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More efficient method development with chromatographic simulation and 3D optimization

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Rational separation design requires understanding the chromatographic space. But without software tools, it's easier said than done.

3D optimization with software

Software can model the effect of multiple separation parameters on method performance, and find the optimal conditions. In 3D optimization, three parameters are varied at once to discover the potential interactions. (By contrast, one-at-a-time optimization is time-ineffective and risks bypassing the optimal conditions.)

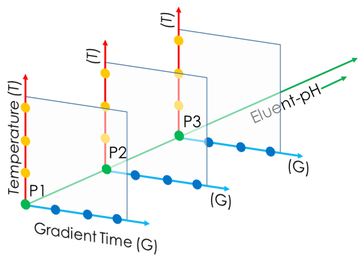

Figure 1. To build a 3D model, at least 2 conditions must be tested for each parameter, for a minimum of 8 conditions. But since some parameters are best modelled with more complex equations, more experiments might be needed to fit a polynomial or logarithmic equation.

Data

Nine compounds were separated using 12 initial methods, which tested 2 gradients (2 to 95% B over 15 min or 45 min), 2 temperatures (30 or 60 °C), and 3 pH values (4.9, 5.39, or 5.86).

Experimental data was generously provided by Jonathan Shackman and Cong Bi from BMS.

Modelling and mapping the resolution

ACD/Method Selection Suite was used to build a 3D model with the experimental data. The gradient was modelled using the equation $\ln k' = a + bX$, the temperature was modelled using the equation $\ln k' = a + bX^{-1}$, and the pH was modelled using the equation $\ln k' = a + bX + cX^2$. These equations are customizable within the software.

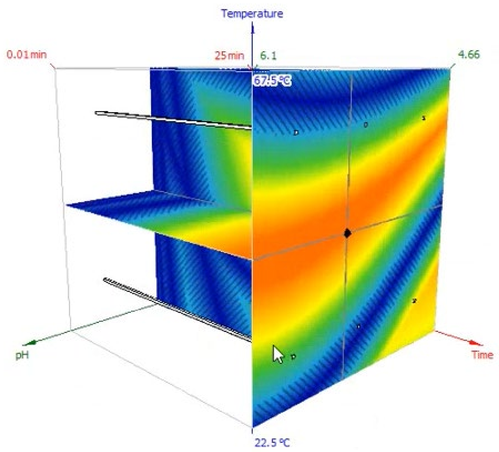

Figure 2. 3D map plotting the resolution as a function of temperature, gradient time, and pH. Red indicates areas of higher resolution, and blue indicates areas of lower resolution.

Table 1. Comparison between experimental and modelled retention times, showing a good fit for all 9 compounds (labelled C1–C9).

Experiment	Solvent B, %	Temp....	pH	C1	C2	C3	C4	C5	C6	C7	C8	C9
1: 1	2-95B (15 min)	30	4.9	3.515 3.515	4.058 4.058	4.687 4.687	4.842 4.842	5.273 5.273	5.933 5.933	6.003 6.003	6.177 6.177	7.950 7.950
2: 2	2-95B (45 min)	30	4.9	5.127 5.127	6.307 6.307	8.863 8.863	8.947 8.947	10.194 10.194	11.457 11.457	12.101 12.101	12.601 12.601	17.170 17.170
3: 3	2-95B (15 min)	60	4.9	2.925 2.925	3.767 3.767	4.697 4.697	4.533 4.533	4.840 4.840	5.485 5.485	5.655 5.655	5.825 5.825	7.312 7.312
4: 4	2-95B (45 min)	60	4.9	3.690 3.690	5.460 5.460	8.645 8.645	7.885 7.885	8.803 8.803	10.055 10.055	10.967 10.967	11.464 11.464	15.326 15.326
5: 5	2-95B (15 min)	30	5.39	3.513 3.513	4.047 4.047	4.800 4.800	4.845 4.845	5.287 5.287	5.943 5.943	6.017 6.017	6.190 6.190	7.965 7.965

Improvement in resolution and suitability

To find the optimal conditions, suitability criteria were defined for resolution, run time, and k' (solvent front proximity). (k* can also be viewed in the peak table.) The software searched a predefined space for conditions that maximized the suitability criteria, and identified new conditions that could resolve all compounds in < 10 min.

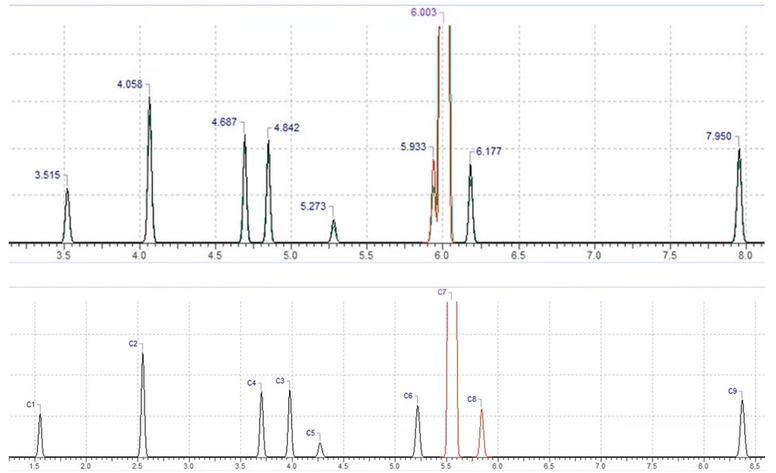

Figure 3. (top) Initial (unoptimized) chromatogram has two unresolved peaks. (bottom) All peaks are clearly resolved in the simulated chromatogram showing optimal conditions.

Using Method Selection Suite, a 3D map was built to model the separation of 9 compounds. The model was then used to improve the separation, cutting down method-development time.