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# Fractional Order and non-linear System Identification algorithms for Biomedical applications

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**Abstract.** We discuss the modelling of dielectric responses of amorphous biological samples. Such samples are commonly encountered in impedance spectroscopy studies as well as in UV, IR, optical and THz transient spectroscopy experiments and in pump-probe studies. In many occasions, the samples may display quenched absorption bands. A systems identification framework may be developed to provide parsimonious representations of such responses. To achieve this, it is appropriate to augment the standard models found in the identification literature to incorporate fractional order dynamics. Extensions of models using the forward shift operator, state space models as well as their non-linear Hammerstein-Wiener counterpart models are highlighted. We also discuss the need to extend the theory of electromagnetically excited networks which can account for fractional order behaviour in the non-linear regime by incorporating nonlinear elements to account for the observed non-linearities. The proposed approach leads to the development of a range of new chemometrics tools for biomedical data analysis and classification.

## 1. Introduction

Many broadband spectroscopic investigations of biomedical interest are performed using femtosecond transient pulse systems, as well as using continuous wave and Fourier domain mode-locked lasers. These spectrometers ensure a persistent excitation of all the modes of the sample across each spectral bin. In these experiments, one often observes Jonscher-like responses that display a fractional order behavior as a function of excitation frequency [1-8]. Furthermore, Havriliak-Negami or Fröhlich mixture [9, 10] type responses are also more faithfully described using fractional order calculus [11, 12]. The use of parametric models to the dielectric spectra of biological tissues has been often discussed in the medical physics community. For example permittivity and conductivity measurements of blood, bone, kidney, liver, spleen, tendon, muscle, skin, fat and brain (Grey and White matter) as well as heart muscle have been characterized and Cole-Cole models have been fitted to those datasets over a large range of frequencies (10 Hz to 100 GHz) by separating the datasets into four different regions and fitting a model for each region [13].

This work provides an overview of modeling approaches that are of relevance to the signal processing of this type of broadband spectra. System identification techniques may be used as a chemometric tool to infer the composition of the sample and observe subtle differences in composition

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between samples on the basis of studying the input and output waveforms from the associated experiments. Modeling techniques enable very parsimonious expressions of the dynamics of the excited samples. On the basis of the generated models, guidelines for optimal excitation using tailored chirped or PRBS sequences can be subsequently developed ensuring optimal signal-to-noise ratio in the experiments. Optimal excitation can be conveniently implemented experimentally using well-established pulse shaping techniques.

The work also highlights the utility of using random *RLC* networks to model the dynamics of multiple excitation/de-excitation processes. These networks can emulate complex diffusive charge transport processes and provide alternatives to existing percolation and spectral density approaches, as well as Archie's law and Kohlrausch-Williams-Watts models. As a consequence, they can also form a basis to extract chemometric information for classification tasks.

## 2. Fractional order calculus and system identification algorithms for the study of the interaction of excitatory waves with biological tissue

In the following sections we discuss generic methodologies for studying the interaction of excitatory waves with biological tissue. The approach considers an emerging area in applied mathematics, that of fractional order calculus and discusses its application within a wider signal processing framework applicable within a biomedical context. We also propose to use 3-dimensional networks containing a different composition of resistive, capacitive and inductive elements to model the dynamic response of biological tissue to excitatory waves. This approach is justified on the basis that the associated dynamics of such networks are of fractional order.

### *2.1. Fractional order models using the forward shift operator*

In linear spectroscopies, the output of a deterministic linear system that describes a biological or chemical process at time instance $k$ can be computed by filtering the excitation input $u(k)$ through a linear filter $G(q)$ which has the dynamic of the system under study. In this formulation, $q$ denotes the forward shift operator $q^{-1}x(k)=x(k\text{-}1)$ which may be associated with its time domain counterpart $z=e^{j\omega}$ in the frequency domain [14-16]. Fractional order linear system identification can be based on parametric methods which would need to describe the true process behavior exactly with a finite number of parameters based on fractional order differential or difference equation models, or non-parametric methods where an infinite number of parameters would be needed to describe the process exactly. Normally, parametric methods will be most appropriate when a relatively low number of parameters need to be determined. Non-parametric methods, however, are generally more flexible, as less structure is imposed on the model in an *a priori* basis.

Usually, the parameters described in parametric models can be extracted in the time, frequency or wavelet domains using least squares, nonlinear optimization or repeated least squares, whereas non-parametric methods would require impulse or transient response analysis or correlation analysis in the time domain, or frequency response, Fourier and spectral analysis in the frequency domain; these techniques are also extendable in the wavelet domain. A general linear fractional order model based on the forward shift operator is shown below:

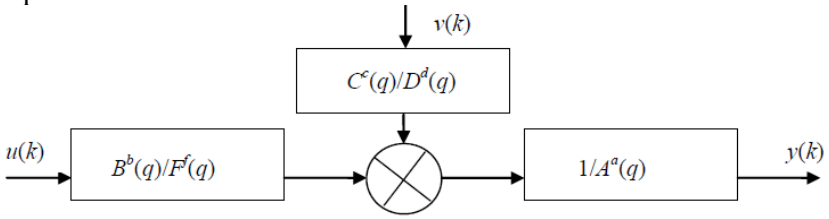


**Figure 1.** Linear fractional order model in generic form.

This generic structure forms the basis for all linear fractional order models that are based on the unit forward shift operator. The fractional order autoregressive with exogenous input (FO-ARX),

autoregressive moving average with exogenous input (FO-ARMAX), output error (FO-OE), Box-Jenkins (FO-BJ), autoregressive-autoregressive with exogenous input (FO-ARARX) and finite impulse response (FO-FIR) models are special cases of the above structure. The identification of the above models is a direct extension from integral order calculus but it also requires an additional step for the estimation of the associated exponents.

*2.2. State space fractional order models*

The dynamics of an unknown medium may also be modeled using an input-output state space representation where a subspace multiple input-multiple output (MIMO) model may be fitted [16-20].

The fractional state space representation for the system is given from:

$$D^{q}\mathbf{x}(t) = A\mathbf{x}(t) + B\mathbf{u}(t) \tag{1a}$$

$$\mathbf{y}(t) = C\mathbf{x}(t) + D\mathbf{u}(t) \tag{1b}$$

where $\mathbf{x} \in \mathbb{R}^n$ is the state vector, $\mathbf{u} \in \mathbb{R}^m$ is the input vector, $\mathbf{y} \in \mathbb{R}^p$ is the output vector and $A \in \mathbb{R}^{n \times n}$, $B \in \mathbb{R}^{n \times m}$, $C \in \mathbb{R}^{p \times n}$ and $D \in \mathbb{R}^{p \times m}$ are the state, input, output and feed-through system constant matrices to be determined. As discussed in [21], such fractional order system is stable if $0 < \alpha < 2$ and $\left|\arg(\lambda_k)\right| > \alpha\pi / 2$ and $-\pi < \arg(\lambda_k) \le \pi$ where $\lambda_k$ corresponds to the $k^{\text{th}}$ eigenvalue of $A$. For time-domain simulations of a system, a recursive distribution of poles and zeros is obtained to approximate the frequency behavior of $s^a$ over an interval $\left[\omega_A, \omega_B\right]$. Because the asymptotic behavior at the low and high limits of the above frequency interval can have a static error between the fractional order model and its approximation, it is common to minimize this using an integrator operating outside that interval. Given a large number of inputs and outputs related to the unknown dielectric system, the goal of the subspace algorithms is to determine the order of the system, $A, B, C, D$ (to a similarity transformation). For simplicity, one may only consider the deterministic case where there is no noise in the measured inputs or process (estimated state) although the proposed approach is also valid to the stochastic case where an explicit augmented model in innovation form can be considered. In that case, an additional step is required to obtain an estimate of covariance matrices of the noise sequences. Simulations using the associated formulations are mentioned elsewhere [22].

*2.3. Combining fractional order calculus models with non-linear system identification models*

Advances in instrumentation and measurement methods have also resulted in a new surge of interest to extend chemometrics algorithms to describe the non-linear phenomena observed in biological sciences. Such problems, arise in 2-photon microscopy, four-wave mixing studies, saturation absorption spectroscopies, Raman spectroscopies, fluorescence lifetime methods or other non-linear spectroscopies using high power laser sources e.g. synchrotrons, free electron lasers etc. Non-linear models need also to be assumed in femtosecond pulse pump-probe experiments where the pump pulse introduces a static non-linearity in the sample which is then observed by the probe pulse at various phase delays. Hammerstein and Wiener models (Figure 2) have been extensively used by the systems identification communities for such purposes. In previous works our group has used integral order calculus with polynomial fitting for the derivation of a static non-linearity [23]. Neural networks, however, are also appropriate to describe the non-linearity in the identification process. Since solute interactions can involve non-linear processes as well as forces acting at a distance, it is quite appropriate to extend such framework to account for processes displaying fractional order dynamics.

Taking into consideration the generic framework shown above, it is appropriate to extend existing Hammerstein-Wiener algorithms to account for fractional order dynamics.

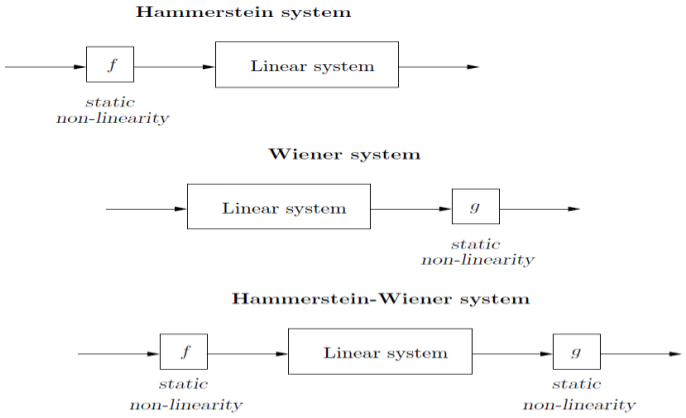


**Figure 2**. Pulse excited systems described by a linear dynamic model preceded and/or followed by static non-linearities.

*2.4. Simulations with randomly connected RLC networks*

In previous works [22, 24] we have discussed the possibility to simulate dynamic processes encountered in spectroscopy experiments using 2-dimensional and 3-dimensional random *RLC* networks. Our work reconfirmed results in the existing dielectrics literature [9, 25-28] and has paved the way for generating parsimonious representation of the excitation and de-excitation dynamics as well as place experimental results within a chemometrics context. For example, it is possible to distinguish between batches of samples prepared in powder form and compressed into pellets as is customary in the pharmaceutical industries by assuming each element in the composition is associated with a capacitive or resistive behavior. Such framework is also of particular relevance to the interpretation of results from laser-induced fluorescence lifetime experiments. By converting the state space responses of these networks into input/output transfer function formulations, it is possible to link the overall admittance observed for the system to few resistive and capacitive components [29]. Classification can then be conveniently performed using very parsimonious representations [30-32]. This work may also be extended to *RLC* networks [33] to account for resonant structures, as would be the case for molecular optics experiments where the electric field resonantly excites the studied molecules. Current work aims to further extend these simulators to Fröhlich mixture type responses as encountered when polarized structures such as membranes are probed, since the observed responses can be highly non-linear. This should be possible by incorporating in the existing networks memristive, memcapacitive and memductive elements.

## 3. Discussion

Although systematic studies of dielectric responses of tissue across the electromagnetic spectrum are regularly being performed using acoustic, nuclear (including functional) magnetic resonance, electron spin resonance, positron emission tomography as well as several other dielectric spectroscopic modalities, in the hope that malignant or diseased tissue can be identified and localized at early stages so that it can be isolated and targeted by therapeutic pharmaceutical modalities in a systematic or in a non-invasive manner through radiation therapies, there is a diverse range of tools currently available to perform parametric and non-parametric identification of such datasets. None of these, however, can fully capture the dynamics of the physical processes associated with the complex observed responses in most samples. This is due to the compositional complexity of the associated tissues. Fractional order modelling approaches can accommodate more complex responses in a manner that is not possible using standard integro-differential equation models. The associated fractional order expressions can capture the dynamics of an arbitrarily complex medium with a greater fidelity (a much smaller residual error in a least squares sense) so small differences in the model structure or parameters can be associated to small changes in the condition of the tissue. The proposed approach should be further explored in a systematic manner within a biomedical dataset classification context e.g. using support vector machine methodologies [34], taking advantage of the parsimonious fractional order expressions so that the generalization ability of the inference engines are not compromised.

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