# A mathematic model of electroretinogram for titanium dioxide ($TiO_2$) neurotoxicity risk assessment*

Petro Samuliak[1,†], Roman Tkachuk[1,†], Pavlo Tymkiv[1,*,†], Oksana Bahrii-Zaiats[2,†] and Oleg Zastavnyy[3,†]

[1] *Ternopil Ivan Puluj National Technical University, Ruska str., 56, 46025 Ternopil, Ukraine*
[2] *Ivan Horbachevsky Ternopil National Medical University, 1, Voli Square, Ternopil, 46001, Ukraine*
[3] *West Ukrainian National University, Lvivska str. 11, Ternopil, 46009, Ukraine*

**Abstract**

The research paper represents the electroretinogram (ERG) math model based on the third-order piecewise polynomial approximation method for the development of the expert assessment system of titanium dioxide (TiO2) nano-particle neurotoxicity for the retina. ERG is considered a sensitive method of early change diagnostics regarding the ability of TiO2 nano-particles to penetrate the blood-retinal barrier and induce structural-functional changes in neurons. The scope of analysis included ERG signals in dark adaptation with the definition of the main phases (a- and b-waves). Their segmentation and third-order polynomial approximation were applied. The proposed model provides smooth segment connections in amplitude and derivative. A heuristic approach to the delimitation of segments in the signals received after the TiO2 exposition was implemented with further parameter identification by the least square method. The results obtained through this method show a decrease in the a- and b-waves amplitudes by 50–60%. This correlates with the experimental in vivo data and proves the efficiency of using the model for early TiO2 neurotoxicity diagnostics.

**Keywords**

Electroretinosignal, mathematical model, parametric identification, titanium dioxide ($TiO_2$) optimization

## 1. Introduction

Nanoscaled titanium dioxide (TiO2) is widely used in cosmetics, paints and varnishes production, food production and multiple other industries. Global annual production of pigmentous TiO2 is about 9.47 million tons, and the forecasts claim that it could reach up to 10 million tons annually in 2025 [1]. The main producers of titanium dioxide are China, the USA, and the EU countries. The studies showed that TiO2 nano-particles can penetrate the blood-brain barrier, and they accumulate in the brain causing oxidating stress, neuroinflammation, and disruption of the neuron's functionality. In this regard, neurotoxicity effects on the visual system is a significant ground in investigations as vision plays a crucial role in life quality and overall well-being of a human.

Electroretinogram remains one of the most powerful tools for visual system functionality evaluation. Electroretinography (ERG) is a non-invasive research method used for retina functionality assessment. The electro retina signal (known as ERS) is formed by the retina cells (namely, by photoreceptors, bipolar, amacrine, ganglion cells and Muller cells) and they usually contain two basic waves: a negative a-wave (featured by the initial downward peak, caused by the photoreceptors' activity) and a following additional b-wave (caused by the depolarization of internal retinal neurons, predominantly bipolar and glial cells). The analysis of the a-wave and b-wave parameters of ERS allows us to evaluate the functionality of photoreceptors and internal

* *CITI'2025: 3rd International Workshop on Computer Information Technologies in Industry 4.0, June 11–12, 2025, Ternopil, Ukraine*
[1,*] Corresponding author.
[†] These authors contributed equally.
argonchik@gmail.com (P. Samuliak); romantkachuk48@gmail.com (R. Tkachuk); t_pavlo_o@ukr.net (P. Tymkiv); bagrijzayats@tdmu.edu.ua (O. Bahrii-Zaiats); olegz80@gmail.com (O. Zastavnyy)
0000-0002-6521-7396 (R. Tkachuk); 0000-0003-1212-3107 (P. Tymkiv); 0000-0002-5533-3561 (O. Bahrii-Zaiats); 0000-0001-8630-8791 (O. Zastavnyy)

retina layer neurons [2-3]. Characteristic changes in the ERS occur under the impact of neurotoxic factors like TiO2 nano-particles. These are wave amplitude reduction and each wave's latency increase. The development of the expert system for the TiO2 neurotoxicity evaluation based on the ERS method requires a mathematical model for these signals to discriminate the informative features and imply the formalized rules for assessment. This approach aligns with recent advances in biosensor modeling using differential and difference equations on lattices, where system stability and parameter identification are crucial for accurate signal interpretation [4]. Such mathematical frameworks support the reliable reconstruction of biological responses under external impacts, which is essential for neurotoxicity assessment models.

The objective of this research paper is the construct a mathematical model of the retina ERS in the form of a piecewise polynomial approximation of its main phases (a- and b-waves) and the development of the concept of the expert system for the automated TiO2 nano-particle neurotoxicity assessment based on this model.

The following materials and methods were employed. The analysis of the electroretinogram signals (ERS) received from the retina in the dark adaptation under a standard light stimulus was performed in the study.

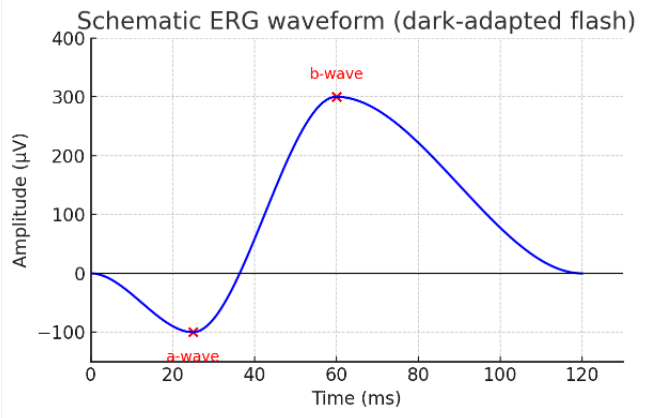


**Figure 1:** A scheme of an electroretinogram with the marking of the main waves: a-wave is an initial negative deflex (of an approximate minimum of 25 ms) and b-wave is the next positive peak (of an approximate maximum of 60 ms). The amplitudes are measured from the isoline: Aa is an a-wave amplitude, and Ab is a b-wave amplitude. The latency (the peak time) is marked as La for the a-wave and Lb for the b-wave.

This ERG signal is featured by the presence of an intense negative a-wave in the beginning, and the advent of the positive b-wave further. When considering a typical dark ERG of a normal retina we can allocate the following segments: an initial a-wave, which is a negative deflex (the curve's subzero decrease) with a minimum at approximately 25 ms; a huge positive b-wave following the previous one with the peak of approximately of 60 ms after stimulation.

After peaking of the b-wave, the signal's amplitude consistently decreases and returns to the isoline (~0 μV) approximately in 120 ms. We divided the ERG curve into three segments according to the main phases for further study. The first segment (I) is an upward and downward part of the a-wave (from the start of the signal to the a-wave minimum's timeline); segment II is the rise of the b-wave from the end of the a-wave to the peak of the b-wave; the segment III is a decrease of the b-wave from its peak to the return of the signal to the isoline.

The segmentation's boundary points were selected by the physiological benchmarks of ERG: the moment of 25 ms (between the segments I–II) is the time of the lowest decrease of a-wave, and a 60 ms benchmark (the boundary point between II–III segments) of the time of b-wave peaking [5,6].

## 2. A third-order piecewise polynomial approximation

The third-order polynomial approximation (also known as cubic approximation) was used for the description of the ERG signal in each segment's boundaries. A third-order polynomial has a brief formula:

$$y(t)=at^3+bt^2+ct+d \quad (1)$$

whereas t – for time (ms), y(t) – for the ERS (μV) at time t; a, b, c, d – for the polynomial's coefficients determining the curve's shape. The approximation was implied separately for each of the segments with the selection of coefficients to provide a smooth segment connection in the boundary points (without breaking amplitudes and the first derivative) [6-8].

In short, the function value and derivatives of polynomials of neighboring segments were aligned at the points t = 25 ms and t = 60 ms, responding to physiological requirements for signal continuity and a smooth transition from a- to b-waves. The boundary conditions for the full integral's edges were implied: at the beginning of the stimulus (t = 0) the amplitude y(0) is 0, and at the end of the record (t = 120 ms), the signal returns to the isoline (y(120) = 0) with no more changes detected (a zero-order derivative). Thus, the system of equations was formed to find each segment's coefficients. By solving this system of equations (using the Gaussian elimination or the symbolic calculation method) we managed to receive clear formulas for the piecewise polynomial ERG signal model. The stability and accuracy of such piecewise models align with findings in lattice differential equation-based biosensor research, where smooth segment connections and parameter identification were critical for predictive validity [7].

### 2.1. The Results

ERG parameters and the polynomial models developed.

Based on the analysis of the experimental ERG signals, the characteristic magnitudes for the reference (intact) retina were determined: the a-wave amplitude (Aa) is about 100 μV (the negative peak), and the b-wave amplitude (Ab) is about 300 μV (the positive peak). The waves' latency (La and Lb) in the dark is equal to approximately 25 ms and 60 ms subsequently. The application of the segmentation method and cubic approximation allowed us to receive the following polynomial equations for each ERG signal (where t — is for time in milliseconds, and y(t) is for the amplitude in microvolts):

Segment I (0–25 ms, a-wave):

$$y_1(t)=0{,}0128\cdot t^3-0{,}480\cdot t^2+0\cdot t+0 \quad (2)$$

With the following coefficients:

a1 = 0,0128, b1 = -0,480, c1 = 0, d1 = 0.

The linear and the constant terms of this equation are zeros. This refers to the zero amplitude and derivative in the start of the signal. This polynom accurately describes the negative a-wave with the minimun of approximately of -100 μV with t = 25t = 25t = 25 ms.

The segment II (25 – 60 ms, the rise of the b-wave):

$$y_2(t)=-0{,}01866\cdot t^3+2{,}379\cdot t^2-83{,}965\cdot t+803{,}79 \quad (3)$$

With the following coefficients:

a2 = -0,01866, b2 = 2,379, c2 = -83,965, d2 = 803,79.

This equation describes a smooth transition from the a-wave minimum to the b-wave maximum. When implying t = 25t = 25t = 25 ms we get an amplitude of -100 μV (the continuity of segment I), while when t = 60t = 60t = 60 ms, the maximal b-wave amplitude remains at the levels of +300 μV. At the peaking, the derivative is zero and this responds to the smooth transition.

The segment III (60–120 ms, the b-wave decline):

$$y_3(t) = 0{,}00278 \cdot t^3 - 0{,}75 \cdot t^2 + 60 \cdot t - 1200 \quad (4)$$

With the following coefficients:

a3 = 0,00278, b3= -0,75, c3 = 60, d3 = -1200.

This equation describes a smooth transition from the a-wave minimum to the b-wave maximum. When implying t = 25t = 25t = 25 ms we get an amplitude of -100 μV (the continuity of segment I), while when t = 60t = 60t = 60 ms, the maximal b-wave amplitude remains at the levels of +300 μV. At the peaking, the derivative is zero and this responds to the smooth transition.

This polynomial fully describes the phase of declining of the b-wave after its maximum. When defining the segment's boundaries, the corresponding values referring to t = 60t = 60t = 60 ms and the amplitude of 300 μV (a smooth connection with the segment II), under the value of t = 120t = 120t = 120 ms. The signal returns to the isoline (0 μV). The smooth transition (a zero derivative) is provided at the connection points,

The results are that the proposed equations fully describe the form of the experimental ERG signal and provide an accurate approximation of all physiologically significant phases of retina response to the light stimulus. The results allow us to clearly track the changes in the signal form induced by the TiO2 neurotoxicity.

The graphic illustration of the piecewise polynomial model is available in image 2 with the segments I, II, and III subsequently colored in red, green, and blue colors. The points on the curve show the basic empiric values (an a-wave minimum, intermediate growth points, b-wave peaks, etc).

It's quite evident that the smooth polynomials interpolate greatly experimental data and they smoothly connect in the boundaries (marked with grey lines). The maximum approximation error remains at the mark lower than a couple of percent from the peaking. This approves this model as the relevant one for the ERG signal description.

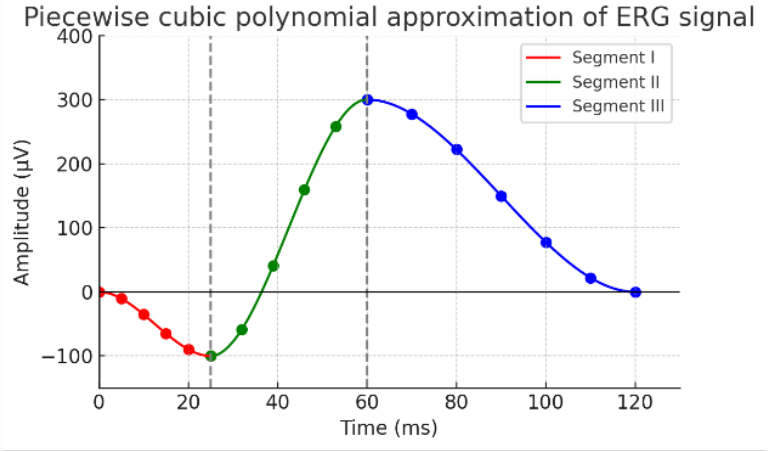


**Figure 2:** A piecewise polynomial approximation of the ERG signal (dark adaptation flash EERG method). Segment I (0–25 ms, a-wave) is marked in red; segment II (25–60 ms, an upward b-wave) is marked in green; segment III (60–120 ms, a b-wave decrease) is marked in blue. The benchmarks show the experimental values for controlling the experiment. Vertical dashlines depict the segments' borders (25 and 60 ms) [1].

## 3. $TiO_2$-induced ERG changes

When developing the model of the ERG signals received from the retina after the impact of TiO2, considerable aberrations from the model's parameters are detected. a- and b-waves amplitudes decreases are the most symbolic signs of neurotoxicity [1].

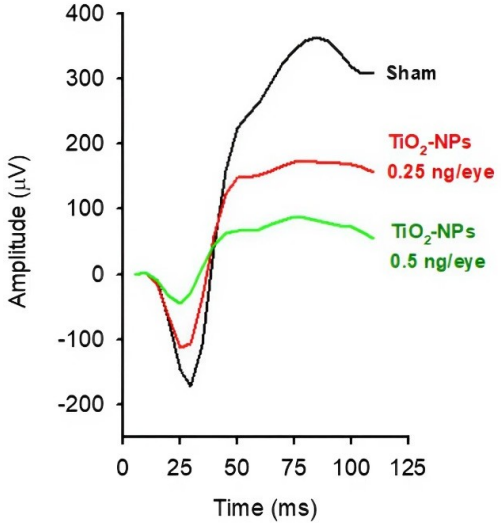


**Figure 3:** Intravitreal exposure of TiO2-NPs impaired the electrophysiology of retina. a ERG recordings were performed in dark room as described in Materials and Methods. Representative ERG α- and β-wave showed damages in their amplitude after TiO2-NP treatments (green and red lines),as compared to sham (black line). b Quantified data showed a great reduced amplitude of at day 7 (both α- and β-wave) and day 14 (α-wave); whereas β-wave amplitude seemed recovery at day 14. *p < 0.05, ***p < 0.001, indicates statistically significant difference from the control (day 0)

According to the research data, an intraocular introduction of the TiO2 nano-particles leads to a considerable reduction in the a-wave, and in the b-wave tracked on the ERG. For example, in experiments on mice, as early as the 7th day after intravitreal injection the TiO2-NP amplitude of the a-wave was reduced by 50-60% on average. The b-wave was reduced by 40–50% compared to the initial results (p<0,001). In particular cases, a moderate b-wave latency increase was detected. This may show the synaptic transition in the retina slowing down.

To approximate the experimental data we decided to imply the third-order piecewise polynomial approximation, which means that the model is determined by particular cubic equations for each of the 5 intervals of the resulting ERS (due to the heuristic approach). This approach allows us to take into consideration local specifics of the function changes except in the cases of overloading of the model by extra parametrization [8-12].

An overall model presentation:

$$y(x)=\begin{cases} a_1x^3+b_1x^2+c_1x+d_1, & x\in[x_0,x_1) \\ a_2x^3+b_2x^2+c_2x+d_2, & x\in[x_1,x_2) \\ a_3x^3+b_3x^2+c_3x+d_3, & x\in[x_2,x_3) \\ a_4x^3+b_4x^2+c_4x+d_4, & x\in[x_3,x_4) \\ a_5x^3+b_5x^2+c_5x+d_5, & x\in[x_4,x_5] \end{cases} \quad (5)$$

With the segmentation borderlines chosen by the heuristic approach implementation, x0 = 7,3; x1 = 14,0; x2 = 18,0; x3 = 25,0; x4 = 34,0; x5= 45,0;

The polynomial coefficients are determined by the least square method for each segment to reduce the difference between the actual value of the test signal considering the value based on the third-order piecewise polynomial model. The results of this ERS modeling featured the following additional coefficients and models which hep evaluate the titanium dioxide neurotoxicity:

$$y(x) = \begin{cases} 0{,}005463x^3 - 0{,}186584\,x^2 + 1{,}957237x + 7{,}333545, & x \in [7{,}32;14{,}00) \\ -0{,}010101x^3 + 0{,}520996x^2 - 8{,}650406x + 59{,}871033, & x \in [14{,}00;18{,}00) \\ 0{,}002101x^3 - 0{,}161157x^2 + 4{,}102519x - 19{,}839512, & x \in [18{,}00;25{,}00) \\ -0{,}001729x^3 + 0{,}149847x^2 - 4{,}260632x + 54{,}709575, & x \in [25{,}00;34{,}00) \\ -0{,}000542x^3 + 0{,}060882x^2 - 2{,}303951x + 44{,}374829, & x \in [34{,}00;45{,}00] \end{cases} \quad (6)$$

## Conclusion

The research study represents a comprehensive approach to the nano-particle neurotoxicity evaluation of titanium dioxide (TiO2). The strategy is based on the analyses of electroretinograms. The math modeling method which works in favor of the retina's ERG signals was offered to sequence separate a- and b-waves. The model developed during the experiment precisely shows the most characteristic ERG parameters like amplitudes, waves' latency, the signals' upward\backward activity etc. At once it helps determine the quantitative value of toxic factors and their parameters.

We offered the third-order partwise polynomial approximation model to approximate the ERG signal in the dark adaptation which guarantees the highest precision of the main signal phases' depiction. The maximum approximation error doesn't exceed 4.2% of the peaking amplitude.

The experimental data showed that after the in vivo introduction of $TiO_2$ nano-particles, the amplitude of a-wave decreased by 51-63%, while the b-wave amplitude decreased up to 43–52% compared to the control group. Subsequently, the increase in the latency of the b-wave by 7.6% is detected. This phenomenon is a showcase depicting the process of the neuro synaptic transmission slowdown. Quantitative regression models, like this, further underscore the utility of parametric identification in detecting pathological deviations from baseline physiological signals [13-17]

The model developed can be used as the experimental system's basis for the expert system of the automated neurotoxicity evaluation caused by the $TiO_2$. The model allows the highlighting of the characteristic functional changes of the normal analyzer at the early stages of toxicant action with the assessment accuracy of up to ±5%.

## Declaration on Generative AI

The authors have not employed any Generative AI tools.

## References


[1] GlobeNewswire. Global Titanium Dioxide Market Analysis and Forecast up to 2028. https://www.globenewswire.com/en/news-release/2023/12/11/2793636/28124/en/Global-Titanium-Dioxide-Market-Analysis-and-Forecast-up-to-2028-Increasing-Use-of-Titanium-Dioxide-in-Plastics-Formation.html

[2] Cornish, E. E., Vaze, A., Jamieson, R. V., & Grigg, J. R. (2021). The electroretinogram in the genomics era: outer retinal disorders. Eye, 35(12), 2406–2418. https://doi.org/10.1038/s41433-021-01659-y

[3] Sun, Y., Wang, Y., Chen, S., & Zhou, Y. (2022). Metallic Engineered Nanomaterials and Ocular Toxicity: A Current Review. Frontiers in Toxicology, 4, 899755.

[4] 6. Martsenyuk, V., Soldatkin, O., Klos-Witkowska, A., Sverstiuk, A., & Berketa, K. (2024). Operational stability study of lactate biosensors: modeling, parameter identification, and stability analysis. In Frontiers in Bioengineering and Biotechnology (Vol. 12). Frontiers Media SA. https://doi.org/10.3389/fbioe.2024.1385459
[5] Tatham, A. J., & Medeiros, F. A. (2017). Detecting Structural Progression in Glaucoma with Optical Coherence Tomography. Ophthalmology, 124(4S), S57-S65.
[6] Robson, A. G., Nilsson, J., Li, S., Jalali, S., Fulton, A. B., Tormene, A. P., Holder, G. E., & Brodie, S. E. (2018). ISCEV guide to visual electrodiagnostic procedures. Doc Ophthalmol, 136(1), 1-26.
[7] 2. Martsenyuk, V., Sverstiuk, A., & Gvozdetska, I. (2019). Using Differential Equations with Time Delay on a Hexagonal Lattice for Modeling Immunosensors. In Cybernetics and Systems Analysis. Vol. 55, Issue 4, 625–637. Springer Science and Business Media LLC. https://doi.org/10.1007/s10559-019-00171-2
[8] Chan, V. T., Tian, Y., Li, Y., Zhou, Y., et al. (2021). Titanium dioxide nanoparticles impair the inner blood-retinal barrier and retinal electrophysiology through rapid ADAM17 activation and claudin-5 degradation. Particle and Fibre Toxicology, 18(1), 1–15.
[9] Cornish, E. E., Vaze, A., Jamieson, R. V., & Grigg, J. R. (2021). The electroretinogram in the genomics era: outer retinal disorders. Eye, 35(12), 2406–2418.
[10] Tymkiv, P. (2021). Analysis of the Complexity of Algorithms for Finding the Coefficients of the Mathematical Model of Low-Intensity Electroretinosignal. In Advanced Applied Energy and Information Technologies 2021: Proceedings of the International Conference (Ternopil, 15-17 of December 2021) (pp. 145-150). Ternopil Ivan Puluj National Technical University.
[11] Nocedal, J., & Wright, S. J. (2016). Optimization methods: A review. SIAM Review, 58(3), 492-525.
[12] Wang, J., Sun, Y., Jiang, Y., & Wang, H. (2023). Hesperidin Attenuates Titanium Dioxide Nanoparticle-Induced Oxidative Stress in Brain. ACS Omega, 8(6), 6132–6140.
[13] Nykytyuk S., Sverstiuk A., Klymnyuk, S., Pyvovarchuk D., & Palaniza Y. (2023). Approach to prediction and receiver operating characteristic analysis of a regression model for assessing the severity of the course Lyme borreliosis in children. Rheumatology, 61(5), 345–352. https://doi.org/10.5114/reum/173115
[14] Musiienko V., Marushchak M., Sverstuik A., Filipyuk A., Krynytska I. (2021). Prediction Factors For The Risk Of Hypothyroidism Development In Type 2 Diabetic Patients. PharmacologyOnLine, Volume 3, 585-594.
[15] Musiienko V., Sverstiuk A., Lepyavko A., Danchak, S., Lisnianska, N. (2022). Prediction factors for the risk of diffuse non-toxic goiter development in type 2 diabetic patients. Polski merkuriusz lekarski: organ Polskiego Towarzystwa Lekarskiegothis link is disabled, 50(296), 94–98.
[16] Chukur O., Pasyechko N., Bob A., Sverstiuk A. (2022). Prediction of climacteric syndrome development in perimenopausal women with hypothyroidism. Menopause Rev; 21(4), 1-6.
[17] Trysnyuk V., Zozulia A., Lupenko S., Lytvynenko I., Sverstiuk A. (2021). Methods of rhythm-cardio signals processing based on a mathematical model in the form of a vector of stationary and stationary connected random sequences CEUR Workshop Proceedings, 3021, 197 – 205.