Skin sensitisation: The implementation of potency predictions in Derek Nexus

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Overview

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  • Data gathering and curation
  • Composition

• EC3 model
  • Methodology
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Background: Derek Nexus and skin sensitisation

- Derek Nexus has 88 alerts for skin sensitisation
  - Based on assay data from mice, guinea pigs and human
- Currently we make qualitative predictions
  - Hazard identification
- We also want to be able to quantitatively estimate skin sensitisation potency
  - To aid in risk assessment
  - Desirable for ethical and regulatory reasons
  - Requires skin sensitisation potency data
Background: The LLNA

- The murine Local Lymph Node Assay (LLNA) is the gold standard assay for predicting skin sensitisation
- Measures the proliferation of T-lymphocytes in the lymph nodes
  - One of the key events in the skin sensitisation Adverse Outcome Pathway (AOP)
- Provides a measure of potency through an EC3 value
  - Estimated concentration of a compound that causes a 3-fold increase in lymphocyte proliferation compared with controls

Background: The LLNA

- EC3 values have been shown to correlate with human skin sensitisation potential
Background: The LLNA

- EC3 values have been shown to correlate with human skin sensitisation potential.
- Sensitisers can be assigned to one of four ECETOC potency categories:

  - **Extreme**
  - **Strong**
  - **Moderate**
  - **Weak**

EC3 (%): 0.1, 1, 10, 100

Kimber et al., Food Chem. Toxicol. 2003, 41, 1799-1809
Lhasa EC3 dataset: Data gathering and curation

- We gathered as much publicly available EC3 data as possible
- The data was curated to ensure it was of high quality
  - Original experimental reports were located and examined
  - Unsuitable/unreliable data were not included in the final dataset
- When more than one LLNA study was found for the same compound the median EC3 value was taken
Lhasa EC3 dataset: Composition

- Data from 1051 LLNA studies were collected, resulting in a dataset containing 664 unique compounds
- Of these, 465 fire only one alert in Derek Nexus
  - These compounds span a good range of EC3 values
  - They include some non-sensitisers that fire a Derek alert
EC3 model: Initial considerations

• We would like to make use of existing knowledge captured in Derek’s alerts for skin sensitisation
  • Each alert space corresponds to a group of chemicals which are believed to react with skin proteins through the same mechanism

• Any model built needs to be transparent and interpretable

• The methodology must be scientifically defensible
EC3 model: Possible methodologies

• Regression models for different structural alerts
  • Some success, but not very interpretable

• Average EC3 values for each structural alert
  • Worked well for some alerts, but not others

• Finding nearest neighbours from within an alert space
  • Provided transparent and interpretable predictions
EC3 model: Possible methodologies

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• Finding nearest neighbours from within an alert space
  • Provided transparent and interpretable predictions
EC3 model: Alert-based nearest neighbours

1. **Query compound**
2. **Match alert in Derek Nexus**
3. **Fingerprint query**
4. **Select NN**
   - ≥ 3 NN
   - < 3 NN: Insufficient data
5. **Fingerprint NN**
6. **Keep up to 10 most similar NN**
7. **Weighted mean** $\frac{MW}{EC3}$
8. **EC3 value predicted**
EC3 model: Alert-based nearest neighbours

- Query compound
  - Match alert in Derek Nexus
  - Fingerprint query
  - Keep up to 10 most similar NN
    - Fingerprint NN
    - Weighted mean $MW/EC3$
  - EC3 value predicted

Lhasa EC3 dataset
- Select NN
  - ≥ 3 NN
  - < 3 NN
    - Insufficient data

Non-sensitiser
Sensitiser
Nearest neighbours (NN)
**EC3 model:** Alert-based nearest neighbours

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**Chemical space**
**EC3 model: Alert-based nearest neighbours**

- **Query compound**
- **Lhasa EC3 dataset**
  - Match alert in Derek Nexus
  - Fingerprint query
  - Select NN
  - Fingerprint NN
  - Keep up to 10 most similar NN
  - Weighted mean $\frac{MW}{EC3}$
  - EC3 value predicted

**Insufficient data**

**Equation:**

$$\frac{MW_q}{EC3_q} = \frac{\sum_{n=1}^{N} (\frac{MW_n}{EC3_n}) T_{q,n}}{\sum_{n=1}^{N} T_{q,n}}$$

- $q$ = query compound
- $N$ = number of nearest neighbours
- $n$ = $n^{th}$ nearest neighbour
- $T_{q,n}$ = Tanimoto index between $q$ and $n$

**Graph:**

- Predicted value
- $MW/EC3$
- Similarity to query

**Non-sensitisers**

A. Natsch et al., *Toxicol. Sci.* **2015**, **143**, 319-332
EC3 model: Alert-based nearest neighbours

- Query compound
- Lhasa EC3 dataset

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Insufficient data

$EC3$

Similarity to query

0 1

1 10

10 100

$E_{EC3}$
EC3 model: Performance

- The model was assessed using a validation set ($n = 46$)
- Predictions were judged as accurate according to two separate criteria:
  - Within a factor of 3 of the experimental EC3 value
  - Within the same ECETOC potency category as the experimental EC3 value
When the model is wrong, it tends to over-predict rather than under-predict the potency.
EC3 model: **Limitations**

1. **Coverage**
   - Directly linked to the size of the Lhasa EC3 dataset
     - This depends on the amount of publicly available LLNA data
   - The EC3 model covers 39 of the skin sensitisation alerts within Derek Nexus
   - Currently there are 49 alerts with fewer than three compounds in our dataset
     - Potential validation compounds: ~80% coverage
     - Do you have data you could share?
EC3 model: **Limitations**

2. Variability in LLNA data

- EC3 values can vary between different assay runs
  - This can be seen in the 87 compounds in the Lhasa EC3 dataset with multiple EC3 values
  - Median = 2.3-fold variation

\[
Fold \ variation = \frac{EC3_{\text{max}}}{EC3_{\text{min}}}
\]

- This will affect the overall accuracy of the model
EC3 model: Demonstration
Conclusions

• We have developed an EC3 model which makes quantitative predictions of skin sensitisation potency
  • Built upon high quality, publicly available LLNA data
• Predictions are made by finding nearest neighbours to the query compound within defined structural alert spaces
  • Makes use of existing knowledge found in Derek Nexus alerts
• The model performs well against a validation set, both in terms of predicting EC3 values and potency categories
  • Provides transparent and interpretable predictions
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Thank you for your attention

Any questions?
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