



Kvik: Interactive exploration of biological pathways

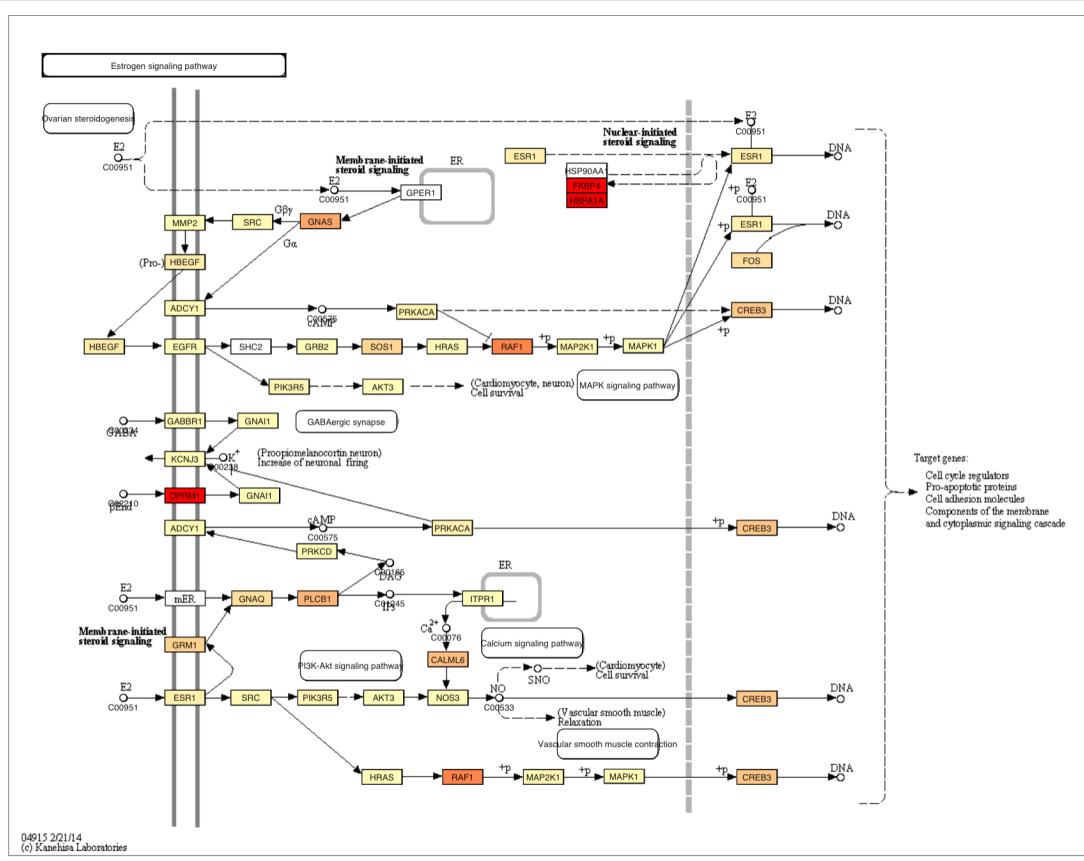
Bjørn Fjukstad

Ph. D. Student / Department of Computer Science

bjorn@cs.uit.no

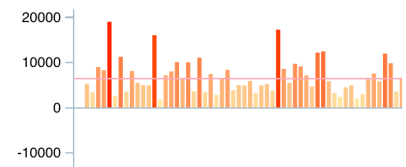
20. October 2014





PLCB1, EIEE12, PI-PLC, PLC-154, PLC-I, PLC154, PLCB1A, PLCB1B

Gene expression values for entire dataset



Mean: 6480.310
 Standard deviation: 3437.448
 Variance: 11816047.351

Similar pathways

- Inositol phosphate metabolism
- Metabolic pathways
- Rap1 signaling pathway
- Calcium signaling pathway
- cGMP-PKG signaling pathway
- Chemokine signaling pathway
- Phosphatidylinositol signaling system
- Adrenergic signaling in cardiomyocytes
- Vascular smooth muscle contraction
- MAPK signaling pathway

me

- Finished my master's in June and became a Ph. D. student in July
- Collaborating with epidemiology researchers at the Dept. of Community Medicine
- I'm not a biologist. Sorry 😊💧



Norwegian Women and Cancer

NOWAC

- Identify relationships between lifestyle and risk of cancer
- Ongoing study since the early nineties
- Lots of data: Over 60 000 blood samples and 800 biopsies

Norwegian Women and Cancer **NOWAC**

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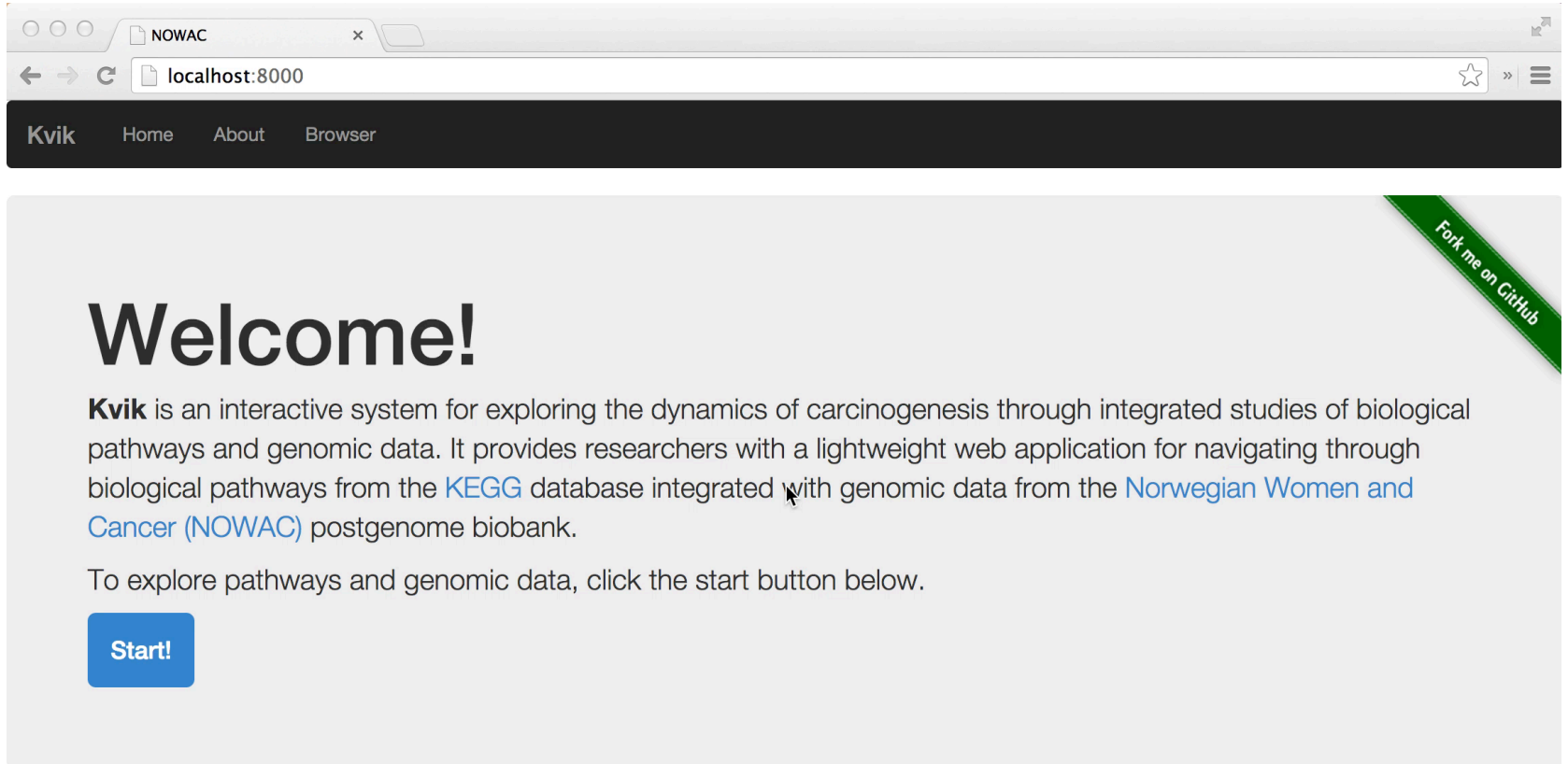
Background and Motivation

- Need a fast and interactive way of looking at many biological processes
- Manually collecting information from different databases is tedious and boring
- Researchers should focus on what they do best

Kvik

- Integrates pathways and other information from KEGG together with data from the NOWAC study
- Makes it accessible through a web application that you can use on any device

Demo



The screenshot shows a web browser window with a single tab titled "NOWAC". The address bar displays "localhost:8000". The browser's navigation bar includes a "Kvik" logo and three menu items: "Home", "About", and "Browser". The main content area features a large "Welcome!" heading. Below the heading, a paragraph describes Kvik as an interactive system for exploring carcinogenesis dynamics, integrating biological pathways from the KEGG database with genomic data from the Norwegian Women and Cancer (NOWAC) postgenome biobank. A blue "Start!" button is positioned below the text. A green diagonal banner in the top right corner of the content area reads "Fork me on GitHub".

localhost:8000

Kvik Home About Browser

Welcome!

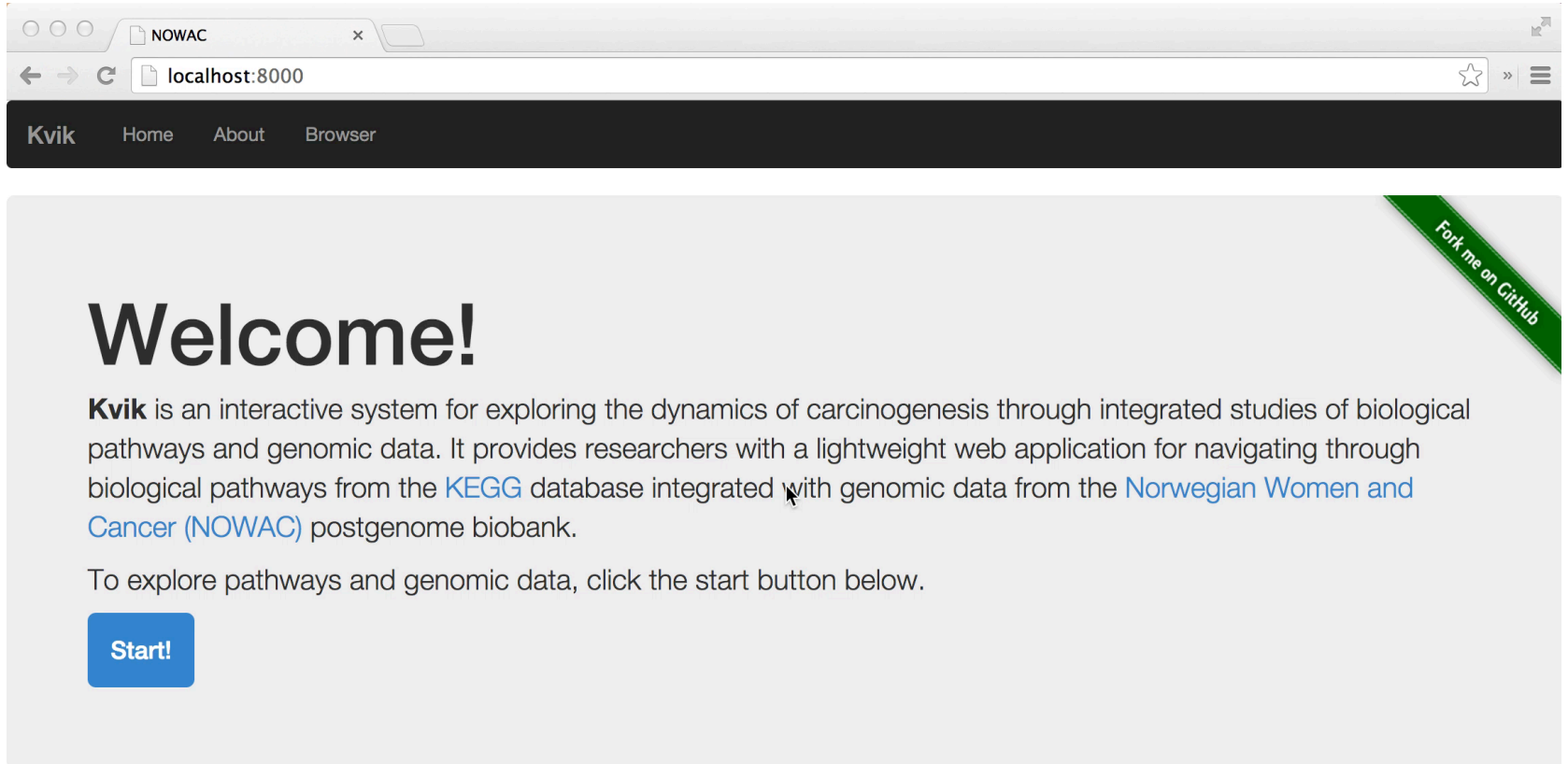
Kvik is an interactive system for exploring the dynamics of carcinogenesis through integrated studies of biological pathways and genomic data. It provides researchers with a lightweight web application for navigating through biological pathways from the [KEGG](#) database integrated with genomic data from the [Norwegian Women and Cancer \(NOWAC\)](#) postgenome biobank.

To explore pathways and genomic data, click the start button below.

[Start!](#)

Fork me on GitHub

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Kvik Home About Browser

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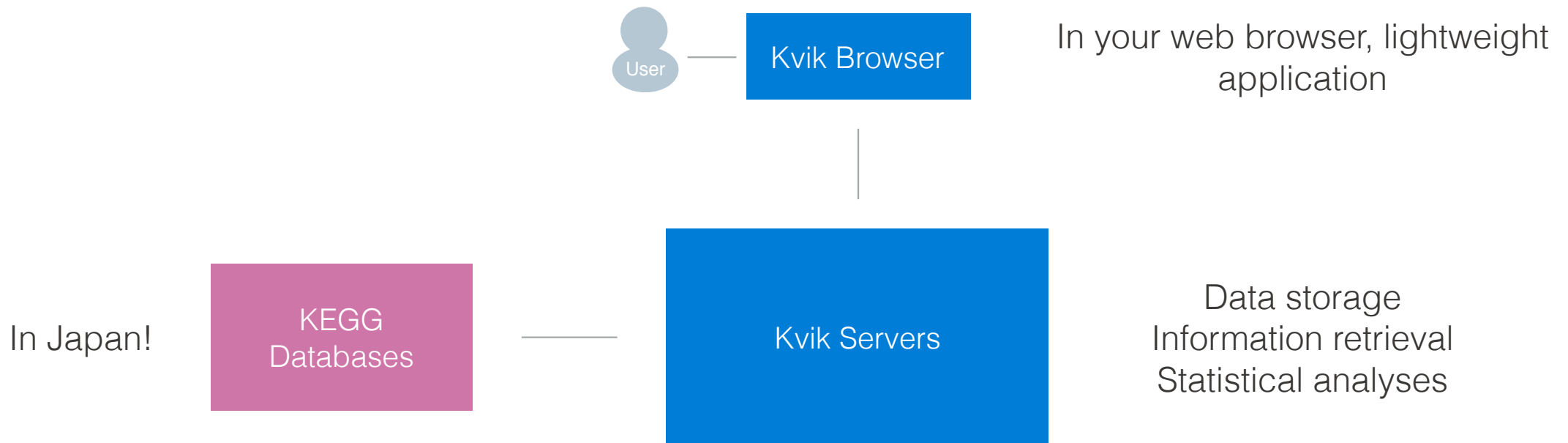
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What's under the hood?



KEGG: Kyoto Encyclopedia of Genes and Genomes

Category	Entry Point	Search & Compute	DBGET Search
Systems information	KEGG PATHWAY KEGG BRITE KEGG MODULE KEGG Mapper KEGG Atlas	Search Pathway Search Brite Reconstruct Module Map Taxonomy	PATHWAY BRITE MODULE
Genomic information	KEGG ORTHOLOGY KEGG Annotation	BlastKOALA <i>New!</i> KO system	ORTHOLOGY
	KEGG GENOME KEGG GENES KEGG Organisms [Species Genus]	SSDB search OC viewer[†] BLAST[†] / FASTA[†] KAAS[†]	GENOME GENES DGENES MGENOME[†] MGENES[†]
Chemical information	KEGG LIGAND KEGG COMPOUND KEGG GLYCAN KEGG REACTION Reaction Modules	SIMCOMP[†] / SUBCOMP[†] KCaM[†] PathSearch[†] PathComp[†] PathPred[†] E-zyme[†]	COMPOUND GLYCAN REACTION RPAIR RCLASS ENZYME
Health information	KEGG DISEASE KEGG DRUG KEGG ENVIRON KEGG MEDICUS	MEDICUS search Drug interaction checker Human diseases Infectious diseases ATC drug classification	DISEASE DRUG DGROUP ENVIRON

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KEGG

- Two options for retrieving data
 - Expensive FTP-licence
 - Free REST API

KEGG REST API

KEGG PATHWAY: hsa05130

www.kegg.jp/dbget-bin/www_bget?pathway+hsa05130

KEGG PATHWAY: hsa05130 [Help](#)

Entry	hsa05130 Pathway
Name	Pathogenic Escherichia coli infection - Homo sapiens (human)
Description	<p>Enteropathogenic E. coli (EPEC) and enterohemorrhagic E. coli (EHEC) are closely related pathogenic strains of Escherichia coli. The hallmark of EPEC/EHEC infections [DS:H00278 H00277] is induction of attaching and effacing (A/E) lesions that damage intestinal epithelial cells. The capacity to form A/E lesions is encoded mainly by the locus of enterocyte effacement (LEE) pathogenicity island. Tir, Map, EspF, EspG are known LEE-encoded effector proteins secreted via the type III secretion system, which is also LEE-encoded, into the host cell. EPEC and EHEC Tir's link the extracellular bacterium to the cell cytoskeleton. Map and EspF are involved in mitochondrion membrane permeabilization. EspG interacts with tubulins and stimulates microtubule destabilization. LEE-encoded adhesin or intimin (Eae) is exported via the general secretory pathway to the periplasm, where it is inserted into the outer membrane. In addition to Tir, two potential host cell-carried intimin receptors, beta1 integrin (ITGB1) and nucleolin (NCL), have so far been identified. The distinguishing feature of EHEC is the elaboration of Shiga-like toxin (Stx). Stx cleaves ribosomal RNA, thereby disrupting protein synthesis and killing the intoxicated epithelial or endothelial cells.</p>
Class	Human Diseases; Infectious diseases BRITE hierarchy
Pathway map	hsa05130 Pathogenic Escherichia coli infection

The diagram illustrates the pathogenic mechanism of EPEC/EHEC. On the left, the bacterium is shown with its flagella and pili. Key components include the Type III Secretion System (T3SS) and the Locus of Enterocyte Effacement (LEE). The T3SS is used to inject effector proteins (Tir, Map, EspF, EspG) into the host cell. Tir binds to the host cell membrane, while Map and EspF interact with the cytoskeleton and mitochondria, respectively. EspG interacts with tubulins. The LEE also encodes the adhesin Intimin (Eae), which is exported to the periplasm and inserted into the outer membrane. On the right, the host cell is shown with the resulting damage, including the formation of attaching and effacing lesions and the production of Shiga-like toxin (Stx), which leads to the inhibition of protein synthesis and ultimately cell death.

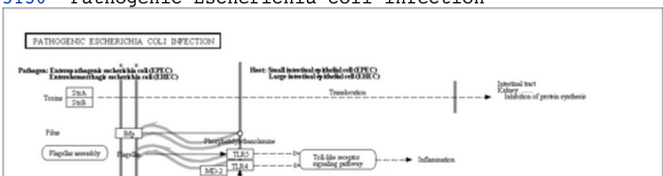
KEGG REST API

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www.kegg.jp/dbget-bin/www_bget?pathway+hsa05130

KEGG PATHWAY: hsa05130 [Help](#)

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rest.kegg.jp/get/hsa05130

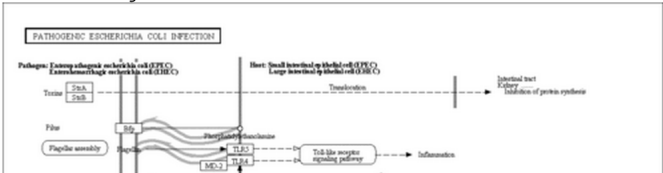
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rest.kegg.jp/get/hsa05130

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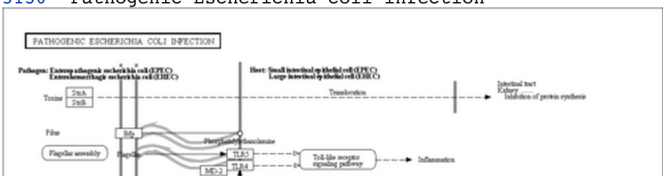
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rest.kegg.jp/get/hsa05130

KEGG REST API

```
rest.kegg.jp/get/hsa05130 x
rest.kegg.jp/get/hsa05130
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CLASS     Human Diseases; Infectious diseases
PATHWAY_MAP hsa05130 Pathogenic Escherichia coli infection
DISEASE   H00277 Enterohemorrhagic Escherichia coli (EHEC) infection
          H00278 Enteropathogenic Escherichia coli (EPEC) infection
ORGANISM  Homo sapiens (human) [GN:hsa]
GENE      7100 TLR5; toll-like receptor 5 [KO:K10168]
          929 CD14; CD14 molecule [KO:K04391]
          7099 TLR4; toll-like receptor 4 [KO:K10160]
          23643 LY96; lymphocyte antigen 96 [KO:K05400]
          10376 TUBA1B; tubulin, alpha 1b [KO:K07374]
          7277 TUBA4A; tubulin, alpha 4a [KO:K07374]
          7278 TUBA3C; tubulin, alpha 3c [KO:K07374]
          7846 TUBA1A; tubulin, alpha 1a [KO:K07374]
          84790 TUBA1C; tubulin, alpha 1c [KO:K07374]
          51807 TUBA8; tubulin, alpha 8 [KO:K07374]
          112714 TUBA3E; tubulin, alpha 3e [KO:K07374]
          113457 TUBA3D; tubulin, alpha 3d [KO:K07374]
          79861 TUBAL3; tubulin, alpha-like 3 [KO:K07374]
          84617 TUBB6; tubulin, beta 6 class V [KO:K07375]
          203068 TUBB; tubulin, beta class I [KO:K07375]
          81027 TUBB1; tubulin, beta 1 class VI [KO:K07375]
          7280 TUBB2A; tubulin, beta 2A class IIa [KO:K07375]
          10381 TUBB3; tubulin, beta 3 class III [KO:K07375]
          10382 TUBB4A; tubulin, beta 4A class IVa [KO:K07375]
          347688 TUBB8; tubulin, beta 8 class VIII [KO:K07375]
```

rest.kegg.jp/get/hsa05130

KEGG REST API

KEGG T01001: 7100

www.kegg.jp/dbget-bin/www_bget?pathway+hsa:7100

KEGG Homo sapiens (human): 7100 [Help](#)

Entry	7100 CDS T01001
Gene name	TLR5, MELIOS, SLEB1, TIL3
Definition	toll-like receptor 5
Orthology	K10168 toll-like receptor 5
Organism	hsa Homo sapiens (human)
Pathway	hsa04620 Toll-like receptor signaling pathway hsa05130 Pathogenic Escherichia coli infection hsa05132 Salmonella infection hsa05134 Legionellosis hsa05321 Inflammatory bowel disease (IBD)
Disease	H00080 Systemic lupus erythematosus
Drug target	Other: D10368
Brite	KEGG Orthology (KO) [BR: hsa00001] Organismal Systems Immune system 04620 Toll-like receptor signaling pathway 7100 (TLR5) Human Diseases Immune diseases 05321 Inflammatory bowel disease (IBD) 7100 (TLR5) Infectious diseases 05130 Pathogenic Escherichia coli infection 7100 (TLR5) 05132 Salmonella infection 7100 (TLR5) 05134 Legionellosis 7100 (TLR5) BRITE hierarchy
SSDB	Ortholog Paralog GFIT
Motif	Pfam: LRR_8 TIR LRR_4 LRR_1 LRR_5 TIR_2 LRR_7 LRRCT Motif

KEGG REST API

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`rest.kegg.jp/get/hsa:7100`

KEGG REST API

```
rest.kegg.jp/get/hsa:7100 x
rest.kegg.jp/get/hsa:7100
ENTRY      7100          CDS      T01001
NAME       TLR5, MELIOS, SLEB1, TIL3
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DRUG_TARGET Other: D10368
BRITE      KEGG Orthology (KO) [BR:hsa00001]
           Organismal Systems
             Immune system
               04620 Toll-like receptor signaling pathway
                 7100 (TLR5)
             Human Diseases
               Immune diseases
                 05321 Inflammatory bowel disease (IBD)
                   7100 (TLR5)
               Infectious diseases
                 05130 Pathogenic Escherichia coli infection
                   7100 (TLR5)
                 05132 Salmonella infection
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                 05134 Legionellosis
                   7100 (TLR5)
POSITION   1q41-q42
MOTIF      Pfam: LRR_8 TIR LRR_4 LRR_1 LRR_5 TIR_2 LRR_7 LRRCT
DBLINKS    NCBI-GI: 16751843
           NCBI-GeneID: 7100
           OMIM: 603031
           HGNC: 11851
           HPRD: 04326
           Ensembl: ENSG00000187554
           UniProt: O60602
STRUCTURE  PDB: 3J0A
AASEQ      858
           MGDHLDLQLLVLMAGPVFVFGIPSCSFDGRIAFYRFCNLTQVPQVLNTERLLLSFNRYRT
           VTASSFPFLEQLQLLELGSQYTPLTIDKEAFRNLPNLRILDGSSKIYFLHPDAFQGLFH
           LFELRLYFCGLSDAVLKDGYFRNLKALTRLDLSKNQIRSLYLHPSFGKLSLKSIDFSSN
           CTM...
```

rest.kegg.jp/get/hsa:7100

KEGG REST API

- There is a lot you can do with it!
- See rest.kegg.jp for more information

KEGG usage in Kvik

Pathway Visualizer
localhost:8000/browser/pathwaySelect=hsa04915

Kvik Home About Browser

Estrogen signaling pathway

Target genes:
 Cell cycle regulators
 Pro-apoptotic proteins
 Cell adhesion molecules
 Components of the membrane and cytoplasmic signaling cascade

PLCB1, EIEE12, PI-PLC, PLC-154, PLC-I, PLC154, PLCB1A, PLCB1B

Gene expression values for entire dataset

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- Rap1 signaling pathway
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- cGMP-PKG signaling pathway
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- Phosphatidylinositol signaling system
- Adrenergic signaling in cardiomyocytes
- Vascular smooth muscle contraction

Logarithmic Absolute Filtering disabled Smoker Hormone Therapy

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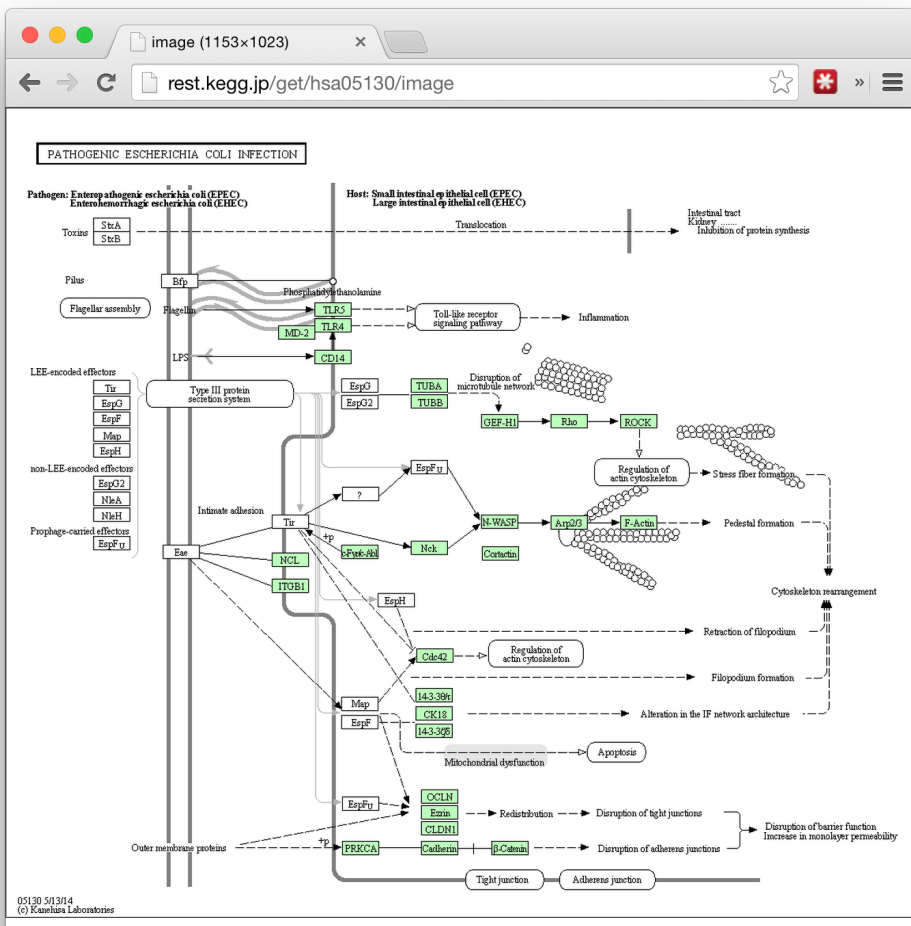
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- Wnt signaling pathway

Logarithmic Absolute Filtering disabled Smoker Hormone Therapy

KEGG Pathways



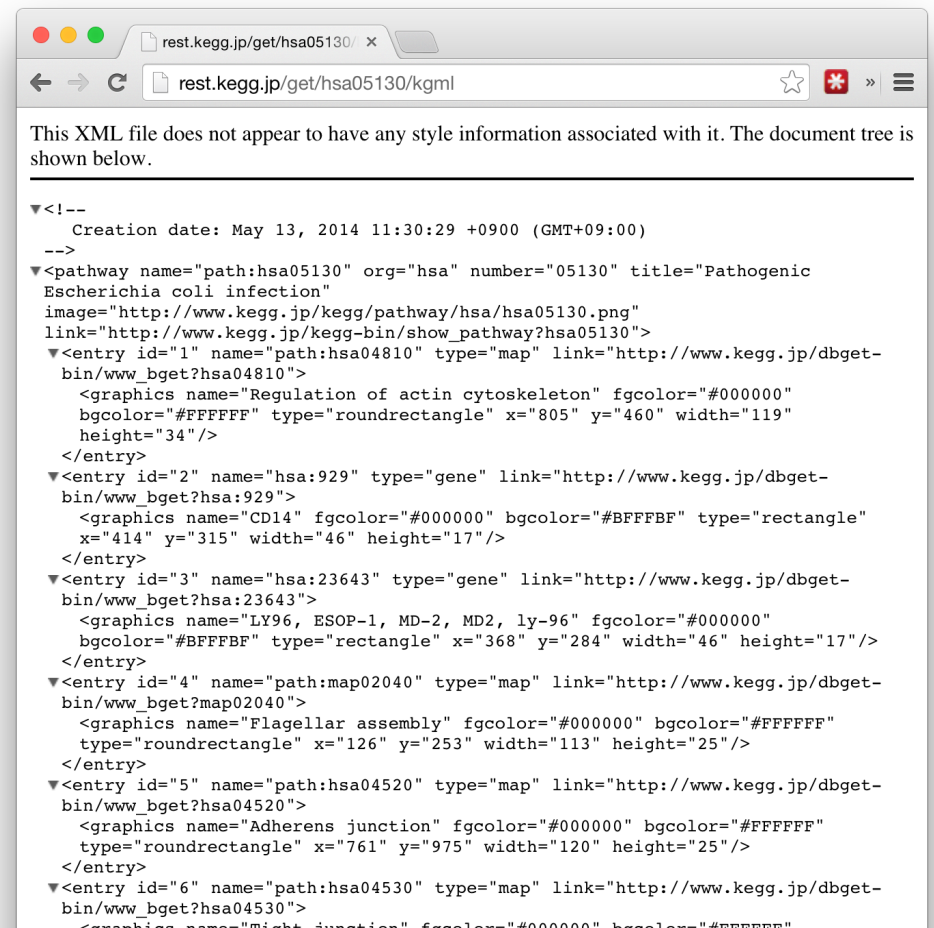
```
rest.kegg.jp/get/hsa05130/
rest.kegg.jp/get/hsa05130/kgml

This XML file does not appear to have any style information associated with it. The document tree is shown below.

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Creation date: May 13, 2014 11:30:29 +0900 (GMT+09:00)
-->
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link="http://www.kegg.jp/kegg-bin/show_pathway?hsa05130">
  <entry id="1" name="path:hsa04810" type="map" link="http://www.kegg.jp/dbget-bin/www_bget?hsa04810">
    <graphics name="Regulation of actin cytoskeleton" fgcolor="#000000" bgcolor="#FFFFFF" type="roundrectangle" x="805" y="460" width="119" height="34"/>
  </entry>
  <entry id="2" name="hsa:929" type="gene" link="http://www.kegg.jp/dbget-bin/www_bget?hsa:929">
    <graphics name="CD14" fgcolor="#000000" bgcolor="#BFFFBF" type="rectangle" x="414" y="315" width="46" height="17"/>
  </entry>
  <entry id="3" name="hsa:23643" type="gene" link="http://www.kegg.jp/dbget-bin/www_bget?hsa:23643">
    <graphics name="LY96, ESOP-1, MD-2, MD2, ly-96" fgcolor="#000000" bgcolor="#BFFFBF" type="rectangle" x="368" y="284" width="46" height="17"/>
  </entry>
  <entry id="4" name="path:map02040" type="map" link="http://www.kegg.jp/dbget-bin/www_bget?map02040">
    <graphics name="Flagellar assembly" fgcolor="#000000" bgcolor="#FFFFFF" type="roundrectangle" x="126" y="253" width="113" height="25"/>
  </entry>
  <entry id="5" name="path:hsa04520" type="map" link="http://www.kegg.jp/dbget-bin/www_bget?hsa04520">
    <graphics name="Adherens junction" fgcolor="#000000" bgcolor="#FFFFFF" type="roundrectangle" x="761" y="975" width="120" height="25"/>
  </entry>
  <entry id="6" name="path:hsa04530" type="map" link="http://www.kegg.jp/dbget-bin/www_bget?hsa04530">
    <graphics name="Tight junction" fgcolor="#000000" bgcolor="#FFFFFF" type="roundrectangle" x="761" y="975" width="120" height="25"/>
  </entry>
</pathway>
```

KEGG Pathways

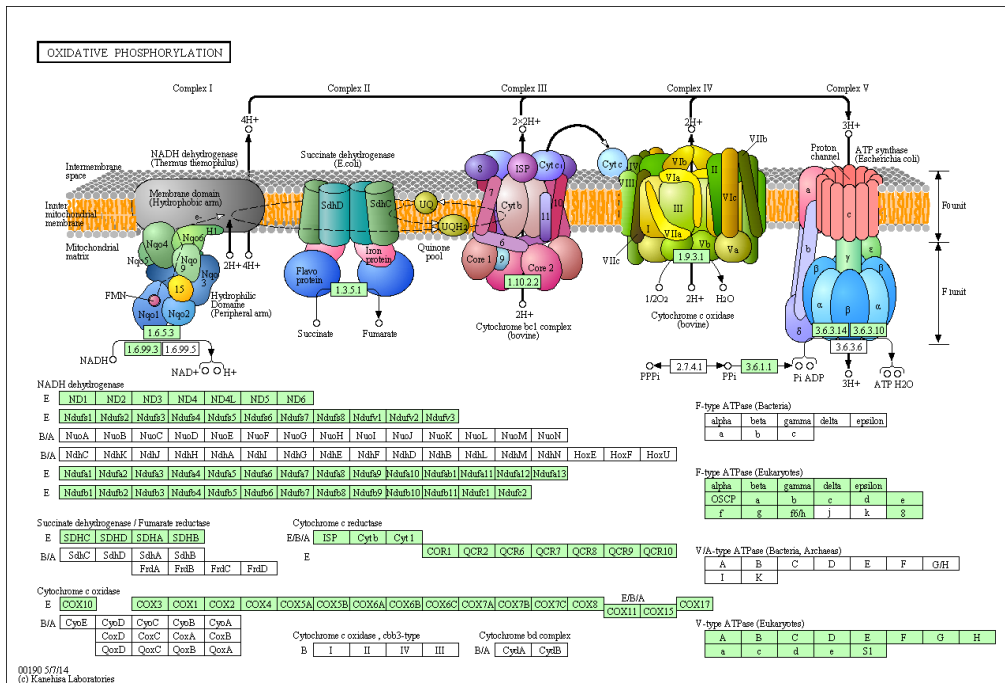
```
<pathway name="path:hsa05130" ... >
  <entry id=1 name="path:hsa048140" ... >
    .
    .
    .
  <relation entryid1=1 entryid2=3 ... >
    .
    .
    .
</pathway>
```



The screenshot shows a web browser window with the address bar containing the URL `rest.kegg.jp/get/hsa05130/kgml`. The page content displays the XML structure of the pathway file, including the following elements:

```
<!--
Creation date: May 13, 2014 11:30:29 +0900 (GMT+09:00)
-->
<pathway name="path:hsa05130" org="hsa" number="05130" title="Pathogenic
Escherichia coli infection"
image="http://www.kegg.jp/kegg/pathway/hsa/hsa05130.png"
link="http://www.kegg.jp/kegg-bin/show_pathway?hsa05130">
  <entry id="1" name="path:hsa04810" type="map" link="http://www.kegg.jp/dbget-
bin/www_bget?hsa04810">
    <graphics name="Regulation of actin cytoskeleton" fgcolor="#000000"
bgcolor="#FFFFFF" type="roundrectangle" x="805" y="460" width="119"
height="34"/>
  </entry>
  <entry id="2" name="hsa:929" type="gene" link="http://www.kegg.jp/dbget-
bin/www_bget?hsa:929">
    <graphics name="CD14" fgcolor="#000000" bgcolor="#BFFFBF" type="rectangle"
x="414" y="315" width="46" height="17"/>
  </entry>
  <entry id="3" name="hsa:23643" type="gene" link="http://www.kegg.jp/dbget-
bin/www_bget?hsa:23643">
    <graphics name="LY96, ESOP-1, MD-2, MD2, ly-96" fgcolor="#000000"
bgcolor="#BFFFBF" type="rectangle" x="368" y="284" width="46" height="17"/>
  </entry>
  <entry id="4" name="path:map02040" type="map" link="http://www.kegg.jp/dbget-
bin/www_bget?map02040">
    <graphics name="Flagellar assembly" fgcolor="#000000" bgcolor="#FFFFFF"
type="roundrectangle" x="126" y="253" width="113" height="25"/>
  </entry>
  <entry id="5" name="path:hsa04520" type="map" link="http://www.kegg.jp/dbget-
bin/www_bget?hsa04520">
    <graphics name="Adherens junction" fgcolor="#000000" bgcolor="#FFFFFF"
type="roundrectangle" x="761" y="975" width="120" height="25"/>
  </entry>
  <entry id="6" name="path:hsa04530" type="map" link="http://www.kegg.jp/dbget-
bin/www_bget?hsa04530">
    <graphics name="Tight junction" fgcolor="#000000" bgcolor="#FFFFFF"
```

Combining image and KGML



(0,0)

x \longrightarrow

y

\downarrow

(180,100)

(180,150)

(180,200)

\longrightarrow

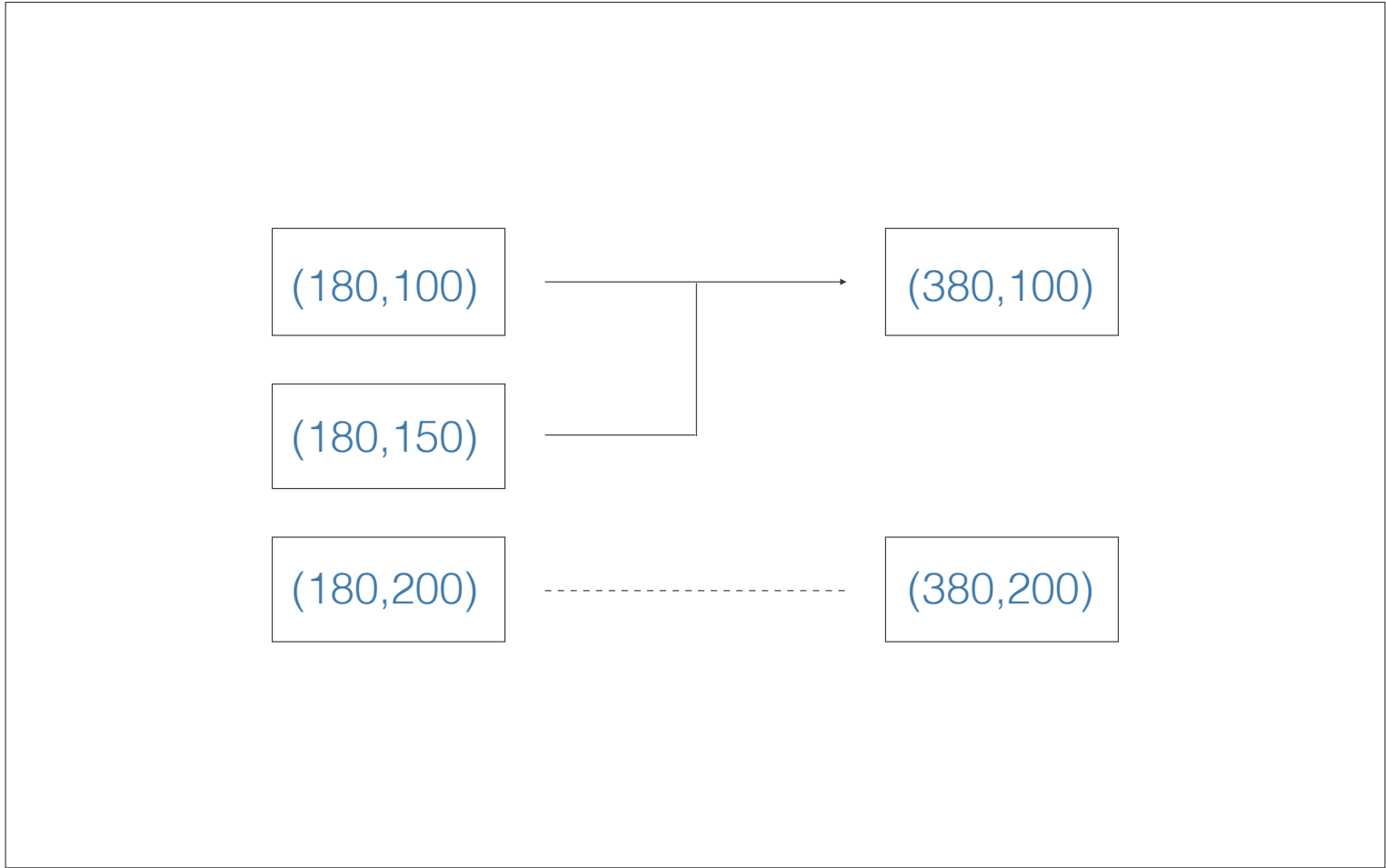
\downarrow

$\cdots\cdots\cdots$

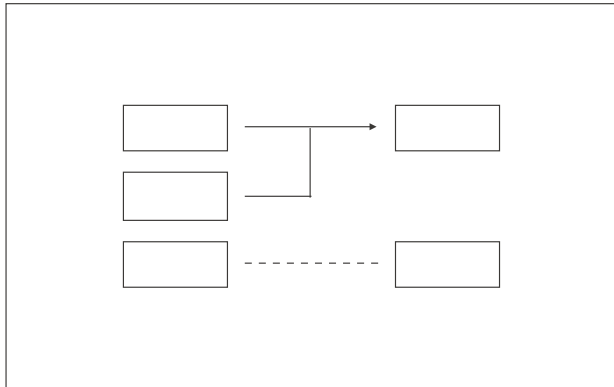
(380,100)

(380,200)

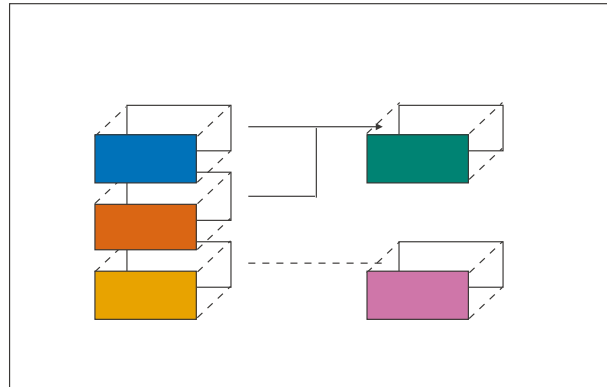
(500,300)



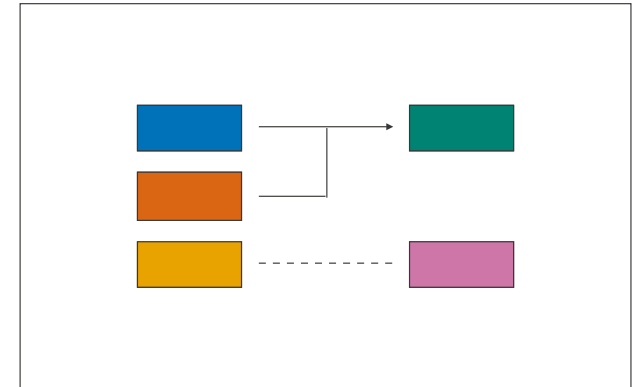
Pathways in Kvik



Static image from
KEGG



Get location from
KGML file, and color
the gene according to
data from NOWAC



Final visualiation

Pathway *similarity*

```
rest.kegg.jp/get/hsa:7100
rest.kegg.jp/get/hsa:7100
ENTRY 7100 CDS T01001
NAME TLR5, MELI05, SLEB1, TIL3
DEFINITION toll-like receptor 5
ORTHOLOGY K10168 toll-like receptor 5
ORGANISM hsa Homo sapiens (human)
PATHWAY hsa04620 Toll-like receptor signaling pathway
hsa05130 Pathogenic Escherichia coli infection
hsa05132 Salmonella infection
hsa05134 Legionellosis
hsa05321 Inflammatory bowel disease (IBD)
DISEASE H00980 Systemic lupus erythematosus
DRUG_TARGET Other: D19368
BRITE KEGG Orthology (KO) [BR:hsa00001]
Organismal Systems
Immune system
04620 Toll-like receptor signaling pathway
7100 (TLR5)
Human Diseases
Immune diseases
05321 Inflammatory bowel disease (IBD)
7100 (TLR5)
Infectious diseases
05130 Pathogenic Escherichia coli infection
7100 (TLR5)
05132 Salmonella infection
7100 (TLR5)
05134 Legionellosis
7100 (TLR5)
POSITION 1q41-q42
MOTIF Pfam: LRR_8 TIR_LRR_4 LRR_1_LRR_5 TIR_2_LRR_7_LRRCT
DBLINKS NCBI-GI: 16751843
NCBI-GeneID: 7100
OMIM: 603031
HGNC: 11851
HFBID: 04326
Ensembl: ENSG00000187554
UniProt: Q60602
STRUCTURE
AASEQ 858
MGDHELDLLGVVLMAGPVFGIPSCSDFGRIFAFYRFCNLTQVPOVLNFTERRALLSPYVIRT
VTASSPFFLEQLQLLELGSQVTPITDKAEAFNLPNLRILDLGSSKIYFLHPDAPQGLFH
LFELRLYFCGLSDAVLKDGYFRNLKALTRLDLSKNQIRSLYHPSFGKLNLSKSIDFSSN
QIFLVCEHELEPLQGKTLSPFLAANSLYSRVSDVWGKCMFPRNMVLEILDVSGNGTVV
DITGNSNAISKQAFSLI LAHHINGAGFGFHNKDPDQNTFAGLAPSSVRHLLDSHGTV
FSLNSRVFTEKQAVLNLAYNKIADAFYGLDNLQVLMLSWELGELSSNFGLP
KVAYIDLQNHAIITDQOTFKLEKIQDLDLSDNALTHIFIPSPIDPFLSGNKLVTLPK
INLTANLHISENRLNLDLFLVFLRVPHLQLLILNQRFSSCSGQDTPSENPSLEQLFL
GENMLQLAWETELEDWDVFEGLSHLQVLYLNHNYLNSLPPGVFSLTALRGLSLSNRLTV
LSHNDLPANLEILDLSRNLAPNDFVLSVLDITHNKFCCECLSTFINWLNHTNVT
IACPDADYQVYVPSFQVLSLESTECQDEEVKSLKLSLFTVCTVLTLELWTLTV
QVSPDQDQVWALQSLMHPNPSGSDRDRWVWVWMLQSSQAFDQVWNLMLWLDQVQ
```


Performance

- Long latency (time to retrieve something) when using the REST API
- Kvik uses *caching* to reduce this latency

Future work

- Visualize more than one pathway at a time
- Make the web-application capable of handling more than one user
- Making it publicly available at kvik.cs.uit.no

Concluding Remarks

- Kvik provides interactive exploration of biological pathways from KEGG and gene expression data from the NOWAC study
- Without any installation or plug-ins, researchers can start exploring the data instantly
- Kvik uses KEGG to provide pathway maps and other information
- Open-sourced at github.com/fjukstad/kvik

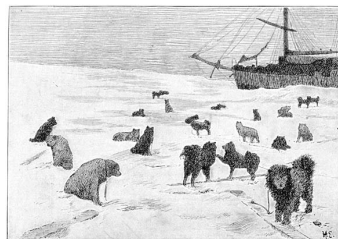
Pathways on the Display Wall

- At the dept. of Comp. Sci. we got a wall-sized display with a 7168x3072 resolution!
- Visualize all the pathways!



Thank you!

Bjørn Fjukstad
bjorn@cs.uit.no



Kvik — Lead sled dog on Fridtjof Nansen's expedition to the North Pole