Organisatorisches

http://www.bioinf.uni-leipzig.de/teaching/currentClasses.html

Diese Spezialvorlesung ist Teil des Moduls “Bioinformatik von RNA- und Proteinstrukturen” (10-202-2208)

Sie kann gemeinsam oder als Alternative zu “Interaktionen und Modifikation von RNAs und Proteinen” (Modul 10-202-2208) besucht werden

Der Stoff baut auf der VO “Einführung in die Bioinformatik von RNA- und Proteinstrukturen” auf und ist ergänzend zu Stoff aus “Interaktionen und Modifikation von RNAs und Proteinen”
Termine

10.04 Kehr, Fallmann  Intro, Levels of RNA Regulation
17.04 Kehr  Annotation of regulatory RNAs
24.04 Fallmann  RNA-protein Interactions I
08.05 Fallmann  RNA-protein Interactions II
22.05 Weinberg  Riboswitches and Regulation
29.05 Bernhart  Triplexe
05.06 Bernhart  Last but not least
Central Dogma of Gene Expression

DNA → RNA → protein

- only about 2% of human DNA is protein coding
- about 80% is transcribed
Non-coding RNAs - ncRNAs

- not translated into aminoacid chain functional at RNA level
  - energetically cheaper
  - faster adapting
  - more flexible

Housekeeping ncRNAs

- 'needed for protein synthesis’
- tRNAs (transfer RNAs), rRNAs (ribosomal RNA), snRNAs (small nuclear RNA), [snoRNAs]

Regulatory ncRNAs

- regulation of all steps of protein synthesis
- e.g. chromatine structure (epigenetic), transcription, splicing, base modification, translation
Developmental complexity

- number of protein coding genes surprisingly static
- amount of ncRNAs scales with increasing complexity

1 Mattick JS, 2011, *FEBS Letters*
Interaction as the key

We talk about regulation of Gene Expression on the RNA level

- For regulation to take place, there has to be interaction
- This means direct contact between two entities of RNA/Protein/DNA
- Or the lack thereof
RNA interactions

As we are concerned with RNA, RNA interactions are important to us.

We distinguish two modes of interaction:

- Intramolecular
- Intermolecular
As we are concerned with RNA, RNA interactions are important to us. We distinguish two modes of interaction:

- **Intramolecular**
  - This is what you already know as basepairing
- **Intermolecular**
  - This is what we are interested in
Why is structure important?
Why is structure important?

Yes, because structure and function are related, but why is structure important for interactions?
Why is structure important?

Yes, because structure and function are related, but why is structure important for interactions?

How many pairings do we allow for a single base?
Why is structure important?

Yes, because structure and function are related, but why is structure important for interactions?

How many pairings do we allow for a single base?

Indeed, just one, so if a base is already paired, can it still interact?
Predicting RNA Interactions → preview

How would you tackle this problem?
How would you tackle this problem?

Co-folding of two sequences, connected by linker, takes care of both, intra- and intermolecular interactions
Can we predict this for all structures possible with one (sub)sequence?
Can we predict this for all structures possible with one (sub)sequence?

Yes, we can!

ACCESSIBILITY

Measure for how much interacting sites are involved in intramolecular bps.
Revert unpaired probabilities $P_{i,j}^u$

into pseudo energy scores via $-RT \log(P_{i,j}^u)$

representing the amount of energy required to unfold a region $i..j$ in order to make it accessible for interactions
Revert unpaired probabilities $P_{i,j}^u$ into pseudo energy scores via $-RT \log(P_{i,j}^u)$ representing the amount of energy required to unfold a region $i..j$ in order to make it accessible for interactions

Important for RNA-RNA as well as RNA-Protein interactions
Non-coding RNAs - ncRNAs

• basepairing
  → secondary structure
  → binding of 'target' sites

• ribonucleoprotein complexes (RNPs)
  → protein catalyzes chemical reaction
  → RNA defines target site
**MicroRNAs - miRNA**

- 21-25 nucleotides long (mature)
- RNA-Induced Silencing Complex (RISC)
- seed region: nts 2-7
- mainly bind 3’-UTRs
- imperfect binding of target (animals) → repression of translation → deadenylation, ribosome activity (EIF)
- perfect binding of target (plants) → prevention of translation → mRNA cleavage
- >400 target per miRNA
- ~60% of mRNA are regulated

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2 Lam JKW, Chow MYT, Zhang Y, Leung SWS, 2015, *Molecular Therapy-Nucleic Acids*
MicroRNAs vs siRNAs

Silencing RNA (siRNA)
- protect cell against exogenous genetic material (e.g. virus RNA)
- perfect complementarity to mRNA
- PIWI domain of RISC
  - direct cleavage of mRNA
- evolutionary origin of miRNAs

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Lam JKW, Chow MYT, Zhang Y, Leung SWS, 2015, Molecular Therapy-Nucleic Acids
Small Nucleolar RNAs - box C/D SnoRNA

- **C/C’ box:** RTGATGA
- **D/D’-box:** CTGA
- Small stem, large loop
- 2’-0-ribose methylation

A: Secondary structure of box C/D snoRNA, B: snoRNA-target RNA interaction, C: kink-turn\(^3\), D: snoRNP\(^4\)

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\(^3\)Bartschat S, Kehr S, Tafer H, Stadler PF, Hertel J, 2014, *Bioinformatics*

Small Nucleolar RNAs - box H/ACA SnoRNA

A: Secondary structure of box H/ACA snoRNA
B: snoRNA-target RNA interaction
C: snoRNP

- H-box: ANANNA
- ACA-box
- Hairpin-hinge-hairpin-tail
- Pseudouridylation

5 Lui L and Lowe T, 2013, Essays Biochem
Diversity of SnoRNA Function

- maturation of rRNA (modification and cleavage)
- snRNAs as targets: small cajal Body RNAs (scaRNAs)
- Further target RNAs (snoRNAs, 7SK RNA, 7SL RNA, mRNAs,..)
- Small derived RNAs (sdRNAs)
  - some miRNA-like function
- Chromatin associated RNAs (caRNAs)
  - decondensation of chromatin
- SnoRNAs associated with cancer
- Telomerase RNA
  - box H/ACA scaRNA domain in animals
Diversity of SnoRNA Function - SNORD115

- SNURF-SNRPN locus
  - snoRNAs effect alternative splicing
  - mRNA editing

Long non-coding RNAs - LncRNA

- length > 200 nucleotides
- estimates vary between 10,000 up to 200,000 LncRNA in human
- differential expressed

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8 Hrdlickova B, Coutinho de Almeida R, Borek Z, Withoff S, 2014, Biochimica et Biophysica Acta
Epigenetic and Transcriptional Function

I. Signaling

II. Decoy

III. Guides

IV. Scaffolds

- act in *cis* and *trans*
- diverse mechanisms and specific functions
- many chromatin regulators (Xist, HOTAIR,...)

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Non-Coding RNA
Non-Coding RNA