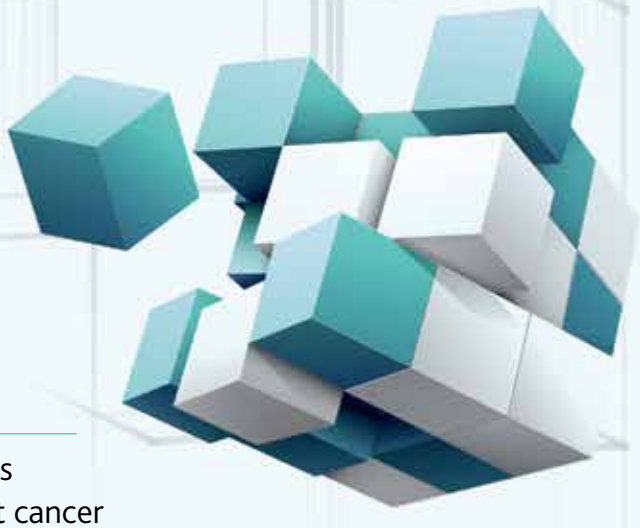
Why 1+1 is greater than 2



Dr Katarzyna Rejniak's collaborative research integrates mathematics, mechanics and biology in the fight against cancer

Can you begin by outlining what your lab does, and how your scientific background led you to work in this field?

My computational group is part of the Integrated Mathematical Oncology (IMO) department at the Moffitt Cancer Center, Tampa, USA. We use computer simulations to test various anticancer treatment strategies, including optimisation of drug properties and drug administration schedules. We are particularly interested in how the components of the tumour microenvironment (physical, chemical, cellular, and the interstitial fluid) influence drug penetration through the tumour tissue, and tumour cell response to chemotherapeutic agents.

We are developing so-called 'agent-based' mathematical models to account for tumour tissue cellular heterogeneity. Our models are also based on physical principles in order to investigate mechanical properties of individual tumour cells while they interact with stromal cells or exert forces to remodel the surrounding extracellular matrix.

My scientific background is in mathematics, computer science and bio-fluid dynamics. These different scientific areas allow me to think outside the box and integrate knowledge across the various fields, from solving mathematical equations, to the use of graph theory, computer graphics algorithms and database management techniques, to the methods of fluid-structure interactions and producing simulation movies. I use all of these tools in my current research on anti-cancer therapeutics, which we have named 'pharmaco-mechanics'.

How useful are your models for testing the comparative effectiveness of different cancer treatments?

One of our projects involves designing more optimal schedules for hypoxia-activated drugs. Standard chemotherapeutic agents only affect dividing cells, meaning that quiescent cells which reside in regions of low oxygen (hypoxia) remain viable, even if exposed to the standard drugs. A new class of drugs that become active in hypoxic regions is now gaining clinical interest, but they often have a very short lifetime, making it important to administer them in an optimal way to maximise their lethal effect against tumour tissues. Using our high-throughput simulations, we can test multiple schedule options in order to determine the optimal timing and dosing of the therapeutic treatment. These schedules will first be tested in mouse models by our collaborators at Moffitt, but once validated they will be used to design clinical trials.

Is this a growing area of research, or do you feel the field demands more attention?

The quantitative benefits offered by computational modelling are gaining attention and momentum. Mathematical oncology at Moffitt is now widely present, but we biomathematicians still have a fair amount of work to do to convince the broader biomedical community of what we can bring to the table. Computational experiments (simulations) can be performed relatively quickly and inexpensively. However, to be meaningful, these mathematical models need to be developed in a close collaboration with experimentalists or clinicians. Only mutual integration of experiments and simulations will be advantageous in the fight against cancer, and the discipline of biomathematics as applicable to cancer research will attain the same broad acceptance as both bioinformatics and biostatistics.

Do you think a greater awareness and understanding of computational methods is desirable for practising medics?

The high-throughput simulations offered by mathematical oncology are well-suited to the concept of personalised medicine, which is now at the forefront of clinical goals. Our group is already using specific histopathology images from mouse experiments to model drug penetration and efficacy, and to test optimal drug combinations and design the most effective drug schedules. My group goal is to apply this approach to standard-of-care data, such as tissue biopsies, which are routinely collected in the Moffitt clinic, in order to provide the patient with a personalised treatment plan.

Does the Moffitt Cancer Center provide a stimulating environment for collaboration? What are the current specific aims of the Institute?

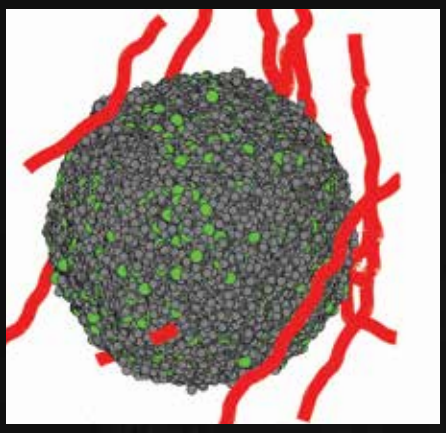
IMO was created five years ago by Drs Robert Gatenby and Alexander Anderson, as a part of Moffitt's mission to contribute to the prevention and cure of cancer. The word 'integrated' is there for a reason – the integration of various anti-cancer approaches and collaboration with different cancer laboratories is at the heart of our research. The Moffitt Cancer Center is also very supportive in providing institutional grant opportunities, and our group has been successful in competing for both the Miles for Moffitt and American Cancer Society Institutional Research Grant for two collaborative projects in sarcoma and pancreatic cancer, respectively.

Crunching cancer with digital drugs

Florida's **Moffitt Cancer Center** is home to an exciting collaborative research project that is using computational modelling to simulate tumour development and the dynamics of anticancer agents

AROUND 200 HUMAN cancers are known to exist, the causes of which are complex and diverse. While some cancers are benign, the invasive, malignant varieties account for an annual global mortality rate of approximately 8 million people – and this figure is growing. Characterised by unregulated cell division, the origins of cancer can be inherited or acquired and risk factors include diet, smoking and environmental pollutants. Recent years have welcomed exciting breakthroughs both in preventative strategies and the efficacy of existing therapeutics, and while a cure is, for the moment, beyond reach, the creative thinking that characterises various research projects around the globe is bringing fresh hope to millions.

Systemic chemotherapy is one of the main anticancer treatments used for most kinds of tumours that are clinically diagnosed. The efficacy of these drugs, however, can be hampered by the physicality of tissue structures which often impede the transport of therapeutic agents to tumour cells in sufficient quantities.



The microPD model for testing optimal administration schedules of drugs supplied through the vasculature (red) and their impact on a growing tumour (individual tumour cells: grey; proliferating cells: green).

This means that drugs that work well *in vitro* sometimes fail at clinical trial when confronted with the complexities of interstitial transport within the tumour microenvironment. However, researchers now believe that at least part of the solution may be found by using computer modelling to simulate the biophysical properties of tumour tissue, interstitial transport, drug properties and interstitial fluid flow, among others. These simulations are helping to improve knowledge of the dynamics of these complex interactions, creating opportunities to test tumour emergence and growth scenarios, as well as various types of therapy, *in silico*.

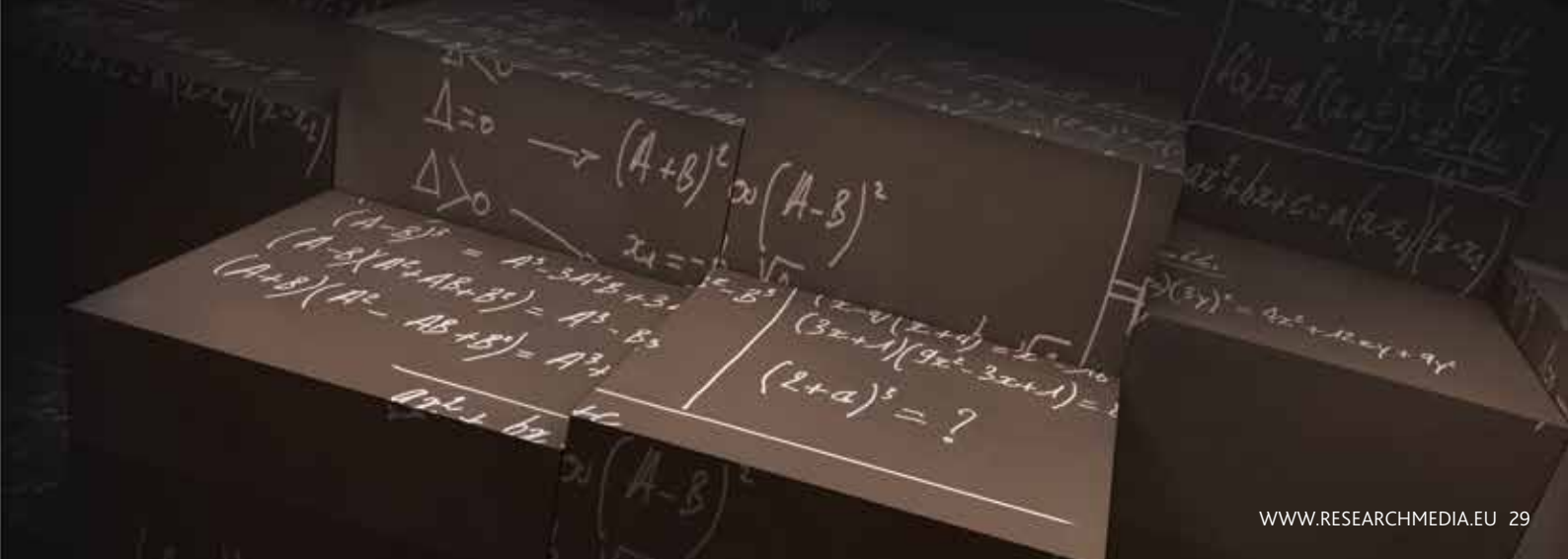
INTEGRATED MODELS

The Integrated Mathematical Oncology (IMO) Department at the Moffitt Cancer Center in Tampa, Florida, USA, is a vibrant environment that brings together scientists from diverse backgrounds and nurtures a broad range of cross-disciplinary projects oriented on employing mathematical models to understand tumour development and design new anticancer strategies. Based at the Center, Dr Katarzyna Rejniak is involved with computational modelling of tumour initiation, progression and treatment – a project integrating mathematics, mechanics and biology in the fight against cancer. Rejniak has developed a computational model known as IBCell (the immersed boundary cell method), which can accurately represent the structure of various soft tissues and the mechanical transformations that occur during their normal development and maintenance, as well as the aberrations that lead to cancers. "*In silico* simulations are well suited for exploring numerous combinations of model parameters which can be varied simultaneously in a controlled manner over a wide range of values," she outlines. "We can explore the whole spectrum of possible simulation results and identify factors which contribute significantly to a given problem."

Due to technical challenges and expense, broadly screening such a range of experimental conditions is rarely possible in laboratory experiments, but computer models enable hundreds of simulations, each with different cellular features, environmental factors and treatment protocols. IBCell has already been leveraged to simulate, for example, the development of epithelial cysts, ductal carcinomas and invasive tumours. It is a flexible model that can be adapted to represent the biomechanical properties of the particular tissue under investigation, and is particularly suitable for small tissue portions such as biopsy samples and experimental 2D and 3D cell cultures. Because the model is agent-based, each cell property can be individualised, allowing the researchers to track both intracellular changes and intercellular interactions. This versatility makes models such as IBCell ideal testing environments for patient-specific treatments.

BETTER THERAPEUTIC TRANSPORT

To understand the complexity of tumour progression and response to treatments, the *in silico* models are developed gradually, but it is relatively easy to incorporate new intracellular or extracellular features. The team is currently working on integrating additional microenvironmental factors into its models, such as extracellular matrix fibril structure, as well as including various metabolic profiles using tissue histology and immunohistochemical staining. Of particular interest is the construction of models of drug penetration within the human body. It is hoped this will lead to higher success rates when testing cancer drugs in clinical trials, as drugs that are potent in cell-culture assays do not always prove as successful in the clinic. Rejniak's group is in the process of developing a suite of pharmacodynamics models (called microPD) which investigate how various drug or biomarker molecules transverse tumour tissue. "Our biomechanical models can help determine properties of therapeutic compounds which



BIOMECHANICAL MODELS IN CANCER

OBJECTIVES

The process of designing effective anti-cancer treatments is complex, and requires collaborative efforts of researches from various disciplines. Biomechanical *in silico* models of cancer and its microenvironment provide a platform for simulating the growth of tumour cells in different tissues and their response to anticancer treatments. When integrated with the experimental and clinical data these quantitative tools can be used to design novel mechanism of drug action, optimal schedules of drug administration and quantitative criteria for clinical trials.

KEY COLLABORATORS

Dr Robert Gillies; Dr David Morse, Moffitt Cancer Center, Cancer Imaging and Metabolism Department

Dr Marilyn Bui; **Dr Damon Reed**, Moffitt Cancer Center, Sarcoma Program

Dr Diane Allen-Gipson, University of South Florida, College of Pharmacology

FUNDING

NIH/NCI Integrative Cancer Biology Program (Vanderbilt-Moffitt ICBP) • NIH/NCI Physical Science-Oncology Center Program (Moffitt PSOC) • Miles for Moffitt Milestone Research Award • American Cancer Society-Institutional Research Grant

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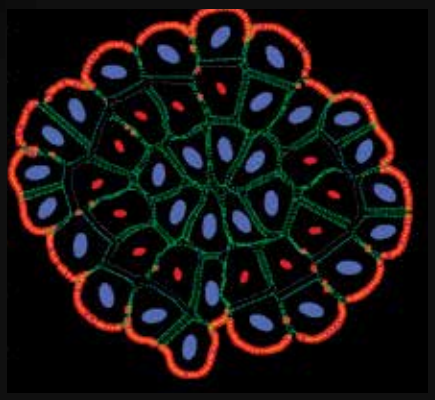
DR KATARZYNA A REJNIAK studied applied mathematics and computer science, gaining her MSc degree from the University of Gdańsk in Poland, and her PhD from Tulane University in New Orleans, USA. She was appointed as a postdoctoral researcher first at the Mathematical Biosciences Institute in Columbus, Ohio, and then at the University of Dundee, UK. Rejniak currently holds a faculty position at the Integrated Mathematical Oncology Department at the H Lee Moffitt Cancer Center & Research Institute at Tampa, Florida. Her research interests include cancer cell mechanotransduction, transition from normal tissue homeostasis to tumours, physical complexity of tumour cell/tissue environment, dynamical changes in tumour tissue metabolic landscape, systems biology of cancer.



A small colony of cells from a developing mammary acinus modelled using the IBCell model. Nuclear staining: blue-viable cells; red-apoptotic cells. Membrane staining: red-integrins; green-cadherins.

optimise their efficient interstitial transport, or aid decisions regarding the most effective drug combinations and scheduling protocols," she explains. "Moreover, mathematical modelling allows the bridging of laboratory experiments with clinical applications by providing a means of extrapolating *in vivo* results from mouse models to humans."

CAMPUS COLLABORATIONS

Modelling tumour growth and its response to treatments is not, however, without its challenges. The models usually involve various cell types and numerous environmental factors, and depend on multiple parameters. Thus, in order to keep biological reality of these mathematical models, it is almost mandatory to find an experimental ally and combine forces.

Rejniak's team collaborates with biologists, pharmacologists and clinicians both at Moffitt and the nearby University of South Florida. Sharing a campus has its advantages, providing the group with easy access to experimental and clinical data to help calibrate their models, and fostering joint efforts working around integrated approaches and experiment design to test model predictions. "We are very fortunate to work at Moffitt, which is not only a National Cancer Institute (NCI) Comprehensive Cancer Center, but a vibrant research institute with over 100 experimental laboratories," enthuses Rejniak. "We believe that only in close collaboration, where both *in silico* models and laboratory experiments inform one another, can new quantitative strategies be developed."

The group is participating in various collaborations, including an ongoing project with Dr David Morse modelling the efficacy of tumour-targeted biomarkers, which can be used both to monitor tumour response to treatment and in intraoperative fluorescence image-guidance, enabling real-time detection of tumour margins during surgery. The researchers are also working with Dr Robert Gillies on designing better administration schedules for hypoxia-activated drugs, and with Drs Marilyn Bui and Damon Reed in predicting how sarcoma tumours respond to standard-of-care chemotherapy. The models are currently in the testing phase but, once ready, will be used to design clinical trials.

TAILORED TREATMENTS

Over the last decade, cross-pollination of ideas across disciplines has become more pronounced and with the onset of the era of personalised medicine, looks set to be increasingly important. Oncology research has become more integrated not only in terms of the synthesis between mathematical modelling and cancer biology, but across different biological disciplines – genetics, intracellular signalling, mechanotransduction, cancer imaging and proteomics are all beginning to share data and mathematical oncology models are no longer merely an academic exercise, but can be calibrated with quantitative biomedical data to bring real-world, tailored benefits to patients with increasing immediacy. It seems likely that computational simulations of various treatment strategies, based on quantitative analysis of standard-of-care clinical data, will become an integral part of personalised medicine.

Despite the fact that most cancer research during the last years has focused chiefly on genetic factors, Rejniak believes that consideration of the mechanical aspects of tumour development and treatment will become increasingly important in new therapeutic strategies. "Tumour cells actually have to do a lot of physical work, displacing other cells in order to grow, adhere and pull on the extracellular matrix in order to move through the stroma," she reflects. "A closer investigation of the mechanotransduction of tumour cells may lead to novel therapeutics."