

PriA Family

Actinobacterial PriA is a promiscuous homologue of enterobacteria HisA enzymatic family. HisA converts ProFAR into PRFAR on histidine pathway, most actinobacteria has lost trpF gene on triptophane pathway, PriA among isomerizing PROFAR also converts PRA into CdRP acting as TrpF on triptophane pathway.

PriA has shown a functional gradient on Actinobacteria that split this family into several enzymatic subfamilies. Among PriA subfamilies there is PriB on Streptomyces that shows little trpF activity and an out of context TrpF gene, there is subHisA on Corynebacteria and Actinomyces that has lost trpF activity, and finally there is subTrpF on Actinomyces that has lost HisA activity.

Some of this enzymes were selected on search of new promiscuous functions, candidate catalized reactions where investigating by exploring substrates chemically similar to native ones.

EvoMining has detected one PriA parologue on Actinobacteria and an expansion conserved on a saxitoxin cluster on Cyanobacteria [@moustafa_origin_2009].

PriA

PriB

SubHisA

subTrpF

PRIA

PriA CORASON All streptomyces have a partially conserved PriA cluster. CT34 has a secondary copy whose best hit on NCBI is Lentzea's PriA with 50% identity 98% coverage

TrpF1 TrpF1 queries gave hits with TrpC enzyme present on every Streptomyces, additionally S rimosus, S coelicolor, S venezuelae and S. NRRL S-1813 had an extra copy. S rimosus TrpC vicinity has PKS and siderophore genes.

TrpF2 Conserved cluster with NRPS sequences flanking TrpF2

TrpF3 Non conserved cluster

TrpF4 purpeofuscus and S bikiniensis

Selected enzymes to investigate affinity of substrates similar to PRA and PRO-FAR

Since on *Streptomyces* has been found representatives from PriA and PriB families, 39 homologue sequences were selected to perform docking enzyme-substrate analysis. This PriA/Prib selected sequences belong to *Streptomyces* evenly distributed on an RpoB species tree with different conditions about TrpF presence/absence. Other chemically characterized PriA Actinobacterial homologues were included on this studio, and finally HisA from *Escherichia coli*, *Arthrobacter Aurescens*, *Salmonella enterica* and *Acidimicrobium ferrooxidans* and Actinobacterial TrpF were added as controls.

When exists cristal structures were used otherwise homologues structures were generated using as template the closest enzyme with cristal structure available.

Controls

HisA Enterobacteria enzymes from *Salmonella enterica* (PDB:5AHE), *Escherichia coli K12 Acidimicrobium ferrooxydans* (PDB:4WD0)

TrpF Actinobacteria Jonesia denitrificans and *Streptomyces* sp Mg1 sequences.

Chemically characterized Actinobacterial enzymes

PriA

Mycobacterium tuberculosis (Mtub PDB:2Y88,2Y89,2Y85,3ZS4) *Streptomyces coelicolor* (Scoe PDB:2VEP,2X30,1VZW),*Streptomyces globisporus*, *Actynomyces urogenitalis* 4X2R *Corynebacterium jeikeum*

subHisA

Corynebacterium diphtheriae *Actinomyces car* (PDB:4X2R)

subTrpF

Arthrobacter aurescens (PDB:4WD0)

PriB

Streptomyces ipomoeae, *Streptomyces sviceus* (PDB:4U28,4TX9)

TrpF controls *Jonesia denitrificans* (PDB:4WUI) *Chlamidya thrachomatis*, *Streptomyces* sp. Mg1 TrpF and *Actinomyces odontolyticus* were included

PriA cristal structures on PDB

```
table <- read.csv("chapter4/EstructurasPDB", row.names = 1,sep="\t")
kable(table, caption = "Enzyme PDB \\label{tab:Enzyme PDB}",caption.short = "Enzyme PDB ")
```

Table 1: Enzyme PDB

	Organismo	Family	Observations	Resolution	Year
4WUI	Jonesia denitrificans	TrpF		1.09	2014
4X9S	Streptomyces sp. MG1	PriB		1.60	2014
5DN1	Streptomyces coelicolor	PriA		1.95	2015
1DL3	Thermotoga maritima	TrpF		2.70	1999
1LBM	Thermotoga maritima	TrpF	RCDRP	2.80	2002
1NSJ	Thermotoga maritima	TrpF		2.00	1996
1V5X	Thermus thermophilus	TrpF		2.00	2003
1VZW	Streptomyces coelicolor	PriA		1.80	2004
2VEP	Streptomyces coelicolor	PriA		1.80	2007
2X30	Streptomyces coelicolor	PriA	R139N	1.95	2010
2Y85	Mycobacterium tuberculosis	PriA	RCDRP	2.40	2011
2Y88	Mycobacterium tuberculosis	PriA	D11N PRFAR	1.33	2011
2Y89	Mycobacterium tuberculosis	PriA	D11N	2.50	2011
3ZS4	Mycobacterium tuberculosis	PriA	PRFAR	1.90	2012
4AAJ	Pyrococcus furiosus	TrpF		1.75	2012
4TX9	Streptomyces sviceus	PriB	ProFAR	1.60	2014
4U28	Streptomyces sviceus	PriB		1.33	2014
4W9T	Streptomyces sp. Mg1	PriB		1.57	2014
4WD0	Arthrobacter aurescens	PriB		1.50	2014
4X2R	Actinomyces urogenitalis			1.05	2014
4AXK	Corynebacterium efficiens	SubHisA		2.25	2013
5AHE	Salmonella enterica	HisA		1.70	2015
5AB3	Salmonella enterica	HisA	D7N, D10G, dup13-15, Q24L, G102A	1.80	2016
5ABT	Salmonella enterica	HisA	D7N, G102A, V106M, D176A	1.65	2016
5AC7	Salmonella enterica	HisA	D7N, D10G, dup13-15	1.90	2016
5AC8	Salmonella enterica	HisA	D10G, dup13-15, G102A	1.70	2016
5AC6	Salmonella enterica	HisA	D7N, D10G, dup13-15, Q24L, G102A	1.99	2016
5A5W	Salmonella enterica	HisA	HisA D7N D176A with ProFAR	NA	2015
5AHF	Salmonella enterica	HisA	HisA D7N with ProFAR	NA	NA
4GJ1	Campylobacter jejuni	HisA		2.15	2012
2W79	Thermotoga maritima	HisA		1.85	2008
1QO2	Thermotoga maritima	HisA		1.85	2000
5LHE	Thermococcus kodakaraensis	TrpF		1.85	2016
5LHF	Thermococcus kodakaraensis	TrpF		1.75	2016

Similar substrates to PRA and PROFAR suggested by Tanimoto distance or previously tested

S1,S2,...S20 substrates were collected from literature and chemoinformatics predictions. S3 PRA and S7 PROFAR are native substrates, S13-S16 are light activated substrates, S17 PRAP, S18 Compound V, were found on literature, S6 GMP, S11 GTP and other were suggested by chemoinformatics.

```
ztable <- read.csv("chapter4/Substrate.data", row.names = 1,sep="\t")
kable(table, caption = "Substrates \\label{tab:substrates}",caption.short = "Substrates ")
```

Table 2: Substrates

Organismo	Family	Observations	Resolution	Year	
4WUI	Jonesia denitrificans	TrpF	1.09	2014	
4X9S	Streptomyces sp. MG1	PriB	1.60	2014	
5DN1	Streptomyces coelicolor	PriA	1.95	2015	
1DL3	Thermotoga maritima	TrpF	2.70	1999	
1LBM	Thermotoga maritima	TrpF	2.80	2002	
1NSJ	Thermotoga maritima	TrpF	2.00	1996	
1V5X	Thermus thermophilus	TrpF	2.00	2003	
1VZW	Streptomyces coelicolor	PriA	1.80	2004	
2VEP	Streptomyces coelicolor	PriA	1.80	2007	
2X30	Streptomyces coelicolor	PriA	R139N	1.95	2010
2Y85	Mycobacterium tuberculosis	PriA	RCDRP	2.40	2011
2Y88	Mycobacterium tuberculosis	PriA	D11N PROFAR	1.33	2011
2Y89	Mycobacterium tuberculosis	PriA	D11N	2.50	2011
3ZS4	Mycobacterium tuberculosis	PriA	PRFAR	1.90	2012
4AAJ	Pyrococcus furiosus	TrpF		1.75	2012
4TX9	Streptomyces sviceus	PriB	ProFAR	1.60	2014
4U28	Streptomyces sviceus	PriB		1.33	2014
4W9T	Streptomyces sp. Mg1	PriB		1.57	2014
4WD0	Arthrobacter aurescens	PriB		1.50	2014
4X2R	Actinomyces urogenitalis			1.05	2014
4AXK	Corynebacterium efficiens	SubHisA		2.25	2013
5AHE	Salmonella enterica	HisA		1.70	2015
5AB3	Salmonella enterica	HisA	D7N, D10G, dup13-15, Q24L, G102A	1.80	2016
5ABT	Salmonella enterica	HisA	D7N, G102A, V106M, D176A	1.65	2016
5AC7	Salmonella enterica	HisA	D7N, D10G, dup13-15	1.90	2016
5AC8	Salmonella enterica	HisA	D10G, dup13-15, G102A	1.70	2016
5AC6	Salmonella enterica	HisA	D7N, D10G, dup13-15, Q24L, G102A	1.99	2016
5A5W	Salmonella enterica	HisA	HisA D7N D176A with ProFAR	NA	2015
5AHF	Salmonella enterica	HisA	HisA D7N with ProFAR	NA	NA
4GJ1	Campylobacter jejuni	HisA		2.15	2012
2W79	Thermotoga maritima	HisA		1.85	2008
1QO2	Thermotoga maritima	HisA		1.85	2000
5LHE	Thermococcus kodakaraensis	TrpF		1.85	2016
5LHF	Thermococcus kodakaraensis	TrpF		1.75	2016

On next figure we can see their chemical structures.

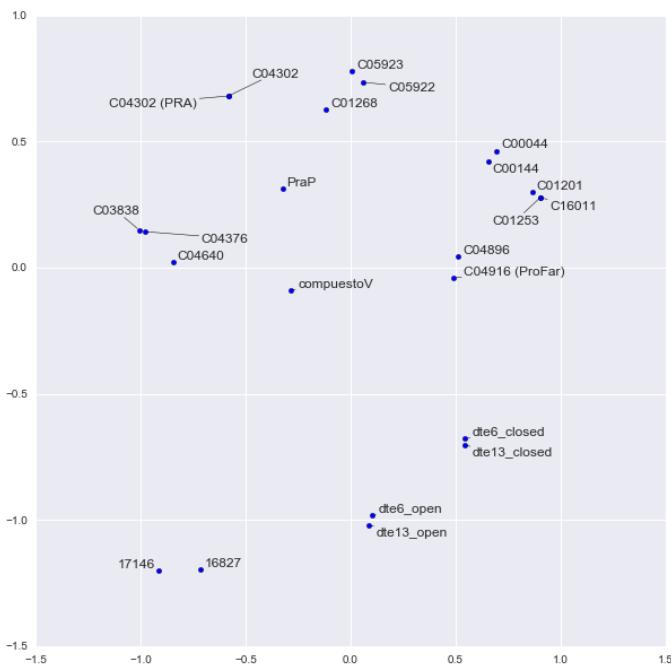
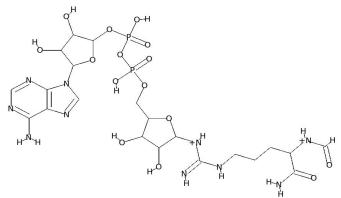
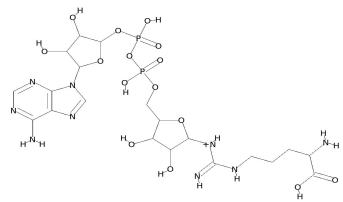


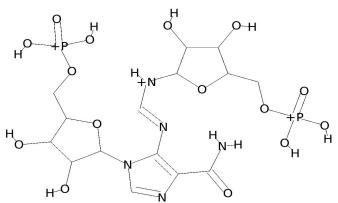
Figure 1: Substrates clustering according to Tanimoto distance



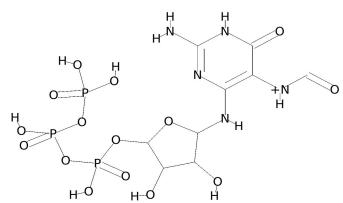
1
ADP-D-ribosyl-[dinitrogen reductase]



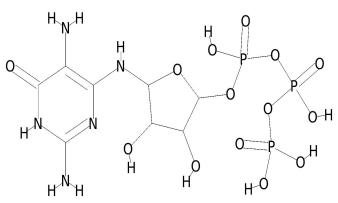
2
N(omega)-(ADP-D-ribosyl)-L-arginine



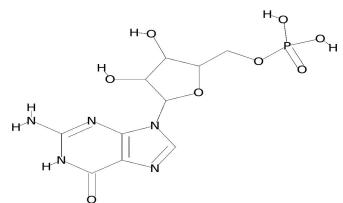
3
5-(5-Phospho-D-ribosylaminoformimino)-1-(5-phosphoribosyl)-imidazole-4-carboxamide



4
Formamidopyrimidine nucleoside triphosphate

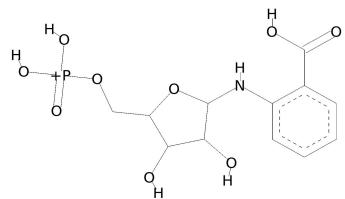


5
2,5-diaminopyrimidine nucleoside triphosphate

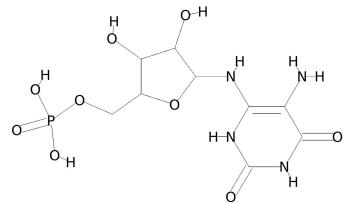


6
Guanosine monophosphate

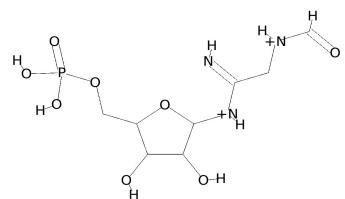
Figure 2: Substrates 1



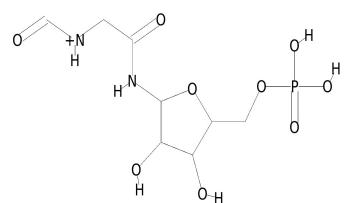
7
N-(5-phospho-D-ribosyl) anthranilate



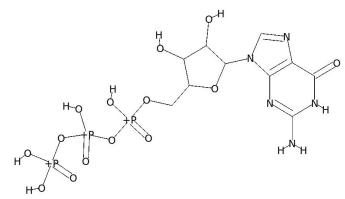
8
5-Amino-6-(5'-phosphoribosylamino)uracil



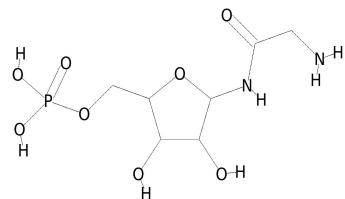
9
2-(Formido)-N1-(5'-phosphoribosyl)acetamidine



10
5'-Phosphoribosyl-N-formylglycinamide

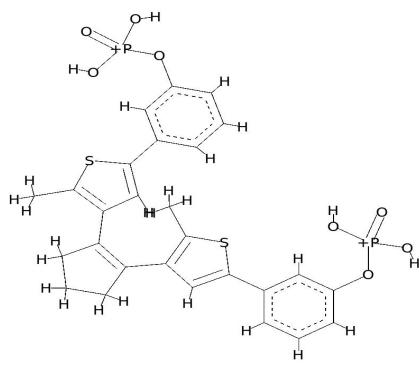


11
Guanosine 5'-triphosphate



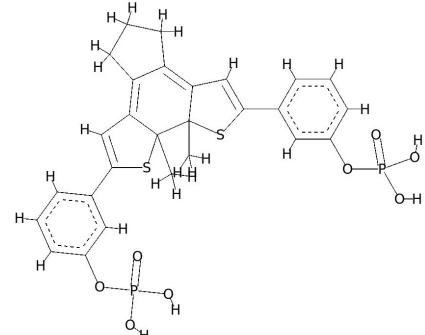
12
5'-Phosphoribosylglycinamide

Figure 3: Substrates 2



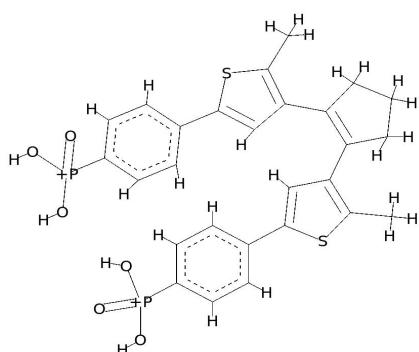
13

DTE-meta-phosphate(dte6_Open form)



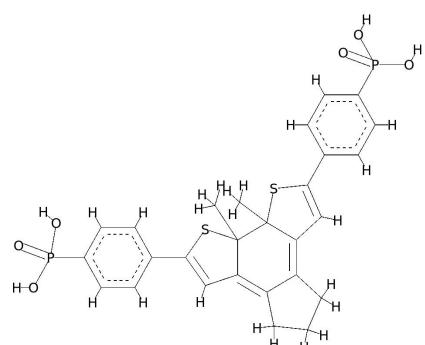
14

DTE-meta-phosphate(dte6_Closed form)



15

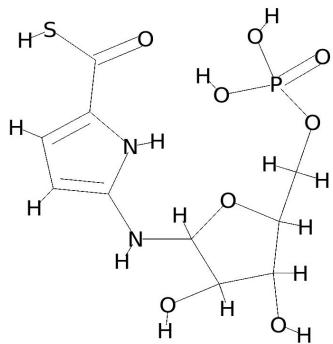
DTE-Para-Phosphonate(dte13_closed form)



16

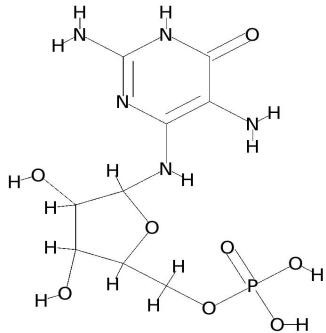
DTE-para-phosphonate(dte13_closed form)

Figure 4: Substrates 3



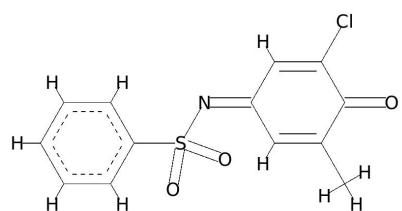
17

4N'-(5'-phosphoribosyl) 4-aminopyrrole-2-carboxilate



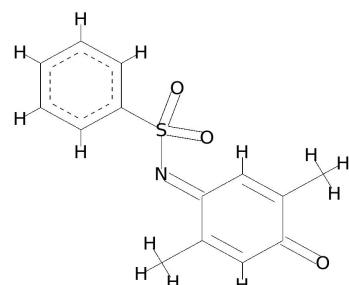
18

2,5-di-amino-6-ribosylamino-4(3H)-pyrimidinone 5'-phosphate



19

(E)-N-(3-chloro-5-methyl-4-oxocyclohexa-2,5-dienylidene)benzenesulfonamide



20

2,5 dimethyl-N-(4-oxocyclohexa-2,5-dienylidene)benzenesulfonamide

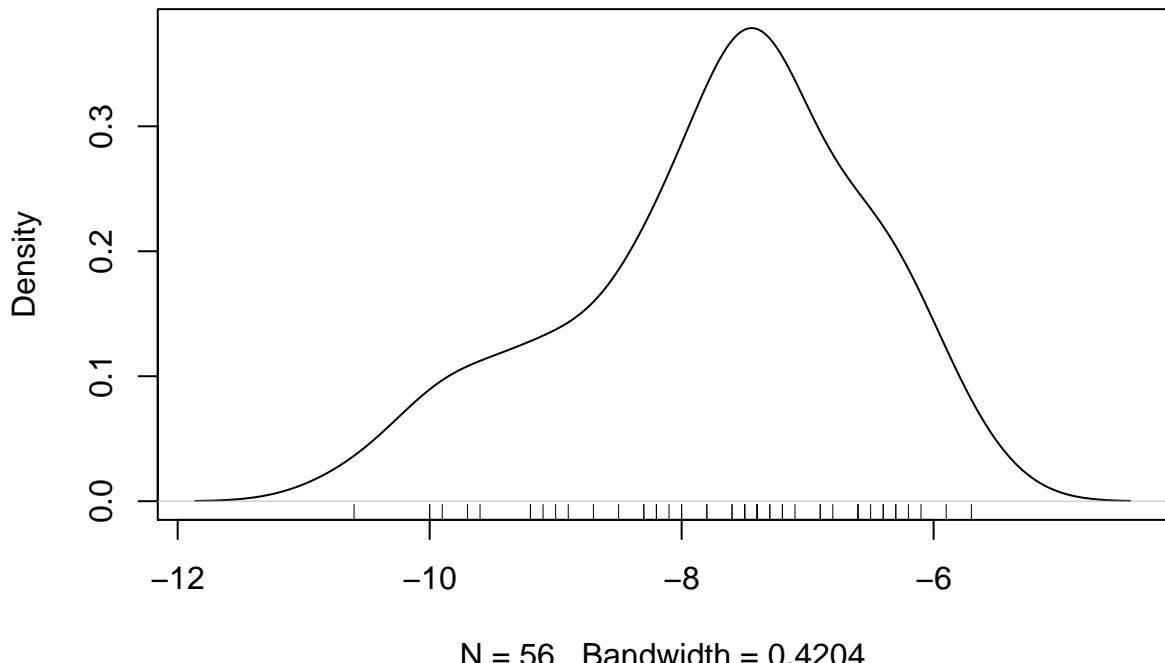
Figure 5: Substrates 4

Docking between PriA enzymes and selected substrates

Docking simulation were calculated for PriA *Streptomyces* enzymes. TrpF enzymes from *Streptomyces Mg1*, *Jonesia denitrificans*, were added as controls

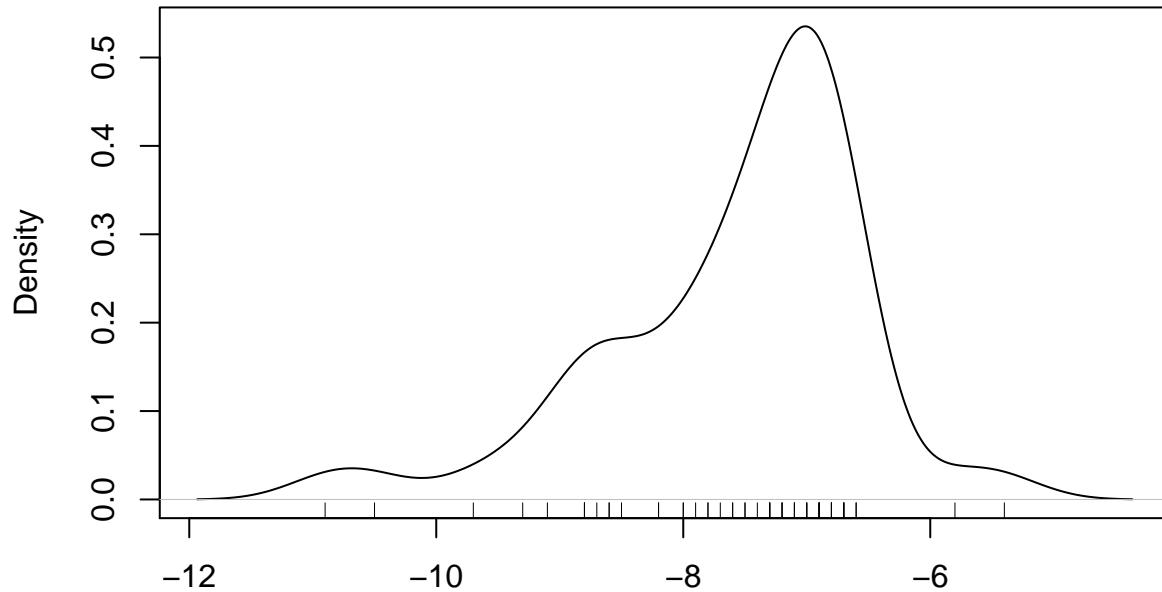
Procedures can be found at Docking Protocols

```
docking <- read.csv("chapter4/SmallHeat.data", header=TRUE, sep="\t")  
  
for (i in 2:21)  
{plot(density(docking[,i],na.rm=T)); rug(docking[,i]); browser()}  
  
density.default(x = docking[, i], na.rm = T)
```



```
## Called from: eval(expr, envir, enclos)
## debug en <text>#4: plot(density(docking[, i], na.rm = T))
```

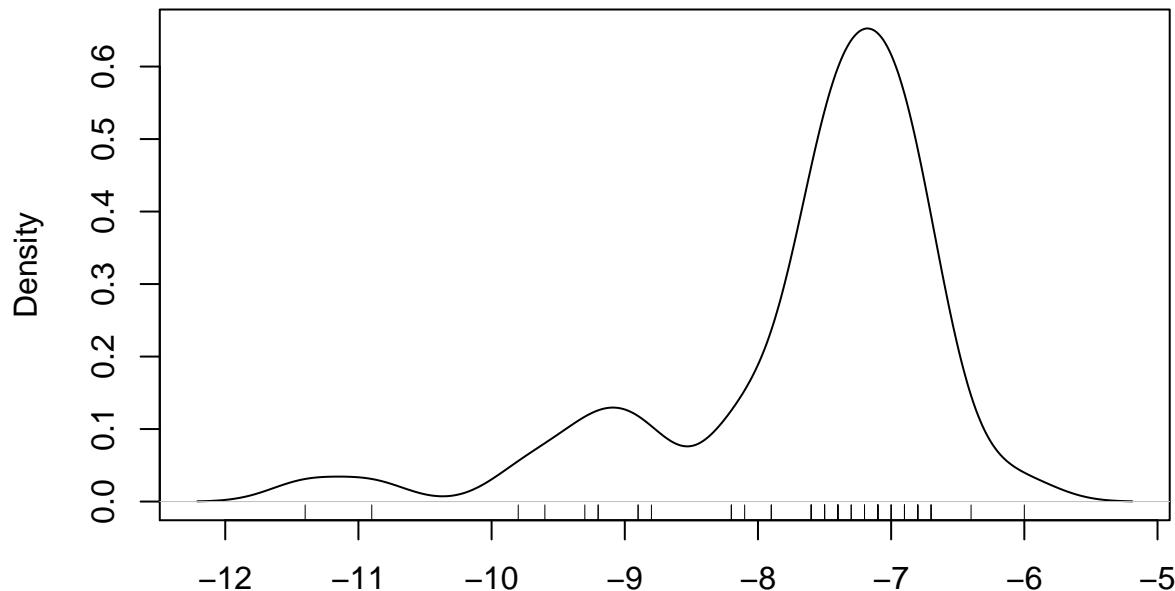
```
density.default(x = docking[, i], na.rm = T)
```



N = 56 Bandwidth = 0.3453

```
## debug en <text>#4: rug(docking[, i])
## debug en <text>#4: browser()
## debug en <text>#4: plot(density(docking[, i], na.rm = T))
```

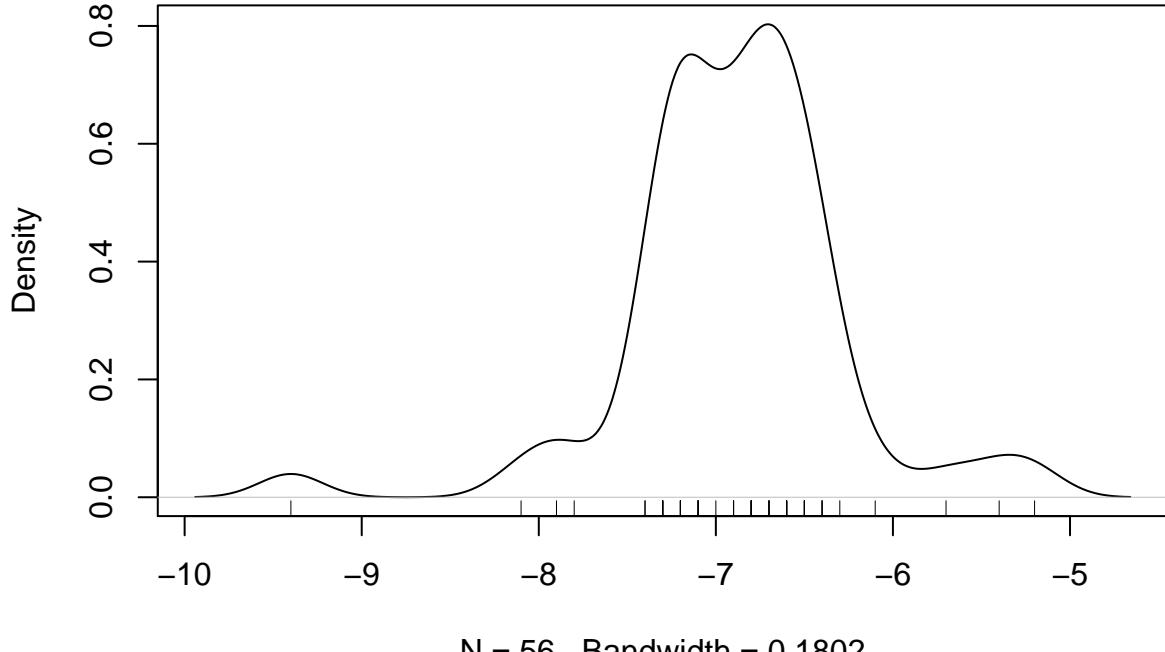
```
density.default(x = docking[, i], na.rm = T)
```



N = 56 Bandwidth = 0.2702

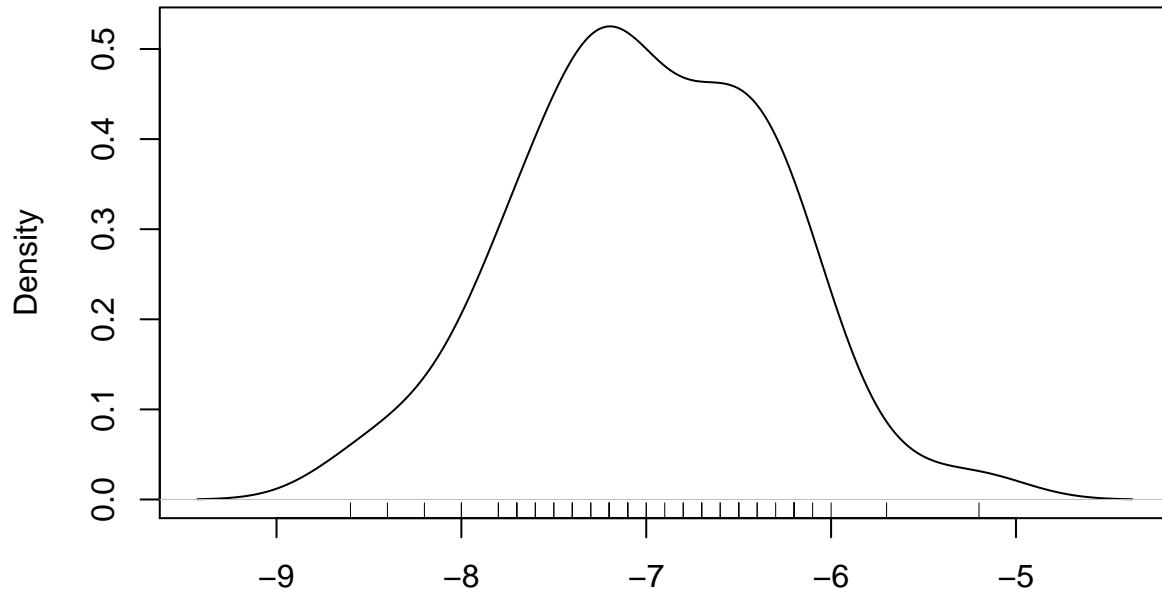
```
## debug en <text>#4: rug(docking[, i])
```

```
## debug en <text>#4: browser()
## debug en <text>#4: plot(density(docking[, i], na.rm = T))
density.default(x = docking[, i], na.rm = T)
```



```
## debug en <text>#4: rug(docking[, i])
## debug en <text>#4: browser()
## debug en <text>#4: plot(density(docking[, i], na.rm = T))
```

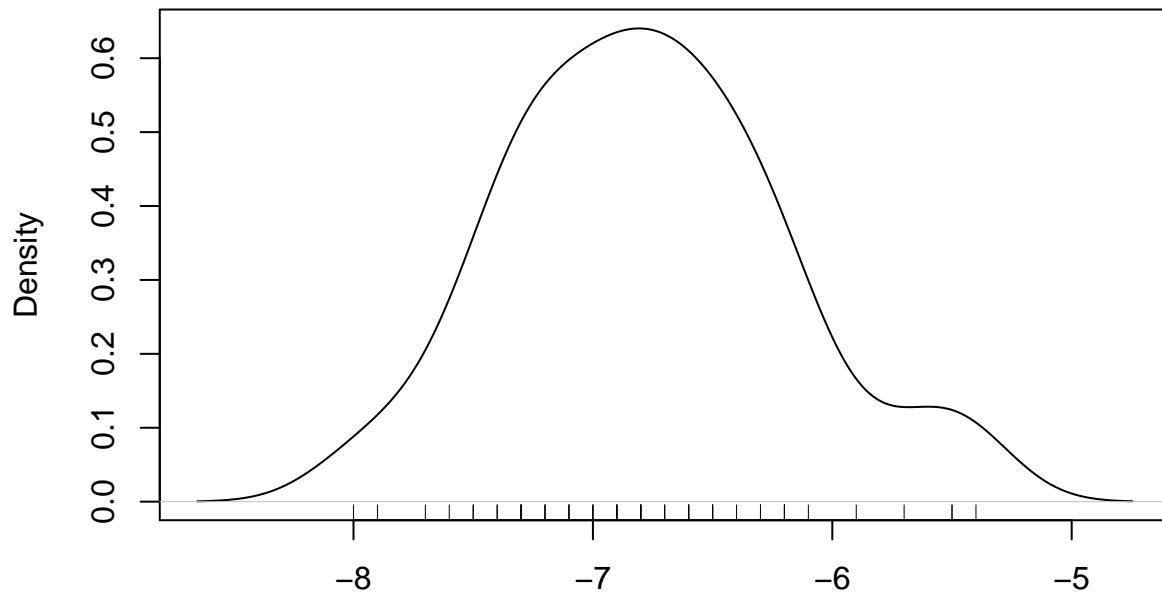
```
density.default(x = docking[, i], na.rm = T)
```



N = 56 Bandwidth = 0.2764

```
## debug en <text>#4: rug(docking[, i])
## debug en <text>#4: browser()
## debug en <text>#4: plot(density(docking[, i], na.rm = T))
```

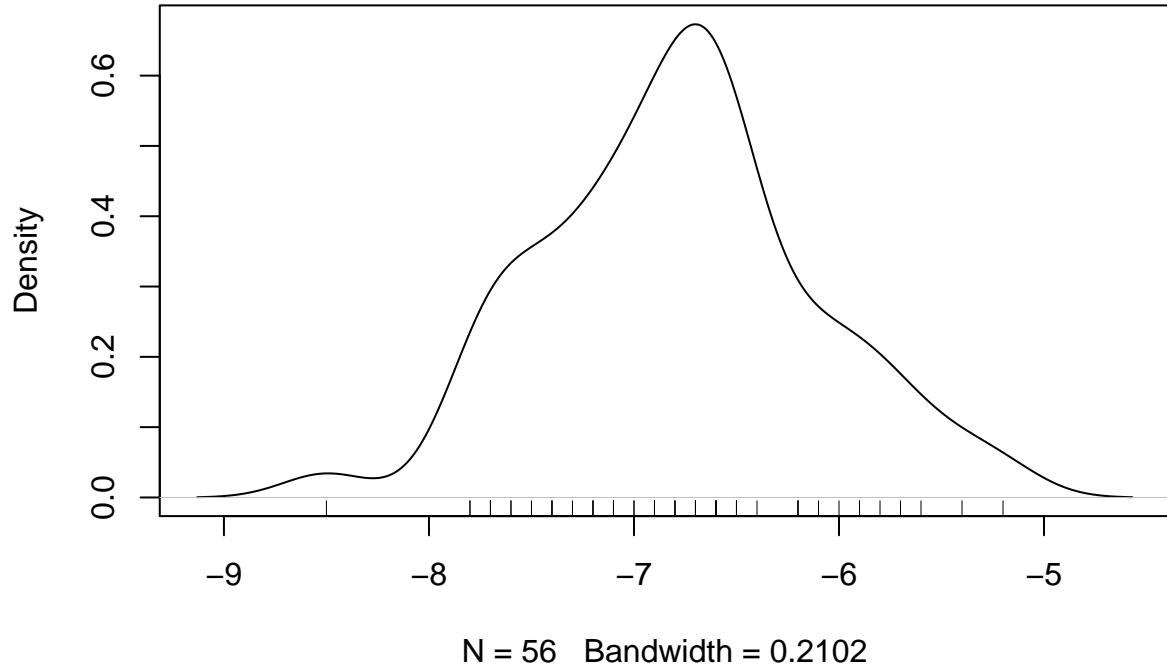
```
density.default(x = docking[, i], na.rm = T)
```



N = 56 Bandwidth = 0.2177

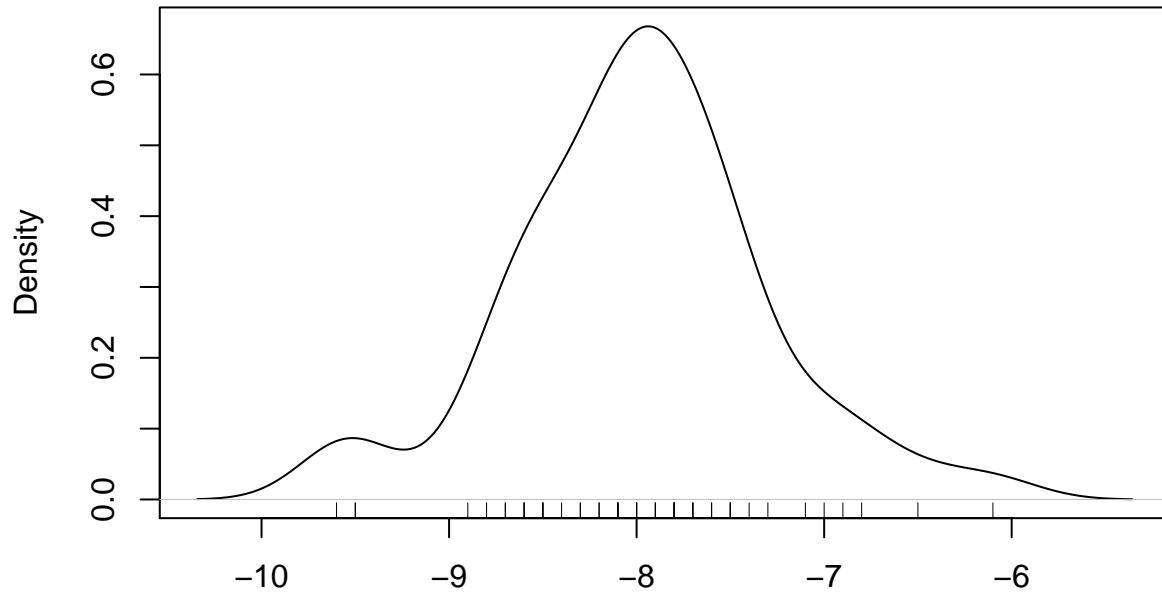
```
## debug en <text>#4: rug(docking[, i])
```

```
## debug en <text>#4: browser()
## debug en <text>#4: plot(density(docking[, i], na.rm = T))
density.default(x = docking[, i], na.rm = T)
```



```
## debug en <text>#4: rug(docking[, i])
## debug en <text>#4: browser()
## debug en <text>#4: plot(density(docking[, i], na.rm = T))
```

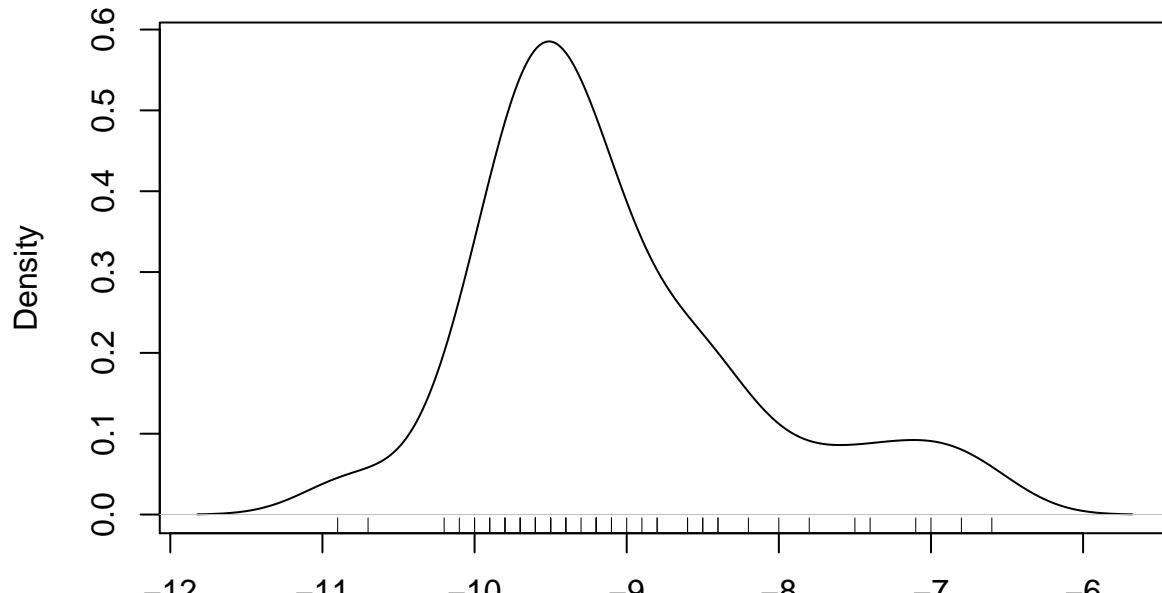
```
density.default(x = docking[, i], na.rm = T)
```



N = 56 Bandwidth = 0.2477

```
## debug en <text>#4: rug(docking[, i])
## debug en <text>#4: browser()
## debug en <text>#4: plot(density(docking[, i], na.rm = T))
```

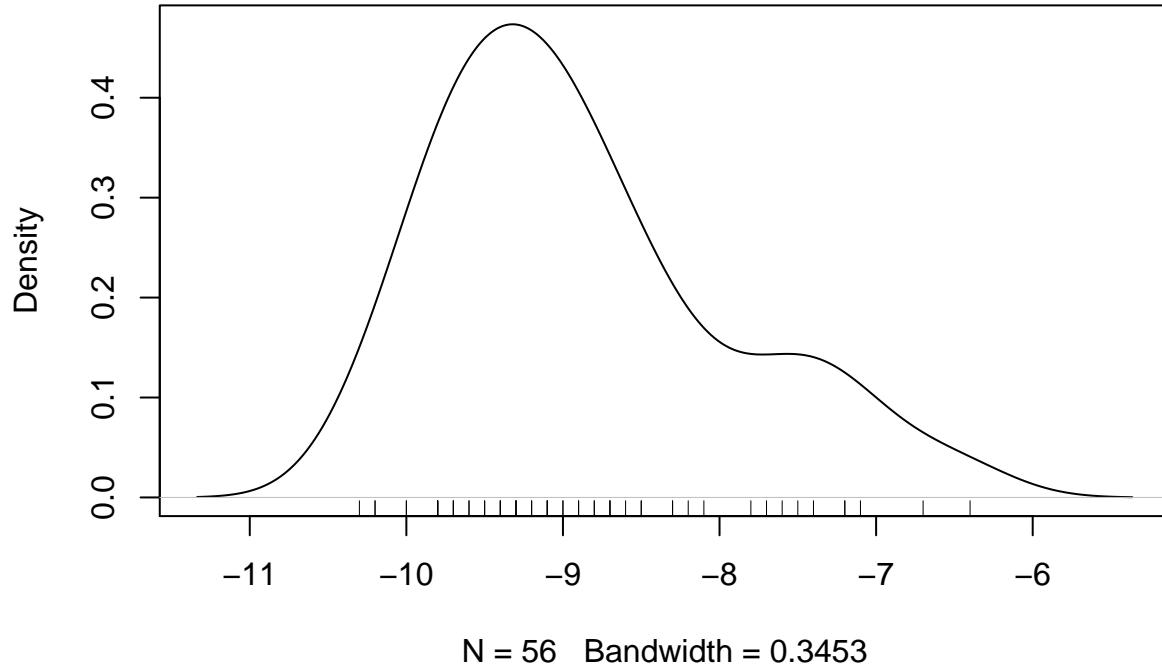
```
density.default(x = docking[, i], na.rm = T)
```



N = 56 Bandwidth = 0.3078

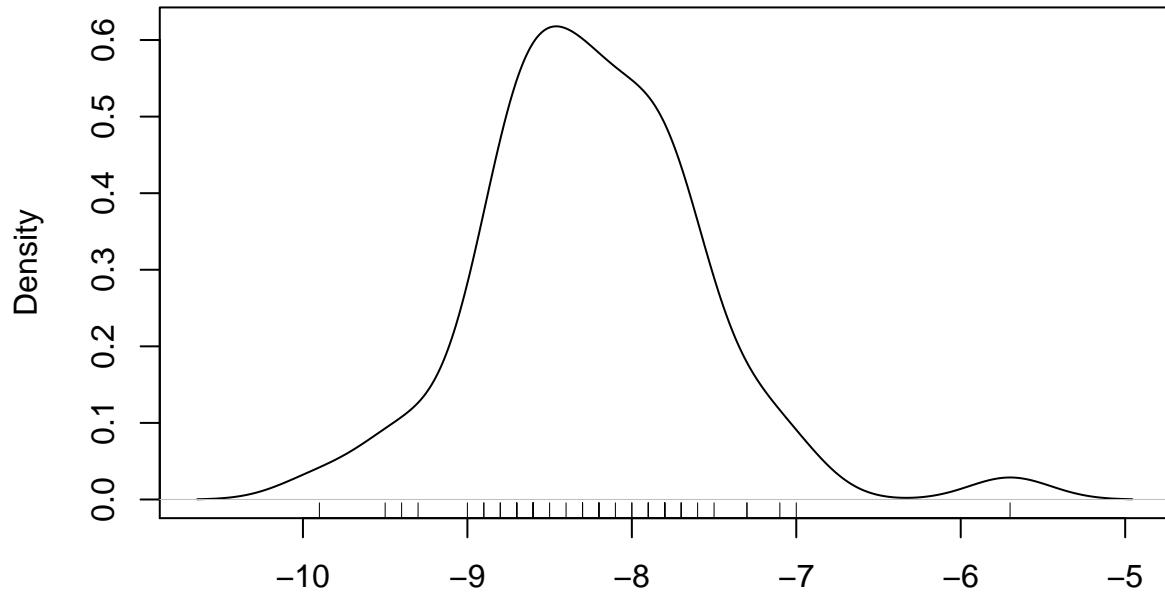
```
## debug en <text>#4: rug(docking[, i])
```

```
## debug en <text>#4: browser()
## debug en <text>#4: plot(density(docking[, i], na.rm = T))
density.default(x = docking[, i], na.rm = T)
```



```
## debug en <text>#4: rug(docking[, i])
## debug en <text>#4: browser()
## debug en <text>#4: plot(density(docking[, i], na.rm = T))
```

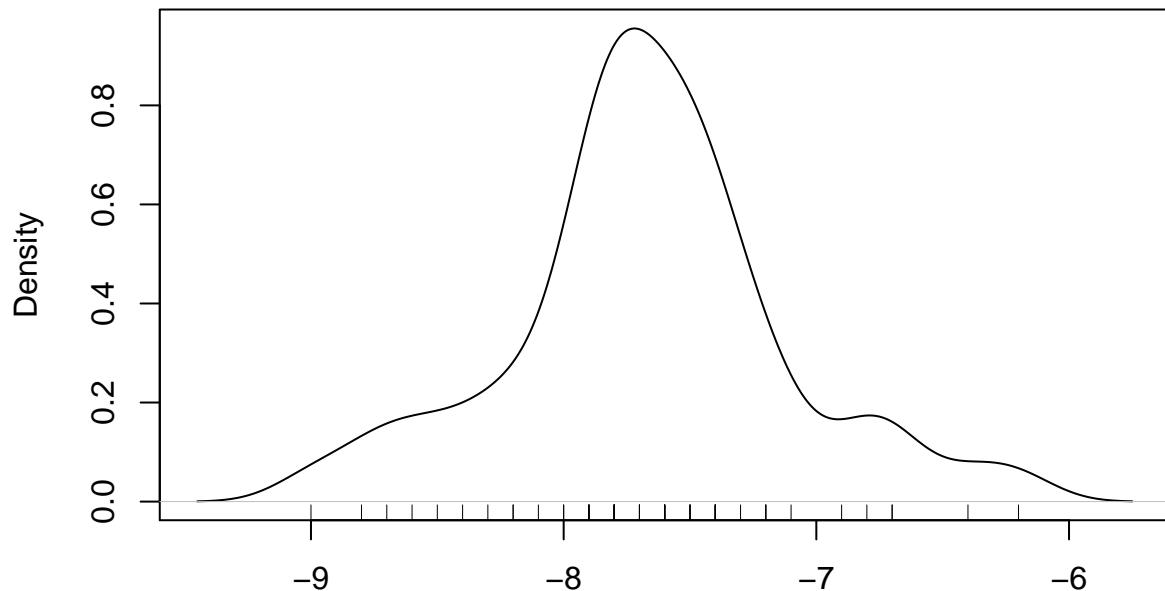
```
density.default(x = docking[, i], na.rm = T)
```



N = 56 Bandwidth = 0.2477

```
## debug en <text>#4: rug(docking[, i])
## debug en <text>#4: browser()
## debug en <text>#4: plot(density(docking[, i], na.rm = T))
```

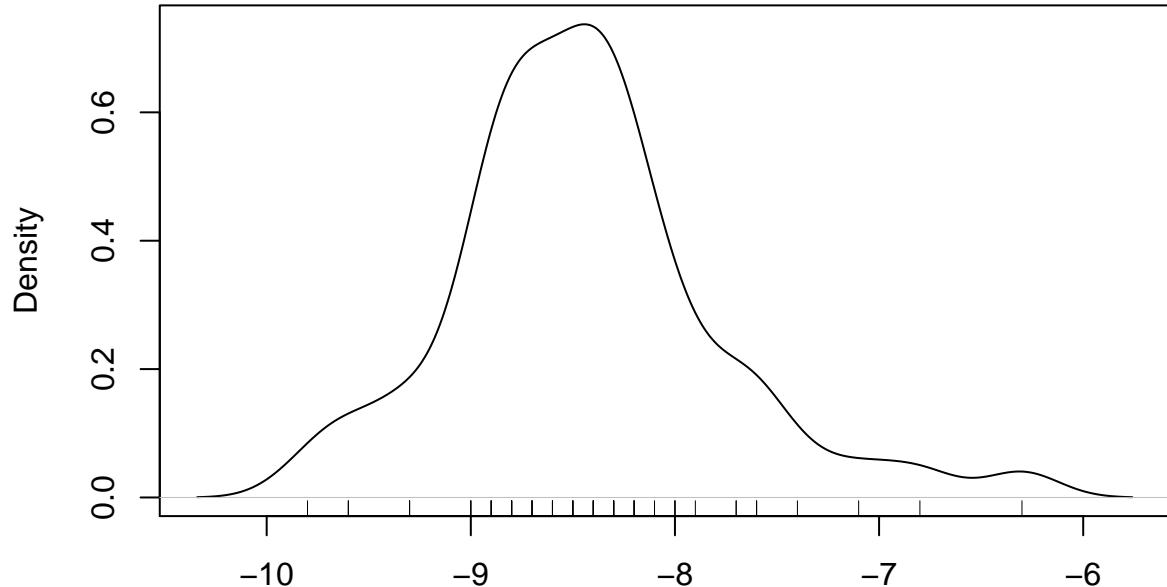
```
density.default(x = docking[, i], na.rm = T)
```



N = 56 Bandwidth = 0.1501

```
## debug en <text>#4: rug(docking[, i])
```

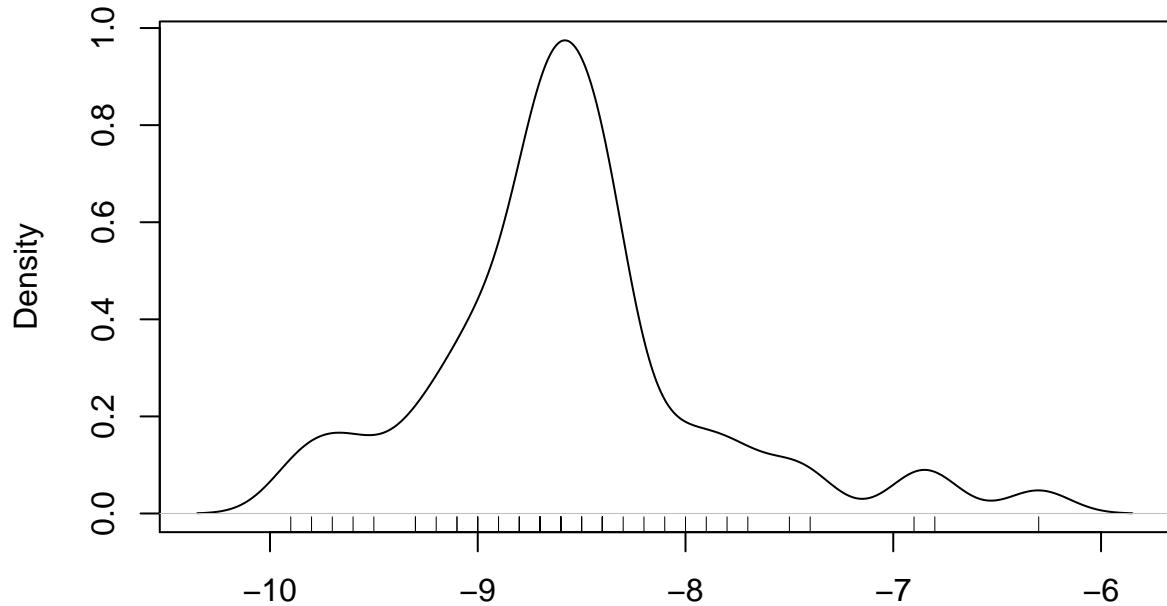
```
## debug en <text>#4: browser()
## debug en <text>#4: plot(density(docking[, i], na.rm = T))
density.default(x = docking[, i], na.rm = T)
```



N = 56 Bandwidth = 0.1802

```
## debug en <text>#4: rug(docking[, i])
## debug en <text>#4: browser()
## debug en <text>#4: plot(density(docking[, i], na.rm = T))
```

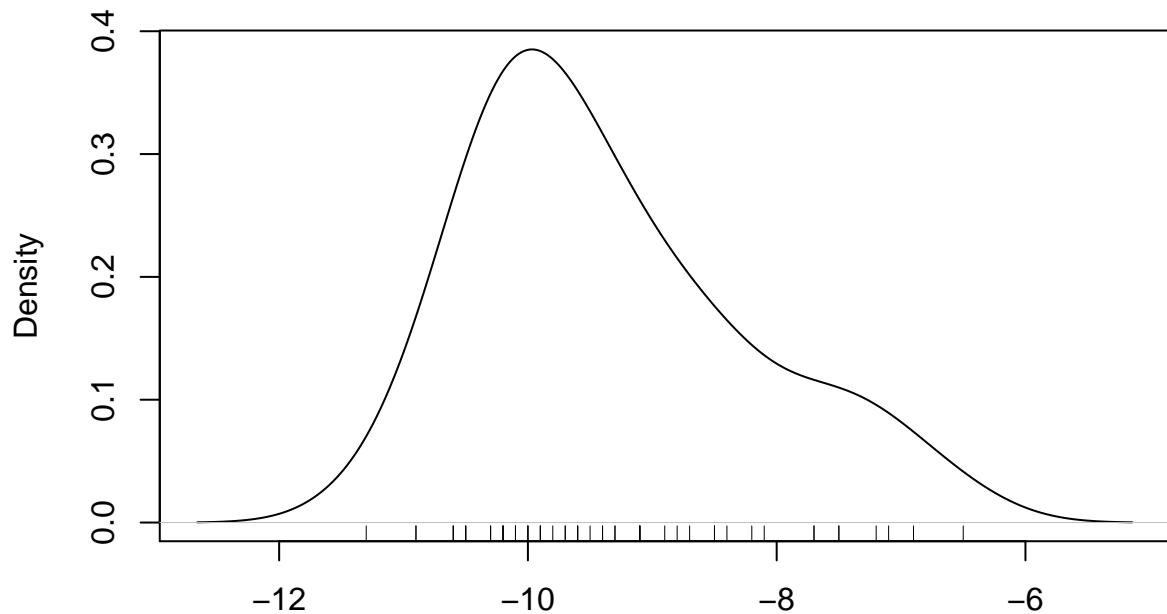
```
density.default(x = docking[, i], na.rm = T)
```



$N = 56$ Bandwidth = 0.1501

```
## debug en <text>#4: rug(docking[, i])
## debug en <text>#4: browser()
## debug en <text>#4: plot(density(docking[, i], na.rm = T))
```

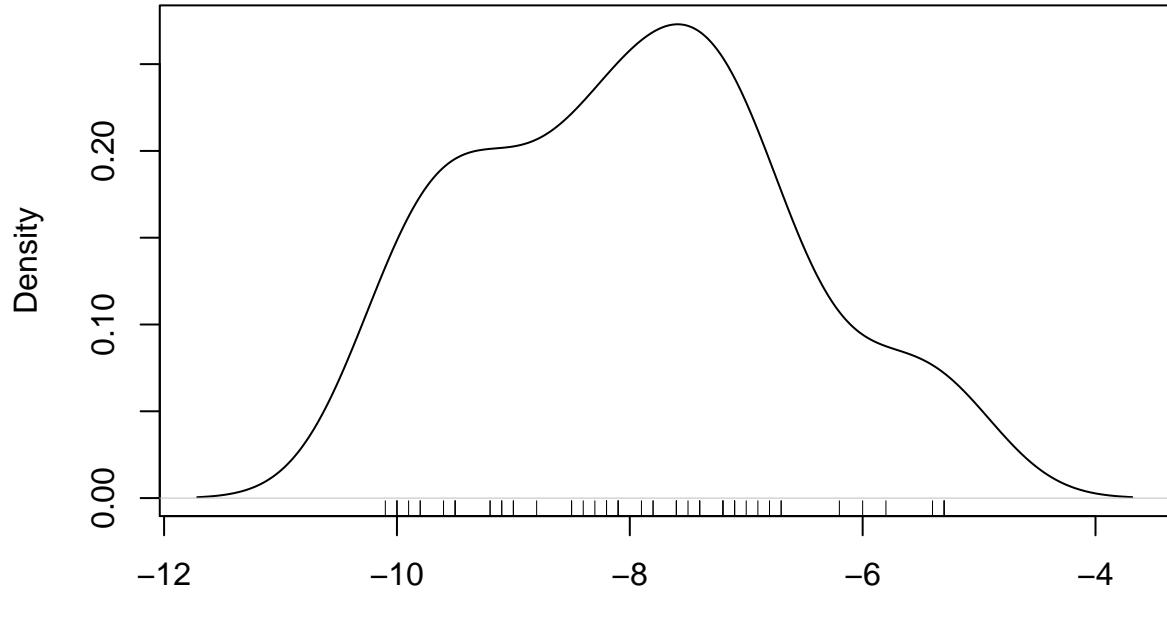
```
density.default(x = docking[, i], na.rm = T)
```



$N = 56$ Bandwidth = 0.453

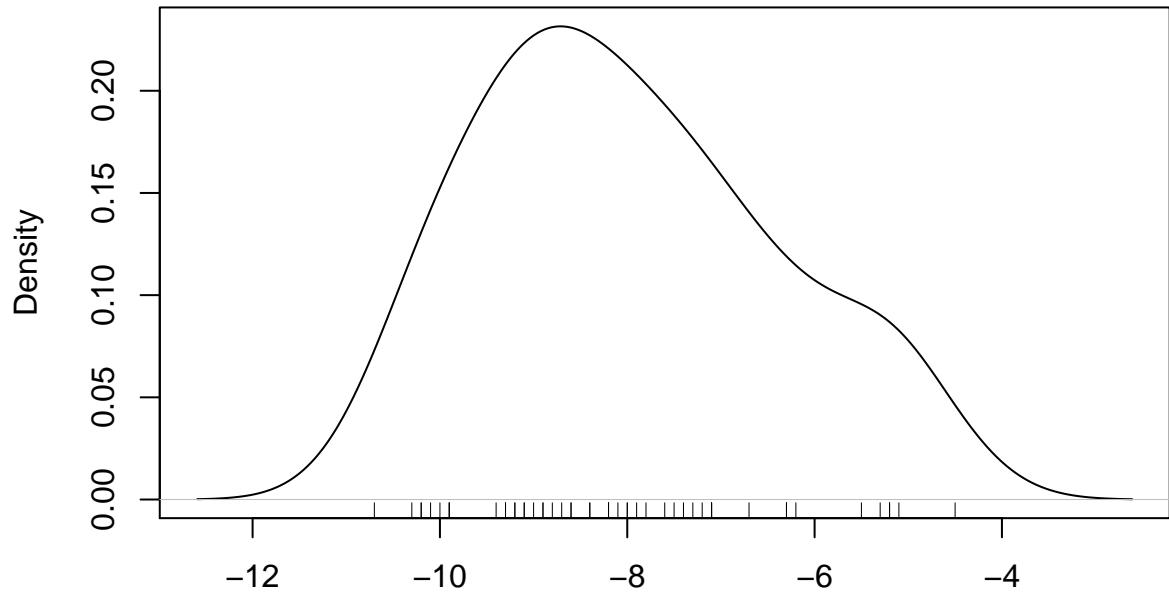
```
## debug en <text>#4: rug(docking[, i])
```

```
## debug en <text>#4: browser()
## debug en <text>#4: plot(density(docking[, i], na.rm = T))
density.default(x = docking[, i], na.rm = T)
```



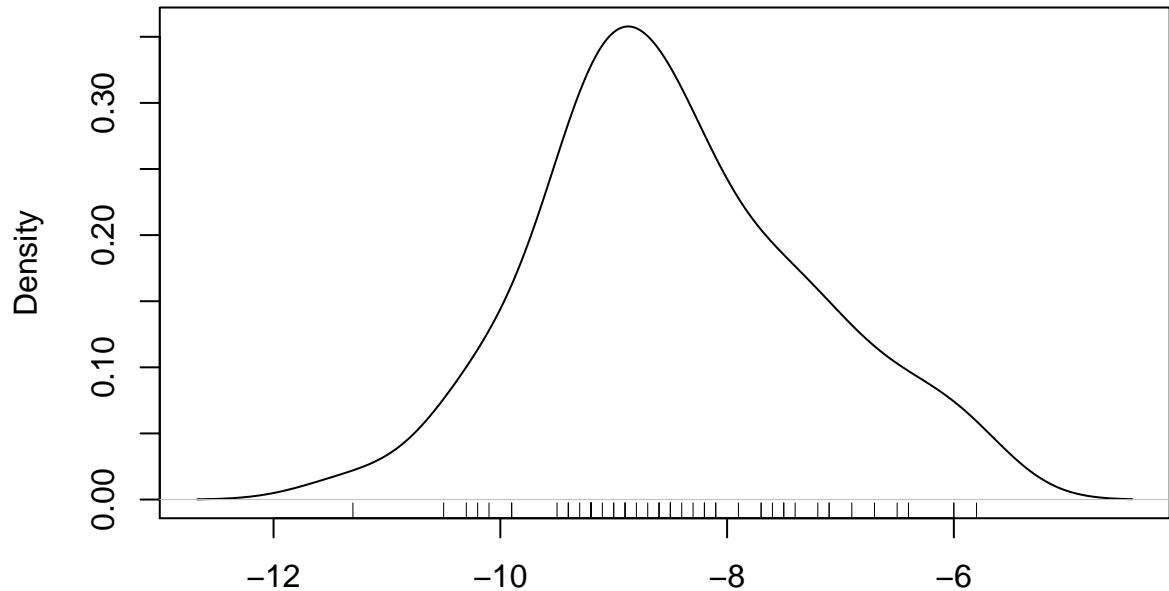
```
## debug en <text>#4: rug(docking[, i])
## debug en <text>#4: browser()
## debug en <text>#4: plot(density(docking[, i], na.rm = T))
```

```
density.default(x = docking[, i], na.rm = T)
```



N = 56 Bandwidth = 0.6305

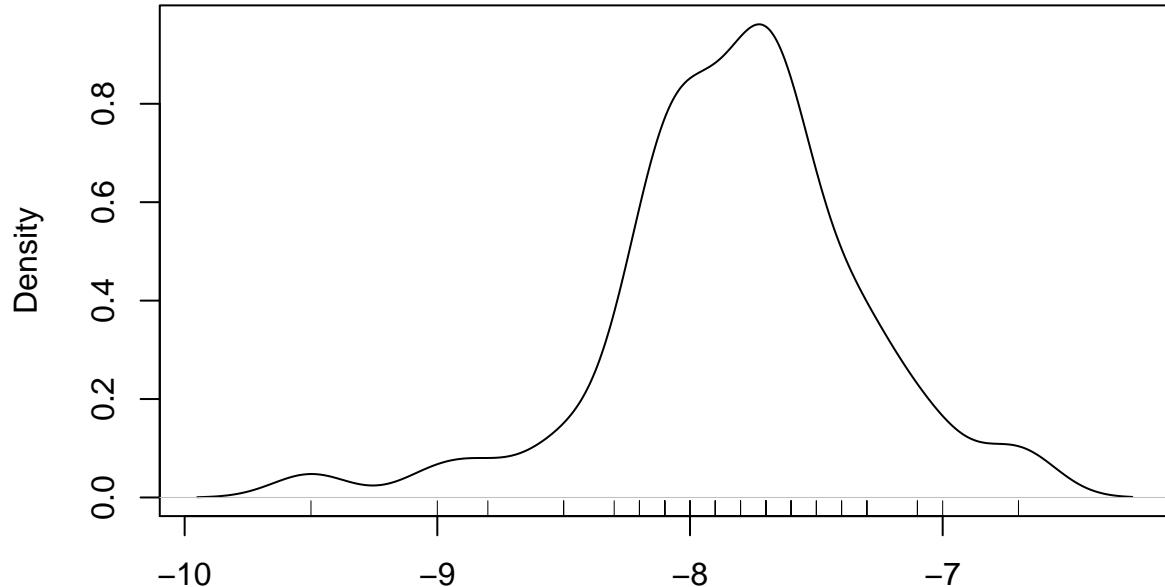
```
## debug en <text>#4: rug(docking[, i])
## debug en <text>#4: browser()
## debug en <text>#4: plot(density(docking[, i], na.rm = T))
density.default(x = docking[, i], na.rm = T)
```



N = 56 Bandwidth = 0.4579

```
## debug en <text>#4: rug(docking[, i])
```

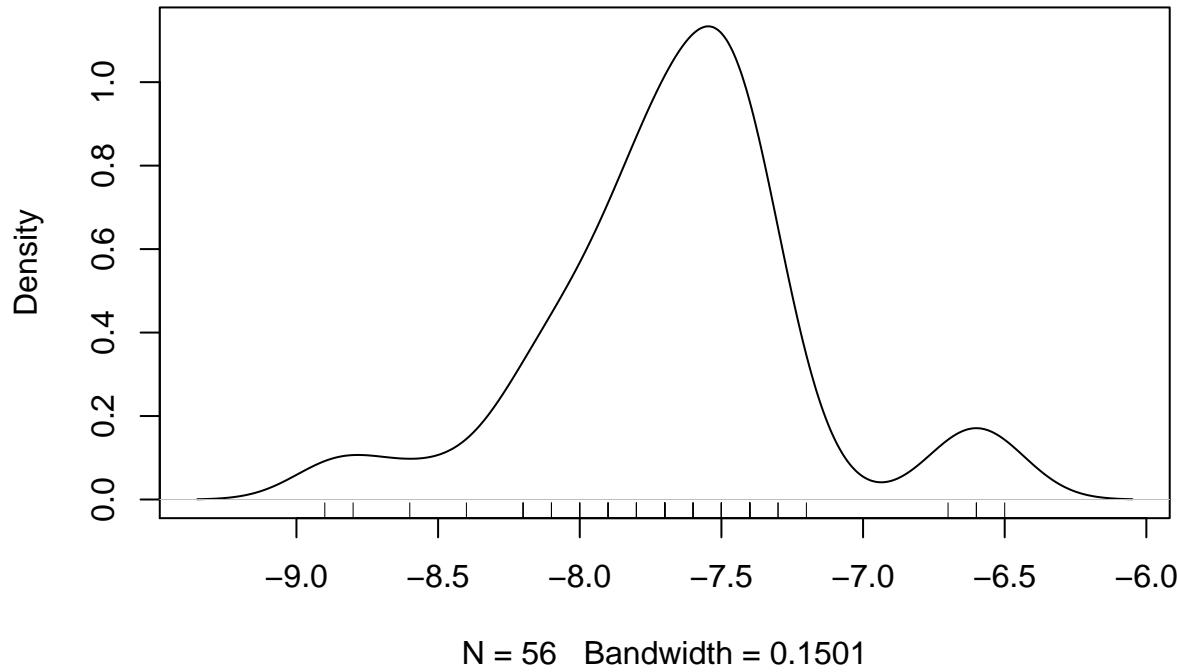
```
## debug en <text>#4: browser()
## debug en <text>#4: plot(density(docking[, i], na.rm = T))
density.default(x = docking[, i], na.rm = T)
```



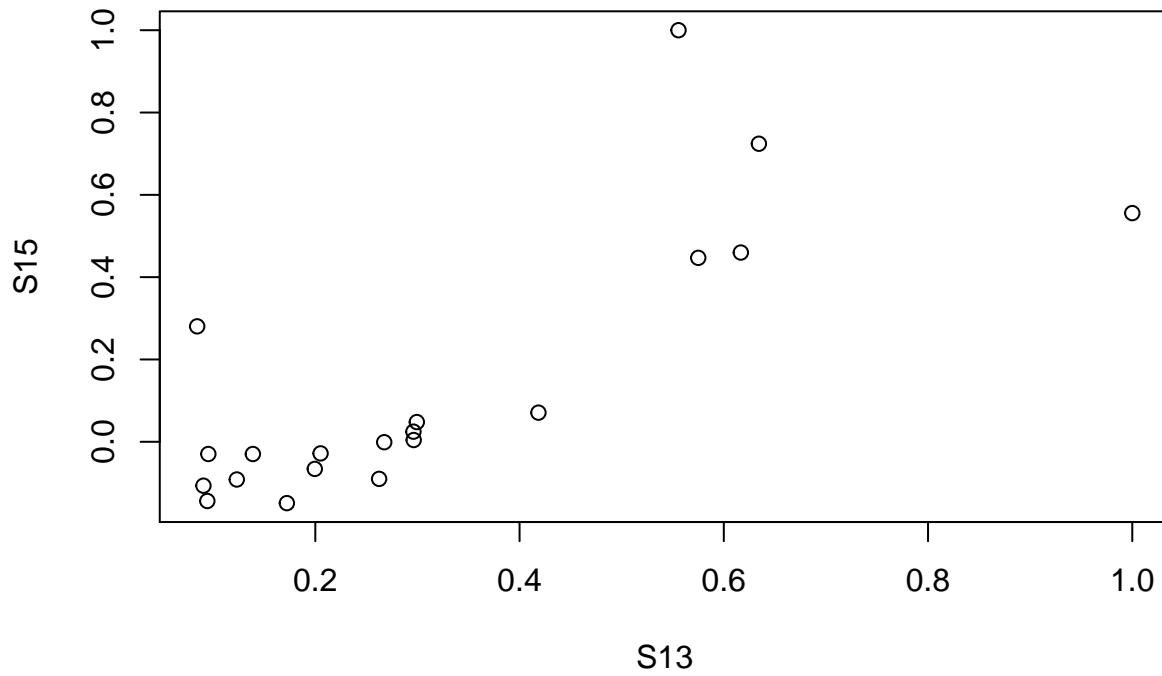
N = 56 Bandwidth = 0.1501

```
## debug en <text>#4: rug(docking[, i])
## debug en <text>#4: browser()
## debug en <text>#4: plot(density(docking[, i], na.rm = T))
```

```
density.default(x = docking[, i], na.rm = T)
```

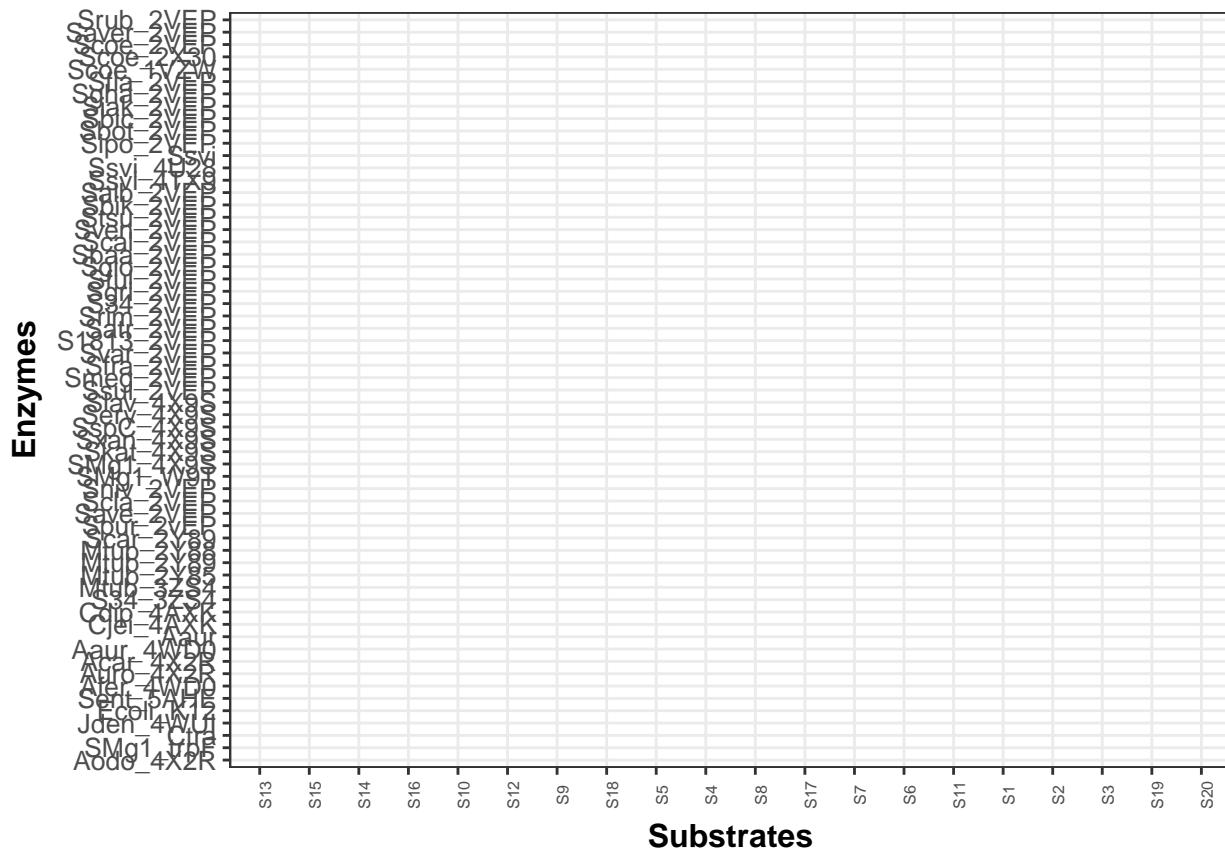


```
## debug en <text>#4: rug(docking[, i])
## debug en <text>#4: browser()
plot(cor(docking[-c(5,12,13,38,51), -1]))
```



```
## Leer sobre la incertidumbre del 2 y explicarla
## Y leer el paper de Julian y el de mauricio sobre reportes de docking
```

```
ggplot(docking.m, aes(x=variable, y=Enzima)) + labs(x = "Substrates", y = "Enzymes",text = element_text
```



GTP is the substrate with best PriA affinity

```
## boxplot de los sustratos
ggplot(docking.m, aes(x=variable, y=value)) + labs(x = "Substrates", y = "Affinity",text = element_text
## Warning: Removed 100 rows containing non-finite values (stat_boxplot).
```

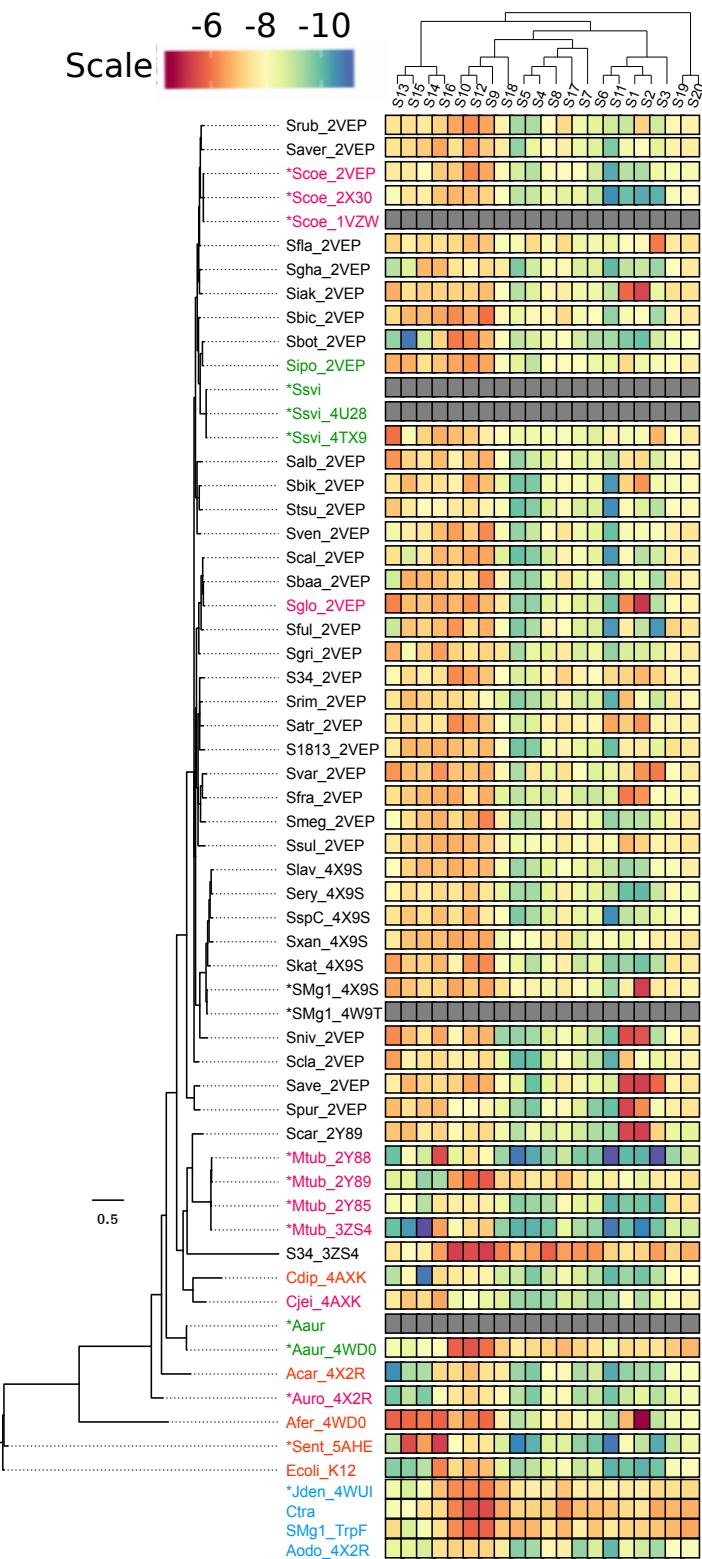


Figure 6: Heatplot docking PriA enzyme Family vs substrates
26

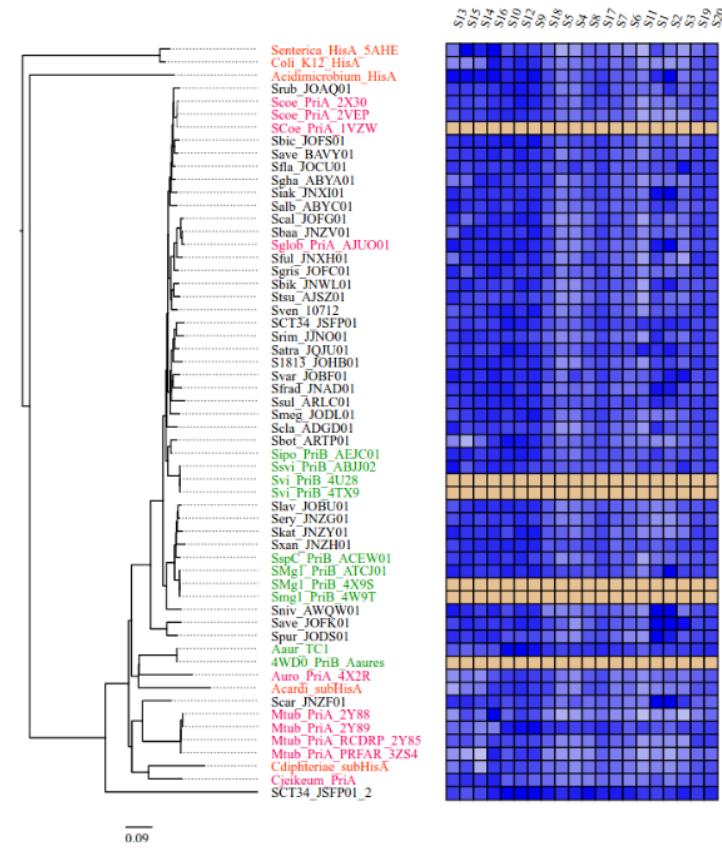
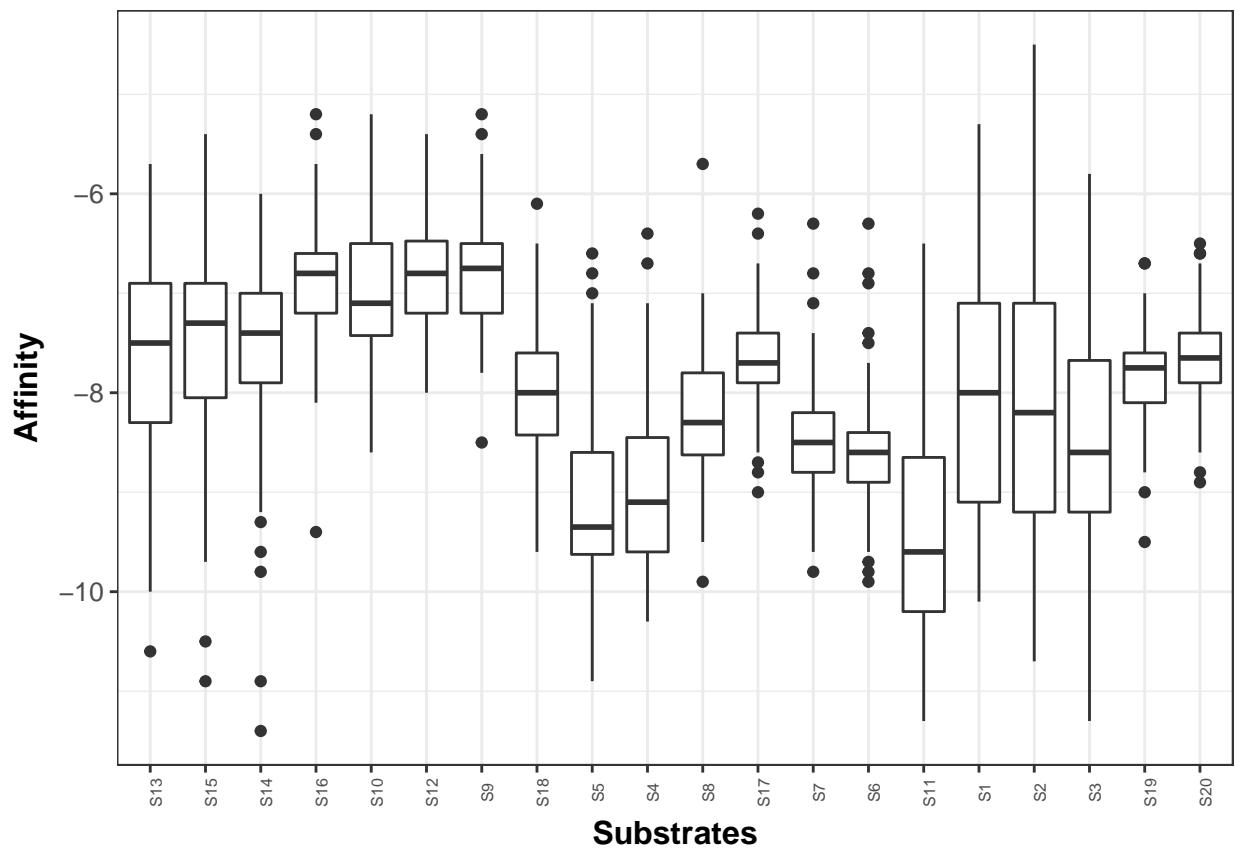


Figure 7: Heat Plot PriA Streptomyces vs other substrates



PriA Activity on GTP

Activity was measured fluorometrically in 96-well plates (Nuc 96-Well Optical Botto Plates) in a TECAN infinite M1000 plate reader (excitation at 286 nm and emission at 386 nm)

Preliminary activity assays were performed on an active PriA from *Streptomyces coelicolor* and an inactive mutant D11A.

Enzymes were cloned on coli V68 strains, overexpression were induced and protein were purified.

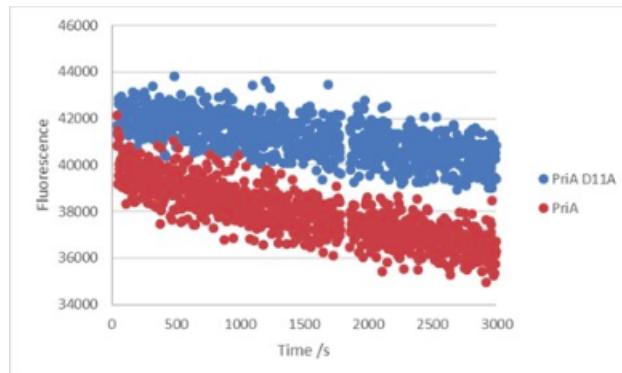


Figure 8: Scoe and non functional Scoe PriA acting on dGTP

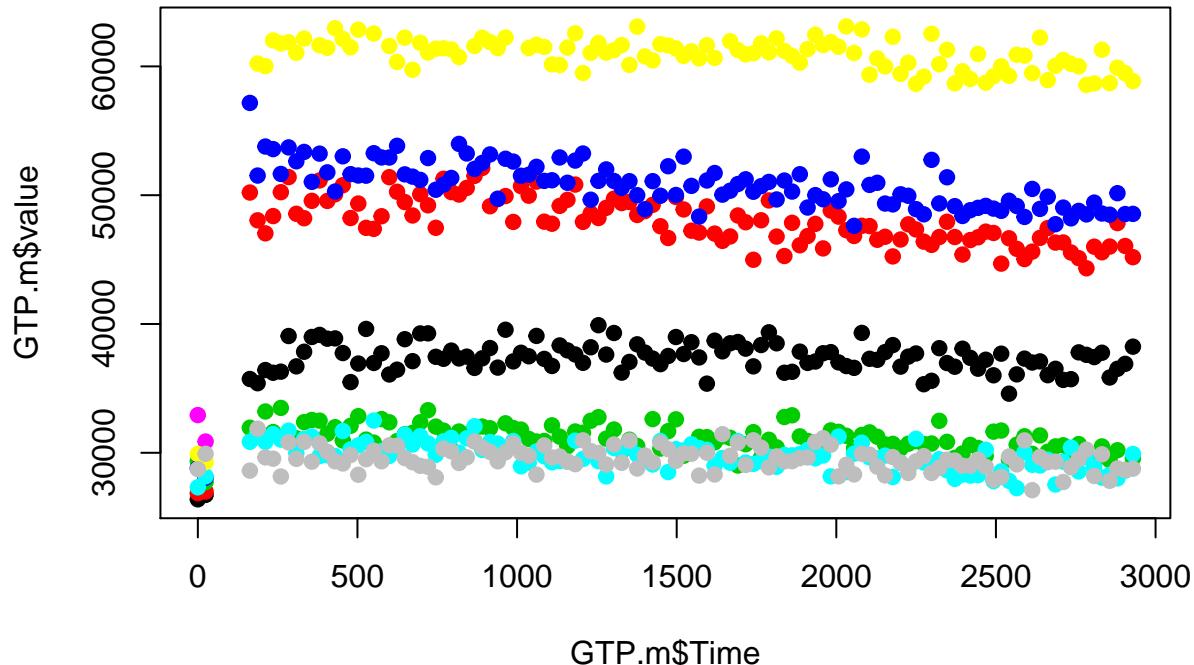
```

GTP <- read.table("chapter4/GTP.activity", header=TRUE, sep="\t")
dGTP <- read.table("chapter4/dGTP.activity", header=TRUE, sep="\t")
GTP.m <- melt(GTP,id="Time")

plot(GTP.m$Time, GTP.m$value, col=GTP.m$variable, pch=19)

```

Warning in xy.coords(x, y, xlabel, ylabel, log): NAs introducidos por
coerción



```

plot.new()
legend("center", legend = unique(GTP.m$variable), col = unique(GTP.m$variable), pch=19)

```

- AMg1
- Ssvi
- Jden
- Tcur
- Sros
- Smeg
- SspC
- Buffer

```

ggplot(GTP.m, aes(x=Time, y=value,color=variable)) + geom_point() + facet_wrap(~ variable) + geom_smooth()

## `geom_smooth()` using method = 'loess'
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : span too small. fewer data values than degrees of freedom.
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : at 227.79
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =

```

```

## parametric, : radius 64.12
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : all data on boundary of neighborhood. make span bigger
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : pseudoinverse used at 227.79
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : neighborhood radius 8.0075
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : reciprocal condition number 1
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : at 1845.3
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : radius 64.12
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : all data on boundary of neighborhood. make span bigger
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : There are other near singularities as well. 64.12
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : zero-width neighborhood. make span bigger
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : zero-width neighborhood. make span bigger
## Warning: Computation failed in `stat_smooth()`:
## NA/NaN/Inf en llamada a una función externa (arg 5)
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : span too small. fewer data values than degrees of freedom.
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : at 474.62
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : radius 15.07
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : all data on boundary of neighborhood. make span bigger
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : pseudoinverse used at 474.62
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : neighborhood radius 3.882
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : reciprocal condition number 1
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : at 1258.8
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : radius 15.07
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : all data on boundary of neighborhood. make span bigger

```

```

## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : There are other near singularities as well. 15.07
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : zero-width neighborhood. make span bigger
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : zero-width neighborhood. make span bigger
## Warning: Computation failed in `stat_smooth()`:
## NA/NaN/Inf en llamada a una función externa (arg 5)
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : span too small. fewer data values than degrees of freedom.
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : at 859.79
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : radius 47.817
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : all data on boundary of neighborhood. make span bigger
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : pseudoinverse used at 859.79
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : neighborhood radius 6.915
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : reciprocal condition number 1
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : at 2256.6
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : radius 47.817
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : all data on boundary of neighborhood. make span bigger
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : There are other near singularities as well. 47.817
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : zero-width neighborhood. make span bigger
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : zero-width neighborhood. make span bigger
## Warning: Computation failed in `stat_smooth()`:
## NA/NaN/Inf en llamada a una función externa (arg 5)
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : span too small. fewer data values than degrees of freedom.
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : at 1084.3
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : radius 0.7208

```

```

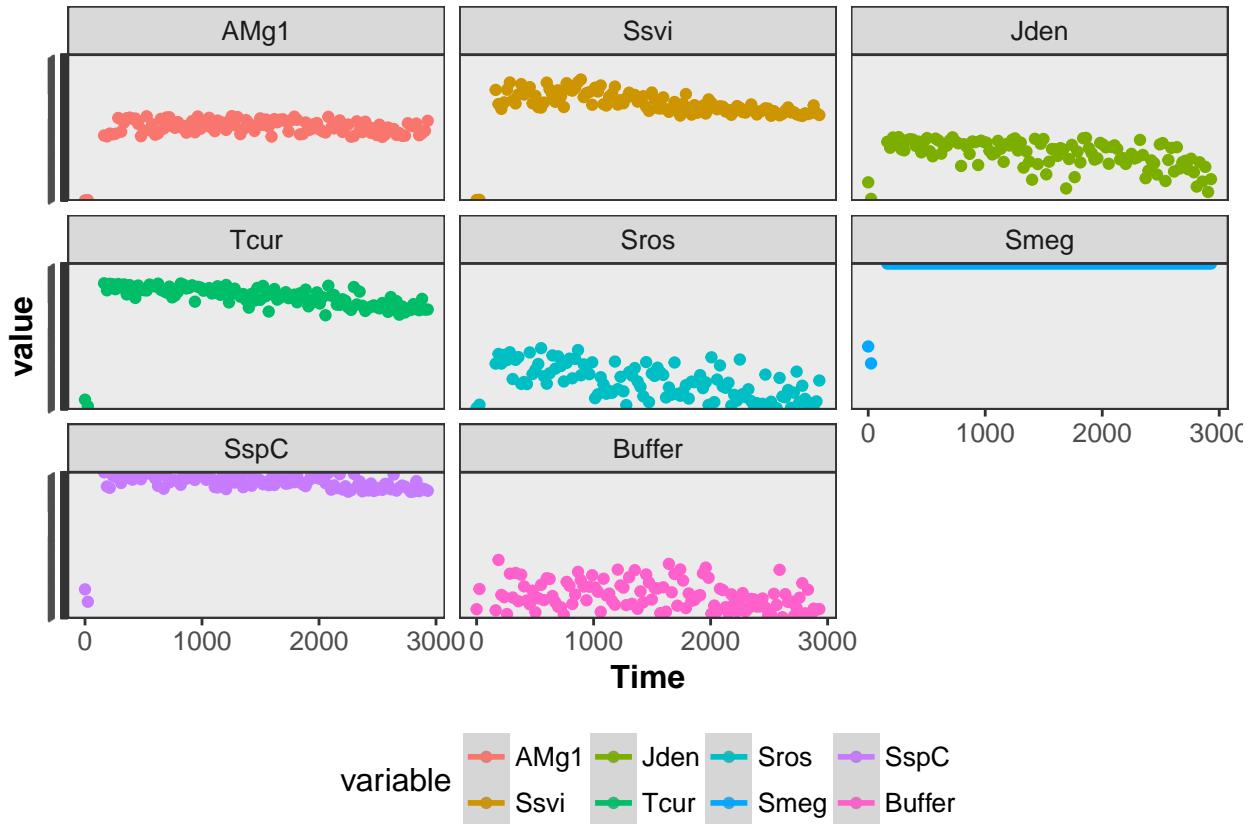
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : all data on boundary of neighborhood. make span bigger
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : pseudoinverse used at 1084.3
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : neighborhood radius 0.849
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : reciprocal condition number 1
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : at 1255.7
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : radius 0.7208
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : all data on boundary of neighborhood. make span bigger
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : There are other near singularities as well. 0.7208
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : zero-width neighborhood. make span bigger
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : zero-width neighborhood. make span bigger
## Warning: Computation failed in `stat_smooth()`:
## NA/NaN/Inf en llamada a una función externa (arg 5)
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : span too small. fewer data values than degrees of freedom.
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : at 1470.5
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : radius 7.7869
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : all data on boundary of neighborhood. make span bigger
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : pseudoinverse used at 1470.5
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : neighborhood radius 2.7905
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : reciprocal condition number 1
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : at 2034.2
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : radius 7.7869
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : all data on boundary of neighborhood. make span bigger

```

```

## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : There are other near singularities as well. 7.7869
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : zero-width neighborhood. make span bigger
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : zero-width neighborhood. make span bigger
## Warning: Computation failed in `stat_smooth()`:
## NA/NaN/Inf en llamada a una función externa (arg 5)
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : span too small. fewer data values than degrees of freedom.
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : at 2612.2
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : radius 2.1199
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : all data on boundary of neighborhood. make span bigger
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : pseudoinverse used at 2612.2
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : neighborhood radius 1.456
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : reciprocal condition number 1
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : at 2906.4
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : radius 2.1199
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : all data on boundary of neighborhood. make span bigger
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : There are other near singularities as well. 2.1199
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : zero-width neighborhood. make span bigger
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : zero-width neighborhood. make span bigger
## Warning: Computation failed in `stat_smooth()`:
## NA/NaN/Inf en llamada a una función externa (arg 5)

```



```
ggplot(GTP.m, aes(x=Time, y=value,color=variable)) + geom_point() + geom_smooth() + theme_bw() + theme(plot.title = element_text(size = 12, face = "bold"))

## `geom_smooth()` using method = 'loess'

## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : span too small. fewer data values than degrees of freedom.

## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : at 1470.5

## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : radius 7.7869

## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : all data on boundary of neighborhood. make span bigger

## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : pseudoinverse used at 1470.5

## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : neighborhood radius 2.7905

## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : reciprocal condition number 1

## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : at 2034.2

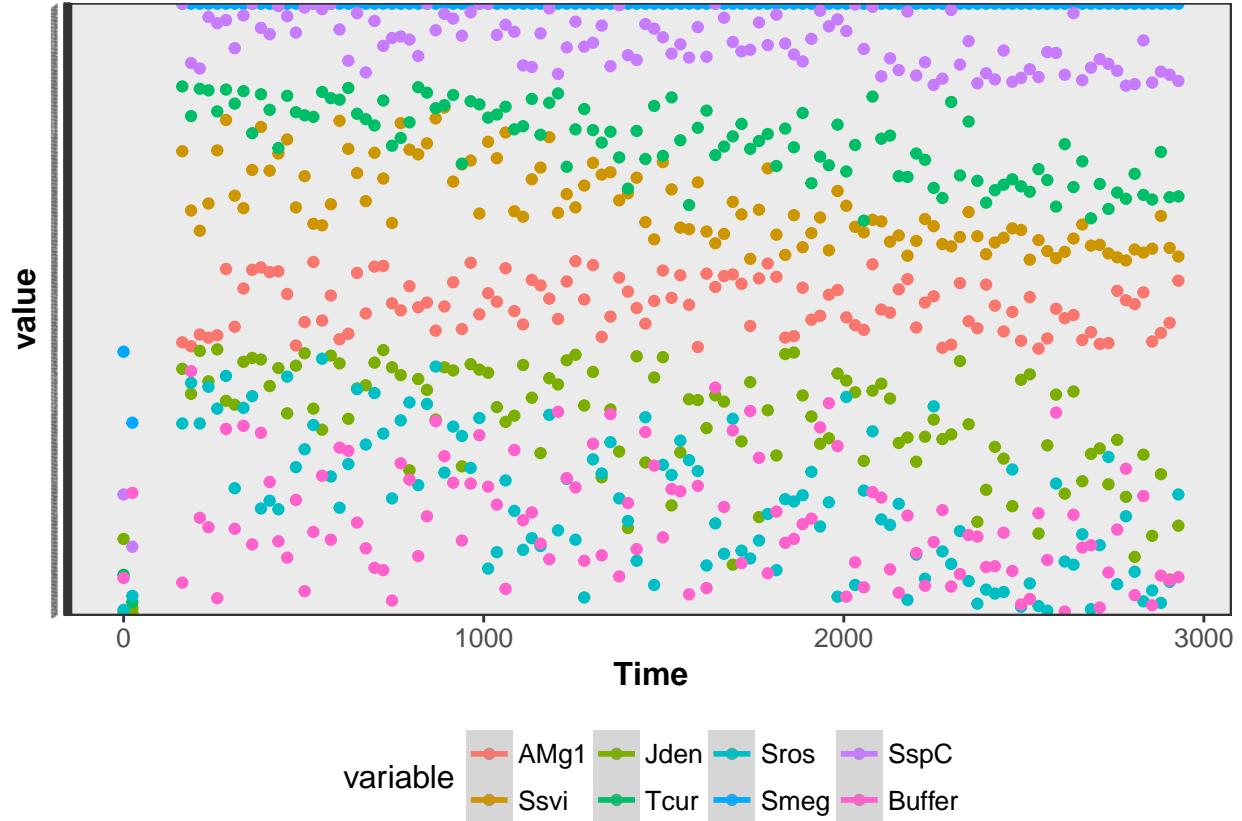
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : radius 7.7869

## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : all data on boundary of neighborhood. make span bigger
```

```

## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : There are other near singularities as well. 7.7869
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : zero-width neighborhood. make span bigger
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric =
## parametric, : zero-width neighborhood. make span bigger
## Warning: Computation failed in `stat_smooth()`:
## NA/NaN/Inf en llamada a una función externa (arg 5)

```



the two enzymes with activity

Thermomonospora curvata thermophilic Actinobacteria from Thermomonosporaceae genus, it can be found in compost and participate in the active degradation of cellulose [@chertkov_complete_2011].

Jonesia trpF shows no activity *Jonesia denitrificans* is classified as a pathogenic organism for animals, reported genome was originally isolated from cooked ox blood [@pukall_complete_2009].

```

docking <- read.csv("chapter4/SmallHeat.data", header=TRUE, sep="\t")
kable(docking, caption = "Enzymes docking \\label{tab:docking}", caption.short = "Enzymes docking ")

```

Table 3: Enzymes docking

Enzima	S13	S15	S14	S16	S10	S12	S9	S18	S5	S4	S8	S17	S7	S6	S11	S1
Srub_2VEP	-7.4	-7.3	-7.5	-7.1	-6.5	-6.2	-6.5	-7.7	-9.4	-9.3	-7.9	-7.2	-8.3	-8.6	-8.9	-9.0
Saver_2VEP	-7.4	-7.2	-7.0	-6.5	-7.3	-6.4	-7.0	-7.5	-9.6	-8.5	-7.9	-7.6	-8.4	-8.7	-9.8	-8.3
Scoe_2VEP	-7.5	-7.5	-7.9	-7.0	-7.0	-6.2	-6.5	-7.8	-8.8	-9.2	-7.8	-7.9	-8.0	-8.9	-10.3	-9.2
Scoe_2X30	-8.1	-7.4	-7.6	-6.9	-6.7	-6.8	-7.1	-7.9	-9.1	-9.0	-8.3	-8.6	-8.5	-9.0	-10.6	-10.0
Scoe_1VZW	NA	NA														

Enzima	S13	S15	S14	S16	S10	S12	S9	S18	S5	S4	S8	S17	S7	S6	S11	S1
Sfla_2VEP	-7.1	-7.6	-7.2	-7.3	-7.2	-6.8	-6.9	-8.1	-8.2	-7.2	-8.2	-7.2	-8.4	-8.3	-8.5	-7.9
Sgha_2VEP	-9.2	-8.7	-6.7	-6.7	-7.4	-7.7	-7.2	-7.5	-9.8	-8.9	-8.2	-7.8	-8.8	-8.7	-10.1	-9.1
Siak_2VEP	-6.6	-7.3	-7.0	-7.1	-7.1	-7.1	-6.8	-8.0	-9.2	-8.7	-7.8	-7.6	-8.3	-8.4	-9.1	-5.8
Sbic_2VEP	-7.2	-6.7	-6.8	-6.5	-6.2	-6.6	-5.9	-7.8	-8.5	-7.8	-7.8	-7.2	-8.2	-8.0	-9.6	-8.2
Sbot_2VEP	-9.6	-10.9	-8.9	-7.1	-6.0	-6.2	-6.7	-8.1	-9.1	-8.8	-8.3	-7.9	-8.9	-9.3	-9.4	-9.8
Sipo_2VEP	-6.6	-6.6	-7.3	-6.9	-6.5	-6.3	-6.5	-8.1	-8.6	-9.1	-8.0	-7.9	-8.0	-8.4	-8.5	-7.2
Ssvi	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Ssvi_4U28	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Ssvi_4TX9	-5.9	-8.2	-7.1	-6.6	-6.8	-7.0	-7.6	-7.9	-8.4	-8.3	-8.2	-8.1	-8.4	-8.7	-7.7	-8.2
Salb_2VEP	-6.3	-7.1	-7.4	-6.8	-7.7	-6.9	-6.6	-8.0	-9.6	-8.9	-8.6	-7.9	-8.6	-8.4	-9.1	-7.4
Sbk_2VEP	-7.4	-6.7	-7.4	-7.3	-7.7	-6.5	-6.8	-8.5	-9.9	-9.8	-8.3	-7.8	-8.2	-8.4	-10.5	-7.1
Stsu_2VEP	-6.9	-7.5	-7.9	-7.8	-7.5	-7.3	-7.7	-8.1	-10.0	-9.7	-8.7	-7.8	-8.8	-8.8	-10.6	-7.8
Sven_2VEP	-8.3	-7.6	-7.5	-6.8	-6.4	-7.0	-6.2	-8.2	-9.6	-9.0	-7.9	-7.4	-8.3	-8.6	-10.0	-8.2
Scal_2VEP	-7.3	-8.8	-7.5	-6.7	-7.0	-6.5	-6.5	-8.7	-10.0	-9.7	-8.8	-7.7	-8.2	-8.6	-10.5	-8.1
Sbaa_2VEP	-8.9	-6.6	-6.7	-6.8	-7.2	-7.2	-6.2	-7.7	-9.6	-9.5	-8.4	-7.4	-8.5	-8.2	-9.7	-8.5
Sglo_2VEP	-6.1	-6.8	-6.9	-6.5	-6.7	-6.3	-6.7	-7.5	-9.6	-9.6	-8.6	-7.8	-8.7	-8.7	-9.9	-6.2
Sful_2VEP	-9.0	-6.9	-7.1	-6.8	-6.3	-7.2	-6.6	-8.1	-9.8	-9.3	-7.7	-8.0	-8.7	-8.8	-10.5	-7.6
Sgri_2VEP	-6.6	-8.2	-7.1	-6.4	-7.1	-7.4	-7.1	-7.4	-9.4	-8.5	-8.6	-7.5	-8.8	-8.4	-9.6	-8.8
S34_2VEP	-7.8	-7.2	-7.6	-7.3	-6.2	-6.5	-6.9	-8.0	-8.8	-8.6	-7.7	-7.1	-7.7	-7.9	-7.2	-7.1
Srim_2VEP	-7.4	-6.8	-7.1	-7.2	-7.2	-7.4	-7.8	-8.6	-9.7	-9.3	-8.8	-7.7	-8.9	-8.7	-10.2	-6.8
Satr_2VEP	-7.6	-7.1	-7.5	-7.4	-6.2	-6.5	-6.9	-8.0	-8.9	-8.7	-7.7	-7.4	-7.7	-7.8	-6.5	-7.0
S1813_2VEP	-7.5	-6.7	-6.8	-6.6	-6.8	-7.0	-6.7	-7.9	-9.9	-9.7	-8.3	-7.7	-8.5	-8.6	-10.0	-7.6
Svar_2VEP	-6.3	-6.8	-7.0	-6.3	-6.9	-6.9	-6.6	-7.8	-9.3	-7.4	-8.5	-7.3	-8.0	-8.7	-8.5	-7.4
Sfra_2VEP	-7.3	-7.0	-6.8	-6.6	-6.5	-7.3	-6.6	-8.6	-9.1	-8.7	-8.9	-7.7	-8.9	-9.0	-8.7	-6.0
Smeg_2VEP	-8.0	-7.3	-6.9	-6.6	-7.2	-6.7	-6.1	-7.6	-9.2	-9.1	-7.8	-7.4	-8.2	-8.5	-9.6	-9.2
Ssul_2VEP	-7.5	-7.0	-6.9	-6.6	-6.6	-6.7	-6.9	-7.7	-8.4	-8.2	-8.2	-7.5	-8.1	-7.7	-8.2	-6.7
Slav_4X9S	-8.0	-7.1	-6.7	-6.9	-6.6	-6.8	-6.7	-8.2	-9.5	-9.1	-8.6	-8.0	-8.4	-8.7	-9.1	-9.5
Sery_4X9S	-7.8	-7.2	-7.6	-7.2	-7.4	-6.9	-7.4	-8.5	-9.4	-9.4	-8.6	-7.6	-8.4	-8.6	-9.1	-10.0
SspC_4X9S	-7.4	-6.9	-7.3	-6.8	-7.3	-6.6	-7.5	-8.0	-9.8	-9.3	-8.7	-7.6	-8.5	-8.4	-10.6	-9.1
Sxan_4X9S	-7.5	-6.9	-6.8	-6.8	-6.5	-6.6	-6.5	-8.3	-8.0	-8.1	-7.6	-7.4	-8.7	-8.1	-8.1	-8.5
Skat_4X9S	-6.4	-7.0	-7.1	-6.7	-7.7	-6.3	-6.2	-8.1	-8.5	-9.2	-8.3	-7.6	-9.0	-8.5	-9.7	-9.5
SMg1_4X9S	-6.5	-6.9	-7.2	-7.1	-6.5	-6.9	-6.4	-7.3	-7.8	-7.7	-8.3	-7.5	-7.9	-8.4	-9.5	-7.6
SMg1_W9T	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sniv_2VEP	-6.2	-6.8	-7.4	-6.5	-7.8	-6.8	-6.7	-9.5	-9.6	-9.4	-8.7	-8.2	-8.6	-9.1	-9.9	-5.4
Scla_2VEP	-6.4	-7.7	-7.4	-7.2	-7.6	-7.5	-7.2	-8.5	-10.1	-10.0	-8.7	-7.9	-8.8	-9.1	-10.2	-6.9
Save_2VEP	-7.6	-6.7	-7.1	-7.2	-7.1	-6.5	-6.6	-7.8	-8.6	-10.0	-8.6	-7.5	-8.3	-8.5	-8.8	-5.3
Spur_2vEP	-6.8	-7.3	-6.9	-6.7	-8.0	-7.9	-7.7	-8.5	-9.5	-9.8	-8.1	-7.8	-8.7	-9.7	-10.0	-5.3
Scar_2Y89	-6.9	-6.8	-7.5	-7.1	-7.8	-7.3	-7.2	-8.3	-9.2	-8.3	-8.9	-8.4	-8.9	-9.3	-9.4	-5.3
Mtub_2Y88	-10.0	-7.8	-8.9	-5.4	-8.6	-7.3	-7.8	-9.5	-10.9	-10.3	-9.5	-9.0	-9.8	-9.8	-11.3	-10.1
Mtub_2Y89	-8.7	-8.6	-9.6	-9.4	-6.4	-5.9	-5.6	-7.1	-7.0	-7.5	-7.3	-6.8	-7.4	-8.4	-7.5	-8.1
Mtub_2Y85	-8.2	-7.9	-9.2	-7.4	-7.6	-7.5	-7.6	-8.4	-9.7	-9.5	-9.3	-7.8	-8.6	-8.6	-10.2	-9.8
Mtub_3ZS4	-10.0	-10.5	-11.4	-6.4	-8.2	-7.2	-7.0	-9.6	-10.2	-10.2	-9.9	-8.5	-9.3	-9.6	-10.9	-10.0
S34_3ZS4	-7.4	-8.0	-7.6	-6.4	-5.2	-5.4	-5.2	-6.1	-6.8	-6.4	-5.7	-6.4	-6.3	-6.3	-7.1	-7.4
Cdip_4AXK	-9.2	-7.8	-10.9	-7.2	-7.5	-7.6	-7.7	-8.9	-9.0	-9.8	-9.0	-8.3	-8.8	-9.2	-10.1	-9.5
Cjei_4AXK	-7.5	-6.9	-7.2	-6.5	-8.4	-8.0	-8.5	-8.7	-9.5	-9.6	-9.4	-8.8	-9.0	-9.5	-9.3	-8.1
Aaur	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Aaur_4WD0	-8.2	-8.5	-8.1	-7.9	-5.7	-5.5	-5.9	-7.0	-7.5	-7.2	-7.1	-6.7	-7.1	-7.4	-8.4	-7.2
Acar_4X2R	-10.6	-9.3	-9.3	-7.2	-7.2	-6.8	-7.3	-7.5	-9.5	-9.8	-8.0	-7.8	-9.3	-8.9	-10.3	-9.6
Auro_4X2R	-9.9	-9.1	-9.8	-8.1	-7.4	-7.1	-7.4	-7.8	-9.2	-9.8	-8.3	-7.8	-9.3	-9.0	-9.9	-9.0
Afer_4WD0	-5.7	-5.8	-6.0	-5.7	-6.7	-6.2	-5.8	-7.6	-9.2	-8.8	-7.8	-7.4	-8.3	-8.4	-9.3	-6.7
Sent_5AHE	-9.1	-5.4	-6.4	-5.2	-8.0	-7.3	-7.4	-8.8	-10.7	-10.2	-8.7	-8.7	-9.6	-9.9	-10.9	-7.8
Ecoli_K12	-9.7	-9.7	-9.2	-6.1	-7.2	-6.6	-6.8	-8.6	-9.5	-9.1	-8.6	-8.2	-9.0	-8.6	-10.2	-9.9

Enzima	S13	S15	S14	S16	S10	S12	S9	S18	S5	S4	S8	S17	S7	S6	S11	S1
Jden_4WUI	-8.3	-8.8	-8.2	-6.8	-6.2	-6.1	-6.0	-6.8	-7.4	-7.6	-7.5	-6.9	-7.6	-7.5	-7.7	-7.5
Ctra	-8.2	-8.0	-7.4	-7.2	-6.1	-5.5	-5.4	-6.5	-7.1	-7.1	-7.0	-6.2	-6.8	-6.8	-6.9	-7.2
SMg1_trpF	-7.2	-8.8	-8.2	-7.3	-6.2	-5.7	-5.7	-6.9	-6.6	-6.7	-7.3	-6.7	-7.6	-6.9	-7.5	-7.1
Aodo_4X2R	-8.5	-8.6	-8.8	-7.3	-7.1	-7.1	-7.1	-7.5	-9.7	-9.4	-7.8	-7.6	-9.6	-8.8	-10.1	-8.4

Enzima	S13	S15	S14	S16	S10	S12	S9	S18	S5	S4	S8	S17	S7	S6	S11	S1
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Molecular dynamics vs experimental data

PriA activity on S3 (PRA)

organism	Family	K_M	k_{cat}	$\frac{k_{cat}}{K_M}$	Pre MD	Pos MD	Reference
Afer	HisA	1.1 ± 0.2	0.05 ± 0.001	0.045	-10.1	-12.3	Noda-García L et al 2015
Ecoli	HisA	1.6	4.9	3.1	-9.9	-16	Henn-Sax et al. (2002)
Sent	HisA	17.0 ± 0.1	7.8 ± 2.4	4.5×10^5	-10.3	-20.1	Söderholm A et al (2015)
Aaur	PriB	2.1 ± 0.5	1.8 ± 0.2	0.9	-7.4		verduzco-castro 2016
Sipo	PriB	3.8 ± 0.2	0.82 ± 0.02	0.21	-8.2	-14.7	verduzco-castro 2016
SspC	PriB	11.4 ± 3.4	2.53 ± 0.74	0.22	-8.5	-12.7	verduzco-castro 2016
SMg1	PriB	13.2 ± 3.4	0.92 ± 0.19	0.069	-8	-15.2	verduzco-castro 2016
Ssvi	PriB	3.9 ± 0.89	0.69 ± 0.04	0.18	-8.2	-16.7	verduzco-castro 2016
Scoe	PriA	3.6 ± 0.7	1.3 ± 0.2	0.4	-8.4	-15	Noda-García et al (2010)
Sglob	PriA	4.2 ± 0.8	0.74 ± 0.03	0.18	-9.2	-16.7	verduzco-castro
Mtub 2Y85	priA	190.23	0.012 – 9.7				Due et al 2011
Mtub 3ZS4	priA	?	-9.9				Due et al 2011 (To be published)
Auro	priA	4.0 ± 0.9	0.2 ± 0.03	0.04	-9.2		Vazquez-Juarez (2016)
Cjei	PriA	2.3 ± 0.2	0.9 ± 0.08	0.39	-8.5		Noda-García et al (2013)
Cdip	subHisA	4.4 ± 0.5	2.6 ± 0.3	0.59	-9.2		Noda-García et al (2013)
SMg1 TrpF	TrpF3	-	-	-	-6.9	-9.6	verduzco-castro 2016
Jden	TrpF3	-	-	- -7.2	-9.4	16.8 ± 3.3	Verduzco-Castro E et al 2016
Acar	SubHisA	0.02					
Aodo	SubTrpF	-	-	-			

PriA activity on S7 (PROFAR) \$\$

organism	Family	K_M	k_{cat}	$\frac{k_{cat}}{K_M}$	Pre MD	Pos MD	Reference
Afer	HisA	-	-	-	-9.2	-9	Noda-García L et al. (2015)
Ecoli	HisA	-	-	-	-9	-11.1	Henn-Sax et al. (2002)
Sent	HisA	-	-	-	-9.6	-10.2	Söderholm A et al (2015)
Aaur	PriB	26.3 ± 6.3	0.37 ± 0.09	0.014	-7.1	-	verduzco-castro 2016
Sipo	PriB	60.8 ± 1.1	8.25 ± 0.4	0.14	-8	-8.5	verduzco-castro 2016
SspC	PriB	149.9 ± 29	1.4 ± 0.12	0.009	-8.5	-10.8	verduzco-castro 2016
SMg1	PriB	129.6 ± 34	0.29 ± 0.04	0.0022	-7.5	-11	verduzco-castro 2016
Ssvi	PriB	24.5 ± 4.0	1.6 ± 0.29	0.067	-8	-9.7	verduzco-castro 2016
Scoe	PriA	5.0 ± 0.08	3.4 ± 0.09	0.7	-8	-9.4	Noda-García et al (2010)
Sglob	PriA	11 ± 1.0	3.8 ± 0.2	0.34	-8.7	-9.4	verduzco-castro 2016
Mtub2Y85	priA	21	3.6	0.17	-8.6		Due et al 2011
Mtub3ZS4	priA				-9.3		Due et al 2011 (To be published)
Auro	priA	23 ± 6.5	0.5 ± 0.05	0.02	-9.3		Vazquez-Juarez (2016)
Cjei	PriA	5.1 ± 1.0	1.6 ± 0.16	0.31	-9		Noda-García et al (2013)
Cdip	subHisA	-	-	-	-8.8		Noda-García et al (2013)
SMg1 TrpF	TrpF3	8.4 ± 1.7	10.5 ± 2.4	1.25	-7.6	-9	verduzco-castro
Jden	TrpF3	16.8 ± 3.3	27 ± 1.6	1.6	-7.6	-7.7	verduzco-castro
Acar	SubHisA	Na	Na	0.02	Na	Na	Na
Aodo	SubTrpF	-	-	-	-	Na	Na

\$\$

Con actividad de FolE i.e activa para el compuesto V Adams et al (2014) Genome size vs Total antismash cluster coloured by order

Non darwinian trayectories

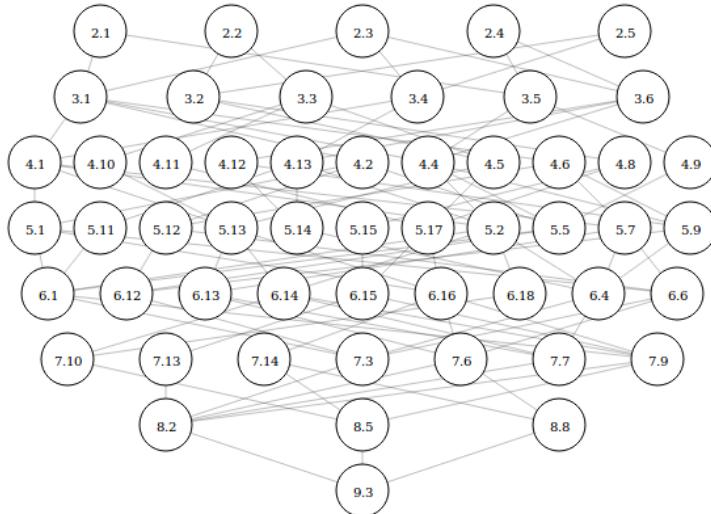


Figure 9: Non darwinian trayectories

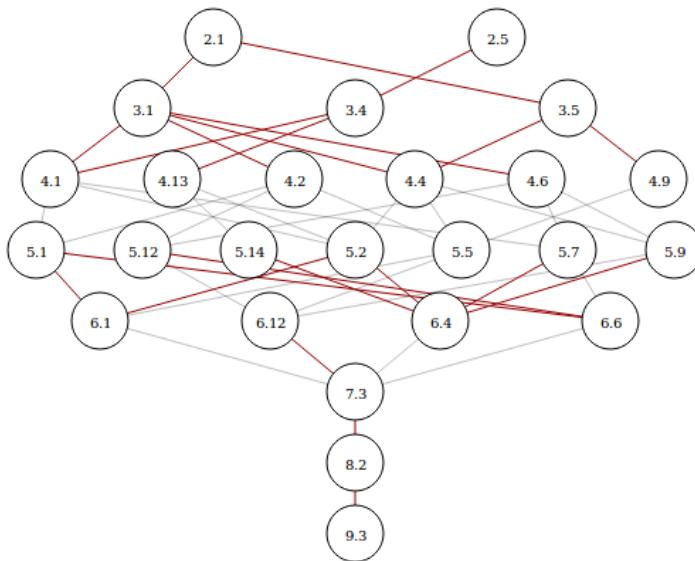


Figure 10: Positive increments on PRA

HisF Arabinosa TrpC TrpD acido antranilico PRPP gliceroles de Ana checar resistencias

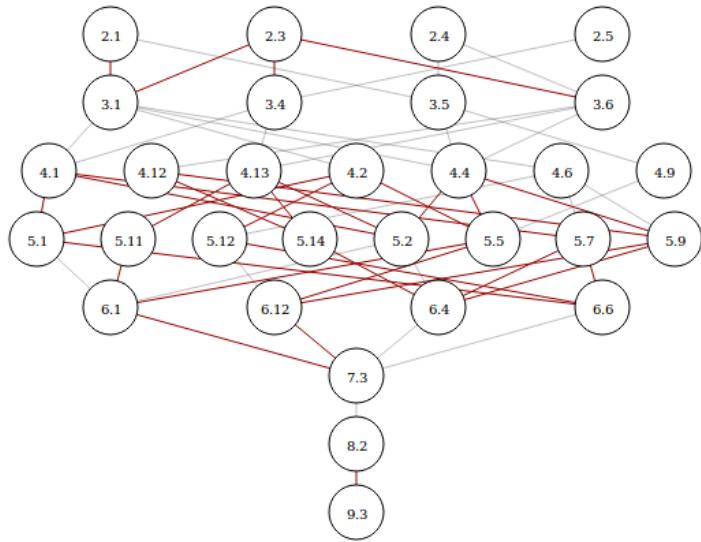


Figure 11: Positive increments on ProFAR



Figure 12: gel

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#sessionInfo()
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