Modeling Drug Degradation

Objective: To Build a Model for Drug Degradation
Diloxanide Furoate is an amoebicide that is administered orally. Once ingested, it becomes hydrolyzed and the active ingredient Diloxanide is released, which subsequently undergoes degradation. In this example, we use REX to obtain a kinetic model for the drug degradation based on experimental data at different temperatures from [1]. The REX zipped file with the complete project can be downloaded here.

Features Illustrated
- Parameter Estimation for Drug Degradation

Experimental Data
In the experiments, a standard solution was prepared by diluting Diloxanide furoate to a 0.2 mg/Lt concentration. Samples of 50 ml were used to measure the degradation at pH=8 and at various temperature values: 40, 50, 55 and 63 C.

The data reports percentage of Diloxanide remaining, as shown in this table:

<table>
<thead>
<tr>
<th>Temperature, (K)</th>
<th>Time, (min)</th>
<th>Diloxanide Remaining, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>336</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>336</td>
<td>5.4095</td>
<td>79.5463</td>
</tr>
<tr>
<td>336</td>
<td>10.305</td>
<td>63.7309</td>
</tr>
<tr>
<td>336</td>
<td>15.2084</td>
<td>46.5249</td>
</tr>
<tr>
<td>336</td>
<td>20.4931</td>
<td>35.456</td>
</tr>
<tr>
<td>336</td>
<td>25.5549</td>
<td>25.3355</td>
</tr>
<tr>
<td>336</td>
<td>30.1376</td>
<td>22.2756</td>
</tr>
<tr>
<td>336</td>
<td>35.3242</td>
<td>15.0321</td>
</tr>
<tr>
<td>336</td>
<td>41</td>
<td>11.1322</td>
</tr>
<tr>
<td>336</td>
<td>45.8573</td>
<td>8.363</td>
</tr>
<tr>
<td>336</td>
<td>50.4209</td>
<td>6.605</td>
</tr>
<tr>
<td>328</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>328</td>
<td>10.6751</td>
<td>76.2062</td>
</tr>
<tr>
<td>328</td>
<td>20.7097</td>
<td>57.248</td>
</tr>
<tr>
<td>328</td>
<td>30.6184</td>
<td>41.7946</td>
</tr>
<tr>
<td>328</td>
<td>40.6548</td>
<td>30.7312</td>
</tr>
<tr>
<td>328</td>
<td>50.6906</td>
<td>22.7583</td>
</tr>
<tr>
<td>328</td>
<td>70.5163</td>
<td>10.9742</td>
</tr>
<tr>
<td>323</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>323</td>
<td>15.5551</td>
<td>76.9946</td>
</tr>
<tr>
<td>323</td>
<td>30.4649</td>
<td>56.4352</td>
</tr>
<tr>
<td>323</td>
<td>45.8831</td>
<td>43.8162</td>
</tr>
<tr>
<td>323</td>
<td>60.6729</td>
<td>32.0782</td>
</tr>
<tr>
<td>323</td>
<td>75.072</td>
<td>23.7584</td>
</tr>
<tr>
<td>323</td>
<td>90</td>
<td>17.4678</td>
</tr>
<tr>
<td>313</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>313</td>
<td>20.801</td>
<td>89.6004</td>
</tr>
<tr>
<td>313</td>
<td>40.1526</td>
<td>77.4819</td>
</tr>
<tr>
<td>313</td>
<td>60.6146</td>
<td>64.1874</td>
</tr>
<tr>
<td>313</td>
<td>80.0662</td>
<td>55.634</td>
</tr>
<tr>
<td>313</td>
<td>100</td>
<td>47.8053</td>
</tr>
</tbody>
</table>
Proposed Model

The degradation reaction is assumed to be as follows:

Degradation: Diloxanide $\rightarrow$ Deg-Diloxanide

We consider a batch reactor with four experimental sets where Temperature is varied. In each set, we enter the mass of active Diloxanide. Usually, in REX the compounds data must be entered in moles, but for this special example we will enter the Diloxanide data as mass in mg. Since this is a simple reaction where atom conservation is not an issue, this transformation to mass basis does not affect the parameter estimation. The only caution is that REX will still report all results on molar basis, so you must replace the REX \textit{gmol} units to \textit{mg} units. The initial Diloxanide is always 0.01 mg for all experiments. Active drug mass for other time values are calculated based on the initial content and the percentage of remaining (active) diloxanide. The following image shows the data for 336K:

Data for the degraded drug amount is not reported. Thus, we have zero values for Deg-Diloxanide in the experimental sets. When we specify the weighting factors, we turn ON the \textit{Ignore Zeros} option to ignore this data. In any case, only Diloxanide mass values are selected in the Weights node as reconciled measurements.

Three parameters are calculated for the degradation reaction: pre-exponential factor, activation energy and Diloxanide order. Bounds are opened for all of them in the Estimation→Parameters node, to allow them to be optimized by REX.
Parameter Estimation: Results

The solution parameters are shown in Results→Parameters node:

The model predictions can be visualized in Model-Data Comparison node. The model match to data is almost perfect; below is shown the evolution of active Diloxanide with time:
An alternative display of model predictions is the Parity Plot for those experimentals:

![Parity Plot](image)

Please note that we directly modeled Diloxanide mass. Although the axis displays \( gmol \) units, these are actually \textit{milligram} of active drug.

References