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From regulation of cell fate decisions towards patient-specific treatments, insights from mechanistic models of signalling pathways

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Cell fate decisions are tightly regulated by complex signalling networks. Disturbed signalling through these networks is prominent in disease development. To elucidate pathway contributions and effects of alterations to the regulation of proliferation, quiescence, senescence, and apoptosis, computational modelling has been essential. Modelling heterogeneity on different scales was shown to be important for cell fate prediction. In recent years, personalised models capturing signalling and cell fate decisions have been developed. Of special interest is the application of these models to predict the response to drugs. In this review, we highlight examples of mathematical models of signalling pathways that regulate disease-relevant cell fate decisions on the path to develop individualised patient models for optimal treatment prediction.

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Introduction

Mammalian cells actively respond to different signals and perturbations. These responses are crucial in various contexts: in developmental processes, the reaction to environmental changes, ageing, shaping disease progression, and reaction to drug treatment. It is well established that these cellular responses are controlled by signalling pathways, which have been studied in great detail to analyse their design, function, and their contribution to different cellular tasks. The analyses showed that important characteristics result from regulations via feedbacks, feedforward loops, or delays leading to overall often nonlinear behaviour such as transient dynamics, oscillations, and switch-like responses due to bistable steady states, which cannot be explained by correlations [1,2]. To capture and investigate this nonlinear behaviour, mechanistic mathematical models of signalling pathways have been developed and have proven to be a valuable tool. Different approaches have been used to model signalling pathways; an introduction is given in Ref. [3]. Important pathway examples include mitogen-activated protein kinase (MAPK) signalling, nuclear factor κB (NF-κB), p53, as well as Wnt signalling [4–12].

The gained insights have been the prerequisite for a more ambitious task: understanding how cell fate decisions are regulated. For certain signals, cells respond with a decision towards a specific cell fate. In the context of not only development and ageing but also diseases and corresponding treatment strategies, critical cell fates comprise proliferation, quiescence, senescence, and apoptosis (Figure 1). Proliferation describes the essential processes of cell growth and division. It is tightly regulated, and dysregulations can lead to neoplasia or imbalances in tissue composition. Stimulation with growth factors or cytokines can lead to signalling through complex networks that ultimately lead to increased proliferation. Important pathways in the regulation of proliferation include MAPK, phosphatidylinositol 3-kinase (PI3K)/AKT, and janus kinase/signal transducer and activator of transcription (JAK/STAT) [13–15]. Apoptosis is a cell death program that is important in the formation and homoeostasis of tissue. Importantly, it can also be induced upon severe DNA damage that cannot be repaired and thereby serves as a protecting mechanism for the organism. The induction of apoptosis is tightly regulated by expression and interaction of proapoptotic and antiapoptotic

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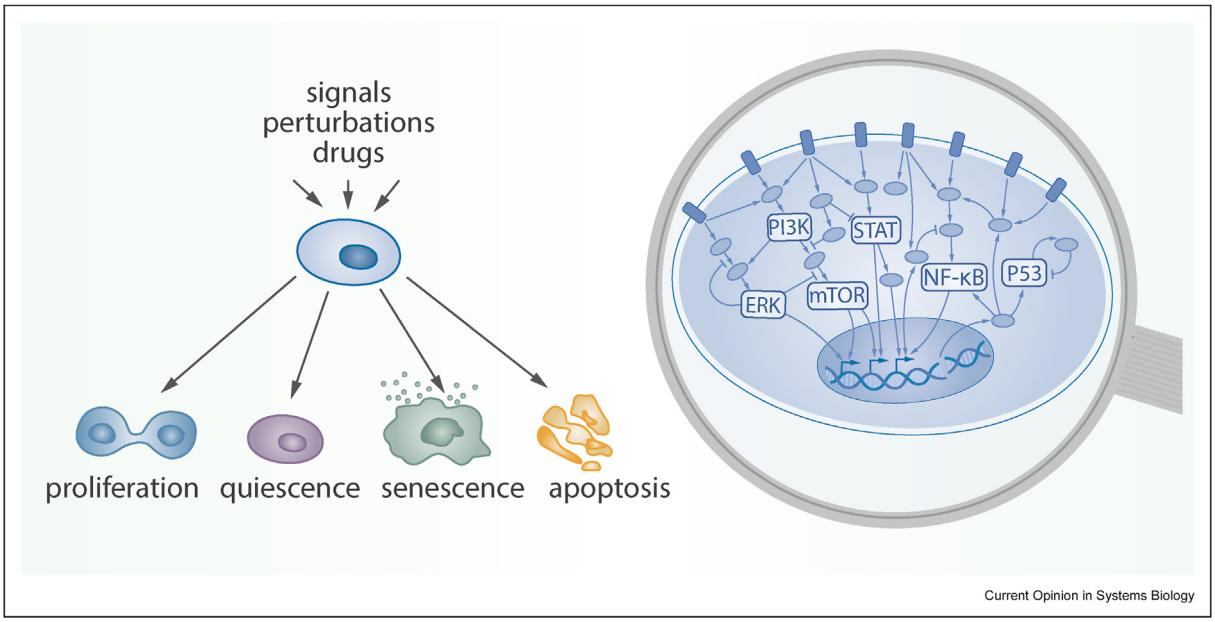
Figure 1



Cell fate decisions and underlying signalling pathways. Upon extraellular and intracellular signals, perturbations as well as drug treatment, cells can obtain different cell fates. The signals can thereby originate from external stimuli interacting with cell surface receptors or internal events such as DNA damage. The decision whether a cell proliferates, enters a transient or permanent cell cycle arrest, senescence, or induces apoptosis is controlled by signalling pathways that are tightly regulated and interconnected. Central pathways that are involved in these decisions to various extents are MAPK, PI3K/AKT, mTOR, JAK/STAT, NF-κB, and p53. Perturbations such as genetic alterations or drugs can interfere with those signalling pathways and therefore modulate cell fate decisions.Abbreviations: MAPK = mitogen-activated protein kinase; PI3K = phosphatidylinositol 3-kinase; mTOR = mammalian target of rapamycin; JAK/STAT = janus kinase/signal transducer and activator of transcription; NF-κB = nuclear factor κB.

factors [16]. The transcription factors p53 and NF-κB induce expression of such factors and have therefore a crucial impact on the cell fate decision between survival and apoptosis [17,18]. P53 is also known for its effect on cell cycle progression. In particular, the expression of one of its target genes, CDKN1A (p21) is linked to DNA damage-induced senescence [19]. This cell cycle arrest state can be induced by several signals linking it to not only ageing and age-related diseases but also tumour development and cancer treatment [20].

An intensively studied disease is cancer, where several cell fate decisions are affected: cells show elevated proliferation rates, avoid apoptosis, enter a senescent state, or follow a different differentiation trajectory [21,22]. As DNA damage is also induced by cancer treatment, the regulation of the decision between survival and apoptosis is of high clinical interest. More recently, the impact of senescence on the efficacy of treatment and therapy outcome came into focus [23]. In context of treatment, the activation of senescence can be beneficial as it counteracts sustained proliferation.

To elucidate the underlying molecular changes in diseases and optimal treatment strategies, the ability of cells to change their cell fate was intensively studied. Many investigations characterise the response of cells to specific stimuli or perturbations in defined conditions. Recently, the insights from these studies have been combined, and disease-specific models have been developed in order to investigate the response of cells to different stimuli and perturbations. Here, we will highlight important mechanistic models capturing processes that regulate cell proliferation, complex decisions between cell survival and cell death, as well as large-scale models that capture these decisions in disease cases. Our focus will be on ordinary differential equation (ODE) models. Overall, we will consider how diverse cell types in various conditions orchestrate their cell fate and find what are the essential characteristics of mathematical models to describe these processes. Such insights will be decisive for our ability to derive personalised disease models, also called digital twins, and to predict optimal treatment strategies.

Regulation of proliferation

In this section, we focus on recent models of signalling pathways that regulate proliferation. These include the MAPK (Ras/Raf/Mek/Erk), PI3K/AKT, mammalian target of rapamycin (mTOR), and the JAK/STAT pathway. Proliferation is strongly connected to cell cycle

progression, which was extensively modelled and was reviewed elsewhere [24–26].

Burbano de Lara et al. [27] investigated the regulation of hepatocyte proliferation in the context of chronic liver disease by an experimental–theoretical approach. Proliferation in hepatocytes is regulated by the MAPK, PI3K/AKT, and mTOR pathways downstream of hepatocyte growth factor. For these pathways, an ODE model was developed and quantified based on time-resolved immunoblotting of primary hepatocytes, first for a preclinical mouse model, fed different diets, and subsequently for patients. The study showed that the only kinetic parameter necessary to be altered between mice fed with different diets is the basal phosphorylation rate of the receptor tyrosine kinase MET. Moreover, this parameter also significantly correlates with patient outcome measures.

The MAPK and PI3K pathways were also analysed and modelled downstream of ErbB in four breast cancer cell lines [28]. Here, a mechanistic model of these pathways was combined with a linear regression model to explicitly model proliferation. This approach allowed to identify differences between the four cell lines representing different breast cancer subtypes and to predict the effect of drug combinations on cell proliferation. The receptor levels and cell-line-specific mutations were identified as main drivers of clinical differences. Targeted, time-resolved proteomics data were the basis for the model fitting, and L_1 regularisation [29] was used to derive cell-line-specific models. Imoto et al. [30] developed a framework for the prediction and analysis of cancer-signalling dynamics based on RNA-sequencing data. Their model captures the MAPK pathway, the PI3K/AKT pathway, and c-Fos induction downstream of ErbB in breast cancer cell lines. The kinetic parameters are derived based on time-series phosphorylation data for three breast cancer cell lines and initial protein levels from gene expression data. Based on a large-scale pan-cancer signalling model [31], Schmucker et al. [32] developed a method to define optimal drug treatment strategies. The model includes ErbB receptors, the RAS and AKT signalling pathways, and the regulation of the MYC and AP1 transcription factors. In this model, proliferation is described as a function of active forms of multiple transcription factors with different weights.

Yip et al. [33] focussed in a modelling–experimental approach on PI3K-inhibitor-sensitive and -resistant breast cancer cells to understand resistance mechanism towards inhibition. Their model includes PI3K/AKT, mTOR, and MAPK signalling downstream of IGF/ErbB and is based on time-course data of critical pathway components. The model is used to predict drug synergies for the inhibitor-sensitive and -resistant cases. The detailed signalling model was extended by a phenotypic module capturing DNA damage, repair, cell cycle phases, and apoptosis. Differences between drug-responders and nonresponders have also been investigated by Raimúndez et al. [34]. They used a model of the EGFR, ERK, and AKT pathways to investigate resistance mechanisms in gastric cancer cell lines.

The JAK/STAT pathway is influencing many processes, including proliferation, differentiation, and apoptosis [35]. In pancreatic β cells, lactogenic hormones promote proliferation and activate the JAK/STAT pathway. In order to investigate heterogeneity in this system, Simoni et al. [36] used a model of the JAK/STAT pathway [37] and modelled a heterogeneous population of cells with varying initial concentrations. Using this approach they could identify proteins, mainly phosphatases, that are strongly influencing the response and therefore might be suitable drug targets. Adlung et al. [38] also studied the cell-to-cell heterogeneity in the JAK/STAT signalling pathway, focussing on the survival–death decision. Here, a mathematical model of the Epo-induced JAK/STAT signalling combined with population and single-cell data was used to understand the sources of cell-to-cell heterogeneity and its impact on survival cell fate.

Overall, these studies show that the elucidation of heterogeneity between cells or cell lines on the level of proteins, protein modifications, or in process rates is critical for the understanding of proliferation and drug responses.

Complex decisions: proliferation, quiescence, senescence, or apoptosis

As exemplified in the study of Yip et al. [33], the regulation of proliferation is embedded in a more complex decision landscape of the cell. For example, in context of DNA damage, cells are required to decide between a transient cell cycle arrest while the damage is repaired, entering senescence or inducing the terminal-fate apoptosis. The transcription factor p53 is upregulated upon DNA damage and induces the expression of numerous target genes. For the decision between transient cell cycle arrest and senescence, the expression levels of one of its target genes, CDKN1A (p21), play an important role. P21 acts as a cyclin dependent kinase inhibitor by binding cyclin—cyclin-dependent kinase complexes and thereby preventing cell cycle progression. To mechanistically understand the regulation of those cell fate decisions, mathematical modelling of p53/p21 signalling as well as NF-κB signalling was applied.

Hsu et al. [39] studied the decision between proliferation and senescence upon DNA damage via chemotherapeutic treatment of cells based on single-cell time-lapse microscopy. They showed how the heterogeneity of cellular dynamics determines cell fate and developed a conceptional model of p21 dynamics after DNA damage.

The model reveals a bistability in p21 states, corresponding to senescence and proliferation. Heldt et al. [40] focussed on the decision between proliferation and quiescence in human cells after mild DNA damage. Based on single-cell data, they created a model for early cell cycle progression containing many cell cycle components as well as p53 and p21. The model shows that two bistable switches integrate DNA damage levels and proliferation signals and mediate the cellular decision. In the case of nonterminal cell fates such as quiescence, the question arises how cell fates are preserved over longer time scales. This was addressed by Reyes et al. [41] in individual human cells using fluorescent reporters for p53 and p21 to characterise their dynamics over several days after irradiation. They reported that not all cells maintain a cell cycle arrest, but some re-enter the cell cycle. Fluctuations in p53 levels led to heterogeneity in the ability to maintain cell cycle arrest. A core model of p53 and a double-negative loop between CDK2 and p21 were used to simulate the effect computationally.

The variability of p53 dynamics among individual cells has been investigated experimentally and theoretically in great detail [42]. Stewart-Ornstein and Lahav analysed on the single-cell level the heterogeneous response of p53 upon DNA damage among 12 different cell lines [43]. Using a mathematical model describing regulation of p53 activity, they could identify the processes causing variability in the p53 dynamics. Yang et al. [44] used a combination of single-cell imaging and a core model of double-strand break-induced activation of the p53 pathway for cell-line-specific modelling in three cell lines. The study characterised the cell type variation in p53 dynamics and cellular response. By creating cell-line-specific models, they identified differences in the protein levels of one of the network components as a critical factor for the p53 response to a DNA-damaging drug. This way, they elucidated a new resistance mechanism to a chemotherapeutic agent. A detailed model of the p53 and PI3K/AKT pathway activation was developed by Hat et al. [45] to describe the regulation of apoptosis and cell cycle processes after DNA damage. The model was subsequently used to predict drug responses of cancer cells for combination treatments [46].

The regulation of cellular survival—death decisions is not only mediated by the p53 and PI3K/AKT pathways but also strongly influenced by NF-κB. NF-κB family members acting as antiapoptotic factors and are regulated via several pathway branches [12]. Based on a comprehensive NF-κB pathway model [47], Roy et al. [48] modelled single-cell fate decisions of proliferation, differentiation, and apoptosis in B-cells. Comparing simulations of different model variants to experimental data revealed the importance of an inhibitory protein—protein interaction regulating a certain NF-κB family member and its necessity for proper B-cell differentiation. NF-κB is also critically involved in the response to DNA damage. The molecular mechanism of NF-κB activation after double strand breaks including poly(ADP-ribose) polymerase 1 (PARP-1) modification has been revealed experimentally [49—51] but has only recently been described by a mechanistic model [52].

In the study of Burt et al. [53], the balance between apoptosis and survival of plasma cells was analysed with a model comprising antiapoptotic and proapoptotic factors that are regulated by the transcription factors FoxO and NF-κB. Quantitatively evaluating the capability of different model variants to reproduce the given data sets allowed to reveal the importance of individual caspase regulation for controlling survival signalling.

The crosstalk of signalling pathways, i.e. the modulating effect of a component from one pathway on the response of another pathway can affect cell fate decisions and has been a subject of modelling approaches disentangling the impact of individual components on the cellular response. In the study of Konrath et al. [54], the impact of NF-κB signalling on the p53 response was investigated, and the processes affected by the crosstalk could be identified based on mathematical modelling and single-cell dynamics. Anderson et al. [55] analysed the impact of AKT/PTEN in TRAIL-induced apoptosis and could demonstrate that AKT is influencing early phases of apoptosis regulation in colorectal carcinoma cells. This demonstrates that the regulation and crosstalk of a range of signalling pathways and processes contribute to the intriguing balance of proapoptic and antiapoptotic factors underlying life—death decisions. Also apoptotic processes downstream of these signalling pathways have been modelled in detail [56,57]. This way, the impact of apoptotic processes on inflammation could be demonstrated [56], and synergies between drug targets promoting effective apoptosis induction in tumour cells could be identified [57].

Large-scale models for cell fate decisions in disease contexts

In order to specify cellular networks for disease cases, to predict the response to various perturbations and allow capturing high-dimensional perturbation data, large-scale models have been developed. These models allow for an integrative view on multiple pathways with their crosstalk and are therefore a step closer to the reality in a cell. Through this integrative view, it becomes possible to understand interactions between perturbations in different pathways. To generate these large-scale models, models for individual pathways and cell fate decision processes are frequently combined and trained using additional data. Often, the aim of these large-scale mechanistic models is the prediction of drugs and drug combinations for optimal targeting of diseases.

Du et al. [58] developed a model of the B-cell-receptor signalling network, including PI3K/AKT, RAS, and NF-κB signalling to model B-cell lymphoma. They combined the detailed signalling model with a tumour growth model to investigate the response to individual and pairs of drugs.

A more comprehensive mechanistic model describing proliferation and cell death by mutated cancer-related signalling pathways was developed by Bouhaddou et al. [59]. This model captures a range of pathways and processes including MAPK and PI3K/AKT pathways, mTOR signalling, DNA damage response via p53 signalling, gene activation by transcription and translation as well as cell cycle and apoptosis. While the focus on this paper is the development and validation of the large-scale model, they also gain detailed mechanistic insights into cell-line-specific responses to mitogen and inhibitor treatment. This model approach was recently developed into a pipeline to allow easy reuse and reparameterisation of the model for different cell types [60]. In addition, the approach enables model extension, demonstrated for expansion via an IFNγ pathway module after analysis of putative crosstalk mechanism [60]. Another large-scale model capturing multiple signalling pathways, cell cycle, DNA damage response and apoptosis was introduced by Miao et al. [61]. The model focusses on pancreatic cancer cells, was fitted to data, and used to analyse the effects of individual and combined drug treatment.

Large-scale signalling networks have been also captured by Boolean and logical modelling approaches that allow reduction of process-related details with respect to the kinetics and parameters [62]. Recently, the approach has been applied to develop patient-specific models [63]. Eduati et al. [64] developed a Boolean model for the extrinsic apoptosis pathway and predicted drug response, first for two cell lines, then for cancer patients, based on biopsy data. Thobe et al. [65] developed personalised models of the signalling network in diffuse large B-cell lymphoma including PI3K, MAPK, JAK/STAT, and NF-κB signalling and investigated the effect of different inhibitors on characteristic marker gene expression. A comprehensive model including many pathways, e.g. MAPK, NF-κB, and PI3K/AKT, as well as proliferation and apoptosis as explicit output nodes allowed Montagud et al. [66] to develop prostate cancer models for individual patients by using the cancer genome atlas (TCGA) data. These personalised models were used for the prediction of treatment responses.

Conclusions and outlook

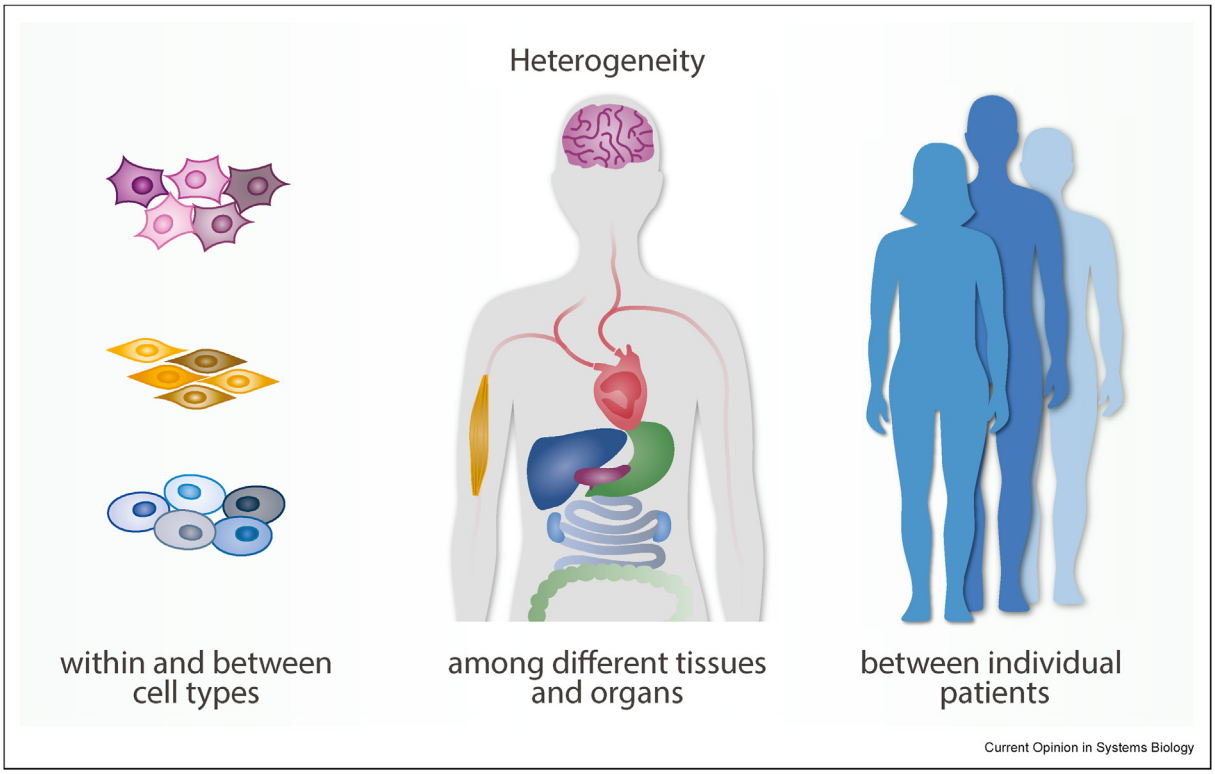
We here highlight studies that successfully modelled processes regulating cell fate decisions and that have been used for the prediction of drug responses. The models often combine and expand individual pathway models that have been studied in great detail before. While several central signalling pathways and processes reoccur in models of different cell fate decisions, their relevance and regulation can vary in different cell types and conditions. The majority of studies used intertwined mechanistic modelling and detailed experimental analyses. Capturing cellular heterogeneity was shown to be an important step of the model-informed identification of critical processes and dynamic patterns. As predicted very early [67], it is critical to distinguish cellular differences that are essential for the function or response of a cell from those that are not. The factors and processes relevant for cellular heterogeneity and fate decisions have been shown to vary greatly in specific systems, e.g. from rates of kinetic processes to receptor levels or dynamical behaviour of key players.

The identification and inclusion of cell-type-specific differences will be relevant for additional aspects: the consideration of the role of the cellular environment and cell−cell interactions in tissues and organs. Here, spatially resolved investigation of signalling can be an instrumental tool [68]. In addition, a consideration of various cell types will highlight differences in their response to drugs and thereby support the prediction of possible drug side-effects.

Based on established models for cell lines, the gained insights are now used to develop personalised disease models for the prediction of optimal therapies. A patient-specific implementation of alteration patterns has been achieved in a number of recent approaches. The aim to implement all relevant patient-specific alterations and possible drug target points simultaneously led to the development of large network models. To that end, models have been frequently expanded in a stepwise manner. For such model expansions, approaches to formulate models in a standardised way for eased reuse and extension are highly useful. Repositories of established models such as Biomodels [69] and JWS online [70] as well as standards for parameter estimation problems such as PEtab [71] greatly support this process. Moreover, a number of tools for the expansion and linkage of existing networks has been recently developed [72−74]. Still, merging-established models often required a detailed investigation of crosstalks and regulations, and while multiple pathways are already included in large-scale mechanistic models, important processes and links are still missing, with processes of the immune response being a prominent example.

Additional challenges for the generation of personalised disease models are as follows: i) the requirement of huge amount of data sets for the training of the large-scale models [31,59] and ii) the mapping of the output of signalling models to phenotypic readouts to capture disease-relevant cell fate decisions. The latter can be

Figure 2



Different layers of cellular heterogeneity. Cellular components such as transcripts and proteins can vary strongly between cells. This cell-to-cell heterogeneity can affect the regulatory network and is therefore important for cell fate decisions. Heterogeneity can originate from different sources. Within a population of cells of the same cell type with an identical genetic background, heterogeneity can arise from the stochastic nature of gene expression (represented by the colour gradient). For cells of different cell types, additional layers of heterogeneity arise based on gene expression changes (represented by the shape). In tissues and organs, the cell-to-cell variability is further increased by differences in the amount and type of stimuli that interact with cells. On the level of patients, the genetic variance and disease-related alterations, e.g. mutations among individuals introduce heterogeneity that can have a strong impact on the outcome of therapies.

realised on different levels of complexity, using individual markers or combinations of markers as a proxy for the phenotype, or by developing phenomenological descriptions, for which a sophisticated approach has recently been developed [75]. Generally, the integration of available omics data by combining machine-learning approaches and mechanistic modelling is a promising approach towards comprehensive personalised disease models [76,77]. An upcoming challenge for such personalised large-scale models is the validation of patient-specific treatment predictions, which require systematic strategies to test and improve such predictions.

So far, it is an open question how much detail is required to capture all relevant patient-specific disease alterations at the same time as cell-type-related heterogeneity (Figure 2). Not all the available details might be necessary to derive effective drug predictions. Once cell type and patient-specific models with sufficient detail are established they will not only guide treatment prediction of developed diseases but also guide our understanding of more subtle changes, e.g. in early disease stages or ageing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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