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Whole-body metabolic modelling and its prospects in precision nutrition

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Abstract

Nutrition has long been investigated with respect to its influence on human health. With the availability of various omics data, such as metagenomics and metabolomics, novel insights have been obtained into the influence of nutrition, particularly concerning the gut microbiome. The gut microbiome plays an important role in the breakdown of food-derived compounds and in producing essential bioactive metabolites required for human health. However, this wealth of information made the interactions between nutrition and human health increasingly intricate, and unravelling these links is complex. This review covers the concepts of genome-scale metabolic modelling as a tool to understand the links between nutrition, the gut microbiome and human metabolism and its applications. Genome-scale metabolic modelling treats metabolism as a mathematical problem which was used to develop models of human metabolism that incorporate physiology and organ-specific metabolism, known as whole-body metabolic models (WBMs). WBMs can incorporate physiological data, such as sex, weight and body fat percentage, as well as nutrition in the form of its metabolite constituents. Finally, the gut microbiome can also be incorporated through a mathematical representation of the species present, based on stool metagenomics. WBMs have already been applied to understand gut microbiome–host co-metabolism in various non-communicable diseases. However, challenges remain, as metabolites measured in food items in public databases typically cover only common metabolites, and engagement with end-users such as nutritionists and policymakers is limited. Nevertheless, WBMs represent a promising step towards digital metabolic twins and thus personalised nutrition and medicine.

Introduction

Nutrition is important for human health as it provides metabolites essential to a healthy life, with roles in, e.g., energy creation, signalling pathways or providing metabolites that cannot be synthesised in the human body[1]. Dietary habits can cause an imbalance of key metabolites that are linked to diseases, such as anaemia and coagulation disorders[2]. Additionally, over- or under consumption of groups of metabolites or macronutrients, such as fibre or saturated fatty acids, are linked to non-communicable diseases, such as cancer, type 2 diabetes and chronic inflammation[3–5]. Conversely, nutrition has been used to treat, alleviate and prevent the same diseases that it can cause, showing the duality of nutrition in human health[6,7].

Investigating the links between nutrition and human health is usually done through analysing associations between various -omics data (e.g., metagenomics, genomics or metabolomics) and dietary questionnaires (e.g., food dairies or food frequency questionnaires)[8,9] (Fig. 1). However, understanding these associations can be difficult as the human body is a complex system. To unravel this complexity, the effects of nutrition on human health can be investigated by studying how the nutrient composition of the diet interact with human metabolism.

Human metabolism is influenced by genetics and health status of the human body, nutrition and the microbiomes which exist on and in us (most notably the gut microbiome)[10,11]. Nutrition can alter the composition of the gut microbiome[12–14], whereas the gut microbiome produces many bioactive compounds for the human host[15,16]. Each individual has their own unique gut microbiome, which will react differently when people are given the same diet[17]. The high variability in gut microbiome composition adds an additional layer of complexity when investigating nutrition and human health. A computational method that allows for disentangling the complex interactions between nutrition, the gut microbiome and the human host is genome-scale metabolic modelling[18] (Fig. 1).

This review outlines the general concepts of genome-scale metabolic modelling and the links between nutrition, the gut microbiome and human metabolism. Current methodologies are highlighted, with which the effect of nutrition on human metabolism through metabolic

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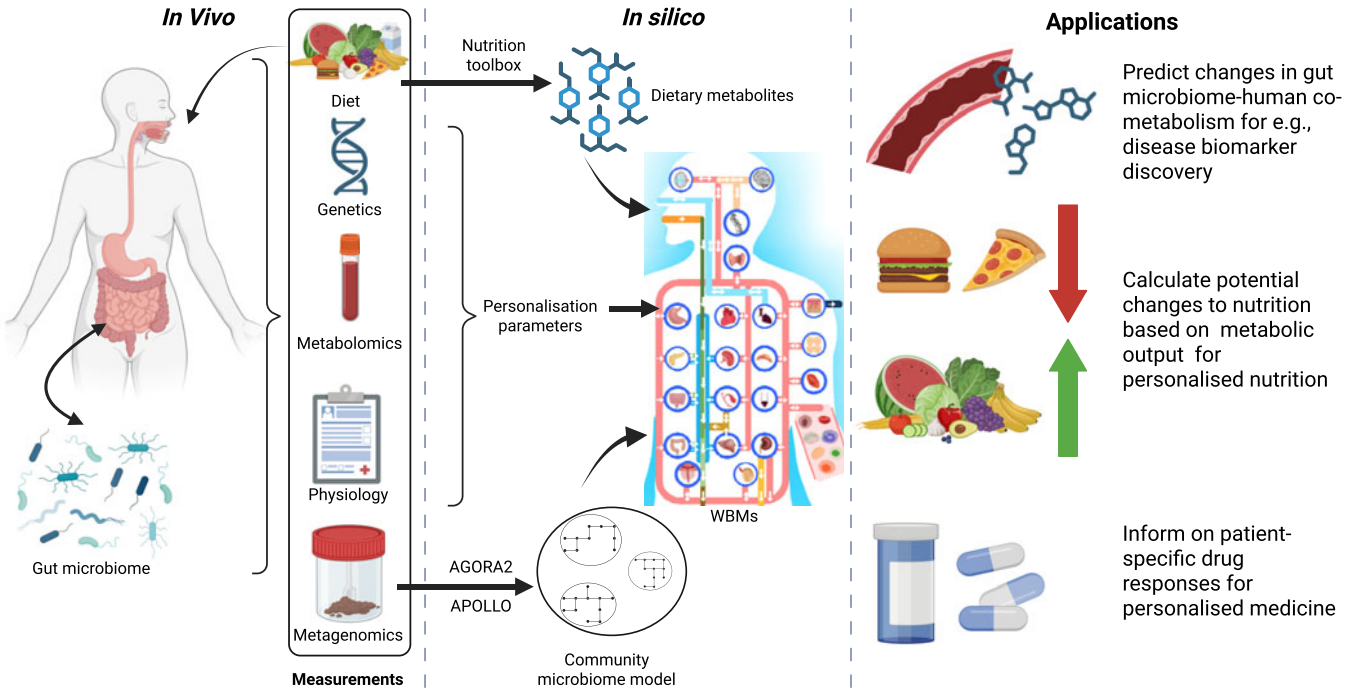

Fig. 1. Schematic overview of factors that can influence human metabolism, which can be measured and incorporated into the whole-body models (WBMs) and how the WBMs can be used in the context of human health. The figure was generated with Biorender.

modelling can be examined. Finally, areas in the use and set-up of WBMs that require further research are discussed as well as potential applications of the mentioned methodologies.

Nutrition and human metabolism

Metabolism describes the collection of biochemical reactions in an organism. These reactions include breaking down (catabolism) or producing (anabolism) molecules. These biochemical reactions are usually catalysed by enzymes encoded in the genome and facilitate reaction rate by several orders of magnitude[19]. In higher organisms, such as humans, metabolism is highly specific, with different organs and cell types exhibiting distinct metabolic capabilities[20–22] and a spatial separation within the cells where enzymes are located in distinct subcellular locations[21].

Human metabolism starts at the digestive tract, which begins in the mouth where food is cut, ground and mixed, and enzymes are added that perform the initial breakdown of macromolecules[23]. The food mixture is passed to the stomach where further enzymatic breakdown of the food occurs. The broken-down food enters the small intestine, where the majority of nutrients are taken up. The small intestine is also where bile is excreted, which contains bile acids that assist in lipid digestion and waste from the liver. The remainder of the metabolites not absorbed in the small intestine move to the large intestine, where additional nutrients are taken up[23]. The large intestine is also the location in the human body with the largest community of microbes, known as the gut microbiome[24,25]. Finally, all the waste from the human body, gut microbiome and undigested metabolites are excreted in the faeces.

It is important to accurately measure which food in which quantities are ingested to understand which nutrients are available to the human body and the gut microbiome. Methods to measure diet composition to understand the foods people consume have been around for decades[26]. Common methods include food frequency questionnaires, recall diets of various time intervals and more recently wearable camera technology[27]. Although these methods give an insight into food consumption, there are limitations to what they can capture. Self-reporting methods are prone to participants over- or under-reporting consumption of food items[27–29]. The wearable camera methods could have difficulties obtaining individual ingredients and consumed amounts for highly mixed foods, such as soups or pies[27,30].

The gut microbiome

The gut microbiome consists of billions of microbes, including archaea, bacteria, fungi and viruses[24,25]. The composition of the gut microbiome is unique to each individual[31]. The gut microbiome assists the digestive system and participates in metabolism by breaking down complex carbohydrates, such as resistant starch and fibre, and producing essential bioactive metabolites, such as short-chain fatty acids (i.e., acetate, propionate and butyrate), neurotransmitters, such as serotonin and dopamine, and vitamins[24,32]. Additionally, the gut microbiome modulates the human immune system and it protects the gut against pathogens[24].

The composition of the gut microbiome is influenced by various factors such as socioeconomic status, geography, sex, age and diet. Of these, diet has shown it can rapidly alter the composition of the gut microbiome[12,14]. Nutrition can thus not only influences what the gut microbiome can produce but also which microbes are present. Influencing the presence and abundance of microbes is important as in many non-communicable diseases the gut microbiome composition is measurably changed[25].

Methods to identify which microbes are present in the gut microbiome have changed and become cheaper and more comprehensive over the last decades[33,34]. The most common methods to discover which microbes are present in a sample are 16S rRNA

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and whole-genome shotgun sequencing[35]. The sequenced data is compared against a reference database containing the sequenced data of known microbes to find the closest related match. Each sequencing technique has its own advantages and disadvantages, 16S rRNA is cheaper but has a decreased sequencing depth, whereas whole-genome shotgun sequencing is more expensive but is able to distinguish microbial species in a microbiome sample[36]. Typically, faecal samples are sequenced to understand which microbes are present in the gut microbiome. This approach assumes that the microbiome found in the faecal sample is representative of the entire large intestine[37,38]. This assumption has yielded valuable insights[25,32,39], but research has shown that the gut microbiome changes considerable depending on the location in the large intestine[38,40]. Other sampling techniques include biopsies, brushing and more recently capsules that capture the microbiome in specific areas of the colon[40,41]. These techniques offer specific microbiome composition in specific areas in the colon but are often invasive or not yet well established.

Once the microbes are identified, they can be characterised by metabolic function, ecological niches or pathogenicity. Additionally, metatranscriptomics[42] (expressed mRNA by the microbiome), metaproteomics (proteins expressed by the microbiome) and metabolomics[38,43] can further provide insights into the functional capabilities of the gut microbiome. These methods, however, often give microbiome-wide associations as opposed to species-specific interactions. Additionally, there are limitations the preparation of these omics, such extraction and yield, and reference databases can be incomplete[44–46]. Another method that aims to elucidate, mechanistically, gut microbiome-human metabolism is genome-scale metabolic modelling.

What is genome-scale metabolic modelling

Genome-scale metabolic modelling is a mathematical approach to metabolism and is the core concept for the constraint-based reconstruction and analysis (COBRA) framework[47]. Converting metabolism of an organism to a mathematical representation is typically done by identifying the biochemical reactions based on its genome. Any missing pathways that have limited genomic annotation or consist of non-enzymatic reactions have to be added manually or through algorithms[48,49]. There are multiple tools available to automate the conversion of the genome of an organism to its corresponding mathematical representation[50–54]. Additionally, metabolic modelling can take information from the biological context to inform its predictions, e.g., consumption of metabolites to ensure maintenance of an organ or the intake of dietary nutrients.

Generally, metabolic modelling does not yet take into account enzyme kinetics or regulation of enzyme expression. Inclusion of these additional constraints requires information on all enzymes in the metabolic system which is often unknown for well-characterised bacteria, let alone for all possible human enzymes. However, there are tools available to add on additional constraints to the metabolic models based on transcriptomics or proteomics[55–57].

Current status of modelling human metabolism

Over the last two decades, metabolic modelling has been used to study bacteria[58], fungi[59], plants[60], animals[43] and humans[18,61,62]. In the context of diet-gut microbiome-human metabolism, metabolic models for the gut microbiome and the human are required. The latest microbiome collections, AGORA2 with over 7000 microbial models[63] and APOLLO with over 230,000 microbial models[64] can be used to create and simulate human microbiome metabolism. AGORA2 and APOLLO have been used to accurately predict changes in gut microbiome metabolism in different non-communicable diseases[65–69].

There are two mathematical models of generic human metabolism, Recond3D[61] and Human1[62], which have been used to simulate cell- and organ-specific metabolism. However, these models do not account for human physiology, organ-organ interactions and biofluid movements, leading to the creation of whole-body metabolic models (WBMs)[18]. The WBMs are sex-specific and have over 20 organs and six cell types that are specific in their metabolic capacities and are connected through 13 different biofluids[18]. WBMs representing infants have also recently been published, which allows for the metabolic modelling of infants from age day 0 to 180[70].

The WBMs can 'consume' a diet as long as the diet is defined by the metabolite constituents. There are eleven *in silico* diets available on the virtual metabolic human website (https://vmh.life) that represent generic diets[71], which allows for investigations into the influence of diet on human metabolism. However, creation of *in silico* diets is time-consuming when done manually and has limited the use of individual diets in WBM modelling, even when dietary information was available. Recently, the nutrition toolbox has been published, which allows for efficient and robust generation of *in silico* diets[72]. When dietary information is available, this toolbox can be used to 'feed' the WBM adjusted to the specific diet that an individual has actually consumed. Additionally, the nutrition algorithm[73] has been adapted to be compatible with the WBMs. The nutrition algorithm calculates the smallest adjustment to an existing diet that is required to achieve the largest change in metabolism. The WBMs can also intake drugs, leading to the ability of predicting drug metabolism, paving the way for personalised medicine.

The WBMs can be further personalised by adjusting physiological parameters, such as weight or body fat percentage, based on an individual. Additionally, the gut microbiome models can be integrated with the large intestinal lumen of the WBMs to account for gut microbiome-host co-metabolism. The WBMs have been used to simulate metabolism in various disease contexts, such as inborn errors of metabolism[18], COVID-19[74], Parkinson disease[75], Alzheimer's disease[76] and metabolic syndrome[77].

Future prospects

The recent advances in genome-scale metabolic modelling outlined above have resulted in an attractive portfolio of computational modelling tools amenable towards the creation of digital metabolic twins (DMTs), i.e., digital replicas of an individual's metabolism, for predictive decision-making along the nutrition-host-microbiome-health axis (Fig. 1).

The constituting resource are continuously updated to capture the growing knowledge content. The human reconstructions have grown from ~3,000 reactions and metabolites (Recon1[78]) to now ~80,000, including sex-, organ- and cell type-specific content in the WBMs[53]. The microbiome efforts originated from reconstructing individual microbes[79] to entire resources now encompassing almost a quarter million microbes[64]. However, the current reconstructions primarily capture the metabolism of endogenous metabolites, i.e., further efforts are required to incorporate information on xenobiotics, including phytochemicals[80]. Currently, *in silico* diets are created based on information derived from publicly available databases, such as the USDA FoodData Central[81] or

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FRIDA[82], which capture individual metabolite-level information for different food items. However, the metabolite coverage remains limited, at least in part due to current challenges in the required analytical measurement challenges in the field of foodomics[83]. Further, efforts are ongoing to specify the molecular composition of complex carbohydrates, such as starch or fibre, which are usually too broadly captured in current databases[84]. Increasing the content of plant-specific metabolism both in current nutrition databases and in the genome-scale reconstructions will allow for more precise and accurate simulations with the WBMs, enabling better prediction of dietary supplementation from foods in the same food groups. Future developments will expand the scope of modelling from diet alone to a more holistic capture of health modulators, such as medication use, physical activity, lifestyle factors or environmental exposures, all of which influence metabolic function. Incorporating such information will allow models to capture diet–host–microbiome interactions in the broader context of modulators of human metabolism (e.g., environmental chemicals or lifestyle factors) and support nutrition strategies tailored to specific clinical conditions or health goals.

Current workflows have emerged primarily from a pre-clinical fundamental research context, with a focus on computational biology. Therefore, the specific tools and skills to generate COBRA-derived mechanism-informed hypotheses remain largely confined to a specialist computational modelling community. To enable *in silico* modelling-enabled decision support systems amenable to providing dietary advice, there is a need to collaborate with the intended end users, such as nutritionists, to create tools which align with their needs and expectations. Ongoing efforts to diversify the modelling user base include, e.g., the creation of the VMH (www.vmh.life) database[71], which hosts and interconnects the current genome-scale modelling resources through a user-friendly web interface.

Thus far, policymaking has relied on population-based statistics for deriving dietary guidelines. Therefore, while largely sound at a general population level, the guidelines may not align with the dietary requirements at an individual level, e.g., relating to the substantial variation in daily energy requirements[85]. It is further suggested that personalised approaches are more effective to catalyse changes in dietary behaviour than conventional approaches[86], i.e., population-level dietary guidelines may be ineffective at addressing ongoing challenges, such as tackling increasing obesity rates and associated co-morbidities[87]. Genome-scale metabolic modelling may therefore be an attractive complement to evidence-based policymaking by enabling the creation of sub-population-derived models for hypothesis testing and validation, including in cases where the corresponding population data may not yet be available. For example, WBMs provide a straightforward solution for testing differences in males compared to females (by using the appropriate sex-specific models), which may help mitigate gender-related biases in large population surveys[88]. Notably, the WBMs can be personalised using different diets, i.e., dietary advice may be tested *in silico* to inform or validate the hypotheses derived from population-based evidence. Therefore, genome-scale metabolic modelling along the diet-host-microbiome-health axis may provide a powerful set of computational tools to inform future evidence-based policymaking efforts.

Overall, the recent advances in metabolic modelling provide a fruitful ground for developing DMTs to test dietary interventions *in silico* before implementation in real life. The current technology development trajectory supports decision-support systems for end users, such as clinicians and dietitians, enabling the comparison of alternative dietary scenarios and identifying interventions most likely to achieve a desired metabolic outcome. Further, integration with wearable devices and other digital health technologies may enable continuous data collection to support, e.g., personalised coaching for nutritional advice to be dynamically adjusted over time. Beyond the metabolic modelling as such, the successful implementation of DMT development will also rely on several enabling technology developments. The generation and availability of high-quality input data is essential, including accurate dietary assessment, expanded food composition databases capturing a comprehensive spectrum of food metabolites and high-resolution multi-omics methodologies to characterise host and microbiome function. Interoperability with established biomedical and nutrition databases, standardised data formats and robust analytical pipelines will be critical to ensure scalability and reproducibility. Ultimately, computational modelling approaches have the potential to empower individuals by providing transparent, biologically grounded explanations of how dietary choices may influence their metabolism and health. However, model predictions represent hypotheses derived from mathematical representations and must be validated and interpreted within the context of evidence-based nutritional practice. Close collaboration between modellers, nutrition professionals, clinicians and regulators will therefore be essential to translate metabolic modelling into safe, effective and sustainable precision nutrition.

Conclusion

Understanding how nutrition influences human metabolism has become more accessible with the rise of novel methodologies. However, that has also increased the complexity of linking the various data type together to formulate and test hypotheses to finally propose dietary advice. Genome-scale metabolic modelling with WBMs can incorporate various types of omics data and physiological parameters to accurately represent an individual's metabolism leading the way to DMTs. Currently, human-microbiome co-metabolism can be modelled through the use of the AGORA2 and APOLLO resources, whereas creation of personalised *in silico* diets have been made more efficient and robust through the nutrition toolbox. Although advances in methodologies and applications for the WBMs have been in development, there are still areas that require further attention. The availability of metabolite content in food databases limits coverage the effects of nutrition on human metabolism simulations and there is of yet limited engagement with potential end users of the simulated results such as nutritionists and policy makers. However, the WBMs represent a crucial step to an efficient and reliable method to understand human metabolism and propose individual-specific dietary changes for health.

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