

Toxicity Prediction

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We aim to use a docking program alongside statistical modelling to predict the toxicity of pesticides.

1 The natural cause and prevention of toxicity

Acetylcholine (ACH) is the natural ligand of the receptor protein acetylcholinesterase (AChE).

ACH is a neurotransmitter that will transmit impulses from a cell to a muscle. This transmission leads to the stimulation of muscle contractions. It is this process that is the cause of toxicity and can eventually lead to the death of the organism.

The main function of AChE is to safely break down the substrate, ACH.

The resulting molecules, acetic acid and choline, are unable to transmit impulses from cells to muscles, therefore preventing muscle contractions and avoiding toxic consequences.

The process can be described in three main steps.

- ACH binds at a specific location on AChE called a binding site.
- The complex formed by AChE and ACH is particularly unstable, leaving ACH vulnerable to hydrolysis, i.e. a reaction with water. The hydrolysis of ACH breaks the substrate down into two smaller molecules, acetic acid and choline.
- The two smaller molecules then leave the binding site of AChE, leaving AChE molecularly unaltered.

After the third step, the molecularly unaltered AChE is then able to bind with other molecules of ACH so that the process can be continually repeated. AChE is said to be *reactivated* after each cycle.

2 How Pesticides Cause Toxicity

Competitive inhibition occurs when both a ligand and a substrate compete for the same binding site of a receptor protein and both can not bind at the same time.

A pesticide is a small molecule that acts as a competitive inhibitor of AChE. If a pesticide binds to AChE, the binding site is blocked and AChE is inhibited from the safe break down of ACH upon release from a cell. A build-up of ACH molecules occurs and it is this build-up that causes toxicity.

We would expect the toxicity of a pesticide to increase

- as the rate of the reaction between AChE and the pesticide increases.
- the more stable the complex formed by AChE and the pesticide is. i.e. The longer they stay bound, the longer AChE is inhibited from the safe break-down of ACH.

3 The Docking Program

AutoDock 4 (Huey *et al.*, 2007) is a docking program that is used to predict the complex formed when a ligand binds with a protein.

The output of AutoDock 4 involves L predicted structures of the complex formed between the ligand and protein, where L can be specified. For each of the L predicted structures, AutoDock 4 estimates

- the *free energy of binding*, ΔG_l^B , for $l = 1, \dots, L$ (including the individual energy terms).
- the *inhibition coefficient*, k_l^I , for $l = 1, \dots, L$.

The free energy of binding and the inhibition constant relate to the rate of the reaction and how stable the predicted complex is.

We aim to use AutoDock 4 to predict the complex formed by AChE and a given subset of pesticides.

Statistical modelling of the output parameters should aid in toxicity prediction.

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References

- Huey, R., Morris, G. M., Olson, A. J. and Goodsell, D. S. (2007) *A Semiempirical Free Energy Force Field with Charge-Based Desolvation*. *Journal of Computational Chemistry*, **28**, 1145-1152.