

# Understanding Cancer through Evolutionary Game Theory

## January 29 – February 2 @Oort

### Science:

1. A concise version of the description and aims of the workshop, including what were the most important scientific questions motivating the workshop.

The aim of this workshop was to bring together experts in evolutionary game theory, cancer biology, oncology and the intersection of these fields, in order to address topics in tumor growth and diversification, metastases, and cancer treatment from a game theoretic perspective. We wanted to explore and advance how game theory can offer a new perspective on understanding, modeling, and treating cancer. We aimed to reveal the strengths and limitations of game theoretic approaches. Of particular interest was how to adapt existing game theoretic models to make them more realistic and directly applicable to experimental and clinical applications. Moreover, we discussed how we can use cancer data to test, parameterize and apply these models and how we can create a lockstep between models, experiments and clinical translation.

2. Is a **tangible outcome** of the workshop expected? If so, please mention – even if it is, as yet, at the level of intention.

Tangible outcomes occurred on three fronts: 1) we are invited to submit work from this workshop to the journal *Games* that is featuring a special issue on cancer and game theory (we shall explore additional avenues for publishing the complementary works of the scientists at the workshop – we have several invitations from other publishers and journals), 2) scientists who otherwise would not know of each other and of each other's work were brought together and formed lasting bonds as colleagues, and 3) new lines of research have developed quickly and we think enduringly among the participants. The discussion groups were particularly successful at spurring research ideas and collaborations. Based on feedback and follow-up conversations we know of several new endeavors.

**Cancer Cachexia** is a wasting away of the body during later stages of cancer and therapies aimed at forestalling or preventing this source of mortality have been only marginally successful. A team with cancer biologists, mathematicians, ecologists and clinicians is working towards modelling the phenomenon, validating the model with actual clinical data, and developing early warning signs of this condition.

**Quality of Life** metrics are crucial for evaluating the costs and benefits associated with therapy and the toxicity that accompanies many treatments. Current ones assume continuous therapy, or other standard of care treatments. And, they have not been updated to incorporate more sophisticated personalized treatments, and adaptive therapies that are fine-tuned to the patients' conditions. A working group made tangible and exciting progress on updating quality of life metrics to consider time-dependent therapies personalized to the individual's cancer state, and individual's experience of debilitating effects of therapy. The group aims to continue this project.

**Who are the players** in the game of cancer and cancer therapy has been a vexing issue. Clearly the cancer cells and the behaviors of the physician represent a kind of predator-prey game, as well as the cancer cells engaging in public goods games, competition games and games of niche construction with each other. But, what of the normal cells? Hitherto it has been a matter of taste whether to include stromal cells, fibroblasts, and immune cells as players or not. Generally, this important issue is discussed informally with participants agreeing to disagree. A group has formed to take flesh out the opportunities and consequences of seeing normal cells as players or not. It should emerge as *Cancer Games: Who are the Players?*

Finally, there were large group presentations, large group discussions, working groups and informal discussions that often went on into the wee hours (we know of one that concluded at 3AM, and science was still the topic of conversation!). Collectively, these have resulted in several seminar invitations, invitations for scientists to visit each other's labs, research collaborations, and invitations for post-docs and graduate programs.

3. Were there any developments which could, already, be termed a (beginning) **scientific breakthrough**? If yes, please tell about it shortly

Some of the topics that are worked on by the workshop participants after the workshop are approached from a completely new (and often very innovative) angle, thus, if successful, these efforts are expected to lead to scientific breakthroughs. There were quite some "out of the box" ideas found during the workshop, thus there is a high chance of such breakthroughs. See the above list of tangible outcomes. Some of these would represent true breakthroughs. Ultimately, the largest emerging breakthrough concerns the integration of mathematics (game theory), experimental cancer biology and clinical practice into adaptive therapy. It has been successfully applied once to metastatic, castrate resistant prostate cancer (published in Nov 2017, *Nature Communications*). The workshop provided a crucial forum for diverse scientists to start tackling the opportunities and challenges of first controlling and then curing metastatic cancer.

4. Did you, or to your knowledge any of the participants, experience notable **"Aha" moments** (for instance, separate scientific communities realizing that they have significantly more in common than they had thought)?

There were certainly such moments, for example when rather theoretical expertise of some participants led to the progress in groups focusing on modeling cancer. For some of the models, understanding of the underlying principles of mathematics made some observations rather obvious, while it also pointed out which of the many parameters used played significant roles and which did not. The discussion of these observations was very much welcomed by the less mathematically trained participants and indeed created some AHA moments. Obvious AHA moments came as modelers and mathematicians were fully apprised of how cancer patients actually die. Almost everyone experienced an AHA moment from expert discussions and presentations of how the immune system interacts with cancer cells within a tumor ecosystem. A number of AHA moments occurred as game theorists and non-game theorists appreciated how similar and sometimes dissimilar their views of science can be. Finally, the biggest AHA moment for most was realizing how everyone at the workshop (and we were a very diverse lot) has something tangible to contribute towards understanding, modeling, experimenting with, and ultimately treating the scourge that is cancer.

#### **Organization/ Format:**

5. How did you experience the **format of the workshop** (the structure of the program, lectures vs discussion time etc.)? Did you try something new (different kind of discussions for instance)? If so, how did it work out? Would you do it again or advise it to others?

We started with series of tutorials introducing the mathematical and biological topics, and after that we asked participants to write down questions that interested them and to which others could sign themselves up - that is how the brainstorming groups were formed. There was considerable time given to group discussions on days 3, 4, and 5, and at the end the groups all presented their outcomes to the others. In the mornings and evenings of days 2,3,4, and 5 we also introduced the inspirational talks which looked on the topics introduced in the tutorials from novel and/or unusual perspectives. The workshop was ended by a talk by Bob Gatenby on evolutionary principles of cancer.

We believe that this format was successful and the working groups were very productive. Most participants were really excited about the topic they were working on, and therefore there was a lot of progress. The vast majority was present during all activities and also stayed until the very end.

There were few participants who did not really actively participate in the discussions and working in the groups. Some of them were there only to learn and/or did not want to/were afraid to express their opinion (this concerned some of the PhD candidates). While this was a bit of pity, fortuitously most of the participants participated actively and with great enthusiasm in the workshop. A lot was learned from each other.

The inspirational talks added much to the main talks, as they gave us very refreshing perspectives on known theory.

6. **Other comments**, suggestions and/or criticism for the Lorentz Center, the scientific advisory boards and/or future organizers.

We really enjoyed the workshop. Everything was arranged very professionally, we got all of the space that we needed for our work. People seemed relaxed and happy and that is the best state of mind to do significant research. Martijn and other people working at the Lorentz Center were very helpful. We received very useful tips during the workshop from Martijn and other staff members. The preparation meeting with the Lorentz Center helped us to sharpen and improve our ideas in finalizing the program. It is clear that the Lorentz Center has much experience with organizing scientific workshops. The beach BBQ that we had as our social event was great, and so was the wine and cheese party. There is not a single negative point we could state here. We appreciate all the support offered by the Lorentz Center; a big THANK YOU to all your team.

#### **Organizers**

Kateřina Stařkov (Maastricht University, the Netherlands)

Joel S. Brown (Moffitt Cancer Center, United States)

Frank Thuijsman (Maastricht University, the Netherlands)

Robert A. Gatenby (Moffitt Cancer Center, United States)