OPINION

Integrative mathematical oncology

Alexander R. A. Anderson and Vito Quaranta

Abstract | Cancer research attracts broad resources and scientists from many disciplines, and has produced some impressive advances in the treatment and understanding of this disease. However, a comprehensive mechanistic view of the cancer process remains elusive. To achieve this it seems clear that one must assemble a physically integrated team of interdisciplinary scientists that includes mathematicians, to develop mathematical models of tumorigenesis as a complex process. Examining these models and validating their findings by experimental and clinical observations seems to be one way to reconcile molecular reductionist with quantitative holistic approaches and produce an integrative mathematical oncology view of cancer progression.

Mathematical modelling of cancer is not new. It goes back over half a century, but experimental biologists have largely ignored it. Today, there are compelling signs of renewed interest[1,2]. What has changed? First, in a broad sense, the discipline of systems biology, of which mathematical modelling is a part (BOX 1), has been widely embraced. Second, there are several key developments, both theoretical and biological, that are distinctively applicable to cancer research and which collude to provide an environment ripe for the mathematical modelling of cancer.

Mathematics and cancer biology
Recent mathematical advances have made it more feasible to model cancer from a mathematical viewpoint. For example, we now have individual-based modelling techniques that better represent the behaviour of cancer cells. These include hybrid models that combine the benefits of discrete and continuous modelling techniques and describe, in a single model, chemical reactions and tissue landscapes. Importantly, multi-scale models have been developed that can capture interactions across different spatial and temporal scales and bring together disparate components of complex systems, including cancer. As these models have developed, the wish to view cancer

from a different vantage point has grown. For example, linear thinking and molecular reductionist approaches, although enormously successful at taking the gene-centric era to fruition, show frustrating limitations at explaining cancer as a complex process. In addition, the capacity to gather experimental or clinical cancer data has grown enormously, to a level that makes the biology inherent in the data difficult to grasp. Such key developments in separate disciplines can address fundamental questions in cancer with novel quantitative tools if merged in a new discipline, integrative mathematical oncology (IMO).

Defining the precise nature of the questions that IMO can tackle requires team science, spirit and constant dialogue between mathematicians and cancer biologists. In our experience, IMO gradually creates a common language that on the one hand enables mathematicians to understand the biology, explain complex mathematics simply and build relevant realistic models, and on the other hand empowers cancer biologists with sufficient mathematical literacy to frame experiments in the context of quantitative models, transposing qualitative hypotheses into quantitative ones. We submit that this emerging discipline will be studied by a diversity of approaches and will be fertile ground for key advancements in both cancer

biology and mathematics. It is also apparent that IMO will not only encompass mathematicians and biologists, but will also need the insight and skills of pathologists, clinical and surgical oncologists, and preclinical and clinical imaging and computer visualisation scientists, to name a few.

Mathematical models of cancer
Traditionally, mathematical models of cancer fall into two broad camps: descriptive and mechanistic. Descriptive models tend to focus on reproducing the gross characteristics of tumours, such as size and cell number, and are generally used to investigate tumour cell population dynamics, without emphasis on cell biological detail[3,4]. By contrast, mechanistic models focus on specific aspects of tumour progression in order to explain the underlying biological processes that drive them[3,5]. These are clearly extreme views of both camps and in reality there are shades in between. The important point is that for a model to offer something useful to a biologist it must be mechanistic to a significant extent.

Although mathematical modelling can be used, if desired, to capture fine mechanistic details of a process, its real power becomes apparent when used to relate multiple components of a complex process to extract fundamental behaviour (FIG. 1). By definition, a complex process is one whose components (possibly complex processes in their own right), by interacting, produce emergent properties that they themselves do not posses individually. That is, the whole is more than the sum of its parts. Emergent properties are often impossible to infer intuitively, certainly not in quantitative terms. Cancer progression is one such complex process — genes interact to produce gene networks, these produce signalling networks that produce cells and these produce tissues, and so on to higher biological scales (FIG. 2). Genes do not have the same properties as cells, though they ultimately cause the emergence of those properties. What is now becoming apparent is that in order to represent cancer progression quantitatively, one needs to integrate multiple processes on multiple scales (FIG. 2). Mathematical modelling is an ideal tool to unveil the fundamental principles governing cancer progression from the molecular

The answer is a resounding yes, if systems biology (SB) is intended as the discipline that 'puts it all together' when analysing biological complex systems. Yet it is only of late that mathematical modelling (MM) is slowly entering the ranks of SB, side by side with bioinformatics, computational biology, high-throughput and data-driven systems approaches. Why the delay? One explanation is sociological: appreciating benefits of MM to current biology requires hard labour. In a nutshell, MM translates qualitative hypotheses into quantitative models directly comparable with experimental data by the process of validation. Although the massive, intuition-defying datasets of modern, 'omics'-dominated biology are obvious material for MM, the process of translation is far from automatic: it requires painstaking, laborious exchanges between experimentalists and mathematicians to reconceptualize a living system in terms of its essential components. A common language must emerge, down to nit-picking clarification of word usage, in consciousness-raising communication efforts sprinkled with "ahh" moments. This time investment is a challenge for busy experimentalists, and mathematicians can sometimes be demotivating if they model living systems purely for the pleasure of mathematical analysis, rather than the goal of biological insight.

Another explanation for the delayed entry of MM into the cohort of SB disciplines is structural: MM directly challenges molecular reductionism, the dominant mode of current biology (albeit also complementing it)[28]. The molecular reductionist view that living systems can be understood in terms of their component parts[29] has produced spectacular advances and changed biology forever. In a natural extension, bottom-up, high-throughput data-driven approaches are the darlings of SB. On the contrary, MM, particularly in its multiscale version (MMM), has strong requirements for top-down views: a living system is more than the sums of its parts — it acquires emergent properties that its individual components may not have[30]. Predicting and explaining these often counterintuitive properties in terms of underlying components is the business of MMM: a reincarnation of holism, its mystical and metaphysical overtones[28] extirpated and replaced by a quantitative inner structure (quantitavive holism, or 'qolism'). Should experimentalists look at biology through 'mathematical spectacles', pay attention to formal theory, think multiscale? It is worth a try, as the pay-off might be huge: insightful multiscale mechanistic descriptions of living systems in a universal language (FIG. 1) that define essential relationships between datasets, however large and complex. Producing the right synthesis of qolistic approaches, such as MMM, with molecular reductionism will advance an SB view of cancer. It is a challenge for cancer biology and mathematics, a sort of cancer evo–devo (broadly, a combination of genetics, development and evolutionary theory)[31] that should launch explorations in exciting directions for both fields.

scale all the way to the population level. Its potential for affecting our understanding of cancer is extensive (BOX 2).

So, how is it done? Are there tangible examples of novel insights into cancer progression produced by mathematical modelling? How is this tool applied? What indications do we have that we are indeed on a viable track? Does the pay-off justify experimental and clinical cancer researchers 'embracing the horror' of equations and calculus? A conservative view is that it is too soon to tell. In these early days opinions vary widely[6]. Reporting our experience might provide insights that are useful to others, as well as material for discussion.

Cancer invasion: emergent behaviour
The transition from non-invasive to invasive forms of cancer is the major issue that our IMO group (see website in Further information) is addressing. To explore this issue we have used several distinct mathematical modelling approaches that share a common aspect: the cancer cell is their fundamental unit (individual-based models, see BOX 2). This might seem an

obvious choice as the cancer cell also appears to be the fundamental unit of cancer research. However, on closer inspection, this choice is not so simple. To understand this statement, it is necessary to briefly consider the concept of biological scales.

A cell can be viewed on many different scales. It can be considered as a collection of genes, or of signalling networks, or of subcellular organelles, or of phenotypic traits (FIG. 2). These scales are intimately connected, as genes ultimately define phenotypic traits. By and large, molecular genetics and molecular biology have been the most productive avenues of cancer research in the past three decades, producing significant advances. The genetic or molecular scales might therefore appear to be the logical places to start modelling cancer, owing to the enormous wealth of data available for testing and validating model predictions. Indeed, there is an abundance of exciting efforts aimed at models of gene and signalling networks in cancer[7–9]. Crucially, however, there is a widening information gap that remains to be filled — how genes and molecules specify the behaviour of a cancer cell. This is aptly described as

genotype-to-phenotype mapping, a complicated problem that itself will probably require novel mathematical approaches to vanquish. This mapping is not one-to-one, in that one gene does not produce one phenotype, but is more likely to be a many-to-one mapping or even a many-to-many mapping. Solving this mapping problem is highly desirable, because it makes it possible to predict cell behaviour mechanistically in terms of its molecular components (similar to the use of statistical mechanics in physics (see Statistical mechanics in Further information)). We will discuss a possible modelling approach that addresses this problem later. In the meantime, our choice of the cancer cell as the main individual acting in our models bypasses the need to wait for the solution of the genotype-to-phenotype problem. However, this compromise makes it more challenging to populate the models with experimental data (model parameterization), as explained below.

The hybrid discrete continuum model
In the remainder of this article, we will exemplify the mathematician–experimentalist synergy required for IMO by discussing results from our hybrid discrete continuum (HDC) model[10] and, briefly, one other model that we are developing[11]. As in biological systems, the *in silico* cell in the HDC model can perform fundamental intrinsic core processes, specifically ones known to drive cancer invasion. As we reported recently[1], the HDC model has great predictive power, even though these core processes are not specified in molecular detail. Such molecular details could be incorporated at a later date to refine the effects of particular core processes (such as the cell cycle, or cell–matrix interactions), owing to the open multiscale architecture of the HDC model (see below). In fact, current HDC model predictions have indicated molecular processes that are in need of better specification and/or parameterization.

In the HDC model, we further focus on the interface between cancer cell phenotype and microenvironment. Again, this captures a biological reality, because the interaction between the cell and its microenvironment is known to have a crucial role in cancer progression[12]. Therefore, in the model we represent cells as points on a lattice that represents the tissue microenvironment (FIG. 3). Each *in silico* cell has a phenotype that comprises a set of traits that include, but are not limited to, proliferation, migration, adhesion and nutrient consumption. By representing the microenvironment as a lattice on which

cells grow and interact, we can implement multiple environmental factors such as density of extracellular matrix (ECM) and the concentrations of nutrients and proteases. How these factors change over time on the lattice is then defined by a set of mathematical equations (FIG. 1).

Overall, the HDC model provides a framework for quantitative analyses of cancer progression and is endowed with an intuitive link between *in silico* and real-life cancer biology, as discussed in the next section.

How can one represent in silico *cell behaviour in this lattice microenvironment?* Each cell is defined by a life cycle that is driven by its phenotype (a collection of traits quantified by coefficients). The cell life cycle describes how each cell lives and dies and, crucially, accumulates trait 'mutations' on the lattice microenvironment. Mutation in this context is defined as changes in the trait coefficients that define a cell's phenotype (FIG. 3). We can now run simulations to see how these cells behave in several distinct circumstances. For example, if trait mutation is not allowed (that is, the initial phenotypes, or trait coefficients, are fixed), cell growth is limited by whether or not a specific phenotype can exploit the tissue microenvironment (A.R.A.A., unpublished data). Conversely, if trait mutations are allowed, the simulation now behaves as an evolutionary process whose outcome cannot easily be grasped intuitively, but emerges as a result of phenotypical competition within a set of microenvironment selective forces. For instance, this evolutionary process may produce tumours with invasive morphology dominated by the most aggressive phenotypes, if it occurs within a harsh microenvironment asserting a strong selection force (FIG. 4, Supplementary information S1, S2, S3 (movies)).

In the HDC simulations, an invasive tumour is characterized by a morphological change from smooth towards fingering margins. Coupled with the development of necrotic areas, the fingering effectively results in the fragmentation of the primary tumour into several independent invasive nests. In real life, such fragmentation is usually an indication of a high-grade tumour as determined by the TNM system[13]. By coupling several microenvironment and cancer cell variables, the HDC simulations provide a mechanistic view of their relative importance in producing invasive outcomes. It is important to underscore that the determining factor of such invasive outcomes is not the property of individual cells (the invasive phenotype), as cells with equally aggressive phenotypes may
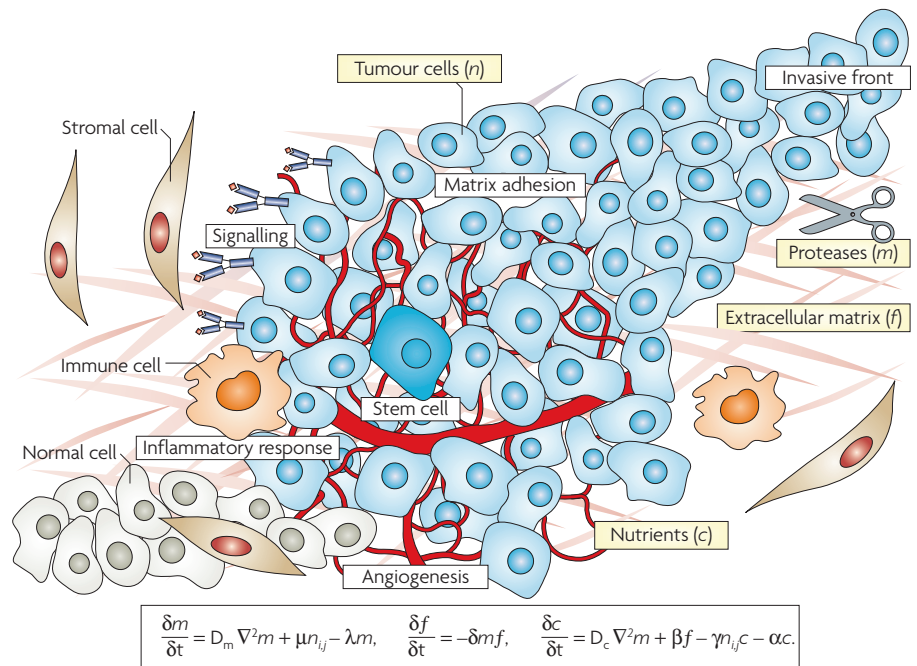

Figure 1 | **Mathematical models and multiple processes.** Cancer is a complex process bridging several spatial and temporal scales and involving many different cell types and processes: stem cells, tumour cells, stroma, inflammatory response, proteinases, angiogenesis, invasion and metastasis, to name but a few. All of these interact in a complex manner to orchestrate cancer growth and progression. Mathematical models offer one way of bringing together multiple processes that bridge scales in quantitative manner. Highlighted in yellow are the subset of variables that we consider in the hybrid discrete continuum (HDC) model, with proteinases (m), extracellular matrix (f) and nutrients (c) being modelled as continuous concentrations through a system of partial differential equations (show below figure) and the tumour cells ($n_{i,j}$ — a tumour cell is located at grid location [i,j]) being modelled as discrete individuals driven by the movement rules (P_0–P_4) as defined in FIG. 3. Proteinases are assumed to diffuse at a rate D_m, be produced by the tumour cells at a rate μ and decay at a rate λ. Extracellular matrix is degraded at a rate δ, proportional to the amount of matrix and proteinases available. Nutrient diffuses at a rate D_c, is produced at a rate β, is consumed by the tumour cells at a rate γ and decays at a rate α.

$$\frac{\delta m}{\delta t} = D_m \nabla^2 m + \mu n_{i,j} - \lambda m, \qquad \frac{\delta f}{\delta t} = -\delta m f, \qquad \frac{\delta c}{\delta t} = D_c \nabla^2 m + \beta f - \gamma n_{i,j} c - \alpha c.$$

or may not produce invasive tumours in the HDC simulations. Rather, the determining factor belongs to the microenvironment: under harsh conditions (strong selective forces are at play, such as hypoxia, low nutrients, difficult to negotiate ECM densities, low growth factors and lack of vascularity) cells collectively behave as invasive; by contrast, cells with similar individual phenotypes do not invade under mild conditions with little or no selection (FIG. 4). This HDC prediction is counterintuitive and is worth validating experimentally because, if correct, it would be a novel insight into the dynamics of cancer cell–microenvironment interactions. Intriguingly, the HDC simulations suggest that the microenvironment has more of a selective than a regulatory effect on invading cancer cells, particularly as conditions become harsh for cell phenotypes. This is rather distinct from the conventional view that the microenvironment is a supporting infrastructure for cancer cells[12].

Unlike histological pathology, which deals with cancer as two-dimensional slices through a three-dimensional tumour, the beauty of mathematics is that models defined in two dimensions can easily be translated to three dimensions, computational power constraints notwithstanding (BOX 2). FIGURE 5 shows results from a full three-dimensional simulation of the HDC model in a harsh microenvironment and displays a more or less spherical morphology with a rough surface. This roughness reflects invasive morphology, as can be appreciated more clearly from the animated sequence of slices through the full three-dimensional structure (Supplementary information S4, S5 (movies)), and agrees well with the equivalent two-dimensional simulations (FIG. 4). It should be noted that this simulation took several days to run on a Dual Core G5 Mac computer, as opposed to 1 h for two-dimensional runs.
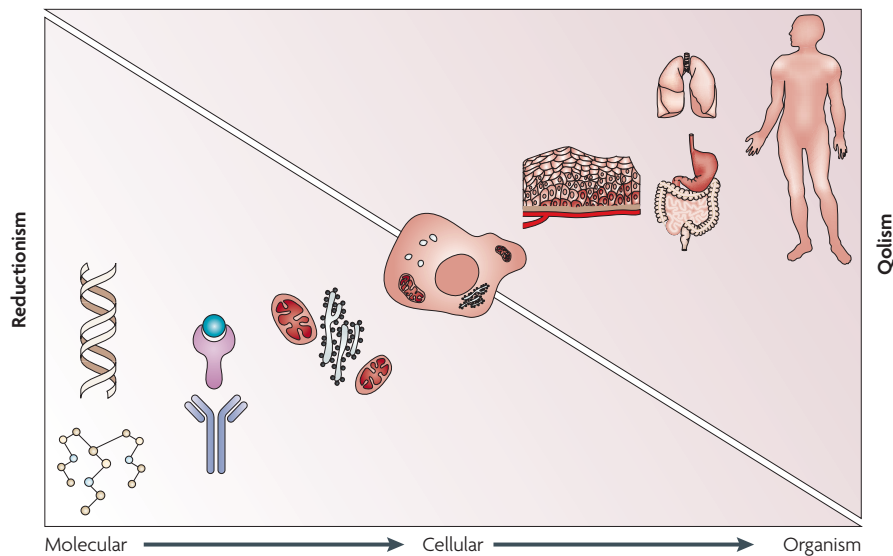
PERSPECTIVES

Figure 2 | **Cancer is multiscale.** Changes at the genetic level lead to modified intracellular signal-ling which causes changes in cellular behaviour and gives rise to cancerous tissue. Eventually, organs and the entire organism are affected. We propose that a focus on the cell as the fundamental unit of cancer naturally links molecular reductionism with quantitavive holism (qolism) (BOX 1).

the current invasive phenotype paradigm, in which invasion is the culmination of a linear cancer progression process.

There are at least three implications from these hypotheses and predictions that are relevant to the message of this Perspective. First, this is an excellent example of what mathematical modelling has to offer to cancer research: it is self-evident that this type of insight is difficult to produce and, perhaps most importantly, to validate, unless such quantitative systems approaches are used. Second, the simulation result points to experiments that would not otherwise be conceived. In fairness, clonal competition experiments between cancer cells were conducted in the 1980s[15], but assessing the relevance of this process in the absence of quantitative computer simulations was diffi-cult and the research was abandoned. Third, it exposes a gap in our knowledge, theoreti-cal and experimental, of the mechanics and dynamics of cancer evolutionary processes.

Selective forces in the microenviron-ment are known to exist, but they are not characterized in quantitative details, perhaps because their crucial importance in the specifics of cancer progression is not appre-ciated. The behaviour of cells in response to these forces is also not difficult to accept, but again their potential to determine widely diverging outcomes is difficult to grasp intuitively. We submit that modelling

HDC model: biological implications

At the moment, the HDC simulations are entirely theoretical, and we are just complet-ing a first round of experimental testing. It is nonetheless worth discussing their implica-tions for a theory of cancer invasion, as the simulations are the result of a model built on mathematical foundations[10] rooted in biologically reasonable assumptions.

In a concise sense, the HDC model pre-dicts that cancer invasion is best explained in terms of the struggle between cancer cell phenotypes. At first glance, this appears to be not particularly novel, because the concept of clonal selection during cancer progres-sion has been accepted for decades[14]. What is fundamentally new, however, is that the HDC model predicts that cancer cells form an invasive tissue because they are compet-ing with each other, as opposed to invading as a consequence of mutations in key genes or a faulty signalling network, or because of intervening regulatory microenvironmental factors (see next section). When competi-tion for resources or space becomes tough (harsh microenvironment), better adapted phenotypes win the competition and grow in an invasive pattern. If competition is low or absent (mild microenvironment), then similar, well-adapted phenotypes evolve but coexist with lesser adaptive ones and form a smooth-margined tumour.

Put another way, the HDC simulations lead to a novel hypothesis: a tumour is composed of individual cells, but it is their collective, rather than individual behaviour

that determines the invasive property of the tumour. The HDC model is able to capture this emergent property because of its intrin-sic multiscale nature: the tumour is repre-sented as a population of individual cells, and invasion is an emergent property of the collective behaviour of this population at the tissue scale (FIG. 3). This is an alternative to

Box 2 | **Mathematical modelling of cancer: a brief overview**

There is a long tradition of mathematical models of tumour growth, ranging from simple temporal population dynamic models to full three-dimensional spatiotemporal models (see REF. 3 for a review). Over the past 10 years or so there has been a rapid growth in deterministic reaction–diffusion models that explicitly consider the tumour as a single continuous density varying in both space and time. Generally these have been used to model the spatial spread of tumours in the form of one-dimensional invading waves or as two-dimensional patterns of cancer cells[2,32–42]. Other numerical approaches have been considered[43–45] but these still treat the tumour as a continuous mass. Although all these models are able to capture the tumour structure at the tissue scale, they fail to describe the tumour at the cellular level. The development of single-cell-based modelling techniques provides such a description and allows one to easily model cell–cell and cell–microenvironment interactions (see REF. 5 for a review). Several different individual-based models of tumour growth have been developed recently, including cellular automata models[1,10,11,46–53], Potts models[54–56], agent-based models[57] or lattice-free models[58,59]. Many of these models are also hybrid by definition and couple the advantages of individual-based models, representing cells, with continuous reaction–diffusion models that better represent environmental variables such as nutrients or tissue. Such hybrid models also allow one to link multiple models across multiple spatial scales, from genes to organ. The ability to bridge scales makes them ideal for cancer modelling as they effectively compartmentalize each scale and allow processes to bridge these compartments[10,11,45,46,54,57,59]. Therefore, these so-called multiscale models are far more accessible to the biologist both in terms of understanding and in terms of experimental validation.

Mathematical models of cancer are often complex and are unlikely to be amenable to standard mathematical analysis and therefore are nearly always solved by means of computational solution. Such computational solutions, either numerical or simulation-based, require a great deal of computing power (especially three-dimensional models, FIG. 5), which has only recently become widely available. It seems clear that we are now seeing the emergence of computational models as the dominant tool in mathematical models of cancer.

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approaches are in fact ideal to characterize these interactive responses, precisely because of their intrinsic ability to address multiple variables over multiple biological scales and connect chemical or physical details of the microenvironment (such as nutrient or ECM constraints) with behaviour at the cellular scale and, most importantly, tissue scale, at which invasion actually happens.

In summary, a cell-based mathematical model exposes the core mechanisms driving cancer progression. The HDC model prediction that cancer cell phenotypes realize their invasive potential by enhanced survival in harsh microenvironment immediately evokes a mechanism of Darwinian natural selection. In the next section, we discuss how close this apparent resemblance is, and possible experimental ways to test its boundaries in the context of current experimental knowledge.

Interfacing with current cancer biology

Placing mathematical models in the context of current schools of thought in modern cancer biology is a key determinant for the success of an IMO group. A dominant school of thought in cancer biology is that cancer is a genetic disease caused by the accumulation of random mutations in oncogene and tumour suppressor gene networks, and that these mutated genes spread through a cancer cell population because they confer a growth advantage[16]. This view emphasizes the occurrence of mutations in cancer-causing genes (mutation pressure) as the mechanism that drives progression. By contrast, the HDC model indicates that at the core of cancer progression lies an evolutionary and adaptive process, and that mutation rates are only one parameter of this process. Put another way, in the HDC model mutation pressure, no matter how high, cannot drive cancer invasion in the absence of a selective process. That is not to say that HDC predictions are inconsistent with or ignore somatic cell mutation rates of cancer-causing genes. On the contrary, the HDC can maximally exploit the empirically determined mutation rates and model their effect on selective and adaptive processes quantitatively, provided they are mapped experimentally to cellular phenotypes. Of course, this is not trivial, because the mapping of genotype to phenotype is not one-to-one, as discussed above. This disconnection between genotype and phenotypical traits means that a given phenotype may be generated by a variety of gene cartels, vastly complicating the interpretation of experimental analyses. Nonetheless, the pay-off of this complex experimentation
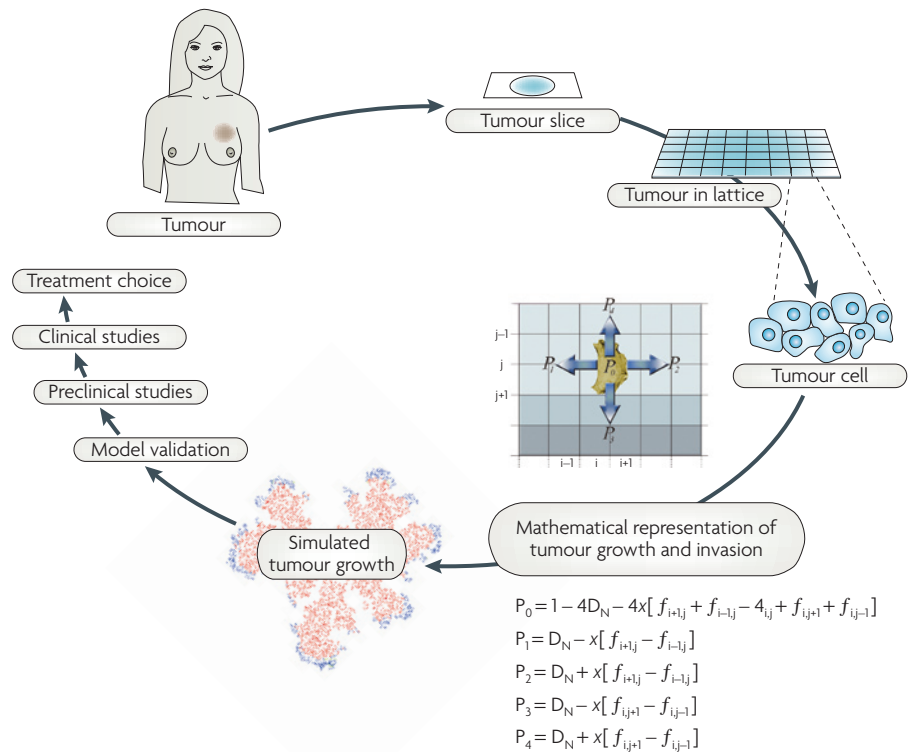
is high, as quantitative analyses of gene mutation spreading in cancer cell populations combined with genotype-to-phenotype mapping can bridge molecular to cellular scales and sensibly connect gene mutations to cancer progression outcomes. Once again, mathematical modelling reveals what experimental information is necessary and why. Furthermore, it provides a quantitative framework in which to interpret the information mechanistically.

Another school of thought stresses the role of the microenvironment in cancer progression[12]. The generally accepted

view is that the microenvironment has an instructive role, that is, it delivers cues or factors that modulate traits of cancerous cells, such as proliferation, differentiation, migration or apoptosis. By contrast, in the HDC model the microenvironment has a selective, rather than instructive, role. That is, it can be viewed as a collection of selective forces acting on cancerous cell populations. The end result of this selective role is the emergence of the fittest cell phenotypes for that microenvironment as the dominant drivers of cancer progression, at the expense of less fit clones.
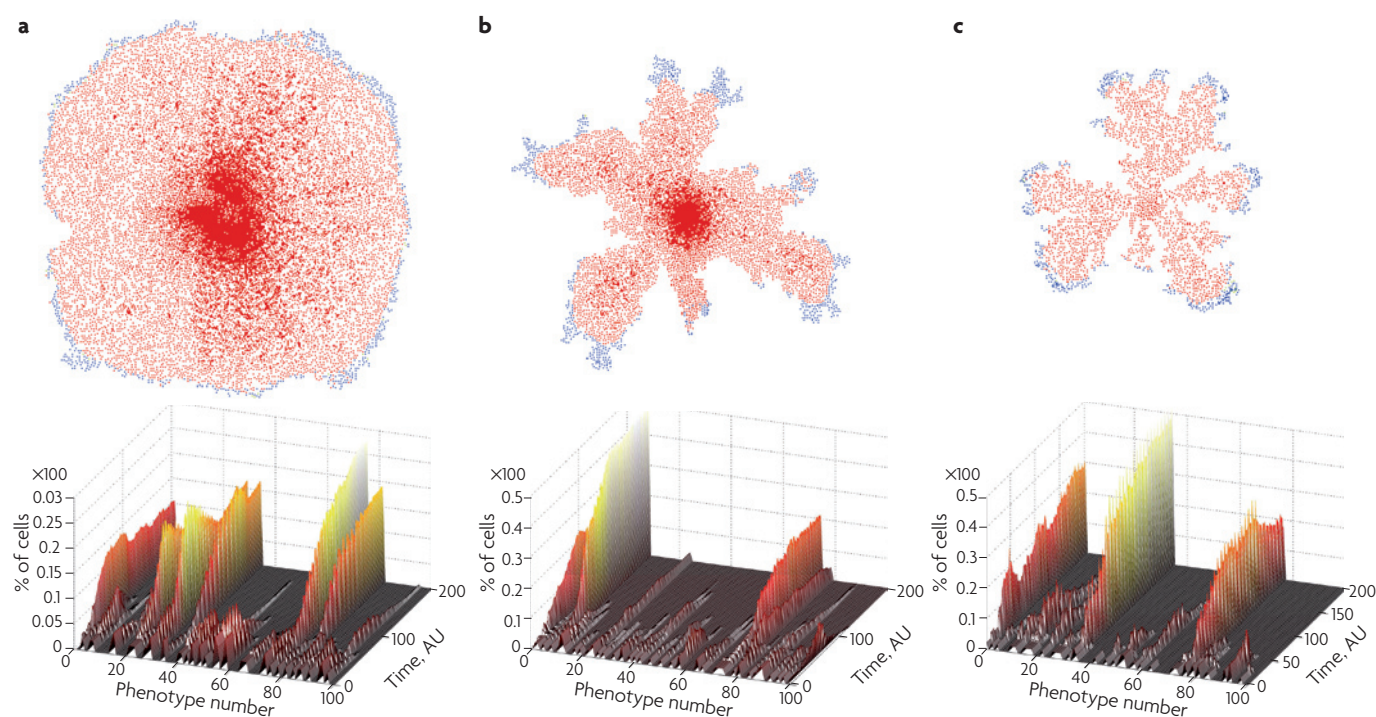

$$P_0 = 1 - 4D_N - 4x[\, f_{i+1,j} + f_{i-1,j} - 4i_{i,j} + f_{i,j+1} + f_{i,j-1}\,]$$
$$P_1 = D_N - x[\, f_{i+1,j} - f_{i-1,j}\,]$$
$$P_2 = D_N + x[\, f_{i+1,j} - f_{i-1,j}\,]$$
$$P_3 = D_N - x[\, f_{i,j+1} - f_{i,j-1}\,]$$
$$P_4 = D_N + x[\, f_{i,j+1} - f_{i,j-1}\,]$$

Figure 3 | **The hybrid discrete continuum model.** Current cancer diagnosis and treatment decisions are centred around a pathologist examining a tissue slice of the tumour at the microscope (histopathology), as well as assessing a few other parameters, including the overall size of the tumour and the presence or absence of tumour in lymph nodes and distant organs. Additional prognostic information that could aid in treatment decisions would be immensely useful; however, to date there has been little improvement over traditional staging methods. A novel approach that might prove useful in the future is the use of mathematical modelling as a predictive tool, with inputs from individual patient data. The hybrid discrete continuum mathematical model represents a first step in this direction, combining microenvironmental and tumour variables to predict tumour phenotype and morphology. The hybrid discrete continuum model builds a quantitative representation of a tumour slice, on a two-dimensional graphical grid (lattice). Each cell is accounted for in the lattice and its behaviour (for example, growth, movement and death) is tracked on the basis of mathematical functions and partial differential equations. Solving these equations in sequential time steps generates a computer simulation of tumour growth. In essence, the shape of the tumour emerges from the properties of individual cells, as well as from input from microenvironmental parameters, such as oxygen concentration and extracellular matrix composition, and evolves with them. Such an approach has the potential to predict disease outcome on the basis of precise quantities measured in the tumour of a specific patient. To be realized, this potential requires stringent validation of the model, by comparing computer predictions with real-life outcomes, followed by preclinical and clinical studies. If successful, the pay-off may be quite high: a rational approach to cancer treatment on a personalized basis.

a

b

c

Figure 4 | **Simulated tumour growth using the hybrid discrete continuum model.** Tumour growth was modelled using three different microenvironments: (**a**) uniform extracellular matrix (ECM), (**b**) grainy ECM and (**c**) low nutrient availability. The upper row shows the resulting tumour cell distributions obtained after 3 months of simulated growth: we can see that the three different microenvironments have produced distinct tumour morphologies. In particular, the homogeneous ECM distribution has produced a large tumour with smooth margins containing a dead-cell inner core and a thin rim of proliferating cells (**a**). The tumour that grew in the grainy ECM also has a dead inner core with a thin rim of proliferating cells; however, it displays a striking, branched fingered morphology of the margins (**b**). This fingering morphology is also observed in the low-oxygen simulation, which produced the smallest tumour (**c**). Note that animations, showing the growth of each of these *in silico* tumours, are available online (Supplementary information S1, S2, S3 (movies)) . One of the major advantages of working with a computational model is the ability to keep track of all variables/parameters at all time points. This allows us to examine the evolution of the tumour phenotype distribution (lower row) as the tumour invaded each of the different microenvironments. We note that there are approximately six phenotypes in the uniform-ECM tumour, two in the grainy-ECM tumour and three in the low-nutrient tumour. These phenotypes have several traits in common: low cell–cell adhesion, short proliferation age and high migration coefficients. In each tumour, one of the phenotypes is the most aggressive and also the most abundant, particularly in (**b**) and (**c**). All parameters used in the simulations are identical with the exception of the different microenvironments. AU, arbitrary units.

One can conclude then, based on the unifying multiscale perspective of the HDC model (paralleled by results from an alternative model that considers both genotype and phenotype[11]), that the cell is a vehicle built and used by genes to interact with the microenvironment. The cellular phenotype therefore bridges two distinct scales and integrates gene expression with microenviromental selection. The dynamics of this selective process drive cancer progression. In this sense, the HDC, or similar multiscale models, have the power to integrate distinct schools of thought in cancer biology.

Tumour evolution in the HDC model
The dynamics of the HDC-outlined selective process remain to be understood. We know what the outcome is, but is selection based on an adaptive mechanism, a purely Darwinian evolutionary mechanism or both? It is worth noting that adaptation and evolution are related, but are not the same[17]. The former may be a temporary adjustment in phenotypic performance, whereas the latter implies a change in the genetic material. The outcome may overlap, but the timescales are different. For evolutionary mechanisms, timescales are usually long, because they entail random mutation followed by nonrandom selection. It is generally agreed that this occurs in multistage carcinogenesis, in which the time is years to decades. In late-stage tumours, considered by the HDC model, the timescale of phenotype change is rapid, probably weeks to months. Is it possible for the genotype to mutate on such short timescales by Darwinian selection and drive the emergence of the fittest phenotype for a given microenvironment? Genome instability might have a role here[18], but one must also consider that increased mutation rates may drive phenotype diversity, but only in concert with selective mechanisms that favour the expansion of mutated clones[19]. Therefore, a better understanding of somatic cell population genetics would be helpful in this context[19].

An alternative possibility is that the cell phenotypes adapt to the microenvironment rapidly, without the need for genetic mutation (phenotype plasticity)[17]. In this case, the best adapting phenotype may end up dominating cancer progression in a given microenvironment[19,20]. It is also possible to envision a combination of evolutionary and adaptive mechanisms[21], such that the former follows the latter. In this case, a fast adaptive response could be fixed by a mutation later.

In order to investigate these hypotheses it is necessary to address these issues experimentally. This example epitomises the integrative nature of the mathematical oncology enterprise, from theoretical to experimental.

Mathematics-driven experimentation

It should be noted that experimental testing of mathematical model-generated hypotheses is non-trivial. It requires an open mind from the experimentalist, and often the development of new quantitative methods. Perhaps its most distinctive feature is that it parallels but definitely does not overlap with conventional hypothesis-driven experimentation focused on the discovery of novel molecules, genes or functions during cancer progression. In a broader sense there are two categories of mathematically-driven experimentation. The first entails experiments specifically aimed at quantifying coefficients of cellular and microenvironmental variables included in the model (model parameterization). These kinds of experiments would be dismissed as descriptive in a conventional biology framework, but they are essential to link a mathematical model with experimental reality. The second category is more challenging, in two ways: first, the experimenter has to analyse model outcomes, translate these into key predictions and formulate testable hypotheses based on these predictions; second, one has to design conclusive experiments to validate these hypotheses. A further challenge is that cancer progression can only truly be tested *in vivo*. The value of this type of experimentation can only be appreciated in the context of theories originated by mathematical models, further supporting the view that theoreticians and experimentalists should be housed together in wet–dry mixed laboratory environments.

As a specific example of experimental procedures driven by the HDC model, we developed a technique to directly measure cell migration by haptotaxis on protein gradients[22]. Other examples include the development of assays for metabolic rates with microphysiometers, assays to directly measure cell–cell adhesion and assays for spatial determinants of invasion (such as the evaluation of fingering on the margins of tumour cell colonies growing *in vitro*).

Just as modelling can spawn new lines of experimentation, many empirical observations, particularly those based on new technology, can stimulate mathematical modelling. Examples include live cell imaging, providing real-time data on cell movement; high-throughput screening assay or gene expression profiling, providing observations on biological variability; and ever-improving imaging technology, providing insights on tumour growth in animals or patients. These datasets, as we mention above, are difficult to grasp

intuitively, and are best explored by modelling. It is perhaps worth noting that, in this arena, alternative modelling approaches that might only consider a single scale might be appropriate, such as models for growth at the tissue scale[23], migration at the subcellular scale[24], or, at the molecular scale, gene expression profiling[25], signalling networks[26] and the cell cycle[27]. Single and multiscale models can sometimes complement each other, for example, a single-scale model could highlight the importance of a specific mechanism at the scale of a single cell that subsequently is incorporated into a multiscale model that considers both the tissue and cell scales. Given the complexity of multiscale models, it might be desirable that certain key mechanisms are tested initially on simpler single-scale models and then incorporated to the full multiscale system, with the caveat that a single-scale model might capture different dynamics owing to the potential for feedback across scales.

Conclusions

In biology, mathematical modelling and mathematics-driven experimentation directly attack the question, what are the underlying principles that drive life processes? In building a mathematical model, it is not so important to include all details of a life process. Rather, the goal is to distil key elements, define their mechanistic principles and subsequently let computation integrate
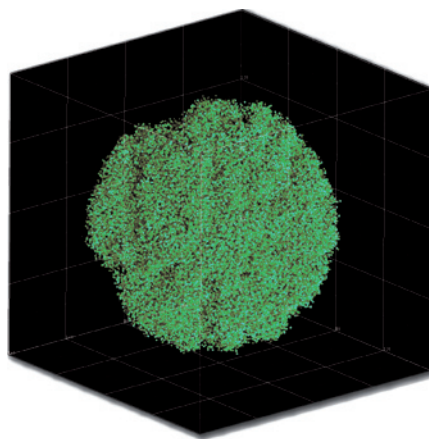

Figure 5 | **A three-dimensional simulation of tumour growth in a grainy extracellular matrix.** The surface of the tumour is largely spherical, although some roughness can be appreciated. This roughness resolves clearly into a fingered morphology (as observed in FIG. 4b) in the animation (see Supplementary information S4, S5 (movies)), which presents a series of slices through this three-dimensional structure. The phenotype distribution (not shown) closely parallels that of the two-dimensional simulations.

them. Care should be taken to make sure that the models generated do not have built-in outcomes. Rather, models should provide unexpected insight into the underlying mechanisms and generate novel hypotheses for experimentation. Further details can be added later or removed as necessary, ideally as dictated by experimental results. Because the model is built in mathematical language, experimental results are naturally positioned in an integrated context that can be compared or enriched with other models, on the same or different scales.

Applying these research principles to the study of cancer is, in a nutshell, the very essence of IMO. We hope this Perspective provided some useful details as to how this could be done and what the eventual pay-off might be for cancer research: a common platform for mathematical modelling, computation, experimentation and translation.

Alexander R. A. Anderson is at the Division of Mathematics, University of Dundee, Dundee, DD1 4HN, Scotland, UK.

Vito Quaranta is at the Department of Cancer Biology, Vanderbilt University School of Medicine, 771 Preston Building, Nashville, Tennessee 37232–36840, USA.

Correspondence to A.R.A.A. and V.Q. e-mails: anderson@maths.dundee.ac.uk; vito.quaranta@vanderbilt.edu

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FURTHER INFORMATION
A. R. A. Anderson's homepage:
http://www.maths.dundee.ac.uk/~sanderso/
Integrative Mathematical Oncology group:
http://www.vanderbilt.edu/VICBC/
Statistical mechanics: http://en.wikipedia.org/wiki/Statistical_mechanics

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MYC — OPINION

MYC in mammalian epidermis: how can an oncogene stimulate differentiation?

Fiona M. Watt, Michaela Frye and Salvador Aznar Benitah

Abstract | MYC in human epidermal stem cells can stimulate differentiation rather than uncontrolled proliferation. This discovery was, understandably, greeted with scepticism by researchers. However, subsequent studies have confirmed that MYC can stimulate epidermal stem cells to differentiate and have shed light on the underlying mechanisms. Two concepts that are relevant to cancer have emerged: first, MYC regulates similar genes in different cell types, but the biological consequences are context-dependent; and second, MYC activation is not a simple 'on/off' switch — the cellular response depends on the strength and duration of MYC activity, which in turn is affected by the many cofactors and regulatory pathways with which MYC interacts.

The epidermis constitutes the outer layer of the skin and functions as a protective interface between the body and the environment. Within the epidermis several types of differentiation can be discerned, including formation of the interfollicular epidermis (IFE), hair follicles and sebaceous glands[1] (FIG. 1a). In each of these regions the cells that have completed the process of terminal differentiation are dead cells that are shed from the tissue and are continually replaced through the proliferation of stem cells. There