

Signaling pathways analysis: HiPathia

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GDA

International Course on
Genomic Data Analysis



PRINCIPE FELIPE
CENTRO DE INVESTIGACION

Outline

1 Signaling pathways

- Methods

2 HiPathia

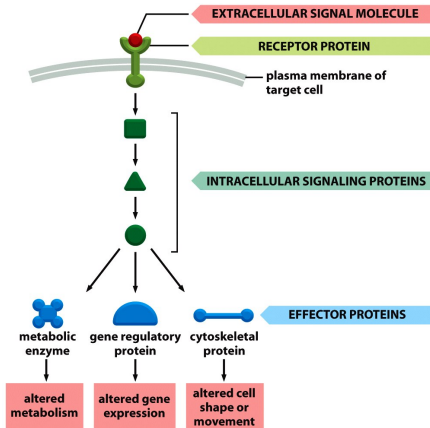
- Preprocess
- Method

3 HiPathia Web Tool

- Usage
- Results



Signaling pathways



Signal transduction

Cellular mechanism which allows the cell to respond to different stimuli by means of biochemical reactions

Signaling pathways

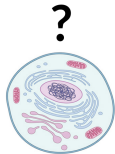
Cascades of protein activations and inhibitions



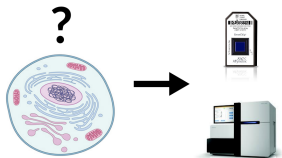
Pathway Methods



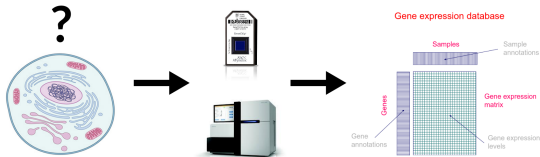
From cell to pathways



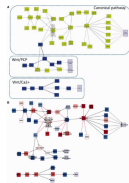
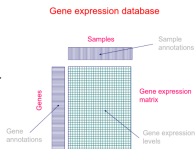
From cell to pathways



From cell to pathways



From cell to pathways



Pathway methods

- **DEGraph**: Based on DE
- **Clipper**: 2 test method
- **SPIA**: Impact factor
- **Sub-SPIA**: Find subnetwork by DE and apply SPIA
- **HiPathia**: Computes signal for each sample



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HiPathia

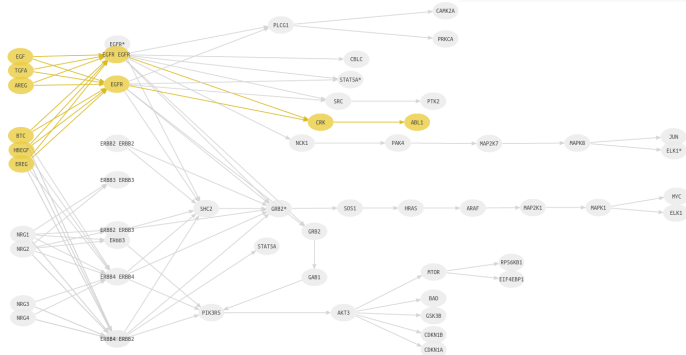
Preprocess



Subpathways

Effector subpathway

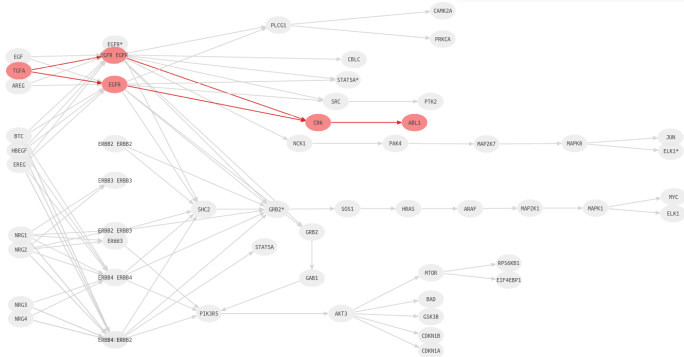
Subgraph of the pathway including any node in a path ending in an effector protein



Subpathways

Decomposed subpathway

Subgraph of the pathway including only one input and one output node



Normalization

Use normalization pipeline depending on technology

Microarray

- Intensities matrix
- RMA
- quantiles

RNA-Seq

- Counts matrix
- TMM
- log transformation

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Expression matrix

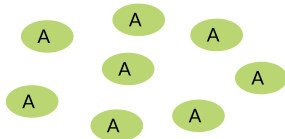
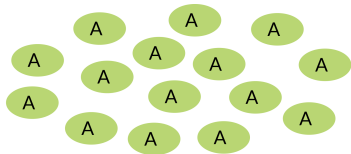


HiPathia

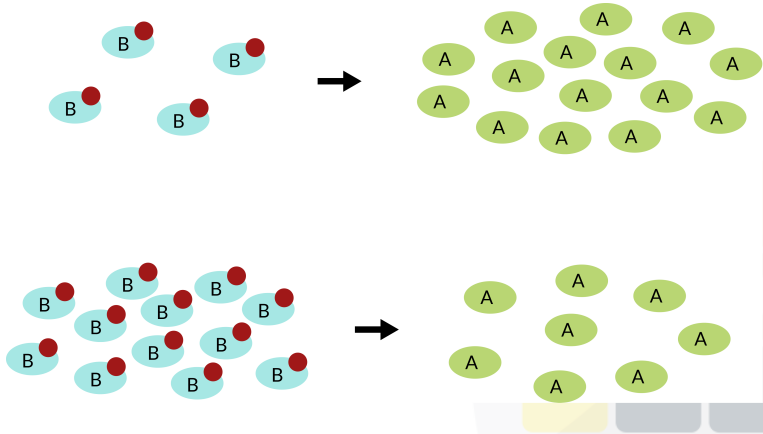
Method



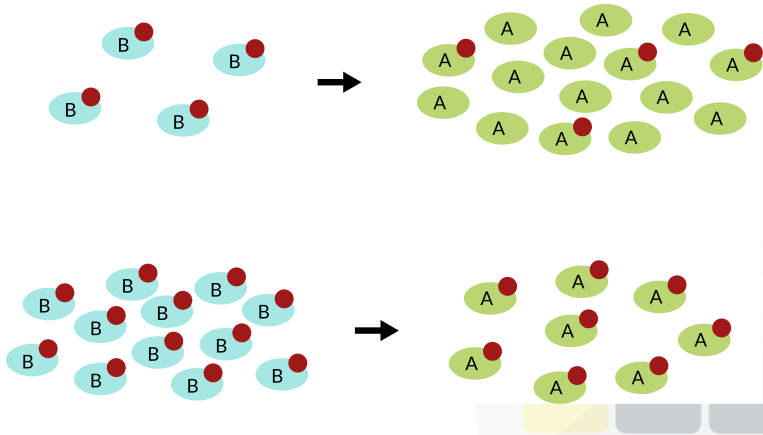
Intuitive idea



Intuitive idea



Intuitive idea



Computing the signal

- 1 Compute a node score based on the expression
- 2 Compute signal passing through each node n

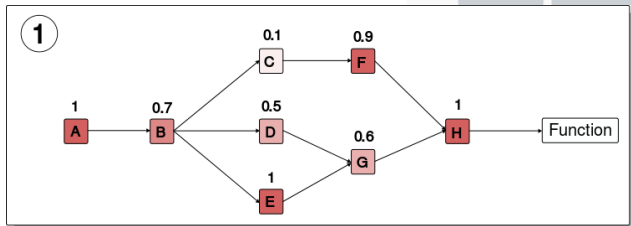
$$S_n = v_n \cdot \left(1 - \prod_{s_i \in A} (1 - s_i)\right) \cdot \prod_{s_j \in I} (1 - s_j)$$

S_n : Signal value through n

v_n : Node value

A : Activation edges

I : Inhibition edges



Computing the signal

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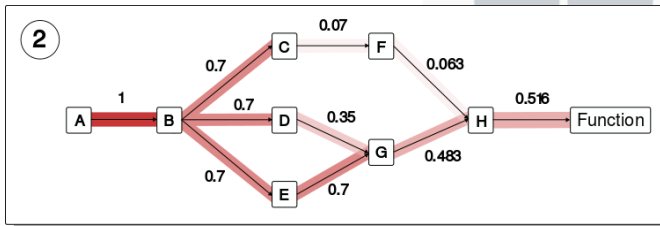
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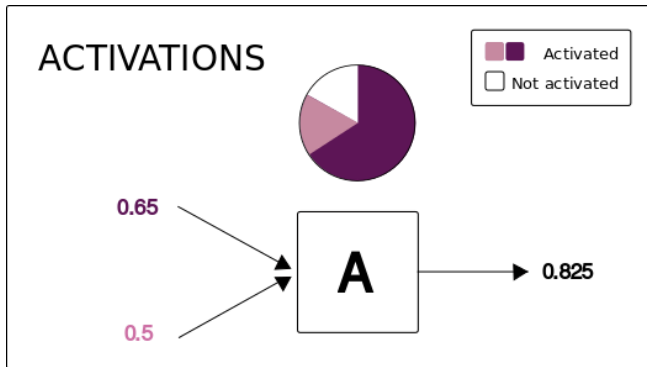
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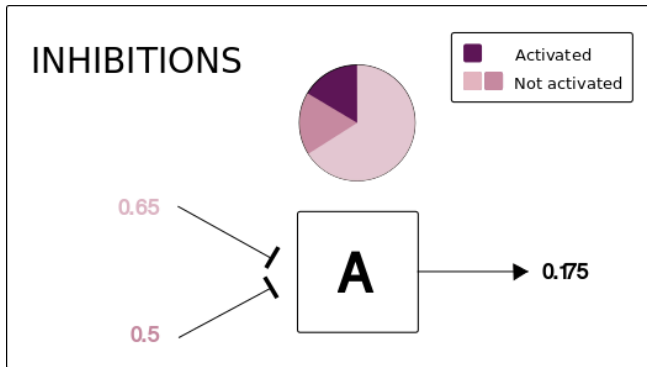
I : Inhibition edges



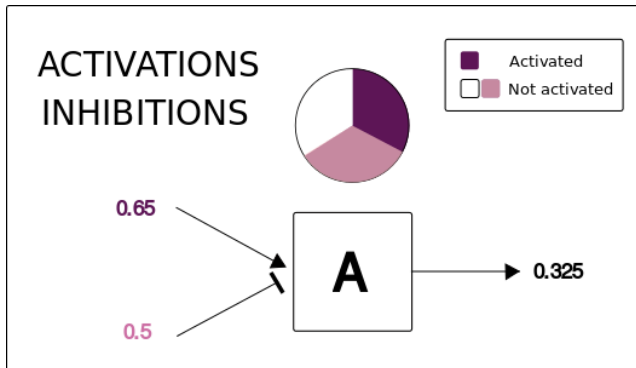
Computing the signal



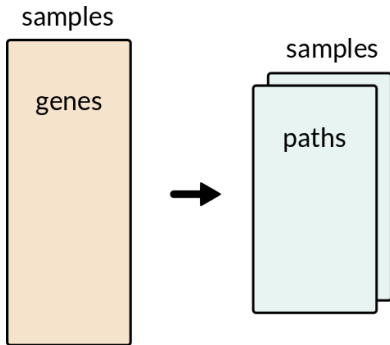
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Computing the signal



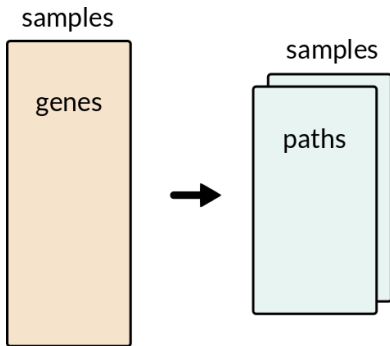
Functional annotation



Functional annotation

We annotate each effector protein to a function

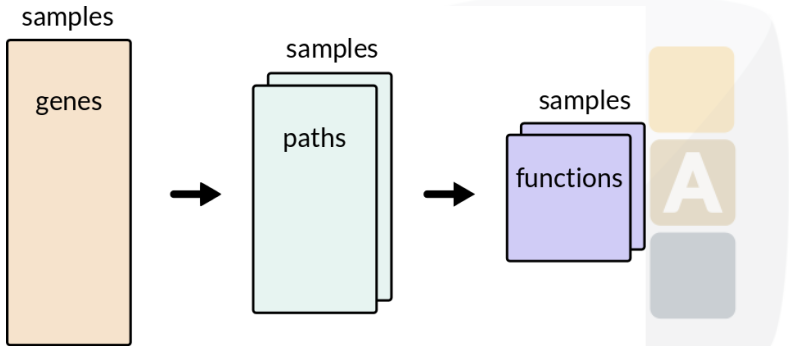
- Uniprot keywords
- GO annotation



Functional annotation

We annotate each effector protein to a function

- Uniprot keywords
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HiPathia

Web tool



Logging in

hipathia.babelomics.org

hiPathia Pathways analysis suite Differential signaling Prediction Login Sign up

hiPathia

HIGH THROUGHPUT PATHWAY
INFERENCE ANALYSIS

1 Start

2 3

hiPathia is a web tool for the interpretation of the consequences of the combined changes of gene expression levels and/or genomic mutations in the context of signalling pathways. hiPathia transforms uninformative gene expression and/or genomic variation data into signalling circuit activities, which carry information on the different cell functionalities triggered by them. Such signalling activities not only account for the underlying molecular mechanisms of diseases or the mode of action of drugs but they can also be used as mechanistic features for the prediction of complex phenotypes.

Note:
hiPathia web application makes an intensive use of the HTML5 standard and other cutting-edge web technologies such as Web Components, so only modern web browsers are fully supported.

hiPathia v1.1.0
Created by Computational Genomics Department
Príncipe Felipe Research Center, Valencia, Spain
2016

Upload data

The screenshot shows the hiPathia web application interface. The top navigation bar includes the hiPathia logo, the text "Pathways analysis suite", and links for "Differential signaling", "Prediction", "My data", "My jobs", "gta2016ciberer", "Profile", and "Logout". The "My data" link is highlighted with an orange box and labeled with a circled "1".

On the left, a "Browse My Data" sidebar is open, showing a file tree with a folder named "gta2016ciberer" containing a file named "Exercise_1". An "Upload" button is highlighted with an orange box and labeled with a circled "3".

The main content area features the hiPathia logo and the text "HIGH THROUGHPUT PATHWAY INFERENCE ANALYSIS". A circled "2" is placed near the top left of the main area. Below the header, there is a paragraph of text describing the application's purpose: "Interpretation of the consequences of the combined changes of gene expression levels and/or genomic mutations in the context of signalling pathways. hiPathia transforms uninformative gene expression and/or genomic variation data into signalling circuit activities, which carry information on the different cell functionalities triggered by them. Such signalling activities not only account for the underlying molecular mechanisms of diseases or the mode of action of drugs but they can also be used as mechanistic features for the prediction of complex phenotypes."

Below the paragraph, a "Note:" section states: "hiPathia web application makes an intensive use of the HTML 5 standard and other cutting-edge web technologies such as Web Components, so only modern web browsers are fully supported."

At the bottom, the footer includes the text "hiPathia v1.1.0", "Created by Computational Genomics Department", "Príncipe Felipe Research Center, Valencia, Spain", and "2016".

Upload data

The screenshot displays the hiPathia web application interface. A 'Browse My Data' panel on the left shows a file named 'Exercise_1'. An 'Upload File' dialog box is open in the center, featuring three numbered steps: 5, 4, and 6. Step 5 highlights the 'File upload:' section with a 'Choose file...' button. Step 4 highlights the 'Bioformat:' section with radio buttons for 'Data matrix expression', 'Variant (VCF)', and 'Experimental design'. Step 6 highlights the 'Upload' button. The dialog also includes a 'Selected file:' field showing 'None', a 'Revalidate' button, a 'File validation log:' table, and a progress bar at 0%. The background shows the main application menu with options like 'Differential signaling' and 'Prediction', and a user profile section.

hiPathia Pathways analysis suite

My data My jobs gda2016ciberer Profile Logout

Browse My Data

gda2016ciberer

Exercise_1

0.0 of 1.0 GB

Upload File

File upload:

Choose file...

Selected file:

None

Revalidate

Bioformat:

☒ Data matrix expression

☐ Variant (VCF)

☐ Experimental design

File validation log:

Line	Type	Message
------	------	---------

Errors: 0 Warning: 0 Info: 0 Lines: 0

0%

Stop

Upload

Notes:

hiPathia web application makes an extensive use of the HTML5 standard and other cutting-edge web technologies such as Web Components, so only modern web browsers are fully supported.

hiPathia v1.0

Created by Computational Genomics Department

Príncipe Felipe Research Center, Valencia, Spain

2016

Workflow

The screenshot shows the hiPathia web application interface. At the top, there is a navigation bar with the text "hiPathia Pathways analysis suite" and two tabs: "Differential signaling" and "Prediction". To the right of the navigation bar are links for "My data", "My jobs", "gda2016ciberer", "Profile", and "Logout".

On the left side, there is a "Browse My Data" panel. It shows a file tree with a folder named "gda2016ciberer" containing a file named "Exercise_1". The file size is 0 B of 1.0 GB. The date is Sep 26, 2016. There are buttons for "Upload" and "Download".

On the right side, the main content area has the title "hiPathia" and the subtitle "HIGH THROUGHPUT PATHWAY INFERENCE ANALYSIS". Below this, there is a paragraph of text: "Interpretation of the consequences of the combined changes of gene expression levels and/or genomic mutations in the context of signalling pathways. hiPathia transforms uninformative gene expression and/or genomic variation data into signalling circuit activities, which carry information on the different cell functionalities triggered by them. Such signalling activities not only account for the underlying molecular mechanisms of diseases or the mode of action of drugs but they can also be used as mechanistic features for the prediction of complex phenotypes."

Below the paragraph, there is a "Note:" section. The note states: "hiPathia web application makes an intensive use of the HTML5 standard and other cutting-edge web technologies such as Web Components, so only modern web browsers are fully supported."

At the bottom of the page, there is a footer that reads: "hiPathia v1.1.0 Created by Computational Genomics Department Principe Felipe Research Center, Valencia, Spain 2016".

Numbered callouts are present: 1 points to the "My data" link, 2 points to the "hiPathia Pathways analysis suite" text, and 3 points to the "Differential signaling" tab.

Workflow

The screenshot displays the hiPathia Pathways analysis suite interface. The top navigation bar includes the hiPathia logo, the text "Pathways analysis suite", and tabs for "Differential signaling" and "Prediction". On the right, there are links for "My data", "My jobs", "Subscribers", "Profile", and "Logout".

Numbered callouts highlight specific features:

- 4**: Points to the "Function level analysis" section, which includes checkboxes for "Gene ontology" and "Uniprot keywords".
- 5**: Points to the "Launch Job" button at the bottom of the "Job information" section.
- 6**: Points to the "My jobs" link in the top navigation bar.
- 7**: Points to the "My data" link in the top navigation bar.
- 8**: Points to the "Differential signaling example" job entry in the "Browse My Jobs" panel.

The "Job information" section includes an "Output folder:" label, a note "You can create folders using the button [icon] inside file browser.", a "File browser" button, a "Job name:" field with the value "Differential signaling job", and a "Description:" field.

The "Browse My Jobs" panel on the right shows a list of jobs:

- ✓ Prediction train example
Prediction Train Done 9/27/2016, 12:03:49 PM
- ✓ Differential signaling example
Differential Signaling Done 9/27/2016, 12:03:46 PM

At the bottom of the panel, it indicates "Total: 2" and has a checkbox for "Enable job notifications".

Tools

① Differential signaling

- Compare signal activity between two conditions
- Correlate path value with a continuous variable

② Prediction

- Construct a predictor from a dataset
- Predict classes from new dataset using the predictor

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HiPathia

Results

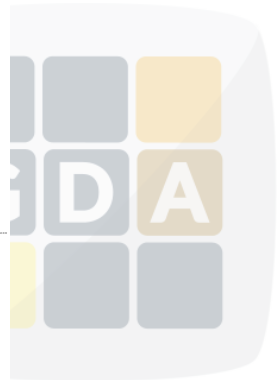
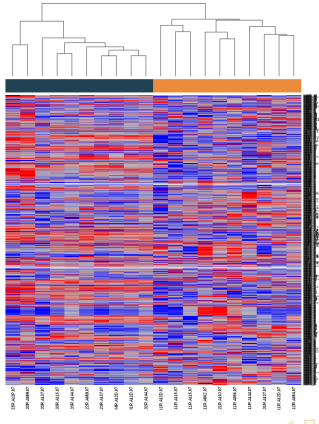


Heatmap

Graphical representation of data where values in a matrix are represented as colors

Path values

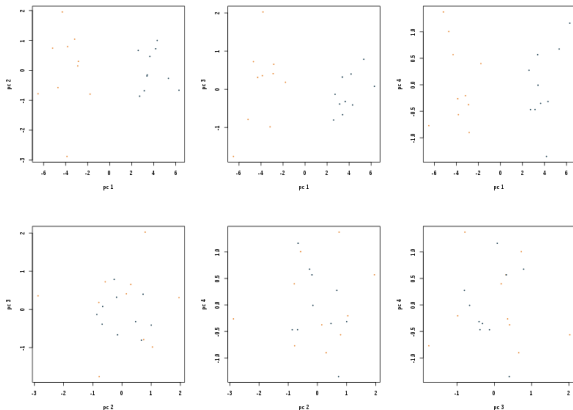
- Path values
- Heatmap



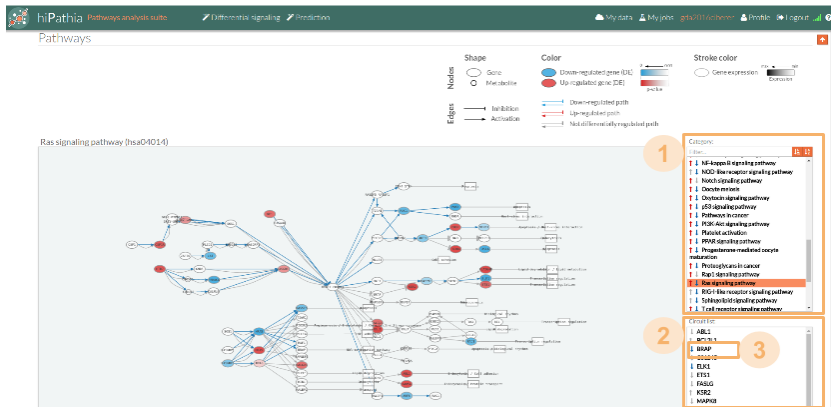
Principal Components Analysis (PCA)

Statistical procedure to convert a set of observations into a set of values of linearly uncorrelated variables

 PCA



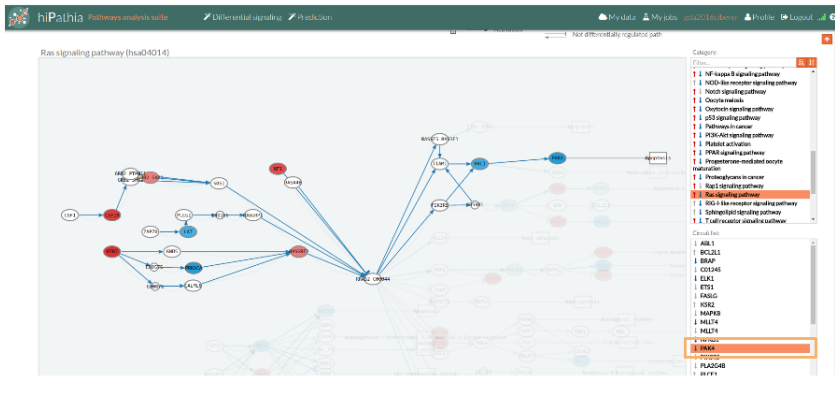
Viewer



Viewer



Viewer





Exercises



HiPathia exercises

Exercise 1

Do the [Differential signaling worked example](#)

Exercise 2

Do the Prediction worked example

- ① Train a predictor following [these steps](#)
- ② Test a new dataset following [these steps](#)

Exercises 3,4,...

Do the [Differential signaling exercises](#)