

# **Molecular Modeling: Application to Computational Toxicology**

# Modeling the Interaction between Environmental Chemicals and Target Macromolecules

- A Computational Approach to Understanding Key Steps in the Mechanisms for Toxicity
- A Tool for Prioritization of Bioassay Requirements

# The Conundrum !!!!!

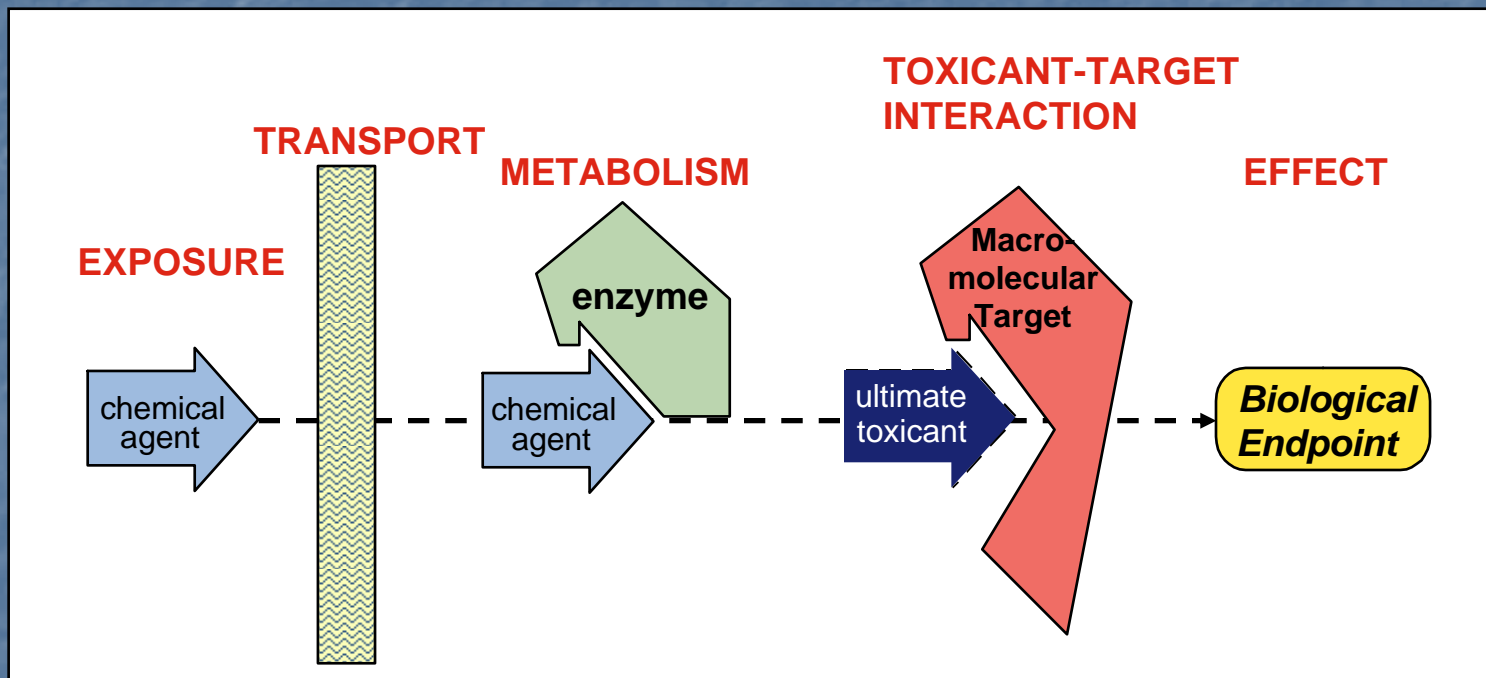
- The application of modern experimental techniques to the study of chemical toxicity has led to an explosion of data that is relevant to the risk assessment process.
- Often that data is not quite the data one would want for evaluating risk.
- How does one use the existing data to obtain the information needed and/or to determine what is the key missing information?

# Extrapolations for Evaluating the Risk Posed by Chemicals

- High Dose to Low Dose
- Route of Exposure to Route of Exposure
- Chemical to Chemical
- Species to Species
- Population Characteristics
  - Sensitive subpopulations
  - Life Stages
- Complex Exposure
  - Dose regime
  - Mixtures of Chemicals

**Knowledge of the Mechanism  
of Toxicity Often Provides a  
Rational Basis for Extrapolation**

# Elements of Toxicity Mechanisms



*vapor pressure  
solubility*

*partition coeff.  
log P  
acidity*

*electronic  
steric  
3D properties  
interaction energies*

For Example,

Will a chemical of unknown activity act as an estrogen?



*Identify a key step in the mechanism of action*

Will the unknown chemical bind to the estrogen receptor?



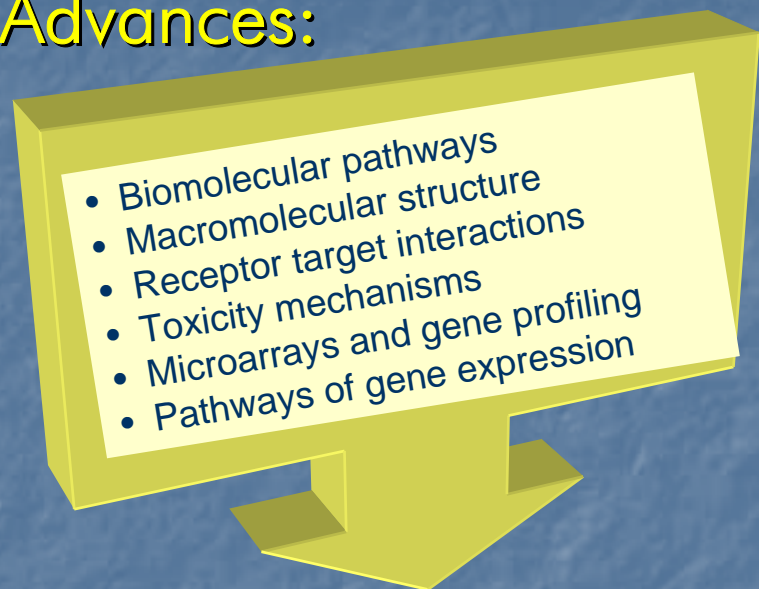
*Model that step*

Does the unknown molecule bind to the estrogen receptor?

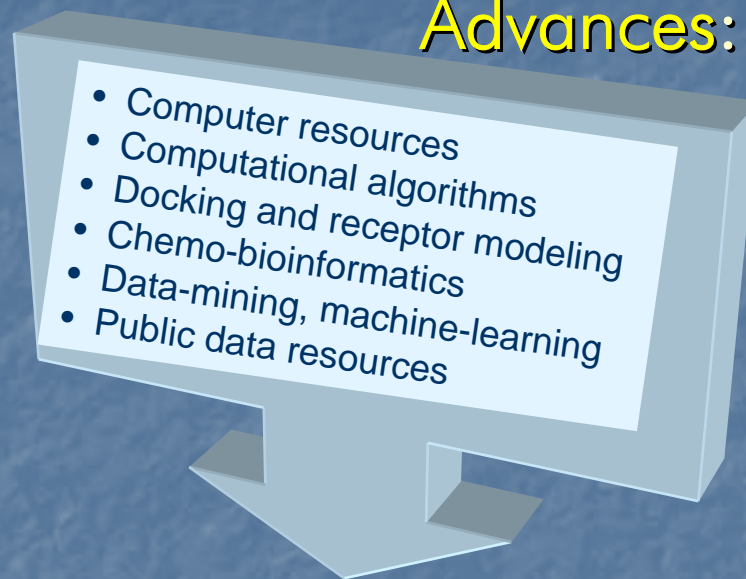
# **Molecular Modeling: Application to Computational Toxicology**

Why now?

## Biological Knowledge Advances:



## Computational Advances:



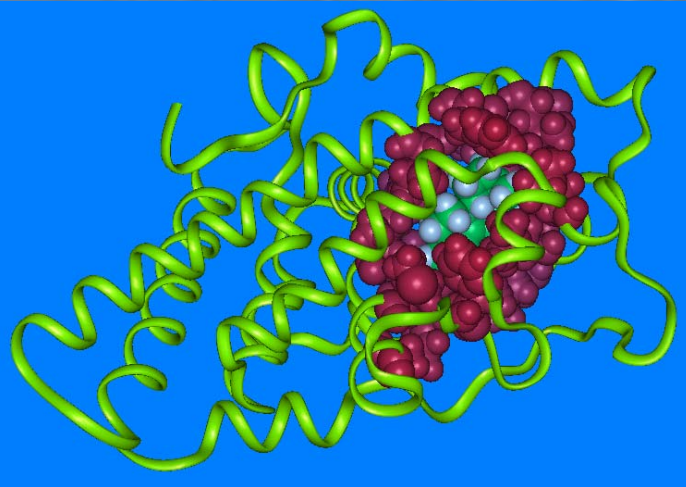
## Leading to improved:

- Mechanism-based framework for SAR models and extrapolations
- Ability to model biological interactions with greater sophistication
- Ability to explore chemical structure associations across toxicity and information domains

- The methods for molecular modeling in biological systems are rapidly improving.
- The engine for this improvement is the pharmaceutical industry and the commercial need to develop new drugs.
- Assessing toxicity is similar to finding new drugs but in important ways it is different.
  - To be a viable drug a molecule must be strong actor
  - Environmental agents are often weak actors
  - If a drug company finds one or a few prospective agents, that is a success
  - We need to test all or almost all of the potential agents
- Our goal is to prioritize testing, so false negatives are much more important than false positives.

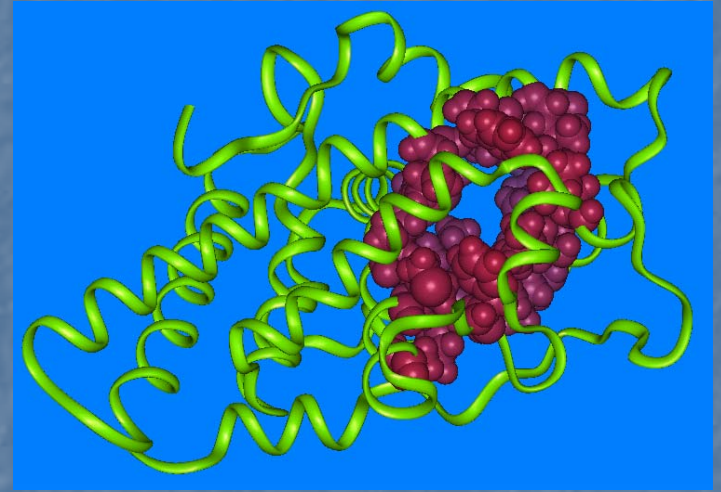
# Docking

Crystal structure  
from the literature



1E3G Human Androgen Receptor  
Ligand Binding Domain with  
Ligand Metribolone (R1881)

Computationally  
created target



1E3G Human Androgen Receptor  
Ligand Binding Domain with  
Ligand removed computationally

# Docking

- The best fit between an unknown potential ligand and the molecular target is then obtained.
  - Using classical methods
  - In this manner a large library of potential ligands could be screened.
  - Scoring function
  - Flexibility
- Models that include more of the underlying physics of the interaction may be used.
  - Electronic structure
  - Targets where what happens after binding is important
    - Enzymes, DNA

## Initial study ----- PAH metabolites binding to the estrogen receptor

- Observations from initial study
  - Many crystal structures of the estrogen receptor with different ligands bound.
    - Targets created from different crystal structures yield different results
    - Protein flexibility
- Conclusion
  - Both protein and ligand flexibility are important.

# New Approach to Docking

- Traditional docking studies
  - One protein target and the comparison of an array of potential ligands
  - The best potential ligands for that target
- New approach
  - A series of (related) protein targets
  - Chemicals to be screened are docked into each target
  - The most likely target for each ligand

LIGAND	Androgen Receptor Mutant 1GS4	Androgen Receptor (rat) 1I37	Androgen Receptor (rat) 1I38	Signalling Protein 1K5D	Estrogen Receptor Alpha 1GWQ	Estrogen Receptor Alpha 1GWR
Vinclozolin	-7.04	-7.77	-7.70	-6.62	-6.80	-7.50
Bisphenol A	-7.89	-8.01	-7.57	-6.80	-8.34	-8.45
Dihydrotestosterone	-9.97	-11.30	-10.51	-7.11	-8.09	-8.60
17b-Estradiol (E2)	-9.49	-10.37	-10.17	-7.53	-10.71	-11.04
Estriol	-9.89	-10.35	-9.88	-8.43	-10.41	-10.99
Progesterone	-10.38	-9.11	-9.91	-6.35	<i>no binding</i>	<i>no binding</i>
Promegestone	-10.10	<i>no binding</i>	-7.93	-6.09	<i>no binding</i>	<i>no binding</i>
Testosterone	-9.98	-10.87	-10.12	-6.99	<i>no binding</i>	<i>no binding</i>
Aldosterone	-10.47	-9.02	-7.63	-6.40	<i>no binding</i>	<i>no binding</i>
Corticosterone	-9.99	-9.27	-8.29	-5.68	<i>no binding</i>	<i>no binding</i>
4-androstenedione	-9.30	-9.90	-9.80	-5.87	<i>no binding</i>	<i>no binding</i>
R 1881	-10.12	-11.27	-9.53	-6.37	-8.43	-9.44
Cyproterone Acetate	-7.94	<i>no binding</i>	<i>no binding</i>	-5.83	<i>no binding</i>	<i>no binding</i>
Linuron	-7.11	-7.66	-7.10	-6.69	-6.99	-6.55
Pregenelone	-10.61	-8.64	-9.69	-6.12	<i>no binding</i>	<i>no binding</i>
Mibolerone	-10.27	-10.92	-9.56	-6.24	-8.92	-9.66
5A-Androstanol	-9.23	-9.40	-9.78	-6.31	<i>no binding</i>	<i>no binding</i>
acetoxypregesterone	-9.29	<i>no binding</i>	<i>no binding</i>	-5.88	<i>no binding</i>	<i>no binding</i>
Trenbolone	-9.79	-10.86	-10.01	-6.06	-8.07	-9.25
Methoxychlor	-7.41	<i>no binding</i>	<i>no binding</i>	-7.75	<i>no binding</i>	-7.79
HPTE	-8.83	-7.33	-6.83	-7.32	-9.33	-9.66
o,p'-DDT	-7.75	<i>no binding</i>	<i>no binding</i>	-6.97	-8.58	-8.85
p,p'-DDE	-7.04	-7.77	-7.70	-6.62	-6.80	-7.50

The best interaction partner for each chemical

1GS4 (Other)	1I37 & 1I38 (Androgen)	1GWR & 1GWQ (Estrogen)
6-Methyl-17-acetoxyprogesterone	Mibolerone	17b-Estradiol (E2)
CYPROTERONE	Dihydrotestosterone	Bisphenol A
ACETATE	TRENBOLONE	Estriol
PROMEGESTONE	R 1881	Methoxychlor
Progesterone	5-ANDROSTAN-17-OL	HPTE
Corticosterone	Testosterone	o,p'-DDT
Aldosterone	4-androstenedione	
PREGNENOLONE	LINURON	
	Vinclozolin	
	p,p-DDE	

# Conclusions

- ❖ Easily available methods for “Docking” show promise
  - ❖ Most of these methods do not allow the receptor to be flexible during docking
  - ❖ This artificially limits the subset of chemicals that bind to receptor

# Conclusions

- When a series of potential macromolecular targets are considered simultaneously, the results are enhanced
- Including a promiscuous receptor for comparison purpose aids in classifying chemicals relative to steroid hormone receptor binding
- Well-constructed data sets obtained with the same protocol from a consistent source will help the process of developing methods for screening

# A Proposal

- Develop a series of macromolecular targets that environmental molecules can be tested against.
  - Choice of targets would result from mechanistic understanding
  - Provide insight into the mechanisms for toxicity
- The appropriate level of interaction between the target and the potential toxicant would be dictated by the mechanism.

# What kind of knowledge would be provided by this approach?

- Feasibility of putative mechanisms of action on the molecular level
- Incorporation of structural information in understanding chemical toxicity
- Screening of chemicals for their capacity to partake in specific mechanisms
  - Predictions on specific chemicals.
  - Prioritization of chemicals for testing

# Collaborations

- NHEERL/RTD
  - Advice and Data
- Duke University
  - Advanced Computational Chemistry
- EPA/Office of Environmental Information
  - Computing and visualization
- SBIR
  - Software developments