

**Original scientific work**

**UDK 575.087.1:575.18**

**DOI 10.7251/SVR1510029M**

# **DEVELOPMENT OF A MODEL OF PREDICTING THE SWEETNESS LEVEL BY USING METHODS OF GENETIC PROGRAMMING**

**Professor Halid Makić PhD<sup>1</sup>, Aida Korčić MA, Bahrudin Hrnjica PhD,  
Samira Dedić MA**

**Samira Hotić MA**

Biotechnical faculty, University in Bihac

**Džemila Agić MA**

The Center for Ecology and Energy Tuzla

**Abstract:** Sweeteners are natural or synthetic substances that leave a sweet feeling and have no or negligible nutritional value when compared to the range of sweetness. All over the world, there is a considerable interest in the development and synthesis of new sweeteners, and developed countries are establishing calories reduction trend, so it resorts to the use of artificial sweeteners. Due to the artificial sweetener use health risks, it is being advised to study sweeteners with a high degree of sweetness, and to reduce quantity intake.

This paper follows development of quantitative models for predicting logSw (logarithm of the relative sweetness) from 132 compounds with a molecular weight of 152.146 to 804.872 and sweetness from 0 to 300000.

In order to find a better link between sweetness and the structure of sweeteners, a great number of natural and artificial sweeteners of different structures will be used. The sweetness degree is correlated with quantum chemical and other molecular descriptors using evolutionary modeling, followed by analysis of the obtained models. The entire dataset is randomly divided into a training set of 26 compounds and test set consisting of 8 compounds, represented by 11 selected molecular descriptors. Values of logSw are provided by GPdotNET software.

For the test set, the correlation coefficients are 0.999326.

The choice of descriptors for model development is selected to be able to interpret and support the AH/B model system according to Shallenberger and Acree.

**Keywords:** *sweetener, relative sweetness, neural networks, evolutionary modeling, model, predict, descriptors*

## **INTRODUCTION**

Sweeteners are synthesized or natural substances that are used for sugar replacement, with the sweetness significantly higher, depending on the

---

<sup>1</sup>Halid Makić, halid\_btf@yahoo.com, 037 228 059

type of sweetener from 10 to 3000 times. The sweetness represents a dimensionless quantity and is used to show the relative sweetness of the substance compared with sucrose, with perception rating of 1. In the world, there is considerable interest of the development and synthesis of new sweeteners, and developed countries establish a trend of calories reduction, so it resorts to the use of artificial sweeteners. There is also a noticeable intensification of discussions regarding the safety of sweeteners that were recently dominant in use (saccharin and cyclamate). The search for new sweeteners is still complicated due to the fact that the relationship between the chemical substances and the exception of sweeteners has not been resolved in a best way. The safety of suitable substances used in diets must be also determined. Also, some other criteria must be met, such as compound should be adequately soluble and stable in a wide range of pH and temperatures, also there should be a clean sweet taste with no other or post-ingestion effects, and it must provide sweet feeling as glucose.

Molecular modeling is a universal term used for theoretical methods (quantum-mechanical and empirical) and use of computer technology, but also for the shape and behavior of molecules. Molecular modeling is used to interpret and predict experimental results in chemistry and physics, for which there are no relevant experimental data, changes of the structure made under different conditions forming the basis for new materials development and the design of biologically active substances. Computer chemistry can be defined as the application of mathematical and theoretical principles to solve chemical problems. We can say that molecular modeling, as a subgroup of computer chemistry, deals with the behavioral predictions of individual molecules in a chemical system (*R. Leach 2001*).

Studies on the synthesis of artificial sweeteners have started in the 19th century and to this day have developed in a number of different types of sweeteners. Emerging trends of sweeteners development is aiming toward an increase of the relative sweetness, i.e., increasing the effect of sweetness by the lowest possible concentration of sweetener. Most researches in the field of model development for predicting the relative sweetness and the connections between the structure and the relative sweetness of sweeteners are moving towards QSAR studies and were carried out on a certain set of related molecules. Until 1963, Robert Shallenberger and Terry Acree proposed AH-B Theory of Sweetness (*Shallenberger and Acree, 1963*). Simply put, they have proposed the theory of sweetness: in order to have a taste of sweet, a compound must contain a hydrogen bond donor (AH) and the Lewis base (B) separated by about 0.3 nanometers. According to this theory, AH-B unit binds sweetener with corresponding AH-B unit on the biological sweetness via receptors for the sweetness sense production.

In addition to this theory, Lemont Kier suggests BX theory in 1972 (*Lemont Kier, 1972*). While previous researchers noted that among some compound groups, sweetness flavors are different, this theory formalized these observations suggesting that the compound should have one third of binding sites (marked X) that could interact with hydrophobic receptors on the sweetness receptor. Later, the researchers statistically analyzed the distance

between superiors AH, B and X of the several types of sweet substances to assess the distance between these interactions on the sweetness receptors.

MPA theory of the multipoint attachment sweetness theory is proposed by Jean-Marie Tinti and Claude Nofre in 1991, which is so far the most elaborated theory (*Tinti and Nofre, 1991*). This theory involves a total of eight interactionsites between a sweetener and the sweetness receptor, although not all sweeteners interact with all eight sites. This model successfully solved the efforts aimed to find very strong sweeteners, including the most powerful types known until now, the guanidine sweeteners. The most powerful of these, lugduname, is about times sweeter than sucrose.

Prior to the modern theories of sweetness, it was popular to associate sweetness with hydroxyl (OH) groups, due to the fact that sugars are saturated by them. However, it was soon being criticized because the polyhydroxy groups differ significantly in sweetness, and many amino acids, some metal salts and unreacted substances, such as chloroform (CHCl<sub>3</sub>) and the saccharin are also very sweet. However, it was obvious that there are some common characteristics among the sweet substances and for the past 75 years, the theory related to the molecular structure and sweet taste has progressed so it explains satisfactorily why certain materials give off a sweet taste. Shallenberger and Acree (*Shallenberger and Acree, 1967*) were the first to suggest the AH/B theory of full flavor substance being common to all components having a sweet taste. That substance is first considered as the combination of covalently bound H proton with electronegative orbital located at a 3Å distance from the protons. Thus, adjacent electronegative atoms of the molecule are essential to the sweetness. Furthermore, one of the atoms must have a proton beingattached to hydrogen bond. The atoms of oxygen, nitrogen and chlorine often fill this role in the sweet molecules and oxygen atoms of hydroxyl groups may serve for the AH or B function in the molecule.

Stereochemical requirements are also compulsory for the AH/B group components of sweet taste so they would be suitable for the receptor's site. The interaction between the active group of sweet molecules and taste receptors is currently considered to be carried through the H-bond AH/B components to a similar structure in taste receptor. The third characteristic is also added to the theory in order to extend its validity to intensely sweet substances. This supplement incorporates appropriate stereochemical arrangements ofregions prone to lipid sweet molecules, usually marked with  $\gamma$ , which are attracted to similar regions prone to lipid taste receptors. These regions of the sweet molecules are usually methylene (-CH<sub>2</sub>-), methyl (-CH<sub>3</sub>) or phenyl (C<sub>6</sub>H<sub>5</sub>) groups. The complete molecule that gives sweet taste is geometrically arranged so that the triangular contactof all active units (AH, B and  $\gamma$ ) with the receptor molecules occursto intensely sweet substances, and this arrangement makes a three-sided sweetness theory.  $\gamma$  side is extremely important feature of intensely sweet substances, but plays a minor role in the sweetness of sugar (*Lemont Kier, 1972*). It appears to be working through theaccess provisioning to certain molecules of unknown receptors, as such, affects the intensity of sweetness. Since sugars are mostly hydrophobic, this feature is expressed in a limited extent for some sugars, such as fructose. This component of sweet taste units is the main factor of sweetness quality variations asobserved for different sweet

substances. Not only this is important for time-intensity perception of sweetness, but it is also related to some interactions between sweet and bitter flavors that some of the components reveals.

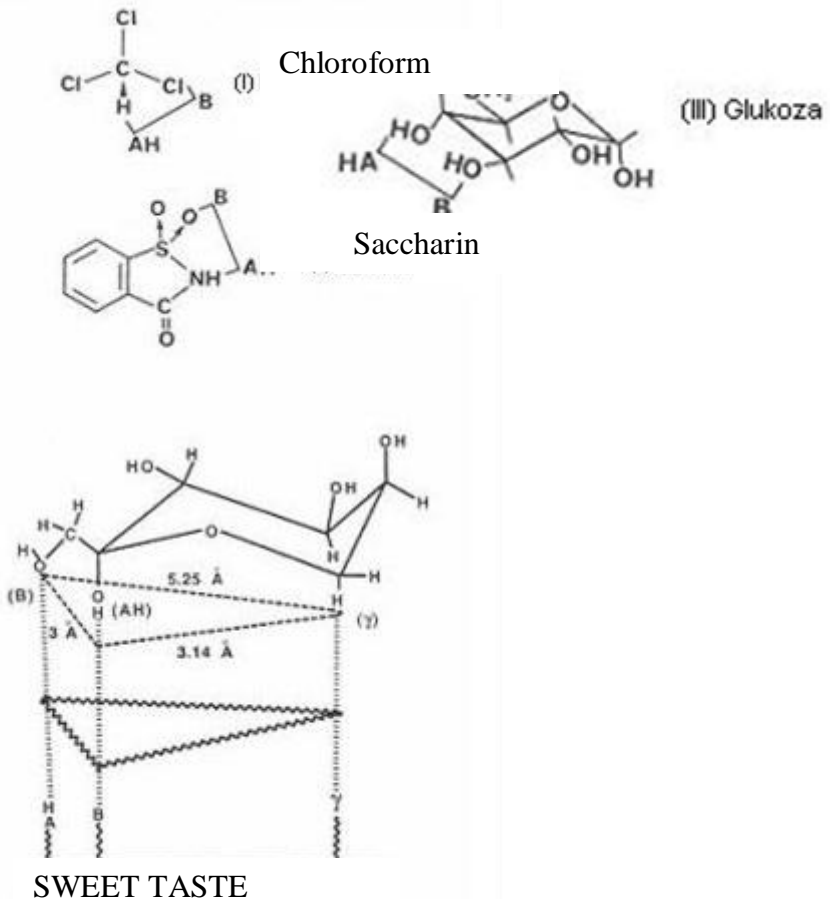


Figure 1: Schematic representation of the links between the AH/B side of  $\beta$ -D-fructopyranose and the sweet taste receptor (Shallenberger and Acree, 1967)

Spillane (William J. Spillane, 1996) noted that the AH/B theory apparently works very well, although extensive, hydrophobic/hydrophilic and electronic effects have significance as well. Shallenberger explains that the sweetness initiates due to the concentrated intermolecular, non-parallel interactions of hydrogen bonds between glycoprotein (*gr. glyks - sweet, phoros-carry*) and dipole receptor. The difficulty in explaining the sweetness of molecules with different chemical structure is also explained by Shallenberger and how it led to the formation of different sweetness theories. Application of sweetness theory in practice shows a very big impact on the food industry.

Large scale experiments with a large sugar number done by Birch and Lee (Birch and Lee, 1971) support Sweetness Theory of Shallenberger and indicate that the fourth hydroxyl group of glucopyranoside is of unique

importance in determining the sweetness, probably by donating AH group proton. It seems that the primary alcohol group has little significance for sweetness. Replacing the acetyl or azide group gives great bitterness to sugar, while replacing benzoyl group causes insipidity.

Computer chemistry can be defined as the application of mathematical and theoretical principles to find solution of chemical problems. We can say that the molecular modeling, as a subgroup of computer chemistry, deals with behavioral predictions of individual molecules in a chemical system (*Leach, 2001*). Today, many different MM models and force fields are in use out of which Gaussian includes: Amber, Dreiding and UFF. MM method is mainly used to handle very large molecules where more accurate methods are practically unfeasible. The molecular mechanics techniques are often empirical methods based on the principles of classical physics and these have the fastest computational speed.

Computer molecular models are the result of mathematical equations that describe the situation and the behavior of electrons and nuclei. Several models were developed and are being used according to the simulation. Basically, there are two conceptually different procedures that, to a greater or lesser extent, can be used in predicting the molecular structures. Mathematical models are divided into classical-mechanical and quantum-mechanical principles (*Carson and Cobelli, 2001*):

**Classical - mechanical approach** pays attention to the molecules as a collection of atoms and bonds treated as balls and elastic threads. Information such as atomic radius and length connection change are used to find the best position of atoms. It is fast, and in most cases, relatively accurate method for locating the optimal geometry of molecules. Here are some methods of molecular mechanics; MM+ method that uses the general force field and AMBER, BIO+, OPLIS methods, using specialized force fields.

**Quantum-mechanical methods** use to solve Schrödinger equation in two ways; semi-empirical and ab initio (which means from the beginning). Semi-empirical methods use experimental data to simplify Schrödinger equation to solve it quickly. For this simplification, many methods have developed including Huckel, Extended Huckel, INDO-S, and MINDO. Each of them has a set of parameters that are based on experimental measurements for different compounds. Some of semi-empirical methods are: Expanded Huckel, INDO, CNDO, MINDO/3, MINDO, AM1, and PM3 (including transition metals), ZINDO/1, ZINDO/S.

On the one hand, ab initio methods use only mathematical approximations. These methods are very theoretically "clean", but on the other hand they are much more computer-complicated and rely on high-speed computers. Some of the STO-G1 methods are made to improve the accuracy of ab initio methods by using smaller number of data.

The question then arises how it is possible to predict the ability of the compounds that are poorly explored or treated by some of the previous methods. During the testing, it is necessary to take a larger number of compounds which are treated by the classical approaches including the synthesis and isolation of the compounds and necessary measurements at the

end. This way, the predictions of precisely defined compound properties are performed.

This paper uses Shallenberger and Acree theories for predicting the sweetness of molecules. As a basic size, relative sweetness is used, that is, its logarithmic value. Relative sweetness is the measure that shows the sweetness of a substance in comparison with sucrose. Chemical-molecular descriptor is the result of logical and mathematical procedures that transforms chemical information into numerical values. Each molecule carries on exactly certain types of information that we're looking at different levels, and based on it, we reach the desired results. The work is based on different structures of molecules that have certain physical, chemical and biological characteristics. A set of 132 molecules, that have the appropriate value of descriptors and relative sweetness, is used in development of the sweetness predicting model. Eleven different descriptors were used for each molecule. In the development of model, each one is treated with 13 descriptors and 132 relative sweetness which make 1716 data in total. The characteristics of each molecule can be seen at different levels and each of them carrying specific types of information.

## METHODS

In this paper, the models of predicting the relative sweetness based on the structure of sweetener molecules are developed. For this purpose, a genetic (evolutionary) modeling is used. In the evolutionary modeling, we got a set of 34 filtrated molecules. A method to develop a model consists of four steps including the preparation of a data set which contains compounds with the experimental sweetness. Then, we did the calculations of molecular descriptors to describe and select the appropriate descriptors for predicting the sweetness and the division of the entire set of data randomly during the training and test set. At the end, we made the models by using methods of genetic modeling. Looking for an answer that is given in this paper, high complexity programs are necessary and their application is persistent in solving mathematical and logistic problems and modeling of molecular systems.

For this purpose were used the following programs:

1. Gaussian 03, GaussView 4.1 (*Gaussian 03, 2004.*)
2. GPdotNET (GPdotNET, 2003)

Gaussian (*Gaussian 03, 2004*) is a software package for the calculation of molecular properties. The package consists of 80 separate programs integrated in a single unit with an auto dialer in the main program. It contains about 800,000 orders. The authors list contains of the names of 82 researchers. According to the number and variety of integrated processes, Gaussian is the richest package for molecular modeling. Because of its universality, the access to the source code and low prices for academic institutions, Gaussian software package represents a worldwide standard for modeling of ab initio, and other methods. These methods may provide energy, the molecular structure and vibrational frequencies of molecular systems, optical and magnetic properties of molecules and substances along with numerous molecular properties derived from these basic computation types.

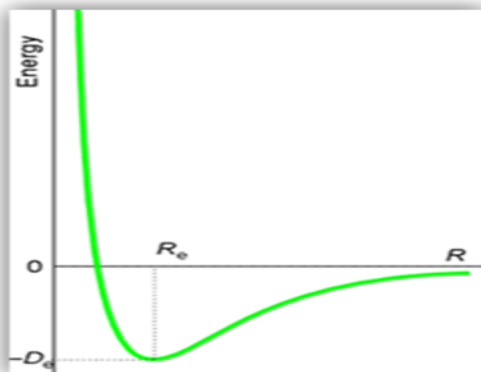


Figure 2. Potential energy as a function of distance within the core of diatomic molecules (Campbell et al., 2006)

Calculations can be performed on the systems in the gas phase or solution, and in their ground or awakened state. Gaussian can serve as a powerful tool to explore the areas of chemical interest such as a replacement effect, reactions of mechanisms, potential energy surfaces and stimulus energies. Gaussian is able to carry out 8 calculation processes sequentially or parallel with that. It can calculate the energy and other related properties for a number of heavy atoms in a matter of minutes. It can submit jobs of few hundred atoms, and can predict the structure of molecules that have up to several hundred atoms of the same size of a computer system. Corresponding bigger systems can be run on supercomputers, based on their specific CPU derived characteristics.

GPdotNET (B.I. Hrnjica 2014) is a tool of artificial intelligence for the application of genetic programming and genetic algorithms in modeling and optimization of various problems of engineering nature. The application was made in .NET (Mono) framework and C# programming language and can be run on Windows and Linux operating systems. The development of the program began in 2006 along with post-graduate work of the modeling and optimization of evolutionary algorithms. As an open source project, GPdotNET was first published on 5th November 2009, on [www.codeplex.com](http://www.codeplex.com) web page. GPdotNET is very easy to use. A person without genetic programming knowledge or genetic algorithm can apply these methods in the program in order to find the solutions of the problems. The application can be used to model any process of engineering that can be presented using exact information, as well as for educating students about evolutionary methods, mostly genetic programming and genetic modeling.

GPdotNET supports the following types of optimization and modeling:

1. **Model for specific data** - modeling with or without predictions of specific data using symbolic regression with genetic programming.

2. **Modeling and optimization for specific data** - modeling with or without predictions of specific data using symbolic regression with genetic programming and optimizing obtained GPdotNET model by using genetic algorithm.

3. **Model of time interval** - the time interval modeling and forecasting data using symbolic regression with genetic programming.

4. **Optimization of analytic functions** - optimization of analytically defined functions using genetic algorithm.



Figure 3: User's interface of the program GPdotNET (Hrnjica B.I. 2014.)

Mathematical modeling with the method of genetic programming by using GPdotNET tools for modeling, optimization and prediction of evolutionary algorithms. Loading and displaying data to train GP models.

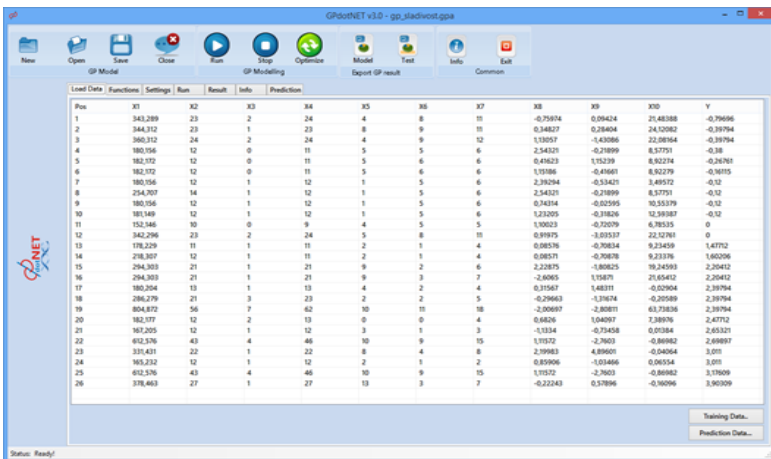


Figure 4: Loading and displaying data (Hrnjica B.I. 2014.)  
 Defining the set of functions that take part in the simulation and the search of the model.



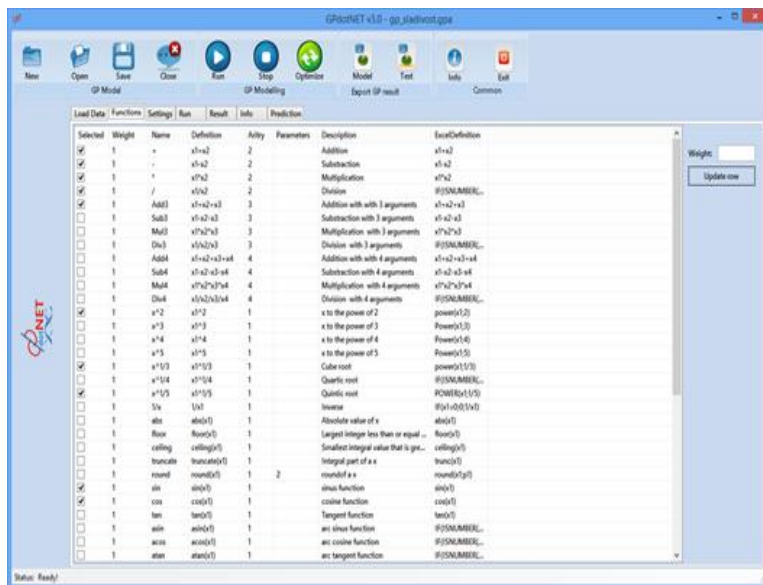


Figure 5: Defining the set of functions (Hrnjica B.I. 2014.)

## RESULTS AND DISCUSSION

One of the first attempts to systematically find the correlation between the structure of a molecule and its sweetness is made by German chemist Georg Cohn, in 1914 and to this day, many studies have been made and different approaches have been used in predicting and finding a quantitative relationship between the structure and the relative sweetness of the sweetener. Many researchers have analyzed the relationship between sweetness and different types of sweeteners as well as their structure by using quantitative (QSAR) models of structure relationships and their activities/properties (Walters, 1995). In 1966, Deutsch and Hansch were among the first ones who conducted QSAR studies on a number of 9 sweet substituent nitroaniline compounds, and showed that distribution coefficient of octanol/water and hydrophobicity of substituents plays an important role in the expression of those sweetness compounds (Deutsch & Hansch, 1966). From 1980 to 1981, Iwamura examines the sweetness in the group of perillartine compounds and aniline derivatives, and some analogs of L-aspartyl dipeptide by using QSAR models, and it showed a high sweetness correlation and the structure of substituents (Iwamura, 1980, Iwamura, 1981). Spillane considered that the sweetness is also important in relation to the hydrophobicity of the compound (William J. Spillane, Ryder and Walsh, 1996). Spillane showed it on amino-succinic derivative groups. Tarko realized that the size of the molecule favorably contributes to the strength of sweetness compound. He analyzed the set for model development of 97 molecules ( $R^2 = 0,83$ ) and the test set that included 24 molecules ( $R^2 = 0,86$ ) (Tarko & Lupescu, 2006).

Recently, researches of Yang and his associates are based on QSAR and QSPR using diverse data sets, and testing the model with other different data sets. These studies aim to build suitable models for the compound sweetness prediction of a bigger number of compounds, even bigger than the compound of previously published studies (Yang *et al.*, 2011). The need of model development resorting for a different set of molecules lies in the fact that the range of sweetness is very wide, molecular weights have a wide range and in structural and conformational diversity of molecules. This is basic concept of this work, except of the application of artificial intelligence and generic modeling on a different set of molecules of natural and artificial sweeteners is used here.

The aim of this study is to find a link between the structure of sweetener molecules and relative sweetness and to develop an acceptable model for forecasting with minimal deviations of the calculated and experimental values. The necessary procedures are carried out and mathematical modeling of evolutionary algorithms is used.

The model was developed by using the *GPdotNET V3.0- artificial intelligence tool* (B.I.Hrnjica <http://gpdotnet.codeplex.com>), while the analysis was performed using 12 descriptors as input variables. The average deviation between the calculated and experimental values is 0,048 with correlation coefficient of 0,999. The results show that the best solution is found in 124.632 generation, with the fitness value of 873,25. Obtained mathematical model is provided in the form of „expression tree“ as shown in Figure 6.

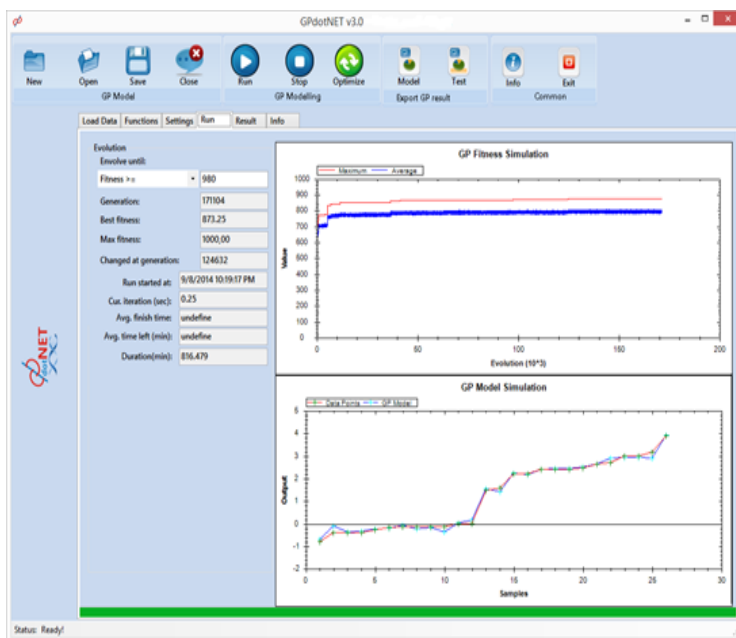


Figure 6: Simulation search solutions (Hrnjica B.I. 2014.)

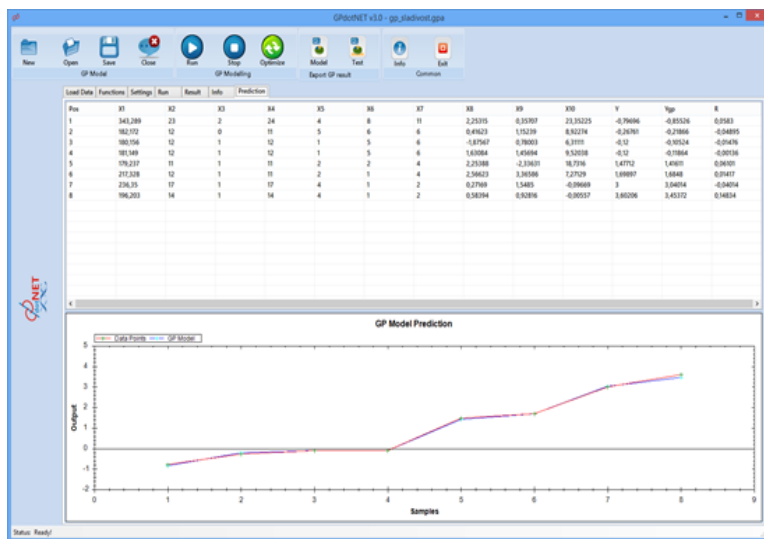


Figure 7: Simulation of test data (Hrnjica B.I. 2014.)

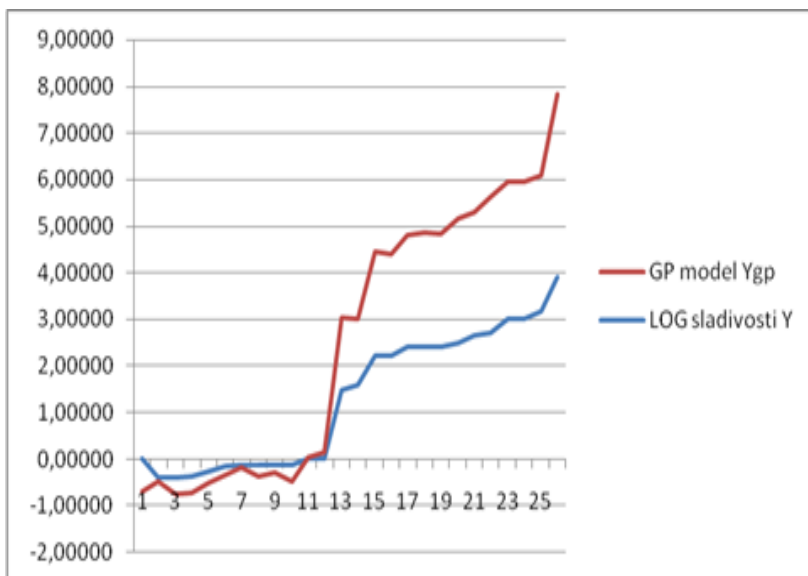
The results are much better than QSAR predictions, as demonstrated by the references of earlier published works (Yang *et al.*, 2011). The explanation lies in the fact that we used larger number of descriptors, and therefore more variables in this work, which favored the use of genetic algorithm. In addition, genetic algorithm has a number of advantages:

- Optimization of continuous or discrete variables;
- Does not require differentiating the objective function;
- Simultaneous search from a wide interval of the objective function;
- The use of a large number of variables;
- Adjustment for parallel computers;
- Optimization of variables with extremely complex functions goal;
- Provides a set of optimal variables, not just one solution.

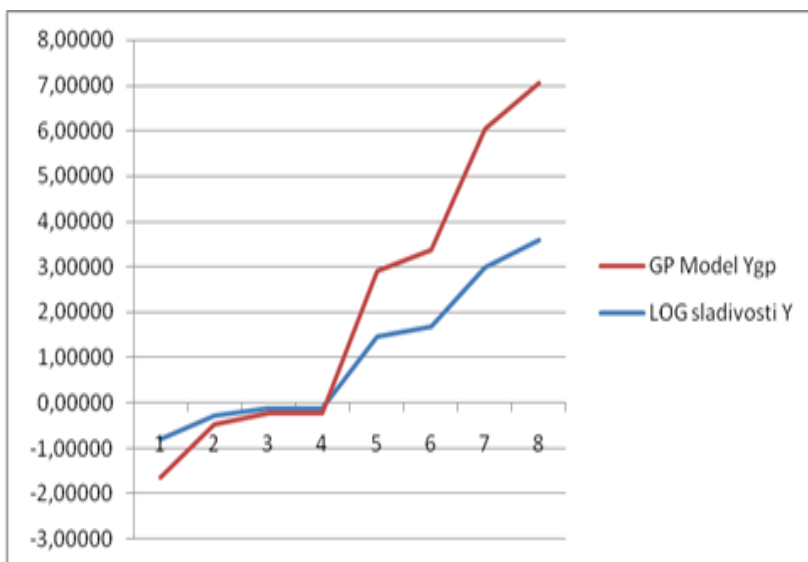
These advantages come in handy when the traditional methods cannot make a satisfactory optimization. Of course, the genetic algorithm is not the best solution to solve any problems. For example, the classical methods of solutions are much better and more quickly calculate the optimum when it concerns analytical functions with several variables (2, 3, etc.). In our work, we found that the combination of descriptors used to predict the relative sweetness component is closely related to logSw. Because of the fact that there are no extreme deviations between experimental and calculated values (Table 4), we concluded that the sweetness is highly related to the properties of atoms, the number of donor and acceptor bonds, molecular weight, and structural properties that are included to provide descriptors. This indicates that the selected molecular descriptors may well interpret the AH/B system.

By developing mathematical model presented in the equation, it is possible to get value of relative sweetness using molecular descriptors for any

newly synthesized molecule. This is confirmed by the fact that the model is developed in the training set, and used again on a test set of randomly selected molecules. The correlation for the training set is 0,99611, and the average deviation is 0,098346.



*Figure 8: Graphic scheme of the error training set*



*Figure 9: Graphic scheme of the error test set*

Table 4: The test set of molecules

Number		1	2	3	4	5	6	7	8
Molecular weight	X1	343,289	182,172	180,156	181,149	180,156	217,328	236,35	196,203
Number of atoms	X2	23	12	12	12	11	12	17	14
Number of rings	X3	2	0	1	1	1	1	1	1
Number of bonds	X4	24	11	12	12	11	11	17	14
Number of rotating bonds	X5	4	5	1	1	2	2	4	4
Donors of H-bonds	X6	8	6	5	5	2	1	1	1
H-bond acceptors	X6	11	6	6	6	4	4	2	2
Dipole 1	X7	2,25315	0,41623	- 1,87567	1,63084	2,25388	2,56623	0,27169	0,58394
Dipole 2	X8	0,35707	1,15239	0,78003	1,45694	- 2,33631	3,36586	1,54850	0,92816
HF	X9	23,35225	8,92274	6,31111	9,52038	18,73160	7,27129	- 0,09669	- 0,00557
LOG of sweetness	X10	- 0,79696	- 0,26761	- 0,12000	- 0,12000	1,47712	1,69897	3,00000	3,60206
GP Model	Yg p	- 0,85525 878	- 0,21865 886	- 0,10523 482	- 0,1186 441	1,4160 9755	1,684 805	3,0401 4097	3,45372 271
RESIDUAL	R	0,06	-0,05	-0,01	0,00	0,06	0,01	-0,04	0,15

The correlation of the test set is 0,999326, and the average deviation is 0,0475.

## CONCLUSION

In this paper, mathematical modeling of genetic programming method has been developed and tested using GPdotNET tools for modeling, optimization and prediction of evolutionary algorithms. It has been shown that the selected molecular descriptors can very well predict the relative sweetness and can also interpret the theory of sweet taste of sweeteners, such as the AH/B theory founded by Shallenberger and Acree that is quite examined.

In the research area of sweeteners, the main trend for the synthesis of high intensity sweeteners is to replace the existing sweeteners studying the mechanism for sweetness. Although many factors affect the sweetness of the compound, this paper discusses the importance of the molecular structure of sweeteners without considering the complicated interactions between the sweetener and its receptors. Models being built in the work will be useful for the new design of intensive sweeteners.

Mathematical modeling of the genetic programming method using GPdotNET tools for modeling, optimization and prediction of relative sweetness of evolutionary algorithms gives proper agreements between experimental and calculated values. The average deviation between the calculated and experimental values is 0,045 and the correlation coefficient is 0,999.

## **RAZVOJ MODELA ZA PREDVIĐANJE STEPENA SLADIVOSTI KORIŠTENJEM METODA GENETSKOG PROGRAMIRANJA**

**Prof. dr Halid Makić, mr sc Aida Korčić, dr sc Bahrudin Hrnjica, mr sc. Samira Dedić, mr sc Samira Hotić, mr sc Džemila Agić**

**Apstrakt:** Sladila su prirodne ili sintetičke tvari koje ostavljaju slatki osjećaj i posjeduju nikakvu ili zanemarivu prehrambenu vrijednost u odnosu na opseg slatkoće. U svijetu postoji znatan interes za razvoj i sintezu novih sladilima, a razvijene zemlje uspostavljaju trend za smanjenjem kalorija, pa se pribjegava i korištenju vještačkih zaslađivača. Zbog zdravstvenog rizika upotrebe vještačkih zaslađivača, pribjegava se istraživanju zaslađivača sa visokim stepenom slatkoće, a smanji količinski unos.

U ovom radu, razvijeni su kvantitativni modeli za predviđanje logSw (logaritam relativne sladivosti) od 132 spoja s molekulskom masom 152,146-804,872 i slatkoće od 0 do 300000.

Kako bi našli bolju vezu između sladivosti i strukture zaslađivača, koristit će se velik broj prirodnih i umjetnih sladila različitih struktura. Stupanj slatkoće je koreliran s kvantnohemijskim i drugim molekulskim deskriptorima korištenjem evolucijskog modeliranja, zatim izvršena analiza dobivenih modela. Cijeli set podataka nasumično je podijeljen u trening set uključujući 26 spojeva i testni set uključujući 8 spojeva, koje zastupa 11 odabranih molekularnih deskriptora. Vrijednosti logSw su predviđene pomoću GPdotNET softvera.

Za testni set, koeficijenti korelacije 0,999326.

Odabir deskriptora za razvoj modela je odabran na način da može tumačiti i podržati AH/B sistem modela po Shallenbergeru i Acreeu.

**Ključne riječi:** zaslađivač, relativna sladivost, neutonske mreže, evolucijsko modeliranje, model, predviđanje, deskriptori

## **REFERENCES**

1. Birch & Lee, (1971.): The chemical basis of sweetness in model sugars, London
2. Campbell, Neil A.; Brad Williamson; Robin J. Heyden (2006.): Biology: Exploring Life. Boston, Massachusetts: Pearson Prentice Hall.
3. Carson E. i Cobelli C. (Eds.) (2001.): Modelling Methodology for Physiology and Medicine, Academic Press, San Diego, CA..
4. Gaussian 03, Revision C.02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J.

- Dannenbergh, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, and J. A. Pople, Gaussian, Inc., Wallingford CT, 2004.
5. Hrnjica B.I. (Bahrudin) (2014.): GPdotNET V3.0- artificial intelligence tool [kompjuterski program], <http://gpdotnet.codeplex.com>, zadnja posjeta 19/06/.
  6. Iwamura, H. (1980): Structure-taste relationship of perillartine and nitro-andcyanioaniline deriavtives. *Journal of Medicinal Chemistry*, 23, 308–312.
  7. Iwamura, H. (1981): Structure-sweetness relationship of L-aspartyl dipeptide analogues. A receptor site topology. *Journal of Medicinal Chemistry*, 24, 572–583.
  8. Lemont Kier (1972.): Molecular theory of sweet taste, *Journal of Pharmaceutical Sciences*, Volume 61, Issue 9, pages 1394-1397.
  9. MATLAB and Statistics Toolbox Release (2012b.): The MathWorks, Inc., Natick, Massachusetts, United States.
  10. McCaleb, Rob (1997): "Controversial Products in the Natural Foods Market". Herb Research Foundation.
  11. Leach, R., (2001.): *Molecular Modelling: Principles and Applications*,
  12. Schallenberger, R.S. i Acre, T.E. (1967.): Molecular theory of sweet taste. *Nature*, 216, 480-482.
  13. Tarko L, Lupescu I. (2006.): QSAR Studies on amino-succinamic acid derivatives sweeteners. *Arkivoc* 13: 22–40.
  14. Tinti JM, Nofre C; (1991.): Design of sweeteners, Walters DE Washington
  15. Yang X, Chong Y, Yan A, Chen J. (2011.): In-silico prediction of sweetness of sugars and sweeteners. *Food Chem* 128(3):653–8.
  16. William J Spillane, Caroline A Ryder, M.Rachel Walsh, Patrick J Curran, Danny G Concagh, Siobhan N Wall, (1996.): Sulfamate sweeteners
  17. Walters Tinti JM, Nofre C; (1991.): Design of sweeteners, Walters DE Washington