AI as an Always-available Oncologist: A Vision for AI-optimized Cancer Therapy Based on Real-time Adaptive Dosing at the Patient Level

Authors: Gabriel Kalweit, Luis García Valiña, Ignacio Mastroleo, Anusha Klett, Joschka Boedecker, Roland Mertelsmann, Maria Kalweit
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Affiliation: University of Buenos Aires, Argentina; FLACSO, Argentina; Collaborative Research Institute Intelligent Oncology (CRIION), Freiburg im Breisgau, Germany
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Gabriel Kalweit\textsuperscript{1,2}, Luis García Valiña\textsuperscript{1,4,6}, Ignacio Mastroleo\textsuperscript{1,4,5}, Anusha Klett\textsuperscript{1}, Joschka Boedecker\textsuperscript{1,2}, Roland Mertelmann\textsuperscript{3}, Maria Kalweit\textsuperscript{1,2}

luisgarciavalina@gmail.com

\textsuperscript{1}Collaborative Research Institute Intelligent Oncology (CRIION), Freiburg, Germany

\textsuperscript{2}Department of Computer Science, University of Freiburg, Freiburg, Germany

\textsuperscript{3}Mertelmann Foundation, Freiburg, Germany

\textsuperscript{4}Program of Bioethics, Facultad Latinoamericana de Ciencias Sociales (FLACSO), Buenos Aires, Argentina

\textsuperscript{5}National Scientific and Technical Research Council (CONICET), Buenos Aires, Argentina

\textsuperscript{6}Department of Philosophy, University of Buenos Aires, Buenos Aires, Argentina
Abstract

This communication presents the long-term vision of AI-optimized cancer therapy based on automated adaptive dosing. The idea is to have an AI-controlled therapeutic system that administers microdoses from information obtained from low-power sensors, which could improve patient quality and survival. While this idea has not been implemented for cancer yet, there are similar health interventions in cancer (not using AI) and in diabetes (using AI) that serve as precedents. However, there are still major challenges to tackle, such as identifying relevant, measurable, and reasonably costly tumor markers and dealing with the enormous combinatorial potential for a rapid and effective response in individual cases. The paper proposes a dual process to address these challenges, involving collecting initial findings in vitro and investigating tumor markers for their transferability to in vivo systems. If successful, this intervention strategy could have vast implications for the treatment of cancer, the second leading cause of death in the world. It is important to consider ethical and regulatory considerations in the development of this strategy.
In May of 2017, after being defeated several times by the Artificial Intelligence (AI) algorithm AlphaGo, the reigning Grand Master of the ancient Chinese game of Go, Ke Jie, declared: “last year, it was still quite human-like when it played; but this year, it became like a god of Go”.\(^1\) Apart from dire forecasts of human obsolescence and machine domination, AI is showing great potential in applications with large search spaces and scenarios of increasing complexity, as the game of Go exemplifies, with \(10^{170}\) possible game combinations.\(^2\) This phenomenal potential for dealing with complexity is what could make AI a game-changer in cancer therapy.

Cancer is a leading cause of death and accounted for 10 million or one in six deaths worldwide in 2020.\(^3\) It is also an elusive and highly complex killer. There are more than a hundred different types of cancer and more potential combinations of carcinogenic mutations than there are atoms in the universe.\(^4\) Each variation affects each person differently and reacts differently to treatment. Also, new drugs, different combinations, and different doses increment the size of the solution space at an exponential level. With this level of complexity, searching for new therapies looks like finding a needle in a haystack.

But AI could be used to tackle this complexity, and the scientific community is currently using it. Machine Learning (ML), a subfield of AI, can foster personalized cancer treatment by allowing computers to learn from experience without rules explicitly imposed by humans. The potential of ML in medicine is enormous, and compared to traditional statistics, it offers a wealth of new possibilities.\(^5-8\)

In oncology, ML tools have been used mainly in AI-assisted diagnosis\(^9-11\) and also in treatment selection\(^12\) to guide the decision-making of medical professionals. What remains missing in real-world implementation is the shift from \textit{AI-optimized diagnosis or treatment selection} to \textit{AI-optimized patient therapy in real-time}.

Currently, some approaches learn optimal treatment strategies using AI, optimizing the sequence of drugs or doses given a set goal (e.g. survival).\(^13,14\) However, the dose and/or drug combinations are not altered in real-time based on the individual patient’s response, despite its potential significance. But with the aid of ML, we could introduce \textit{real temporality} in doses and combinations of drugs, making them change as a response to the evolution of the disease. This could improve treatment.

For example, some studies have investigated using lower-than-maximum tolerated doses and different frequencies (adaptive dose) that might better manage cancer and reduce the severe side effects of cancer therapies. An example of a
non-real-time adaptive dose regime of proven drugs for metastatic castrate-resistant prostate cancer, based on the idea of evolutionary dynamics of cancer and game theoretic mathematical models, showed signals of improvement (e.g. delay of drug resistance, less overall drug use, etc.) in an observational study\(^\text{15}\) of new non-validated practice\(^\text{16}\) (a.k.a. “innovative care”). This adaptive approach could be combined with ML to personalize treatment to the specificities of the patient and the disease in real-time. This has not been done yet for cancer, though a similar idea has been envisioned for sepsis.\(^\text{13(p 1719)}\)

In the future, a medical device based on measurements from low-powered sensors would always monitor the cancer patient and deliver targeted therapy in the form of just-needed doses of the appropriate drug(s) in a more precise and timely manner to control the disease within clinically meaningful limits for the patient. This is what a new paradigm of AI-optimized cancer therapy may look like. An AI-based system as an always-available oncologist that seamlessly remembers and analyzes the highly individual course of the disease in real-time; always adapting and learning. The development of an AI-automated insulin pump for diabetes, currently in the final stages of approval, shows a doable and real-life example of this general vision of AI-optimized therapy.\(^\text{17}\)

However, translating this vision into a workable solution for cancer therapy still faces major challenges. First, is the problem of finding appropriate tumor markers that fairly correlate with the course of the disease. Second, once found, solving the almost inextricable combinatorial complexity with only a few data points. In a nutshell, the system must generalize from little accessible training data and find a solution that is safe, timely, and effective.

This latter fundamental problem could be solved with a “two-track system” (see Figure 1) based on patented technology by two of the authors.\(^\text{18-20}\) First, initial findings would be collected in vitro. Sensors such as imaging microscopes or fluid sensors could record cells in a medium under given drugs and analyze samples for any components like fragments of the cellular membrane and other cellular structures, cell-derived exosomes, small non-coding RNAs or miRNAs which are involved in gene regulation and cellular processes and metabolites secreted from the cells. Once a system is set up, the first data set recorded this way could subsequently be optimized by reinforcement learning. Reinforcement learning (RL) is a type of ML in which the system is not told which action to take, but instead is placed in a space with rewards and punishments and must learn by trial and error.
which sequence of actions yields the most expected accumulated rewards.\textsuperscript{21} Through a well-sorted selection of drugs and probably significant measurement points, compiled and selected by human experts, the data efficiency and thus the feasibility could be increased. Nevertheless, as in numerous other real-world scenarios, the readout may exhibit substantial variance, necessitating that the RL method demonstrates robustness to noise in the immediate reward.\textsuperscript{22}

In a subsequent step, the tumor markers found would have to be investigated for their transferability to \textit{in vivo} systems both non-clinical and clinical. For example, fast forwarding to clinical contexts, if a generalizable group of tumor markers could be found, it would be possible for an RL agent, in a small number of case studies with patients for whom other forms of therapy are not clinically useful (e.g. some cases of pancreatic cancer), to administer proven drugs (e.g. folic acid and methotrexate (MTX)) at “off-label” dose and frequency within known safety and toxicity boundaries, while monitoring the course of the disease, analogous to long-term administration in rheumatic diseases but in real-time. Such case studies would fall within the ethics and regulation of new non-validated practice\textsuperscript{16} and hence, if positive results were registered, clinical trials should follow.

![Diagram of two-track system](image)

**Figure 1.** Two-track system towards a medical device based on measurements from low-powered sensors monitoring the patient and delivering targeted cancer therapy in real-time.
Technical problems aside, ethical and regulatory aspects of this approach will remain unsettled. First, we must consider its social value. Of the 10 million cancer-related deaths in 2020, 70% occurred in low- and middle-income countries. On the one hand, this shows that any scientifically valid, safe, and effective AI-optimized cancer therapy has a promising social value not only for high-income countries (HICs) but especially for low- and middle-income ones (LMICs). On the other hand, this is also a challenge to our current way of developing health interventions. We may expect that, at least initially, such an AI-optimized cancer therapy would be costly and biased towards the context of development (e.g. leading cancer centers in urban areas of HICs). Therefore, questions of health equity and benefit sharing with LMICs will have to be addressed.

Second, we must examine the ethical aspects associated with clinical translation; that is, the process of combining AI and non-AI components of a health intervention to unlock its clinical utility. During this process, any harm caused by using AI interventions with poor or no adherence to good clinical and scientific practices, whether in innovative practice (e.g. case studies) or research contexts (e.g. clinical trials), will amount to undue harm to patients or research participants.

Third, there are questions regarding data capturing through implants and other medical devices. Privacy and consent are paramount here, as questions of liability in case of malfunction, wrong recommendations or adverse events.

Lastly, we should also mind governance issues. The scientific integrity of researchers, innovators, and organizations, in charge of developing an AI intervention for health, requires a sufficient level of both internal and external review and transparency, and a regulatory environment that finds the “golden mean” between laissez-faire and stifling innovation.

The purpose of this short communication was to introduce the long-term vision of an AI-optimized cancer therapy based on real-time adaptive dosing at the patient level. It is still far from reality, but it is nevertheless a feasible idea with practical implications since once the scientific community envisions a target, it is more likely to achieve it. We may remember that the insulin pump also seemed impossible when it was proposed. But it succeeded, and now its use is being approved in some countries, along with hundreds of other new AI-assisted devices.

A final point of resemblance between the automated insulin pump and this proposal concerns what is probably the most difficult change we must make in our
conception of cancer treatment. Ultimately, it may be necessary to reevaluate that curing cancer is the optimal goal in all instances. Instead, we should consider controlling the disease as the ideal solution for certain cases, which would amount to a paradigm shift in oncology.

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About the Authors

Gabriel Kalweit holds a PhD in machine learning from the University of Freiburg. Initially focused on fundamental reinforcement learning, his research now encompasses the entire spectrum of artificial intelligence, with a particular emphasis on advancing oncology. Dr. Kalweit has a dual appointment, serving both as a Postdoctoral Researcher at the Neurorobotics Lab, University of Freiburg, and as the Head of Fundamental AI Research at the Collaborative Research Institute for Intelligent Oncology (CRIION), Freiburg.

Luis L García Valiña is a philosopher and writer based in Buenos Aires, Argentina. With expertise in American pragmatism, political philosophy and ethics, he is currently interested in exploring the impact of artificial intelligence on medicine, society, and politics.

Ignacio Mastroleo is the Head of Philosophy of AI for Health at the Collaborative Research Institute Intelligent Oncology (CRIION), Freiburg, he is also Assistant Director of the Program of Bioethics, Instituto de Investigaciones Sociales de América Latina (IICSAL), Facultad Latinoamericana de Ciencias Sociales (FLACSO), Argentina and Researcher the National Scientific and Technical Research Council (CONICET), Buenos Aires, Argentina.

Anusha Klett is the Biology Research Team Leader at the Collaborative Research Institute Intelligent Oncology. She is part of a team working towards a vision of AI-optimised cancer therapy based on real-time adaptive dosing at the patient level. Originally from India, Anusha completed her Bachelor's degree in Microbiology before moving to Germany for her Master's degree. Her PhD in Biology focused on the molecular mechanisms of HSV-1-induced apoptosis.

Joschka Bödecker is the Scientific Director at the Collaborative Research Institute Intelligent Oncology (CRIION) and Professor at the Department of Computer Science, Universität Freiburg.

Prof. em. Dr. Dr. h.c. mult. Roland Mertelsmann, Chairman of the Board of the Mertelsmann Foundation.

Maria Kalweit (Huegle), is the Head of Applied AI Research at the Collaborative Research Institute Intelligent Oncology (CRIION) and postdoc at the Department of Computer Science, Universität Freiburg.