

Backstory

Interdisciplinary approaches to metastasis

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SUMMARY

Interdisciplinary research is making a significant contribution to understanding metastasis - one of the grand challenges in cancer research. Examples drawn from apparently unconnected areas of physics, and described at a recent workshop on metastasis, illustrate the value of interdisciplinary thinking.

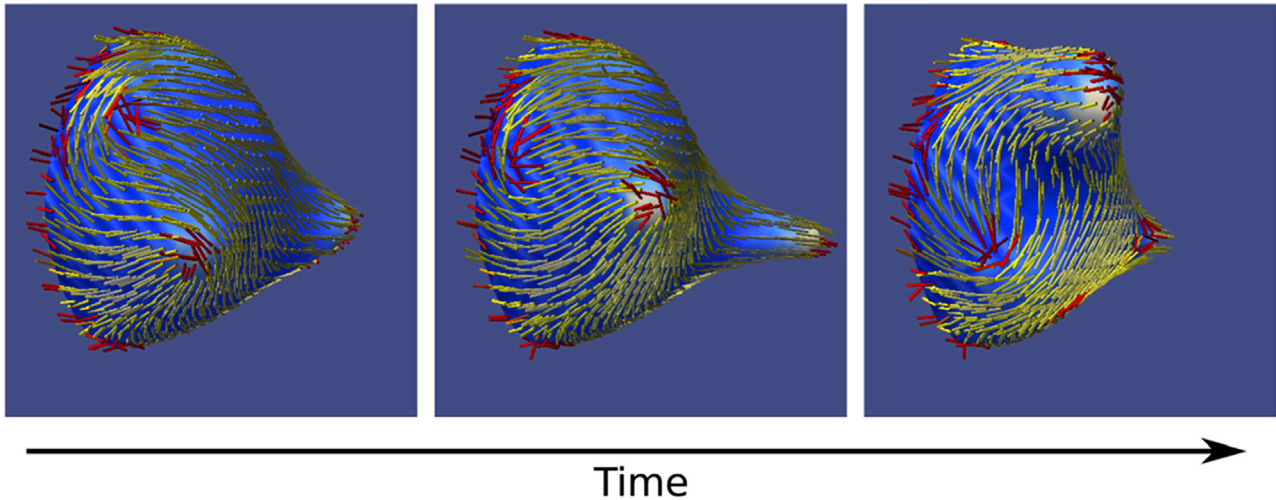
What is the rationale for promoting interdisciplinarity approaches to science in general and cancer research in particular?

Perhaps the simplest and most compelling answer is that metastases are the cause of death in 95% of cancer patients who die from the disease and the prognosis of patients with common (e.g., lung, breast, prostate, pancreas, etc.) metastatic cancer has changed little in the past 50 years. In treatment of metastatic prostate cancer, for example, Jemal et al. found that, despite the advent of multiple new treatments in the past decade, 5-year overall survival is lower in 2017 than in 1977 (PubMed PMID: 28376154; PMCID: PMC5409140). The need for an interdisciplinary approach emerges from increasing recognition of cancer as a complex, adaptive, dynamic system. For decades, cancer investigation has been highly reductionist, focusing on detailed molecular analysis of cancer cells, with the implied assumption that continual improvements in data acquisition would achieve some threshold at which full understanding would be achieved. This has not happened. Based on historical physical science experiences in converting large data sets to knowledge (e.g. Kepler and then Newton in defining planetary motion), it seems clear that active “systems-based” investigations are necessary to identify first principles and a comprehensive theoretical framework for understanding cancer biology. This approach could easily become hubristic, and it is certainly the case that neither the physical nor the biological sciences have a monopoly on identifying principles that underlie disease mechanisms (see, for example, <https://www.ukri.org/blog/understanding-the-physics-of-life/>).

From the outset, cancer treatment has been characterized by significant contributions from a wide range of disciplines, which extend beyond medicine and biology. For example, radiotherapy—still a mainstay of much cancer treatment—has its origins in the physics laboratories of more than century ago, while clinical imaging has a similar genesis and is a core element of cancer diagnosis and therapy. Remarkable advances

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Tentacle growth at a topological defect in a model active nematic (Figure 2C reprinted with kind permission from Metselaar et al. (2019))
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in molecular technology have produced enormous data sets which have certainly increased the understanding of biology of cancer, yet the slow progress in alleviating the personal and societal burdens of cancer suggests progress in deciphering the complexity of the disease is dependent on different disciplines working even more closely.

However, successful cross-disciplinary collaborations are challenging as biological sciences, which emerge from a tradition emphasizing description and classification, have in the past been separated by language and philosophy from the physical sciences, where the integration of mathematical methods into empirical investigations is the long-established research paradigm. Thus, achieving truly interdisciplinary investigations to address critical dynamics in cancer biology currently requires sustained time and commitment from diverse investigators to overcome these barriers.

Interdisciplinary approaches to cancer research

Promotion of interdisciplinarity is an increasingly prominent element of the strategies promoted by major cancer research funders—no aspect of cancer is entirely within the domain of a single specialism. For example, Cancer Research UK has a long-standing multidisciplinary award scheme which is delivered in partnership with the UK's Engineering and Physical Sciences Research Council (<https://www.cancerresearchuk.org/funding-for-researchers/how-we-deliver-research/our-research-partnerships/epsrc-working-in-partnership-to-deliver-multidisciplinary-research>), and many different disciplines are represented in the global Grand Challenge award scheme (<https://cancergrandchallenges.org/>). The US National Cancer Institute has a major interdisciplinary funding program—the Physical Sciences in Oncology (<https://physics.cancer.gov/>) which, perhaps significantly, includes a network of researchers from a wide range of disciplines engaged in research projects. There are numerous similar programs in Europe, including, for example, the wider Physics of Life program funded by the Dutch Research Council (<https://www.nwo.nl/en/physics-life-pol>).

The Rosetrees Trust also has a long history of promoting interdisciplinary research and is currently funding a Physics of Medicine network, which is embedded within a wider Physics of Life network funded by UK Research and Innovation (<https://www.physicsoflife.org.uk/physics-of-medicine.html>), briefly described in a previous Backstory (iScience 24, 102877, August 20, 2021).

Bringing scientists together

The core of the Rosetrees' program is a series of workshops each aimed at promoting interdisciplinary approaches to some of medicine's Grand Challenges. As a physicist working at the interface with medicine and biology, S.W.S. has found one of the most common problems encountered by colleagues in the physical and biological sciences is getting sustained engagement with the clinical research community. As a

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physician working at the same interface, R.A.G. has found absence of experience in complex biological and clinical studies, often leading mathematicians to underestimate the difficulty of performing such investigations and overestimate the accuracy of data obtained from them. Framing workshops and subsequent research in terms of clinical challenges is particularly helpful in drawing in the medical research community. One of the underlying principles of the Rosetrees' program, which is applicable more generally to interdisciplinary research, is to start discussions between disciplines by focusing on a clinical "grand challenge" and then considering how other disciplines may contribute to better understanding of the challenge, rather than starting with a particular scientific technique and hoping it may find application in medicine. In particular, clinical engagement helps ensure that techniques drawn from the physical and mathematical sciences are clinically relevant and biologically grounded.

Cancer research is replete with clinical and scientific challenges, one of which is how to better understand and treat metastatic disease, which poses a major hurdle to improving clinical outcomes, even with novel biological and immunotherapies.

Cancer metastasis: Lessons learned from interdisciplinary collaborations

A virtual workshop on metastasis, funded through the Rosetrees program and jointly organized with Cancer Research UK, was held in November 2021 (see <https://www.physicsoflife.org.uk/metastasis-workshop.html>). The workshop included many examples of collaborative research involving mathematics, soft matter and quantum physics, and molecular and cellular biology, with speakers from leading groups in the US, Spain, Italy, Germany, and the UK. Ongoing research described at the workshop provided vivid examples of how interdisciplinarity can play out in practice and a number of these are selected to illustrate the scientific insights gained by strong interdisciplinary working.

Kairbaan Hodivala-Dilke, Deputy Director of the Cancer Research UK Bart's Centre and a distinguished cell biologist (<https://www.bartscancer.london/staff/professor-kairbaan-hodivala-dilke/>), opened the workshop by framing the challenge of metastasis. This has also been set out in many articles, including a recent review by Fares et al. (2020), which builds on the wider and seminal work of Hanahan and Weinberg (2011), in which activation of invasion and metastasis is considered one of the key characteristics of tumor behavior. As Fares et al. (2020) note "The development of metastases requires cancer cells to leave their primary site, circulate in the bloodstream, endure pressure in blood vessels, acclimate to new cellular surroundings in a secondary site, and escape deadly combat with immune cells (Massague and Obenauf 2019; Maitra 2016)". These steps are mediated by a series of molecular and physical interactions, which govern the motility and plasticity of cancer cells. It is therefore not surprising that one of the fruitful areas for interdisciplinary approaches to metastasis is to consider chemotaxis, in which the orientation and movement of tumor cells are governed by external signals. At first sight, it may appear unsurprising that cells move along gradients in the concentration of particular chemicals. However, computational modeling and experimental observation by Robert Insall et al show that, when cells generate their own chemoattractant concentration gradients by breaking down chemical attractant locally, the results really are startling as it enables cells to navigate long and complex paths through tissue without making mistakes (Tweedy et al., 2020). This deceptively simple process is likely to be an important contributor to tumor spread and is a beautiful example of "simplicity from complexity" noted above.

The work also illustrates the value of mathematical modeling in biology, which is a characteristic feature of the broader Physics of Life.

Translating theory

One of the constant surprises in interdisciplinary research is how theories in one domain can apply to other fields; for example, soft matter physics is now a prominent source of new ways of looking at metastasis. Julia Yeomans' group in the Physics Department at Oxford has a long-established program of research in active matter, which is distinguished from passive matter by its continuous use of energy from the surroundings. In particular, the study of active droplets shows that a wide variety of different droplet shapes are predicted, assuming a simple active stress mechanism (Ruske and Yeomans 2021). These shapes arise from the existence of active turbulence—a key feature of active droplets—with strong vorticity and dynamic topological line defects, which are created and destroyed. Ruske and Yeomans note that the interplay between these processes can produce finger-like protrusions—"budding"—in the droplet, akin to the emergence of bud-like tips seen in Hydra (Maroudas-Sacks et al., 2021) and moving groups of cancer cells during tissue

invasion. This suggests that the theory, which successfully explains the morphology of active droplets, may also be relevant to the dynamics of tumor shape.

Understanding the processes that govern the shape of tumors may, at first sight, seem to have limited immediate clinical relevance. The work of Victor Perez-Garcia et al from a wide range of disciplines (Perez-Garcia et al., 2020) used tumor imaging and metabolic data from different cancers to show that tumors obey a so-called superlinear scaling law of the form $Z = \alpha V^\beta$, where Z is a measure of tumor metabolic activity, V is a measure of tumor volume, α is a rate constant, and β represents the scaling exponent (West et al. 1997). $\beta \sim 1.25$ (hence “superlinear”) for growing tumors, in contrast with $\beta \sim 0.75$ (sublinear), which characterizes the relationship between body mass and metabolic rates for a wide range of species (Kleiber 1932). The significance of the value of β was beautifully shown by the analysis of Perez-Garcia et al who used a nonlocal Fisher-Kolmogorov equation to show that if the tumor comprised a single clone, it would display sublinear growth dynamics, but if the tumor contained several different clonal populations, it would demonstrate superlinear growth as the fitter clones grew preferentially. The explosive growth associated with a superlinear scaling law is often a precursor to metastasis, and thus, the volume growth exponent may become a measure of potential lethality. The same concepts, when applied to brain metastases, may allow genuine tumor relapses to be differentiated from inflammatory reactions to radiation therapy, providing key information for the clinical management of the disease (Ocaña-Tienda et al., 2022).

Having shown that perspectives from the physical sciences can provide real insights into the dynamics of tumors, the workshop also included examples of where interdisciplinary approaches are proving valuable in improving therapies for metastatic disease. A particularly powerful example was provided by the work of Gatenby et al at in a broadly interdisciplinary team (including 9 mathematicians and 2 evolutionary biologists) at the Moffitt Cancer Centre in the US, who are leading the development of evolution-based therapies for cancer. One strategy (termed “adaptive therapy”) build on the well-recognized role of evolutionary dynamics in the growth of tumors (Michor et al., 2004) by developing mathematical models of tumor clonal dynamics during drug therapy. These models are similar to those developed to describe predator-prey population dynamics in ecology, describing the development of the resistant clones in the tumor, while assuming that resistant clones tend to be suppressed initially by their interactions with the treatment-sensitive clones (Cunningham et al., 2020; Thomas et al., 2018). The models are used to inform an adaptive treatment regime in which drug therapy is stopped when a prespecified tumor response is seen—in the case of metastatic castration-resistant prostate cancer, this is a given reduction in the level of prostate-specific antigen (PSA)—and only resumed when the PSA level reaches a threshold level. Unlike conventional drug regimens that administer drugs at maximum tolerated dose continuously until progression, the adaptive regime reduces treatment application to maintain tumor control without accelerating the emergence of the resistant clones. A clinical trial of this approach in metastatic castration-resistant prostate cancer has shown real promise (Zhang et al., 2019) and, crucially, has also shown how longitudinal trial data can inform model parameters and that subsequent simulations applied to each patient in the trial can provide novel insights into the underlying evolutionary dynamics led to the observed outcomes.

“Interdisciplinary approaches are key to making real scientific progress, not least in addressing the truly grand challenge—to develop an integrated understanding of life from single molecules to systems biology.”

The work on adaptive therapies at the Moffitt Cancer Centre is based on a deep understanding of the role of Darwinian selection in tumor development. Given the central role that clonal selection plays in tumor dynamics, cancer therapy would greatly benefit from the ability to control the evolutionary trajectory of a tumor. At first sight, given the stochastic nature of clonal mutations and the strong sensitivity of complex dynamic systems to initial conditions, this would appear to be unachievable. However, the work of Michael Hinczewski et al (Iram et al., 2021) is a superb example of how a truly interdisciplinary approach can offer a potential solution to a seemingly intractable problem. Drawing on an approach developed to steer a quantum system through a particular set of quantum states—counterdiabatic driving—the group have shown that it is possible to control the speed and distribution of evolutionary trajectories of a tumor by varying the concentrations of therapeutic drugs. If realized in the clinic, this approach would have very significant consequences for cancer therapy.

Future perspectives

From the perspective of the physical sciences, living systems use information and energy to maintain a stable low entropy state while far from thermodynamic equilibrium. Although unique in nature, the complex dynamic systems that form life, including cancer, must fundamentally obey the first principles of physics which, in turn, produce the evolutionary first principles of biology.

The examples given above demonstrate the value of interdisciplinary science more widely and I hope they also demonstrate that being alert to the wider implications of a technique or tool can lead to some remarkable science. [Brown et al. \(2015\)](#) have rehearsed five underlying principles which support the development of interdisciplinary research, while these are developed for medicine in particular in an article by [Smye and Frangi \(2021\)](#).

Perhaps the most authoritative and comprehensive recent review of the Physics of Life is that published by the US National Academies (2022), which is replete with recommendations aimed at promoting the development of interdisciplinary approaches to the science, including ensuring that funding mechanisms and academic career development reflect the importance of this vibrant and intellectually demanding area.

Given that the ultimate justification for the promotion of interdisciplinarity is that it leads to better science, it is pleasing to see that journals increasingly recognize this even if different fields are still highly variable in their engagement with different disciplines ([Van Noorden 2015](#)). The development of this open mindset in early career researchers (ECRs) in particular is an important element, and the role of interdisciplinary networks in promoting opportunities for informal cross-discipline discussions is also central. S.W.S.'s experience with the Rosetrees/UKRI Physics of Life and Medicine workshops, held virtually during the pandemic, is that the various online platforms have been able to support these discussions to a surprising degree. Some ECRs find such platforms easier to use as a means of opening debate with senior researchers, though others miss the informal "water cooler" moments that arise during in-person meetings. Other approaches designed to promote interdisciplinary thinking in the ECR community engaging in the Physics of Life network include the provision of summer schools, promotion of interdisciplinary resources, bursaries, funding for sandpits and placements—for example, see <https://www.physicsoflife.org.uk/early-career-researchers.html>. In the UK, the ambition and excitement generated by the recent announcement by UKRI and the Wellcome Trust of nine major awards funded by the £18m Physics of Life Strategic Priorities Fund—<https://www.ukri.org/news/using-physics-to-transform-our-understanding-of-life/>—will also be an important driver of engagement between different disciplines.

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Conclusions

Understanding metastasis is only one challenge in cancer biology, which, in turn, is only one facet of the Physics of Life. The US National Academies (2022) report on Physics of Life notes that:

This report argues that breadth is an essential part of the excitement in biological physics. The physicist's approach to understanding the phenomena of life is yielding fascinating results in contexts ranging from the folding of proteins to the flocking of birds, from the internal mechanics of cells to the collective dynamics of neurons in the brain, and more. We see glimpses of the sorts of unifying ideas that we hope for in physics, cutting across this huge range of scales. At the same time, each of these problems also connects to a larger community of biologists, sometimes reaching as far as applications in medicine and technology ... ([National Academies of Sciences, Engineering, and Medicine, 2022](#)).

Interdisciplinary approaches are key to making real scientific progress, not least in addressing the truly grand challenge—to develop an integrated understanding of life from single molecules to systems biology. This is an immensely compelling prospect, worthy of as much attention as the Higgs boson, quantum computing, or the search for dark matter. Different and previously disparate areas of science are now

converging on this challenging area and the prospects of making significant advances are very promising. In short, this a field with a truly exciting future.

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AUTHOR CONTRIBUTIONS

S.W.S. led the organization of the Workshop on which this article is based (see above) and wrote the original draft. R.A.G. gave a keynote lecture at the Workshop and reviewed and edited the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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