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Research review paper

Predicting drug-microbiome interactions with machine learning

Laura E. McCoubrey, Simon Gaisford, Mine Orlu, Abdul W. Basit *

University College London, London, United Kingdom

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ABSTRACT

Pivotal work in recent years has cast light on the importance of the human microbiome in maintenance of health and physiological response to drugs. It is now clear that gastrointestinal microbiota have the metabolic power to promote, inactivate, or even toxify the efficacy of a drug to a level of clinically relevant significance. At the same time, it appears that drug intake has the propensity to alter gut microbiome composition, potentially affecting health and response to other drugs. Since the precise composition of an individual's microbiome is unique, one's drug-microbiome relationship is similarly unique. Thus, in the age of evermore personalised medicine, the ability to predict individuals' drug-microbiome interactions is highly sought. Machine learning (ML) offers a powerful toolkit capable of characterising and predicting drug-microbiota interactions at the individual patient level. ML techniques have the potential to learn the mechanisms operating drug-microbiome activities and measure patients' risk of such occurrences. This review will outline current knowledge at the drug-microbiota interface, and present ML as a technique for examining and forecasting personalised drug-microbiome interactions. When harnessed effectively, ML could alter how the pharmaceutical industry and healthcare professionals consider the drug-microbiome axis in patient care.

1. Uncovering the drug-microbiome relationship

Described as the 'last organ', the human microbiome encompasses trillions of microorganisms residing within a myriad of ecological niches of the human body. Bacteria, fungi, and archaea represent key living microbes, known as microbiota; whereas phages, viruses, and plasmids are principal non-living elements of the microbiome (Berg et al., 2020). Collectively, these microorganisms present a dynamic, diverse, and complex genetic reservoir that exists in interactive flux with itself and human cells (Huttenhower et al., 2012). The scale of the microbiome is substantial; commensal bacteria alone are more numerous than human cells and encode for 150 times more unique genes than their human host (Qin et al., 2010; Sender et al., 2016). The majority of microbiota reside in the lower gastrointestinal (GI) tract and are known as the human gut microbiome (HGM). In possessing such genetic diversity, the HGM can be considered as having the metabolic capacity of the liver (Scheline, 1968).

Pioneering work of the 19th century by Nobel Laureate Robert Koch and Louis Pasteur cast light on bacteria as causes of disease (Koch (Biographical, 1967). Whilst marking a medical milestone, and facilitating the treatment of countless infectious diseases worldwide, the perception of microorganisms as solely pathogenic has widely persisted. As such, the presence of microorganisms on, within, and in proximity to the human body is often regarded negatively, and widespread global overuse of antimicrobials persists (Malik and Bhattacharyya, 2019). In reality, the importance of the microbiome for human health, and the significance of maintaining microbial diversity, are now only being realised (Manor et al., 2020; Proctor et al., 2019; Uzan-Yulzari et al., 2021). Numerous diseases, including metabolic syndrome, autoimmune dysfunction, inflammatory bowel disease, and neurological disorders have been linked to a dysbiotic HGM with varying degrees of mechanistic insight (Cryan et al., 2020; Jostins et al., 2012; Markle et al., 2013; Vrieze et al., 2012). Generally, the microbiome's metabolic functions enable physiological processes critical for human health. Microbial enzymes possess significant functional redundancy, capable of transforming many chemically distinct substrates (Tian et al., 2020). For example, gut microbiota regulate half of all intestinally derived serotonin, synthesise several vitamins, and break down macronutrients (such as fibre) that are otherwise indigestible by human cells (Fung et al., 2019; Oliphant and Allen-Vercoe, 2019).

While the role of the HGM in maintaining good health is broadly recognised, it is not well understood. The extent to which the microbiome affects the physiological action of drugs has only recently begun to emerge. The first case of microbial drug metabolism was discovered in

* Corresponding author.
E-mail address: a.basit@ucl.ac.uk (A.W. Basit).

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the 1930s when an early sulphonamide antibiotic, Prontosil, was found to require activation by intestinal bacteria for therapeutic action (Fuller, 1937). Despite this early realisation most known drug-microbiome interactions have only been characterised following the turn of the century, enabled by advancing genomic, metabolomic, and microbiological methods (Huttenhower et al., 2012). Over 180 drugs are now recognised as substrates for gut bacterial enzymes, and thus vulnerable to direct enzymatic transformation *in vivo* (Hatton et al., 2019; Zimmermann et al., 2019a). It is becoming clear that microbial metabolism can significantly affect the clinical response to drugs. An individual's microbiome composition is thought to be as unique as a fingerprint (Franzosa et al., 2015). Consequently, microbiome heterogeneity may represent a significant cause of variability in patients' physiological, and thus clinical, response to drug treatment (Vinarov et al., 2021). In addition, the drug-microbiome relationship can be regarded as bidirectional: as the microbiome can affect drugs, the administration of drugs can similarly affect the microbiome. With new studies linking dysbiosis to disease frequently emerging, it is prudent to understand how drugs may impact commensals and therefore, human health (Maier et al., 2018).

In clinical practice, variability in patients' drug response frequently leads to dosing difficulties, adverse reactions, and failures in clinical trials (Harrison, 2016; Madla et al., 2021). If drug-microbiome interactions could be predicted at the individual patient level, then a portion of this variability could be forecast and thus accounted for. Moreover, prediction of how drugs may affect individuals' microbiome compositions could lead to changes in treatment, whereby microbiome health is a considered factor at the point of prescribing. As such, the occurrence of drug-induced dysbiosis could be substantially lessened and the selection of an optimal treatment and dose would become easier. Machine learning (ML) stands to be an enabling tool for the characterisation and prediction of drug-microbiome interactions. Enumerate factors shape one's microbiome composition including the presence of disease, age, sex, diet, genome, and lifestyle (Chaudhari et al., 2020; Keohane et al., 2020). ML techniques can interpret extremely large datasets, considering thousands of patients and factors, and identify intrinsic drug-microbiome patterns (Elbadawi et al., 2021a). Frequently, ML can identify patterns at speeds and accuracies far exceeding human capabilities (Silver et al., 2017). With these patterns elucidated, prediction of drug-microbiome interactions can be made for new patients, based on how they compare to those examined in the original dataset. Medicine is increasingly adopting ML, and other forms of artificial intelligence, to streamline and optimise every stage of the patient pathway, from symptom recognition to treatment, discharge, and patient support (Gilvary et al., 2019; May, 2021). The pharmaceutical industry is also embracing ML for the streamlined development of new drugs (Damiati, 2020; Elbadawi et al., 2021c). In coming years, it is likely that ML will be frequently harnessed for use in microbiome medicine (Fig. 1) (McCoubrey et al., 2021a).

In this review, current knowledge at the drug-microbiome interface is examined, with consideration for how ML can be leveraged to explain and predict interactions. We highlight how gut microbiota modulate drug response both directly and indirectly, and explore how medicines can affect HGM composition for the better or worse. We present ML as an emerging tool, describing how it is currently used in microbiome medicine, its strengths, challenges, and implications for future practice.

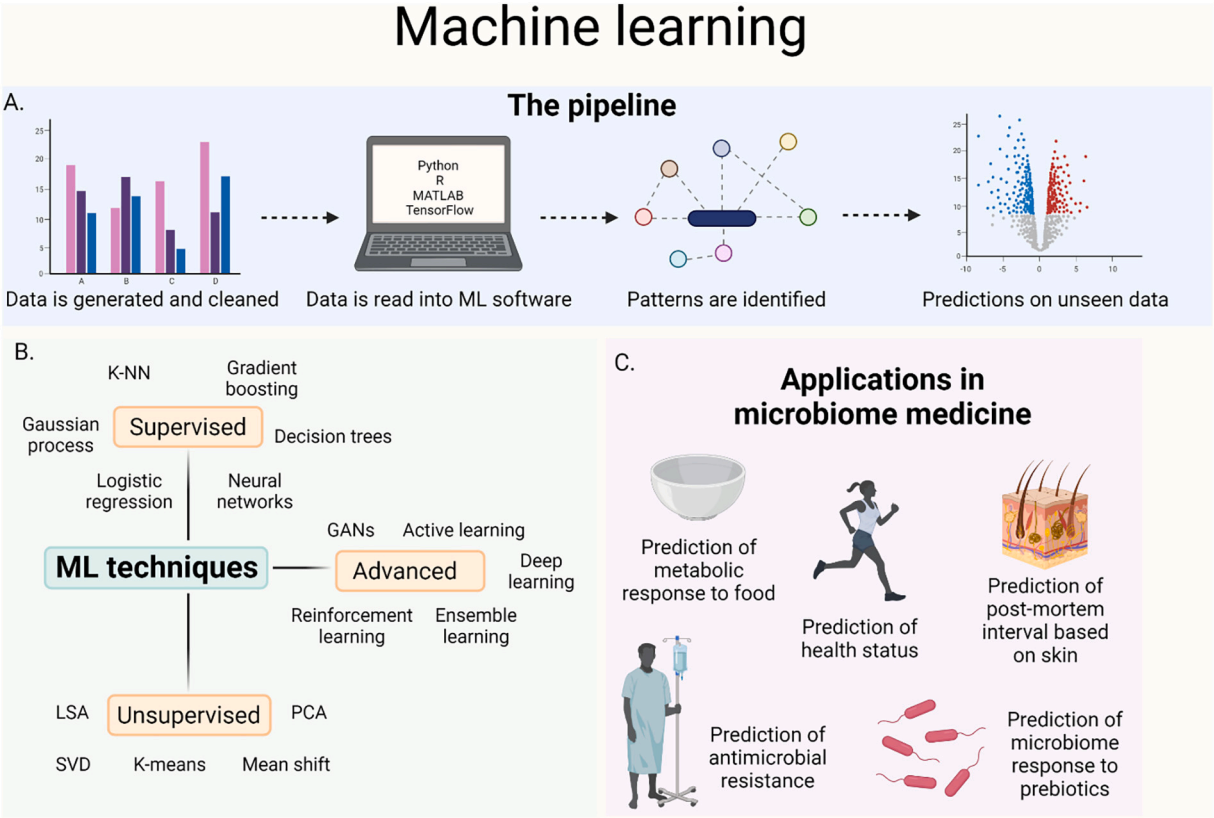


Fig. 1. A: The machine learning (ML) project workflow; B: common ML techniques, separated into supervised, unsupervised, and advanced categories. K-NN: k nearest neighbour, GANs: generative adversarial networks, LSA: latent semantic analysis, SVD: singular value decomposition, PCA: principal component analysis; C: existing applications of ML in microbiome medicine include prediction of metabolic response to food (Berry et al., 2020), health status (Gupta et al., 2020), post-mortem interval based on skin microbiome (Johnson et al., 2016), antimicrobial resistance (Khaledi et al., 2020), and microbiome response to administration of prebiotics (Luo et al., 2018).

2. Direct microbial metabolism

Currently, the most characterised mechanism of microbiome-mediated drug metabolism is direct enzymatic transformation of drugs within the GI tract (Basit et al., 2002; Clarke et al., 2019; Yadav et al., 2013). The density and composition of microorganisms residing within each region of the digestive system varies substantially, affected by parameters such as pH; oxygen availability; nutrient supply; motility; luminal fluid volume; and host immune activity. Multiple niches also exist within the same GI region; for example, microbiota inhabiting the luminal fluid are distinct to those populating the epithelial mucosal surface (James et al., 2020). Microorganism density and diversity progressively increases from the proximal to distal gut: from 10^1 to 10^3 bacterial colony-forming units (CFU) per mL in the stomach, to 10^{10}–10^{12} bacterial CFU/mL in the colon (Martinez-Guryn et al., 2019). There is less knowledge on the spatial organisation of non-bacterial elements of the HGM, which account for a minor but physiologically important proportion of GI microorganisms (Gregory et al., 2020; van Tilburg Bernardes et al., 2020). Bacteria in all regions of the GI tract produce enzymes with high functional redundancy, capable of transforming a diverse array of substrates (Tian et al., 2020; Varum et al., 2020a; Varum et al., 2020b). Such enzymes have evolved to digest dietary nutrients, aid lipid absorption, maintain microbial homeostasis, and detoxify ingested poisons (Joice et al., 2014). Interaction between drugs and microbial enzymes can result in both positive and negative changes to original drug mass, with common transformations including oxidation, reduction, deacetylation, hydrogenation, hydroxylation, and acetylation (Zimmermann et al., 2019a) (Table 1). Biologics can also be affected (Wang et al., 2015; Yadav et al., 2016). It is not just orally administered drugs that are susceptible to enzymatic metabolism by gut microbiota: parenteral drugs can reach the gut through excretion in bile acids or diffusion from systemic circulation.

In recent years, the scale of enzymatic drug transformation in the gut has become clear. Two key studies within the field have used high throughput *in vitro* screening to identify instances and mechanisms of direct drug metabolism by intestinal bacteria (Javdan et al., 2020; Zimmermann et al., 2019a). In the first, Zimmerman et al. investigated 76 strains of human GI bacteria for their ability to chemically modify 271 oral drugs (Zimmermann et al., 2019a). The researchers incubated each drug with each bacterial strain for 12 h and used liquid chromatography mass spectrometry to identify instances of drug transformation. From the 20,596 drug-bacteria interactions assessed, two-thirds (176) of the investigated drugs were found to undergo chemical modification by at least one strain of gut bacteria. This, understandably, includes many drugs with known inter-individual variabilities in pharmacological response. In the study, Zimmerman et al. investigated bacterial metabolism as a cause of inter-patient variability using the model drug dexamethasone. It was known from the *in vitro* screen that dexamethasone undergoes sidechain cleavage by *Clostridium scindens* (ATCC 35704), liberating an androgen metabolite. When dexamethasone was delivered orally to both germ-free and *C. scindens* mono-colonised gnotobiotic mice, the colonised mice had significantly lower levels of caecal and plasma drug concentrations, with correspondingly higher levels of androgen metabolite. This showed that the screening experiment correctly identified dexamethasone's microbial metabolism *in vivo*. Further, anaerobic incubation of dexamethasone with faecal cultures from 28 human donors showed significant variation in individual drug metabolism. This highlights how strain-level differences in HGM profile can directly affect physiological drug handling.

In the second key study, Javdan et al. built on growing knowledge to ascertain greater mechanistic insight into metabolism variability (Chankhamjon et al., 2019; Javdan et al., 2020). Whereas Zimmerman et al. primarily worked with monocultures of gut bacteria, Javdan et al. used batch culturing of whole gut bacteria communities (Javdan et al.,

Table 1
Examples of drugs susceptible to direct transformation by microbial enzymes produced in the gastrointestinal tract.

Drug	Reaction	Causative agent	Experimental model	Effect
Brivudine	Cleaving of tetrahydrofuran ring	*Bacteroides thetaiotaomicron* encoding *bt4554* gene	Mice (sex unspecified)	Increased conversion to hepatotoxic metabolite, bromovinyluracil (BVU) in the caecum, resulting in higher BVU serum levels (Zimmermann et al., 2019b).
Dexamethasone	Desmolysis (sidechain cleaving)	*Clostridium scindens*	Mice (both sexes)	Reduced drug concentration in the caecum, and increased androgen metabolite concentration in the caecum and serum (Zimmermann et al., 2019a).
Digoxin	Lactone ring reduction	*Eggerthella lenta* producing cardiac glycoside reductase enzyme	Mice (male)	Formation of an inactive metabolite, dihydrodigoxin (Haiser et al., 2014). Reduction in digoxin bioavailability (Haiser et al., 2013).
Diltiazem	Deacetylation	*Bacteroides thetaiotaomicron* encoding *bt4096* gene	*Ex vivo* human microbiota from faeces (64% male)	Differences in diltiazem metabolising capacity, correlating with *bt4096* homolog abundance (Zimmermann et al., 2019a).
Doxifluridine	Deglycosylation	*Escherichia coli* encoding *deoA* or *upd* genes	*In vitro* incubation with bacterial strains	Premature activation to 5-fluoruracil, potentially increasing risk of intestinal toxicity (Chankhamjon et al., 2019).
Hydrocortisone	Deacetylation (by unidentified enzyme) and subsequent ketone reduction by 20β-HSDH	*Bifidobacterium adolescentis* encoding the 20β-HSDH gene	*Ex vivo* human microbiota from faeces (sex unspecified)	Formation of 20β-dihydrocortisone (Javdan et al., 2020).
Levodopa	Decarboxylation	Bacterial tyrosine decarboxylases	Humans (both sexes)	Peripheral conversion of levodopa to dopamine. Abundance of intestinal tyrosine decarboxylase explains increased oral levodopa dose requirements in Parkinson's disease patients (van Kessel et al., 2019).
Mycophenolate mofetil	Ester hydrolysis	Unknown	*Ex vivo* human microbiota from faeces (sex unspecified)	Formation of mycophenolic acid, a metabolite linked to gastrointestinal toxicity. Metabolism shows inter-individual variability (Javdan et al., 2020).
Progesterone	Likely reduction	Unknown	*Ex vivo* human microbiota from faeces (males)	Progesterone is degraded by faecal microbiota within 2 h. Potential metabolites include 5α and 5β-pregnanolone (Coombes et al., 2020).
Sulfasalazine	Cleavage of azo bond	Bacterial azoreductases (widely produced across species)	*Ex vivo* human microbiota from faeces (sex unspecified)	Rapid metabolism of the prodrug sulfasalazine (within 120 min) to its active compound, 5-aminosalicylic acid (Sousa et al., 2014).
Tacrolimus	C9 keto-reduction	*Faecalibacterium prausnitzii*	Humans (both sexes)	Production of metabolite, M1, with 15-fold lower immunosuppressant activity (Guo et al., 2019). *F. prausnitzii* abundance positively correlates with oral tacrolimus dose requirements in adult kidney transplant patients (Lee et al., 2015).

2020). Beginning with a screen of 438 drugs in the presence of a single donor's gut bacteria, the researchers found 57 of drugs (13%) to be chemically transformed. These drugs spanned 28 pharmacological classes, including the antiepileptic clonazepam; the anticancer prodrug capecitabine; the anti-Parkinson's tolcapone; and the immunosuppressant mycophenolate mofetil. Chemical analysis was used to characterise the nature of the reactions and specific metabolites formed. The results could substantially aid researchers in predicting the clinical significance of bacterial drug metabolism, as metabolite identification facilitates prediction of downstream physiological effects. In a second part to their study, Javdan et al. used whole gut bacteria cultures from 20 healthy donors to assess variability in microbial metabolism of 23 drugs. They found cases of unanimous drug stability (ketoconazole, ropinirole); unanimous drug depletion (spironolactone, misoprostol); and inter-donor variability (levonorgestrel, capecitabine, hydrocortisone) (Fig. 2). Spironolactone was determined to undergo thioester hydrolysis to the active 7α-thiospironolactone. Misoprostol was consistently metabolised to its active acid form, *via* ester hydrolysis. Capecitabine was variably deglycosylated to deglycocapecitabine, a previously unknown metabolite formed primarily by Proteobacteria. Hydrocortisone was also variability converted, forming androgenic 20β-dihydrocortisone through ketone reduction, likely *via* oxidoreductases produced by Bifidobacteria. This latter reaction has begun to be explored for the microbiome-mediated management of androgen-dependent diseases (Doden et al., 2019).

Within the clinic, notable examples of direct HGM metabolism of critical drugs include tacrolimus (Guo et al., 2019), digoxin (Haiser et al., 2014), and levodopa (van Kessel et al., 2019).

These results have implications for how individual microbiome composition is understood to directly affect pharmacokinetics. However, it is important to recognise the limitations of *in vitro* and *ex vivo* studies when considering whether results translate to drug-microbiome reactions *in vivo*. For example, the work by Zimmerman et al. measured drug metabolism by individual bacterial isolates (Zimmermann et al., 2019a). In the intestines, many different species of microbiota coexist symbiotically alongside each other within diverse ecological niches (Donaldson et al., 2016). Because the metabolic activities of distinct microbial species within heterogenous communities are often interdependent, the behaviour of individual bacterial isolates *in vitro* may not always reflect their behaviour *in vivo*. Furthermore, *in vitro* screening methods often do not consider that the presence of food, bile acids, and hormones within the intestinal lumen can also affect microbial dynamics (Kelly et al., 2020). Whilst the study by Javdan et al. did consider drug metabolism within multi-species microbiome models, by using faeces, the findings of their study may still not fully map to interactions *in vivo* (Javdan et al., 2020). For one, drug metabolism screening was completed using liquid broth populated with faecal microbiota, a medium that does not reflect the multi-niche intestinal environment (Donaldson et al., 2016). Additionally, results are based on microbiota from 20 healthy donors. In reality, it is often patients with diseases who take medicines, and because microbiome composition can be affected by host disease, findings may differ in these individuals (Proctor et al., 2019). Limitations aside, the studies have substantially expanded awareness of microbial drug metabolism due to their high throughput methodology. The *in vitro* results can now be validated with human studies. This work has already been completed for severable drugs, notable examples being the critical drugs tacrolimus (Guo et al., 2019), digoxin (Haiser et al., 2014), and levodopa (van Kessel et al., 2019).

3. Indirect microbial effects on drugs

Whilst direct enzymatic drug metabolism has been most widely explored to date, indirect microbial effects on drug response are no less significant or prominent. Physiological response to drugs can be indirectly mediated by gut microbiome effects on bile acids; epithelial permeability; intestinal drug transporters; gut motility; and hepatic metabolism (Fig. 3).

Drug absorption from the GI tract is a sensitive process. To be absorbed into circulation, drug molecules must be dissolved in GI fluid and either diffuse or be transported across the epithelium. Any factor that affects drug dissolution or membrane permeation can thus affect the amount of drug absorbed into circulation, and therefore a patient's response to the drug (Ong et al., 2021). The microbiome's extensive metabolic activity has substantial impact on the intestinal environment. For one, bile acids undergo significant metabolism by colonic microbiota. The bile-microbiota relationship is symbiotic: bacteria prevent toxic accumulation of bile acids, whilst bile acids prevent bacterial overgrowth and support a stable and diverse gut microbiome (Ridlon et al., 2014). Bile acids also play an important role in the solubilisation of lipids in the GI tract, including lipophilic drugs. There is therefore the possibility that disruptions in gut microbiome composition could affect bile acid homeostasis, and thus affect the absorption of lipophilic drugs (Enright et al., 2018). In liver transplant recipients, it has been observed that ursodeoxycholic acid, a secondary bile acid, significantly and variably affects the absorption of ciclosporin, a lipophilic immunosuppressant (Caroli-Bosc et al., 2000). In another study, microbial enzyme activity was found to impact bile salts' solubilisation capacity for nine oral drugs, including the critical antiepileptic, phenytoin (Enright et al., 2017). Research on the impact of bacterial bile acid metabolism on drug absorption is still in its infancy. Other emerging mechanisms of microbiome-mediated effects on drug absorption are *via* changes to epithelial permeability (Takashima et al., 2020), gut motility (Roager et al., 2016), and intestinal drug transporters (González-Sarrías et al., 2013). Additionally, HGM effects on response to checkpoint inhibitor immunotherapies (*e.g.*, nivolumab and pembrolizumab) are currently receiving substantial scrutiny. Whilst the mechanism has not been fully elucidated, it is known that several species of gut bacteria modulate patients' drug response through production of the metabolite inosine (Mager et al., 2020). Such effects could orchestrate patients' chance of sufficient drug response and progression-free cancer survival (Hakozaki et al., 2020).

Hepatic drug metabolism can also be affected by the microbiome. Enzymatic degradation of drugs in the liver is a crucial element of physiological drug response. In the liver, drugs are transformed to typically inactive and excretable metabolites. If hepatic metabolism is impaired, then drug clearance can be reduced, increasing risk of toxicity. The HGM and liver directly communicate *via* the portal vein and bile duct; metabolites from the gut travel to the liver *via* venous blood, and bile acids produced in the liver pass through the gut before excretion. Gut microbiota are known to modulate hepatic gene expression. A study comparing hepatic gene expression in germ free and colonised mice found over 4000 transcripts to be differentially expressed in the livers of the two groups (Montagner et al., 2016). A number of these are involved in the detoxification of drugs, including the cytochrome P450 (CYP450) enzymes, *Cyp3a11* and *Cyp2b10*. The CYP3A subfamily are known to metabolise approximately half of all marketed drugs (Gandhi et al., 2012). Elsewhere, a cluster of 112 genes connected to hepatic drug metabolism have been proven as being microbiome-mediated (Björkholm et al., 2009). In this study, researchers exposed germ free and colonised mice to pentobarbital, and confirmed that the presence of microbiota significantly increased time of anaesthesia.

4. Do no harm

Clearly, the HGM plays an important and emerging role in the physiological handling of drugs. Microbiome composition is a dynamic process, altered by numerous factors such as diet, lifestyle, health, age, and importantly, medication use (Asnicar et al., 2021; Chaudhari et al., 2020; Jostins et al., 2012; Mulder et al., 2020). Both drugs with and without intended antimicrobial actions have been shown to significantly alter the diversity and density of the microbiome (Table 2) (Maier et al., 2018; Mulder et al., 2020). Due to the numerous and interconnected

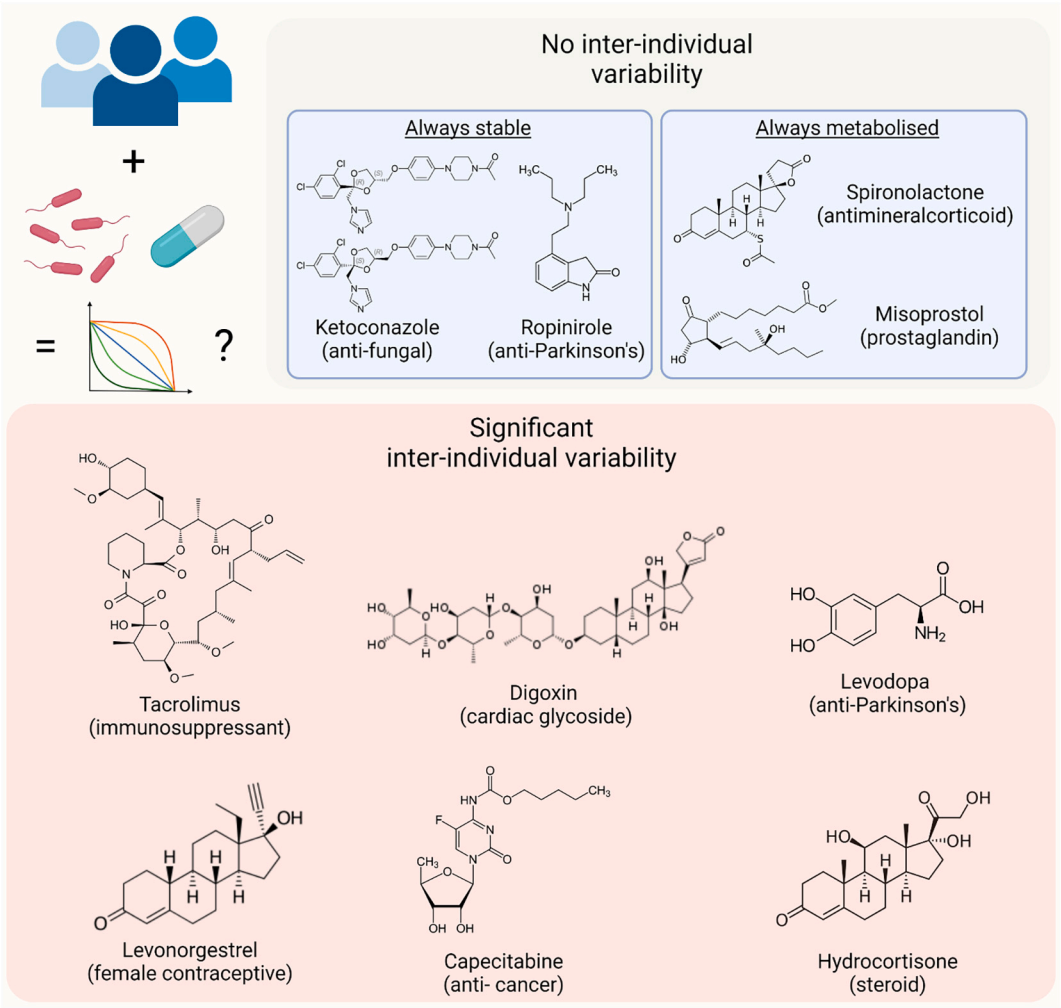


Fig. 2. Direct drug metabolism by microbiota can be a source of significant pharmacokinetic variability (Haiser et al., 2013; Javdan et al., 2020; Lee et al., 2015; van Kessel et al., 2019).

functions of the microbiome, even seemingly small changes in composition could affect host health (Liu et al., 2020). First and foremost, it is essential to do patients no harm during treatment. Therefore, it is important to recognise how drugs could negatively impact microbiome functioning.

Whilst frequently lifesaving, antibiotic administration has ruinous and long-lasting effects on the microbiome (Montassier et al., 2021). A study by Mulder et al. investigated the microbiome composition of 1413 individuals in relation to antibiotic exposure over 4 years (Mulder et al., 2020). They found that macrolides and lincosamides were associated with significantly lowered faecal microbiome diversity for up to 4 years after prescription. Decreased diversity was noted for at least one year after prescription of beta-lactams and quinolones. Faecal microbiome diversity is recognised as an important indicator of health. Low faecal microorganism diversity has been linked to several disease states, including reduced immune functioning (Gregory et al., 2020); metabolic syndrome (Singer-Englar et al., 2019); and various neurological impairments (Cryan et al., 2020). Whilst strain-level interactions and functions are more descriptive measurements of microbiome health than overall diversity measurements, the changes to microbial diversity clearly demonstrate the widespread impacts of antimicrobials (Park et al., 2020). In the study by Mulder et al., it was identified that antimicrobials with substantial activity against anaerobes increased the ratio of gut Firmicutes to Bacteroidetes, a signature associated with obesity (Singer-Englar et al., 2019). Recently, it was also found that antibiotic exposure during the neonatal period impairs child growth for the first 6 years of life, due to perturbations in gut microbiota colonisation (Uzan-Yulzari et al., 2021). The anti-commensal effects of antimicrobials may also impact the physiological response to other drugs (Cussotto et al., 2021). This has been clinically demonstrated with warfarin; antibiotics with substantial activity against *Bacteroides fragilis* were associated with higher risk of excessive anticoagulation in a study of 1185 patients (Yagi et al., 2021).

Perhaps even more surprising are the effects of human-targeted drugs on the HGM (Roberti et al., 2020). A study by Maier et al., in which over 1000 drugs were screened for *in vitro* activity against 40 gut bacteria strains, found that 27% of non-antibiotic drugs inhibit the growth of at least one bacteria strain (Maier et al., 2018). The drugs with anti-commensal activity spanned a diverse array of indication areas, with antipsychotics, antineoplastics, and calcium-channel blockers accounting for the highest number of anti-bacteria hits. These important findings highlight how commonly prescribed drugs can exert unexpected off-target effects on gut microbiota. Work should now clarify the clinical relevance of such drug-microbiome interactions; in some areas this is already underway. For example, alterations to microbiota composition by proton pump inhibitors significantly increase intestinal permeability in mice (Takashima et al., 2020). It should also be recognised that alteration of microbiome composition may form part of a drug's therapeutic action. For example, metformin's microbiota effects contribute towards its treatment of type 2 diabetes mellitus (Wu et al.,

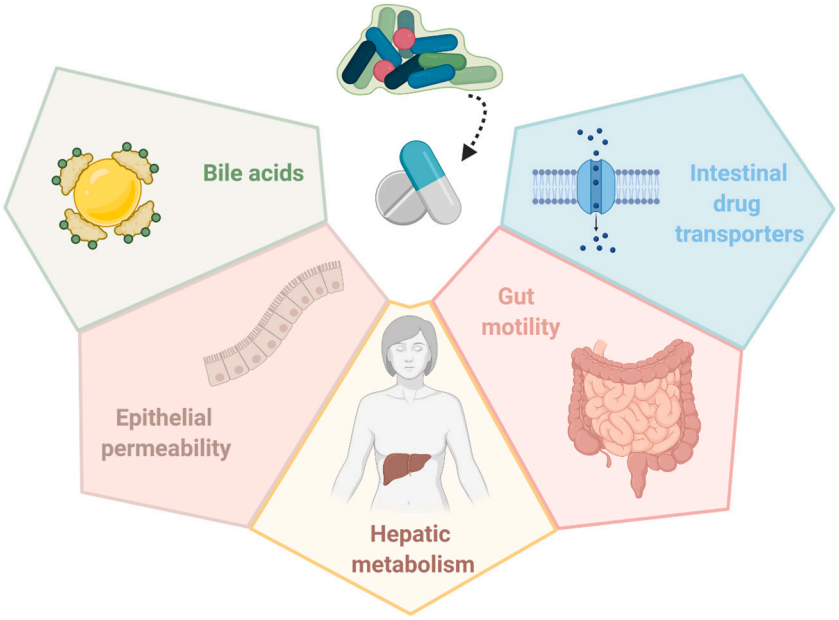


Fig. 3. Mechanisms of indirect gut microbiome effects on drug bioavailability. Microbiome-mediated alteration of bile acids, epithelial permeability, gut motility, and intestinal drug transporters can change the absorption of intraluminal drugs into systemic circulation. Alterations in hepatic metabolism can modify the half-lives of drugs in circulation.

2017); the immunostimulatory effects of antitumour CTLA-4 targeted antibodies are dependent on interactions with commensal *B. fragilis* (Vétizou et al., 2015); and diversification of microbiome composition, mediated by statins, may be protective against obesity (Vieira-Silva et al., 2020). Most recently, methotrexate has been found to alter gut microbiome composition, with subsequent shifts in microbial metabolism reducing host immune activation, supporting the drug's action in rheumatoid arthritis (Nayak et al., 2021).

5. The power of prediction

The ability to predict drug-microbiome interactions could reshape how medicines are prescribed. Increasingly, research is illustrating how the uniqueness of one's microbiome impacts response to medical and nutritional interventions (Wang et al., 2021). Prediction of individuals' microbial drug metabolism or susceptibility to microbiome alteration by drugs could facilitate a new hallmark of personalised medicine. Prior to prescription, clinicians could predict how patients' microbiota may alter physiological drug response, and assess the risk of anti-commensal effects on individual health. Currently, this goal has not been realised due to the complexity of the task. Due to the microbiome's individual nature, thousands of factors may contribute towards drug-microbiota interactions. Moreover, until recently, there has not been sufficient evidence characterising the drug-microbiome relationship to form reliable predictions. Now, the breadth of drug-microbiome research means there is capacity to gain insights for individual patient behaviour. ML is a natural tool to facilitate such predictions (McCoubrey et al., 2021b). For one, ML is capable of handling and interpreting very large datasets (Cammarota et al., 2020). Secondly, ML techniques can be trained to continuously learn as new evidence emerges, avoiding constant reprogramming of algorithms as knowledge advances (Ariane Christie et al., 2019). A good introduction to ML in biological applications has been published by (Camacho et al., 2018).

Within the general field of drug design and development, ML is being progressively applied to optimise traditional processes (Bannigan et al., 2021). For example, algorithms have been demonstrated to streamline multiple aspects of pharmaceutical formulation, including the design of solid dispersions (Dong et al., 2021), prediction of tablet properties (Onuki et al., 2012), formulation of personalised medicines (Elbadawi et al., 2021b), and prediction of protein therapeutic stability (Gentiluomo et al., 2020; King et al., 2011). ML has additionally been used to better characterise the relationship between microbiome composition and health. For instance, (Gupta et al., 2020) trialled a random forest model to predict human health status based on species-level gut microbiota composition. Further, (Ma et al., 2021) successfully predicted patient's colorectal cancer status based on microbial single nucleotide markers, using classification techniques. Similarly, the use of ML to harness microbiome big data for precision cancer medicine has been explored by (Cammarota et al., 2020).

Whilst ML has been less frequently used to characterise the drug-microbiome relationship, there are several examples to date. In their study of drug metabolism by gut microbiota, Zimmerman et al. used a clustering algorithm to identify how drug structure can increase susceptibility to enzymatic transformation in the gut (Zimmermann et al., 2019a). They noted that the presence of lactone, urea, azo, and nitro functional groups increase the chance of bacterial metabolism (Fig. 4A). Elsewhere, a dataset composed of 491 bacterial genomes, 324,697 enzymes, and 1609 molecules was used to predict direct microbial metabolism of drugs (Sharma et al., 2017). The researchers employed random forest ML to learn how structural fingerprints of drugs affect vulnerability to transformation by specific bacterial enzymes. The result was a model that could predict microbial enzymatic metabolism of commercial drugs with over 90% accuracy. Such a model could be combined with individuals' microbial genomic reads to predict drug-enzyme reactions in the GI tract. The effects of drugs on the microbiome have also begun to be predicted using ML. A group have successfully developed a classification algorithm that can predict adverse drug effects on the growth of 40 gut bacterial strains (McCoubrey et al., 2021a) (Fig. 4B). Another group have employed ML to identify disturbances in oral-gut microbiota interactions following oral application of thonzonium bromide in rodents (Fig. 4C) (Simon-Soro et al., 2021). Elsewhere, the development of probiotic therapeutics has been optimised using ML (Westfall et al., 2021).

Whilst ML has been demonstrated as a useful tool for the prediction of drug-microbiome interactions, there remains a lack of translation to clinical use. Here, the field of nutrition can provide inspiration. The Personalised Responses to Dietary Composition Trial (PREDICT 1) study has recently shown it possible to predict food-microbiome relationships

Table 2
Effects of drugs on the gut microbiome and health.

Drug(s)	Effects	Experimental model
Atypical antipsychotics (PO) (including clozapine, olanzapine, risperidone, quetiapine, asenipine, ziprasodone, lurasidone, aripiprazole, paliperidone, and iloperidone)	Decreased bacterial species diversity in females (potentially explaining why females are more prone to antipsychotic-induced weight gain). Both sexes showed increased abundance of *Lachnospiraceae* and decreased abundance of *Akkermansia* and *Sutterella*.	Adult humans (both sexes) (Flowers et al., 2017).
Benzylpenicillin in combination with gentamicin (IV)	Reduced bacterial richness, particularly decreased abundance of Bifidobacteria for 2 years. Attenuation of weight and height gain in boys for first 6 years of life. Higher body mass index in both sexes.	Human neonates in first 48 h of life (both sexes) (Uzan-Yulzari et al., 2021).
Fluoxetine (PO)	Decreased abundance of *Turicibacter sanguinis*, leading to increased serum triglyceride levels and reduced white adipose tissue in females (but not males)	Mice (both sexes) (Fung et al., 2019).
Metformin (PO)	Treatment for 4 months altered abundance of 86 bacterial strains, mostly γ-proteobacteria (*e.g.*, *Escherichia coli*) and Firmicutes. Increased abundance of *Akkermansia muciniphila*. Altered bacterial gene expression and improved host glucose tolerance.	Human adults (both sexes) and mice (male) (Wu et al., 2017).
Methotrexate (PO)	Decreased abundance of Bacteroidetes and increased abundance of Actinobacteria. Expression of 6409 bacterial genes altered. Reduced inflammatory potential of microbiota.	GF female mice colonised with human microbiota (both sexes); bacterial isolates; humans (both sexes) (Nayak et al., 2021).
Omeprazole (PO)	Treatment for 4 weeks altered bacterial taxa associated with *C. difficile* infection (Enterococcaceae and Streptococcaceae, Clostridiales) and GI bacterial overgrowth (increased Micrococcaceae and Staphylococcaceae).	Humans (both sexes) (Freedberg et al., 2015).
Paracetamol (PO)	Higher abundance of Streptococcaceae	Humans (both sexes) (Jackson et al., 2018).
Statins (PO) (simvastatin 48%, 31% atorvastatin, 21% other statins)	Protective against the Bacteroides2 (Bact2) enterotype, a gut microbiome configuration associated with systemic inflammation and obesity. This may be due to attenuated inflammation.	Human adults (both sexes) (Vieira-Silva et al., 2020).

GF: germ free, IV: intravenous, PO: oral administration.

with regression and classification ML (Asnicar et al., 2021). The team illustrated how faecal microbiota composition is a good predictor of circulating postprandial triglyceride and insulin concentrations. Gut microbiota were shown to account for greater inter-person variability in postprandial response than meal macronutrients, demonstrating the importance of microbiome variability in metabolism (Berry et al., 2020). This study is an excellent example for how drug-microbiome interactions may be predicted using clinical data. The study, based on data from 1098 individuals, is now applying its methodology to the commercial market, thus widening its accessibility[1]. At-home kits are designed to provide personalised dietary recommendations for users; such a model could be adapted for the pharmaceutical market, whereby professionals are provided with therapeutic recommendations for individual patients based on their microbiome profile.

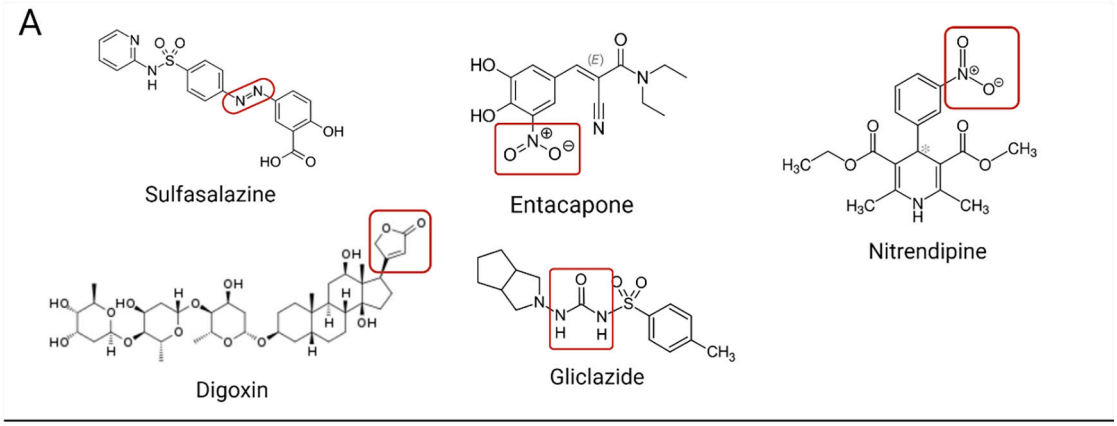
There remain several challenges in achieving clinical translation of ML for prediction of drug-microbiome interactions. For one, researchers must prove the mechanisms underlying more interactions in clinical studies. To build robust ML models, these studies should be large-scale, or at least be additive to existing studies. The field is currently lacking large, accessible datasets focused on *in vivo* drug-microbiome interactions. At present, high throughput *ex vivo* studies (Javdan et al., 2020; Zimmermann et al., 2019a) or general observation microbiome studies (Everett et al., 2021; Huttenhower et al., 2012; Proctor et al., 2019) are the best sources of data for ML. A few databases have also been built to collect disease-microbiome or drug-microbiome interactions in a single place (Janssens et al., 2018; Sun et al., 2018). Secondly, to be clinically relevant, professionals require cost-effective, fast, and non-invasive tests that can detect biomarkers underlying microbiome-drug interactions, which are feedable into predictive ML algorithms (Pollard et al., 2020). Healthcare structures will need to adapt policies and guidelines, and ML outputs should be robustly validated and explainable, to ensure user trust (Silcox et al., 2020). In addition, existing work on the drug-microbiome relationship focuses almost entirely on bacteria of the distal gut; to understand the full picture it is essential to elucidate any roles of non-bacterial elements of the microbiome across multiple sites (Borrel et al., 2020; Carrieri et al., 2021; Freire et al., 2020; Liang and Bushman, 2021). Whilst there are evidently challenges facing ML uptake in this field, the outcome of improved patient care, and the growing adoption of ML in medicine as whole, make it a likely feature of the near future. Going forward, the pharmaceutical industry will have to adapt their pre-clinical development of therapeutics to consider possible interactions with the microbiome. Early identification of drug-microbiome interactions will guide subsequent pharmacokinetic studies, toxicology profiling, and may facilitate drug repurposing for precision microbiome medicine (Ghyselinck et al., 2021; Khan et al., 2021). Here, ML can be utilised to predict likely interactions, guiding subsequent investigations using *in vitro* and animal models.

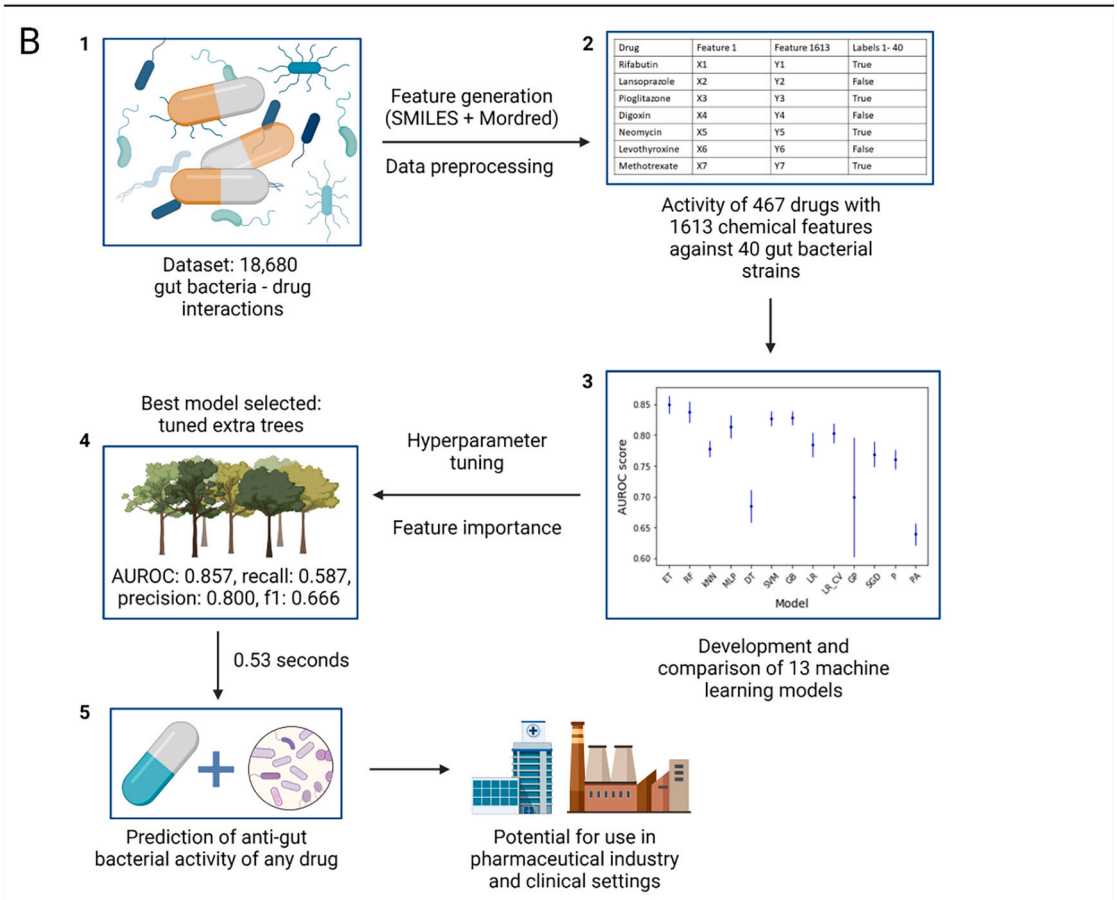
6. Conclusions

Increasingly, research is highlighting the importance of the human gut microbiome for health and response to drugs. As more and more evidence emerges, the complexity of the drug-microbiome relationship is coming to light, highlighting how many questions remain before its full clinical impact can be characterised. It is now known that over 180 drugs are susceptible to direct metabolism by intestinal bacteria, often leading to significant inter-patient variability in drug response. In addition, intestinal microbiota can indirectly alter drug response through effects on bile acids; epithelial permeability; intestinal drug transporters; gut motility; and hepatic metabolism. Furthermore, as microbiota can affect drugs, drugs can also affect microbiota. Drug effects on commensals have the potential to lead to dysbiosis-induced disease in patients (Moens et al., 2019). On the other hand, drug effects on microbiota could be essential for therapeutic action. This differentiation is something that will need to be unpicked on a drug-by-drug basis.

Clearly, the drug-microbiome relationship is complex and likely unique to individuals. Due to its proficiency in handling large and complex data, ML offers a powerful way to explore and better understand the drug-microbiome relationship. An eventual goal will be using

[1] ZOE website. https://joinzoe.com/, 'Understand how your body responds to food'. Accessed 14th February 2021.





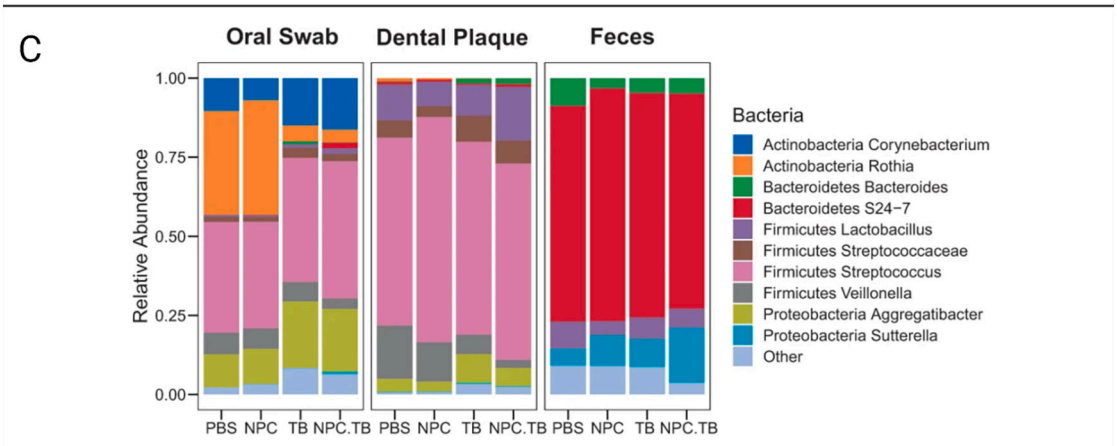


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Fig. 4. A: a ML clustering algorithm known as principal component analysis has identified certain functional groups (azo, nitro, lactone, and urea) to increase drugs' likelihood of bacterial metabolism. The drugs shown are all significantly transformed by gut bacterial enzymes (Zimmermann et al., 2019a). B: the construction workflow of a ML pipeline generating an extra trees algorithm that can predict adverse drug effects on gut bacterial growth (McCoubrey et al., 2021b). C: (Simon-Soro et al., 2021) have used machine learning to identify disturbance in the gut microbiomes of rodents, leading to increased abundance of *Sutterella*, following topical oral application of thonzonium bromide. PBS: control group, NPC: empty nanoparticles, TB: free thonzonium bromide, NPC.TB: thonzonium bromide-loaded nanoparticles. All reproduced images have been used with permission from their source.

ML to predict interactions and pharmaceutical outcomes for individual patients, facilitating personalised prescriptions. To date, ML has been applied to predict *in vitro* drug-microbiome interactions with early success, highlighting its future potential. Going forward it is essential that more human studies characterise *in vivo* drug-microbiome interactions across diverse patient populations and drug classes. The current sparsity of this information goes some way to explain why there remains to be any formally validated ML tools for prediction of drug-microbiome interactions. However, as these studies inevitably emerge, given the heightening interest in microbiome medicine, it is likely that ML will be frequently harnessed to analyse and elevate findings. As this happens, healthcare providers and the pharmaceutical industry will be increasingly called upon to consider drug-microbiome interactions in their guidelines and policies, for the ultimate benefit of patients.

Declaration of Competing Interest

None.

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