

# Mechanistically-driven identification of novel structural alerts for mitochondrial toxicity

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## OBJECTIVES

- AOP provides a model for mechanistic understanding of toxicity
- Most in silico models for mitochondrial toxicity lack this
- Availability of new data allows identification of structural alerts directly linked to mechanism of action

## APPROACH

- Data source: Seahorse respirometric assay
- Structural alerts: KNIME workflow based on iterative Bayes statistics
- Verify mechanism: Literature search

## MAIN RESULTS

- 11 structural alerts with literature evidence for mechanism of action (8 of these are novel)
- Including these alerts improves the performance of existing alerts published by Nelms et al., 2015

## IMPACT

- Progress toward a more complete AOP for mitochondrial toxicity
- Current coverage of mechanistic space is limited
- **For more information, contact: Charles Gong (cg588@cam.ac.uk)**

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## OBJECTIVES

- Molecular Initiating Event links chemical properties of molecules to biological responses
- Many current models do not incorporate mechanism of action, limiting our understanding
- New data allows linking structural alerts directly to mechanism of action

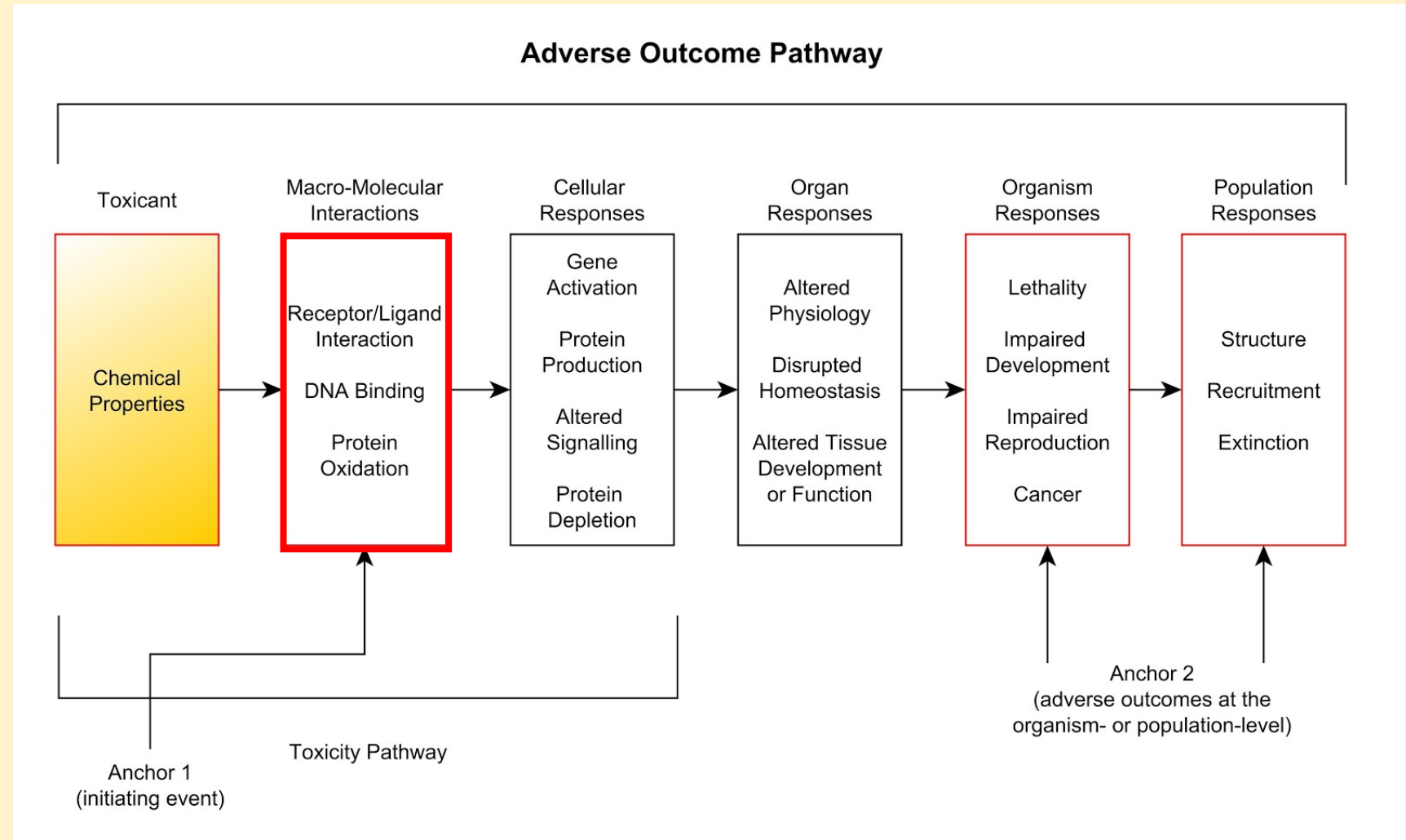
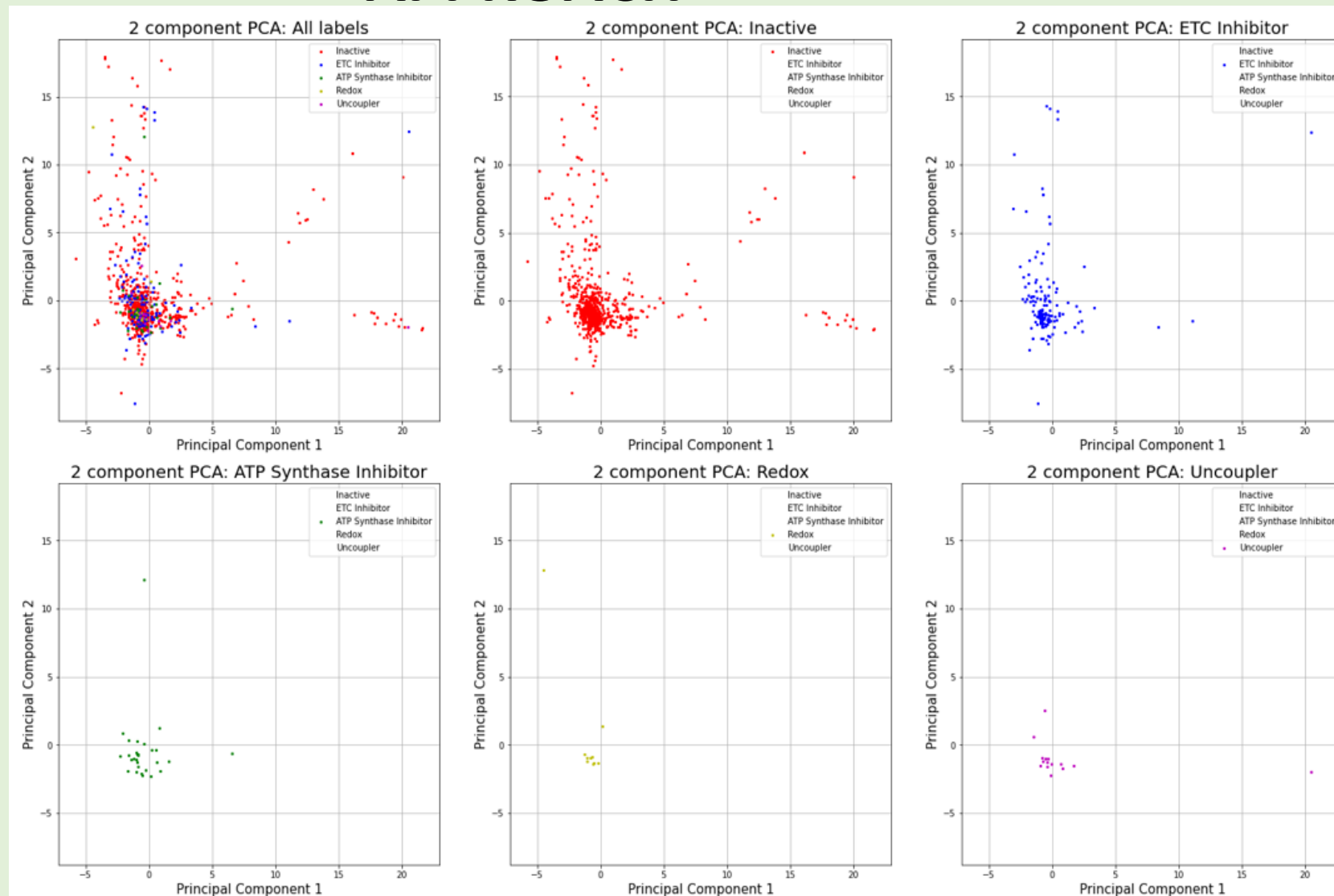


Diagram adapted from Allen et al., 2014

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## APPROACH

- Data source: Hallinger et al., 2020
- Seahorse respirometric assay



# Mechanistically-driven identification of novel structural alerts for mitochondrial toxicity

## APPROACH

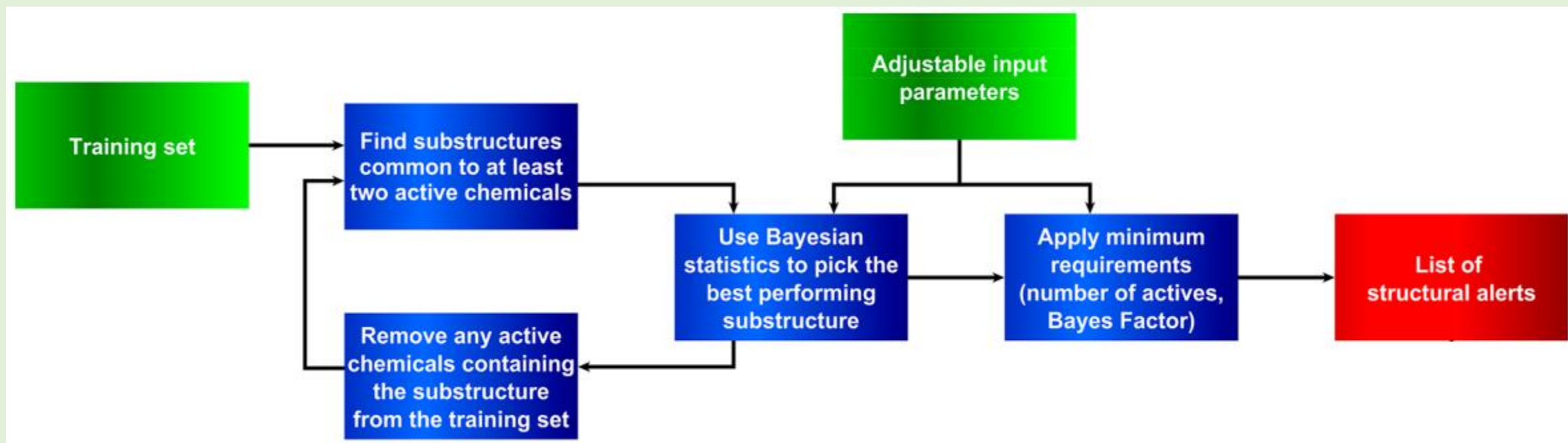


Diagram adapted from Wedlake et al., 2020

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## APPROACH

Group alerts by mechanism

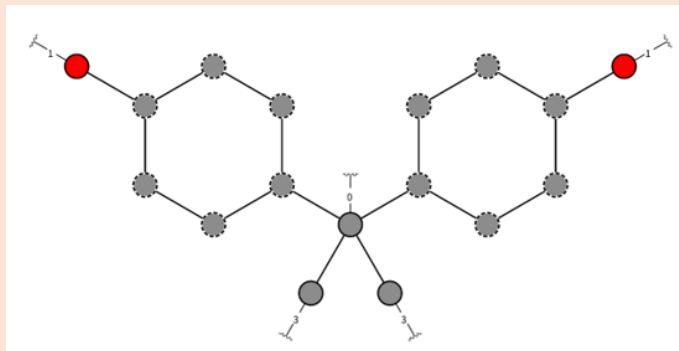
```
graph TD; A[Group alerts by mechanism] --> B[Look for literature evidence for activity]; B --> C[Modify alert based on remaining compounds];
```

Look for literature evidence for activity

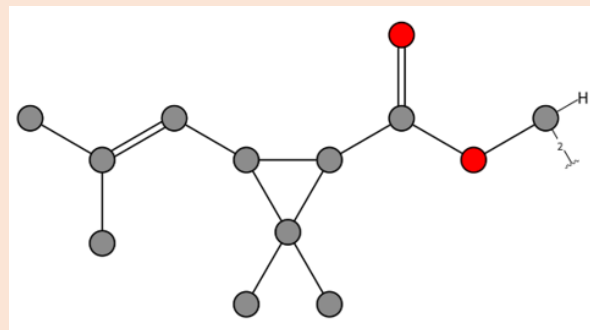
Modify alert based on remaining compounds

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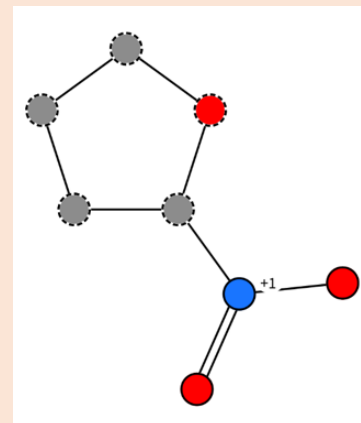
## MAIN RESULTS



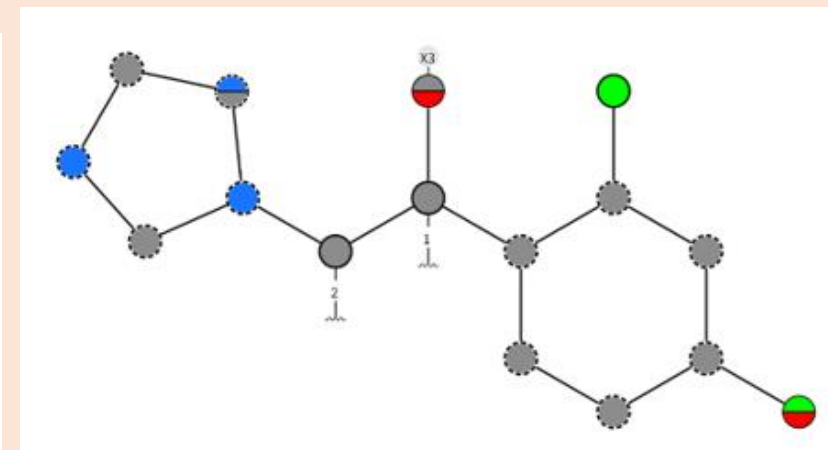
ETC inhibitor



ETC inhibitor



Redox cycler



ETC inhibitor (already known)

Validation on external data (data source: Hemmerich et al., 2020)

<u>Model</u>	<u>Accuracy (%)</u>	<u>Sensitivity (%)</u>	<u>Specificity (%)</u>	<u>MCC</u>
Derek Nexus	82.1	16.3	93.1	0.1197
Nelms alerts	<b>85.8</b>	16.6	<b>97.3</b>	0.2322
Nelms alerts + this work	85.7	<b>20.8</b>	96.6	<b>0.2574</b>

(Nelms et al., 2015)

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## IMPACT

- Improve predictive power of existing models by accounting for more mechanisms of action
- Coverage of mechanistic space is limited for now, but AOP framework allows gradual build-up

## REFERENCES

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- Allen, T. E. H., Goodman, J. M., Gutsell, S. and Russell, P. J., 2014. Defining Molecular Initiating Events in the Adverse Outcome Pathway Framework for Risk Assessment. *Chemical Research in Toxicology*, 27(12), pp.2100-2112.
- Hallinger, D., Lindsay, H., Paul Friedman, K., Suarez, D. and Simmons, S., 2020. Respirometric Screening and Characterization of Mitochondrial Toxicants Within the ToxCast Phase I and II Chemical Libraries. *Toxicological Sciences*, 176(1), pp.175-192.
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- Hemmerich, J., Troger, F., Füzi, B. and Ecker, G. F., 2020. Using Machine Learning Methods and Structural Alerts for Prediction of Mitochondrial Toxicity. *Molecular Informatics*, 39(5), p.2000005.