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DESIGN OF MOLECULES FOR PARETO-OPTIMUM FUNCTIONALITIES

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ABSTRACT

The proposed work involves optimization algorithms based on response surfaces and computer aided molecular design. This approach is based on the arrangement of individual atoms rather than the arrangement of certain clusters of atoms known as groups. Multi-objective optimization was performed instead of single-objective optimization using the response surface method based upon self organizationconcept. Besides optimizing the number of atoms of different chemical elements in a chemical compound, the number of different types of bonds are also optimized. This approach distinguishes among possible isomers with the same chemical formula.

INTRODUCTION

As new environmental regulations are enforced and the designs of refrigeration systems improve, the need to design and produce better refrigerants becomes more profound. Traditional ways of designing, producing and testing a new chemical compound generally involve design heuristics coupled with direct experimental and computational studies. Some of the most important thermodynamic properties are the freezing point, boiling point, vapor pressure, enthalpy of vaporization and liquid specific heat.

Montreal and Kyoto protocols enforce certain restrictions and limit the use and production of many refrigerants due to their harmful effects on the atmosphere. Consequently, other properties are also desirable such as low Ozone Depletion Potential (ODP), very low Global Warming Potential (GWP), short atmospheric lifetime, low Green House Gas (GHG) emission and biodegradability. Little effort has been done in the past to address all these issues simultaneously.

Commercially available software packages such as the *Estimation Program Interface (EPI)* suite have been developed for the estimation of a wide variety of chemical, physical and environment related properties. For example, the atmospheric oxidation [1] (U.S. Environmental Protection Agency 2008) prediction and biodegradability probability [2] (U.S. Environmental Protection Agency 2009) of an organic compound may be performed by inputting its *Simplified Molecular Input Line Entry System* (SMILES) [3] notation in the user interface of the *Atmospheric Oxidation Program for Microsoft Windows* (AOPWIN) [1] and *Biodegradation Probability Program* (BIOWIN) [2].

In our particular application there will be several simultaneous objectives that are often contradictory. Each of these objectives depends on the number of chemical elements constituting a given refrigerant, the number of atoms of each of these elements and the number and type of bonds among each of these atoms. All of these parameters thus, represent design variables that could be optimized in order to create an entire set of new refrigerants that will have the best trade-off among the desired multiple objectives as defined earlier. In general, we could have m such objective functions each depending on n design variables. A set of inequality and equality constraints must also be specified which limit the values that individual design variables and/ or combinations of design variables (and/ or objective functions) may achieve in order to guarantee the physical relevance of the numerical results obtained from the optimization algorithm.

Calm and Didion [3] summarized the results and observed trends of many past attempts to search for new refrigerants. The major findings are summarized below:

a) Increasing the number of carbon atoms in the refrigerant molecules not only increases the molecular weight, it generally also results in an increase in the normal boiling temperature and the heat capacity.
b) Presence of a large number of hydrogen atoms in the molecule generally decreases the atmospheric lifetime of the organic compound. Compounds with lower atmospheric lifetimes are known to have lower ODP and GWP. However, compounds with large number of hydrogen atoms tend to have higher flammability, especially when the number of hydrogen atoms in the refrigerant molecule becomes greater than the number of halogen atoms in the molecule.
c) An increase in the number of oxygen atoms results in a decrease in the ODP and GWP because it results in reduced stability of the particular compound in the atmosphere. It has also been associated with increased reactivity, flammability and toxicity.
d) The increase in the number of fluorine atoms increases the GWP. Perfluorinated compounds are examples which support this observation. Perfluorinated compounds belong to the family of organic compounds in which all the hydrogen atoms on a carbon chain are replaced with fluorine atoms and the molecule contains at least one different functional group.
e) An increase in the chlorine content generally results in an increased ODP and toxicity. It also generally results in an increased lubricant miscibility.
f) An increase in the bromine content also generally increases the ODP of the organic compound. However, increased bromine content in the molecule has also been linked with reduced flammability of the compound. In general, a larger number of halogen atoms in the molecule results in an increase in the atmospheric lifetime, ODP and GWP. This trend is especially observed for perhalogenated compounds. Perhalogenated compounds belong to the family of organic compounds in which all the hydrogen atoms on a carbon chain are replaced with a particular halogen atom and the molecule contains at least one different functional group.
g) Presence of a large number of nitrogen atoms in the molecule has been associated with an increased reactivity of the compound, thereby reducing stability of the molecule. Increased nitrogen content is also linked with an increase in the toxicity. Presence of sulfur also shows similar effects on the toxicity and the stability of the compound.
h) Presence of boron in the molecule makes the compound more reactive and generally toxic. Iodine atoms in the molecule also increase the reactivity of the compound and some volatile iodine containing compounds have been rejected in the past because of their high toxicity. Because of their higher reactivity, organic compounds having iodine generally have lower atmospheric lifetime. Consequently, this also reduces their potential use as refrigerants, because of similar issues related to their long term stability inside the refrigeration system.

RESEARCH OBJECTIVES

This research aims to test and evaluate the performance of a different approach in designing new refrigerants. Freon-12 will be used as the reference refrigerant. The performance of the newly designed refrigerants will be evaluated on the basis of the normal boiling temperature, latent heat of vaporization, vapor pressure variation over the operating range, half-life in troposphere and biodegradability. Thus, this research represents an endeavor of finding an alternative strategy for designing new functional molecules.

PROPOSED METHODOLOGY

The rationale behind the newly developed molecular design methodology is very similar to the basis of a group/ atom/ bond contribution approach [5]. It is the fact that intermolecular forces in a molecule are determined by the nature and the number of the chemical elements constituting the particular molecule, types and locations of bonds between a particular pair of atoms and the arrangement of atoms themselves. Thus, a given set of structural variables describing a topology of a molecule should be linked to a unique set of property values for such a molecule.

An initial pool of organic compounds was constituted. The compounds included in this pool were chosen while considering currently used refrigerants, the availability of experimental data and/ or accurate property estimation models and stability criteria required by an organic compound to be used as a refrigerant. This initial pool of

organic compounds comprised of the general family of alkanes, halogen substituted alkanes, alkenes, halogen substituted alkenes, ethers and halogen substituted ethers. These chemicals were chosen in such a way that none of them had more than four constituting carbon atoms.

Following is the sequence of operations which together constitute the newly developed methodology for performing multi-objective optimization of the molecular structure of refrigerants.

1. Selection of compounds & their properties for the initial data pool
2. Parameterization of the molecular structure and creation of design variables
3. Creation & integration of the surrogate model for approximating the objective functions
4. Specification & integration of constraints and other system parameters
5. Iterative use of the optimization algorithm until the requirements are satisfied
6. Obtain the optimum sets of design variables
7. Transform the optimized sets to molecular structures
8. Validate the results

A methodology to mathematically represent the molecular structures of those compounds was also developed. Using this methodology, the molecular structures of all the compounds in the initial data set were represented by a unique set of twenty eight structural design variables. This approach of mathematically representing the molecular structure was also found capable of differentiating between isomers of a particular compound.

Using the available data, multi-dimensional surrogate models/ response surfaces were developed to approximate the objective functions. The weighted approximation method [6] and modified radial basis functions based method were considered for creating the response surfaces. The results were analyzed, and it was found that estimates from the weighted approximation method were more accurate than the ones which were produced from the radial basis functions based method.

Constraints for governing the individual value of all the design variables, enforcing limits on the combination of constraints and setting the lower and/ or upper bounds of the desired property values, were formulated. Constraints were specifically developed and enforced to ensure the chemical feasibility of a generated molecular structure.

Along with the constraints, the information regarding the meta-models was used in the process of optimization. The optimization was performed using the commercially available multi-objective optimization software package, IOSO NM version 1.0 [7].

PARAMETERIZATION OF THE MOLECULAR STRUCTURE

The developed methodology is based on the creation and evaluation of 28 structural design variables, used for representing the molecular structure of any compound considered in this study. The methodology has been designed to handle molecules which have up to four carbon atoms. Apart from carbon atoms, the other elements which might be present in the molecule are restricted to hydrogen, chlorine, fluorine, bromine and oxygen. The compound is only allowed to have any of the following types of seven bonds:

a) Carbon-carbon single bond
b) Carbon-carbon double bond
c) Carbon-hydrogen single bond
d) Carbon-chlorine single bond
e) Carbon-fluorine single bond
f) Carbon-bromine single bond
g) Carbon-oxygen single bond

Each of the four carbon atoms is associated directly with seven out of a total of twenty eight structural design variables. Each of these seven structural design variables physically represents the number of a particular type of bond associated with the particular carbon atom.

Table 1 shows the twenty eight structural design variables (X_1, X_2, X_3…, X_{27}, X_{28}). The first row of the design variables, X_1, X_2, X_3 and X_4, represents the number of carbon-carbon single bonds associated with each of the carbon atoms designated by C_1, C_2, C_3 and C_4, respectively.

Similarly, the second row of design variables, X_5, X_6, X_7 and X_8, represents the number of carbon-carbon double bonds associated with each of the four carbon atoms designated by C_1, C_2, C_3 and C_4, respectively. In a similar manner, X_9, X_{10}, X_{11} and X_{12} represent the number of carbon-hydrogen single bonds associated with C_1, C_2, C_3 and C_4, respectively; X_{13}, X_{14}, X_{15} and X_{16} represent the number of carbon-chlorine single bonds associated with C_1, C_2, C_3 and C_4, respectively; X_{17}, X_{18}, X_{19} and X_{20} represent the number of carbon-fluorine single bonds associated with C_1, C_2, C_3 and C_4, respectively;

X_{21}, X_{22}, X_{23} and X_{24} represent the number of carbon-bromine single bonds associated with C_1, C_2, C_3 and C_4, respectively and X_{25}, X_{26}, X_{27} and X_{28} represent the number of carbon-oxygen single bonds associated with C_1, C_2, C_3 and C_4, respectively.

A set of inequality and equality constraints must be specified which limit the values that individual design variables and/ or a combinations of design variables (and/ or objective functions) may achieve in order to guarantee the physical relevance of the numerical results obtained from the optimization algorithm.

Table 0. Structural design variables used in the molecular design methodology for refrigerants with 4 carbon atoms

	C_1	**C_2**	**C_3**	**C_4**
Number of C-C bonds	X_1	X_2	X_3	X_4
Number of C=C bonds	X_5	X_6	X_7	X_8
Number of C-H bonds	X_9	X_{10}	X_{11}	X_{12}
Number of C-Cl bonds	X_{13}	X_{14}	X_{15}	X_{16}
Number of C-F bonds	X_{17}	X_{18}	X_{19}	X_{20}
Number of C-Br bonds	X_{21}	X_{22}	X_{23}	X_{24}
Number of C-O bonds	X_{25}	X_{26}	X_{27}	X_{28}

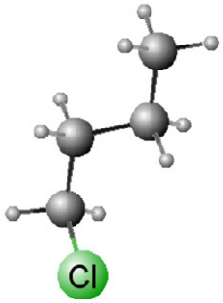
The developed design methodology is capable of differentiating between structural isomers of an organic compound. In addition, it differentiates between different structural isomers by generating unique sets of twenty eight structural design variables for each of the structural isomers.

Isomers are compounds that have the same molecular formula, but differ in the arrangement of individual atoms in the molecule. For example, the molecular formula C_4H_9Cl may correspond to any of the following organic compounds:

a) 1-chlorobutane
b) 2-chlorobutane
c) 1-chloro-2-methylpropane
d) 2-chloro-2-methylpropane

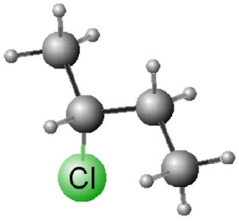
The molecular structure of 1-chlorobutane, 2-chlorobutane, 1-chloro-2-methylpropane and 2-chloro-2-methylpropane, respectively. Even though they are represented by the same molecular formula, distinct structural features can be clearly seen in their molecular structures.

Values of the corresponding sets of twenty eight structural design variables show that the proposed design methodology represents the molecular structure of all the four compounds in a unique manner. Hence, it successfully differentiates between the four isomers of the organic compound having the formula C_4H_9Cl. Examples for two of these isomers are shown in Figure 1 and Figure 2.



Number of	C_1	C_2	C_3	C_4
C-C bonds	1	2	2	1
C=C bonds	0	0	0	0
C-H bonds	2	2	2	3
C-Cl bonds	1	0	0	0
C-F bonds	0	0	0	0
C-Br bonds	0	0	0	0
C-O bonds	0	0	0	0

Figure 1. Molecular structure of 1-chlorobutane and the corresponding set of 28 structural design variables.



Number of	C_1	C_2	C_3	C_4
C-C bonds	1	2	2	1
C=C bonds	0	0	0	0
C-H bonds	3	1	2	3
C-Cl bonds	0	1	0	0
C-F bonds	0	0	0	0
C-Br bonds	0	0	0	0
C-O bonds	0	0	0	0

Figure 2. Molecular structure of 2-chlorobutane and the corresponding set of 28 structural design variables.

Multi-objective optimization using Indirect Optimization on the basis of Self Organization (IOSO) software

The capabilities of IOSO technology algorithms have been documented in the past in detail [6-9]. This algorithm is based on the application of response surface methodology and the adaptive use of global and middle range multi point approximation. These techniques allow for a more accurate response surface fit in the vicinity of the optimum of the most recent optimization cycle. Another advantage of using these techniques is that they are capable of generating accurate response surfaces, even when very small amount of data (candidate solutions) is available. IOSO also achieves this by implementing a number of independent highly efficient evolutionary self organizing algorithms. The selection of a particular algorithm is done internally and adaptively and it depends on the specific problem.

Any iteration of IOSO essentially comprises of the creation of surrogate models [6-9] that analytically approximate the objective functions and subsequently of optimization of this approximation function in the current search region. Between two successive iterations, the experiment plan is modified; the current search space is adaptively selected and modified; a global or a middle range response function is chosen and the response surface is transformed; the parameters and the structure of the optimization algorithms are modified and if necessary, new potentially promising points are selected within the current search region. Because of the small number of points in the points are selected within the current search region. Because of the small number of points in the initial *Design of Experiments* (DOE) and a large search space, the accuracy of the process during initial stages could be poor. During each iteration, the behavior of the objective functions, inside the current search space, near the extremum, is stored and the response function is made more accurate. The number of points in the search region is increased and the search space itself is progressively reduced. This results in an increase in the approximation function accuracy, which in turn increases the efficiency of the whole optimization process. The entire process is fully automatic.

Preparation of the data set for optimization

Because of the non-availability of experimental/ estimated values of many of such properties in the public domain, this study is limited to the use of normal boiling temperature, enthalpy of vaporization, vapor pressure, half-life in the atmosphere and biodegradability. Different sources were identified and used to extract the information about each compound selected in this study.

Currently used refrigerants involve an extensive use of chlorofluorocarbon (CFC), hydrochlorofluorocarbon (HCFC), perfluorocarbon (PFC) and other halogenated hydrocarbon based compounds. Non-fluorochemical, fluorochemical and hydrofluoroethers based compounds are also used as refrigerants in some applications [10-12].

Only those compounds which have four or fewer carbon atoms were selected in this study. Duvedi *et al.* [13] reported that molecules with larger number of carbon atoms do not exhibit vapor pressures in the range desired for refrigerants. It is also observed that compounds having double or higher bonds show stability problems by spontaneously decomposing or by polymerizing in a short period of time. In many situations stability problems can be avoided by simply ensuring that the new refrigerant does not have double or triple bonds. Therefore, compounds containing any triple bonds are not considered. However, this study uses compounds with carbon-carbon double bonds to prevent any elimination of potentially good molecules.

Compounds containing nitrogen atoms were not considered, because of primarily two reasons. They are:

1. When both halogen and nitrogen groups exist in a low boiling compound, the compound shows strong tendencies to explode [12]
2. We could not find a sufficiently large number of nitrogen containing compounds, with their properties available. Consequently, such compounds would not be represented well in the data pool.

Compounds containing other elements like sulphur, phosphorous, iodine, *etc*. are also not considered. Again, this is because of the fact that the number of such compounds for which either experimental or estimated property data could be found, is not sufficient to be incorporated in the data pool. An insufficient representation in the data pool would result in a decrease in the accuracy of the response surface. Because of the above concerns, compounds belonging to the generic class of alkanes, alkenes, alkyl halides, ethers and halogenated ethers only were considered for selection in the present effort.

In all, 295 compounds were selected in the data pool. As described earlier, each molecular structure is represented by a unique set of values of the 28 structural design variables (Table 1). Algorithms applied on the initial data, which actually is a pool of different sets of these 28 design variables, generate newer sets of design variable values. Since each of these new sets of design variables, in essence, represents a unique molecular structure, it is highly important that each of these sets of values correspond to a feasible molecular structure. This is ensured by binding the values of the design variables by different equality and inequality constraints. These constraints not only limit the values that can be attained by the design variables; they also place restrictions on how a design variable needs to be combined with other design variables. These equations remain valid for each and every organic compound considered during the construction of meta-models. At the same time, the satisfaction of these equations or constraints remains necessary for any new molecule. The following sections list some of the different constraints which are important from the point of view of obtaining a feasible molecular structure. The sections also explain the necessity and importance of some of the many such constraints.

All the 28 design variables (Table 1) are strictly integers as they represent the number of different bonds. It should be noted at this point, that resonance effects in the molecular structure are not considered. The design variables X_1, X_2, X_3 and X_4 represent the number of single bonds used by the respective carbon atom to bond itself to the remaining three carbon atoms. In general, no carbon atom can have more than four carbon atoms attached to it *via* single bonds and no carbon atom can have less than zero number of carbon atoms attached to it *via* single bonds. However, since the total number of carbon atoms in the refrigerant molecule, considered in this study, was restricted to four, a carbon atom may be attached to a maximum of three other carbon atoms *via* carbon-carbon single bonds. Mathematically, this fact can be represented by the following equation.

$$0 \leq X_i \leq 3 \; for \;\; i = 1,2,3,4 \tag{1}$$

The design variables X_5, X_6, X_7 and X_8 represent the number of carbon atoms attached to each of the four carbon atoms *via* carbon-carbon double bonds. Only a maximum of two carbon atoms may get attached to a given carbon atom and there cannot be fewer than zero carbon atoms that are attached to any carbon atom *via* carbon-carbon double bonds. Hence, the following relationship remains satisfied.

$$0 \leq X_j \leq 2 \; for \;\; j = 5,6,7,8 \tag{2}$$

Similarly, the design variables X_9, X_{10}, X_{11} and X_{12} can only take values between 0 and 4. The reason for this is the fact that in order for the octet rule to be valid, there cannot be more than four hydrogen atoms attached to a single carbon atom and there cannot be fewer than zero hydrogen atoms attached to a carbon atom. Mathematically, this can be represented by the following relationship.

$$0 \leq X_k \leq 4 \; for \;\; k = 9,10,11,12 \tag{3}$$

Using a similar argument, it can be concluded that there cannot be more than four chlorine/ fluorine/ bromine atoms attached to a single carbon atom *via* single bonds. Hence, the following relation holds true.

$$0 \leq X_l \leq 4 \; for \;\; 13 \leq l \leq 24 \tag{4}$$

The same argument also remains true in the case of oxygen atoms bonded to a carbon atom *via* single bonds. Thus, the number of oxygen atoms attached to a carbon atom *via* a single bond may vary between zero and four. However, the initial

pool of 295 data had molecules which either lacked an oxygen atom or contained just a single oxygen atom. Because of this reason, no carbon atom was found, in the original dataset, to be associated with more than one carbon-oxygen single bond. Hence, equation 5 needs to be satisfied.

$$1 \leq X_m \leq 1 \; for \;\; m = 25, 26, 27, 28 \qquad (5)$$

Multiple equality and inequality constraints were formulated to regulate the combinations of the structural design variables. These constraints ensured structural feasibility of the generated sets of the 28 design variables after optimization.

RESULTS OF OPTIMIZATION

As discussed earlier, the primary objective of the study is to develop refrigerants which are better than the currently used refrigerants (specifically Freon-12) in as many aspects as possible. Hence, the property constraints depend on the property values of Freon-12.

Using 265 candidate refrigerants for which all six objectives were available (see below), response surfaces generating algorithm was used [6] for fitting the 28-dimensional response surfaces for each of the following design objectives.

P1 = Normal boiling temperatures
P2 = Enthalpy of vaporization
P3 = Tropospheric half-life time
P4 = Root mean squared value of the difference in the vapor pressure of the particular organic compound and that of Freon-12
P5 = Biodegradability obtained from BIOWIN 5

Table 2. Minimum and maximum values of the six objectives for the initial set of 265 refrigerants

Objective	Minimum value	Maximum value
Normal boiling temperature(^{o}C)	-82	163
Enthalpy of vaporization (kcal/mol)	2.94	13.07
Tropospheric half-life time (days)	0.16943	89120.37
Vapor pressure indicator (kPa)	0	8859.464
BIOWIN 5 estimation result	-0.0569	0.6415

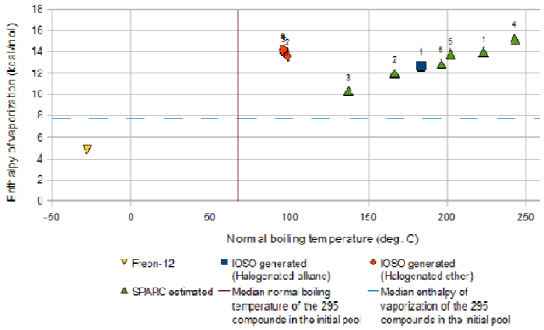


Figure 3. Pareto-optimal results of maximizing enthalpy of evaporation and maximizing boiling temperature: Properties of the molecular structures obtained using IOSO software for optimization and their consequent comparison with those generated through SPARC online calculator. A yellow triangle designates Freon-12.

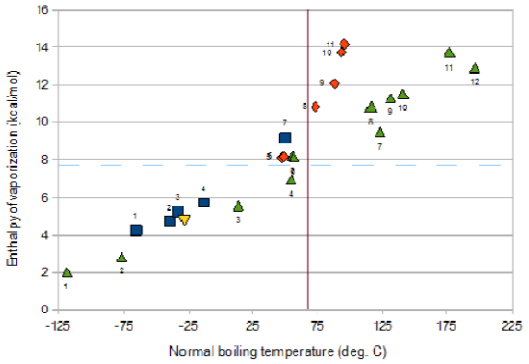


Figure 4. Pareto-optimal results of maximizing enthalpy of evaporation and minimizing normal boiling temperature: Properties of the molecular structures obtained using IOSO software for optimization and their consequent comparison with those generated through SPARC online calculator. A yellow triangle designates Freon-12.

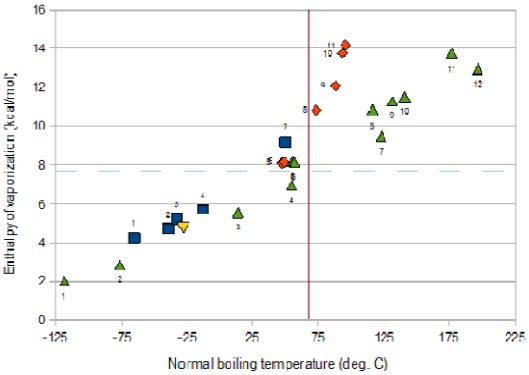


Figure 5. Pareto-optimal results of maximizing enthalpy of evaporation and minimizing tropospheric half-life time: Properties of the molecular structures obtained using IOSO software for optimization and their consequent comparison with those generated through SPARC online calculator. A yellow triangle designates Freon-12.

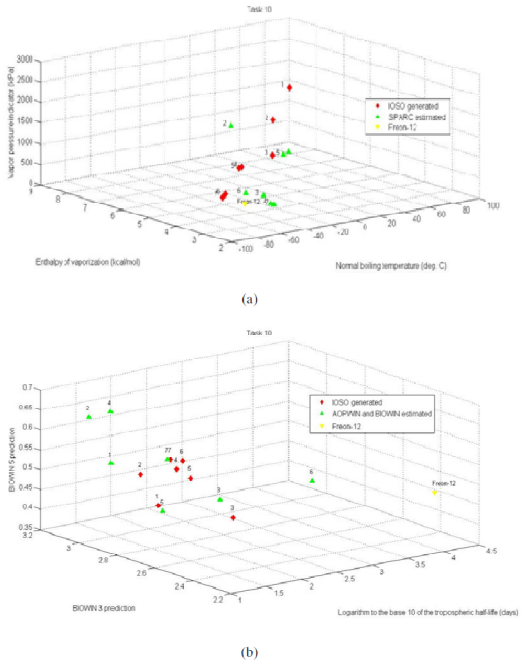


Figure 6. Pareto-optimal results of the simultaneous maximization of the normal boiling temperature, the maximization of the enthalpy of vaporization, and the minimization of the tropospheric half-life time showing distribution of the newly generated molecules in the (a) thermodynamic property space, and (b) environmental property space. A yellow triangle designates Freon-12.

CONCLUSIONS

Multi-objective design optimizations were successfully performed using an initial pool of data, constraints which also ensure the structural feasibility of any generated molecule and meta models. It was found that the methodology successfully generated several candidate solutions which were generally found better than Freon-12 in one or more objectives. Errors between the property predictions using IOSO software and those obtained through property prediction models used in this study were also calculated.

REFERENCES

[1] U.S. Environmental Protection Agency. *Atmospheric oxidation program for microsoft windows (AOPWIN) v 1.92a.* June 2008.

[2] U.S. Environmental Protection Agency. *BIOWIN v 4.10.* March 2009.

[3] *SMILES Tutorial.* February 2009. http://www.epa.gov/med/Prods_Pubs/smiles.htm (accessed December 2009).

[4] J. M. Calm and D. A. Didion, Trade-offs in refrigerant selection: Past, present and future. *International Journal of Refrigeration* 21, no. 4 (1998) p. 308-321.

[5] L. E. K. Atchenie, R. Gani and V. Venkatasubramanian, *Computer Aided Molecular Design: Theory and Practice.* Amsterdam: Elsevier, 2003.

[6] Sigma-Technology Company, Approx-Version 1. Moscow, August 2009.

[7] Sigma Technology, IOSO NM version 1.0 Multiobjective non-linear optimization software. *Reference Manual.* Moscow, 2009.

[8] I. N. Egorov-Yegorov, G. V. Kretinin, I. A. Leshchenko, and S. V. Kuptcov, Multi-objective robust optimization using IOSO technology Part 1: Main features, *Fifth Conference on Evolutionary Methods for Design, Optimization and Control Appl. to Industrial and Societal Problems.* (2003) p. 120-121.

[9] I. N. Egorov, G. V. Kretinin, I. A. Leshchenko, and S. V. Kuptzov, Multi-objective approach for robust design optimization problems, *Inverse Problems in Science and Engineering* 15, no. 1 (2007) p. 47-59.

[10] A. Sekiya and S. Misaki, The potential of hydofluorothers to replace CFCs, HCFCs and PFCs, *Journal of Fluorine Chemistry*, no. 101 (2000) p. 215-221.

[11] J. M. Calm, The next generation of refrigerants - Historical review, considerations, and outlook, *International Journal of Refrigeration* (Elsevier) 31 (2008) p. 1123-1133.

[12] M. Mohanraj, S. Jayaraj, and C. Muraleedharan, Environment friendly alternatives to halogenated refrigerants - A review, *International Journal of Greenhouse Gas Control* 3 (2009) p. 108-119.

[13] A. P. Duvedi and L. E. K. Achenie, Designing environmentally safe refrigerants using mathematical programming, *Chemical Engineering Science* 51, no. 15 (1996) p. 3727-3739.