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NDEx: Accessing Network Models and Streamlining Network Biology Workflows

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Abstract

NDEx, the Network Data Exchange (https://www.ndexbio.org) is a web-based resource where users can find, store, share and publish network models of any type and size. NDEx is integrated with Cytoscape, the widely used desktop application for network analysis and visualization. NDEx and Cytoscape are the pillars of the Cytoscape Ecosystem, a diverse environment of resources, tools, applications and services for network biology workflows. In this article, we introduce researchers to NDEx and highlight how it can simplify common tasks in network biology workflows as well as streamline publication and access to data. Finally, we show how NDEx can be used programmatically via Python with the 'ndex2' client library, and point readers to additional examples for other popular programming languages such as JavaScript and R.

Keywords

Cytoscape; enrichment analysis; JavaScript; NDEx; neigh-borhood query; network biology; network models; pathway; python; R; REST API; subnetwork; systems biology

INTRODUCTION

Networks are a powerful and flexible paradigm that facilitate communication and computation about interactions of any type, whether social, economic, or biological. In recent years, the vast amount of biomedical data generated through omics approaches has contributed to a massive increase in publications featuring biological network models of cancer and other human diseases. This data is often provided as figures and tabular data files in supplementary materials, thus making its access and re-use laborious and time consuming. NDEx, The Network Data Exchange (Pillich, Chen, Rynkov, Welker, & Pratt,

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2017; Pratt et al., 2017; Pratt et al., 2015) is an online commons providing infrastructure and data resources to facilitate the use of biological networks in research. NDEx enables new modes of collaboration and publication using biological networks, and simplifies access to and re-use of network models.

Scientists can use NDEx to find networks to use in analysis applications: with 5913 publicly available networks, NDEx provides easy access to a wide variety of biological network data, including but not limited to resources such as BioGRID (Oughtred et al., 2021), SIGNOR (Licata et al., 2020), Wikipathways (Kutmon et al., 2016), DrugBank (Wishart et al., 2018), and BioPLEX (Huttlin et al., 2021).

Individuals and organizations can store and manage networks in their NDEx accounts, and can also make their networks publicly available, providing an easy distribution channel for both small pathways and very large interaction data sets. NDEx users can request DOIs (Digital Object Identifiers) for their networks and use them to link to the data from publications. Unlike a spreadsheet of interaction data in supplementary materials, readers can immediately visualize and inspect the data interactively in NDEx. Since 2017, NDEx has been an official repository for Springer Nature and the PLoS family of journals.

In addition, NDEx is fully integrated with Cytoscape (Shannon et al., 2003), a desktop application for network visualization and analysis, thus enabling networks to seamlessly flow from a journal article to a user's NDEx account straight into Cytoscape for subsequent data integration and analysis. Therefore, storing and distributing networks with NDEx promotes FAIR data principles, where networks become archival resources that are Findable, Accessible, Interoperable, and Re-usable.

Notebooks in Python and R have become a preferred software environment for bioinformaticians and experimental biologists; NDEx exposes a powerful REST API allowing Jupyter notebooks and other programs in Python to access NDEx via the ndex2 Python package, as shown in Basic Protocol 3. Client libraries are also available in R, Java, and JavaScript, positioning NDEx to serve as a framework for integration between bioinformatics applications and content resources. Examples of use of NDEx by applications include NAGA (Network Assisted Genomic Analysis) (Carlin et al., 2019), a web application and supporting service that uses NDEx in multiple capacities, and CRAVAT (Cancer-Related Analysis of Variants Toolkit; Masica et al., 2017), a toolkit for the interpretation of variants in the context of known mechanisms.

As scientific analysis systems increasingly shift to the cloud, NDEx and Cytoscape are moving to a primarily cloud-based network analysis ecosystem, where containerized services, applications, and data resources are easily accessible and fully interoperable.

BASIC PROTOCOL 1 GETTING STARTED WITH NDEX

In this first protocol, we will introduce the fundamental aspects of the NDEx web user interface (hereafter, NDEx UI) and prepare the ground for the "real world" use cases presented in Basic Protocols 2, 3, and 4. You will learn to use the NDEx UI to search for networks, become familiar with the NDEx Network Viewer (NNV), and create your

own NDEx account. NDEx accounts are free to use and provide you with 10 gigabytes of cloud storage space for your networks. It is not necessary to install the Cytoscape desktop application for this protocol, but it is required in Basic Protocol 2, so we recommend that you install the software now to avoid interruptions in the workflow. Here is a breakdown of the topics covered in this protocol:

- Overview of the NDEx landing page

- Network search feature

- The NDEx Network Viewer (NNV)

- Querying a network to extract subnetworks of interest

- Convenience features: Open in Cytoscape

- Creating and managing an NDEx account

- Saving a network to your NDEx account.

Necessary Resources

Hardware—A computer with stable internet connection

Software—Web browser (recommended: Google Chrome or Mozilla Firefox)

While we don't discourage the use of alternative web browsers, we cannot guarantee that all features will be available and functioning as intended. If you run into problems using a browser other than those specified above, please let us know! You can easily report a bug in NDEx using our web form. Please make sure to always update your browser to the latest available version.

Cytoscape desktop application (optional but recommended)

Please visit https://cytoscape.org to download and install the Cytoscape desktop application compatible with your operating system.

Other—Please add support@ndexbio.org to your e-mail contacts before proceeding. This is particularly important if you use a Gmail address, and necessary to ensure that you receive e-mails from the NDEx server to validate your account or reset your password (if necessary).

1.   Overview of The NDEx landing page.

To begin, launch a browser window and navigate to https://www.ndexbio.org to load the NDEx landing page (Fig. 1).

In the left corner of the top bar, the NDEx logo shows the current software version (2.5.1). Next, several menu items provide access to documentation, bug report/contact forms, and the FAQ page (Fig. 1A). Finally, in the top right corner, you can find the

Login/Register button (Fig. 1B), which you will use later in this protocol to create your account.

> You can click the underlined version number to access the **Release Notes** for details about new features, improvements, and bug fixes.

Below the logo, a cluster of three buttons (Fig. 1C) allows you to browse the latest network, explore the collection of NDEx featured networks, and visualize search examples. Click the **Featured Networks** button to open a dropdown menu with a variety of high-quality network models of different types and from different sources.

2. Network search feature.

You can run a custom network search using the textbox (Fig. 1D). The most popular ways to search for networks are by keyword or gene name.

> When searching for genes, you can decide to activate Search Term Expansion by marking the available checkbox: this feature will expand your search terms to include all possible aliases, thus returning networks that contain your genes of interest even if they have unofficial names. This feature only works for human genes. Mouse over the small blue icon to display a tooltip with additional information.

Keyword search: Type leukemia in the textbox and click the magnifier (or press Enter) to run the search: the results will be displayed as a table of networks that include leukemia in the network's name or description, or in a node name (Fig. 2).

The number of search results is displayed at the bottom left corner of the table (red oval).

For each network, you can see several property columns (such as number of edges, owner or date last modified).

Mouse over the network name to display a tooltip with a detailed network description (if applicable): try this with the first network in the results page, Acute Myeloid Leukemia.

Click the browser's Back button to go back to the NDEx landing page.

Gene search: Now type FLT3 in the textbox and run the search: the results page will contain all networks that include FLT3 in that network's name or description, or in one of its node's name or alias properties. Please make note of the number of Total Items in your search results.

Go back to the landing page and repeat the same search, but this time mark the checkbox to perform **Search Term Expansion** (Fig. 1D): if you compare the Total Items in the expanded search results with what you noted earlier, you'll notice that you now find a few additional networks that refer to FLT3 by one of its aliases.

> When searching for genes, using Search Term Expansion will expand your search terms to include all possible aliases, thus returning results (networks) that contain your gene(s) of interest even if they carry

unofficial names. This feature only works for human genes. Mouse over the small blue info icon to display a tooltip with more information.

For additional types of searches, please select the **Search Examples** button to view examples and access the advanced search documentation. The NDEx Search Feature is case-insensitive.

3.   The NDEx Network Viewer (NNV).

Click the network called **Acute Myeloid Leukemia** to open the network view page. The network view page is shown in Figure 3 and consists of Main Canvas, Info Panel, Query Feature, Action Buttons, and Menu Buttons.

Main Canvas: This area occupies about two thirds of the screen and is where the network model is drawn and visualized (Fig. 3A). Use the navigation buttons to zoom in/out and re-center the graphic view.

Click a graphic element (node or edge) to open a pop-up window and inspect the data.

Hold the Ctrl key on your keyboard and use your mouse or touchpad to perform a multiple selection (nodes and edges): with a multiple selection, you can inspect the data associated to nodes and edges by clicking the relative tabs in the info panel (Fig. 3B).

For small networks like the pathway we are looking at, graphic rendering is achieved using cytoscape.js. For large networks, NDEx uses a new, high-performance rendering engine called the Large Graph Renderer (LGR). It achieves the performance required for the display of millions of elements by using a different underlying technology and supporting only a limited subset of Cytoscape visual styling.

Info panel: This is located on the right-hand side, next to the Main Canvas, and occupies about one third of the screen (Fig. 3B). By default, the Info Panel shows the Network tab that provides information about the displayed network, including its description, reference publication, licensing information, and other properties.

The Info Panel has two additional tabs, Nodes and Edges, that become available only when you perform a multiple selection in the Main Canvas.

Query feature: It is located at the bottom left of the network view page (Fig. 3C). The Query Feature lets you search the displayed network for a subnetwork (or neighborhood) of interest.

Type TP53 in the query textbox and click the magnifier (or press Enter) to run the query. The screen will split and display the original network and the retrieved subnetwork.

Click the X in the Query Feature to close the result and restore the original network page

You can choose among 7 different types of query by using the dropdown selector. The default query type is "1-Step Neighborhood"; click the info button next to the query type selector to reveal embedded documentation explaining the different types of query.

Action buttons: These buttons are located at the bottom right corner of the network view page and let you perform several actions on the displayed network (Fig. 3D), e.g., edit network properties, share the network with others, or request a DOI. However, the most convenient action is the possibility to open your network in the Cytoscape desktop application with just one click.

If the requirements to use this feature are satisfied, the **Open in Cytoscape** button will be enabled (colored orange); otherwise, it will be disabled (colored gray). Mouse over the button to display a tooltip with info.

Minimum requirements: you must have Cytoscape 3.6.0 or higher running on your computer (default port: 1234) and the CyNDEx-2 app installed.

Recommended requirements: always use the latest Cytoscape version available (currently 3.8.2), as it comes with the CyNDEx-2 app pre-installed. If the CyNDEx-2 App needs to be updated, Cytoscape will notify you upon startup.

Menu buttons: These buttons are located at the top left corner of the screen (Fig. 3E) and perform the same functions as the items in the top menu bar of the NDEx landing page: clicking the logo will bring you back to the landing page. The user avatar allows you to login/register an account while the three vertical dots provide access to the top menu items (contact form, FAQ, etc.).

Finally, the largest button, "SWITCH TO CLASSIC MODE" lets you view the network using our legacy network viewer where you can access a few features that haven't been ported over to NNV yet, such as the ability to clone a network and automatically save the copy to your account.

4. Create an account.

Now that you are familiar with the NDEx landing and NNV pages, let's guide you through the process of creating your own NDEx account.

You can do this by clicking the **Login/Register** button (Fig. 1B) in the landing page or by clicking the **User Avatar** button (Fig. 3E) on any NNV page.

In the pop-up window, choose whether you want to **Sign in/Sign Up with Google** (Fig. 4A) or if you prefer to proceed manually (Fig. 4B).

If you have a Google account, we highly recommend that you Sign In/Sign Up with Google, as it makes the process simpler and faster. With this option, you will create your account with two clicks, and don't need to verify your e-mail address to activate the account.

The NDEx server will still send you a confirmation e-mail that contains a system-generated password: you will need this password to access your account programmatically later in Basic Protocol 4, so please make sure you keep it handy. You can also change the system-generated password to your favorite one from your account settings; we'll show you how to do this shortly.

If you don't have a Google account or prefer to create your NDEx account manually, click the link as shown in Figure 4B, fill out the registration form, accept the Terms & Conditions, and click the Sign Up button.

Next, check your e-mail and verify your e-mail address by clicking the activation link you received.

You can now go back to the NDEx landing page or NNV page and sign in to your new NDEx account with the username and password you have chosen.

5.   Manage your account.

Once logged in, your account page will look like Figure 5. On the left-hand side, expand the **Account Settings** button, then choose **Change Password:** in the pop-up window, you can change the password to access your account.

If you have created your account using Google in the previous step, you may want to change the system generated password with something you'll remember more easily.

Now expand the **Account Settings** button again, then choose **Edit Settings**: in the pop-up window, you can adjust several settings including changing the e-mail address associated to your account, add a personal image or opt-out of monthly usage statistics e-mails for your networks (Fig. 6).

To add a personal image, you must provide the URL where the image can be fetched from. You cannot upload an image from file.

6.   Add your first network.

Now that you have an account and 10 gigabytes of free cloud storage for your networks, let's add a network to your account.

From your account's page, click the magnifier in the top right corner (Fig. 5) to open the Search modal window, which has the same features as the Search interface on the landing page.

Type leukemia in the textbox and run the search.

In the results page, click the **Acute Myeloid Leukemia** to display the network.

Now type MDM2 TP53 in the query textbox (Fig. 3C) and press Enter.

When the query result is displayed in split screen, you will notice that a blue floppy disk icon is now available in the query control bar: click it to save the

query result to your account, then navigate back to your account page using the User Avatar in the top left of the page.

Now you should see your account page populated with one network, the query result that you just saved.

Your network's visibility is PRIVATE, which means your network is only visible to you.

Now click the network's name to open its page and display it.

In the bottom right corner where the Action Buttons are located, you can click the "pencil" button and access the network property editor (Fig. 7), where you can modify a variety of network properties, including the network's visibility.

Make the network PUBLIC using the visibility dropdown, then click the green button to save your changes.

> The network property editor screen also shows the NDEx Score for the network: the NDEx Score is calculated based on the amount of annotation a network has. The more information associated to a network, the higher its score. The score is considered by the NDEx server to rank search results; this way, networks that are well annotated will be ranked higher while those poorly annotated will be ranked lower. We strongly recommend that you annotate your networks thoroughly before making them publicly available, so that they will be more easily found in searches and be more informative to your audience.

Now that you are familiar with the NDEx UI, let's move on to Basic Protocol 2 go through a typical workflow to prepare your networks for submission, peer-review and publication in a scientific journal.

BASIC PROTOCOL 2 USING NDEx AND CYTOSCAPE IN A PUBLICATION-ORIENTED WORKFLOW

As seen in the previous protocol, an NDEx account unlocks several features not available to anonymous users such as the ability to save networks, manage their visibility, or open them in Cytoscape for subsequent analysis, visual styling, and layout. In this second protocol, we will describe the NDEx features that support collaboration, peer-reviewed publication, and distribution of network models. You will learn how to connect Cytoscape with NDEx and export (save) a network to your NDEx account, share it with collaborators, and finally request a DOI to make your network accessible as a stable reference resource. Basic Protocol 2 uses one of the sample networks available in Cytoscape; however, we encourage you to follow the protocol using your own research network model if possible. If you are not familiar with the Cytoscape Desktop application, please refer to the manual at https:// manual.cytoscape.org/en/stable/. Here is a breakdown of the topics covered in this protocol:

- Launch Cytoscape.

- Open the sample network

- Use the Cytoscape NDEx interface to sign into your account from Basic Protocol 1.

- Export the network to your NDEx account.

- Go to the NDEx website and select the new network.

- Annotate the network.

- Enable the network's "Share URL"

- Request a DOI.

Necessary Resources

Hardware—A computer with a stable internet connection

Software—Web browser (recommended: Google Chrome or Mozilla Firefox)

While we don't discourage the use of alternative web browsers, we cannot guarantee that all features will be available and functioning as intended. If you run into problems using a browser other than those specified above, please let us know! You can easily report a bug in NDEx using our web form. Please make sure to always update your browser to the latest available version.

Cytoscape desktop application

Please visit https://cytoscape.org to download and install the Cytoscape desktop application compatible with your operating system.

1. To begin, launch the Cytoscape desktop application on your computer and wait for startup.

2. Once Cytoscape has loaded, you will see a **Welcome Screen** (Fig. 8A) as well as a **Control Panel** on the left-hand side (Fig. 8B).

   Did you know that you can search for networks in NDEx directly from the Cytoscape **Control Panel**? Just type your search term(s) or gene names(s) in the NDEx text box (Fig. 8C) and press Enter to display the results, then double-click any results to immediately open the networks in Cytoscape.

3. In the **Welcome Screen**, click the "Affinity Purification" sample session tile (Fig. 8D) to open and display the network.

4. Click the **NDEx Button** in the Cytoscape toolbar and choose **Sign In/Sign Up** (Fig. 9).

5. In the pop-up window, input your username and password (created earlier in Basic Protocol 1) and click the **Sign In** button to connect Cytoscape with your NDEx account.

The pop-up window also offers the option to reset your NDEx password or create an NDEx account directly from Cytoscape, using the same methods described in step 4 in Basic Protocol 1.

6. Once signed in, Cytoscape will display the network browser window displaying all the networks stored in your NDEx account (Fig. 10). The **My Networks** checkbox (Fig. 10A) lets you choose what networks are displayed; removing the check mark will show all public networks available in NDEx. When you do that, the search box above (Fig. 10B) is enabled and allows you to search networks in NDEx by keyword or gene name, as we have already seen in Basic Protocol 1. Finally, the tile in the top right corner (Fig. 10C) shows the NDEx account (profile) you are currently connected to, lets you to set up additional profiles, or sign out of the currently connected profile.

This feature is useful in situations where a computer is shared among multiple users: in fact, they will be able to use Cytoscape on the same computer, each accessing their own network models stored in their personal NDEx accounts.

7. Click the **Close Dialog** button at the bottom right to close the window and go back to Cytoscape.

8. Now that Cytoscape and NDEx are connected, you are ready to save the Cytoscape sample network to your NDEx account: click the **NDEx Button** in the Cytoscape toolbar (Fig. 9) and this time choose **Export Network to NDEx**.

9. A new window will be opened as shown in Figure 11. If desired, you can add information to the network using the available property fields. When done, click the blue button at the bottom right corner to save the network to your NDEx account.

Depending on the size of the network and the speed of your internet connection, it might take some time to complete the process (up to a couple of minutes). When the process is complete, a notification will be displayed.

10. Use the web browser to visit your NDEx account page. Select the network you just saved to display it in the network viewer. Your network is PRIVATE; you are the only one who can view it.

11. To share this network with collaborators or include it in a peer-reviewed article submission, click the **Share** action button (Fig. 3D) in the bottom right corner of the NNV page, and choose **Share**.

12. The NDEx UI will show the permission management screen; here, click the **Enable Share URL** button to activate a sharable link that you can copy and paste in documents, e-mails, slide decks, etc.

This feature is like the sharable links used in Dropbox and Google Docs. It is very convenient to grant access to your networks only to people you select (collaborators, reviewers) while maintaining the

confidentiality of your data prior to its public release. Please remember anyone with the Sharable URL can access your network!

13. When collaboration on the network is finished or the peer-review process has formally accepted your submission and your network model is ready for publication and distribution, you can request the assignment of a Digital Object Identifier (DOI) that will turn your network model into a permanent, stable reference dataset. To request a DOI, click the **Share** action button (Fig. 3D) in the bottom right corner of the NNV page, and this time choose **Request DOI**.

14. The NDEx UI will show the Request DOI page (Fig. 12), where you need to populate all the network property fields. Please double check the "Contact Email" field, as this is the e-mail address we will use to communicate with you. When done, click the green Request DOI button at the bottom right of the screen.

> Some of the required DOI property fields (such as "rights", "reference" and "publication date") have little blue info buttons: mouse over to display details and click to access relevant documentation that will be opened in a new browser tab.

15. A final pop-up window will be displayed: please review all information, then click the blue button to submit your DOI request. After the request is submitted, you'll be sent back to the network's NNV page: at the top of the info panel, below the network's name, you'll see a badge that says **DOI Status: Pending**. If necessary, you can delete the DOI request by clicking the gray trashcan icon next to the badge.

> Once the DOI is minted and assigned, you will be notified by e-mail. At that time, the badge will change and display the actual DOI. After the DOI is assigned, you will not be able to delete the request or operate on the network anymore.

BASIC PROTOCOL 3 WORKING WITH NDEx NETWORKS IN PYTHON

Programmatic access and interactive display via Python, R, and JavaScript enable a broad range of applications in network analysis and visualization. The ndex2 Python client library provides a convenient wrapper around the NDEx server API: NDEx networks are transferred using the CX (Cytoscape Exchange) format and ndex2 includes the NiceCX Python object to simplify the use of CX data. As NiceCX does not provide common network manipulation functionality, for this purpose data is cast into other data models such as NetworkX or iGraph. This protocol consists of a Jupyter Notebook that demonstrates how to use the ndex2 Python client and NiceCX class to perform the following operations:

- Load a network starting from an existing network in NDEx and display it in the notebook

- Copy and apply a style from an existing template in NDEx

- Apply a layout using NetworkX

- Save a network to your account in NDEx.

The Sphinx documentation for the ndex2 client is available at https://ndex2.readthedocs.io/en/latest/.

The CyJupyter documentation is available at https://github.com/cytoscape/cytoscape-jupyter-widget.

Additional Jupyter Notebook examples are available at https://github.com/ndexbio/ndex-jupyter-notebooks.

Examples for JavaScript and R can be found in the tutorial "Automation in the Cytoscape Ecosystem" available at https://github.com/cytoscape/cytoscape-ismb-2020/blob/master/README.md.

Necessary Resources

Hardware—A computer with stable internet connection

Software—Python 3.6 or higher

ndex2 Python Client

The ndex2 Python client module can be installed from the Python Package Index (PyPI) repository using PIP: pip install ndex2

If you already have an older version of the ndex2 client installed, you can use this command instead: pip install --upgrade ndex2

CyJupyter Widget

The CyJupyter module can be installed from the Python Package Index (PyPI) repository using PIP: pip install cyjupyter

Once installed, you must enable it: jupyter nbextension enable --py -- sys-prefix cyjupyter

Jupyter Notebook installed

Web browser (recommended: Google Chrome or Mozilla Firefox)

Files—Jupyter Notebook file "Working with NDEx Networks in Python"

This notebook is provided as a single file in Supplementary File 1. Alternatively, you can obtain it together with several other Python tutorials by cloning this repository: https://github.com/ndexbio/ndex-jupyter-notebooks.

1. Load network from NDEx.

In this first step, you will import a public network from NDEx into the python environment. Every network in NDEx is assigned a Universal Unique ID (UUID) that can be used to reliably reference a specific network. You will load the network called "Sonic hedgehog" available at http://ndexbio.org/viewer/

networks/cfd3528f-a7a4-11eb-9e72-0ac135e8bacf. Please click the link to look at the network before we move forward with the next steps.

The first block of code (Fig. 13) shows how you can make a request to the specified NDEx server using the UUID of the network using the ndex2.create_nice_cx_from_server() call. The server returns the network in CX format which is used to create a NiceCX object.

The second block of code lets you print out a summary of the network.

The third block of code allows you to display the network within the notebook using the CyJupyter widget, while the fourth block generates a clickable link that you can use to view the page of the network you just imported from NDEx (for convenience, this same link is provided earlier in this paragraph).

2. Copy and apply visual style.

One of the easiest ways to apply a visual style to a network is to copy that style from another network. This allows you to work on the style of your network in Cytoscape using the interactive style editor, then save the network to NDEx for future use as a template. The NiceCX class provides a special method for this common operation, both downloading the template and copying the style to the target network. You specify the network to use as template by defining its UUID, and the apply_template() method copies the visual style and applies it to the 'Sonic Hedgehog' network you imported from NDEx in the previous step (Fig. 14).

3. Save (upload) network to NDEx.

NiceCX networks have a convenient one-step upload method. Saving a network to your account requires you to provide your NDEx 'username' and 'password'. You will now save the 'Sonic Hedgehog' network with its colorful visual style to the NDEx account you created earlier on, in Basic Protocol 1.

You use the first three blocks of code (Fig. 15) to set the credentials required to access your NDEx account.

> You will need the credentials (account name and password) of the NDEx account you created during Basic Protocol 1. Please have the credentials handy before moving forward with this protocol. Also, please be beware of typos and make sure you hit the ENTER key in each field to set the input value!

The fourth block of code assigns a new name to your network and saves it to your account using the upload_to() method. The function returns the URL of the network's RAW JSON, which you can use to generate a clickable URL to visualize your new network.

> Your new network is saved to your NDEx account as a 'private' network, so when you click the link to visualize it, you will be asked

to login unless you already have a browser window opened and you are logged in to your NDEx account.

Using the CyJupyter widget, you can also display your new 'Sonic Hedgehog colorful (ndex2)' networks and compare the visual style differences with the original 'Sonic Hedgehog' network imported at the beginning of this notebook.

4. Apply a layout.

The ndex2 client and NiceCX class do not provide network manipulation functionalities; for such operations, the data must first be cast into a different data model, in this case a NetworkX object (Fig. 16).

In the first block of code, you start from our NiceCX network and generate a NetworkX object using the NiceCX to_networkx() method; then, you use the NetworkX spiral_layout() method to assign positions to the nodes. The result of the layout operation is a Python dictionary of positions keyed by node IDs that you assign to the variable 'pos'. You can display the network with the new layout using the NetworkX draw method, passing in the NetworkX object and dictionary of positions.

To apply the new layout to our NiceCX network, you need to transform the NetworkX positions into a CX cartesianLayout aspect. This is achieved in the second block of code by iterating through the dictionary of positions to create a list of Cartesian coordinates that you then apply to the NiceCX network via the set_opaque_aspect() method.

The minus sign in front of the 'y' coordinates in line 7 (Fig. 16) is required to ensure that the layout of your NiceCX network will be identical to what you previewed when drawing the NetworkX network in the previous block of code. The reason for this is that NetworkX uses one convention for the zero position of Cartesian coordinates (zero at bottom left) while Cytoscape/cytoscape.js/CX use another (zero at top right). So, omitting the minus sign in line 7 would result in a NiceCX network with a vertically flipped layout (Fig. 17). You can experiment yourself by removing the minus sign and saving a new copy of the network, then compare it with the previous one.

5. Save (update) network to NDEx.

NiceCX networks also have an update_to() method to update an existing network instead of creating a new one. You will now update the 'Sonic Hedgehog colorful (ndex2)' network you saved in step 3 above with its updated version boasting the new spiral layout (Fig. 18) and display it in the notebook.

The target network to be updated is specified by its UUID, and this MUST be the first argument passed to the update_to() method.

You can now verify that the 'Sonic Hedgehog colorful (ndex2)' network in your account has been replaced (updated) by the latest version that contains the spiral layout we added using NetworkX.

COMMENTARY

Background Information

As seen in the three protocols described above, NDEx provides a convenient way to store network models in the cloud in a safe and easily accessible manner. Users can decide to use NDEx anonymously, as a resource where they can find and query a variety of networks; alternatively, they can create a free account, get 10 gigabytes of cloud storage space, and unlock many additional features only available to registered users. All these features aim to simplify network biology workflows by allowing seamless communication between data resources and other services/applications, by providing interactive access to data, and by promoting its immediate use and re-use in an intuitive, transparent manner. In this respect, NDEx advocates and fully supports FAIR data principles. One of the most important workflows for scientists is that related to publishing their research findings; NDEx can simplify pre-publication collaboration between researchers, provide live data access to reviewers during the peer-review process, and turn network models into permanent, archival resources by minting DOIs. Hence, the NDEx infrastructure is a useful asset not only for the individual researcher, but also for the larger or-ganization that can use it as publishing and distribution channel for its scientific data output.

Critical Parameters

The NDEx UI and ndex2 Python client communicate with the NDEx server via the internet; it is therefore of critical importance that you use a fast, stable broadband connection to the internet when working with networks in NDEx. The NDEx UI and Python client are capable of catching errors and ex-ceptions, and present users with clear, under-standable error messages; however, sometime networking errors happen that neither the user nor the software have control over; if you encounter any problems while executing op-erations that you have already executed suc-cessfully before, please try resetting your internet connection, or try again later. In addition, some convenience features in the NDEx UI require certain conditions to be met. For example, in order to use the "Open in Cytoscape" feature, you must have Cytoscape installed on your machine, running and accessing its default port (1234).

Troubleshooting

For troubleshooting information, please refer to Table 1.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Internet Resources

https://www.ndexbio.org

The NDEx landing page.

https://home.ndexbio.org/faq/

The NDEx FAQ page.

https://home.ndexbio.org/quick-start/

The NDEx user manuals and technical documentation pages.

https://github.com/ndexbio/ndex-jupyter-notebooks

The NDEx Jupiter notebook tutorials repository (in-cludes the notebook described in Basic Protocol 3).

https://ndex2.readthedocs.io/en/latest/

The Sphinx documentation for the ndex2 Python client.

https://github.com/cytoscape/cytoscape-jupyter-widget

The CyJupiter documentation.

https://cytoscape.org

The Cytoscape homepage.

https://manual.cytoscape.org/en/stable/

The Cytoscape user manual.

https://github.com/cytoscape/cytoscape-ismb-2020/blob/master/README.md

The tutorial "Automation in the Cytoscape Ecosys-tem".
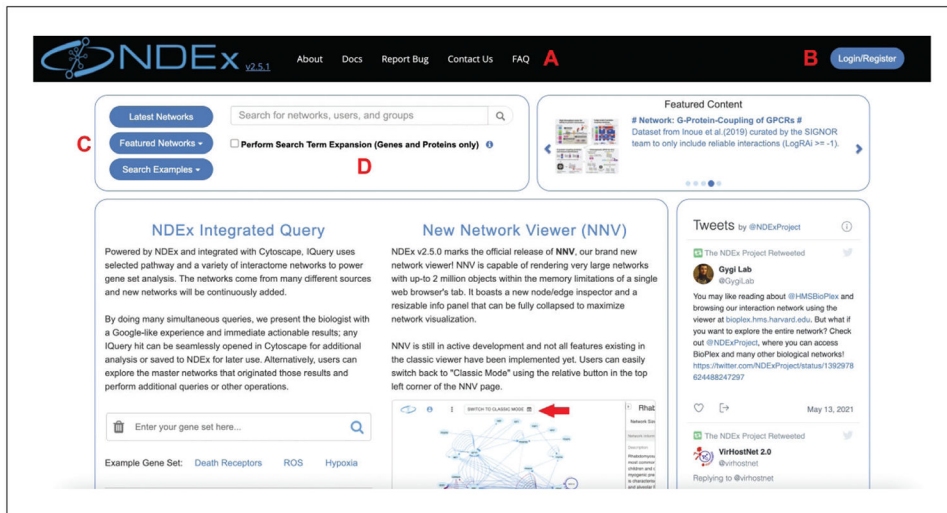
Figure 1.

NDEx landing page. (**A**) Top menu; (**B**) Login/register button; (**C**) Featured networks; (**D**) Network search feature.

Figure 2.
Search results table. The total number of results is displayed in the bottom left corner of the table as indicated by the red oval.
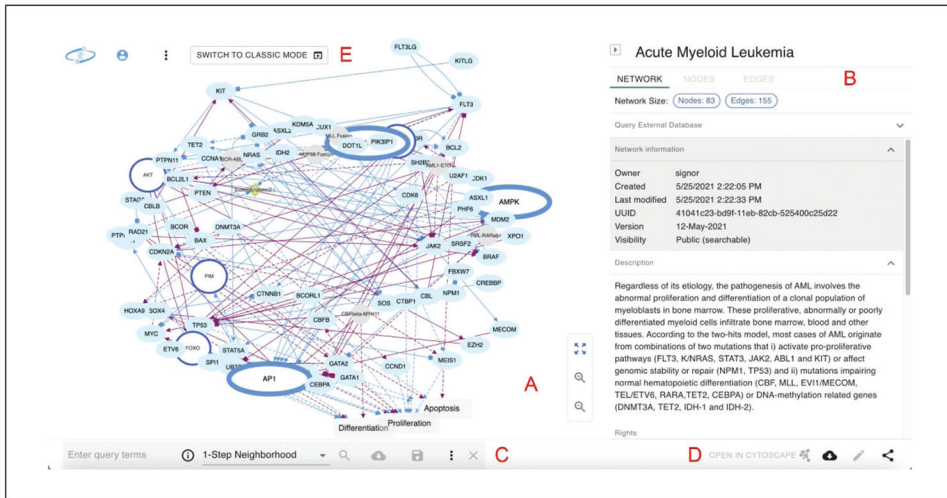
Figure 3.
NDEx Network Viewer (NNV) page. (**A**) Main canvas; (**B**) Info panel; (**C**) Query feature; (**D**) Action buttons; (**E**) Menu buttons.
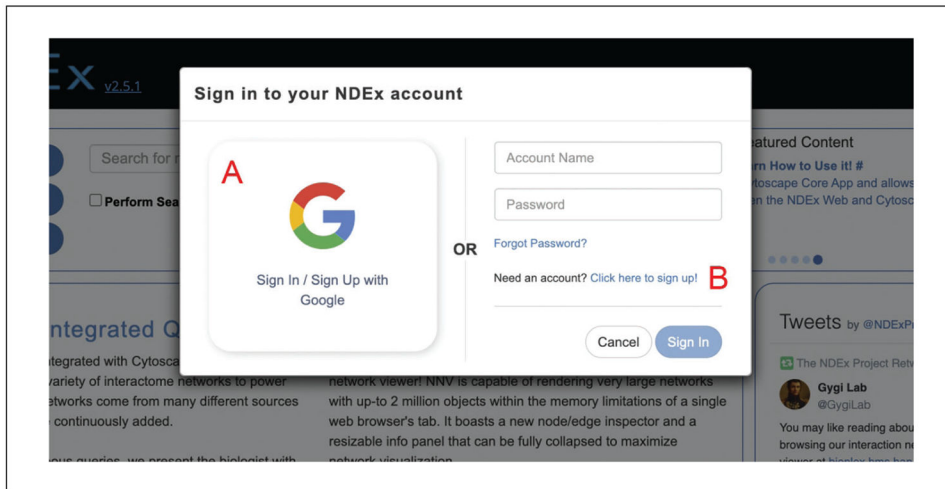
Figure 4.
Login/register window. Users can choose to create an account either using Google as identity provider (**A**), or manually (**B**).
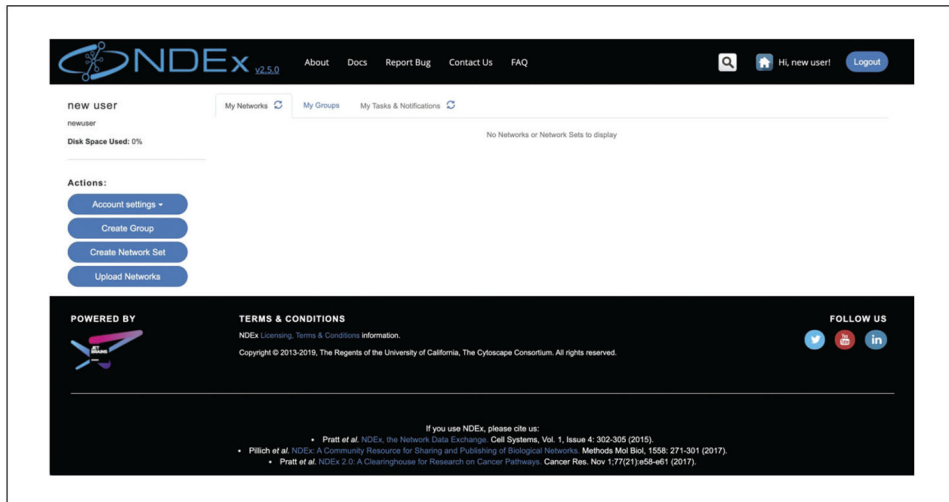
Figure 5.
NDEx account page. A newly created user account page can be managed using the Actions buttons on the left-hand side.
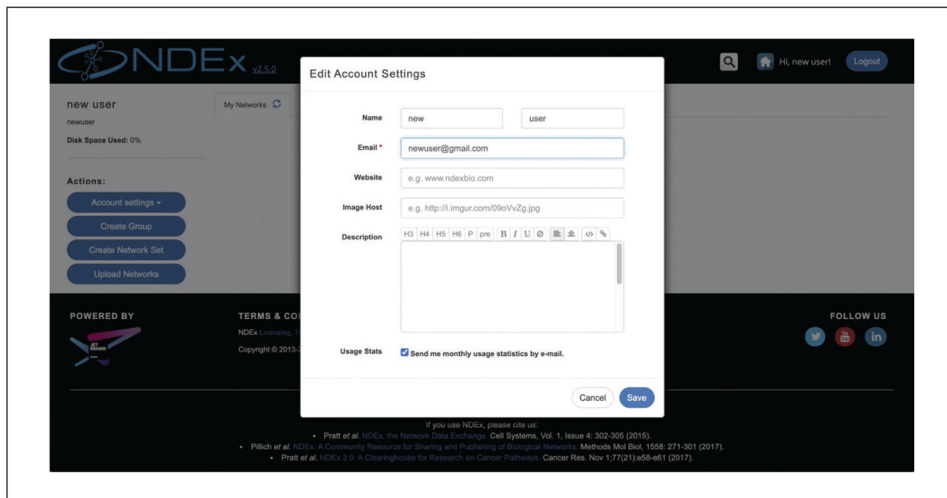
Figure 6.
Edit account settings window. The interface lets users modify and personalize their account page; for example, they can change the e-mail address associated to the account, set a custom image, or opt out of monthly usage statistics e-mails.
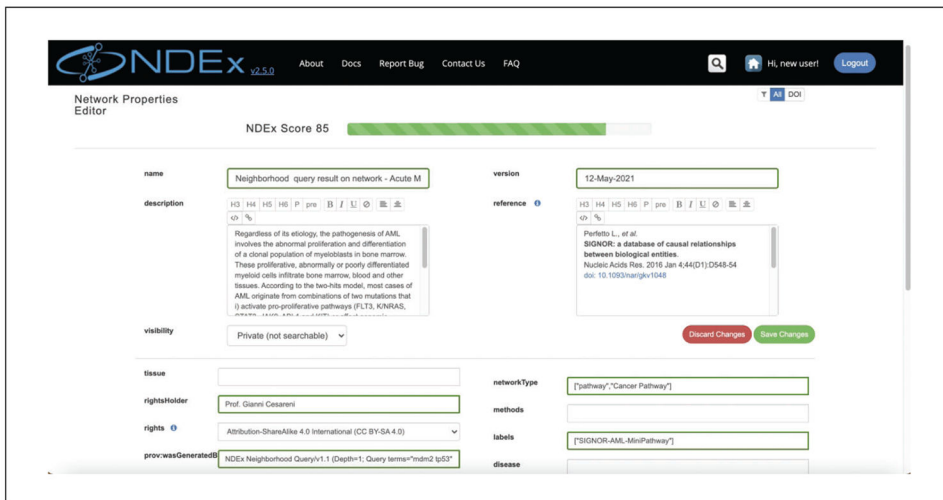
Figure 7.
Network property editor page. The interface lets users add/modify metadata to annotate their networks; for example, users can control a network's visibility or version, specify a published reference, and select a license. The NDEx score at the top of the page is a measure of the degree of annotation of the network and is used to rank the network in search results: the more the properties are annotated, the higher the score, the better the rank in search results.
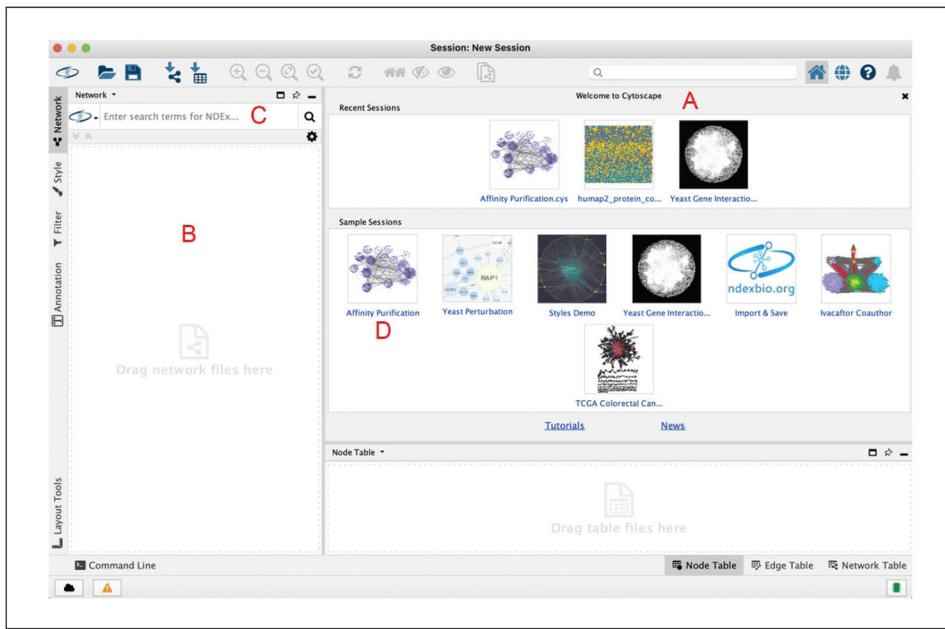
Figure 8.
Cytoscape desktop application interface. (**A**) Welcome screen; (**B**) Control panel; (**C**) NDEx
Search module; (**D**) Sample session tile.
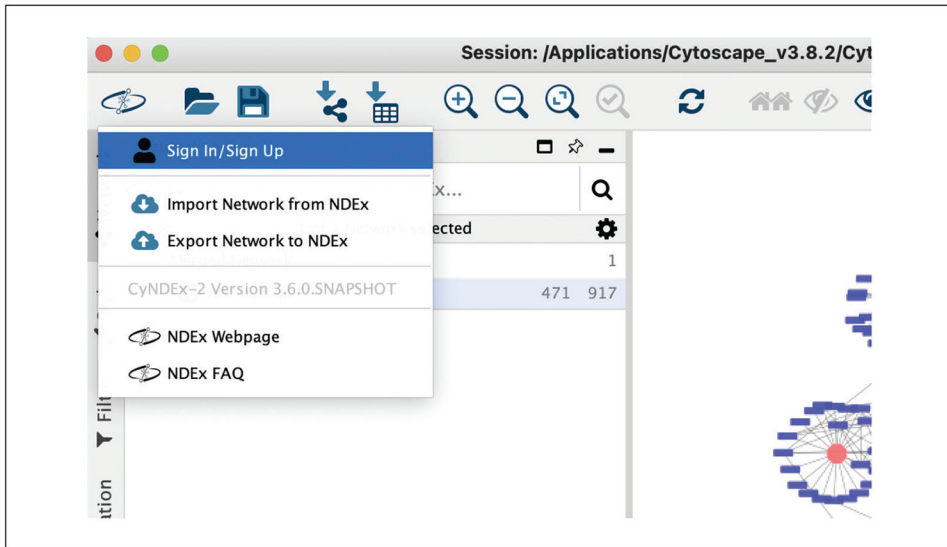
Figure 9.
NDEx button in the Cytoscape toolbar. The NDEx button in the Cytoscape toolbar allows users to connect their NDEx account with Cytoscape, import and export networks, as well as display the NDEx FAQ and Landing pages using your default web browser.
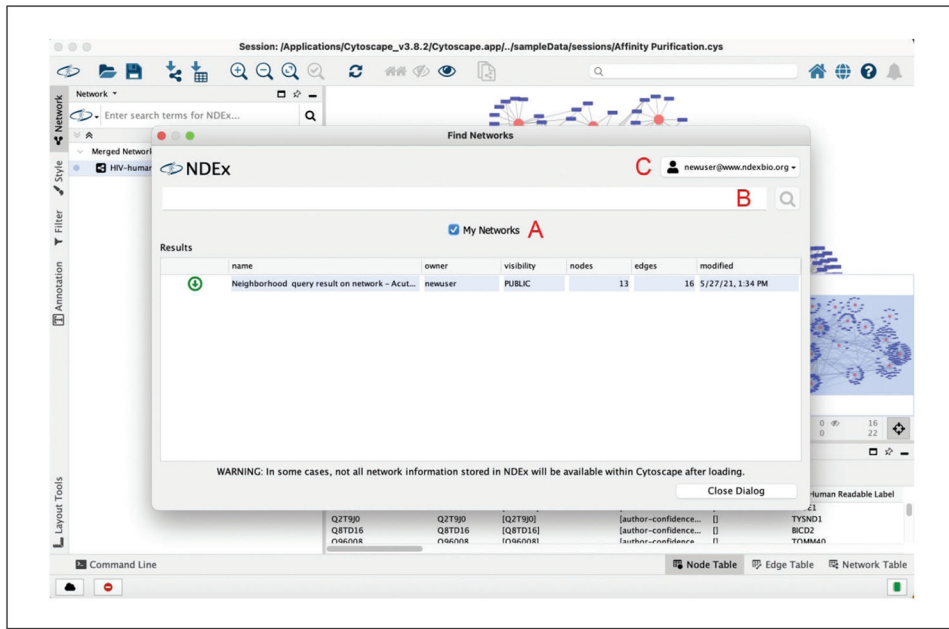
Figure 10.
Network browser window. (**A**) My networks checkbox; (**B**) Network search box; (**C**) NDEx account (profile) tile.
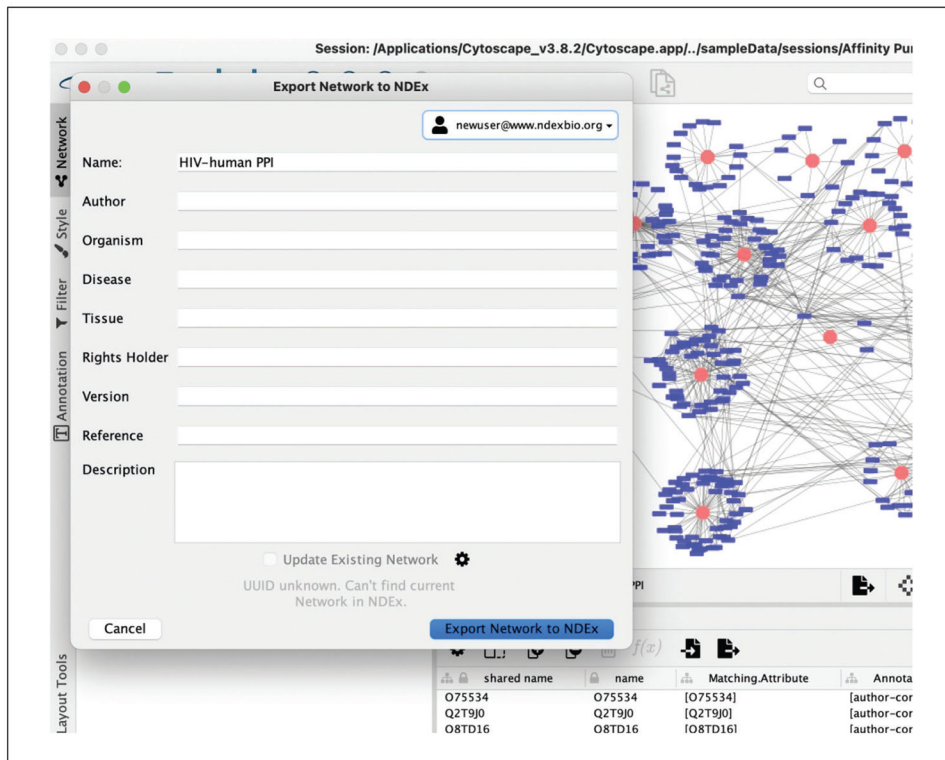
Figure 11.
Export network to NDEx. Users can add properties to their network prior to saving it to NDEx and decide whether they want to save a new copy or update an existing one.

Figure 12.
Request DOI page. All network properties must be populated in order to request a DOI. The small blue info icons provide additional information and access to relevant documentation.

```
 1  import ndex2
 2
 3  SERVER = 'http://ndexbio.org'
 4  NETWORK_UUID = 'cfd3528f-a7a4-11eb-9e72-0ac135e8bacf'
 5
 6  #This is used to create clickable links to view the networks in NDEx
 7  NETWORK_BASE_URL = 'http://ndexbio.org/viewer/networks/'
 8
 9  # Load a public network from NDEx
10  nice_cx_network = ndex2.create_nice_cx_from_server(SERVER, uuid=NETWORK_UUID)
```

```
 1  # Use the "print_summary()" convenience function to get a summary of the imported network
 2  nice_cx_network.print_summary()
```

We can also capitalize on the cyjupyter widget to display our network in the notebook using cytoscape.js

```
 1  from cyjupyter import Cytoscape
 2
 3  # Convert the NiceCX object into a CX JSON object and visualize it with the CyJupyter widge
 4  nice_cx_network_viz = nice_cx_network.to_cx()
 5  Cytoscape(data=nice_cx_network_viz, format='cx')
```

Or simply generate a link to view our network in the browser:

```
 1  # Click this link to view the network you just imported from NDEx in your browser
 2  print("Network's URL (click to view!): " + NETWORK_BASE_URL + NETWORK_UUID)
```

Figure 13.
Load network from NDEx. The code displayed loads a network from NDEx, prints a summary, and lets you display it in the notebook.

```
1    TEMPLATE_UUID = 'b8ff8c89-a7b0-11eb-9e72-0ac135e8bacf'
2
3    # Copy the style from a template network in NDEx and apply it to our NiceCX network
4    nice_cx_network.apply_template(SERVER, TEMPLATE_UUID)
```

Figure 14.

Apply a visual style. This code lets you copy the visual style from an existing template
stored in NDEx and apply it to your network.

```
1  # This is used to prompt users for NDEx credentials in this notebook
2  import getpass
```

```
1  # Watch out for typos and be sure to hit enter in the field to set the value!!!
2  NDEXUSER = getpass.getpass()
```

```
1  # Watch out for typos and be sure to hit enter in the field to set the value!!!
2  NDEXPASSWORD = getpass.getpass()
```

```
1   # Let's first rename our modified network
2   nice_cx_network.set_name('Sonic Hedgehog colorful (ndex2)')
3
4   # Then save it to NDEx and return the URL of the network's page as well as its UUID
5   response = nice_cx_network.upload_to(SERVER, NDEXUSER, NDEXPASSWORD)
6   my_network_uuid = response.split('/')[-1]
7
8   print ('=' *15)
9   print("Network's URL (click to view!): " + NETWORK_BASE_URL + my_network_uuid)
10  print("Network's UUID: " + my_network_uuid)
11
12  # Convert the NiceCX object into a CX JSON object and visualize it with the CyJupyter widge
13  nice_cx_network_viz = nice_cx_network.to_cx()
14  Cytoscape(data=nice_cx_network_viz, format='cx')
```

Figure 15.

Save network to NDEx. This code prompts users for their NDEx account credentials and saves their network. It also returns a clickable link to view the network in a browser page and displays it in the notebook via the cyJupyter widget.

```
1  import networkx as nx
2
3  # Convert the network to a NetworkX object
4  NX_NETWORK = nice_cx_network.to_networkx(mode='default')
5
6  # Create layout and visualize it
7  pos = nx.drawing.layout.spiral_layout(NX_NETWORK, scale=700)
8  nx.draw(NX_NETWORK, pos)
```

```
1  # Transfer new layout back to original network
2  new_cart_layout = []
3  for node_id, coordinates in pos.items():
4      new_cart_layout.append({
5          'node': node_id,
6          'x': coordinates[0],
7          'y': -coordinates[1]
8      })
9  nice_cx_network.set_opaque_aspect(ndex2.constants.CARTESIAN_LAYOUT_ASPECT, new_cart_layout)
```

Figure 16.

Apply a layout. This code casts the network into a networkx object, applies a spiral layout, and then transfers the new node coordinates back to the original network by setting the CX cartesianLayout aspect.
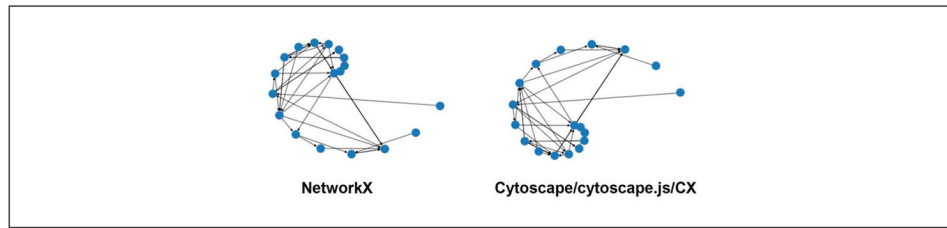
Figure 17.
Cartesian Coordinates. NetworkX and Cytoscape/cytoscape.js use different conven-tions for the zero position of Cartesian coordinates. NetworkX assumes the zero position is at the bottom left while Cytoscape/cytoscape.js set the zero to the top left. As a result, a minus sign is necessary in the code in line 7 in Figure 16 to ensure that the orientation of the CX network is not flipped vertically as compared to the NetworkX network.

```
1  # First, let's rename our modified network
2  nice_cx_network.set_name('Sonic Hedgehog colorful spiral (ndex2)')
3
4  # Update existing network in NDEx and return the URL of the network's page
5  # as well as its UUID
6  nice_cx_network.update_to(my_network_uuid, SERVER, NDEXUSER, NDEXPASSWORD)
7
8  print ('=' *15)
9  print("Network's URL (click to view!): " + NETWORK_BASE_URL + my_network_uuid)
10 print("Network's UUID: " + my_network_uuid)
11
12 # Convert the NiceCX object into a CX JSON object and visualize it with the CyJupyter widge
13 nice_cx_network_viz = nice_cx_network.to_cx()
14 Cytoscape(data=nice_cx_network_viz, format='cx')
```

Figure 18.

Update network in NDEx. This code shows how to update a network in NDEx by overwriting it with a new network. The UUID of the target network to update is the first argument that must be passed to the update method.

Table 1

Troubleshooting Information

Problem	Possible cause	Solution
I didn't receive my account activation e-mail	E-mail blocked by spam filter	Check your spam folder. Add support@ndexbio.org to your contacts
	Error when typing your e-mail address during account creation	Repeat the account creation process and type your e-mail address carefully
'Open in Cytoscape' is grayed-out and unavailable	The Cytoscape desktop application is not running on your computer	Start up the Cytoscape desktop application and wait for it to loads
	The Cytoscape desktop application is not listening on its default port (this is uncommon)	In case you modified this previously, reset Cytoscape to access its default port (1234)
My search in NDEx doesn't return any results	Error when typing your search term(s)	Check the spelling of your search term(s). Review the search documentation at https://home.ndexbio.org/finding-and-querying-networks/#searchexamples.
	There are no results matching your search term(s)	Try searching with a different term(s)
I can't log into my account	Wrong password	Reset your password