes and other biological concepts. This work sets the stage for the development of new information technologies that will help researchers overcome information overload, caused by rapid growth of the scientific literature, and help increase the speed of scientific discovery.

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210 MATERIALS AND METHODS

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212 **Implementation**

213 Biofactoid is written in JavaScript. The backend server uses a microservice
 214 architecture, with Node.js, Express, and RethinkDB. Client-server data synchronization,
 215 supporting automatic saving and concurrent editing, uses websockets and a model similar to
 216 differential synchronization (Fraser, 2009). The front end uses React and Cytoscape.js
 217 (Franz et al., 2016), for network drawing and is optimized for desktop and mobile devices.
 218 An administrative dashboard, as well as user curation workflow automation features (e.g.
 219 automatic email generation) are integrated into the Biofactoid system to aid system
 220 scalability.

221

222 **Availability**

223 Biofactoid is available to biomedical researchers for data sharing and exploration via
 224 the <https://biofactoid.org> website. To support bioinformaticians and software developers, all
 225 user-contributed pathway data is openly accessible in multiple standard formats, including
 226 raw data in JavaScript Object Notation (JSON), the Systems Biology Graphical Notation
 227 Markup Language (SBGNML) pathway visualization format (Process Description visual
 228 language) (Le Novère et al., 2009; van Iersel et al., 2012), and the Biological Pathway
 229 Exchange (BioPAX) language (Demir et al., 2010). All source code, documentation and data
 230 are open source and freely available through GitHub
 231 (github.com/PathwayCommons/factoid), and containerized components are freely available
 232 on DockerHub (hub.docker.com/r/pathwaycommons/factoid) enabling others to build on and
 233 improve our software.

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247 **COMPETING INTERESTS**

248 None declared.

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406 FIGURES

A

ras mediates nerve growth factor receptor modulation of three signal-transducing protein kinases: MAP kinase, Raf-1, and RSK.
K W Wood, C Sarnecki, T M Roberts, J Blenis
Cell 68 (1992)

p21 c-ras

p21 c-ras

p21 c-ras (Homo sapiens)

Type ☒ Gene or gene product ☐ DNA ☐ RNA ☐ Protein

Synonyms C-BAS/HAS; C-H-RAS; C-HA-RAS1; CTLO; H-RASIDK; p21ras; c-has/bas p21 protein; RASH1; HRAS1; Ha-Ras1 proto-oncoprotein;

More information NCBI Gene

Select a better match for "p21 c-ras"

SUBMIT

B

ras mediates nerve growth factor receptor modulation of three signal-transducing protein kinases: MAP kinase, Raf-1, and RSK.
K W Wood, C Sarnecki, T M Roberts, J Blenis
Cell 68 (1992)

Activated ras

p21 c-ras

GTP

Interaction type

- ☒ Binding
- ☐ Transcription/translation
- ☐ Post-translational modification
- ☐ Phosphorylation
- ☐ Dephosphorylation
- ☐ Methylation
- ☐ Demethylation
- ☐ Ubiquitination
- ☐ Deubiquitination
- ☐ Other

Raf-1

Submitted

407

C

Activated ras

p21 c-ras

GTP

Raf-1

ras mediates nerve growth factor receptor modulation of three signal-transducing protein kinases: MAP kinase, Raf-1, and RSK.
K W Wood, C Sarnecki, T M Roberts, J Blenis
Cell 68 (1992) PubMed Google Scholar

Abstract

p21c-ras plays a critical role in mediating tyrosine kinase-stimulated cell growth and differentiation. However, the pathways through which p21c-ras propagates these signals remain unknown. We report that in PC12 cells, expression of a dominant inhibitory mutant of ras, c-Ha-ras(Asn-17), antagonizes growth factor- and phorbol ester-induced activation of the erk-encoded family of MAP kinases, the 85-92 kd RSKs, and the kinase(s) responsible for hyperphosphorylation of the proto-oncogene product Raf-1. In addition, we find that expression of the activated ras oncogene is sufficient to stimulate these events. These data indicate that ras mediates nerve growth factor receptor and protein kinase C modulation of MAP kinases, RSKs, and Raf-1.

Recommended articles

Ras controls coupling of growth factor receptors and protein kinase C in the membrane to Raf-1 and B-Raf protein serine kinases in the cytosol.
A dominant negative mutant of Ras, M17 Ras, was used to study the role of Ras in receptor coupling of Raf-1 and B-Raf protein serine/threonine kinases (PSKs). We found that mutant Ras blocks serum- and T2-O-tetradecanoyl phorbol 13-acetate-induced activation of Raf-1 kinase in NIH3T3 cells and Raf-1 as well as B-Raf PSK stimulation by nerve growth factor (NGF) in PC12 pheochromocytoma cells. Mitogen stimulation of Raf kinase was measured by determination of Raf
J Troppmair, J T Bruder, H App, ..., U R Rapp
Oncogene 7 (1992)

MEK kinase activity is not necessary for Raf-1 function.
p21c protein kinase has been identified as an interm...
W M Yee, P F Worley
Mol. Cell. Biol. 17 (1997)

Rheb interacts with Raf-1 kinase and may function to integrate growth factor- and protein kinase A-dependent signals.
Rheb is a recently described member of the Ras family that was originally identified as an immediate-early gene in brain but is also widely expressed in other tissues. Here we demonstrate that Rheb interacts with and appears to regulate Raf-1 kinase, an essential component of the H-Ras signaling pathway. In direct contrast to H-Ras, however, the interaction of Rheb with Raf-1 is potentiated by growth factors in combination with agents that increase cyclic AMP (cAMP) levels. Protein kinase A-dependent phosphorylation of serine 43 within the
W M Yee, P F Worley
Mol. Cell. Biol. 17 (1997)

Rit contributes to nerve growth factor-induced neuronal differentiation via activation of B-Raf-extracellular signal...

408

409 **Figure 1. The Biofactoid curation tool.**

410 Curation in Biofactoid involves creating a visual network representing relationships between
411 genes or molecules. (A) Genes and chemicals are represented by circular shapes (nodes)
412 where users provide a label, the type of gene product, and the organism. A custom search
413 engine matches the label to a corresponding record from a database of genes or chemicals.
414 (B) Relationships are represented by connecting participants with lines, arrows, to indicate
415 activation, or 'T-bars' to represent repression. Users select the mechanism that best
416 describes the interaction. Complexes are represented as participants enclosed by a box,
417 which users can label. (C) Submitted pathways are made publicly available for exploration
418 (browsing) on the Biofactoid website. Users can view information about the article and can
419 access related information, such as other published articles mentioning a particular
420 interaction or participants of an interaction.