

Cancer metastasis and the immune system response: modeling the micro-environment by Ising hamiltonian

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To overcome the cancer seeding and late metastasis, the immune system oportune response is essential. Recently, the system biology approach is relevant for better understanding the highly complex process of cancer metastasis and the immune system response CM-IS. Diverse mathematical modeling and algorithmic simulations have been introduced in the tumor immune research. In spite of that, the comprehension is far away to be satisfactory. In this paper, we introduce an Ising Hamiltonian energy function to model the micro-environment of CM-IS, focus on the innate immune system response.

Keywords: Cancer metastasis; immune system; tumor immune interaction; Ising Hamiltonian energy function.

Para preservar la salud y superar el nacimiento y posterior metástasis de cáncer, la respuesta oportuna del sistema inmune es esencial. Recientemente, el enfoque de biología de sistemas es relevante en la comprensión de este proceso, altamente complejo, de metástasis de cáncer y respuesta del sistema inmune CM-IS (por sus siglas en Inglés). Se han presentado diversos modelos matemáticos y algoritmos en la investigación sobre cáncer *versus* sistema inmune. Pese a ello, la comprensión de tal proceso dista mucho de ser satisfactoria. En este artículo, introducimos una función de energía de modelo de Ising para modelar el micro-ambiente de CM-IS, con foco en la interacción del sistema inmune inato.

Descriptores: Metástasis de cáncer; sistema inmune; interacción inmune tumoral; función de energía hamiltoniana.

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1. Introduction

Cancer is a multifactorial illness which growth comes from individual genetic inheritance joined to lifestyle conditions [1,2]. Genetic difference makes diverse tendencies in cancer deploy [1]; from the analyses on patient's clinical record files, the conclusion is that the 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 breathing 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 drops out from the primary tumor and, by entering in the arterial bloodstream, the angiogenesis occurs. Angiogenesis disseminates CC, and, some of them may invade other organs' tissues [1]. If the organ invasion grows and attracts more CC it becomes colonization and the

cancer metastasis CM started, see Fig. 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 to PMN formation; previously, the organs of metastasis are selected to be modified by the primary tumor, before metastatic dissemination occurrence. The formation of PMN comprises the process of sowing the seed of metastasis. Sowing is made by the action of tumor-secreted factors and tumor-shed extracellular vesicles. Both enable the soil at distant metastatic sites to stimulate the outgrowth of the incoming cancer cells.

Cancer metastasis and the 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.

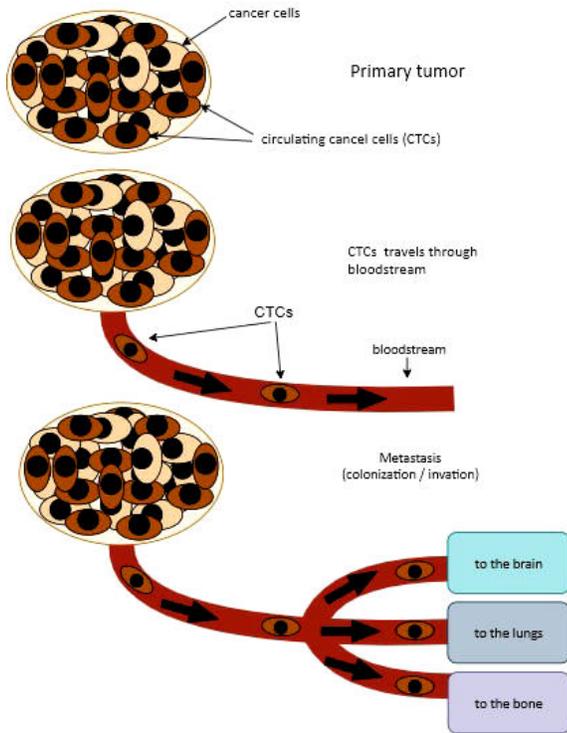


FIGURE 1. Some cancer cells drop out from the primary tumor and entry in the arterial blood stream for angiogenesis occurrence; then disseminate and could invade other organs' tissues.

It refers to 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 the 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 life being tissues. To illustrate the microenvironment of CM-IS, see Fig. 2.

CM-IS is a biology system battle that needs a better understanding 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 results. The analysis and multidisciplinary approach advance 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. An 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 a metaphor for gaming may be heavy to follow. So, the de-

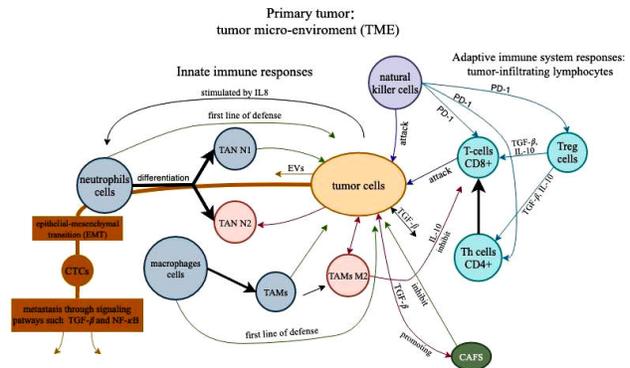


FIGURE 2. CM-IS in TME. The innate and adaptative immune system interaction: the tumor associated neutrophils (TANs) and macrophages (TAMs) can became anti-tumoral or pro-tumoral. Initially, the fibroblasts (CAF's) inhibits the tumor growth but can became pro-tumoral trough TGF-β; as well, initially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

demand was for an easier explanation, providing that the biochemical issues close the gap to medical dialogue. Start the formalization of CM-IS microenvironment interaction without the metaphor of Go gaming is the focus of this paper.

1.1. 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.

1.2. 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 low 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 Sec. 2, the CM-IS formal modeling by means of the Ising Hamiltonian is followed, with the simulation and results illustration in Sec. 3. The discussion in Sec. 4 lengthens this research and the conclusions close the paper.

2. Ising function for CM-IS microenvironment

The Ising model energy function has 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 ferromagnetism of spins interaction [2] which formulation follows

$$H = -\frac{1}{2} \sum_{i,j}^n w_{ij} x_i x_j - \sum_i^n h_i x_i. \quad (1)$$

Value of w_{ij} 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 of an element, for example, the tumor size or the number of IS cells.

$$x_i = cn_i. \quad (2)$$

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

$$w_{ij} = Q_{ij} P_{ij}. \quad (3)$$

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

$$Q_{ij} = \sum_u a_u q_u^{ij}, \quad (4)$$

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

For example, in the tumor micro-environment (Fig. 2), the tumor associate macrophages (TAMs) are re-programmed to inhibit lymphocyte functions through the release of inhibitory cytokines such IL-10, prostaglandin 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 is 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 Fig. 2, we only consider the tumor and the IIS structures, showing in Table I.

TABLE I

Structural elements	
Tumor cells	x_1
Neutrophil cells	x_2
Tumor associate neutrophil N1 (TAN N1)	x_3
Tumor associate neutrophil N2 (TAN N2)	x_4
Macrophages	x_5
Tumor associate macrophages (TAMs)	x_6
Tumor associate macrophages M2 (TAMs M2)	x_7
Natural killers	x_8

To show how the interactions take place, the arrangement is presented in Table II.

TABLE II

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

Table II is not a matrix array. Their elements have the following properties:

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

Since each interaction occurs with a given probability, therefore, in Eq. (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:

TABLE III

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

Table III is also not a matrix and their elements have the same properties that elements of Table II.

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

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

$$P_{1,3} = 1 - P_{1,4} \quad (5)$$

$$P_{1,6} = 1 - P_{1,7}. \quad (6)$$

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

Thus if AT denotes anti-tumor action and PT pro-tumor action, then:

$$P_{1,3} = P(AT|TAN N1) \quad \text{and} \quad P_{1,4} = P(PT|TAN N2)$$

$$P_{1,6} = P(AT|TAMs) \quad \text{and} \quad P_{1,7} = P(PT|TAMs M2).$$

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 Eq. (1) is:

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

3. 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 the strength of cancer tumor *versus* the immune response are made. Graphs that illustrate the Strong-Strong, Medium-Strong, and Weak-Strong combinations are shown in the Figs. 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 greater the difference between biological systems, the greater the rapid and noticeable success of the stronger.

Simulations are made regarding the following condition: 100 time units (days) for each. The anti- or pro-tumor behavior that the immune system response plays is considered. The macrophages and neutrophils as part of the innate immune system both can act anti- or pro-tumor. Different probability in each simulation is regarded 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.

3.1. 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 Figs. 3, 4 and 5. It is necessary to take into

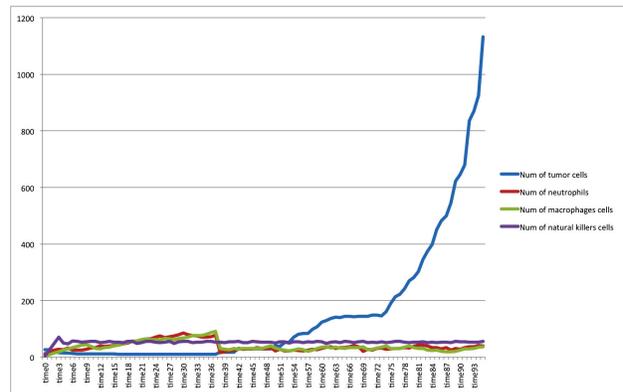


FIGURE 3. Strong - Medium: the graph of fight shows a hard growth of cancer tumor

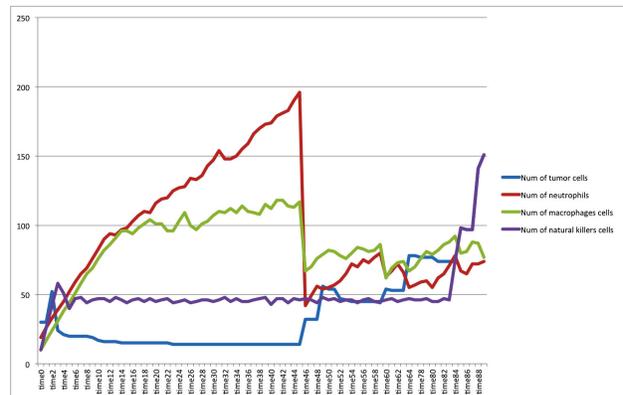


FIGURE 4. Strong-Strong. In this simulation, the neutrophil and macrophage cells are strong anti-tumor, and their lines show this behaviour that makes the IS defeats cancer tumor.

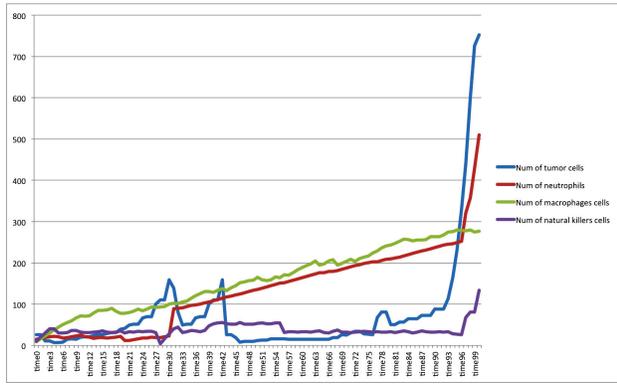


FIGURE 5. Strong-Strong. In this simulation, the cancer tumor defeats the immune system.

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.

3.2. Graphs of medium cancer

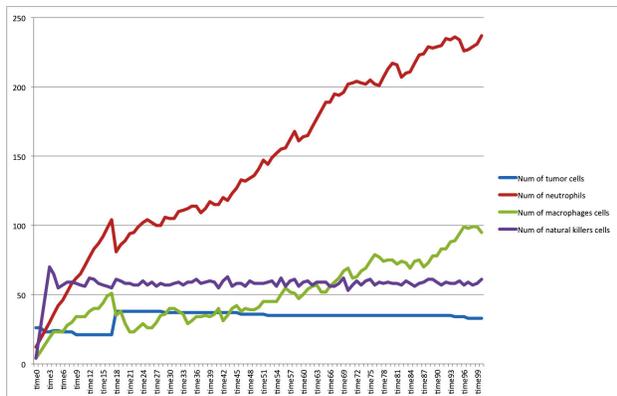


FIGURE 6. Medium-Strong: the graph shows the superiority of the immune response. The cancer tumor not disappears but it has a low intensity.

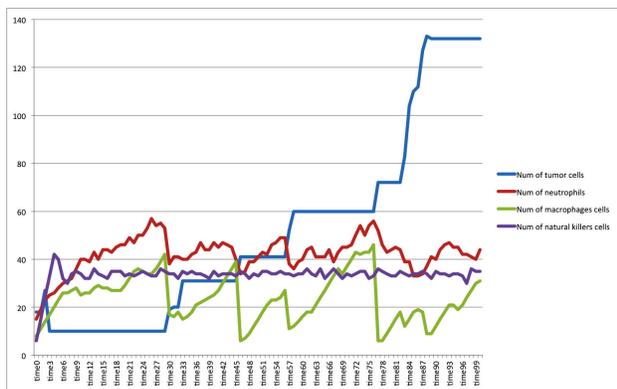


FIGURE 7. Medium-Medium. In this simulation, the cancer tumor efeats the immune system-strongly. This is the plausible scenario half of the times.

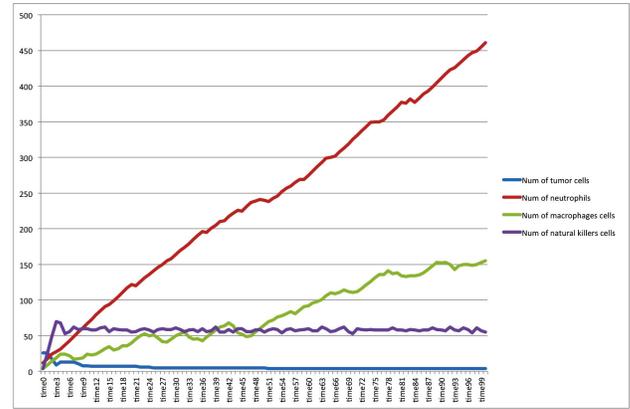


FIGURE 8. Weak-Medium: weak cancer looks like not a real challenge for a not fair healthy immune system. This may correspond the circumstance of average population. However, more test simulations are required for truth statement.

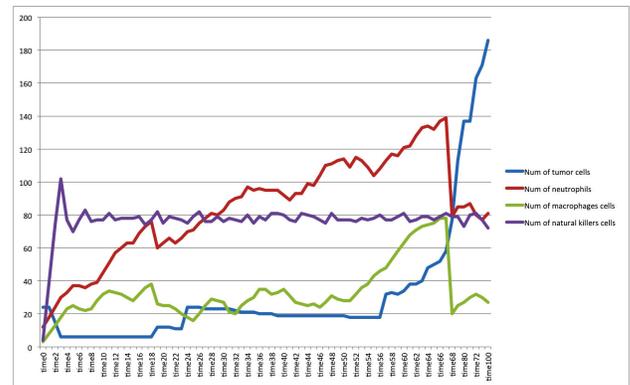


FIGURE 9. Weak-Weak. In this simulation, the cancer tumor defeats immune system. The difference with the medium-medium simulation in the previous graph is that the required times (ticks) are longer than there.

3.3. Graphs of weak cancer

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.

4. Discussion

CM-IS is a complex emergent process that involves chemical, physical and biological assorted interaction processes [16], in turn 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 a database 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 a 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 correlate with the strength of the cancer dissemination. The strength of CM or IS during the fight determines the success each 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 tests and file records, are required to estimate the 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 Ref. [8]. This paper follow up that approach without the Go game metaphor, that for a not Go gamer may be hard to grasp.

5. 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 in 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 greater the difference between biological systems, the greater the rapid and noticeable success of the stronger. Patients' real data from clinical lab tests 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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