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Fractional models in electrical impedance spectroscopy data for glucose detection☆

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ABSTRACT

The article presents a methodology to discriminate glucose levels using electrical impedance spectroscopy technology. The method is based on an adequate estimation and assessment of the impedance data followed by identification of a general rational fractional model. The methodology is illustrated on a group of saline–protein–glucose solutions at physiological concentrations, and shows the ability of the fractional models to discriminate glucose levels. The method exhibit significant differences in the zero position of the fractional model for different glucose concentrations allowing discriminate the glucose effect on the impedance data along different matrix solutions. The results based on fractional model method are compared with classical circuit models and rational integer models. Even when the different methodologies perceive variations in the impedance data given glucose alterations, the fractional models present low uncertainty allowing discriminating small glucose alterations in the physiological range.

1. Introduction

Conditions for a continuous blood glucose monitoring include high accuracy, high sensitivity and short measurement time [1–4]. These conditions establish electrical impedance spectroscopy (EIS) as one of the most suited techniques, since it allows distinguishing, in a single measurement, multiple individual contributions from different constituents of the system under test [5–10].

Unfortunately, the relation between the structure of the system, the analyte concentration and the impedance behavior is not straightforward. The relation can be complex and requires a suitable model that allows interpreting the measurement results while reduces the uncertainty in parameters. There are different approaches to establish a system's model. The ideal method is to develop a mathematical model that correlates and quantifies each one of the physical–chemical processes that probably occur in the system. However, such a method requires plenty knowledge and critical understanding of all processes that could take place in the system. Other extended alternative is to use analog electrical circuit models where the circuit's elements and connections represent physical processes that are likely present in the system. In this sense, the designed circuit is believed to be the most appropriate design [5,6]. However, there exist difficulties to obtain the exact or correct circuit model for a particular process or system. The principal ones can be reported as: (1) it is possible to find more than one equivalent circuit that follows the spectrum impedance. (2) From the different circuits that can be identified, it is not possible to say what configuration is correct, and (3) it is always possible to obtain a more accurate fitting over the experimental data adding more circuits elements [11]. Fractional models for NaCl-glucose solutions have been previously reported in [12] under the fix $\sqrt{s}$ or Warburg variable showing important result reducing the model order. In the current work a general fractional model is introduced and assessed over different glucose solutions showing the capability of the method to discriminate glucose content at physiological levels.

In order to develop a glucose measurement system based on EIS technology, the present article is concerned in an appropriate excitation signal strategy, followed by data analysis and a convenient modeling procedure. In general two steps are considered:

- Measure and quantify the quality of the measured data: A convenient excitation signal that improves the EIS experimentation is a multisine excitation. This signal reduces the measurement time, offers full control of the excitation harmonics and shape of the power spectra keeping the properties of pseudorandom signals. This excitation allows estimating the additive noise and discriminate between even and odd nonlinear contributions present in

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the system, while allowing to calculate the best linear approximation (BLA) of the impedance, as well as assessing the stationarity of the process [13]. All this information is important since electrochemical systems are prone to be highly non-linear, while out of controlled conditions could present high levels of noise. In this sense, the quality of the measurements is quantified based on the level of noise and levels of non-linear distortions present in the system.

- The second step is identification based on fractional models. Fractional order systems are described by integro-differential equations involving fractional order derivatives. They are a generalization of the traditional calculus. Similar concepts and tools are applied, but with a wider generalization. [14–17]. The drawback, however, is that fractional models are non-linear in the parameters and require an initial estimation to guarantee convergence to the solution. In the present method the initial estimation is obtained by an algorithm based on the linear integer model in the Laplace domain [18].

The methodology is illustrated on a group of fundamental solutions (saline–glucose and albumin–saline–glucose) where the electrolyte concentration have been modified from average physiological to hiponatremia and hipocloremia levels (low levels of Cl and Na). In all cases the discrimination of the glucose was possible using fractional models, while circuit models and integer models showed high uncertainty avoiding discriminating the glucose levels. In this sense, the proposed methodology presents high capabilities to improve analyte detection based on EIS.

There are several areas in science and engineering where fractional models have been successfully applied. Some examples in medical/biomedical applications are: fractional model structure describing the hemodynamics in functional magnetic resonance imaging (fMRI) [19], fractional order models to quantify the respiratory mechanical properties of the respiratory system [20], description of the fractional behavior of the deoxyribonucleic acid code [21], fractional models to understand the dynamics of human immunodeficiency virus infecting the CD4+T lymphocytes [22,23], fractional calculus models of complex dynamics in biological tissues [24]. In the field of electrochemistry, the use of fractional elements to model the impedance spectral data are described in [6,25]. In [26] the data analysis of mass-transfer electrochemical systems using fractional models is analyzed showing reduction in the number of parameters compared with integer models. A survey using fractional circuits models to fit impedance data in biomedicine and biology are presented in [27]. A review of the history of fractional calculus is found in [28].

The article is organized as follows: Section 2 the methodology for glucose analyte detection based on EIS is presented. In this section the excitation signal and the fractional model identification procedure are described. Section 3 the result and analysis of the impedance measurements and modeling are presented. Section 4 compares the results using fractional models with those obtained by circuits models and rational integer models. Section 5 presents the general conclusions of the present work.

2. Methodology

The methodology includes two general steps: Estimates the BLA of the impedance system, assess the measured data, and identify a parametric fractional model.

2.1. Impedance measurement

From the different signals that allow broadband excitation (maximum length binary sequence, noise excitation, chirp, discrete interval binary sequence, multisine excitations among others), the random phase multisine reduces the measurement time, allows full control of the excitation spectra while allows identifying the level of noise and the level of non-linearities present in the system. The random phase multisine signal is a periodic signal formed by the sum of N harmonically related sine waves with amplitudes A_k and uniform distributed random phases ϕ_k in the interval $[0, 2\pi[$

$$r(t) = \frac{1}{\sqrt{N}} \sum_{k=1}^{N} A_k \sin(j\omega_k t + \phi_k) \tag{1}$$

ω_k are the excited frequencies ($\omega_k = \frac{2\pi k}{N} f_s$) and f_s the sampling frequency.

From the different signals that could be generated by (1) this article uses an odd random phase multisine (ORPM) signal. In this signal most of the odd harmonics are excited, called excited odd harmonics. The even harmonics are not exited, called non-excited even harmonics. And in a group of predefined and consecutive odd harmonics one of them is randomly non-excited ($A_k = 0$), called non-excited odd harmonics. In the multisine the lowest frequency is the fundamental and define the period of the signal. The maximum frequency is limited by the Nyquist theorem. This kind of signal is periodic, and from here the leakage is not a problem in the impedance estimation.

In order to have good impedance estimation the measurements need to be done in steady state. To reach this condition a waiting or stabilization time (t_W) is required. This time depends on the time constant of the system and the frequency resolution [29,13]. For P measured periods, the measurement time using ORPM excitation (t_{ORPM}) is:

$$t_{ORPM} = t_W + P\frac{1}{f_{\min}} \tag{2}$$

with (f_{min}) the lower excited frequency. The waiting time (t_W) is considered only once, which reduces the measurement time compared with (equivalent) single-sine excitations, where the waiting time (t_W) need to be counted for each excitation frequency. On the other hand the ORPM is a broad band excitation signal and reduces the measurement time compared to swept–sine excitations [13,30].

The reduction of the excitation time is important since diminish de risk of estimating the impedance during changes in the system. However, it does not imply that the system behaves stationary. In order to assess the presence of non-stationary contributions, the levels of noise at excited and non-excited frequencies can be used. The variance of the noise should be a smooth function of the frequency. So, the noise level at excited and non-excited frequencies should be approximate the same. If the system is non-stationary, the noise estimation at the excited frequencies will contain information not only of the noise but of the non-stationary behavior in the system, generating a difference between the noise estimations (at excited and non-excited lines) [31–34]. More information on the measurement analysis using multisine excitations can be found in [35,36].

2.2. Identification based on fractional models

Once the measurements have been assessed and the BLA of the impedance system estimated, the next step is to establish the relationship between changes in the impedance given changes in the system by variations in glucose concentration. In order to establish such relation fractional models are developed.

Modeling a fractional system using integer order models require a high number of parameters to reach a satisfactory approximation [37]. The high number of parameters will increase their uncertainty making difficult to identify small changes in the impedance