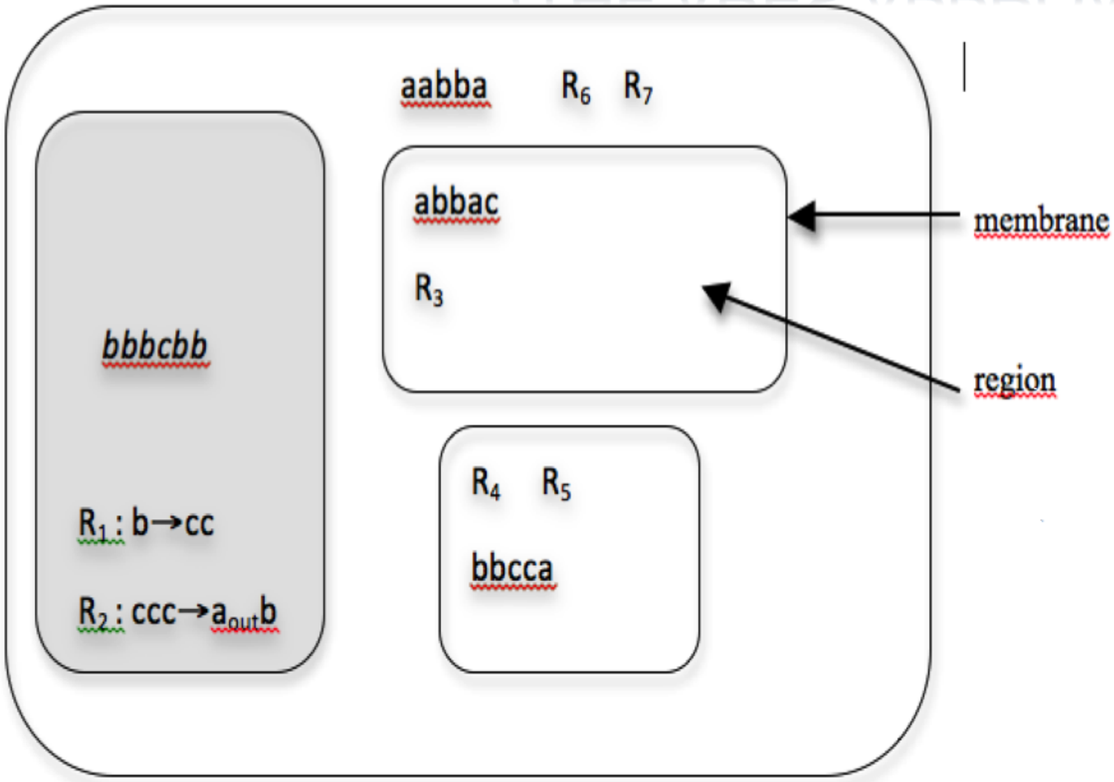
MEMBRANE COMPUTING SIMULATOR PROTOTYPE AND THEORETICAL MODEL SCENARIO OF P-SYSTEM FOR MICROBIAL ECOSYSTEMS (THE ARES APPROACH)



WP-7

Membrane computing
EVOTAR approach
http://www.evotar.eu

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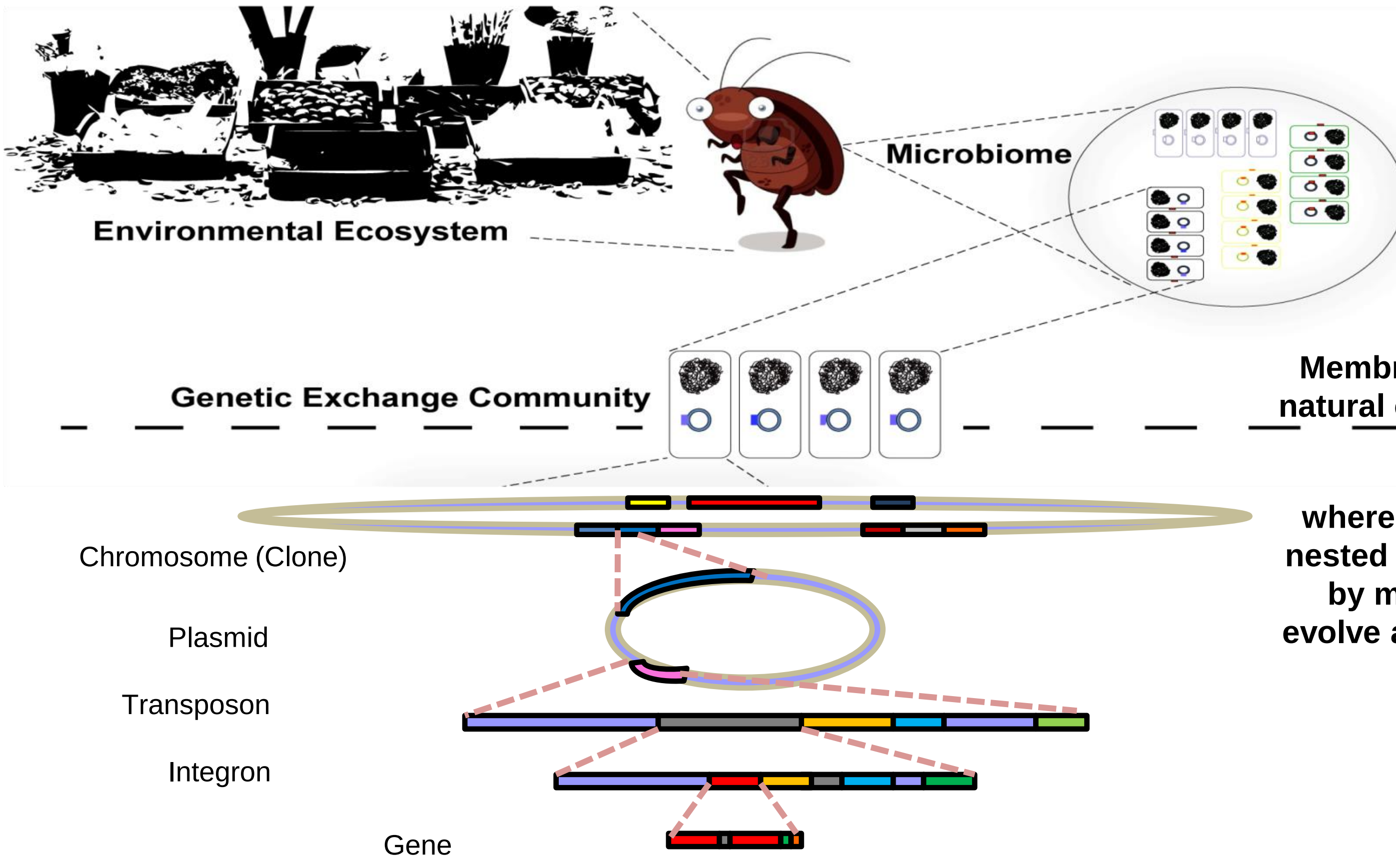
Membrane Computing Antibiotic Resistance and P systems

$$\prod = (V, \mu, W_1, \ldots, W_n, (R_1, \rho_1), \ldots, (R_n, \rho_n))$$



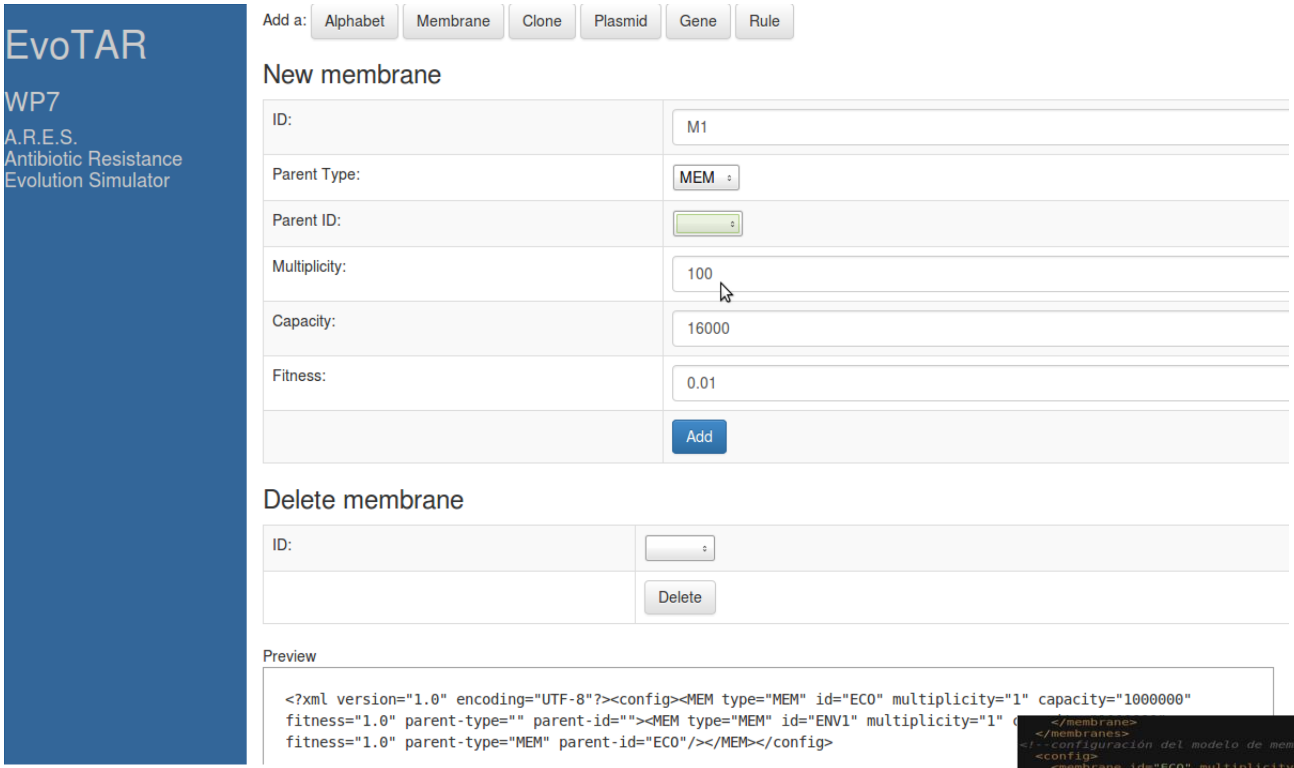
Membrane Computing is a natural computing formalism

where objects separated in nested compartments limited by membranes and that evolve according to a defined set of rules

TO KNOWN MORE

http://ppage.psystems.eu
http://www.p-lingua.org/wiki/index.php/Main_Page

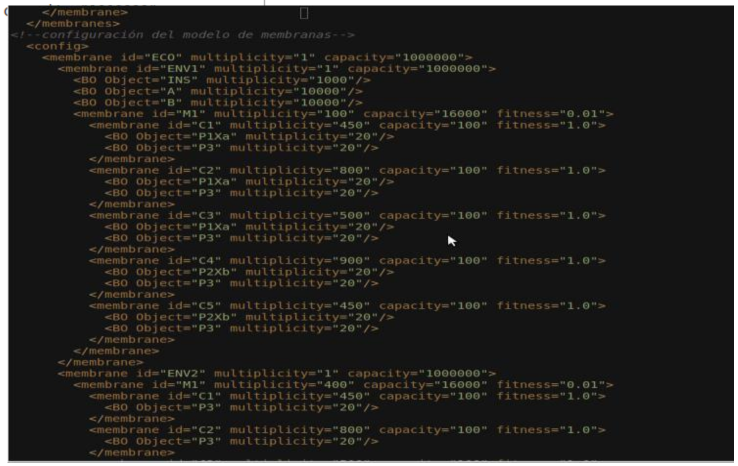
ARES: Front-End Interface



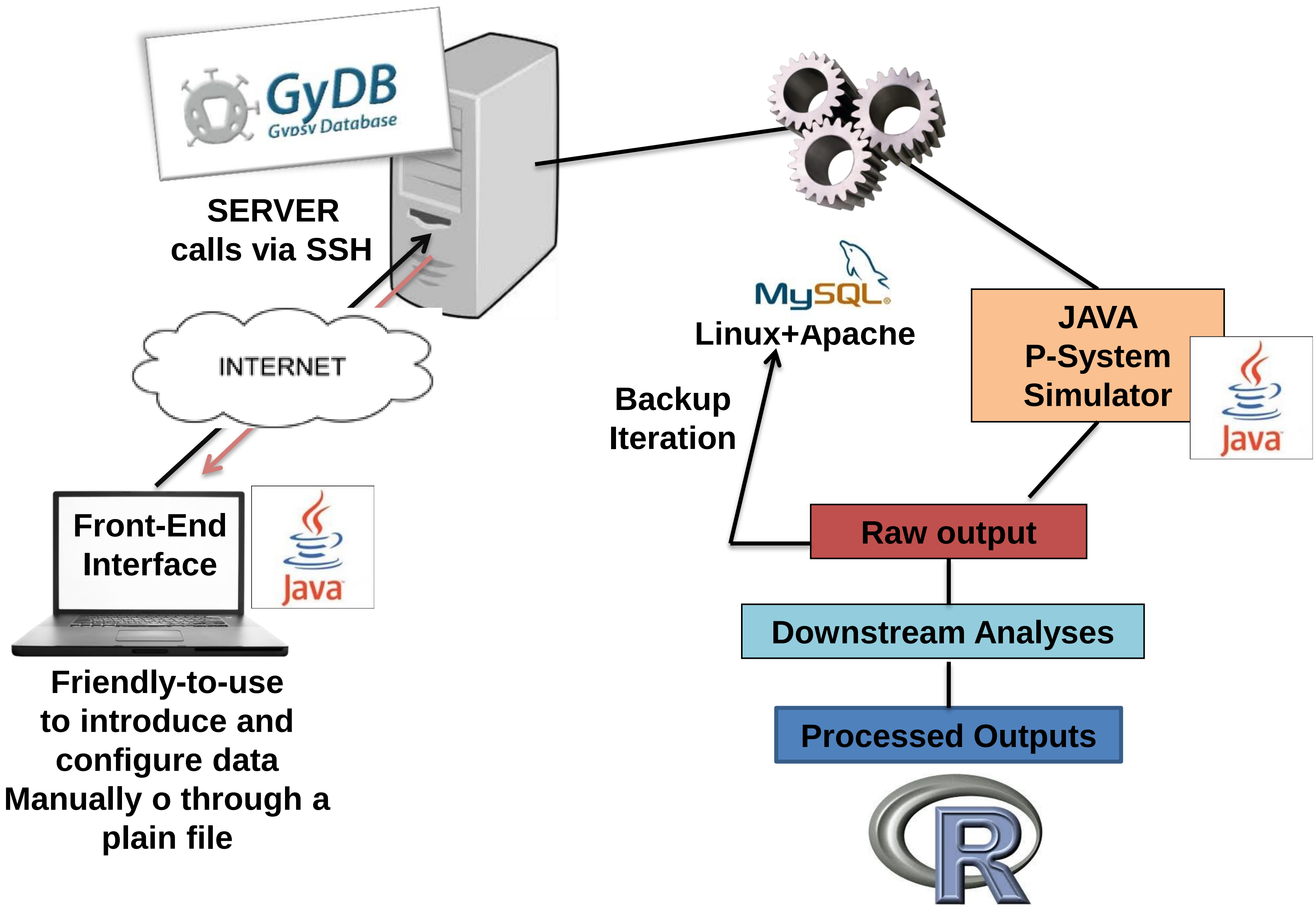
Easy to use

Avanced informatics Skill not required

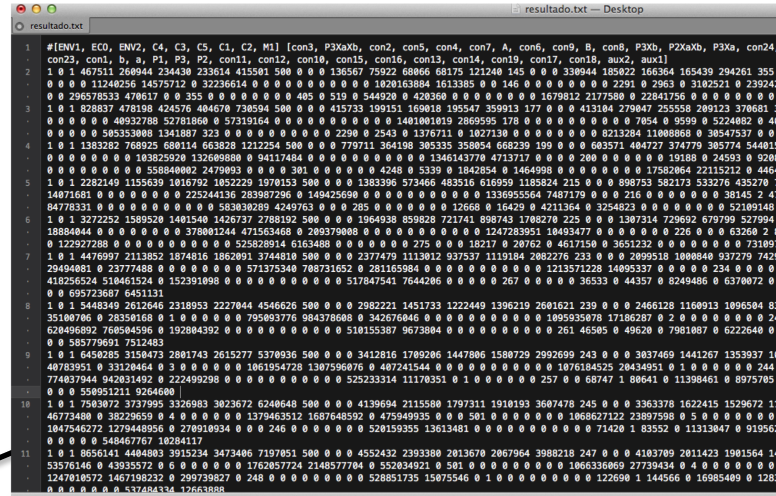
The XML is automatically generated



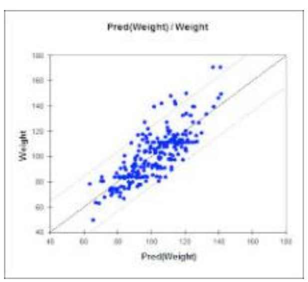
ARES: Server Pipeline



ARES output and tools for Downstream Analysis

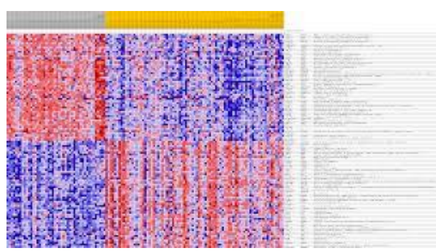


Statistics



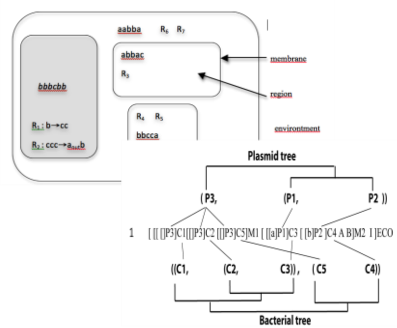
- Frequency
- Average,
- Covariance
- Price Equation
- Distribution

Diversity



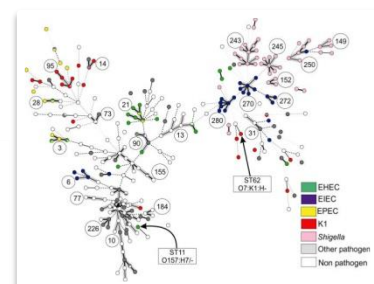
- *Heatmap*
- Rarefaction
- Diversity indexes
- Fitness Lanscapes

Drawing



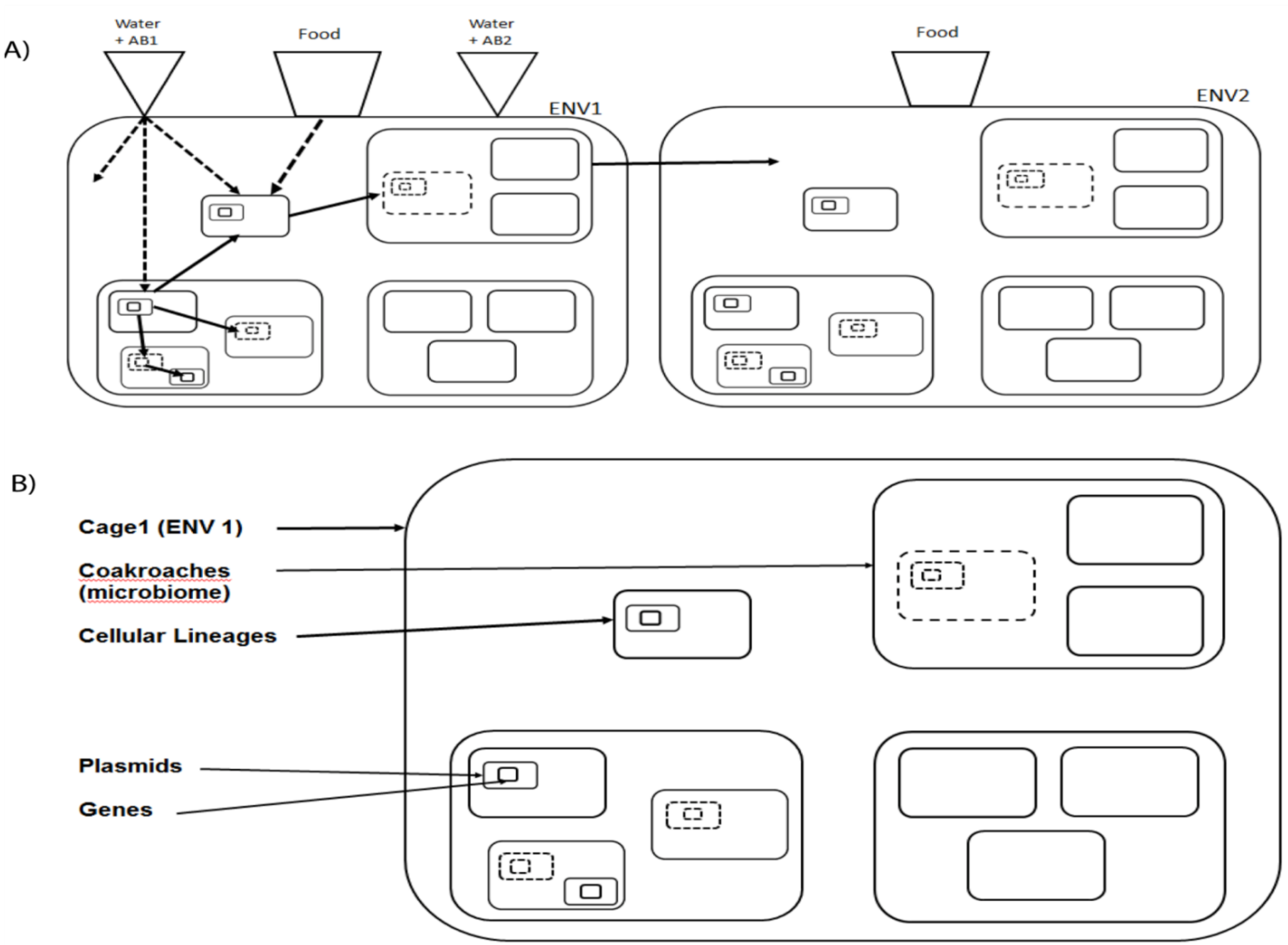
- Newick strings
- Venn Diagrams

Network



- Graph reconstruction
- Power law analysis

Case Study: Cockroach Farm



Aims

- Comparing Scenarios for Testing Null hypotheses under diverse interventions
- Make predictions under changing parameters
- Modeling the spatio-temporal dynamics of resistance genes, or any other units of selection
- Experimental validation
- Debugging of ARES

Applying Rules of Evolution

Rules for movement and/or transference of objects

$$[\ [\ ]_{Mn}\ ]_{ENV1}\ [\ ]_{ENV2} \rightarrow [\ ]_{ENV1}{}' \ [\ [\ ]_{Mn}\ ]_{ENV}{}'$$

- We consider the possibility of migratory flows between the populations of both environments (ENV1 and ENV2) with a rate M1
- Microbes released from intestinal discharge from cockroaches go into the environment and have the possibility of being re-acquired by other cockroaches with a rate M2.
- Cockroaches infect food with bacteria that have the subsequent possibility to colonize again cockroach gut with a rate M3.
- Antibiotic AB1 enters from water to the cockroach gut with a rate M4
- Antibiotic AB2 enters from water to the cockroach gut with a rate M5
- Antibiotic AB1 enters from environment to the bacterial cell with a rate M6
- Antibiotic AB2 enters from environment to the bacterial cell with a rate M7
- Antibiotic AB1 enters from cockroach gut to the bacterial cell with a rate M8
- Antibiotic AB2 enters from cockroach gut to the bacterial cell with a rate M9
- Plasmids can be horizontally transferred via conjugation from a bacterial clone to another with rate M10 which comprises a relation among the growth rate (ψ) number of transconjugants (T) and the donors (D) and the receptors (R) in a plasmid population
- P1 recruits gene “b” from plasmid P2 with a rate M11
- P2 recruits gene “a” from plasmid P1 with a rate M12
- P3 recruits gene “a” from plasmid P1 with a rate M13
- P3 recruits gene “b” from plasmid P2 with a rate M14

Applying Rules of Evolution

Rules for mortality or loss

$$[AB1]_{Cn} \rightarrow [I]$$

- 6-months old cockroaches die by natural causes according to rate D_1
- 5-months old cockroaches die by stress or competition according to rate D_2
- 4-months old cockroaches die by stress or competition according to rate D_3
- 3-months old cockroaches die by stress or competition according to rate D_4
- 2-months old cockroaches die by stress or competition according to rate D_5
- 1-months old cockroaches die by stress or competition according to rate D_6
- Cockroaches will die due to bacterial infection according to rate $D_{7,}$ being the ratio between the total number of bacteria within a cockroach individual (CLobs) at a given generation and the maximum bacterial population size allowed in a cockroach microbiome (CLmax).
- Under food restrictions, a fraction of the cockroach population will starve to death according to rate D_8
- A Gram negative bacterial clone will die under a concentration X_1 of Antibiotic AB_1
- A Gram positive clone will die under a concentration X_2 of Antibiotic AB_2
- Bacteria cells in stationary phase will naturally die under rate D_9 which is equal to R_1. In the stationary phase there is equilibrium between cell division and death.
- Bacterial cells constituting a microbiome M_i will die if their cockroach host die
- Plasmids of bacterial cells are lost by degradation with a rate D_{10}
- Plasmids of bacterial cells will be lost by segregation during bacterial replication according to rate D_{11}

Applying Rules of Evolution

Rules for drinking and feeding

- ENV1 water includes a concentration of antibiotic AB1 of X_3 units/ml
- ENV1 water includes a concentration of antibiotic AB2 of X_4 units/ml
- An amount of food will be daily supplied to both populations ENV_1 and ENV_2 with a rate F_1
- A cockroach individuals feeds food with a rate F_2
- A cockroach individual drinks water with a rate F_3
- Cockroaches will release faeces to the environment with a rate F_4

Rules for environment maintenance

- Boxes representing environments ENV1 and ENV2 will be clean from faeces remains with a rate A_1
- Boxes representing environments ENV1 and ENV2 will be clean from food remains with a rate A_2
- Boxes representing environments ENV1 and ENV2 will be clean from both faeces and food remains with a rate A_3
- Plasmids with gene "a" express ab1 protein with a rate M15
- Plasmids with gene "b" express ab2 protein with a rate M16
- ab1 neutralize AB1 in every clone
- ab2 neutralize AB2 in every clon

Rules for modification

Under values of R_8 below 1 time (T_1) necessary to apply R8 within ENV_1

- Under values of R_8 below 1 time (T_2) necessary to apply R8 within ENV_2

Applying Rules of Evolution

Rules for drinking and feeding

- ENV1 water includes a concentration of antibiotic AB1 of X_3 units/ml
- ENV1 water includes a concentration of antibiotic AB2 of X_4 units/ml
- An amount of food will be daily supplied to both populations ENV_1 and ENV_2 with a rate F_1
- A cockroach individuals feeds food with a rate F_2
- A cockroach individual drinks water with a rate F_3
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Rules for environment maintenance

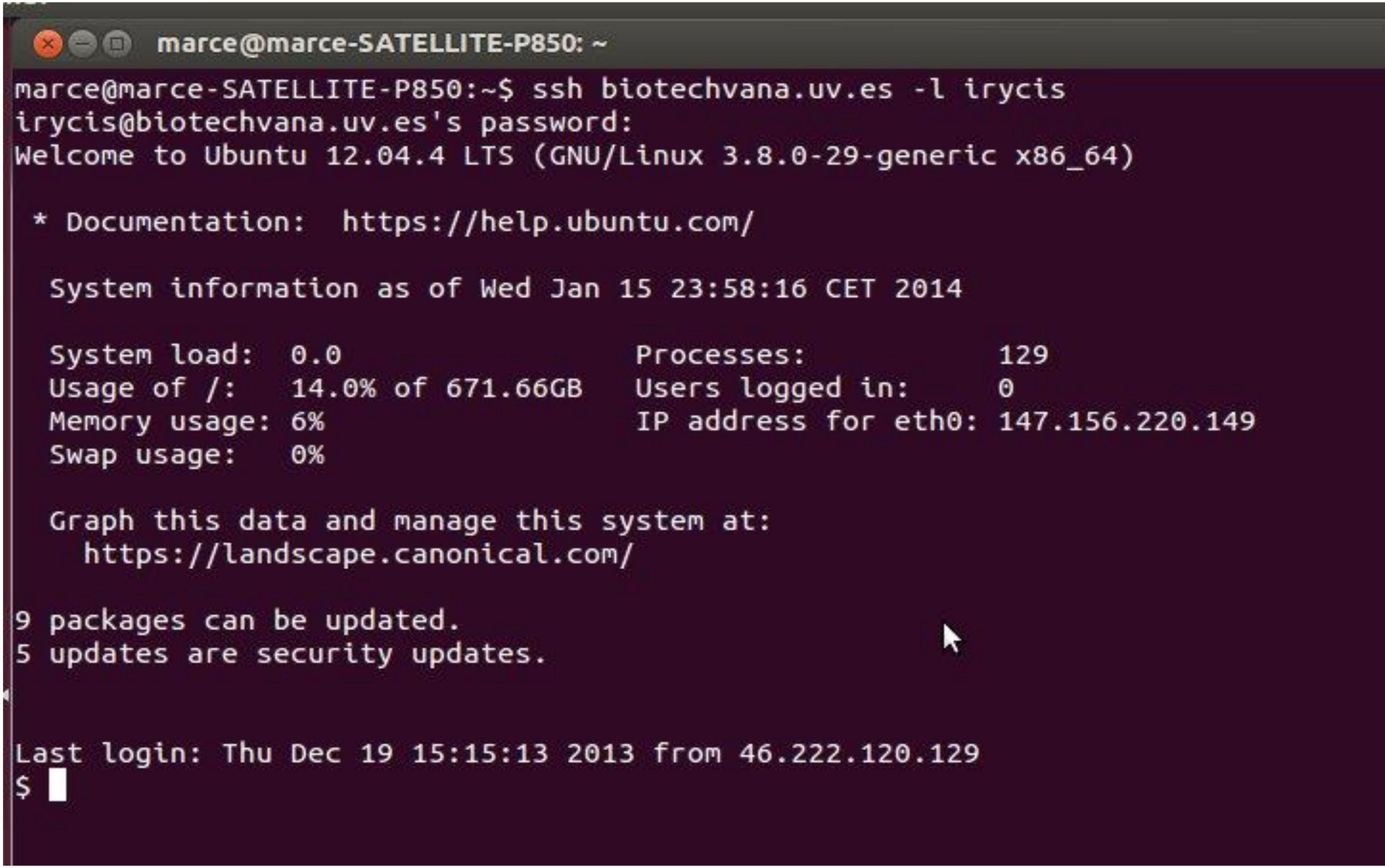
- Boxes representing environments ENV1 and ENV2 will be clean from faeces remains with a rate A_1
- Boxes representing environments ENV1 and ENV2 will be clean from food remains with a rate A_2
- Boxes representing environments ENV1 and ENV2 will be clean from both faeces and food remains with a rate A_3
- Plasmids with gene "a" express ab1 protein with a rate M15
- Plasmids with gene "b" express ab2 protein with a rate M16
- ab1 neutralize AB1 in every clone
- ab2 neutralize AB2 in every clon

Rules for modification

Under values of R_8 below 1 time (T_1) necessary to apply R8 within ENV_1

- Under values of R_8 below 1 time (T_2) necessary to apply R8 within ENV_2

Server


marce@marce-SATELLITE-P850: ~
marce@marce-SATELLITE-P850:~$ ssh biotechvana.uv.es -l irycis
irycis@biotechvana.uv.es's password:
Welcome to Ubuntu 12.04.4 LTS (GNU/Linux 3.8.0-29-generic x86_64)
* Documentation: https://help.ubuntu.com/
System information as of Wed Jan 15 23:58:16 CET 2014
System load: 0.0
Processes: 129
Usage of /: 14.0% of 671.66GB
Users logged in: 0
Memory usage: 6%
IP address for eth0: 147.156.220.149
Swap usage: 0%
Graph this data and manage this system at:
https://landscape.canonical.com/
9 packages can be updated.
5 updates are security updates.
Last login: Thu Dec 19 15:15:13 2013 from 46.222.120.129
$

Server

```
marce@marce-SATELLITE-P850: ~
$ cd simulador
$ ./executa_auto
#[ENV1, ENV2, ECO, C4, C3, C5, C1, C2, M1] [con3, P3XaXb, con2, con5, con4, con7, A, con6, con9, B, con8, P3Xb, P2XaXb, P3Xa, con24, P1Xa,
 P1Xb, P2Xb, con20, P1XaXb, P2Xa, con21, INS, con22, con23, con1, b, a, P1, P3, P2, con11, con12, con10, con15, con16, con13, con14, con19
, con17, con18]
1 1 0 900000 500000 450000 450000 800000 500 0 0 0 261000 145000 130500 130500 232000 145 0 0 0 639000 355000 319500 319500 568000 355 0 0
 501 0 0 0 0 0 0 0 0 0 0 0 0 7000000 0 5400000 0 0 0 0 0 0 0 0 21600000 28000000 0 62000000 0 0 0 0 0 0 0 0 0 0 0 0 146 0 0 0 0 0 0 0
0 0 0 0 5950000 0 4590000 0 0 0 0 0 0 0 0 18360000 23800000 0 17980000 0 0 0 0 0 0 0 0 0 0 0 0 355 0 0 0 0 0 0 0 0 0 0 0 0 1050000 0 810
000 0 0 0 0 0 0 0 0 3240000 4200000 0 44020000 0 0 0 0 0 0 0 0 0 0 0 0
1 1 0 1741708 954718 821609 851461 1520581 500 0 0 0 606018 331328 298399 290904 526423 177 0 0 0 1135690 623390 523210 560557 994158 323
501 0 0 0 0 0 0 0 0 0 0 0 0 0 0 13491400 0 10365100 0 0 0 0 0 0 0 0 82920800 107931200 0 117801540 0 0 0 0 0 0 0 0 0 0 0 0 178 0 0 0 0 0 0 0
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40 0 1910460 0 0 0 0 0 0 0 0 15283680 19499520 0 76740100 0 0 0 0 0 0 0 0 0 0 0 0
1 1 0 3351906 1793638 1486845 1589917 2877223 500 0 0 0 1307635 709333 655052 609769 1130802 199 0 0 0 2044271 1084305 831793 980148 17464
21 301 0 0 0 0 501 0 0 0 0 0 0 0 0 0 0 25796100 0 19867620 0 0 0 0 0 0 0 0 238411440 309553200 0 221990580 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 2
00 0 0 0 0 0 0 0 0 0 0 20067180 0 15384460 0 0 0 0 0 0 0 0 184613520 240806160 0 88251820 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 301 0 0 0 0 0 0 0
0 0 0 5728920 0 4483160 0 0 0 0 0 0 0 0 53797920 68747040 0 133738760 0 0 0 0 0 0 0 0 0 0 0 0
1 1 0 4908679 2763933 2129827 2448305 4453663 500 0 0 0 1872292 1068906 900746 920673 1701013 215 0 0 0 3036387 1695027 1229081 1527632 27
52650 285 0 0 0 501 0 0 0 0 0 0 0 0 0 0 0 40588460 0 29454460 0 0 0 0 0 0 0 0 471271360 649415360 0 334088140 0 0 0 0 0 0 0 0 0 0 0 0 0 0
216 0 0 0 0 0 0 0 0 0 0 0 30341640 0 22099480 0 0 0 0 0 0 0 0 353591680 485466240 0 129272600 0 0 0 0 0 0 0 0 0 0 0 0 0 0 285 0 0 0 0 0 0
0 0 0 0 0 10246820 0 7354980 0 0 0 0 0 0 0 0 117679680 163949120 0 204815540 0 0 0 0 0 0 0 0 0 0 0 0
1 1 0 6700839 4084601 2910829 3610446 6572605 500 0 0 0 2622110 1620939 1305747 1423802 2614797 225 0 0 0 4078729 2463662 1605082 2186644
3957808 275 0 0 0 0 0 0 0 501 0 0 0 0 0 0 0 60266000 0 40561640 0 0 0 0 0 0 0 0 811232800 1205320000 0 477586400 0 0 0 0 0 0 0 0 0 0 0 0 0
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 0 0 0 0 0 0 15906720 0 10288280 0 0 0 0 0 0 0 0 205765600 318134400 0 285838500 0 0 0 0 0 0 0 0 0 0 0 0
1 1 0 8421367 5373882 3687486 4742129 8646778 500 0 0 0 3661466 2440954 1787859 2126389 3899838 233 0 0 0 4759901 2932928 1899627 2615740
4746940 267 0 0 0 0 0 501 0 0 0 0 0 0 0 0 0 85276640 0 54643020 0 0 0 0 0 0 0 0 1311432480 2046639360 0 617432840 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 234 0 0 0 0 0 0 0 0 0 0 65063000 0 42331700 0 0 0 0 0 0 0 0 1015960800 1561512000 0 278330120 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 267 0
0 0 0 0 0 0 0 0 20213640 0 12311320 0 0 0 0 0 0 0 0 295471680 485127360 0 339102720 0 0 0 0 0 0 0 0 0 0 0 0
1 1 0 9720079 6373028 4278072 5615786 10251147 500 0 0 0 4541712 3113288 2256696 2751283 4985448 239 0 0 0 5178367 3259740 2021376 2864503
 5265699 261 0 0 0 0 0 0 0 0 0 0 501 0 0 0 0 105087580 0 65661000 0 0 0 0 0 0 0 0 1838508000 2942452240 0 724762240 0 0 0 0 0 0 0 0 0 0 0 0
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1 1 0 10527306 7011837 4640101 6176287 11279093 500 0 0 0 4970688 3450122 2484538 3084259 5543930 243 0 0 0 5556618 3561715 2155563 309202
8 5735163 257 0 0 0 0 0 0 0 0 0 501 0 0 0 0 0 0 116504240 0 71822020 0 0 0 0 0 0 0 0 2298304640 3728135680 0 792692480 0 0 0 0 0 0 0 0 0 0 0 0
 0 0 0 0 0 0 0 0 244 0 0 0 0 0 0 85268780 0 53857280 0 0 0 0 0 0 0 0 1723432960 2728600960 0 390670740 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
 0 257 0 0 0 0 0 0 31235460 0 17964740 0 0 0 0 0 0 0 0 574871680 999534720 0 402021740 0 0 0 0 0 0 0 0 0 0 0 0
```
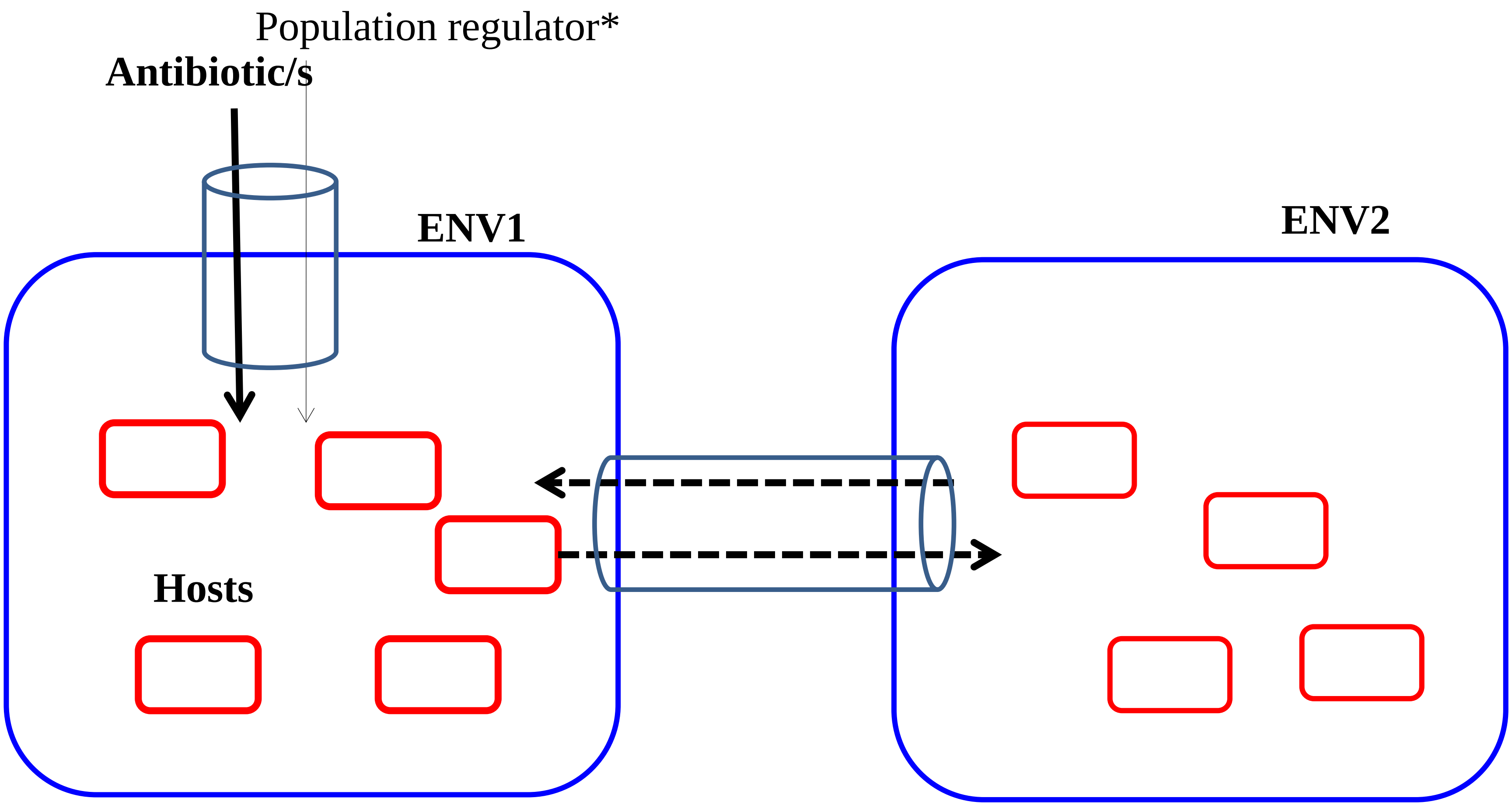
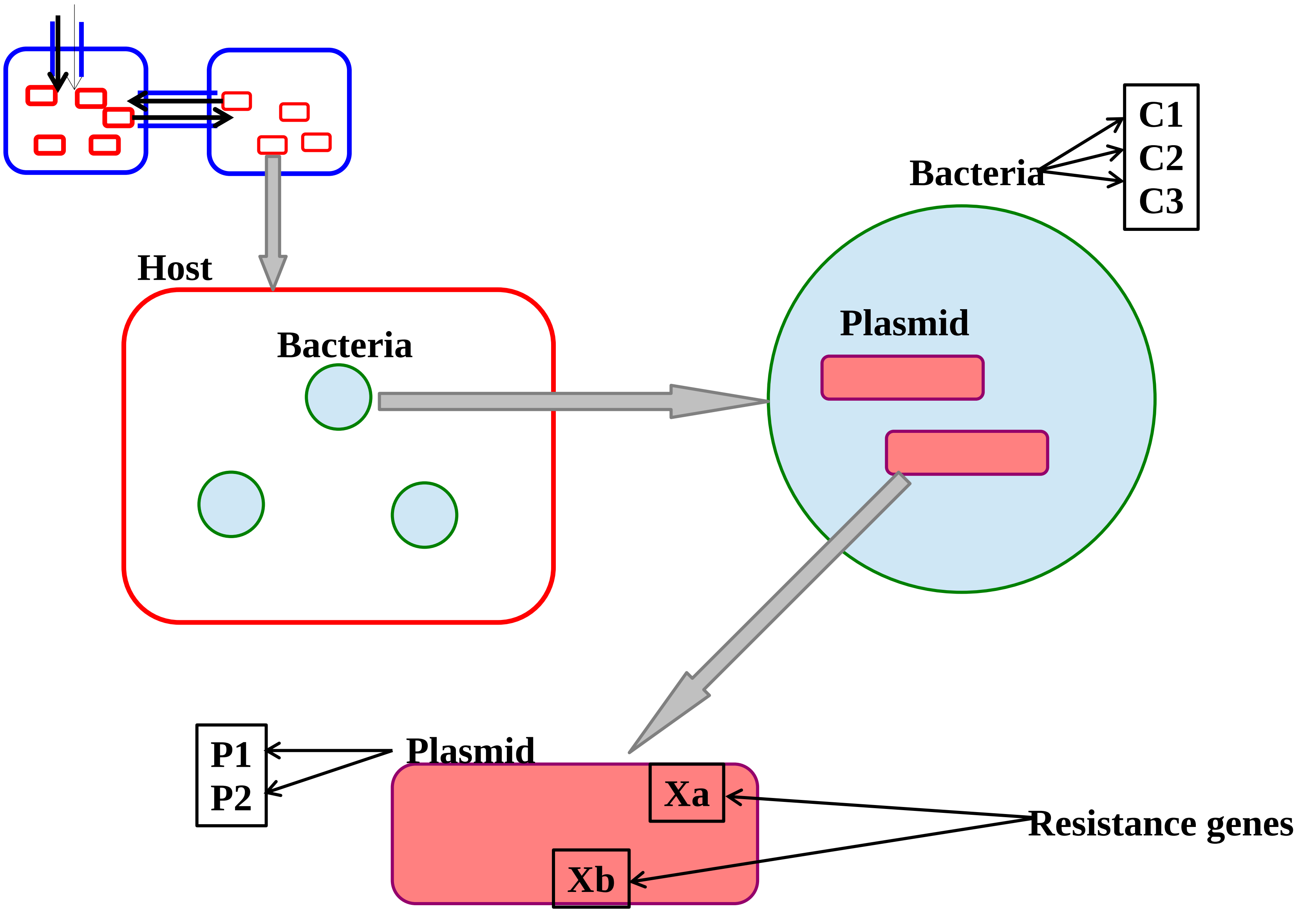

The Scenario



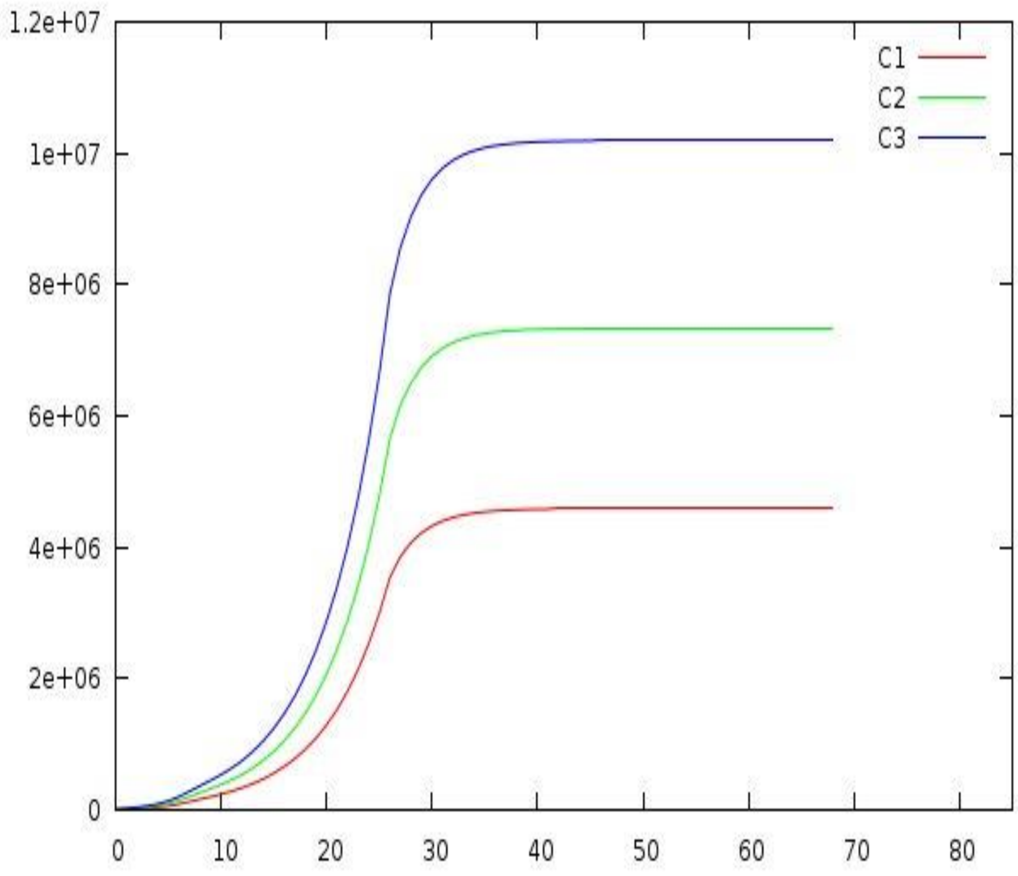
* Insecticide (*Blatella*)

The Scenario

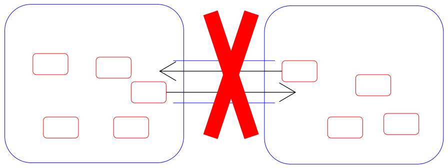


Experiments

ENV1



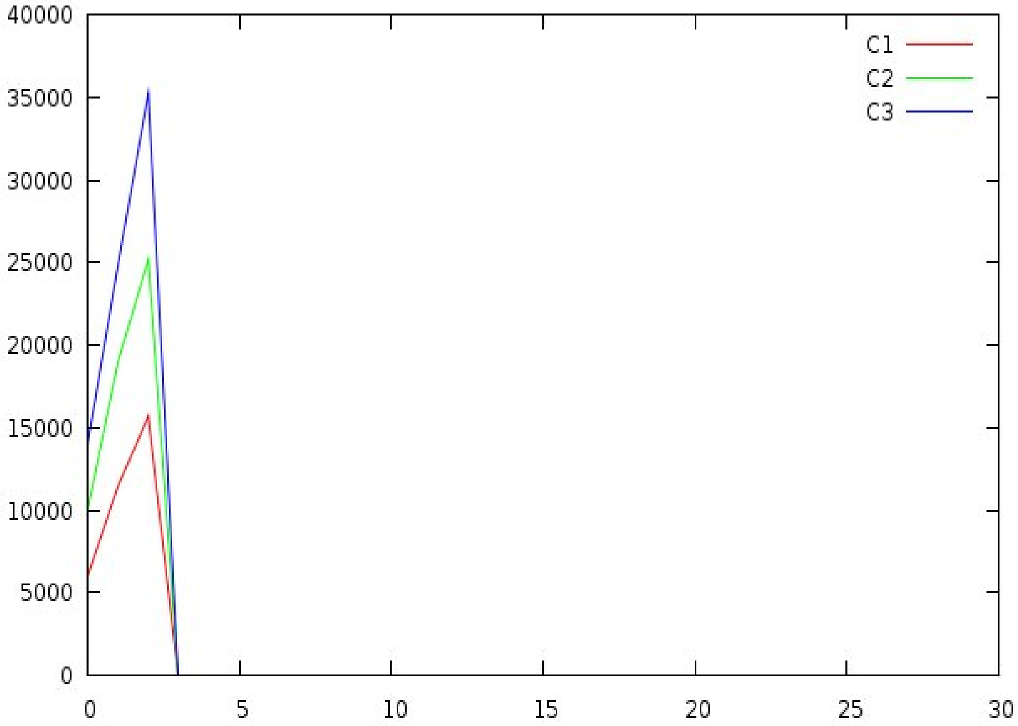
Scenario:
-No path between ENV1 and ENV2



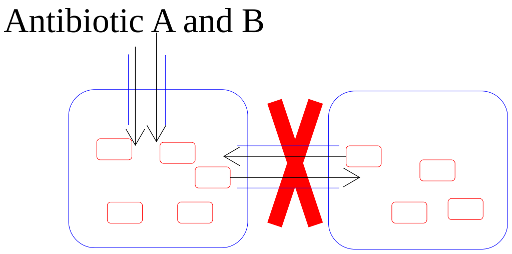
Observations:
-Normal growth of bacteria

Experiments

ENV1



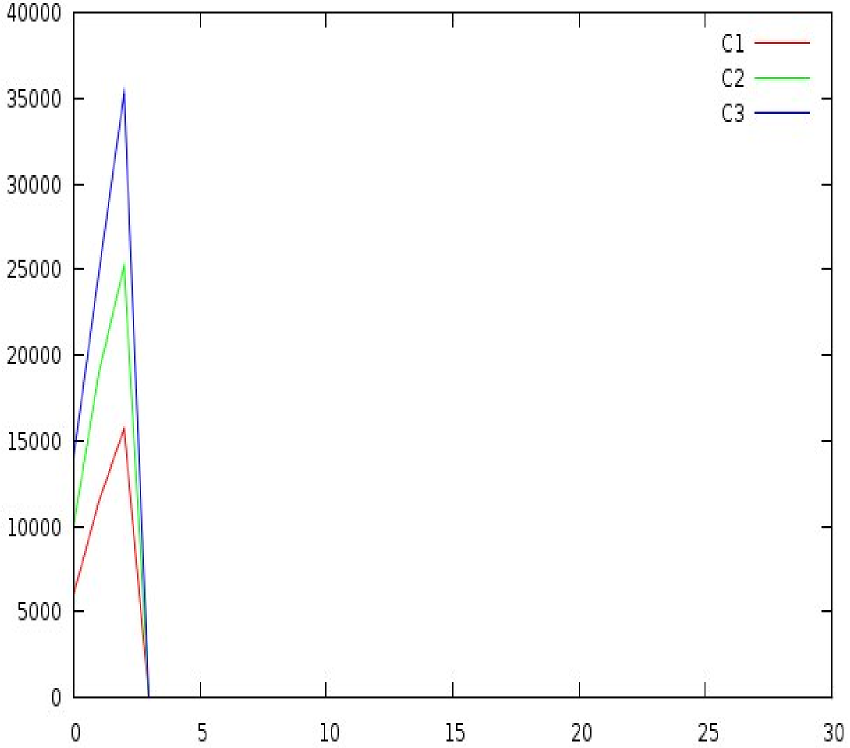
Scenario:
-No path between ENV1 and ENV2
-Challenge with Antibiotics A and B



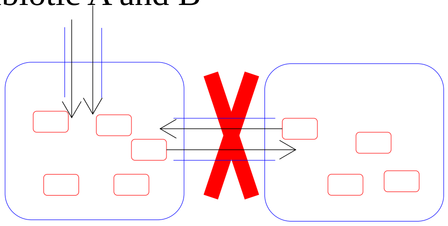
Observations:
- Susceptible bacteria are eliminated

Experiments

ENV1



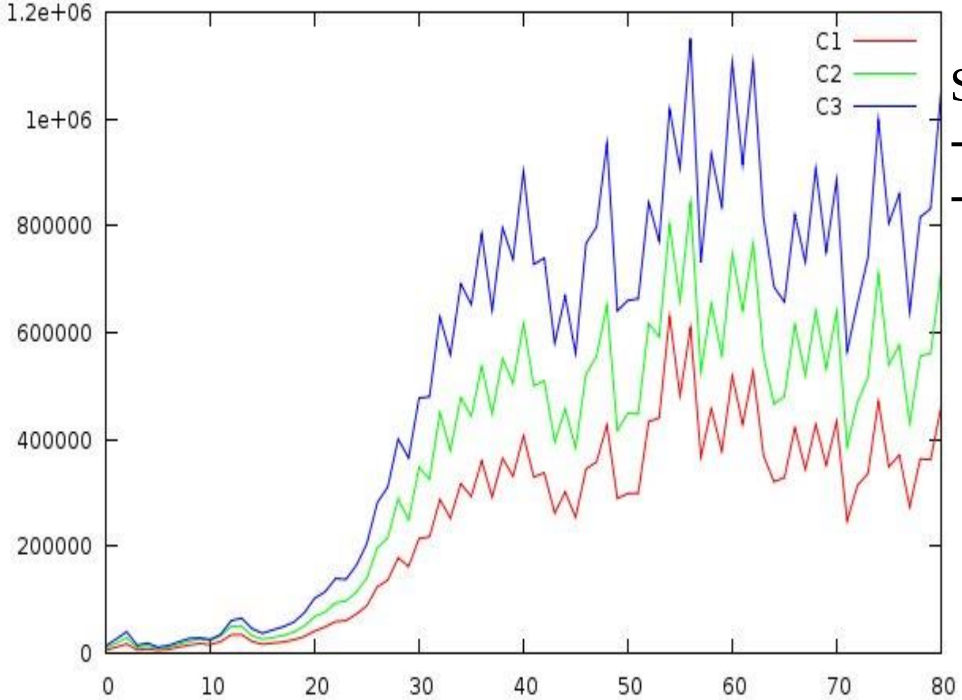
Scenario:
-No path between ENV1 and ENV2
-Challenge with antibiotics A and B
-Clone C1 from ENV1 containd a plasmid P1 with the resistance gene to A



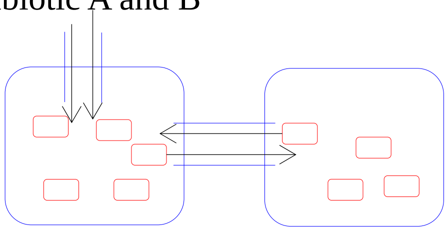
Observations:
-Bacteria suceptible to A and B are eliminated
-Antibiotic B kill Clone 1 resistant to A

Experiments

ENV1



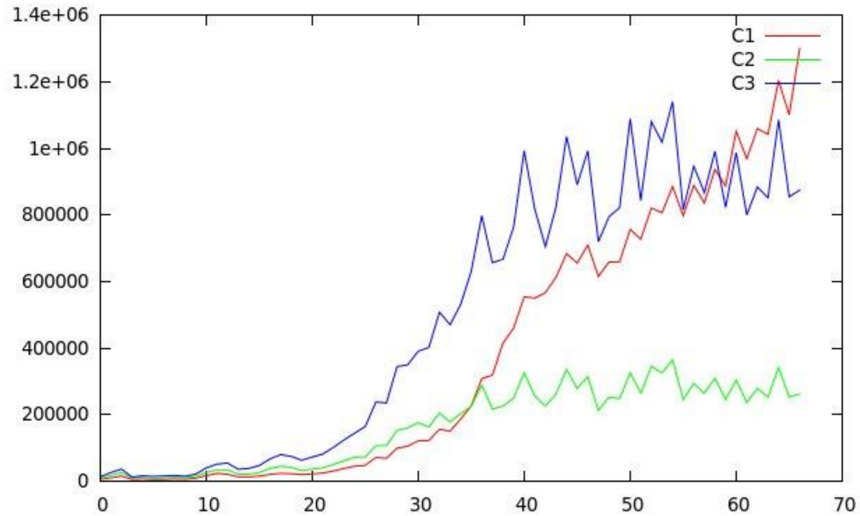
Scenario:
-Open path between ENV1 and ENV2
-Challenge with antibiotics A and B in ENV1

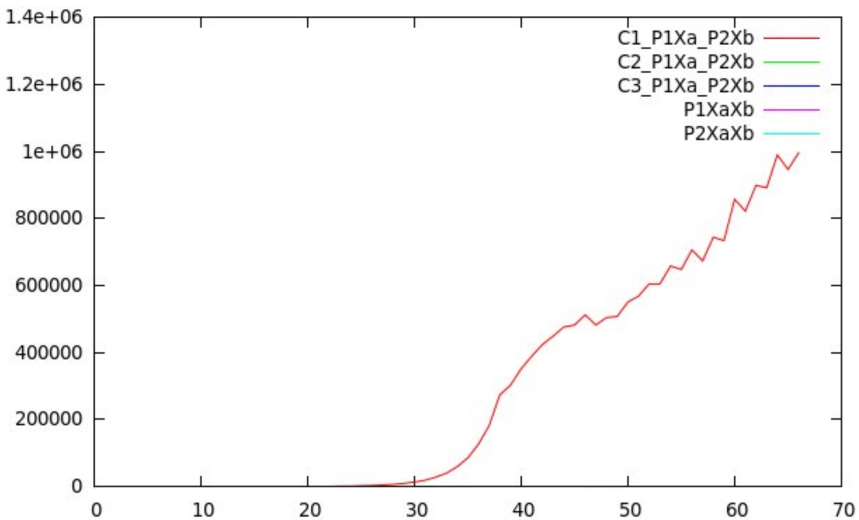


Observations:
-There is a constant flow of bacteria from ENV2 to ENV1. Because of this bacteria are not fully eliminated from in ENV1
-The noise in the graph is caused for the dead and migrations of bacteria in every step

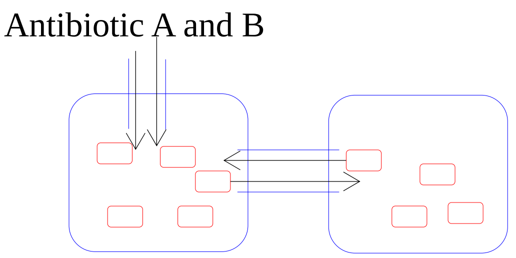
Experiments

ENV1





Scenario:
-Open path between ENV1 and ENV2
-Challenge with antibiotics A and B
-C1 from ENV1 have P1 with resistance to A
-C2 from ENV2 have P2 with resistance to B



Observations:

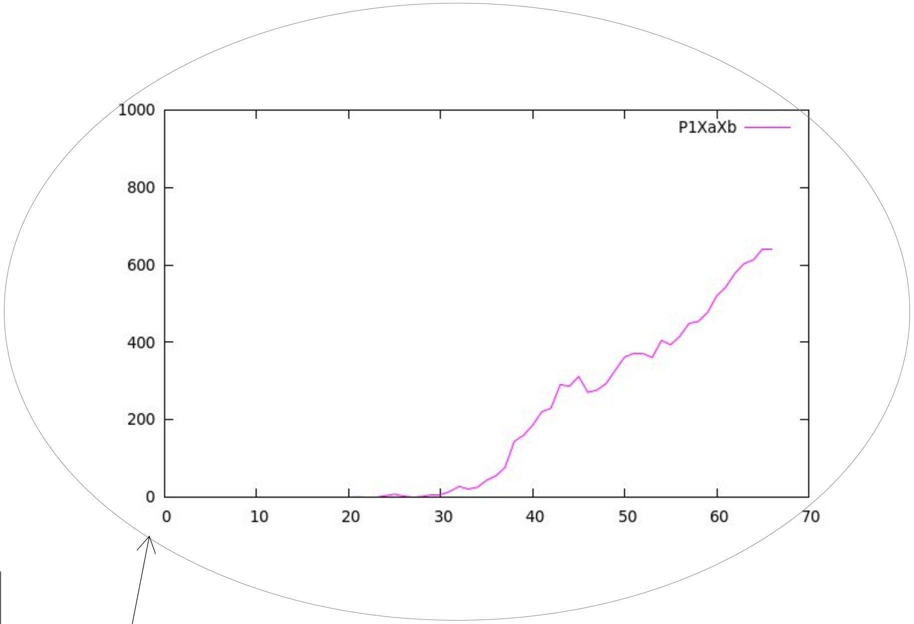
-Clone 2 with resistance to B move from ENV2 to ENV1 and transfer P2 to Clone 1

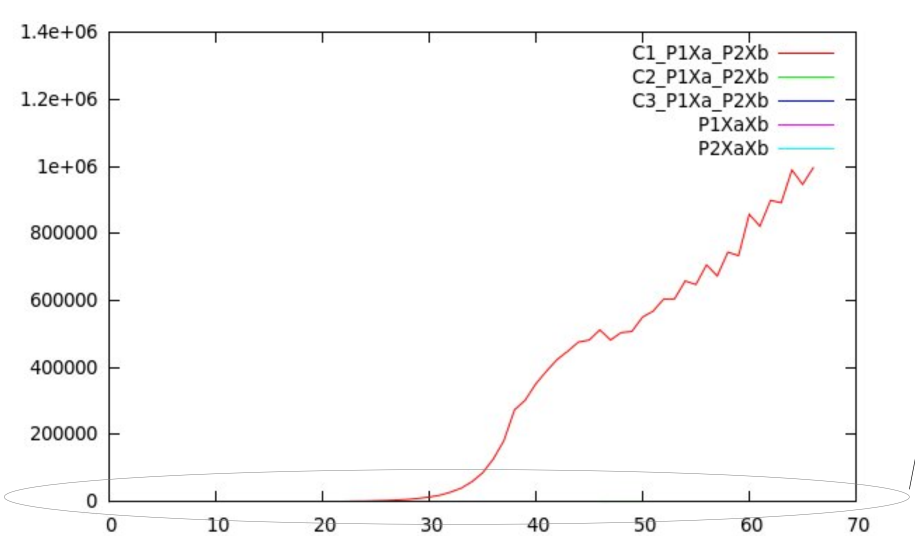
- Clone C1 resisting both antibiotics survive and spread

Experiments

Observations:

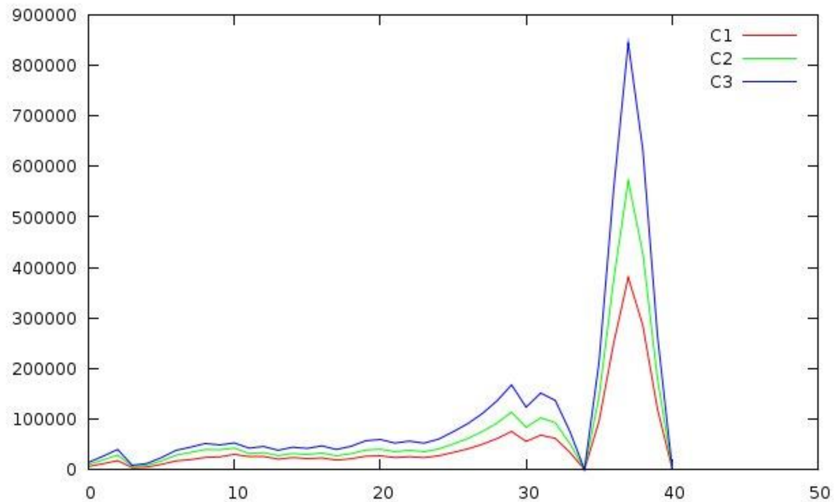
If the number of bacteria with plasmid P1 with a gene of A-resistance, and plasmid P2 with a gene of B- resistance survive and grow, the probability of P1 or P2 transfer to the other plasmid increase, leading to resitance to both antibiotics.

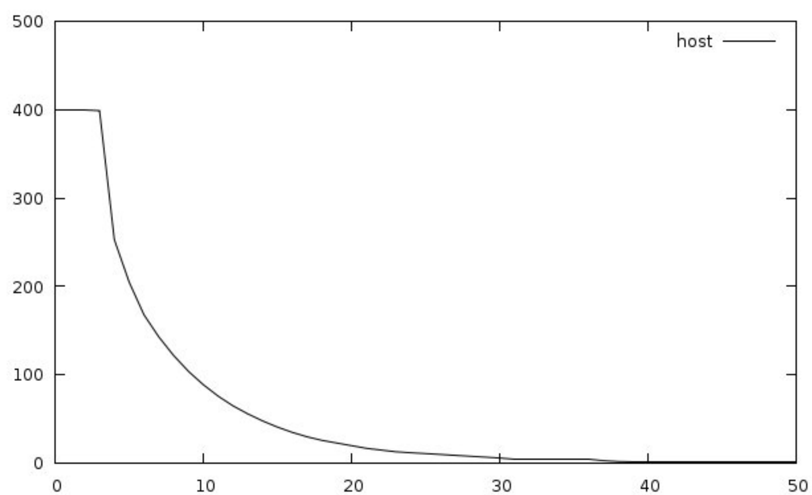




Experiments

ENV1





ENV1 + ENV2

Scenario:

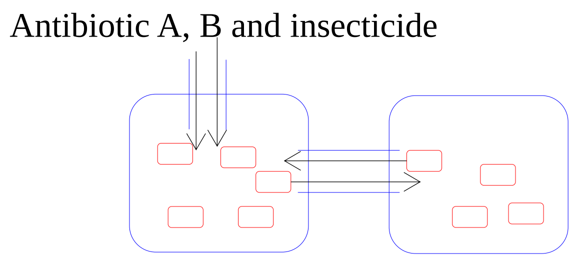
-Open path between ENV1 and ENV2

-Challenge with A and B antibiotics

-A proportion of hosts are eliminated (insecticide in *Blatella*)

-C1 from ENV1 has P1 with gene of A-resistance

-C2 from ENV2 has P2 with gene of B-resistance



Observations:

If the number of susceptible hosts decrease, resistant organisms are disappearing.

Future research and work in progress

- Refinement of the rules
- Stochastic/Probabilistic approach: migration to PDP systems
- Interfaces for input and output data
- Generalization of the experiments
- Connection with other sowftwares (i.e. R packages)