Combining Aggregation with Pareto Optimization: A Case Study in Evolutionary Molecular Design

Johannes W. Kruisselbrink, Michael T.M. Emmerich*, Thomas Bäck*,*
Andreas Bender+, Ad P. IJzerman+, Eelke van der Horst+
+Leiden/Amsterdam Centre of Drug Research, Leiden University
**Leiden Institute for Advanced Computer Science (LIACS), Leiden University*
The Netherlands

Research question

How can we deal with optimization problems with many criteria that can be partitioned into objectives and fuzzy constraints?

General approach

Model fuzzy constraints as objectives using Derringer desirability functions

Map the objective function values to the interval [0,1] to allow for aggregation of the objectives

Group the objectives and constraints into logically separable groups and aggregate their objective scores using the desirability index concept

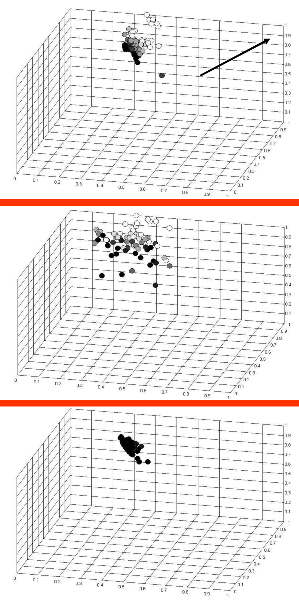
Apply Pareto optimization using the desirability index scores of the different groups

Problem class

Multi-objective design optimization problems with a small number of objectives and a number of fuzzy (or soft) constraints:

$$\begin{aligned} &\min\ f_i(x), \qquad i = 1, \ldots, N \\ &s.t.\ \ g_j(x) \gtrsim 0,\ j = 1, \ldots M \end{aligned}$$

- x can be of any domain D
- $\gtrsim$ is a fuzzified version of $\geq$ with the linguistic interpretation $g_j(x)$ is essentially greater than 0



Typical Pareto front approximations of the three approaches: top: approach 1, middle: approach 2, bottom: approach 3

Remodeling of the objectives

The objectives can be transformed using:

$$\hat{f}_i(x) = \exp\left(d_i \cdot (f_i^* - f_i(x))\right) \rightarrow \max,\ i = 1, \ldots, M$$

Here, f^* is an estimation of the global minimum.

Remodeling of the constraints

Constraints are of the following forms:

$$A_j \lesssim g_j(x) \text{ or } g_j(x) \lesssim B_j \text{ or } A_j \lesssim g_j(x) \lesssim B_j$$

Modeled by desirability functions using:

$$d_j(x) = \begin{cases} 0 & , g_j < \mathrm{LB}_j \\ \left(\frac{g_j(x) - \mathrm{LB}_j}{A_j - \mathrm{LB}_j}\right)^{l_j} & , \mathrm{LB}_j <= g_j(x) < A_j \\ 1 & , A_j <= g_j(x) <= B_j \\ \left(\frac{g_j(x) - \mathrm{UB}_j}{B_j - \mathrm{UB}_j}\right)^{u_j} & , B_j < g_j(x) <= \mathrm{UB}_j \\ 0 & , g_j(X) > \mathrm{UB}_j \end{cases}$$

Here, LB_j and UB_j are absolute lower and upper cutoff values.

Approach 1:

Aggregate the objectives and aggregate the constraints. Do Pareto optimization on the aggregated scores of those two groups:

$$f_{\text{objectives}} = \hat{f}_1 \cdot \hat{f}_2 \cdot \ldots \cdot \hat{f}_N$$

$$f_{\text{constraints}} = \hat{g}_1 \cdot \hat{g}_2 \cdot \ldots \cdot \hat{g}_M$$

Approach 2:

Combine the constraints into one desirability score and keep the objectives separate. Pareto optimization using the separate objectives scores and the aggregated constraint score.

Approach 3 (benchmark):

Aggregate objectives and constraints into one scoring value for single objective optimization.

A Case Study in Molecular Design

The study is motivated by a problem scenario in automated drug design. Particular test case: search for estrogen receptor antagonists.

Objectives:

Activity models (support vector machines) :

- f_1: predictor based on ECFP6 fingerprints
- f_2: predictor based on AlogP2 Estate Counts
- f_3: activity predictor based on MDL

Constraints:

Lipinski's drug-likeness criteria and a minimized energy confirmation test. These are fuzzy constraints with the bounds:

Descriptor	LB	A	B	UB
Num H-acceptors	0	1	6	10
Num H-donors	0	1	3	5
Molecular solubility	-6	-4	NA	NA
Molecular weight	150	250	450	600
ALogP	0	1	4	5
Minimized energy	0	0	80	150

Experiments

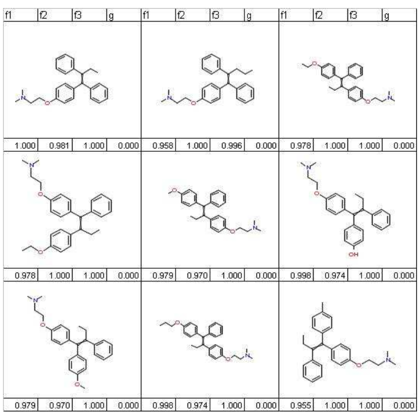
The three approaches were tested on an evolutionary algorithm implementing graph-based genetic operators.

For the Pareto optimization, an NSGA-II selection scheme was used.

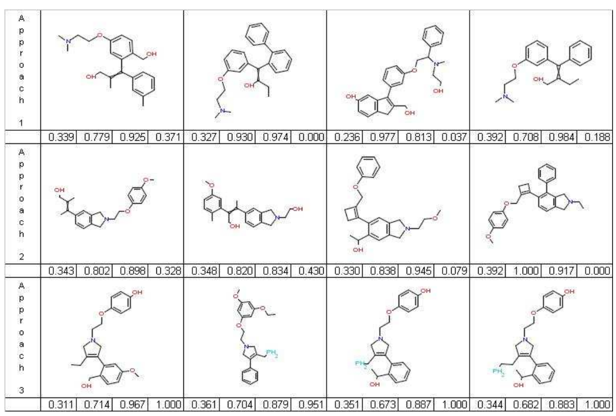
Parameter settings:

- Strategy: (80+120)-EA
- Generations: 1000
- Runs per approach: 4

(computation time per run: approx. 14 hours)



A high quality subset of the solutions found by run 3 of approach 2 containing the well known drug Tamoxifen



Random subsets from the Pareto optimal solutions obtained in run 1 of each approach. The diversity seems slightly better for approach 2, but this is only marginal.

- Combining objectives into logically separable groups using desirability indexes is a good way to reduce the number of objectives
- The proposed method is especially useful when dealing with fuzzy constraints which can be remodeled as objectives
- In some cases, it is better to do partial aggregation and perform Pareto optimization on the remaining objectives than to do full aggregation