

DISEÑO E IMPLEMENTACIÓN DE UN SISTEMA DE INFORMACIÓN EN β -LACTAMASAS



Luis M. Rodríguez R.

Trabajo de grado dirigido por
Emiliano Barreto Hernández, cPhD

AGENDA

Introducción

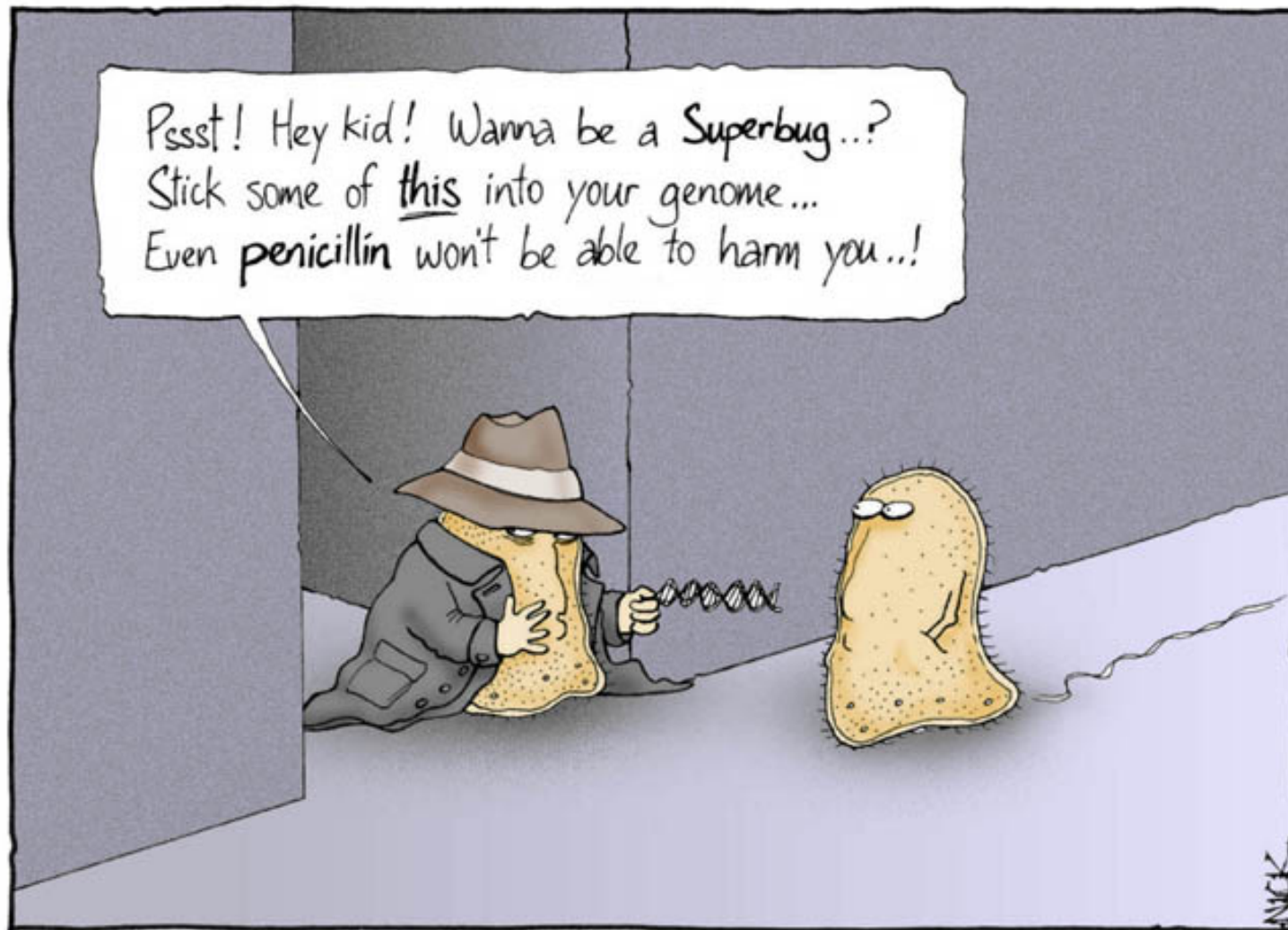
Métodos

Resultados

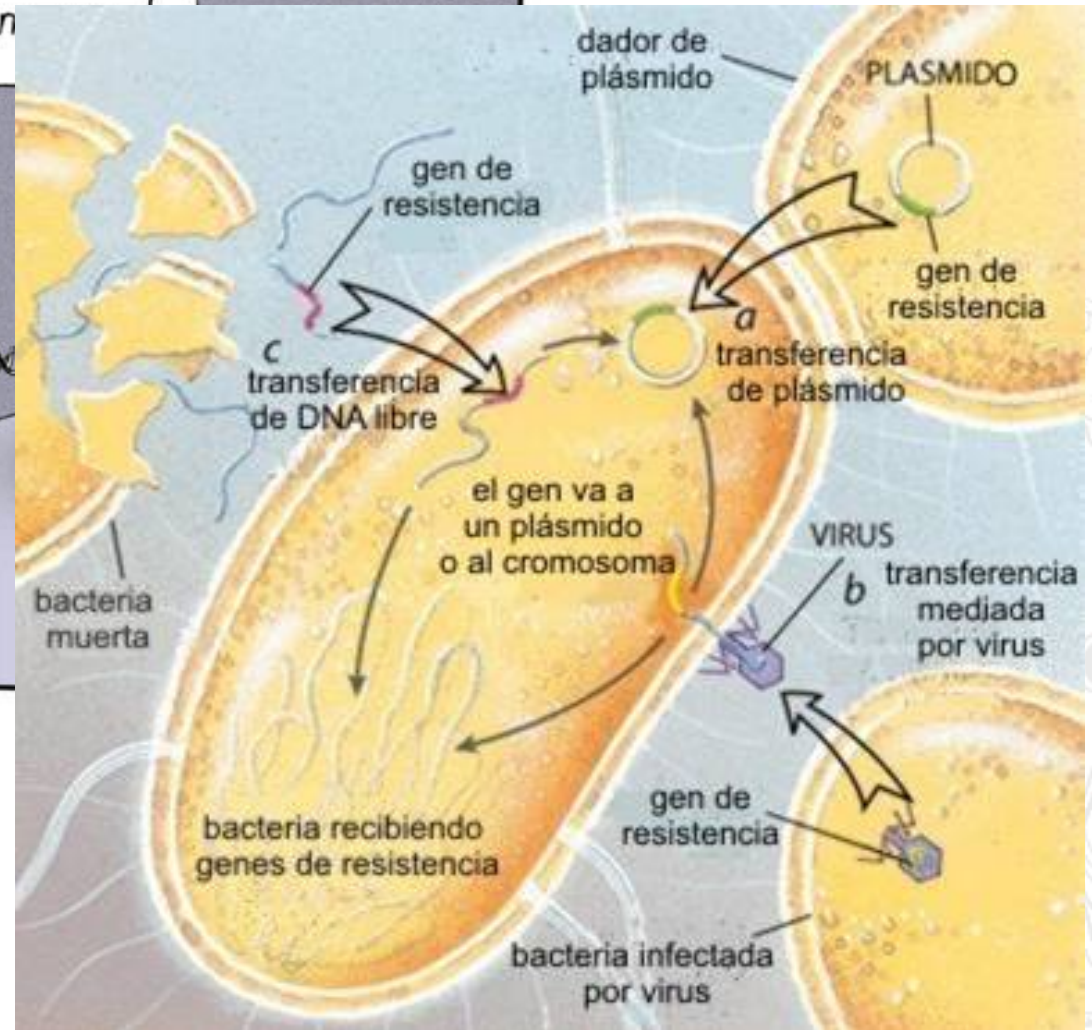
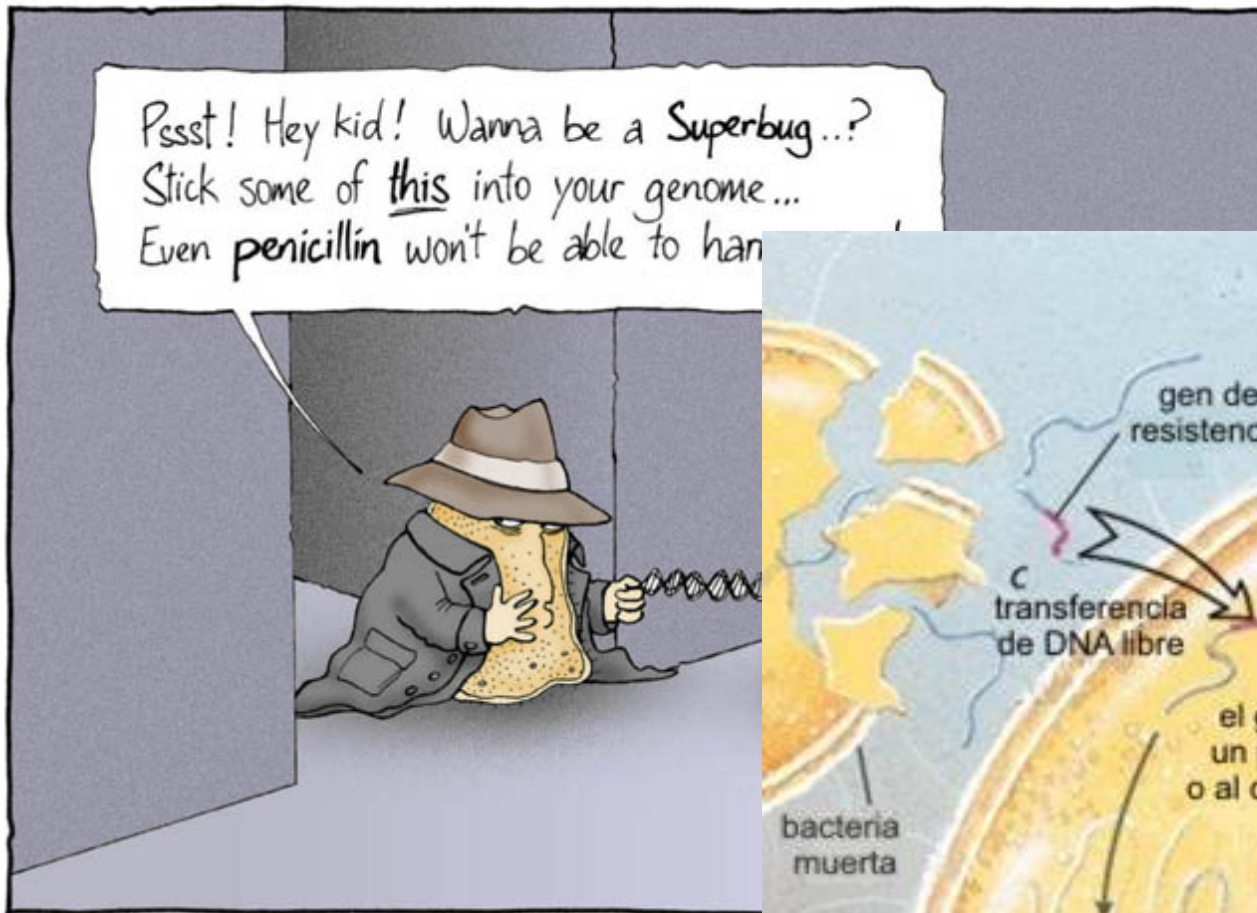
Conclusiones y perspectivas



Introducción: resistencia

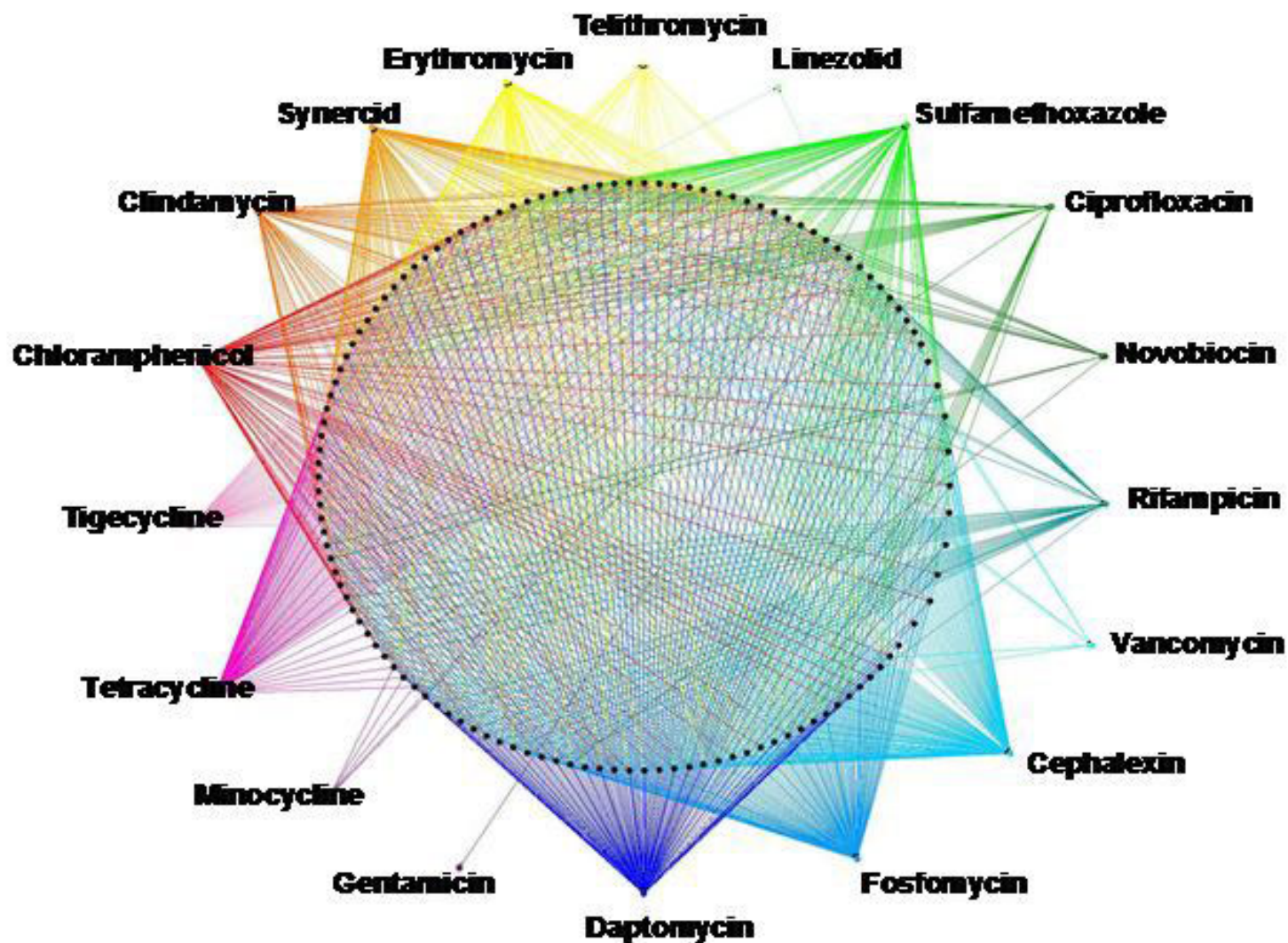


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Sánchez de Rivas C. 2006. ¿Antibióticos, ayer, hoy y mañana...? QuímicaViva 5(2).

Luis M. Rodríguez R.

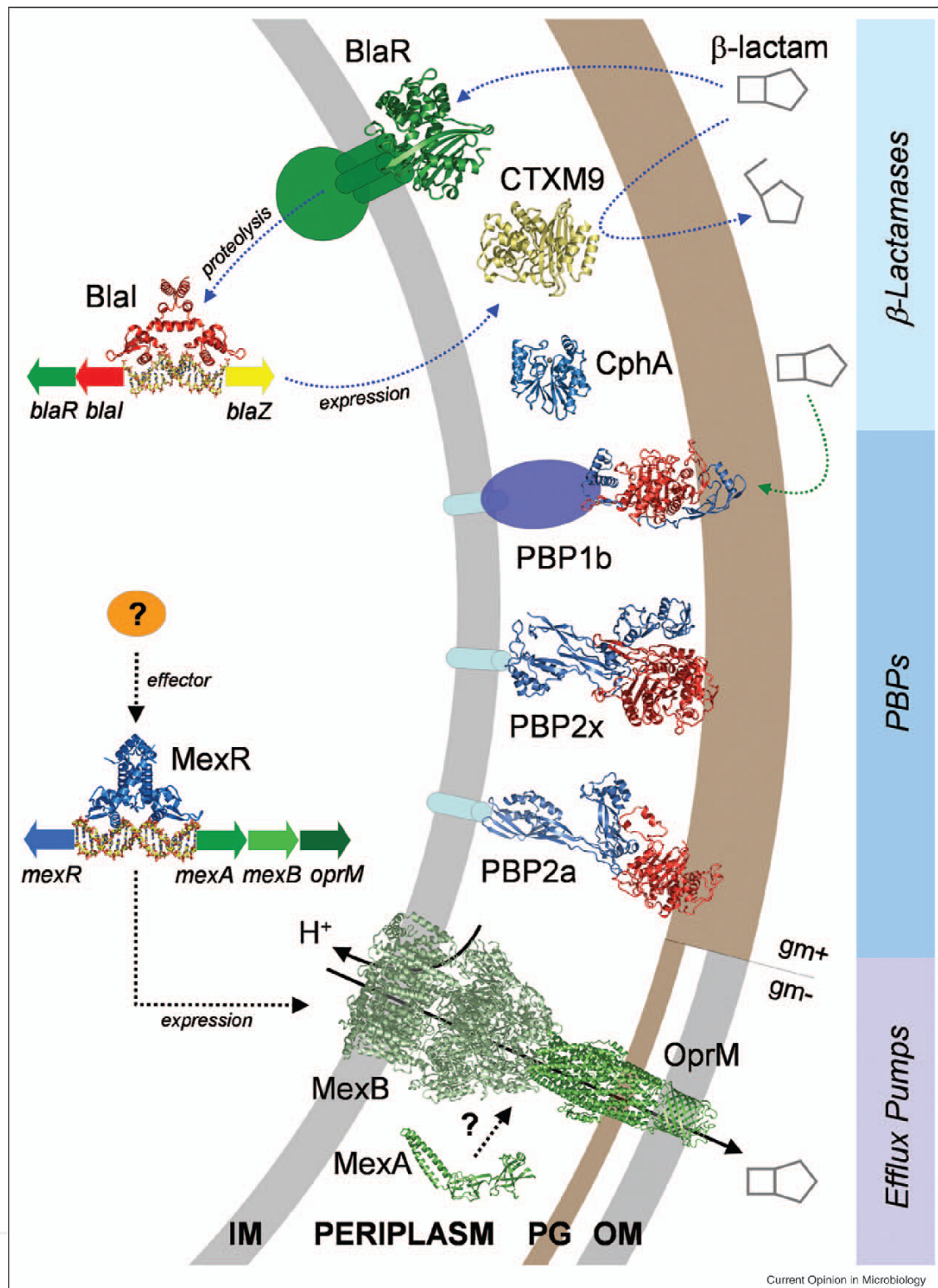


D'Costa VM, McGrann KM, Hughes DW, Wright GD.
2006. Science 311(5759):374-7.

Luis M. Rodríguez R.

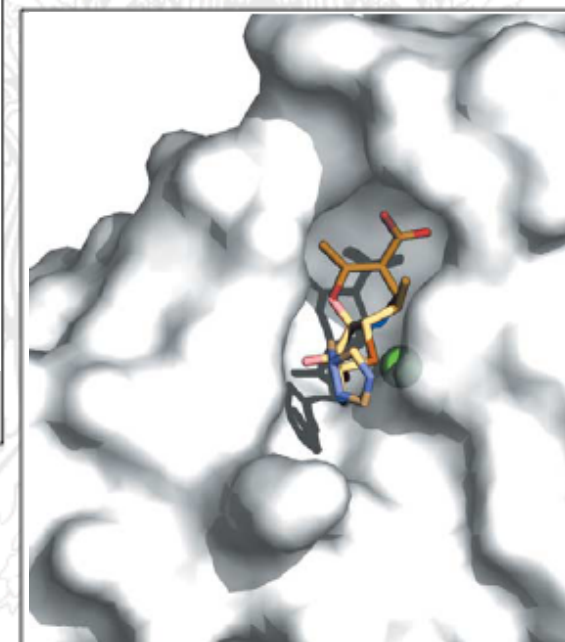
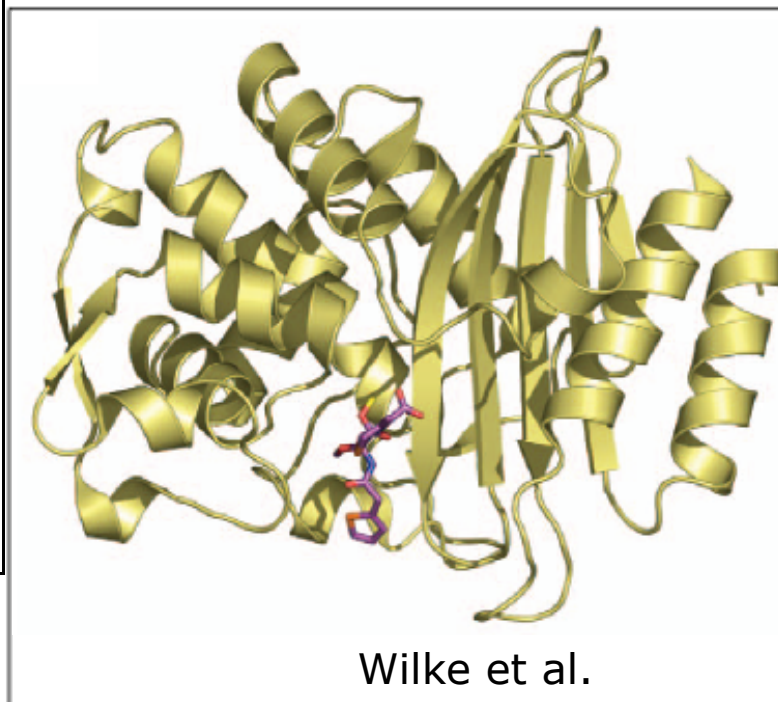
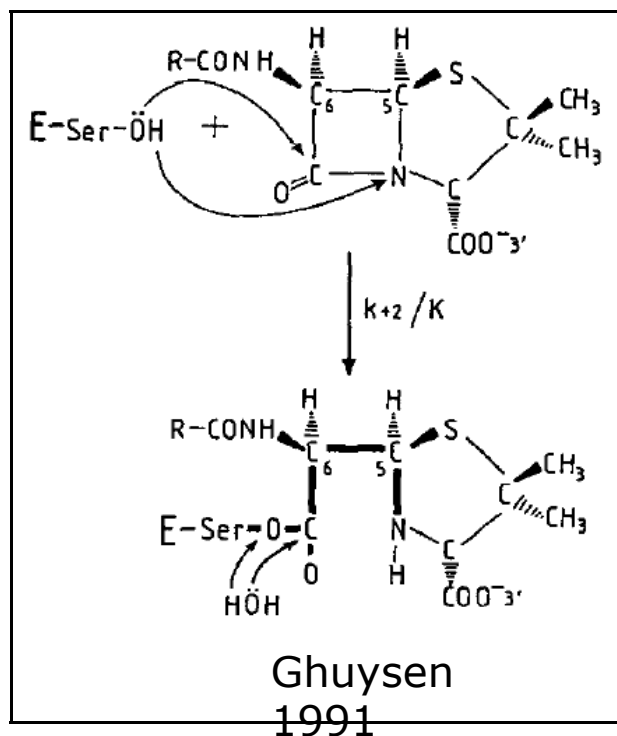
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Reproduction rights obtainable from
www.CartoonStock.com





Wilke MS, Lovering AL, Strynadka NCJ.
2005. β-lactam antibiotic resistance: a
current structural perspective. Current
Opinion in Microbiology 8:525-533.

Introducción: las β-lactamasas



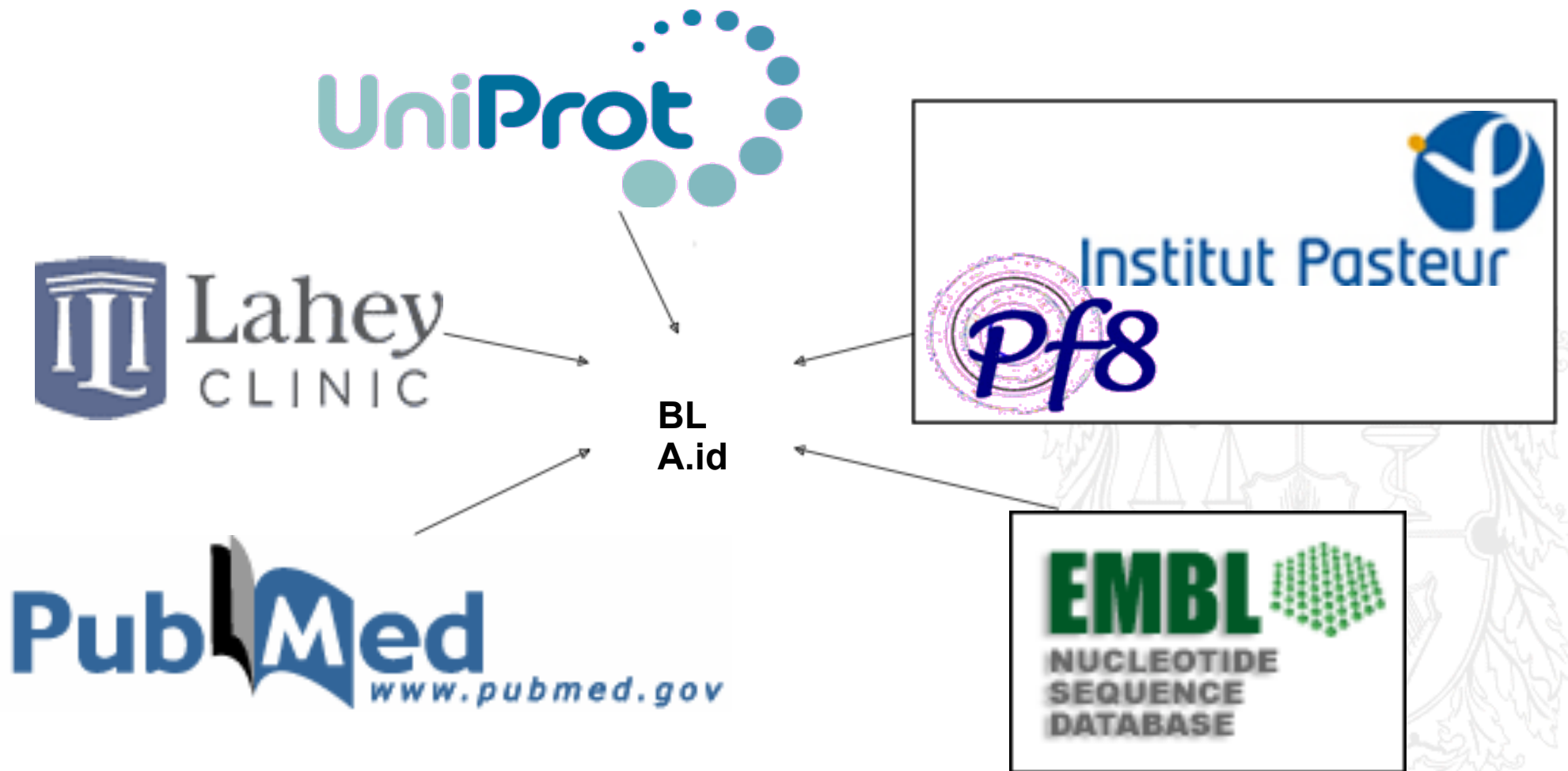
Garau et al. 2005

Ghuysen J-M. 1991. Serin β-lactamases and penicillin-binding proteins. *Annual Review of Microbiology* 45:37-67.

Garau G.; Bebrone C.; Anne C.; Galleni M.; Frère J-M.; Dideberg O. 2005. A Metallo-β-lactamase Enzyme in Action: Crystal Structures of the Monozinc Carbapenemase CphA and its Complex with Biapenem. *Journal of Molecular Biology* 345:785-795.

Wilke M.S.; Lovering A.L.; Strynadka N.C. 2005. β-Lactam antibiotic resistance: a current structural perspective. *Current Opinion in Microbiology* 8:525-533.

Introducción: el reto computacional



AGENDA

Introducción

Métodos

Resultados

Conclusiones y perspectivas



Métodos: obtención de datos

CTX-M-type β -Lactamases

β -Lactamase

Nucleotide

Reference

CTX-M-1
CTX-M-2
CTX-M-3
CTX-M-4
CTX-M-5
CTX-M-6
CTX-M-7
CTX-M-8
CTX-M-9
CTX-M-10
CTX-M-11
CTX-M-12
CTX-M-13
CTX-M-14
CTX-M-15 (UOE-1)
CTX-M-16
CTX-M-17
CTX-M-18
CTX-M-19
CTX-M-20
CTX-M-21
CTX-M-22
CTX-M-23
CTX-M-24
CTX-M-25
CTX-M-26
CTX-M-27
CTX-M-28
CTX-M-29
CTX-M-30
CTX-M-31
CTX-M-32
CTX-M-33
CTX-M-34
CTX-M-35
CTX-M-36
CTX-M-37

X92506
X92507
Y10278
Y14156
U95364
AJ005044
AJ005045
AF189721
AF174129
AF255298
AY005110
AF305837
AF252623
AF252622
AY044436
AY029068
AY033516
AF325133
AF325134
AJ416344
AJ416346
AY080894
AF488377
AY143430
AF518567
AY157676
AY156923
AJ549244
AY267213
AY292654
AJ567481
AJ557142
AY238472
AY515297
Assigned
AB177384
AY649755
^Y822595

AAC40:509, 1996
AAC40:509
AAC42:827
AAC42:125
AAC42:198
FEMS Microbiol Lett
FEMS Microbiol Lett
AAC44:193
AAC44:197
AAC45:616
AAC45:214
AAC 46:630
AAC 46:630
FEMS Microbiol Lett
AAC 45:226
AAC 46:121
AAC 45:335
AAC 45:335
FEMS Microbiol Lett
J. Infect. Dis
JAC 54:401
JAC 57:143
AAC 48:48
JAC 51:194
JAC 52:29
J. Infect. Dis
AAC 48:44
AAC 47:28
AAC 48:23
Int. J. Antimicrob Agents
JAC 56:115

Enzyme	pl value	2	4	9	11	12	1	0	275	278	Reference(s)	Accession number(s)
		(-)	(-)	(5)	(7)	(8)		(69)	(274)	(277)	(Reference)	
OXY-1-1	7.5	L	S	T	L	M			S	E	1	Z30177
OXY-1-2	7.7	.	.	.	.	.		.	.	.	5	AJ871864, AJ871865
OXY-1-3	N. A.	.	.	.	.	.		.	.	.	2	AY077482
OXY-1-4	N. A.	.	.	.	.	.		.	.	.	2	AY077483
OXY-1-5	N. A.	.	.	.	.	.		.	.	.	2	AY077486
OXY-1-6	5.25	.	.	.	.	.		.	.	K	3	Y17715
OXY-1-7	7.4	.	.	.	.	.		.	.	.	4	M27459
OXY-2-1	N. A.	I	.	I	M	L		.	N	.	5	AJ871866
OXY-2-2	N. A.	I	.	I	M	L		.	N	.	5	AJ871867
OXY-2-3	N. A.	I	.	I	M	L		.	N	.	2	AY077488
OXY-2-4	N. A.	I	.	I	M	L		.	N	.	3	Y17714
OXY-2-5	N. A.	I	.	I	M	L		.	N	.	2	AY077487
OXY-2-6	N. A.	I	.	I	M	L		.	N	.	2	AY077485
OXY-2-7	N. A.	I	.	I	M	L		.	N	.	1	Z49084
OXY-2-8	N. A.	I	.	I	M	L		.	N	.	6	AY055205
OXY-3-1	6.7	I	T	S	.	I		L	.	D	2	
OXY-4-1	7.7	.	.	S	.	.		.	.	.	2	
OXY-5-1	7.2	.	.	.	.	.		.	.	.	5	

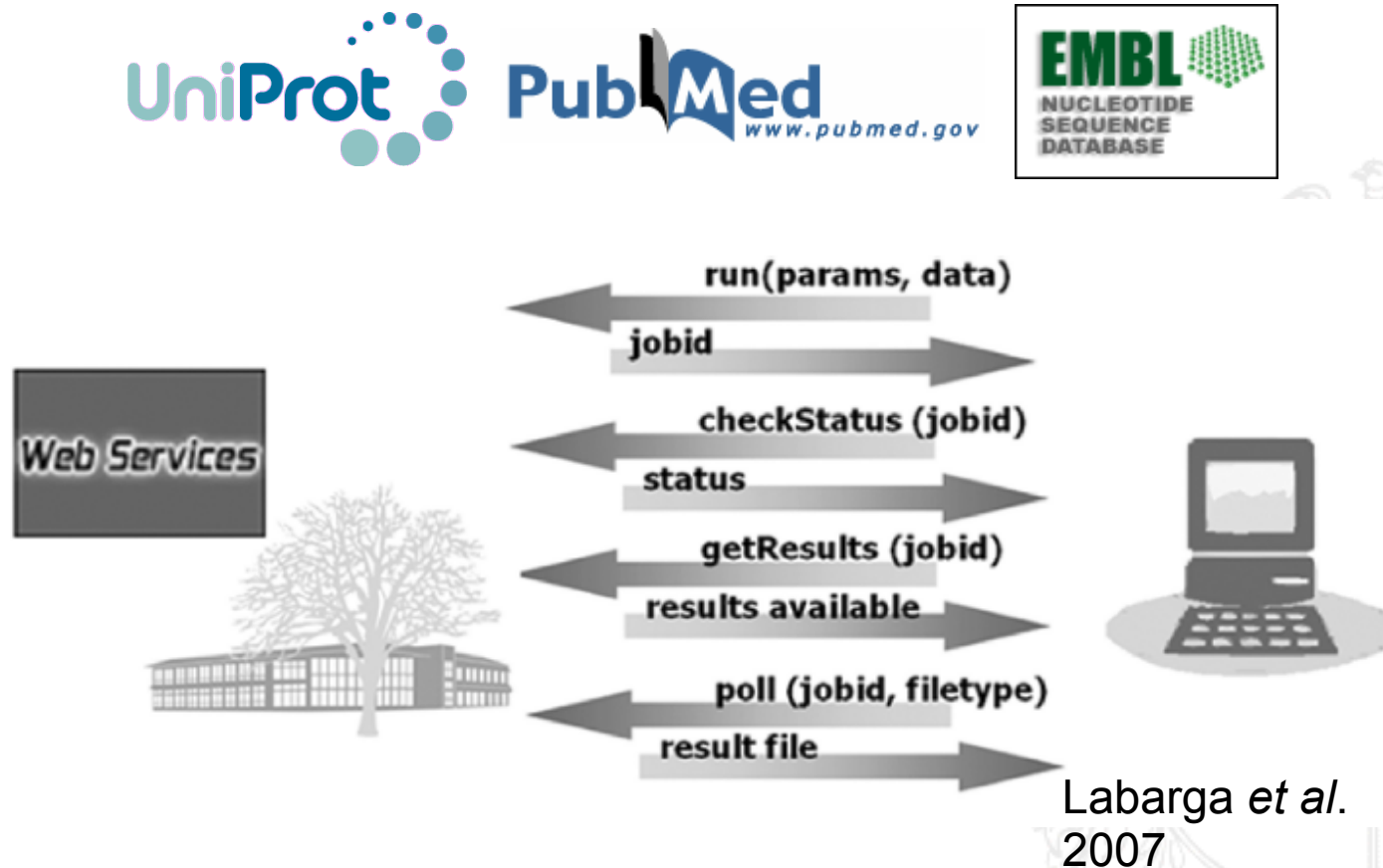
www.pasteur.f

AAC49:4745,2005
Int. J. Antimicrob Agents 27:573, 2006

www.lahey.or

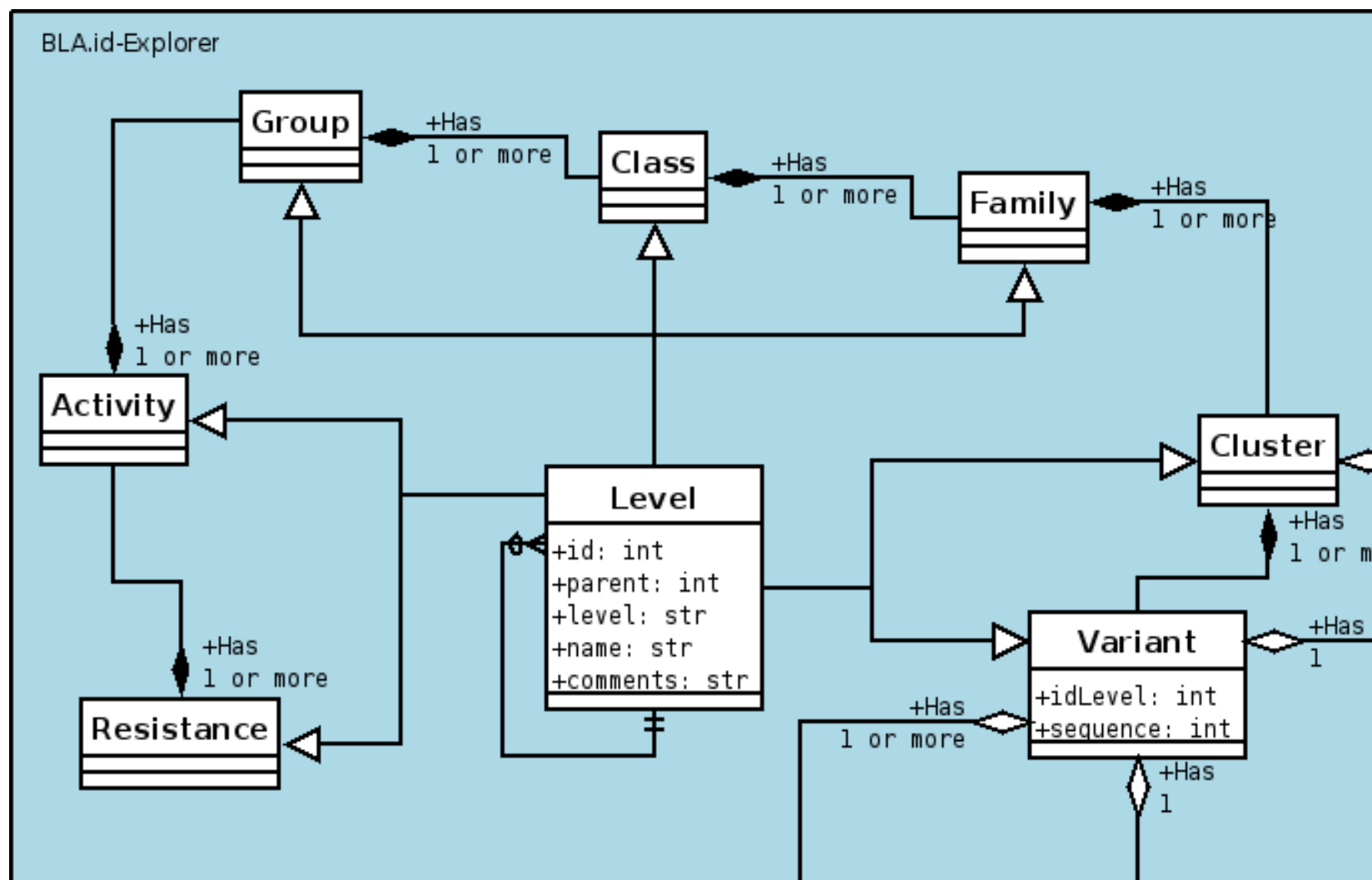
9 Luis M. Rodríguez R.

Métodos: obtención de datos

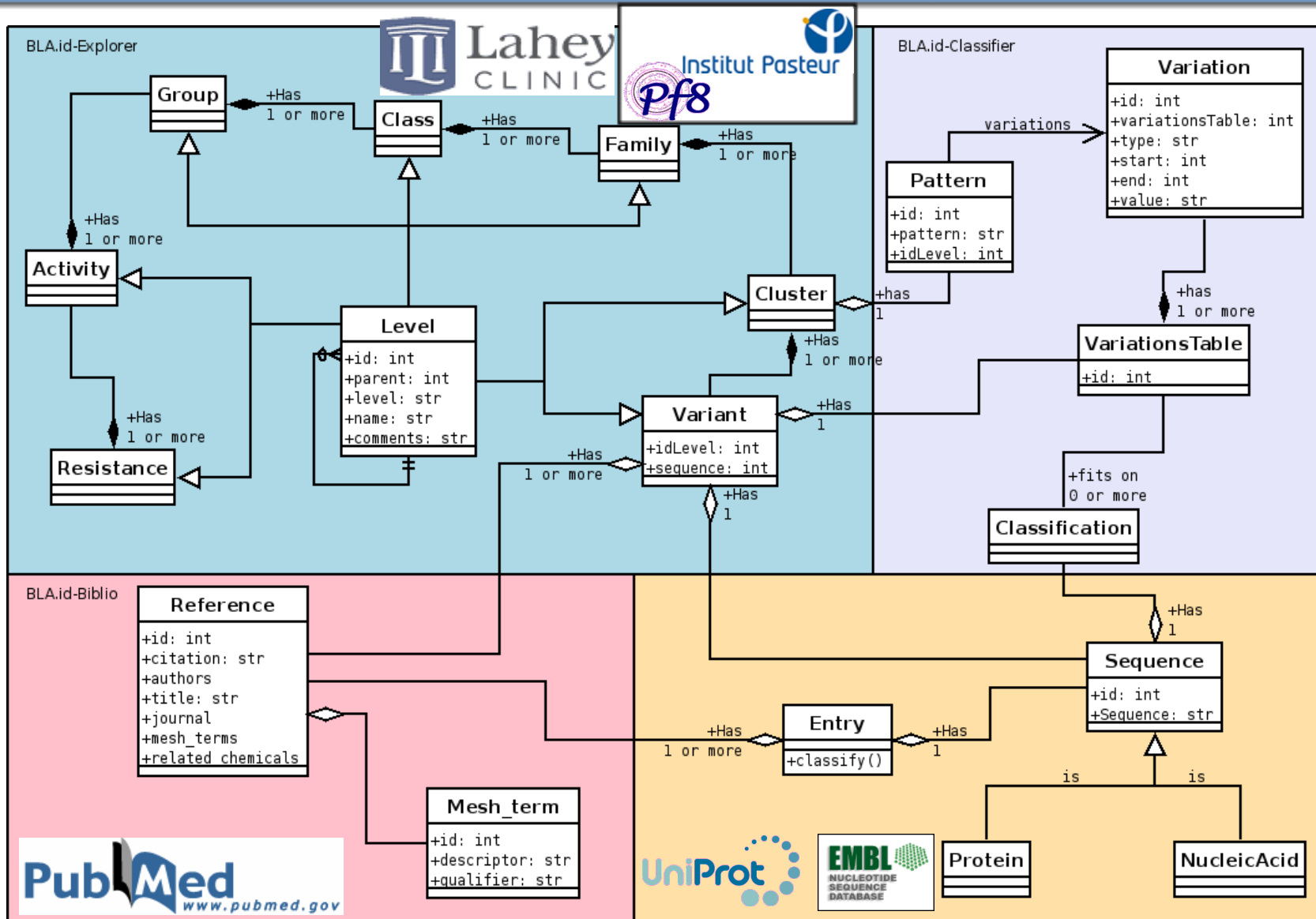


Labarga, A.; Valentin, F.; Andersson, M.; López, R. 2007. Web services at the European Bioinformatics Institute. *Nucleic Acids Research* 35:W6-W11.

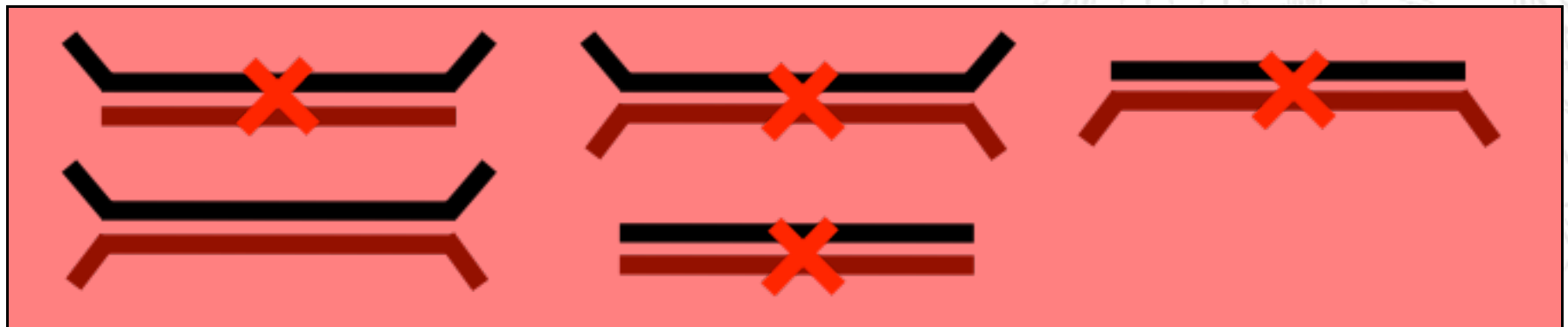
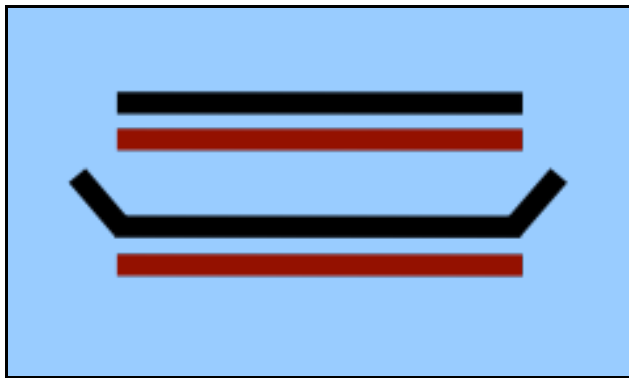
Métodos: estructura y organización

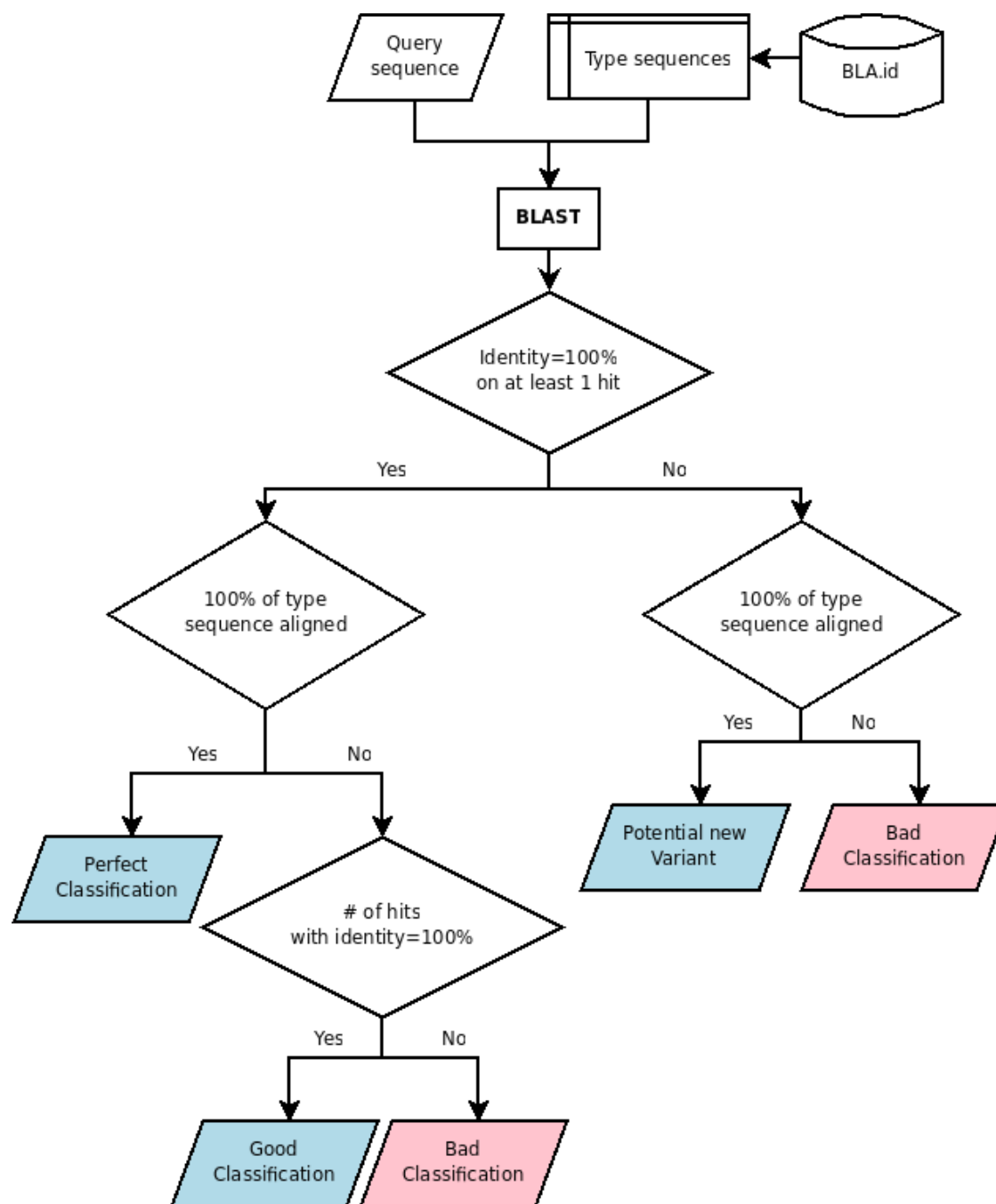


Métodos: estructura y organización



Métodos: clasificación





Métodos: implementación

PHP

JavaScript

C / C++

(bio)Perl

R

XML

MySQL

Apache

Linux

SOAP

AJAX



<xml />



AGENDA

Introducción

Métodos

Resultados

Conclusiones y perspectivas



Resultados: Web-GUI

Acción

☒ Clasificar ☐ Buscar Proteínas ☐ Buscar Ácidos Nucléicos

Tipo de secuencia

☒ Proteína ☐ Ácido nucleico

Introduzca su secuencia

```
>|cl|2|CME-2: CME_2 extended spectrum  
beta-lactamase.  
MKKIILLFILTSQVLVAQHTSILNDINAVTKDKKATVAVSVLGIENDFQF  
SNANGNLKMPMLSVFKFHIALAVLNQVDKGNLTLDQKILIKKSDLLENTW  
SPLREKYPDGNVELPLSEIITYTVAQSDNNGCDILLRLIGGKTQVQLMD  
VNGVKNFQIKYNEEEMHKNDVKTLANYTTTASMVKTLKAFYKGMFLSKR  
STIFLMDIMTKTNTGMSKLPGLLPKVRMARKTGSSGKMKNGLTIAENDSG  
IVTLANGKHAI AVFVKDSMESEEVNCGIIAQVSKI VWDALNKKNKP
```

o desde un archivo

Acción

☒ Clasificar ☐ Buscar Proteínas ☐ Buscar Ácidos Nucléicos

Tipo de secuencia

☒ Proteína ☐ Ácido nucléico

Introduzca su secuencia

```
>|cl|2|CME-2: CME_2 extended spectrum  
beta-lactamase.  
MKKIILLFILTSQVLVAQHTSILNDINAVTKDKKATVAVSVLGIENDFQF  
SNANGNLKMPMLSVEKFHIALAVLNQVDKGNLTLDQKILIKKSDLLENTW  
SPLREKYPDGNVELPLSEIITYTVAQSDNNGCDILLRLIGGKTQVQKLM  
VNGVKNFQ  
STIFLMDII  
IVTLANGKI
```



Su secuencia ha sido clasificada con éxito.

o desde un archivo

Enviar

RESULTADO

Su secuencia se ha clasificado exitosamente como

CME-2 (297 aa)

Identidad: 100%

E-value: 3e-168

Longitud del alineamiento: 297

ARCHIVOS ORIGINALES

[Ver la secuencia original](#)

[Ver el resultado en xml](#)

[Ver el resultado en html](#)

REFERENCIA (BLAST)

Altschul, Stephen F., Thomas L. Madden, Alejandro A. Schäffer, Jinghui Zhang, Zheng Zhang, Webb Miller, and David J. Lipman (1997), "Gapped BLAST and PSI-BLAST: a new generation of protein database search programs", Nucleic Acids Res. 25:3389-3402.

- > Actividad β -lactamase
 - > Grupo Serin-protease
 - > Clase A
 - > Familia CME
 - > Familia CTX-M
 - > Familia GES
 - > Familia OXY
 - > Familia KPC
 - > Clado KPC-2
 - > Variante KPC-1
 - > Variante KPC-2
 - > Variante KPC-3
 - > Variante KPC-4
 - > Variante KPC-5
 - > Variante KPC-6
 - > Variante KPC-7

> Actividad β-lactamase

> Grupo Serin-protease

> Clase A

> Familia CME

> Familia CTX-M

> Familia GES

> Familia OXY

> Familia KPC

> Clado KPC-2

> Variante KPC-1

> Variante KPC-2

> Variante KPC-3

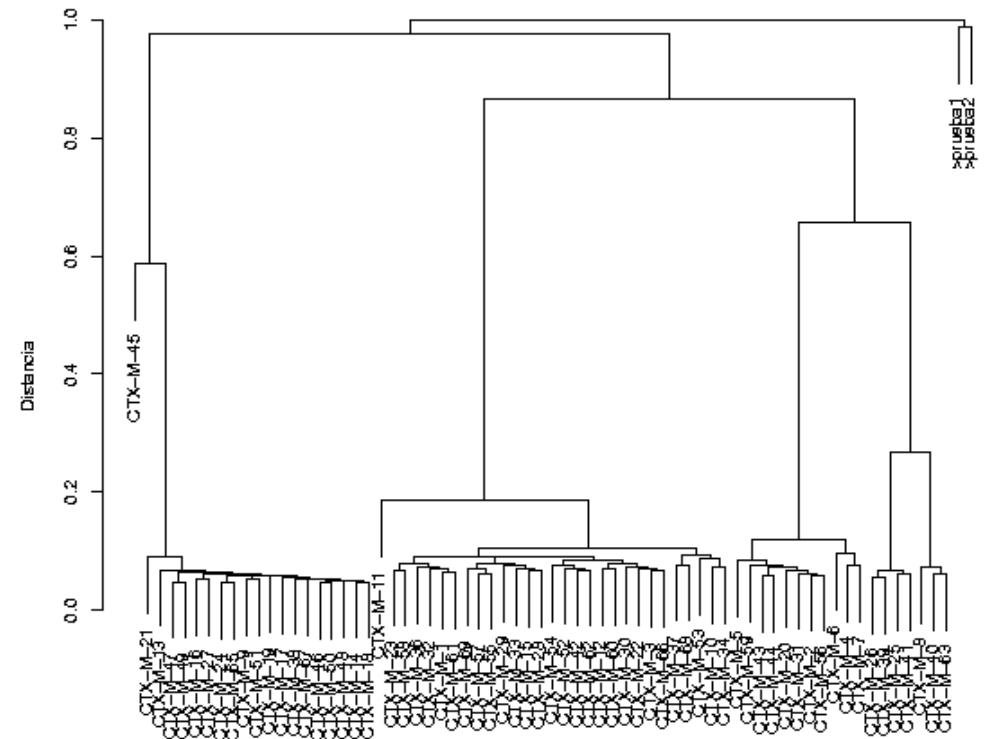
> Variante KPC-4

> Variante KPC-5

> Variante KPC-6

> Variante KPC-7

Dendrograma de Familia CTX-M y 2 ramas extra.



Hecho con BLA.id: <http://bioinf.ibun.unal.edu.co/BLA.id/0.3/> 13 Jul 2008.

This denomination was deprecated after the publication of erratum from Yigit H et al (2001) on February 2008. The sequence reported on 2001 had an erroneous codon, and corrected sequence is identical to that of Variante KPC-2.

Aceptar

ADMINISTRATION TASKS

SUBMIT A SEQUENCE TO THE DATABASE

Node to link sequence (may be blank)

KPC-7 (variant)
KPC-6 (variant)
KPC-5 (variant)
KPC-4 (variant)
KPC-3 (variant)
KPC-2 (variant)
KPC-1 (variant)
OXY-6-4 (variant)
OXY-6-3 (variant)

Database in which sequence is stored (may be blank)

☐ UniProt ☐ EMBL

Entrypname on the database (may be blank)

Sequence (this must be filled only if database or entryname are blank)

Comments

[Back to the main menu.](#)

::: Biblio

BLA.ID-BIBLIO

Colección de referencias bibliográficas relacionadas con β-lactamasas, con información adicional obtenida de Medline.

INFORMACIÓN GENERAL

Título	The structure of beta-lactamases.
Autores	Ambler RP .
Revista	Philosophical transactions of the Royal Society of London. Series B, Biological sciences .
Referencia cruzada	PubMed: 6109327  .
Cita	Ambler RP. The structure of beta-lactamases. Philos Trans R Soc Lond B Biol Sci. 1980 May 16;289(1036):321-31.

RESUMEN

The beta-lactamases are widely distributed in both Gram-positive and Gram-negative bacteria. They all inactivate penicillins and cephalosporins by opening the beta-lactam ring. Many varieties of the enzyme can be distinguished on the basis of their catalytic and molecular properties, but only amino acid sequence determination gives information upon which a molecular phylogeny can be based. The present evidence suggests that the beta-lactamases have a polyphyletic origin. All the beta-lactamases of currently known amino acid sequence belong to one homology group, here called class A enzymes. Class B consists of the mechanistically distinct *Bacillus cereus* beta-lactamase II, which preliminary partial sequence analysis suggests to be structurally unrelated to the class A enzymes. It is predicted that sequence analysis will show that further classes will need to be created to account for particular beta-lactamases of distinctive molecular and mechanistic properties.

Resultados: anotación y curaduría

5 casos típicos de anotación y curaduría: nodos problemáticos

Clase C

Familia LEN

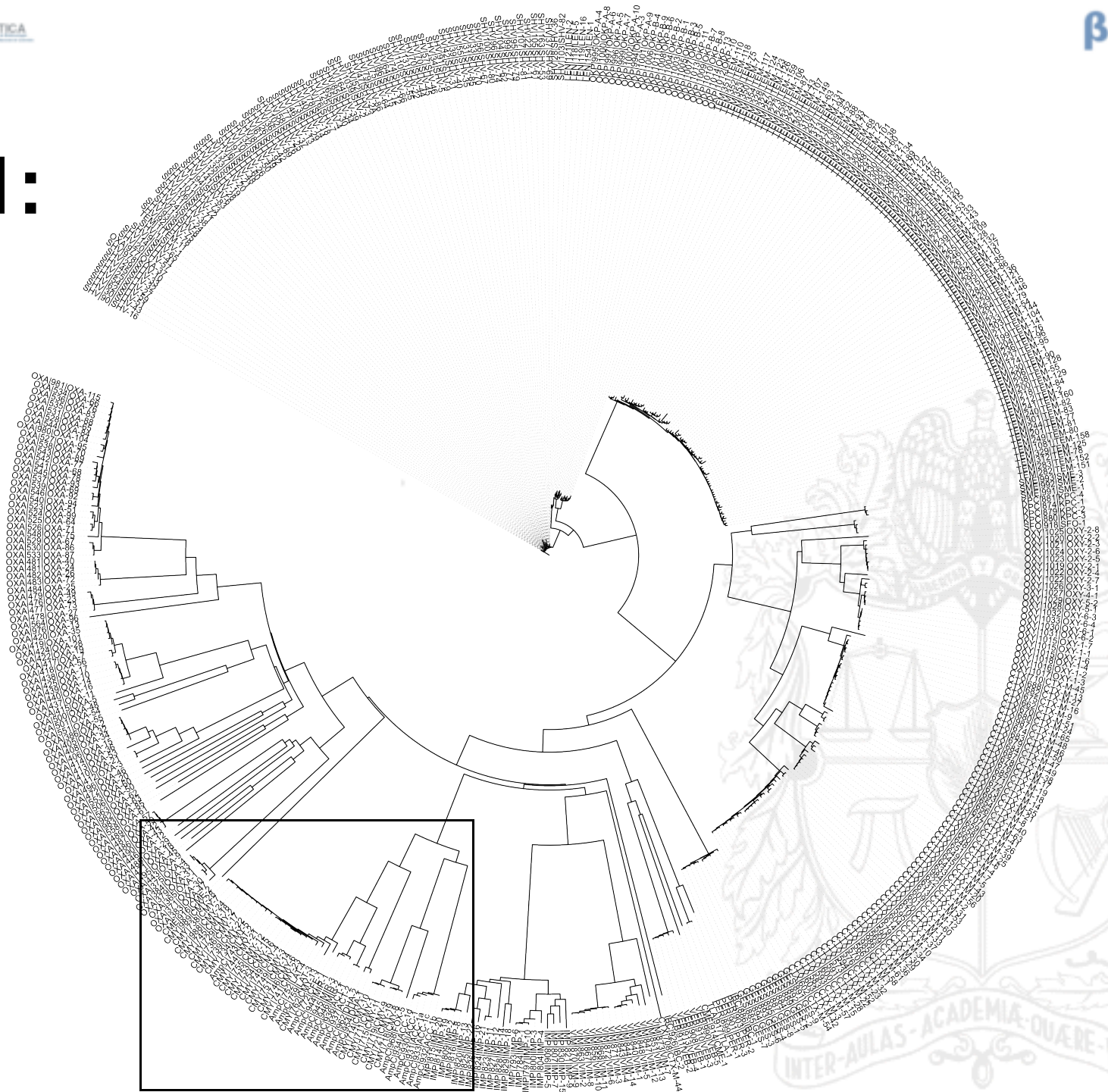
Clado OKP-B

Variante IBC-1

Familia FONA / SFO



Caso 1: Clase C



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Figure 1:

The figure displays a phylogenetic tree illustrating the evolutionary relationships among various beta-lactamase variants. The tree is rooted at the top left and branches downwards. The variants are labeled along the branches, including CMY989, CMY738, CMY988, CMY745, CMY729, CMY736, CMY739, CMY734, CMY743, CMY744, CMY755, CMY753, CMY754, CMY749, CMY751, CMY746, AmpC752, AmpC762, AmpC759, AmpC725, AmpC944, AmpC945, AmpC946, AmpC936, AmpC937, AmpC962, AmpC954, CMY714, CMY715, CMY719, CMY721, CMY718, AmpC968, AmpC934, AmpC930, AmpC931, AmpC933, and AmpC932. Colored circles (yellow, blue, green, red) highlight specific clusters or groups of variants.

Caso 2: Familia LEN



Caso 3: Clado OKP-B

› Variante OKP-B-8



› Variante OKP-B-9



› Variante OKP-B-10



› Variante OKP-B-11



› Variante OKP-B-12



› Variante OKP-B-13



› Variante OKP-B-14



› Variante OKP-B-15



› Variante OKP-B-16



› Variante OKP-B-17



› Variante OKP-B-18



› Variante OKP-B-19



› Variante OKP-B-20



Caso 4: Variante IBC-1

Download:



CLASSIFICATION

Group	Serin-proteasa
Class	A
Family	GES
Variant	GES-7

VARIANT DATA

BLA.id entry	PR885
Registered entries	PR885 PR886 PR1143
Reference	Giakkoupi P; Tzouveleakis LS; Tsakris A; Loukova V; Sofianou D; Tzelepi E. 2000. IBC-1, a novel integron-associated class A beta-lactamase with extended-spectrum properties produced by an <i>Enterobacter cloacae</i> clinical strain. <i>Antimicrob. Agents Chemother.</i> , 44, 2247-2253.

ENTRY DATA

Description	Class A beta-lactamase.
Organism	Enterobacter cloacae . [DSMZ] [Taxonomy]
xRef	Uniprot: Q9L8E3_ENTCL
Bibliographic reference	PubMed: 10952563
Sequence	Isoelectric Point: 7.6222 (Calculated on the basis of sequence) Length: 287 Update: 01-JUN-2003 Sequence >>

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Caso 5: Familia FONA / SFO

FONA-type	Identity	Similarity
FONA-1	95.3%	98.0%
FONA-2	95.6%	97.3%
FONA-3	96.3%	97.3%
FONA-4	95.6%	98.0%
FONA-5	95.9%	96.6%
FONA-6	96.6%	97.6%

Comparación de las secuencias de SFO-1 con las
6
variantes FONA

Sinónimos

Family	Synonyms on variants
CTX-M	4
GES	2
OXA	1
OXY	1
SFO	6
SHV	5
TEM	57
Total	76



Referencias geográficas

Proc. Natl. Acad. Sci. USA
Vol. 75, No. 8, pp. 3737–3741, August 1978
Biochemistry

Nucleotide sequence of the ampicillin resistance gene of *Escherichia coli* plasmid pBR322

(protein sequence/secretion signal/ β -lactamase/DNA chemistry)

J. GREGOR SUTCLIFFE*

The Biological Laboratories, Harvard University, Cambridge, Massachusetts 02138

Communicated by Walter Gilbert, June 14, 1978



Referencias geográficas

Proc. Natl. Acad. Sci. USA
Vol. 75, No. 8, pp. 3737–3741, August 1978
Biochemistry

Nucleotide of *Escheric*.

(protein sequence/

J. GREGOR SUTCL

The Biological Laboratories

Communicated by Walt

JOURNAL OF BACTERIOLOGY, Jan. 1974, p. 56–62
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Vol. 117, No. 1
Printed in U.S.A.

Molecular Specificities of R Factor-Determined Beta-Lactamases: Correlation with Plasmid Compatibility

R. W. HEDGES, NAOMI DATTA, POLYXENI KONTOMICHALOU, AND J. T. SMITH

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Department of Bacteriology, Clinic of Therapeutics, University of Athens, Athens, Greece; and
Microbiology Section, Department of Pharmaceutics, The School of Pharmacy University of
London, London WC1N 1AX, England

Received for publication 19 September 1973

Referencias geográficas

Proc. Natl. Acad. Sci. USA
Vol. 75, No. 8, pp. 3737–3741, August 1978
Biochemistry

Nucleotide of *Escheric*.

JOURNAL OF BACTERIOLOGY, Jan. 1974, p. 56–62
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Vol. 117, No. 1
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JOURNAL OF BACTERIOLOGY, Oct. 1970, p. 34–44
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Molecular Specification of B Factor Determined
Vol. 104, No. 1
Printed in U.S.A. npatibility

J.

T

C

Circular R-Factor Molecules Controlling Penicillinase

Synthesis, Replicating in *Escherichia coli* Under
Either Relaxed or Stringent Control

J. T. SMITH

W12 OHS England;
is, Greece; and
University of

POLYXENI KONTOMICHALOU,¹ MICHIKO MITANI,² AND
ROYSTON C. CLOWES

Division of Biology, The University of Texas at Dallas, Dallas, Texas 75230

Received for publication 20 April 1970

Referencias geográficas

Proc. Natl. Acad. Sci. USA
Vol. 75, No. 8, pp. 3737–3741, August 1978
Biochemistry

Nucleotide of *Escheric*

JOURNAL OF BACTERIOLOGY, Jan. 1974, p. 56–62
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Vol. 117, No. 1
Printed in U.S.A.

JOURNAL OF BACTERIOLOGY, Oct. 1970, p. 34–44
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Vol. 104, No. 1
Printed in U.S.A.

J.

T

C

Circular R-Factor Molecules Controlling Penicillinase

Synthesis Replicating in *Escherichia coli* Under

JOURNAL OF BACTERIOLOGY, Apr. 1975, p. 250–256
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J. T. SMITH

in W12 OHS England;
is, Greece; and
University of

Vol. 122, No. 1
Printed in U.S.A.

Origin of the TEM Beta-Lactamase Gene Found on Plasmids

FRED HEFFRON,* R. SUBLETT,¹ R. W. HEDGES, ALAN JACOB, AND STANLEY FALKOW

Department of Microbiology, University of Washington, Seattle, Washington 98195,* and the Department of
Bacteriology, Royal Postgraduate Medical School, London, England

Received for publication 4 November 1974

Resultados: datos almacenados

484 variantes, 2254 secuencias, 606 entradas bibliográficas con más de 1000 términos MeSH con calificadores, 63 comentarios y 67 referencias geográficas revisadas de 24 países.

Acceso libre desde <http://bioinf.ibun.unal.edu.co/BLA.id/>.



AGENDA

Introducción

Métodos

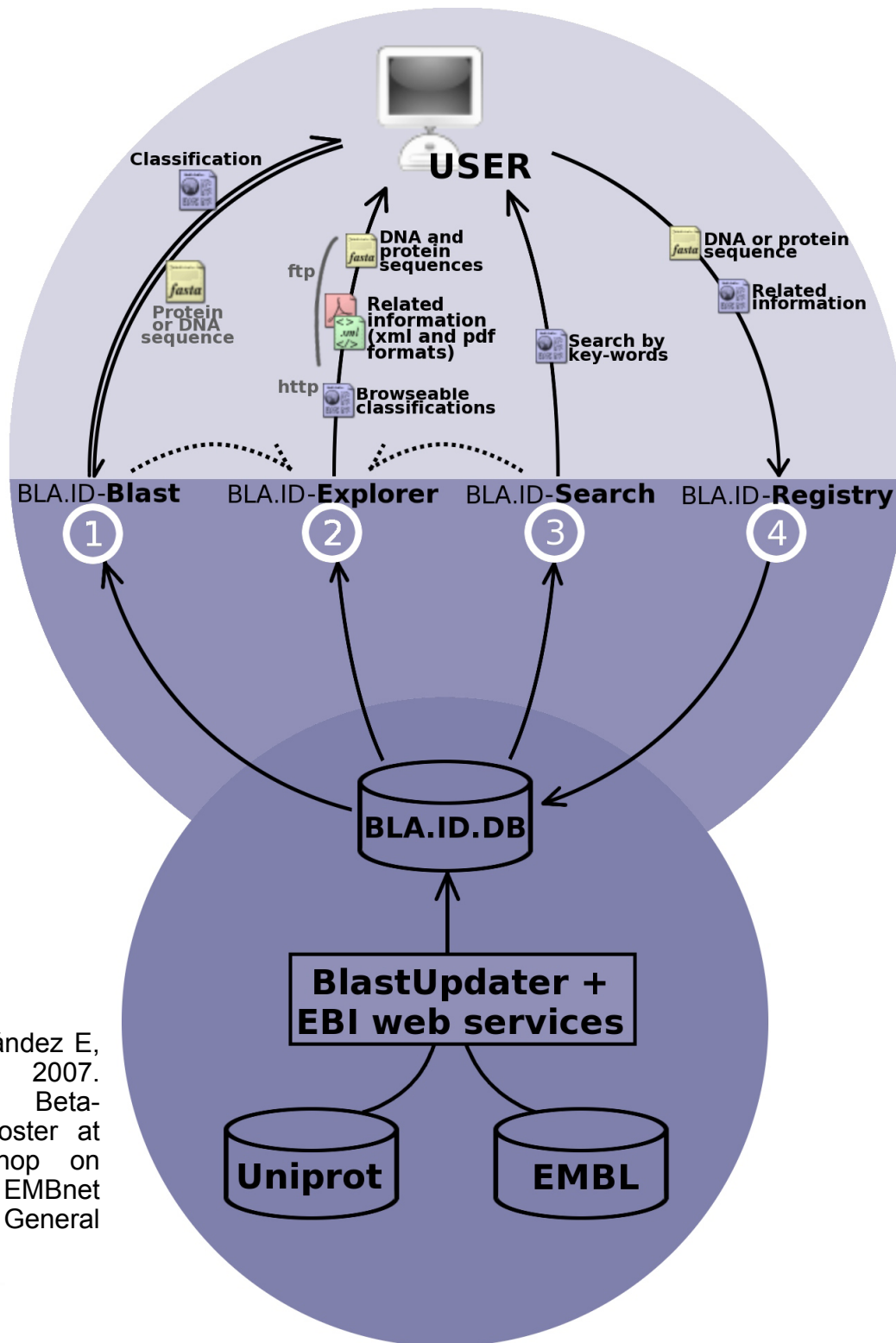
Resultados

Conclusiones y perspectivas



Conclusiones

- ¿Qué puede hacer un usuario?
 - ☐ Clasificar secuencias.
 - ☐ Buscar secuencias similares reportadas.
 - ☐ Encontrar información relacionada centralizada:
 - Bibliografía.
 - Anotación manual.
 - Referencias geográficas
 - ...
 - ☐ Generar dendrogramas de secuencias reportadas y/o provistas por el usuario.
- ¿Qué hemos encontrado?



Rodríguez RLM, Barreto-Hernández E, Reguero Reza MT. 2007. BLA.ID.CLINIC: A new Beta-lactamases web resource. Poster at Bioinformatics 2007: Workshop on Collaborative Bioinformatics, EMBnet Annual Meeting, RIB Annual General Meeting. Torremolinos, Spain.

Conclusiones

- ¿Qué puede hacer un usuario?
- ¿Qué hemos encontrado?
 - ☐ Nodos problemáticos.
 - ☐ Sinónimos.
 - ☐ Secuencias no reportadas como tipo.
 - ☐ Problemas en la referenciación geográfica.



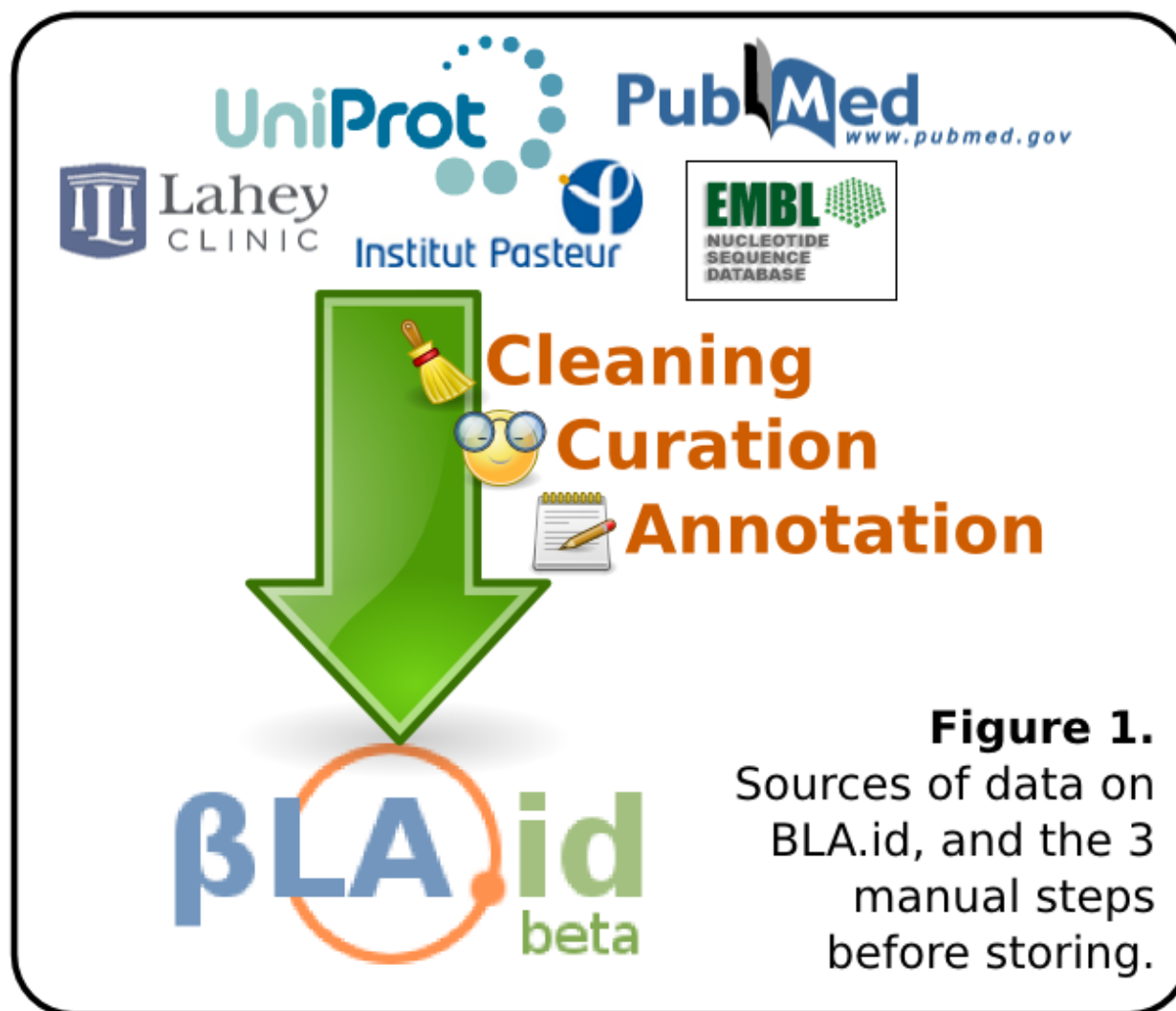


Figure 1.
Sources of data on
BLA.id, and the 3
manual steps
before storing.

Rodriguez L, Mantilla R, Falquet L, Reguero MT, Barreto E. 2008. Storage, classification and molecular patterns detection of beta-lactamases sequences. Abstract 70. Poster at EMBnet Conference 2008: 20th Anniversary Celebration: Leading applications and technologies in bioinformatics. Martina Franca, Taranto, Italy.

Perspectivas

- Herramientas de web 2.0 para mejorar el flujo de información.
- Perfiles AMSA (HMM-like).
- Antibióticos.
- No solo β -lactamasas.
- Minería de textos.



Final

. Agradecimientos

- ☐ Familia, amigos, compañeros, profesores.
- ☐ Emiliano Barreto Hernández, María Teresa Reguero, Ramón Mantilla, Laurent Falquet.
- ☐ Usuarios tempranos.



Colciencias.



Universidad Nacional de Colombia

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Instituto de Biotecnología

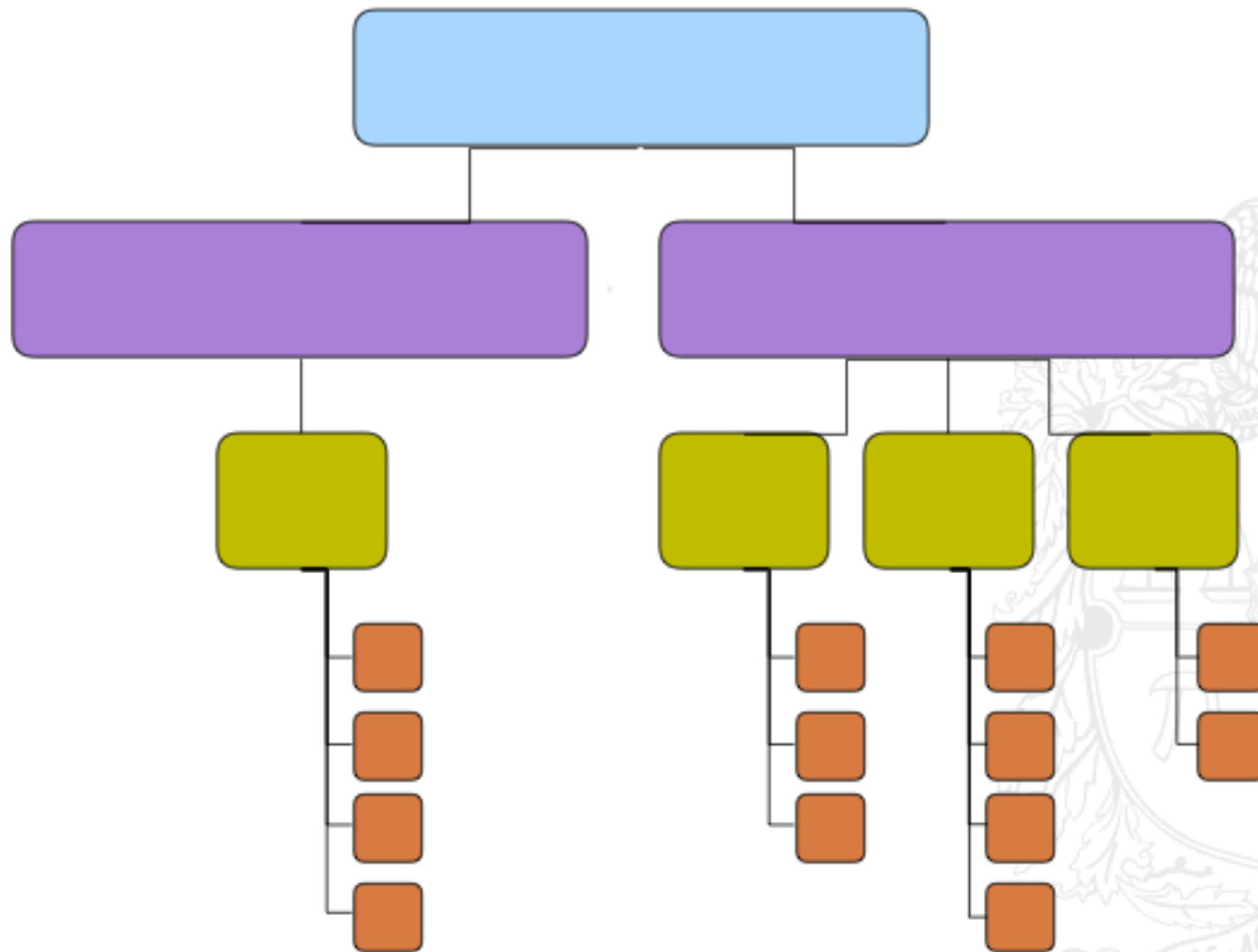
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Departamento de Biología

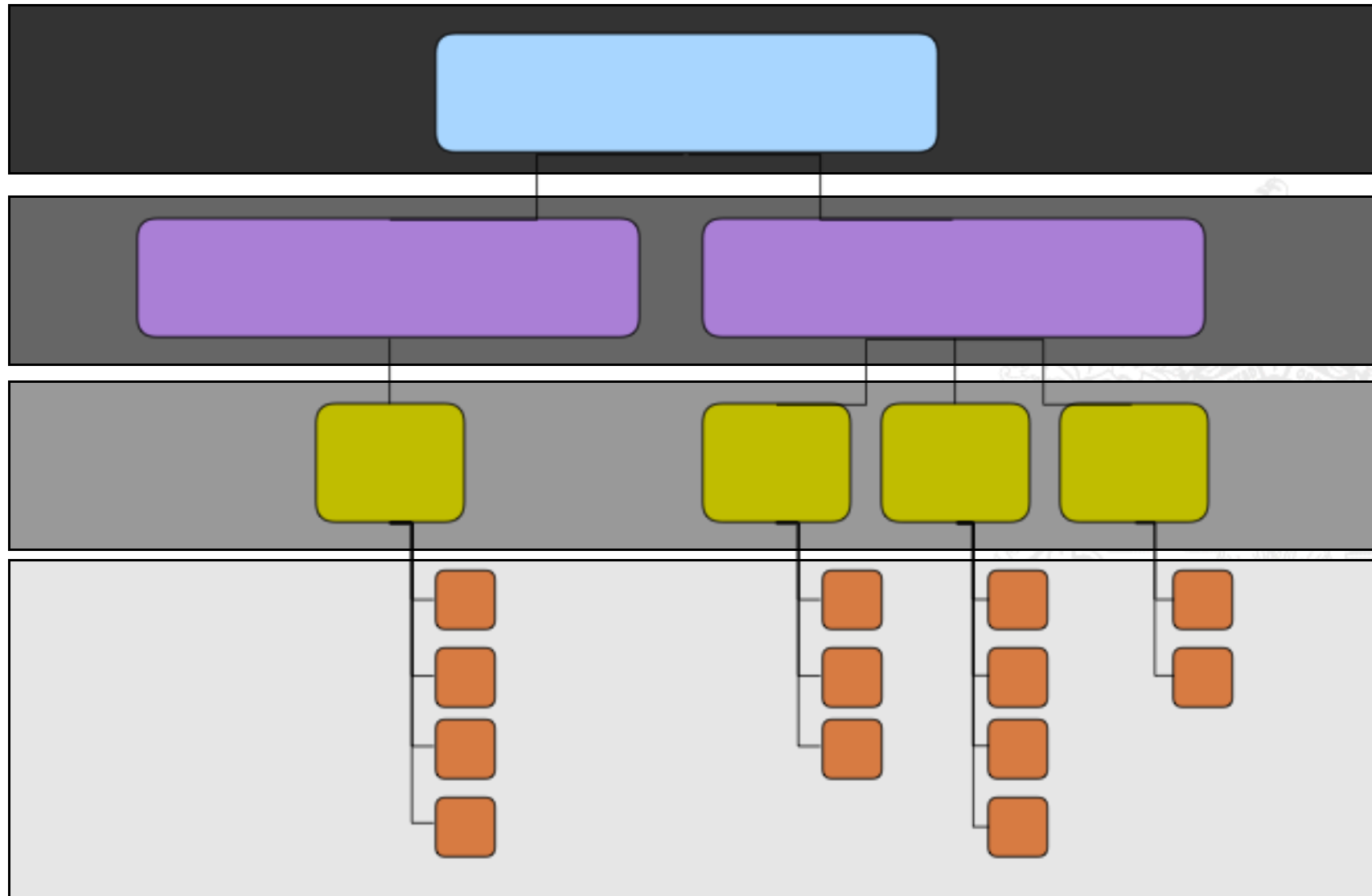
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Dirección de Investigación Sede Bogotá, Universidad Nacional de Colombia

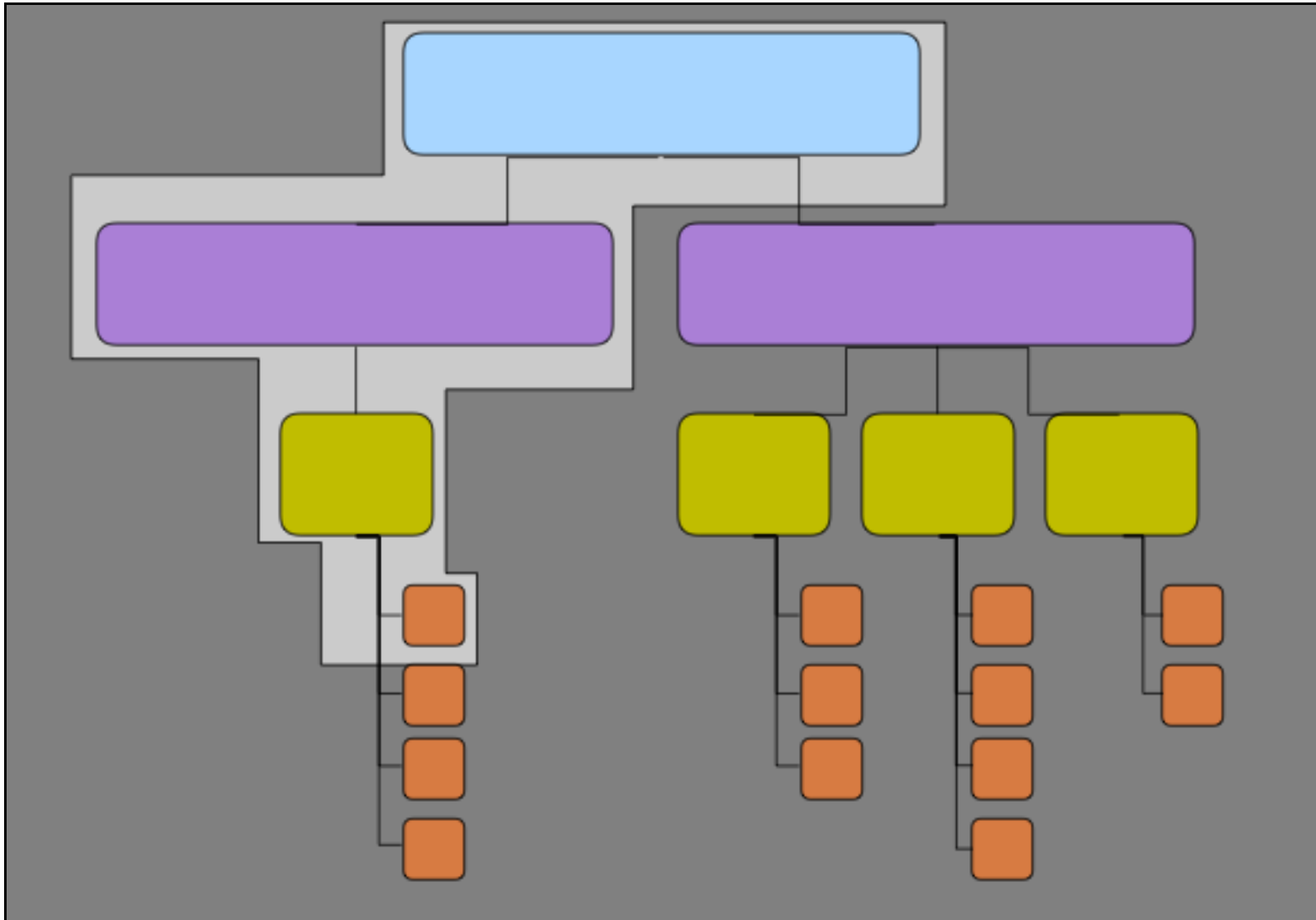
Métodos: estructura y organización



Métodos: estructura y organización

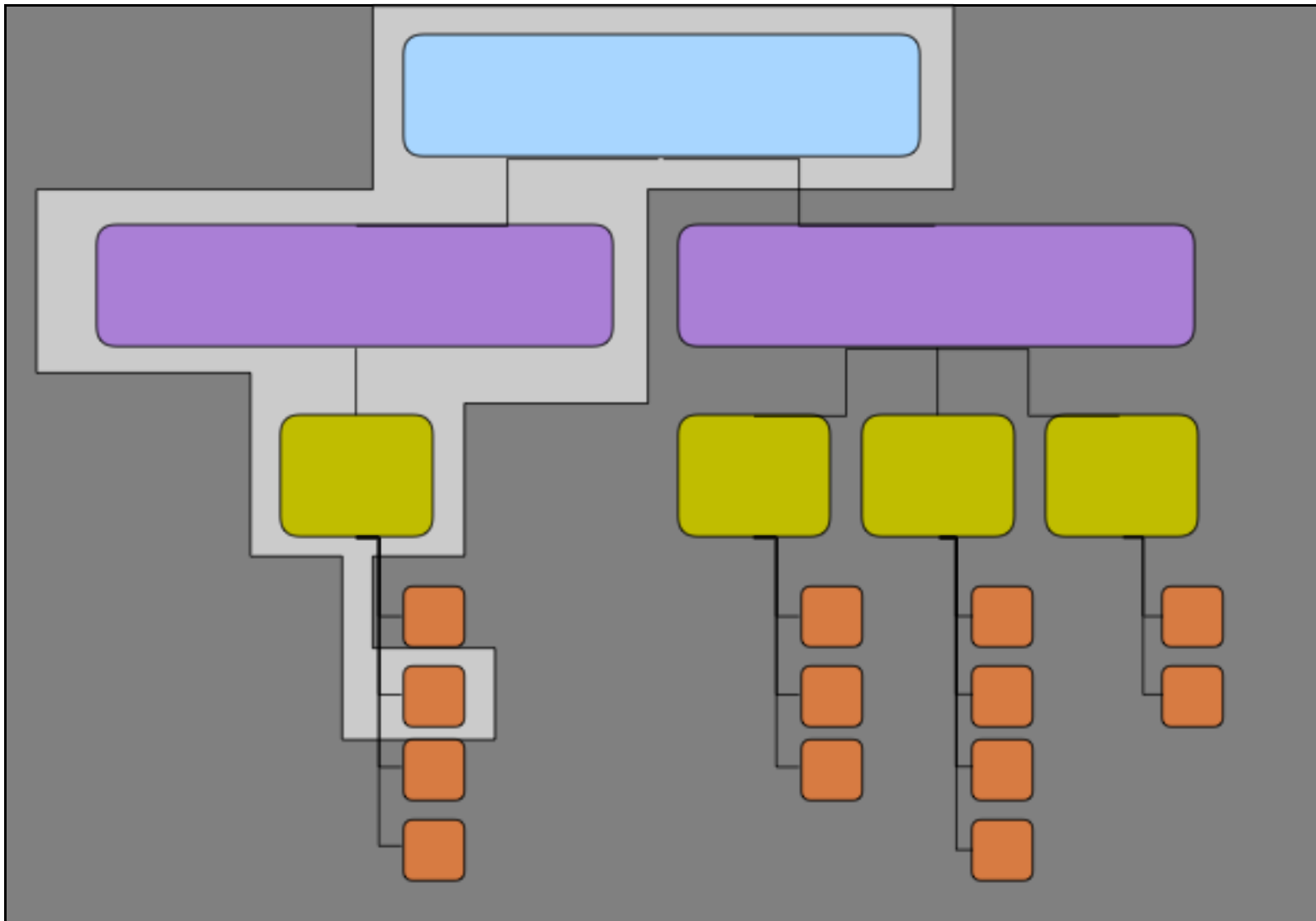


Métodos: estructura y organización

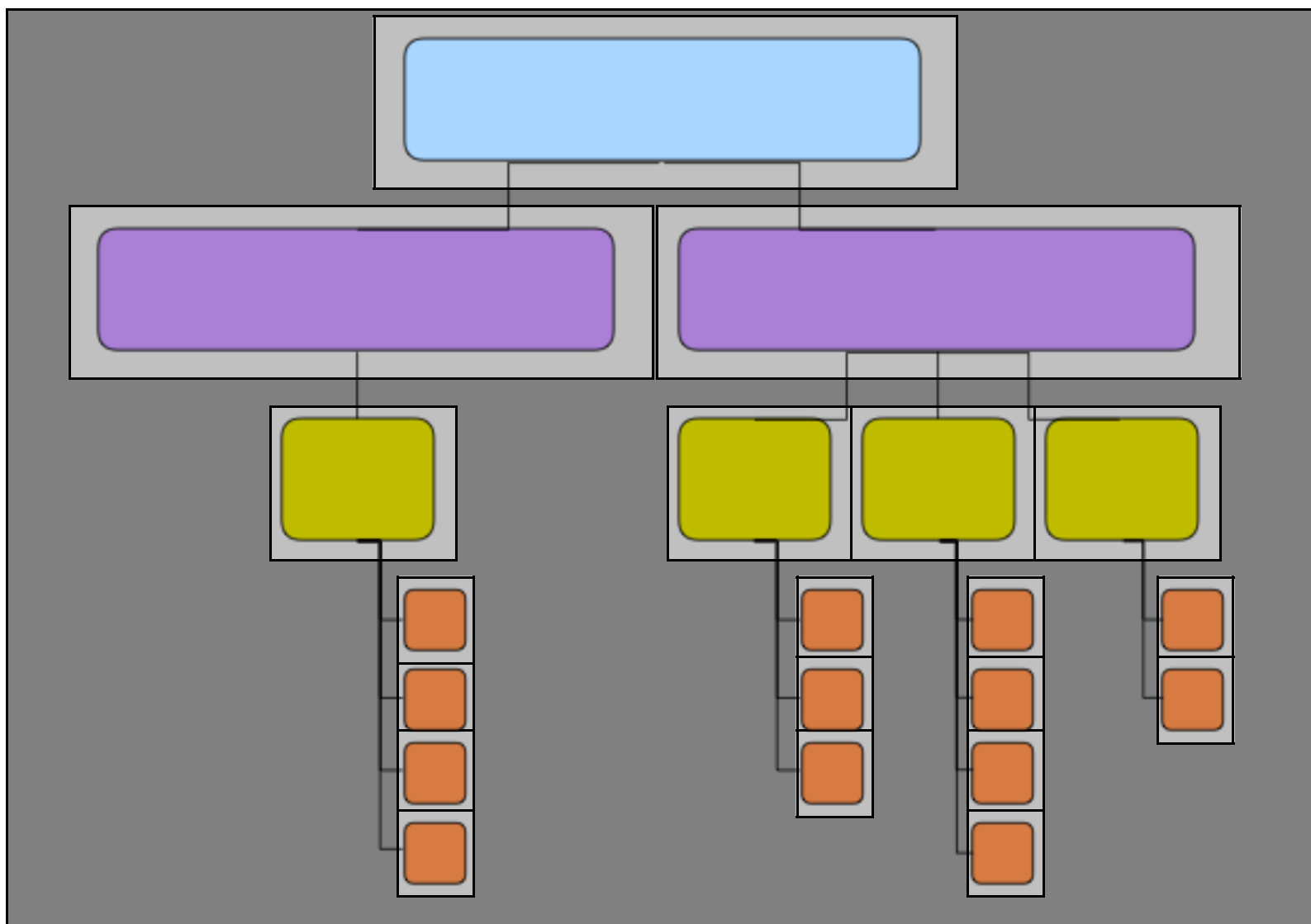


Luis M. Rodríguez R.

Métodos: estructura y organización



Métodos: estructura y organización



Métodos: implementación

Recopilación de datos



<xml />



Métodos: implementación

Almacenamiento de datos



Métodos: implementación

GUI / Web



Métodos: implementación

PHP

JavaScript

C / C++

(bio)Perl

R

XML

MySQL

Apache

Linux

SOAP

AJAX



<xml />

