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# Cancer Metastasis and the Immune System Response: CM-IS Modeling by Ising Model

Matias Alvarado[1], Renato Arroyo[2]

[1] Centro de Investigación y de Estudios Avanzados,
Instituto Politécnico Nacional,
Mexico

[2] Universidad de Guadalajara,
Centro Universitario de Ciencias Exactas e Ingenieria,
Mexico

matias@cs.cinvestav.mx, salomonarroyo@gmail.com

**Abstract.** The modeling of cancer metastasis and the immune system (CM-IS) response is of top interest for cancer diagnosis and therapy. CM-IS is a highly complex biological process. From interaction of basic cancer cells emerges the cancer growth and late cancer metastasis. The immune systems reaction for organism protections should avoid the cancer proliferation. The strength of the IS response against cancer spring correlates the success (or not) of the cancer growth. In this paper we outline the use of the Ising model for CM-IS interaction modeling. Ising model is classic in physics, biology and chemistry for the modeling of emergent interaction phenomena. Hence the convenience to use for CM-IS formal and computational intelligence approach.

**Keywords:** cancer-metastasis, immune-system, interaction, Ising-model.

## 1 Introduction

CM-IS is a highly complex biological process [8] of top interest for cancer diagnosis and therapy. The next sub-processes are CM-IS involved: the cancer tumor seeding; the cancer cells CC cooperation for tumor growth and metastasis; the immune system cells ISC cooperation strategies for protecting the organism against cancer proliferation; the CM-IS dynamic of fighting –short or long depending on diverse factors. The CM-IS analysis and comprehension requires a multidisciplinary approach to advance regarding the scalability and precision involved in [3]. The last years use of mathematical and algorithmic methods [5, 13, 16] contributes for CM-IS better understanding; as well as for the agile finding of results [17].

Ising model is classic for mathematical modeling of complex interaction phenomena in chemistry, physics and biology [5]. Usually, these phenomena are determined by pressure or temperature as essential thermodynamics parameters.

CM-IS concerns –direct or indirectly– temperature or pressure parameters [13]. But it looks like more complex as an emergent process that involves chemical, physical and biological assorted interaction process [10].

We use Ising model to sketch a formalization of CM-IS. We start with the parametrical description of tissues, and, of some of the effects from CC over tissues for cancer tumor growth or metastasis; as well, the parametrical description of elements of IS process that confront tumor cancer growth and metastasis. We introduce an initial definition of Ising model energy function to formalize the CM-IS interaction: the cooperation among CC or among ISC; as well as the dynamic of CM-IS fighting [3]. On the base of the Ising model formalism computer simulations are practiced and the analysis of results provides conclusions that may help for therapies design.

Next follows a short review of the hallmarks of cancer. Then the literature review on CM modeling, with differential equations, Markov decision processes, agent-based systems and Hamiltonian formulas. The Ising model formalism for CM-IS is introduced and illustrated. A short section for Discussion follows and Conclusions close the paper.

### 1.1 Hallmarks of Cancer and Conditions to Deploy

Cancer is a multifactorial illness that grows from individual genetic inheritance joins to life style conditions [8, 11]. Genetic difference make different tendencies to cancer deploy [8]. But, cultural factors like habits of life, food quality and person's living conditions, it makes the difference of low or high frequency in a population; or the individual intensity of cancer deploy [6]. Aerobic exercise practice strongly prevents the risk of cancer seed and late deployment [2].

Cancer starts with a disordered replication of malignant cells over a tissue shaping the first solid cancer tumor [8]. The transiton growth factor TGF-$\beta$ play an important role in the tumor micro-enviroment (TME). At early stages of tumorigenesis can acth like tumor suppressing and tumor promoting later on [8, 4], see Fig. 1. Some cells from the cancer tumor may disseminate on distant tissues making invasions [15]. The CC dissemination is by arterial blood flow or angiogenesis [8]. If the invasion in an organ grows and attracts more CC it becomes successful cancer colonization in the organ. This is cancer metastasis, the fatal step of cancer growth in the live organism [15]. Metastasis implies that cancer is out of a bounded site and is organism spreading. The IS surveillance will have serious difficulties to overcome cancer when metastasis occurs [8]. In Fig. 2 the metastatic process is depicted.

IS reaction to confront and bound cancer spring is clever for health care [5]. The firm IS response makes difficult success of any invasion [3]. Otherwise the weak IS response facilitates the cancer tumor growth and proliferation of metastasis springs [9]. The first IS response is by means of the innate immune system IIS, that recruits macrophages and natural killer cells to eliminate CC invasion [15]. CC antigens are detected by IS cells activating reaction to kill CC. But, mutations of CC complicate the IIS action. A mutant CC is not identified by IIS cells.

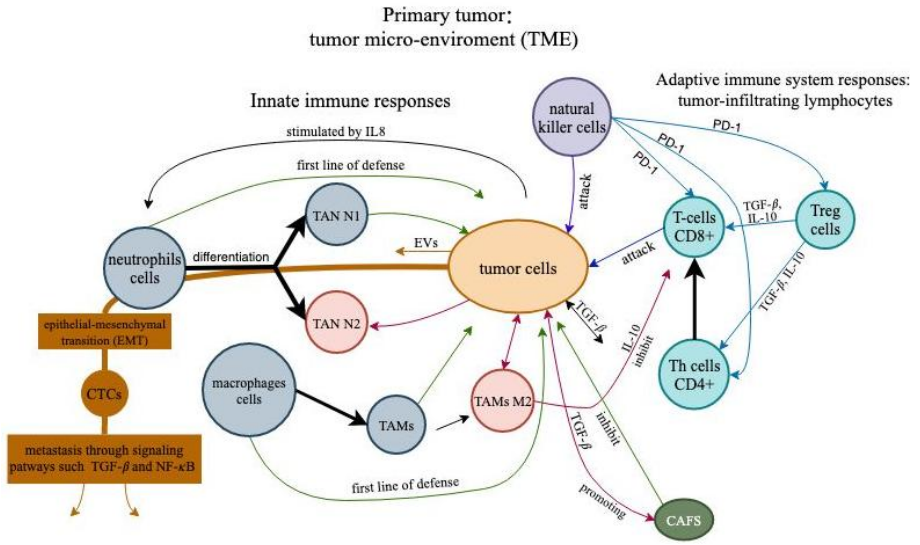


**Fig. 1.** Interaction of tumor and immune system cells in tumor micro-enviroment (TME).The innate and adaptative immune system interacts in differents forms: neurophils, in form of tumor associate neutrophils (TAN) and macrophages, in form of tumor associate macrophages (TAMs) can be anti-tumoral (TAN N1 and TAMs) or pro-tumoral. Cancer associate fibroblasts (CAFS) initially inhibits the tumor growth, but at the same time can be pro-tumoral trougth TGF-$\beta$. The natural killers attacks tumor cells but at the same time regulates the proliferation of adaptative tumors cells.

Therefore, when IIS response is not enough to eliminate cancer tumor, the adaptive immune system AIS action is required. The AIS implements a set of strategies to fight cancer growth and metastasis springs; it activates the recruitment of T cytotoxic cells and other macrophages [7]. A war of biological strategies started. This behavior is available to be formulated then computer simulation on the basis of Ising model.

## 2 Related Literature Review

In the computational **agent-based** approach each agent is a basic element in a social virtual environment. From the agents interaction usually 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 take advantages from computational tools, get scalability and different conditions for testing experiments [7].

In the modeling with **differential equations** [1], cancer growth functions use input parameters that represent the back elements for growth dynamics.

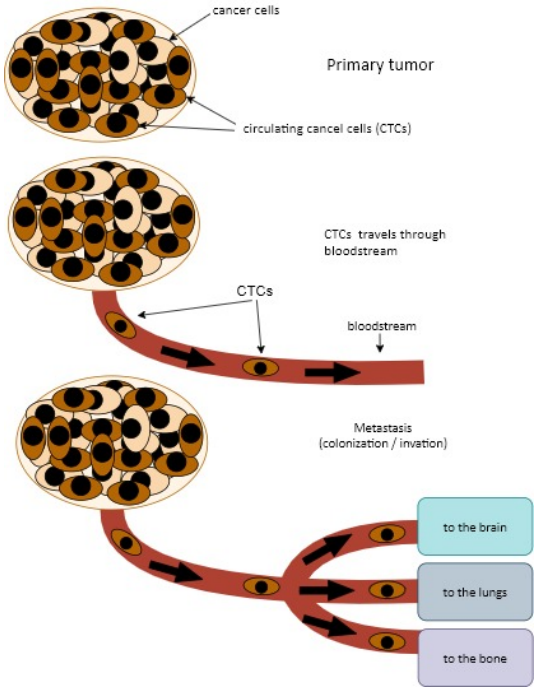


**Fig. 2.** Diagram of metastatic process. When tumor cells adquire the epithelial-mesenchymal transition, cancer cells can leave the primary tumor in form of circulating tumor cells (CTCs) and travel trough bloodstream. Consequently cancer cells can metastasize (invade) some organs.

As usual, the differential equations depend on the initial and border conditions of the phenomena. However, cancer initial conditions could not be clearly defined, and, border limit conditions less even.

In [14] cancer metastasis from an organ primary tumor is statistically featured. From statistics of 446 patients, the frequency of metastasis for the first site and the sequence of metastasis sites were calculated. As an instance, from breast or prostate cancer the most frequent metastasis site is bone (34%), liver (16%) and lung (15%). Main claim is that the first metastasis strongly influence the deploy sequence of the next metastasis sites; as well, the probability of patient's survival. In addition, a **Markov chain model** of random walks for prediction of the order of spatial metastasis sites is proposed.

## 3 CM-IS in Systems Biology and Game Theory

The growth of a cancer primary tumor is an illness invasion on live organ tissues. Cancer metastasis is the dispersion of illness, by invasions, to other body organs.

To invade new body tissues (positions), cancer follows kind of strategies. The most usual is the mutation of CC, e. g. PDL1- mutates to PDL1+; it conveys that a mutated CC is no more detected by IS cells that attack it previous mutation. The avoidance of immunity actions accelerates the cancer metastasis. One biology system emerges from primary cancer tumor and late metastasis in a net of lively cancer tumors.

The immune response to a cancer invasion is an IS action of reduction to stop the tumor growth, and the late complete CC elimination. For preventing CC spreading and eventual metastasis, the strengthening of immune surveillance is essential. IIS and AIS construct nets of immunity structures for bounding cancer tumor and metastasis [18] That construction of immune nets obeys kind of strategic composition of IS reductions. The strategies for cancer reductions it involve the recruitment of cytokines T cells and macrophages. Coordination of IS elements is required for the success of surveillance actions. This coordinate immune response is a biology system too.

CM-IS is a two biology system battle to occupy live being tissues. One biology system is the cancer primary tumor and late net of metastasis; the other is built from the immune actions and reactions to preserve health. Hence, CM-IS comprehension requires a system biology approach [10]. As well, the kind of competition to occupy the organs tissues puts CM-IS in a game theory perspective [12]: The goal of each MC-IS gamer is keep control of the organism, by cancer or by health.

## 4 CM-IS Ising Model Formalism

The Hamiltonian of Ising model [3] for pherromagnetism of spins interaction follows. Value of $w_{ij}$ is the energy interchange between $x_i$ $x_j$; $-h_i$ is the energy of the field that affects $x_i$:

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

The Hamiltonian of Ising model is expressive enough for including the biochemical and biophysical parameters of CM-IS fighting interaction. Notation of parameters in CM-IS process are in Table 1.

Equation (2) is the formal description of molecules in CM-IS; CC molecules is $c_i = -1$ and the IS molecules is $c_i = 1$:

$$x_i = c_i(n_i + r_0^{k_i}). \tag{2}$$

Parameter $n_i$ sets the amount of CC or IS in the molecule. Parameter $r_0$ sets the rate of TGF-$\beta$; and $k_i$ the growth rate of a cancer molecule. The value $w_{ij}$ is the energy interchange between molecules $x_i$ $x_j$. $w_{ij}$ is calculated from the interaction energy of molecules that cooperate with or confront to $x_i$ $x_j$:

$$w_{ij} = \sum_{k}^{m} r_{t,x_t^{ij}}. \tag{3}$$

**Table 1.** Parameters in CM-IS process.

| CC/metastasis tumor | Parameter | Immune system | Parameter |
|---|---|---|---|
| Initial tumor cells | $n_i$ | Innate immune system | $m_i$ |
| TGF-$\beta$ | $r_0$ | Natural killers | $c_i$ |
| IL-8 | $\lambda$ | Adaptative immune system | $t_i$ |
| Tumor derived factors | $\tau$ | Fibroblasts | $f_i$ |
| PD-11 | $\pi$ | Fibroblasts | $f_i$ |

Parameter $r_t$ is the coefficient for weighting the strength of tactics of cancer or immune response. The tactics of invasion, reductions, nets and connections among molecules of the CM-IS process. In Table 2 the list of draft percentages for tactics is propose. The higher the percent values of tactics it is the higher the strength of each biology system.

**Table 2.** List of draft percentages for tactics is propose.

| Tactic | Notation | Percentage of strength of cancer / Immune system | | |
|---|---|---|---|---|
| | | Weak | Medium | Strong |
| Invation | $r_{in}$ | 0.1 | 0.4 | 0.7 |
| Reduction | $r_{rd}$ | 0.1 | 0.4 | 0.8 |
| Net | $r_{nt}$ | 0.2 | 0.5 | 0.7 |
| Conection | $r_{ct}$ | 0.2 | 0.5 | 0.7 |

Percentages for tactics are just draft values. Current simulations are made as proof of concept with such values. Thoroughly test and adjustments would allow the tune convergence to real values. Patients' real data are required to estimate probabilities on the basis of them. The best the data samples the best the calculi of suitable probabilities; in addition to a wide enough diversity of data is required.

A house-made Netlogo application is used for simulations. Breast cancer primary tumor and bone metastasis simulations are practiced in rough manner. Results show an expected tendency: the equal force of each biology systems splits the percentage of success. And, the proportional strength of one biology system with respect to the other it corresponds to the each other proportional success.

## 5 Discussion

CM-IS concerns the analysis of biochemical and physiological process for understanding the relationship of an organ primary tumor and the late metastasis

on far organs' tissues. Statistics from data base of patients are being emerging in recent years. CM-IS statistics needs of several years periods to get relevant observations on the cancer evolution, for both metastasis behavior and survival periods. Depending of the type of primary tumor and first metastasis site the evolution is observed with differences. We think that may obey a probability distribution function. It should need a deep analysis for concluding this hypothesis.

The CM-IS biological system can be seen as a game competition to occupy the body. Go game concerns a fight on territory control. First automation that beat top human experts was AlphaGo [16]. Go gaming comparison with CM-IS and formalization by Ising model [3] is an antecedent of current work. Chemo-, radio-therapies or vaccines for cancer treatment may add to CM-IS game theory perspective.

## 6 Conclusions

From CC interaction emerges the cancer growth and metastasis. The strength of the immune systems reaction against cancer spring and metastasis it determines the success to beat them. CM-IS is a highly complex biological process. We use the Ising model for CM-IS modeling. The CM-IS emergent biological phenomena is well formalized by using this stochastic mathematical tool. A Netlogo program supports the initial simulations. Draft case study involves breast cancer and bone metastasis as the first metastasis site.

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