Cancer metastasis and the innate and adaptive immune system responses: modeling by Ising Hamiltonian*

Renato Arroyo† and Matías Alvarado‡
Authors' institution and/or address
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To overcome the cancer seeding and late metastasis, the immune system opportune response is essential. The system biology approach is for better understanding the complex process of cancer metastasis and the immune system response CM-IS. Mathematical modeling and algorithmic simulations has improved the tumor immune research. In this paper we introduce an Ising Hamiltonian energy function to model the innate and adaptive immune system response of CM-IS. The level of modeling is the CM-IS microenvironment. The case analyzed is breast cancer that makes metastasis to bone, lung and liver;these organs are the most frequently suffering breast cancer metastasis.

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I. INTRODUCTION

Cancer is a multifactorial illness which growth comes from individual genetic inheritance joined to life style conditions [1, 2]. Genetic difference makes diverse tendencies in cancer deploy [1]; from the analyses on patient's clinical record files, conclusion is that, cancer spread, also depends on the patients' life habits and living conditions: quality of feed and the environmental conditions [2, 3]; the ingestion of meals with preservatives ingredients stimulates cancer growth; the aerobic exercise practice makes difference on cancer frequency in a population [4]; the toxic air breading or the contaminated water consumption both grows up the risk of cancer [5]. All these cultural aspects influence the cancer raise and strongly induce the CM dissemination.

Cancer starts with a disordered replication of cells on an organ tissue shaping the solid primary tumor [1]. From the initial cancer cells CC, the transition growth factor TGF$-\beta$ sizes the tumor. Some CC drop out from the primary tumor and by entry in the arterial blood stream the angiogenesis occurs. Angiogenesis disseminates CC, and, some of them may invade other organs' tissues [1]. If organ invasion grows and attracts more CC it becomes colonization and the cancer metastasis CM started, see Figure 1. The immune system surveillance will have serious difficulties to overcome cancer when metastasis occurs, and, CM is frequently the patient's fatal step.

Premetastatic niche PMN formation is a condition for CM [6]. Out of the primary tumor, cancer cells invaders contribute on PMN formation; previously, the organs of metastasis are selected to be modified by the primary tumour, before metastatic dissemination occurrence. The formation of PMN comprises the process of sowing the seed of metastasis. Sowing is made by the action of tumour-secreted factors and tumour-shed extracellular vesicles. Both enable the soil at distant metastatic sites to stimulate the outgrowth of the incoming cancer cells.

Cancer metastasis and Immune System response (CM-IS) is an emergent complex biological process [7]. IS is twofold, innate and adaptive. The innate immune system arranges the genetic inherited immune actions. The adaptive IS results from a live permanent training process. The training is deployed from the successful immune response to unedited diseases; kind of libraries are deployed as long as IS overcomes a disease and immunity is achieved for this sick. Concerns the stimulation from the biochemical signaling mechanisms of cytokines.

The opportune/sloppy IS response difficult/easies the cancer tumor growth and proliferation of metastatic springs. The immune response from the innate immune system IIS recruits macrophages and natural killer cells to eliminate invasions [6]. CC antigens are detected by IS cells activating reaction to eliminate CC. However, CC mutations complicate the IIS action. A mutant CC is not identified by IIS cells. Therefore, the more elaborated IIS response is needed to eliminate cancer tumor. The adaptive immune system AIS action implements strategies to fight cancer growth and metastatic springs; AIS activates the recruitment of T cytotoxic cells and other macrophages [1, 8]. A war of biological strategies started to occupy live being tissues. To illustrate the microenvironment of CM-IS, see Figure 2.

* A footnote to the article title
† Also at Physics Department, XYZ University.
‡ Second.Author@institution.edu

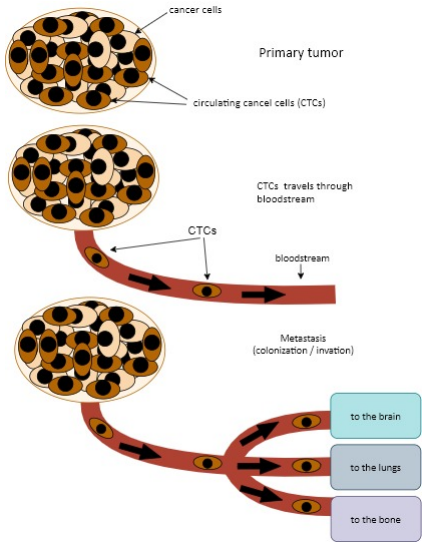

Figure 1: Some cancer cells drop out from the primary tumor and entry in the arterial blood stream for angiogenesis occurence; then disseminate and could invade other organs' tissues.

CM-IS is a biology system battle which best comprehension needs of a system biology approach [9]: The use of mathematical and algorithmic methods is a clever way for CM-IS better understanding as well as for the agile finding of results. The analysis and multidisciplinary approach advances on the diverse scalability and precision involved in CM-IS comprehension [10]. The CM-IS emergent phenomena, so the tumor microenvironment (TME) of CM-IS interaction is modeled by an Ising model energy function. Antecedent of this paper is the use of Ising Hamiltonian for modeling the Go gaming and the suggestive comparison with CM-IS [8] –my last collaboration with Germi Cocho. CM-IS as metaphor of Go gaming may be heavy to follow. So, the demand to easier explanation providing the biochemical issues that close the gap to medical dialogue. Start the formalization of CM-IS microenvironment interaction without the metaphor of Go gaming is the focus in this paper.

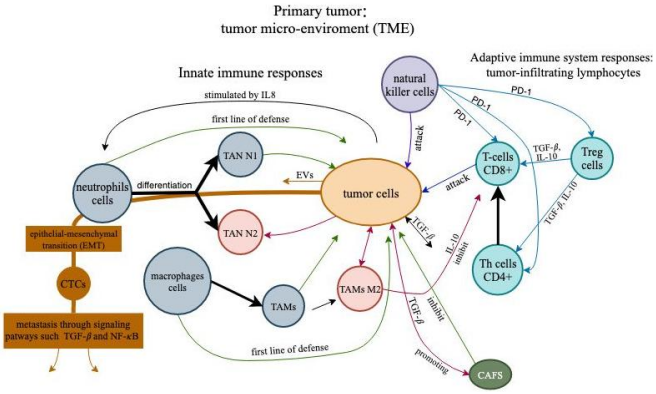

Figure 2: CM-IS in TME. The innate and adaptative immune system interaction: the tumor associated neutrophils (TANs) and macrophages (TAMs) can became anti-tumoral or pro-tumoral. Initially, the fibroblasts (CAFS) inhibits the tumor growth but can became pro-tumoral trougth TGF-β; as well, initially the natural killers NK cells attacks CC and at the time regulates the proliferation of adaptive CC.

A. System biology

System biology approaches [10] focus on different scales on cancer and immune response: Immune-related tumor mechanobiology; tumor-associated vasculature in the immune response; tumor-associated lymphatics and lymph nodes; tumor immunotherapy; tumor-enhancing immune cells; and, intra-tumor heterogeneity. Since the system biology perspective the approaches may classify as deterministic or stochastic, continuous or discrete; and, bottom up or top down that means micro- or macro- environment scale.

In the computational agent-based approach [11] from the agents interaction emerges a behavior not reduced to the linear addition of the agents' behavior. By means of the agent-based model, some CM-IS sub-processes get scalability and different conditions for testing experiments [7]. This is in the discrete and stochastic approaches.

In the continuous approaches that use ordinary or partial differential equations modeling [12] functions use input parameters to represent the elements for growth dynamics. The required initial and border conditions, however, frequently are not well defined. This is a main weakness in this proposals.

B. Immune mediate theory of metastasis

The metastasis sequence of biological processes comprises the development, growth, local invasion of a primary tumor; the preparation of a pre-metastatic niche; the entrance into or intravasation, travel through or circulation, and the exit from the vascular system or extravasation; and the growth and development of a secondary metastatic tumor [1, 6].

From the growing experimental and clinical evidence is learned that the immune response to cancer is anti-tumor but pro-tumor as well [13]. The immune system supplies for growth pro-angiogenic factors and defense against cytotoxic immune attacks. This immune system role is formalized in the immune-mediated theory of metastasis [14]. It includes anti- and pro-tumor immune effects, and the experimental observation of tumor-induced phenotypic plasticity of immune cells. The so called immune cells "tumor education" could explain the observed law performance of immunotherapies and metastatic phenomena like blow-up, dormancy, and the own metastasis to injured organs. Instance for tumor-immune interactions at two anatomically distant sites, confronts experimental data in order to predict the preparation of the PMN; by pro-tumor educated immune cells prior to the

arrival of any tumor cells. It reproduces the relative magnitude and timing of this PMN preparation.

In Section 2 the CM-IS I+A formal modeling by means of the Ising Hamiltonian is followed with the simulation and results illustration in Section 3. Discussion in Section 4 lengthen this research and Conclusions close the paper.

II. ISING FUNCTION FOR CM-IS I+A MICROENVIRONMENT

Ising model energy function has the enough flexibility to express such diversity in a stochastic manner. For modeling the CM-IS microenvironment we use the Hamiltonian of Ising model, a classic in the pherromagnetism of spins interaction [2] which formulation follows.

$$H = -\frac{1}{2}\sum_{i,j}^{n} w_{ij}x_i x_j - \sum_{i}^{n} h_i x_i \tag{1}$$

Value of $w_i j$ is the energy interchange between x_i, x_j; h_i is the energy of the field that affects x_i.

The Ising model energy function for CM-IS follows. Equation (2) is the formal description of molecules in CM-IS. The constant $c = 1, -1$ represents the membership of an element x_i to the immune system ($c = 1$) or to a cancer cell ($c = -1$); n_i is the number of cells or an element, for example the tumor size or the number of IS cells.

$$x_i = cn_i \tag{2}$$

In (3), the value of w_{ij} is calculated from the interaction of molecules that cooperate or confront among in the nearby of x_i x_j.

$$w_{ij} = Q_{ij}P_{ij}. \tag{3}$$

The **Q** matrix indicates the intensity of interactions between x_i and x_j. Each Q_{ij} is given by

$$Q_{ij} = \sum_{u} a_u q_u^{ij}, \tag{4}$$

where each q_u^{ij} is a biochemical (signal) elements that weight the interaction of either cancer or immune response structures.

For example in the tumor micro-environment (Figure 2), tumor associate macrophages (TAMs) are reprogrammed to inhibit liymphoscyte functions through release of inhibitory cytokines such IL-10, prostaglandis or ROS [15]. This is reflected in our model as follows; considering that tumor cells are represent by x_1 and TAMs by x_6, the interaction between these structures in given by:

$$Q_{1,6} = a_1 q_1^{1,6} + a_2 q_2^{1,6},$$

where $a_1 q_1^{1,6}$ and $a_2 q_2^{1,6}$ represent the levels of IL-10 and ROS respectively.

Based on the tumor micro-environment shown in Figure 2 we only consider the tumor and the IIS structures, showing in table 1:

Structural elements	
Tumor cells	x_1
Innate IS	
Neutrophil cells	x_2
Tumor asociate neutrophil N1 (TAN N1)	x_3
Tumor asociate neutrophil N2 (TAN N2)	x_4
Macrophages	x_5
Tumor asociate macrophages (TAMs)	x_6
Tumor asociate macrophages M2 (TAMs M2)	x_7
Natural killers	x_8
Adaptative Immune System	
T cells (CD8+)	x_9
Th cells (CD4+)	x_{10}
Treg cells	x_{11}

Table 1

To show hos interactions take place, we show the following arrangenent

$$\begin{bmatrix}
0 & Q_{1,2} & Q_{1,3} & Q_{1,4} & Q_{1,5} & Q_{1,6} & Q_{1,7} & Q_{1,8} & Q_{1,9} & Q_{1,10} & Q_{1,11} \\
Q_{2,1} & 0 & Q_{2,3} & Q_{2,4} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
Q_{3,1} & Q_{3,2} & 0 & Q_{3,4} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
Q_{4,1} & Q_{4,2} & Q_{4,3} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
Q_{5,1} & 0 & 0 & 0 & 0 & Q_{5,6} & Q_{5,7} & 0 & 0 & 0 & 0 \\
Q_{6,1} & 0 & 0 & 0 & Q_{6,5} & 0 & Q_{6,7} & 0 & 0 & 0 & 0 \\
Q_{7,1} & 0 & 0 & 0 & Q_{7,5} & Q_{7,6} & 0 & 0 & Q_{7,9} & 0 & 0 \\
Q_{8,1} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & Q_{8,9} & Q_{8,10} & Q_{8,11} \\
Q_{9,1} & 0 & 0 & 0 & 0 & 0 & Q_{9,7} & Q_{9,8} & 0 & Q_{9,10} & Q_{9,11} \\
Q_{10,1} & 0 & 0 & 0 & 0 & 0 & 0 & Q_{10,8} & Q_{10,9} & 0 & Q_{10,11} \\
Q_{11,1} & 0 & 0 & 0 & 0 & 0 & 0 & Q_{11,8} & Q_{11,9} & Q_{11,10} & 0
\end{bmatrix}$$

Table 2

Table 2 is not a matrix array. Their elements has the following properties:

$$\text{Table 2} = \begin{cases} Q_{ij} = Q_{ji} & \text{is symetric.} \\ Q_{ii} = 0 & \text{diagonal elements are zero.} \\ Q_{ij} = 0 & \text{only if structural elements} \\ & \text{not interact.} \end{cases}$$

Since each interaction occurs with a given probability, therefore in (3) P_{ij} represents the probability of interaction among the structural elements with biochemical signals. In the same way we can write these probabilities within the following arrangement:

$$\begin{bmatrix} 0 & P_{1,2} & P_{1,3} & P_{1,4} & P_{1,5} & P_{1,6} & P_{1,7} & P_{1,8} & P_{1,9} & P_{1,10} & P_{1,11} \\ P_{2,1} & 0 & P_{2,3} & P_{2,4} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ P_{3,1} & P_{3,2} & 0 & P_{3,4} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ P_{4,1} & P_{4,2} & P_{4,3} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ P_{5,1} & 0 & 0 & 0 & 0 & P_{5,6} & P_{5,7} & 0 & 0 & 0 & 0 \\ P_{6,1} & 0 & 0 & 0 & P_{6,5} & 0 & P_{6,7} & 0 & 0 & 0 & 0 \\ P_{7,1} & 0 & 0 & 0 & P_{7,5} & P_{7,6} & 0 & 0 & P_{7,9} & 0 & 0 \\ P_{8,1} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & P_{8,9} & P_{8,10} & P_{8,11} \\ P_{9,1} & 0 & 0 & 0 & 0 & 0 & P_{9,7} & P_{9,8} & 0 & P_{9,10} & P_{9,11} \\ P_{10,1} & 0 & 0 & 0 & 0 & 0 & 0 & P_{10,8} & P_{10,9} & 0 & P_{10,11} \\ P_{11,1} & 0 & 0 & 0 & 0 & 0 & 0 & P_{11,8} & P_{11,9} & P_{11,10} & 0 \end{bmatrix}$$

Table 3

Table 3 is also not a matrix and their elements has the same properties that elements of table 2.

$$\text{Table 3} = \begin{cases} P_{ij} = P_{ji} & \text{is symetric.} \\ P_{ii} = 0 & \text{diagonal elements are zero.} \\ P_{ij} = 0 & \text{only if structural elements} \\ & \text{not interact.} \end{cases}$$

The reviewed literature [15] suggests that the probability of successful interaction between certain structural elements complies with the following rules.

$$P_{1,3} = 1 - P_{1,4} \tag{5}$$

$$P_{1,6} = 1 - P_{1,7}. \tag{6}$$

Equation (5) reflex that the probability of success interaction between tumor asociate neutrophil N1 (TAN N1) and tumor cells is an event complementary of the probability of success interaction between tumor asociate neutrophil N2 (TAN N2) and tumor cells. In the same way, equation (6) reflex the same between tumor associate macrophages (TAMs), tumor associate macrophages M2 (TAMs M2) and tumor cells.

Since this; if AT denotes anti-tumor action and PT pro-tumor action, then:

$P_{1,3} = P(AT|\text{TAN N1})$ and $P_{1,4} = P(PT|\text{TAN N2})$
$P_{1,6} = P(AT|\text{TAMs})$ and $P_{1,7} = P(PT|\text{TAMs M2})$.

Therefore $P_{1,3}$ weights the anti-tumor intensity and $P_{1,4}$ the complement; the respective measuring with $P_{1,6}$ and $P_{1,7}$.

Taking in consideration the above definitions, the explicit form of equation (1) is:

$$H = -\frac{1}{2}\sum_{i,j}^{n} Q_{ij} P_{ij} x_i x_j - \sum_{i}^{n} h_i x_i \tag{7}$$

III. SIMULATIONS AND RESULTS

On the base of the Ising model formalism computer simulations are practiced. A Netlogo application is used for dozens of simulations on CM-IS: Combinations of strength of cancer tumor *versus* the immune response are made. Graphs that illustrate the Strong - Strong Medium - Strong and Weack - Strong combinations are shown in the figures 3 to 11. Results show an expected tendency: the equal force of both biology systems, cancer tumor and immune system, splits the percentage of success, and, the fight duration is quite long. The more the difference between each other biology system the more the fast and notorious success of the stronger.

Simulations are made regarding the next conditions: 100 time units (days) for each. The anti- or pro-tumor behavior that the immune system response plays is considered. The macrophages and neutrophiles as part of

the innate immune system both can act anti- or pro-tumor. Different probability in each simulation is regard for them. Complementary probability for TAN N1 and TAN N2 as well as for TAMs and TAMs M2 are quantified. The mentioned probabilities may vary pseudo-randomly and may provoke abrupt changes; this circumstance may correspond to patients with unexpected changes. A neighborhood-based variance on that probabilities might tune the changes smoothly, and that might correspond to the average CM-IS dynamic.

A. Graphs of strong cancer

The scenario of strong cancer *versus* medium and strong immune system response are simulated and the resulting graphs are shown in figures 3, 4 and 5.It is necessary to take into account that macrophages and neutrophils, when in contact with tumor cells, can become anti-tumor or pro-tumor action cells. This behavior can promote or inhibit tumor growth.

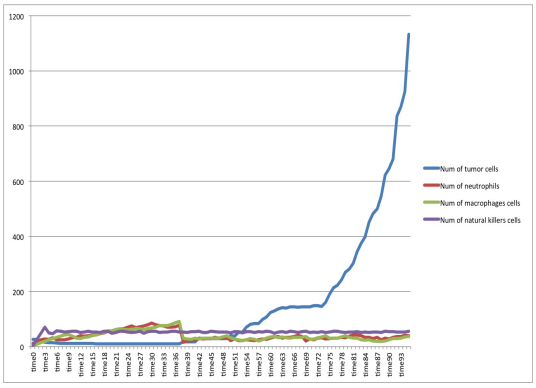

Figure 3: Strong - Medium: the graph of fight shows a hard growth of cancer tumor

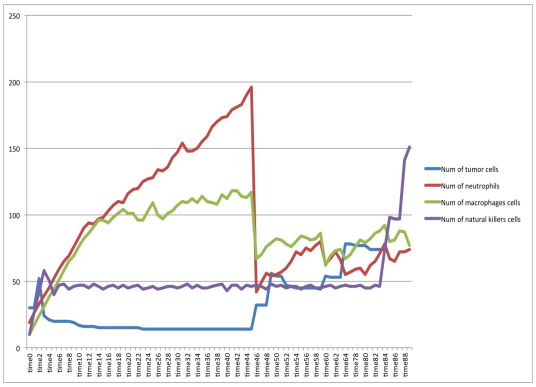

Figure 4: Strong - Strong. In this simulation neutrophil and macrophage cells are strong anti-tumor and their lines show this behaviour that makes the IS defeats cancer tumor.

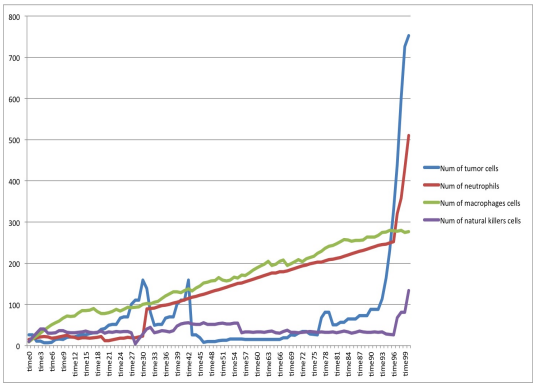

Figure 5: Strong - Strong. In this simulation cancer tumor defeats the immune system.

B. Graphs of medium cancer

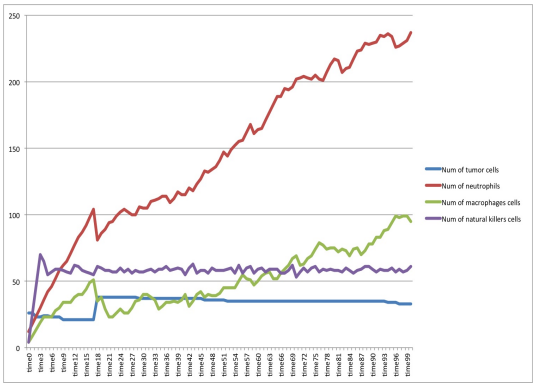

Figure 6: Medium - Strong: the graph shows the superiority of immune response. Cancer tumor not disappears but is down intensity

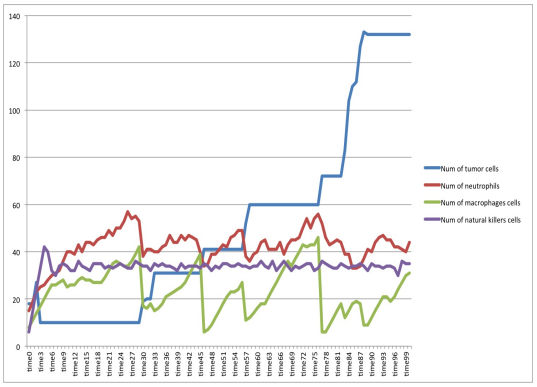

Figure 7: Medium - Medium. In this simulation cancer tumor defeats immune system -strongly. This is the plausible scenario the half of the times.

C. Graphs of weak cancer

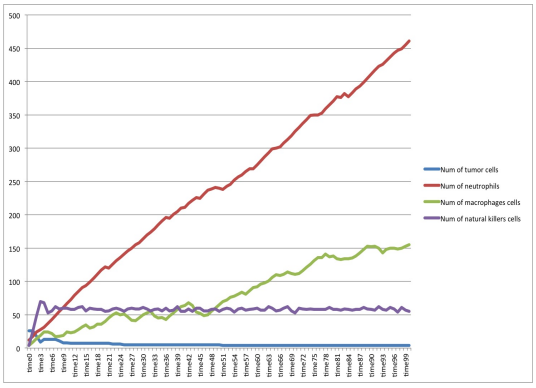

Figure 8: Weak - Medium: weak cancer looks like not a real challenge for a not fair healthy immune system. This may correspond the circumstance of average population. But a lot of more test simulations are required for truth statement.

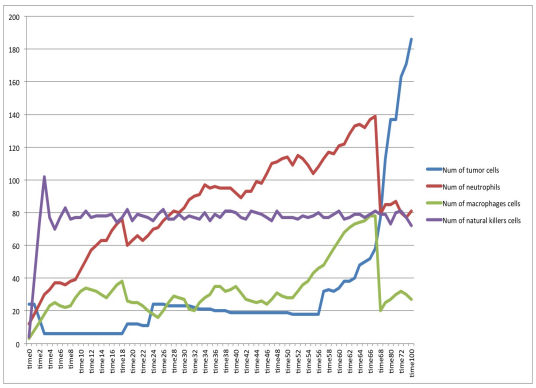

Figure 9: Weak - Weak. In this simulation the cancer tumor defeats immune system. Difference with the medium - medium simulation in the previous graph is that the required times (ticks) is longer than there.

Some remarks could be achieved from an ample statistical analysis. Hundreds at least, and even better, thousands of simulations are required. The sensitive analysis that captures the specific conditions that may correspond to different patients is a relevant task to the future.

IV. DISCUSSION

CM-IS is a complex emergent process that involves chemical, physical and biological assorted interaction process [16], in turns determined by parameters of pressure or temperature. In order to clarify the cancer dynamic of an organ primary tumor and the late set of metastasis on distant organs' tissues [17], statistics from data base of patients suffering cancer and metastasis were analyzed. From the analysis of the clinical records and data of patients suffering CM in a 60 year period, calculi of suitable probabilities are proposed: a power-law-like distribution of probability is observed [18, 19]. Given a cancer primary tumor, few organs have high probability to suffer metastasis: bone or lymphatic nodes; half dozens of organs suffer media frequency of metastasis, among them liver or lung; and two dozens of organs present low frequency risk [18, 19]. The strength of the IS response against cancer spring should correlates the strength of the cancer dissemination. The strength of CM or IS during the fight determines the success each more probably achieves.

Current simulations are made as proof of concept. Thoroughly test and adjustments would allow the tune convergence to precise values on CM-IS. Additional patients' data, from clinical test and file records, are required to estimate right probabilities. CM-IS statistics needs of several time periods to get relevant observations on the cancer evolution, for both metastasis behavior and survival periods. A wide diversity of data is required.

The competition to keep control of the organism, by cancer or by health, puts CM-IS in a game theory perspective [20]. Go game concerns a fight on territory control [21] quantified by an Ising model energy function in [8]. This paper follow up that approach without the Go game metaphor, that for not Go gamer may be hard to grasp.

V. CONCLUSIONS

CM-IS is a highly complex emergent biological process, and, a flexible and expressive enough formal tool is required for its right modeling. We use the Ising model for CM-IS micro-environment modeling, focus the innate immune response. On the base of that model, a Netlogo application allows clarifying simulations. The equal strength of both biology systems, cancer tumor and immune system, makes similar the percentage of success of each of them, as well as the fight duration. The more the difference between each other biology system the more fast and notorious success of the stronger. Patients' real data from clinical lab test and records are required to precise the values of probabilities concerning the metastasis occurrence in the organs. Construction of statistics data sets of patients with cancer metastasis regarding genetic and live conditions criteria is a challenge to take on.

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