Validation of Short-Term Blood Glucose Prediction Algorithms

Evgeniia L. Litinskaia, Pavel A. Rudenko, and Kirill V. Pozhar
Institute of Biomedical Engineering, National Research University of Electronic Technology, Zelenograd, Moscow, Russian Federation
Email: zheka101993@yandex.ru, rudenko.pavel.a@gmail.com, kir-p@ramler.ru

Nikolai A. Bazaev
Sechenov University, Moscow, Russian Federation
Email: bazaev-na@yandex.ru

***Abstract*—Algorithms for model predictive control as well as mathematical models themselves need effectiveness evaluation. In the work are considered physiological, neural network based and empirical models, their special aspects and methods of approbation. DirecNet open-access database clinical protocols were processed and used for empirical sigma-model based algorithm tests. The general concept of developed short-term prediction algorithm based sigma-model is to compare the measured and the modeled BG. Processing this data the algorithm generates its outputs and performs further BG prediction. The DirecNet data allows providing effective prediction algorithm and empirical mathematical model evaluation. Primary tests show that sigma-model based algorithm is unsusceptible to patient physiological quasi-constant parameters variability and is susceptible to noise level. Relative deviation of prognosis with added 25% normal noise is less than 20%.**

***Index Terms*—diabetes mellitus, closed-loop system, blood glucose prediction, mathematical model, approbation**

I. Introduction

Diabetes mellitus is widespread endocrine disease that occurs when pancreas is no longer available to produce enough insulin and characterized by chronic increase of blood glucose concentration (BG).

Nowadays the most widely used method for diabetes mellitus type I compensation is pump insulin therapy based on on-time exogenous insulin infusion.

The closed-loop system for blood glucose level control based on insulin pump combined with glucose meter may improve efficiency of insulin therapy and enable to compensate diabetes automatically. The key part of such a system is a feedback on blood glucose dynamic prediction performed by corresponding algorithms.

Bioengineering system comprised of portable closed-loop system and a patient is to provide high accuracy and reliability of blood glucose dynamic prediction. Moreover, it is highly important to achieve the best operation of algorithms as a part of portable device software, proper functioning in a processing unit.

Manuscript received September 16, 2018; revised February 23, 2019.

Prediction algorithms are based on mathematical models, describing blood glucose dynamic. Approbation of algorithms and models is a nontrivial task due to their complexity and mathematical nature.

Blood glucose mathematical models may be divided into three main groups depending on their basic principles:

1) *physiological models;*
2) *neural networks based models;*
3) *empirical models.*

Physiological models [1]-[4] usually are based on ordinary differential equations taking into account a lot of physiological parameters. The goal of such models is the highest correspondence to real physiological human processes. However, they may not be able to perform accurate long-term prognosis, because it can not to take into account a number of processes and long-term variability of physiological constants. Besides, complicated high order differential equations generally use immeasurable parameters, which are also variable for different patients.

Models based on neural networks [5]-[8] are aimed at the most accurate prediction without a strict description of physiological processes. The most accuracy is achieved by feedback and continuous education. However, the main disadvantage of the neural networks is an unknown and hardly predictable process of prognosis construction. That makes this type of models less sufficient and reliable as a part of the closed-loop system. It stands to mention that neural networks models are learning and operates well with one particular patient and need reeducation for different patients. Moreover, using neural networks in firmware is rather complicated because it demands high resources of the processing unit.

Taking into account all disadvantages of previously described model types we suggest another model type – empirical models. Their goal is to build the accurate prognosis by crisp logic. Empirical models [9], [10] are physiologically independent, because they take into account mainly constant physiological parameters and are not oriented to repeat real physiological (human) processes. They don't need the feedback and may use

doi: 10.18178/ijpmbs.8.2.34-39

neural network only for education. Empirical models also should be reeducated or calibrated for different patients, but it takes much less time and computing power in comparison with neural networks based models. Therefore, using such models as a base for prediction algorithm allows providing sufficient high accuracy and reliability of the closed-loop system with simple mathematical base.

The main task of blood glucose dynamic prediction applicable for mentioned bioengineering system is to exclude (minimize) hypoglycemia and longtime hyperglycemia in patients with diabetes mellitus type I. Therefore, the empirical model is more relevant to use in bioengineering system of the portable closed-loop system and a patient.

II. Materials and Methods

A. Approbation Methods

Let us consider main methods for mathematical models and algorithms on its basis approbation:

1) *virtual data;*
2) *real data from databases;*
3) *real data based on clinical trials.*

Virtual data (virtual patient) is available and convenient way to approbate the developed model. However, it is based on the mathematical model itself that gives the method some disadvantages. First of all, the base model used in virtual patients may have its own errors or deviations in modeling. Additionally, it uses unknown physiological parameters that are difficult to take into account. Finally, it makes only identical model with similar structure and parameters to show the best results during approbation.

Nowadays, one of the most widely used virtual data based methods for mathematical models and prediction algorithms approbation is the in silico system [11], [12]. The system of virtual patients is realized in special software that is certified by FDA.

Real data methods are based on models approbation by using daily BG tracks. These methods are divided into ones based on clinical trials and data from databases.

Clinical data capture provides highly accurate and reliable information about a real patient BG dynamic. Furthermore, it allows receiving all essential physiological parameters performing necessary investigations. The main disadvantage of the method is data capture complication and low availability. Besides, incorrect operation of data receiving devices and human factor may have influence on received data and cause errors.

Databases are the most available and simple method for getting real patient data. Although it provides less essential data then clinically captured one, it is sufficiently accurate and reliable for model approbation. However, data from databases may be incomplete and unsorted and demand processing to make it more convenient to use. As database information is received the same way as clinical data, it also may be influenced by human factor or device errors.

Nevertheless, being the most available and enough accurate real data source, databases are the most relevant methods for mathematical models approbation, especially empirical ones.

B. DirecNet Database

DirecNet is an available wide database of clinical trials of patients with diabetes mellitus [13]. This database includes not only BG dynamic data, but also information about factors affecting it: food intake, insulin infusion, physical activities.

Information from DirecNet is unprocessed and is presented in protocols as it has been collected from glucose meters and sensors. Tracks may include incorrect values of BG monitors and are difficult to analyze without additional processing.

For that end, special software was developed in Matlab. The software consists of two programs: processing and visualization programs.

The former provides DirecNet data structuring. Initial information about trials includes a protocol file about measuring parameters and conditions and one table-file with all measurements results for all patients. The processing program allows dividing all this data in separate tables with information about one parameter for one patient. Once performed, the processing provides more convenient analysis of presented data.

As a result BG tracks for all patients were formed, third part of which had incorrect information (rapid long-term BG level deviation near physiological limits and constant BG value during long time). Such tracks were excluded from the resulting set of data.

Finally, the processing program combines daily BG tracks got from different glucose meters obtained with different frequency. Glucose meters data were adjusted with the meters accuracy. As reference points clinical blood count data were used. Mean track was interpolated using data from fingerstick meters (FreeStyle Flash and OneTouch Ultra) and constant glucose monitor (CGMS) with discretization period of 5 minutes. Combined track are more accurate and have the highest discretization (Fig. 1). In further researches these tracks were used as ideal reference tracks.

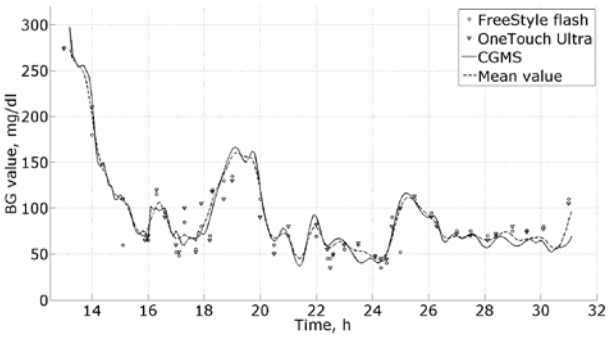


Figure 1. Combined track of One Touch Ultra, FreeStyle Flash and CGMS Medtronic MiniMed BG meters.

Then, visualization program made as a graphical interface combines final track with food intake and

insulin infusion data. Developed interface allows graphical data visualization with comfortable parameter control (Fig. 2).

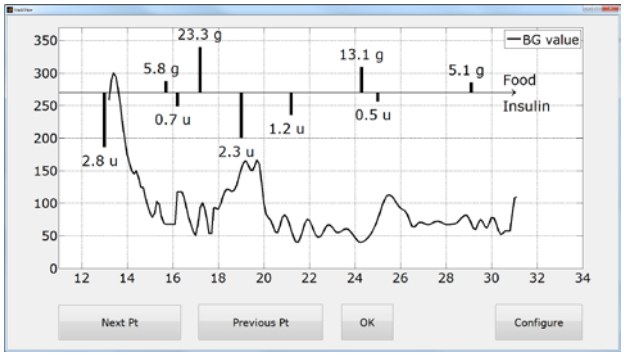


Figure 2. Graphical interface for BG tracks visualization.

C. Short-Term Prediction Alrorithm

Developed short-term prediction algorithm is based on improved empirical Sigma-model presented in [14]. The model is based on logistic function or sigma-function. That is why it is called sigma-model. The model describes BG dynamic taking into consideration food intake and insulin infusion data and assumes that glucose dynamic is strongly connected to regulation of insulin, amylin, epinephrine and glucagon. Ascents of BG are mainly caused by food intake as well as glycogenolysis and gluconeogenesis activated by glucagon and epinephrine. Descents of BG are caused by glycolisys and glycogenesis activated by insulin and amylin.

The general concept for algorithm is to compare two data sets – the measured BG and the modeled BG. Processing this data the algorithm generates its outputs and performs further BG prediction.

At the start of the algorithm the initial prediction point is defined, that is the state after the closed-loop system is powered on or recalibrated. After the patient enters meal/insulin data or bolus insulin data is received from the pump the model is recalculated, thus recalculates the prediction. It is also done if no data events happen but the prediction time interval passed. Summing up there are several points for prediction renewing: powering on the closed-loop, its recalibrating, meal data from the patient and insulin data from either the patient or the insulin pump.

After the prediction is done, several levels are built: a large interval and a small one surrounding the prediction. These ranges are used to classify the measured value into one of the following categories: reliable, reasonable reliable and unreliable. The width of the intervals varies over time: the more time has passed since the last recalibration, the wider the intervals are. Fig. 3 illustrates the intervals around the prediction value.

After the measurement is performed the got BG value is being compared to the prediction value using the around intervals. As the measured value is within one of the ranges, it can be applied to some category. The categories, reliability intervals, and their verbal description are given in Table I.

Owing to classification intervals, it is possible to detect such situations as incorrect patient data input, glucose errors and insulin pump faults. Besides them, several errors can be detected by the closed-loop components by themselves: glucometer alarms or infusion failures. The detected problems are reported about to the main control unit of the closed-loop system, which generates alarms and notifies.

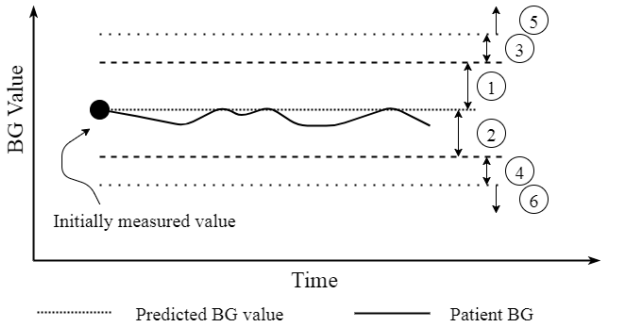


Figure 3. The schematic interval illustration around the prediction value.

After the algorithm detects the meal intake, it starts the calculation of bolus insulin dose for compensating the taken carbohydrates and keeping the patient BG within safe values. This calculation is performed using the mathematical model of blood glucose dynamics.

TABLE I. CLASSIFICATION OF BG MEASUREMENTS

Interval	***Classification***	***Algorithm react***
1, 2	Small difference, reliable value	Moving the prediction to the measured value
3	Large positive difference	BG refinement mode, possible incorrect meal data
4	Large negative difference	BG refinement mode, possible incorrect insulin data
5, 6	Unreliable measurement	Glucometer fault

D. Short-Term Prediction Alrorithm Validation

Approbation of developed prediction algorithm based on empirical sigma-model was performed by the computer simulation using DirecNet database. The method allows one to work with large amount of data and to repeat experiments with different controlled settings.

During validation of developed prediction algorithm it was necessary to take into account errors that occur in the BG track. It was simulated by addition to the processed track points normal noise with levels of 0, 10, 15, 20 and 25 %. The experiment goal is to evaluate prospects of the algorithms applicability in the real closed-loop system.

To quantify clinical accuracy of patient estimates of their current blood glucose as compared to the blood glucose value obtained in their meter the Clarke error grid analysis (EGA) [15] is used. On X-axis, there are real BG and on Y-axis – measured ones. In the case of prediction algorithm approbation on Y-axis, there are prognoses.

During approbation eight patient data from one of DirecNet studies was used. Patients 7, 10, 37, 41, 55, 59, 61, 69 had the most complete set of data about meal and insulin injections and had a track without noisy or empty zones.

For each patient were made 10 noisy tracks for each level of noise: 0, 10, 15, 20 and 25% and 1 clean track. In every experiment, the algorithm operation was estimated with EGA and averaged relative deviation (ARD) the prognosis from real BG values. Estimation results were added in the common protocol for further additional analyzing.

The algorithm validation was performed according to the following criteria:

- algorithm response on BG measurements error;
- BG prognosis quality in different patients with similar set of parameters;
- prognosis quantity parameters repetition with fixed experiment parameters, but different time distribution of measurement errors.

III. Results

For algorithm response on errors analysis for each patient were made single tables with ARD and EGA results for every noise level. Tables include averaged results for all ten experiments for the patients.

As an example, analysis results for patient 59 are presented in Table II. Fig. 4 shows an example of EGA analysis for the same patient. Common approbation results including all patients' data on all errors are shown on Fig. 5.

TABLE II. EGA and ARD Analysis Results for Patient 59

Noise level, %	ARD, %	Averaged Clarke error grid values, %				
		A	*B*	*C*	*D*	*E*
0	2.0	100.0	0	0	0	0
10	3.0	99.98	0.02	0	0	0
15	6.6	92.96	6.17	0	0.87	0
20	7.4	91.92	4.41	0	3.67	0
25	13.7	81.83	14.86	0	3.31	0

Results demonstrate that the algorithm operation depends on BG measurement accuracy. With the measure error increase raises algorithm's ARD. However, as Fig. 4 and Table II shows with noise increase from 10 to 25% the amount of values from Zone A of the Clarke error grid falls only from 99% to 80%. Taking into account unadjusted mathematical model parameters for every single patient and results averaging this fall may be considered as unessential.

To estimate BG prognosis quality in different patients with similar set of mathematical model parameters, data from the common protocol was divided into separate tables for every noise level. Tables included patient number, ARD and EGA results. Prognosis results for all patients on noise level 10% are presented in Table III.

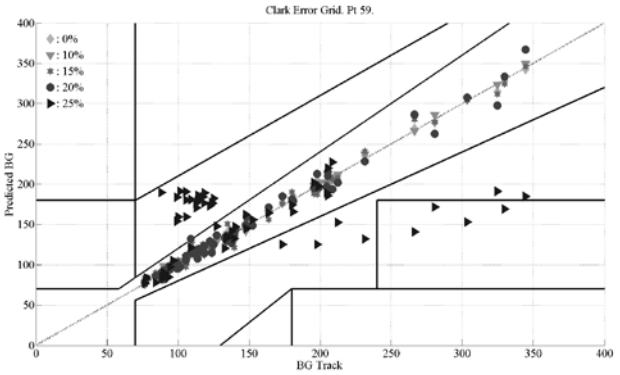


Figure 4. Prediction EGA for patient 59.

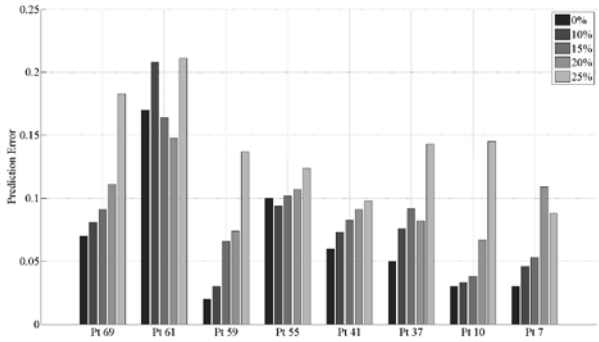


Figure 5. Approbation results with different noise levels.

TABLE III. Analysis Results on 10% Noise Level for All Patients

Patient	ARD, %	Averaged Clarke error grid values				
		A	*B*	*C*	*D*	*E*
7	4,6	94,5	5,5	0	0	0
10	3,3	97,1	2,9	0	0	0
37	7,6	89,0	10,3	0,4	0,1	0,2
41	7,3	89,3	10,7	0	0	0
55	9,4	82,9	16,9	0	0,2	0
59	3,0	99,8	0,02	0	0	0
61	20,8	65,9	33,1	0,2	0,6	0,2
69	8,1	89,4	10,5	0,1	0	0

As it could be noticed from the Table III, the algorithm shows different results for different patients with similar set of parameters. Especially, patient 61 had the most significant influence on the results. Therefore, parameters should be accurately adjusted (chosen) for every patient during calibration to achieve the best algorithm performance. However, for all patients with BG measurement error of 10% ARD is less than 20%, while without patient 61 it is even less than 10%. From there, it could be considered that the closed-loop on the basis of the developed algorithm will allow verifiable prognosis even in the case of parameters change in time. Besides, it will show better results being properly calibrated.

Then, there was analyzed the influence of different time distribution of measurement errors on prognosis

quantity parameters repetition with fixed experiment parameters. For that end, the common protocol was divided into separate tables for every patient and noise level. Tables included ARD and EGA results for all ten iterations of the experiment. Such a table for the patient 10 and for 15% noise level is demonstrated by Table IV.

It may be noted that developed short-term algorithm is unsusceptible to the different time distribution of measurement errors.

TABLE IV. ANALYSIS RESULTS FOR PATIENT 10 ON 15% NOISE LEVEL FOR ALL TEN ITERATIONS

Iteration	ARD, %	Averaged Clarke error grid values				
		A	*B*	*C*	*D*	*E*
1	4	97,5	2,5	0	0	0
2	3	98,6	1,4	0	0	0
3	3	99,5	0,5	0	0	0
4	4	96,3	3,7	0	0	0
5	5	95,3	4,7	0	0	0
6	4	96,0	4,0	0	0	0
7	4	96,8	3,2	0	0	0
8	4	99,3	0,7	0	0	0
9	3	99,6	0,4	0	0	0
10	4	96,5	3,5	0	0	0

Further experiments should be performed with the data of all possible patients from all DirecNet studies in order to get more verifiable statistical results.

IV. CONCLUSIONS

We have marked out three groups of blood glucose mathematical models and considered methods of their approbation. Empirical models of blood glucose dynamic allow effective operation of bioengineering system of patient and the closed-loop system based on noninvasive glucometer and insulin pump. In combination with physiological independence, it provides sufficient high accuracy of prognoses and is not resource-intensive.

The short-term prediction algorithm based on the empirical sigma-model was described. Approbation of the algorithm was performed using DirecNet database. The available DirecNet data allows providing effective prediction algorithm and empirical mathematical model evaluation.

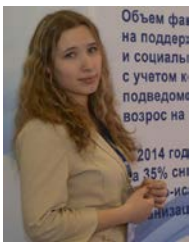
Primary tests show that sigma-model based algorithm is unsusceptible to patient physiological quasi-constant parameters variability and is susceptible to noise level. Relative deviation of prognosis with 25% error of BG meter is less than 20%.

ACKNOWLEDGMENT

The work was financed by the Ministry of Education and Science of Russian federation: agreement № 14.578.21.0186, project ID: RFMEF157816X0186.

REFERENCES

[1] R. N. Bergman, "Toward physiological understanding of glucose tolerance: Minimal-model approach," *Diabetes*, vol. 38, no. 12, pp. 1512-1527, 1989.
[2] J. Sturis, K. S. Polonsky, E. Mosekilde, and E. Van Cauter, "Computer model for mechanisms underlying ultradian oscillations of insulin and glucose," *American Journal of Physiology*, vol. 260, no. 5, pp. E801-E809, 1991.
[3] K. Engelborghs, V. Lemaire, J. Belair, and D. Roose, "Numerical bifurcation analysis of delay differential equations arising from physiological modeling," *Journal of Mathematical Biology*, vol. 42, no. 4, pp. 361-385, 2001.
[4] D. L. Bennett and S. A. Gourley, "Asymptotic properties of a delay differential equation model for the interaction of glucose with the plasma and interstitial insulin," *Applied Mathematics and Computation*, vol. 151, no. 1, pp.189-207, 2004.
[5] Z. Trajanoski and P. Wach, "Neural predictive controller for insulin delivery using the subcutaneous route," *IEEE Transaction on Biomedical Engineering*, vol. 45, no. 9, pp. 1122-1134, 1998.
[6] S. G. Mougiakakou, *et al*., "A neural network based glucose-insulin metabolism models for children with type I diabetes," in *Proc. International Conference of the IEEE Engineering in Medicine and Biology Society*, 2006.
[7] E. Teufel, M. Kletting, W. G. Teich, H-J. Pfleiderer, and C. Tarin-Sauer, "Modeling the glucose metabolism with backpropagation through timetrained Elman nets," in *Proc. the 13th IEEE Workshop on Neural Network for Signal Processing*, 2003, pp. 789-798.
[8] W. A. Sandham, D. J. Hamilton, A. Jappx, and K. Pattersod, "Neural network and neuro-fuzzy systems for improving diabetes therapy," *Proceedings of the 20th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, vol. 20, no. 3, pp. 1438-1441, 1998.
[9] N. A. Bazaev, K. V. Pozhar, and P. A. Rudenko, "Mathematical modeling of blood glucose concentration dynamics," *Biomedical Engineering*, vol. 48, no. 6, pp. 292-296, 2015.
[10] N. A. Bazaev, K. V. Pozhar, E. L. Litinskaia, and P. A. Rudenko, "Mathematic model of blood glucose dynamics," *The International Journal of Artificial Organs*, vol. 40, no. 8, pp. 437-438, 2017.
[11] B. P. Kovatchev, M. D. Breton, M. C. Dalla, and C. Cobelli, "In silico preclinical trials: A proof of concept in closed-loop control of type 1 diabetes," *Journal of Diabetes Science and Technology*, vol. 3, no. 1, pp. 44-55, 2009.
[12] B. P. Kovatchev, M. D. Breton, M. C. Dalla, and C. Cobelli, "In silico model and computer simulation environment approximating the human glucose/insulin utilization," *Food and Drug Administration Master File MAF 1521*, 2008.
[13] K. J. Ruedy, R. W. Beck, D. Xing, and C. Kollman, "For the diabetes research in children network (DirecNet) study group diabetes research in children network: Availability of protocol data sets," *Diabetes Sci. Technol*, vol. 1, no. 5, pp. 738-745, 2007.
[14] N. A. Bazaev and K. V. Pozhar, "Blood glucose prediction for 'artificial pancreas' system," in *Gluconeogenesis*, W. Zhang, Ed. Rijeka, Croatia: InTech, 2017, pp. 55-73.
[15] W. L. Clarke, D. Cox, L. A. Gonder-Frederick, W. Carter, and S. L. Pohl, "Evaluating clinical accuracy of systems for self-monitoring of blood glucose," *Diabetes Care*, vol. 10, no. 5, pp. 622-628, 1987.



Evgeniia L. Litinskaia was born in Gubkin, Russia, in 1993. She received B.S. degree in biomedical engineering in 2015 and M.S. degree in electronics and microelectronics in 2017 and now is a PhD student (1 year) in National Research University MIET, Institute of Biomedical Systems. Since 2015, she has been an engineer of Institute of Biomedical Systems, National Research University MIET. She is an author of more than 15 articles and has one invention. Her research interests include non-invasive device for blood glucose measurement and closed-loop system for diabetes mellitus type 1 therapy. She is a member of Institute of Electrical and Electronics Engineers (IEEE) since 2016 a member of Society of Photo-Optical Instrumentation Engineers (SPIE) since 2017.

Pavel A. Rudenko was born in Moscow, Russia, in 1991. He received B.S. degree in computer science in 2012, M.S. degree in computer science in 2014 and now is a PhD student (4 year) in National Research University MIET, Institute of Computer Science. Since 2012 he has been an engineer in different departments (Institute of Computer Science and Control Systems, Institute of Biomedical Systems, all National Research University MIET). He is an author of more than 15 articles. His research interests include computer science, embedded systems, programming and modeling of control systems.

Kirill V. Pozhar was born in Donetsk, USSR, in 1991. He received B.S. degree in biomedical engineering in 2012 and M.S. degree in electronics and microelectronics in 2014 and now is a PhD student (4 year) in National Research University MIET, Institute of Biomedical Systems. Since 2015 he has been an Assistant teacher of Institute of Biomedical Systems, National Research University MIET. He is an author of more than 30 articles and 4 inventions. His research interests include biophysics and optical glucose detection.

Nikolai A. Bazaev was born in Moscow, USSR, in 1984. He received PhD degree in Engineering sciences in 2011 in National Research University MIET. He is the author of more than 50 articles and 5 inventions. His research interests include wearable artificial kidney for renal replacement therapy, non-invasive device for blood glucose measurement. He is the winner of President scholarship (the Russian Federation, 2012-2014) and Presidential Grant (Russian Federation, 2016-2017), the winner of international conference on biomedical engineering (Russian German Conference, 2012, 2016). Since 2016, member of European Society of Artificial Organs (ESAO). Since 2017, member of European Renal Association (ERA-EDTA).