VPH SUCCESS STORY

Respiratory healthcare by design: Computational approaches bringing respiratory precision and personalised medicine closer to bedside

Himanshu Kaul

Michael Smith Foundation for Health Research Trainee, School of Biomedical Engineering, University of British Columbia, Vancouver, Canada
Correspondence Address: himanshu.kaul@ubc.ca

Abstract

Precision medicine represents a potentially powerful means to alleviate the growing burden of chronic respiratory diseases. To realise its potential, however, we need a systems level understanding of how biological events (signalling pathways, cell-cell interactions, tissue mechanics) integrate across multiple spatial and temporal scales to give rise to pathology. This can be achieved most practically in silico: a paradigm that offers tight control over model parameters and rapid means of testing and generating mechanistic hypotheses. Patient-specific computational models that can enable identification of pathological mechanisms unique to patients' (omics, physiological, and anatomical) profiles and, therefore, personalised drug targets represent a major milestone in precision medicine. Current patient-based models in literature, especially medical devices, cardiac modelling, and respiratory medicine, rely mostly on (partial/ordinary) differential equations and have reached relatively advanced level of maturity. In respiratory medicine, patient-specific simulations mainly include subject scan-based lung mechanics models that can predict pulmonary function, but they treat the (sub)cellular processes as 'black-boxes'. A recent advance in simulating human airways at a cellular level to make clinical predictions raises the possibility of linking omics and cell level data/models with lung mechanics to understand respiratory pathology at a systems level. This is significant as this approach can be extended to understanding pathologies in other organs as well.

Here, I will discuss ways in which computational models have already made contributions to personalised healthcare and how the paradigm can expedite clinical uptake of precision medicine strategies. I will mainly focus on an agent-based, asthmatic virtual patient that predicted the impact of multiple drug pharmacodynamics at the patient level, its potential to develop efficacious precision medicine strategies in respiratory medicine, and the regulatory and ethical challenges accompanying the mainstream application of such models.

Introduction

Chronic diseases remain a source of great fiscal and economic burden on our society. In Europe, chronic diseases like cancer, chronic respiratory disorders, diabetes, and mental illnesses contribute to 85% of all deaths [1]. In addition to the treatment costs, chronic diseases depress wages, labour productivity, workforce participation whilst increasing disability and early retirement [1]. The costs associated with treatment of these diseases is increasing given increased life expectancy of Europeans as well as the rising prevalence in multiple chronic diseases in an individual: a phenomenon referred to as multimorbidity [1]. It is estimated that over 50 million people in Europe suffer from multimorbidities, likely due to shared pathological mechanisms, shared risk profile, or random events [2].

Pharmacotherapy and medical devices represent the most common healthcare alternatives available today. Of these, medical devices tend to be quite efficacious, albeit with a narrow field of influence. Pharmacotherapy, on the other hand, represents the most pervasive treatment option. However, the one-size-fits-all approach is not efficient and for numerous chronic diseases pathological mechanisms are not well understood and, as such, the extent of treatment is limited. Pharmacotherapy especially struggles when it comes to diseases that emerge from the loss of critical cell populations that are incapable of regenerating following this loss. The regenerative medicine paradigm where stem cells can be differentiated to mature cell populations or tissues and administered to patients represents a powerful therapeutic approach [3]. However, we currently lack strategies to develop such cell-based therapies ex vivo and administer them at clinical scale [4].

Alleviating the burden of chronic disease and ensuring the delivery of sustainable health services requires precise treatment strategies that will reduce inpatient days, enhance understanding of molecular signatures that contribute to chronic pathology [5], and cost-effective treatment decision-making pipelines. The fundamental barrier to achieving these

goals is a lack of understanding of the systems-level pathological mechanisms that underpin chronic pathology, especially multimorbidities. In this article, I discuss how computational modelling is already playing a crucial role in addressing some of these challenges and how current advancements in respiratory medicine have poised computational approaches to play an ever more significant role in clinics, industry, and laboratories to bring precision and personalised healthcare closer to reality at a clinically meaningful scale.

Our inability to integrate omics', cellular, and organ-level events is a critical bottleneck to precision healthcare

The crucial challenge to understanding disease pathology and developing personalised therapies is that pathology, much like function, emerges from an integration of events at multiple spatial and temporal scales. For example, genes mediate cellular activity, which together form tissues and organs, downstream of which the various organ systems act synergistically to yield functionality at the human (organism) level. The organism itself exists in a continuous exchange with the environment. Pathology, similarly, is a multiscale event, where departure from normal functionality at the gene, cell, tissue, organ levels lead to diseases at the human level. Asthma, for example, emerges from interactions between multiple genes and between genes and environmental factors – not as a result of a single mutation in a single gene [6]. Integrating information or mechanisms or data structures across these dynamically linked hierarchies, referred to as dynamic assimilation [7], is a non-trivial endeavour and requires predictive computational models that can generate quantitatively testable mechanistic hypotheses linking the various hierarchical levels. The rationale being that following validation such models will be able to reveal how parametric changes, related to input signals or gene mutations or transcriptomic profile, lead to pathology and offer insights into how these pathological mechanisms can be silenced or reversed. Computational models are important here as, unlike in vitro or in vivo models, they offer precisely controlled parameters that can be easily manipulated individually or collectively inside a model with a lot of undesired complexity abstracted away.

There are a variety of mathematical paradigms that can be employed at each hierarchical level. For example, gene regulatory networks (GRNs) [8] help understand how a network of molecular regulators that interact with each other and other intracellular components regulate cell functionality. GRNs are composed of nodes, which represent genes and their

regulators, and edges, which represent the regulatory relationships between the nodes. At the cellular level, rule-based paradigms, such as the cellular automata [9,10] or agent-based modelling [11], are employed to understand how a multicellular system evolves based on interactions between cells. The strength of these rule-based approaches is that they do not discount system heterogeneity and consider lower-level system details, thereby allowing the user to investigate emergent phenomena. At the tissue and organ levels, the continuum methodology has been utilised quite successfully. Such methods are based on physical laws and/or constitutive principles and employ partial (P) or ordinary (O) differential equations (DEs) to capture tissue or organ behaviour. As long as the underlying cellular or transcriptional heterogeneity can be ignored, the continuum assumption works extremely well at this scale. Finally, statistical and probabilistic approaches can be utilised to make predictions at the organism level, though such models are generally not mechanism-oriented [12]. Other mathematical approaches, beyond the ones enumerated here, can also be applied [12-15].

Some of these approaches, especially the continuum assumption based PDE models, have covered tremendous ground in predicting organ functionality and interactions between medical devices and organ physiology. Guo et al. (2018) [16] used a multiscale, multicompartmental poroelasticity model to evaluate transport of blood, cerebrospinal fluid, and interstitial fluid in the brain. They used MRI-based subject brain morphology with tissue anisotropy maps and patient-specific vascular flow to create their domain (Fig. 1A).

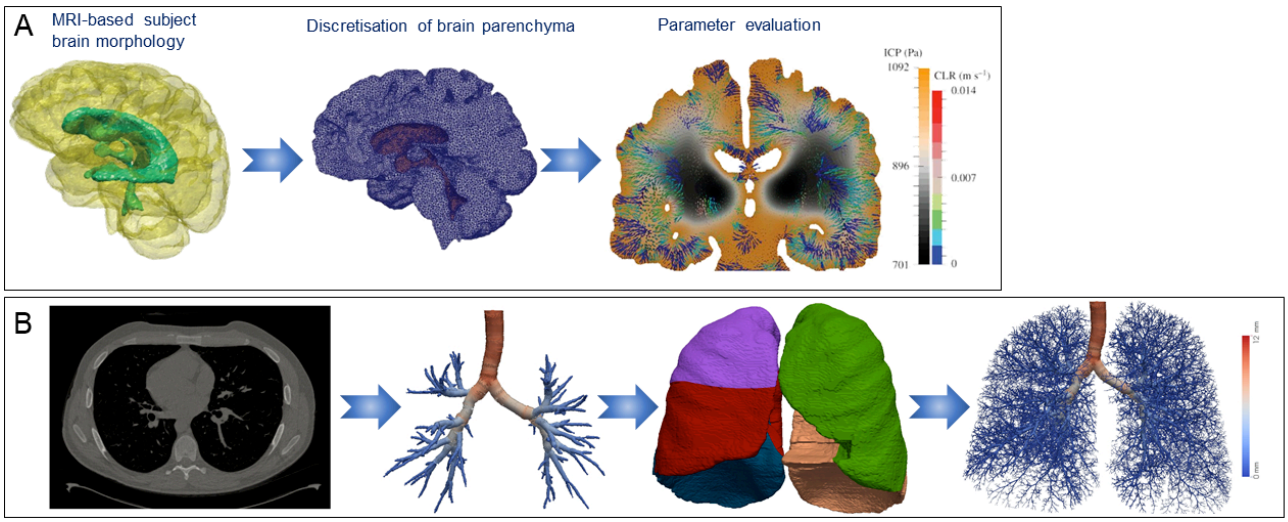

Figure 1. *Continuum models have played a key role in understanding pathology and making*

patient-specific predictions. A. A computational model that utilised MRI-based subject brain morphology to predict differences in parameters, such as CSF accumulation and clearance, for normal vs MCI subject. Model pipeline was constructed using a multiple-network poroelasticity theory-based model of cerebral parenchyma, image-based model personalisation workflow, and subject-specific boundary conditions. Reprinted with permission from © (2018) Guo et al, Interface Focus, 8:20170019, under Creative Commons Attribution License. B. Development of patient-based complete conducting airway model. The CT image is used to generate the central airway, which are rendered as a series of tubes. The complete conducting airway tree (colour coded by airway radius) is generated using the lobar segmentations. Reprinted from © (2015) Bordas et al, PLoS One, 10(12): e0144105, under Creative Commons Attribution License.

The brain parenchyma was discretized and the poroelastic equations were solved via the finite element approach. This enabled the investigators to evaluate parameters like inter-cranial pressure, capillary bed perfusion, and interstitial fluid clearance in a healthy male subject compared against a male subject with mild cognitive impairment (MCI). Their model showed a marginally reduced clearance of cerebrospinal fluid (CFS) and interstitial fluid (ISF), elevated parenchymal tissue displacement and CSF/ISF accumulation. The approach has implications to understanding the mechanisms underpinning dementia and identifying new biomarkers related to vascular risk factors of Alzheimer's disease. Peach et al (2014) [17], on the other hand, used computational fluid dynamics (CFD) to evaluate the performance of minimally invasive interventional devices, i.e. flow diverters, for the treatment of cerebral aneurysms. They created an anatomically accurate representation of brain vasculature with an aneurysm and into it positioned the device virtually. Solving the haemodynamic equations led to the quantification of flow inside the aneurysm sac. A significant advantage of this approach is that based on the reconstructed patient anatomy, the investigators can test multiple devices virtually to determine the design that will have the most optimal therapeutic impact. This is precisely what the investigators did with designs showing as high as 70% reduction in aneurysm inflow. This example is an excellent representation of the state-of-the-art in patient-specific in silico modelling of medical devices.

Furthermore, continuum models have been successfully utilised in cardiac modelling, and have progressed to the level of the whole heart [5]. Building on a foundation that is more than half-a-century old [18], the application of diffusion tensor magnetic resonance imaging [19] has enabled organ level modelling. This has led to models with unprecedented structural and biophysical detail that includes electromechanics [20] and fluid dynamics of blood flow within the left ventricle [21]. The models have offered insights

into myocardial ischemia [22], mechanisms of arrythmia in the setting of idiopathic dilated cardiomyopathy [23], and channelopathies [24]. Patient-specific formulations of these models are being used to interrogate advanced methods of cardiac resynchronisation therapy in dyssynchronous heart failure [25]. Additionally, the models are being used for the evaluation of novel antiarrhythmic therapies [5,26].

In respiratory medicine, a variety of continuum models have been developed that capture the impact of changes in airway anatomy on lung function. These include realistic subject-based models of lung functions by Tawhai *et al*. (2009) [27,28]. This model has been used to assess density and pleural pressure gradients in healthy subject-based models. It relies on finite element discretisation of the organ geometry and applies finite deformation elasticity. The model assumes the lung-air matrix to be a compressible, nonlinearly elastic continuum with homogeneous and isotropic material properties. Creating clinically-relevant subject-specific lung models entails segmenting airways from computed tomography (CT) images, generating subject-specific computational models, and comparing the effect of airway geometry before and after simulated interventions (Fig. 1B) [28-30]. This patient CT data-based approach has been advanced to generate patient-based complete conducting airway models to predict patient airway ventilation and airflow dynamics by comparing computational predictions with clinical pulmonary function tests [29]. As illustrative examples: Bordas *et al*. (2015) [29] created patient-based airway models that showed significant difference in airway resistance of severe asthmatics vs healthy subjects. Their model predictions, further, correlated with the patient forced expiratory volume in one second (FEV1). Recently, Foy *et al*. (2019) [31] utilised the similar overall approach to demonstrate that narrowing small airways greatly impact the forced oscillation technique (FOT) derived resistance at 5Hz minus 20Hz. FOT is a non-invasive technique to assess bronchial hyperresponsiveness in adults and children. It superimposes a series of pressure oscillations over a range of frequencies (typically 5-35 Hz) on normal breathing [32]. Foy and co-authors further established forced oscillation R5-R20 as a marker of anatomical narrowing in small airways, and that small airway narrowing has a marked impact on both asthma and quality of life.

While majority of patient-specific continuum models make use of patients' anatomical specificity, they are not entirely suitable for generating molecular signatures of diseases. This, instead, requires models and modelling approaches that can dynamically assimilate [7] information and data across the various gene, cell, tissue hierarchies: a critical challenge faced by computational medicine currently. The main reason computational models have

been unable to achieve this stems from the fact that there is no single locus origin of functionality [5] or pathology, which means that the emergence of function or loss of function cannot be distilled to a single event (except in certain genetic disorders, e.g.: monogenic disorders) and tends to typically be a multi-loci event. This is further complicated by the fact that synergy between biochemical agonists and antagonists has profound impact on functionality and pathology. This overall complexity makes predicting patient-level outcomes quite challenging, if not impossible. Overcoming this challenge will require a strategy that links these hierarchies, which will enable the development of patient-specific models, precision medicine strategies, and guide efficient regenerative medicine protocols.

Multi-paradigm modelling represents an important milestone in patient-specific modelling

The advantages of employing continuum (ODE/PDE) models that rely on the homogeneity assumption include their ability to conduct rapid analyses and a broad exploration of the parameter space efficiently, offering insights that can form the basis for the computationally expensive discrete (rule-based) simulations [33]. The limitations of these models have been highlighted previously in literature [7,34]. To summarise, as they assume system homogeneity and ignore the lower-level system detail, such models struggle to account for system heterogeneity. They, therefore, are unable to deal with the complexity of the evolving system and capturing emergent phenomenon [11]. Therefore, by themselves, they struggle to integrate information across multiple biological hierarchies.

To account for system heterogeneity, one can rely on cell-level models that include the cellular automata and agent-based models. Both modelling techniques are forms of discrete mathematical approaches that break down a system into sub-components that interact with each other based on a rule-set assigned to each component at each discrete time point [4]. The rule-set, in the context of asthma for example, can contain a *rule* that states *if a patient is genetically predisposed to aggressive inflammation, the number of eosinophils in their airways will be x-times higher than a healthy subject*. Their chief advantage lies in the fact that they account for system heterogeneity and are, thus, optimal to quantifying emergent phenomena. However, it is because they offer the most logical interface between intracellular 'omics (genomic, proteomic, transcriptomic) information

and tissue- and organ-level (anatomical, physiological, biopsy) models that makes the rule-based formulations ineluctable for patient-specific modelling.

This was best tested via an in silico trial [35] that was conducted in parallel with the clinical trial [35] of severe asthmatics with the drugs Mepolizumab [36] and Fevipiprant [37]. Asthma is an airway disease that results in a narrowed airway, which results in reduced airflow and forced expiratory volume (FEV1). It is a heterogeneous disease with patients showing symptoms on a spectrum: eosinophilic, non-eosinophilic, severe, moderate, mild asthma, for example. The human airway is composed of epithelial, mesenchymal, and inflammatory components. The lumen of the airway is surrounded by the epithelium, which includes columnar and goblet cells in the first layer followed by a basal cell layer. This is followed by the mesenchyme, which includes fibroblasts and airway smooth muscle (ASM) cells. Finally, the capillaries in this region act as the conduit for inflammatory cells (mast cells, eosinophils, etc) into the airways.

In health, interactions between these airway components are harmonious, and the airway can respond normally to any challenges (allergen, virus, etc). However, when the interactions lack this normal harmony, they result in pathological remodelling that ultimately leads to inflammation, disrupted epithelium, and increased muscle mass, which constricts and narrows airways [35]. Pathological remodelling is a classic example of emergent phenomenon, where the emerging loss of functionality is a decentralised, multi-loci event. Understanding these events from a mechanistic perspective requires an approach that can account for the heterogeneous interactions between system components. To achieve this, Kaul et al. (2019) [38] developed an agent-based model, creating a virtual airway with epithelial (columnar, goblet, basal), mesenchymal (fibroblasts, airway smooth muscle), and inflammatory (eosinophils and 'universal' inflammatory) cells to simulate interactions between these airway components. In their model (Fig. 2A), a disrupted epithelium triggered fibroblast proliferation, also activating the recruitment of inflammatory cells into the virtual airway.

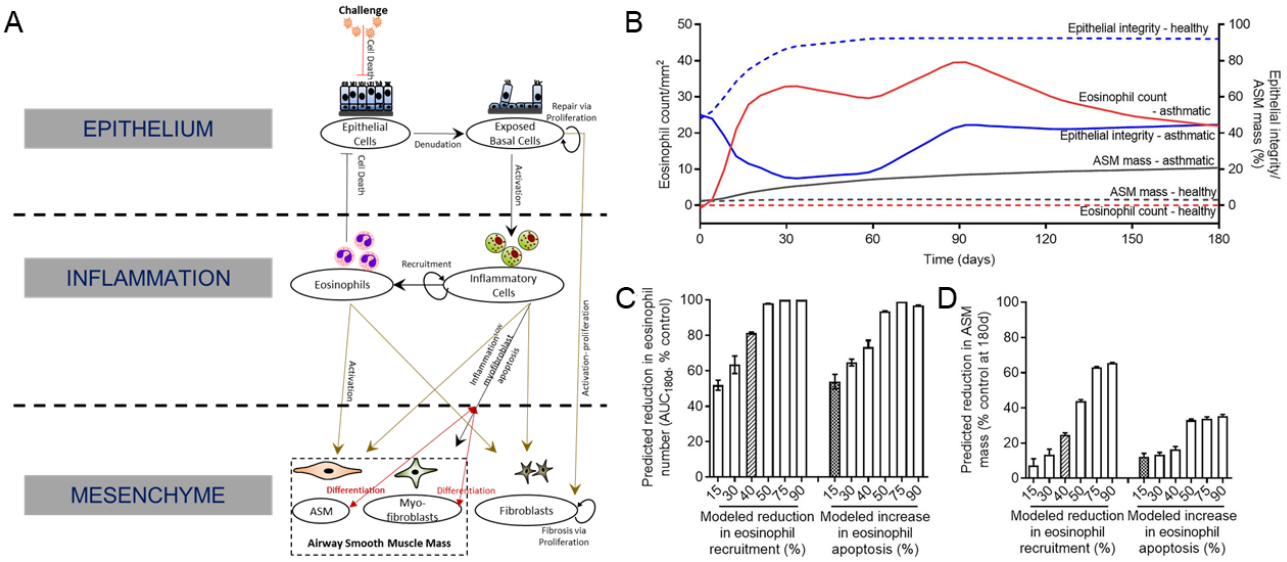

Figure 2. *A patient-level agent-based model of asthma pathogenesis. A. The schematic depicts interactions between the various cellular components of the human airway. These interactions were transformed into rules that were used to develop the model. B. The model captured the hallmarks of asthma. Healthy model showed high epithelial integrity and low eosinophil count & ASM mass following a challenge. The asthmatic model showed low epithelial integrity and a heightened eosinophil count & ASM mass. C. The model was used to predict the impact of Fevipiprant (decreased recruitment of inflammatory cells) and Mepolizumab (induction of apoptosis in eosinophils). The chequered bars represent drug 'dosages' (x-axis) that led to clinically observed reduction in eosinophilia. D. The clinically relevant dosages (chequered bars) were used to predict the reduction in ASM mass. While the clinically relevant anti-IL5 dosage did not lead to significant reduction in ASM mass, the suggests a way to optimise anti-IL5 therapy. Reprinted from © (2019) Saunders R, Kaul H, Berair R et al, Science Translational Medicine, 11: eaao6451, with permission from the American Association for the Advancement of Science.*

The inflammatory cells in their lifetime within the airway released cytokines that recruited more inflammatory cells and caused the muscle cells to undergo hypertrophy and, eventually, contraction. These pro-inflammatory cytokines induced fibroblasts to differentiate into myofibroblasts, thereby adding to the airway muscle mass together with the ASM cell hypertrophy. The release of pro-inflammatory cytokines, if beyond a certain threshold, eventually recruited eosinophils that travelled through the sub-mucosa to the epithelium where they degranulated to release cytotoxic proteins that killed epithelial

cells, further disrupting the epithelium. The parameters in the model were derived from existing clinical, animal, and in vitro literature (in that order of priority).

Saunders et al. (2019) [35] used this model to understand Fevipiprant pharmacodynamics. To achieve this, the investigators first demonstrated that the model capturing a healthy airway resulted in normal remodelling after a challenge (Fig. 2B). They then conducted a sensitivity analysis to determine which alterations in epithelial, mesenchymal, and inflammatory parameters will result in the clinical hallmarks of asthma. The clinical hallmarks of asthma were defined as [35]: (i) eosinophilic inflammation (defined as eosinophils/mm^2 submucosal area) of >10, (ii) epithelial integrity of <70%, and (iii) airway muscle mass of ≥10 and ≤50%. Their analysis showed that single perturbations from normal behaviour did not yield the hallmarks of asthma, pointing to the robustness of the system. In fact, the hallmarks emerged when multiple parameters were perturbed. This is consistent with growing literature that suggests asthma to be an outcome of multiple perturbations, and not single mutation [6]. Interestingly, they captured a range of asthma phenotypes: severe asthma, non-severe asthma, non-eosinophilic asthma. This was an important finding as asthma severity exists on a continuum, which had not been captured computationally. This has opened an avenue of exploring the precise parameters and interactions responsible for the various asthma phenotypes. Importantly, the ability to predict the interactions responsible for the various phenotypes means the ability to identify appropriate interventions.

The most parsimonious set of parametric conditions that resulted in the hallmarks of asthma was used as the 'virtual patient' and used to conduct an in silico trial [39] with drugs Mepolizumab, an anti-Interleukin (IL)5 agent, and Fevipiprant, a Prostaglandin D2 type 2 receptor (DP2) antagonist. DP2 is expressed by inflammatory cells and in ASM bundles. A range of 'drug' dosages were tested for both drugs. The model suggested that an anti-IL5 dose that triggers apoptosis in 15% eosinophil tissue population will lead to ~54% reduction in eosinophilia versus the computational placebo control, which was consistent with Mepolizumab clinical data (~55%) [36]. For Fevipiprant, the model suggested that a 40% reduction in eosinophil recruitment will result in ~81% reduction in eosinophilia compared to the computational placebo control, which was also consistent with the clinical trial (~80%). Following this clinical validation (Fig. 2C), the model was used to predict a concomitant reduction in muscle mass. For the mepolizumab virtual trial, consistent with the clinical trial, the model predicted ~12% relative reduction in muscle mass. However, for the fevipiprant virtual trial, the model showed ~25% relative reduction

in muscle mass, though this was less than the clinically observed reduction in muscle mass. This suggested that Fevipiprant had a direct impact on ASM mass, in addition to its impact by reducing eosinophilia. This was confirmed in vitro, when the drug molecules were observed to reduce migration of ASM cells derived from the patients. When this feature was added to the model, it revealed reduction in muscle mass consistent with the fevipiprant clinical trial (~45% computational relative reduction vs ~45% clinical reduction).

This investigation showed the capability of mechanistic mathematical models, especially agent-based models, in making clinically-relevant predictions at the patient level [35,40]. It also demonstrated the model's potential as a drug design and optimisation tool [41]. This is evident in Fig. 2C which shows how an anti-recruitment therapy, for the same 'dosage' will be comparatively more efficacious, but also shows how an anti-apoptosis therapy can be improved to show significant reduction in muscle mass. This also means that much like Peach and coworkers'model [17] that allowed them to determine the best flow diverter design given patient anatomy, this model can be used to determine the optimal drug type and dosage before it is administered to the patient. This is also made possible due to the fact that the model considers interactions between various cellular components that would persist across scales. Therefore, agent-based approaches can be utilised to simulate organ behaviour and use it to test drug efficacy in silico.

Importantly, this agent-oriented approach can be extended to design and optimise regenerative medicine therapies: a method that has shown immense potential in treating chronic diseases that arise due to lack of critical cell populations [42], but that has underperformed due to our inability to control and scale-up tissue design ex vivo [4]. Agent-based modelling can be particularly effective here as it i) considers system-level heterogeneity (as opposed to continuum models), ii) simulates the spatiotemporal evolution of the system based on interactions between system components, and iii) the approach adequately accounts for the decentralised nature of biological interactions [11]. In fact, multiple examples exist where the agent-based approach has been utilised to understand biological mechanisms [43-49]. However, the amenability with which ABMs can be coupled with other methodologies is what makes them ideal to develop strategies that will scale up regenerative medicine therapies to meet clinical demands.

Towards this end, Kaul et al. (2013) [50] coupled an agent-based framework with the transport equation to capture dynamic reciprocity [51] – the mutually reciprocal dynamic interactions between cells and their microenvironment [52] – within a bioreactor. The

underlying rationale for capturing dynamic reciprocity was that cells shape their environment, which in turn provide them developmental (biochemical, mechanical, architectural, spatial) cues thereby shaping cellular development in turn. The quantification of this relationship is critical if we are to predictively control morphogenesis ex vivo, and scale-up this process so we can meet the healthcare demands at clinical scale. Kaul and co-workers noted the approach was able to capture this dynamic relationship, and demonstrated how changes in transport and flow can alter the growth dynamics profoundly. While the use of computational fluid dynamics (CFD) and other continuum approaches have been previously used to optimise bioreactor design [53-57], it is the assimilation of virtual cells via agents within these bioreactors that will potentially provide more nuance in terms of the precise spatial and temporal biochemical fingerprints that cells are exposed to within the bioreactors. This offers more control over the ex vivo growth and a way to predictively regulate growth of desired tissues and organs at clinical scale ex vivo.

The future is in silico

Mathematical and computational paradigms have over the last two decades made tremendous strides in aiding healthcare. This has been achieved by models that explore pathological mechanisms, assist in predicting the optimal course of intervention, and design and development of new drugs, medical devices, and bioreactors. Examples also abound of deep learning and artificial intelligence algorithms [58-60] that have performed as well as physicians in identifying pathology from image-based patient data, with the implication that such techniques will speed up diagnoses.

The most significant milestone, however, is represented by the ability to run patient-specific simulations, where model initial conditions are derived from the patient's 'omics profile, cell- (biopsy) and tissue-/organ-level (anatomy, imaging, FEV1, for example) data to predict their response to interventions, before they are administered to the patients. As argued here, this can be achieved via multi-paradigm models that couple agents, which can capture cell interactions and gene networks, with organ-level models. Such in silico pipelines (Fig. 3) and digital patients represent the future of healthcare where we can acquire patient data, process it to develop useful models to simulate the impact of drugs or devices, and use the insights to create improved methods for disease diagnosis and treatment.

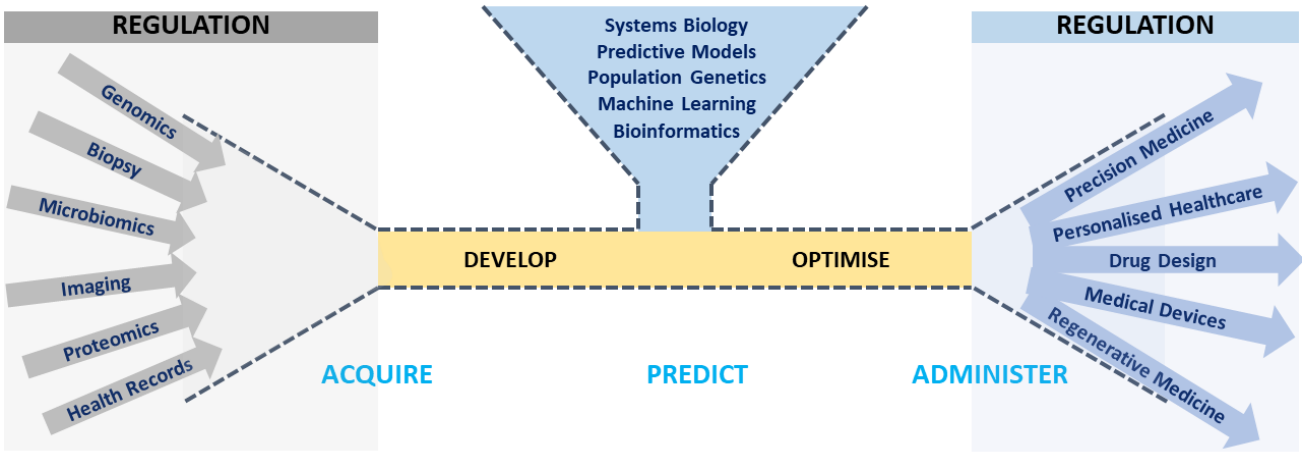

Figure 3. *Patient-specific in silico pipeline. Patient-specific models in future will be able to integrate patient omics and higher-level (cell-, tissue-, organ-level) information to predict optimal interventions tailored to individual patients. Such pipeline will entail acquisition of the patient data and its processing to develop computational models via a variety of approaches discussed in this article (and beyond). The models will be used either to predict patient outcomes to therapies or model drug pharmacodynamics to optimise drug/therapy design. The personalised interventions thus identified will be administered to patients. Both ends of the spectrum (i.e. Acquire and Administer) will need to be amenable to ethical, legal, and industrial regulatory criteria to ensure standardised, reliable, and consistent delivery of computationally-driven personalised healthcare.*

However, such pipelines necessitate that the computational community work closely with regulatory bodies and stakeholders at both ends of the pipeline. At the patient end, this includes addressing ethical concerns pertaining to the ownership, privacy, and storage of patient data. At the innovation end, this entails garnering appropriate approval to clinical software that will come fitted with one of these predictive models or machine learning algorithms, training clinicians in their application, as well as addressing ethical and legal concerns that will emerge from a shift to computation-aided healthcare. This will ensure standardised, consistent, and reliable delivery of computationally-driven personalised healthcare. To this extent, the recently released discussion paper by the US Food and Drug Administration (FDA) to regulate artificial intelligence-based products used in healthcare that continually adapt based on new data is a key milestone. While the scope of this discussion paper [61] encapsulates criteria to determine when an AI based product will require FDA approval before commercialisation, it will inevitably widen as products coupling AI with predictive mathematical models become the norm in future.

Conclusion

Computational models are fast elevating the clinical landscape and have moved rapidly to predicting outcomes at the patient level. Certain approaches have shown promise in terms of capturing patient-specificity. While the patient-specificity in these models emerges from patient anatomy, a current challenge in healthcare remains lack of a modelling approach that can integrate events across multiple biological hierarchies. Agent-based modelling is a powerful approach that can fulfil this role as it offers an optimal mathematical representation of cells and, hence, can act as the appropriate interface between patients' omics' profile and higher-level (cell/tissue/organ) function. Moving closer to a reality where precision healthcare is available at clinical scale will require this computational pipeline to be robust, computationally practical in terms of speed, and amenable to regulatory standards.

Acknowledgements

The work on the virtual patient was supported by the Airway Disease Predicting Outcomes through Patient Specific Computational Modelling (AirPROM) project, funded through the Seventh European Union Framework grant # 270194. Himanshu Kaul is currently supported by the Michael Smith Foundation for Health Research Trainee Award.

Declaration of interest

No interest declared

References

[1] Brennan P, Perola M, van Ommen GJ, Riboli E, Consortium EC. Chronic disease research in Europe and the need for integrated population cohorts. Eur J Epidemiol. 2017;32(9):741-749.
[2] Struckmann V, Snoeijs S, Melchiorre MG, et al. Caring for people with multiple chronic conditions in Europe. Eurohealth International. 2014;20(3):35-40.
[3] Peerani R, Zandstra PW. Enabling stem cell therapies through synthetic stem cell-niche engineering. J Clin Invest. 2010;120(1):60-70.

[4] Kaul H, Ventikos Y. On the genealogy of tissue engineering and regenerative medicine. Tissue Eng Part B Rev. 2015;21(2):203-217.
[5] Winslow RL, Trayanova N, Geman D, Miller MI. Computational Medicine: Translating Models to Clinical Care. Sci Transl Med. 2012;4(158).
[6] Thomsen SF. Genetics of asthma: an introduction for the clinician. Eur Clin Respir J. 2015;2: 10.3402/ecrj.v2.24643.
[7] Kaul H. A multi-paradigm modelling framework for simulating biocomplexity. Oxford: Engineering Science, University of Oxford; 2013.
[8] Davidson E, Levine M. Gene regulatory networks. Proc Natl Acad Sci USA. 2005;102(14):4935-4935.
[9] Von Neumann J, Burks AW. Theory of self-reproducing automata. Urbana,: University of Illinois Press; 1966.
[10] Fortuna L, Frasca M, Fiore A, Chua L. The wolfram machine. Int J Bifurcat Chaos. 2010;20(12):3863-3917.
[11] Kaul H, Ventikos Y. Investigating biocomplexity through the agent-based paradigm. Brief Bioinform. 2015;16(1):137-152.
[12] Viswanathan S, Zandstra PW. Towards predictive models of stem cell fate. Cytotechnology. 2003;41(2-3):75-92.
[13] Brehme M, Koschmieder S, Montazeri M, et al. Combined Population Dynamics and Entropy Modelling Supports Patient Stratification in Chronic Myeloid Leukemia. Sci Rep. 2016;6:24057.
[14] Trefois C, Antony PM, Goncalves J, Skupin A, Balling R. Critical transitions in chronic disease: transferring concepts from ecology to systems medicine. Curr Opin Biotechnol. 2015;34:48-55.
[15] Ghalati PF, Samal SS, Bhat JS, Deisz R, Marx G, Schuppert A. Critical Transitions in Intensive Care Units: A Sepsis Case Study. arXiv. 2019.
[16] Guo L, Vardakis JC, Lassila T, et al. Subject-specific multi-poroelastic model for exploring the risk factors associated with the early stages of Alzheimer's disease. Interface Focus. 2018;8(1):20170019.
[17] Peach TW, Ngoepe M, Spranger K, Zajarias-Fainsod D, Ventikos Y. Personalizing flow-diverter intervention for cerebral aneurysms: from computational hemodynamics to biochemical modeling. Int J Numer Meth Bio. 2014;30(11):1387-1407.
[18] Noble D. Cardiac action and pacemaker potentials based on the Hodgkin-Huxley equations. Nature. 1960;188:495-497.

[19] Helm PA, Tseng HJ, Younes L, McVeigh ER, Winslow RL. Ex vivo 3D diffusion tensor imaging and quantification of cardiac laminar structure. Magn Reson Med. 2005;54(4):850-859.
[20] Gurev V, Lee T, Constantino J, Arevalo H, Trayanova NA. Models of cardiac electromechanics based on individual hearts imaging data: image-based electromechanical models of the heart. Biomech Model Mechanobiol. 2011;10(3):295-306.
[21] Sugiura S, Washio T, Hatano A, Okada J, Watanabe H, Hisada T. Multi-scale simulations of cardiac electrophysiology and mechanics using the University of Tokyo heart simulator. Prog Biophys Mol Biol. 2012;110(2-3):380-389.
[22] McDowell KS, Arevalo HJ, Maleckar MM, Trayanova NA. Susceptibility to arrhythmia in the infarcted heart depends on myofibroblast density. Biophys J. 2011;101(6):1307-1315.
[23] Bayer JD, Narayan SM, Lalani GG, Trayanova NA. Rate-dependent action potential alternans in human heart failure implicates abnormal intracellular calcium handling. Heart Rhythm. 2010;7(8):1093-1101.
[24] Benson AP, Al-Owais M, Holden AV. Quantitative prediction of the arrhythmogenic effects of de novo hERG mutations in computational models of human ventricular tissues. Eur Biophys J. 2011;40(5):627-639.
[25] Kerckhoffs RC, McCulloch AD, Omens JH, Mulligan LJ. Effects of biventricular pacing and scar size in a computational model of the failing heart with left bundle branch block. Med Image Anal. 2009;13(2):362-369.
[26] Moreno JD, Zhu ZI, Yang PC, et al. A computational model to predict the effects of class I anti-arrhythmic drugs on ventricular rhythms. Sci Transl Med. 2011;3(98):98ra83.
[27] Tawhai MH, Nash MP, Lin CL, Hoffman EA. Supine and prone differences in regional lung density and pleural pressure gradients in the human lung with constant shape. J Appl Physiol. 2009;107(3):912-920.
[28] Burrowes KS, Iravani A, Kang W. Integrated lung tissue mechanics one piece at a time: Computational modeling across the scales of biology. Clin Biomech (Bristol, Avon). 2018.
[29] Bordas R, Lefevre C, Veeckmans B, et al. Development and Analysis of Patient-Based Complete Conducting Airways Models. Plos One. 2015;10(12).
[30] Tawhai MH, Hunter P, Tschirren J, Reinhardt J, McLennan G, Hoffman EA. CT-based geometry analysis and finite element models of the human and ovine bronchial tree. J Appl Physiol. 2004;97(6):2310-2321.
[31] Foy BH, Soares M, Bordas R, et al. Lung Computational Models and the Role of the Small Airways in Asthma. Am J Respir Crit Care. 2019.

[32] Oostveen E, MacLeod D, Lorino H, et al. The forced oscillation technique in clinical practice: methodology, recommendations and future developments. Eur Respir J. 2003;22(6):1026-1041.
[33] Murray PJ, Walter A, Fletcher AG, Edwards CM, Tindall MJ, Maini PK. Comparing a discrete and continuum model of the intestinal crypt. Phys Biol. 2011;8(2):026011.
[34] Parunak HV, Savit R, Riolo RL. Agent-based modeling vs. equation-based modeling: A case study and users ' guide. Multi-Agent Systems and Agent-Based Simulation. 1998;1534:10-25.
[35] Saunders R, Kaul H, Berair R, et al. DP2 antagonism reduces airway smooth muscle mass in asthma by decreasing eosinophilia and myofibroblast recruitment. Sci Transl Med. 2019;11(479):eaao6451.
[36] Flood-Page PT, Menzies-Gow AN, Kay AB, Robinson DS. Eosinophil's role remains uncertain as anti-interleukin-5 only partially depletes numbers in asthmatic airway. Am J Resp Crit Care. 2003;167(2):199-204.
[37] Gonem S, Berair R, Singapuri A, et al. Fevipiprant, a prostaglandin D2 receptor 2 antagonist, in patients with persistent eosinophilic asthma: a single-centre, randomised, double-blind, parallel-group, placebo-controlled trial. Lancet Respir Med. 2016;4(9):699-707.
[38] Kaul H, Brightling C, Smallwood R. Clinical level agent-based model of pathological airway remodeling in asthma. In. University of Leicester: Figshare; Dataset: 2019. https://doi.org/10.25392/leicester.data.7610933.v1
[39] Saunders RM, Kaul H, Berair R, et al. Fevipiprant (qaw039) Reduces Airway Smooth Muscle Mass In Asthma Via Antagonism Of The Prostaglandin D2 Receptor 2 (dp2). Am J Resp Crit Care. 2017;195.
[40] Chachi L, Diver S, Kaul H, Rebelatto MC, Boutrin A, Nisa P, et al. Computational modelling prediction and clinical validation of impact of benralizumab on airway smooth muscle mass in asthma. Eur Respir J, 2019. DOI: 10.1183/13993003.00930-2019.
[41] Kaul H, Brightling C, Smallwood R. Clinically-relevant computational model of airway remodelling to design and optimise interventions to treat asthma. Eur Respir J. 2017;50(Supplement 61):PA1046. DOI: 10.1183/1393003.congress-2017.PA1046
[42] Murry CE, Keller G. Differentiation of embryonic stem cells to clinically relevant populations: Lessons from embryonic development. Cell. 2008;132(4):661-680.
[43] Kaul H, Hall BK, Newby C, Ventikos Y. Synergistic activity of polarised osteoblasts inside condensations cause their differentiation. Sci Rep. 2015;5:11838.
[44] Adra S, Coakley S, Kiran M, McMinn P. An Agent-Based software platform for modelling systems biology. In Epitheliome Project Report:2008:58.

[45] Adra S, Sun T, MacNeil S, Holcombe M, Smallwood R. Development of a Three Dimensional Multiscale Computational Model of the Human Epidermis. PLoS One. 2010;5(1):Article No.: e8511.
[46] Sun T, Adra S, Smallwood R, Holcombe M, MacNeil S. Exploring Hypotheses of the Actions of TGF-beta 1 in Epidermal Wound Healing Using a 3D Computational Multiscale Model of the Human Epidermis. PLoS One. 2009;4(12):Article No.: e8515.
[47] Walker D, Sun T, Macneil S, Smallwood R. Modeling the effect of exogenous calcium on keratinocyte and HaCat cell proliferation and differentiation using an agent-based computational paradigm. Tissue Eng. 2006;12(8):2301-2309.
[48] Li X, Upadhyay AK, Bullock AJ, et al. Skin stem cell hypotheses and long term clone survival--explored using agent-based modelling. Sci Rep. 2013;3:1904.
[49] Pierce SM, Skalak TC, Papin JA. Multiscale biosystems integration: coupling intracellular network analysis with tissue-patterning simulations. IBM J Res Dev. 2006;50(6):601-615.
[50] Kaul H, Cui Z, Ventikos Y. A multi-paradigm modeling framework to simulate dynamic reciprocity in a bioreactor. PLoS One. 2013;8(3):e59671.
[51] Bissell MJ, Hall HG, Parry G. How does the extracellular-matrix direct gene expression. J Theor Biol. 1982;99(1):31-68.
[52] Kaul H, Ventikos Y. Dynamic reciprocity revisited. J Theor Biol. 2015;370:205-208.
[53] Kaul H, Ventikos Y, Cui ZF. A computational analysis of the impact of mass transport and shear on three-dimensional stem cell cultures in perfused micro-bioreactors. Chinese J Chem Eng. 2016;24(1):163-174.
[54] Cioffi M, Boschetti F, Raimondi MT, Dubini G. Modeling evaluation of the fluid-dynamic microenvironment in tissue-engineered constructs: A micro-CT based model. Biotechnol Bioeng. 2006;93(3):500-510.
[55] Maes F, Van Ransbeeck P, Van Oosterwyck H, Verdonck P. Modeling Fluid Flow Through Irregular Scaffolds for Perfusion Bioreactors. Biotechnol Bioeng. 2009;103(3):621-630.
[56] Consolo F, Caronna M, Montevecchi FM, Flore GB, Redaelli A, Asme. A CFD computational model for the optimization of transport phenomena in a rotating hollow fiber bioreactor for artificial liver. Proceedings of the Asme Summer Bioengineering Conference 2008, Pts a and B. 2009:477-478.
[57] Bilgen B, Sucosky P, Neitzel GP, Barabino GA. Flow characterization of a wavy-walled bioreactor for cartilage tissue engineering. Biotechnol Bioeng. 2006;95(6):1009-1022.

[58] Krause J, Gulshan V, Rahimy E, et al. Grader Variability and the Importance of Reference Standards for Evaluating Machine Learning Models for Diabetic Retinopathy. Ophthalmology. 2018;125(8):1264-1272.
[59] Gulshan V, Peng L, Coram M, et al. Development and Validation of a Deep Learning Algorithm for Detection of Diabetic Retinopathy in Retinal Fundus Photographs. JAMA. 2016;316(22):2402-2410.
[60] Poplin R, Varadarajan AV, Blumer K, et al. Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning. Nat Biomed Eng. 2018;2(3):158-164.
[61] FDA. Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) - Discussion Paper and Request for Feedback. In:2019.