

Time-fractal modulation of modulated electro-hyperthermia (mEHT)

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Introduction

Local hyperthermia in oncology is well-known from the ancient time. Unfortunately, oncological hyperthermia has no wide acceptance in the modern oncotherapies, it is much rarely applied than would be optimal. Contrary to its remarkable results and its opportunity applying complementary to almost any state-of-art oncological methods, it is suffering much of the negligence, it had no breakthrough in clinical practices. According to my opinion, one of the major factors of the missing applications is the thinking about hyperthermia as simple heating, like a "kitchen" method considering the devices as the hear-providing oven where the patients are "cooked". Indeed, the thinking about its control is also kitchen like: for how long and on what temperature it is applied, just like when we make a cake or biscuit at home. Our objective would genuinely like to break with the kitchen category and take into account the living physiology in the oncologic hyperthermia.

Methods

The complexity is one of the central properties of the living organisms. The self-organized and consequently self-similar structure [1] characterizes the complexity in its complete form. The study of biological complexity raised a new discipline: the fractal physiology (FP) [2]. FP is rigorously based on natural sciences, like physics, chemistry and of course mathematics, [3]. The dynamism, how the parts interact and change in time, is an important character of FP. The dynamism of the bio-systems can be described in spatio-temporal frame, having the bio-structure with the bio-processes in complex unity [4], [5]. The method applying FP in oncological hyperthermia is the modulated electro-hyperthermia (mEHT, oncothermia) [6], as a renewal of the historical heating methods, applying the synergy of the bio-electromagnetism with FP. The basic physiological and biophysical differences of malignant cells from their healthy counterpart make the mEHT method special: (1) the accurate selection of the tumor, [7]; (2) control the homeostatic correction feedbacks [8]; (3) select the malignant cells [9]; (4) the electromagnetic excitation of the clusters of transmembrane proteins by the beta/delta dispersion [10] (5) induce apoptosis by excitation with electromagnetic field [11]; (6) activate the immune system recognizing the tumor [12]. The homeostasis of the organism is a well-defined equilibrium, where the energy dissipation is well balanced with the metabolic energy controlling the dynamic fluctuations in a certain fractal range [13]. The fluctuations have a correlation in time, following the chemical and structural changes in dynamical equilibrium. The correct electromagnetic signal correlates with the healthy changes, act in time repeatedly which is in correlation with the steps of metabolic activity (autocorrelation of the signal). This signal follows a time-fractal fluctuation, which selectively supports or blocks the preferred (healthy) or avoidable (malignant) processes at the cellular membrane, respectively. This signal is taken by the amplitude

modulation of the carrier frequency (13.56MHz), and is demodulated by the rectification of the membrane potential. This dynamical effect well expands the above selection mechanisms, which are mostly structure connected.

Results

Morphological difference of modulated (mEHT) and unmodulated (EHT) treatments were measured in vivo for HT29 (human colorectal carcinoma, xenograft) and C26 (murine colorectal carcinoma, allograft) models, and analyzed 48h after treatment. Results favor the mEHT by 66.4% and 17.4%, for H29 and C26 in vivo measurements, respectively. In case of 4T1 breast cancer cell-line in balb/c mice the result 96h after treatment was 83.6% gain in mEHT case compared to the same treatment with EHT. The immune-response differs too. The CD3 T cell marker distribution in the living part of the treated tumor was higher in the modulated cases relative to untreated references 91.4% at EHT 104.6% in mEHT compared to their individual untreated sham samples. It is even more important that the Ki67 proliferation marker was significantly suppressed by modulation compared to the unmodulated treatment, [14]. The massive domains of sample patterns show better reaction on the modulation than on the mixed formations. This supports the noise-selection facilities of cancerous and non-cancerous tissue [15]. The destruction of the malignant cells is dominantly apoptotic, [16], preparing antigen recognition cells to produce helper and killer T-cells. This allows direct systemic effect to kill the malignant cells over the body, finding the disseminated cells and distant metastases, (abscopal effect) [17]. The results clearly show the additional effects of the fractal modulated EMF to the other heating methods [18].

Conclusion

mEHT is a new hyperthermia method using fractal modulation to improve the effective selection and killing the malignant cells. It is a controlled, reproducible and reliable treatment: it treats locally and acts systemically, (abscopal effect) [19].

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Objective

**Most local hyperthermia devices in oncology use bio-
electromagnetic effects with various frequencies.**

**The chosen frequency may optimize the energy-absorption and
the consequent changes in the malignant cell.**

Outline

☐ Specialties of modulated electro-hyperthermia

☐ Concept of spatio-temporal fractals

☐ Modulated carrier frequency and its effects

Success of modulated electro-hyperthermia

Selection by

1

Electric conductivity
(Metabolic differences, Warburg effect)

Due to high metabolic rate, the tumor ionic concentration is high and consequently its **conductivity selects**

2

Dielectric permittivity
(autonomy of malignant cells; Szentgyorgyi effect)

Due to missing cellular network, extracellular matrix of malignant cells have high dielectric **permittivity selects**

3

β/δ frequency dispersion
(lipid resonance absorption; Schwan effect)

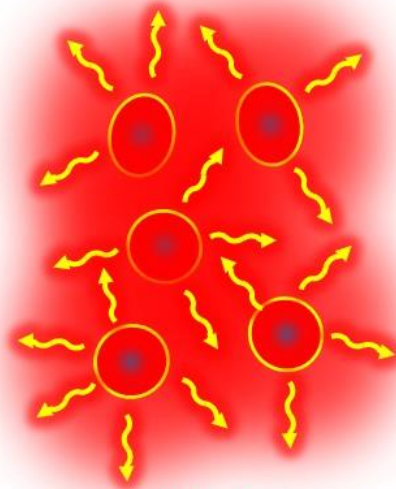
Due to large number of clusters of transmembrane proteins the protein-lipid complex attacked, **frequency dispersion selects**

4

Time-fractal modulation
(lipid resonance absorption; Schwan effect)

Produce damage associated molecular pattern (DAMP) and immunogenic cell death (ICD), **synchronization selects**

Selective, heterogenous heating
(targeted molecules of selected cells)



mEHT solution

The heating is heterogenic, only the malignant cells are selected

← **Objective of my presentation**

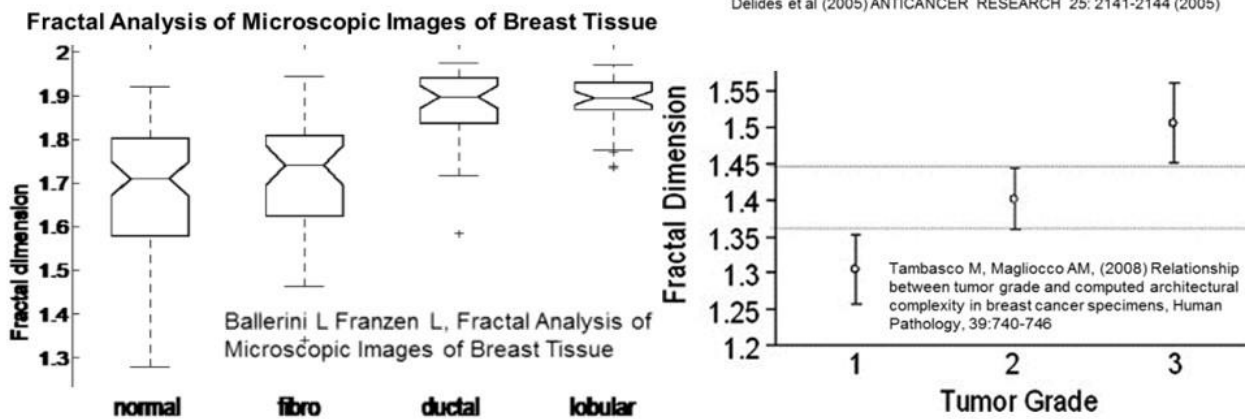
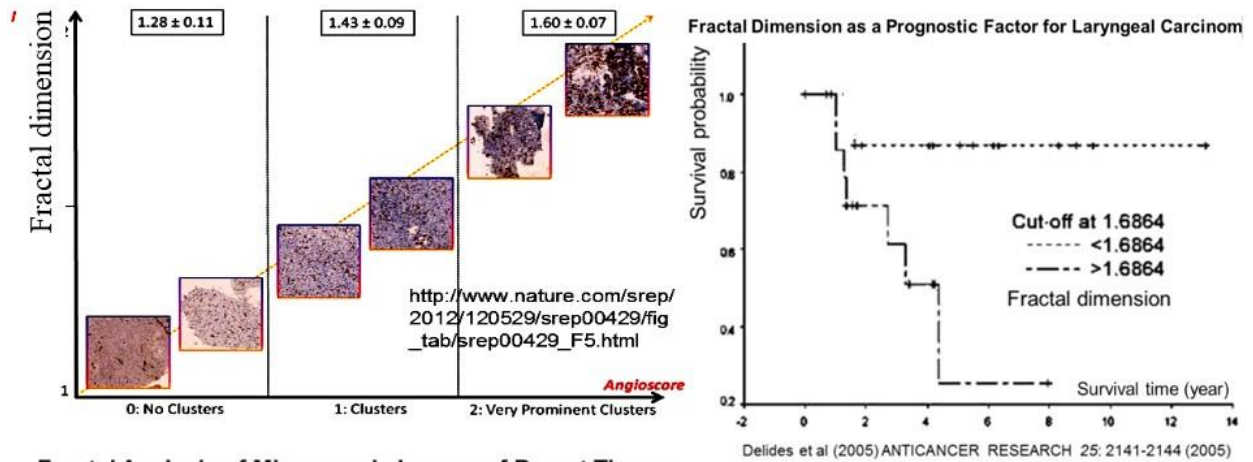
Outline

☐ Specialties of modulated electro-hyperthermia

☐ Concept of spatio-temporal fractals

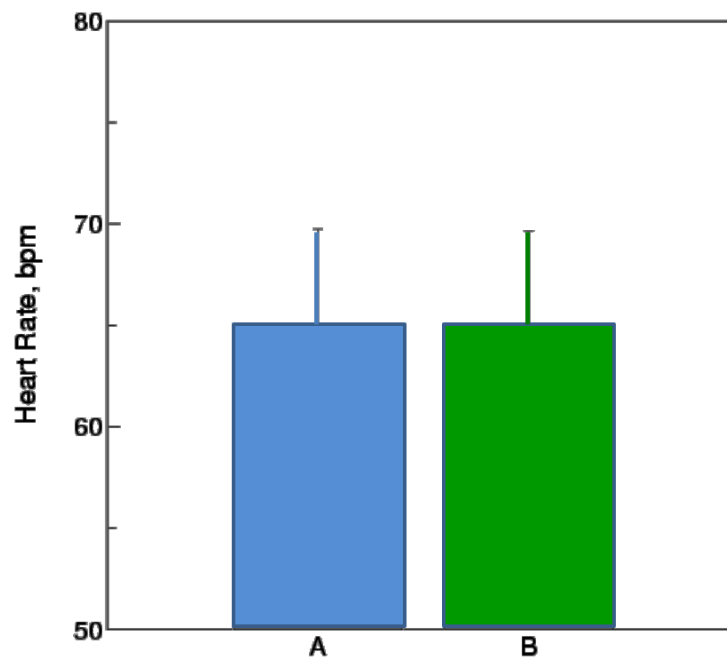
☐ Modulated carrier frequency and its effects

Structural fractals

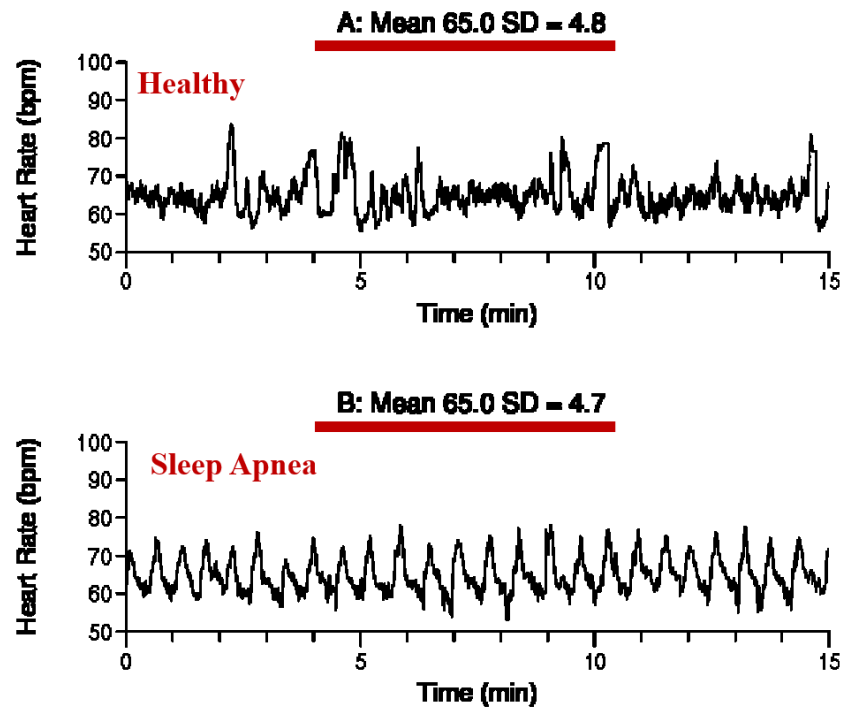


Quiz

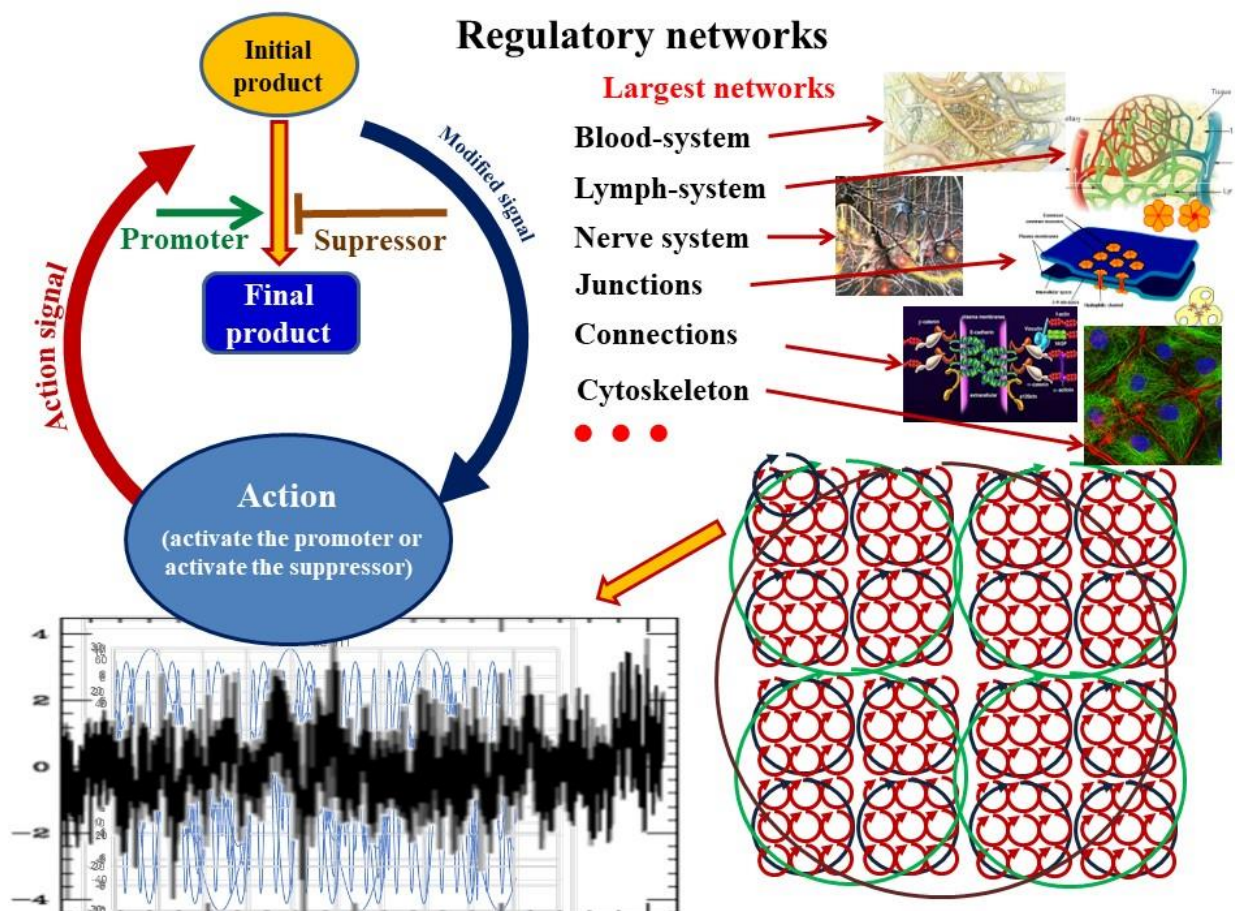
Which subject is healthier?



Quiz



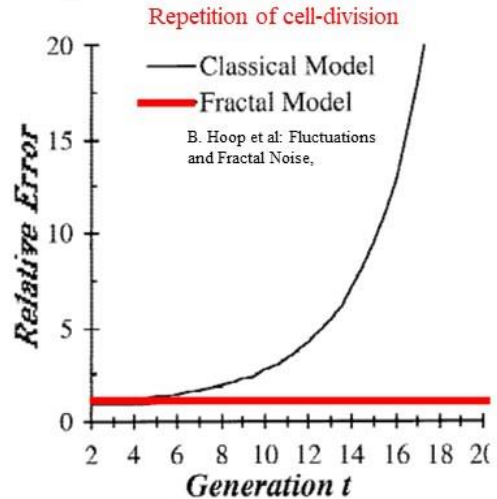
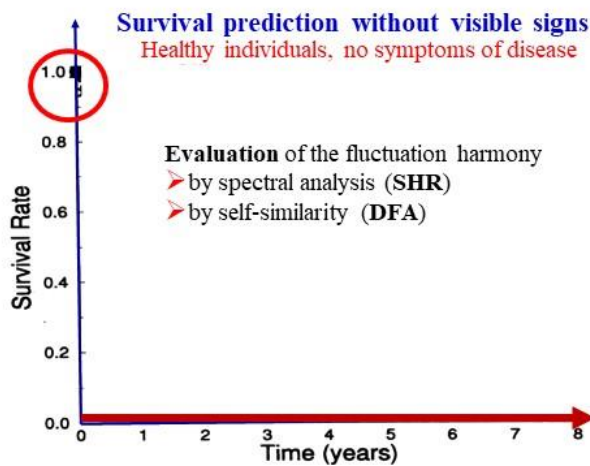
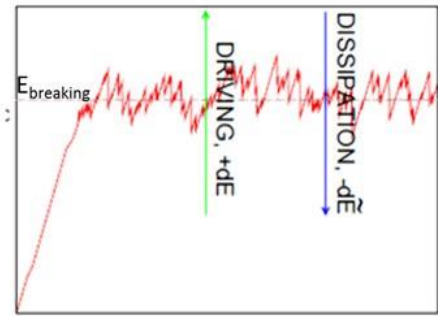
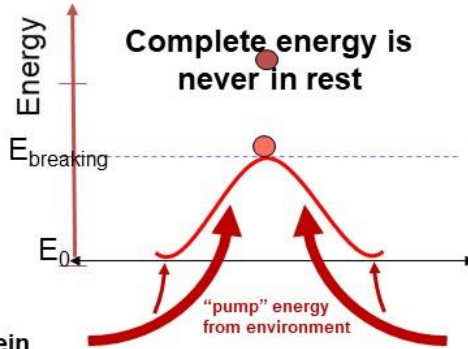
The variability of the signal has a role, not only the averages



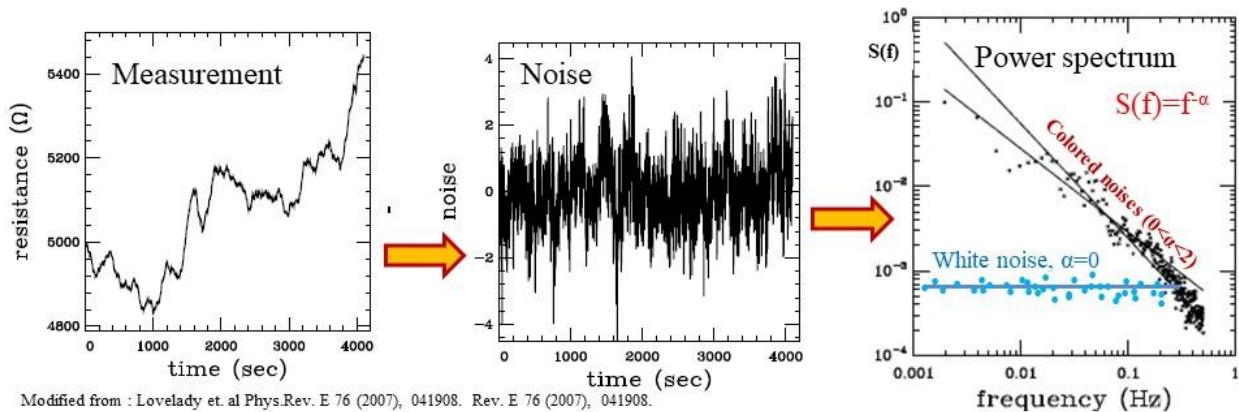
Homeostasis in fractal physiology



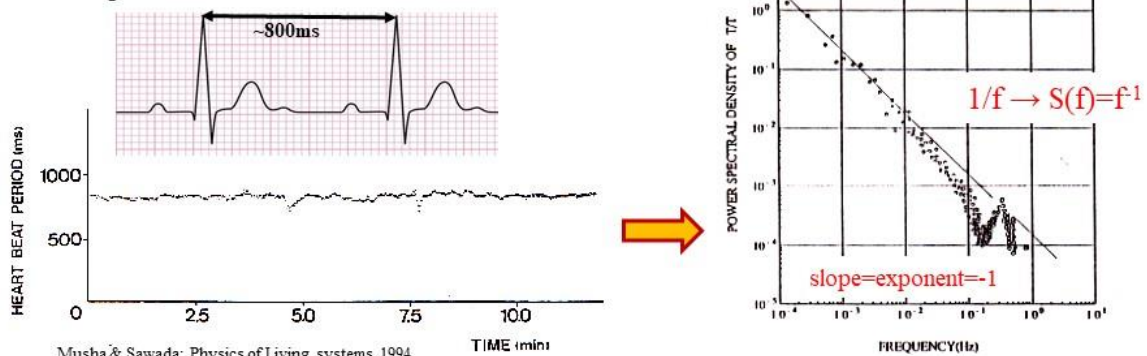
"Life is like riding a bicycle.
To keep your **balance**, you
must keep moving" **A. Einstein**



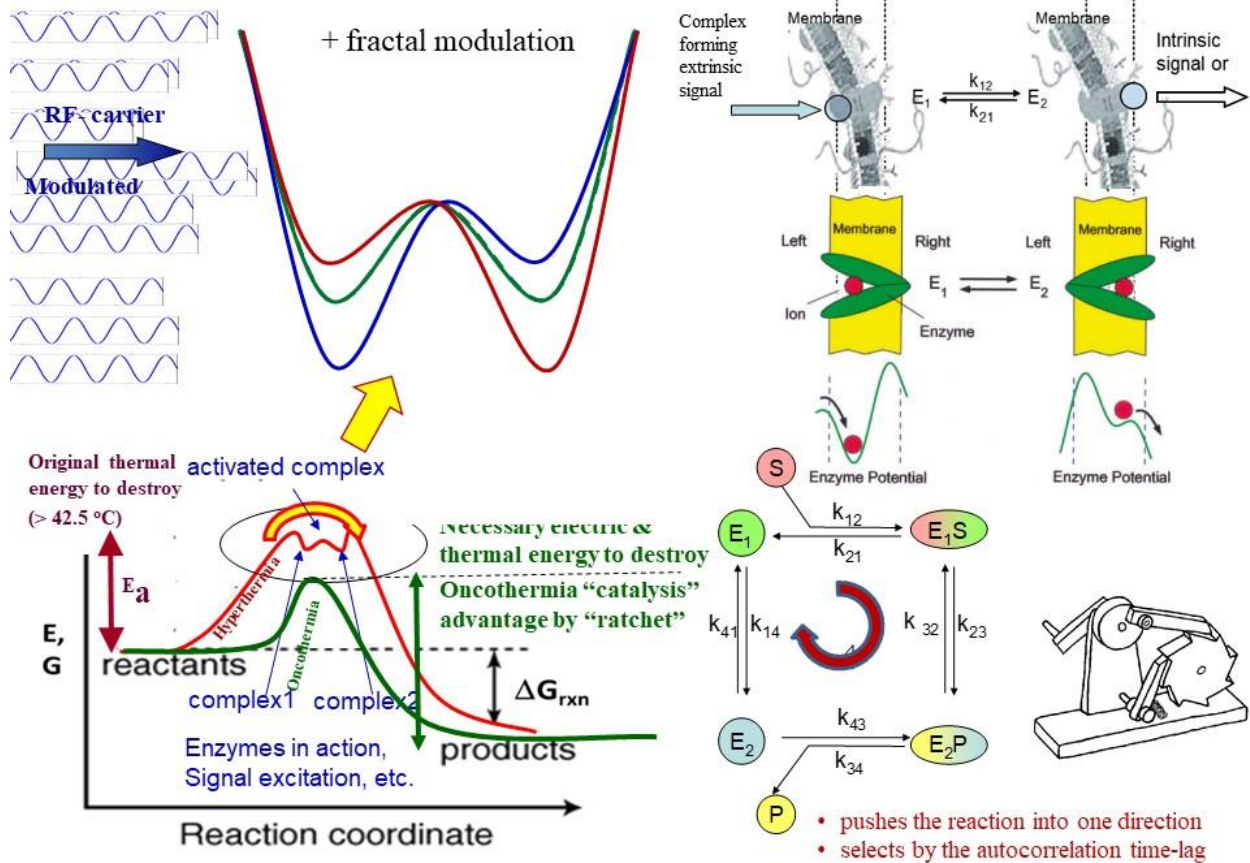
Dynamism of fractal structures



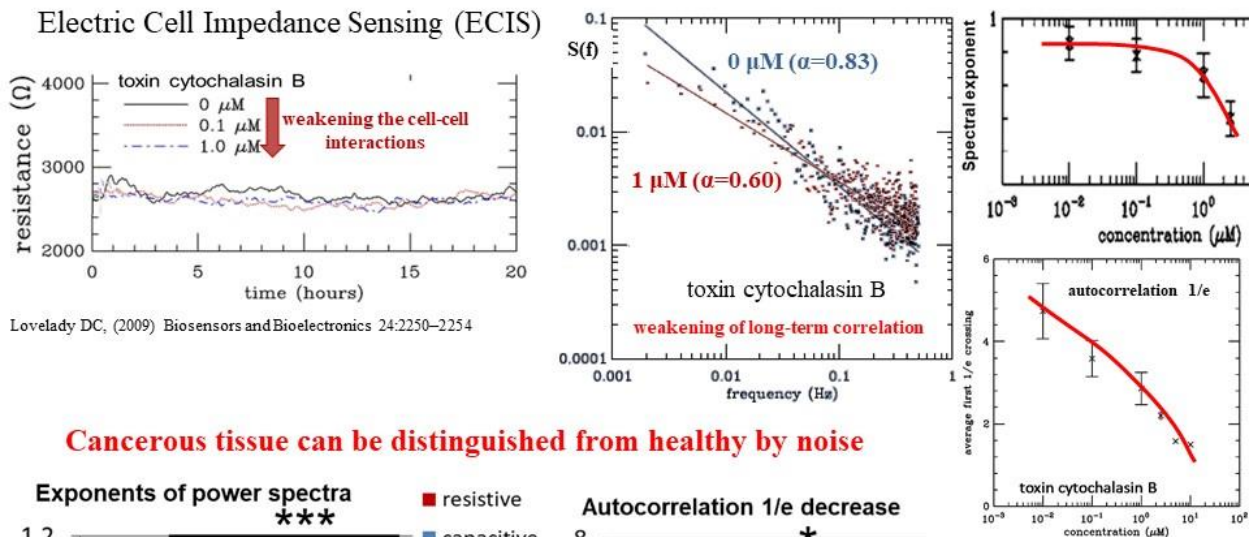
Example: fluctuation of R-R interval of heart-beat



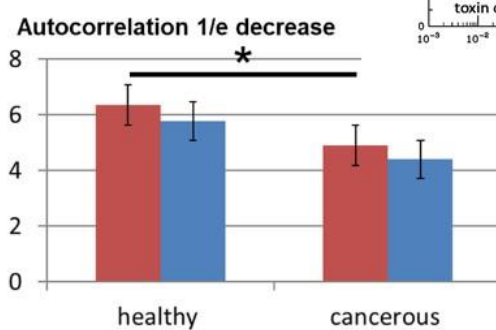
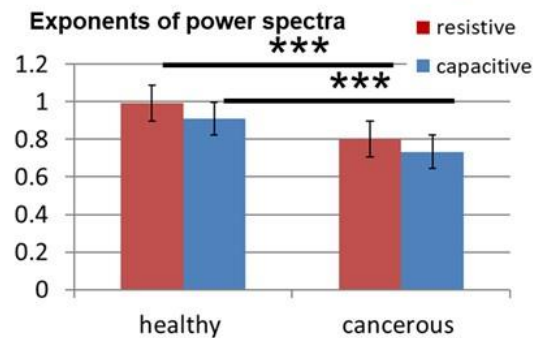
Stochastic resonant “ratchet”



The fluctuations (noise) defines the cellular interactions



Cancerous tissue can be distinguished from healthy by noise

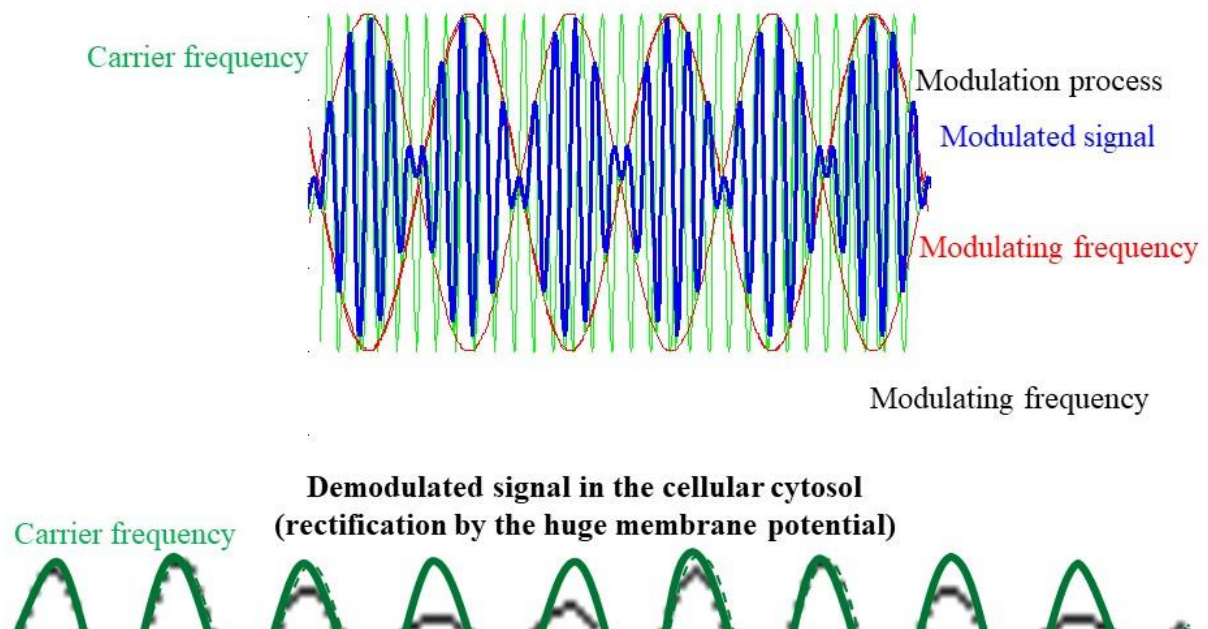


Lovelady et. al: Rev. E 76 (2007), 041908.

Outline

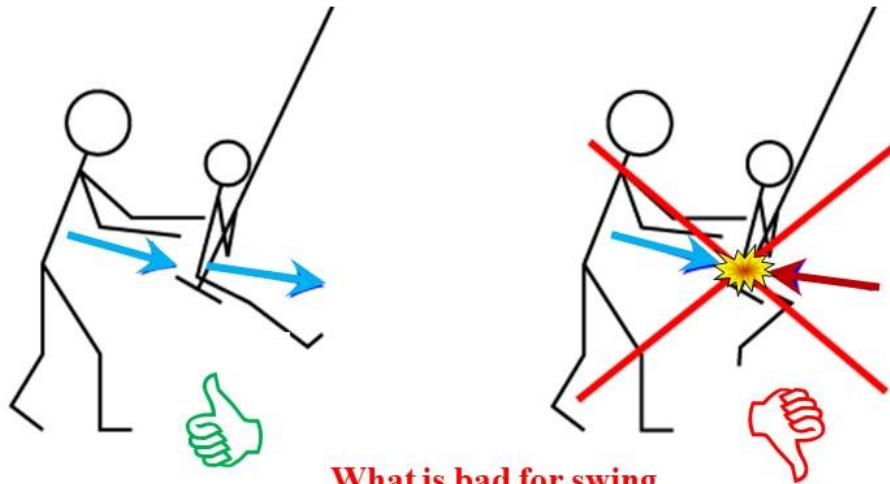
- ❑ Specialties of modulated electrohyperthermia
- ❑ Concept of spatio-temporal fractals
- ❑ Modulated carrier frequency and its effects

Modulation process



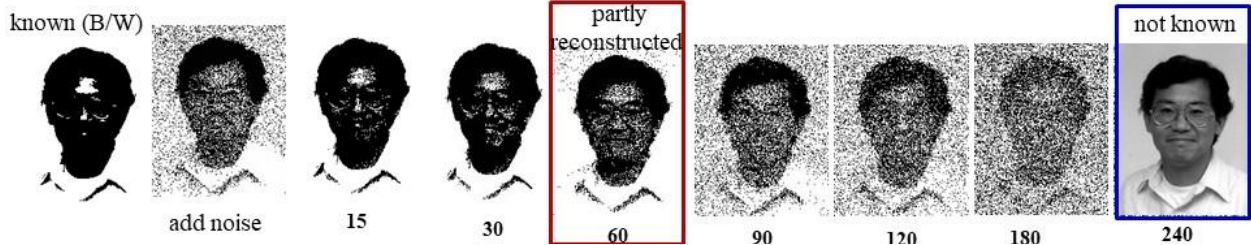
This excites the missing apoptotic pathways in sequences of the autocorrelation of the demodulated signal

Selection by modulation



What is bad for swing
is good for exciting special receptors and signal pathways

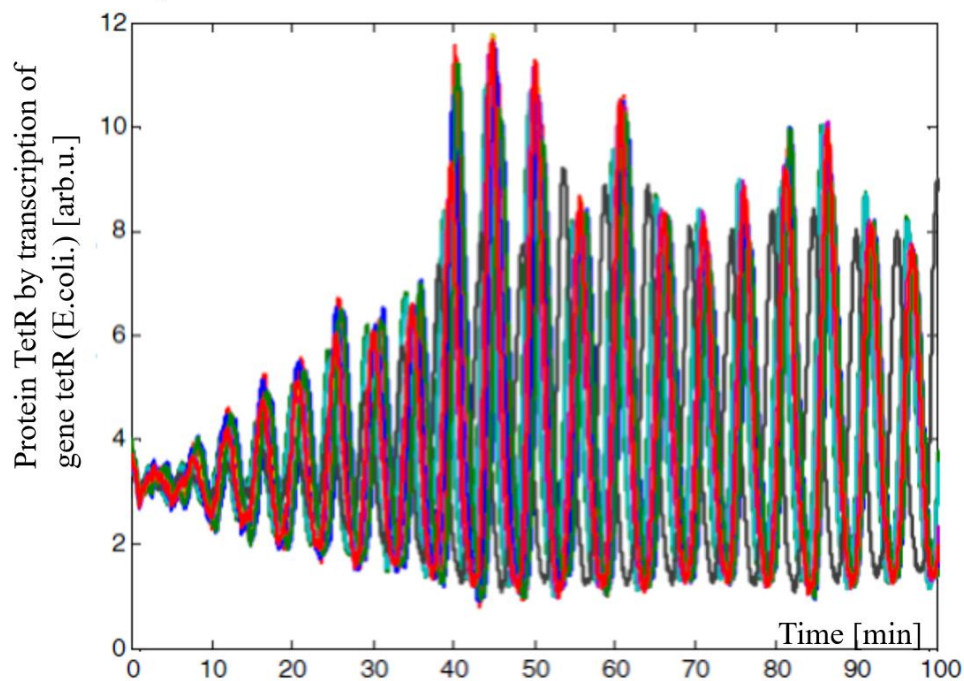
It is stochastic process like for example the photo-reconstruction by noise



Example: genetic synchronization by extrinsic noise

Ten coupled genetic oscillators

Synchronization cannot be achieved under intrinsic kinetic parameter fluctuations and extrinsic molecular noise.

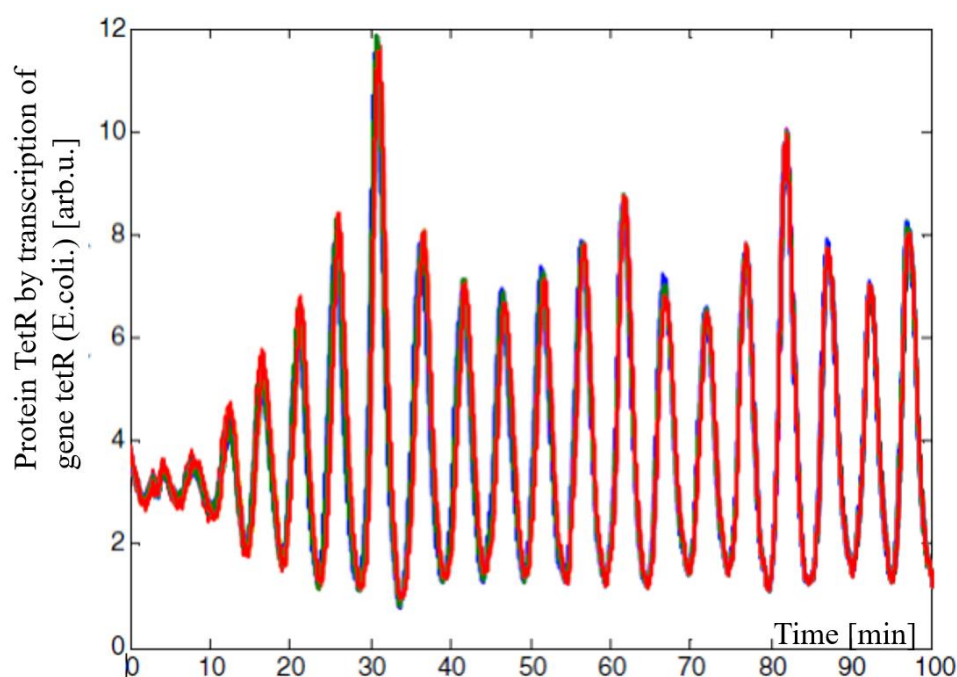


Chen B-S, Hsu C-Y; Robust synchronization control scheme of a population of nonlinear stochastic synthetic genetic oscillators under intrinsic and extrinsic molecular noise via quorum sensing; BMC Systems Biology 2012, 6:136

Example: genetic synchronization by extrinsic noise

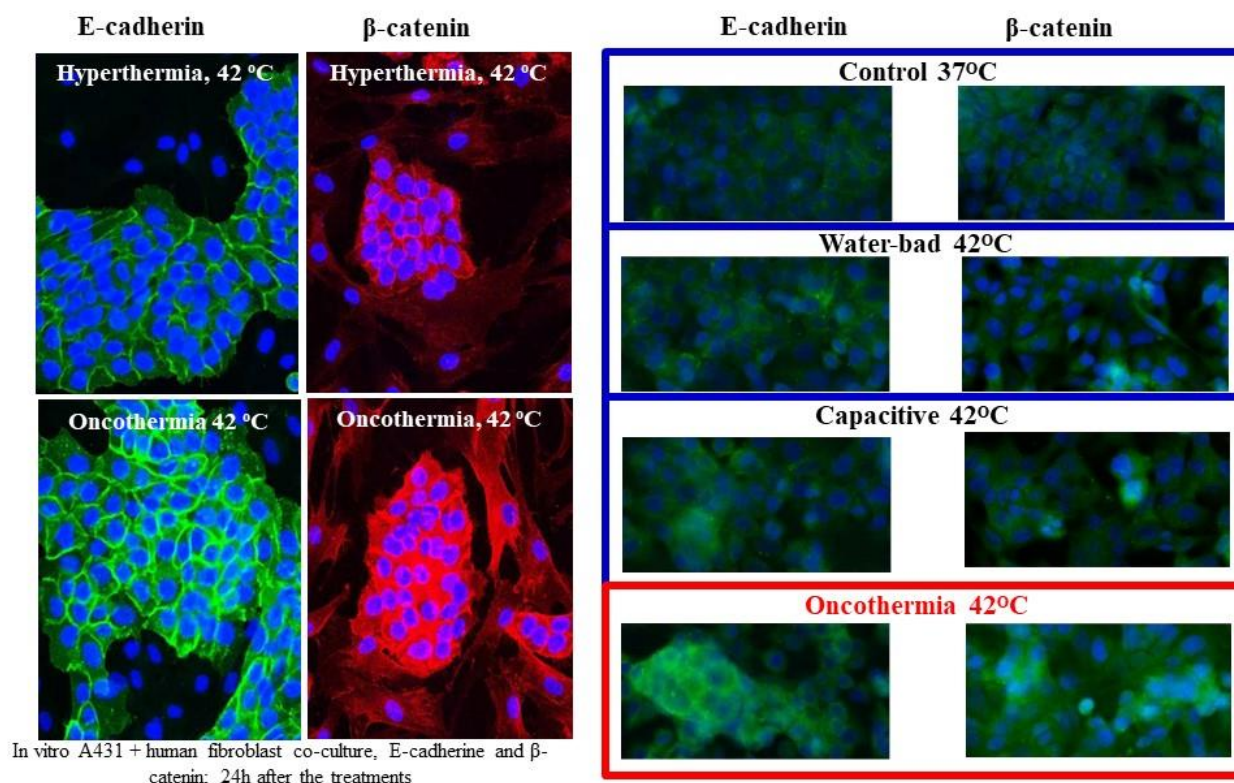
Ten coupled genetic oscillators

The robust synchronization result by extrinsic noise.



Chen B-S, Hsu C-Y; Robust synchronization control scheme of a population of nonlinear stochastic synthetic genetic oscillators under intrinsic and extrinsic molecular noise via quorum sensing; BMC Systems Biology 2012, 6:136

Block the invasion and dissemination



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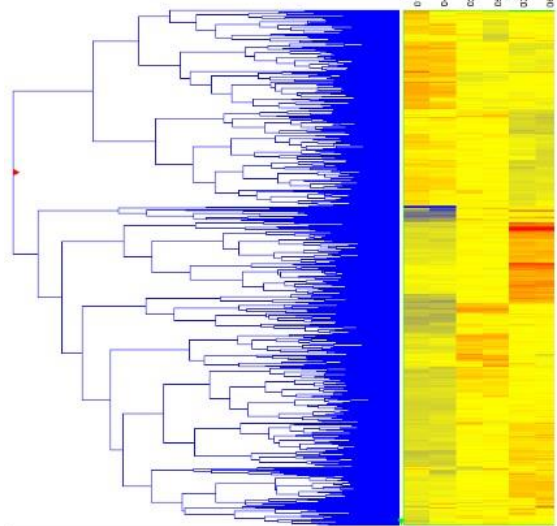
Oncothermia heats differently (mRNA-based info)

Human lymphoma U937 cell (in-vitro)

1. Control (37°C)

2. Water-bath (42°C)

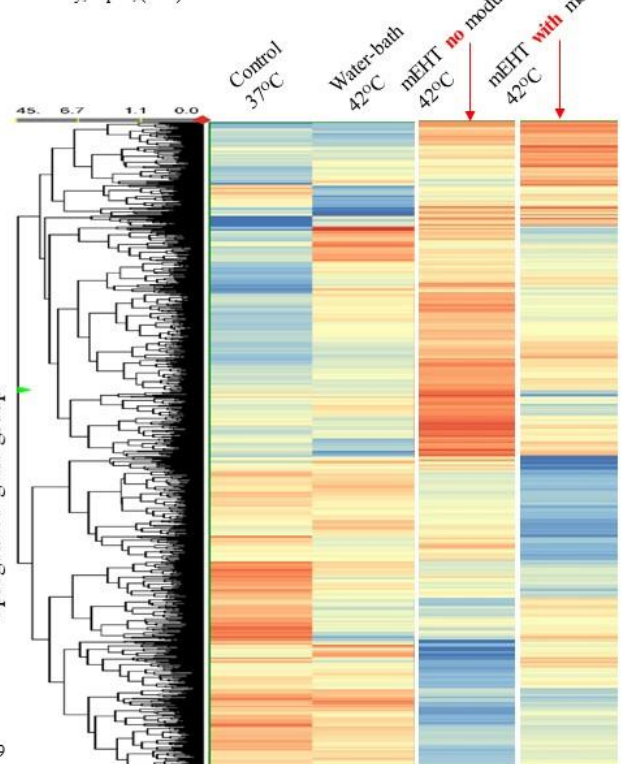
3. mEHT (42°C)



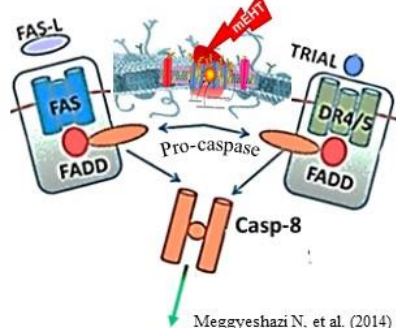
Andocs G, et al. (2016) Cell Death Discovery (Nature Publishing Group), 2, 16039

C26 allograft (in-vivo)

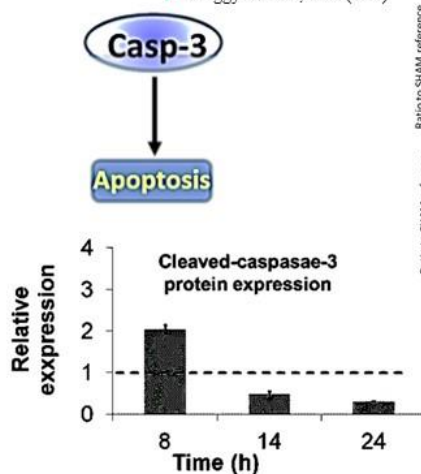
Andocs G, Kondo T. Toyama University, Japan, (2018)



Excite membrane rafts: extrinsic pathways of apoptosis

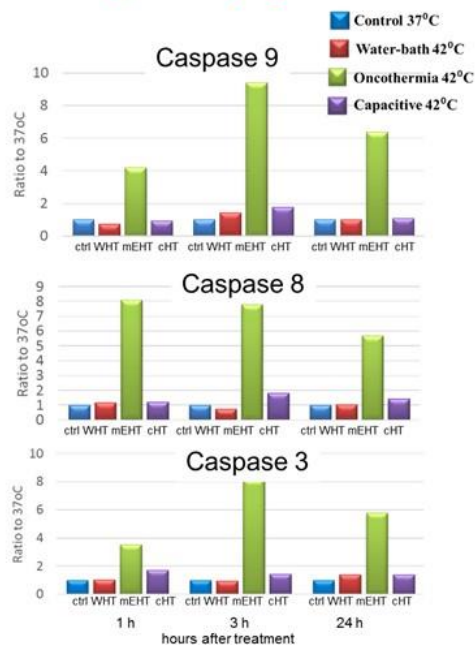
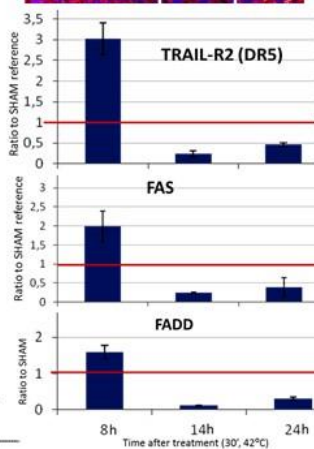
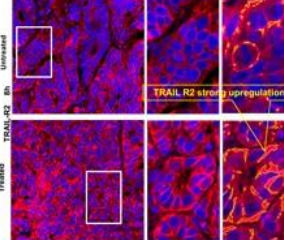


Meggyeshazi N, et al. (2014)



HT29 cell-line, mEHT (42°C)

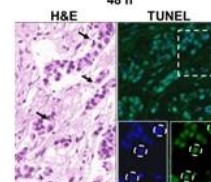
Oncothermia induced ICD-TRAIL R2 (DR5)



Yang K-L, et al., Oncotarget, oi: 10.18632/oncotarget.11444,

DNA fragmentation

Meggyeshazi N, et al. (2014)



Challenge of tumor-specific immune support (abscopal)

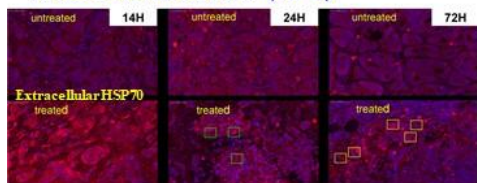
Malignancy is a systemic disease !!

Produce DAMP and ICD

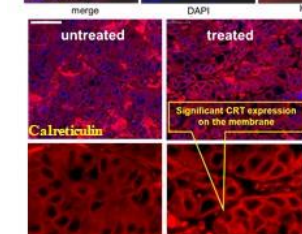
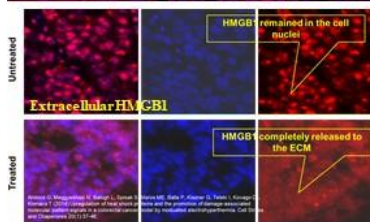
tumor-specific immune reaction, like vaccination

Andocs G, et al. (2014) Cell Stress and Chaperones 20(1):37-46

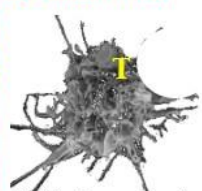
HT29 cell-line, mEHT (42°C)



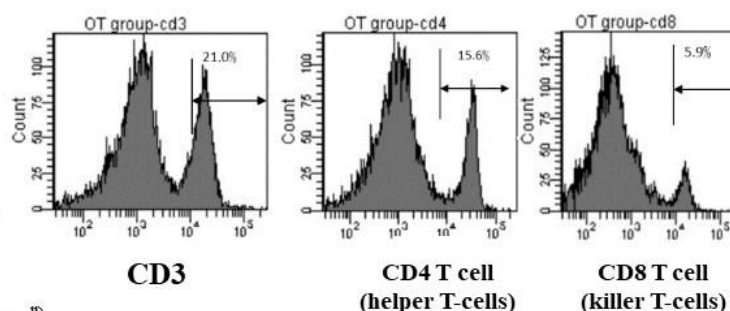
- CRT „eat me” signal
- ATP „find me” signal
- HMGB1 „danger” signal
- HSP70 “info” signal



DC maturation

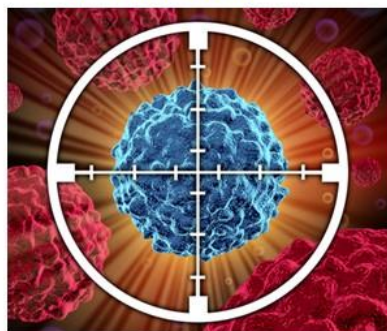


APC (antigen presenting cell)

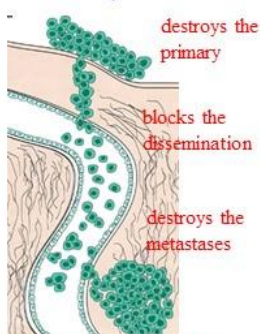


mEHT fits well to the modern oncology

Targeted therapy to malignant cells

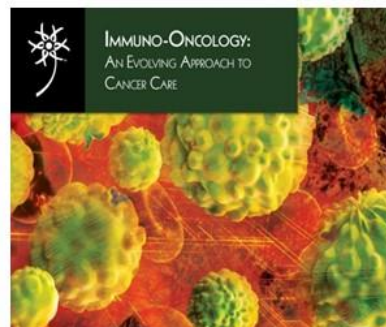


Complex therapy to system



ACTS SYSTEMICALLY

Direct and effective way to immuno-oncology



mEHT is a new kind of hyperthermia

- Heats selectively
- Physiology compatible
- It has applicable dose

Thank you for your attention

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