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Can major breakthroughs in cancer be achieved through theoretical models ?

Comment on ‘Improving cancer treatments via dynamical biophysical models’
by M. Kuznetsov, J. Clairambault and V. Volpert

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The review by Kuznetsov, Clairambault and Volpert [1] presents a state-of-the-art in mathematical oncology focusing on dynamical biophysical models and their application to therapy.

It first presents the different model types (ODEs, PDEs and Agent-Based Models) and their respective potential for describing various tumour properties (spatiality, age, phenotypes) at the individual cell level or at the tumour scale. It also shows how the main therapeutic means including chemotherapy (targeted and antiangiogenic therapies), immunotherapy and radiotherapy are classically represented in the models. The review then specifically highlights – through well-chosen examples – how models are used to optimize, combine, adapt the therapies with the aims to maximize the efficiency, to reduce the toxicity, to avoid the emergence of resistance to treatment.

This is a timely review since we are reaching the exponential growth regime of mathematical models development in oncology while experiencing the growing frustration of not being able to more successfully bring them to the clinic. Why are models predictions still rarely used by clinicians ? As spotted by the authors, one main reason is that clinicians do not trust models. Since there is too much at stakes they prefer to rely on their acquired experience and continue to act empirically.

It is however undeniable that models can help fight cancer. The examples given show that models proved very useful to bring some insights on many therapeutic aspects, to understand why and how: therapeutic combinations can succeed or fail; lowering the dose can help manage resistance through metronomic chemotherapy; treatment can be optimally scheduled through chronotherapy; resistance and recurrence might occur. Most of these successes highlight general principles, however we would like models to be predictive at the scale of the individual. This makes the all difference between precision and personalized medicine [2,3].

In this quest towards personalized therapy, a holistic approach is required. Systems biology aims at integrating the different model components or models combinations, often by means of hybrid modelling [4]. Examples of the potential of such models are shown in the review as well as their limits. Indeed the rise in complexity makes the parameters too numerous and often impossible to obtain from experiments, and the models untractable mathematically.

There is a drift towards too much complexity, mostly encouraged by biologists who tend to envision models as a virtual match of the biological reality. In the same way the obsession for data fitting should not be the main driver for model development. It should be reminded that the purpose of a model is to answer one specific question and that its domain of applicability and validity is always restricted. So, is the power of mathematical models in oncology limited to there potential in question solving such as therapeutic optimization? Or can we expect theoretical models to lead to major breakthroughs in the fight against cancer?

For this, models should be rethought in their true nature - where they are more likely to lead to a breakthrough - which is to test new concept and hypotheses inspired by the biology and not strictly mimicking the biology itself. This requires to think out of the box in a transdisciplinary way, this requires to make theories.

The added value of this review is precisely to address the importance of theories : the Somatic Mutation Theory (SMT) *versus* the Tissue Organization Field Theory (TOFT) for the origin of cancer. Both theories are based on opposite hypotheses regarding the default status of the cell, quiescent for SMT, proliferative for TOFT which creates an intellectually stimulating and highly debated paradigm shift [5,6,7]. The review especially advocates the atavistic theory, that provides an explanation for the characteristics of the cancer cell behaviour - including the desinhibition of proliferation, migration, and the favoured glycolytic metabolism - as a reversion to a primordial monocellular ancestral state through progressive dedifferentiation [8]. Once again the theory drastically changes the way to think by proposing a different perspective to reinterpret the knowledge accumulated so far. Regardless of being right or wrong, the atavistic theory opens up new avenues and stimulates new experimental or theoretical researches.

Testing such a theory using mathematical modelling may well generate the expected breakthrough.

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