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Artificial intelligence applied to model the sulphur absorption process - a possible application in cure with sulphurous mineral water

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Abstract

The presence of Sulphur in human body is estimated to be around .25 percent from total body weight. The modern therapy includes among others the usage of Sulphur us spring waters as crenotherapy or external use like - therapeutic and preventive treatment for a large category of diseases. High levels of hydrogen sulphide are extremely toxic and as result the model of absorption of Sulphur could be useful as predictor in a daily treatment during a cure with sulphurous mineral water.

This quantity of chemical elements from a specific diet rich in these elements absorbed in human organism is one of the most important characteristics of a benefic cure in medical diseases. The most studied mechanisms of absorption were studied for Zinc, Magnesium, Iron and Calcium. The most common way to develop a mathematical model is to use the pharmacokinetic equations based on Michaelis-Menten approach (first order model) and to develop it thereafter for quantitative relations. In some cases, only experimental data can exists and the pharmacokinetic model is not completely elucidated or a simplified model doesn't exist yet.

A model based on genetic programming is proposed in order to discover a mathematical relationship between dietary sulphate (mmol/day) and total sulphate in ileostomy fluid (mmol/day) using experimental data published in literature.

The set of terminals that are used in genetic programing – GP (using Polish notation) is reduced to basic operation (sum, difference, multiplication and division) along with the most plausible operations that could have physical meaning: rooted square, exponential and power. The formulas discovered by GP using experimental proved a good fit of data with discovered mathematical formula, e.g. the rooted mean square error below 1.5% and $R^2 \approx 94.36\%$.

Mathematical formulas discovered by genetic programming can be used as an alternative to pharmacokinetic model in order to predict sulphate and sulphite absorption and excretion. The usage of this method is especially efficient when the mechanism of absorption in not elucidated enough to provide a compartmental model given by a set of equations. A correlation with pharmacokinetic equations in the case that these exist will help the improvement of terminals and alphabet used by genetic programming in order to have a model closer to one that have a physical meaning.

Key words: *Sulphur absorption, sulphurous mineral water, mathematical model, genetic programming,*

Introduction

Several minerals that are necessary for existence of life are present in diet in various amounts (the 7 elements are: Ca, P, Mg, Na, K, Cl, and S). Several other elements, micro minerals (or trace minerals) are required in much smaller amounts (milligrams to micrograms each day) for existence of life (1). The most abundant mineral element in the human body is calcium, phosphorus and sulfur, in this order. The most studied mechanisms of absorption along with mathematic models were studied for Zinc, Magnesium, Iron and Calcium. Human intestinal absorption and skin absorption mathematical models that are proposed in literature are verified by experimental data and its represent an approximation of chemical or physical phenomenon (2). High levels of hydrogen sulphide are extremely toxic and as result a model of absorption of sulphur could be useful for prediction in a daily treatment for a cure with sulphurous mineral water. The sulphur is available in our usually diets, derived almost only from proteins but also from 2 of the 20 amino acids that present sulphur in their composition (3). Sulphurous mineral waters are traditionally used for respiratory, skin, and musculoskeletal disorders, but more recently, the beneficial effects proved to be on the other disorders (arterial hypertension pulmonary, atherosclerosis, ischemia-reperfusion injury, peptic ulcer, heart failure, and acute/ chronic inflammatory diseases (4,5,6,7). The sulphur (in the form of hydrogen sulphide) is the main responsible for effects of mineral waters, sulphurous mud, or plods that are made using sulphurous mineral water (4, 8). Experiments with baths with mineral water proved that the useful minerals from water can be absorbed by the skin. In an experiment using human skin at 98.6°F, the authors of (9) found that sulfates pass fast the skin barrier, meanwhile magnesium did not. Even the propagation of transdermal magnesium is scientifically unsupported (10); the transdermal percutaneous models for other mineral can be used in order to evaluate the accumulation of mineral and to develop a treatment schema based on time slicing.

Materials and methods

The method used in this paper is (10). The equation of evolution of the apical iron uptake as function of time and initial parameters from (10) is computed using Genetic Programming (GP) (11). GP is a branch of evolutionary algorithms (EA), which have a number of applications to optimization problems that mimics Darwin's evolutionary theory. The basic operations in GP are similar to GA (Genetic Algorithms): selection (in most of situation the elitist selection), crossover and mutation. Different from GA, in GP all the operations are made using chromosomes in that are functions (representation of mathematical formulas as trees in reverse Polish notation), figure 1.

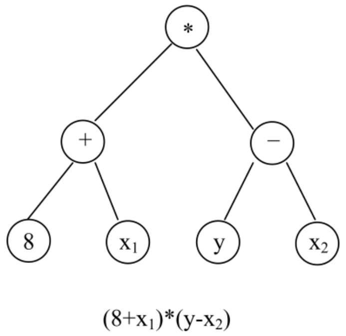

Figure 1. *A simple formula in GP.*

The crossover and mutation operate in the manner as genetic algorithms (GA) but using the sub trees, figure 2 and 3. The main steps in GP are: generation of population, evaluation of each individual, selection, crossover, mutation, and generation of a new population. A first population of individuals is created using a random generator (usually uniform distribution). The common values are between 50-500 individual. The algorithm used fixed population in GP, but in GA, there are algorithms for variable size of population during generations.

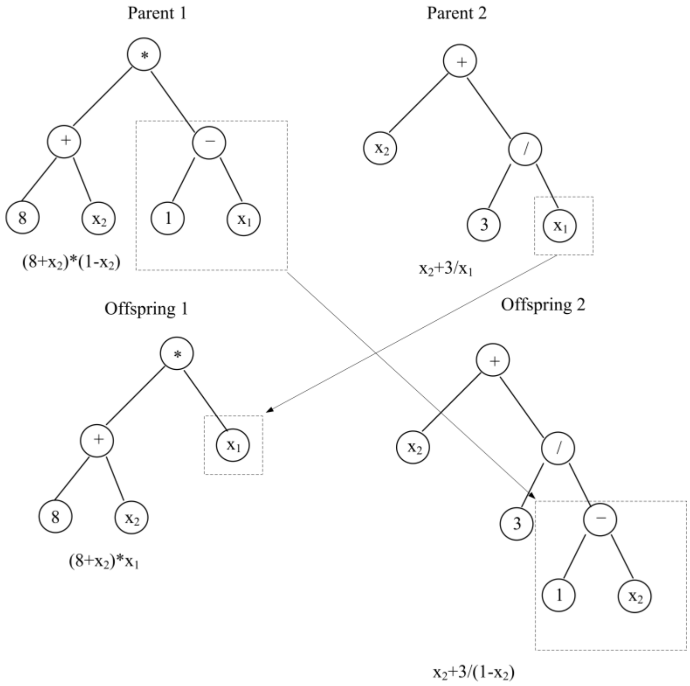

Figure 2. *The crossover (single point cut) in GP.*

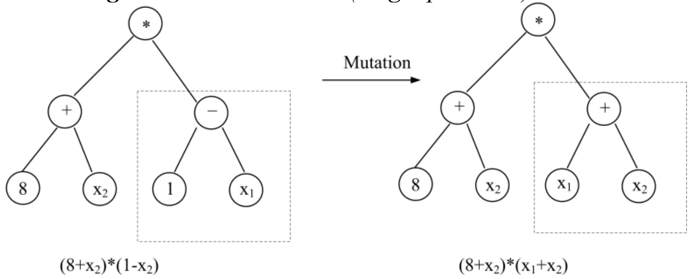

Figure 3. *Mutation operator in GP.*

Each individual from population is evaluated according to fitness function. The fitness function can be defined according to different criteria, and one of the most common measure is the RMS (Rooted Mean Square Error) among the experimental data and the values given by model represent by obtained function using GP. Using the fitness function, the selection operator selects the pairs of individuals (according to selection mechanism: roulette, tournament, stochastic sampling, etc.) in order to apply the crossover operator to create new individuals. The less performing individuals are discarded and the best individuals are grouped in a new generation. Mutations are performed in order to prevent the premature convergence and elitism disadvantages. The population is evaluated again and the loop continues until stop conditions are fulfilled. The stop condition can be a predefined number of iterations or a number of steps (usually 50-100 generation) that cannot produce an improvement of fitness for the best individual from population.

Results

The experimental data from paper (12) are used in construct an analytical model using GP.

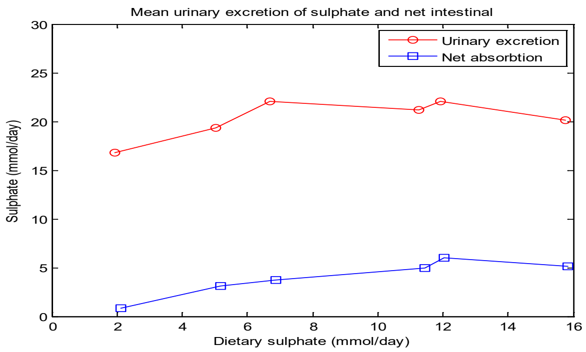

Figure 4. *Mean urinary excretion of sulphate and net intestinal sulphate absorption in dietary sulfate experiment (from (11)).*

In figure 4 is presented Mean urinary excretion of sulphate and net intestinal sulphate absorption (dietary - total ileal sulphate) v dietary sulphate in the ileostomies. Mean urinary excretion of sulphate is correlated with intestinal absorption according to (11,12). The scope is to find out a mathematical relation (function) y = f(x), as in figure 5.

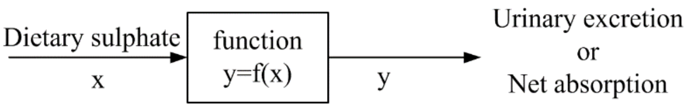

Figure 5. *The mathematical relation that must be found using GP.*

The Parameters Values/criterion, used in GP algorithm is:

- population size 200
- number of generations 60
- recombination probability 0.9
- mutation probability 0.1
- elitism selection : keep the best
- function set cos(), sin(), +, −, *, /, ab, sqrt, exp()
- terminals set, random value between 1 and +10
- initial population Ramped-Half-and-Half
- tree depth limit 16
- selection method Tournament
- fitness function Root Mean Square Error (RMSE).

In the further experiments, a more generalization error, given by the Jackknife Mean Squared Error (MSEJK), at the end of the process will be used. In order to find out the function f(x), the GPTIPS 2.0 toolbox for Matlab was used (13, 14,15,16). Best fitness achieved, RMSE=0.05723, a very good result (figure 6 and figure 7).

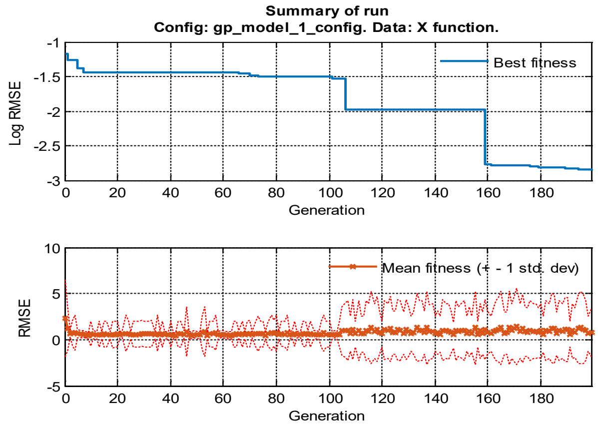

Figure 6. *The fitness evolution during generations until stop conditions for urinary excretion*

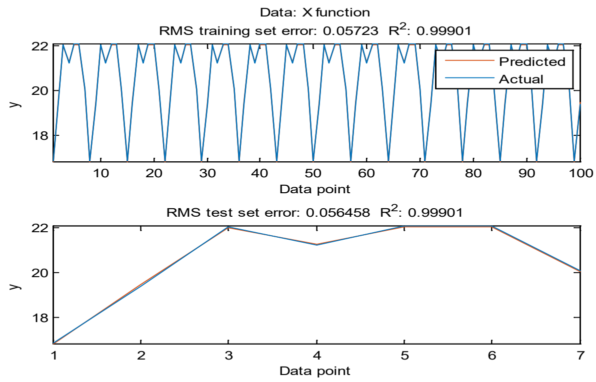

Figure 7. *The fitting experimental date vs model and the RMS plot for all the points from experimental data from (10), urinary excretion.*

A special mention must be done for stop condition (16, 17). There are few available options but the most used are: the reach of a predefined number of iterations, the reach of maxim error criterion, and the maximum depth of the tree (in GP case). The criteria fit R^2 is given in figure 8. The generated tree used for formula extraction is given in figure 9.

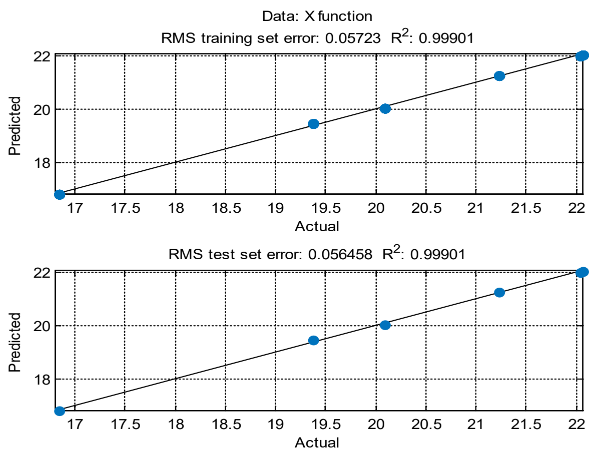

Figure 8. *The R^2 criteria for training case and testing case for data (urinary excretion according to (11))*

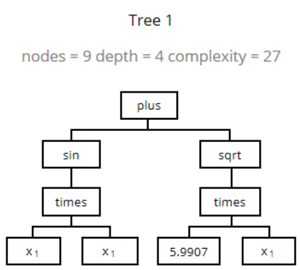

Figure 9. *Tree discovered by GP used in construction of equation thhat are used along with constants thta join the two trees in multigene approach (1)*

The formula extracted from tree (Polish notation) for y = f(x) is:

$$y= f(t)=0.574\cdot\sin(t^2)+1.622\cdot e^{\cos(t)}+5.9907\cdot t^{1/2}+14.09. \qquad \textbf{(1)}$$

In a similar manner, the formula for sulphate excretion is given by (RMSE = 0.0030371):

$$y=g(t)=(t-7.876)\cdot(2\cdot x+\sin(t))\cdot 0.01735-1.874\cdot\sin(t-7.72)+2.535. \qquad \textbf{(2)}$$

The RMSE and R^2 for net absorption is given in figure 10. There are another interesting application (3), urinary excretion of sulfates and creatinine during consumption of a standard diet, over a period of 48 hours.

$$y=\sin(\sin(t)-t+0.0198)\cdot 0.0346-\cos(4.792\cdot t^2)\cdot 0.1144-0.1144\cdot t^{1/2}+((t-6.5527\cdot\cos(t^{1/2}))^{1/2}+0.8953. \qquad \textbf{(3)}$$

The graphic from (3) is presented in figure 11. The formula found it after 25 restarted initial populations is (best fitness RMSE = 0.062431) is given in equation (3).

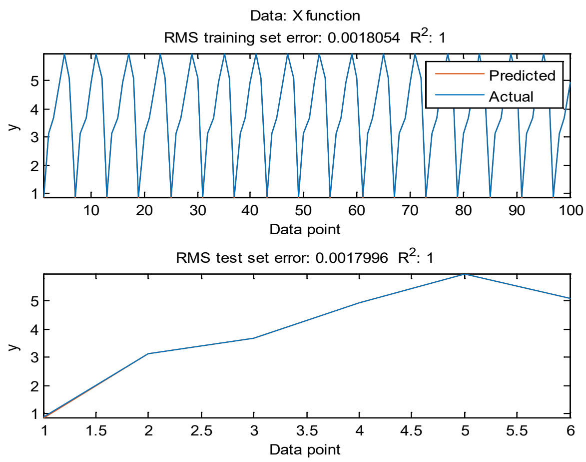

Figure 10. *RMSE and R^2 for net absorption*

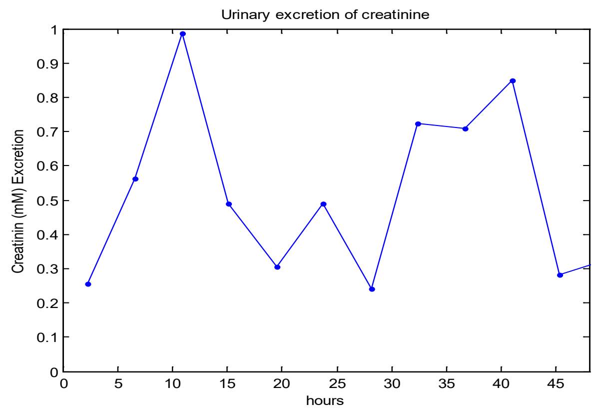

Figure 11. *RMSE and R^2 for experimental data from (3)*

It is known that the convergence solution of evolutionary algorithms including GP can depend on initial populations. In order to overcome this shortcoming, this usually solution is to restart many times the algorithm with random populations. In this paper, for all the applications, a maximum number of 25 restarts proved to be enough for a satisfactory solution.

Conclusion

The relations obtained by GP in most of the cases are not connected with equations of the real world. The mathematical formulas that approximate a curve can expressed in many different analytical forms that have all good results in approximation.

The accuracy of the model depends of the number of samples collected from experimental data (for statistical significance, the number of samples must be greater than 31, a known results from statistical theory). In particularly case, the formulas given by GP can be used for prediction of sulphate absorption and it can be useful in evaluation of the cure with mineral sulphurous water. In the further applications, a dive in models using GP will be used that is, the selection of function will be made using a statistical analysis of credibility related to physical phenomena.

Declaration of conflict of interests

There is no conflict of interest for any of the authors regarding this paper.

Informed consent

An informed consent was obtained from the patient included in this study.

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