Cell Communication III:
Steroid Hormones

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10/12/10

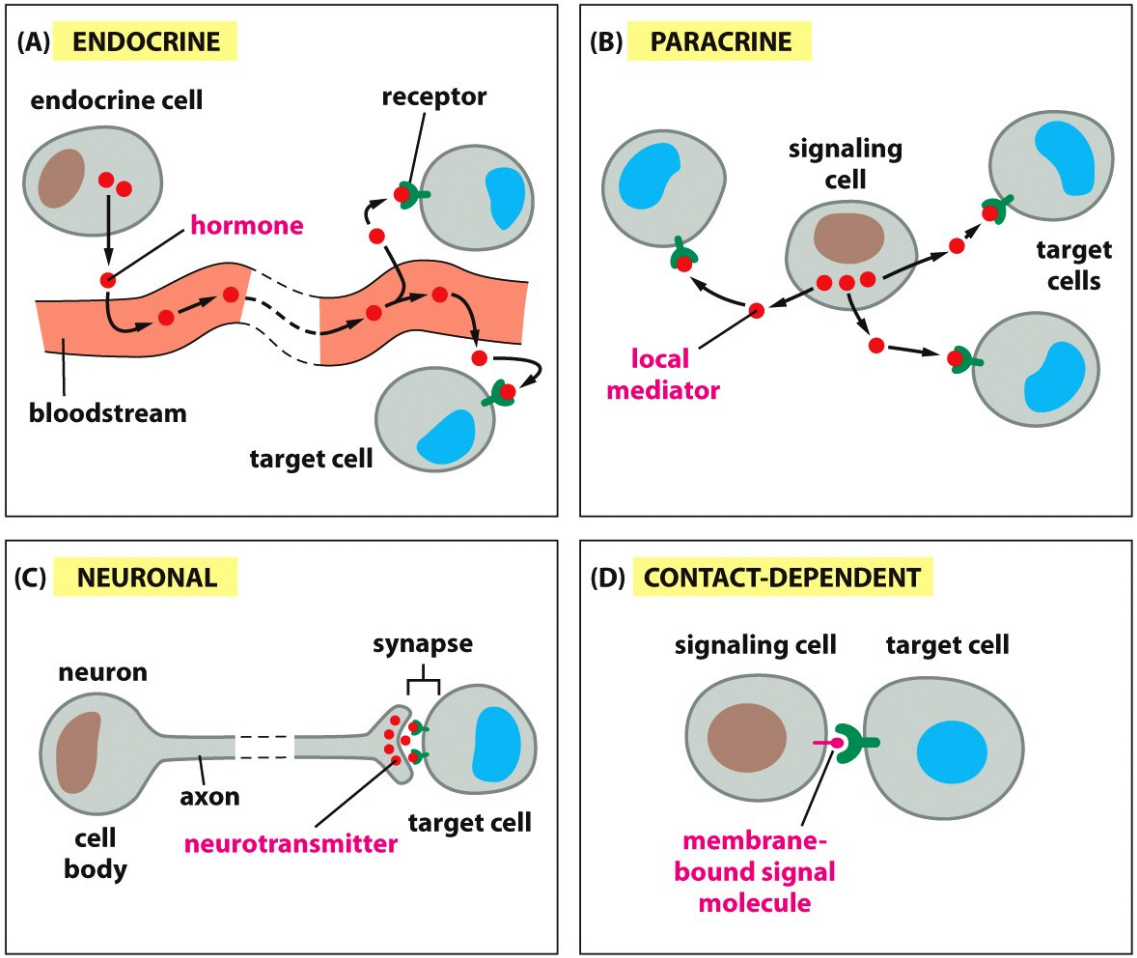
Cell Communication Review

- Small Molecules
  - Example molecule?
  - What are its chemical characteristics?

- Peptides and Proteins
  - Example hormone?
  - Characteristics of this peptide hormone?

Cell Communication Review II

- How do these signals get around?

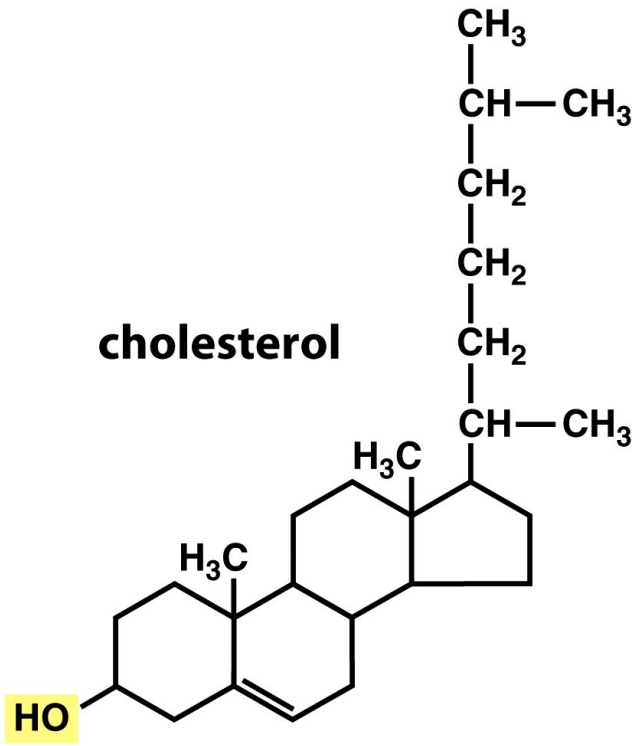


Steroid Hormones

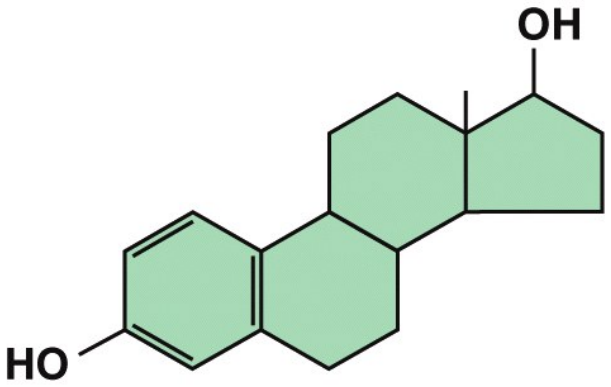
- Different class of hormone
  - Structure
  - Transport
  - Receptors
  - Function

  - Estrogen will be the model steroid hormone for this lecture
  - Contrast to Insulin and NO

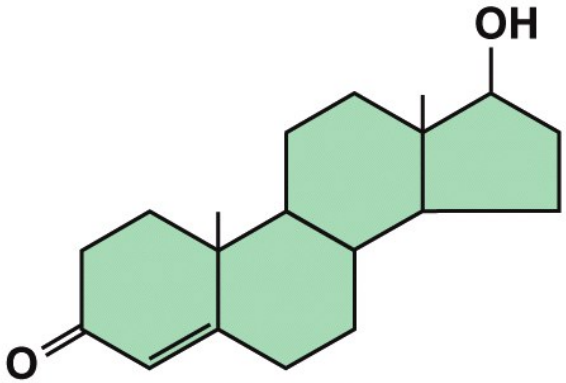
Derived from Cholesterol



cholesterol



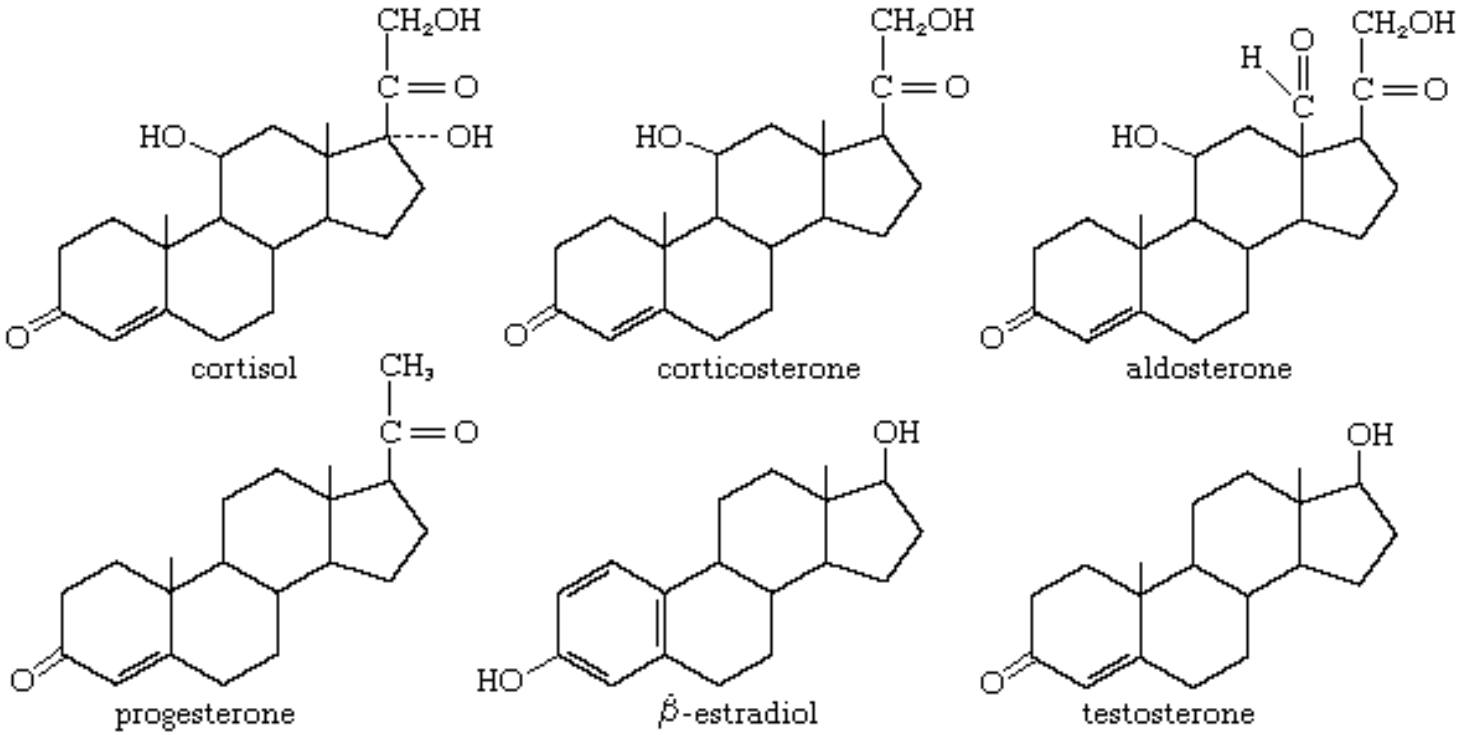
estradiol



testosterone

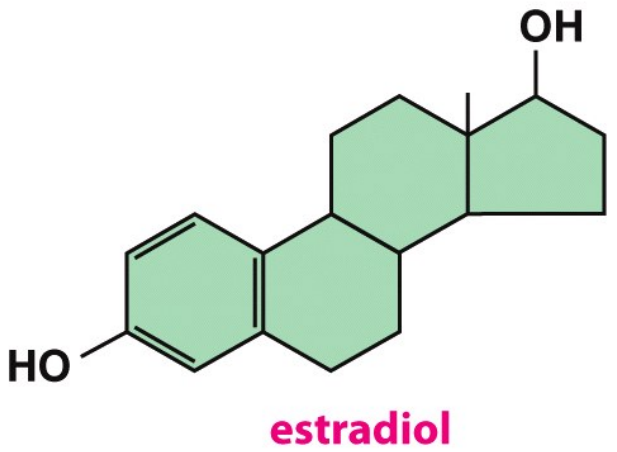
Steroid Hormones

- Generally:
  - Considered small molecules
  - Very similar chemical structures
  - Fundamentally _____

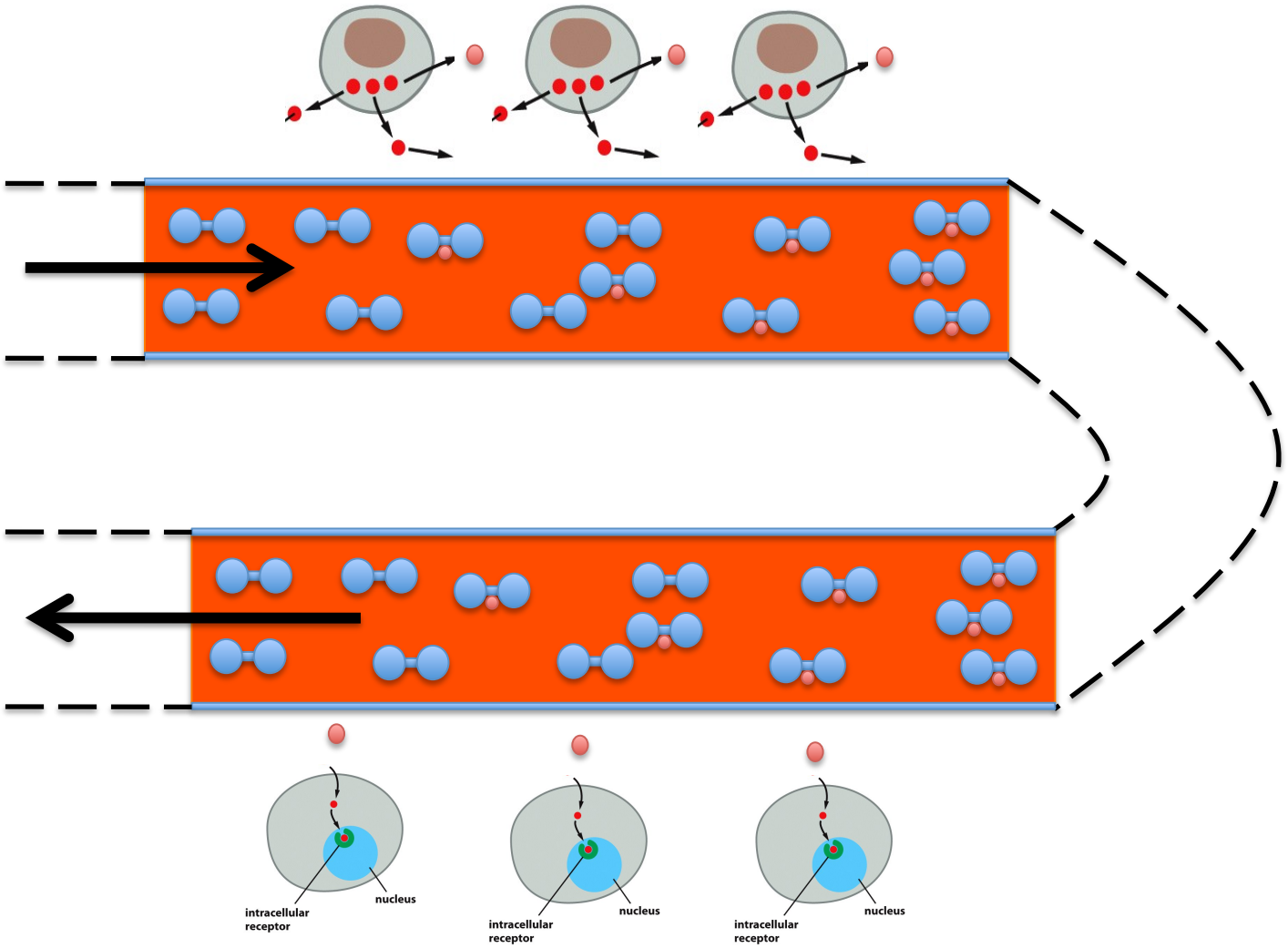


Consequences of Hydrophobic Hormones

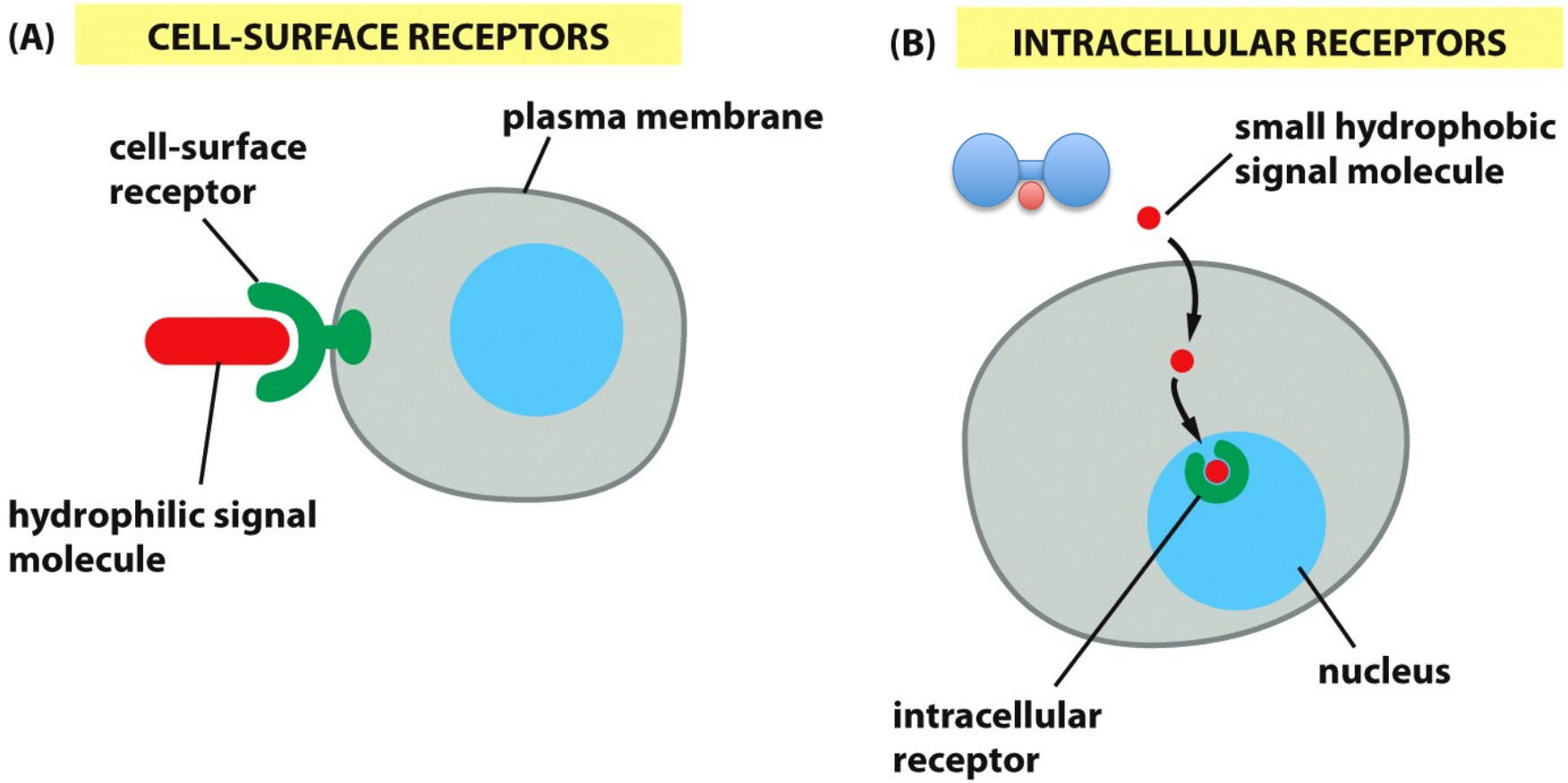
- Solubility in water?
- Solubility in lipid membrane?
- How does this affect its transportation in blood?



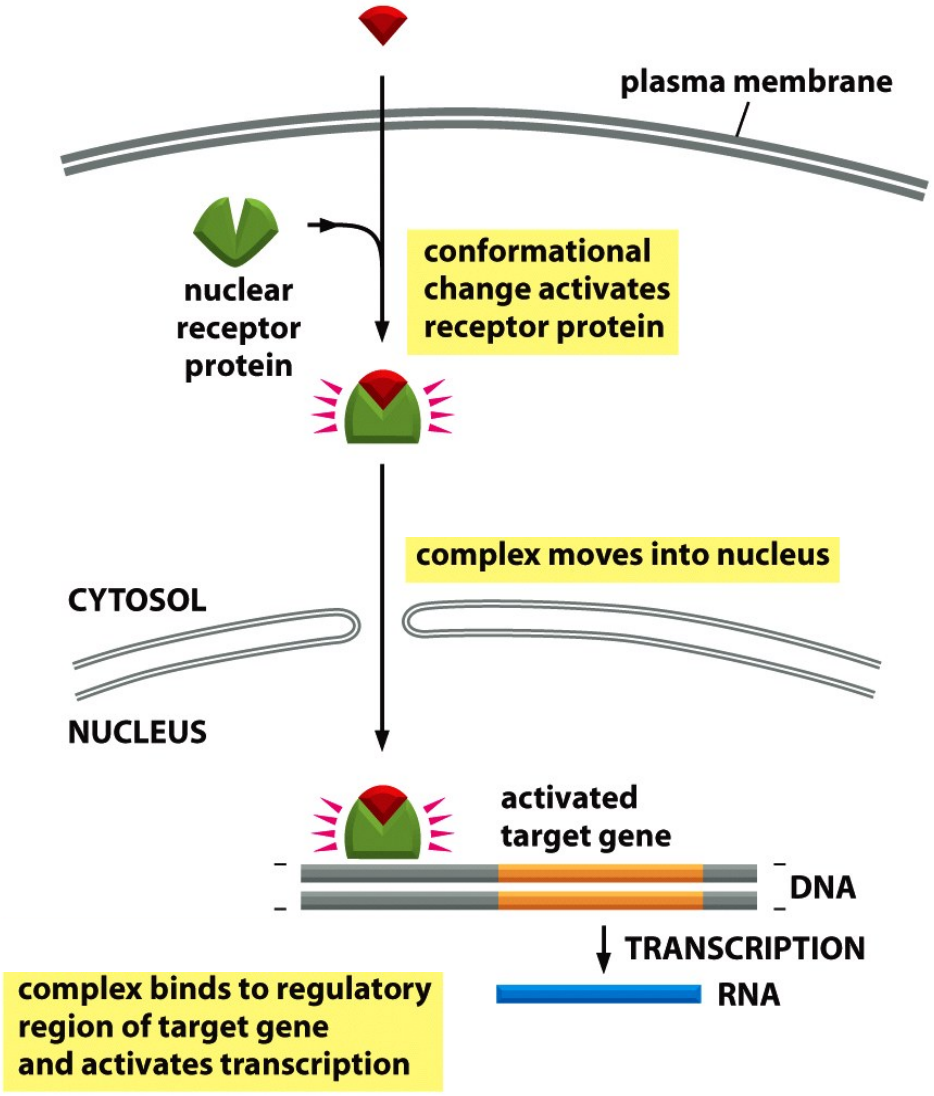
Steroid Hormones catch a ride on Carrier Proteins



How are receptors different?



Basic Nuclear Receptor Activation



Lets get specific:
The Estrogen Receptor

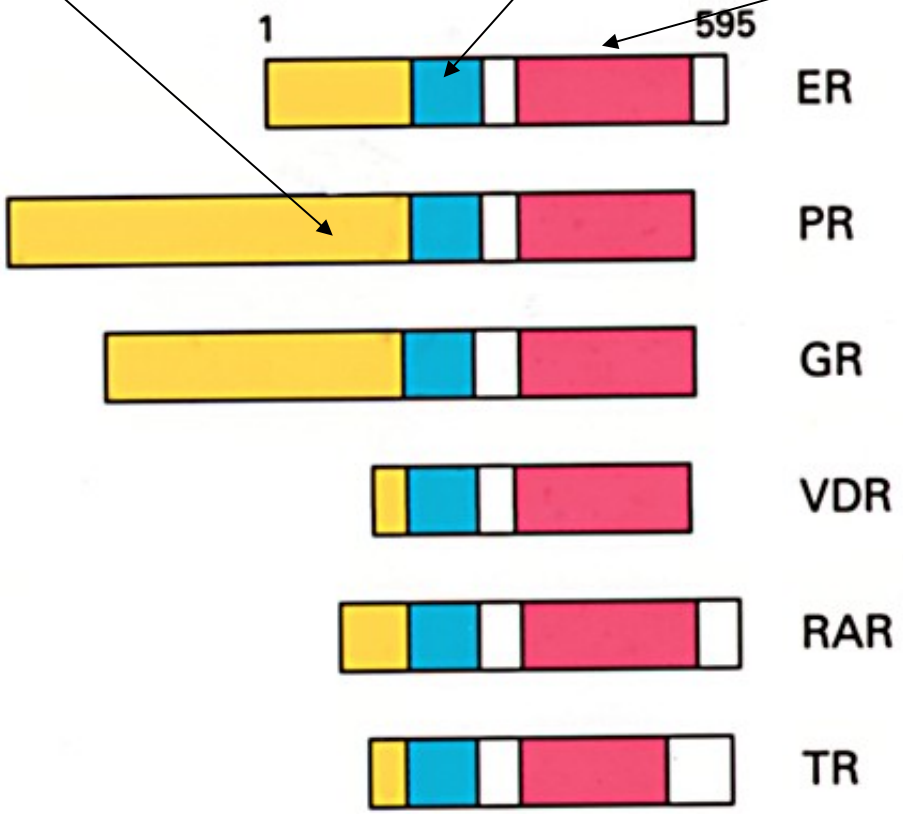
- A nuclear receptor
- Binds Estrogen and affects DNA transcription
- Changes pattern of gene expression
- Affect on organism is slow (minutes to days)

Nuclear Receptor Subfamily

Yellow shows the highly variable activation domain

Blue shows the highly conserved DNA binding domain- ~66 amino acids

Red shows the hormone binding domain



estrogen receptor

glucocorticoid receptor

RCSB Protein Data Bank - Structure Summary for 1A52 - ESTROGEN RECEPTOR ALPHA LIGAND-BINDING DOMAIN COMPLEXED TO ESTRADIOL

http://www.rcsb.org/pdb/explore/explore.do?structureId=1A52

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ESTROGEN RECEPTOR ALPHA LIGAND-BINDING DOMAIN COMPLEXED TO ESTRADIOL

1A52

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DOI:10.2210/pdb1a52/pdb

Primary Citation

Crystallographic comparison of the estrogen and progesterone receptor's ligand binding domains.

Tanenbaum, D.M., Wang, Y., Williams, S.P., Sigler, P.B.

Journal: (1998) Proc.Natl.Acad.Sci.USA **95:** 5998-6003

PubMed: 9600906
PubMedCentral: PMC27574
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PubMed Abstract:

The 2.8-A crystal structure of the complex formed by estradiol and the human estrogen receptor-alpha ligand binding domain (hERalphaLBD) is described and compared with the recently reported structure of the progesterone complex of the human progesterone receptor ligand binding domain,...

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Molecular Description Hide

Classification: Receptor
Structure Weight: 60742.57

Molecule: ESTROGEN RECEPTOR
Polymer: 1 **Type:** polypeptide(L) **Length:** 258
Chains: A, B
Fragment: LIGAND-BINDING DOMAIN

Source Hide

Polymer: 1

Scientific Name: Homo sapiens Taxonomy **Common Name:** Human **Expression System:** Escherichia coli

Ligand Chemical Component Hide

Identifier	Name	Formula	Binding Affinity (BindingDB)	Interaction View
AU	GOLD ION	Au		Ligand Explorer
EST	ESTRADIOL	$C_{18}H_{24}O_2$	EC50 : 0.007 - 5.7 nM IC50 : 0.5 - 570 nM Kd : 0.2 - 0.87 nM Ki : 0.113 - 100 nM	Ligand Explorer

Biological Assembly 1

More Images...

View in Jmol SimpleViewer
Other Viewers Protein Workshop

Biological assembly 1 assigned by authors and generated by PISA (software)

Deposition Summary Hide

Authors: Tanenbaum, D.M., Wang, Y., Sigler, P.B.

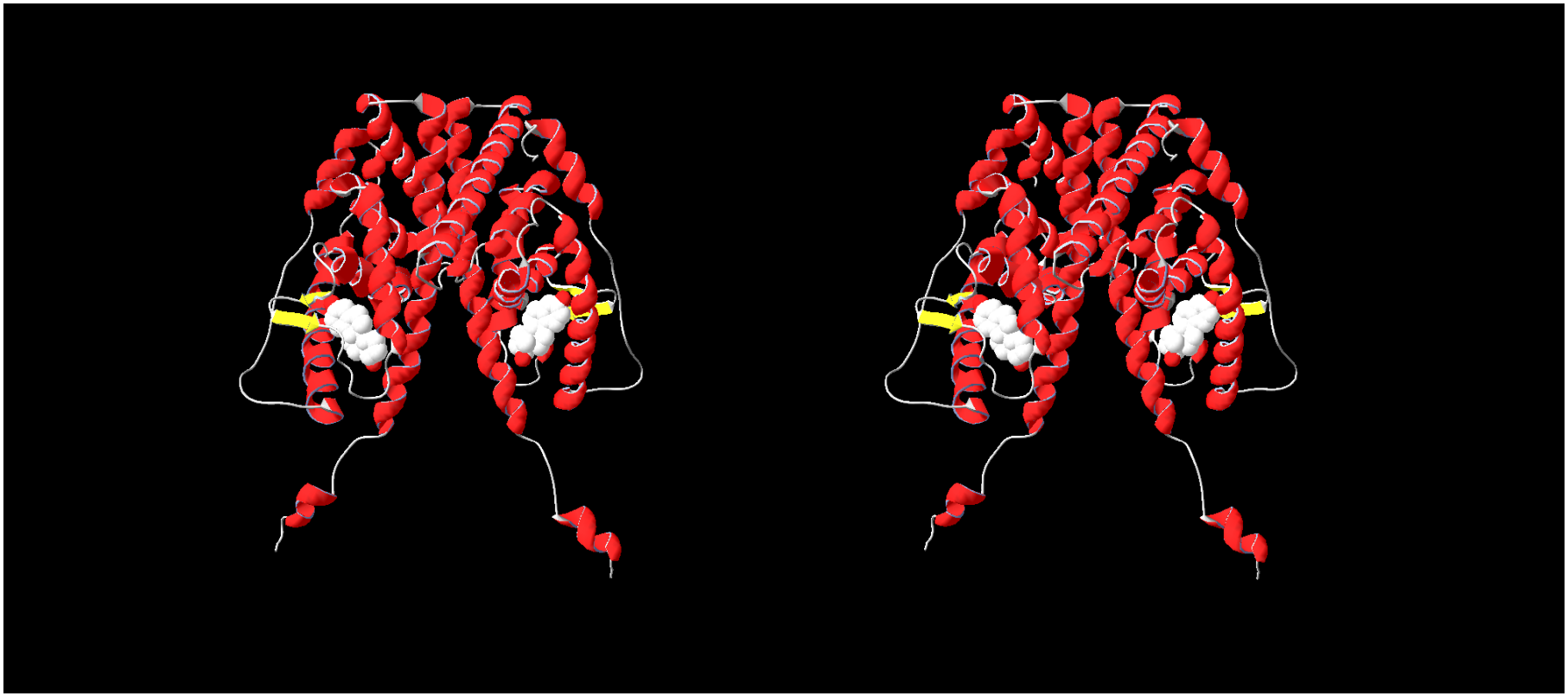
Deposition:	1998-02-19
Release:	1998-09-16
Last Modified (REVDAT):	2009-02-24

Experimental Details Hide

Method: X-RAY DIFFRACTION
Exp. Data: Structure Factors

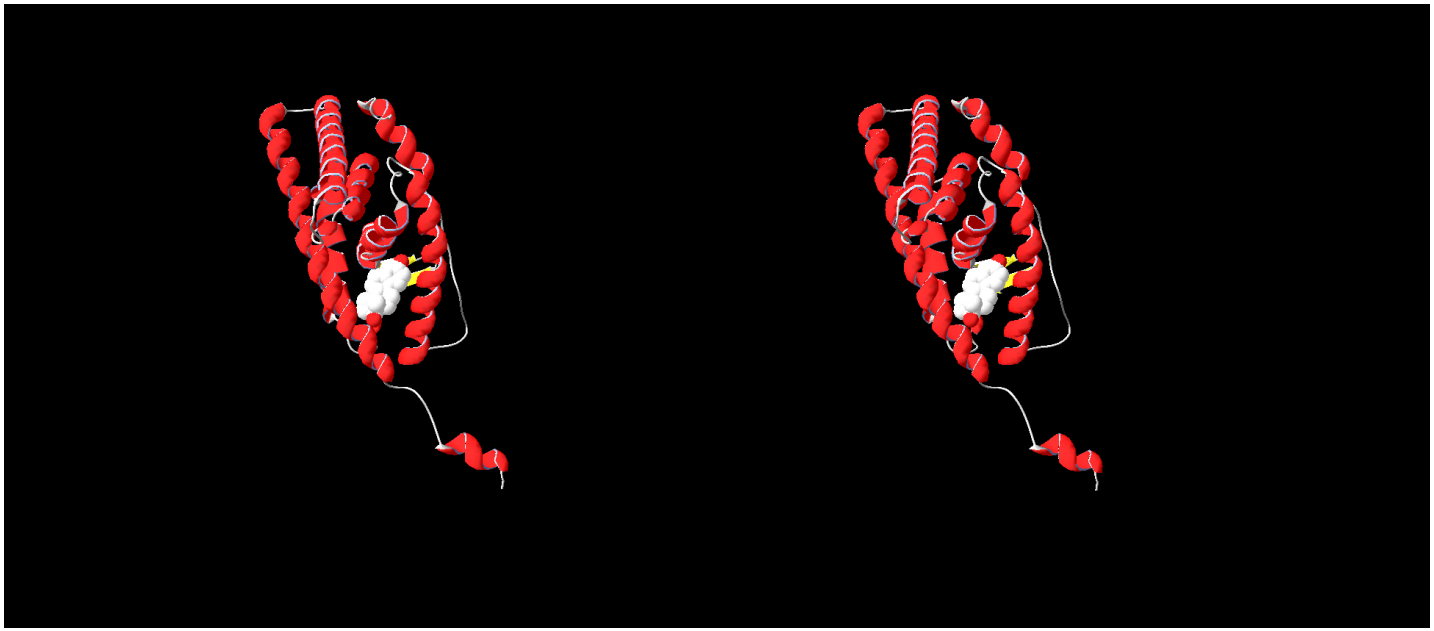
Resolution[Å]:	2.80
R-Value:	0.223 (obs.)
R-Free:	0.274
Space Group:	H 3 2
Unit Cell:	

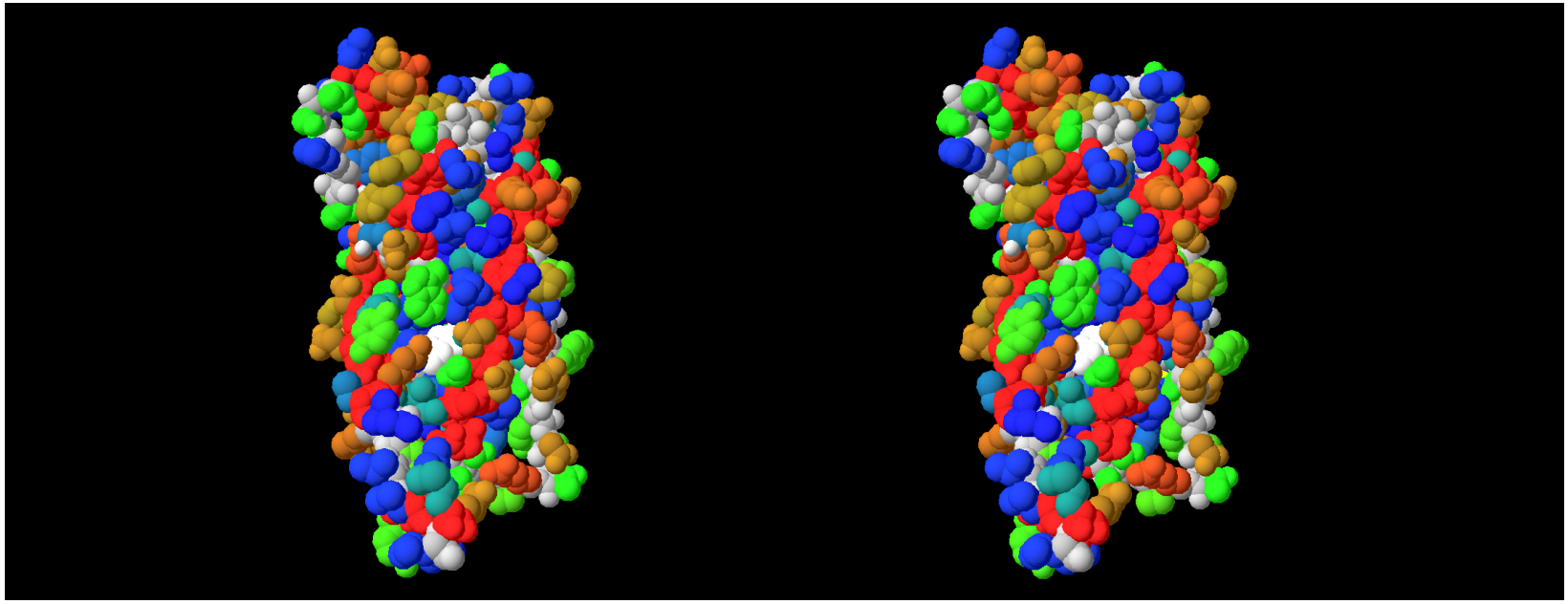
Estrogen Receptor: Ligand Bound



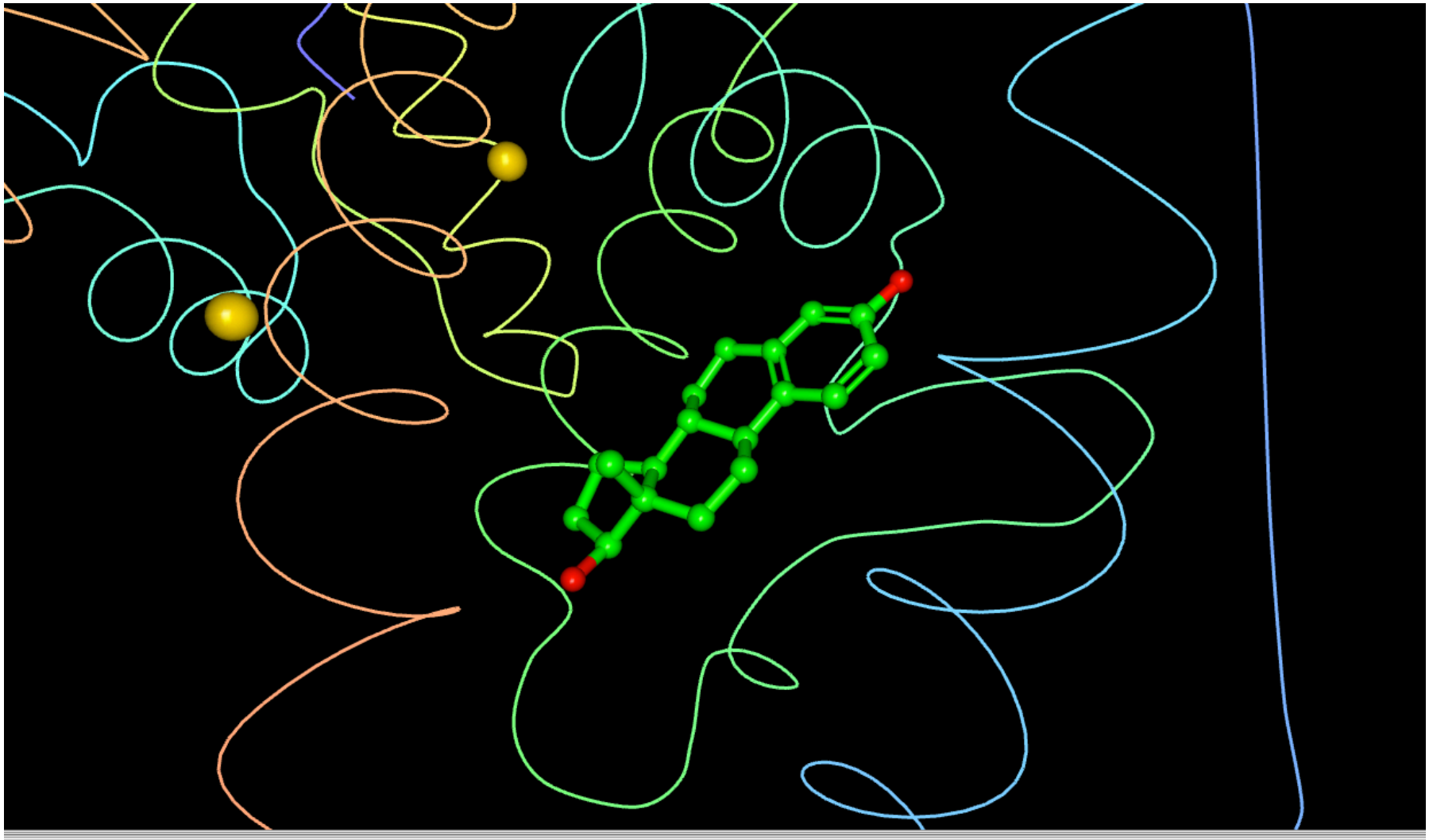
PDB # 1A52

Additional views

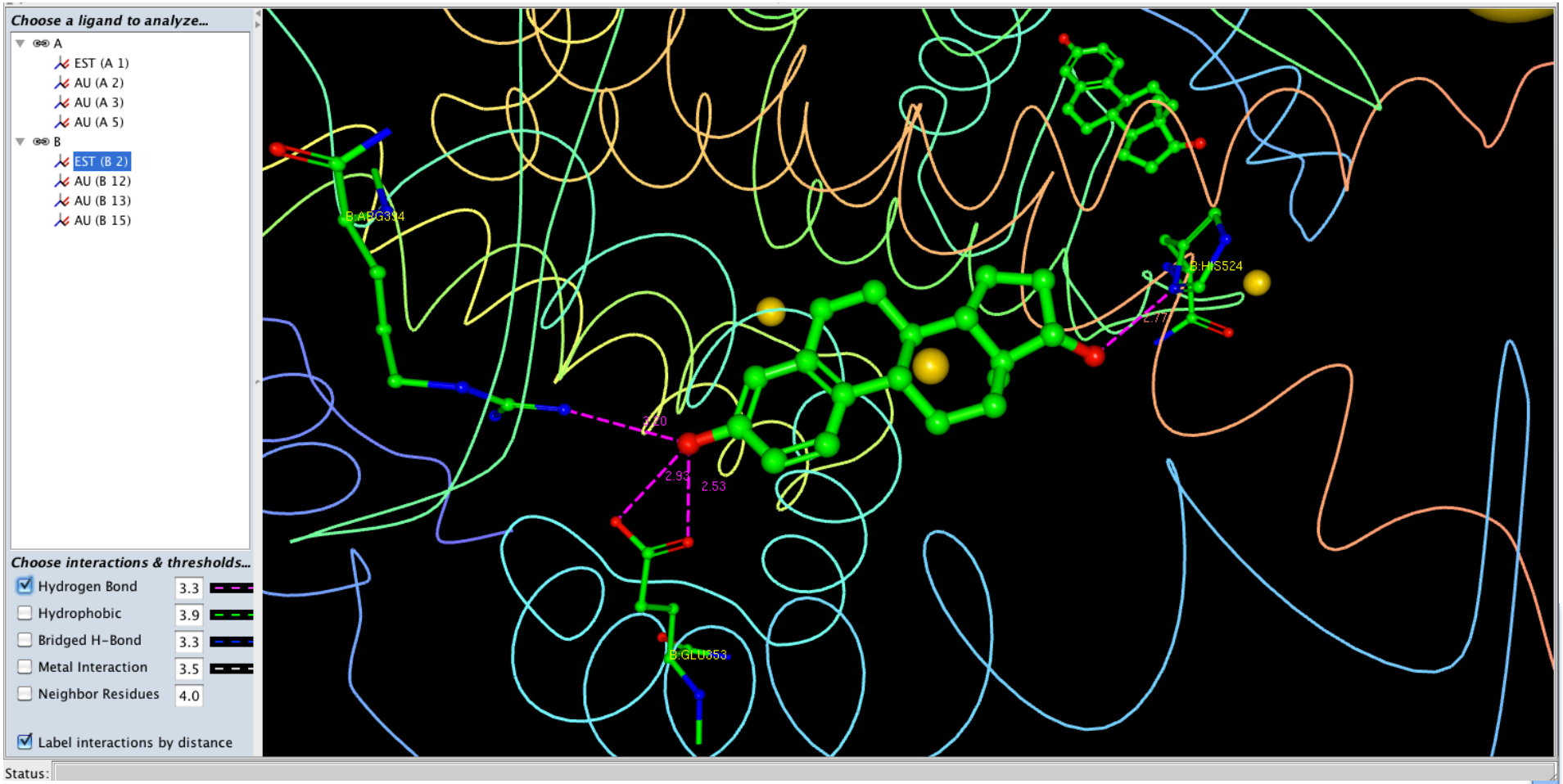




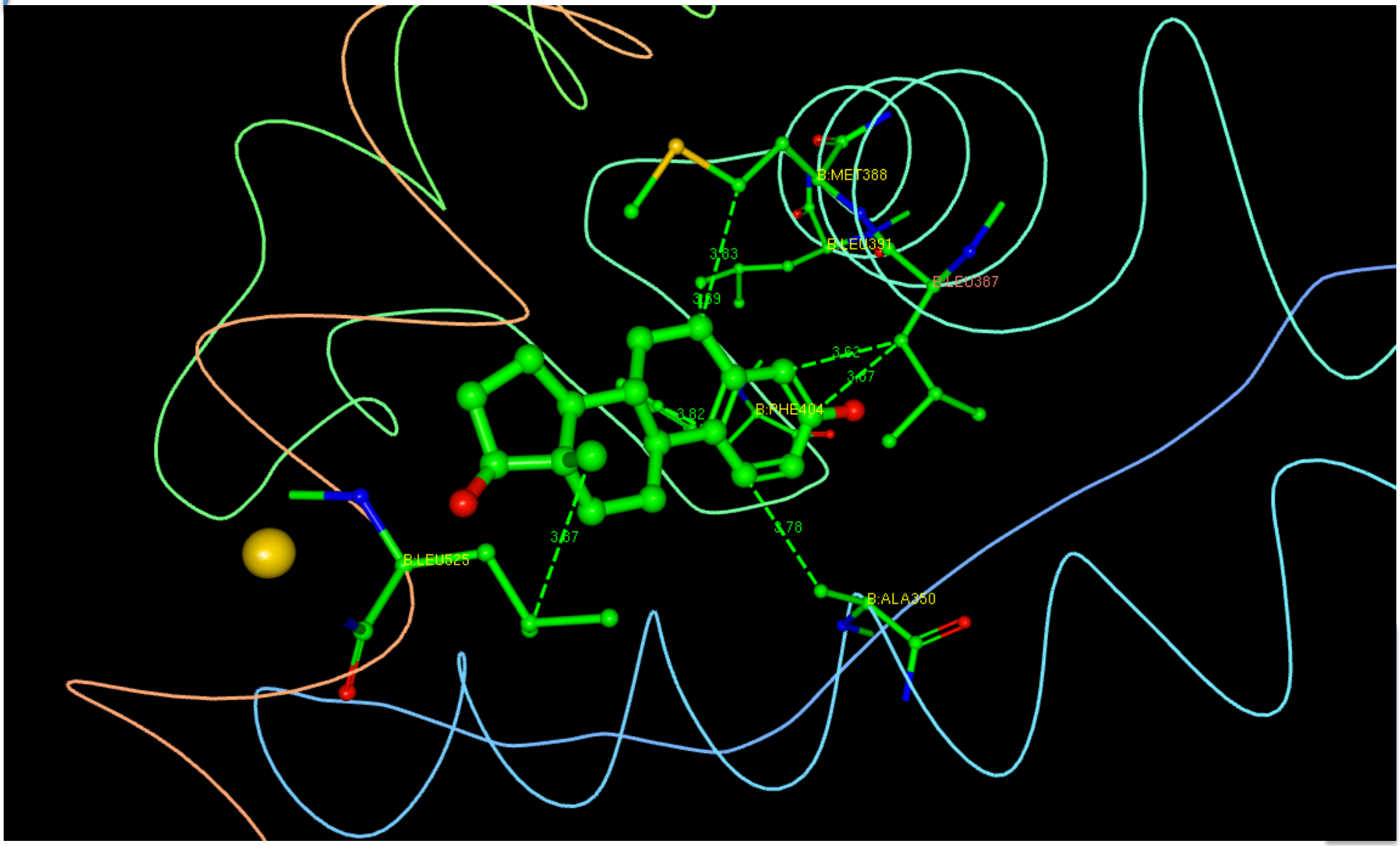
Estrogen Bound to receptor



Hydrogen Bonds

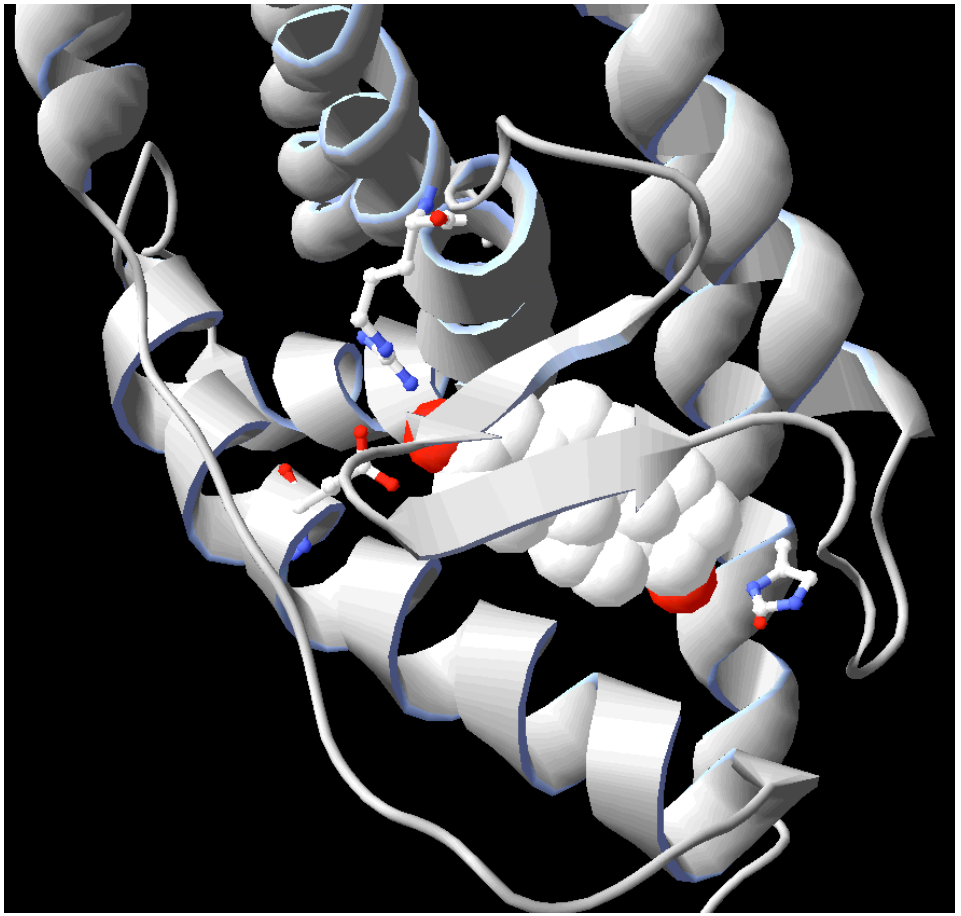


Hydrophobic Contacts



Estrogen bound to Ligand binding domain

- Deep pocket
- Specific H-bonds
- Very Hydrophobic



PDB # 1A52

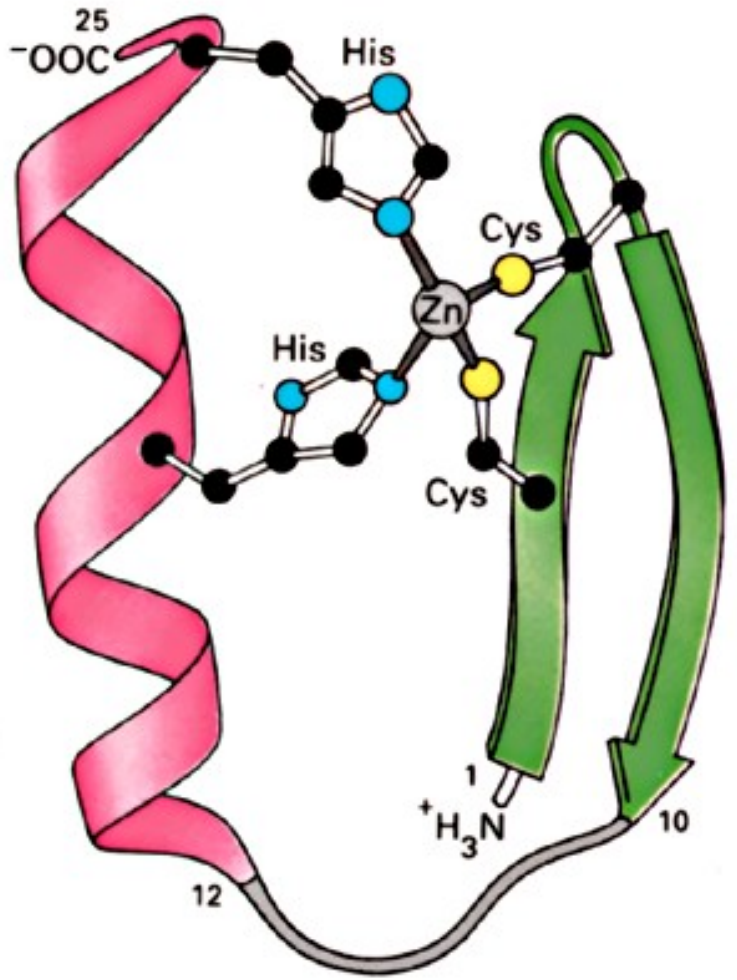
Binding Triggers Activity

- How could this happen?

- We know:
  - Only active when _____
  - One estradiol per ER monomer
  - Forms dimers
  - Ligand binding domain is connected to DNA binding domain (Not shown yet)

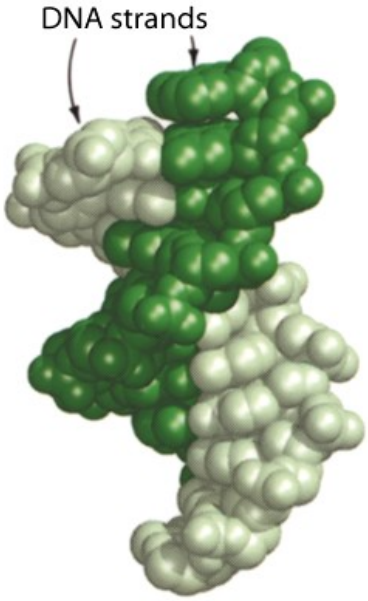
DNA Binding Domain

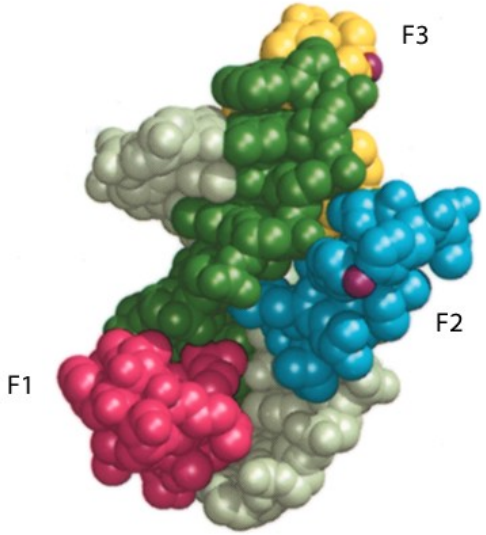
- Zn finger
- >700 genes include this fold
- Zif268, a classic Zn finger is shown here
- The _____ interacts with the DNA



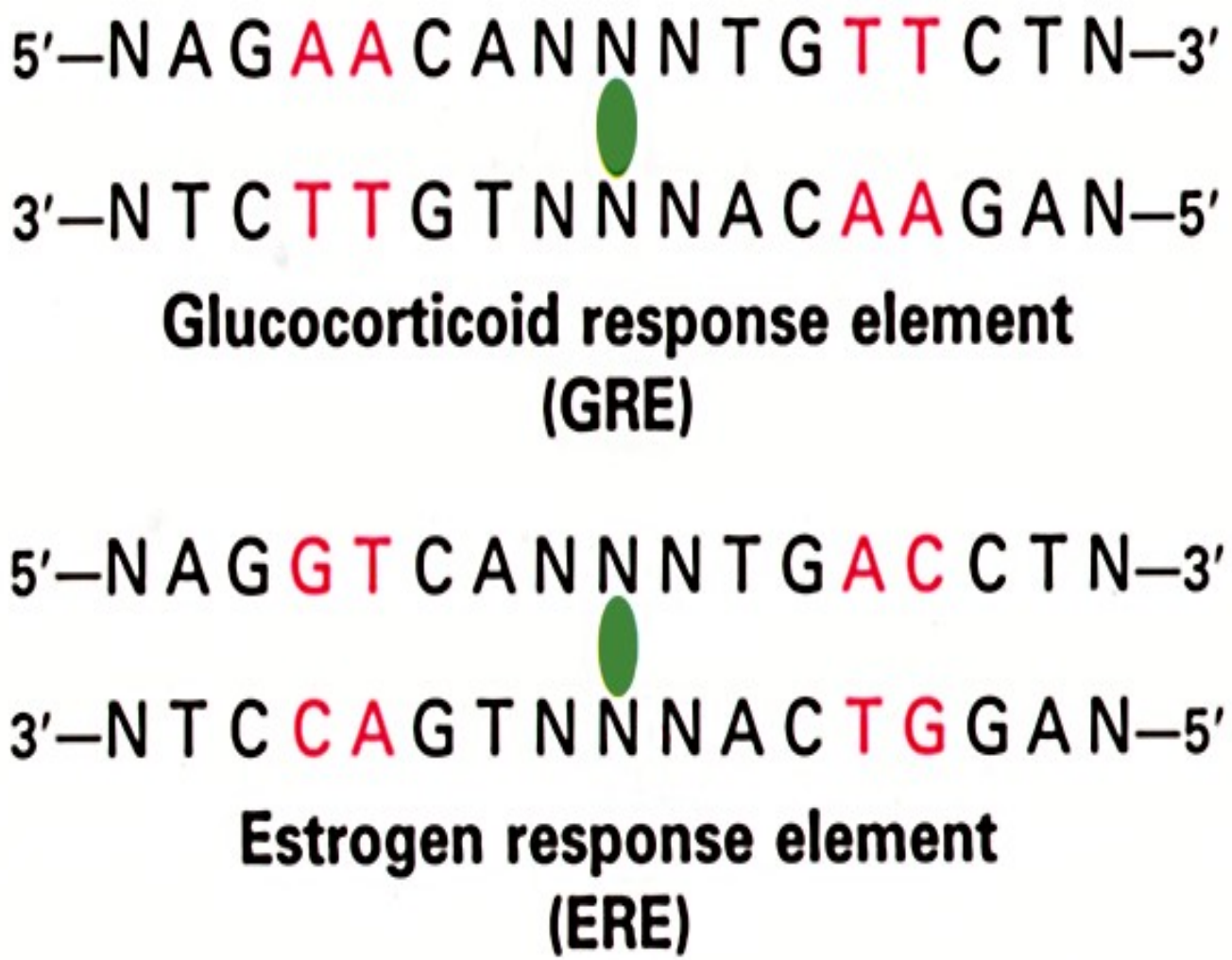
Steroid Receptors use Zn fingers

- Structural motif is highly versatile
- Proteins can have 1 to 37 of these fingers
- More fingers, longer DNA sequence recognized
- Recognition is based of non-covalent, complementarity between amino acids on helix and base pair sequence of DNA

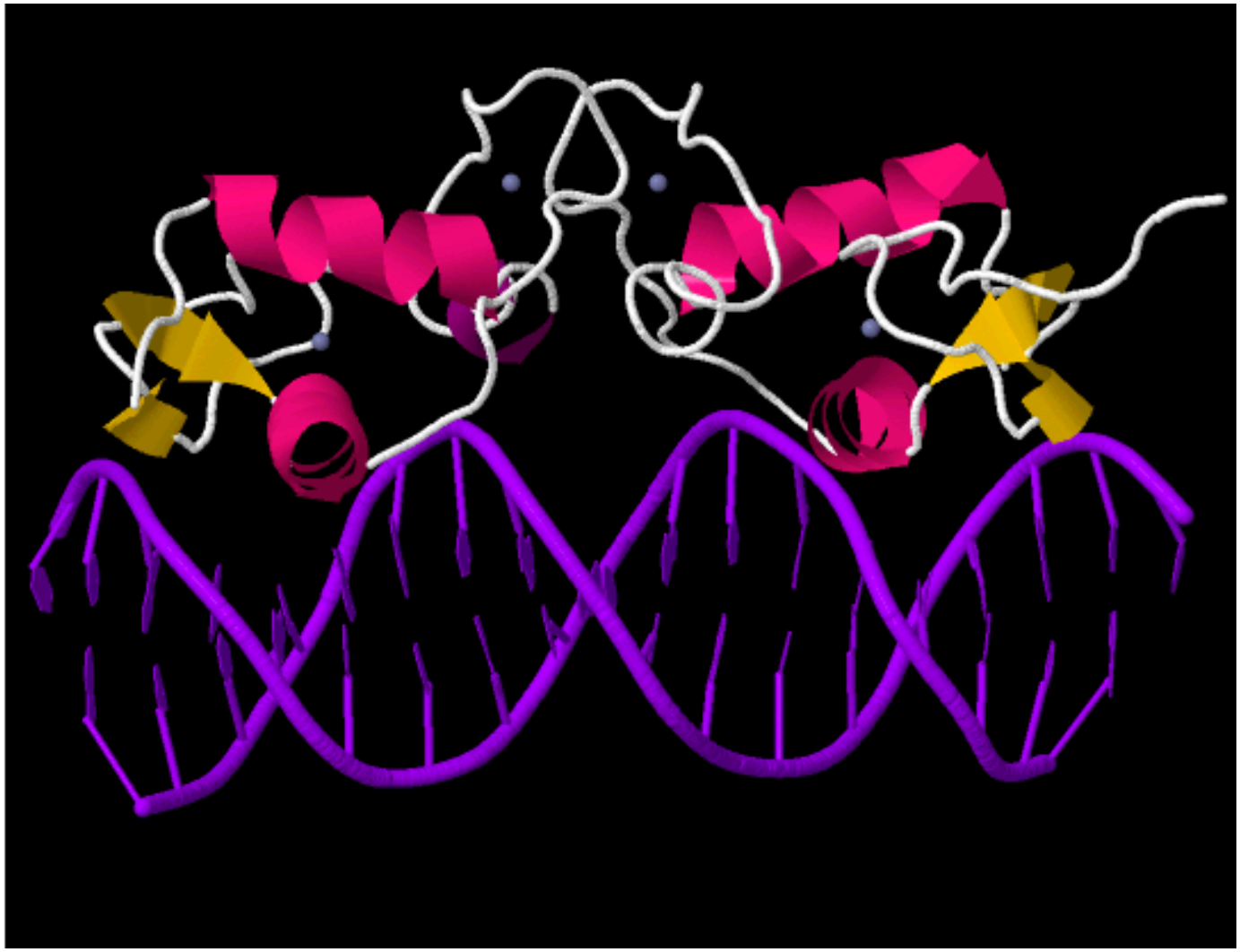




Steroid receptors recognize related DNA sequences



ER DNA binding domain



PDB 1HCQ

Un-natural Signaling?

- Non-natural non-steroidal ligands
- Environmental Estrogens
  - _____: from plants but remember plants don't have cholesterol so must be non-steroidal pathways to derivatives.
  - _____: "Other" estrogens
    - DDT (the most potent estrogenic mimic known, much stronger than estrogen)
    - Bisphenol A – Nalgen recalled its plastic water bottles due to this compound