What Can an AI Competition do for You?

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Today’s Goal


I WANT YOU
TO THINK ABOUT
AI COMPETITIONS
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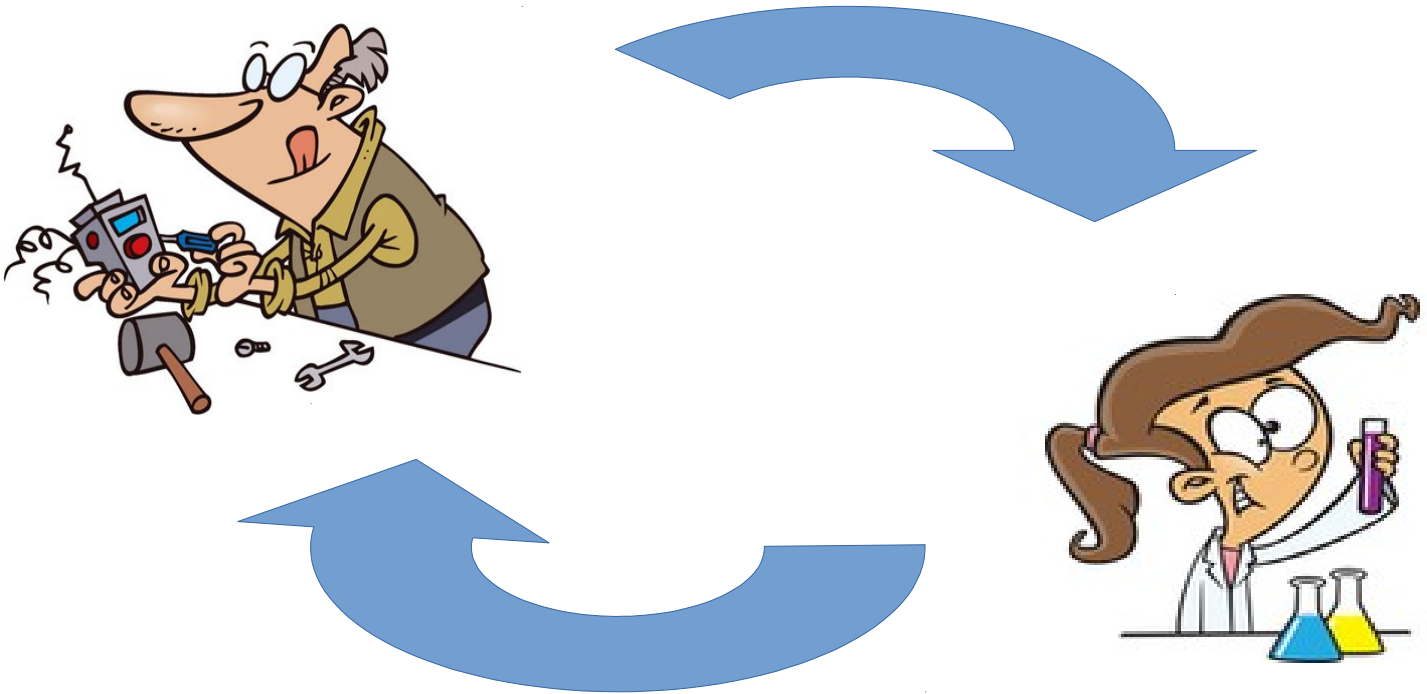
Methods and Discovery



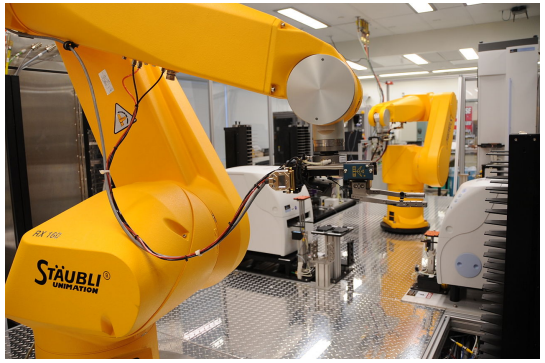
Methods and Discovery

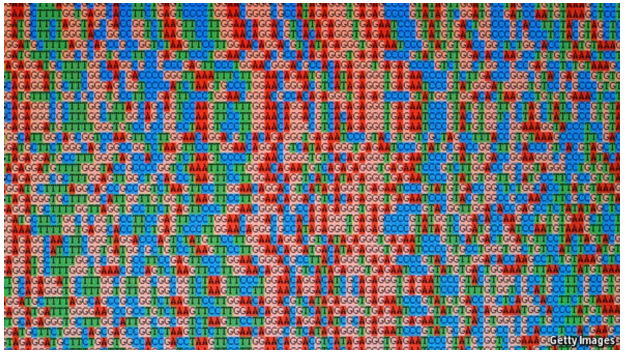
- Patch clamping
- Mass spec
- RNASeq
- Bioinformatics
- CRISPR

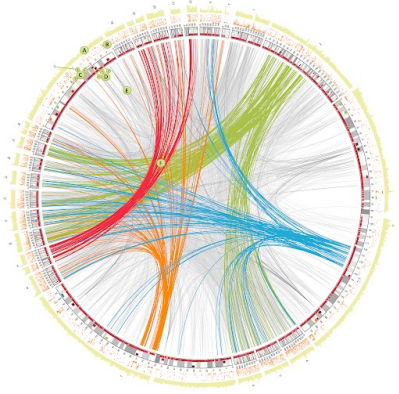
- Ion channels
- Protein expression
- Gene regulation
- Everything
- CRISPR

Science is Symbiotic

Genomics:
More Data than Knowledge







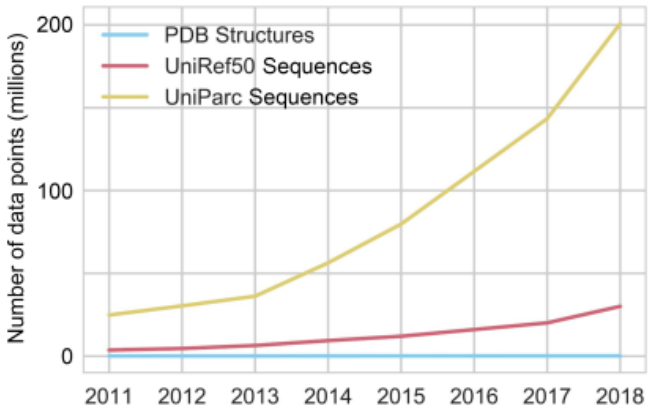
Predictive Models in Biology

- Data are abundant, but knowledge is lacking
  - Protein Sequence to Structure
  - Protein Sequence to Function
  - Image to Phenotype
  - Phenotype to Genotype
  - Genotype to Phenotype
  - Symptoms to Disease

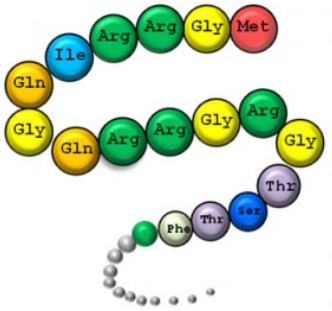
There are Many Methods to do one thing: Which is Best?

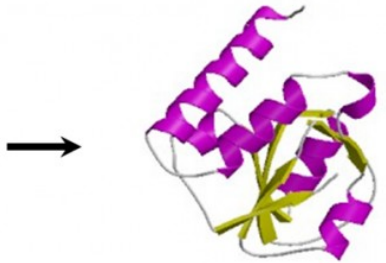
What is “Best”?

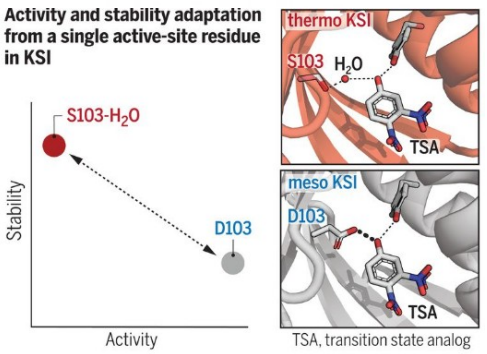
The Protein Structure Prediction Problem



Credit: Mohammed AlQuraishi







Pinney *et al* Science(2021) **371**:6533

Sequence data: easy to obtain; Structure data: hard to obtain

An important problem: structure tells us how the protein functions

A hard problem: there is a large search space

CASP: Critical Assessment of Structure Prediction

Problem: protein folding, or, predicting structure from sequence

Communities: Structural biologists & bioinformaticians

Challenge set: proteins whose structures were experimentally determined.

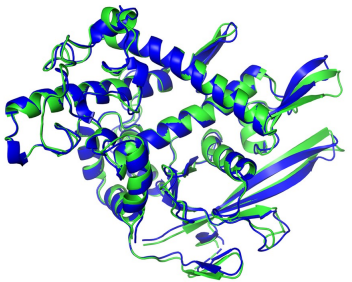
Assessment metrics: Root Mean Square Deviation, GDT_TS, etc.

Sequence of unknown structure

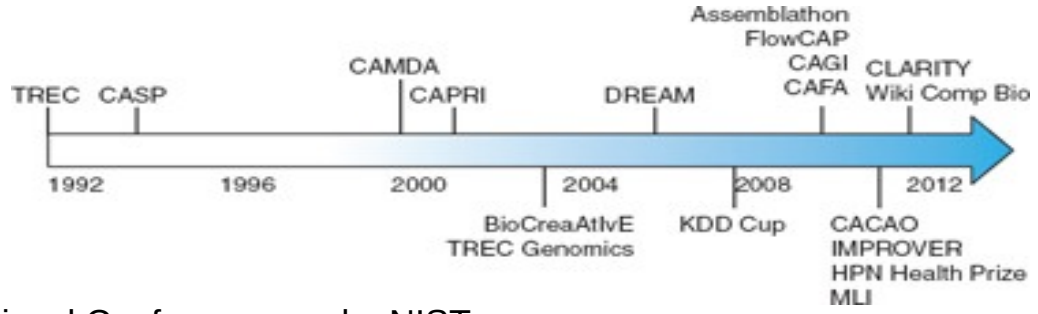
Predictions

Experimental data

Scoring



History of Competitions



TREC: Text Retrieval Conference run by NIST

CASP: structure prediction

CAPRI: Protein Interaction

BioCreative: Text mining

DREAM: umbrella – many biomedical challenges

CAGI: genotype / phenotype

CAFA: Function

CACAO: educational

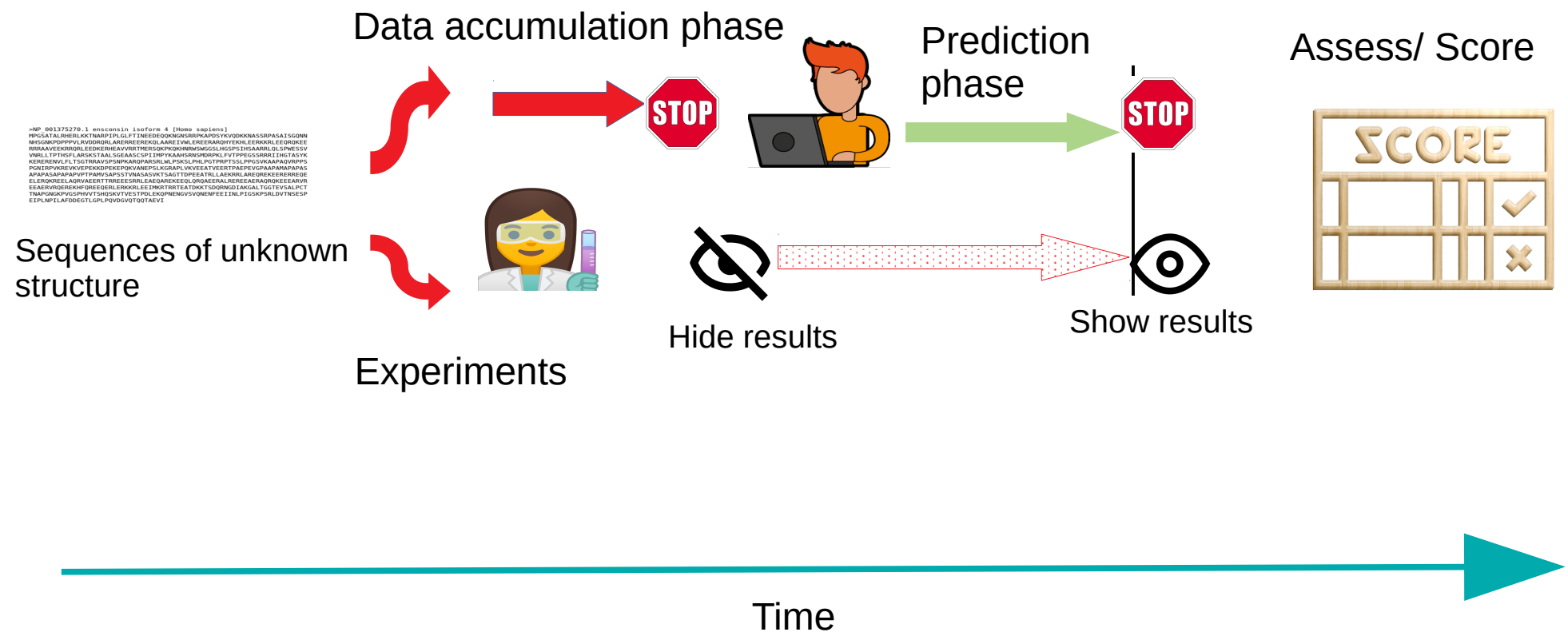
CAFA

- Critical Assessment of Function Annotation
  - Predict function from amino-acid sequence
- **Community**: function predictors, ontologists, experimental biologists
- **Problem**: given a protein, which functions are associated with it?
- **Challenge set**: proteins that organizers know their functions, but predictors don’t

Example: CAFA

- Critical Assessment of Function Annotation
  - Predict function from amino-acid sequence
- Community: function predictors, ontologists, experimental biologists
- Problem: given a protein, which functions are associated with it?
- Challenge set: proteins that organizers know their functions, but predictors don’t
- Assessment Metrics: oh, boy...

Competition Timeline: Getting Benchmark data

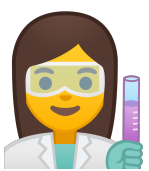


Big Data competitions: use a time challenge

Data accumulate over time **mostly after** the prediction phase ends

Sequences of unknown functions

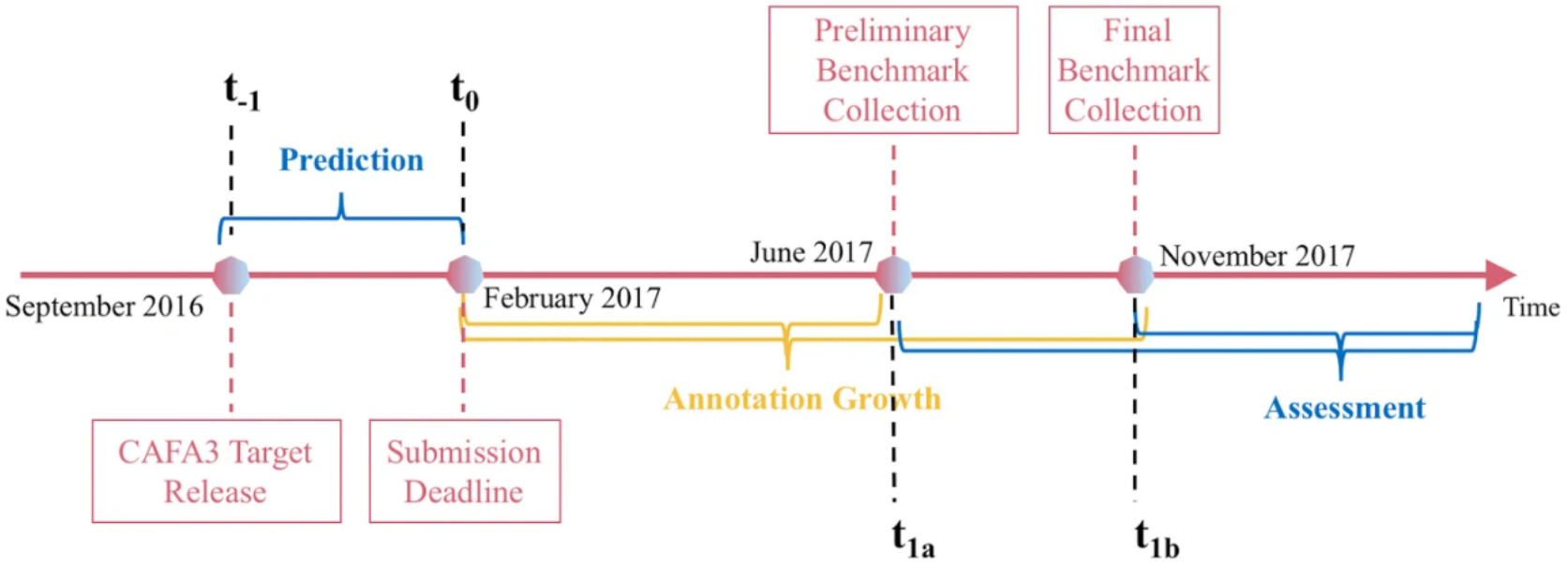
Prediction phase



Data accumulation phase

Time

CAFA Timeline



CAFA3 timeline

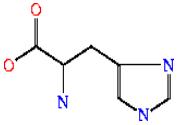
What is Protein Function?

Histidine amino lyase

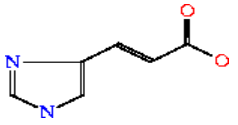
(HAL, Histidase)

Biochemical

10^{-9} m



L-histidine



Urocanate

$+NH_3$

What is Protein Function?

Biochemical

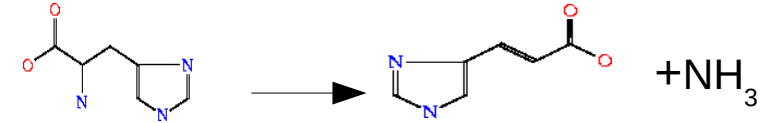
Cellular

10^{-9} m

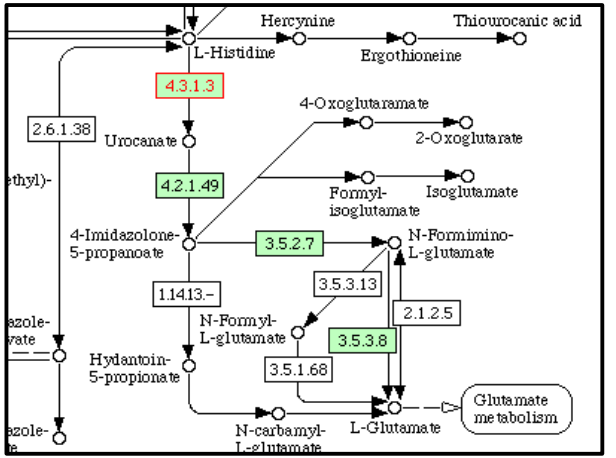
10^{-6} m

Histidine amino lyase

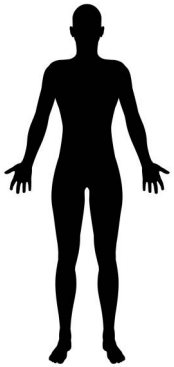
(HAL, Histidase)



L-histidine Urocanate $+NH_3$



What is Protein Function?



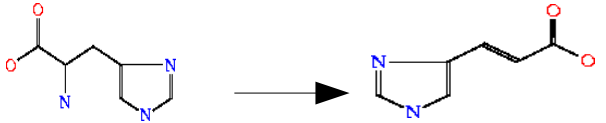
Biochemical — 10^{-9} m

Cellular — 10^{-6} m

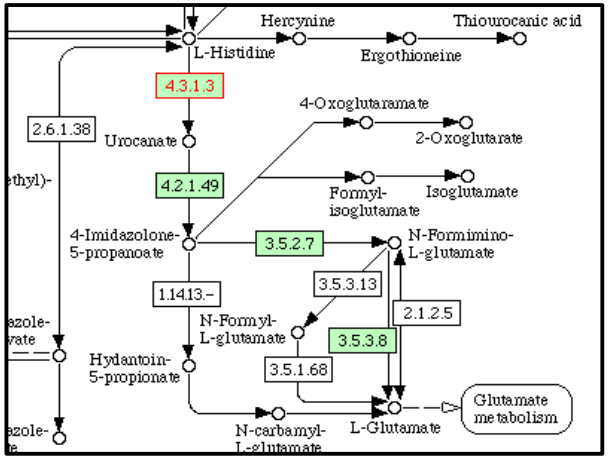
Phenotype — 10^{-1} m

Histidine amino lyase

(HAL, Histidase)



L-histidine → Urocanate



Mutation: Histidinemia

(Mental impairment and speech defect)

Natural Language isn't standard!

"HAL—which is the first enzyme in the degradation pathway of L-histidine—catalyzes the non-oxidative deamination of its substrate to trans-urocanic acid".

László Poppe, (2001) COCB

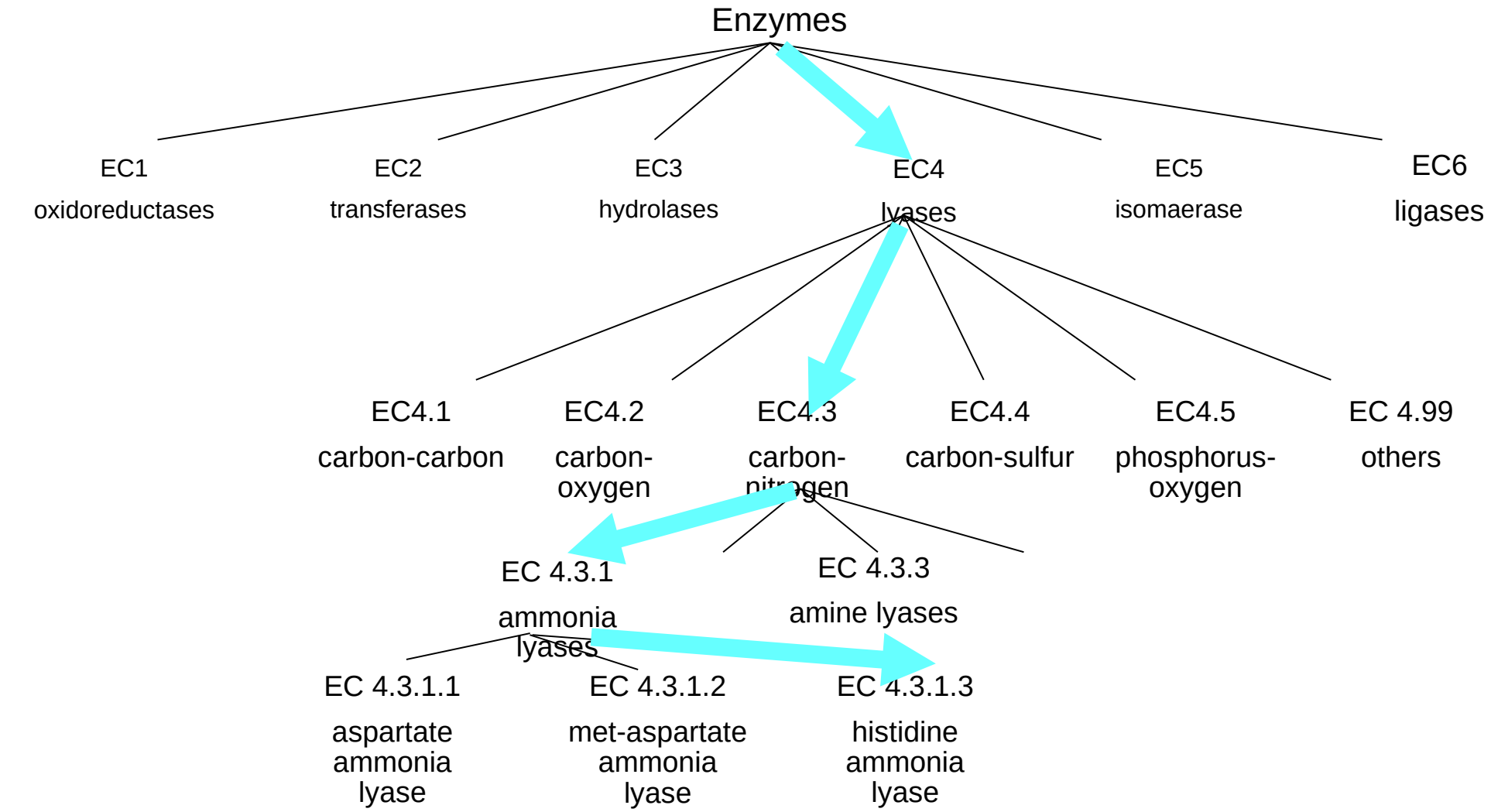
"Histidase catalyzes the elimination of the alpha-amino group of histidine using a 4-methylidene-imidazole-5-one (MIO), which is formed autocatalytically from the internal peptide segment 142Ala-Ser-Gly."

Baedecker & Schultz, (2002) Eur J Biochem

Too many words, synonyms, meanings…

“An **ontology** is the formal naming and definition of the types, properties, and interrelationships of the entities that really or fundamentally exist for a particular domain of discourse”

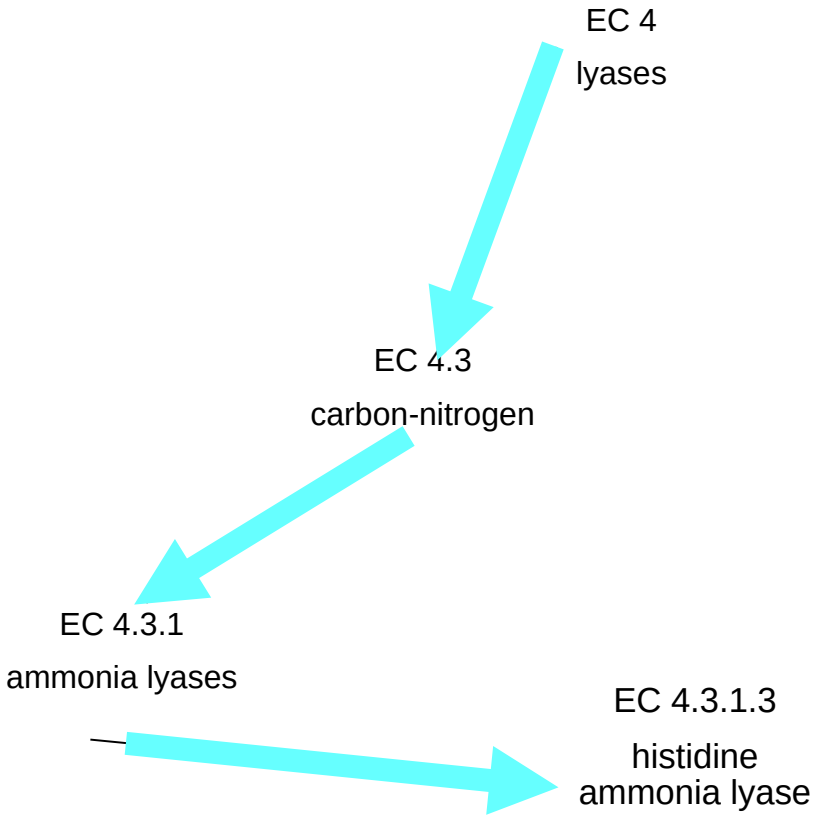
A Simple Ontology: the Enzyme Commission Classification



Enzyme Commission Classification

E.C. Provides a relationship description by:

1) Using a **controlled vocabulary**
2) Going from the general to the specific
3) Defining the scope of interest



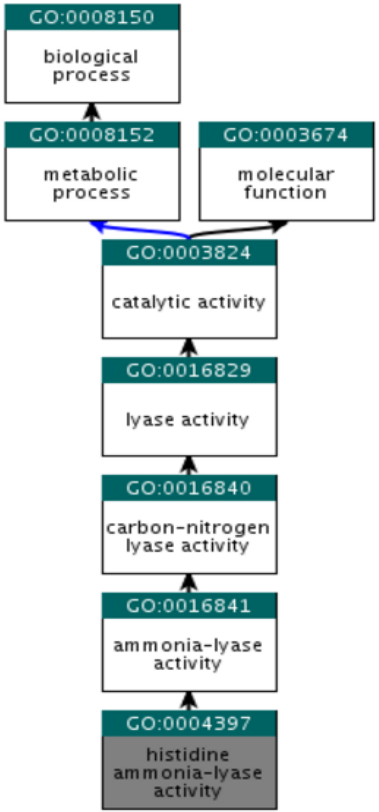
What do we need?

- A standardized functional vocabulary
- A comprehensive vocabulary
- Capture different functional aspects
- Capture different relationship types

The Gene Ontology (GO) Project

- A major project standardizing the representation of genes and gene product attributes.
- Major Goals:
  1) Develop and maintain a controlled vocabulary and relationships of gene and gene product attributes
  2) Annotate genes and gene products
  3) Provide tools to access data provided by the GO project

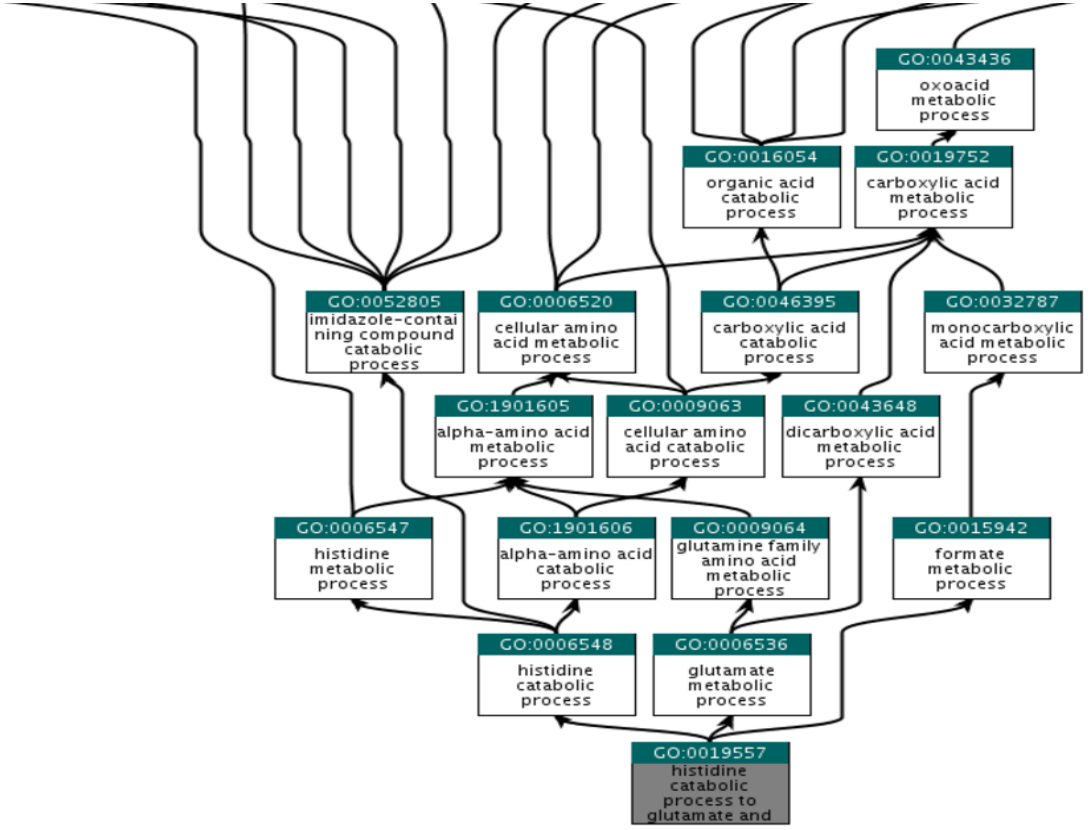
Open the Ontology, HAL...



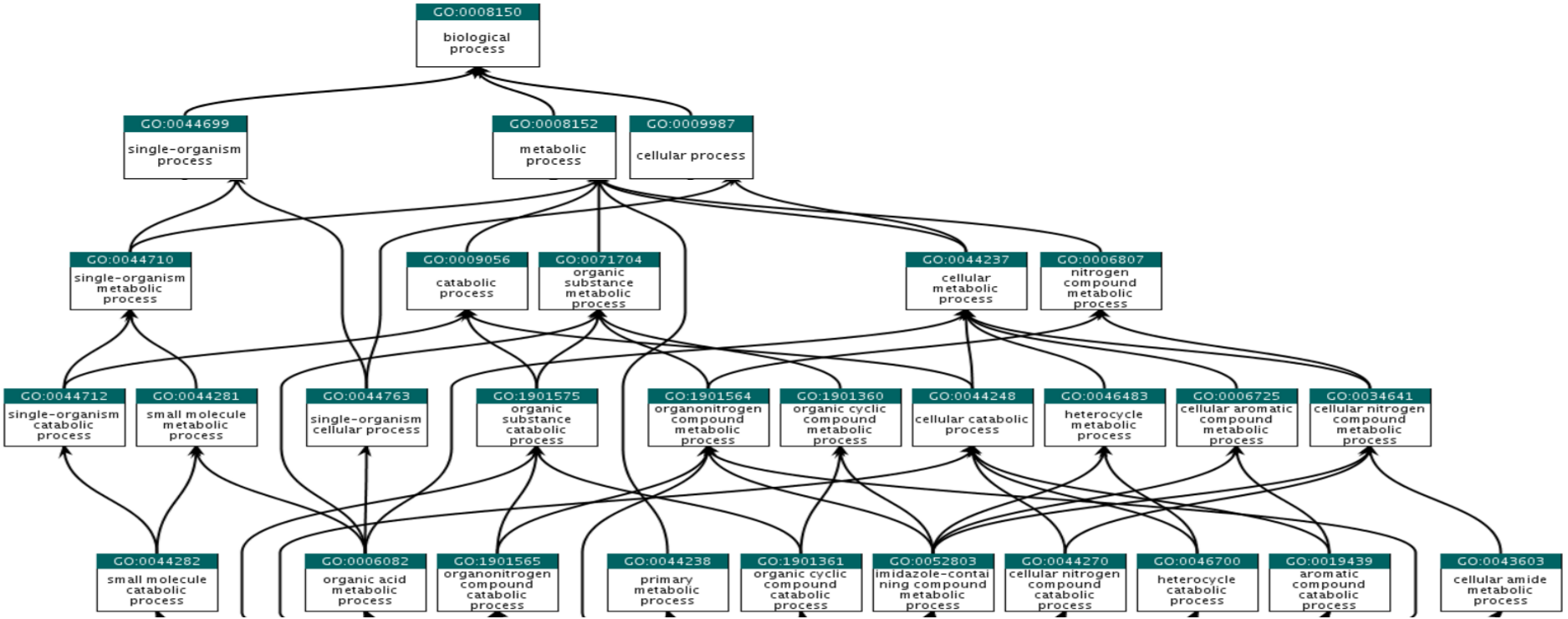
Search for GO term: ebi.ac.uk/QuickGO

Search for protein: UniProtKB

Biological Process



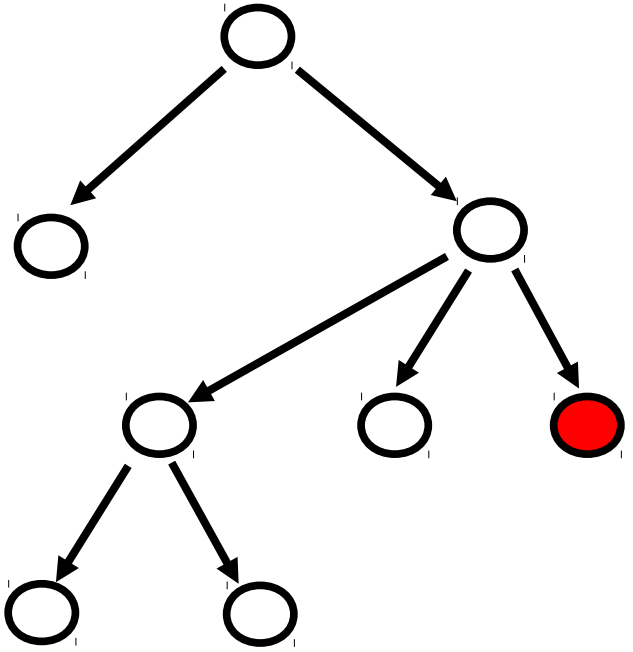
Going up...


GO:0008150
biological process
GO:0044699
single-organism process
GO:0008152
metabolic process
GO:0009987
cellular process
GO:0044710
single-organism metabolic process
GO:0009056
catabolic process
GO:0071704
organic substance metabolic process
GO:0044237
cellular metabolic process
GO:0006807
nitrogen compound metabolic process
GO:0044712
single-organism catabolic process
GO:0044281
small molecule metabolic process
GO:0044763
single-organism cellular process
GO:1901575
organic substance catabolic process
GO:1901564
organonitrogen compound metabolic process
GO:1901360
organic cyclic compound metabolic process
GO:0044248
cellular catabolic process
GO:0046483
heterocycle metabolic process
GO:0006725
cellular aromatic compound metabolic process
GO:0034641
cellular nitrogen compound metabolic process
GO:0044282
small molecule catabolic process
GO:0006082
organic acid metabolic process
GO:1901565
organonitrogen compound catabolic process
GO:0044238
primary metabolic process
GO:1901361
organic cyclic compound catabolic process
GO:0052803
imidazole-containing compound metabolic process
GO:0044270
cellular nitrogen compound catabolic process
GO:0046700
heterocycle catabolic process
GO:0019439
aromatic compound catabolic process
GO:0043603
cellular amide metabolic process

Let’s review

- Critical Assessments can help develop and improve methods
- Need: interesting problem, community, rules
- **Computational representation of problem and method performance**

Assessment of Function Prediction Using Ontologies

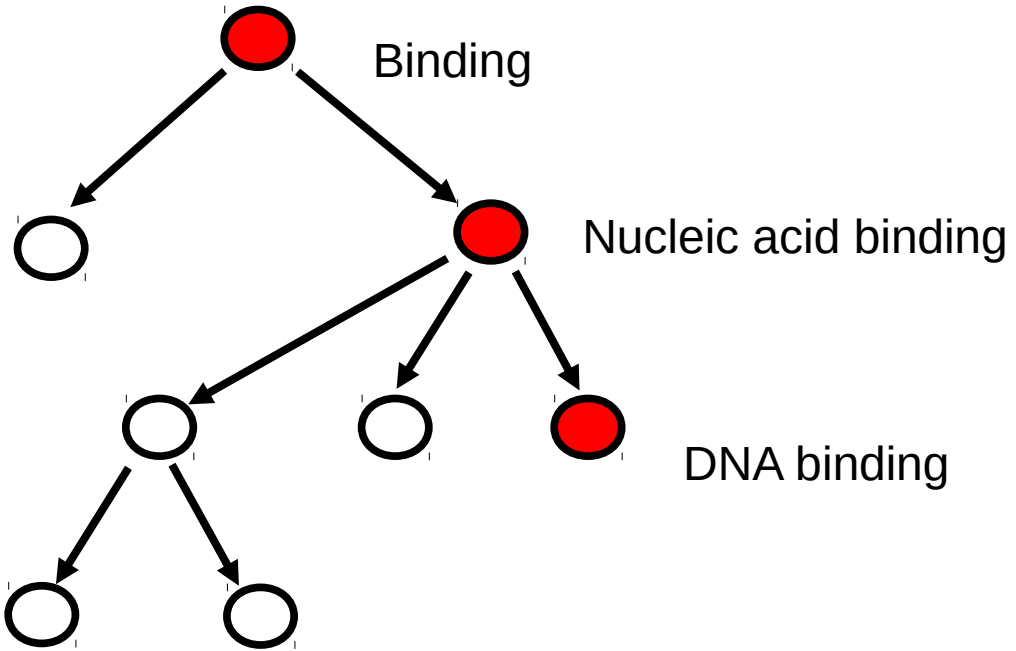


DNA binding

True function

Predicted function

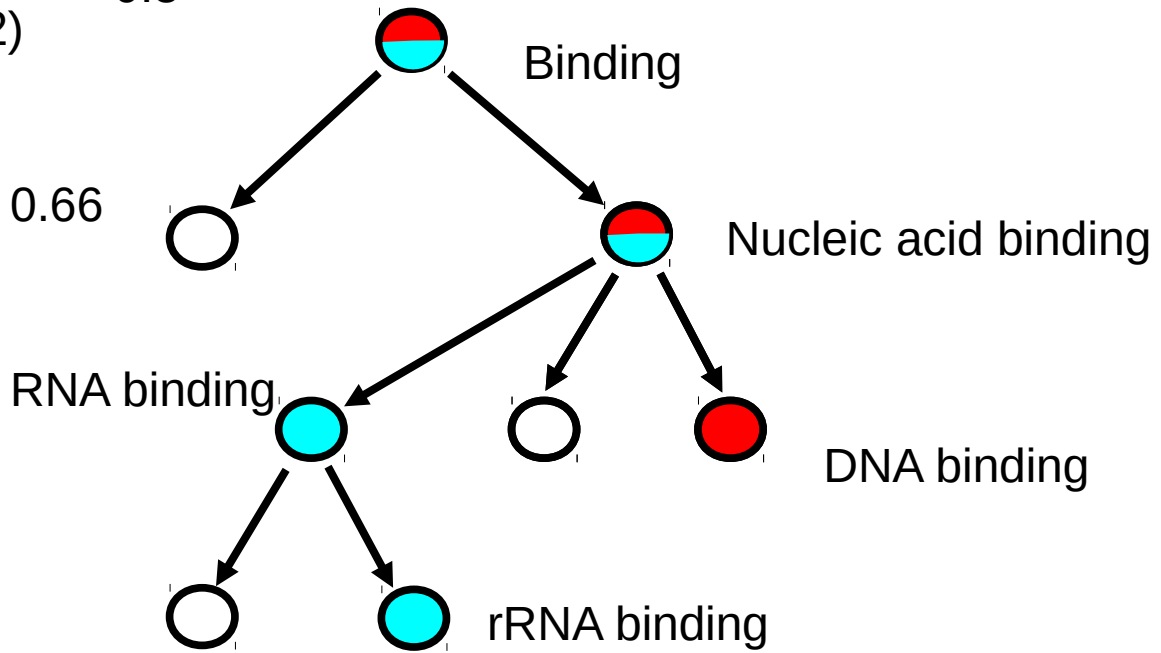
Assessment of Function Prediction Using Ontologies



Assessment of Function Prediction Using Ontologies

$$\text{Precision} = \frac{TP(2)}{TP(2)+FP(2)} = 0.5$$

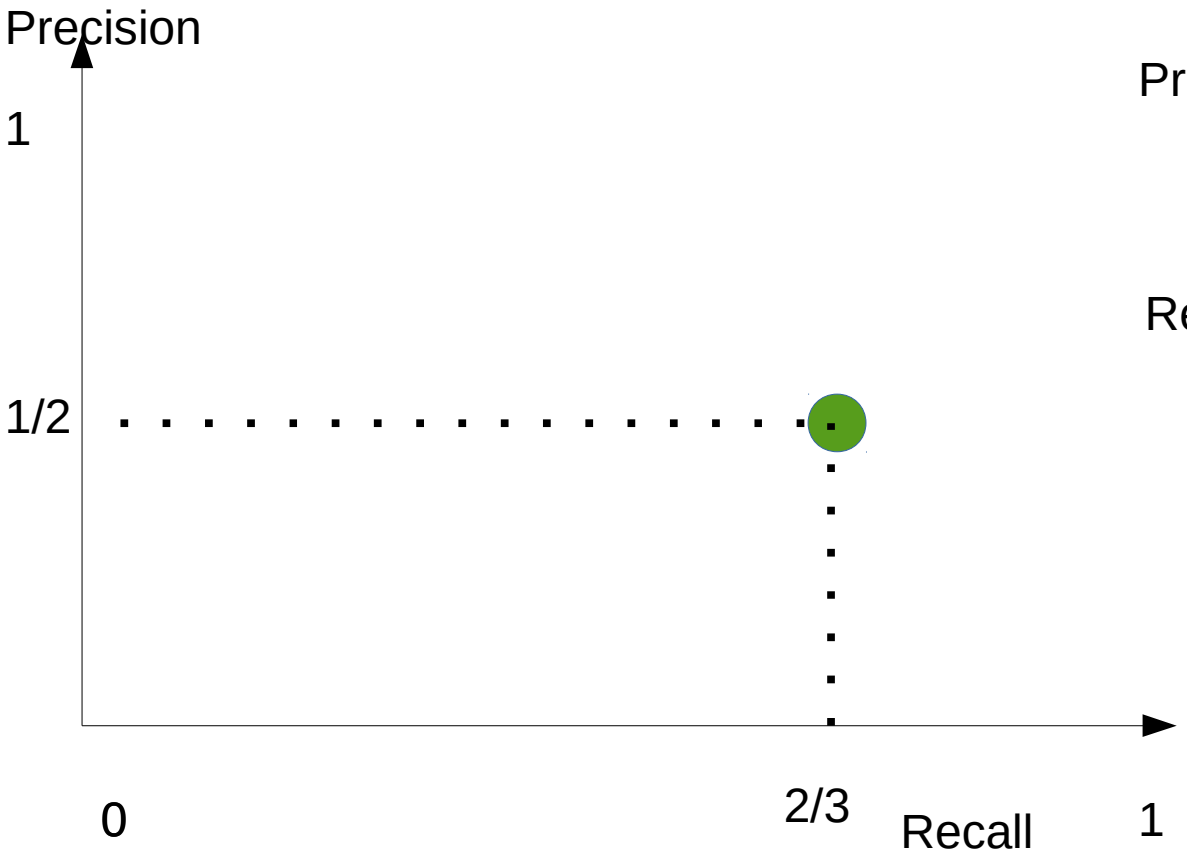
$$\text{Recall} = \frac{TP(2)}{TP(2)+FN(1)} = 0.66$$



True Positives : 2
False Positives: 2
False Negatives: 1

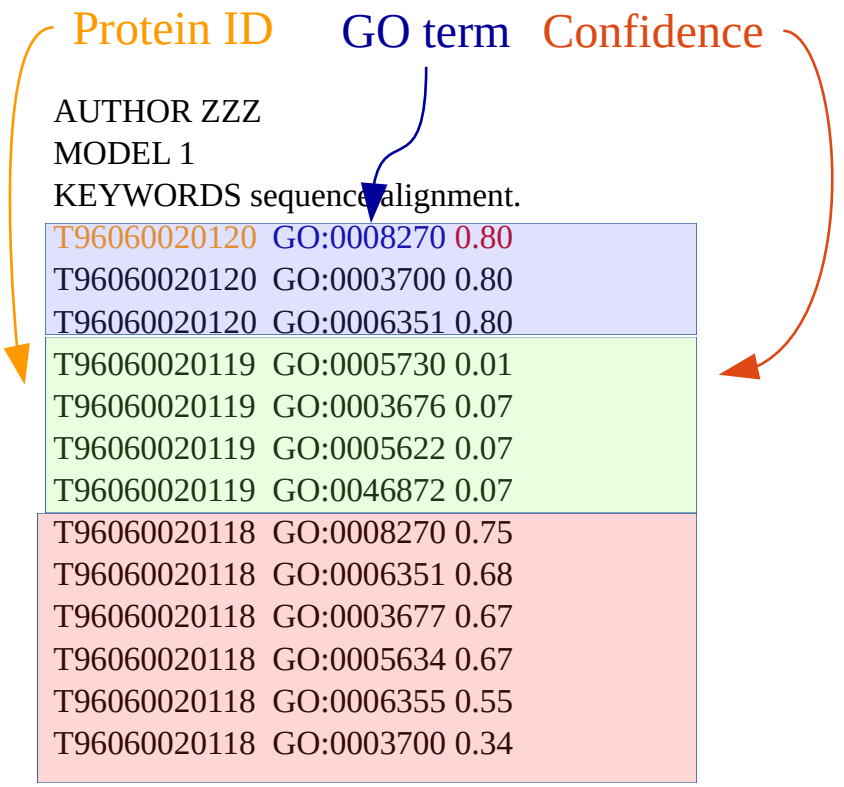
True function
Predicted function

Precision Recall

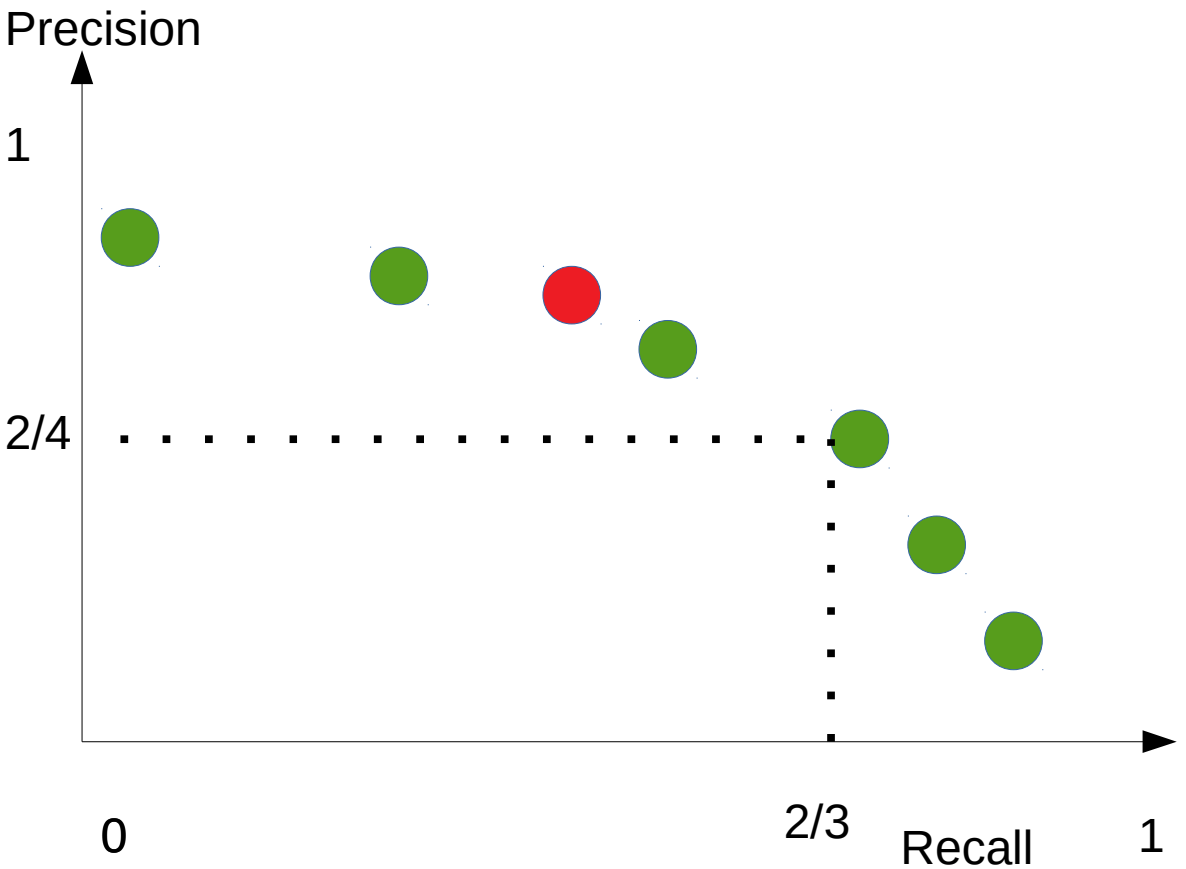


$$\text{Precision} = \frac{TP}{TP + FP}$$

$$\text{Recall} = \frac{TP}{TP + FN}$$


Protein ID
GO term
Confidence
AUTHOR ZZZ
MODEL 1
KEYWORDS sequence alignment.
T96060020120 GO:0008270 0.80
T96060020120 GO:0003700 0.80
T96060020120 GO:0006351 0.80
T96060020119 GO:0005730 0.01
T96060020119 GO:0003676 0.07
T96060020119 GO:0005622 0.07
T96060020119 GO:0046872 0.07
T96060020118 GO:0008270 0.75
T96060020118 GO:0006351 0.68
T96060020118 GO:0003677 0.67
T96060020118 GO:0005634 0.67
T96060020118 GO:0006355 0.55
T96060020118 GO:0003700 0.34

Precision Recall Curve



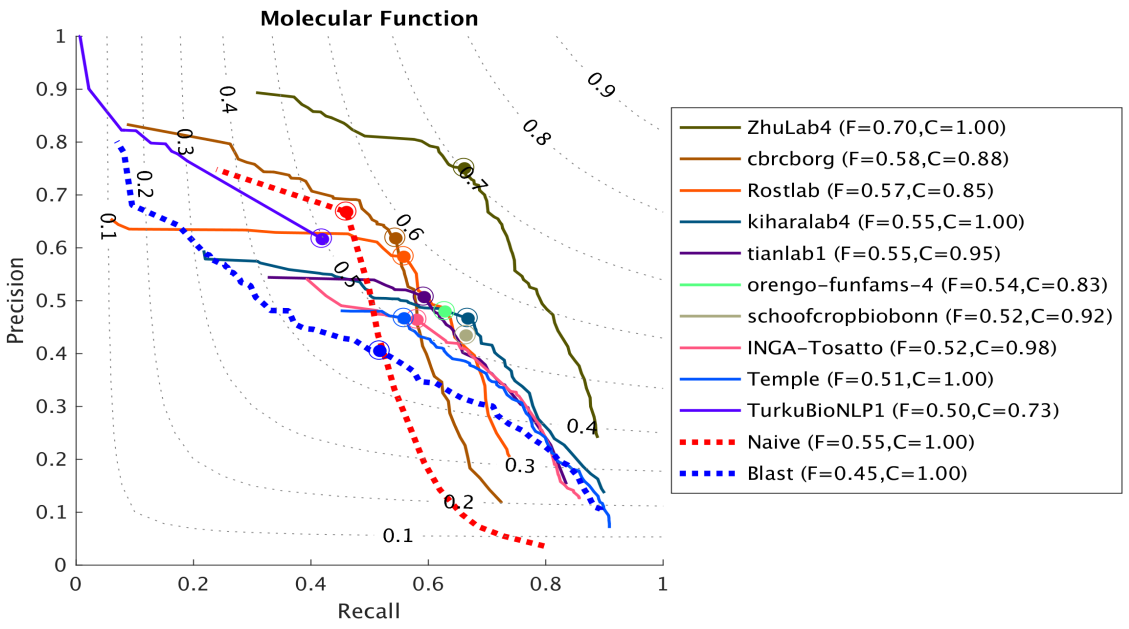
$$\text{Precision} = \frac{TP}{TP + FP}$$

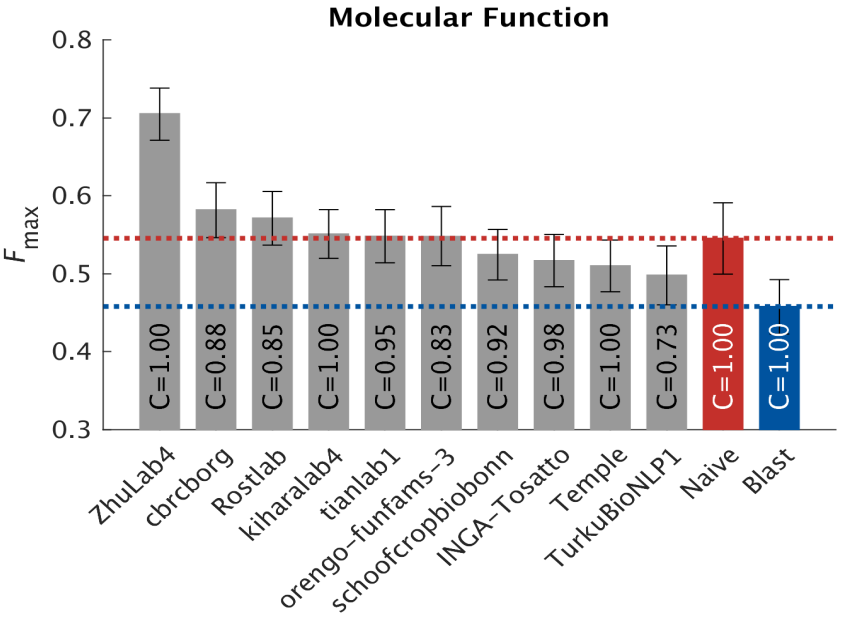
$$\text{Recall} = \frac{TP}{TP + FN}$$

$$F1 = \frac{Pr \times Rc}{Pr + Rc}$$

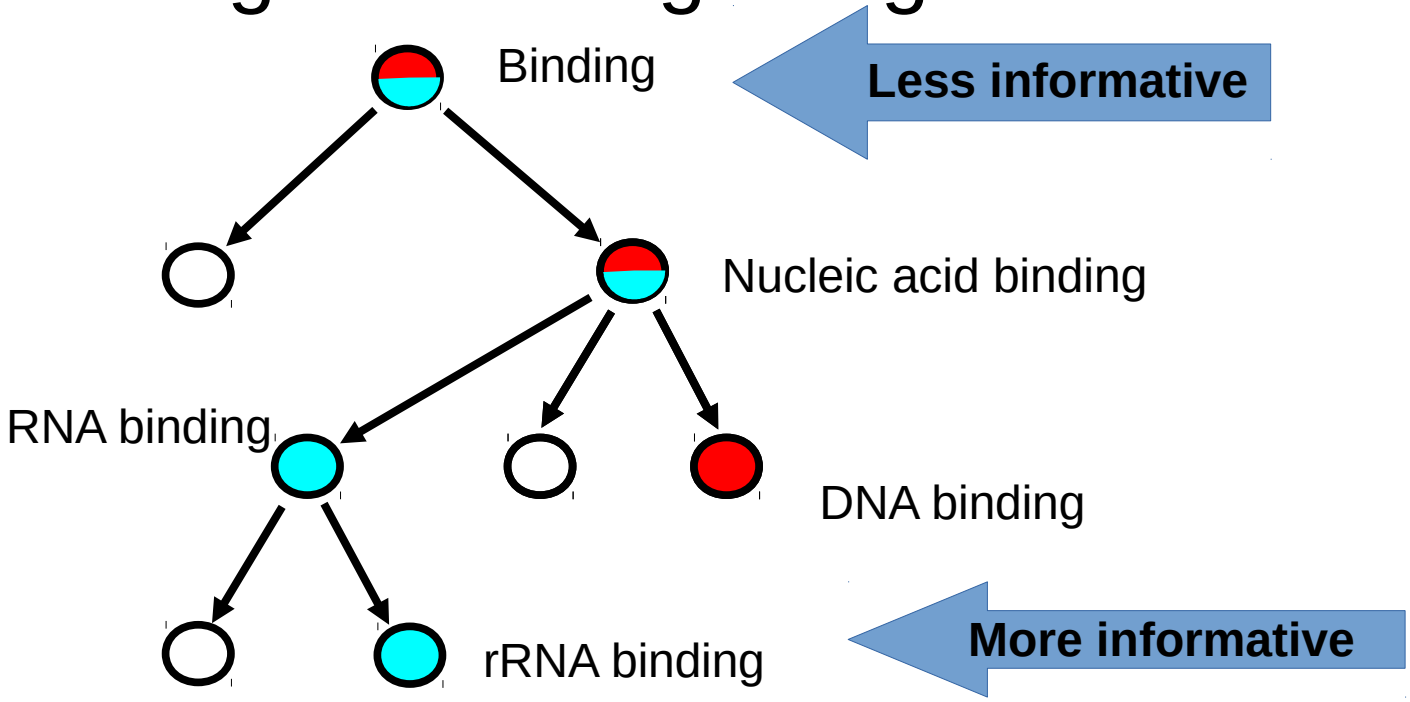
Molecular Function

Benchmark: all species Type: no knowledge Mode: full Metric: F-max





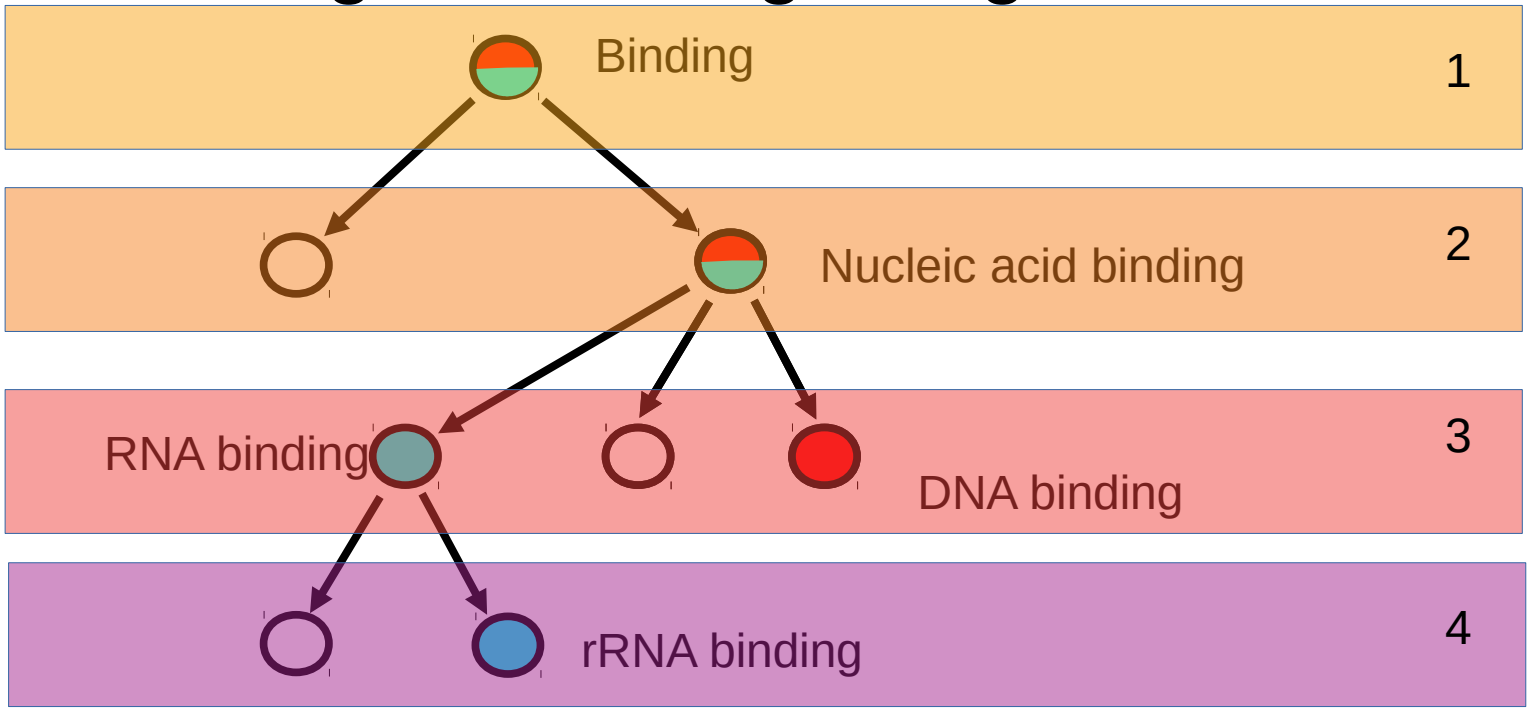
Assessment of Function Prediction Using Ontologies: Adding Weight



True Positives : 2
False Positives: 2
False Negatives: 1

True function
Predicted function

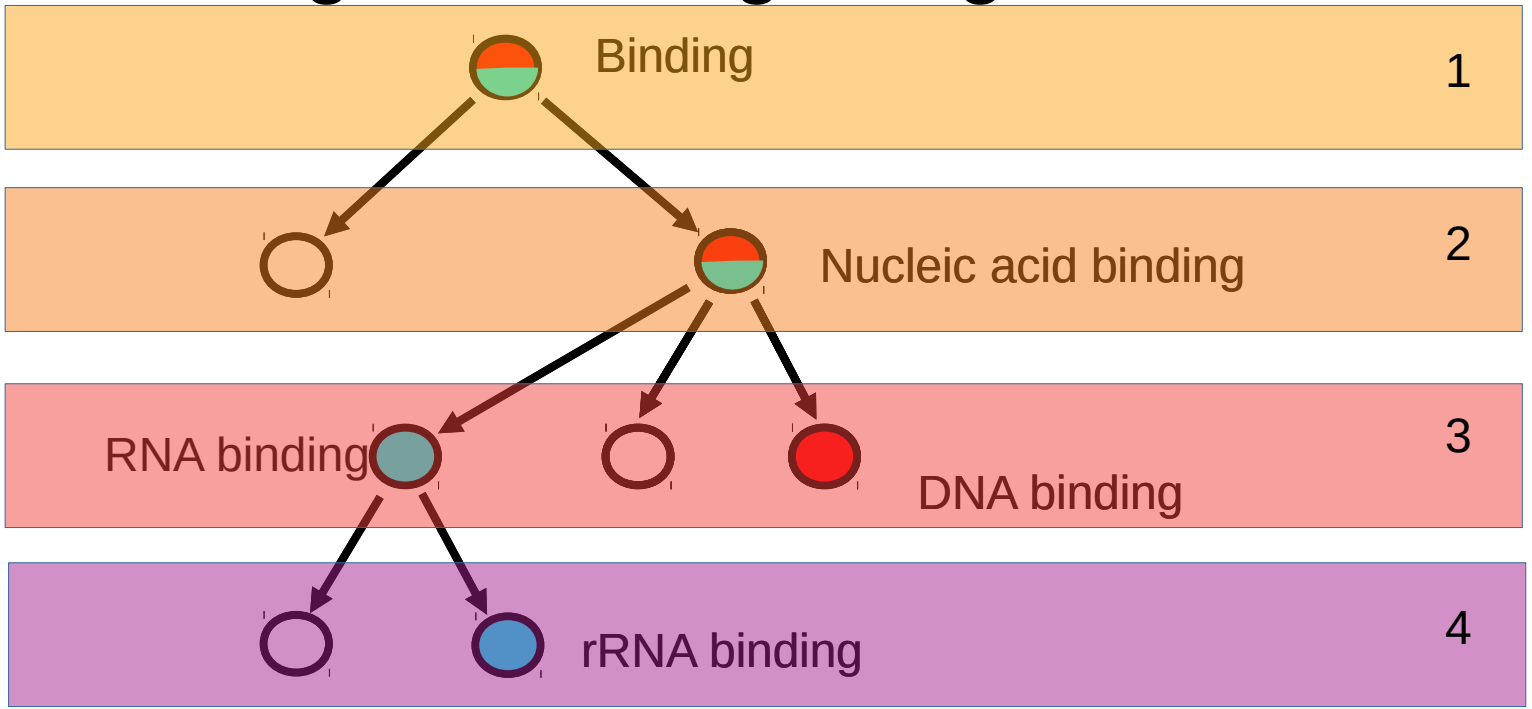
Assessment of Function Prediction Using Ontologies: Adding Weight



True Positives : 1+2 = 3
False Positives: 1*3 = 3
False Negatives: 3+4 = 7

True function
Predicted function

Assessment of Function Prediction Using Ontologies: Adding Weights



	-W	+W
Pr	0.5	0.5
Rc	0.66	0.3

True Positives : 1+2 = 3
False Positives: 1*3 = 3
False Negatives: 3+4 = 7

True function
Predicted function

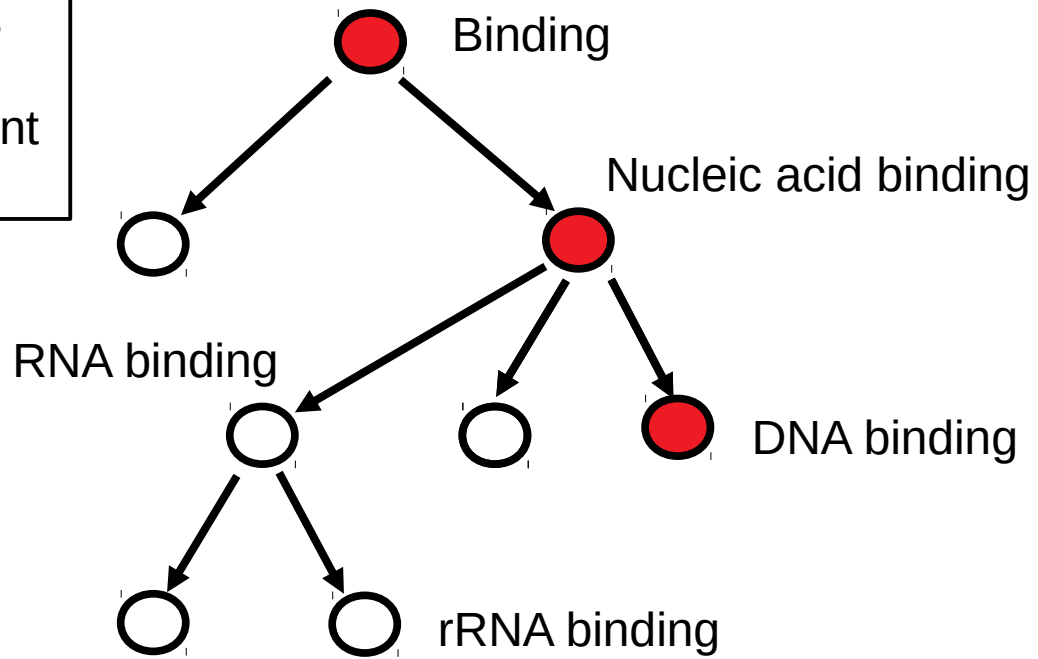
Assessment of Function Prediction Using Ontologies: Information Theory

T: set of true nodes
v: node
i: information content
ia: accumulated *i*

$$i(T) = \log \frac{1}{\Pr(T)}$$

$$\Pr(T) = \prod_{v \in T} \Pr(v|\mathcal{P}(v))$$

$$\begin{aligned} i(T) &= \log \frac{1}{\prod_{v \in T} \Pr(v|\mathcal{P}(v))} \\ &= \sum_{v \in T} \log \frac{1}{\Pr(v|\mathcal{P}(v))} \\ &= \sum_{v \in T} ia(v) \end{aligned}$$



Clark & Radivojac. *Bioinformatics*. **29**: i53 (2013).

Assessment of Function Prediction Using Ontologies: Information Theory

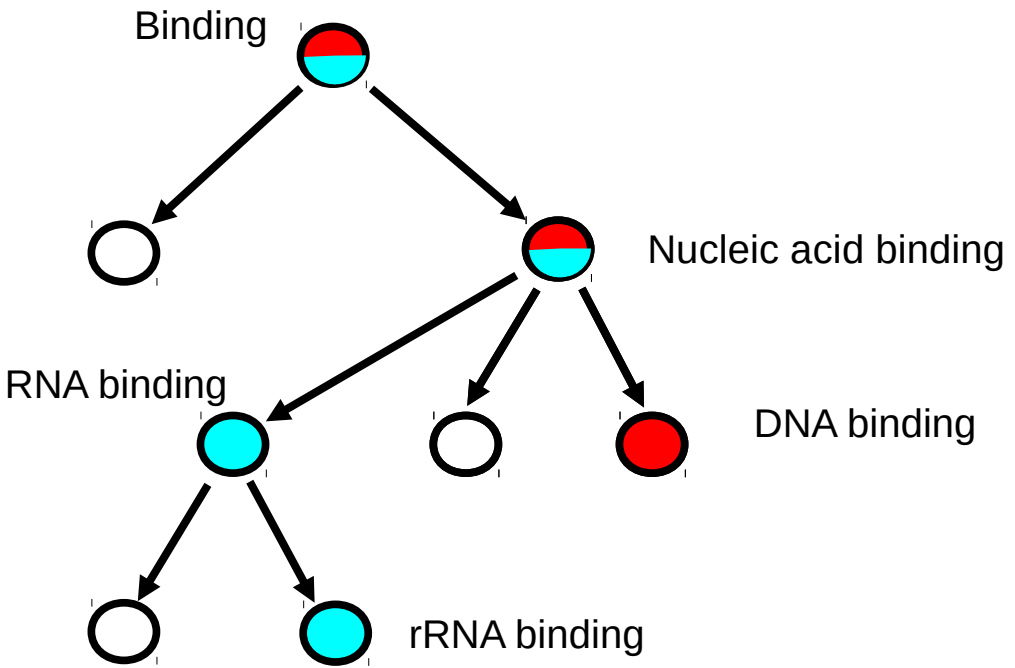
Misinformation
(accumulated IC of FP):

$$mi(P,T) = \sum_{v \in P-T} ia(v)$$

Remaining uncertainty
(false negatives):

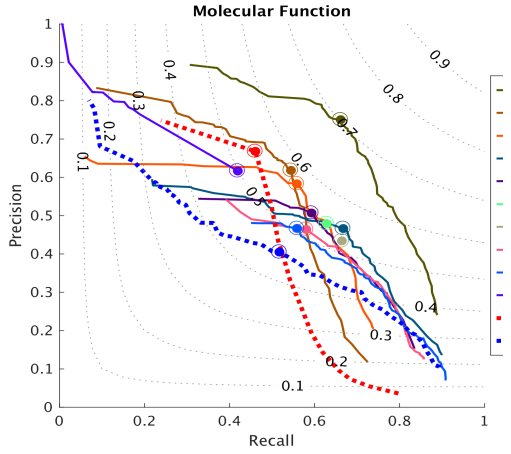
$$ru(P,T) = \sum_{v \in T-P} ia(v)$$

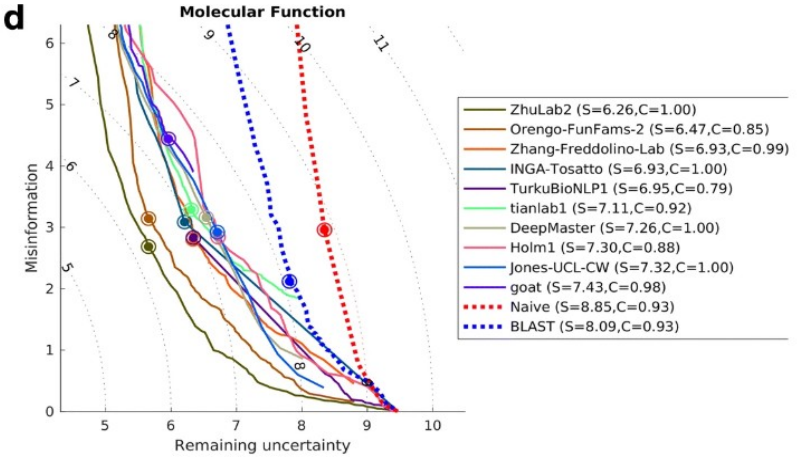
Goal: minimize ru and mi

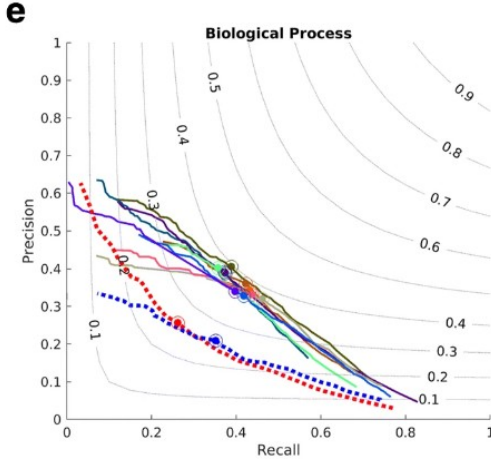


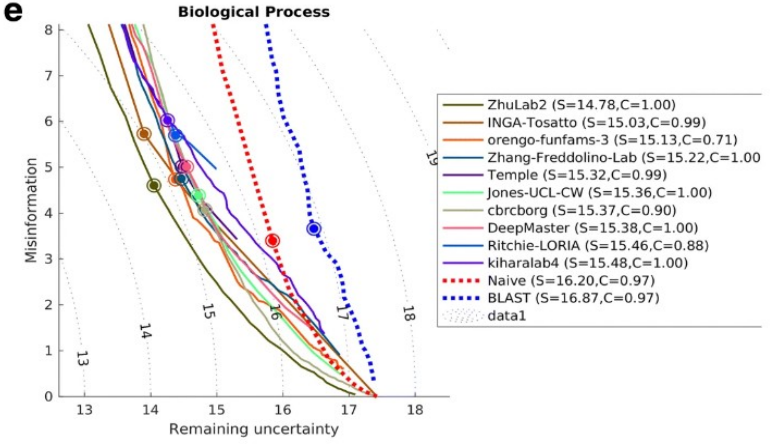
True function
Predicted function

Precision / Recall vs. ru / mi





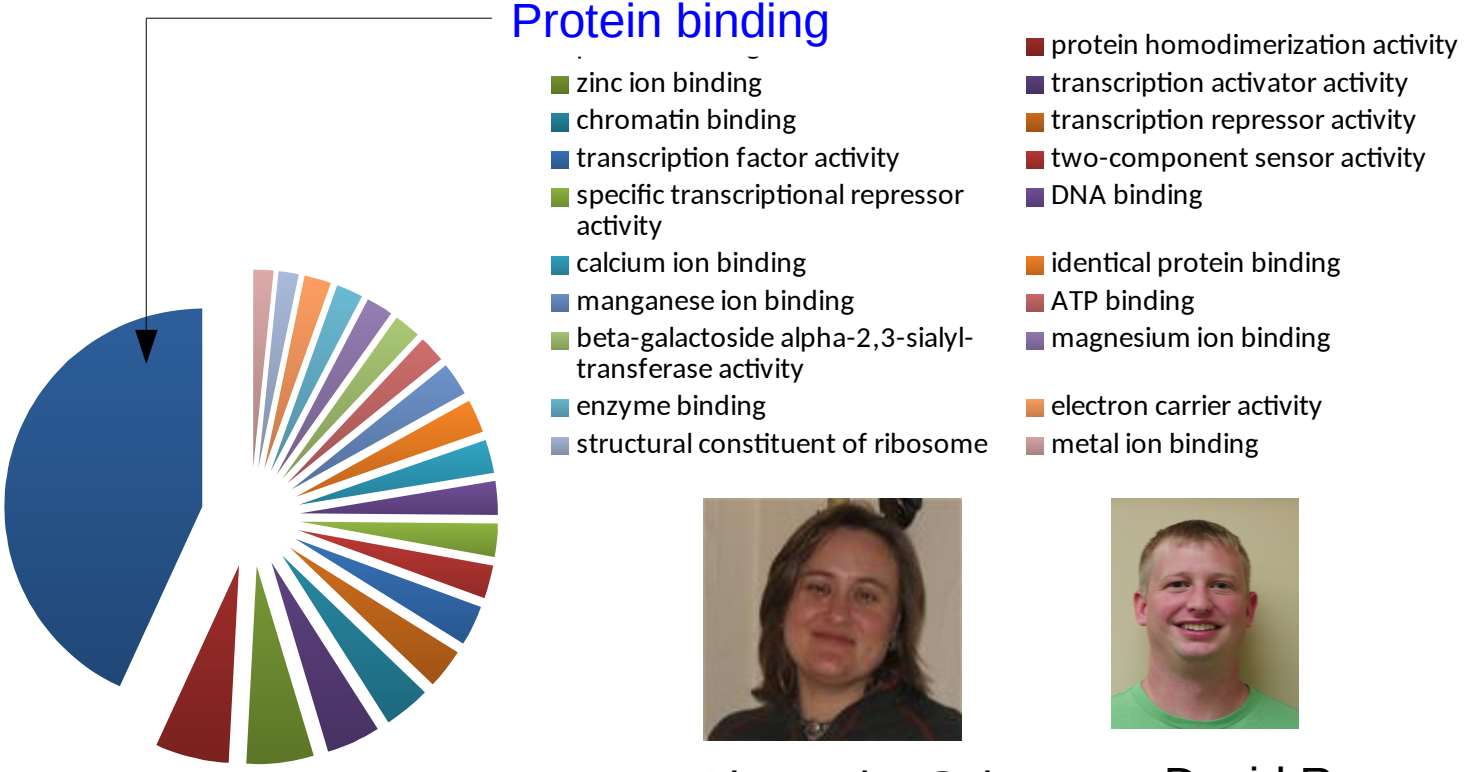




About Assessment Metrics

- One metric rarely captures all information
- Multiple metrics are advised
- Learn and update as the competition matures

Databases are biased...



Alexandra Schnoes

David Ream

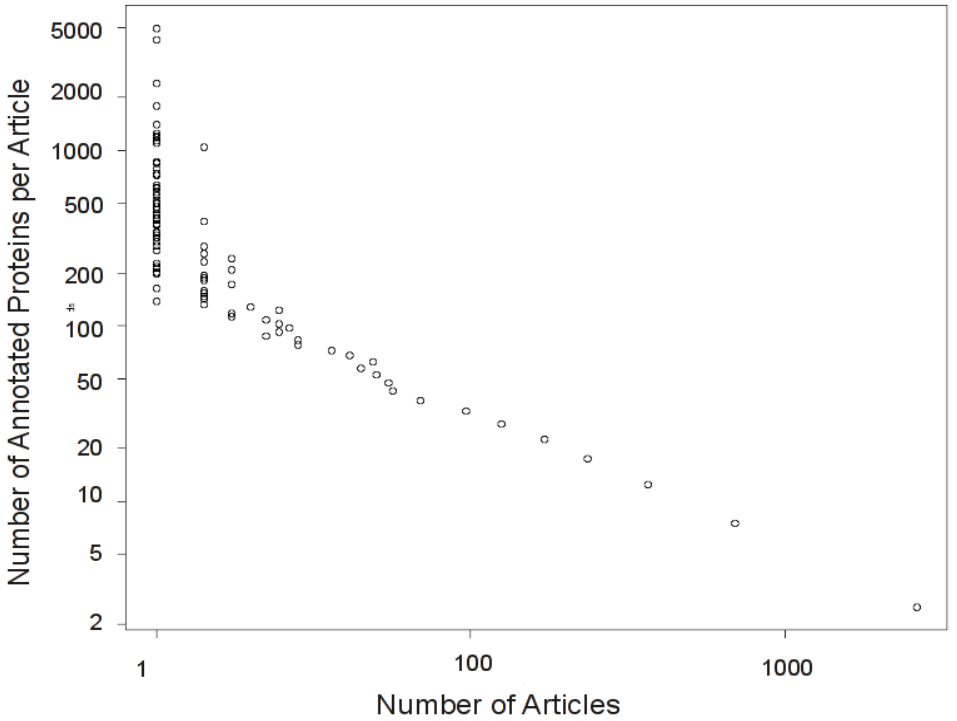
Alexander Thorman

PLOS COMPUTATIONAL BIOLOGY

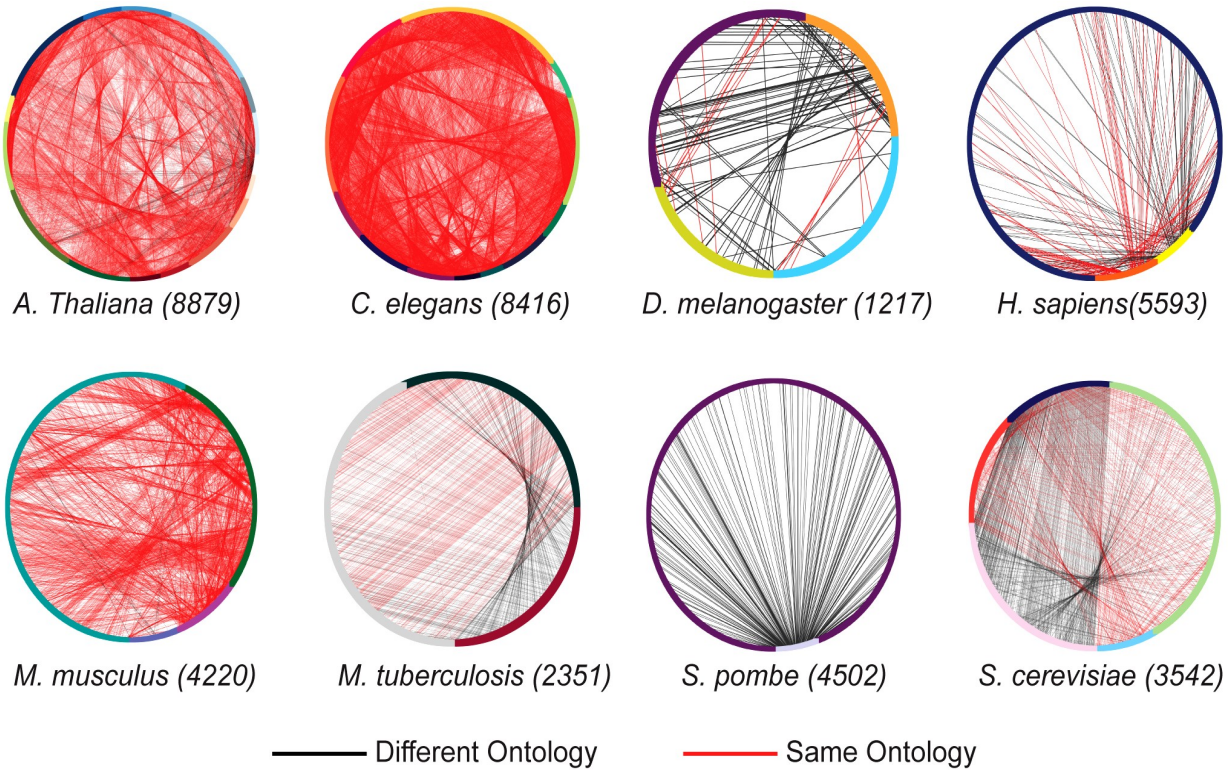
Best Function Prediction Program (confidential source code)

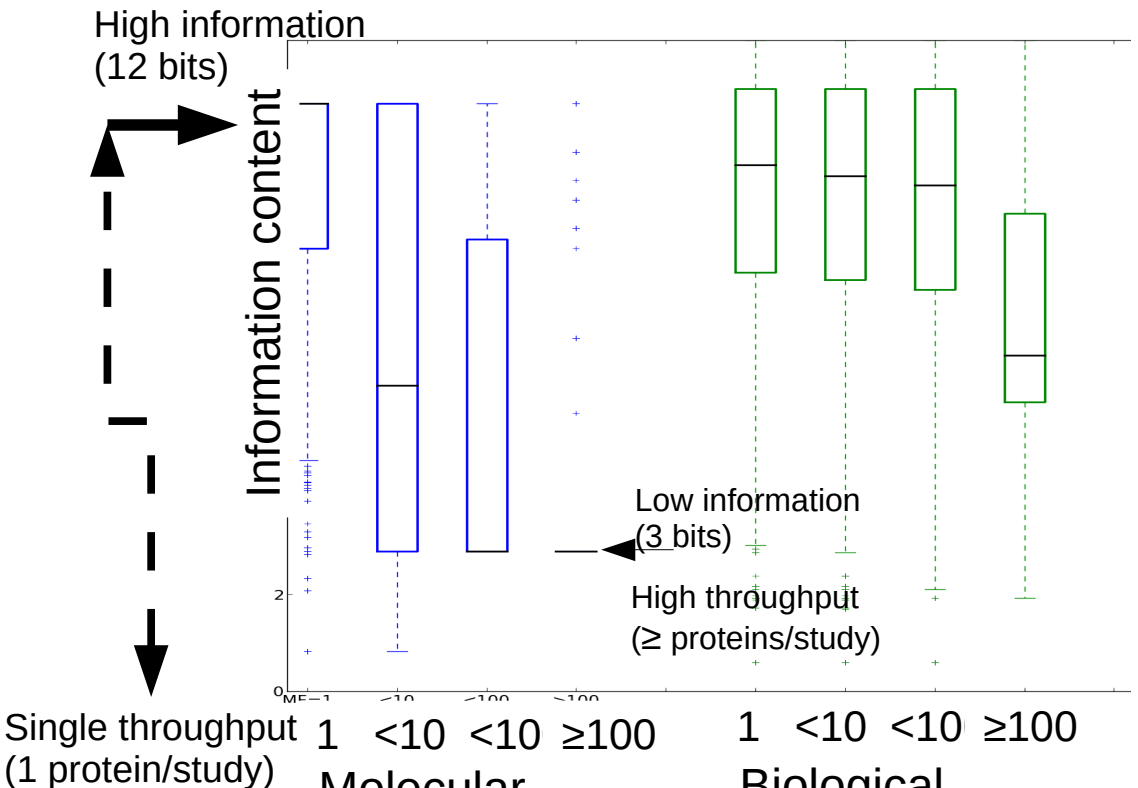
```
def best_predictor_ever(inseq):
        print “protein binding”
```

Annotations per article



Annotation redundancy





Schnoes *et al* (2013)

High throughput Experiments

The Bad

- Bias our knowledge
- Bias priors for function prediction programs
- Are less informative than low-throughput experiments

The Good

- Exclusively annotate genes otherwise unknown
- Fewer $$$
- Fast results
- Consistency

DIALOGUE FOR **R**EVERSE **E**NGINEERING **A**SSESSMENT AND **M**ETHODS

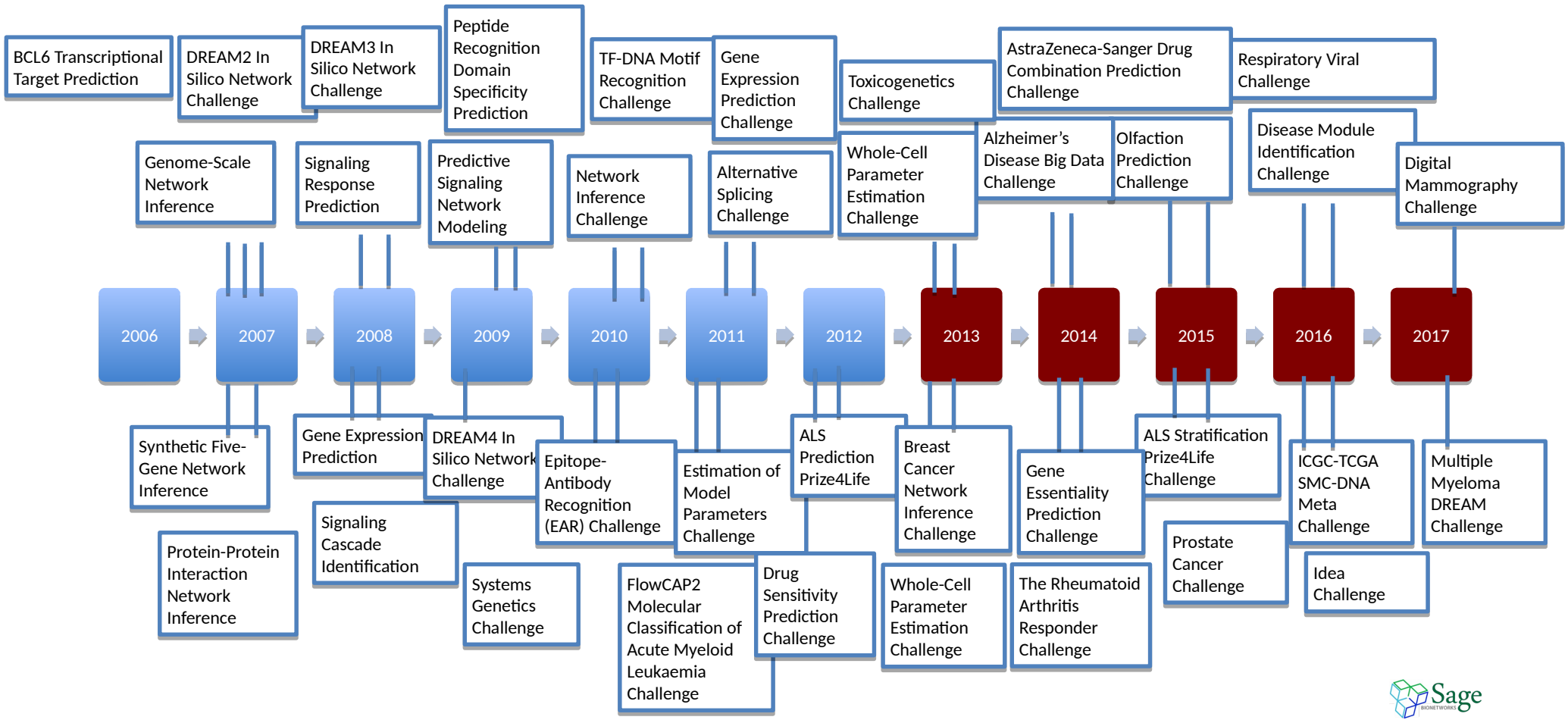
Crowdsourcing innovation in biomedicine

DREAM Challenges

DIALOGUE FOR **R**EVERSE **E**NGINEERING **A**SSESSMENT AND **M**ETHODS

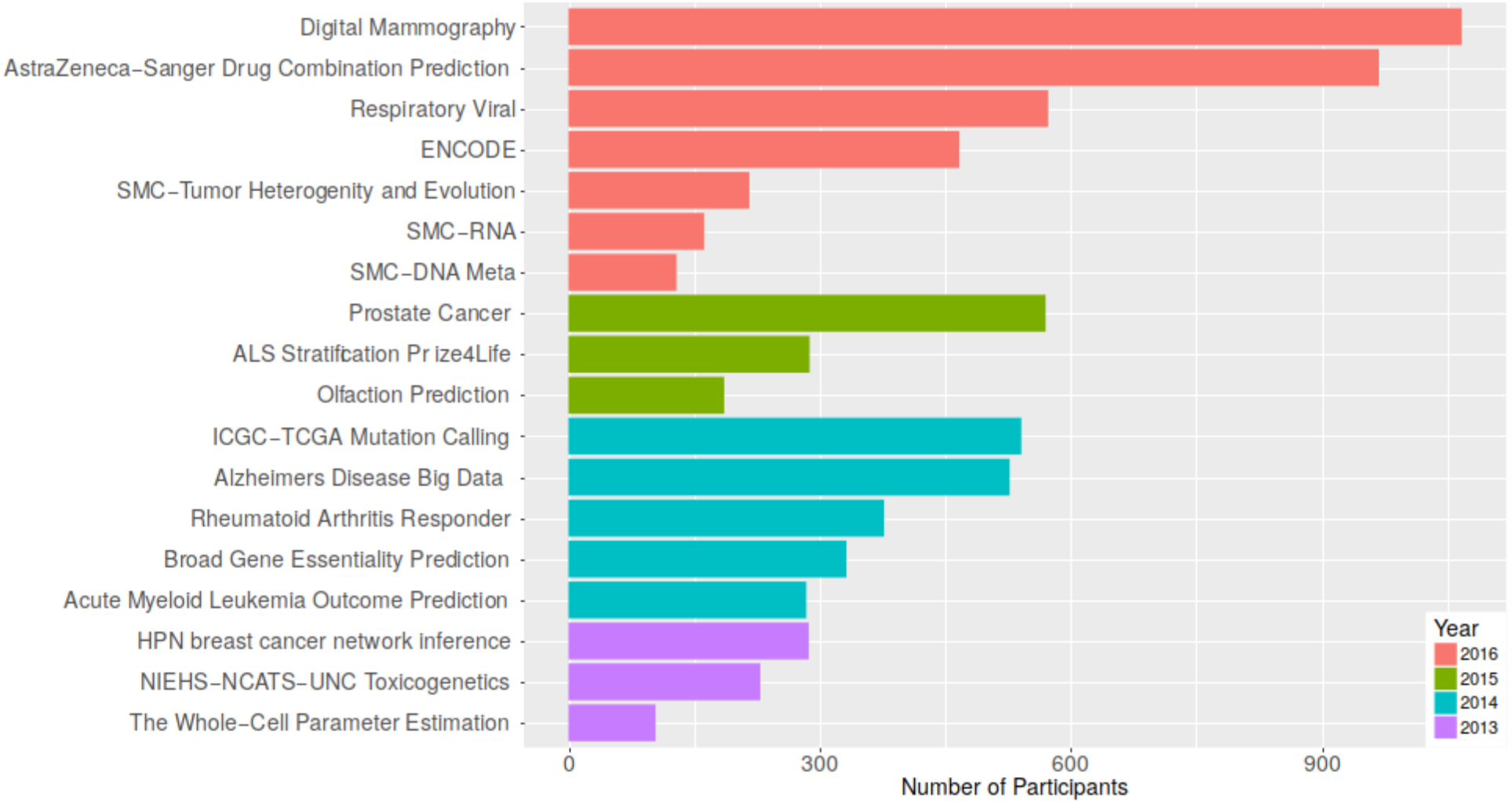
- A crowdsourcing effort that poses quantitative, biomedical questions
- Mission:
  - to contribute to the solution of important biomedical problems
  - to foster collaboration between research groups
  - to democratize data
  - to accelerate research
  - to objectively assess algorithm performance

DREAM over the years



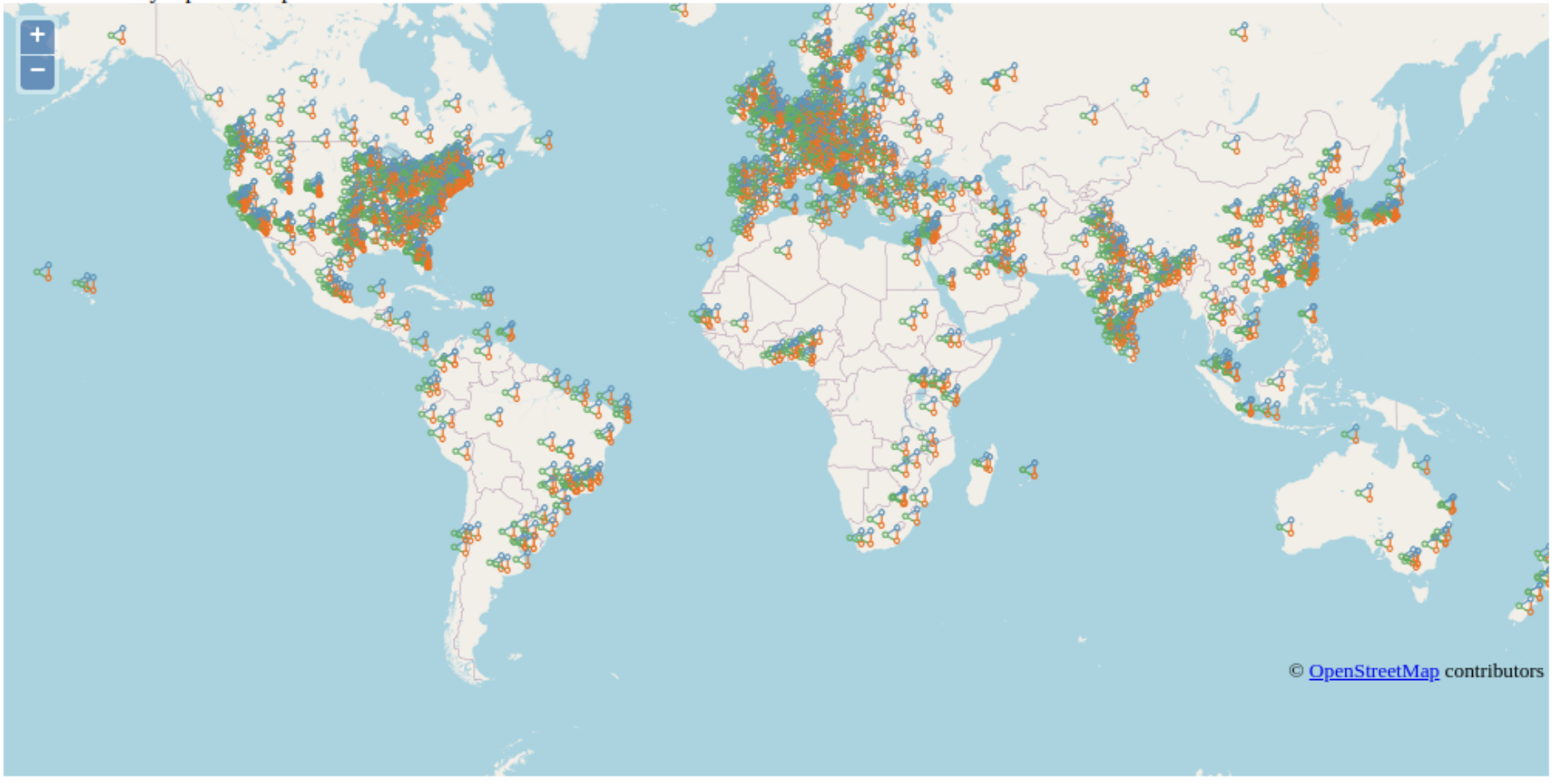
Sage BIONETWORKS

Some challenge participation figures



Where in the World are Synapse Users?

These 11383 Synapse users provide a 'location' in their User Profile. Scroll down to see locations of Teams.

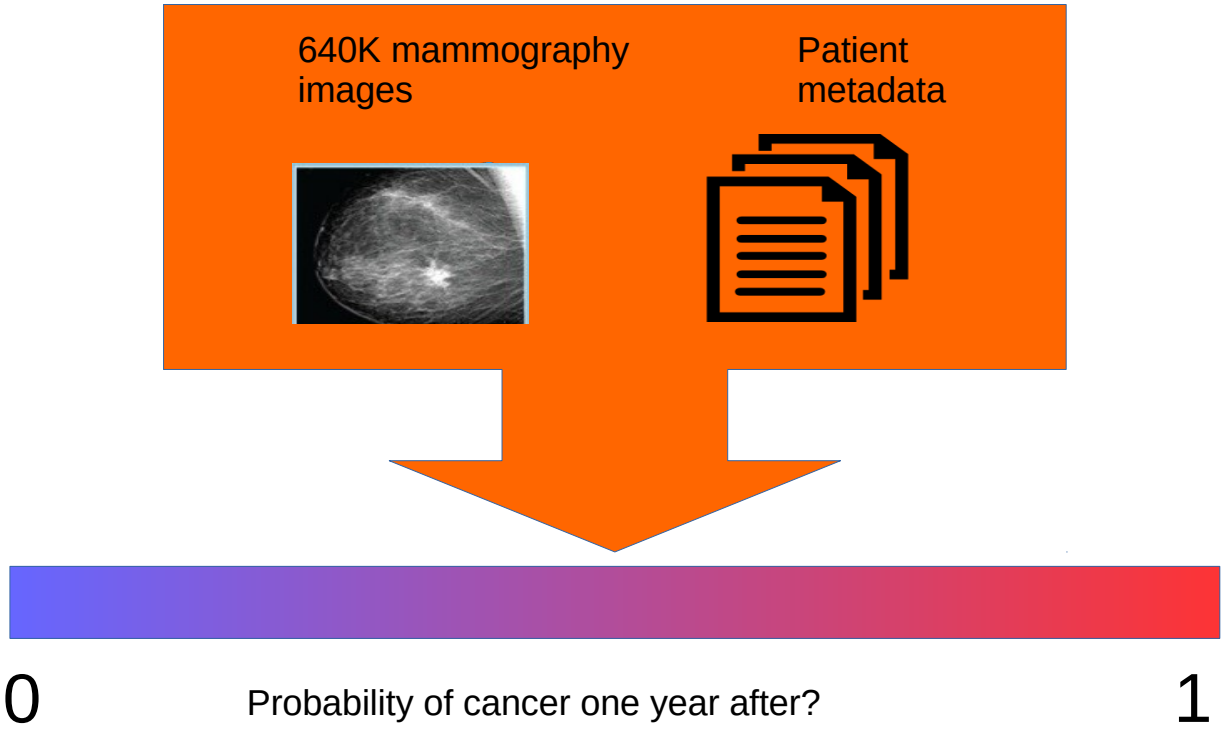


Mammography DREAM Challenge

TP: patient sick, predicted sick
FP: patient healthy, predicted sick
TN: patient healthy, predicted healthy
FN: patient sick, predicted healthy

Sensitivity: TP/(TP+FN)

Specificity: TN/(TN+FP)



https://www.synapse.org/Digital_Mammography_DREAM_Challenge

Mammography DREAM Challenge

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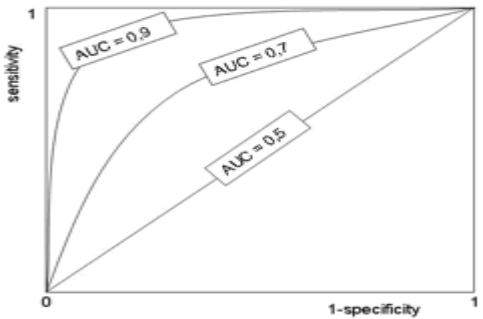
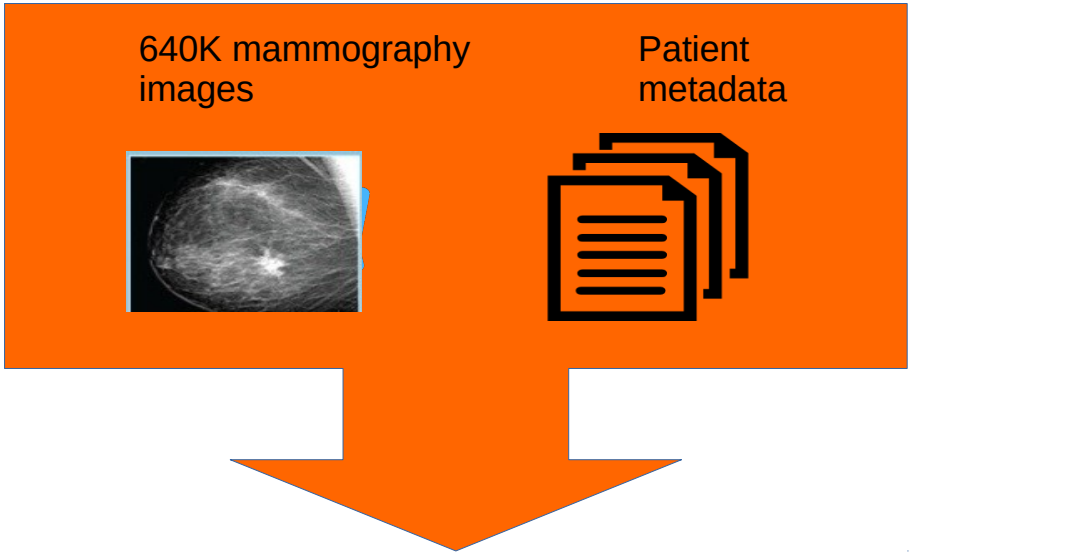


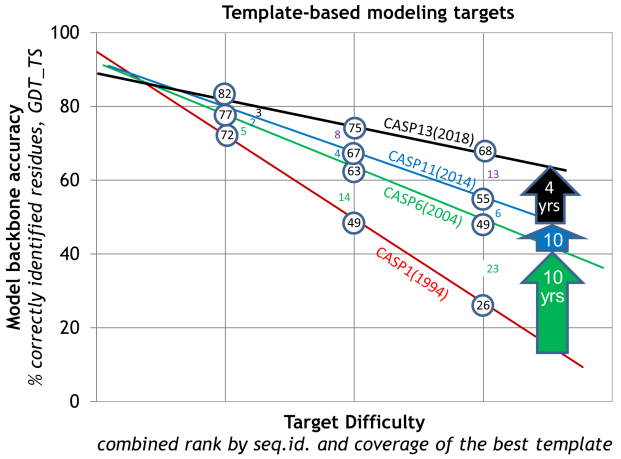


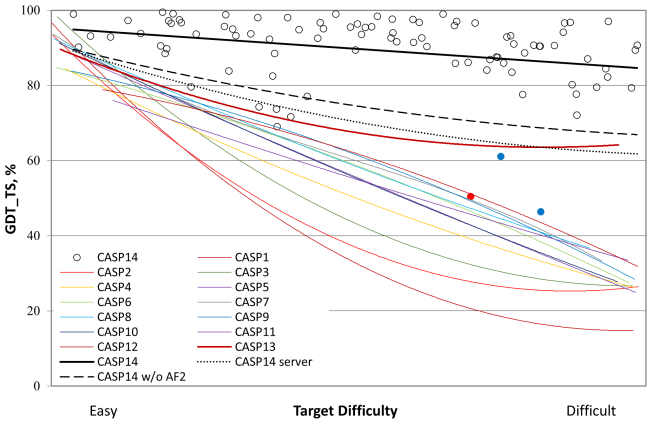
0 Probability of cancer one year after? 1

https://www.synapse.org/Digital_Mammography_DREAM_Challenge

Do Computational Challenges Improve Methods?

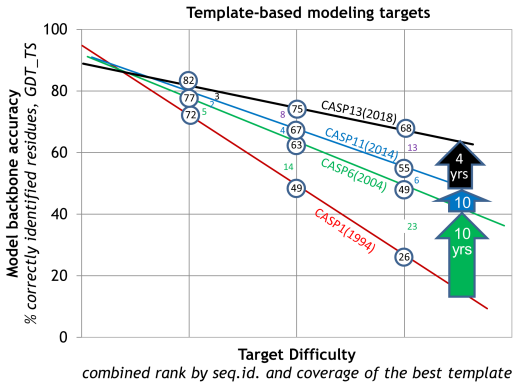
Critical Assessment of Structure Prediction

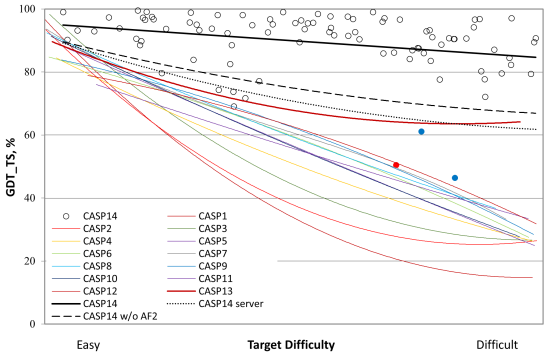




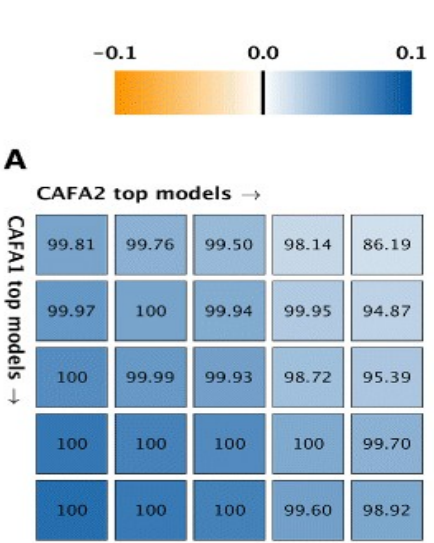
Do Computational Challenges Improve Performance?

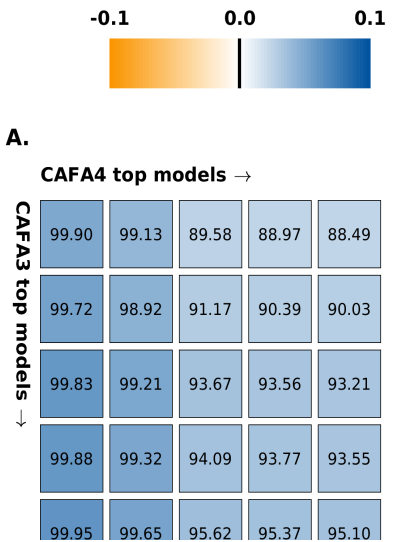
Critical Assessment of Structure Prediction





Critical Assessment of Function Annotation





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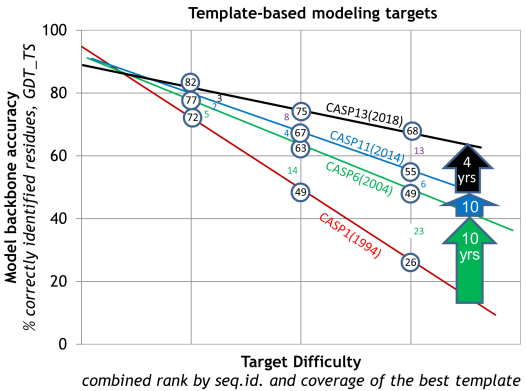
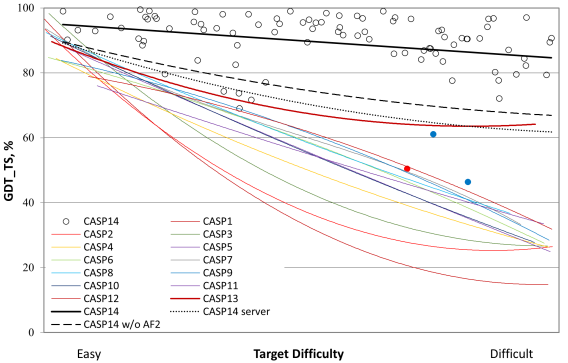
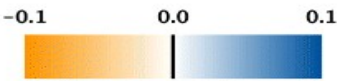
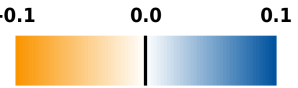
Critical Assessment of Structure Prediction

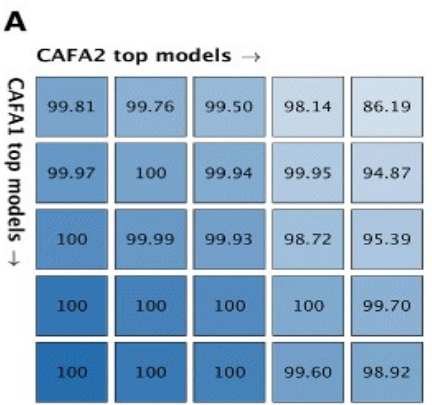


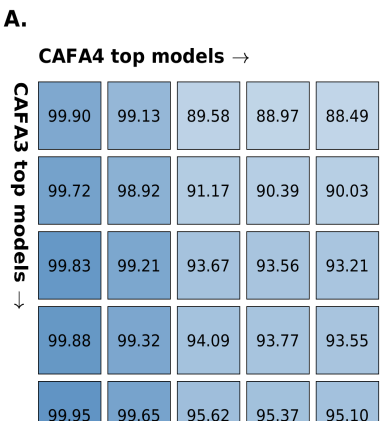


Critical Assessment of Function Annotation

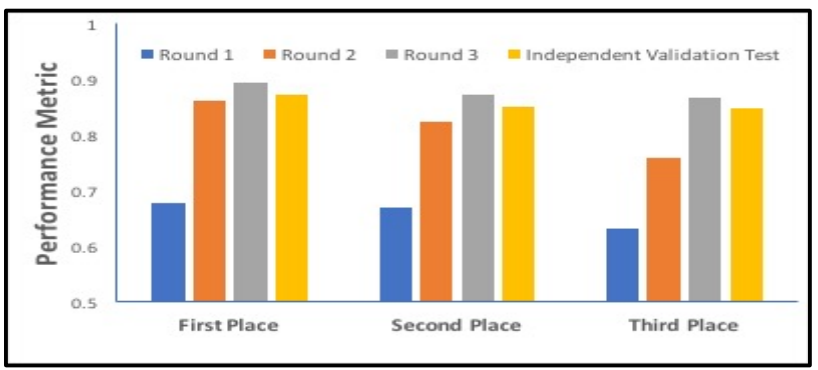






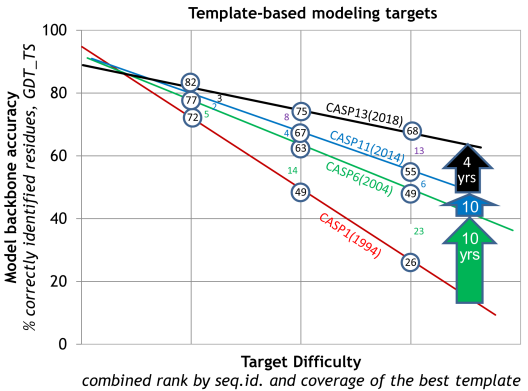


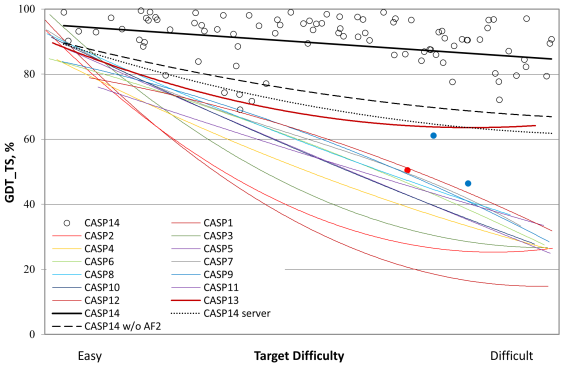
Mammography DREAM challenge



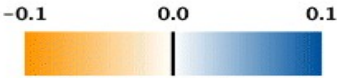
Do Computational Challenges Improve Performance?

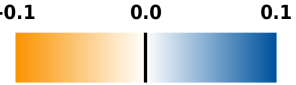
Critical Assessment of Structure Prediction

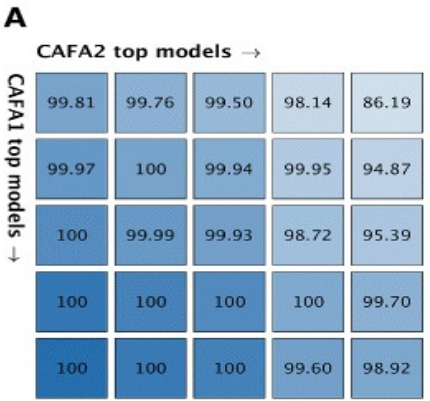


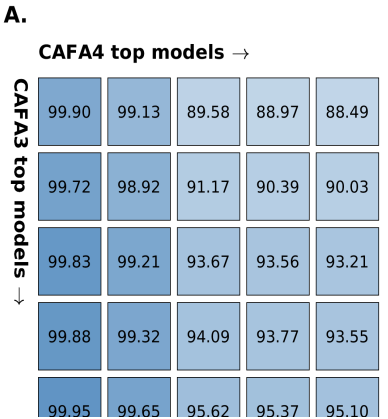


Critical Assessment of Function Annotation

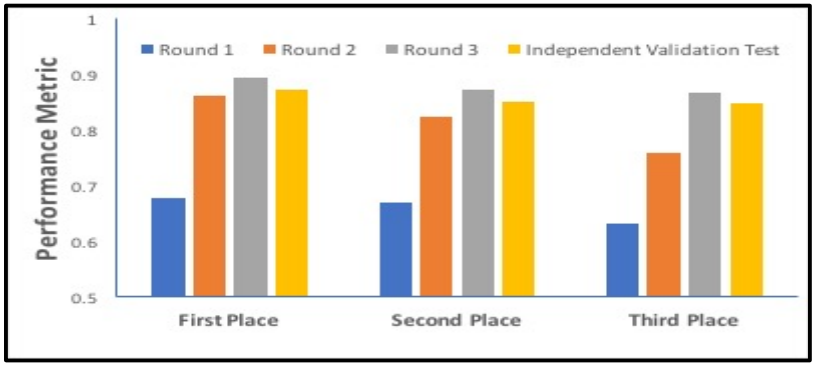








Mammography DREAM challenge



More Information

- Kaggle (general AI challenges)
- BioFunctionPrediction.org

Mark Your Calendars! JULY 10-14, 2022

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INTERNATIONAL SOCIETY FOR COMPUTATIONAL BIOLOGY

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Acknowledgments


Casey Greene


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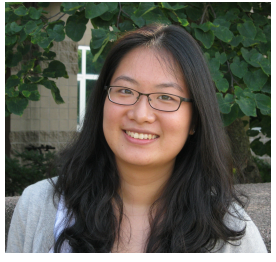
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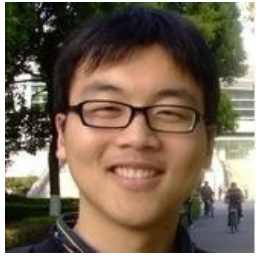
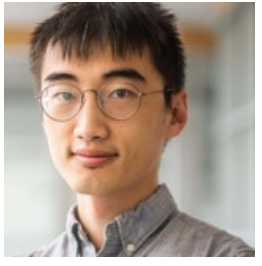

Yuxiang Jiang


Yisu Peng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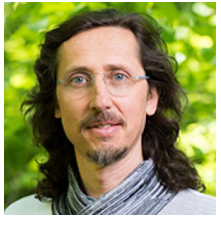
Marc RR


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Principal Investigators


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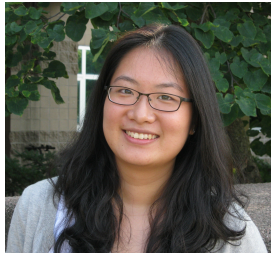
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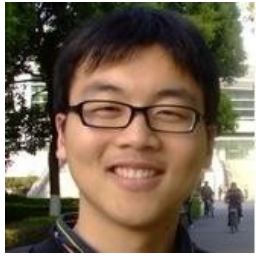
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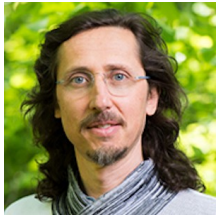
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Students & Staff


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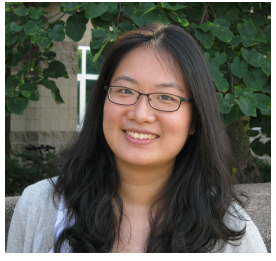
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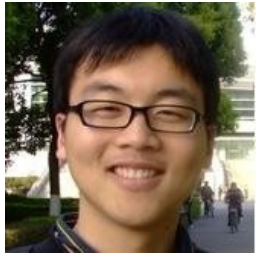
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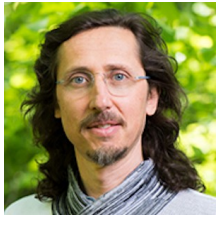
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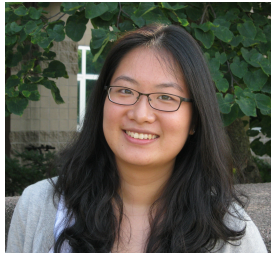
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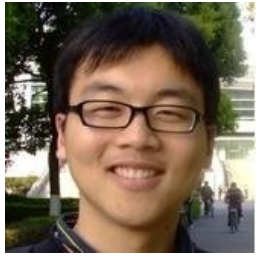
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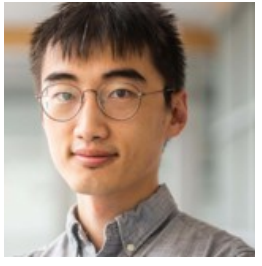

Yisu Peng

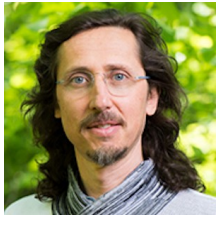

Tim Bergquist


Balint Kacsoh


Scott Zarecor


Burkhard Rost


Christine Orengo


Marc RR


Dannie Durand


Steven Brenner

Acknowledgments

Steering Committee


Casey Greene


Predrag Radivojac


Sean Mooney

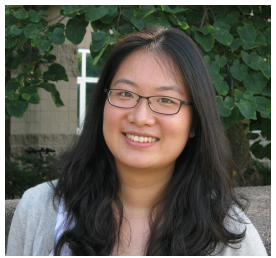

Deb Hogan


Gio Bosco


Mark Wass


Kimberly Reynolds


Wyatt Clark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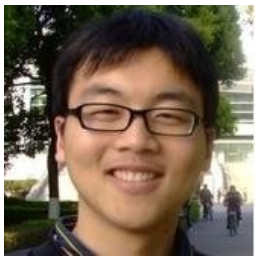
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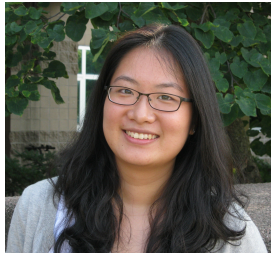
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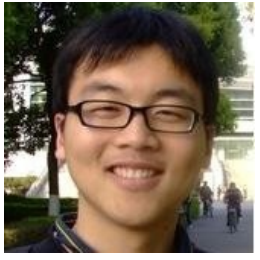
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Acknowledgments

>60 participating CAFA groups
from 25 countries

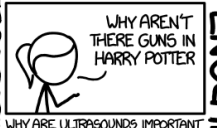
QUESTIONS

FOUND IN GOOGLE AUTOCOMPLETE

WHY DO WHALES JUMP
WHY ARE WITCHES GREEN
WHY ARE THERE MIRRORS ABOVE BEDS
WHY DO I SAY UH
WHY IS SEA SALT BETTER
WHY ARE THERE TREES IN THE MIDDLE OF FIELDS
WHY IS THERE NOT A POKEMON MMO
WHY IS THERE LAUGHING IN TV SHOWS
WHY ARE THERE DOORS ON THE FREEWAY
WHY ARE THERE SO MANY SVCHOST.EXE RUNNING
WHY AREN'T THERE ANY COUNTRIES IN ANTARCTICA
WHY ARE THERE SCARY SOUNDS IN MINECRAFT
WHY IS THERE KICKING IN MY STOMACH
WHY ARE THERE TWO SLASHES AFTER HTTP
WHY ARE THERE CELEBRITIES
WHY DO SNAKES EXIST
WHY DO OYSTERS HAVE PEARLS
WHY ARE DUCKS CALLED DUCKS
WHY DO THEY CALL IT THE CLAP
WHY ARE KYLE AND CARTMAN FRIENDS
WHY IS THERE AN ARROW ON AANG'S HEAD
WHY ARE TEXT MESSAGES BLUE
WHY ARE THERE MUSTACHES ON CLOTHES
WHY ARE THERE MUSTACHES ON CARS
WHY ARE THERE MUSTACHES EVERYWHERE
WHY ARE THERE SO MANY BIRDS IN OHIO
WHY IS THERE SO MUCH RAIN IN OHIO
WHY IS OHIO WEATHER SO WEIRD
WHY ARE THERE MALE AND FEMALE BIKES
WHY ARE THERE BRIDESMAIDS
WHY DO DYING PEOPLE REACH UP
WHY AREN'T THERE VARICOSE ARTERIES
WHY ARE OLD KLINGONS DIFFERENT
WHY AREN'T THERE DINOSAUR GHOSTS
WHY DO IGUANAS DIE
WHY DO TESTICLES MOVE
WHY ARE THERE PSYCHICS
WHY ARE HATS SO EXPENSIVE
WHY IS THERE CAFFEINE IN MY SHAMPOO
WHY DO YOUR BOOBS HURT
WHY ARE THERE SLAVES IN THE BIBLE
WHY DO TWINS HAVE DIFFERENT FINGERPRINTS
WHY ARE AMERICANS AFRAID OF DRAGONS
WHY IS HTTPS CROSSED OUT IN RED
WHY IS THERE A LINE THROUGH HTTPS
WHY IS THERE A RED LINE THROUGH HTTPS ON FACEBOOK
WHY IS YKK ON ALL ZIPPERS
WHY IS HTTPS IMPORTANT

WHY ARE THERE WEEKS
WHY DO I FEEL DIZZY
WHY AREN'T ECONOMISTS RICH
WHY DO AMERICANS CALL IT SOCCER
WHY ARE MY EARS RINGING
WHY ARE THERE SO MANY AVENGERS
WHY ARE THE AVENGERS FIGHTING THE X MEN
WHY IS WOLVERINE NOT IN THE AVENGERS
WHY ARE THERE SWARMS OF GNATS
WHY IS THERE PHLEGM
WHY ARE THERE SO MANY CROWS IN ROCHESTER, MN
WHY IS PSYCHIC WEAK TO BUG
WHY DO CHILDREN GET CANCER
WHY IS POSEIDON ANGRY WITH ODYSSEUS
WHY IS THERE ICE IN SPACE
WHY IS THERE LAVA
WHY ARE DOGS AFRAID OF FIREWORKS
WHY IS THERE NO KING IN ENGLAND
WHY ARE THERE ANTS IN MY LAPTOP
WHY IS EARTH TILTED
WHY IS SPACE BLACK
WHY IS OUTER SPACE SO COLD
WHY ARE THERE PYRAMIDS ON THE MOON
WHY IS NASA SHUTTING DOWN

WHY IS THERE AN OWL IN MY BACKYARD
WHY IS THERE AN OWL OUTSIDE MY WINDOW
WHY IS THERE AN OWL ON THE DOLLAR BILL
WHY DO OWLS ATTACK PEOPLE
WHY ARE AK 47S SO EXPENSIVE
WHY ARE THERE HELICOPTERS CIRCLING MY HOUSE
WHY ARE THERE GODS
WHY ARE THERE TWO SPOCKS
WHY ARE MY BOOBS ITCHY
WHY ARE CIGARETTES LEGAL
WHY ARE THERE DUCKS IN MY POOL
WHY IS JESUS WHITE
WHY IS THERE LIQUID IN MY EAR
WHY DO Q TIPS FEEL GOOD
WHY DO GOOD PEOPLE DIE
WHY ARE THERE FEMALE MR MIMES
WHY IS LIFE SO BORING
WHY IS MT VESUVIUS THERE
WHY DO THEY SAY T MINUS
WHY ARE THERE OBELISKS
WHY ARE WRESTLERS ALWAYS WET
WHY ARE OCEANS BECOMING MORE ACIDIC
WHY IS ARWEN DYING
WHY AREN'T MY QUAIL LAYING EGGS
WHY AREN'T MY QUAIL EGGS HATCHING
WHY AREN'T THERE ANY FOREIGN MILITARY BASES IN AMERICA



WHY ARE ULTRASOUNDS IMPORTANT
WHY ARE ULTRASOUND MACHINES EXPENSIVE
WHY IS STEALING WRONG

WHY ARE THERE TINY SPIDERS IN MY HOUSE
WHY DO SPIDERS COME INSIDE
WHY ARE THERE HUGE SPIDERS IN MY HOUSE
WHY ARE THERE LOTS OF SPIDERS IN MY HOUSE
WHY ARE THERE SPIDERS IN MY ROOM
WHY ARE THERE SO MANY SPIDERS IN MY ROOM
WHY DO SPIDER BITES ITCH
WHY IS DYING SO SCARY
WHY IS THERE HELL IF GOD FORGIVES
WHY IS PROGRAMMING SO HARD
WHY IS THERE A 0 OHM RESISTOR
WHY DO AMERICANS HATE SOCCER
WHY DO RHYMES SOUND GOOD
WHY DO TREES DIE
WHY IS THERE NO SOUND ON CNN
WHY AREN'T POKEMON REAL
WHY AREN'T BULLETS SHARP
WHY DO DREAMS SEEM SO REAL
WHY IS THERE NO GPS IN LAPTOPS
WHY DO KNEES CLICK
WHY AREN'T THERE E GRADES
WHY IS ISOLATION BAD
WHY DO BOYS LIKE ME
WHY DON'T BOYS LIKE ME
WHY IS THERE ALWAYS A JAVA UPDATE
WHY ARE THERE RED DOTS ON MY THIGHS
WHY IS LYING GOOD
WHY IS GPS FREE