Computational prediction of intrinsic disorder
FROM HUMBLE BEGINNINGS TO MODERN RESOURCES

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Intrinsic disorder

**Intrinsically disordered proteins**\(^1\) (IDPs) have at least one **intrinsically disordered region** (IDR). IDR\(\)s lack a stable structure in isolation and take form of conformational ensembles. “**Intrinsic**” reflects the fact that the disordered state is encoded in the sequence.

\(^1\) also called floppy, pliable, rheomorphic, flexible, mobile, partially folded, natively denatured, natively unfolded, natively disordered, intrinsically unstructured, intrinsically denatured, intrinsically unfolded, ...
Intrinsic disorder

Abundant in nature
- computational studies estimate that 30 to 50% of eukaryotic proteins have one or more long IDR

Involved in numerous molecular functions
- signaling, regulation, assembly, molecular recognition (proteins and nucleic acids), translation and transcription

Only about 1,600 IDPs (3,500 IDR) are annotated experimentally
- experimental data are used to develop and validate computational models
- computational prediction often plays a key role to produce initial hypothesis about presence and function of disorder

VCU College of Engineering
http://biomine.cs.vcu.edu
Prediction of intrinsic disorder

P06701 (UniPRot) / DP00530 (DisPRot): **silent information regulator (Sir3p) from yeast**

Native annotation
Prediction of intrinsic disorder

P06701 (UniPRot) / DP00530 (DisPRot): silent information regulator (Sir3p) from yeast

Prediction of intrinsic disorder

Annual #

Number of predictors in a given year

Total number of predictors

CASP5
CASP10
CAID

0 1 2 3 4 5 6 7 8 9

Prediction of intrinsic disorder

Functions of intrinsic disorder

Molecular partners
- **Protein** (417 IDRs)
- **DNA** (76 IDRs)
- **RNA** (33 IDRs)
- Lipid (30 IDRs)
- Metal (39 IDRs)
- Small molecule (32 IDRs)
- Inorganic Salt (1 IDR)

Molecular functions
- **Entropic Chain** (186 IDRs)
  - Molecular Recognition: Assembler (232 IDRs)
  - Molecular Recognition: Effector (181 IDRs)
  - Molecular Recognition: Chaperone (30 IDRs)
  - Molecular Recognition: Display Site (23 IDRs)
  - Molecular Recognition: Scavenger (17 IDRs)

Prediction of intrinsic disorder function

1st protein-partner predictor

1st DNA & RNA-partner predictor

1st linker predictor

1st moonlighting predictor

Number of predictors in a given year
Total number of predictors

0 1 2 3 4 5

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Modern resources for disorder prediction

Databases of predicted disorder
- MobiDB at [http://mobidb.bio.unipd.it/](http://mobidb.bio.unipd.it/)
- D²P² at [http://d2p2.pro/](http://d2p2.pro/)

Disorder prediction center

Quality assessment for disorder predictions
MobiDB

http://mobidb.bio.unipd.it/

Predictions of intrinsic disorder and protein-partner regions for 75 million proteins

P06701 (UniPRot) / DP00530 (DisPRot): **silent information regulator (Sir3p) from yeast**

Piovesan D, Tabaro F, …, Tosatto S. MobiDB 3.0: more annotations for intrinsic disorder, conformational diversity and interactions in proteins. *Nucleic Acids Res.* 46(D1):D471-D476, 2018
DEPICTER
DisorderEd Prediction cenTER
http://biomine.cs.vcu.edu/servers/DEPICTER/

Webserver for integrated prediction of disorder and disorder functions

P06701 (UniPRot) / DP00530 (DisPRot): silent information regulator (Sir3p) from yeast

QUARTER
QUality Assessment for pRotein inTrinsic disorder pRedictions
http://biomine.cs.vcu.edu/servers/QUARTER/
Webserver for quality assessment of disorder predictions

P06701 (UniPRot) / DP00530 (DisPRot): silent information regulator (Sir3p) from yeast

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QUAlity Assessment for pRotein inTrinsic disorder pRedictions
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Webserver for quality assessment of disorder predictions

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Summary

80+ predictors, **23 years** of history

Intrinsic disorder **can be accurately predicted directly from the sequence**

Methods that **predict selected IDR functions** are available

**Modern resources** emphasize convenience and predictive quality
- pre-computed disorder predictions
- integrated prediction of disorder and disorder functions
- indication of predictive quality/uncertainty at the amino acid level
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