If the data does not come to R, R must go to the data

Olga Kalinina

Helmholtz Institute for Pharmaceutical Research Saarland, Saarland University

FOSDEM PGDay 2019

Who am I?

Who am I?

- Bioinformatics = computational biology

Who am I?

- Bioinformatics = computational biology
  - Analysis of data to gain new biological insights

Who am I?

- Bioinformatics = computational biology
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  - Molecular biology

Who am I?

- Bioinformatics = computational biology
  - Analysis of data to gain new biological insights
  - Molecular biology
- Head of research group for drug bioinformatics at Helmholtz Institute for Pharmaceutical Research Saarland

Who am I?

- Bioinformatics = computational biology
  - Analysis of data to gain new biological insights
  - Molecular biology
- Head of research group for drug bioinformatics at Helmholtz Institute for Pharmaceutical Research Saarland
  - Find new bioactive compounds

Data in (life) sciences

Data in (life) sciences

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#chr	to1	ref	alt	GeneSymbol	ClinicalSignificance	ReviewStatus	PhenotypeList	uniprot_ac	uniprot_pos	aa1	aa2
chr1	949608	G	A	ISG15	Benign	criteria provided, single submitter	not specified	P05161 83	S N	benign	3rt3
chr1	955563	G	C	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	4 R	P	benign
chr1	955596	C	G	AGRN	Benign	criteria provided, single submitter	not provided	O00468-6	15 P	R	benign
chr1	955601	C	T	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	17 L	F	possibly
chr1	957605	G	A	AGRN	Pathogenic	no assertion criteria provided	Congenital myasthenic syndrome	O00468-6	76 G		
chr1	957693	A	T	AGRN	Pathogenic	no assertion criteria provided	Congenital myasthenic syndrome	O00468-6	105 N		
chr1	976577	T	C	AGRN	Benign	no assertion criteria provided	not specified	O00468-6	251 V	A	probably damagin
chr1	976598	C	T	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	258 T	I	probably
chr1	976963	A	G	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	353 Q	R	benign
chr1	977028	G	T	AGRN	Benign	criteria provided, multiple submitters,	no conflicts	not provided;not specified		O00468-6	
chr1	978628	C	T	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	465 P	L	benign
chr1	978762	G	A	AGRN	Benign	criteria provided, multiple submitters,	no conflicts	not specified	O00468-6	510 G	
chr1	978974	G	A	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	554 V	M	probably
chr1	979310	G	A	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	636 G	S	probably
chr1	979748	A	T	AGRN	Benign	criteria provided, multiple submitters,	no conflicts	not specified	O00468-6	728 E	
chr1	980552	G	A	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	756 A	T	possibly
chr1	980840	C	T	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	825 R	C	probably
chr1	980868	G	A	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	834 R	Q	probably
chr1	981131	A	G	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	852 Q	R	benign
chr1	981226	C	T	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	884 R	C	probably
chr1	981353	C	T	AGRN	Benign	criteria provided, single submitter	not provided	O00468-6	897 A	V	possibly
chr1	981942	C	A	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1026 T	N	probably
chr1	982213	G	C	AGRN	Benign	criteria provided, multiple submitters,	no conflicts	not provided;not specified		O00468-6	
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chr1	983221	C	T	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1233 R	W	benign
chr1	983243	C	T	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1240 P	L	probably
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chr1	983604	C	T	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1322 R	W	probably
chr1	984261	G	T	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1374 V	L	benign
chr1	984426	C	T	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1429 R	C	benign
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chr1	985070	G	A	AGRN	Benign	criteria provided, multiple submitters,	no conflicts	not specified	O00468-6	1547 E	
chr1	985126	G	C	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1565 Q	H	benign
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chr1	985826	G	A	AGRN	Benign	criteria provided, multiple submitters,	no conflicts	not specified	O00468-6	1666 V	
chr1	985853	G	A	AGRN	Pathogenic	no assertion criteria provided	Congenital myasthenic syndrome	O00468-6	1675 G		
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chr1	986143	G	T	AGRN	Pathogenic	no assertion criteria provided	Congenital myasthenic syndrome;Myasthenic syndrome, congenital,				
chr1	986165	G	A	AGRN	Benign	criteria provided, multiple submitters,	no conflicts	not specified	O00468-6	1734 R	
chr1	986849	G	A	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1796 R	H	benign
chr1	987116	G	A	AGRN	Benign	criteria provided, single submitter	Myasthenic syndrome, congenital, 8	O00468-6	1858		
chr1	987155	G	A	AGRN	Pathogenic	no assertion criteria provided	Congenital myasthenic syndrome	O00468-6	1871 G		
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chr1	989207	G	C	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1909 S	T	benign
chr1	989224	C	T	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1915 R	W	probably
chr1	990213	C	T	AGRN	Benign	no assertion criteria provided	not specified	O00468-6	1997 P	L	benign ?
chr1	990242	A	G	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	2007 K	E	probably
chr1	1167674	C	T	B3GALT6	Pathogenic	no assertion criteria provided	Ehlers-Danlos syndrome, progeroid type, 2	Q96L58 6			
chr1	1167675	G	A	B3GALT6	Benign	no assertion criteria provided	not specified	Q96L58 6	R Q	possibly damaging	
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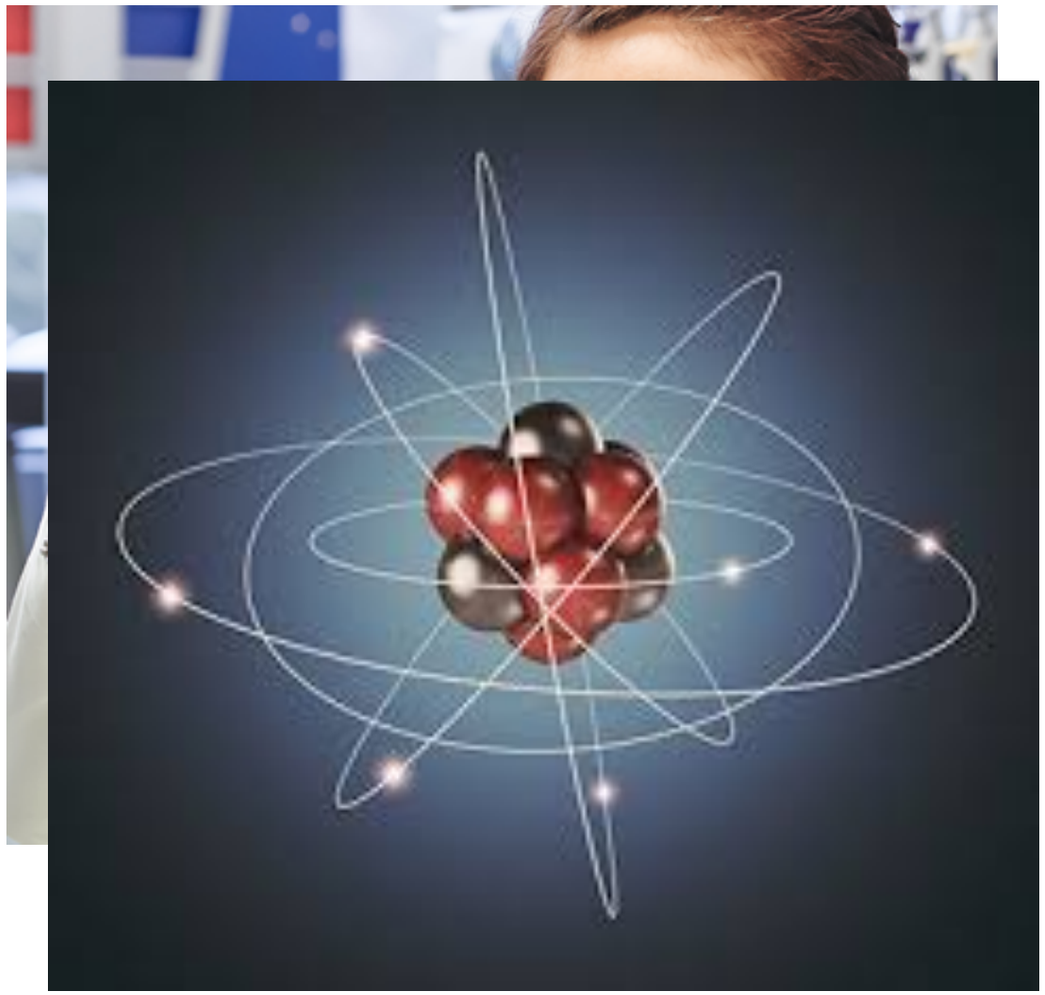
Data in (life) sciences



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chr1	955596	C	G	AGRN	Benign	criteria provided, single submitter	not provided	O00468-6	15 P	R	benign
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chr1	976577	T	C	AGRN	Benign	no assertion criteria provided	not specified	O00468-6	251 V A	probably damagin	
chr1	976598	C	T	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	258 T	I	probably
chr1	976963	A	G	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	353 Q	R	benign
chr1	977028	G	T	AGRN	Benign	criteria provided, multiple submitters, no conflicts	not provided;not specified	O00468-6			
chr1	978628	C	T	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	465 P	L	benign
chr1	978762	G	A	AGRN	Benign	criteria provided, multiple submitters, no conflicts	not specified	O00468-6	510 G		
chr1	978974	G	A	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	554 V	M	probably
chr1	979310	G	A	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	636 G	S	probably
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chr1	980552	G	A	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	756 A	T	possibly
chr1	980840	C	T	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	825 R	C	probably
chr1	980868	G	A	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	834 R	Q	probably
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chr1	981353	C	T	AGRN	Benign	criteria provided, single submitter	not provided	O00468-6	897 A	V	possibly
chr1	981942	C	A	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1026 T	N	probably
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chr1	983604	C	T	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1322 R	W	probably
chr1	984261	G	T	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1374 V	L	benign
chr1	984426	C	T	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1429 R	C	benign
chr1	984669	C	T	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1451 P	L	benign
chr1	984971	G	A	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1514 A	T	benign
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chr1	987116	G	A	AGRN	Benign	criteria provided, single submitter	Myasthenic syndrome, congenital, 8	O00468-6	1858		
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chr1	987191	G	A	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1883 E	K	benign
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chr1	989224	C	T	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1915 R	W	probably
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chr1	990242	A	G	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	2007 K	E	probably
chr1	1167674	C	T	B3GALT6	Pathogenic	no assertion criteria provided	Ehlers-Danlos syndrome, progeroid type, 2	Q96L58 6	R Q	possibly damaging	
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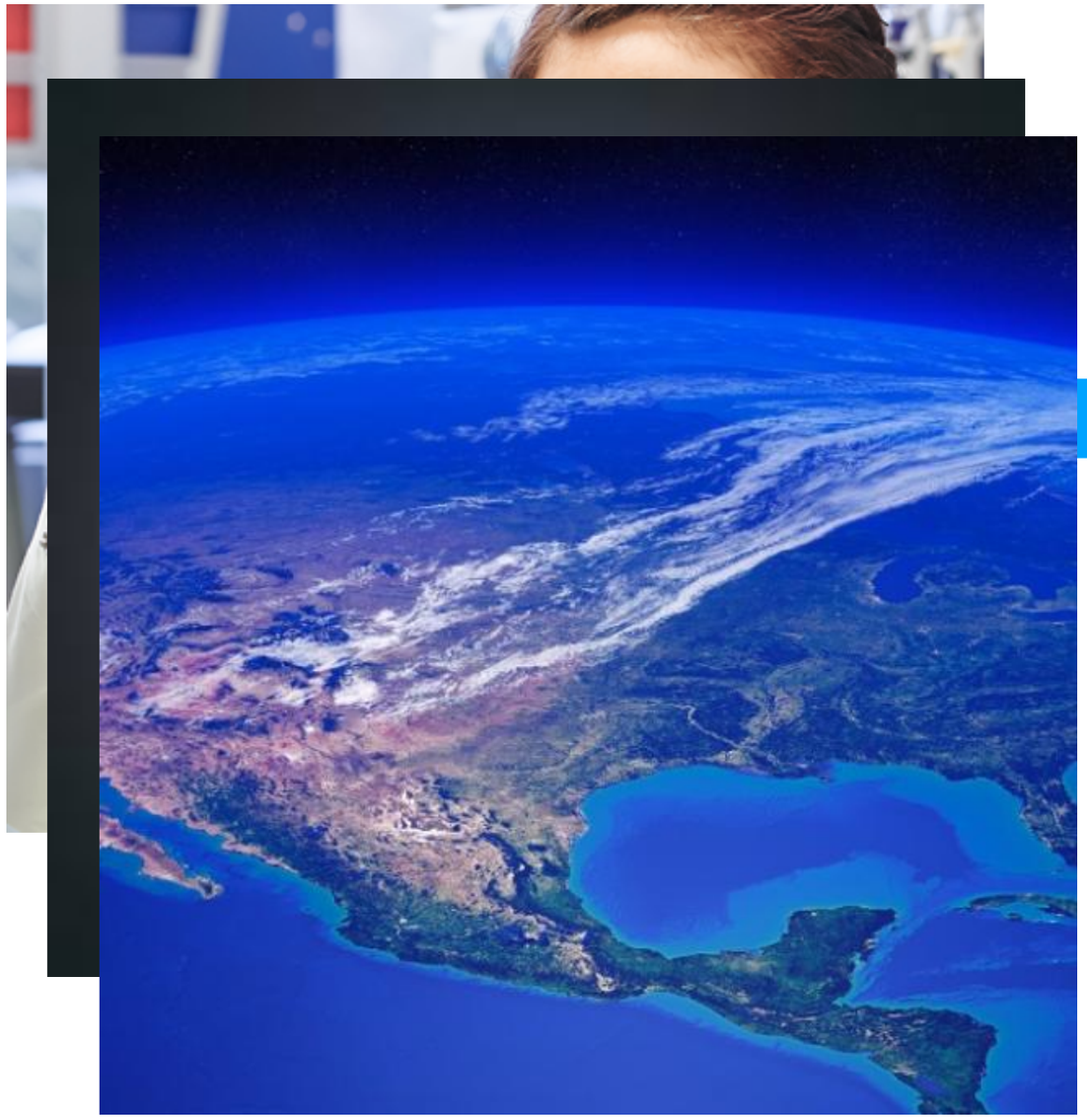
Data in (life) sciences



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chr1	955596	C	G	AGRN	Benign	criteria provided, single submitter	not provided	O00468-6	15 P	R	benign
chr1	955601	C	T	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	17 L	F	possibly
chr1	957605	G	A	AGRN	Pathogenic	no assertion criteria provided	Congenital myasthenic syndrome	O00468-6	76 G		
chr1	957693	A	T	AGRN	Pathogenic	no assertion criteria provided	Congenital myasthenic syndrome	O00468-6	105 N		
chr1	976577	T	C	AGRN	Benign	no assertion criteria provided	not specified	O00468-6	251 V A	probably damagin	
chr1	976598	C	T	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	258 T	I	probably
chr1	976963	A	G	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	353 Q	R	benign
chr1	977028	G	T	AGRN	Benign	criteria provided, multiple submitters, no conflicts	not provided;not specified	O00468-6			
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chr1	979310	G	A	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	636 G	S	probably
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chr1	980552	G	A	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	756 A	T	possibly
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chr1	980868	G	A	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	834 R	Q	probably
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chr1	986143	G	T	AGRN	Pathogenic	no assertion criteria provided	Congenital myasthenic syndrome;Myasthenic syndrome, congenital,				
chr1	986165	G	A	AGRN	Benign	criteria provided, multiple submitters, no conflicts	not specified	O00468-6	1734 R		
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chr1	987159	G	A	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1872 R	Q	benign
chr1	987191	G	A	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1883 E	K	benign
chr1	989207	G	C	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1909 S	T	benign
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chr1	990213	C	T	AGRN	Benign	no assertion criteria provided	not specified	O00468-6	1997 P	L	benign ?
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chr1	1167680	T	G	B3GALT6	Benign	criteria provided, single submitter	not specified	Q96L58 8	W G	benign ?	

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chr1	955563	G	C	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	4	R	P benign
chr1	955596	C	G	AGRN	Benign	criteria provided, single submitter	not provided	O00468-6	15	P	R benign
chr1	955601	C	T	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	17	L	F possibly
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chr1	976577	T	C	AGRN	Benign	no assertion criteria provided	not specified O00468-6	251	V	A	probably damagin
chr1	976598	C	T	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	258	T	I probably
chr1	976963	A	G	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	353	Q	R benign
chr1	977028	G	T	AGRN	Benign	criteria provided, multiple submitters, no conflicts	not provided;not specified	O00468-6			
chr1	978628	C	T	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	465	P	L benign
chr1	978762	G	A	AGRN	Benign	criteria provided, multiple submitters, no conflicts	not specified	O00468-6	510	G	
chr1	978974	G	A	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	554	V	M probably
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chr1	980552	G	A	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	756	A	T possibly
chr1	980840	C	T	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	825	R	C probably
chr1	980868	G	A	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	834	R	Q probably
chr1	981131	A	G	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	852	Q	R benign
chr1	981226	C	T	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	884	R	C probably
chr1	981353	C	T	AGRN	Benign	criteria provided, single submitter	not provided	O00468-6	897	A	V possibly
chr1	981942	C	A	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1026	T	N probably
chr1	982213	G	C	AGRN	Benign	criteria provided, multiple submitters, no conflicts	not provided;not specified	O00468-6			
chr1	982722	A	G	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1135	Q	R probably
chr1	983221	C	T	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1233	R	W benign
chr1	983243	C	T	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1240	P	L probably
chr1	983506	C	T	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1289	P	L benign
chr1	983604	C	T	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1322	R	W probably
chr1	984261	G	T	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1374	V	L benign
chr1	984426	C	T	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1429	R	C benign
chr1	984669	C	T	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1451	P	L benign
chr1	984971	G	A	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1514	A	T benign
chr1	985070	G	A	AGRN	Benign	criteria provided, multiple submitters, no conflicts	not specified	O00468-6	1547	E	
chr1	985126	G	C	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1565	Q	H benign
chr1	985407	C	A	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1623	F	L benign
chr1	985826	G	A	AGRN	Benign	criteria provided, multiple submitters, no conflicts	not specified	O00468-6	1666	V	
chr1	985853	G	A	AGRN	Pathogenic	no assertion criteria provided	Congenital myasthenic syndrome	O00468-6	1675	G	
chr1	985955	G	C	AGRN	Pathogenic	no assertion criteria provided	Congenital myasthenic syndrome;Myasthenic syndrome, congenital,				
chr1	986143	G	T	AGRN	Pathogenic	no assertion criteria provided	Congenital myasthenic syndrome;Myasthenic syndrome, congenital,				
chr1	986165	G	A	AGRN	Benign	criteria provided, multiple submitters, no conflicts	not specified	O00468-6	1734	R	
chr1	986849	G	A	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1796	R	H benign
chr1	987116	G	A	AGRN	Benign	criteria provided, single submitter	Myasthenic syndrome, congenital, 8	O00468-6	1858		
chr1	987155	G	A	AGRN	Pathogenic	no assertion criteria provided	Congenital myasthenic syndrome	O00468-6	1871	G	
chr1	987159	G	A	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1872	R	Q benign
chr1	987191	G	A	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1883	E	K benign
chr1	989207	G	C	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1909	S	T benign
chr1	989224	C	T	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	1915	R	W probably
chr1	990213	C	T	AGRN	Benign	no assertion criteria provided	not specified O00468-6	1997	P	L	benign ?
chr1	990242	A	G	AGRN	Benign	criteria provided, single submitter	not specified	O00468-6	2007	K	E probably
chr1	1167674	C	T	B3GALT6	Pathogenic	no assertion criteria provided	Ehlers-Danlos syndrome, progeroid type, 2				Q96L58 6
chr1	1167675	G	A	B3GALT6	Benign	no assertion criteria provided	not specified Q96L58 6	R	Q	possibly damaging	
chr1	1167680	T	G	B3GALT6	Benign	criteria provided, single submitter	not specified Q96L58 8	W	G	benign ?	

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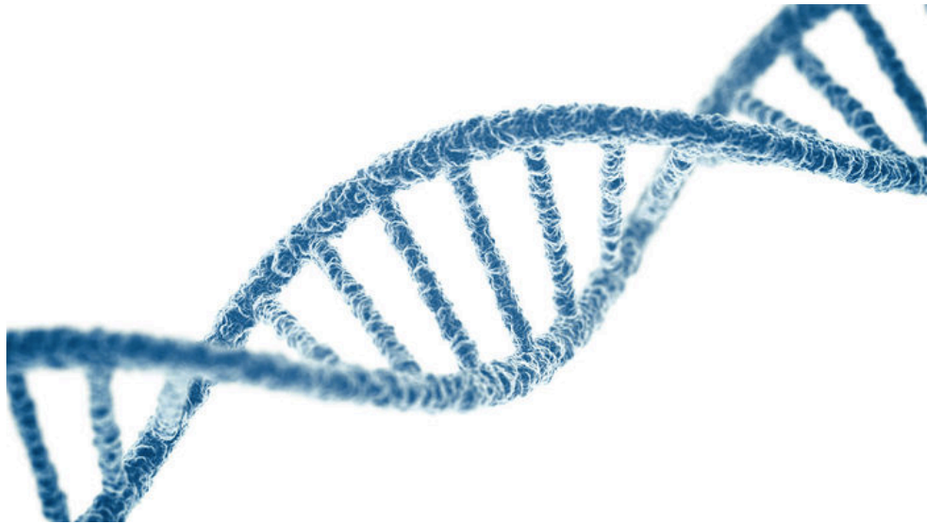

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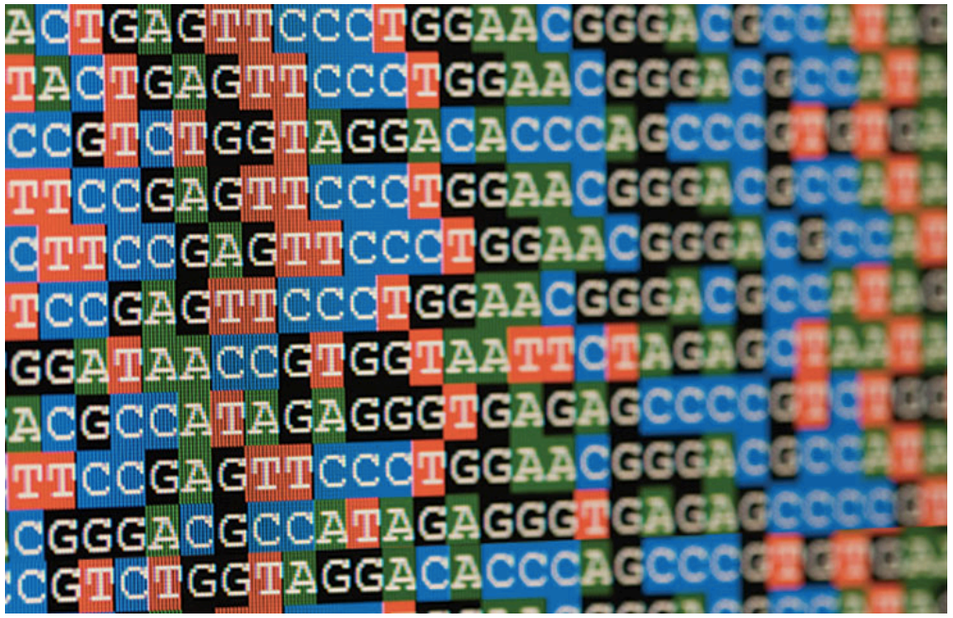

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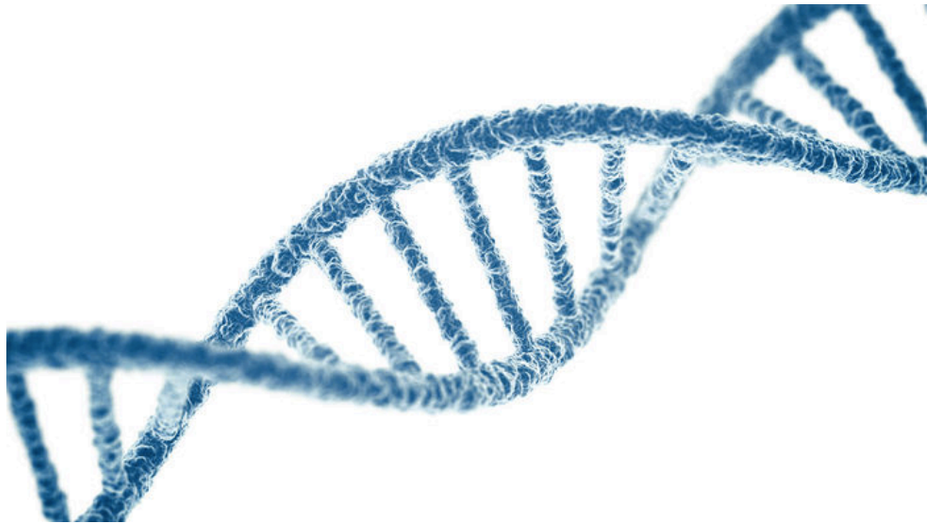

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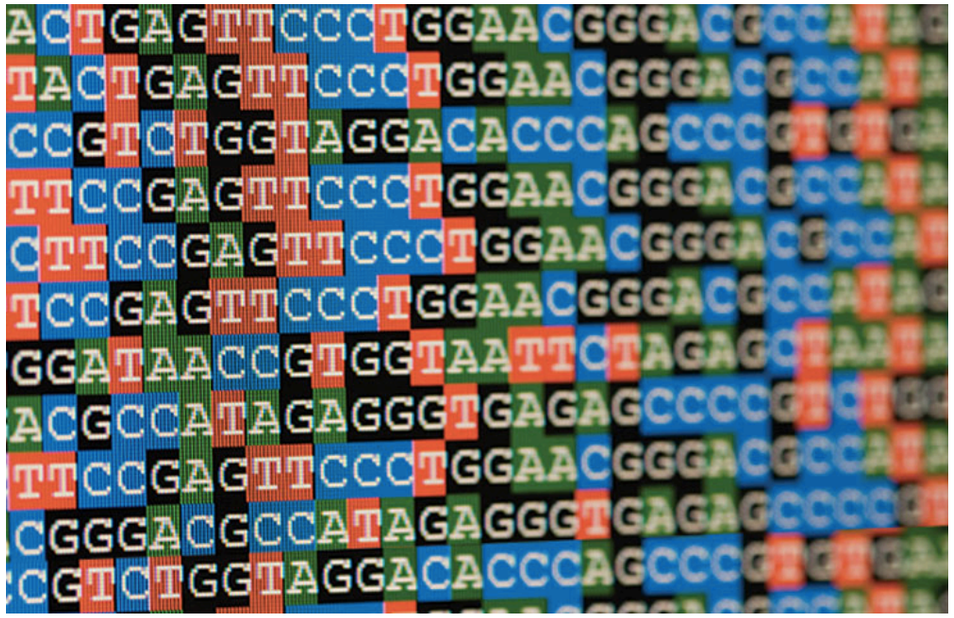

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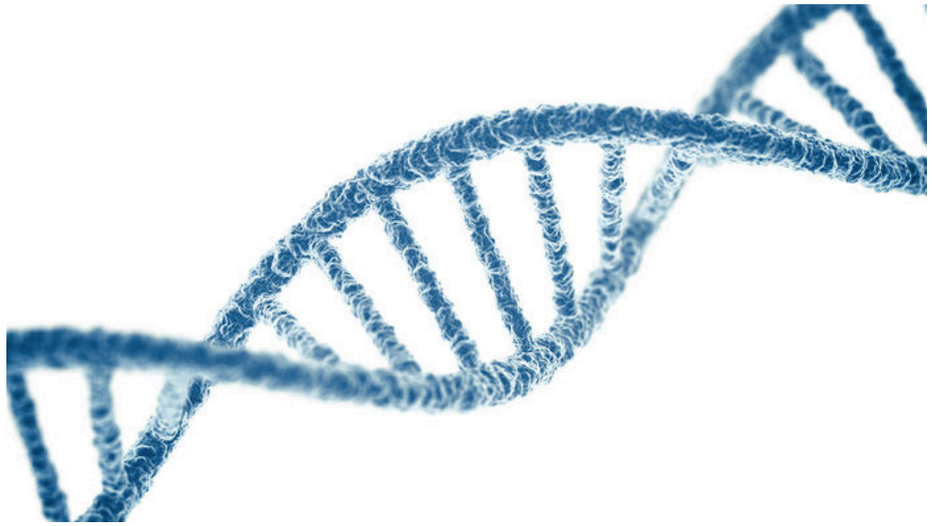

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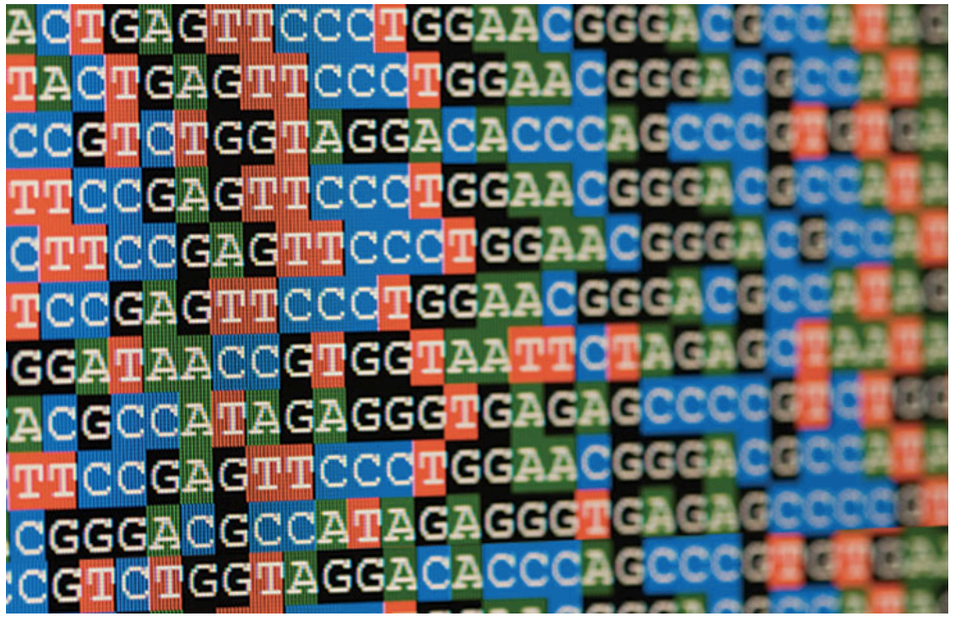

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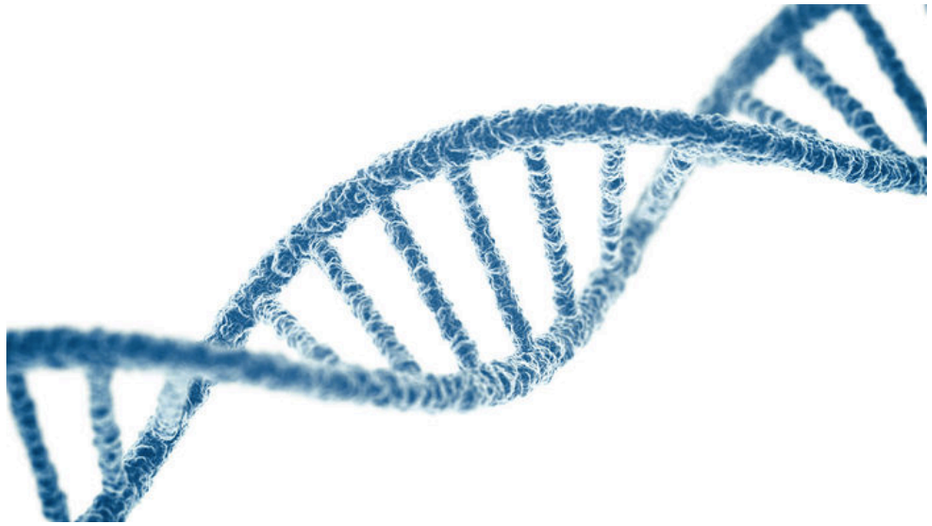

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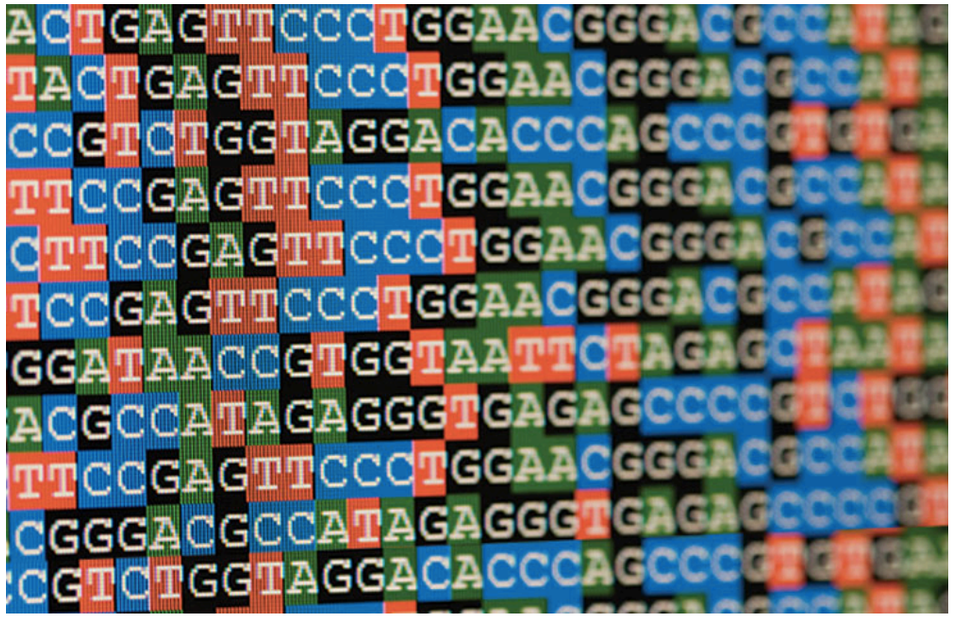

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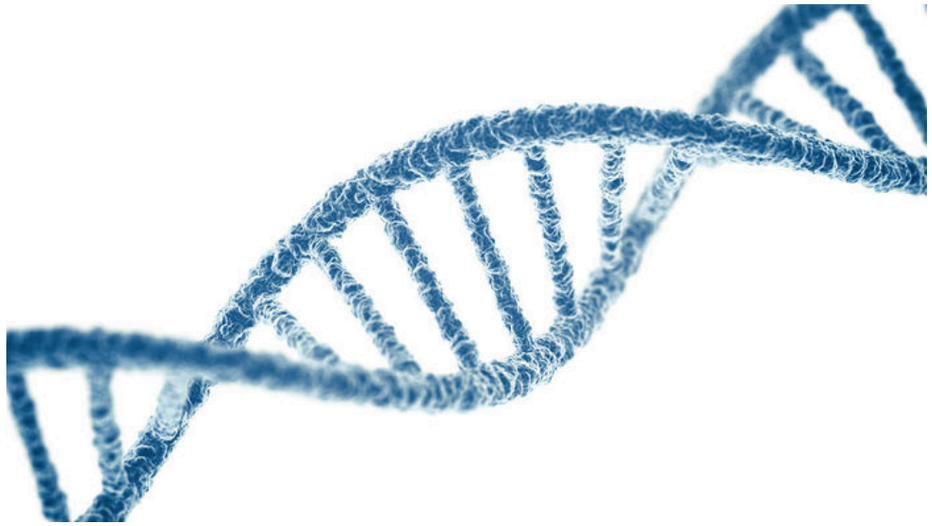

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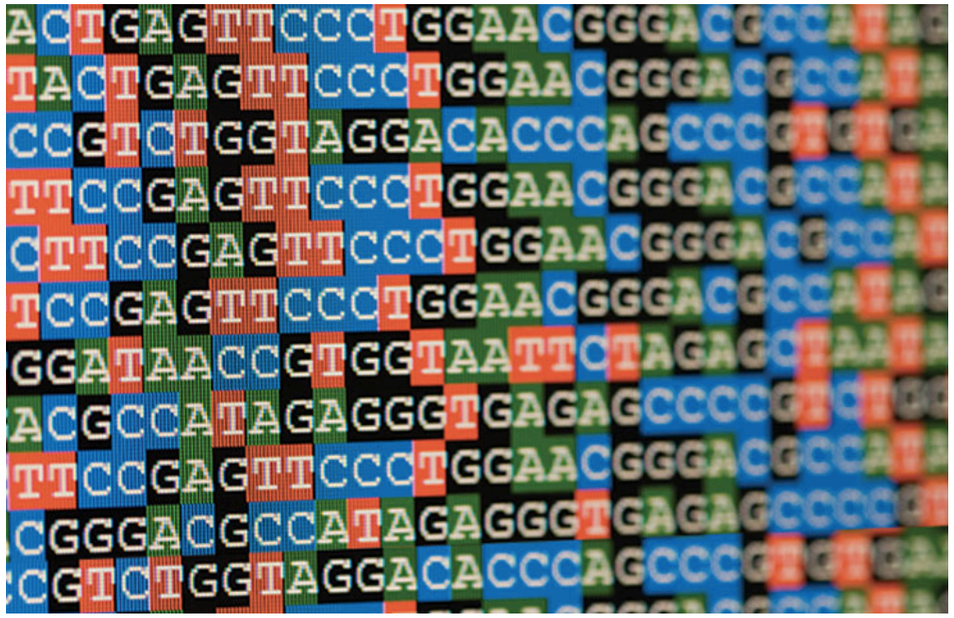

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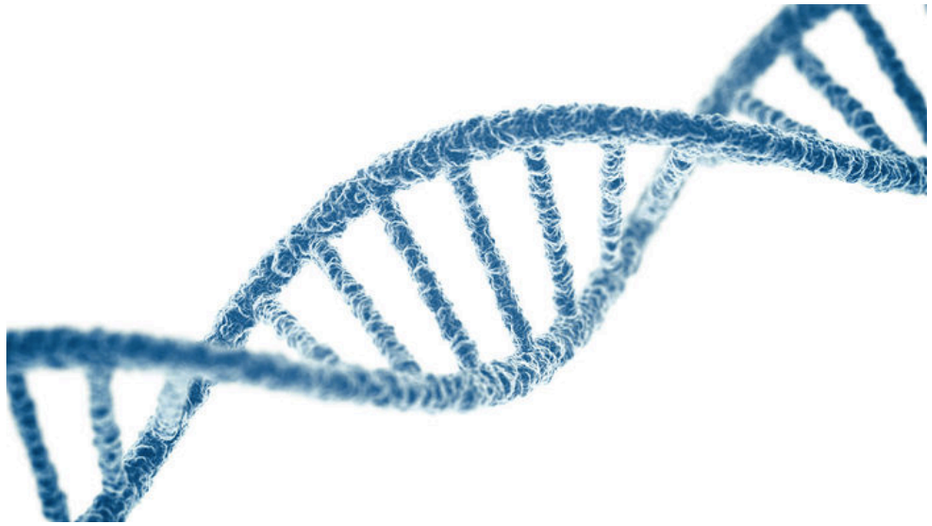

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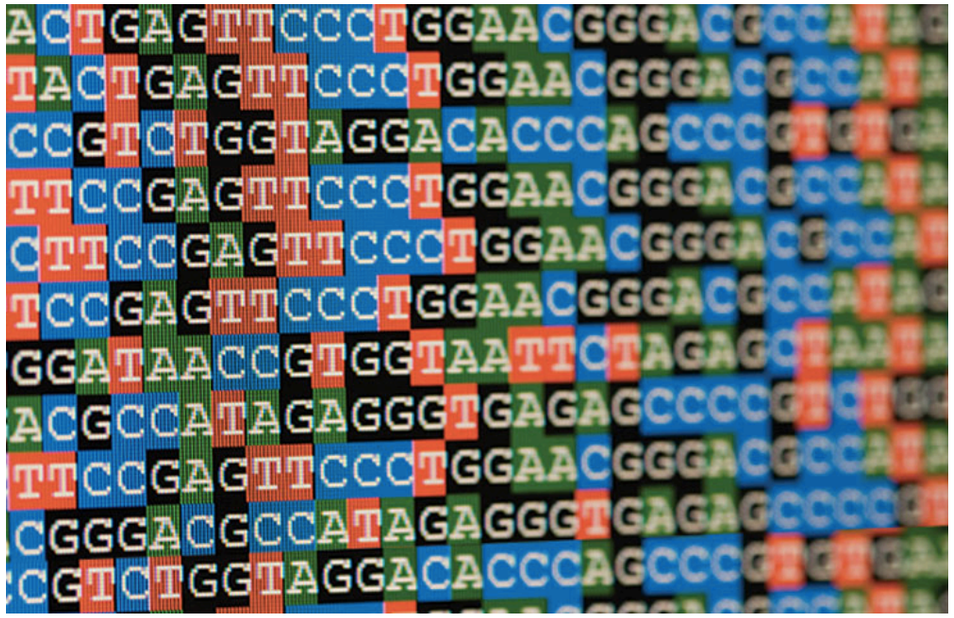

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  - (Cross-references from human proteins to other data sources: 147 MB = 6,026,631 rows)

Typical data analysis pipeline

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Experiment (up to TBs of data)

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↓

Initial data processing, cross-referencing

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Initial data processing, cross-referencing

↓

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Store in a DB

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Select relevant data

Typical data analysis pipeline

Experiment (up to TBs of data)

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Typical data analysis pipeline

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Write to disc (text files, MBs to GBs)

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Analyze with dedicated statistical software (Python, SAS, R), typically in RAM

R programming language

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- Free software environment for statistical computing and graphics

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- CRAN — 13,626 packages for various types of analysis: https://cran.r-project.org/

R

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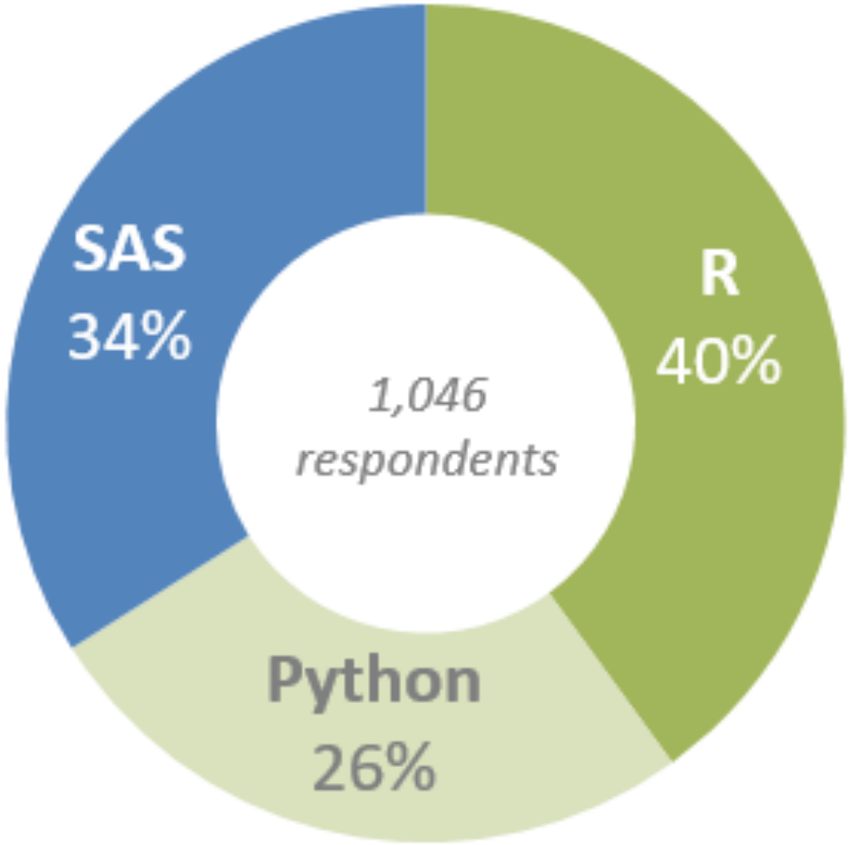

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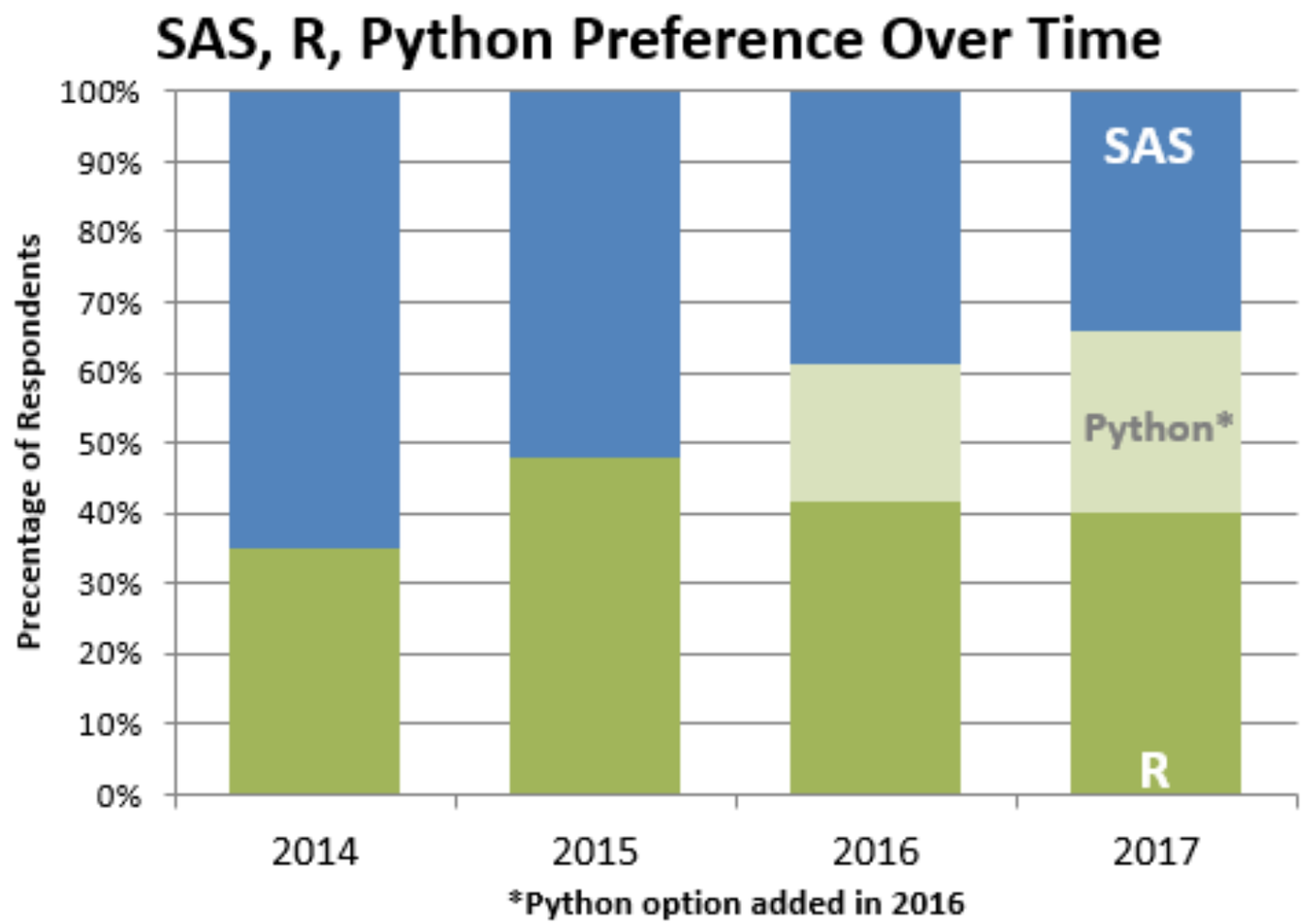

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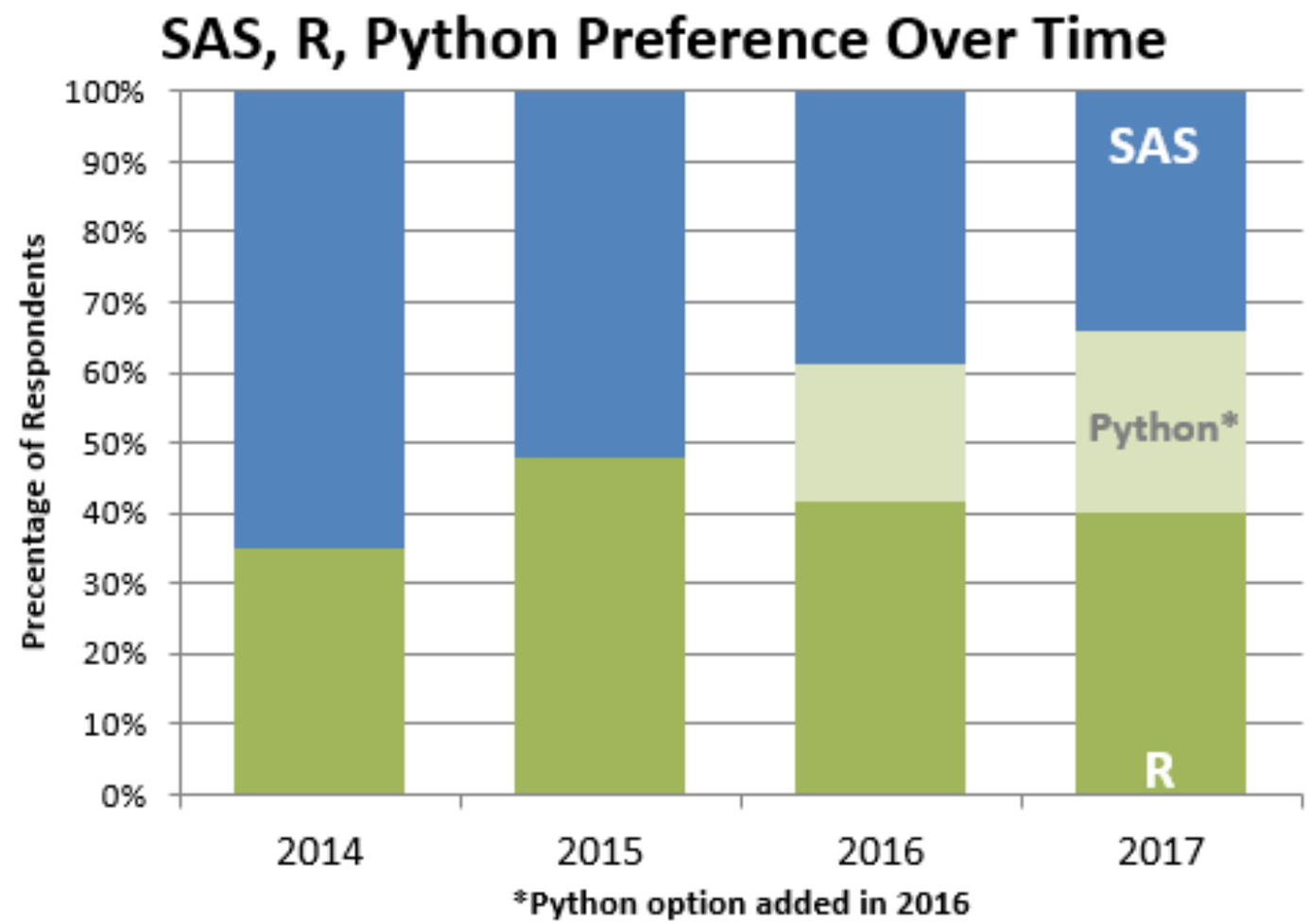

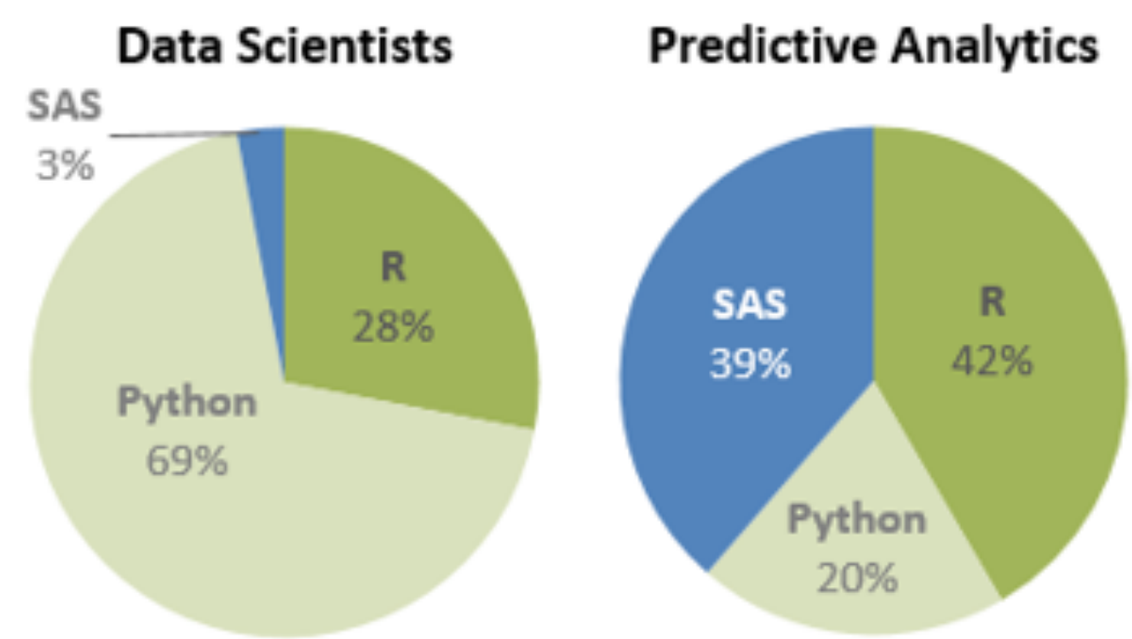

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R

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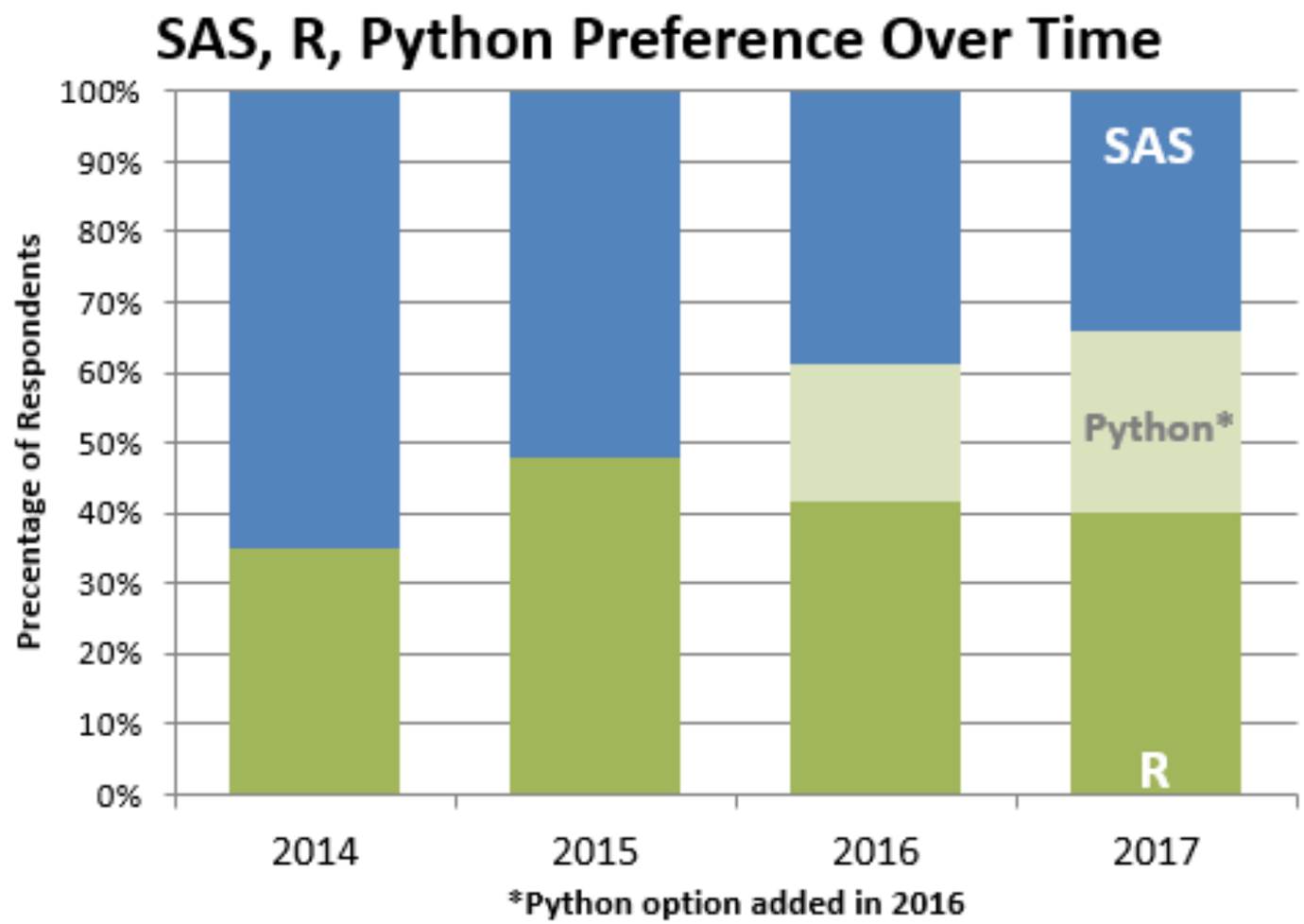

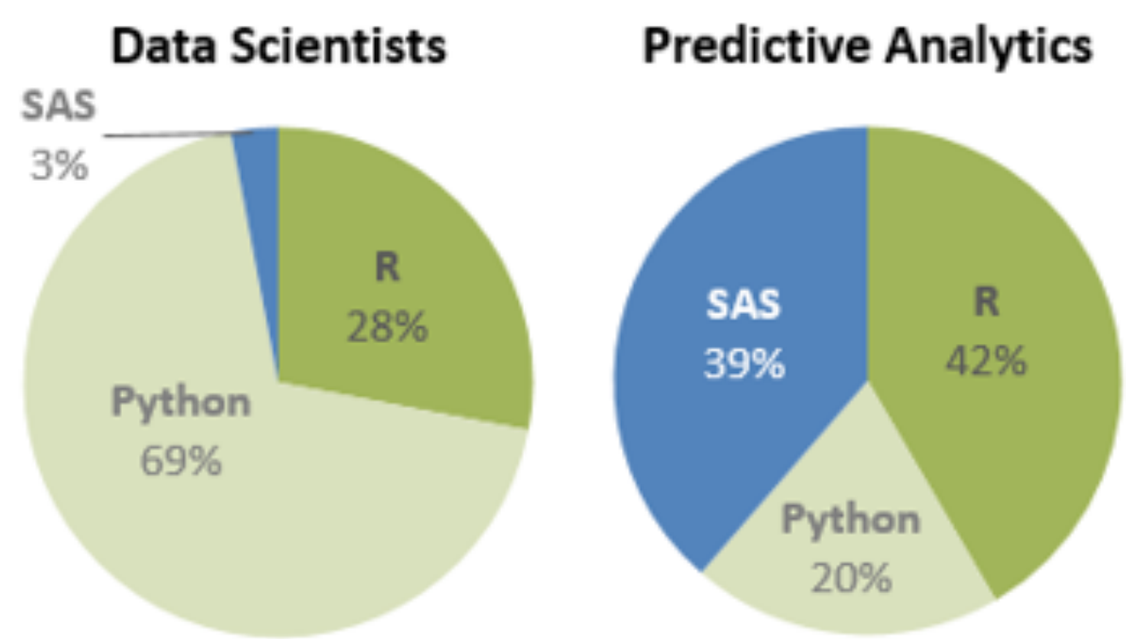

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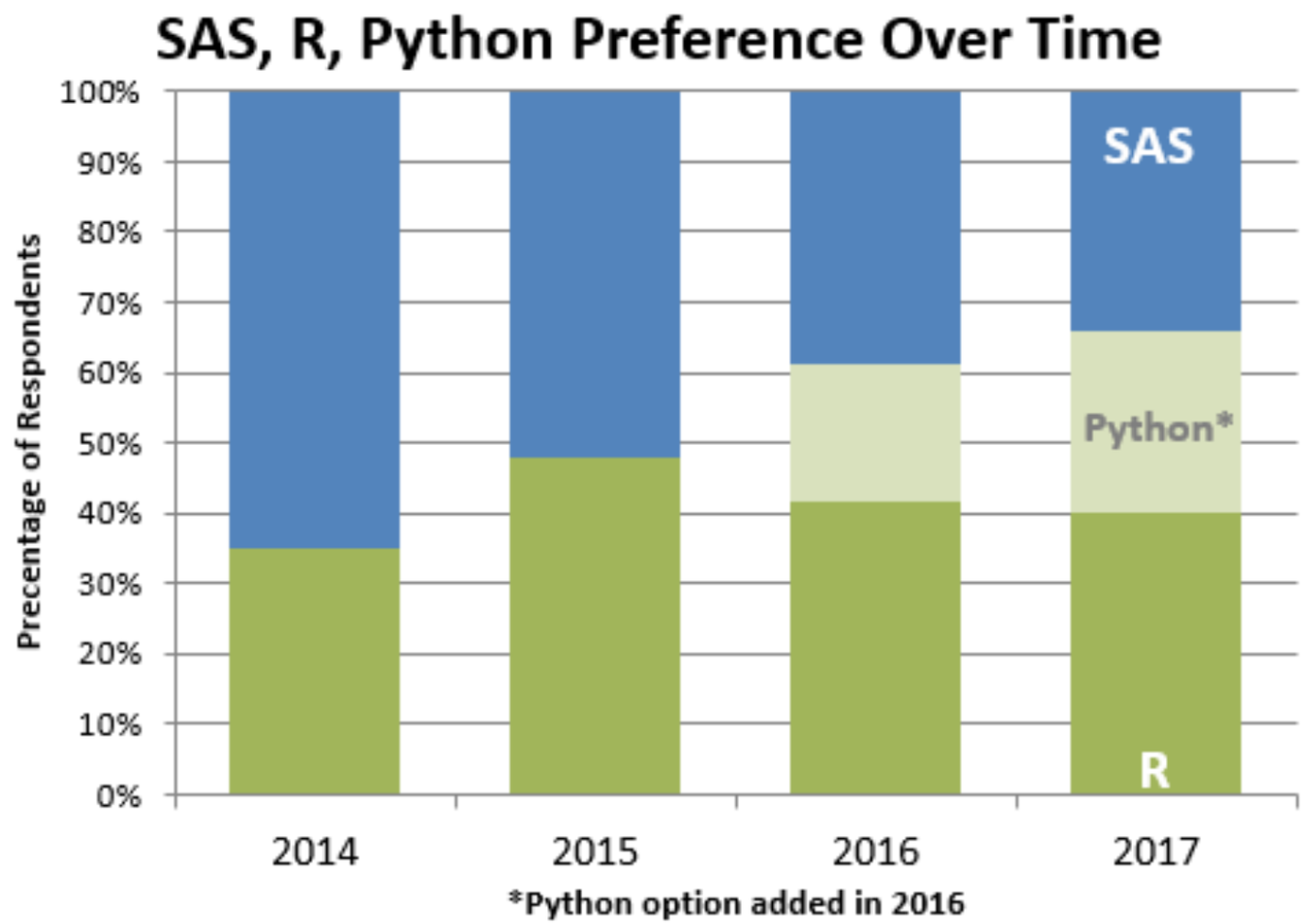
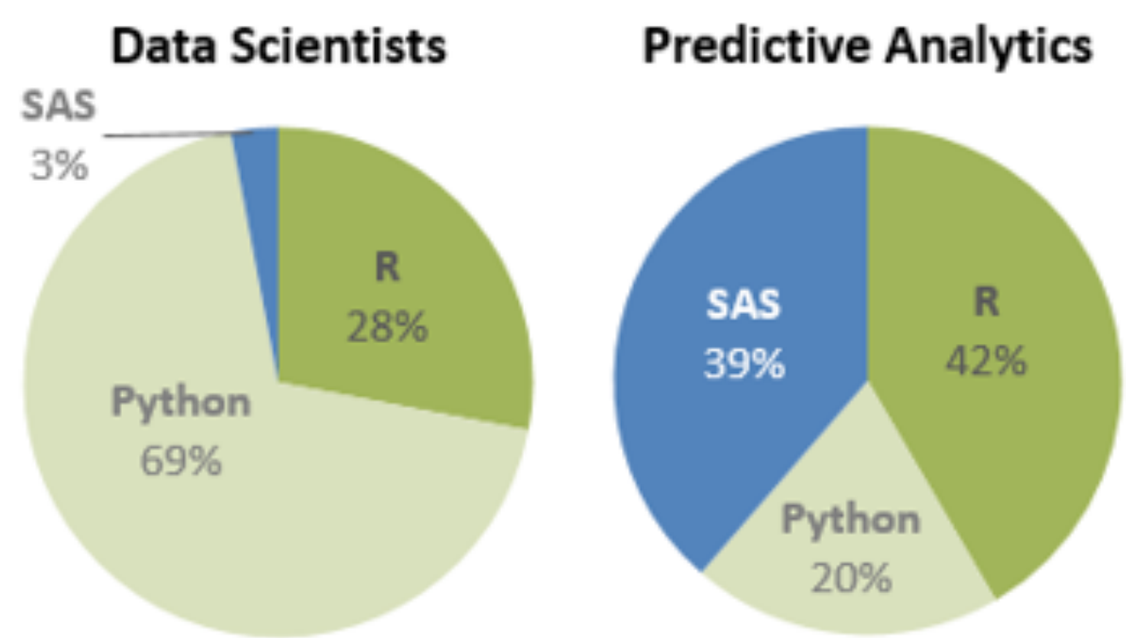
R

- R is still widely used, especially in academia
- R is very well suited to do statistical / machine learning
- Due to details of implementation, calculations in R are very efficient





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- Developed by Joe Conway since 2003
- Implements full R functionality

This talk

- No technical details of implementation or management
- User perspective

Is it possible to do full cycle of data analysis using only PL/R?

Biology for dummies

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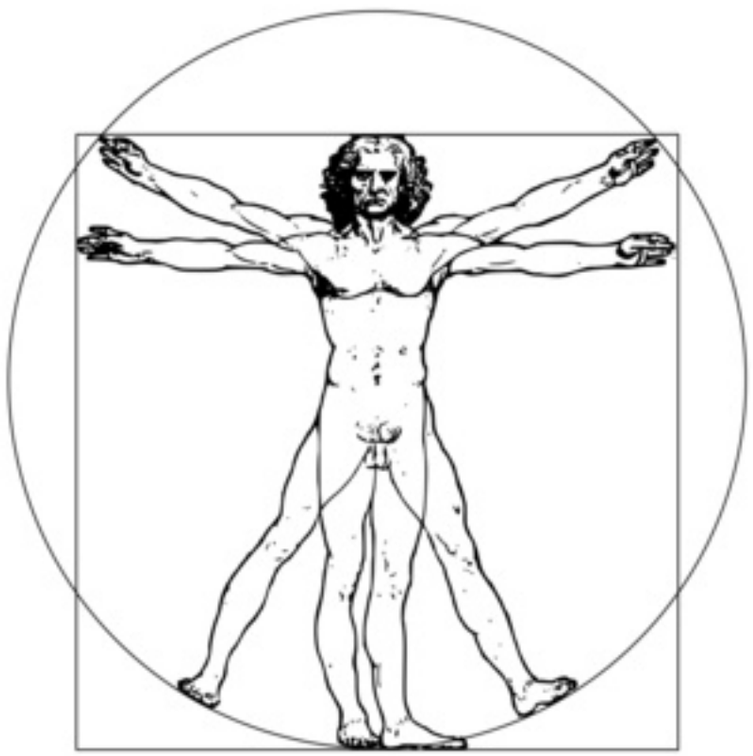

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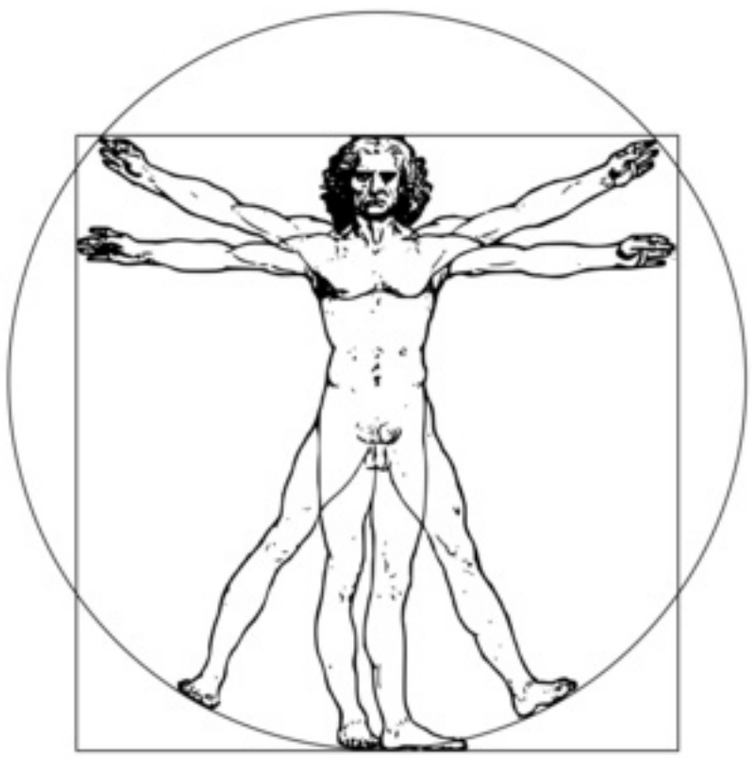

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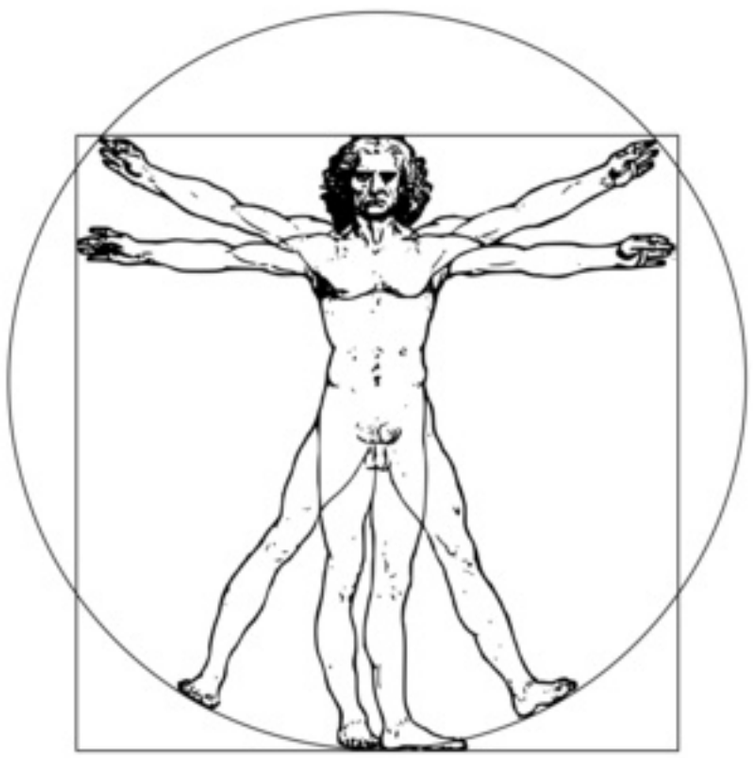

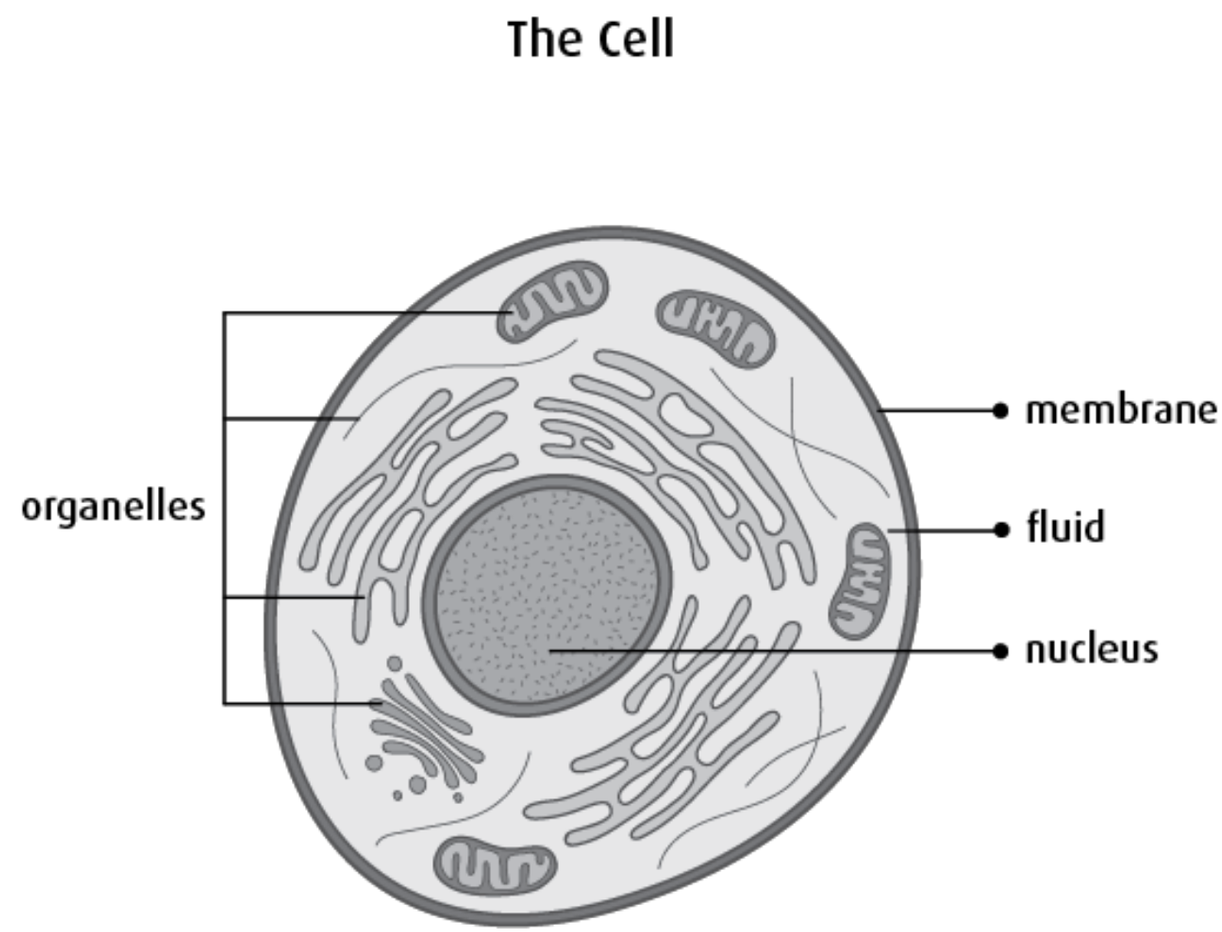

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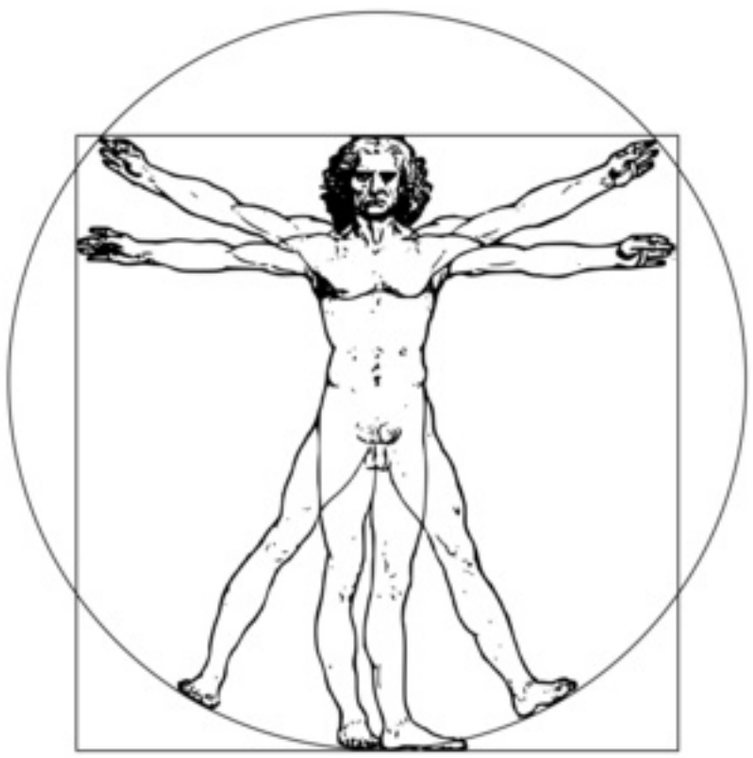

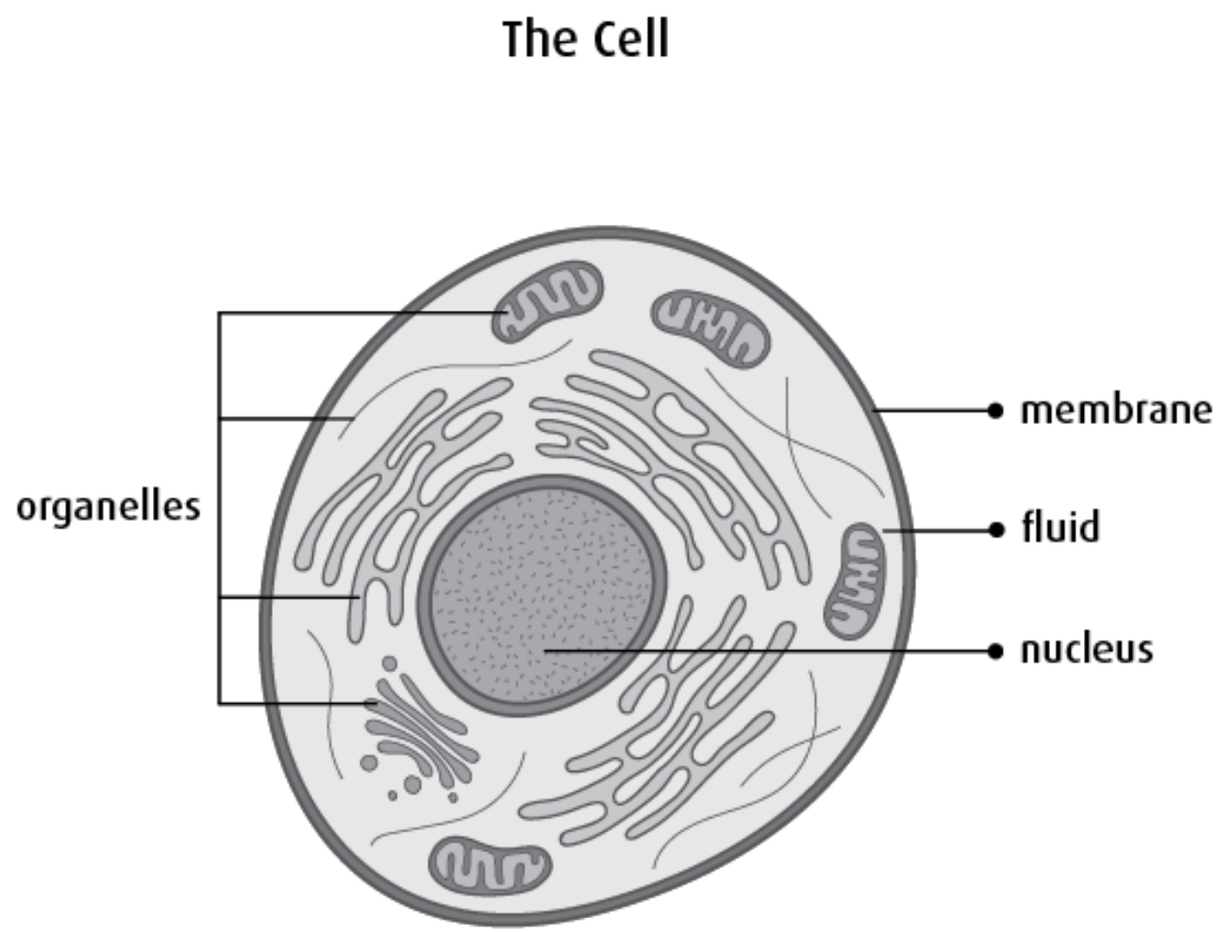

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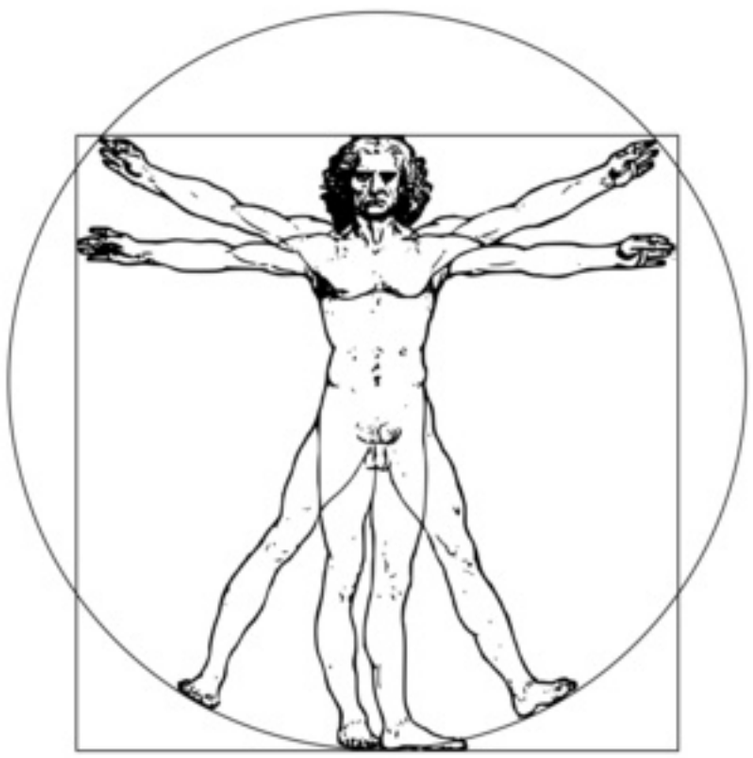

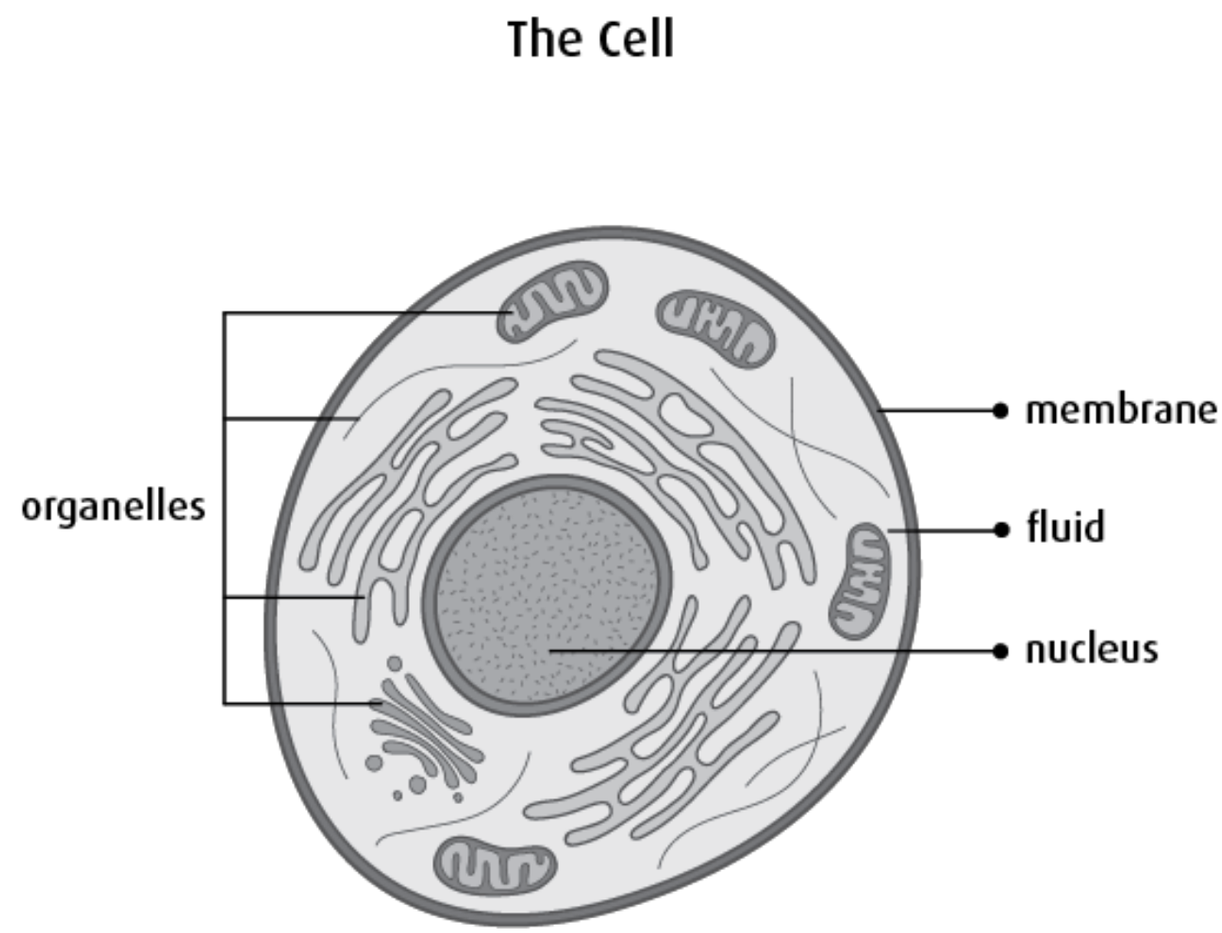

Biological molecules: DNA, RNA, proteins

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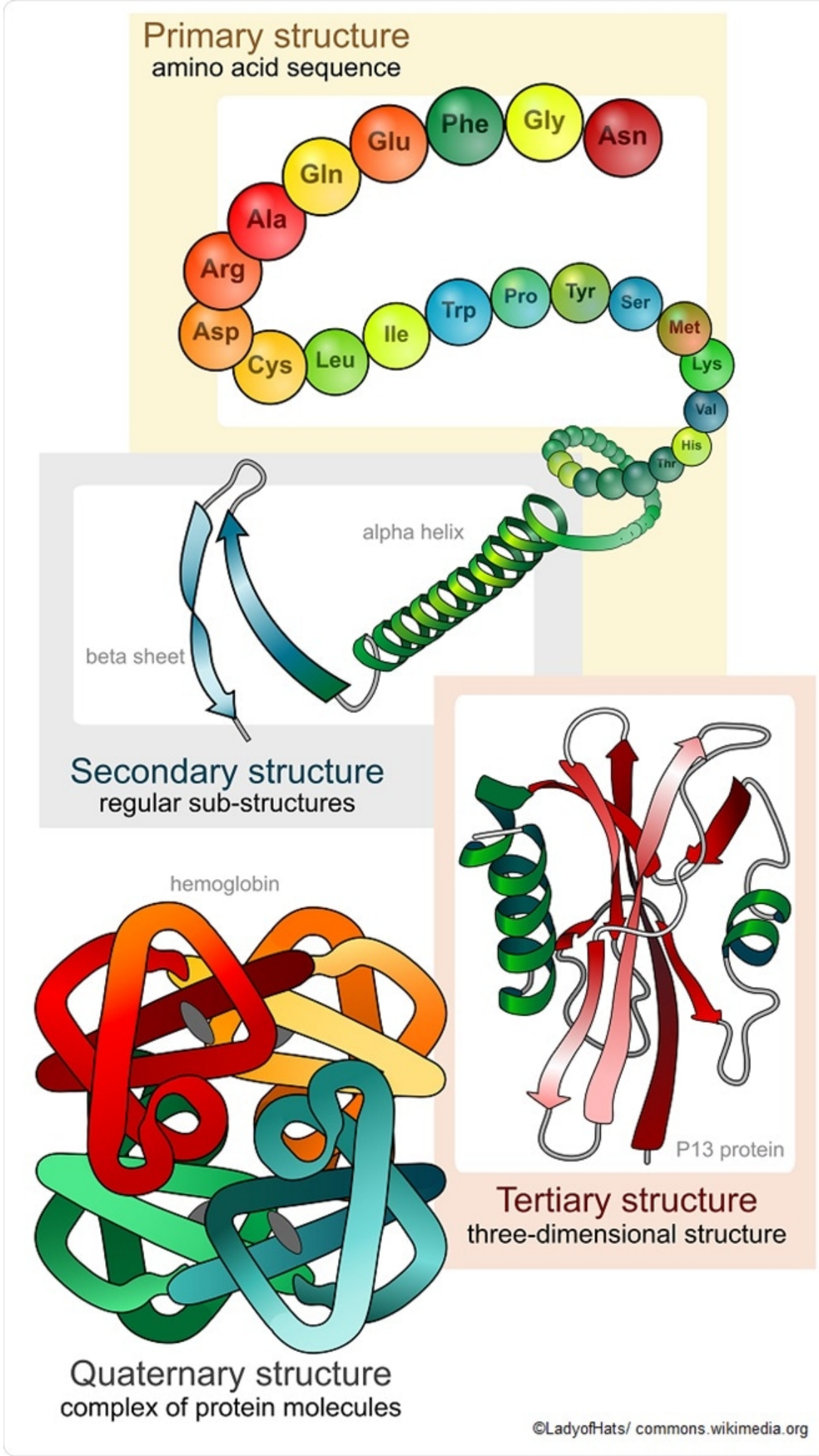
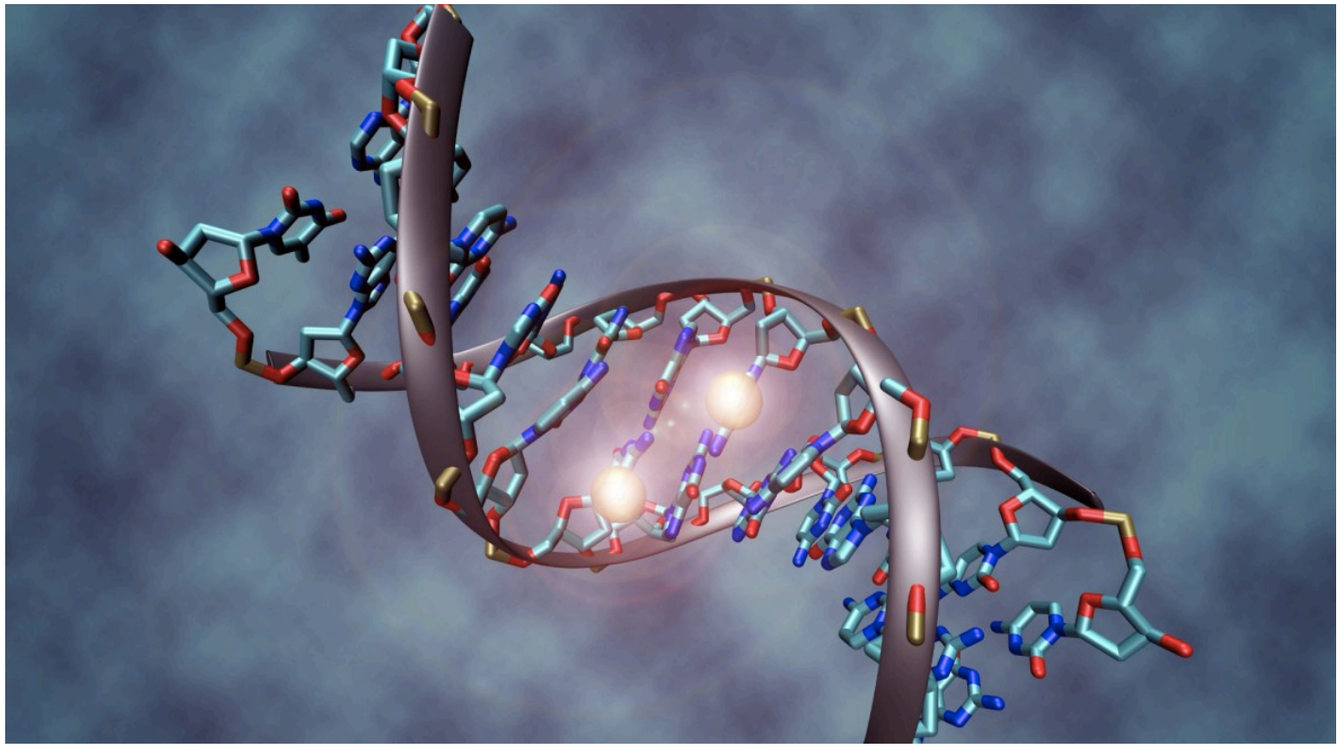


Mutations



Mutations

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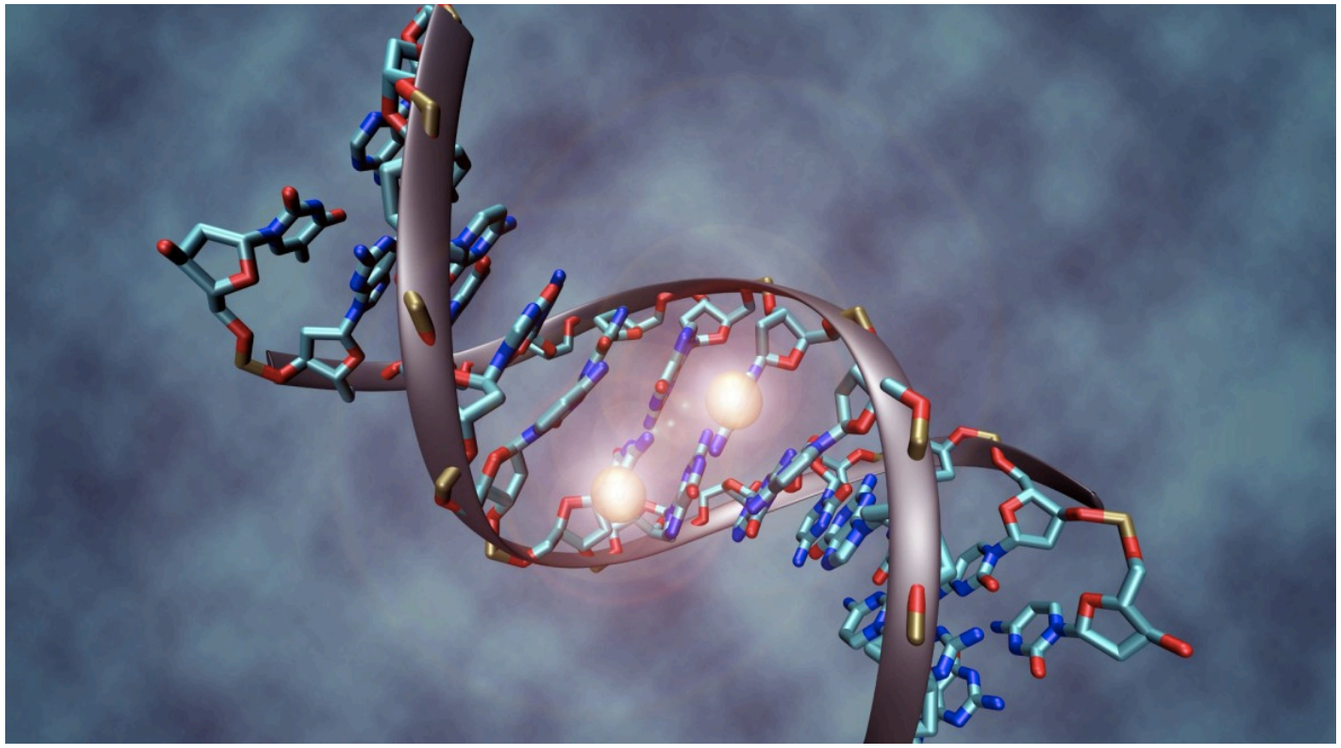

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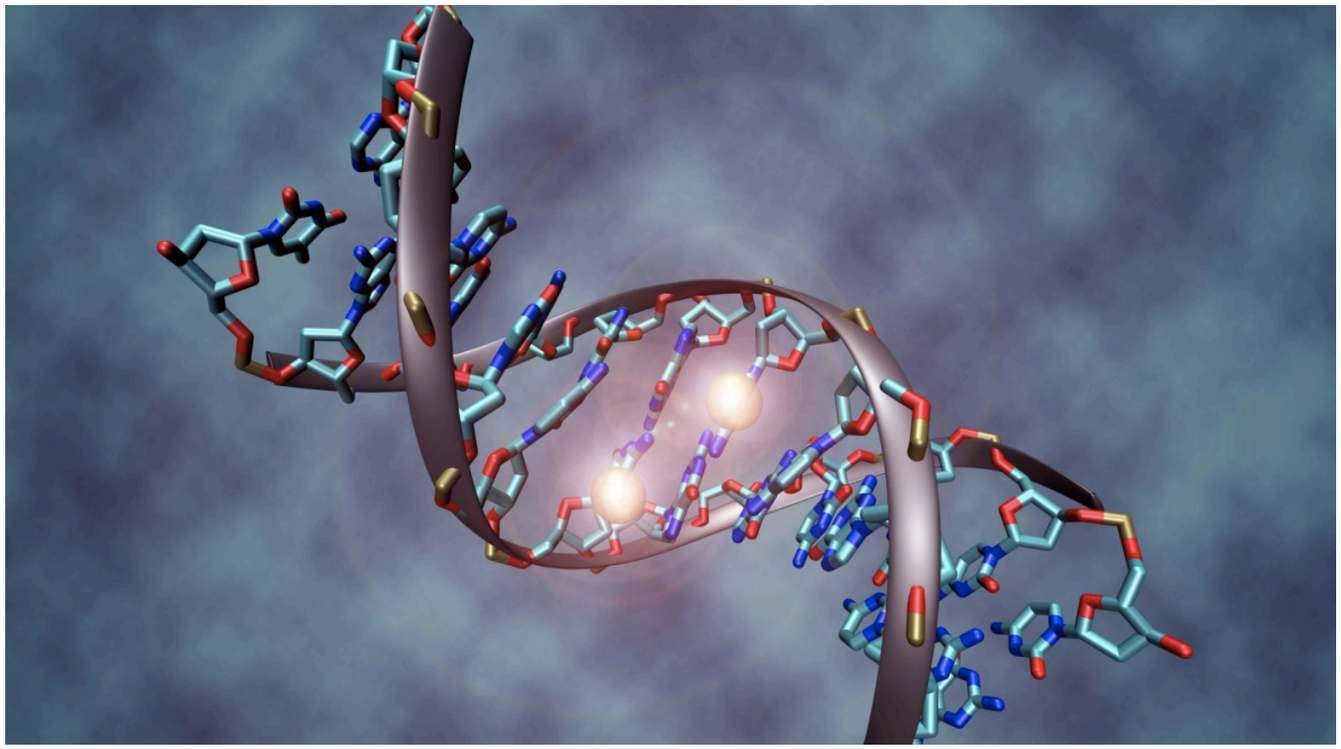

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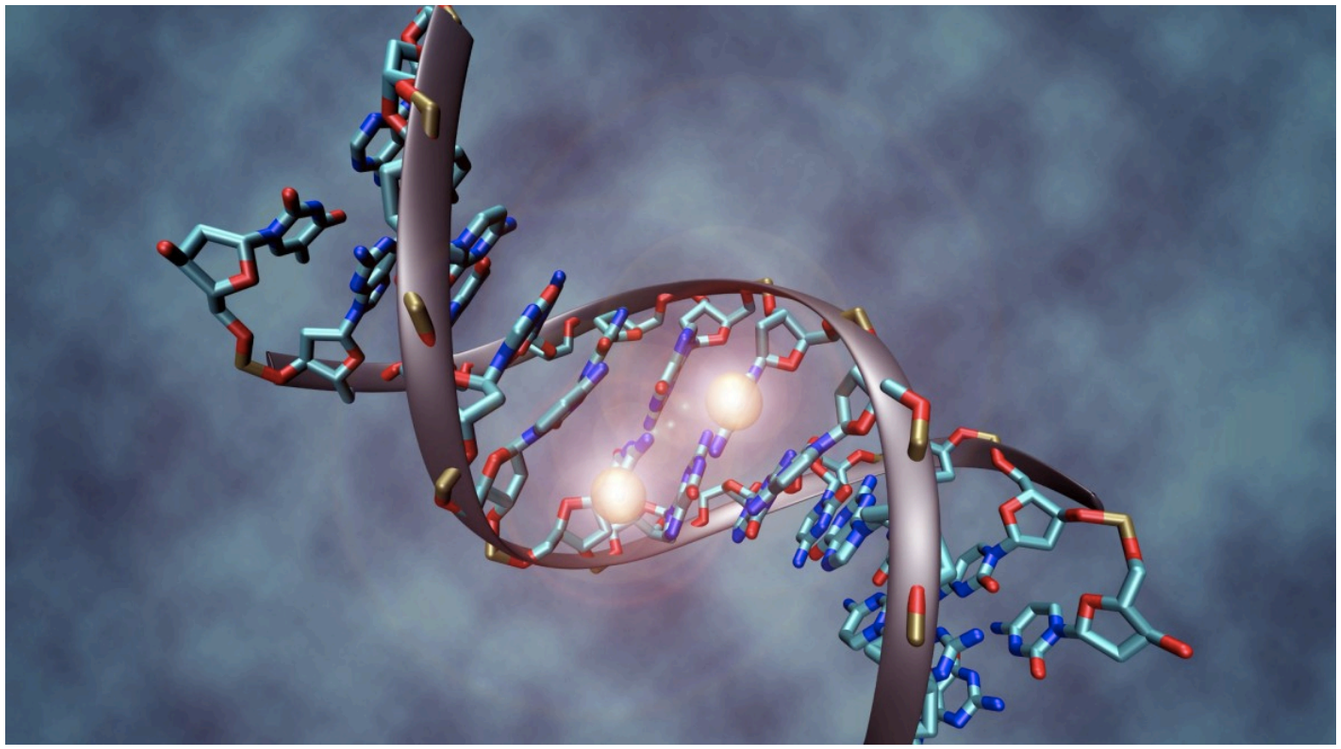

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- Repair mechanisms => 1 mutation in **10^{10}** nucleotides per cell division

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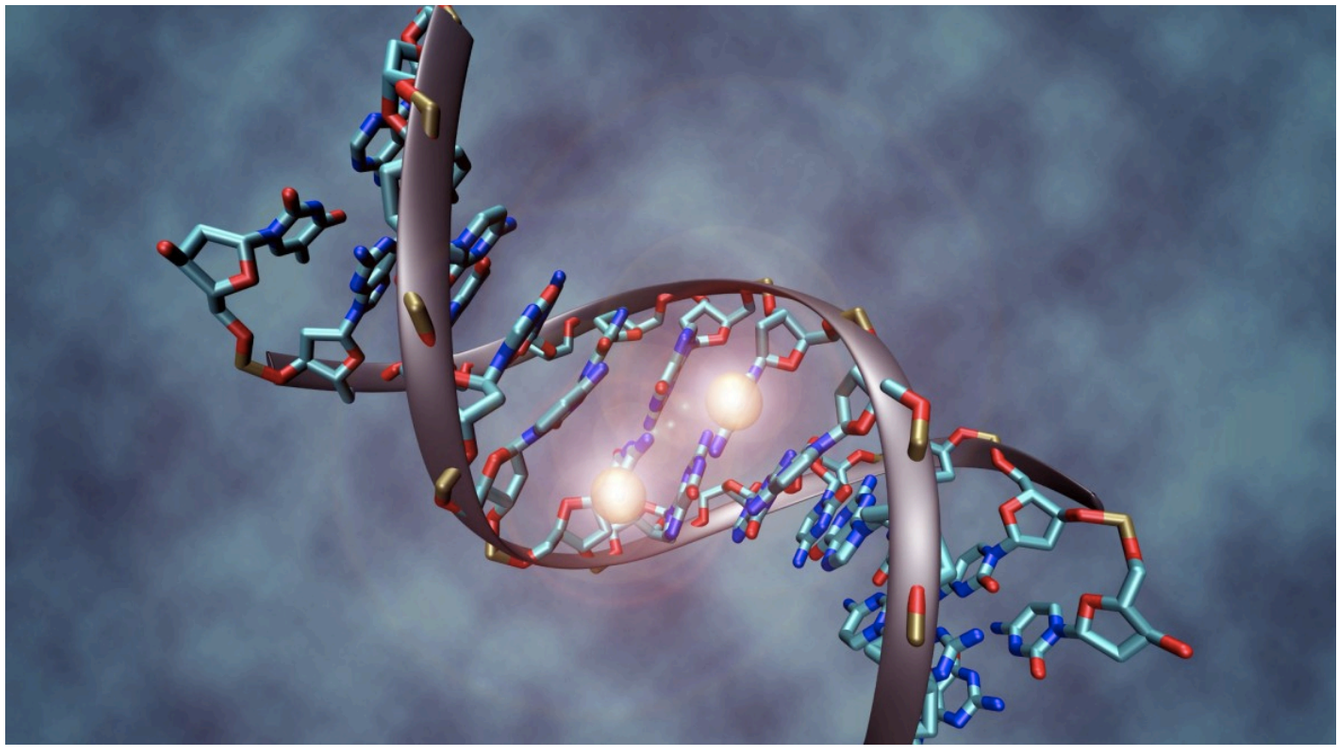

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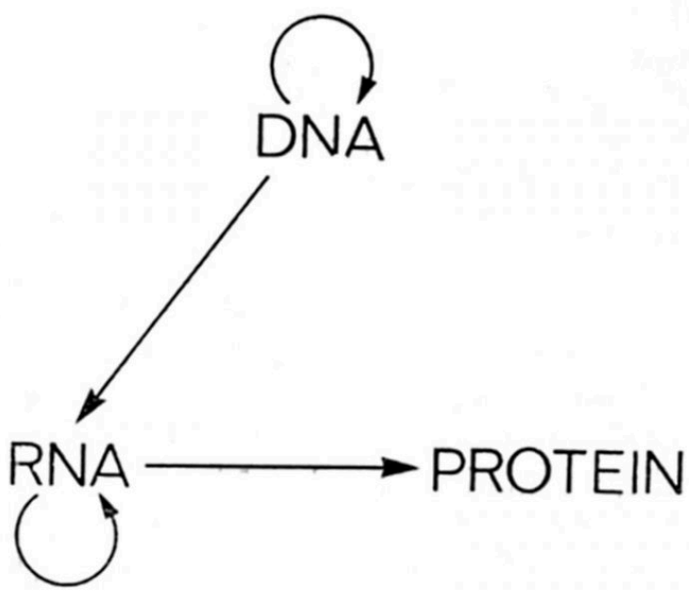
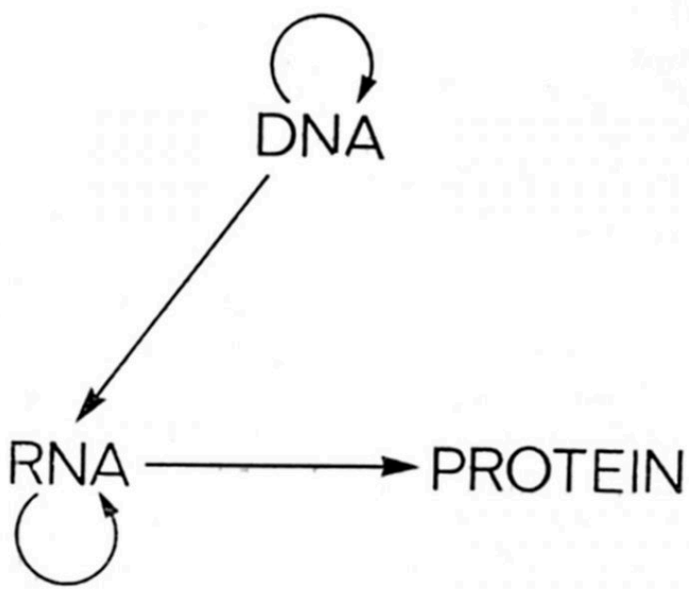
  - Endogenous DNA damage
  - Exogenous DNA damage
- Repair mechanisms => 1 mutation in **10^{10}** nucleotides per cell division
- Cf. human genome size: **3×10^{9}** bp

The Central Dogma: flow of information in the living cells



Crick's 1958 version of the "central dogma" of biology from Crick (1970, Figure 3, p. 562).

The Central Dogma: flow of information in the living cells



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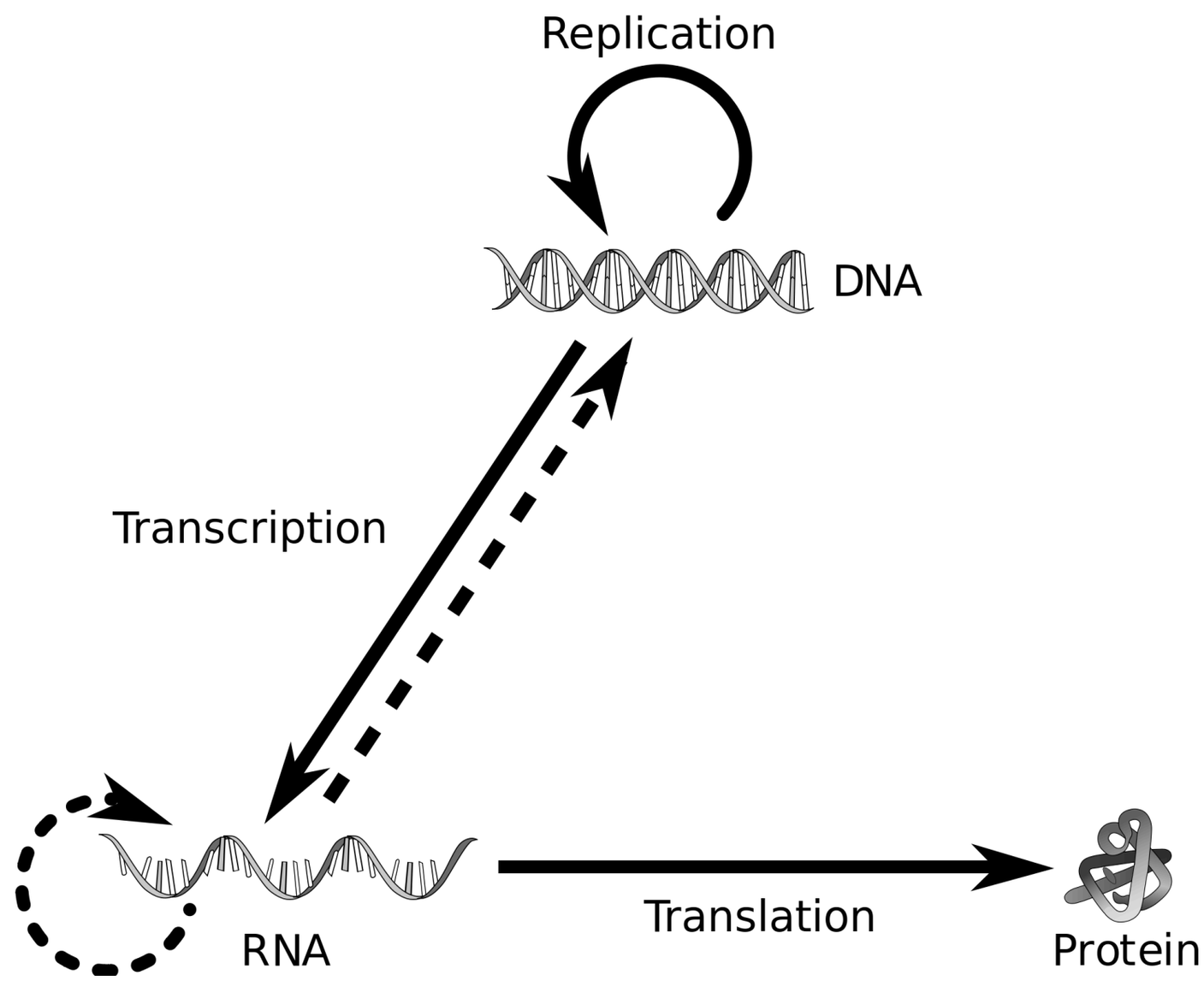

https://commons.wikimedia.org/wiki/File:Central_dogma_of_molecular_biology.svg

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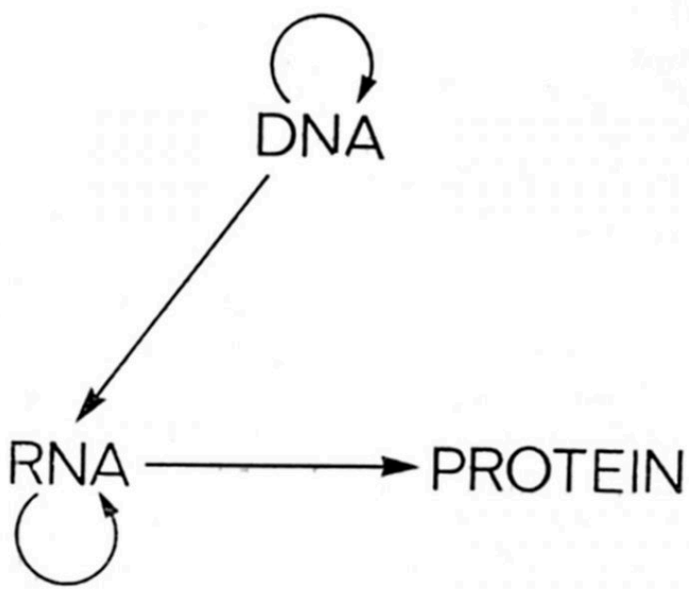

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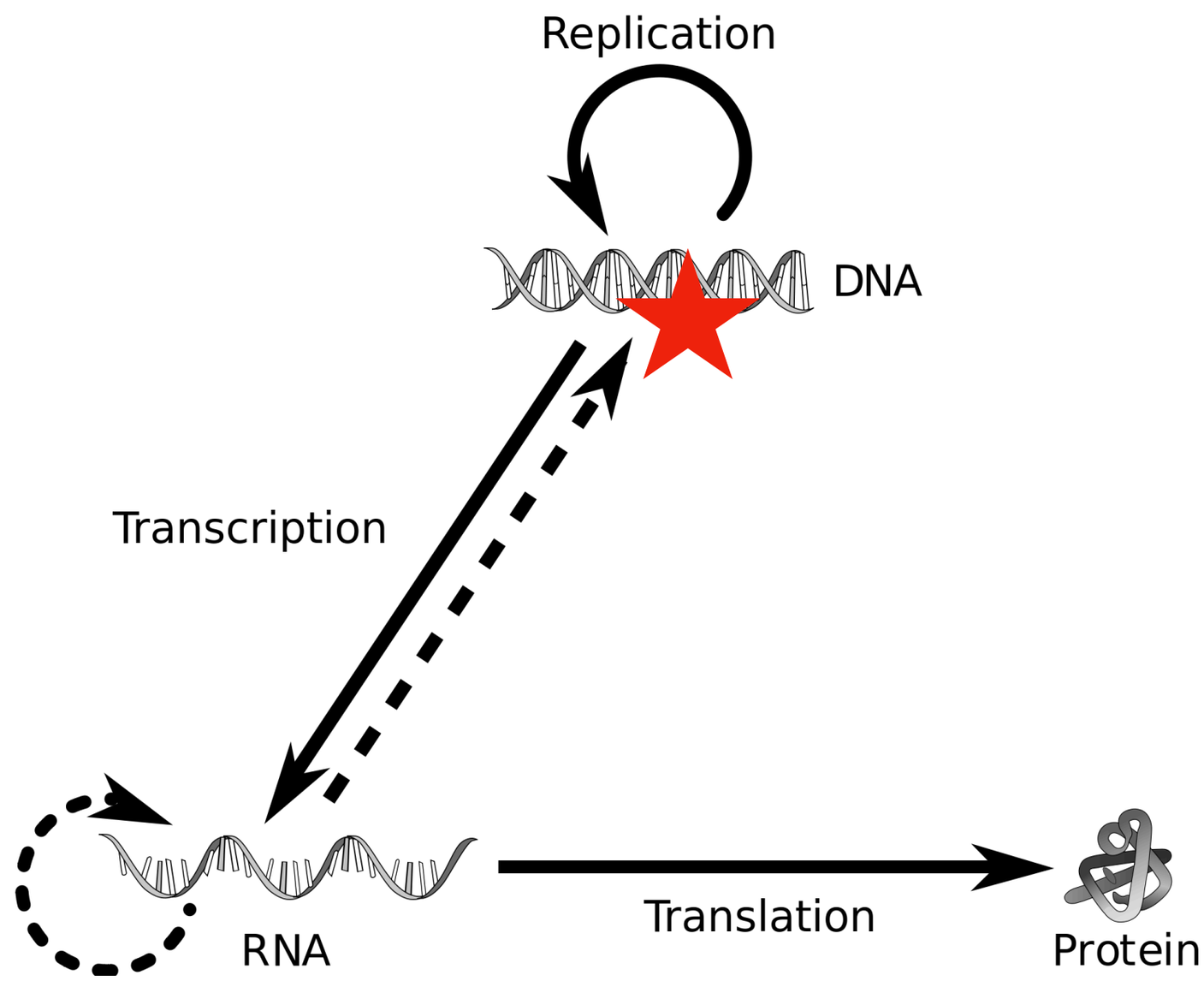

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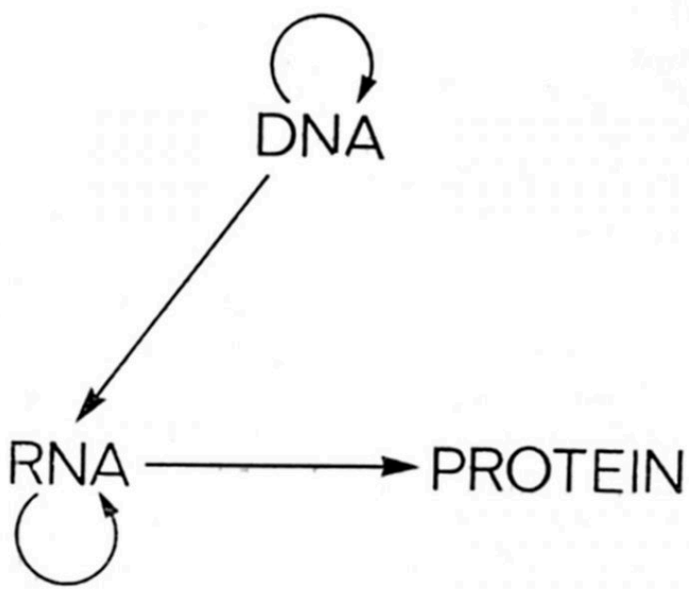

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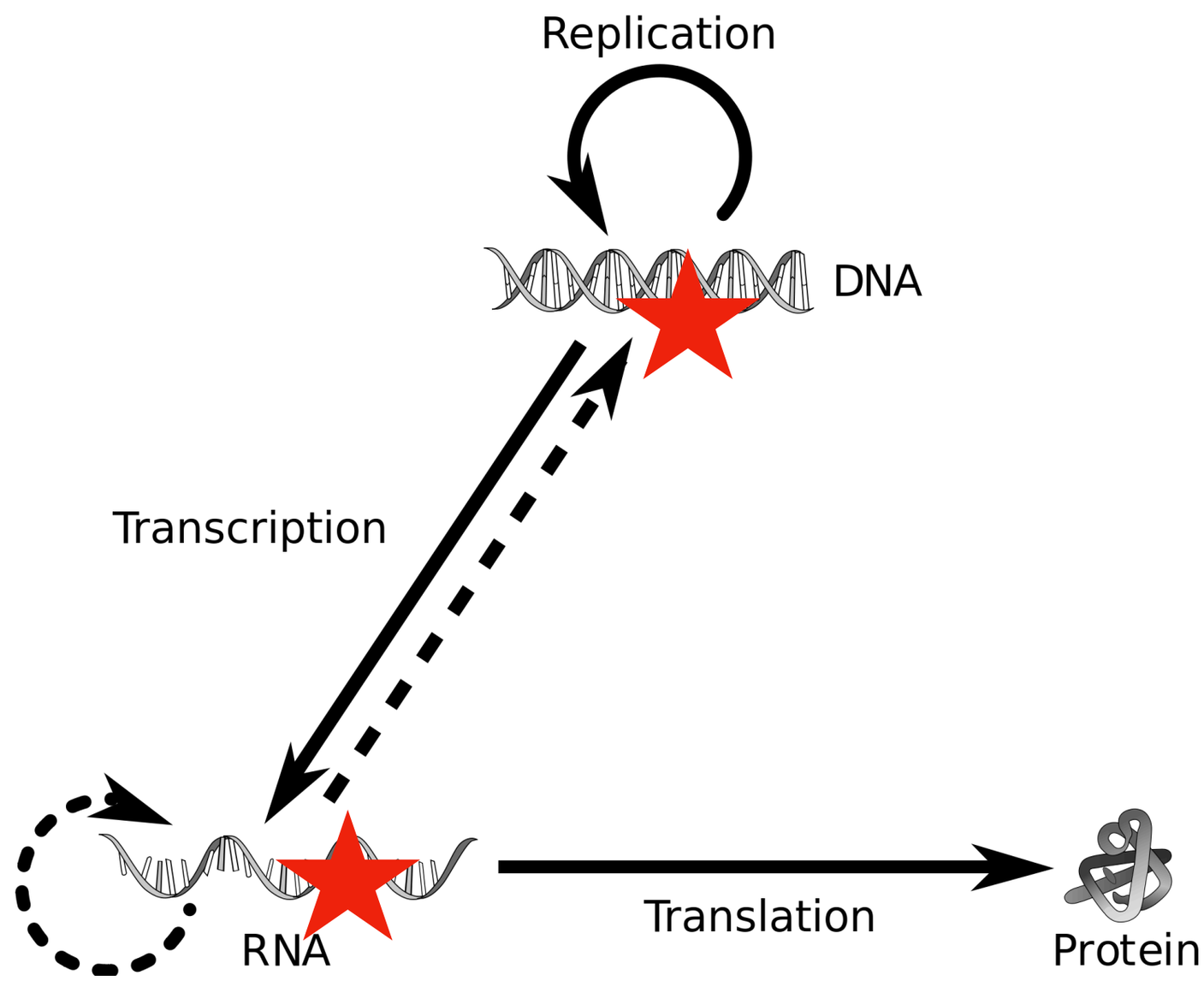

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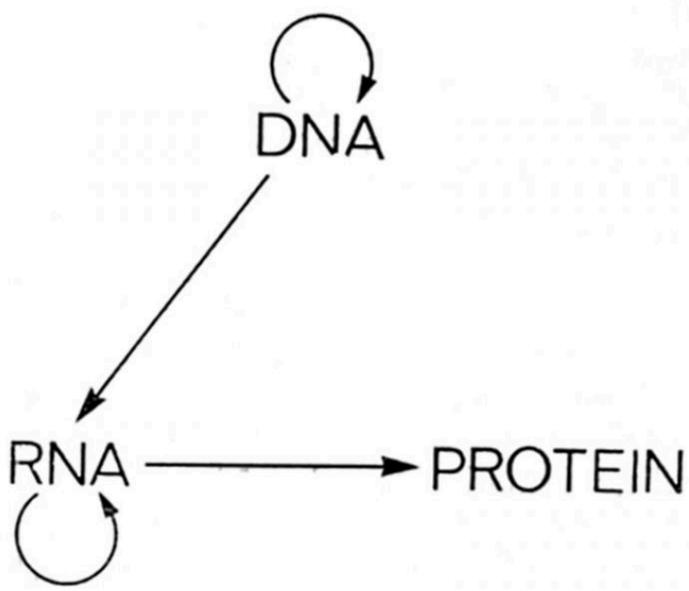

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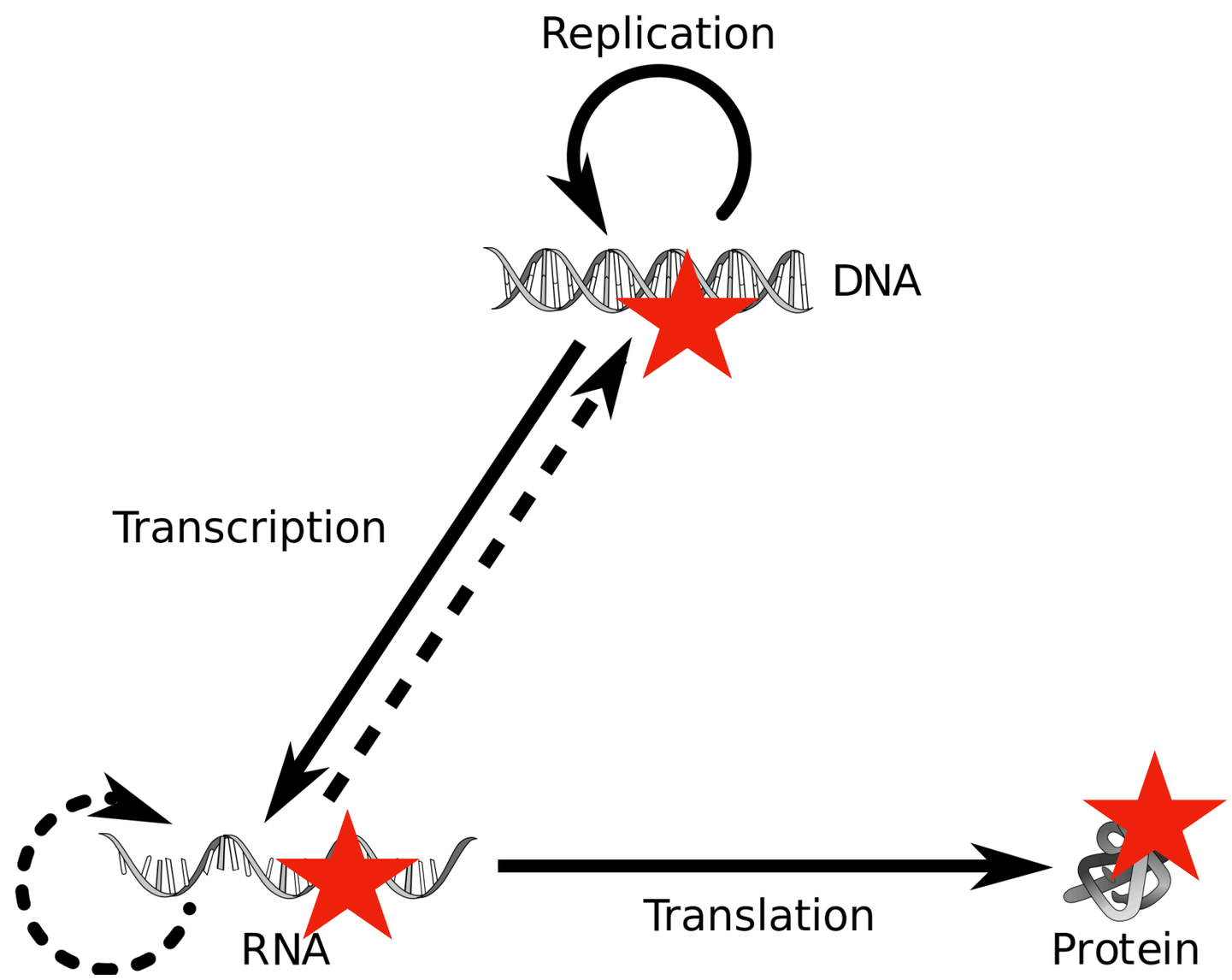

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Protein thermodynamic stability

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- Simple case: protein can unfold and refold rapidly, reversibly, via a two-state mechanism

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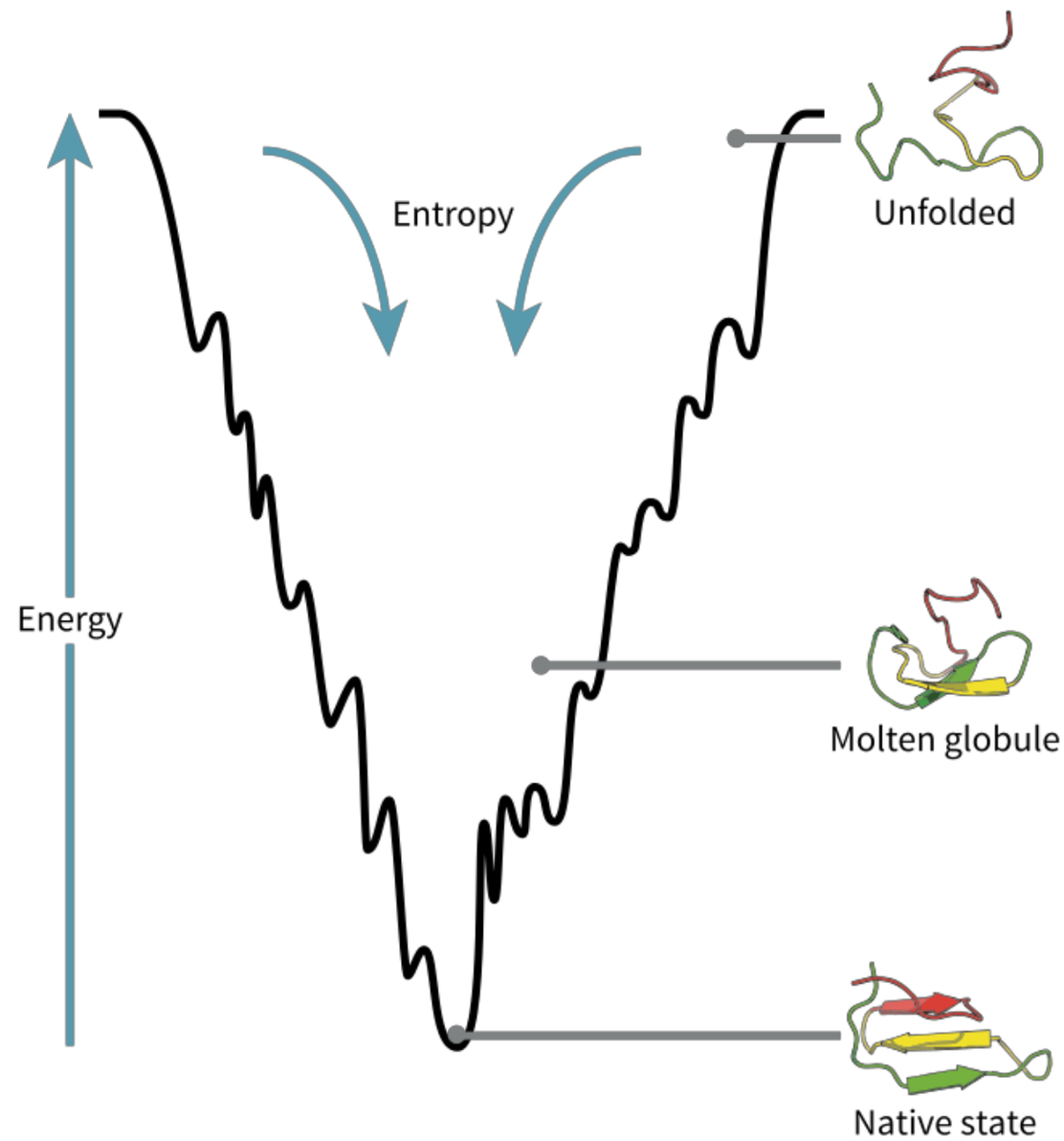

https://commons.wikimedia.org/w/index.php?curid=28353539

Some data (real-life)

- **ΔΔG** estimates upon mutations

#chr	Gene	ClinicalSignificance	uniprot_ac	uniprot_pos	aa1	aa2	FX_ddG
chr1	ISG15	Benign	P05161	83	S	N	-0.517133
chr2	DNMT3A	Pathogenic	Q9Y6K1	583	C	Y	33.0787
chr1	AGRN	Benign	O00468-6	15	P	R	?

…

- 84,426 rows (13 MB)

Reading the data (R)

```
> x<-read.table("clinvar.main.pph.ddg.uniprot.tsv",
sep='\t', header=T)
> x[ x == "?" ] <- NA
> nrow(x)
84426
```

- => **data frame**

Reading the data (Postgres)

```
kalinina=# CREATE TABLE clinvar (chr text, to1 bigint, ref text,
alt text, GeneSymbol text, ClinicalSignificance text,
ReviewStatus text, PhenotypeList text, uniprot_ac text,
uniprot_pos int, aa1 char(1), aa2 char(1), prediction text,
PDB_id text, PDB_pos text, PDB_ch char(1), ident float, FX_ddG
float, IM_ddG float, M_ddG float, M_conf float);
CREATE TABLE

kalinina=# COPY clinvar FROM 'clinvar.main.pph.ddg.uniprot.tsv'
WITH (NULL '?', DELIMITER E'\t');
COPY 84426
```

Calculate median (R)

```
>median(x$FX_ddG)
[1] NA
```

Calculate median (R)

```
>median(x$FX_ddG)
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>median(x$FX_ddG, na.rm=TRUE)
[1] 0.974858
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```
>median(x$FX_ddG)
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>(x[x$ClinicalSignificance=='Pathogenic',]$FX_ddG)
[1] 1.7756
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Calculate median (R)

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>median(x$FX_ddG)
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>(x[x$ClinicalSignificance=='Pathogenic',]$FX_ddG)
[1] 1.7756

> aggregate(FX_ddG ~ ClinicalSignificance, data = x, FUN =
median)
    ClinicalSignificance FX_ddG
1                 Benign 0.62209
2             Pathogenic 1.77560
```

Calculate median (PL/R)

```
kalinina=# CREATE or REPLACE FUNCTION r_median(_float8) RETURNS
float AS '
median(arg1)
' LANGUAGE 'plr';
CREATE FUNCTION

kalinina=# CREATE AGGREGATE median (
sfunc = plr_array_accum,
basetype = float8,
stype = _float8,
finalfunc = r_median
);
CREATE AGGREGATE

kalinina=# SELECT clinicalsignificance, median(fx_ddg) FROM clinvar
GROUP BY clinicalsignificance ORDER BY clinicalsignificance;

clinicalsignificance | median
---------------------+----------
Benign               | 0.6220875
Pathogenic           | 1.7756
(2 rows)
```

Summary statistics (R)

```
> aggregate(FX_ddG ~ ClinicalSignificance, data = x, FUN = summary)
    ClinicalSignificance FX_ddG.Min. FX_ddG.1st Qu. FX_ddG.Median FX_ddG.Mean FX_ddG.3rd Qu. FX_ddG.Max.
1                 Benign    -5.77969       -0.04082       0.62209     1.37172       1.91954     62.08970
2             Pathogenic   -18.09830        0.30438       1.77560     3.21887       4.21793     52.26050
```

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2             Pathogenic   -18.09830        0.30438       1.77560

FX_ddG.Mean FX_ddG.3rd Qu. FX_ddG.Max.
    1.37172       1.91954     62.08970
    3.21887       4.21793     52.26050
```

You need additional code if you need to preserve a specific order of categories

Summary statistics (PL/R)

```
kalinina=# CREATE or REPLACE FUNCTION r_summary(_float8) RETURNS _float8 AS '
summary(arg1)
' LANGUAGE 'plr';
CREATE FUNCTION

kalinina=# CREATE AGGREGATE summary (
sfunc = plr_array_accum,
basetype = float8,
stype = _float8,
finalfunc = r_median
);
CREATE AGGREGATE

kalinina=# SELECT clinicalsignificance, SELECT summary(fx_ddg) FROM clinvar GROUP BY
clinicalsignificance ORDER BY clinicalsignificance;

clinicalsignificance | summary
---------------------+-----------------------------------------------------------------
Benign               | {-5.77969,-0.040819875,0.6220875,1.37171750416516,1.9195375,62.0897}
Pathogenic           | {-18.0983,0.3043845,1.7756,3.21886833468419,4.217925,52.2605}
(2 rows)
```

Boxplot (R)

```
>boxplot(x[ x$ClinicalSignificance == ‘Pathogenic’, ]$FX_ddG)
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- Syntax for subsetting:

```
x[ x$<someFactor> == ‘<someValue>’, ]
```

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- Output directly to active graphic device

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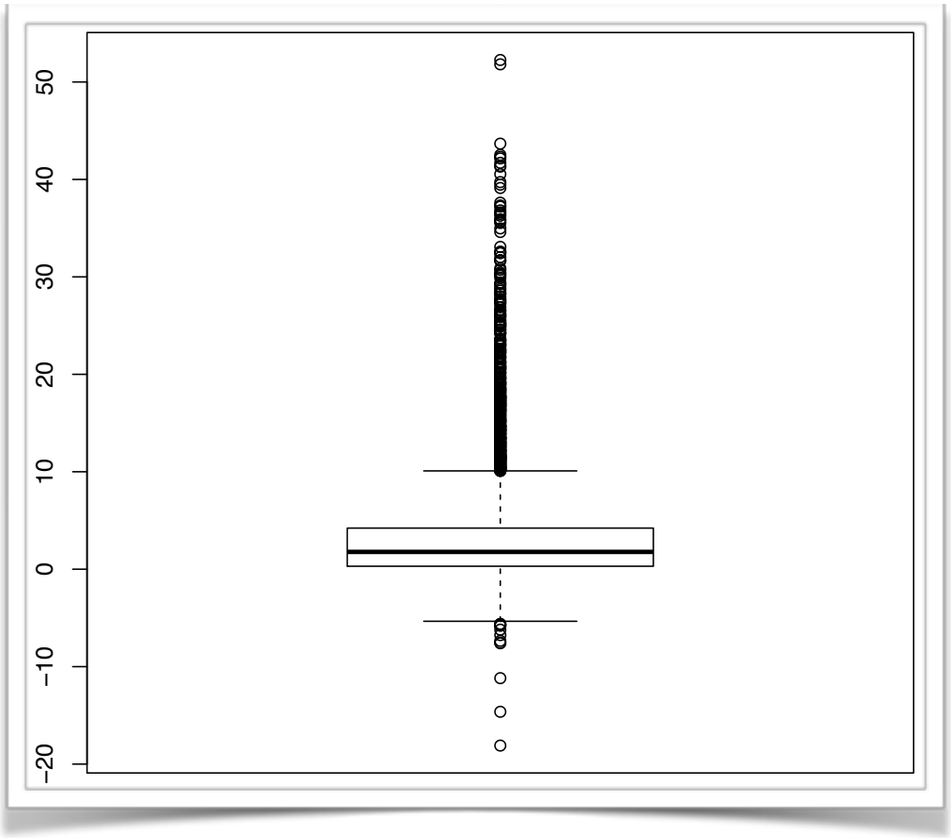


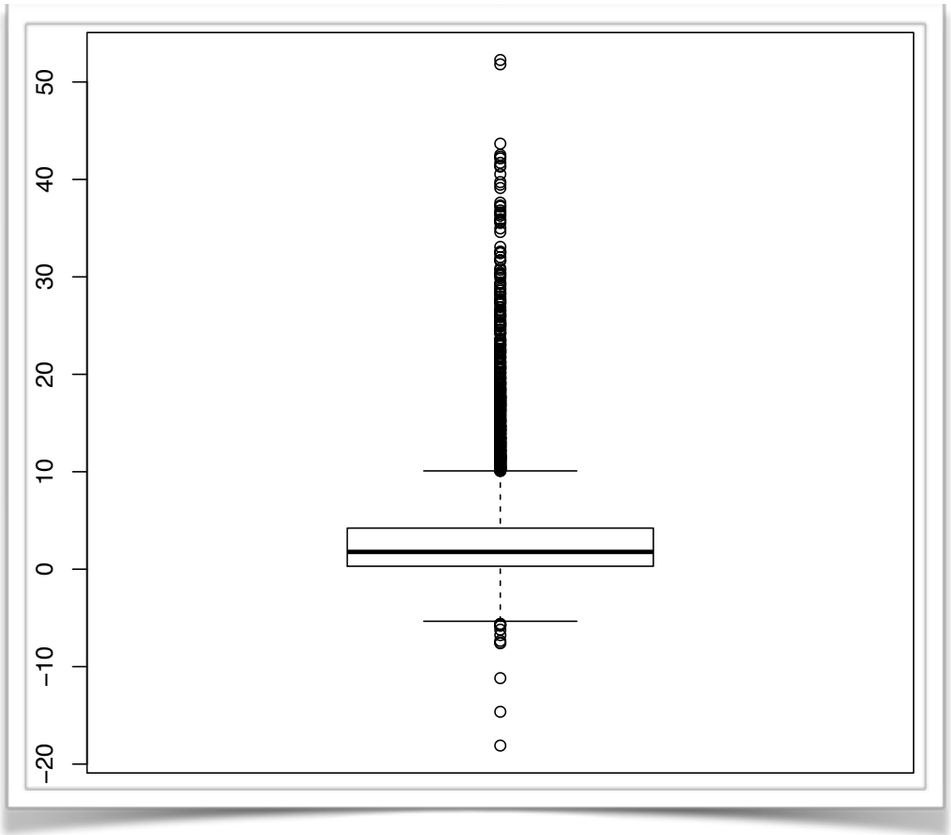
Boxplot (PL/R)

```
CREATE or REPLACE function
r_boxplot2(_float8) RETURNS void AS '
pdf("~/Work/ddG/test.pdf")
boxplot(arg1)
dev.off()
' language 'plr';
CREATE FUNCTION

kalinina=# CREATE AGGREGATE boxplot2pdf (
sfunc = plr_array_accum,
basetype = float8,
stype = _float8,
finalfunc = r_boxplot2
);
CREATE AGGREGATE

kalinina=# SELECT boxplot2pdf(fx_ddg)
FROM clinvar WHERE clinicalsignificance =
'Pathogenic';
 boxplot2pdf
-------------

(1 row)
```



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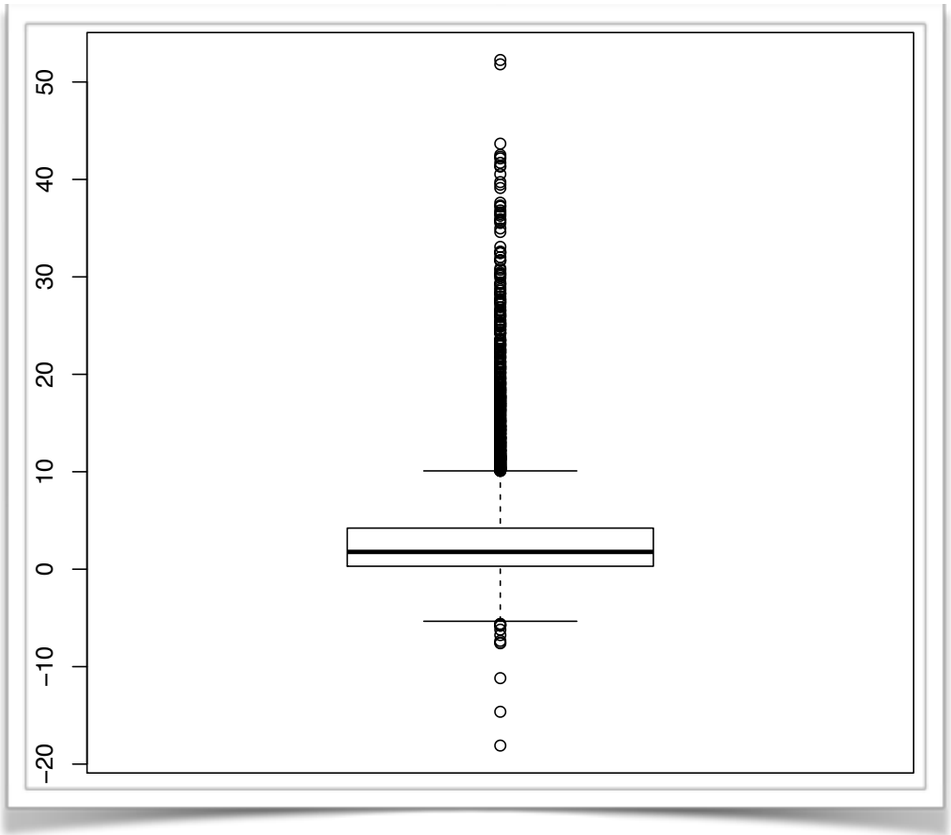
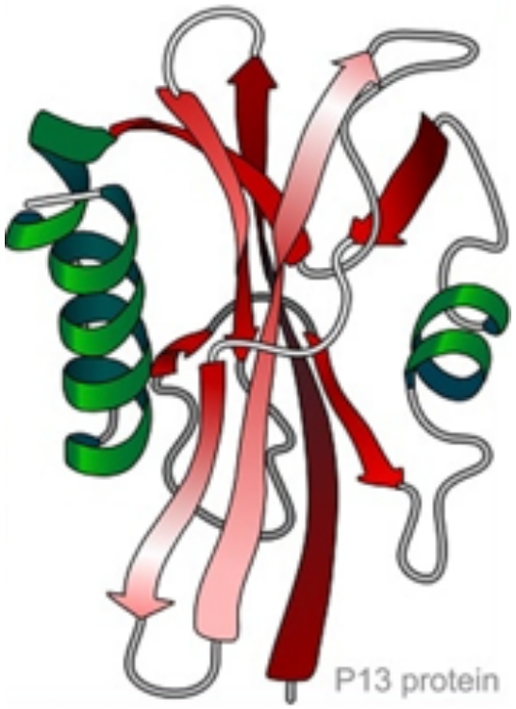
'Pathogenic';
 boxplot2pdf
-------------

(1 row)
```

Only output to file



More data (real-life)



- **Structural annotation** of the human proteome

#AC	Mut	Species	Tags	Surface/Core	**Class**
P30613	R498	HUMAN	None	Surface	**Ligand**
P30613	G411	HUMAN	None	Core	**Core**
P30613	R559	HUMAN	None	None	**Disorder**

- Every protein position is classified as `Surface`, `Core`, `Ligand`, `Metal`, `Protein`, `DNA`, `RNA`, or `Disorder` (8 categories)
- 23,095,049 rows (1.9 GB)

Pie chart (R)

```
> p <- read.table("proteome.classification.tsv", sep="\t")
> p[ p == "None" ] <- NA
> pp <- p[p$Class <> 'Disorder', ]
> piedata <- aggregate(pp$AC, by=list(Category=pp$Class), FUN=length)
> piedataOrdered <- piedata[ order(-piedata$x), ]
> piedataOrdered
  Category       x
7  Surface 6411178
1     Core 4519347
5  Protein 2228705
3   Ligand  934970
4    Metal  830419
2      DNA  265432
6      RNA   69701

> pie(piedataOrdered$x/nrow(pp),
  labels=piedataOrdered$Category)
```

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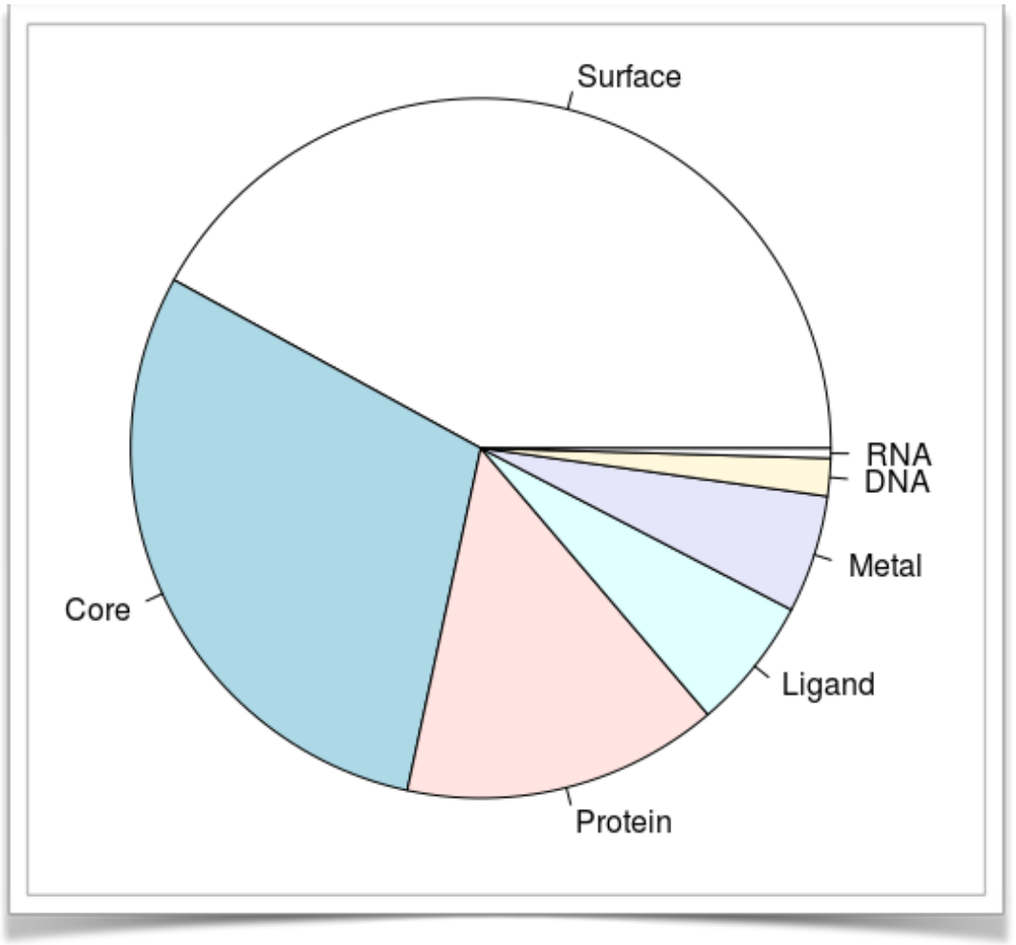

Pie chart (PL/R)

```
kalinina=# CREATE VIEW piechart AS SELECT class, CAST(count(ac) AS float)/(SELECT
count(ac) FROM structman WHERE class <> 'Disorder') AS percentage FROM structman
WHERE class <> 'Disorder' GROUP BY class ORDER BY percentage DESC;
CREATE VIEW

kalinina=# CREATE or REPLACE function r_pie(_float8) RETURNS void AS '
pdf("~/Work/ddG/testpie.pdf")
pie(arg1)
dev.off()
' language 'plr';
CREATE FUNCTION

kalinina=# CREATE AGGREGATE pie2pdf (
sfunc = plr_array_accum,
basetype = float8,
stype = _float8,
finalfunc = r_pie
);
CREATE AGGREGATE

kalinina=# SELECT pie2pdf(percentage) FROM piechart;
 pie2pdf
---------

(1 row)
```

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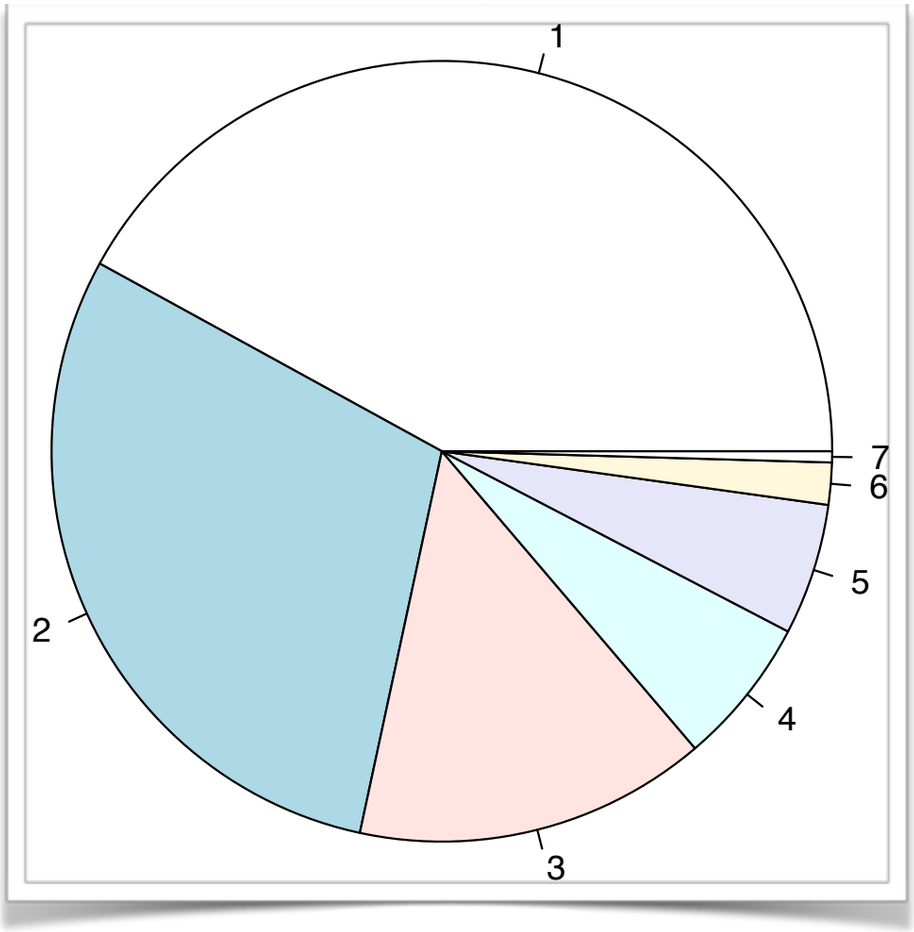
 pie2pdf
---------

(1 row)
```



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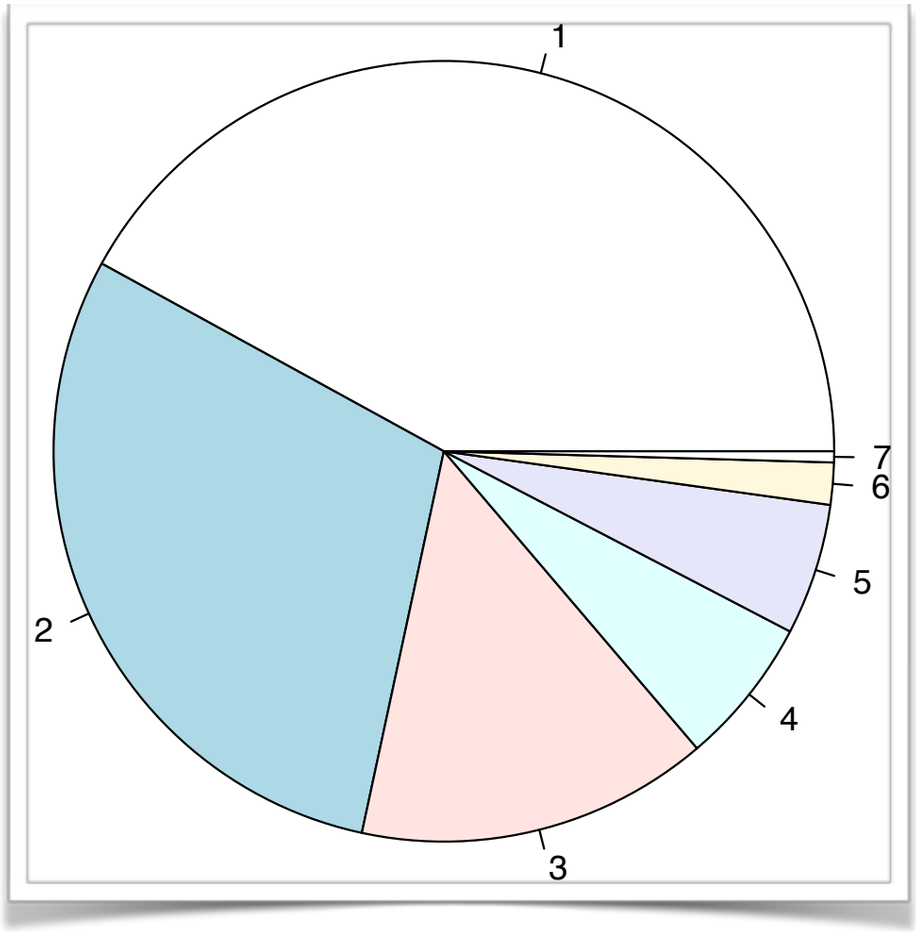
 pie2pdf
---------

(1 row)
```

No clean solution to pass the names of the categories



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- `pp` (all rows except ‘Disorder’) has 15,259,752 rows

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- The most expensive command in R:

```
aggregate(pp$AC, by=list(Category=pp$Class), FUN=length)
```

takes ~6.3 sec to execute

Now it starts to pay off

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- The most expensive command in R:
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Now it starts to pay off

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- The most expensive command in R:
  `aggregate(pp$AC, by=list(Category=pp$Class), FUN=length)`
  takes ~6.3 sec to execute
- Selection from `piechart` in the database takes 1.97 sec
- On the other hand, running `median` grouped by `Class` will never finish: full table scan

Statistical significance

- R has implementations of a variety of statistical tests, e.g. Wilcoxon test:

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```
> wilcox.test(x[x$ClinicalSignificance==‘Pathogenic',]$FX_ddG),
x[x$ClinicalSignificance==‘Benign',]$FX_ddG))

    Wilcoxon rank sum test with continuity correction

data:  x[x$ClinicalSignificance == "Pathogenic", ]$FX_ddG and
x[x$ClinicalSignificance == "Benign", ]$FX_ddG
W = 4419800, p-value < 2.2e-16
alternative hypothesis: true location shift is not equal to 0
```

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x[x$ClinicalSignificance == "Benign", ]$FX_ddG
W = 4419800, p-value < 2.2e-16
alternative hypothesis: true location shift is not equal to 0

> wilcox.test(x[x$ClinicalSignificance==‘Pathogenic',]$FX_ddG),
x[x$ClinicalSignificance==‘Benign’,]$FX_ddG))$p.value
[1] 1.033810e-167
```

Passing two arrays of datapoint

```
kalinina=# CREATE TABLE ddg (pathogenic float, benign float);
CREATE TABLE
kalinina=# INSERT INTO ddg(pathogenic) SELECT fx_ddg FROM clinvar
WHERE clinicalsignificance = 'Pathogenic';
INSERT 0 20336
kalinina=# INSERT INTO ddg(benign) SELECT fx_ddg FROM clinvar
WHERE clinicalsignificance = 'Benign';
INSERT 0 64090
kalinina=# CREATE TABLE ddg_all (ddg float);
CREATE TABLE
kalinina=# INSERT INTO ddg_all(ddg) SELECT pathogenic FROM ddg;
INSERT 0 84426
kalinina=# INSERT INTO ddg_all(ddg) SELECT benign FROM ddg;
INSERT 0 84426
```

…and calculating statistical significance

```
kalinina=# CREATE OR REPLACE FUNCTION r_wilcox(_float8) RETURNS float AS
'
x<-arg1[1:length(arg1)/2]
y<-arg1[length(arg1)/2+1:length(arg1)]
wilcox.test(x,y)$p.value
' language 'plr';
CREATE FUNCTION

kalinina=# CREATE AGGREGATE wilcox (
sfunc = plr_array_accum,
basetype = float8,
stype = _float8,
finalfunc = r_wilcox
);
CREATE AGGREGATE

kalinina=# SELECT wilcox(ddg) FROM ddg_all;
        wilcox
-----------------------
 1.03380966840586e-167
(1 row)
```

…draw plots with two series

```
kalinina=# CREATE OR REPLACE FUNCTION r_plottwo(_float8) RETURNS float AS
'
pdf("testtwo.pdf")
x<-arg1[1:length(arg1)/2]
y<-arg1[length(arg1)/2+1:length(arg1)]
boxplot(x,y)
dev.off()
' language 'plr';
CREATE FUNCTION

kalinina=# CREATE AGGREGATE plottwo (
sfunc = plr_array_accum,
basetype = float8,
stype = _float8,
finalfunc = r_plottwo
);
CREATE AGGREGATE

kalinina=# SELECT plottwo(ddg) FROM ddg_all;
        plottwo
-----------------------

(1 row)
```

…draw plots with two series

```
kalinina=# CREATE OR REPLACE FUNCTION r_plottwo(_float8) RETURNS float AS
'
pdf("testtwo.pdf")
x<-arg1[1:length(arg1)/2]
y<-arg1[length(arg1)/2+1:length(arg1)]
boxplot(x,y)
dev.off()
' language 'plr';
CREATE FUNCTION

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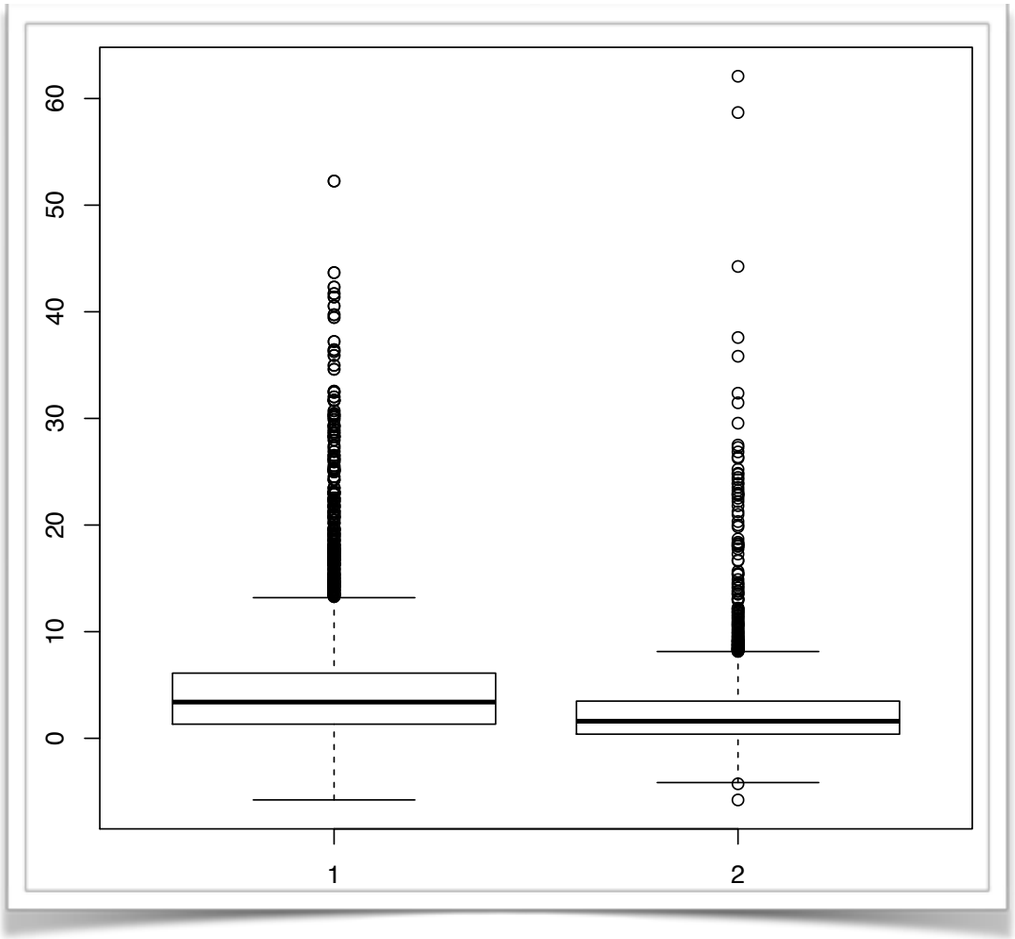

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```

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```
x: chr Gene   ClinicalSignificance uniprot_ac uniprot_pos aa1 aa2 FX_ddG

p: AC Mut  Species Tags  Surface/Core  Class


> library (dplyr)
> joined_data <- t %>% inner_join(p, by = c(c(x$uniprot_ac == p$AC)),
c(x$uniprot_pos == p$Mut)))
Error in Ops.factor(x$uniprot_ac, p$AC) : level sets of factors are
different
```

- You have to have the same set of identifiers in both tables!

Joins (PL/R)

```
kalinina=# SELECT DISTINCT structman.ac AS ac,
clinicalsignificance, fx_ddg INTO core FROM clinvar INNER JOIN
structman ON structman.ac = clinvar.uniprot_ac AND structman.mut
= clinvar.aa1||clinvar.uniprot_pos WHERE structman.class =
'Core';
SELECT 6637

kalinina=# SELECT DISTINCT structman.ac AS ac,
clinicalsignificance, fx_ddg INTO notcore FROM clinvar INNER JOIN
structman ON structman.ac = clinvar.uniprot_ac AND structman.mut
= clinvar.aa1||clinvar.uniprot_pos WHERE structman.class <>
'Core';
SELECT 13430
```

Joins (PL/R)

```
kalinina=# SELECT clinicalsignificance, median(fx_ddg) FROM clinvar GROUP BY
clinicalsignificance;
 clinicalsignificance |  median
----------------------+-----------
 Pathogenic           |    1.7756
 Benign               | 0.6220875
(2 rows)

kalinina=# SELECT clinicalsignificance, median(fx_ddg) FROM core GROUP BY
clinicalsignificance;
 clinicalsignificance | median
----------------------+---------
 Pathogenic           |  3.4113
 Benign               | 1.55485
(2 rows)

kalinina=# SELECT clinicalsignificance, median(fx_ddg) FROM notcore GROUP BY
clinicalsignificance;
 clinicalsignificance |  median
----------------------+----------
 Pathogenic           | 1.003565
 Benign               | 0.424089
(2 rows)
```

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- However, one can benefit from data handling in the database
- **Feedback**: https://2019.fosdempgday.org/f