Quantitative Complexity Theory: Applications in Medicine

WHITE PAPER
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OntoMed LLC

Abstract

Even though the so-called “complexity science” has been around for a few decades, it has failed to produce workable definitions and metrics of complexity. In fact, complexity still today is being seen as a series of phenomena of un-orchestrated self-organization and emergence in which their complexity is never measured. In early 2005 the first Quantitative Complexity Theory (QCT) has been established by J. Marczyk. According to this theory, complexity is no longer seen as a process but as a new physical property of systems. Complexity, therefore, just like for example energy, is an attribute of every system. In nearly a decade, the QCT has found numerous applications in diverse fields. One of them is medicine.

Because modern science lacks a holistic perspective, favouring super-specialization, a patient is rarely seen and treated as multi-organ dynamic system of systems. Due to this cultural limitation and because of the overwhelming complexity of the human body, only on rare occasions is medical science quantitative. This paper describes how the QCT can help provide the medical community with quantitative and holistic information on the state of a patient, as well as on the impact of treatment. To that end, a variety of applications of QCT in medicine are reviewed.

Background of QC Technology

Complexity is a natural and holistic property of every system. The complexity of a system having state vector \{x\} of N components is defined as a function of Structure and Entropy as follows:

\[ C = f(S \odot E) \]

where \( S \) represents an \( N \times N \) adjacency matrix, \( E \) is an \( N \times N \) entropy matrix, “\( \odot \)” is the Hadamard matrix product operator and \( f \) is a norm operator. Given that \( S \) has no units and since entropy is measured in bits the units of \( C \) are also bits. The above equation represents a formal definition of complexity and it is not used in its computation. Instead, the adjacency matrix is determined via a patented multi-dimensional algorithm which determines if entry \( S_{ij} \) is 0 or 1. This establishes the structure of the system in question.

The intensity of relationships between the components of \{x\}, the so-called generalized correlation, is computed based on concepts of entropy and Shannon’s Information Theory. This approach has been chosen because it avoids the drawbacks of conventional model-based techniques whereby one attempts to describe data via regression models, cluster analysis or other methods. The huge advantage of our “model-free” approach is that it is independent of numerical conditioning of the data and its ability to identify the existence of structures where conventional methods fail.

Once the entropy matrix and the adjacency matrix have been obtained, one may compute the complexity of a given system as the following matrix norm:

\[ C = \| S \odot E \| \]

A fundamental property of the above measure of complexity is that it is bounded. The upper bound, the so-called critical complexity, \( C_U \), as well as the lower bound, \( C_L \), are also computed based on entropy concepts. In proximity of the lower complexity bound, a given system functions in a deterministic structure-dominated fashion. In proximity of critical complexity system functioning is uncertainty-dominated and relationships between the various state vector entries are fuzzy and therefore characterized by very low generalized correlations.
System structure, which depicts the interdependencies between the components of \( \{x\} \) spanning a period of time \( T \), is illustrated in Figure 1.

![System structure](image)

**Figure 1.** Representation of structure (adjacency matrix \( S \)). The nodes (state-vector components) are aligned along the diagonal. Such maps are known as System Maps.

System complexity can be measured if data is available. Examples of data which may be processed using QCT techniques implemented in OntoMed’s software products are:

- Multi-channel data recorded in an ICU (Intensive Care Unit) or OR (Operating Room)
- ECGs
- EEGs
- Certain classes of images

Both real-time data as well as off-line data may be analyzed. The important aspect of OntoMed’s technology is that raw data may be used, without the need of pre-conditioning or filtering.

QCT makes it possible to quantify for the first time the instantaneous stability of a patient. Based on streaming multi-channel data available in an ICU or OR, stability is defined as the rate of change of complexity over time:

\[
\lambda(t) = \frac{\partial C(t)}{\partial t}
\]

Stability is expressed in percentage terms, whereby values close to 0% reflect highly unstable patients while values in proximity of 100% correspond to stable situations. Stability may be measured in real-time using the COSMOS™ (Complexity-based Stability Monitoring System) and is useful in issuing early-warnings. This is because complexity fluctuations have been found to precede critical or life-threatening situations.

QCT finds an important application in quantifying the impact of treatment (surgery, drugs, implant, etc.). Provided that pre and post-treatment data is available, such as ECG or EEG, it is possible to quantify the “distance” between the two situations. This is done by comparing not only the values of the single components of \( \{x\} \), but also the topologies of the respective System Maps. The technique, therefore, delivers a holistic reflection of the evolution of patient’s state-of-health precisely because it takes into account all the couplings between the different parameters, not just their instantaneous values.

The simplest application of QCT is to rank and classify patients and/or risk stratification. Complexity, because it takes into account the components of \( \{x\} \) as well as all the significant couplings and their structure \( (S) \) it reflects, via one scalar measure, the entire system. Measurements of complexity may be performed over short or long time periods \( (T) \).
Given the fact that complexity is a function of both structure and entropy, it is important to understand which of these two components is responsible for high or low values thereof. The predominance of the structural component over entropy points to essentially deterministic behaviour. When entropy dominates system behaviour is chaotic and forecasts or estimates of future states may be very difficult. However, this distinction is not crucial in a real-time setting in which the rate of change of complexity is of particular interest.

In the following sections various applications of QCT are described.

**Real-time applications**

COSMOS™ is a real-time software system for monitoring patients in the ICU or OR. Application of the tool at the US Army Institute of Surgical Research (USAISR) has shown that fluctuations of complexity precede deterioration in vital signs during hypoxic cardiac arrest. In [1] and [2] it is shown how, in an experiment with live animals “During asphyxia, traditional vital signs remained non-indicative of demise until abrupt occurrence of LOAP. At a mean time of 5 min. 24 sec before LOAP, a critical change (rise) in OSC was identified.” The Graphical User Interface of the tool is illustrated in Figure 2.

COSMOS™ computes patient’s stability in short, medium and long term as well the corresponding instantaneous complexity. A bar chart – known as the Complexity Profile - provides a quantitative breakdown of complexity according to the different data channels (components of \{x\}). Like all plots, it too is updated in real-time and indicates, in percentage terms, how much each data channel contributes to the instantaneous value of complexity. In practice, it indicates which vital signs are contributing, and in what measure, to patient’s stability (or instability). It is difficult to stress the relevance of such information.

The COSMOS™ system is a single software module, available for integration into any IT infrastructure in hospitals. Its simple data transfer protocols make it easy to integrate and deploy.
Cardiology

There are numerous applications of QCT in cardiology. As illustrated in Figure 1, QCT algorithms may be used to process intracavitary EGM signals to improve arrhythmia detection and discrimination as well as help track performance over time. In particular, the technology can be used to improve patient management by reducing inappropriate shocks, not to mention alerts of worsening patient condition.

![Figure 1. Examples of complexity-based rhythm discrimination](image)

Figure 3. examples of complexity-based rhythm discrimination. Complexities of each signal are indicated as well as the corresponding System Maps.

A QCT-based index has been used to validate Baseline HRV (Heart Rate Variability) as being predictive in terms of clinical events in Heart Failure patients implanted with Cardiac Resynchronization Therapy (CRT) [3]. The award-winning paper points out that "Even if results are drawn from a small sample of patients with a limited proportion of events, the analysis of these data showed that the HR-Complexity (HR-Co) index carries relevant prognostic information on outcome of patients implanted with CRT. In particular, HF patients with higher HR-related complexity, representing a less compromised autonomic function, are prone to have better clinical response. On the other hand, baseline HR-Co, being the only parameter correlated to a clinical response in this setting, may be used to identify patients with a poor response, which may require additional interventions and/or better adjustment of the therapy. In this study, a significant increase of HR-related complexity indices and their variation are strongly correlated with the recovery of autonomic parameters and with a positive clinical response to CRT at 1 year”.

The study is innovated in that a novel approach has been devised to process the HRV diagrams stored in the memory of a device (ICD, pacemaker). While conventional approaches measure the area of the HRV diagram, the new QCT-based approach was adopted to actually measure the complexity of the image, see Figure 4.
idea is that complexity of the image footprint takes into account not only the area its edges embrace but also the internal characteristics of the image and contour distribution.

Figure 4. Mapping of an HRV diagram onto a QCT-based System Map. The 32 columns of pixels correspond to the entries of the map located on its diagonal.

A recent application of QCT technology is in measuring the actual impact of CRT therapy [4]. The concept, however, applies equally to all sorts of therapies (surgery, drugs, device implant, etc.) provided that pre and post treatment data is available. The first step is to obtain data and to synthesize the corresponding System Maps for pre and post treatment situations. This is implemented in the OntoCare™ system. An example of ECG mapping onto a System Map is illustrated in Figure 5.

Figure 5. Mapping of a multi-channel ECG diagram onto a QCT-based System Map. The 12 ECG channels correspond to the entries of the map located on its diagonal.
Once both data sets have been read and processed, OntoCare™ performs a topological map comparison in order to establish the degree of data similarity. If the maps are similar, this points to a low impact of therapy. If, on the other hand, data similarity is low, this points to a large impact of therapy (independently of whether it has been successful or damaging to the patient – this is up to the physician). An example is illustrated in Figure 6.

![Example of OntoCare™ Graphical User Interface](image)

Figure 6. Example of OntoCare™ Graphical User Interface, illustrating per and post ICD implant System Maps as well as examples of ECG channel time-histories as well as 2D scatter plots.

In the case in question the data set similarity of 36.8% points to an impact of therapy of $100 - 36.8 = 62.2\%$. The tool also provides additional and fundamental information, namely by identifying how the impact of therapy is distributed among the various parameters used to monitor the patient’s health. This is illustrated in Figure 7.

![Figure 7. Breakdown on therapy impact](image)

Figure 7. Breakdown on therapy impact for the case depicted in Figure 6. The bar chart provides a ranking of ECG channels in terms of contribution to the difference between pre and post-treatment ECGs. In the case in question channel V4 contributes approximately 28% of the 62.2% therapy impact.

Such information is invaluable as it can help locate areas (in this case in the myocardium) which are more receptive to therapy and help target better future interventions.
Neurology

Neurology is another field of medicine in which the QCT finds fertile ground. Similarly to ECG processing EEGs can be processed to yield complexity time-histories such as the ones depicted in Figure 8, corresponding to a healthy (left) and a patient in coma (right) are shown.

Figure 8. Complexity time-histories of a healthy patient (left) and one in a state of coma. Both time-histories are based on 10-minute EEGs.

OntoCare™ is being be used to measure the topological difference between EEGs recorded with eyes open/closed as well as to quantify the impact of artefacts. Figure 9 illustrates two examples.

Figure 8. Examples of System Maps of a healthy patient (upper maps) and one in a state of coma (lower maps).

In the case of a healthy patient, EEG complexity with eyes open is 21.7 while with eyes closed it is 58.8, reflecting a clear difference. System map topologies differ significantly. In the case of a comatose patient, there is very little difference in complexities: 229.4 (eyes open) versus 209.9 (eyes closed). System maps have almost identical topologies and densities. Similar information may be used to rank patients, i.e. establish a quantitative
“measure of coma” in analogy to the Glasgow coma scale. While the Glasgow scale score is based on eyes opening, verbal and motor response a complexity-based ranking is performed based entirely on patient’s EEG. It is therefore an objective index and takes into account the entire EEG as well as its structure. Finally, complexity may be used to measure the effects of artefacts or filtering on an EEG.

QCT-based techniques can be applied to measure the intensity of epileptic seizures as well as to quantify the effectiveness of treatment. An example is shown in Figure 9, where two system maps, based on 96-channel EEG, corresponding to pre-seizure and during mid-seizure are illustrated.

![System Maps of a patient before and during epileptic seizure.](image)

Figure 9. Examples of System Maps of a patient before and during epileptic seizure. The length of the red vertical arrow is proportional to the intensity of the seizure.

It is clear how during seizure all areas of the brain function in strong correlation, leading to a densely interconnected System Map. Complexity increases by approximately a factor of 5 with respect to pre-seizure.

These few examples illustrate the broad applicability of QCT to medicine. Research is currently being performed with various institutions (US Army Institute of Surgical Research, USA, Ospedale Sacro Cuore Don Calabria, Italy, Azienda Ospedaliera CTO, Italy, Hospital Universitario Sao Paulo, Brazil and Boston Scientific, Italy) in order to establish new applications and to further validate the technology.

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