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ABSTRACT

One of the key issues of solving engineering tasks is the search for a robust solution. Robustness is extremely important when developing health -based instruments, because a wrong instrumental diagnosis of a patient can cause the patient life. Robustness is also important in respect of the instrument electronics and the associated evaluation software. Our robustness research experience, which we gained in the field of robot structure and software research, began to be used in medical research and developments based on impedance spectroscopy, what we also researched and developed. In this article, I briefly try to summarize the problem and justify legitimacy of our research.

Keywords: *impedance spectroscopy, robustness, optimization, inverse problem, healthy*

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Introduction

Electrical impedance spectroscopy (EIS) is a popular non-destructive material test procedure. In EIS process with AC current had been excited in a test environment, and the excitation response is measured at one or more points on the surface of the examined environment. The recorded characteristics can be represented on Bode or on Nyquist diagrams. Spectrum presents the frequency dependence of the complex electrical resistance of the tested substance at different excitation frequencies. For EIS, depending on electrochemical or biological processes the frequency range, the frequency response can be analytically determined by the equivalent circuit elements. These elements include standard resistance and capacitors, but these are often unsuitable for biological measurement developments (e.g., diffusion, ion migration, etc.). Therefore, other special "circuits" have also been developed for the use of this method. There is still a need to overcome several technological barriers to present reliable future applications. Now, the sensitivity, accuracy, and reproducibility of methods are major shortcomings in applications.

Our research group had been developed measuring instruments for measuring spectroscopy, for four and eight-channel high precision spectroscopy. Our instruments measure impedance spectrum in 1mHz and 2MHz frequency range. Our multi-channel electrical impedance meter is based on digital lock-in technology. We have a self-developed algorithm for solving inverse problems on impedance networks. We make physical validation of a residual impedance rejection method during ultra-low frequency bio-impedance spectral measurements [Vizvari Z. (2020)].

In several medical biology research, we use EIS technologies. Some interesting research topics would be listed in the domain of bioimpedance-based measuring device for

- The primary tumor detection [Vizvari Z. (2021)].
- The study of hypoxic and hyperoxic conditions in cell cultures [Filotas N. (2021)].
- The diagnosis of Non-Alcoholic Fatty Liver Disease NAFLD [Gyorfi N. (2021)].
- The development of graphene coated measuring plate for the investigation of “dark” neurons [Berta K, (2021)].
- Preparation and validation of self-developed bioimpedance electrode array for tumor cells measurement [Nadasdi L, (2021)].

The results of impedance spectroscopic measurements usually contain quite a lot of uncertainty. The source of uncertainty may result from different sources, such as noise, nonlinearity, crosstalk, etc. These effects may have been greatly deformed by the results which occurred while solving the inverse problem. This can be very critical, for example, during medical applications or accompanied by critical chemical processes.

Robustness is a fundamental issue for assessing research results and engineering applications. We have research / development experience to measure the robustness of complex systems [Kecskés I. (2021)].

We used multi-objective and multi-scenario-based optimization research during our research of hexapod walking robot. In the case of hexapod robot research, many degrees of freedom should also be solved. Similar problems occur in the evaluation of impedance spectroscopy measurement results too. Analysis of research results as well as measurement results justify our expectations.

Application of Heuristic Optimization in Bioimpedance Spectroscopy Evaluation

- An effective and robust self-developed Method in Support of Measuring the Cole-Cole Parameters.
- A Modified Cole-Cole Model Used in the Evaluation of Low-Frequency Electrical Impedance Spectroscopy Measurements.

We want to measure the impedance properties of a cell culture. Cell cultures, depending on the type and nature of the cells, result in different transmission functions. These transmission functions can be approached with their electrical ($\boldsymbol{Z}_{domain}$, R and C elements, Figure 1) equivalent, single-pole, two-pole, three-pole approximations. In addition to the cell nature effect, the effect of excitation contacts ($\boldsymbol{Z}_{in}$, $\boldsymbol{Z}_{out}$) also appears in the measurement results, which changes from the case, but we do not know to what extent. In order to characterize the nature of the cell culture examined ($\boldsymbol{Z}_{domain}$), the R and C values must be estimated using the measurement results.

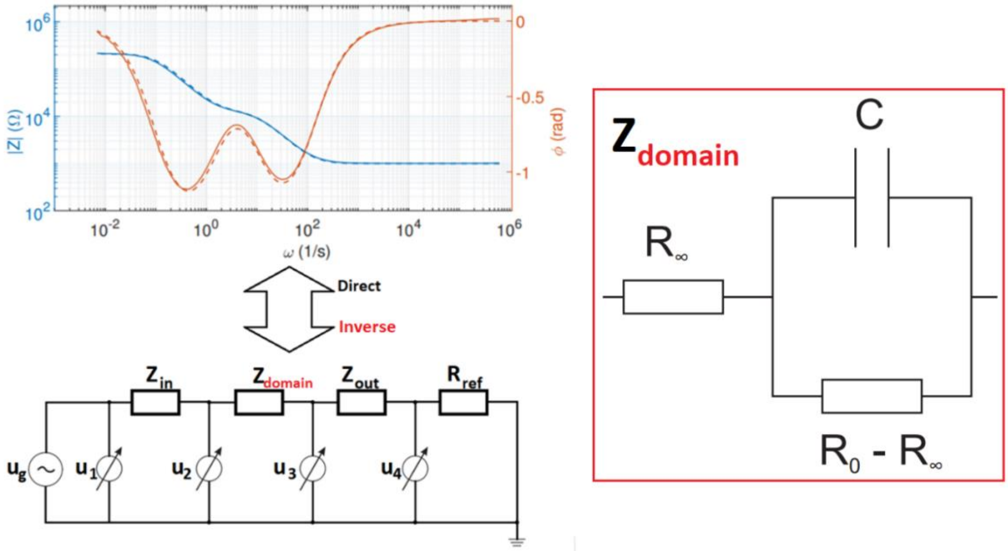
Impedance Spectroscopy

The Electrical Impedance Spectrum (EIS) procedure is based on a precise impedance measuring device which can measure at a given frequency. In order to be able to measure the impedance spectrum, the measuring device must be suitable for measuring impedance in the interesting frequency range. Impedance value should be measured with lock-in amplifier-based instrument, when we want to measure it with high accuracy (our instrument works on this principle). The details of the instrument and the measurement procedure are described in [Vizvari Z. (2020)]. It is important that the measurement process is automatically done from one frequency value to another in the desired range. At a given frequency the impedance spectrum can be represented with two values: with the absolute value of impedance and the phase value. The measurement results can be presented graphically on a Nyquist or Bode diagram.

The most basic method of implementing BIS methods is the four-electrode technique. One electrode is called a driver electrode, through which the current signal is injected and the other (three) electrodes, through which the frequency - dependent potentials were measured, are called sensor electrodes.

To develop an algorithm, it is advisable to simulate single-pole, two-pole circuits with so-called phantoms. First, we approach cell culture behavior with a single-pole model. In addition to the single-pole cell model, the circuit phantom is also built into the R-C element simulation of the excitation branch. The schematic diagram of the phantom circuit is on Figure 1, the u_1 is voltage of the sinus drive generator, and the u_2, u_3 and u_4 can be measured in the points, but the voltage and phase at specific points.

Figure 1. *Presentation of Direct and Inverse Data Transformation of Measured Results*



In different applications we need to determine the parameters of structural elements of the environment. From the impedance spectrum the structural elements can only be determined by inverse methods. Inverse mathematical methods have high sensitivity to input results, which requires that the measurement results are particularly accurate. The accuracy of our self -developed instrument in the measurement range: <1ppm for damping and <0.001° for angle. This error range is sufficient to estimate the values obtained as a result of the inverse problem.

EIS is a valuable tool for a wide range of substances determination because it is capable for characterization of wide range of transport and reaction routes. The use of EIS in the case of a wide range of electrochemical/biological phenomena is a significant challenge in interpret data. Complex physical processes are likely to contribute to the value of the measured impedance, often generating significantly overlapped answers in the frequency range. Various basic methods are used for the analysis of EIS data, making the most typical. These are "method of dominant quantity" or "modeled circuit elements". These methods require careful selection of equivalent circuit elements (with using an inverse method). This is needed, because we want to clearly present the physical processes, in the system under investigation. However, equivalent circuit models (ECMS) are often not unique and/or incomplete their physical meaning, limiting the accessible insight in structure. As a result, in recent years, they have increased interest in inversion algorithms, which estimate the underlying physical distributions such as relaxation time (DRT) and the distribution of diffusion times (DDT). This allowed to detailed EIS analysis, without the priori construction of ECMS. The location, magnitude and forms of recovered distributions can be used to determine their physical origin.

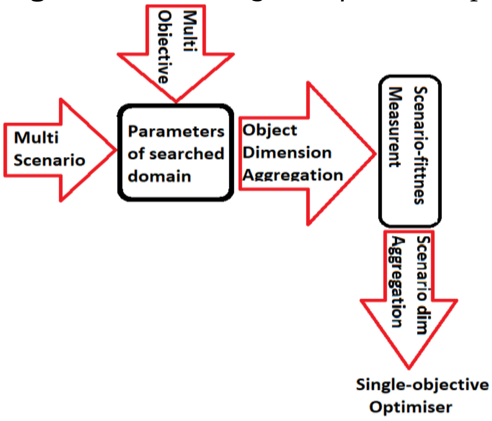
Robust Optimization

The Multi-Objective optimization process has many objective functions, and when searching for an optimal solution, the criteria include finding the best fitness values while compromising between goals. The definition and scope of the robust optimum is examined in detail in the literature [Deb K. (2006)]. In practice, users are not always interested in finding so-called global best solutions, especially if these solutions are quite sensitive to changing perturbations that cannot be avoided in practice. The optimum is robust if the performance is stable for the expected changes in the environmental parameters or in any sense for various scenarios. Such perturbations of parameters appear in different environmental parameters, different numeric calculation methods, different missions, uncertainty of measurements and uncertainty of model parameters or design parameters. One of the latest recommended methods for robust optimization converts is a single objective robust optimization problem into a bi-objective optimization problem that can be solved with multiple objective optimization algorithms [Yu, W.-J. (2017)].

Multi-objective and multi-scenario optimization were described in literature. In the case of simulation models, in which the equipment is intended to implement many or infinite missions, the typical scenarios for planned use can represent the entire scenario set. Thus, the purpose of the test system has a multi-scenario property. In case of multi-objective problems where preferences are difficult to determine. To find an optimal solution, the decision-maker must determine the requirements and quantify the quality. For many objective problems, preferences are very difficult and complex. From time to time it is impossible to determine the requirements.

The robustness test process we developed a new method with which the automatic summary of goals and scenarios has become feasible (see Figure 2). Then, an objective search algorithm could be used as a result. Robustness was increased by the proper parameterization of the aggregation process. These goals were achieved using minimal mathematical apparatus. But we used soft computing methods with the highest possible extent. Optimization of the utility function’s weights by a multi-scenario approach.

Figure 2. *Block Diagram of Robust Optimization Procedure*



Contrary to summary methods, product-based aggregation offers an advantage: the participation of individual objects from the resulting global criterion. A method of weighted multiplication, where exponent-type weights indicate the relative importance of each objective functions and exponential weights help to present a non -linear character too. We present the utility functions with the following types of functions [Kecskés I. (2021)]:

$$f = \prod_{m=1}^{M} (b_m + f_m(X))^{e_m}$$

$$g_1 : \frac{1}{M} \sum_{m=1}^{M} b_m = 1 \quad g_2 : \prod_{m=1}^{M} e_m = 1.$$

Sensitivity analysis with the robustness index, approaches to multi-purpose robust optimization problems, where performance functions are very sensitive to small changes in design variables and/or design environment parameters. According to this research, the robust index (RI) is the highest eigenvalue of the sensitivity Jacoby matrix.

During the development, our goal is to teach a robust system that appreciates the C and R_0 values as accurately as possible from these measured voltages, regardless of the values of C_{in}, R_{in}, C_{out}, R_{out}.

The voltage and phase value measurements are performed at the following frequencies: $f_i=10^{-1.8+i0.2}$, $i =\{0, 1,..., 33\}$. The 34 points between 0.0158Hz and 63096Hz are equidistant on the logarithmic axis. The circular frequency from this: $\omega_i = 2\pi f_i$.

Mathematical Model for Optimization

We first built the mathematical model of the circuit in MATLAB. Then we validated the model with some measurements. After that, with the validated mathematical model, we created thousands of examples, variations, a dataset, this dataset is later data base on a trained and optimized system.

Each impedance values are calculated with the following formulas:

$$Zin_i = \frac{1}{\frac{1}{Rin} + j\omega_i Cin}, where\ i = \{0,1, \dots 33\}$$

$$Zout_i = \frac{1}{\frac{1}{Rout} + j\omega_i Cout}$$

$$Zdomain_i = R_\infty + \frac{1}{\frac{1}{R0 - R_\infty} + j\omega_i C}$$

where, j is the imaginary unit. We can calculate the normalized voltage values:

$$I_i = \frac{U1}{Zin_i + Zbody_i + Zout_i + Rref}$$

$$Zdomain = \frac{U3 - U2}{I}$$

$$U4 = Rref \cdot I$$

$$U3 = (Zout + Rref) \cdot I$$

$$U2 = (Zbody + Zout + Rref) \cdot I$$

$$U1/4 = \frac{U1}{U4} \quad \text{and} \quad U2/4 = \frac{U2}{U4}$$

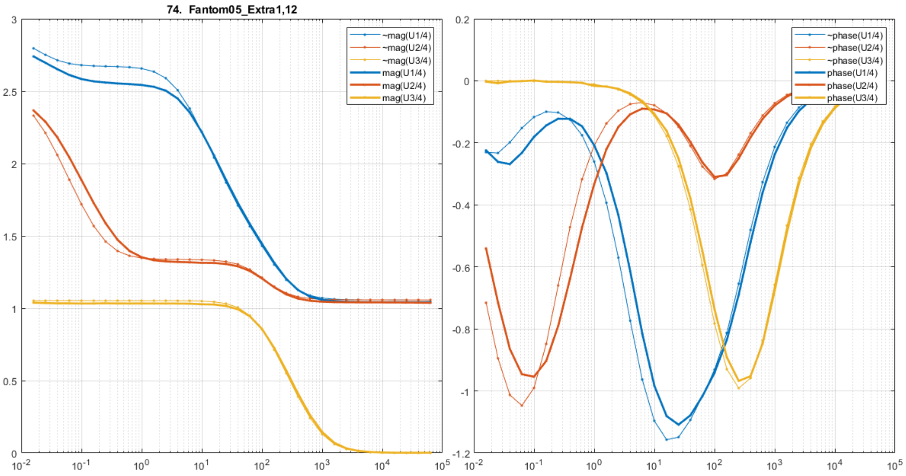
The data set contains a 34 -length complex vector for each impedance combination: *U1/4*, *U2/4*, and the associated solution: R_0 and *C*. From these, we generate magnitude and phase values. The $R_\infty = 1k\Omega$ és $R_{ref} = 96\Omega$, $U_1 = 12V$ have constant value. The R_{in}, C_{in}, R_{out}, C_{out} are varied from a logarithmic weight set, in the Table 1.

Table 1. *Training Dataset Parameters*

Variables	Num. of Variants	Unit	Simulated set
R_0	26	$k\Omega$	1, 1.2, 1.5, 1.8, 2.2, 2.7, 3.3, 4.1, 5, 6, 7.4, 9, 11, 13.5, 16.4, 20.1, 24.5, 30,36.6, 44.7, 54.6, 66.7, 81.5, 99.5, 121.5 148.4
C	37	mF	0.05, 0.06, 0.08, 0.11, 0.14, 0.17, 0.22, 0.29, 0.37, 0.47, 0.61, 0.78, 1, 1.28, 1.65, 2.12, 2.72, 3.49, 4.48, 5.75, 7.39, 9.4900, 12.18, 15.64, 20.1, 25.79, 33.1200, 42.52, 54.6, 70.1 90, 115.58, 148.41, 190.57, 244.7, 314.2, 403.43
R_{in}, R_{out}	9	$k\Omega$	5, 10, 20, 30, 50, 100, 200, 300, 500
C_{in}, C_{out}	7	mF	0.1, 0.3, 1, 3, 10, 30, 100

The training data set contains 26*37*9*7 = 60606 cases. Similarly, we generated a test data set with slightly different values, 16*19*7*4 = 8512.The measurement database contains 91 measurement results, like the above, which plays the role of external validation in the development of the network. One of these is presented in Figure 3.

Figure 3. *The Simulation Model Shows Similar Curves Compared to Measured*



Results of Applied Robust Inverse Process for Decision Results

We taught a Feedforward with a small neural network with 40 neurons in a hidden layer. Learning algorithm was used by Levenberg-Marquardt Backpropagation (*Trainlm*). This solution system is a relatively simple structure that can easily measure the possibility of solving the problem. The input is *2x34* Magnitude voltage *(U1/4 and U2/4)* + *2x34* phase, i.e., a total of 136-dimensional inverse solution system.

The *U1/4* and *U2/4* normalized voltage values (network inputs) show no linear character with output estimated values (R_0 *and* C), so the result vector range is transformed in a logarithmic range ($T1 = log_{10}R_0$, $T2 = log_{10}C$). In our experience, the logarithmic output has given much more robust solutions. The performance of the estimate was estimated with Pearson correlation; Table 2 summarizes the results of the estimation.

Table 2. *The Results of the Performance Estimation*

Neural network output	**Training, n=60606**	**Test, n=8512**	**Validation, n=91**
$\boldsymbol{T1 = \log_{10} C_0}$	r=0.8	r=0.62	r=0.72
$\boldsymbol{T2 = \log_{10} C}$	r=0.83	r=0.57	r=0.84

The training and the test showed a similar distribution, but the test results were weaker. This may indicate some over-learning. The validation kit, on the other hand, shows quite a good result, although a larger sample set would be needed to estimate the exact performance.

Future Work

The parameters and hyperparameters of the neural network could be tuned in such a way that the various cases (scenarios), or phantom variations, achieve the best possible estimates. Estimates R and C can be considered as two parallel objectives, so multi-objective multi-scenario optimization could refine the network or other similar estimating systems.

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