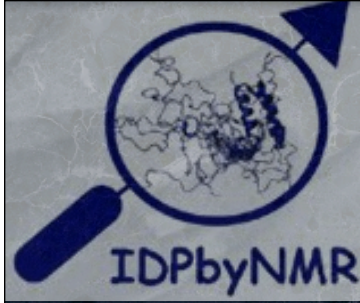
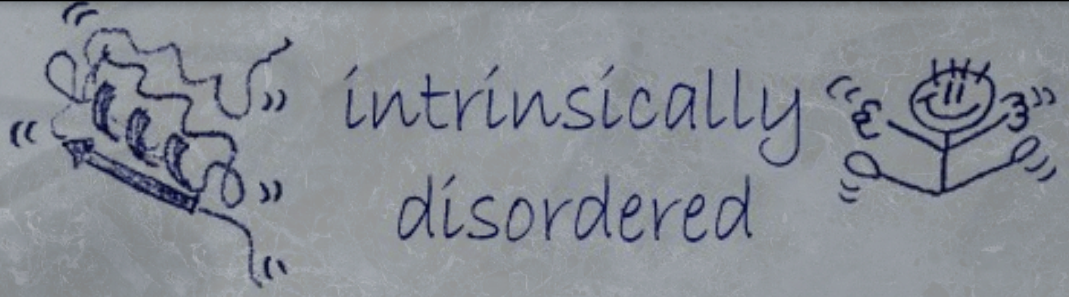




NMR study of viral IDPs

Tomáš Hošek,
CERM, Italy

Presentation overview

- IDPs & viruses
- Studied viral oncoproteins:
  - E7 from Human Papilloma virus 16
  - E1A from Adenovirus 2/5

Intrinsically Disordered Proteins

- function coded by short AA sequence (Short Linear Motifs)
- highly prevalent in eukaryotes
- also vastly exploited by viruses
- viral IDPs involved in cancer development

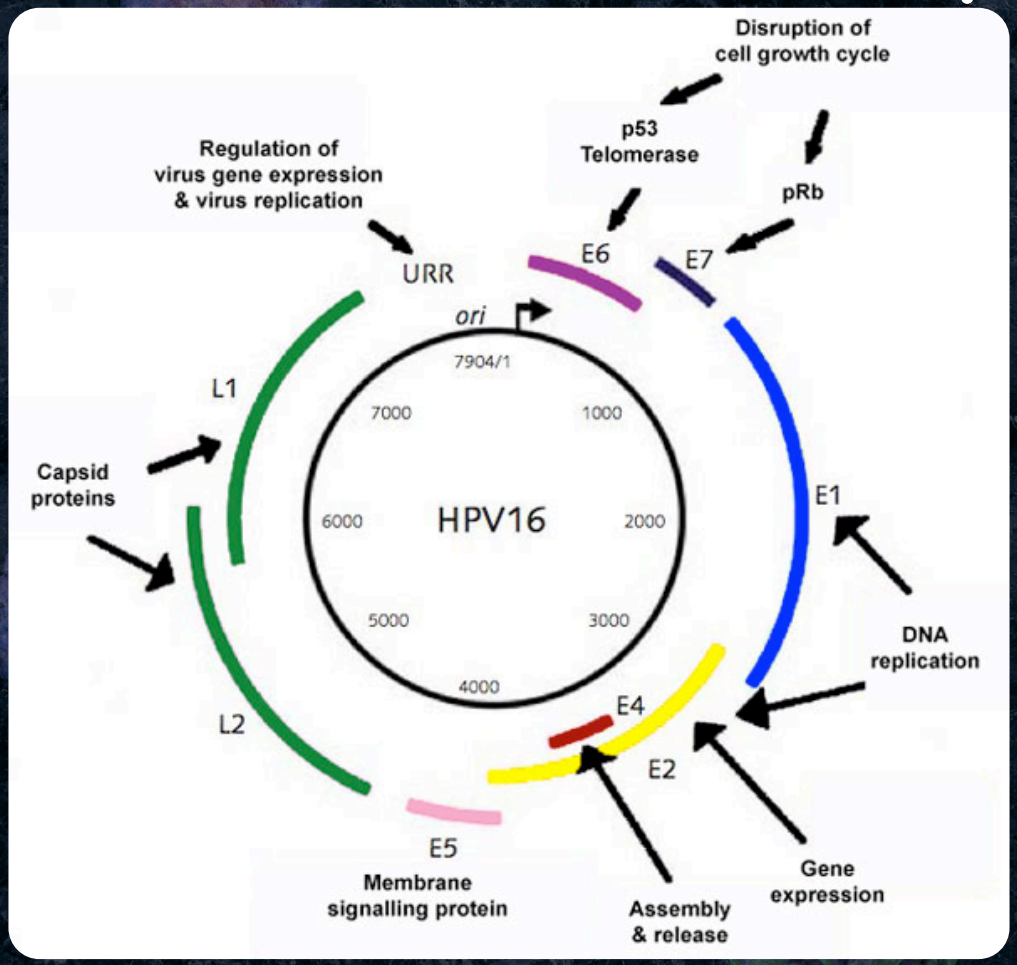
Dunker, A. K. (2001). Intrinsically disordered proteins. Journal of Molecular Graphics and Modelling, 19(1), 26–59.
Tompa, P. (2002). Intrinsically unstructured proteins. Trends in Biochemical Sciences, 27(10), 527–533.
Davey, N. E., Travé, G., & Gibson, T. J. (2011). How viruses hijack cell regulation. Trends in Biochemical Sciences, 36(3), 159–169.
Uversky, V. N., & Dunker, A. K. (2008). Controlled chaos. Science (New York, N.Y.), 322(5906), 1340–1341.

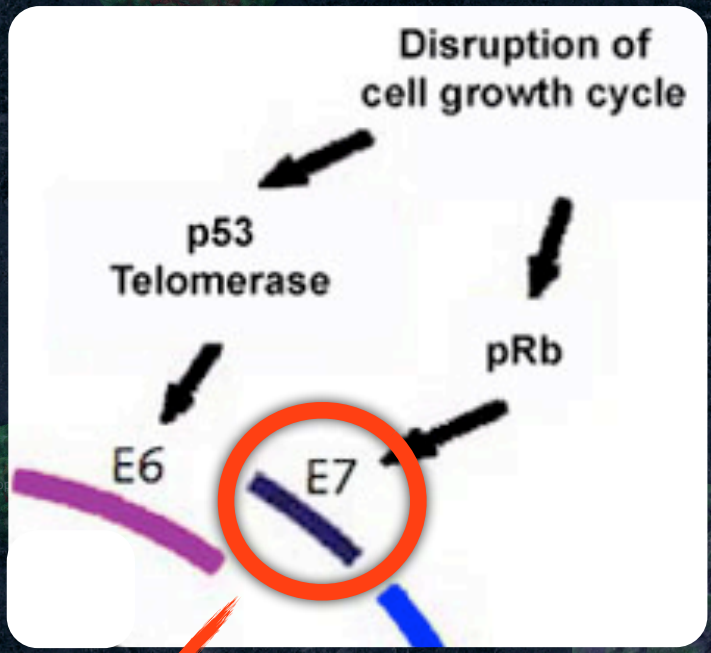
Human Papilloma viruses

- non-enveloped dsDNA viruses
- infect keratinocytes of skin or mucous membrane
- can cause cervix and throat cancer
  - low-risk (HPV-6, HPV-11)
  - moderate-risk (HPV-26, HPV-53)
  - high-risk (HPV-16, HPV-18) = oncogenic

Uversky et al. (2006). Protein Intrinsic Disorder and Human Papillomaviruses: Increased Amount of Disorder in E6 and E7 Oncoproteins from High Risk HPVs. Journal of Proteome Research, 5(8), 1829-1842.

Human Papilloma virus





CR1 | CR2 | CR3

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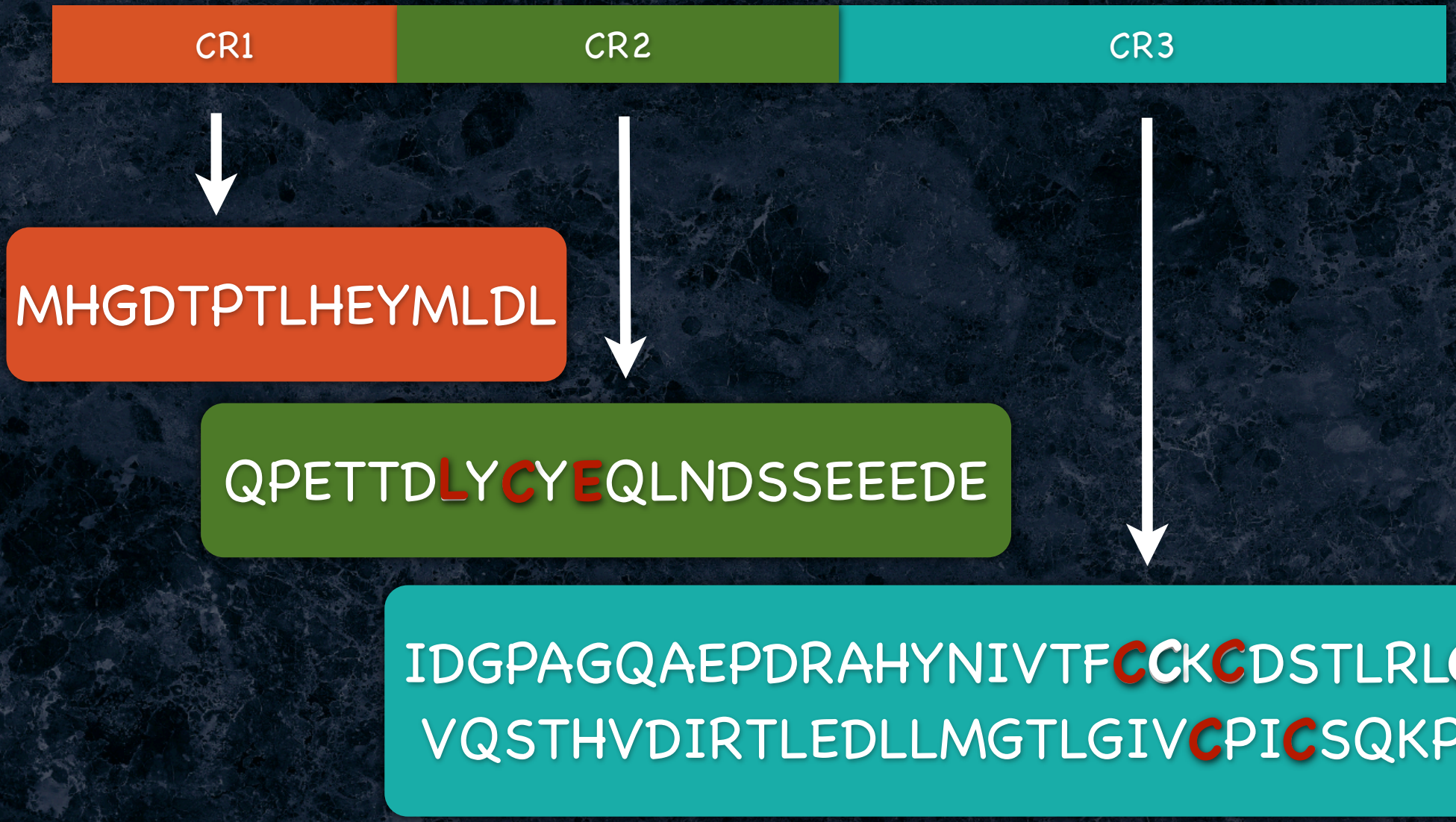
HPV 16 E7 oncoprotein



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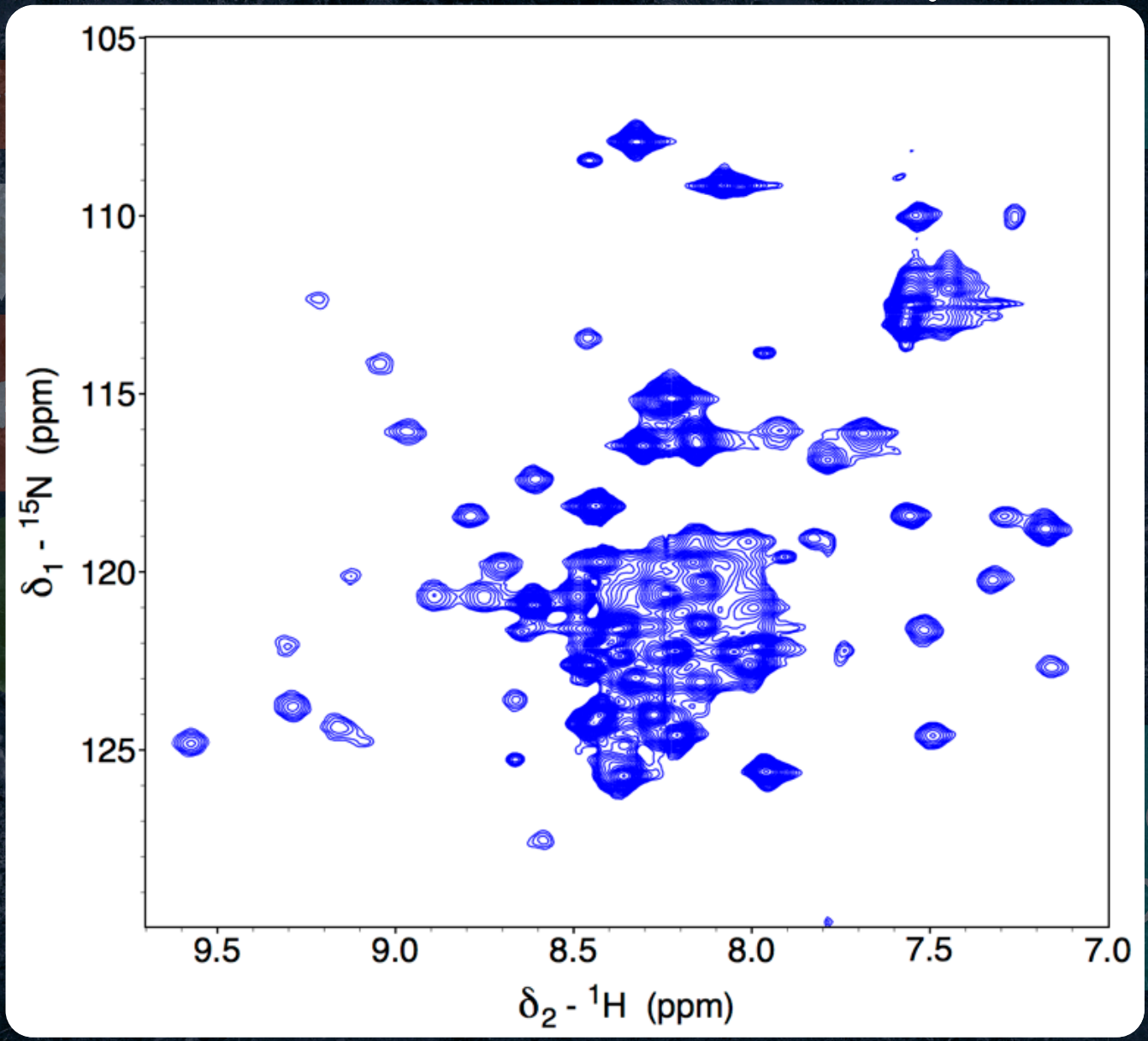
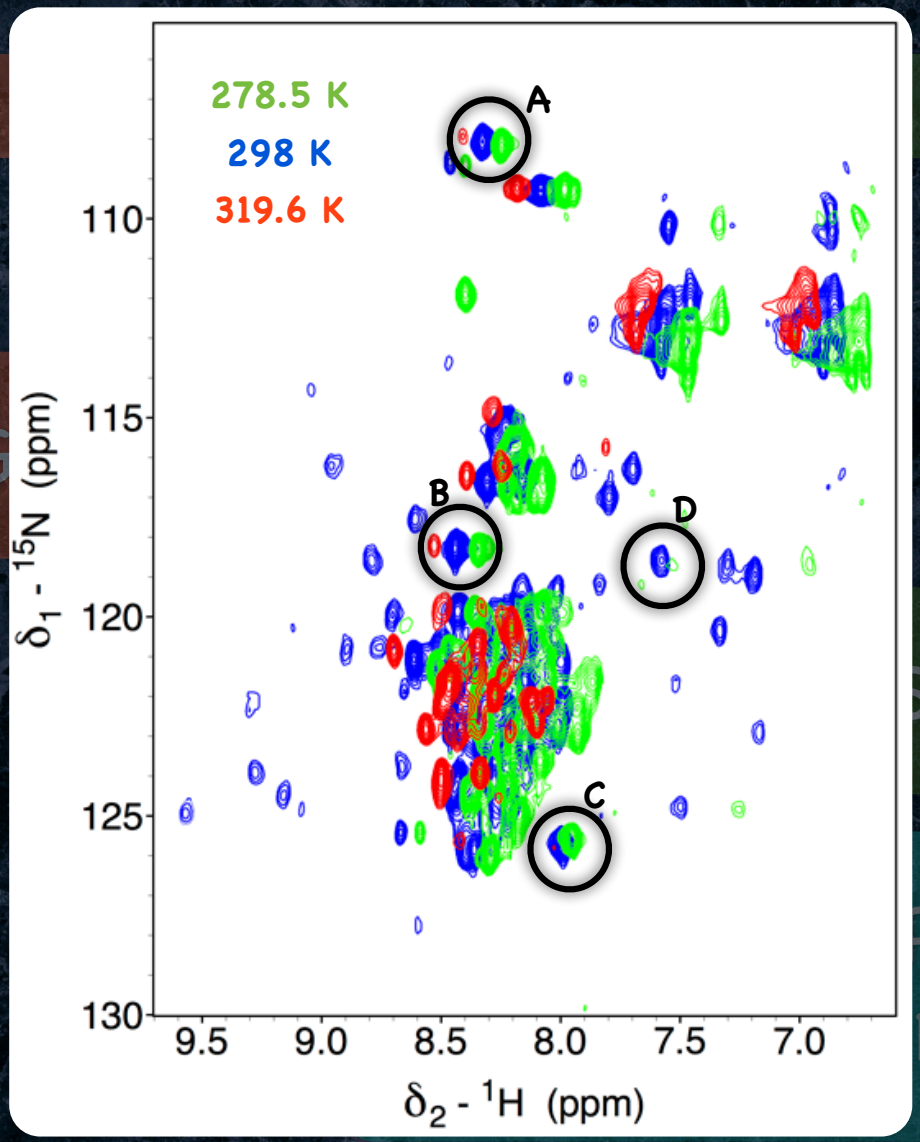
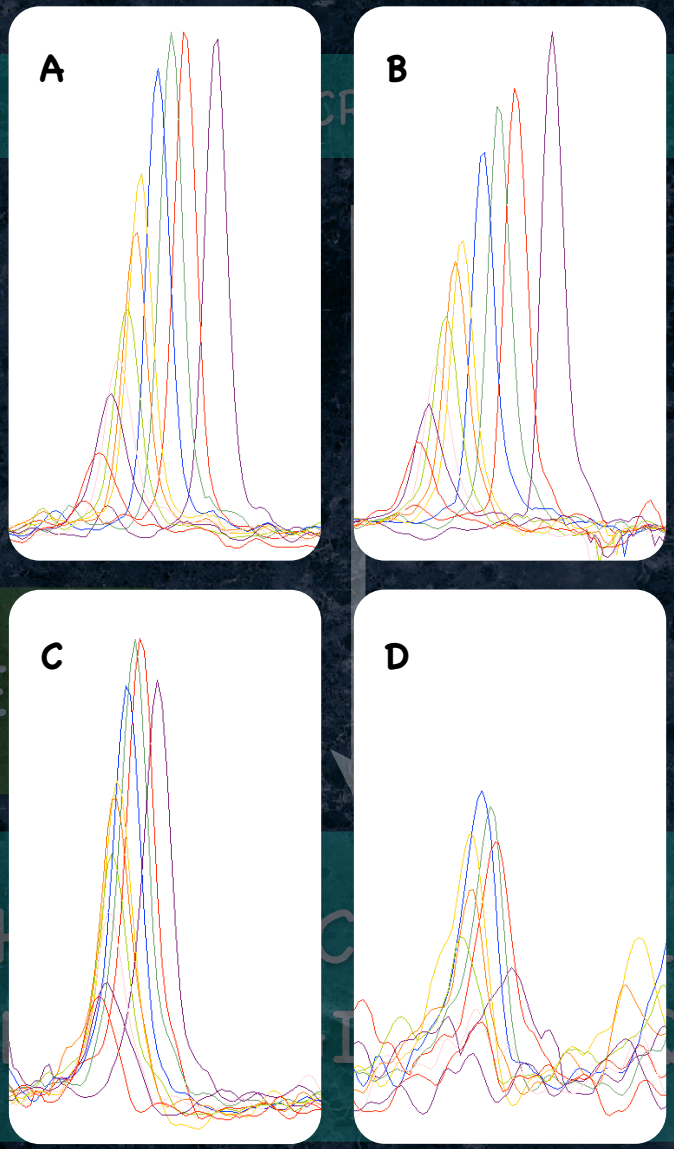
HPV 16 E7 oncoprotein

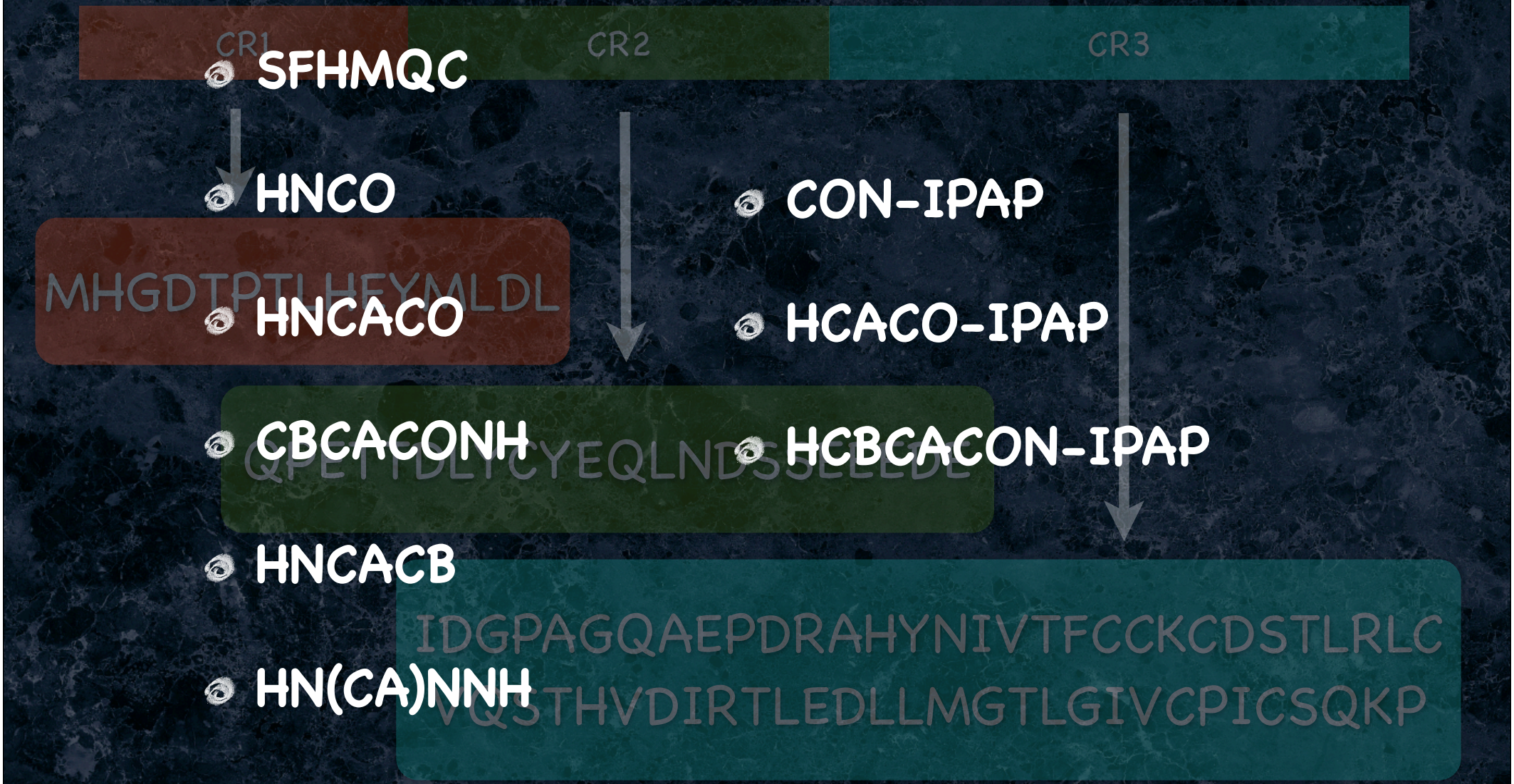


Temperature dependence





Assignment of HPV 16 E7



Assignment of HPV 16 E7

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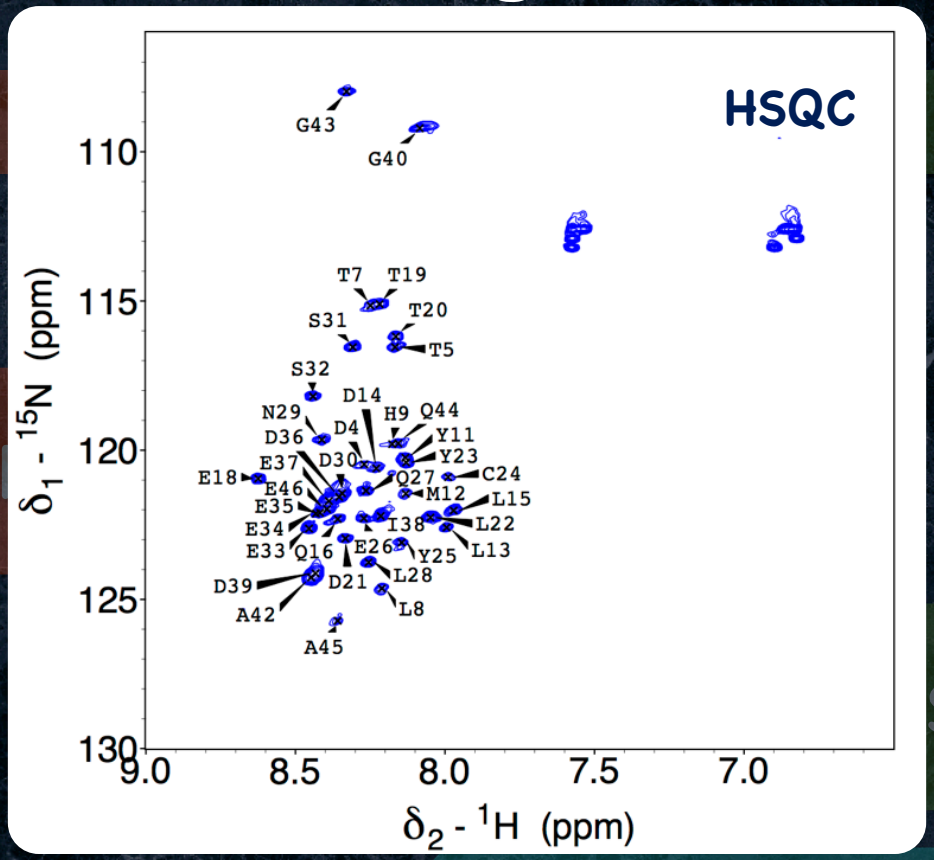
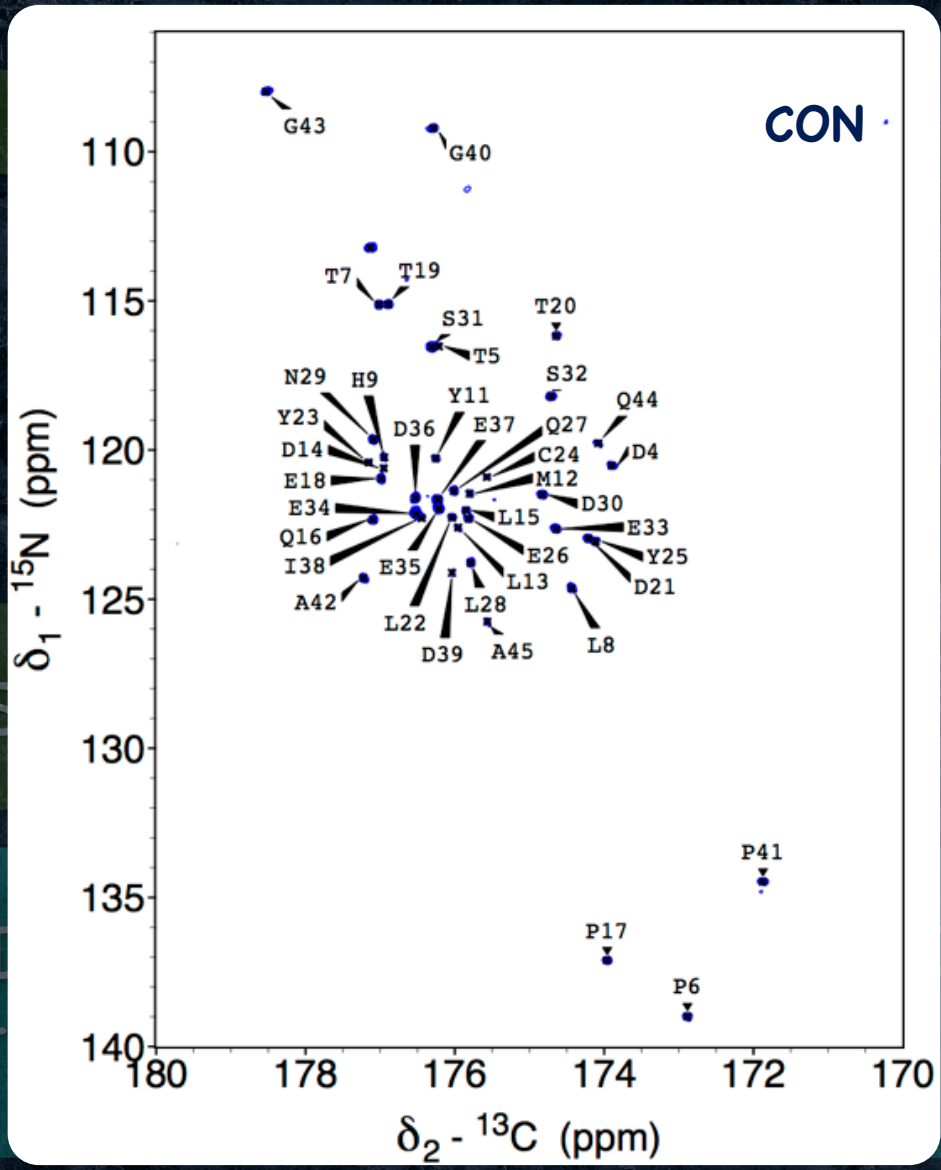
Assignment of HPV 16 E7





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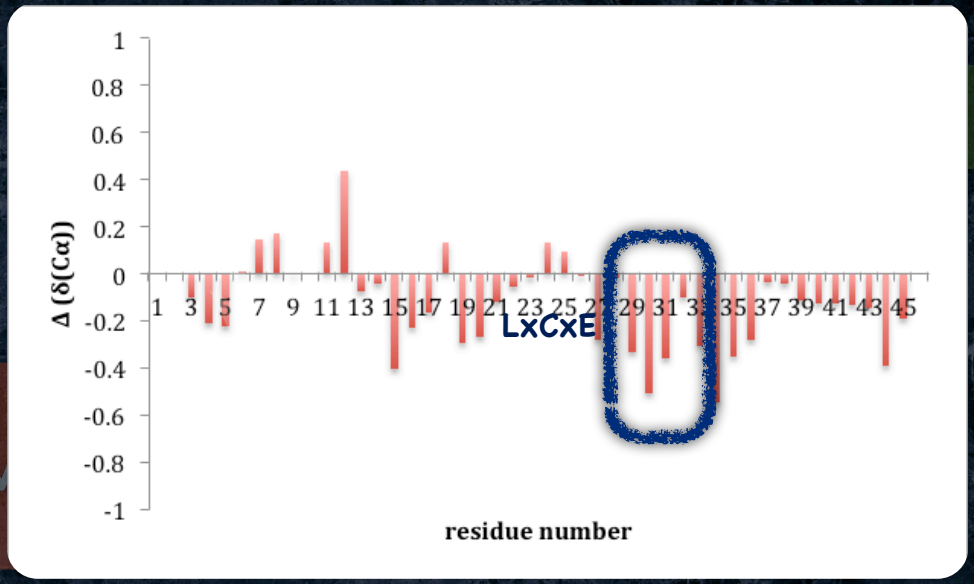
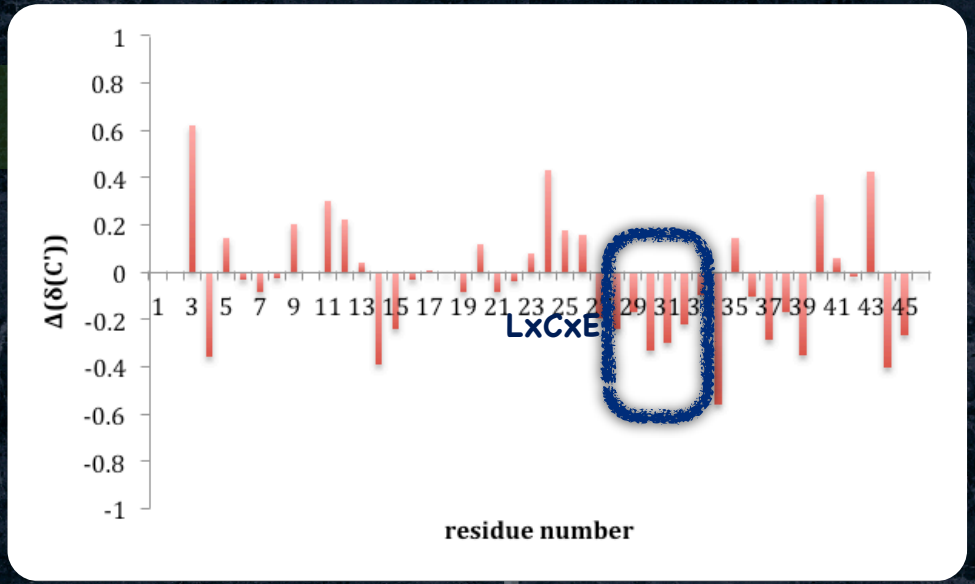
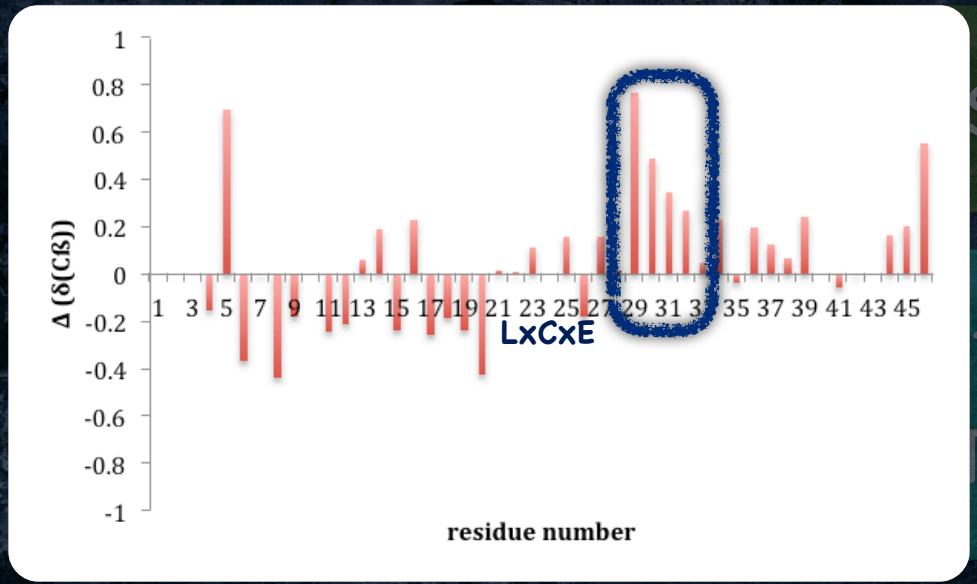
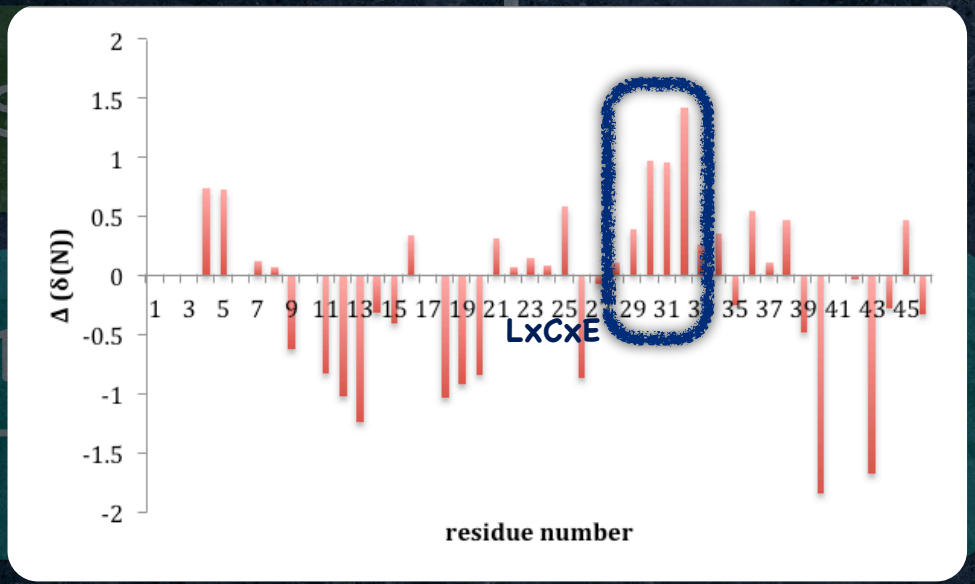
Chemical Shift Index









Lee, J., Russo, A. A., Pavletich (1998). Structure of Retinoblastoma tumor-suppressor pocket domain bound to a peptide from HPV E7. Nature, 391(6670), 859–865.

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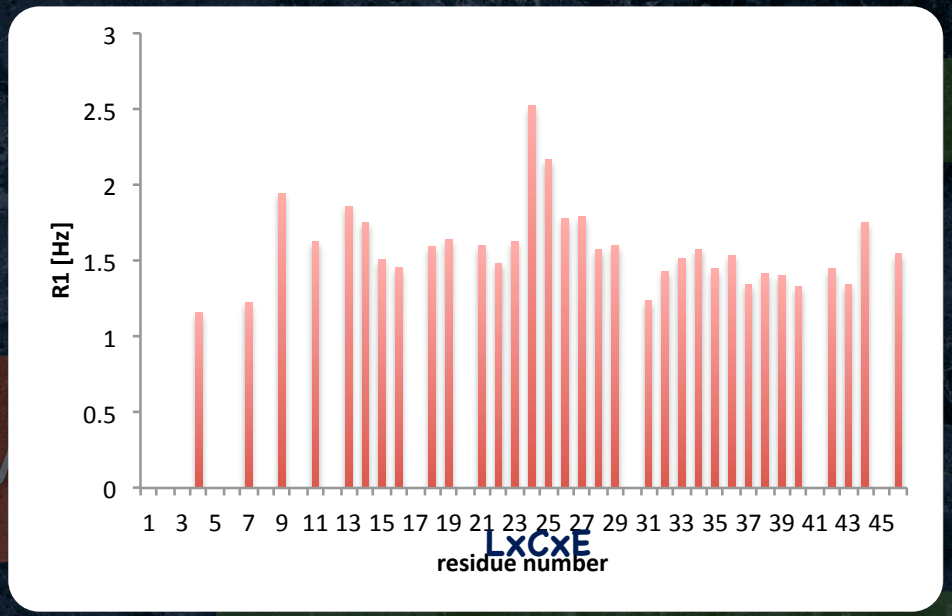
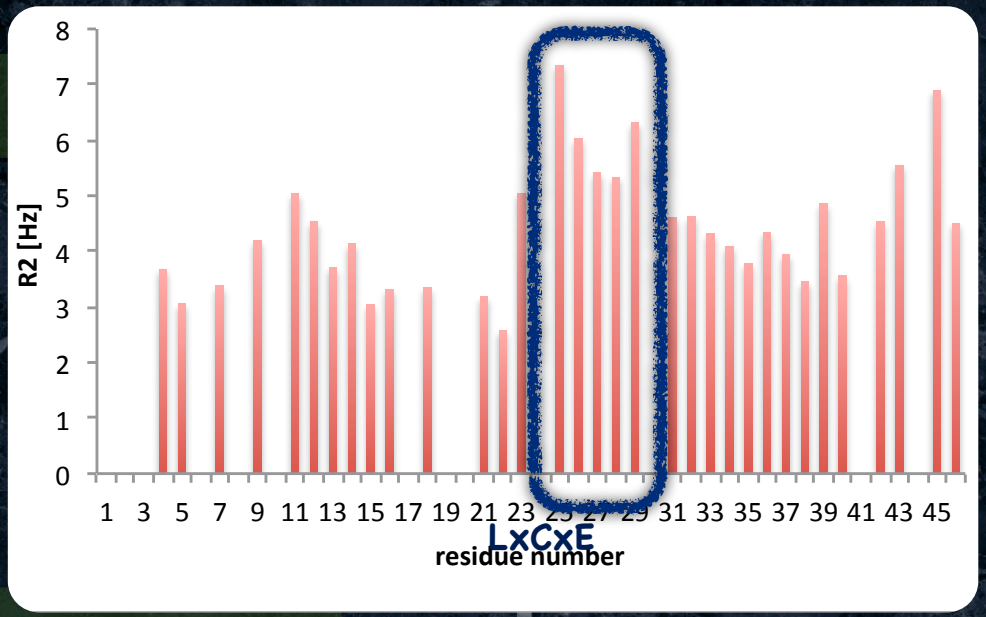
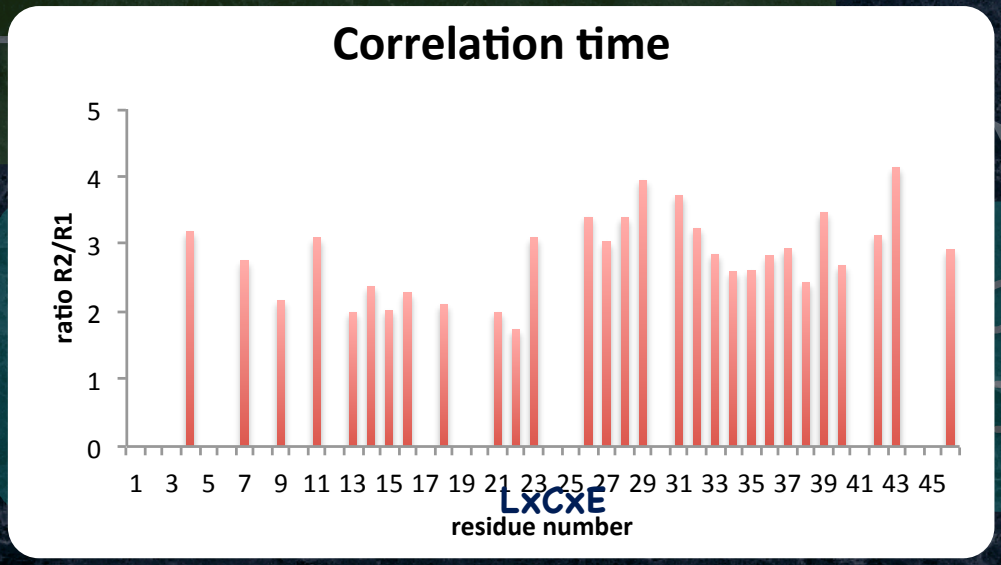
^{15}N relaxation experiments







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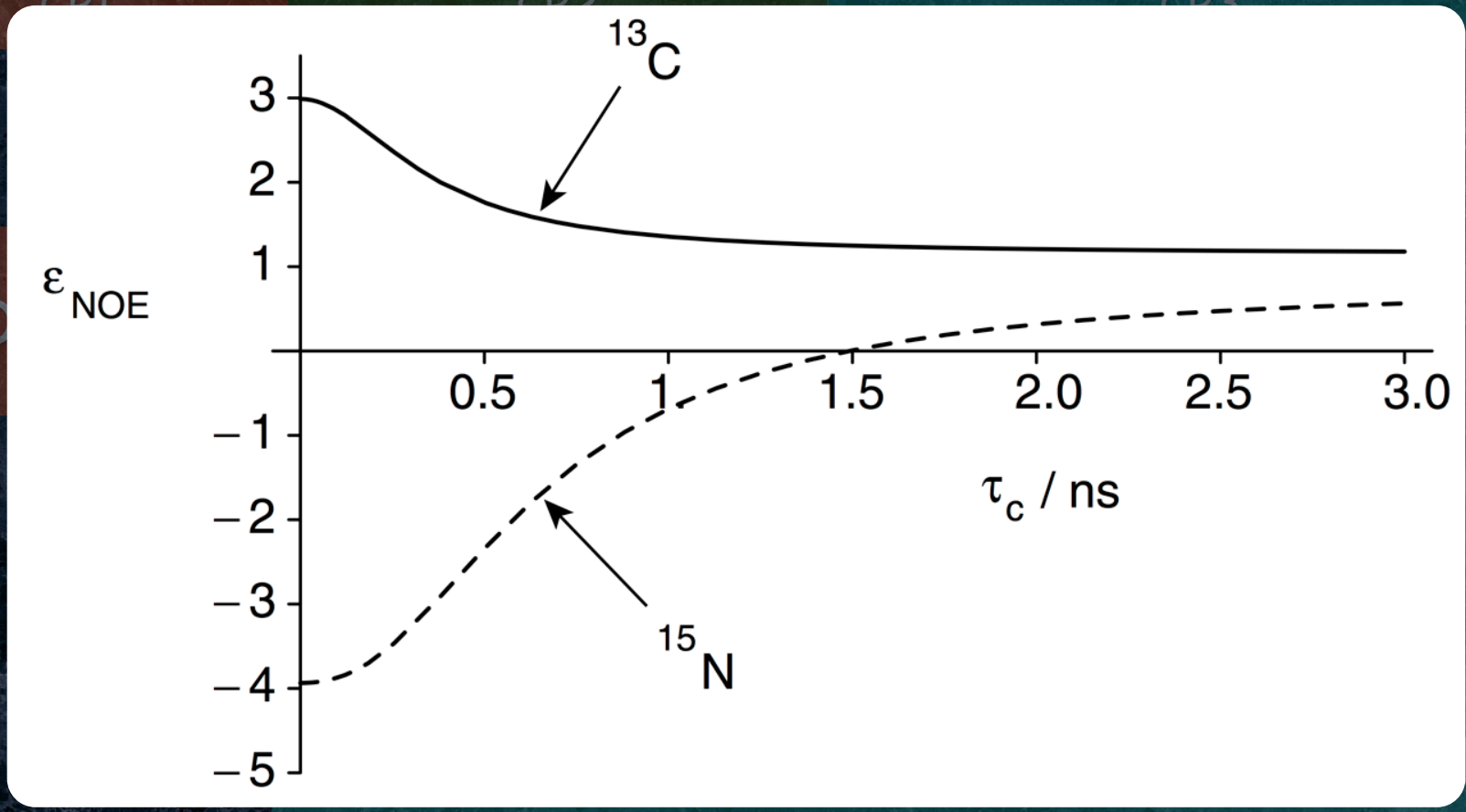
heteronuclear NOE



Malcolm H. Levitt, Spin Dynamics: Basics of Nuclear Magnetic Resonance - 2nd ed., Chichester: John Wiley & Sons Ltd., 2009

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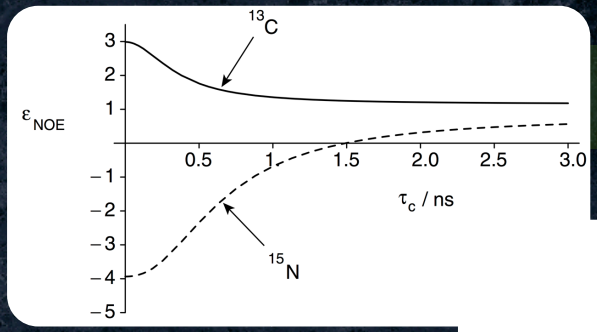
$^{1}H-^{15}N$ heteronuclear NOE

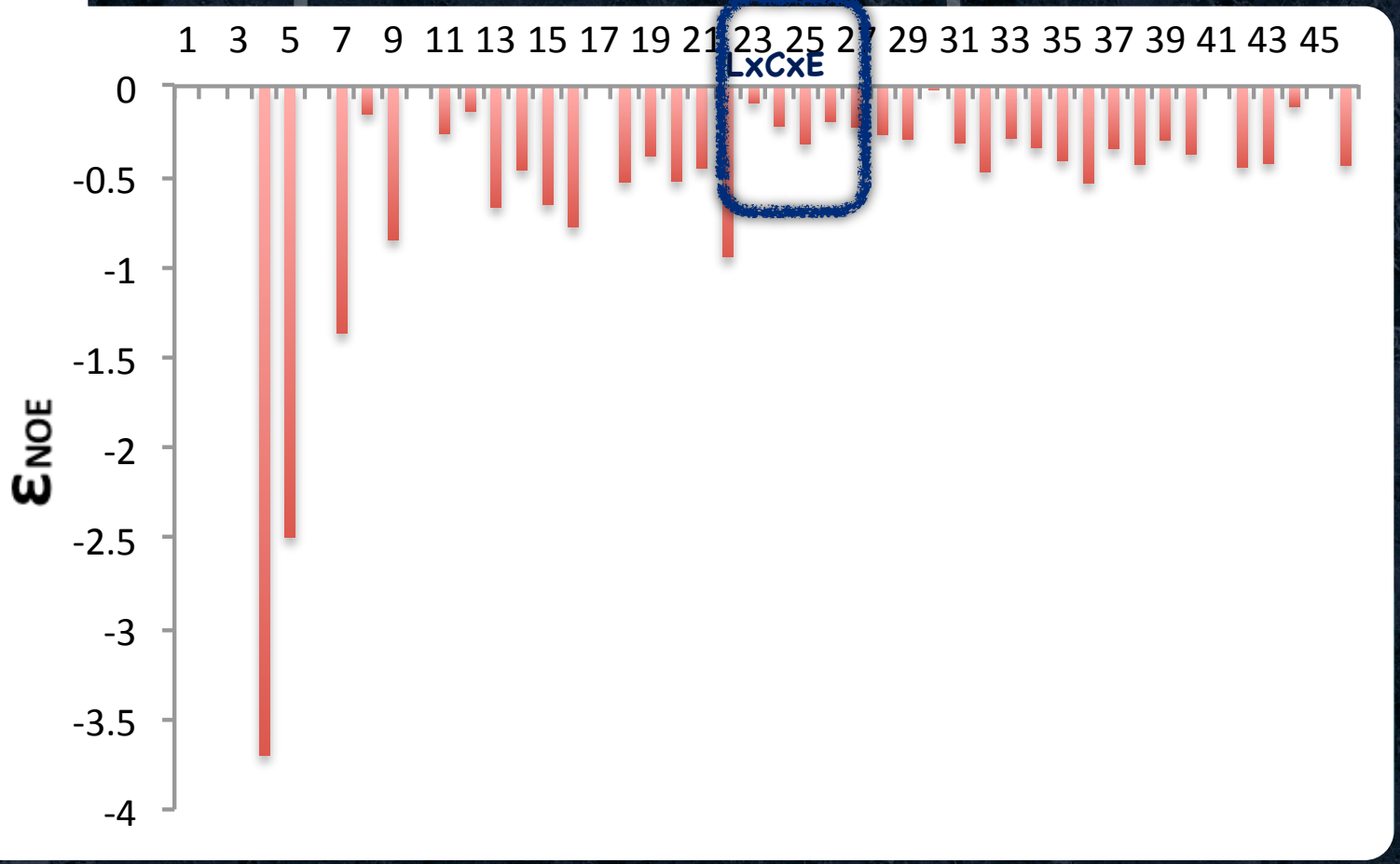


CR2

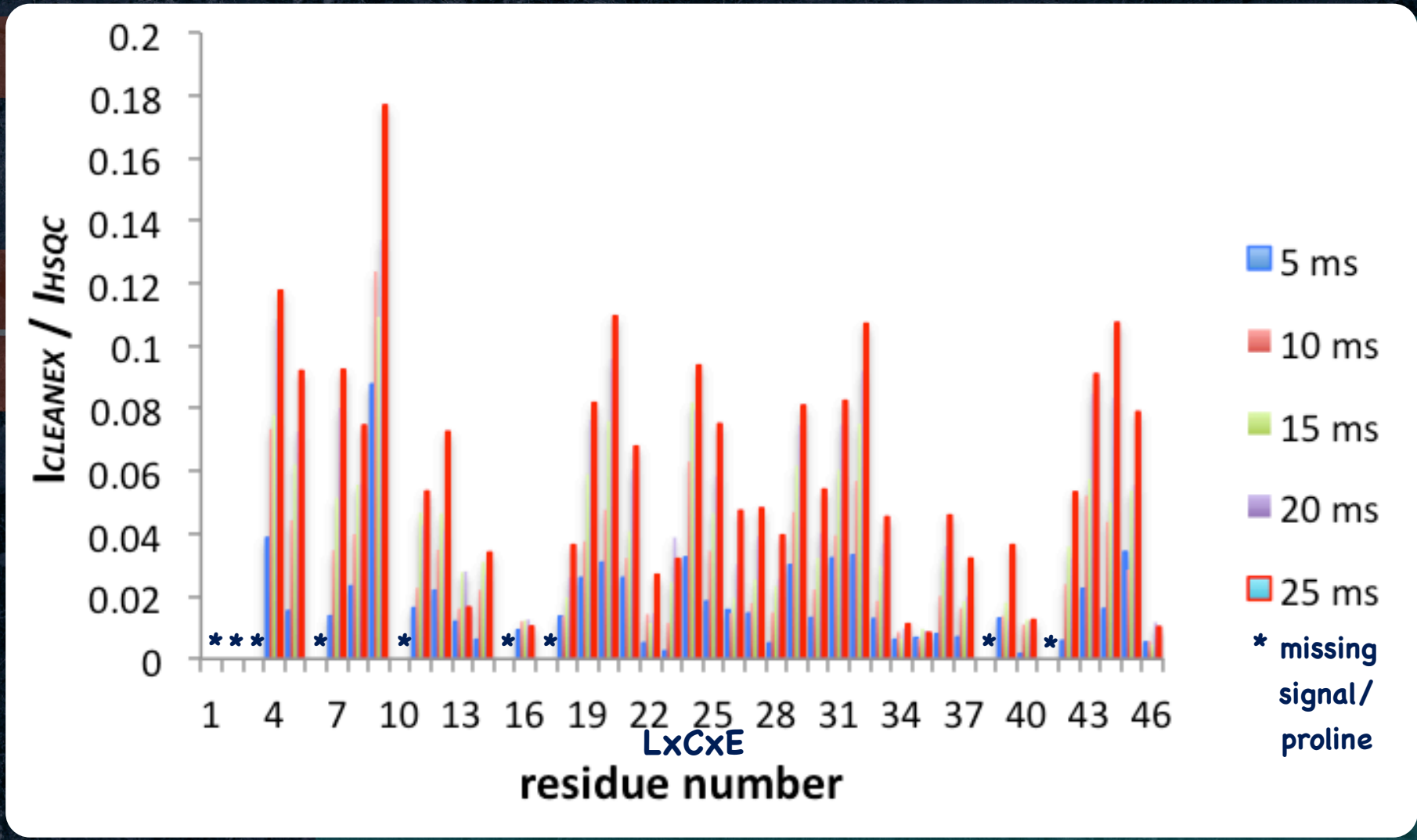
CR3

MHGDTPTLH

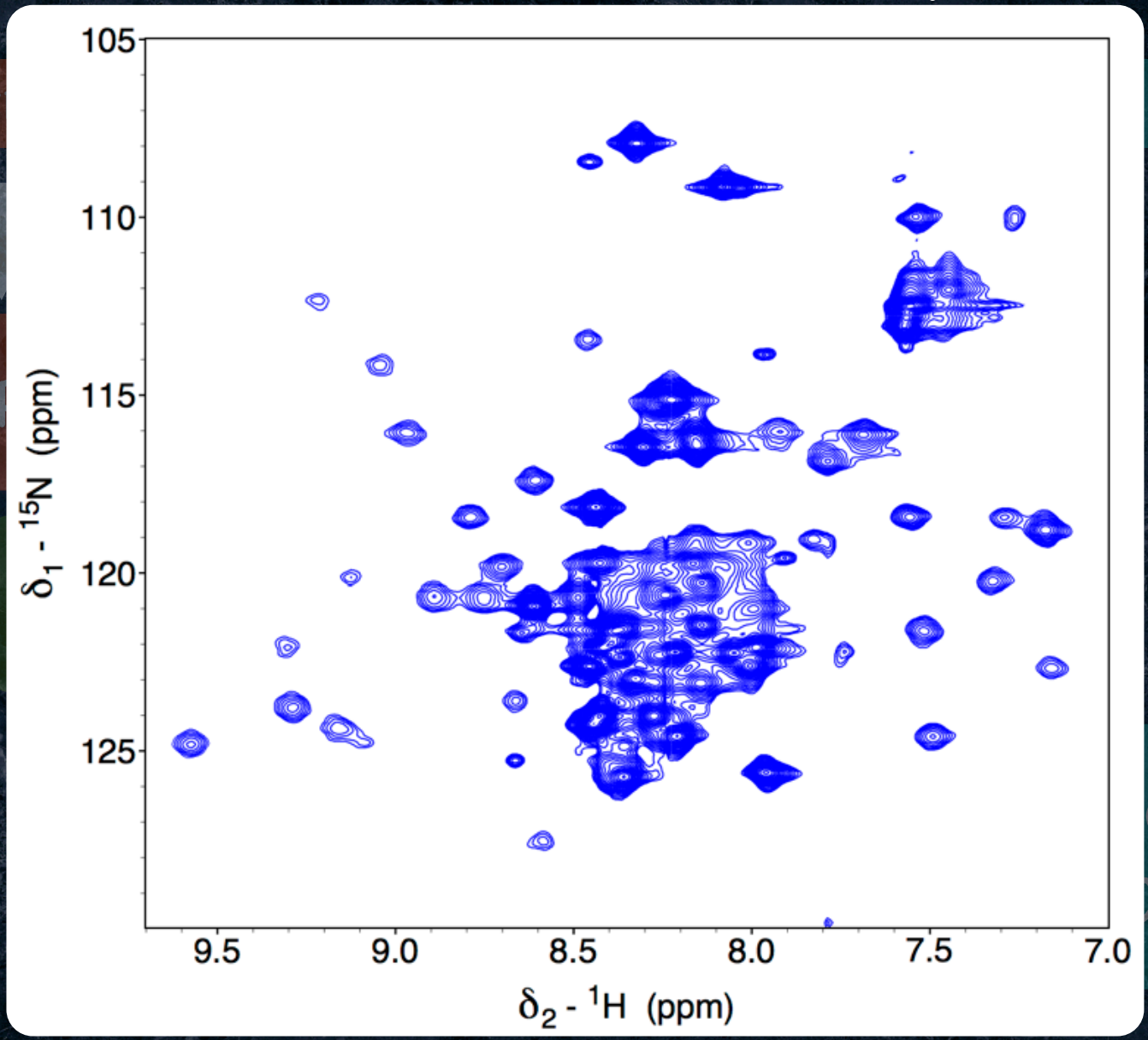
QPET



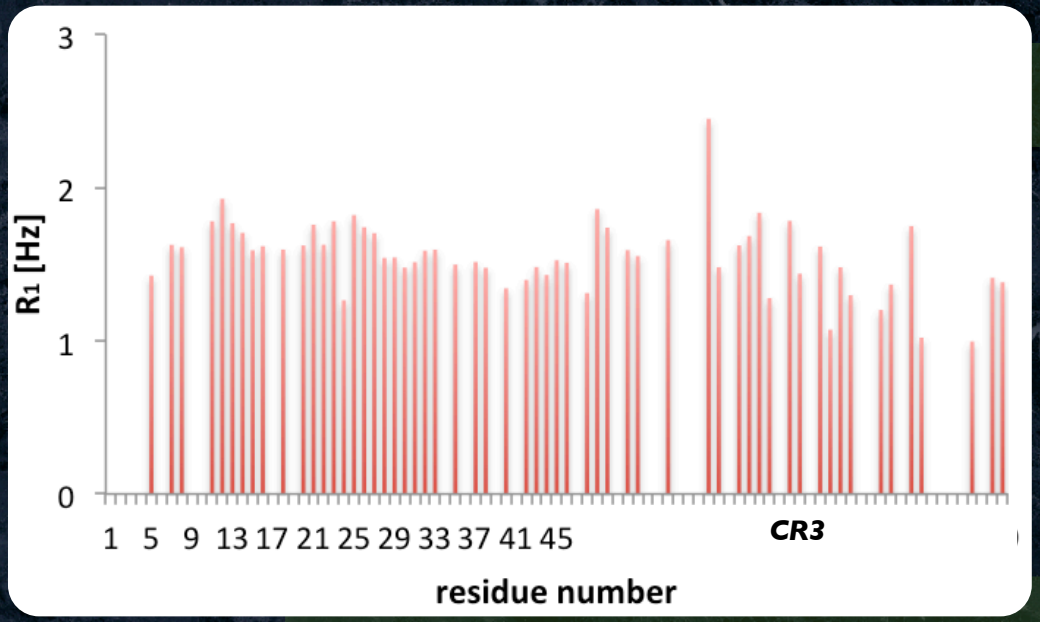
HN-H_2O exchange rates

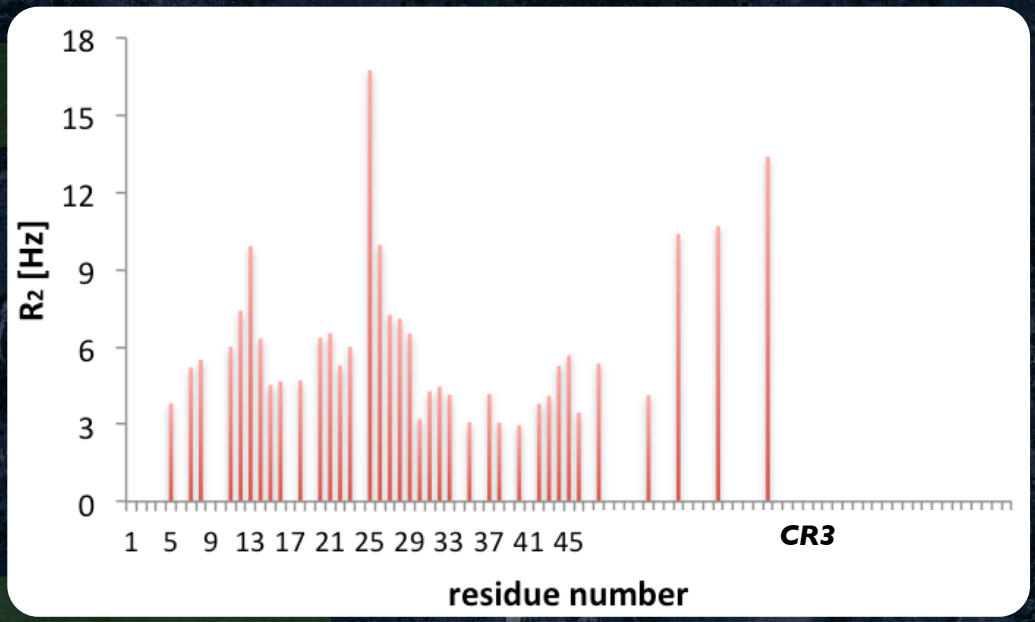


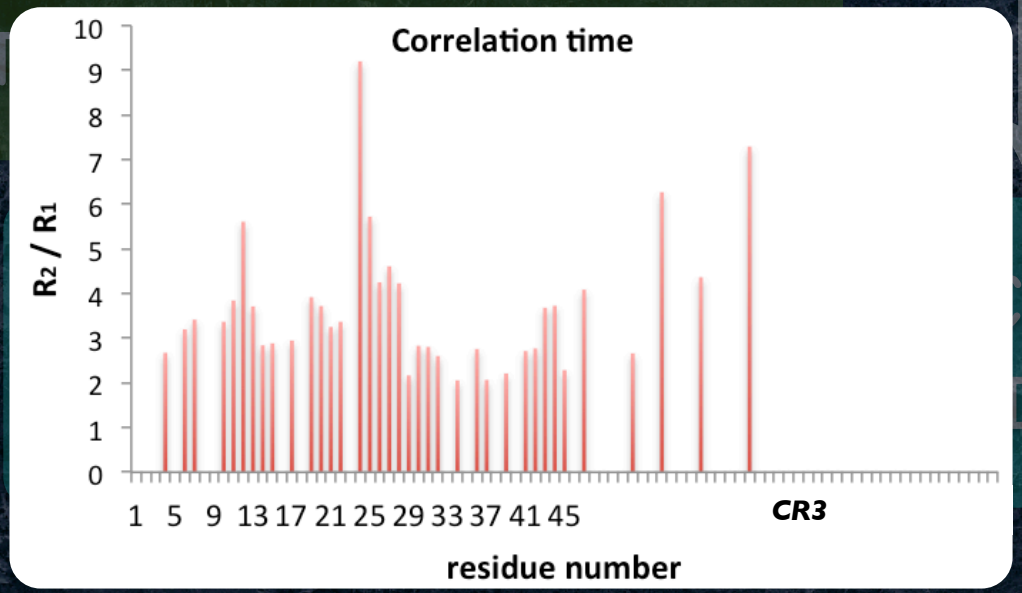
HPV 16 E7 oncoprotein



^{15}N relaxation experiments







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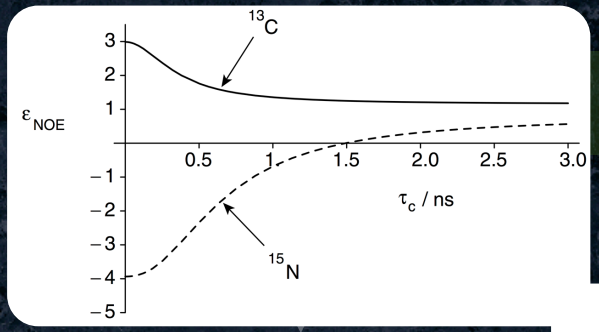
$^{1}H-^{15}N$ heteronuclear NOE

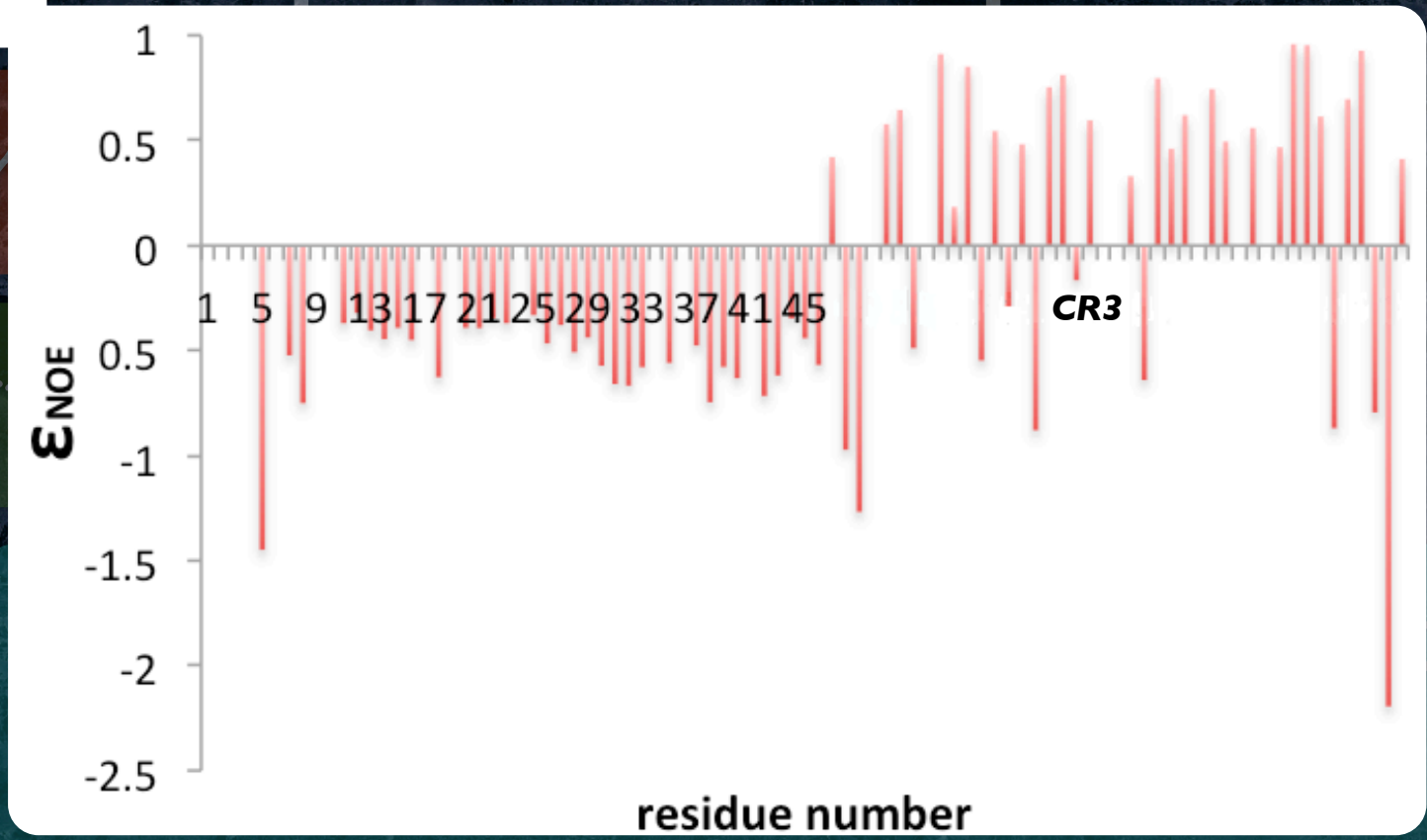


CR2

CR3

MHGDTPTLHEY

QPETT



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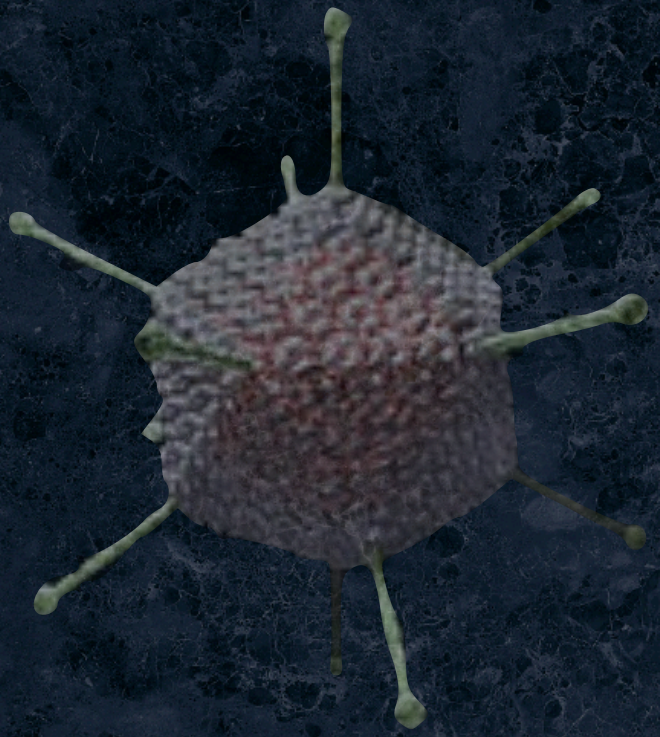
Adenovirus

- non-enveloped dsDNA virus
- involved in many infections:
  - acute respiratory
  - gastrointestinal
  - ocular
- can induce cancer, but also suppress tumorigenicity



Pelka, P. et al.(2008). Intrinsic Structural Disorder in Adenovirus E1A: a Viral Molecular Hub Linking Multiple Diverse Processes. Journal of Virology, 82(15), 7252–7263.

Adenovirus E1A protein

- can induce cancer (rodent)
- but also suppress tumorigenicity (human)
- around 50 known binding partners
- two main forms (289AA and 243 AA)

Pelka et al. (2008). Intrinsic Structural Disorder in Adenovirus E1A: a Viral Molecular Hub Linking Multiple Diverse Processes. Journal of Virology, 82(15), 7252–7263.

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AdV 2/5 289R E1A protein

MRHIICHGGVITEEMAASLLDQLIEEVLADNLPPPSHFEPPTLHELYDLDVTAP

EDPNEEAVSQIFPESVMLAVQEGIDLFTFPPAPGSPEPPHLSRQPEQPEQRAL

GPVSMPNLVPEVIDLTCHEAGFPPSDDEDEEGEEFVLDYVGHPGHGCRSCHYH

RRNTGDPDIMCSLCYMRTCGMFVYSPVSEPEPEPEPEPEPARPTRRPKLVPAIL

RRPTSPVSRECNSSTDSCDSGPSNTPPEIHPVVPLCPIKPVAVRVGGRRQAVE

CIEDLLNEPGQPLDLSCKRPRPLEHHHHHH

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AdV 2/5 289R E1A protein

MRHIICHGGVITEEMAASLLDQLIEEVLADNLPPPSHFEPPTLHELYDLDVTAP

EDPNEEAVSQIFPESVMLAVQEGIDLFTFPPAPGSPEPPHLSRQPEQPEQRAL

GPVSMPNLVPEVIDLTCHEAGFPPSDDEDEEGEEFVLDYVGHPGHGCRSCHYH

RRNTGDPDIMCSLCYMRTCGMFVYSPVSEPEPEPEPEPEPARPTRRPKLVPAIL

RRPTSPVSRECNSSTDSCDSGPSNTPPEIHPVVPLCPIKPVAVRVGGRRQAVE

CIEDLLNEPGQPLDLSCKRPRPLEHHHHHH

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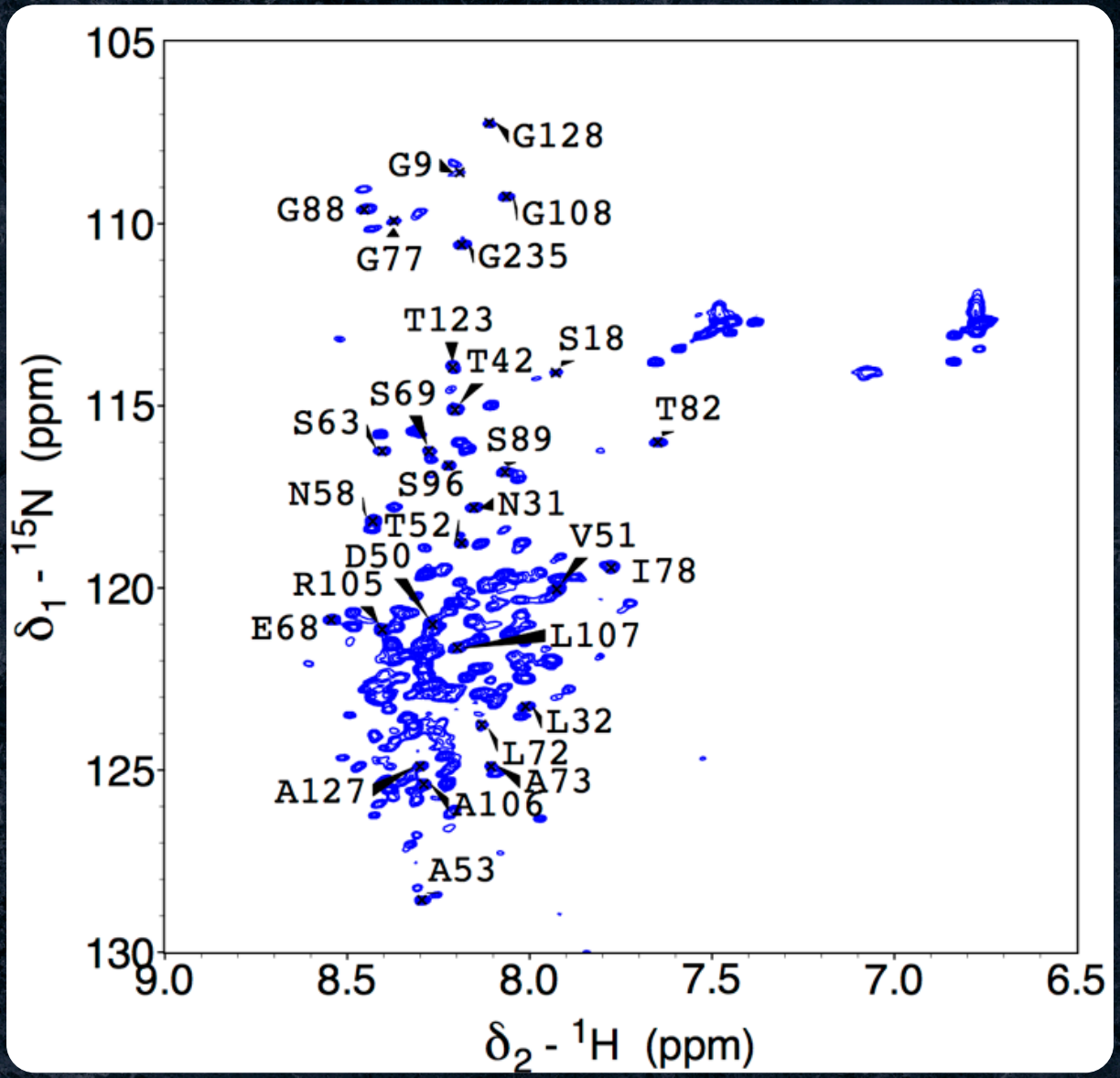
AdV 2/5 289R E1A protein



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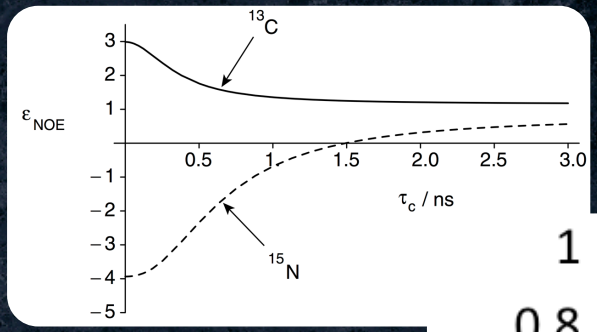
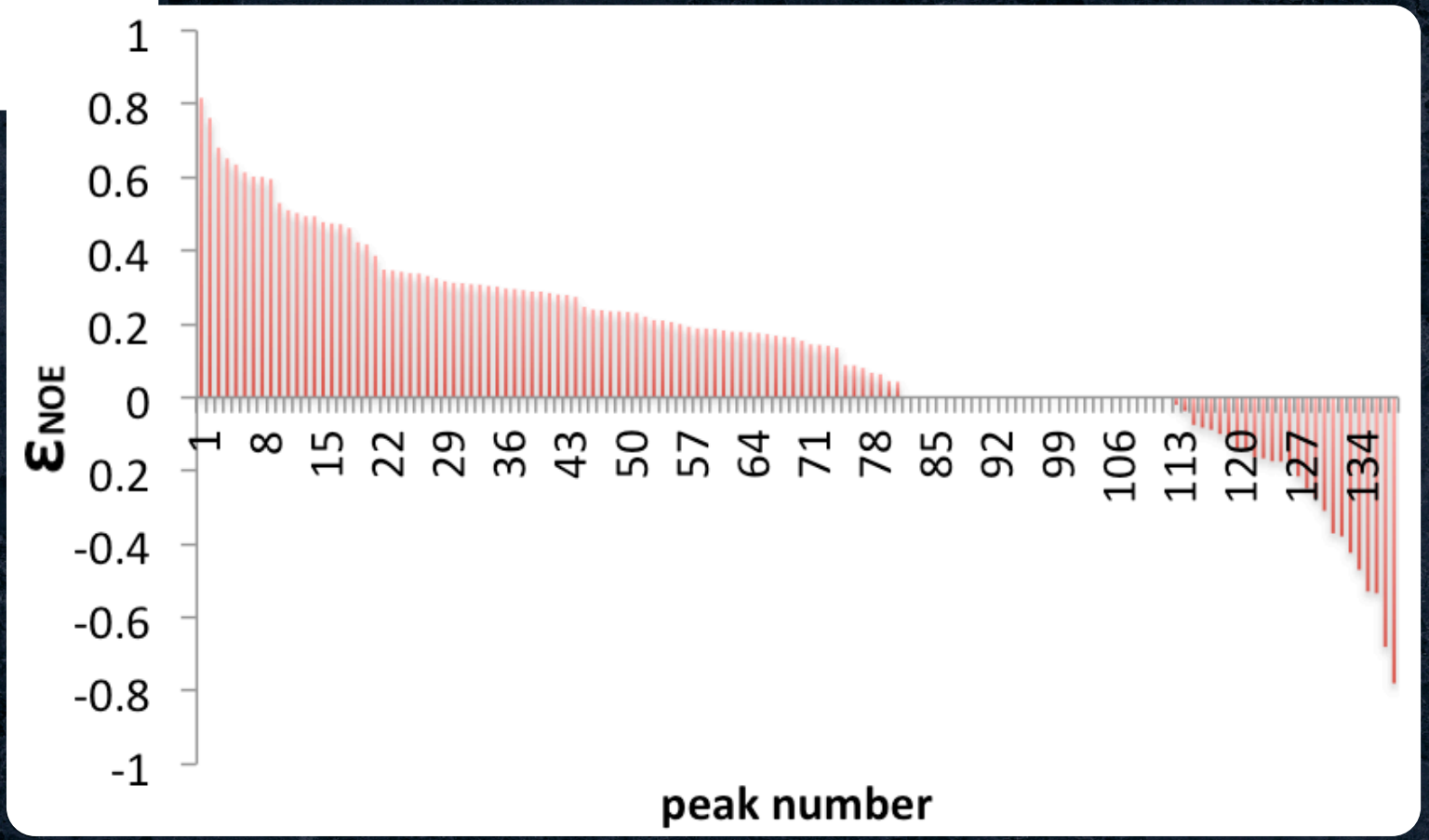
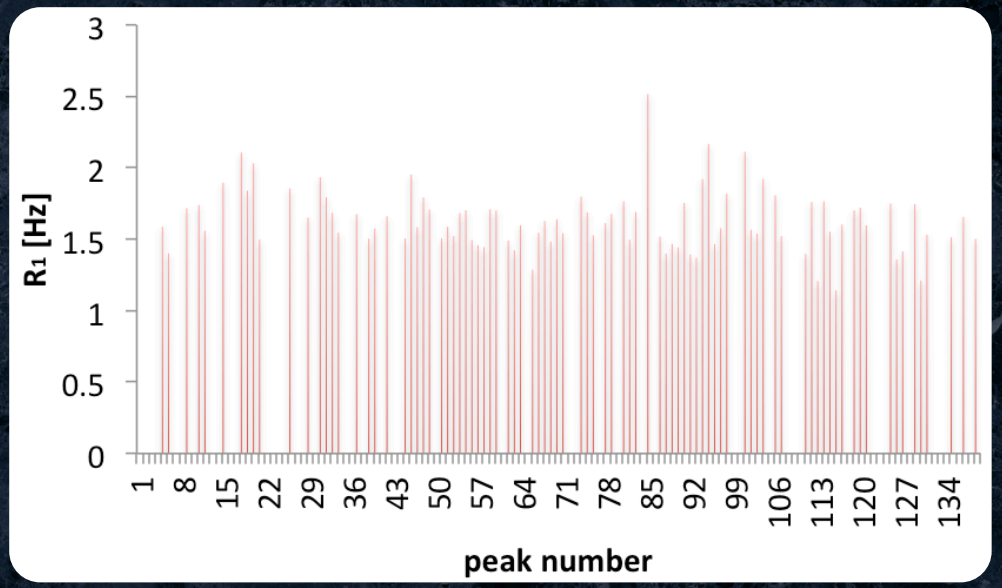
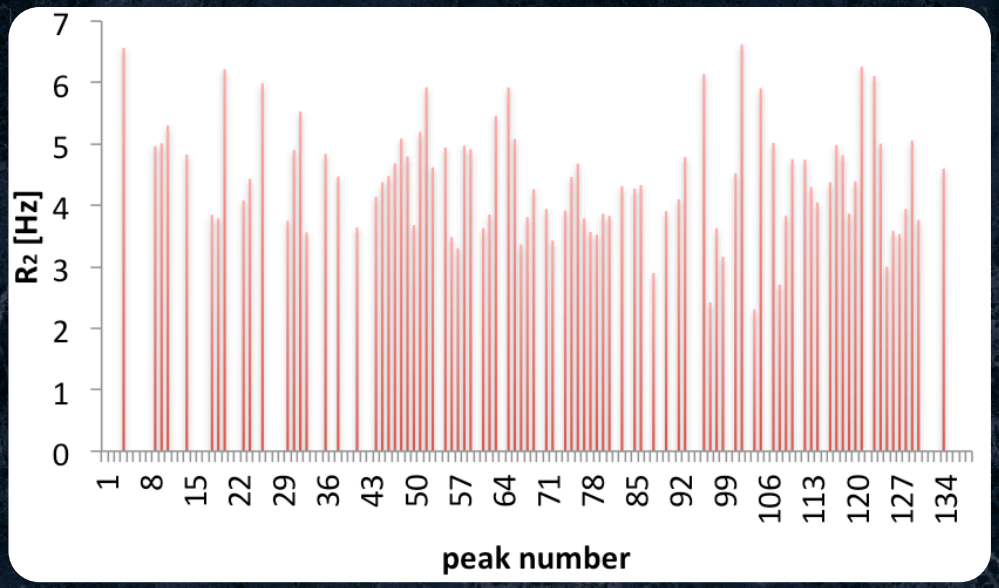
$^{1}H-^{15}N$ heteronuclear NOE

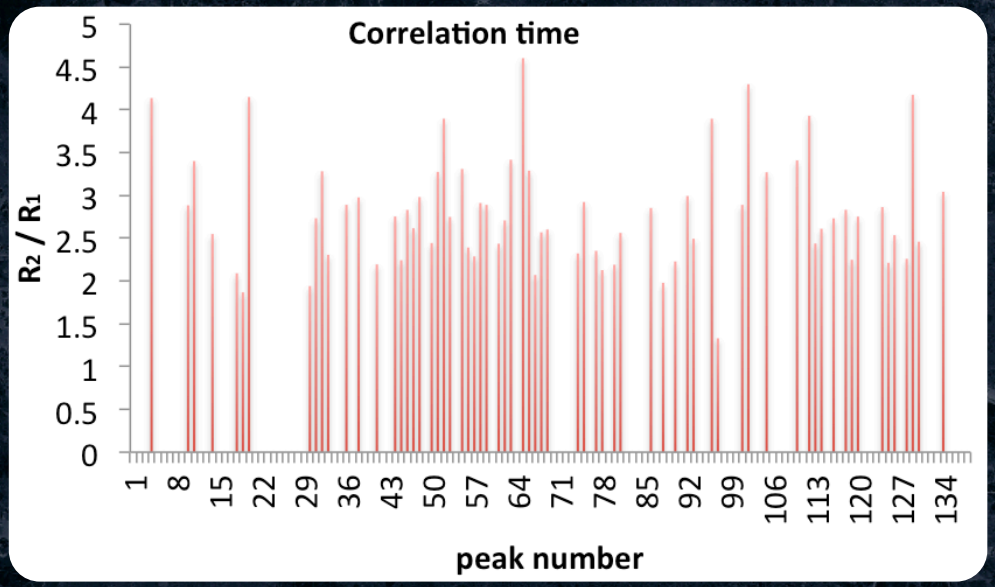




^{15}N relaxation experiments







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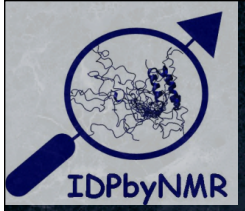
Acknowledgement

- prof. Isabella C. Felli, prof. Roberta Pierattelli
- Eduardo Calçada
- CERM
- IDPbyNMR



Thank you!

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