Interaction sources comparison: NicheNet VS Omnipath

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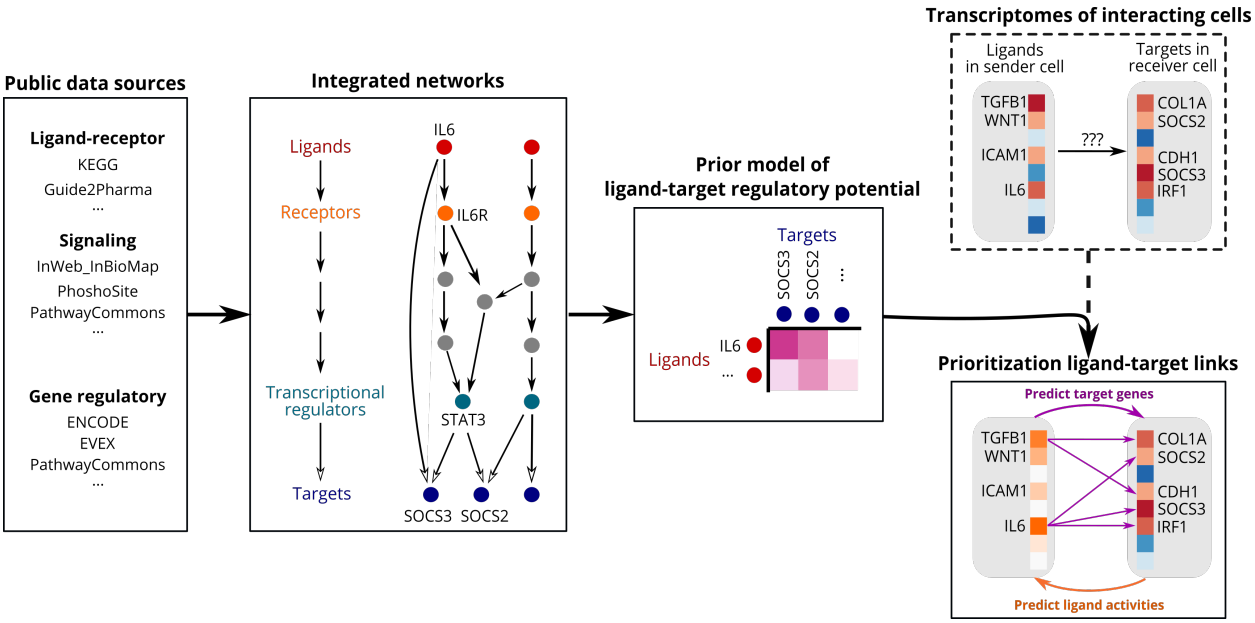
Abstract

This vignette shows a comparison between the protein interaction sources used in the NicheNet method and the ones available on Omnipath.

The NicheNet Method

NicheNet (https://github.com/saeyslab/nichenetr) is a method to predict ligand-target links between interacting cells by combining their data with prior knowledge on signaling and gene regulatory networks (Browaeys et al 2019). **NicheNet** has already been applied to predict upstream niche signals driving Kupffer cell differentiation (Bonnardel et al. 2019).

The figure below shows a graphical representation of the NicheNet workflow. Interactions inferred from several complementary ligand-receptor, signaling and gene regulatory data sources were aggregated in respective integrated networks from which ligand-target regulatory potential scores were calculated. This model of prior information on potential ligand-target links can then be used to infer active ligand-target links between interacting cells. NicheNet prioritizes ligands according to their activity (i.e., how well they predict observed changes in gene expression in the receiver cell) and looks for affected targets with high potential to be regulated by these prioritized ligands(Browaeys et al 2019).



You can find below the list of public resources used to generate the prior model of ligand-target regulatory potential.

Database	Source	Reference
cpdb	cpdb_interaction	Kamburov et al. (2013)
cpdb	cpdb_complex	Kamburov et al. (2013)
evex_expression	lr_evex_regulation_expression	Van Landeghem et al. (2012)
evex_expression	evex_regulation_expression	Van Landeghem et al. (2012)

Database	Source	Reference
evex_signaling	evex_catalysis	Van Landeghem et al. (2012)
evex_signaling	evex_regulation_other	Van Landeghem et al. (2012)
evex_signaling	evex_phosphorylation	Van Landeghem et al. (2012)
evex_signaling	evex_regulation_binding	Van Landeghem et al. (2012)
evex_signaling	evex_binding	Van Landeghem et al. (2012)
guide2pharmacology	pharmacology	Pawson et al. (2014)
harmonizome	harmonizome_KEA	Lachmann and Ma'ayan (2009)
harmonizome	harmonizome_PhosphoSite	Hornbeck et al. (2015)
harmonizome	harmonizome_kinase_substrate_predictions	Rouillard et al. (2016)
harmonizome	harmonizome_DEPOD	Duan et al. (2015)
harmonizome_gr	harmonizome_CHEA	Lachmann et al. (2010)
harmonizome_gr	harmonizome_ENCODE	Consortium (2004)
harmonizome_gr	harmonizome_JASPAR	Mathelier et al. (2014)
harmonizome_gr	harmonizome_TRANSFAC_CUR	Matys et al. (2006)
harmonizome_gr	harmonizome_TRANSFAC	Matys et al. (2006)
harmonizome_gr	harmonizome_MOTIFMAP	Xie et al. (2009)
harmonizome_gr	harmonizome_GEO_TF	Edgar et al. (2002)
harmonizome_gr	harmonizome_GEO_KINASE	Edgar et al. (2002)
harmonizome_gr	harmonizome_GEO_GENE	Edgar et al. (2002)
harmonizome_gr	harmonizome_MSIGDB_GENE	Subramanian et al. (2005)
HTRIDB	HTRIDB	Bovolenta et al. (2012)
inweb_inbiomap	inweb_inbio_interaction	Li et al. (2017)
inweb_inbiomap	inweb_inbio_interaction_pathway	Li et al. (2017)
inweb_inbiomap	inweb_inbio_pathway	Li et al. (2017)
kegg	kegg_cytokines	Kanehisa et al. (2016)
kegg	kegg_cams	Kanehisa et al. (2016)
kegg	kegg_neuroactive	Kanehisa et al. (2016)
kegg	kegg_ecm	Kanehisa et al. (2016)
omnipath	omnipath_directional	Türei et al. (2016)
omnipath	omnipath_undirectional	Türei et al. (2016)
ontogenet	ontogenet_coarse	Jojic et al. (2013)
pathwaycommons_expression	lr_pathwaycommons_controls_expression_of	Cerami et al. (2011)
pathwaycommons_expression	pathwaycommons_controls_expression_of	Cerami et al. (2011)
pathwaycommons_signaling	pathwaycommons_controls_phosphorylation_of	Cerami et al. (2011)
pathwaycommons_signaling	pathwaycommons_controls_state_change_of	Cerami et al. (2011)
pathwaycommons_signaling	pathwaycommons_catalysis_precedes	Cerami et al. (2011)
pathwaycommons_signaling	pathwaycommons_controls_transport_of	Cerami et al. (2011)
pathwaycommons_signaling	pathwaycommons_interacts_with	Cerami et al. (2011)
pathwaycommons_signaling	pathwaycommons_in_complex_with	Cerami et al. (2011)
ppi_prediction	ppi_lr	
ppi_prediction	ppi_l_bidir	
ppi_prediction	ppi_bidir_r	
ppi_prediction	ppi_bidir_bidir	
ppi_prediction_go	ppi_lr_go	
ppi_prediction_go	ppi_l_bidir_go	
ppi_prediction_go	ppi_bidir_r_go	

Database	Source	Reference
ppi_prediction_go	ppi_bidir_bidir_go	
ramilowski	ramilowski_known	Ramilowski et al. (2015)
regnetwork	regnetwork_source	Liu et al. (2015)
regnetwork	regnetwork_encode	Liu et al. (2015)
Remap	Remap_5	Griffon et al. (2015)
trrust	trrust	Han et al. (2015)
vinayagam	vinayagam_ppi	Vinayagam et al. (2011)

Omnipath Resources

As we can see in the previous figure, **NicheNet** used many different publically available resources to build a prior knowledge network. Their final integrated network is composed of three individual networks:

- A network of ligand-receptor interactions (Inter-cellular)
- A network of signaling interactions (Intra-cellular)
- A network of gene regulation (Intra-cellular)

The new versin of the **Omnipath** (http://omnipathdb.org/) database contains curated interactions belonging to these three categories. One can therefore build an integrated network equivalent to the one used in **NicheNet** by only fetching the **Omnipath** webserver. This can significantly ease the integration of different databases, each one of them storing data in distint formats and whose interaction show different levels of reliability.

We therefore here compare the interactions used in the **NicheNet** method with those freely available in the **Omnipath** database. You can find below three sections comparing each one of three different interaction categories.

Ligand-Receptor Interaction Network

We first load the ligand-receptor interactions used to build the **NicheNet** model.

```
## We first load the required libraries to run this script
library(OmnipathR)
library(dplyr)
library(VennDiagram)
library(readr)
```

```
## We read the data which are freely available via Zenodo and we display
## how they look like.
lr_Network_Nichenet <-
    readRDS(url("https://zenodo.org/record/3260758/files/lr_network.rds"))
lr_Network_Nichenet
## # A tibble: 12,651 x 4
##    from  to    source         database
##    <chr> <chr> <chr>          <chr>
##  1 CXCL1 CXCR2 kegg_cytokines kegg
##  2 CXCL2 CXCR2 kegg_cytokines kegg
##  3 CXCL3 CXCR2 kegg_cytokines kegg
##  4 CXCL5 CXCR2 kegg_cytokines kegg
##  5 PPBP  CXCR2 kegg_cytokines kegg
##  6 CXCL6 CXCR2 kegg_cytokines kegg
##  7 CXCL8 CXCR2 kegg_cytokines kegg
##  8 CXCL6 CXCR1 kegg_cytokines kegg
##  9 CXCL8 CXCR1 kegg_cytokines kegg
```

```
## 10 CXCL9 CXCR3 kegg_cytokines kegg
## # ... with 12,641 more rows
```

We show the total number of ligand-receptor interactions after removing duplicates:

```
lr_Network_Nichenet_Unique <- lr_Network_Nichenet %>%
    dplyr::distinct(from, to)
nrow(lr_Network_Nichenet_Unique)
## [1] 12019
```

Omnipath possess a dedicated dataset storing these type of interactions (*LigrecExtra*). We now fetch the **Omnipath** web service to get these interactions.

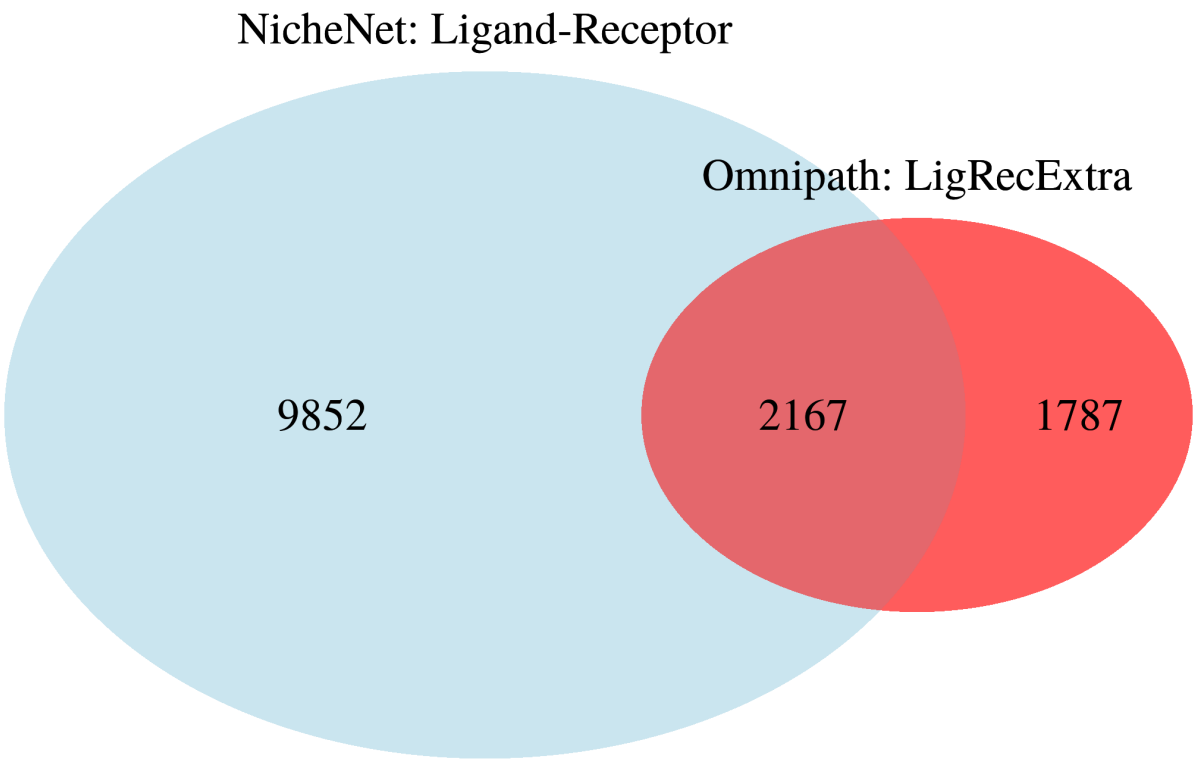
```
## We access to the Omnipath webservice usign the OmnipathR package and we
## display how the interactions look like.
lr_Network_Omnipath <- import_ligrecextra_interactions()
lr_Network_Omnipath[1:6,c(3,4,5,6,7,12)]
##   source_genesymbol target_genesymbol is_directed is_stimulation is_inhibition
## 1             CALM1             TRPC3           1              0             1
## 2            NOTCH1              JAG2           1              0             1
## 3              JAG2            NOTCH1           1              1             1
## 4              DLL1            NOTCH1           1              1             0
## 5            NOTCH1              DLL1           1              1             1
## 6              IGF1             IGF1R           1              1             0
##
## 1
## 2
## 3                                                 Baccin2019;CellPhoneDB;EMBRACE;Fantom5;HPMR;HPRD;IC
## 4                                                       Baccin2019;CellPhoneDB;EMBRACE;Fantom5;HPMR;
## 5
## 6 Baccin2019;CA1;CellPhoneDB;DIP;EMBRACE;Fantom5;Guide2Pharma;HPMR;HPRD;KEGG;Kirouac2010;LRdb;ProtMa
```

We show the total number of ligand-receptor interactions available in the **Omnipath** *LigrecExtra* dataset after removing duplicates:

```
## We also remove self-interactions in case they exist
lr_Network_Omnipath_Unique <- lr_Network_Omnipath %>%
    dplyr::distinct(source_genesymbol,target_genesymbol) %>%
    dplyr::rename(from=source_genesymbol, to=target_genesymbol) %>%
    dplyr::filter(from != to)
nrow(lr_Network_Omnipath_Unique)
## [1] 3954
```

We display the number of matching interactions between different sources with a Venn diagram:

```
Venn_plot <- draw.pairwise.venn(nrow(lr_Network_Nichenet_Unique),
    nrow(lr_Network_Omnipath_Unique),
    nrow(dplyr::intersect(lr_Network_Nichenet_Unique,
    lr_Network_Omnipath_Unique)),
    category = c("NicheNet: Ligand-Receptor", "Omnipath: LigRecExtra"),
    lty = rep("blank", 2), fill = c("light blue", "red"), alpha = rep(0.4, 2),
    cat.pos = c(0, 0), cat.dist = rep(0.025, 2), cex= 1.5, cat.cex=1.5,
    verbose = FALSE)
grid.draw(Venn_plot)
```



In **NicheNet**, the authors predicted ligand–receptor interactions by searching in protein–protein interaction databases for interactions between genes annotated as ligands and receptors (Browaeys et al 2019).

We can also do something similar using **Omnipath**. The new version of **Omnipath** also contains protein annotations describing roles in inter-cellular signaling, e.g. if a protein is a ligand, a receptor, an extracellular matrix (ECM) component, etc... Thus, we selected proteins annotated as ligand or receptors and we searched for interactions between them (with ligands as sources of interactions and receptors as sources). The process is described in the following code chunks:

```
## We import Omnipath Inter cellular annotations
InterCell_Annotations <- import_omnipath_intercell()

## We filter those proteins which are mainly annotated as receptor or ligand
Ligands_Receptors <- InterCell_Annotations %>%
    dplyr::filter(category %in% c("receptor","ligand"))

## There are also some complexes. We are going to deal with them by including
## each of its individual proteins in our list
Ligand_Receptors_class <- character()
Ligand_Receptors_name <- character()
for (i in seq(nrow(Ligands_Receptors))){
    if (Ligands_Receptors$entity_type[i] == "complex"){
        Genescomplex <-unlist(strsplit(gsub("COMPLEX:", "",
            Ligands_Receptors$genesymbol[i]),"_"))
        class <- rep(Ligands_Receptors$category[i],length(Genescomplex))
        Ligand_Receptors_name <- c(Ligand_Receptors_name,Genescomplex)
```

```
        Ligand_Receptors_class <- c(Ligand_Receptors_class,class)

    } else {
        Ligand_Receptors_name <-
            c(Ligand_Receptors_name, Ligands_Receptors$genesymbol[i])
        Ligand_Receptors_class <-
            c(Ligand_Receptors_class, Ligands_Receptors$category[i])
    }
}
```

We remove duplicates and we display the number of proteins that we have annotated as ligand or receptors.

```
Ligand_Receptors_df <- data.frame(GeneSymbol = Ligand_Receptors_name,
    Class = Ligand_Receptors_class, stringsAsFactors = FALSE) %>%
    dplyr::distinct()
AllLigands_vec <-
    dplyr::filter(Ligand_Receptors_df, Class == "ligand") %>%
    dplyr::pull(GeneSymbol)
AllReceptors_vec <-
    dplyr::filter(Ligand_Receptors_df, Class == "receptor") %>%
    dplyr::pull(GeneSymbol)
table(Ligand_Receptors_df$Class)
##
##   ligand receptor
##     1049     2328
```

We next get protein-protein interactions from the different datasets availabe in **Omnipath**

```
AllInteractions <-
    import_post_translational_interactions(exclude = "ligrecextra") %>%
    dplyr::select(source_genesymbol, target_genesymbol) %>%
    dplyr::distinct() %>%
    dplyr::rename(from=source_genesymbol, to=target_genesymbol)
```

```
nrow(AllInteractions)
## [1] 77799
```

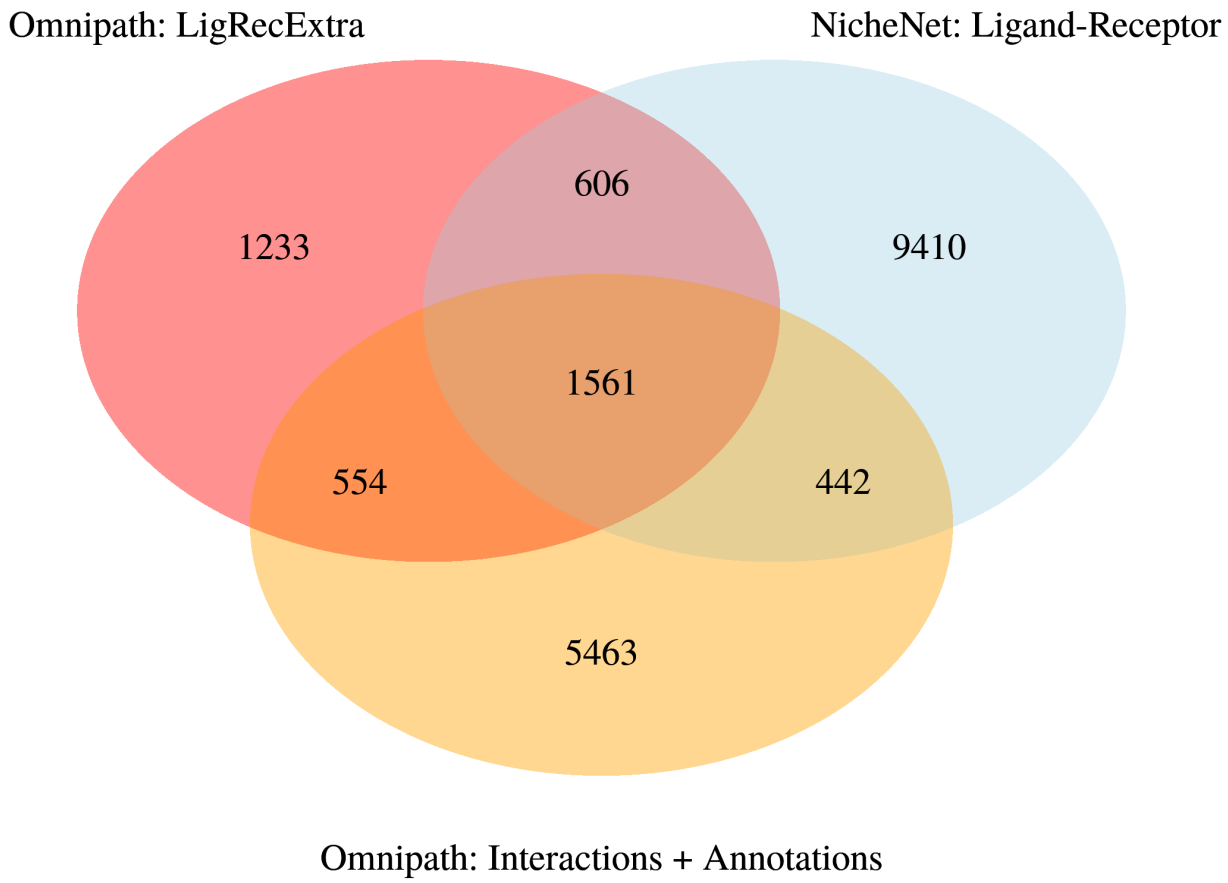
Now, we search for pairs of proteins annotated as ligand and receptor with an interaction between them.

```
## Do the other way around? I only used from=ligands and to=receptors
Matching_Interactions_Annotations <- AllInteractions %>%
    dplyr::filter(from %in% AllLigands_vec) %>%
    dplyr::filter(to %in% AllReceptors_vec) %>%
    dplyr::distinct()
nrow(Matching_Interactions_Annotations)
## [1] 8020
```

We finally display the number of matching interactions between the different sources with a Venn diagram:

```
Venn_plot <- draw.triple.venn(nrow(lr_Network_Nichenet_Unique),
    nrow(lr_Network_Omnipath_Unique),
    nrow(Matching_Interactions_Annotations),
    n12 = nrow(dplyr::intersect(lr_Network_Nichenet_Unique,
        lr_Network_Omnipath_Unique)),
    n23 = nrow(dplyr::intersect(lr_Network_Omnipath_Unique,
        Matching_Interactions_Annotations)),
    n13 = nrow(dplyr::intersect(lr_Network_Nichenet_Unique,
```

```
        Matching_Interactions_Annotations)),
    n123 = nrow(dplyr::intersect(dplyr::intersect(lr_Network_Nichenet_Unique,
        lr_Network_Omnipath_Unique),
        Matching_Interactions_Annotations)),
    category = c("NicheNet: Ligand-Receptor", "Omnipath: LigRecExtra",
        "Omnipath: Interactions + Annotations"),
    lty = rep("blank", 3), fill = c("light blue", "red","orange"),
    alpha = rep(0.25, 3), euler.d = TRUE, scaled=TRUE,
    rotation.degree = 0, reverse=TRUE, cex=1.25, cat.pos = c(330, 30 , 180),
    cat.dist = rep(0.075, 3), cat.cex = 1.25)
grid.draw(Venn_plot)
```



Signaling Network

In this section, we compare the singaling network used to build **NicheNet** with the one available through **Omnipath**. We first load the signaling interactions used to build the **NicheNet** model.

```
## We read the data which are freely available via Zenodo and we display
## how they look like.
sig_Network_Nichenet <-
    readRDS(url("https://zenodo.org/record/3260758/files/signaling_network.rds"))
sig_Network_Nichenet
## # A tibble: 3,621,987 x 4
##    from    to    source                                    database
##    <chr>   <chr> <chr>                                     <chr>
```

```
##  1 BTRC    PDCD4 omnipath_directional                    omnipath
##  2 RPS6KB1 PDCD4 omnipath_directional                    omnipath
##  3 RPS6KB1 PDCD4 pathwaycommons_controls_phosphorylation... pathwaycommons_signal...
##  4 RPS6KB1 PDCD4 pathwaycommons_controls_state_change_of  pathwaycommons_signal...
##  5 RPS6KB1 PDCD4 harmonizome_KEA                         harmonizome
##  6 RPS6KB1 PDCD4 harmonizome_PhosphoSite                 harmonizome
##  7 AKT1    PDCD4 omnipath_directional                    omnipath
##  8 AKT1    PDCD4 pathwaycommons_controls_phosphorylation... pathwaycommons_signal...
##  9 AKT1    PDCD4 pathwaycommons_controls_state_change_of  pathwaycommons_signal...
## 10 AKT1    PDCD4 harmonizome_KEA                         harmonizome
## # ... with 3,621,977 more rows
```

We show the total number of ligand-receptor interactions after removing duplicates:

```
sig_Network_Nichenet_Unique <- sig_Network_Nichenet %>%
    dplyr::distinct(from, to)
nrow(sig_Network_Nichenet_Unique)
## [1] 2475457
```

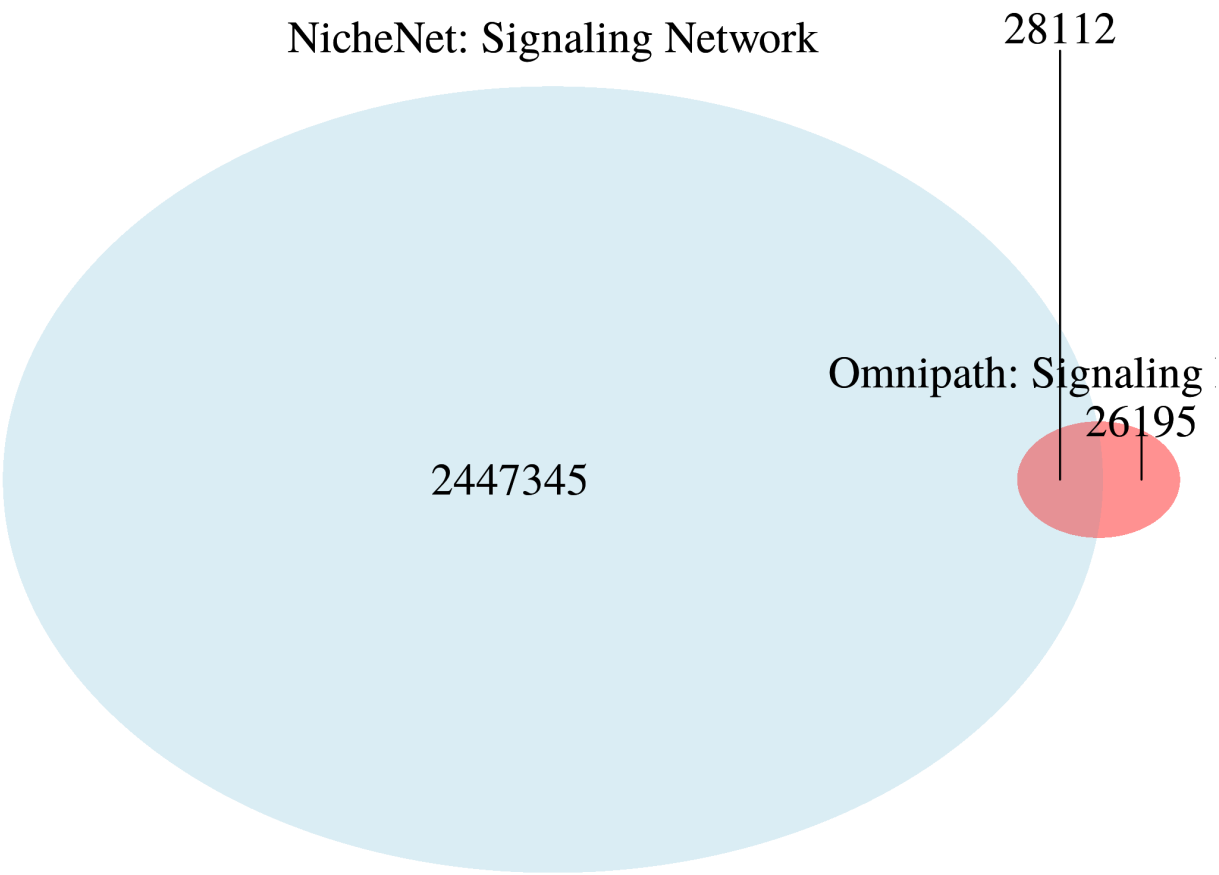
We generate a signaling network using **Omnipath** resources:

```
sig_Interactions_Omnipath <-
    import_post_translational_interactions(exclude = "ligrecextra") %>%
    dplyr::rename(from=source_genesymbol, to=target_genesymbol) %>%
    dplyr::filter(consensus_direction == "1") %>%
    dplyr::distinct(from, to, .keep_all = TRUE)  %>%
    dplyr::select(from, to)

sig_Network_Omnipath <- sig_Interactions_Omnipath %>%
    dplyr::distinct()
nrow(sig_Network_Omnipath)
## [1] 54307
```

We finally display the number of matching interactions between the different sources with a Venn diagram:

```
Venn_plot <- draw.pairwise.venn(nrow(sig_Network_Nichenet_Unique),
    nrow(sig_Network_Omnipath),
    nrow(dplyr::intersect(sig_Network_Nichenet_Unique,
    sig_Network_Omnipath)),
    category = c("NicheNet: Signaling Network",
        "Omnipath: Signaling Network"),
    lty = rep("blank", 2), fill = c("light blue", "red"), alpha = rep(0.25, 2),
    cat.pos = c(0, 0), cat.dist = rep(0.025, 2), cex= 1.5, cat.cex=1.5)
grid.draw(Venn_plot)
```



Gene Regulatory Network

In this section, we compare the GRN network used to build **NicheNet** with the **DoRothEA** regulons available through **Omnipath**. We first load the GNR interactions used to build the **NicheNet** model.

```
## We read the data which are freely available via Zenodo and we display
## how they look like.
gr_Network_Nichenet <-
    readRDS(url("https://zenodo.org/record/3260758/files/gr_network.rds"))
gr_Network_Nichenet
## # A tibble: 3,592,299 x 4
##    from  to      source           database
##    <chr> <chr>   <chr>            <chr>
##  1 KLF2  DLGAP1  harmonizome_CHEA harmonizome_gr
##  2 KLF2  DTNB    harmonizome_CHEA harmonizome_gr
##  3 KLF2  BHLHE40 harmonizome_CHEA harmonizome_gr
##  4 KLF2  RPS6KA1 harmonizome_CHEA harmonizome_gr
##  5 KLF2  PXN     harmonizome_CHEA harmonizome_gr
##  6 KLF2  UBE2V1  harmonizome_CHEA harmonizome_gr
##  7 KLF2  MSRA    harmonizome_CHEA harmonizome_gr
##  8 KLF2  TEX14   harmonizome_CHEA harmonizome_gr
##  9 KLF2  CYLD    harmonizome_CHEA harmonizome_gr
## 10 KLF2  RYBP    harmonizome_CHEA harmonizome_gr
## # ... with 3,592,289 more rows
```

We show the total number of ligand-receptor interactions after removing duplicates:

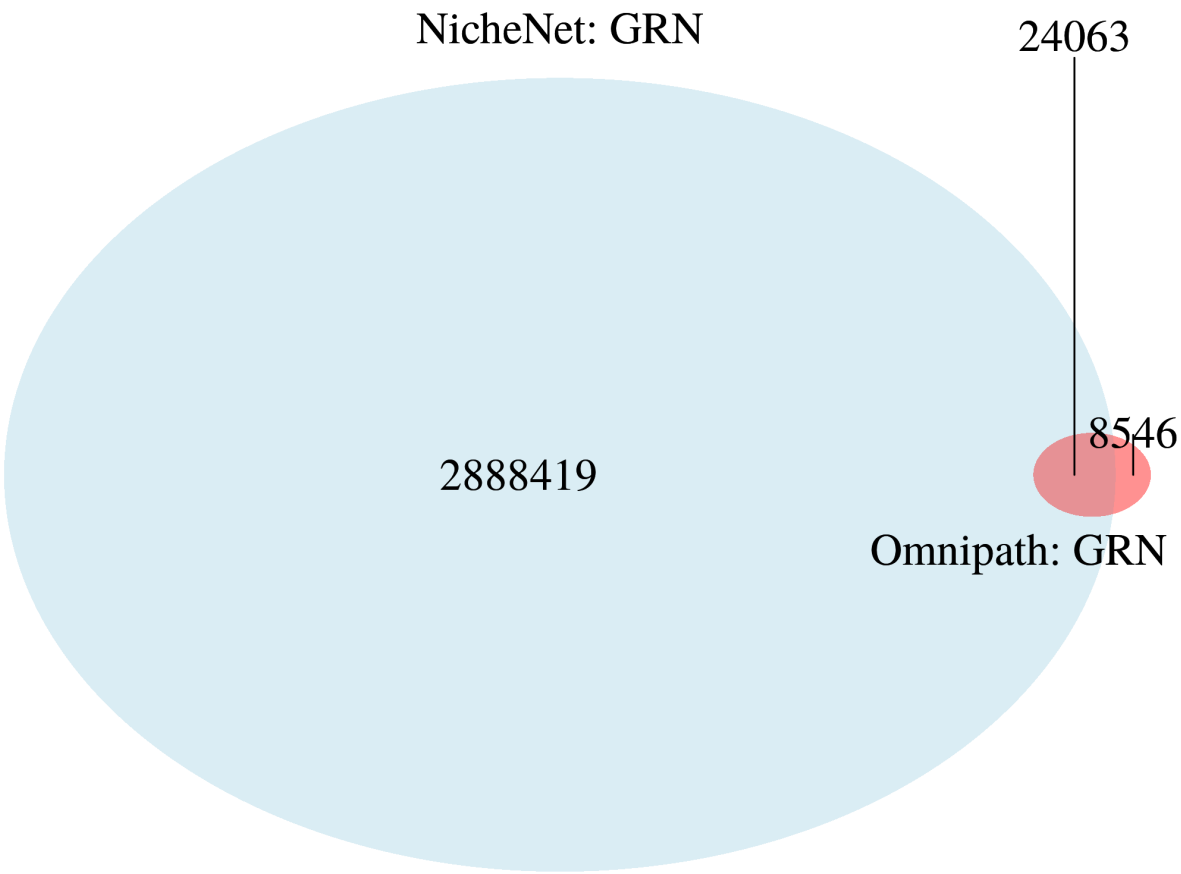
```
gr_Network_Nichenet_unique <- gr_Network_Nichenet %>%
    dplyr::distinct(from, to)
nrow(gr_Network_Nichenet_unique)
## [1] 2912482
```

We generate a GRN network using **Omnipath** resources:

```
gr_Interactions_Omnipath <-
    import_dorothea_interactions(dorothea_levels = c('A','B','C')) %>%
    dplyr::select(source_genesymbol, target_genesymbol) %>%
    dplyr::rename(from=source_genesymbol, to=target_genesymbol) %>%
    dplyr::distinct(from, to)
nrow(gr_Interactions_Omnipath)
## [1] 32609
```

We finally display the number of matching interactions between the different sources with a Venn diagram:

```
Venn_plot <-
    draw.pairwise.venn(nrow(gr_Network_Nichenet_unique),
    nrow(gr_Interactions_Omnipath),
    nrow(dplyr::intersect(gr_Network_Nichenet_unique,gr_Interactions_Omnipath)),
    category = c("NicheNet: GRN", "Omnipath: GRN"),
    lty = rep("blank", 2), fill = c("light blue", "red"), alpha = rep(0.25, 2),
    cat.pos = c(0, 215), cat.dist = rep(0.025, 2), cex= 1.5, cat.cex=1.5)
grid.draw(Venn_plot)
```



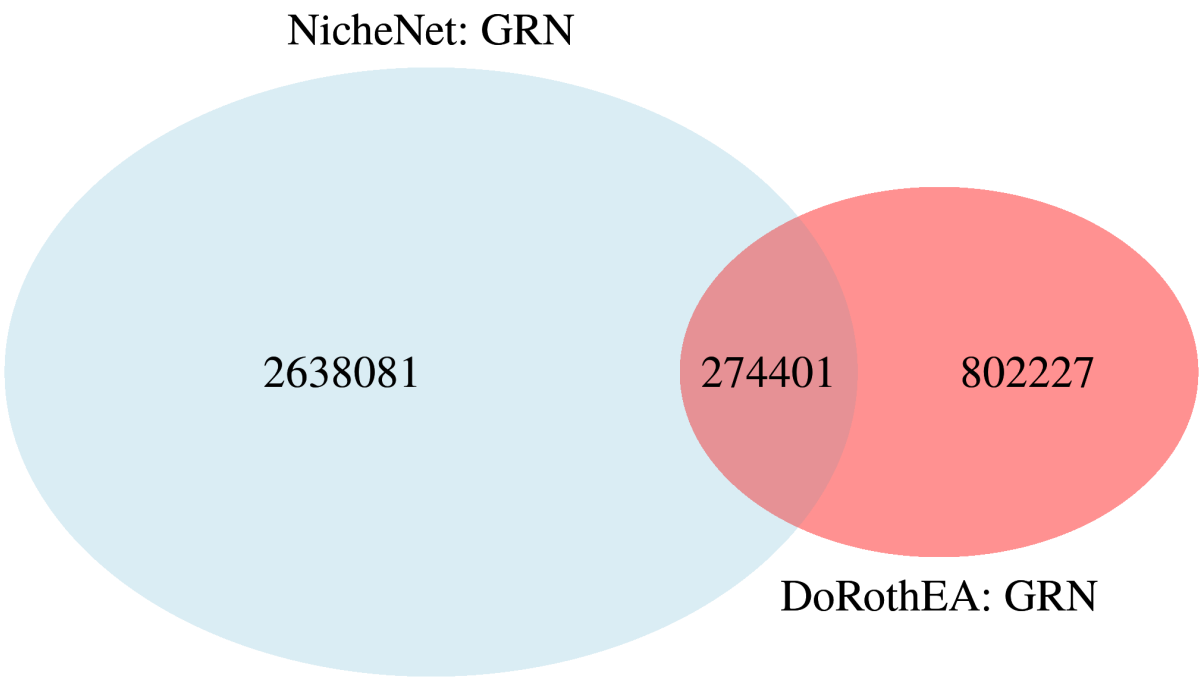
it is to note that **DoRothEA** contains some additional interactions which are not available in the **Omnipath**

web server. We now compare **NicheNet** gene regulatory interaction with the all **DoRothEA** regulons.

```
## To download from:
## https://github.com/saezlab/DoRothEA/tree/master/data/TFregulons/consensus/table
full_dorothea <- read_csv("DoRothEA/database.csv")

full_dorothea_unique <- full_dorothea %>%
    dplyr::select(TF,target) %>%
    dplyr::rename(from=TF, to=target) %>%
    dplyr::distinct(from,to)
nrow(full_dorothea_unique)
## [1] 1076628
```

```
Venn_plot <- draw.pairwise.venn(nrow(gr_Network_Nichenet_unique),
    nrow(full_dorothea_unique),
    nrow(dplyr::intersect(gr_Network_Nichenet_unique,
    full_dorothea_unique)),
    category = c("NicheNet: GRN", "DoRothEA: GRN"),
    lty = rep("blank", 2), fill = c("light blue", "red"), alpha = rep(0.25, 2),
    cat.pos = c(0, 180), cat.dist = rep(0.025, 2), cex= 1.5, cat.cex=1.5)
grid.draw(Venn_plot)
```



References

Bonnardel et al. Stellate Cells, Hepatocytes, and Endothelial Cells Imprint the Kupffer Cell Identity on Monocytes Colonizing the Liver Macrophage Niche. Immunity (2019) doi:10.1016/j.immuni.2019.08.017

Browaeys, R., Saelens, W. & Saeys, Y. NicheNet: modeling intercellular communication by linking ligands to target genes. Nat Methods (2019) doi:10.1038/s41592-019-0667-5