EvoMining

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## EvoMining 2.0: A customizable computational pipeline for evolutionary reconstructions during genome mining

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## Abstract

Microbial natural products has importance in human health and life. Due to the abundance of genomic and metagenomic data, new natural products research by genome mining is a growing field. Traditional genome mining approaches explored bacterial genomes localizing marks of previously knwon secondary metabolism enzymes organized on biosynthetic gene clusters (BGCs). Here we present EvoMining a downloadable visual genome mining tool that incorporates evolution theory into genome mining. On EvoMining databases are customizable, its based on enzyme expansions not on BGCs. The advantage of this method is that every expanded enzyme family is a candidate to explore recruitments, and all prokatyiotic genome, even the unexplored Archaea kingdom. On this study EvoMining was applied to several database such as Cyanobacteria, Actinobacteria, Pseudomonas and Archea studying expansions for enzyme families such as TauD and other enzymes recently recruited onto secondary metabolism. Finally the genomic plasticity of Streptomyces coelicolor known BGCs i explored generlizind applying the open/Close pangenome approach to a BGCs. This Evolutionary methods open the door to discover not previously knwon chemical compounds at private genome collections and prioritize them according to their genomic plasticity.

## Introduction

Natural products are synthesized by biosynthetical gene clusters (BGCs) codified on the genome of a wide range of microorganisms. Enzymes that belong to a BGC can either be mainly restricted to secondary metabolism, or be a recent recruitment acting as accesory enzymes.  
With the genomic era and 500,000 prokaryotic genomes available at NCBI, there has been a oom of development of specilized genome mining software. Traditional approaches are based on recognize marks of enzymes devoted to secondary metabolism (**???**), or domains (**???**) lattely Evolution (**???** nadine).  
On prokaryotic genomes enzyme families are expanded frequently either by duplication or by horizontal gene transfer and that this expansions are acting as evolutionary raw material being recruited into secondary metabolism to perform nobel chemical functionalities. A proof of concept of EvoMining idea was provided by the discovery of an arseno compound on Streptomyces coelicolor (Cruz-Morales et al. 2016), nevertheless.

Despite EvoMining analysis has recently being present on the natural products field (Blin et al. 2017,Alanjary et al. (2017),Ziemert, Alanjary, and Weber (2016),Miller, Chevrette, and Kwan (2017)) EvoMining software has not been released, on this work we free EvoMining as a downloadable stand alone tool implemented on a docker container. EvoMining is free and open to all users and there is no login requirement. Despite Actinobacteria are great natural product producers (**???**) other microrganisms can be explored.

Here we present the EvoMining expansions analysis using different genome-DB such as Actinobacteria, Cyanobacteria, Pseudomonas and Archaea. To enrich possibilities of central DB an example of what we called backward EvoMining was incorporated: BGCs from S coelicolor available at Mi-BIG were analyzed EvoMining backwards and all enzyme families expanded but not over represented were followed.

Finally to prioritize which clusters possess more metabolite variations, assuming a link between genomic and metabolite plasticity we introduce the idea of classifying the saturation of a pangenome as open/closed pangenome measuring BGCs as open / closed BGC.

## Results and Discussion

### Figure 1 EvoMining pipe-line

EvoMining is a visual, evolutionary based genome mining tool with the milestone of prioritize non standard secondary metabolite pathways. The algorithm follows enzyme families from central pathways on their recruitment as components of natural products biosynthetic gene clusters (BGCs) within a genomic database.

Figure1  
Pipeline

EvoMining inputs are a (1) a custom genomic database (genomic-DB), (2) a central pathways database (central-DB) and (3) a natural product database (natural-DB) composed of genes that belongs to experimentally tested BGCs. These three databases are provided and can be modified, replaced and expanded by the user. In this work genomic-DB are collection of up to date genomes in RAST format from taxonomically related organisms such as Actinobacteria, Cyanobacteria, Pseudomonas and Archaea. Selection of this taxa obeys to the possibility of comparing well known NPs producing organisms such as Actinobacteria and Cyanobacteria in contrast with Archaea that has been poorly investigated. The central-DB contains nine central pathways from Actinobacteria previously curated (Barona-Gómez, Cruz-Morales, and Noda-García 2012), plus an update of seed metabolic enzymes identified after manual curation congruent with the central EvoMining paradigm. The natural-DB currently comprises all sequences that belongs to some BGCs from The Minimum Information about a Biosynthetic Gene cluster (MIBiG) (Medema et al. 2015).

As output EvoMining identifies on the genomic-DB those expanded families from the central-DB that has at least a recruited member onto the natural-DB, proceeding then to the reconstruction of the evolutionary history of the enzyme family. Given an enzyme from the central-DB, the product of EvoMining analysis is a color coded tree of the expanded enzyme family that provides information about the metabolic fate. Specifically, enzymes from central metabolism are differentiated from known Natural Products enzymes and those expansions with potential activity into secondary metabolism are emphasised as putative novel recruitments. Further analysis of these hits allows visualization of the genomic vicinity guiding to the discovery of novel BGCs. In addition to the updates associated to the workflow of EvoMining, the version to be released will include the possibility of defining the dynamics of the gene content of any given BGC to explore the chemical plasticity related to EvoMining hits. This allows to prioritize which clusters possess more metabolite variations, therefore unmasking biosynthetic darkmatter (Medema and Fischbach 2015, Blin et al. 2017).

EvoMining code and components (blast, muscle, FastTree, newick utilities, Gblocks,apache and SVG perl module) are wrapped on the docker container nselem/newevomining downloadable at the Docker hub. Code is available at at github: nselem/EvoMining and manual at <https://github.com/nselem/EvoMining/wiki>. EvoMining tool will allow researchers to examine their own genomes and their own enzyme families in the search of expansions involved on nobel secondary metabolism.

EvoMining will identify those expanded families of the central-DB within the genomic-DB that has at least a recruited member onto the natural-DB, proceeding then to the reconstruction of the evolutionary history of the enzyme family. Given an enzyme from the central-DB, the product of EvoMining analysis is an interactive color coded tree of the enzyme expanded family where best bidirectional hits (BBH) of central-DB are differentiated from Natural Products members and those expansions close to a Natural Product sequence that are not BBH with central-DB enzymes are emphasised as putative nobel recruitments into secondary metabolism.

### Figure 2 Expansions on some databases

Archaea Cyanobacteria, and Actinobacteria based on central metabolism from actinobacteria  
2.1 Expansions same central  
Expansions other central  
To acotate the search for enzymes of recent recruitment into natural products TauD

GenomicDatabases ### Figure 3.1 Expansions on genomic dinamics  
3.2(Bakward EvoMining)  
Coelicolor clusters  
Esto se hará solo sobre Streptomyces de los 1246

table <- read.csv("Figuras/CoelicolorMiBIG", row.names = 1,sep="\t")  
kable(table, caption = "Coelicolor\\label{tab:Coelicolor MiBig}",caption.short = "CoelicolorMiBig ")

Coelicolor

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Full...partial | Main.product | Biosynthetic.class | Organism | X..Backward.EvoMining.Hits | Open.closed |
| BGC0000038 | Full | coelimycin | Polyketide | Streptomyces coelicolor A3(2) | NA | NA |
| BGC0000194 | Full | actinorhodin | Polyketide | Streptomyces coelicolor A3(2) | NA | NA |
| GC0000315 | Full | calcium-dependent antibiotic | NRP | Streptomyces coelicolor A3(2) | NA | NA |
| BGC0000551 | Full | sapB | RiPP | Streptomyces coelicolor A3(2) | NA | NA |
| BGC0000595 | Full | SCO-2138 | RiPP | Streptomyces coelicolor A3(2) | NA | NA |
| BGC0000849 | Full | gamma-butyrolactone | Other | Streptomyces coelicolor A3(2) | NA | NA |
| BGC0000940 | Full | desferrioxamine B | Other | Streptomyces coelicolor A3(2) | NA | NA |
| BGC0000324 | Partial | coelibactin | NRP | Streptomyces coelicolor A3(2) | NA | NA |
| BGC0000325 | Partial | coelichelin | NRP | Streptomyces coelicolor A3(2) | NA | NA |
| BGC0000660 | Partial | albaflavenone | Terpene | Streptomyces coelicolor A3(2) | NA | NA |
| BGC0000663 | Partial | hopene | Terpene | Streptomyces coelicolor A3(2) | NA | NA |
| BGC0000910 | Partial | melanin | Other | Streptomyces coelicolor A3(2) | NA | NA |
| BGC0000914 | Partial | methylenomycin | Other | Streptomyces coelicolor A3(2) | NA | NA |
| BGC0001063 | Partial | undecylprodigiosin | NRP / Polyketide | Streptomyces coelicolor A3(2) | NA | NA |
| BGC0001181 | Partial | geosmin | Terpene | Streptomyces coelicolor A3(2) | NA | NA |

# Expansions of enzime sequences from MiBIG from S coelicolor will be explored within the scope of the genomic database Streptomyces. The goal is to recover those enzymes that are not yet been considered as common on secondary metabolism.   
## Moda is the most common copy number on an organism, Organisms with an extra copy are the ones that may have this copy recrutied into secondary metabolism  
# This extra copy on at least 4 organismos  
## In addtiion the distribution of the enzyme is deseried present on at least half o the organisms (Not to exclusive)  
## Too exclusive means only belong to secondary metabolism, we are looking for switches   
## looking for an esay number between 0 and one that reflects too expanded, too exclusive  
# y el exp number, mas entre .2<= Exp <=.6 y analizar eso árboles.   
# One minus average organisms that contains one copy.  
# More copies than organisms this number tends to one ## too expanded  
# few copies on homogeneously on few organisms tends to cero ## too particular   
# two copies by organism .5 , that is not usually the case because there is some variance   
  
  
#### Functions   
OneOrMode <- function(x){ #max between 0 and one  
a = table(x) # x is a vector  
moda=a[which.max(a)]  
inte=max(1,as.integer(names(moda)))  
return(inte)  
}  
  
Mode <- function(x){ ## mode  
a = table(x) # x is a vector  
moda=a[which.max(a)]  
inte=as.integer(names(moda))  
return(inte)  
}  
  
  
OrganismsExtraCopy <- function(x){ ##how many organisms has an extra copy than the mode  
 a = table(x) # x is a vector   
 moda=a[which.max(a)]  
 inte=as.integer(names(moda)) #the moda  
 subx<-as.integer(a[which(as.integer(names(a))>inte)]) ## vector of organisms with extra copies  
 suma<-sum(subx) ## how many  
return(suma)  
}  
  
OrgAtLeastOneCopy <- function(x){ ##how many organisms has a copy   
 a = table(x) # x is a vector   
 subx<-as.integer(a[which(as.integer(names(a))>0)]) ## vector of organnisms with at least one copy  
 suma<-sum(subx) ## how many  
return(suma)  
}  
  
  
Copies <- function(x){ ##how many organisms has an extra copy than the mode  
 suma<-sum(x) ## how many  
return(suma)  
}  
  
######## Reading and sorting data   
## Read EvoMining tables  
tableExp <- read.csv("Figuras/ExpansionBlast.data", header=TRUE, sep="\t")   
  
tableCentral <- read.csv("Figuras/Central.data", header=TRUE, sep="\t")   
tableDistribution <- read.csv("Figuras/Enzymes.Distribution", header=TRUE, row.names=1,sep="\t")   
tableCentralDistribution <- read.csv("Figuras/CentralEnymes.Distribution.csv", header=TRUE, row.names=1,sep="\t")   
  
#necesito poner el valor de names de moda en el renglon con el mismo valor en enzima  
#number of organisms greater than mode at least tenpercent of the genome  
##Reducing tableExp to those I have distribution  
tableExp=tableExp[tableExp$Enzyme %in% names(tableDistribution),]  
tableExp <- tableExp[order(tableExp$Enzyme),]   
tableDistribution <- tableDistribution[,order(names(tableDistribution))]   
  
tableExpOriginal <- read.csv("Figuras/ExpansionBlast.data", header=TRUE, sep="\t")   
tableExpOriginal=tableExp[tableExp$Enzyme %in% names(tableDistribution),]  
tableExpOriginal <- tableExp[order(tableExp$Enzyme),]   
  
################# Processing functions BGC data   
modaOrOne=apply(tableDistribution,2, OneOrMode)   
moda=apply(tableDistribution,2, Mode)  
ExtraCopy=apply(tableDistribution,2, OrganismsExtraCopy)  
OneCopy=apply(tableDistribution,2, OrgAtLeastOneCopy)  
CopiesEvo=apply(tableDistribution,2, Copies)  
Average=colMeans(tableDistribution)  
#names(moda)  
tableExp$Moda=moda  
tableExp$Average=Average  
tableExp$ExtraCopy=ExtraCopy  
tableExp$OneCopy=OneCopy  
tableExp$CopiesEvo=CopiesEvo  
#modaOrOne  
#moda  
#ExtraCopy  
#OneCopy  
CopiesEvo

## Enzyme\_1 Enzyme\_10 Enzyme\_100 Enzyme\_101 Enzyme\_102 Enzyme\_103   
## 535 191 9140 20 9690 22   
## Enzyme\_104 Enzyme\_105 Enzyme\_106 Enzyme\_107 Enzyme\_108 Enzyme\_109   
## 30 18 10 6359 241 1617   
## Enzyme\_11 Enzyme\_110 Enzyme\_111 Enzyme\_112 Enzyme\_113 Enzyme\_114   
## 131 53 946 9664 6094 2429   
## Enzyme\_115 Enzyme\_116 Enzyme\_117 Enzyme\_118 Enzyme\_119 Enzyme\_12   
## 1696 469 320 592 140 632   
## Enzyme\_120 Enzyme\_121 Enzyme\_122 Enzyme\_123 Enzyme\_124 Enzyme\_125   
## 892 3583 547 2431 2362 376   
## Enzyme\_126 Enzyme\_127 Enzyme\_128 Enzyme\_129 Enzyme\_13 Enzyme\_130   
## 370 1347 1000 6912 468 6576   
## Enzyme\_131 Enzyme\_132 Enzyme\_133 Enzyme\_134 Enzyme\_135 Enzyme\_136   
## 6628 551 3499 9711 4078 3832   
## Enzyme\_137 Enzyme\_138 Enzyme\_139 Enzyme\_14 Enzyme\_140 Enzyme\_141   
## 996 9784 1915 821 1871 4   
## Enzyme\_142 Enzyme\_143 Enzyme\_144 Enzyme\_145 Enzyme\_146 Enzyme\_147   
## 1234 1726 3845 678 121 6868   
## Enzyme\_148 Enzyme\_149 Enzyme\_15 Enzyme\_150 Enzyme\_151 Enzyme\_152   
## 6489 993 399 1001 6 375   
## Enzyme\_153 Enzyme\_154 Enzyme\_155 Enzyme\_156 Enzyme\_157 Enzyme\_158   
## 1818 412 347 378 454 1268   
## Enzyme\_159 Enzyme\_16 Enzyme\_160 Enzyme\_161 Enzyme\_162 Enzyme\_163   
## 4788 352 1649 216 9719 6193   
## Enzyme\_164 Enzyme\_165 Enzyme\_166 Enzyme\_167 Enzyme\_168 Enzyme\_169   
## 5403 87 64 8326 1717 100   
## Enzyme\_17 Enzyme\_170 Enzyme\_171 Enzyme\_172 Enzyme\_173 Enzyme\_174   
## 421 6409 7253 1170 1709 226   
## Enzyme\_175 Enzyme\_176 Enzyme\_177 Enzyme\_178 Enzyme\_179 Enzyme\_18   
## 2695 1124 1820 36 36 1061   
## Enzyme\_180 Enzyme\_181 Enzyme\_182 Enzyme\_183 Enzyme\_184 Enzyme\_185   
## 1501 92 799 36 9742 696   
## Enzyme\_186 Enzyme\_187 Enzyme\_188 Enzyme\_189 Enzyme\_19 Enzyme\_190   
## 1806 2291 1057 5814 1013 531   
## Enzyme\_191 Enzyme\_192 Enzyme\_193 Enzyme\_2 Enzyme\_20 Enzyme\_21   
## 538 774 1496 456 1070 877   
## Enzyme\_22 Enzyme\_23 Enzyme\_24 Enzyme\_25 Enzyme\_26 Enzyme\_27   
## 670 645 423 447 1403 1605   
## Enzyme\_28 Enzyme\_29 Enzyme\_3 Enzyme\_30 Enzyme\_31 Enzyme\_32   
## 33 2007 3547 4958 1161 501   
## Enzyme\_33 Enzyme\_34 Enzyme\_35 Enzyme\_36 Enzyme\_37 Enzyme\_38   
## 16 438 251 1263 9757 7222   
## Enzyme\_39 Enzyme\_4 Enzyme\_40 Enzyme\_41 Enzyme\_42 Enzyme\_43   
## 9766 320 1518 440 583 7190   
## Enzyme\_44 Enzyme\_45 Enzyme\_46 Enzyme\_47 Enzyme\_48 Enzyme\_49   
## 9019 8844 2741 359 6764 319   
## Enzyme\_5 Enzyme\_50 Enzyme\_51 Enzyme\_52 Enzyme\_53 Enzyme\_54   
## 4365 267 274 271 272 295   
## Enzyme\_55 Enzyme\_56 Enzyme\_57 Enzyme\_58 Enzyme\_59 Enzyme\_6   
## 237 625 20 2965 1555 117   
## Enzyme\_60 Enzyme\_61 Enzyme\_62 Enzyme\_63 Enzyme\_64 Enzyme\_65   
## 1238 6264 29 1160 275 7203   
## Enzyme\_66 Enzyme\_67 Enzyme\_68 Enzyme\_69 Enzyme\_7 Enzyme\_70   
## 9495 6726 1078 9750 9741 3495   
## Enzyme\_71 Enzyme\_72 Enzyme\_73 Enzyme\_74 Enzyme\_75 Enzyme\_76   
## 3490 1038 821 159 2306 9508   
## Enzyme\_77 Enzyme\_78 Enzyme\_79 Enzyme\_8 Enzyme\_80 Enzyme\_81   
## 13 7836 9743 1576 142 30   
## Enzyme\_82 Enzyme\_83 Enzyme\_84 Enzyme\_85 Enzyme\_86 Enzyme\_87   
## 740 527 145 3197 9734 2744   
## Enzyme\_88 Enzyme\_89 Enzyme\_9 Enzyme\_90 Enzyme\_91 Enzyme\_92   
## 3857 9778 3507 6278 5371 487   
## Enzyme\_93 Enzyme\_94 Enzyme\_95 Enzyme\_96 Enzyme\_97 Enzyme\_98   
## 462 729 1611 830 3292 3842   
## Enzyme\_99   
## 3844

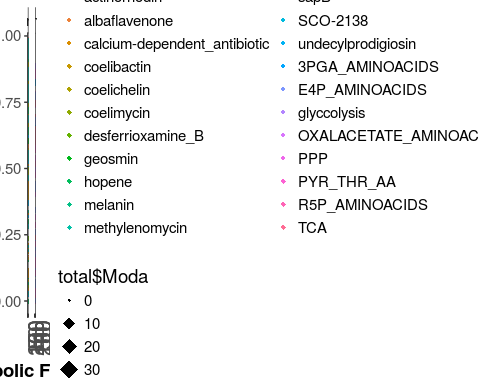
#Average  
#CopiesEvo  
sum(tableDistribution$Enzyme\_108)

## [1] 241

tableExpOriginal$Moda=moda  
tableExpOriginal$Average=Average  
tableExpOriginal$ExtraCopy=ExtraCopy  
tableExpOriginal$OneCopy=OneCopy  
tableExpOriginal$CopiesEvo=CopiesEvo  
  
################# Processing functions central data   
 CentralmodaOrOne=apply(tableCentralDistribution,2, OneOrMode)  
Centralmoda=apply(tableCentralDistribution,2, Mode)  
CentralExtraCopy=apply(tableCentralDistribution,2, OrganismsExtraCopy)  
CentralOneCopy=apply(tableCentralDistribution,2, OrgAtLeastOneCopy)  
CentralCopiesEvo=apply(tableCentralDistribution,2, Copies)  
CentralAverage=colMeans(tableCentralDistribution)  
  
tableCentral$Moda=Centralmoda  
tableCentral$Average=CentralAverage  
tableCentral$ExtraCopy=CentralExtraCopy  
tableCentral$OneCopy=CentralOneCopy  
tableCentral$CopiesEvo=CentralCopiesEvo  
  
#One minus average organisms that contains one copy.  
#More copies than organisms this number tends to one ## too expanded  
# few copies on homogeneously on few organisms tends to cero ## too particular   
# two copies by organism .5 , that is not usually the case because there is some variance   
#tableExp$ExpNum=(modaOrOne-tableExp$OneCopy/tableExp$CopiesEvo)/(modaOrOne)   
#tableCentral$ExpNum=(CentralmodaOrOne-tableCentral$OneCopy/tableCentral$CopiesEvo)/(CentralmodaOrOne)   
  
tableExp$ExpNum=1-tableExp$OneCopy/tableExp$CopiesEvo  
tableCentral$ExpNum=1-tableCentral$OneCopy/tableCentral$CopiesEvo  
  
  
tableExp<-tableExp[order(tableExp$Order),]  
#tableCentral$Order=tableCentral$Order+193  
tableCentral$Order

## [1] 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23  
## [24] 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46  
## [47] 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69  
## [70] 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92  
## [93] 93

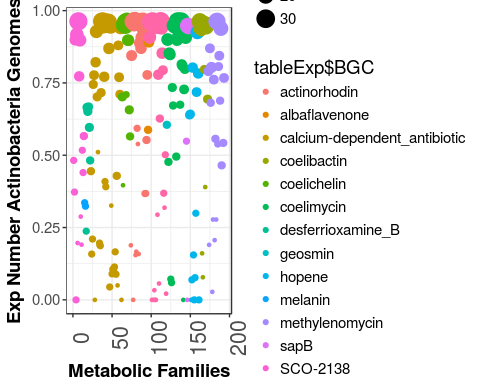
tableCentral<-tableCentral[order(tableCentral$Order),]  
tableEnzymeReduced=subset(tableExp,tableExp$ExpNum<=.6 & tableExp$ExpNum>= .2 )  
  
total <- rbind(tableExp,tableCentral)  
todosImage<-ggplot(total,aes(x=total$Order, y=total$ExpNum, color=total$BGC, size = total$Moda))+facet\_wrap(~ total$Type)+ geom\_point(shape=20) + labs(x = "Metabolic Families", y = "Exp Number Actinobacteria Genomes",text = element\_text(size=12)) + theme\_bw()+theme(plot.title = element\_text(size = 20, face = "bold"), text = element\_text(size = 14), axis.title = element\_text(face="bold"), axis.text.x=element\_text(angle = 90,size = 16), legend.position = "right")  
  
ggplot(total,aes(x=total$Order, y=total$ExpNum, color=total$BGC, size = total$Moda))+facet\_wrap(~ total$Type)+ geom\_point(shape=18) + labs(x = "Metabolic Families", y = "Exp Number Actinobacteria Genomes",text = element\_text(size=12)) + theme\_bw()+theme(plot.title = element\_text(size = 20, face = "bold"), text = element\_text(size = 14), axis.title = element\_text(face="bold"), axis.text.x=element\_text(angle = 90,size = 16), legend.position = "right")



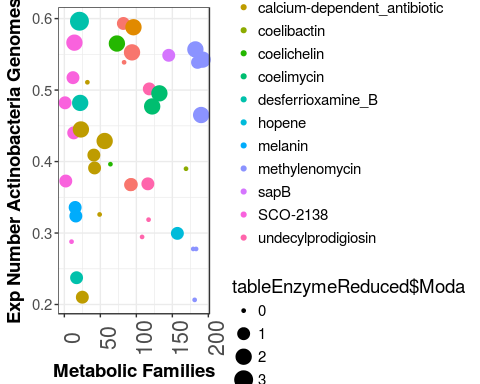
ggsave(file="todosImage.svg", plot=todosImage, width=30, height=8)  
   
#str(tableExp)  
#tableExp$Enzyme  
## ploting images  
require("svglite")

## Loading required package: svglite

#save the plot in a variable image to be able to export to svg  
 imageBGC=ggplot(tableExp,aes(x=tableExp$Order, y=tableExp$ExpNum, color=tableExp$BGC, size = tableExp$Moda))+ geom\_point() + labs(x = "Metabolic Families", y = "Exp Number Actinobacteria Genomes",text = element\_text(size=12)) + theme\_bw()+theme(plot.title = element\_text(size = 20, face = "bold"), text = element\_text(size = 14), axis.title = element\_text(face="bold"), axis.text.x=element\_text(angle = 90,size = 16), legend.position = "bottom")  
 ggsave(file="imageBGC.svg", plot=imageBGC, width=20, height=8)  
   
 ggplot(tableExp,aes(x=tableExp$Order, y=tableExp$ExpNum, color=tableExp$BGC, size = tableExp$Moda))+ geom\_point() + labs(x = "Metabolic Families", y = "Exp Number Actinobacteria Genomes",text = element\_text(size=12)) + theme\_bw()+theme(plot.title = element\_text(size = 20, face = "bold"), text = element\_text(size = 14), axis.title = element\_text(face="bold"), axis.text.x=element\_text(angle = 90,size = 16), legend.position = "right")



imageCentral= ggplot(tableCentral,aes(x=tableCentral$Order, y=tableCentral$ExpNum, color=tableCentral$BGC, size = tableCentral$Moda))+ geom\_point() + labs(x = "Metabolic Families", y = "Exp Number Actinobacteria Genomes",text = element\_text(size=12)) + theme\_bw()+theme(plot.title = element\_text(size = 20, face = "bold"), text = element\_text(size = 14), axis.title = element\_text(face="bold"), axis.text.x=element\_text(angle = 90,size = 16), legend.position = "right")  
 ggsave(file="imageCentral.svg", plot=imageCentral, width=20, height=8)  
  
   
  
 ggplot(tableEnzymeReduced,aes(x=tableEnzymeReduced$Order, y=tableEnzymeReduced$ExpNum, color=tableEnzymeReduced$BGC, size = tableEnzymeReduced$Moda))+ geom\_point() + labs(x = "Metabolic Families", y = "Exp Number Actinobacteria Genomes",text = element\_text(size=12)) + theme\_bw()+theme(plot.title = element\_text(size = 20, face = "bold"), text = element\_text(size = 14), axis.title = element\_text(face="bold"), axis.text.x=element\_text(angle = 90,size = 16), legend.position = "right")



#kable(tableExp, caption = "CoelicolorExpansions\\label{tab:Coelicolor Expansions}",caption.short = "CoelicolorExpansions")

Presence Absence EvoMining was run over enzymes with expansion number between .1 and .6 Figuras/GenomicDBS.svg ### Figure 4 Pan cluster Idea on closed Streptomyces

Cluster visualization

Cluster visualization

Open /closed coelicolor How spread is the cluster How to describe the cluster  
Conservation  
Enzymes that appear x%

Variability How variable is the region  
derivative of rarefaction curve

Took 15 clusters from Streptomyces coelicolor on MiBig Analize its open/close pancluster according to EvoMining backwards  
O sea 15 corasones, no necesito escoger las query enzyme, al menos 3 por cluster... y que no sean NRPS o PKS

## MEthodology

[@dufresne\_algorithmique\_2016,@blin\_recent\_nodate,@kurtboke\_revisiting\_2017,@miller\_interpreting\_2017,@schniete\_expanding\_2017,@kim\_recent\_2017,@robertsen\_toward\_2017,@juarez-vazquez\_evolution\_nodate,@chavali\_bioinformatics\_nodate,@tracanna\_mining\_2017,@ren\_breaking\_2017,@choudhary\_current\_2017,@alanjary\_antibiotic\_2017,@chevrette\_sandpuma:\_2017,@wohlleben\_antibiotic\_2016,@weber\_secondary\_2016]

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