A new frontier in molecular applications of ecological stoichiometry to understand global soil organic matter decomposition

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Abstract.

Coupled biogeochemical cycles drive ecosystem ecology by influencing individual-to-community scale behaviors; yet the development of integrative process-based models remains elusive. Soil organic matter (SOM) decomposition in particular is regulated by resource stoichiometry that dictates microbial nutrient acquisition (‘ecological stoichiometry’). Ecological stoichiometry has revealed promising patterns of global ecosystem functions and informed process-based biogeochemical models. Despite its basis in biogeochemical modeling, ecological stoichiometry is largely absent from implementations of high-resolution microbial measurements, and the metabolic models they inform. Such fine-scale studies are critical components of larger scale models by developing transferrable relationships. One of the challenges to integrating models across molecular resolutions is that models of each scale use different underlying frameworks with few common threads to connect them. To address this challenge, we contend that ecological stoichiometry provides a framework for merging state-of-science biogeochemical models with microbial metabolic models to predict SOM decomposition. This article discusses new approaches to genome-enabled experiments and to models leveraging stoichiometric theory. We highlight two gaps that limit our understanding of SOM decomposition: (1) understanding how individual microorganisms alter metabolic strategies in response to substrate stoichiometry and (2) translating this knowledge to the scale of biogeochemical models. We suggest iterative information exchange to refine the objectives of high-resolution investigations and to specify limited dynamics for representation in large-scale models through integrated genome-enabled reaction networks. We propose that advancing technologies in the context of stoichiometric theory provides an untapped framework for interpreting molecular data and further distilling this information into reduced complexity SOM decomposition models.

Key words: carbon use efficiency, carbon cycling, nitrogen cycling, ecosystem models, soil nutrients, microbiome

Introduction.

The world's soil ecosystems contain a pool of carbon (C, ~1500 Gt C) that is larger than vegetation and atmospheric stocks combined, and its destabilization has the potential to dramatically alter future climates (Crowther et al. 2019). Much of this belowground C is contained by soil organic matter (SOM). Soil organic matter decomposition is regulated by resource availability that determines the metabolic pathways used for microbial nutrient acquistion (Hungate et al. 2003; Wang & Houlton 2009; Zhang et al. 2014). It is rate-limited by microbial processes that are notoriously difficult to measure and predict beyond the scale of localized experimental plots (Bond□Lamberty et al. 2016; Naylor et al. 2020). While microbial processes can now be measured using state-of-science molecular approaches, and theoretically used to establish scalable principles, interpreting vast molecular data types using standard statistical approaches is challenging. Therefore, SOM decomposition at scales most relevant to climate change largely continues to be predicted through generalized environmental proxies such as moisture, temperature, minerology, and total soil C or nutrient pool sizes (Bailey et al. 2018). These parameters leave a substantial amount of uncertainty surrounding model predictions (Todd-Brown et al. 2014; Todd-Brown et al. 2013). The shortcomings of predicting SOM decomposition beyond localized scales point to a need to incorporate more understanding of scalable spatial and biochemical processes into SOM decomposition models (Todd-Brown et al. 2013). Recent work has improved conceptual, empirical, and numerical representations of mineral protection and hydrologic mechanisms that regulate microbial access to SOM (Blankinship et al. 2018; Brangarí et al. 2020; Waring et al. 2020; Woolf & Lehmann 2019). In contrast, detailed representations of the microbial metabolisms that directly convert SOM into carbon dioxide are still missing from predictive models at the ecosystem-scale.

Progress in understanding the processes that drive SOM decomposition historically has advanced in parallel between biogeochemical and microbial research domains (Fig. 1). Recent attempts have represented fine- (individual microbial metabolisms and metabolites), intermediate- (groups of microorganisms and/or elemental pool composition), and coarse-resolution (multiple interacting microbial groups and/or elemental pool sizes) connectivity of microbial drivers and biogeochemical outcomes in predictive models at a particular level of resolution (Fig. 1 and 2). Yet, we lack integrative process-based models that link across molecular to ecosystem scales and can enable more robust predictions of SOM decomposition in next-generation models (Chowdhury et al. 2019). Translating the depth of information that now can be obtained by molecular approaches to the ecosystem-level is pressing line of scientific inquiry (Hall et al. 2018). A major challenge to this effort is that that models of each scale use different underlying frameworks such that there are few common threads with which to connect models.

While many biogeochemical models are built on the principles of ecological stoichiometry (i.e., the role of elemental composition in regulating ecological interactions, Sterner & Elser 2002; Van de Waal et al. 2018) through nutrient-regulated decomposition rates, ecological stoichiometry is largely absent from research using high-resolution molecular measurements that allow unprecedented insight into soil microbiomes. Ecological stoichiometry uses the elemental (e.g.., C:H:N:O:P:S) imbalance between organisms and their substrates to predict that nutrient limitations universally control biological activity (Elser et al. 2000; Elser et al. 1996; Reiners 1986; Sterner 1995). It has been leveraged to decipher overarching patterns in the processes governing SOM decomposition (Billings & Ballantyne IV 2013) and is the guiding framework for decades of biogeochemical investigations that provide the foundation for many process-based models.

Here, we argue that by using an ecological stoichiometry framework to combine new microbiological and computational tools with biogeochemistry, we have a currently unexploited opportunity to integrate predictive models across measurement scales and to better understand global patterns in microbial SOM decomposition. Our intent in this paper is not to comprehensively review all existing types of microbiological and biogeochemical models, rather to highlight an opportunity for future research while providing necessary background information. We propose the use of top-down and bottom-up information exchange guided by ecological stoichiometry to iteratively (1) refine the objectives of high molecular resolution investigations and (2) specify a limited set of dynamics for representation in large-scale models through integrated genome-enabled reaction networks (Fig. 3). Top-down approaches leverage bulk biogeochemical pool sizes to identify nutrient limitation (s) that then guide parameters selection and calibration of reduced complexity models. Bottom-up approaches use stoichiometric principles to guide the analysis and interpretation of large molecular datasets by establishing predictive rules that are translatable across scales. By using ecological stoichiometry as a conceptual framework to transfer knowledge across scales and couple to existing models, we have the potential to develop a new generation of reduced complexity genome-enabled models.

Ecological Stoichiometry as a Guiding Framework in Soil Organic Matter Decomposition.

Microbial (i.e., fungal, bacterial, archaeal, and viral) degradation of chemically diverse SOM is central to global C cycles and is reliant on broader organismal and soil stoichiometry

(Buchkowski et al. 2015; Buchkowski et al. 2019; van Groenigen et al. 2006). Nutrient availabilities in soil determine the metabolic pathways (and their efficiencies) and substrates that are used during SOM decomposition. Much belowground N and S is stored within organic matter that is mineralized by soil microbial communities to provide inorganic nutrients accessible to plants (Freney 1986; Jenkinson 1990; Kirkby et al. 2011). While P availability is often associated with mineral weathering; the decomposition of organic matter is a key source of P in many ecosystems (Heuck et al. 2015; Margalef et al. 2017). Microbial decomposition also increases the bioavailability of SOM by cleaving polymeric compounds into simple C substrates that can be directly assimilated by microorganisms. This process is often catalyzed by extracellular enzymes (EE) that release nutrients from organic matter, connecting C, N, S, and P cycling (Allison et al. 2014). Viral predation can also influence these dynamics by lysing specific clades of microorganisms and by influencing organic matter accessibility to microorganisms (Kuzyakov & Mason-Jones 2018; Weinbauer 2004; Wilhelm & Suttle 1999). Global patterns in the importance of these mechanisms in governing SOM decomposition, and the specific environmental conditions under which certain metabolic pathways are favored by microbial communities, are active areas of research.

Understanding SOM decomposition mechanisms across different ecosystems is challenging because heterogeneity in nutrient statuses, substrate quailities and energetics, and microbial communities can lead to different apparent controls in different soils (Milcu et al. 2011; Sullivan et al. 2014). Rates of decomposition have been linked to microbial adjustments in the acquistion of specific elements in response to differences between microbial biomass and substrate stoichiometries (i.e., nutrient limitations, Billings & Ballantyne IV 2013; Billings & Ziegler 2008; Frost et al. 2005; Manzoni 2017; Manzoni et al. 2008; Spohn 2016; Sterner &

Elser 2002). This work is rooted in the paradigm that organisms exhibit stoichiometric homeostasis in which they maintain stable biomass elemental ratios regardless of substrate stoichiometry. It leads to the prediction that nutrient limitations universally regulate biological activity (Spohn 2016). Specifically, the relative strength of the relationship between microbial metabolisms involved in N, S, or P acquisition and SOM decomposition should be strongest in soils with the lowest underlying proportion of that element. Major enzymatic pathways associated with organic N-, S-, and P- acquisition (e.g., proteases, sulfatases, and phosphatases) should therefore vary across soils based on nutrient status. Indeed, the stoichiometry of microbial biomass features little global variation (60:7:1 C:N:P) (Cleveland & Liptzin 2007) and substrate stoichiometries are highly variable (Frost et al. 2005; Manzoni 2017; Manzoni et al. 2008; Spohn 2016; Sterner & Elser 2002), supporting a dynamic in which microorganisms must adapt to account for soil nutrient concentrations.

The dependency of SOM decomposition on soil nutrients has been investigated most frequently using a suite of biogeochemical techniques in observational or fertilization studies such as CO_2 flux, mass loss, bulk chemistry (e.g., C:N), microbial biomass measurements, and/or potential EE activity measurements (Sullivan et al. 2014). In contrast to current 'omics approaches that can directly measure the metabolic pathways involved in SOM decomposition, each of these approaches provides indirect evidence for nutrient-regulated microbial decomposition using comparatively low molecular resolution. Additionally, the majority of researchers quanitfy total or coarsely-defined lumped C pools with minimal characterization of the abundance of specific SOM compound classes or their stoichiometry. For instance, the classical pool and flux model focuses on three or four operationally defined C pools that are connected by biological drivers of decomposition, namely extracellular enzymes (Abramoff et al.

2018). As such, current estimates of nutrient limitations on SOM decomposition vary widely (Cleveland et al. 2006; Grandy et al. 2008; Kirkby et al. 2013; Kirkby et al. 2014; Sullivan et al. 2014; Takriti et al. 2018), and the majority of research has focused on a few elements, generally on linkages between C and N cycling (Cleveland et al. 2006; Grandy et al. 2008; Khan et al. 2016; Kirkby et al. 2013; Kirkby et al. 2014).

Potential EE activity remains the primary tool in biogeochemical research for measuring the decomposition of specific compound classes in SOM pools. EEs are ubiqutous in soils and catalyze the depolymerization of complex SOM compounds into simpler molecules for direct uptake (Allison et al. 2010). The standard suite of enzyme assays target organic substrates including including proteins, carbohydrates, amino sugars, organic phosphates, and lignins (Allison et al. 2007; Burns 1982; Sinsabaugh & Shah 2011). However, certain extracellular enzymes (e.g., NAG, BG, phosphatases) are more widely assayed than others (e.g., phenol oxidase, sulfatases), and methodological limitations have constrained the development of accurate assays for some extracellular enzymes (Allison et al. 2010; Graham et al. 2019). Additionally, while the ratios of EE activities have been used to assess nutrient limitations (Grandy et al. 2008; Hill et al. 2014; Jing et al. 2020; Moorhead et al. 2013; Sinsabaugh et al. 2008), these assays can be influenced by pH and only provide potential rates. They are low molecular resolution compared to many ‘omics-based apporaches because they target chemical bonds contained by classes of SOM rather than specific molecules, and they can have long turnover times that decouple them from SOM cycling at a specific point in time (Schimel et al. 2017).

Microbial investigations into nutrient-regulated SOM decomposition have traditionally used a complementary set of tools, revealing differences in metabolic strategies to maintain stoichiometric homeostasis using lumped traits(e.g. community-level variation between bacteria and fungi or copiotrophic and oligotrophic metabolisms, Elser et al. 2003; Fierer et al. 2007; Strickland & Rousk 2010). Changes in microbial heterotrophy has also been suggested to vary microbial preferences for C vs. N globally, an inference drawn from primarily biogeochemical data (Taylor & Townsend 2010). Understanding how changes in metabolic strategies of individual microorganisms respond to changes in substrate stoichiometry scale to a microbial community's elemental use efficiency and capacity for decomposition is a key unknown in process-based modelling.

To address this challenge, we propose using ecological stoichiometry to inform the collection and analysis of high-resolution microbial data types. This approach guides the development of more precise model representations that in turn can be valuable tools for interpreting new high-resolution datasets.

'Omics-based characterization of microbial communities (i.e., metagenomic, metatranscriptomic, metaproteomic, and metabolomic) and other high molecular resolution approaches (e.g., chemical probes) provide direct means to evaluate how stoichiometry regulates the ecology of decomposition. 'Omics approaches have been highlighted as emerging tools in ecological stoichiometry but are not yet widely implemented (Van de Waal et al. 2018). Microbial genes and their expression patterns can reveal the genetic potential (genes), expression (transcripts), and translation (proteins) of specific enzymes involved in SOM decomposition and more directly evaluate if N, S, and P acquisition vary predictably with SOM stoichiometry. While these modern microbial approaches have their own limitations (e.g., data annotation and discrepancies in turnover time when compared to rates), they provide a more complete representation of biogeochemical cycles than EE potential assays.

Several potential analysis targets for stoichiometric regulation of SOM decomposition have been identified in ‘omics pipelines. For example, Finn et al. (2020) and Wilhelm et al. (2019) proposed lists of relevant KO and CaZY annotations. These contain enzymes involved in the decomposition of organic C as well as N, S, P, and iron cycles, including EEs commonly measured in EE assays. They span the following classes of enzymes: (1) cellulose (e.g., cellobiosidase, endoglucanase), hemi-celluloses (e.g., xylanase), lignin (ligninase), and cellobiose (e.g., beta-glucosidase) degradation; (2) mineral and organic N cycling (e.g., chitinase; leucine-aminopeptidase, N-acetyl glucosaminidase; and nitrate, nitrite and nitrous oxide reductases); (3) N-fixation (nitrogenase); (4) P cycling (monophosphatases); (5) methane cycling (e.g., methyl coenzyme M reductase, particulate methane monooxygenase); and (6) assimilatory and dissimilatory sulfate reductases. New annotations for molecular markers involved in SOM decomposition continue to be discovered, and our ability for molecular resolution into stoichiometry-based processes can help illuminate patterns where traditional biogeochemical methods have been insufficient.

Ecological Stoichiometry in SOM Decomposition Modelling.

While ongoing research is steadily improving the accuracy of SOM decomposition models, the enormous amount of soil chemical and biological diversity and the depth of new molecular data types complicates efforts to formulate predictions based on stoichiometric relationships. These relationships underlie the kinetics of SOM decomposition and therefore are essential to genome-enabled model structures and calibrations. Still, data interpretation remains challenging for empiricists (Jansson & Hofmockel 2018), and most current SOM decomposition models do not yet incorporate cutting-edge molecular approaches to represent detailed microbial processes. Additionally, there is a need to move beyond pool-based models, which rely on separating SOM by chemical, physical, and functional properties that can be difficult to measure (Abramoff et al. 2018), to more fluid and continuous relationships between belowground SOM, microorganisms, and decomposition (Jinyun & Riley 2020; Waring et al. 2020). Microbial data mining approaches have made incremental advances to this effort, but remaining obstacles highlight an opportunity for broader use of ecological stoichiometry to guide targeted investigations. Below, we discuss the current state of microbial models across different scales of community hierarchies as well as their counterparts in biogeochemical modelling (Fig. 1). We also discuss existing modelling approaches that integrate across fields and their use of ecological stoichiometry as a guiding framework (Fig. 2). Finally, we highlight opportunities for ecological stoichiometry to guide the development of high-resolution models such as genome-enabled reaction networks and their assimilation at larger scales via reduced complexity models (Fig. 3).

Many models emerging from microbiology are rooted in ecological representations at individual-to-community scales. At the individual level, common modeling approaches depict individual's growth rates and/or specific metabolic processes without consideration of stoichiometric balance. Single cell metabolic models typify process-based microbial models at the individual scale. This suite of models considers inputs in the context of a model organism's genome to make predictions of growth dynamics or specific metabolomic products (e.g., GEMS, Duarte et al. 2004; Loira et al. 2012; Lu et al. 2019). With respect to ecological stoichiometry at the individual scale, microorganisms maintain stoichiometric balance by adjusting growth rate or biomass stoichiometry and/or mining or excreting nutrients. This understanding could be integrated into individual-scale models by adjusting active metabolic processes based on environmental nutrient context, for instance through metabolic flux analysis. At an intermediate scale (i.e., small groups of microorganisms), ecological stoichiometry operates by impacting the growth rates of organisms with particular traits – for example, microorganisms with specific nutrient acquisition pathways, r- and K- life strategies, stress tolerance, or other competitive advantages. However, stoichiometry is not captured in current process-based models at intermediate-scales. These models simulate interactions between individuals, limited sets of individuals, or their characteristic traits, to predict metabolic outputs or changes in the growth of specific organisms (Bouskill et al. 2012; Follows & Dutkiewicz 2011; Malik et al. 2020; Reed et al. 2014). Incorporation of stoichiometric principles such as substrate stoichiometry and/or environmental nutrient status at the intermediate scale can guide an individual's expressed metabolisms in the context of other microorganisms as well as the interactions of their metabolites and extracellular enzymes. Finally, at the community-scale (i.e., groups of microbial guilds), models tend to represent interactions among groups of several organisms through core ecological processes such as dispersal/transport, predator/prey, and mortality with limited consideration of stoichiometry (Abel et al. 2015; D'Acunto et al. 2019; Mattei et al. 2015); while ecological stoichiometry induces compositional shifts in metabolic or growth tendencies and/or subtle changes to community biomass C:N:P:S ratios. Changes in community stoichiometric balance should change along with compositional changes to inform community-level metabolism based on nutrient availability and substrate stoichiometries.

On the other hand, biogeochemical models, in particular those at intermediate to large scales, often employ stoichiometric principles. Fine-scale biogeochemical models include reaction networks and reactive transport models that represent molecular-level processes (e.g., those involving specific SOM molecules, EEs, or inorganic nutrients, Porta et al. 2018; Riley et al. 2014; Wilson et al. 2019). While stoichiometric principles underlying nutrient limitation(s) influence the elemental composition of organic matter and excretion of extracellular enzymes, these processes are mostly implicitly considered through the concentrations of specific molecules in fine-scale biogeochemical models. Thus, they represent an opportunity for model refinement through minimal adjustments. At intermediate scales, biogeochemistry considers the composition of pools of elements, often through relatively coarse parameters such as fast vs. slow cycling SOM pools, mineral SOM, chemical classes or C:N ratios of SOM, and/or organic vs. inorganic nutrient pools. Biogeochemical models at this scale are often built upon stoichiometric principles, as they constrain rates of SOM decomposition with parameters that represent nutrient availability, stoichiometries of organic substrates or microbial biomass, and carbon and nutrient use efficiencies. Process-based models at the intermediate scale have been a primary focus of many recent research efforts and include advances such as MEND (Wang et al. 2015), RESOM (Tang & Riley 2015), and MIMICS-CN (Kyker-Snowman et al. 2020). Finally, the largest scale considered here is comprised of seminal models that are generalized across environments, typified by the foundational CENTURY model (Parton 1996). These models focus on elemental stocks (e.g., total C, N, and/or P) and adjust SOM decomposition rates through nutrient limitations in line with ecological stoichiometry. Recent progress in large-scale pool models proposes increased accuracy from a tighter coupling of C and N dynamics (Berardi et al. 2020).

State-of-science SOM models use ecological stoichiometry to integrate between microbiology and biogeochemistry at intermediate scales. Due to computational limitations, these models generally are based on C pools with lumped characteristics and include two elements at most (Abramoff et al. 2018; Moorhead et al. 2012; Sulman et al. 2019; Wang et al. 2015; Wieder et al. 2015). They use a small set of coarse parameters to denote microbial processes, in particular C and nutrient use efficiencies (CUE, NUE), that describe C and nutrient assimilation into microbial biomass (Allison et al. 2010; Cleveland & Liptzin 2007; Geyer et al. 2016; Min et al. 2016; Sihi et al. 2016; Sinsabaugh et al. 2013; Sinsabaugh et al. 2016; Wang et al. 2015; Wieder et al. 2014). CUE and NUE are typically estimated from stoichiometries of organic matter and microbial biomass or from the ratios of C- vs. nutrient-acquring enzymes (Manzoni et al. 2012; Sinsabaugh et al. 2016). As such, CUE and NUE incorporate the principles of ecological stoichiometry into microbial-explicit models by serving as proxies for generalized microbial processes. Under nutrient limitation, microorganisms reduce their C uptake, acquire nutrients, and/or respire or excrete excess C such that C assimilation into biomass often declines (Anderson et al. 2005; Del Giorgio & Cole 1998; Manzoni 2017; Manzoni et al. 2017; Manzoni et al. 2008; Middelboe & Søndergaard 1993; Milcu et al. 2011; Mooshammer et al. 2014b; Smith & Prairie 2004; Sterner & Elser 2002). Thus, CUE typically decreases when nutrients are limiting. In contrast, when nutrients exist in excess, microorganisms adjust their uptake or rate of respiration/excretion to decrease NUE (Milcu et al. 2011; Mooshammer et al. 2014a).

The balance of these processes is difficult to predict due in part to microbial interactions (i.e., stoichiometry influences individual behavoir rather than community-level behavoir that ultimately regulates SOM decomposition, Manzoni 2017; Manzoni et al. 2012; Sterner & Elser 2002). There is also large variation in microbial CUE and NUE, and their relationships to SOM decomposition, due to spatial and temporal changes in resource availability, microbial community structure, and soil physical properties (Frey et al. 2013; Herron et al. 2009; Malik et al. 2018; Manzoni et al. 2012; Qiao et al. 2019; Sinsabaugh et al. 2013; Sinsabaugh et al. 2016). Biogeochemical models have shown that small changes in CUE can have large impacts on SOM decomposition (Li et al. 2014; Six et al. 2006; Wieder et al. 2013), offering an intriguing possibility for model improvement through detailed representations of nutrient-regulated microbial metabolic pathways to develop scalable and integrated genome-enable reaction networks (Hagerty et al. 2018).

Opportunities for Ecological Stoichiometry and High-Resolution Measurements in SOM Decomposition Modelling.

Recent work biogeochemical modelling has improved predictions of SOM decomposition by more explicitly accounting for the stoichiometries of microbial biomass and SOM (Buchkowski et al. 2019) (Fig. 2). Fatichi et al. (2019) have proposed direct representation of microbial communities involved in coupled SOM and nutrient cycling, an approach that could not only aid in increasing the accuracy of SOM decomposition predictions but also become a useful tool for empiricists to interpret multidimensional microbial data. Below, we highlight opportunities to improve fine-scale predictive models as well as integration between biogeochemical and microbial models across scales of molecular resolution through stoichiometric principles that underly the kinetics of SOM decomposition.

At the finest molecular resolution, there is a limited set of modelling approaches that currently predict rates of molecular processes involved in SOM decomposition, primarily arising from microbial modelling efforts. Genome-enabled metabolic models, in particular, infer function from molecular data types by placing annotations within the context of a cell's biochemical abilities to consume substrates, grow, and produce energy (Cuevas et al. 2016). These models are constrained by a set of biochemical reactions that define the possible functions of a microorganism or group or community of microorganisms and provide a structure in which to root functional annotations (Seaver et al. 2020). Commonly used in systems biology to represent interconnected metabolic processes (Lieven et al. 2020; Seaver et al. 2020), they are capable of including thousands of genes, metabolites, fluxomes, transcriptomes, proteomes, and associated reactions. Flux balance analysis is widely used within genome-enabled model constructs to predict fluxes through the reactions in a metabolic network (Cuevas et al. 2016; Orth et al. 2010). Genome-enabled models can also be coupled to other methods of decoding high-resolution molecular data, such as thermodynamic theory (Garayburu-Caruso et al. 2020; Song et al. 2020), deep learning (Zampieri et al. 2019), or network modelling (Kessell et al. 2020; McClure et al. 2020) to further extend their applicability. In order for fine-scale models to be used to develop transferrable understanding, continued expansion of these techniques under stoichiometrically constrained conditions is needed, with acknowledgement of the compositional nature of many stoichiometric metrics (Gloor et al. 2017; Tsilimigras & Fodor 2016).

In an idealized scenario, direct modelling of individual substrate uptake and release by all individuals in a soil ecosystem, as well as their interactions, should alleviate errors due to scaling across levels of community organization. To do so, microbial-explicit biogeochemical models would need to leverage genome-enabled or metabolic flux models that represent metabolic processes and species interactions at the individual-to-community scales. However, it is currently computationally unfeasible to model all microbial processes in a soil ecosystem as well as their intereactions with each other, necessitating *a priori* choices of which metabolic pathways to include in a genome-enabled models. There are thousands of different metabolic pathways influencing SOM decompostion, and a large proportion of soil microbial communities consists of dark matter for which we can assign no function. Therefore, it is necessary to have a guiding framework for determining which pathways to include in any metabolic model and further scale high molecular resolution predictions to the scale of a soil ecosystem (Zakem et al. 2020).

Ecological stoichiometry can address this need and link microbial and biogeochemical models across scales of molecular resolution through (1) top down approaches to inform model structures and (2) bottom up approaches for model calibration (Fig 3).

In top down approaches, ecological stoichiometry can be leveraged via bulk biogeochemical measurements to first identify nutrient limitation(s) that then guide model development at higher molecular resolutions. Patterns in nutrient concentrations and biochemical transformations can inform the selection of targeted parameters for inclusion in and calibration of reduced complexity models. For example, nutreint limitations identified from bulk measurements define a set of reactions that should most strongly impact rates of SOM decomposition. Examples include representing amino acid metabolism for N limitation, microbial biomass recycling for P limitation, and/or organosulfatases for S limitation (or combinations therein in the case of nutrient co-limitation) in integrated genome-enabled reaction networks (Fig. 3). Outcomes from this suite of models can then further refine parameters, pointing to specific microbial genes/transcripts/proteins in pathways associated with the rate limiting step in SOM decomposition. Using this approach, we can narrow down molecular data to specific microbial metabolisms or ‘omics markers of interest to build genome-enabled models including only the most relevant parameters that are scalable to the level of soil ecosystems.

Conversely, stoichiometric theory can be used in bottom-up approaches to guide parameterization and calibration across scales of molecular resolution (Fig 3). Bottom-up approaches start with high-resolution measurements and use ecological stoichiometry as a framework for their interpretation. For example, data mining could be driven by a focus on nutrient acquisition metabolic pathways (e.g., peptidase-, phosphatase-, and sulfatase-including metabolic pathways) in order of hypothesized nutrient limitations. Metabolic pathways with the most predictive power of SOM decomposition, inferred from transcripts, proteins, and metabolites mapping to metabolic pathways involved in nutrient regulation of SOM decomposition, then guide the portions of intermediate-scale models where greater resolution may lead to more accurate predictions. This could result in inclusion and/or calibration of specific portions of SOM pools that are most tightly coupled to decomposition rates [e.g., protein pools (low C:N) or necromass (low C:P)] or in the direct assimilation of specific metabolic pathways for representation instead of lower resolution measurements such as CUE and NUE. Dynamically activating genome-enabled reaction networks for a specific nutrient status could provide the maximum benefit of including high molecular resolution in SOM decomposition models while being computationally tractable. In turn, parameters and rate estimates made at the intermediate scale can then influence the relative importance of variables in low molecular resolution models such as CUE/NUE, bacterial:fungal biomass, and/or biomass C:N:S:P.

The result of these approaches, used in combination, is a new suite of models that represent a limited set of microbial metabolisms, guided by stoichiometric principles and high-resolution molecular measurements, that are computationally feasible and more accurately predict SOM decomposition (Fig. 3). This addresses a major challenge to the next generation of predictive models—deriving integrated genome-enabled reaction networks that can represent SOM decomposition mechanisms across molecular-to-ecosystem scales.

Opportunities afforded by investments in new molecular and computational technologies

The power of ecological stoichiometry to guide model integration across scales of biological complexity can increase even further when leveraged in combination with new advances in molecular technologies and machine learning algorithms. Research that simultaneously investigates microbial roles in C, N, S, and P cycling is rare, and EE assays are imprecise relative to ‘omics or probe-based assays. Additionally, in EE assays, targeted enzymes and substrates must be determined *a priori*, and several enzymes involved in SOM decomposition—notably phenol oxidases, peroxidases, and sulfatases—are underinvestigated due to methodological challenges (Sinsabaugh 2010). Investments in untargeted molecular approaches are opening new doors into soil microbial analyses by allowing detection of active metabolisms. These are nascent technologies that have the potential to improve our understanding of SOM decomposition but need greater usage and development to surmount remaining challenges. Stable isotope probing (SIP, Bernard et al. 2007; Dumont & Murrell 2005; Pepe-Ranney et al. 2016) paired with ‘omics-based approaches and new ultrahigh-resolution metabolomics (Tfaily et al. 2017) methods in particular are promising techniques that can overcome major limitations of EE assays. Below, we describe these technologies, interesting aspects of their potentials in the context of ecological stoichiometry, and current barriers to widespread usage. Our intent is to highlight emerging technologies that are beyond the suite of high-resolution measurements that are now common (e.g., metagenomics) and present a new class of technologies from which we can derive even more information.

In SIP, substrates enriched in heavy isotopes (e.g., ^{13}C, ^{18}O, ^{15}N) are amended to microbial communities and then isotope-labeled biomarkers of active microbial populations are recovered and analyzed (Bernard et al. 2007; Dumont & Murrell 2005; Pepe-Ranney et al. 2016). While SIP has long been used in biogeochemistry, recent advances are increasing the tractability of SIP within amplicon profiles, metagenomes, metatranscriptomes, and metaproteomes (Barnett & Buckley 2020; Jameson et al. 2017; Pepe-Ranney et al. 2016; Wilhelm et al. 2019; Youngblut et al. 2018a; Youngblut et al. 2018b). For instance, metaproteomic SIP can detect active metabolic pathways by assessing the rate of incorporation of heavy isotopes into proteins (Grob et al. 2015; Jehmlich et al. 2016; Von Bergen et al. 2013), and when SIP is used in metagenomic investigations, sequence assembly and binning into microbial genomes is vastly improved (Barnett & Buckley 2020; Wilhelm et al. 2019). These approaches have been used in environmental applications such detecting ^{13}C transfer into microorganisms and metabolites (Li et al. 2019; Starr et al. 2018) and assessing taxon-specific growth rates (Hungate et al. 2015; Papp et al. 2020; Purcell et al. 2019) among other uses (Grob et al. 2015; Wilhelm et al. 2019).

SIP could be employed in the context of ecological stoichiometry for maximum benefit in either top down or bottom up approaches. For example, in a bottom up approach, broad ^{13}C (e.g., ^{13}C-labelled amino acids) and ^{15}N (e.g., $^{15}NO_3$) tracers can evaluate linkages of C and N cycling with SOM decomposition by denoting microorganisms (via 16S rRNA or metagenonmic sequencing) or active microbial pathways (via transcriptomics, proteomics, and metabolomics). In soil ecosystems that are constrained by N-availability, N cycles should notable impact SOM decomposition. An ecological stoichiometry framework therefore sets *a priori* expections for pathways of interest in SOM decomposition (e.g., rate limiting pathways). In a top down approach, ecosystem nutrient status and/or the impact of specific portions of elemental cycles on SOM decomposition (e.g., amino acid cycling) can inform the choice of substrates used in SIP (e.g., a specific amino acid) to provide greater resolution into active microorganisms and metabolic pathways.

However, ‘omics-based SIP still faces a number of challenges to reach its full potential. The amount of label incorporation needed for downstream ‘omics measured can vary by technology, posing logistical issues because subsamples from a single isotopic enrichment cannot be easily analyzed for signatures in DNA, RNA, proteomic, and metabolomic data types. An unlabelled set of samples is needed in addition to enriched samples in many instances, doubling sample sizes in experimental designs. Further, extensive prototyping is often needed because label incorporation itself varies with time, across sample sets, and with microbial GC content. Addtionally, microbial cross-feeding can present difficulties in tracing label incorporation (Coyotzi et al. 2016; Schwartz et al. 2016), and there is no standardized software available for data analysis. These drawbacks come at a large monetary cost that have constrained widespread application of SIP in ‘omics investigations. For SIP to reach its full potential, investment is needed to increase accessibility, determine the approppropriate label amounts, incubation duration for specific soil types, and standardized software for data analysis as well as to streamline ‘omics integration with SIP.

In parallelel, ultrahigh-resolution metabolomics, such as Fourier transform ion cyclotron resonance mass spectrometry (FTICR-MS, Tfaily et al. 2015; Tfaily et al. 2017), can illuminate new aspects of SOM decomposition by enabling the determination of elemential stoichiometry in thousands of SOM molecules simultaneously (Tfaily et al. 2017). In FTICR-MS, soils are extracted with a choice of solvent depending on the portion of the SOM pool of interest. Extractions can then be ionized via Electrospray ionization (ESI) to assist the transfer of ions from solution into the gaseous phase and injected into the FTICR-MS instrument to yield extremely high mass resolving power (>1M) and mass measurement accuracy (<1 ppm). Formulas assigned via ultrahigh-resolution metabolomics are a promising tool for evaluating metabolisms influenced by ecological stoichiometry by providing information on the abundance of molecules with specific stoichiometries (e.g., C:N ratios of SOM molecules in a standing pool) or changes in these molecules during the course of experiments.

Yet, development of ultrahigh-resolution metabolomics and increased access to relevant technologies by the broader scientific community are needed to push its current boundaries. A primary constraint is that ionization efficiency and biases vary across soil types, and in some cases, even within soils in a single experiment. This makes quantification of metabolites unreliable such that data is most accurately used in a presence/absence format. Another weakness is that SOM must be extracted prior to analysis via most metabolomic technologies; however, there has been significant improvement in the development of new extraction techniques to minimize inefficiencies and target a suite of chemically distinct organic matter pools (Tfaily et al. 2015). Despite its limitations, ultrahigh-resolution metabolomics has been used to evaluate the relative balance of OM thermodynamics vs. N availability in regulating aerobic respiration, revealing its power when leveraged with ecological stoichiometry (Garayburu-Caruso et al. 2020). Particularly when combined with other ‘omics technologies, it can provide molecular resolution into nutrient-regulated microbial metabolic pathways (Song et al. 2020). Investment in the use of tailored standards and advances in the calculation of ionization biases as well as improvements in extraction efficiencies can help these technologies reach their full potential.

In parallel with technological opportunities, the interpretation of untargeted molecular approaches is complicated by the inadequate description of metabolic pathways for soil microorganisms in existing databases and the unsuitability of standard statistical approaches in ecology for combining diverse multidimensional data types. Unsupervised machine learning is emerging as a tool both to decipher hidden patterns in complex data and to eliminate the needs for *a priori* relationships between genes (e.g., via metabolic pathways or metagenome-assembled genomes) and for gap filling to infer absent data. There is an enormous diversity of machine learning algorithms with varying levels of complexity that are well-suited to discern patterns in data (Rana et al. 2020; Were et al. 2015). Techniques such as K-nearest-neighbor (Peterson 2009), artificial neural network(ANN, Sarle 1994), support vector machines (SVM, Wang 2005), neuro-fuzzy (Nauck et al. 1997), decision tree classifiers (Safavian & Landgrebe 1991), and random forests (Liaw & Wiener 2002) are most commonly employed in microbiology and environmental disciplines, often in combination due to the various strengths and weaknesses of each (e.g., Cai et al. 2019; De Clercq et al. 2019; Dong & Chen 2019; Qdais et al. 2010; Rahimian Boogar et al. 2019; Thompson et al. 2019; Wang et al. 2020). Data-driven machine learning has been employed in a variety of gene annotation pipelines to reveal microbial dark matter (Arakawa et al. 2006; Aziz et al. 2008; Faria et al. 2018; Hyatt et al. 2010; Notebaart et al. 2006), metabolite identification (Djoumbou-Feunang et al. 2019; Shen et al. 2013), gap-filling (Oyetunde et al. 2019), assimilation of multiple lines of data (Rana et al. 2020), pathway enrichment (Luo et al. 2009), and phenotype prediction (LaPierre et al. 2019; Pasolli et al. 2016). Still, we lack rigorous machine learning investigations in which sampling and experimental designs move beyond feature identification to translating selected features into meaningful ecological outcomes.

Machine learning approaches are particularly important for soils in which the vast majority of microorganisms have not been cultured. These methods have recently been used to describe complex environmental problems such as deriving microbial indicators of disturbances (Beall et al. 2016; Glasl et al. 2019), assessing microbial community dynamics (Cai et al. 2019; Guo et al. 2015; Lesnik & Liu 2017; Wang et al. 2020), and predicting soil C content (Chen et al.

2019; Hengl et al. 2017; Jardine & Siikamäki 2014; Keskin et al. 2019; Morellos et al. 2016) among other applications (Graham et al. 2018; Rahimian Boogar et al. 2019; Thompson et al. 2019). Yet such applications are mostly descriptive and independent of any theoretical framework as a foundation for interpretation. Pairing machine learning with ecological theory for experimental hypothesis testing is needed to push fundamental biology forward (Rana et al. 2020; Were et al. 2015). Using new high-resolution molecular data types in spatially- and temporally-distributed sampling, paired with machine learning, can offer unprecedented untargeted resolution into the nutrient-regulated pathways by which microorganisms decompose SOM (Manzoni et al. 2017; Mooshammer et al. 2014b).

Specifically, within the context of ecological stoichiometry, we propose that machine learning can parse nutrient-regulated mechanisms that control SOM decomposition rates across all scales of molecular resolution. For examine, at the finest molecular resolution, machine learning can uncover signals in gene, transcript, protein, or metabolite data (alone or in combination) that correspond to SOM decomposition rates. Signals can be interpreted within the context of stoichiometry informed *a priori* hypotheses to infer possible casual relationships for evaluation with experiments. Similar approaches can also be used in combination with metabolic pathway mapping or other grouping strategies (e.g., by N, S, or P cycle involvement) to further distill relationships into casual units that are representable in models.

Complementarily, investment in targeted approaches can improve the accuracy of existing enzyme-based approaches. Activity-based protein profiling (ABPP, Killinger et al. 2019), for example, leverages chemical probes that react irreversibly with protein families to identify enzymes binding to specific molecules, and when paired with mass spectrometry-based approaches, can also quantify rates of enzyme activity (Killinger et al. 2019). In contrast to EE assays that reveal potential enzyme rates, ABPP has the potential to dramatically improve investigations of SOM decomposition by revealing the true expression of decomposition enzymes; however, it is rarely used in soils (Sadler & Wright 2015; Whidbey & Wright 2018; Zegeye et al. 2020). Major challenges to soil-based ABPP include complexation with diverse chemical structures in soils (i.e., non-specificity) and probe extraction from the soil matrix (Killinger et al. 2019). A broad range of chemical probes have been developed to target enzymes such as serine hydrolases (Sanman & Bogyo 2014), cysteine proteases (Sanman & Bogyo 2014), metalloproteases (Saghatelian et al. 2004), kinases (Patricelli et al. 2007), glycosidases (Chauvigné-Hines et al. 2012), and ammonia monooxygenases (Bennett et al. 2016). These provide a solid foundation for further development and deployment in soils. ABPP could be employed in similar ways to the current usage of potential EE activities to evaluate stoichiometruc relationships that underlie SOM decomposition with more precision. As ABPP use becomes more common in microorganisms (Sharifzadeh et al. 2018) and the diversity of available probes continues to expand (Killinger et al. 2019), there is potential for ABPP-based approaches to move beyond the coarse resolution of EE assays and to target specific enzymes involved in nutrient-regulated decomposition (Sadler & Wright 2015).

Conclusions.

Dynamic soil environments have led to the evolution of a large repository of interconnected microbial mechanisms for energy acquisition. Nutrient-driven metabolic regulation is the ultimate control over many biogeochemical processes including SOM decomposition (Manzoni et al. 2017; Mooshammer et al. 2014b). The stoichiometry of SOM decomposition in particular regulates biological activity across individual-to-community scales.

Ecological stoichiometry is largely absent from more modern implementations of high-resolution molecular measurements, despite promising relationships uncovered by decades of biogeochemical research that guide large scale predictive models. Using ecological stoichiometry as a framework to guide technological and model-based advances at the molecular scale can expedite progress towards overcoming a major challenge to understanding global SOM decomposition — intrepreting the massive amount of data generated by high-resolution approaches to investigating diverse soil microbial communities. Ecological stoichiometry can provide a tractable set of metabolic reactions and parameters to depict detailed SOM cycling in genome-enabled reaction networks and scale across levels of molecular resolution within a common framework, yet it has not been leveraged in state-of-science experiments and models. We propose that investing in and deploying new technologies in the context of stoichiometric theory provides an untapped and promising framework for interpreting the vast amount of data we can now generate and further distilling this information into reduced complexity models that predict SOM decomposition.

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Declarations.

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Availability of data and material (data transparency). Not applicable.

Code availability (software application or custom code). Not applicable.

Authors' contributions. EBG conceived and wrote the manuscript with significant contributions from KSH.

Figures.

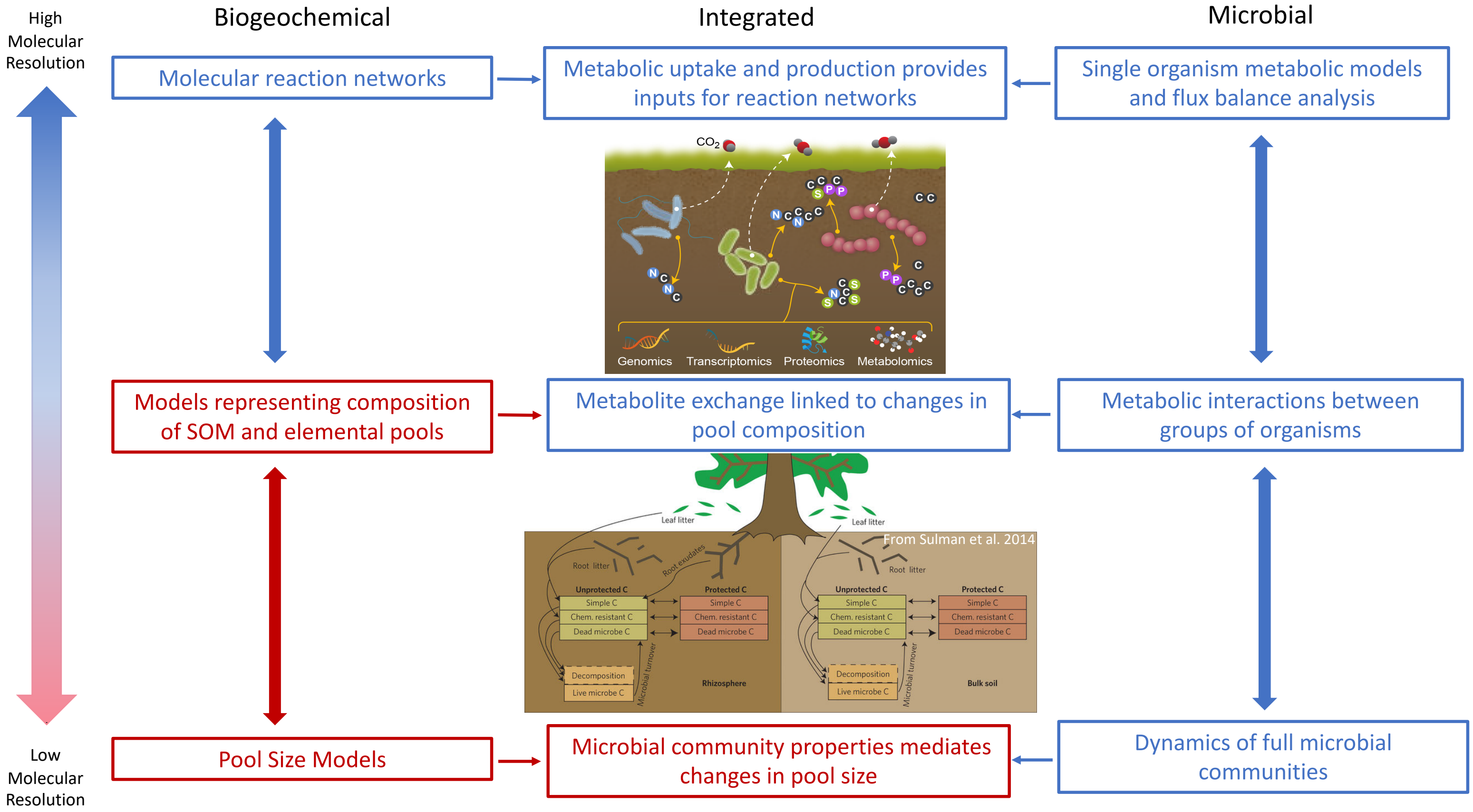

Fig 1. Parallel development of processed-based biogeochemical and microbial models across scales of molecular resolution. Ecological stoichiometry has guided the development of many biogeochemical models at relatively coarse molecular resolution but has not yet been assimilated into high-resolution modelling frameworks that are principally informed by microbiology. We present opportunities for stoichiometry to serve as an underlying framework to integrate state-of-science SOM decomposition models across

ecological hierarchies – from individual microorganisms to bulk pools and fluxes – as well biogeochemical and microbial disciplines. Examples of common modelling frameworks are arranged vertically by level of molecular resolution and horizontally by scientific domain. Information exchange is denoted by arrows. Modelling frameworks that leverage ecological stoichiometry are presented in red, and opportunities to use these principles to guide multiscale model development are presented in blue. Insets denote the role of stoichiometry in SOM decomposition (top) and an example of state-of-science SOM decomposition models (bottom).

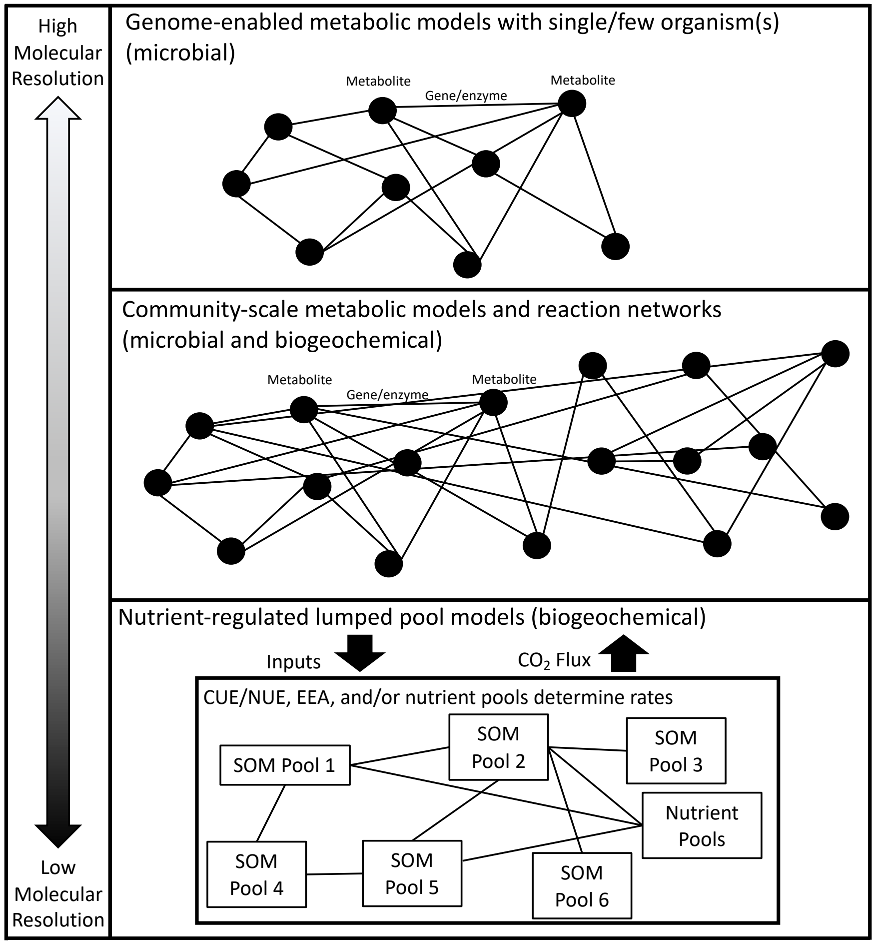

Fig 2. State-of-science SOM decomposition models across scales of molecular resolution. State-of-science models across scales of ecological hierarchies arise from different scientific domains. At the highest level of molecular resolution (top), genome-enabled models predict the production and consumption of specific metabolites by specific microorganisms or groups of microorganisms. This

class of models is rooted in fundamental microbiology. At intermediate scales, community-scale metabolic models and reaction networks have been largely separately developed in microbiology and biogeochemistry, respectively. Finally, at coarser levels of molecular resolution, biogeochemical models predict SOM decomposition using nutrient-regulated exchange between lumped SOM pools with specific chemical attributes.

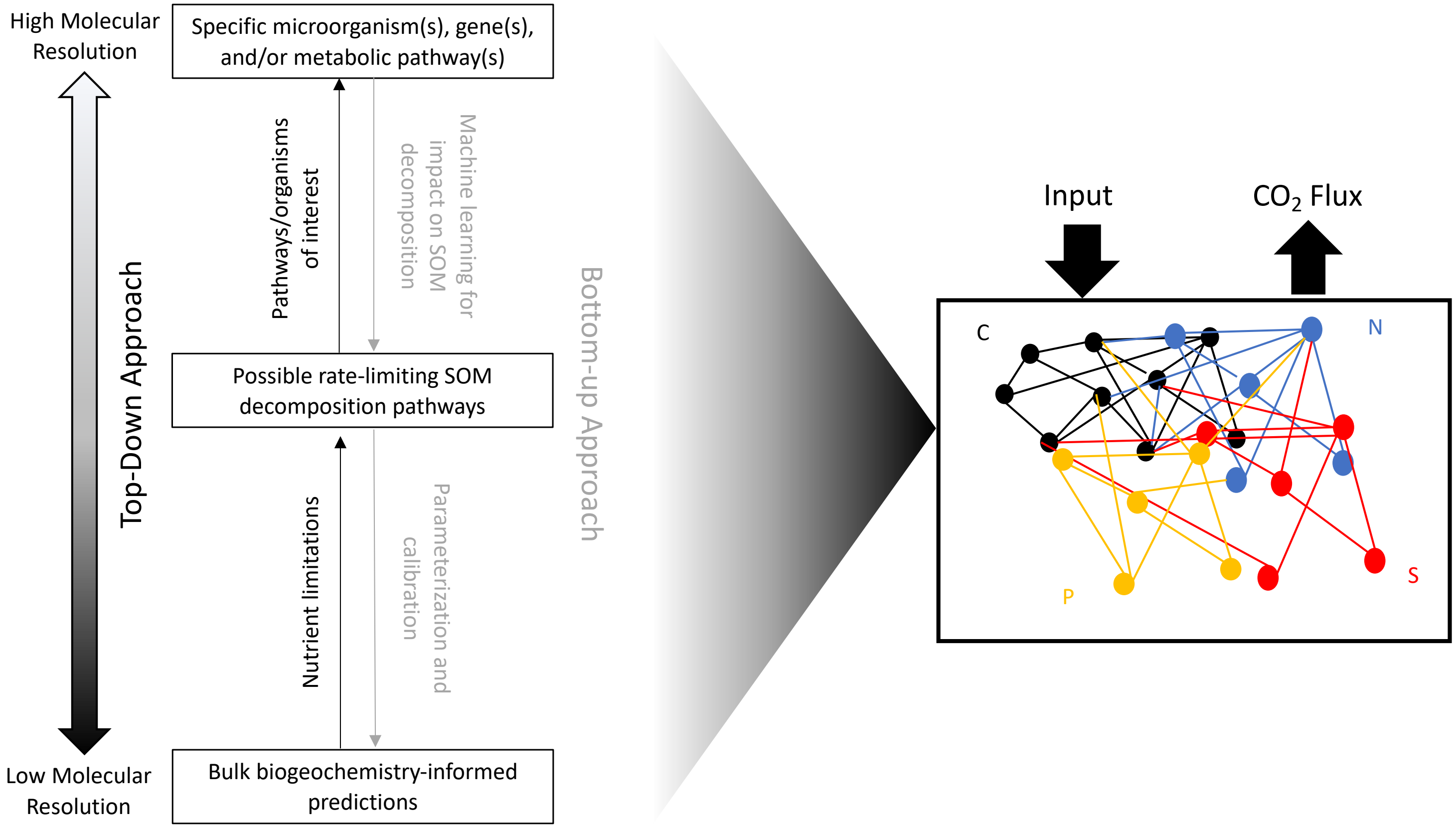

Fig 3. Schematic of opportunities for ecological stoichiometry to guide iterative approaches that generate genome-enabled reduced complexity models. Ecological stoichiometry can guide a cycle of top-down and bottom-up approaches for more efficient generation of next generation models. Top-down approaches use nutrient limitations inferred from bulk biogeochemical measurements to guide the determination of rate-limiting pathways in SOM decomposition. In turn, rate-limiting pathways can reveal specific metabolic pathways and/or microorganism for detailed representation in predictive models. Bottom-up approaches use ecological

stoichiometry as a framework for guiding the interpretation of high molecular resolution data streams with the help of new machine learning algorithms, for example by focusing on metabolic pathways that tend to be involved in nutrient acquisition. Using these approaches to identify the rate-limiting steps of SOM decomposition can then aid in the parameterization and calibration of larger-scale models by informing the tuning of substrate use efficiencies and/or by revealing pathways for more detailed representation. By using both approaches iteratively, we can identify specific portions of genome-enabled reaction networks that add predictive power with detailed representation in large-scale SOM decomposition models.

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