

TECHNOLOGY

The COSMOS™ system works based on complexity measures developed by Ontonix. The concept is to measure fluctuations of complexity versus time to quantify stability.

WHY COMPLEXITY?

Because modern science lacks a holistic perspective favoring 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 medicine a quantitative science. Our mission is to deliver a technology which will provide the medical community with quantitative and holistic information on the state of a patient, as well as on the impact of treatment.



Measuring patient stability in the OR and in the ICU. In real-time!

Sudden changes in complexity indicate an imminent crisis.

COSMOS™

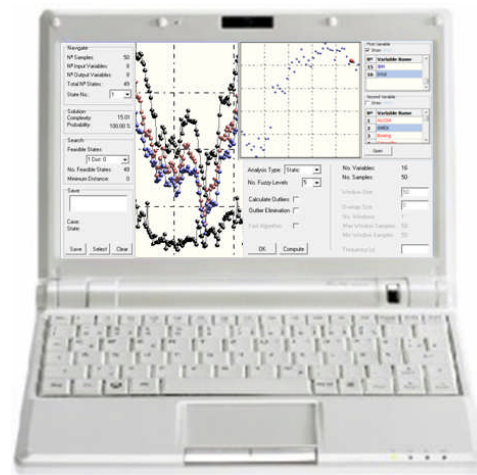
COSMOS™ (COMplexity-based Stability MONitoring System) is a PC-based multi-channel real-time system which quantifies the stability of hospitalized patients. Based on streaming data, originating from sensors and other monitoring devices such as those in an Operating Room or an Intensive Care Unit, the device computes the instantaneous degree of stability of a patient. The system also signals when the mentioned stability undergoes changes due to traumas, side-effects of treatment or any other dynamic mutations within the patient's organism. The device is unique in that it processes simultaneously all channels, analyzing all the potential cross-relationships, delivering a truly holistic view of the patient.

Model-free data processing

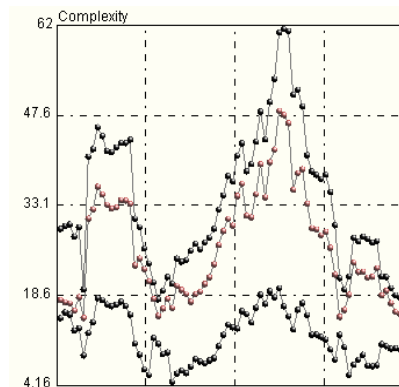
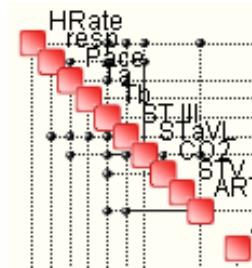
An important feature of our technology is that the collected data is processed to a model-free technique. This means that the measure of stability of the patient is not flawed by any particular mathematical approach.

Once defined, a model is condemned to deliver only what has been hard-wired into it. This is why the adoption of a particular math model automatically influences the conclusions one will derive from the underlying data. In other words, models can distort the information given data contains.

Data in an ICU is complex and of dynamical nature. It is characterized by strong variability and is highly non-stationary, presenting couplings of varying degree between the different channels. Our complexity-based technology allows one to capture and integrate different OR or ICU-specific data to generate a single, holistic measure which is indicative of patient stability. An example of complexity evolution versus time is shown on the right (40 simultaneous data channels).

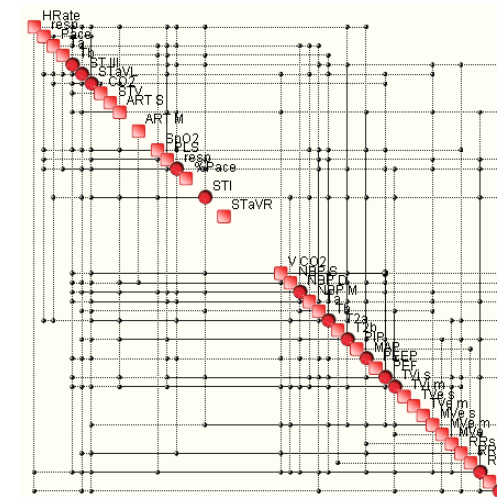


Complexity Science at the Service of Medicine



The Concept behind crisis anticipation.

The first step in the process of measuring the complexity of data originating from other monitoring devices is to establish a map of the relationships between the various data channels. This is done in real-time using a proprietary algorithm. An example of such map is shown below and a detail is illustrated on the left.



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Complexity Technology Facts

Q: What happens in the proximity of critical complexity?

A: When a given dynamical system finds itself functioning close to its critical complexity it becomes capable of delivering unexpected behavior. It is this property of highly complex systems that makes people intuitively try to avoid them as they are very difficult to understand and manage. The amount of complexity in a



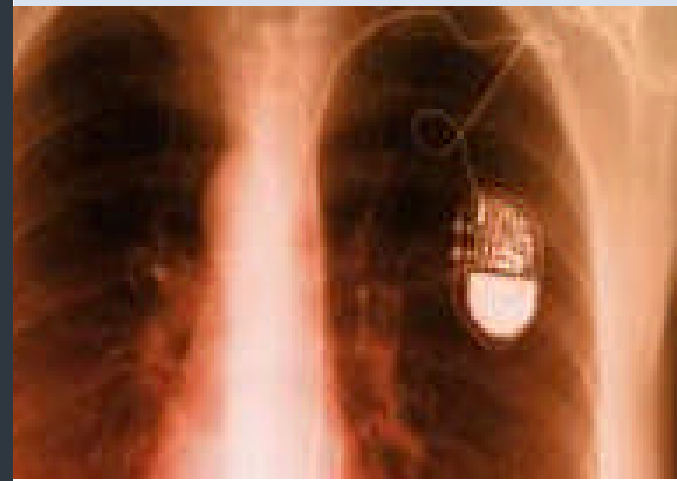
system is proportional to the effort that is needed in order to manage it. In proximity of critical complexity, not only complexity is high – a critically complex system has the capacity to behave according to numerous modes and to suddenly switch from one mode to another. This is a further source of difficulty when it comes to understanding and running the system. This explains why certain systems fail without early-warning.

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Measuring the impact of Cardiac Resynchronization Therapy

Complexity is an ideal means of measuring a patient's response to therapy, implants or surgery.

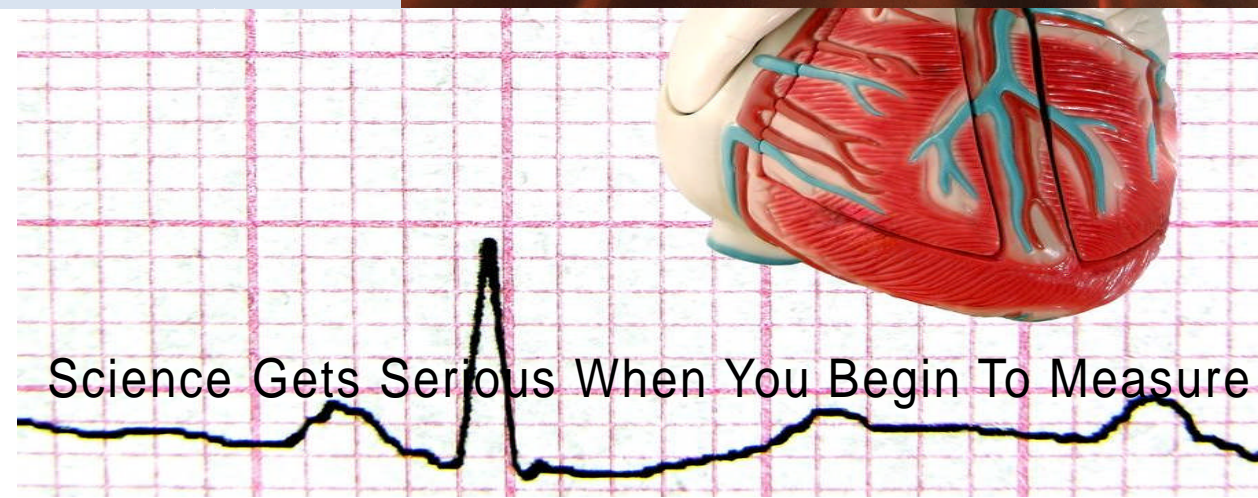
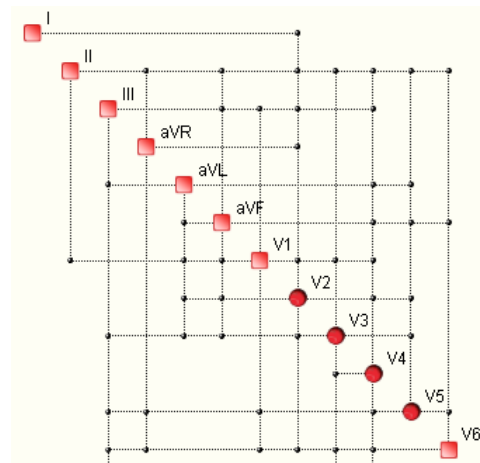
Cardiac Resynchronization Therapy (CRT)

In a healthy heart, the lower chambers (ventricles) pump at the same time and are in sync with the heart's upper chambers (atria). When a patient has heart failure, it happens that the right and left ventricles do not pump together. When contractions are not synchronized, the left ventricle is incapable of pumping sufficient amounts of blood to the body. This ultimately leads to increase in heart failure symptoms, such as breath shortness, fatigue, or irregular heartbeat. Cardiac Resynchronization Therapy coordinates the heart, so both chambers beat in sync. CRT uses a device that functions as a pacemaker or defibrillator (Implantable Cardiac Defibrillator) that is implanted under the skin. The device provides electrical impulses that synchronize the contractions of the ventricles.

Cardiac Resynchronization Therapy, adopted with NYHA class III and IV status patients, has been shown to improve the symptoms of heart failure and patient's overall quality of life. CRT is generally beneficial to patients with a moderate ejection fraction (EF).

Our technology allows us to express in quantitative terms the degree of success of the therapy based on pre and post implant ECG analysis or on the data stored in the device itself.

Reduced Heart Rate Variability, or the RR variability, is recognized as a predictor of mortality after myocardial infarction. There are numerous ways of measuring HRV, such as SDNN, SDANN or RMSSD. An innovative means of measuring HRV is via analysis of the HRV diagram. A conventional approach is to measure the footprint of the HRV diagram at patient discharge and at follow up. A more advanced approach is to actually measure the complexity of the diagram and not its area. A measure of the area gives no idea as to the internal structure of the image.



Science Gets Serious When You Begin To Measure

What Complexity Maps reflect.

Our analyses produce the so-called Complexity Maps. These are generated automatically based on raw data, such as EKG, EEG or any other real-time or off-line source. They reflect how information flows within a system, illustrating all the significant couplings, indicating sources of complexity and criticality. Complexity Maps (see example on the left) are fundamental towards better understanding of the dynamics of systems and of their potential failure modes.

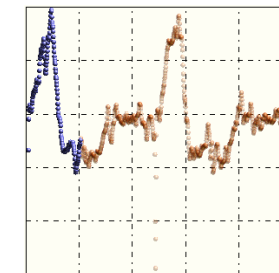
What inputs are needed.

CRT complexity analysis is performed using data gathered before and after the implant of the device. Typically the ECG data, in the form of tensions (mV) at each electrode, are used. The ECG is recorded over the same given period of time before implant and upon follow-up.

A second source of data is the device (ICD) itself which often has the capability of storing relevant information with a certain frequency.

What results are obtained.

The fundamental result of an implant complexity analysis is quantification of the degree of patient's response to the implant. The difference in complexity of the data, whether it is ECG or data downloaded from the ICD, reflects, in a quantitative fashion, the intensity of the patient's response to the therapy.



Complexity Technology Facts

Q: Does the User need to provide the maps of relationships between parameters?

A: No, it is COSMOS™ that determines these relationships based on raw data. There is no need for the user to try to establish a-priori which parameters of a system are significant. It is up to COSMOS™ to decide this. In any event, doing this manually would be impractical



since even with a few tens of parameters there are potentially thousands of significant relationships. Therefore, the process must be automated. It also makes little sense to a-priori try to reduce the number of parameters because COSMOS™ is very fast. Besides, any aprioristic assumptions as to which parameters are important and which are not are always very dangerous. It is up to the tool to make decisions in this respect.

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Advanced EEG and ECG processing.

Measuring and ranking the magnitude of disorders via a radically new look at data.

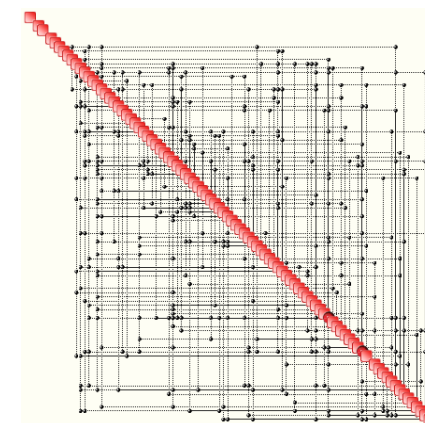
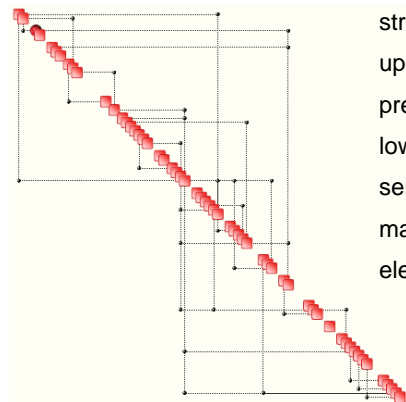
Electroencephalography is a technique that reads scalp electrical activity generated by brain structures. The electroencephalogram (EEG) is a reflection of the electrical alternating type activity recorded at the scalp's surface by means of metallic electrodes. Electroencephalographic readings are completely non-invasive procedures which may be applied repeatedly.

Brain patterns generally form sinusoidal waves. They normally range from 0.5 to 100 μV in amplitude. EEG signals, which are significantly weaker than those of an ECG, are processed using Fourier transforms so as to identify the frequency content of the signal's spectrum. There are four basic categories of brain waves that dominate the power spectrum:

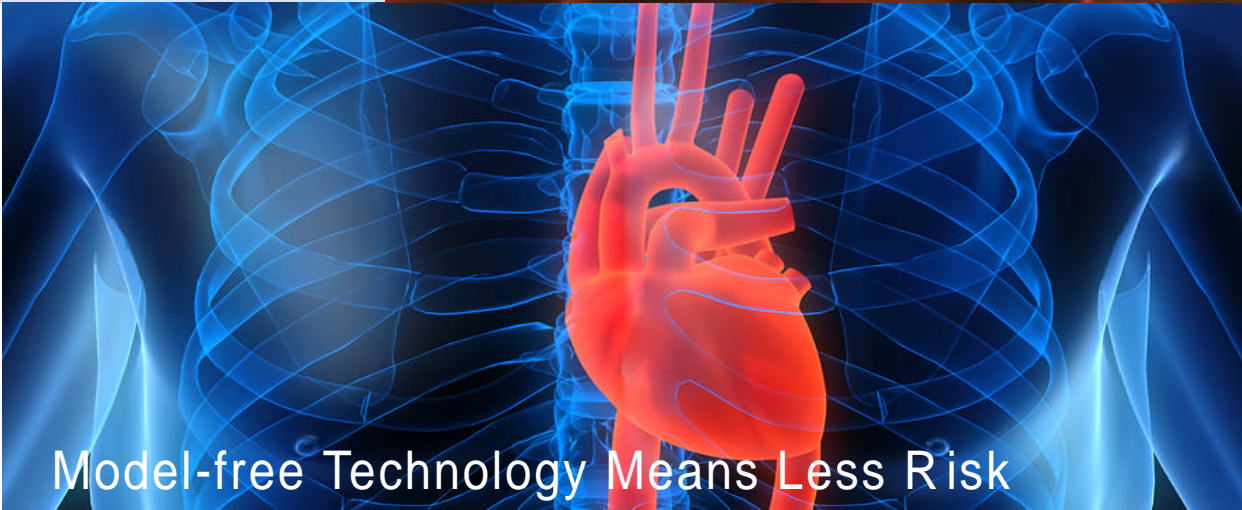
- beta (>13 Hz)
- alpha (8-13 Hz)
- theta (4-8 Hz)
- delta (0.5-4 Hz)

EEGs are used for a wide variety of cases, such as:

- monitor alertness, coma
- locate areas of damage
- control anesthesia depth
- investigate epilepsy
- test epilepsy drug effects
- test drugs for convulsive effects
- investigate sleep disorders



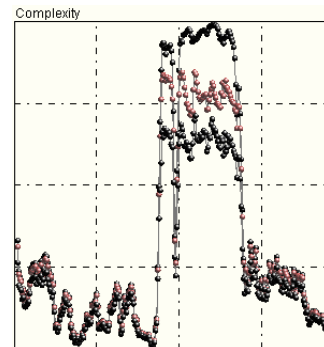
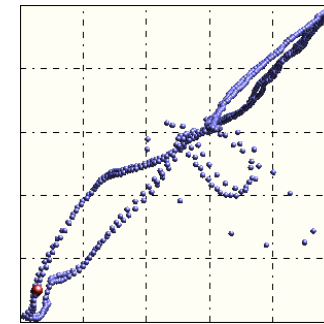
Just like in the case of an ECG, our technology offers the possibility to actually measure the intensity and magnitude of the mentioned disorders. In the case of epilepsy, for example, the difference between the complexity of the EEG before and during seizure is a measure of seizure intensity. Below, two Complexity Maps are illustrated. The maps reflect the multi-dimensional structure of the EEG. The upper one corresponds to a pre-seizure state while the lower one corresponds to seizure. Each node of the maps corresponds to a single electrode.



Model-free Technology Means Less Risk

The fundamental task of (ECG) processing is to detect the R-peaks. The typical difficulties in ECG processing derive from irregular distance between peaks, irregular peak form or low-frequency components due, for example, to breathing. ECG is useful in the detection and analysis of various heart disorders such as:

- Atrial Fibrillation (AF or A Fib)
- Atrial Flutter (AFL)
- Ventricular Tachycardia (VT)
- Ventricular Fibrillation (VF)
- Long QT Syndrome (LQTS)



Complexity-based analysis of ECG data allows us to measure objectively the magnitude of these disorders. Thanks to complexity-based ECG processing it is also possible to classify patients in an innovative fashion, not just based on age, sex or NYHA class. In fact, complexity establishes a new means of heart risk ranking and stratification.

Complexity Technology Facts

Q: What is a model-free approach?

A: A model-free approach, such as the one adopted in COSMOS™, does not rely on math models. Instead of using stats, regression models, artificial neural nets or cluster analysis, COSMOS™ processes the data in its original form without any distortions that originate from the usage of the said modeling techniques.



A model-free approach does not try to fit any a-priori structure on top of the data but rather tries to determine the inherent structure in the data, without any pre-filtering or data pre-conditioning. This guarantees that the original information in the data is preserved. The future of science depends greatly on its ability to learn how to identify the patterns of Nature and not to enforce simplistic models on top of observations.

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