SHEDDING LIGHT
THE SCIENCE OF OUR DAY-TO-DAY LIVES, AND BREAKING THE ORDINARY DOGMAS

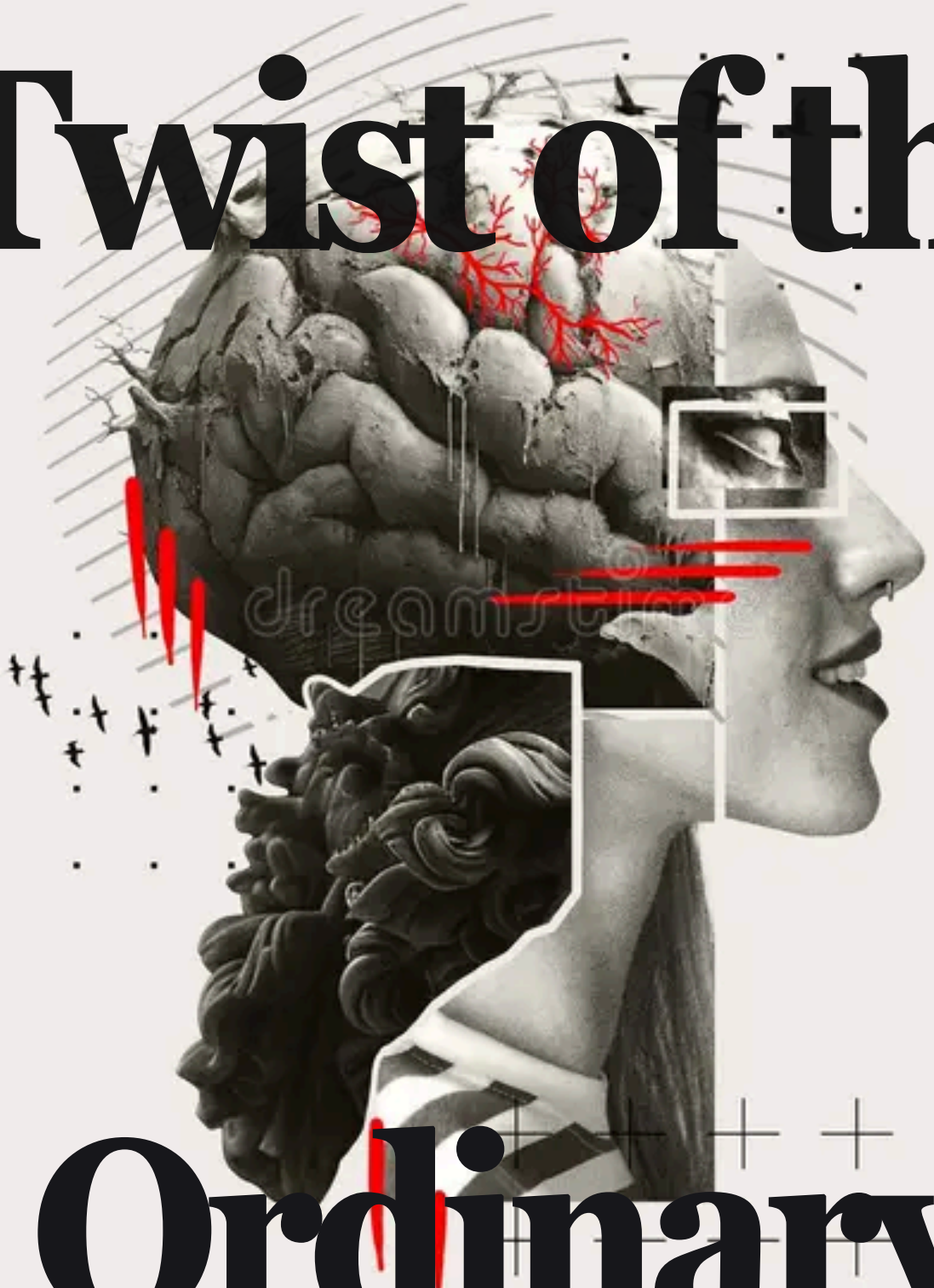
MAPPING GUT DYSBIOSIS IN ALZHEIMER'S USING ML:

THE SECRETS BURIED BENEATH EARTH'S SURFACE:

GREEN FOUNDATIONS

NOVEMBER 2026 ISSUE #7

Twist of the Ordinary



THE CENTRIFUGE

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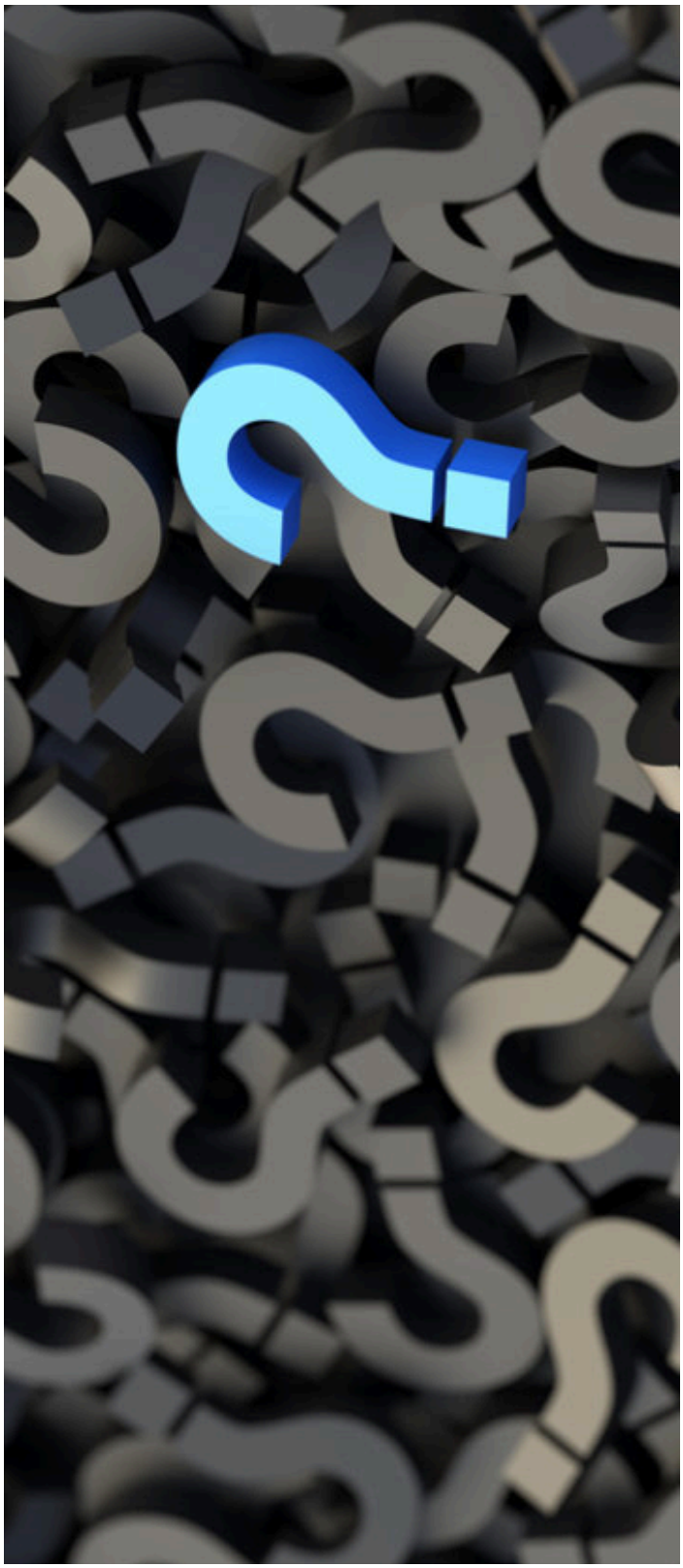
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OUR THEME - A TWIST OF THE ORDINARY



We live our day-to-day lives with a few certainties– whether they are things we were taught as children or wisdom picked up through our own experience. These dogmas we create are extremely important for our survival; we cannot live our entire lives in constant uncertainty, endlessly questioning the pillars that guide us.

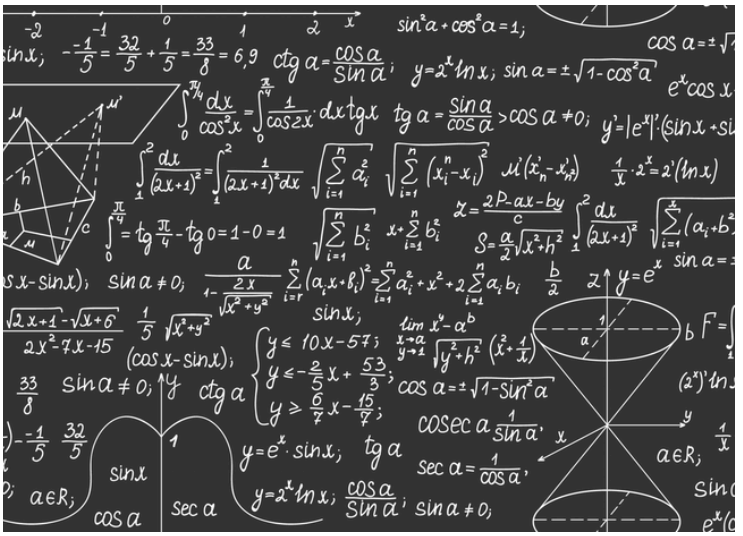
Although dogmas are often necessary for a manageable life, when searching for the truth, we must reevaluate our beliefs and verify that what seems imperceptibly constant actually provides as solid a foundation as we once believed. We learn and live by the certainty of chemical reactions, biological processes, and the accuracy of the algorithms delivering our daily updates.

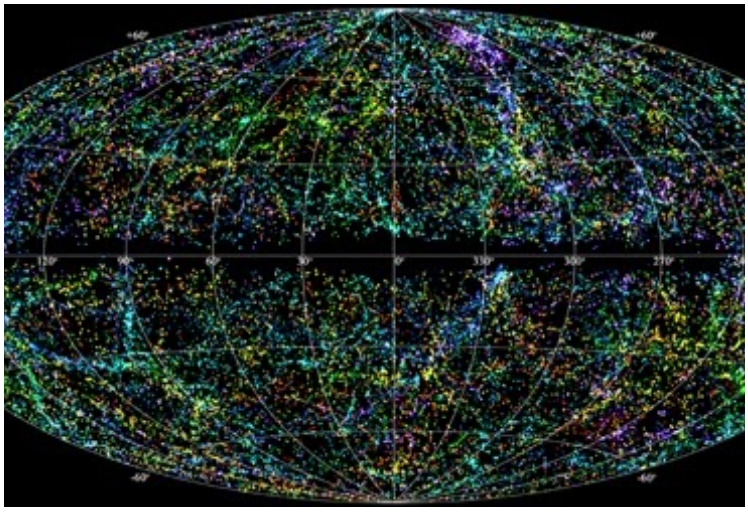
While that certainty is usually reliable, truly understanding the world around us requires exploring the exceptions. What happens when a constant changes? Why does it change? How do the rules that have always applied suddenly seem to shift?
These are the exact questions this issue answers. We examine the disruptions to our daily routine and uncover the hidden rules governing nature's seamless exceptions– exploring why elements that should never react suddenly form chemical bonds, how two grand theories fall just short of aligning, and how our complex planet creates something as ordinary as the fuel we use every day.

OUR WRITERS

RITISHA AGARWAL

HAILING FROM LONDON, RITISHA IS DRIVEN BY THE BELIEF THAT MATHEMATICS IS NOT JUST AN ABSTRACT LANGUAGE, BUT A PRACTICAL LENS THROUGH WHICH WE CAN DECODE THE WORLD. SHE IS PASSIONATE ABOUT THE REAL-WORLD APPLICATION OF MATHEMATICAL CONCEPTS, CONSTANTLY SEEKING TO BRIDGE THE GAP BETWEEN THEORY AND EVERYDAY LIFE. A LIFELONG LEARNER AT HEART, SHE THRIVES ON EXPLORING DIVERSE TOPICS AND CONNECTING WITH A GLOBAL COMMUNITY OF THINKERS WHO SHARE HER RELENTLESS DRIVE FOR DISCOVERY.





IBRAHIM CHISHTI

IBRAHIM CHISHTI IS A SIXTH FORM STUDENT FROM LONDON. HE IS FASCINATED BY THE UNIVERSE WE LIVE IN AND THE WAYS THAT WE QUANTIFY AND UNDERSTAND IT. WITH A PARTICULAR PASSION FOR ASTRONOMY AND ENGINEERING, HE IS DRIVEN BY THE IDEA OF HUMAN EXPLORATION BEYOND EARTH AND HOPES TO ONE DAY HELP WITH SUCH EXPLORATION. HE ENJOYS BOTH LEARNING ABOUT AND SHARING KNOWLEDGE ON OUR PLACE IN THIS VERY BIG WORLD.

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PUNEETH NUNNA IS A STUDENT AT SHREWSBURY SENIOR HIGH SCHOOL WHO IS PASSIONATE ABOUT THE FOREFRONT OF MODERN TECHNOLOGY, PARTICULARLY THE EVOLVING INTERSECTION OF THE PHYSICAL AND DIGITAL WORLDS. AS TOOLS SUCH AS ARTIFICIAL INTELLIGENCE AND ADVANCED HARDWARE BECOME MORE ACCESSIBLE, HE STRIVES TO USE THEM FOR MEANINGFUL, ORIGINAL RESEARCH AND TO CREATE RESOURCES THAT LET OTHERS BUILD ON HIS WORK. HIS INTERESTS SPAN ROBOTICS AND ENGINEERING TO ARTIFICIAL INTELLIGENCE AND ENVIRONMENTAL SUSTAINABILITY, AND HE IS EXCITED TO KEEP EXPLORING THESE FIELDS THROUGH RESEARCH, INNOVATION, AND COLLABORATION.



UNNATI MISHRA

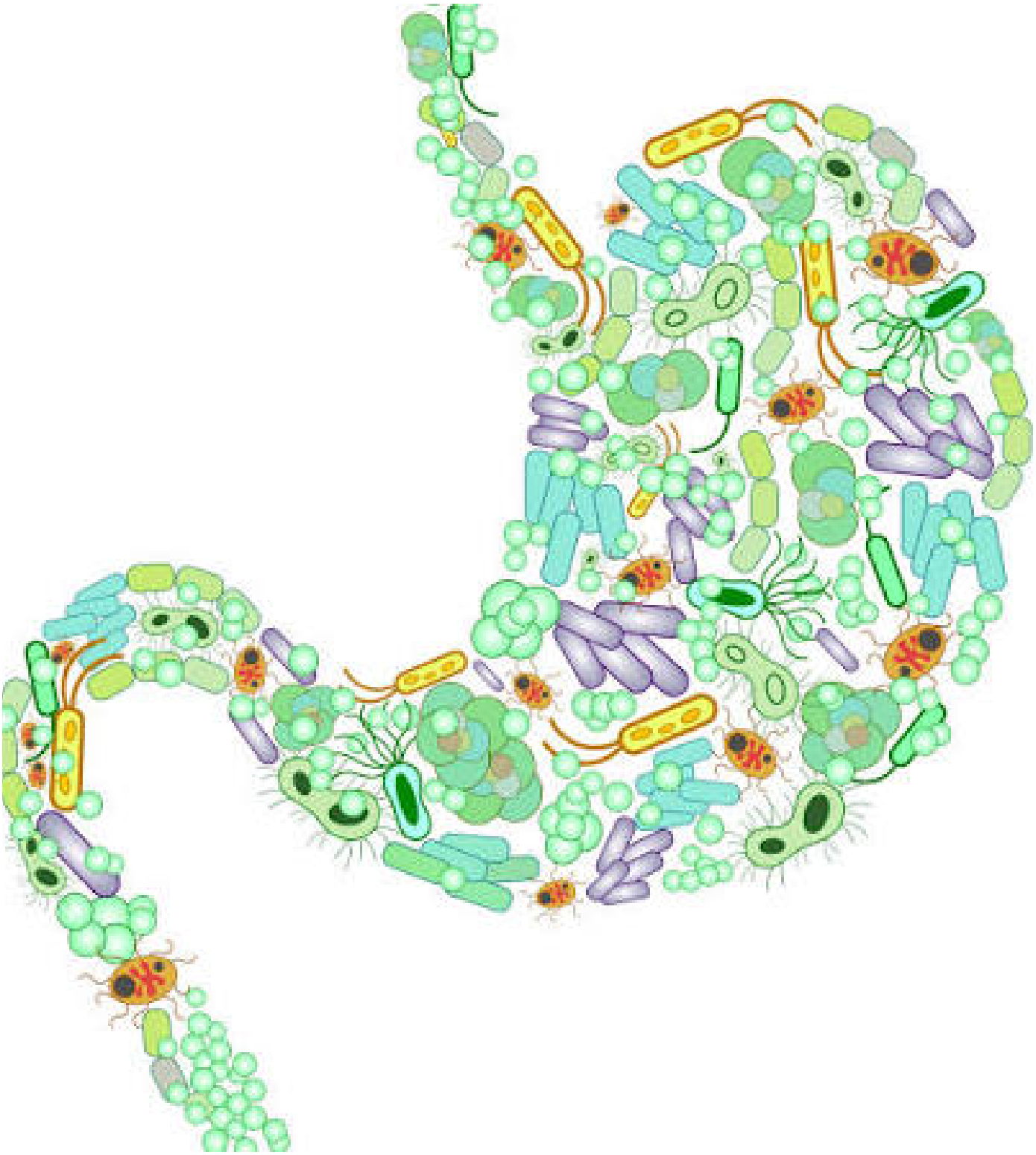


UNNATI MISHRA IS A RISING BIOMEDICAL ENGINEERING STUDENT AT THE UNIVERSITY OF SOUTHERN CALIFORNIA. THEY DEVELOPED A PASSION FOR RESEARCH IN HIGH SCHOOL THROUGH INDEPENDENT AND GROUP PROJECTS, PARTICULARLY IN EXPLORING THE EFFECTS OF ENVIRONMENTAL CHEMICALS ON HUMAN HEALTH. THEY ARE ESPECIALLY INTERESTED IN THE INTERSECTION OF BIOMEDICAL ENGINEERING AND GLOBAL HEALTH POLICY, AND HOPE TO CONTINUE CONDUCTING RESEARCH THAT IMPROVES HEALTHCARE ACCESSIBILITY. WHEN NOT IN THE LAB,



MAPPING GUT DYSBIOSIS IN ALZHEIMER'S USING ML: A MACHINE-LEARNING DRIVEN METAGENOMIC PROFILING OF GUT DYSBIOSIS FOR EARLY ALZHEIMER'S DISEASE RISK PREDICTION

By Pranav Kumar



ABSTRACT

Alzheimer's disease is a progressive, currently irreversible, neurodegenerative disorder associated with the accumulation of β-Amyloid (Aβ) plaques between cells and tau (τ) tangles within cells. The gut-brain axis has been implicated in Alzheimer's disease (AD) pathogenesis, yet experimental results regarding a gut microbial signature associated with AD remain inconsistent. In this study, I reprocessed a publicly uniformly reprocessed four publicly available fecal 16S rRNA cohorts (PRJNA554111, PRJNA489760, PRJNA633959, PRJNA734525; 413 samples, 218 AD / 195 controls) through a common amplicon-sequence-variant pipeline and evaluated cross-cohort generalizability using leave-one-dataset-out (LODO) validation across five machine-learning algorithm families. Cohort of origin was predictable from genus composition with 92.7% accuracy (chance 25%), whereas disease status reached only 0.74–0.81 AUC within studies and 0.57–0.64 AUC under LODO, a consistent generalization gap of approximately 0.17 AUC across all five models. Naive per-cohort standardization did not rescue LODO performance. Of 168 genera tested, 12 showed consistent direction across all four cohorts and survived FDR correction and showed depletion of butyrate-producing taxa in AD. The strongest signal was Lachnospira, detected in 46.8% of AD versus 75.9% of control samples (Fisher $p = 1.2 \times 10^{-9}$), consistent in direction across all four cohorts. SHAP feature attribution showed only Lachnospira and Akkermansia important in all four folds, corroborating the differential-abundance result. Together these results indicate that technical variation between studies exceeds disease-associated variation in AD microbiome data and that certain taxa, primarily butyrate producers whose prevalence was reduced, replicate across independent cohorts.

INTRODUCTION

Biological context

Alzheimer's disease (AD) is the most common cause of dementia and is defined pathologically by the accumulation of Aβ plaques in the extracellular space and neurofibrillary tangles of hyperphosphorylated τ. However, decades of investigations focusing on amyloid build-up have yielded only modest disease-modifying benefits, and the initiating events of the disease prior to observable proteinopathy remain unresolved [1]. This gap in amyloid research has shifted attention towards other contributors to neurodegeneration, such as chronic systemic inflammation and its interaction with neural immune signaling. Genome-wide association studies have implicated microglial risk loci such as TREM2 and CD33, positioning the resident immune compartment of the central nervous system (CNS) as a mediator of susceptibility instead of a bystander to plaque deposition [2,3]. Yet, microglial phenotypes are not determined solely by intrinsic genetic cues; microglial maturation and reactivity are shaped by signals of peripheral origin and the gut microbiome is among the sustained sources of such signals in the host.

The gut microbiome-brain (gut-brain) axis provides several plausible routes through which intestinal microbial communities could modulate AD pathology. Germ-free of amyloid-overexpressing transgenic mice markedly reduces the presence of cerebral Aβ, and perturbation of the microbiome with antibiotics alters plaque load in the same models, implying that the effect is contingent on microbial colonisation [4,5].

Colonisation also mediates microglial maturation and immune capabilities, with short-chain fatty acids (SCFAs) having been identified as key signals [6]. SCFAs produced in the gut microbiome such as butyrate, propionate, and acetate signal through FFAR2/3 and support blood-brain barrier integrity while reducing microglial reactivity; dysbiosis-associated increases in intestinal permeability allow for the translocation of microbe-associated molecular patterns like lipopolysaccharide which interacts with TLR4 and causes NF-κB and NLRP3 inflammasome activation. Further, microbially derived metabolites such as trimethylamine N-oxide, secondary bile acids, and tryptophan catabolites alter the balance between indoles which are neuroprotective and kynurenines which are neurotoxic [7]. Importantly, these mechanisms act on abundance-weighted community function rather than the presence or absence of any single genera, an important point for modelling this compositional data.

Human observational studies have sought to characterize the AD-associated gut microbiome, primarily using 16s rRNA amplicon sequencing. Reported biosignatures include reduced α-diversity, depletion of Firmicutes and butyrate-producing genera like Faecalibacterium and Roseburia, enrichment of pro-inflammatory taxa including Escherichia, and other signals [8,7,9,10]. Similar shifts have been identified in preclinical AD (amyloid-positive but no clinically significant cognitive symptoms). However, findings are frequently inconsistent between cohorts, with contradictory directions of effect for taxa such as Bacteroides, Bifidobacterium and Alistipes, and this heterogeneity has been attributed in part to differences in geography, sequencing region, and analytical methodology [11,10]. Univariate differential-abundance testing is poorly matched to this structure, motivating multivariate machine learning approaches to accommodate interaction and non-linearity when relating community composition to AD status.

Methodological Considerations

Methodological factors are a particular concern. Early studies typically relied on operational taxonomic units (OTUs) and older reference databases, whereas modern pipelines use amplicon sequence variants (ASVs) that offer single-nucleotide resolution and improved cross-study comparability [12,13]. Reanalyses of datasets with updated tools have, in at least one case, failed to reproduce the original disease-specific signatures: a 2025 reanalysis of PRJNA554111 reported no distinct microbial composition separating AD from controls [14]. Independently, large integrative meta analyses pooling many public cohorts have shown that study-of-origin (batch) effects can explain more compositional variance than disease status itself [10], underscoring the fragility of single-cohort microbiome classifiers.

Here I reprocessed BioProject PRJNA554111 (originally described by Zhuang et al. [9]) along with three additional fecal 16S V3-V4 amplicon sequencing cohorts, with a fully current ASV pipeline, and came up with a focused methodological question: can AD status be predicted from gut community composition, and if so, how sensitive is that predictability to model family? I further quantified per-taxon differential abundance and reconciled it with community-level predictability. Finally, I conducted a cross-cohort, leave-one-dataset-out validation to test generalizability, motivated by the recognized irreproducibility of AD microbiome signatures [14,11,10].

THEORY OF CHANGE

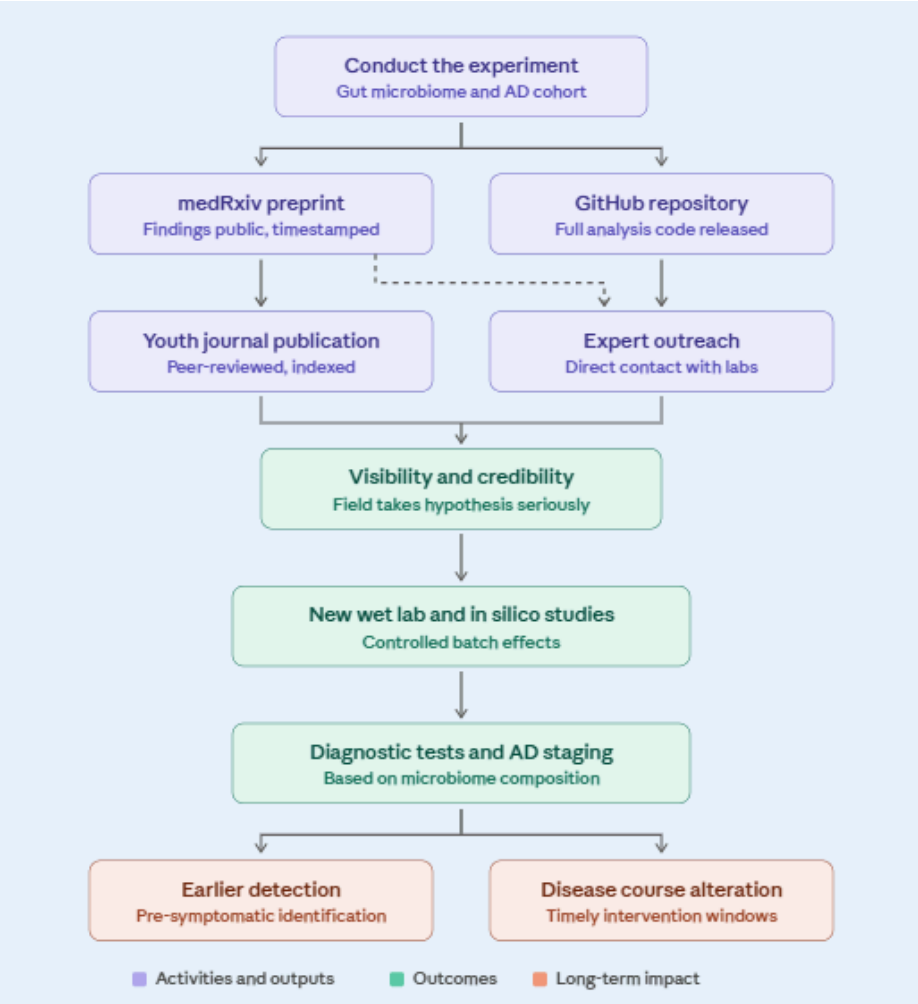


Figure 1. General outline of steps of a theory of change.

The process by which a change is expected to be effected is detailed in Figure 2. Note there are a few assumptions and uncertainties of significance in relation to carrying out this theory of change. It is assumed that this paper is of sufficient quality to be published in a youth journal and that its findings are significant enough to garner interest from experts and associated labs. Assuming both of these ends are achieved, it is supposed that the field of gut microbiology would take the hypothesis of this study and further research directions seriously though this may not be the case as by the time visibility is achieved, new professional findings may supersede this study's. Lastly, it is assumed that the new studies carrying into effect the further research directions discussed below shall lead to new diagnostic tests and AD staging criteria, but this necessarily presupposes that these new studies will not obtain null results.

METHODS

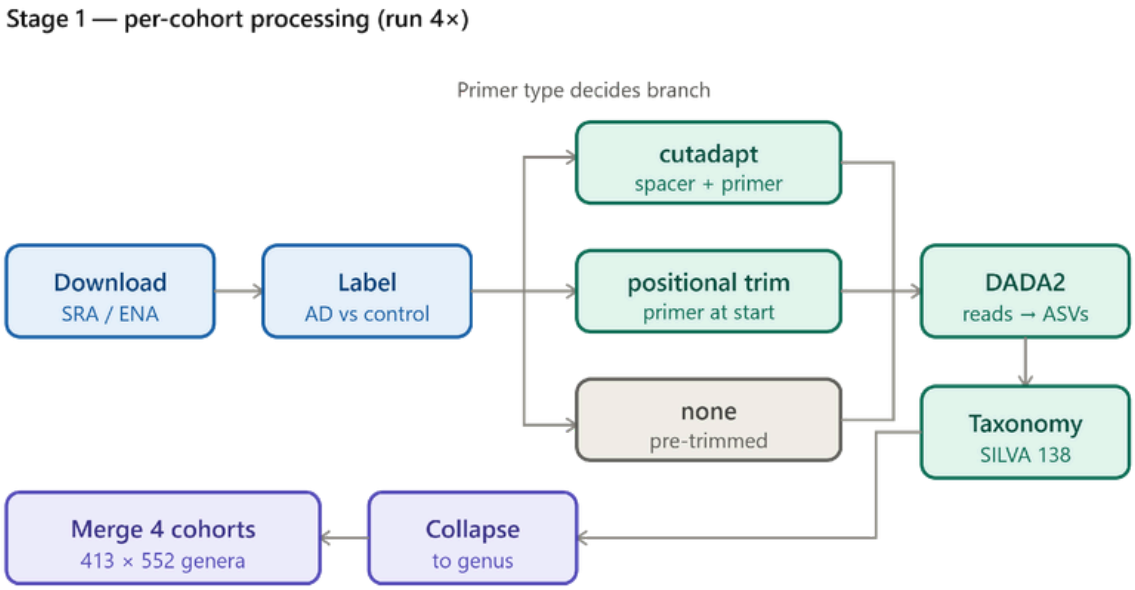


Figure 2. Per-cohort processing procedure step sequence.

Four publicly available fecal 16s rRNA amplicon sequencing BioProjects with AD and control groups were obtained the NCBI Sequence Read Archive/European Nucleotide Archive: PRJNA554111 (cohort 1), PRJNA489760 (cohort 2), PRJNA633959 (cohort 3), and PRJNA7345425 (cohort 4). Disease-group labels were not consistently formatted or organized in SRA metadata fields and thus were reconstructed for each cohort based on the sample-naming conventions or library_name attribute, then verified against the expected group sizes based on Zhuang et al. [9], Li et al. [11], and Liu et al. [15] for cohorts 1, 2, and 3, respectively.

Cohort-specific curations of these datasets were necessary. In PRJNA489760, samples of both fecal and blood specimens across AD, mild cognitive impairment (MCI), and control groups were present; only fecal AD and control samples were retained (60 of 180 runs). In PRJNA734525, library_name distinguished the AD group from the healthy control group, with prefixes such as AD, ADH (an AD subtype), MCI, and C (for control); MCI samples were excluded, and two additional samples were excluded because their reads were only present in an untrimmed form inconsistent with the other reads in the cohort. The final data composition is given in Figure 2 below and Table 1 in Appendix II in thecentrifugemag.com.

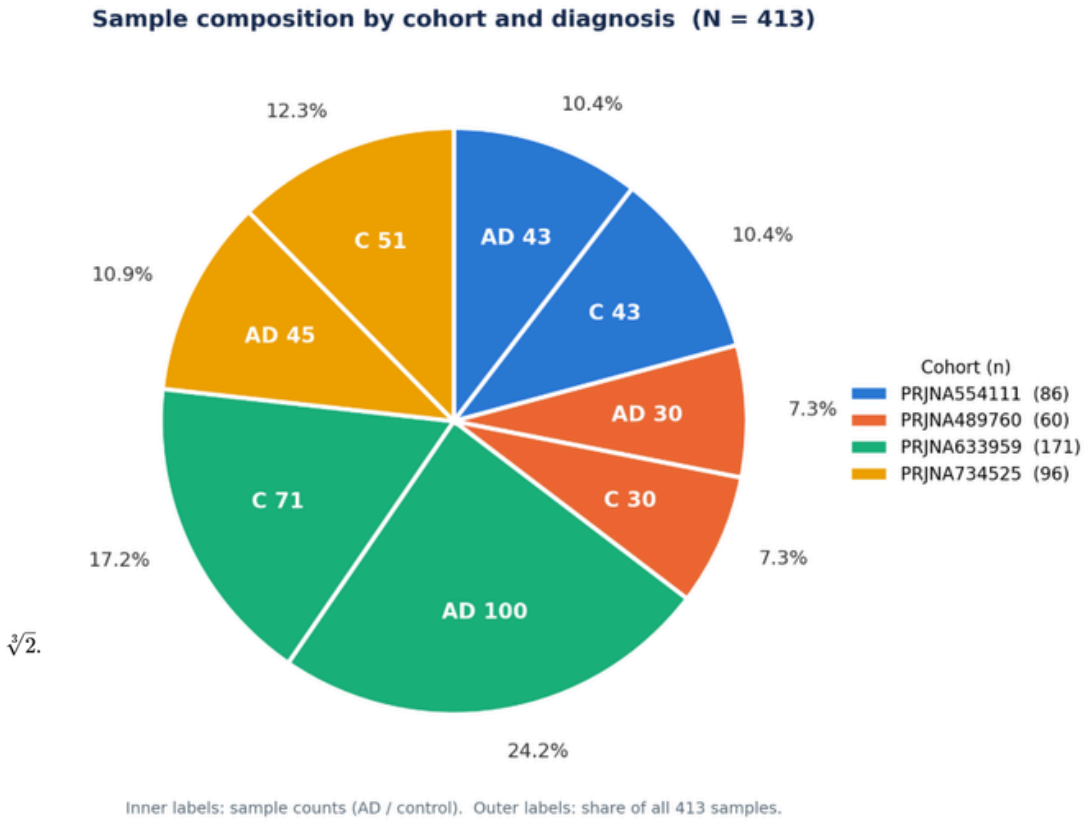


Figure 3. Cohort composition and processing parameters

Note that only the forward read of PRJNA734525 was retained while the remaining datasets were all processed as paired-end reads.

Sequence Processing

Reads were imported into QIIME 2 (2024.10) [13,22] and processed per cohort using DADA2. The manner in which primers were to be handled for each cohort was determined by inspection of read starts. If primers were preceded by a variable heterogeneity spacer, they were removed with cutadapt [16] using the 341F (CCTACGGGNGGCWGCAG) and 805R (GACTACNVGGGTATCTAATCC) sequences; if primers occurred at the first base position, they were removed by fixed positional trimming (17 nt forward and 21 nt reverse), as sequence based matching failed in this scenario. In cohort 3, primers had already been removed by the submitter.

Truncation lengths were selected for each cohort based on interactive quality profiles in QIIME 2 View, subject to retaining sufficient overlap to merge the approximately 427 nt primer-free V3-V4 amplicon. Cohort 4 was processed single-end because submitter trimming had produced two distinct read-length groups (approximately 233 and 284 nt), preventing a uniform paired-end truncation. Genus-level assignment, which was used throughout the study, is adequately supported by single-end V3-V4 reads.

Amplicon sequence variants (ASVs) were identified with DADA2 [12]. Taxonomy was assigned by consensus alignment against SILVA 138 (99%) [17] using VSEARCH [18] at 80% identity and 80% query coverage. Feature tables were collapsed to genus level (L6) for all subsequent analysis as the genus level is the finest resolution comparable across cohorts differing in read structure and processing.

Cross-Cohort Merging and Preprocessing

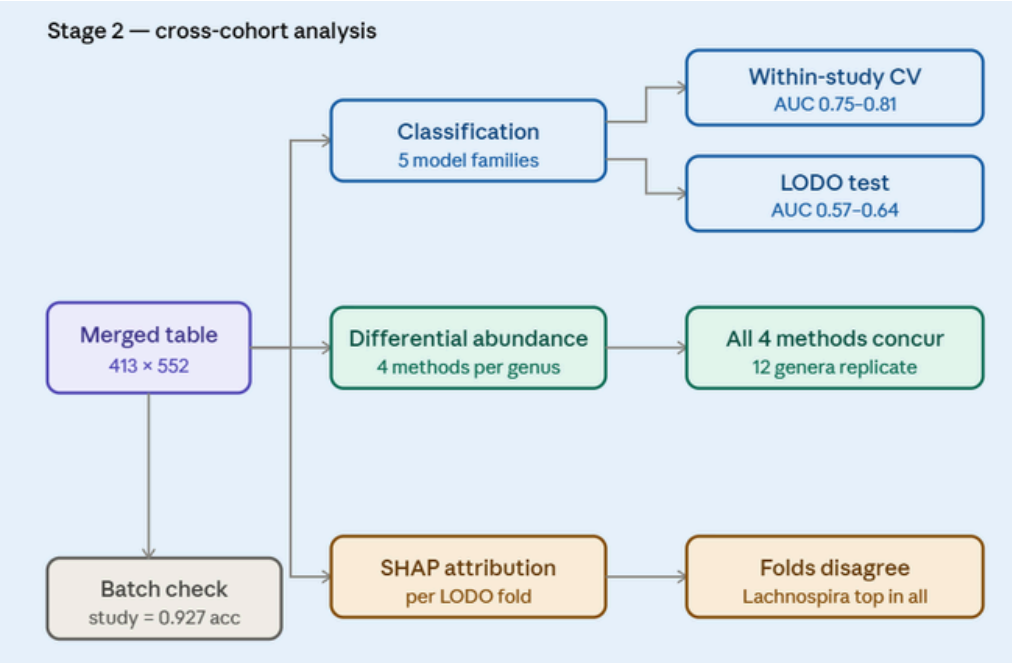


Figure 4. Steps of Cross-cohort analysis

Genus tables were exported and merged across cohorts by union of genus labels, thus yielding 413 samples and 552 genera. For modelling, counts were converted to relative abundance, genera present in under 10% of samples were dropped (168 genera retained), and values were log-transformed. For differential abundance, a centered log-ratio (CLR) transform was additionally applied, with zeros imputed at half the minimum observed non-zero value.

Classification and leave-one-dataset out validation

Five algorithm families were evaluated: elastic-net logistic regression, random forest, gradient boosting, linear support vector machine (probability-calibrated), and k-nearest neighbours (k = 15), implemented in scikit-learn [19]. Two evaluations were performed for each. Within-study performance was estimated by 5-fold stratified cross-validation separately within each cohort and averaged. Leave-one-dataset-out (LODO) performance was estimated by training on three cohorts and testing on the fourth which was completely excluded from training, rotating through all four as testing data.

The magnitude of the study effect was quantified by training a random forest to predict cohort of origin from genus composition under 5-fold cross-validation.

To test whether batch adjustment improves cross-cohort transfer, LODO was repeated after per-cohort standardization (each cohort was centered and scaled using its own samples), a correction that prevents the leaking of held-out label information.

Differential abundance and cross-cohort replication

Instead of pooling samples, each genus was tested within each cohort separately (Mann-Whitney U), and results were combined by Fisher's method with Benjamini-Hochberg FDR correction. A genus was considered replicated only if it achieved $q < 0.05$ and showed the same directional effect in all four cohorts. This analysis was performed on both log-relative-abundance and CLR-transformed data. For taxa with high zero-inflation, prevalence (proportion of samples with non-zero abundance) was compared by Fisher's exact test, as fold-change estimates are unstable under zero imputation. ANCOM-BC [20] was additionally applied per cohort for comparison with the above methods.

Pipeline validation via synthetic data

To confirm the analysis pipeline could recover a transferable signal replicated across cohorts when present, I generated synthetic genus tables matching the real cohort sizes, feature count, and batch structure, with a disease effect of tunable strength applied in the same direction across all four simulated cohorts and processed them through the aforementioned LODO pipeline with a Random Forest classifier. The generation of the synthetic genus tables is discussed in more depth in Appendix I.

Data volume estimation using synthetic data

To determine the volume of samples needed for AUC > 0.85 to be achieved by a classifier, I generated synthetic genus tables with varying sample counts and batch effect magnitude. These sets of genus tables were then processed through the aforementioned LODO pipeline with a Random Forest classifier. The generation of these tables and the manner in which the batch effect was controlled are discussed in greater depth in Appendix I.

RESULTS

Uniform processing across four cohorts

All four cohorts were processed to genus-level tables with high-quality taxonomic assignment (0% unassigned ASVs in the cohorts examined). Retention varied by cohort: PRJNA554111 and PRJNA489760 retained approximately 72-80% of reads as non-chimeric, PRJNA734525 76%, while PRJNA633959 showed an elevated intrinsic chimera rate (approximately 46% non-chimeric) that persisted after correcting primer removal, indicating a library-preparation characteristic rather than a processing artifact. Sequencing depth remained adequate in all cohorts (minimum per-sample depths of 21,765; 12,905; and 20,529 in the cohorts assessed). The merged matrix comprised 413 samples and 552 genera (168 after prevalence filtering).

Study of origin is far more predictable than disease status

A random forest trained to identify cohort of origin from genus composition achieved 92.7% accuracy (chance = 25%). By contrast, the same feature space supported only modest discrimination of disease status. This establishes that between-study technical variation is the dominant structure in the merged data.

A consistent generalization gap across five model families

Within-study cross-validation yielded mean AUCs of 0.736–0.807, whereas LODO validation yielded 0.575–0.641. The resulting generalization gap was remarkably consistent, 0.158 to 0.182 AUC, across all five algorithm families (Figure 5 below and Table 2 in Appendix II), indicating that the loss is a property of the data rather than of any particular learner.

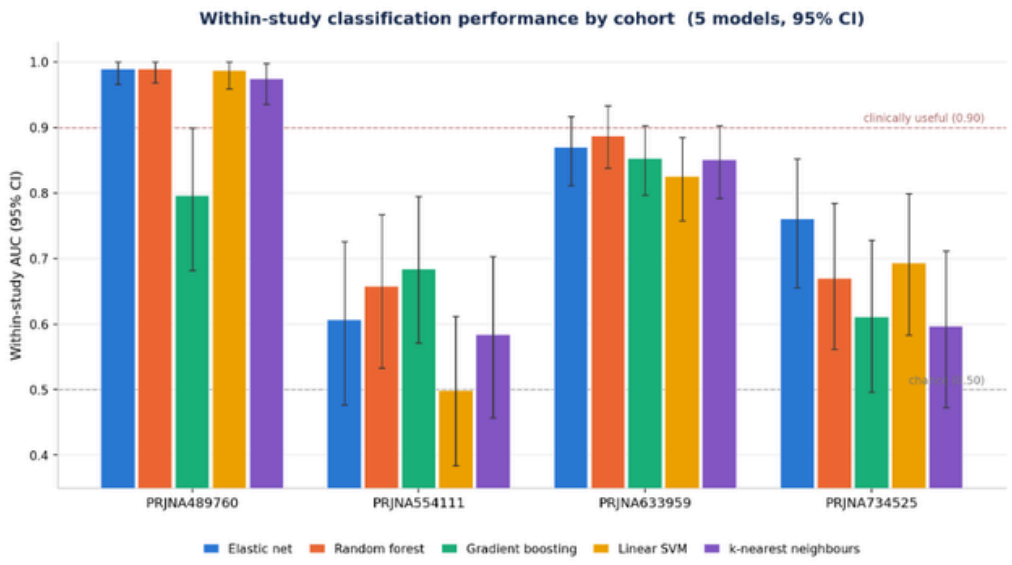


Figure 5. Per-cohort and average AUC values by cohort and classifier.

On average across the four cohorts, the elastic classifier performed with an AUC value of 0.807, the random forest performed with an AUC of 0.801, the gradient boosting classifier performed with an AUC of 0.736, the Linear SVM classifier performed with an AUC of 0.751, and the k-nearest neighbors classifier performed with an AUC of 0.752.

Notably, LODO performance remained modestly above chance for most models, indicating a weak but non-zero transferable signal. Per-cohort LODO results were heterogeneous (Figure 6 below and Table 3 in Appendix II): PRJNA633959 was predicted best when held out (0.59–0.74), whereas PRJNA554111 was predicted at essentially chance level by every model (0.51–0.58).

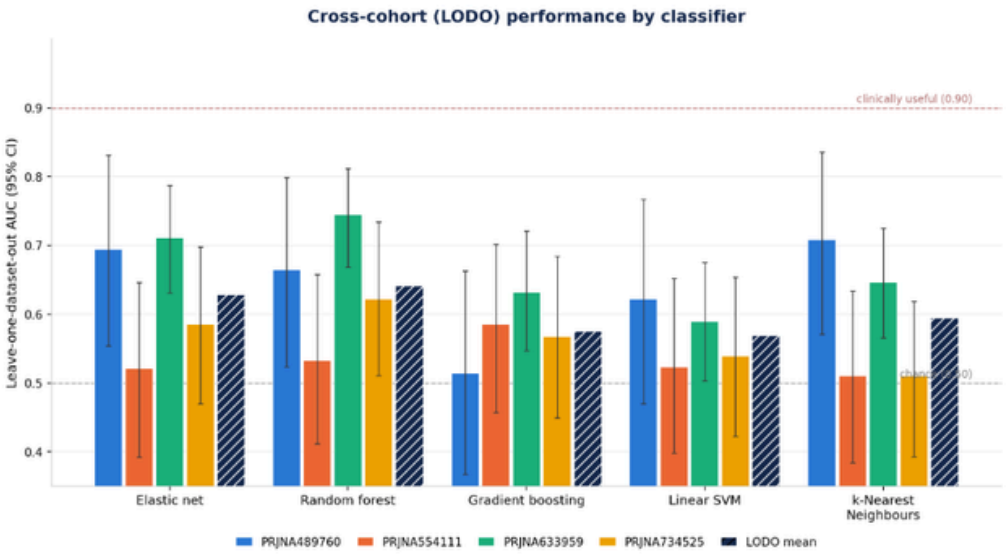


Figure 6. LODO AUC values by classifier and held-out cohort

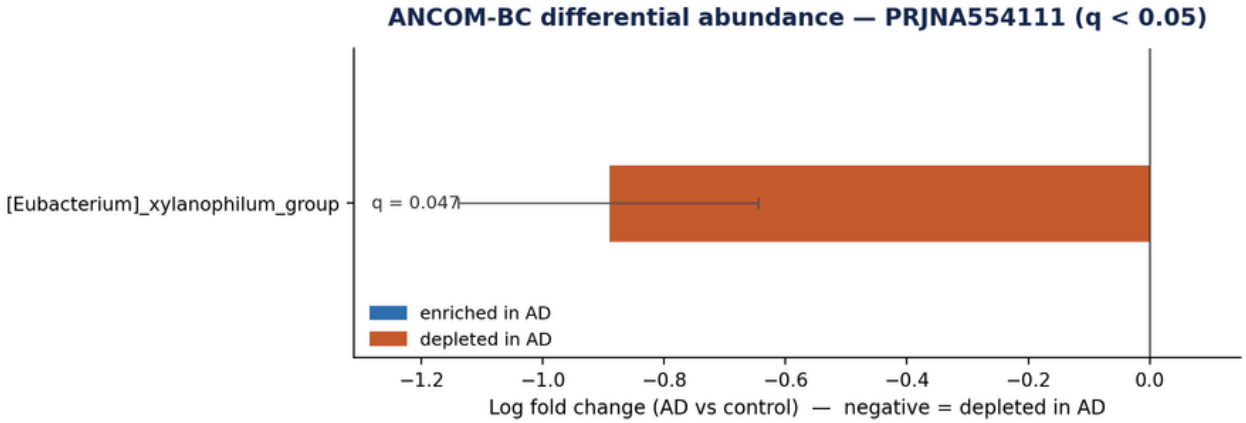
Naive batch correction does not rescue transfer

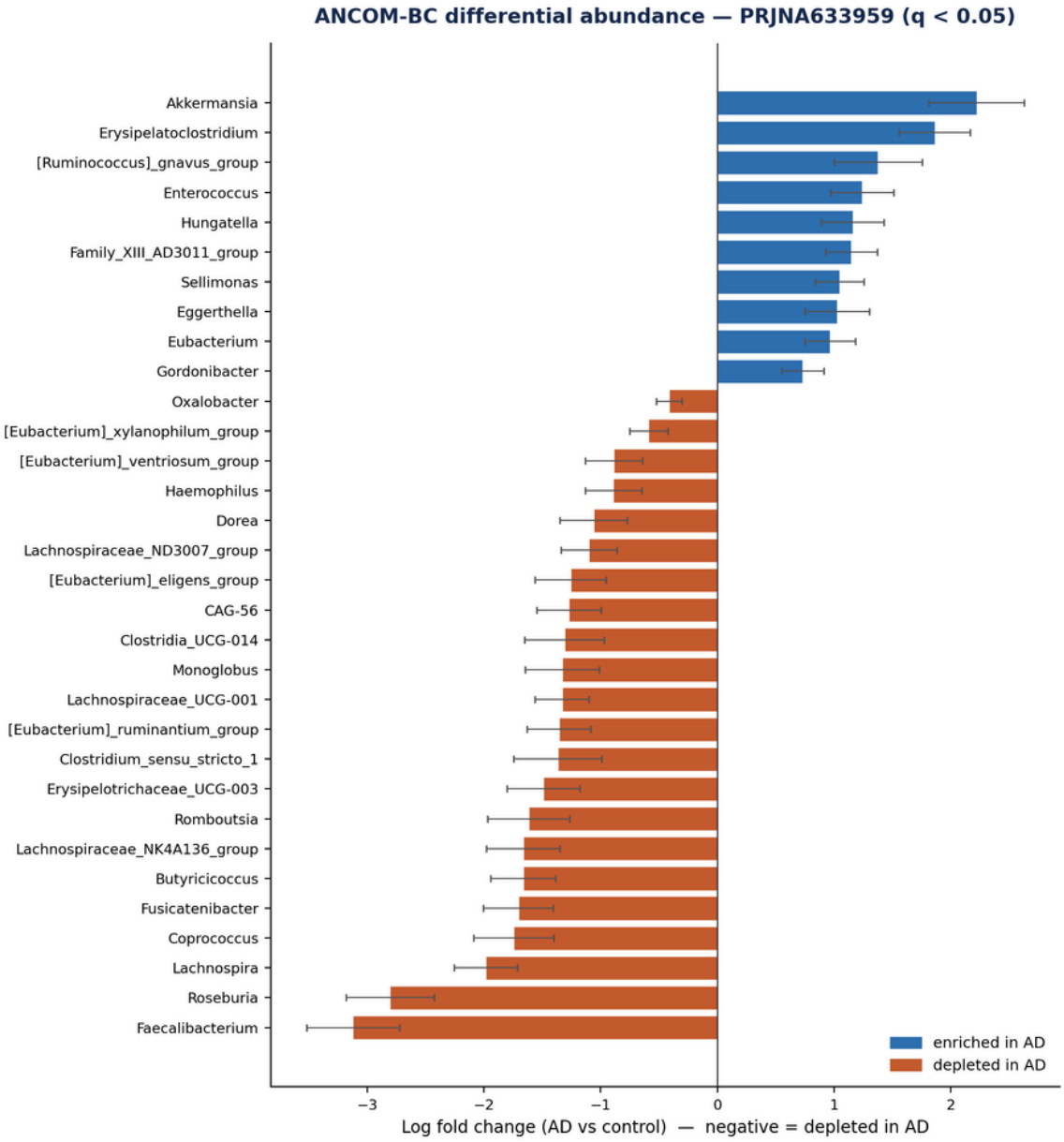
Per-cohort standardization reduced mean LODO AUC for elastic net (0.628 → 0.573) and left random forest essentially unchanged (0.641 → 0.628). The decrease was driven almost entirely by PRJNA734525, which fell from 0.58 to 0.39 (below chance). I interpreted this as centring removing disease-associated variation along with batch offset in a cohort whose case/control ratio differs from the training cohorts; covariate-preserving methods (e.g. MMUPHin, ConQuR), which explicitly protect the disease variable, would be the appropriate comparison and were not evaluated here.

ANCOM-BC agrees with the other methods

ANCOM-BC was applied per cohort as a fourth differential-abundance method. Reading the group-effect column (groupAD, where a positive LFC denotes a higher abundance in AD), ANCOM-BC's direction of effect agreed with the raw relative abundances for every significant genus tested. Of the 55 genera considered significant ($q < 0.05$) in PRJNA633959, all 55 (100%) matched the raw between-group direction. ANCOM-BC was similarly concordant with the raw relative abundance method in the other cohorts. As an example, in PRJNA633959, Faecalibacterium and Roseburia were reported as depleted in AD, agreeing with the raw relative abundances (4.26% vs 15.94% and 1.59% vs 7.49%, AD vs control) and the CLR-based Wilcoxon results. Hence, all four methods (raw relative abundance, Mann-Whitney on log-relative abundance, CLR-based Wilcoxon, and ANCOM-BC) were mutually concordant in direction of effect, strengthening confidence in the replicated genera that have been reported in Section 3.6.

Twelve genera replicate across all four cohorts





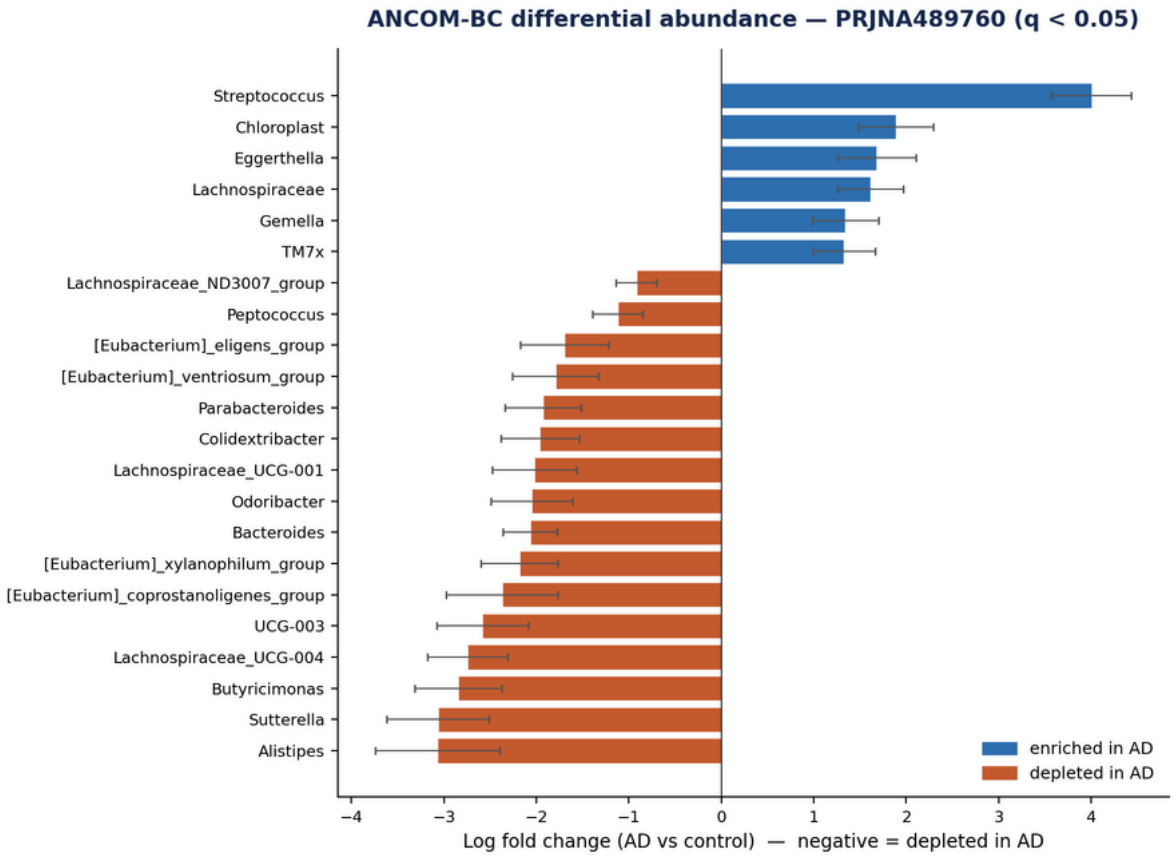


Figure 7. Significant genera across all cohorts

Note that PRJNA734525 did not produce any significantly differentially abundant genera. Testing each genus within each cohort (Figure 7 above) and combining by Fisher's method, 12 of 168 genera achieved $q < 0.05$ with consistent direction in all four cohorts (Table 4 in Appendix II). Six were also recovered by the log-relative-abundance analysis, with identical directions.

Half of the replicated genera are butyrate- or short-chain-fatty-acid–associated taxa depleted in AD (Lachnospira, Faecalibacterium, Butyricicoccus, two Lachnospiraceae groups, Romboutsia). Genera significant in only one cohort should be regarded as suggestive.

Model feature attribution disagrees between cohorts except for two genera

To examine which taxa the classifiers relied on, SHAP values were computed for each leave-one-dataset-out random forest, applied to the held-out cohort. Overlap in the top 20 attributed features between folds was low (Jaccard index 0.14–0.38), indicating that models trained on different cohort combinations depend on substantially different taxa. Only two of 168 genera, Lachnospira and Akkermansia appeared in the top 20 of all four folds.

Lachnospira ranked 1st, 3rd, 4th and 1st across the four folds, and Akkermansia 3rd, 6th, 14th and 4th. Both were also identified as replicated by the independent differential-abundance analysis (Section 3.6), providing convergent evidence from two methodologically unrelated approaches. Conversely, the fold with the weakest performance (PRJNA554111, AUC 0.533) relied on an idiosyncratic feature set (Erysipelatoclostridium, Sellimonas, Ruminococcus gnavus group) not prominent in any other fold. Because LODO AUCs ranged from 0.53 to 0.75, these attributions describe model behaviour rather than established biology, and are reported as supporting evidence for the low cross-cohort transferability rather than as independent biological findings.

Lachnospira is a prevalence difference, not a fold-change

Lachnospira showed extreme CLR values in PRJNA633959 driven by zero-inflation rather than abundance shift, and is therefore best characterised by prevalence. It was detected in 46.8% of AD versus 75.9% of control samples overall (Fisher $p = 1.2 \times 10^{-9}$), with the same direction in every cohort: 70.0% vs 86.7% (PRJNA489760), 55.8% vs 69.8% (PRJNA554111), 22.0% vs 63.4% (PRJNA633959, $p = 9.1 \times 10^{-8}$), and 77.8% vs 92.2% (PRJNA734525). Absolute abundances were low throughout (medians 0–0.4%), consistent with expected values for this genus.

Presence of a transferable signal can be detected by the pipeline

As a positive control, the pipeline returned AUC = 0.505 under a null and AUC > 0.83 under a moderate injected effect (cohort-of-origin predictable at 1.000, comparable to 0.927 in real data), confirming the pipeline can detect a transferable signal when present and manufactures none when absent. The real-data LODO AUC (~0.6) corresponds to a weak injected effect.

Presencé of a transferable signal can be detected by the pipeline

Strong, realistic batch effects in cohorts caused AUC values to collapse to chance as the number of samples (n) grew (AUC = 0.602 at n = 90 to AUC = 0.502 at n = 5000). However, in synthetic cohorts where batch effects were negligible, increasing sample counts did cause AUC values to rise to moderate significance (AUC = 0.726 at n = 90 to AUC = 0.807 at n = 5000). Thus, it is unlikely that any amount of current data shall lead to a model with a clinically useful cross-cohort AUC value as these models are necessarily limited by strong batch signatures.

Discussion

Three findings emerge. First, technical variation dominates: cohort of origin was recoverable from genus composition with 92.7% accuracy while disease status reached at most 0.64 AUC out-of-cohort. To test whether this ceiling reflected limited sample size or a barrier intrinsic to the data, synthetic data was generated. Cross-cohort AUC rose toward 0.81 with increasing sample size when batch effects were negligible, but plateaued near chance under realistic batch heterogeneity regardless of sample size, indicating that technical variation between studies rather than insufficient data limit cross-cohort classification. This finding is consistent with the failure of naive batch correction and the model-independent generalization gap described below.

Second, within-study performance is not generalizable. The 0.16–0.18 AUC gap was near-identical across bagged trees, boosted trees, a regularized linear model, a margin classifier and an instance-based learner, indicating a property of the data rather than of model choice. Published AD microbiome classifiers validated only within a single cohort should be expected to lose comparable performance on new data. That LODO nevertheless remained modestly above chance for most models indicates a weak transferable signal does exist, an intermediate conclusion between "diagnostic signature" and "no signal at all." The heterogeneity across held-out cohorts is itself informative: PRJNA554111, the cohort underlying widely cited original claims, was the least predictable from the others.

The SHAP analysis adds a mechanistic dimension to this. The models did not merely perform differently across held-out cohorts, they reasoned differently, sharing only 14-38% of their top-ranked features. This suggests the classifiers are largely fitting cohort-specific structure rather than a common disease signal, which is precisely what the generalization gap would predict. That Lachnospira nevertheless ranked in the top four of every fold, and was independently flagged by the statistical analysis, makes it the most defensible single finding in this study.

Third, a small, biologically coherent set of taxa replicates. Six of twelve replicated genera are butyrate-associated and depleted in AD, consistent with reduced short-chain-fatty-acid production capacity; butyrate supports gut barrier integrity and has been implicated in neuroinflammation. Lachnospira was the most consistent and is best described as reduced prevalence rather than reduced abundance.

Several limitations apply. Only four cohorts have been processed, and the Control/AD ratios across cohorts differ. Further, all four cohorts are Chinese, limiting geographic generalizability. Cohorts differed in read structure, requiring one to be processed single-end, and one exhibited an elevated intrinsic chimera rate; both were handled by analyzing at genus level, but residual technical heterogeneity remains. Clinical metadata (medication, diet, comorbidity, disease stage) were unavailable, precluding confounder adjustment. Only a naive batch correction was evaluated; covariate-preserving methods may perform better and should be tested. Finally, several replicated genera were individually significant in only one cohort, and their combined significance is driven principally by the largest study.

CONCLUSION

Uniform reprocessing and leave-one-dataset-out validation of four AD gut microbiome cohorts shows that study of origin is far more predictable than disease status, that within-study classification performance overstates cross-cohort performance by approximately 0.17 AUC regardless of algorithm, and that a weak but non-zero AD signal transfers across cohorts. Twelve genera replicate in direction across all four studies, dominated by depletion of butyrate-producing taxa, with reduced prevalence of Lachnospira the most consistent finding.

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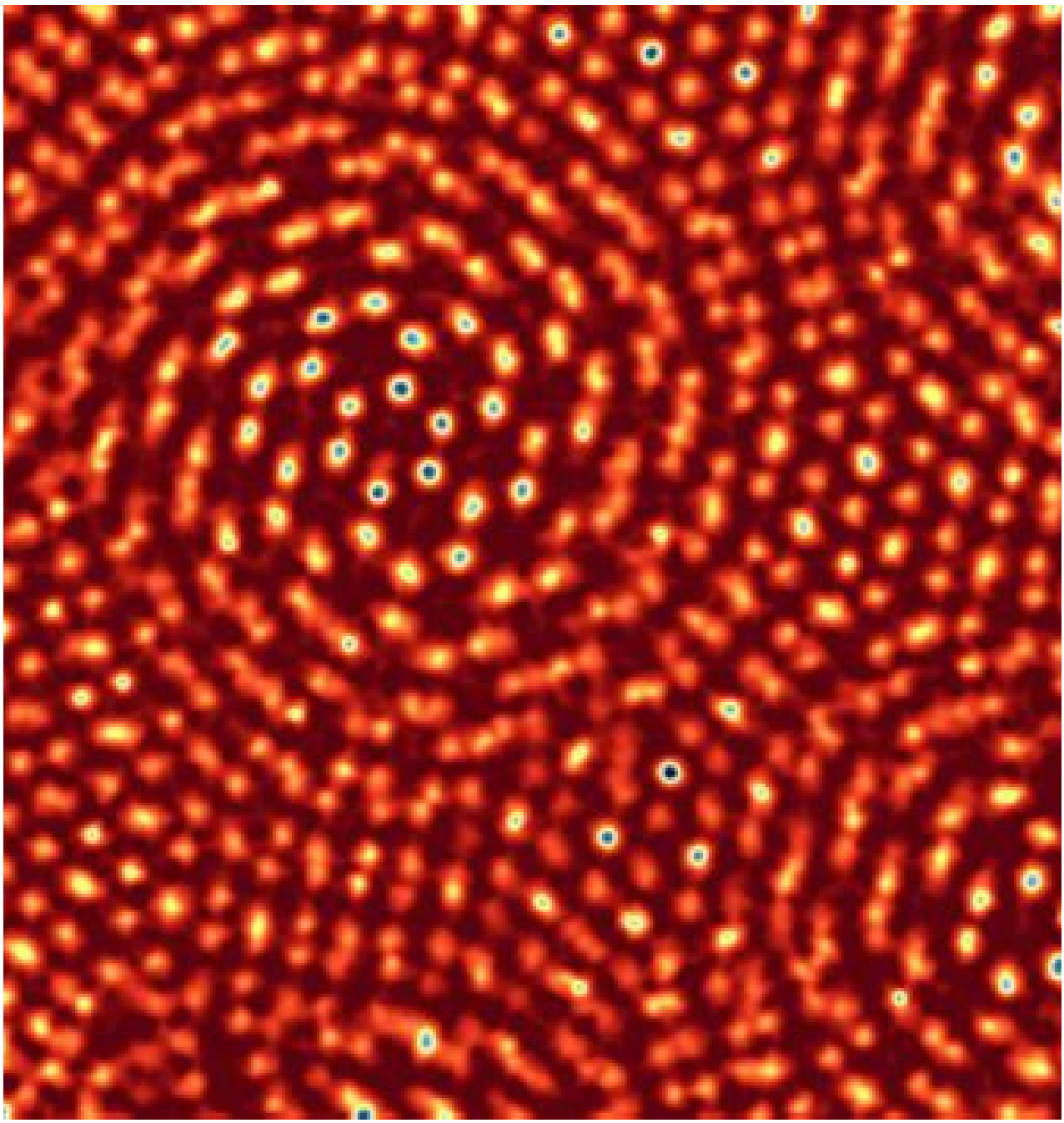
FURTHER RESEARCH

While this study did not identify a significant and consistent AD signal in gut microbiota, the replicated set of 12 bacterial taxa warrants additional research. As mentioned above, the current study was performed with cohorts of East Asian patients. It is necessary to conduct further studies to determine whether the same signal survives when other demographies are included as well or whether a distinct signal results. In addition, as this study only utilized 16S rRNA amplicon sequencing data, it may be worthwhile to utilize shotgun metagenomic sequencing data [21] to enable potentially greater taxonomic resolution, cross-kingdom profiling, and functional information, though the greater cost and host DNA contamination would have to be accounted for. Further, other classifiers such as Graph Neural Networks (GNNs) and transformer-based architectures may be studied to determine whether they would be better suited for gut microbiome data.

The results from the analysis of synthetic data suggest that while the pipeline was indeed a valid setup, the nature of the data available, specifically the strength of the batch effects, prevented a clinically useful AUC value from being achieved as strong batch effects in the synthetic data were determined to cause AUC values to collapse as sample size increased, explaining the drop from within-study to LODO AUC values across all classifiers. Hence, to arrive at significant results beyond what has been achieved in this study, it is not sufficient to increase just sample size but also necessary to control the magnitude of the batch effect. Additional studies utilizing a unified design and identical pipelines are needed to obtain data with minimal batch effects for use in novel analyses to identify an AD signal in gut microbiota.

THE ELEMENTS THAT BROKE THE RULES

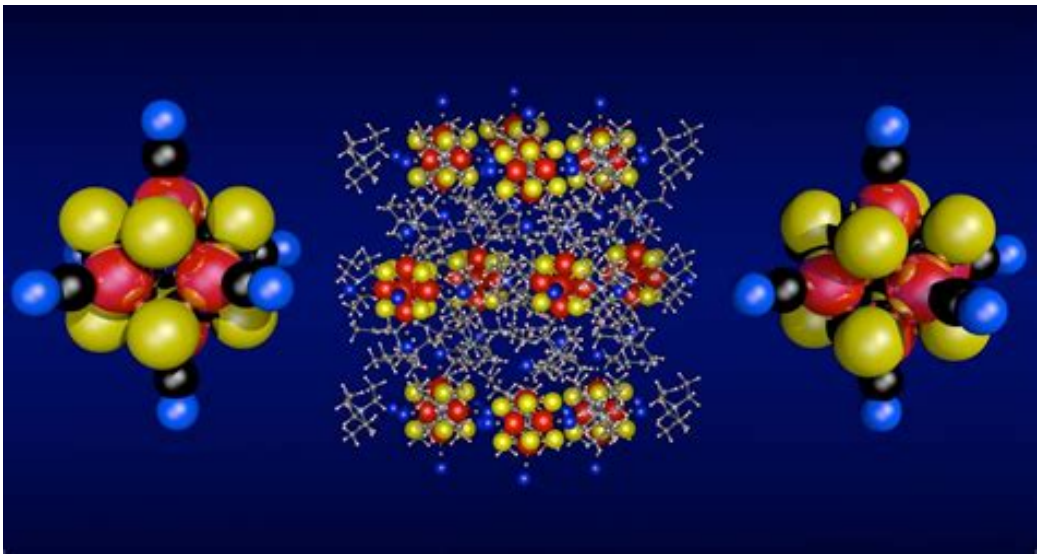
Aaria Rathi



I learned in school that noble gases do not react. They have a full outer shell, so they are stable and basically uninterested in bonding with anything else. That is how they are usually introduced. It is also not quite true. In 1962, a chemist named Neil Bartlett was working with platinum hexafluoride, a blood-red gas that is extremely reactive. He noticed something interesting. The energy needed to remove an electron from xenon was very close to the energy needed to remove one from oxygen. Oxygen reacted with platinum hexafluoride, so Bartlett wondered what would happen if xenon did the same thing. He tried it and got a yellow solid. The noble gas had reacted.

At first, people were skeptical. Xenon was supposed to be inert, and that was practically its defining characteristic. Some chemists thought Bartlett must have made a mistake. But other researchers repeated the experiment and got similar results. Before long, scientists had made compounds containing xenon, and later compounds of krypton and radon as well. The interesting part is that the rule had never really been a rule. It was an assumption based on what we had observed up to that point. Helium and neon still resist forming ordinary compounds, but the heavier noble gases turned out to be much less unwilling than their name suggested.

That makes me question how many other things we learn in chemistry that are technically true only because we leave out the exceptions. Take aluminium. Aluminium is a metal. It conducts electricity, forms positive ions and generally behaves like the kind of element we expect a metal to be. But when a small number of aluminium atoms are grouped together, something strange happens. Certain aluminium clusters can behave chemically like completely different elements. A cluster containing thirteen aluminium atoms, for example, can have electronic properties resembling those of a halogen. These are called superatoms. They are not new elements. Nothing about the aluminium atoms has changed into another element. What changes is the way their electrons behave when the atoms are grouped together. The same element can therefore behave very differently depending on how its atoms are arranged.

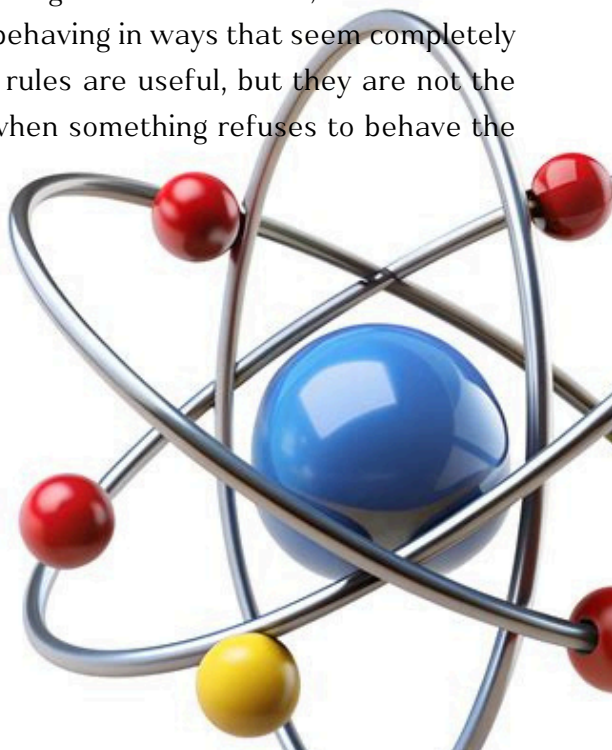


Superatomic structures

Then there is gold. We tend to think of gold being yellow as simply one of its properties, like its density or melting point. But the colour actually comes from some surprisingly complicated physics. Gold has seventy-nine protons, which means its inner electrons move fast enough that relativistic effects become important. Those effects change the energies of the electron orbitals. Because of this, the energy gap between certain orbitals shifts into the range of visible light. Gold absorbs some blue light more strongly and reflects much of the remaining visible light, which is why we see it as yellow. Without those relativistic effects, gold would look much more like silver. That is one of those facts that sounds like an exaggeration until you realise it comes directly from the physics.

Relativity also helps explain mercury's strange behaviour. Mercury has eighty protons, so relativistic effects are important there too. Its outer electrons are held unusually tightly, which contributes to weaker bonding between mercury atoms. As a result, mercury has an unusually low melting point for a metal. It melts at about -39°C and is liquid at ordinary room temperature. A property that seems completely ordinary when we first learn about mercury is actually connected to some very non-obvious physics happening inside the atom.

None of this is particularly new. Bartlett's xenon experiment happened in 1962. Superatoms have been studied since the late twentieth century, and the relativistic chemistry of heavy elements has been understood for decades. Yet we still teach the simpler versions: noble gases do not react, aluminium is a metal, and gold is yellow because gold is yellow. I understand why. The simple rules are useful. You cannot introduce every exception every time you teach a basic concept, and most of these rules work well enough for the situations we usually encounter.
But I think the exceptions are more interesting than the rules. They show that chemistry is not really a list of categories where every element stays neatly in its assigned box. Change the environment, the number of atoms, or the way electrons are arranged, and an element can start behaving in ways that seem completely unexpected. That is probably what I like most about chemistry. The rules are useful, but they are not the end of the story. Sometimes the most interesting chemistry starts when something refuses to behave the way you were told it should.



THE SECRETS BURIED BENEATH EARTH'S SURFACE

HOW PRESSURE, POROSITY, AND PERMEABILITY SHAPE
THE UNDERGROUND JOURNEY OF OIL

Stella Maris Ivana Sihotang



Imagine trying to move through a city where every building is solid, the streets are invisible, and the only way forward is through tiny gaps between the walls. Surprisingly, this is somewhat similar to how petroleum moves underground. Beneath Earth's surface, oil travels through microscopic spaces within certain rocks rather than through enormous empty caves. Its journey depends on a combination of geological structures and physical principles that determine whether it can move freely or remain trapped for millions of years



Image 1. credit: Stanley Paxton / U.S. Geological Survey (USGS).

A World of Tiny Spaces

To understand how oil moves, we first need to look at the rocks that hold it. Petroleum reservoirs are commonly found in sedimentary rocks, such as sandstone and some types of limestone. Although these rocks appear solid, they may contain countless tiny openings called pores.

The amount of space within a rock is described by its porosity. A rock with high porosity can hold a relatively large volume of fluid, while a rock with low porosity has less available space. However, having space to store oil does not necessarily mean that the oil can move through it.

This is where permeability becomes important. Permeability describes how easily fluids can pass through a material via connected pores and pathways. Think of porosity as the number of rooms in a building and permeability as the hallways connecting them. A building might have many rooms, but without connecting hallways, moving between them would be difficult. Similarly, a rock can have high porosity but low permeability if its pores are poorly connected. These properties are fundamental to understanding fluid movement through porous materials (Marle, 2006).

This distinction helps explain why not every rock containing petroleum can produce oil efficiently. The size, arrangement, and connectivity of its pores all influence how easily petroleum can travel.

What Makes Oil Move?

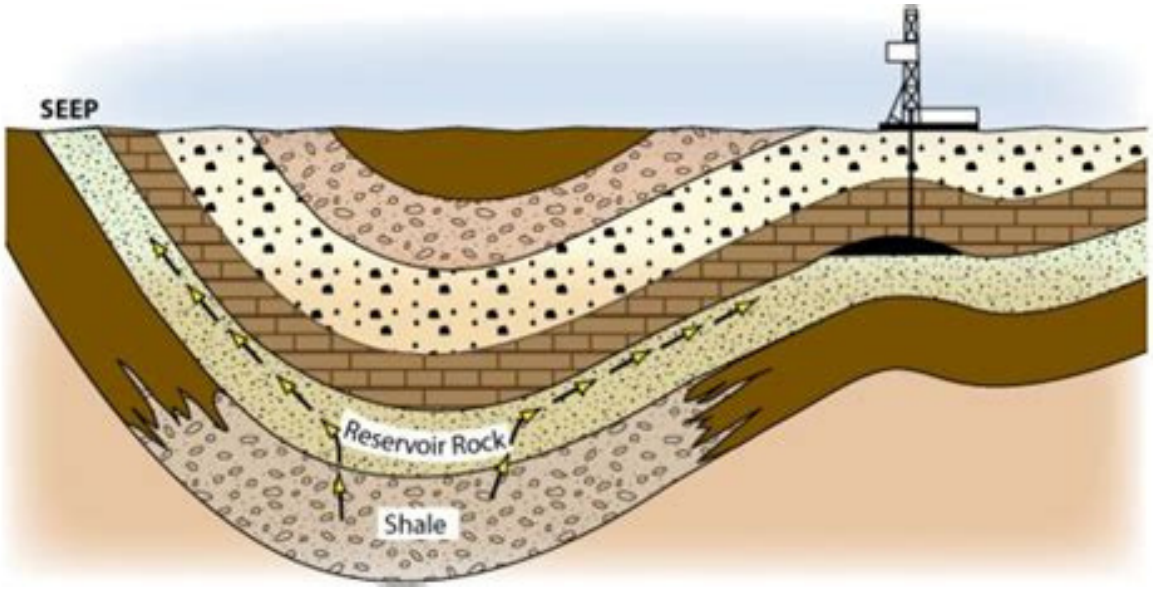
Even when a rock has connected pores, oil does not simply flow through them without a driving force. One of the most important factors is pressure.

Fluids generally move in response to differences in pressure, flowing from regions of higher pressure toward regions of lower pressure. Underground, pressure conditions can be influenced by the weight of overlying rock, the presence of other fluids, geological changes, and the conditions within the reservoir itself.

When a pressure difference exists across a permeable rock formation, it can drive petroleum through the connected pore spaces. However, the rate of movement depends on more than pressure alone.

Another important factor is viscosity, which describes a fluid's resistance to flow. Honey, for example, flows more slowly than water under similar conditions because it has a higher viscosity. Petroleum also varies in viscosity: some oils flow relatively easily, while others are much thicker and more resistant to movement.

Consequently, two reservoirs experiencing similar pressure differences may behave very differently. Oil in a highly permeable rock with relatively low viscosity may move more readily than oil in a tight formation containing more viscous petroleum. These relationships form part of the physical basis used to analyze fluid flow through reservoir rocks (Marle, 2006).



What Makes Oil Move?

Scientists and engineers need ways to predict how fluids behave underground. One of the fundamental tools they use is Darcy's law, developed from experiments conducted by French engineer Henry Darcy in the nineteenth century.

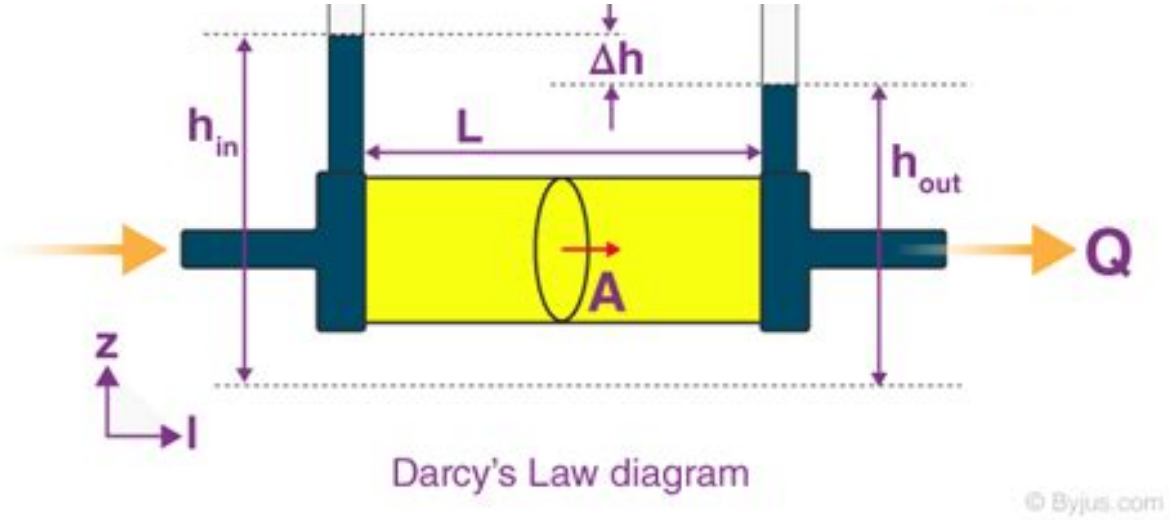
In its simplest form, Darcy's law relates fluid flow through a porous material to the material's permeability, the fluid's viscosity, and the pressure gradient across the material. A pressure gradient describes how pressure changes over a given distance. The law provides a mathematical foundation for describing fluid flow through porous media (Marle, 2006).

The principle is straightforward: under the conditions described by the basic law, greater permeability and a stronger pressure gradient generally allow more fluid to flow, while greater viscosity reduces the flow rate.

This relationship provides a useful starting point for understanding petroleum reservoirs. Engineers can use measurements of rock properties and fluid behavior to estimate how readily oil might move through a formation.

However, real reservoirs are more complicated than the idealized conditions of the basic law. Oil reservoirs may contain oil, water, and natural gas simultaneously. These fluids can interfere with one another's movement, and the rocks themselves may vary significantly from one location to another. As a result, applying Darcy's law to multiphase petroleum flow presents challenges that require more advanced analysis (Govindarajan et al., 2025).

For these reasons, reservoir engineers often use more advanced models that account for multiple fluids, changing pressure conditions, and differences in rock structure.



From Underground Physics to Petroleum Engineering

Understanding how oil moves through rock is essential to petroleum exploration and production. Before engineers can estimate how much petroleum a reservoir may yield, they need to understand its geological structure and the properties of its fluids.

Scientists gather information from rock samples, well measurements, and other geological data to estimate porosity, permeability, and fluid characteristics. These measurements help engineers build models of underground reservoirs and predict how petroleum may respond to changing pressure conditions.

This knowledge also helps explain why extracting oil is not as simple as drilling a hole and waiting for it to flow. Some reservoirs have enough natural pressure to drive fluids toward a well, while others may require additional methods to improve recovery. Even then, not all the oil within a reservoir can necessarily be extracted, because some remains trapped in tiny pores or is difficult to move through the rock.

The same physical principles are relevant beyond petroleum production. Understanding fluid movement through porous materials also contributes to groundwater studies, geothermal energy systems, and the underground storage of gases such as carbon dioxide.

The Physics Beneath Our Feet

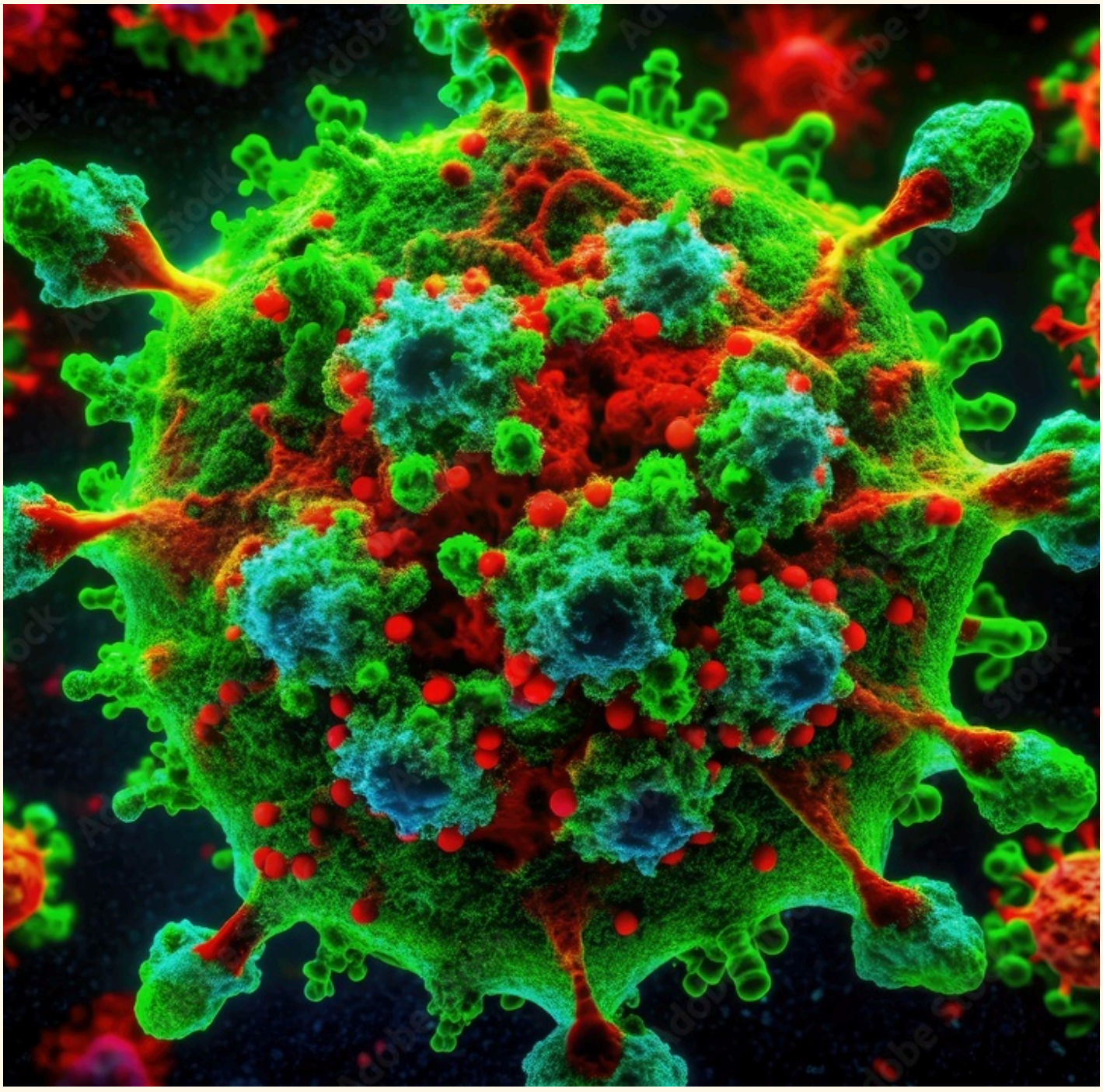
The movement of petroleum is a reminder that some of Earth's most important processes happen at scales too small for us to see directly. Beneath seemingly solid rock, countless pores and interconnected pathways create a complex environment where fluids respond to pressure, viscosity, and the structure of their surroundings.

Porosity determines how much space a rock can contain, permeability influences how easily fluids can travel through it, and pressure differences help drive that movement. Together, these factors provide the foundation for understanding the behavior of underground petroleum reservoirs.

What appears from the surface to be an immovable mass of stone is, on a microscopic scale, a network of pathways governed by physics. By studying these hidden spaces, scientists and engineers can better understand how oil moves through Earth's crust—and why some of its underground journeys are far easier than others.

REPROGRAMMING THE IMMUNE SYSTEM: THE PROMISE AND RISKS OF CAR-T CELL THERAPY

BY NATALIE KHON

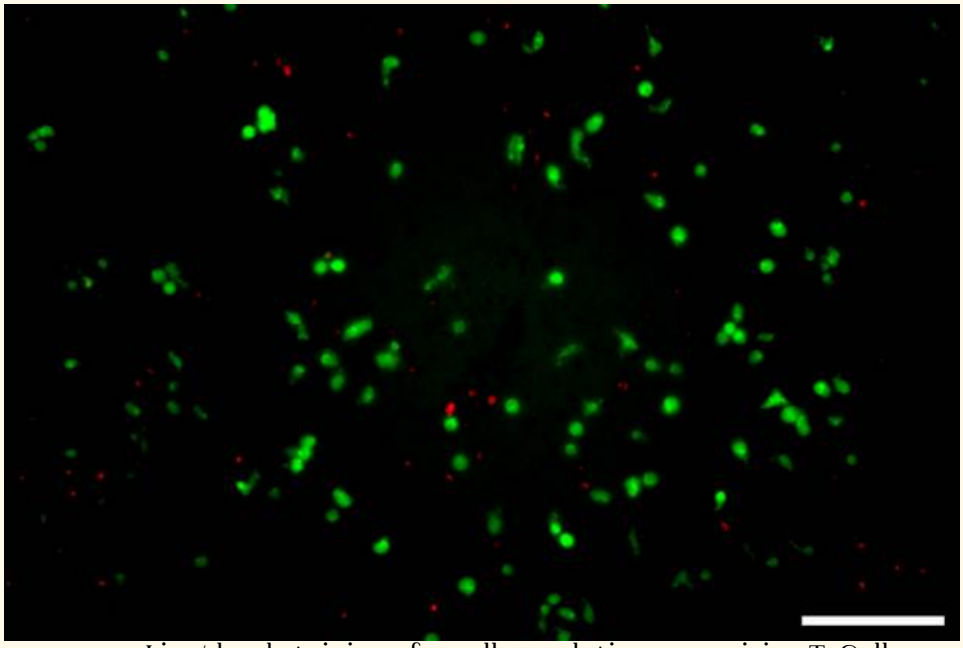


INTRODUCTION

Few medical innovations have so dramatically leveraged the immune system as both a weapon and source of healing as CAR-T cell therapy. When conventional chemotherapy fails and relapse occurs, physicians have turned to this technology as a way of redirecting the body's immune cells to target cancerous ones. CAR-T cell therapy holds promise in its ability to attack the cancer with the person's immune system internally, but the treatment is incredibly expensive, not always geographically accessible, and comes with potentially life-threatening side effects; however, these risks and the overall success rate for lymphomas and leukemia make it an appropriate choice therapy for those who have exhausted other options.

CAR-T cell therapies are genetically engineered white-blood cell-based immunotherapies, meaning they manipulate the patient's immune system to attack the cancerous cells within the body. These white blood cells are known as T cells, which this therapy converts into living drugs that produce receptors that give the cells the ability to detect and latch onto the antigens present in the cancerous cells. Called "chimeric antigen receptors" or CARs, these binding agents ultimately eliminate the cells from the body [1]. Currently, CAR-T cell therapies are only FDA approved for treating blood cancers like lymphoma, leukemia, and myeloma, but researchers are actively working toward developing consistent methods of harnessing this therapy on solid tumors and autoimmunity disorders [2].

While groundbreaking for its ability to utilize the patient's own immune system to attack cancerous cells, receiving CAR-T cell therapy is a long and intricate process [3]. Still, for those with few other options, the treatment holds appeal for targeting the source of a cancer without requiring external interventions, such as chemotherapy or radiation. To begin, patients get their blood drawn, which allows doctors to extract T cells [4]. This process allows scientists in specialized laboratories to personalize the treatment by synthetically creating the chimeric antigen receptors and attaching them to the genetic makeup of the cells. Because the cells reproduce with these receptors, CAR-T cell therapy has generally been effective in helping patients achieve long-term remission [5].



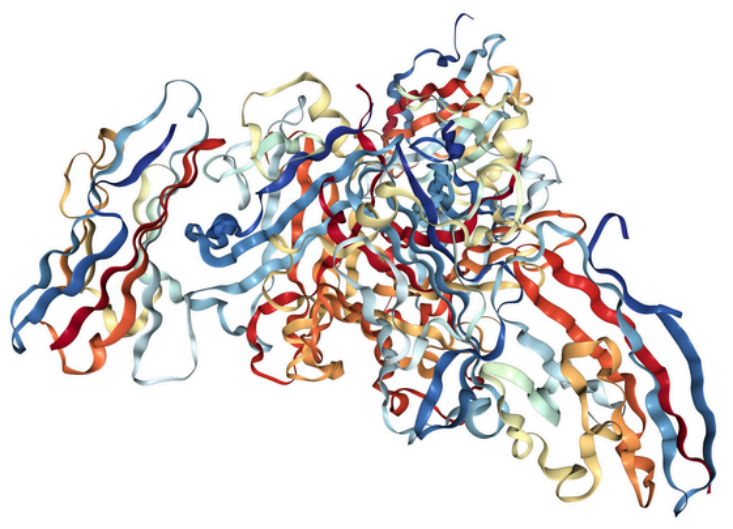
Live/dead staining of a cell population comprising T-Cells

Primary Benefits of CAR-T Cell Therapy

The success of CAR-T cell therapy owes, in large part, to the flexibility of the structure of the CAR. The CAR is made up of many proteins that combine into a fusion protein, known as the "chimera." The bonding area contains several distinct regions, allowing scientists to alter where the CAR attaches and thus tailor the treatment to the person. Typically, the presence of MHC proteins determines T cell activation, but CAR-T cells do not require MHC expression, allowing them to detect more cancer cells, which makes the treatment more effective overall [6].

As cells reproduce, they remember previous encounters with the disease, allowing the immune system to respond in cases when the same threat returns. As a result, CAR-T cell therapy has been associated with improved remission outcomes. Scholler et al. (2012) examined over 200 patients who had received the treatment over the course of eleven years, noting the presence of the engineered T cells in 98% of study participants [7]. In another study, Kalos et al. analyzed engineered CAR-T cells in vivo, tracking their expansion 1000-fold and their ability to function at a high level for a minimum of six months [8]. The persistence of these CAR-T cells enables the benefits of the therapy to remain in the body without immunosuppression, enabling the engineered cells to continue monitoring and attacking cancer cells.

The novel structure of the CAR-T cell has resulted in widespread treatment success, including in patients whose cancer reappeared after an initial remission period. Research out of Rutgers Cancer Institute has noted the promise of CAR-T cell therapy in patients with aggressive cancers that other therapies fail to treat. For example, in a study examining the long-term success of the treatment, researchers found that 42% of adults with lymphoma were in remission fifteen months after receiving CAR-T cell therapy [9]. These results suggest the potential of CAR-T cell therapy to provide lasting disease control for patients who previously had very limited therapeutic options.



CAR protein complex

DOMINANT TRETAMENTS

CAR-T cell therapy can be adapted to different cancer types by identifying variations in antigen expression and engineering T cells to recognize specific targets. In a study on patients with advanced leukemia, Kalos et al. determined that CD19 targeting CAR was particularly effective [8]. Later research identified several additional potential targets—including CD33, CD123, FLT3, LeY, CLL-1, CD7, and NKG2D—in preclinical studies of acute myeloid leukemia [10]. In patients with acute lymphoblastic leukemia, allogeneic CAR-T cell therapies, which use modified T cells from healthy donors rather than the patient's own cells, have also produced remission with limited serious complications, including cytokine release syndrome [11]. This range of clinically effective potential CAR targets is one reason why the therapy has been so effective for patients with leukemia.

Although CD19-targeted therapies have become a dominant approach for treating leukemia, they have required modification to improve their effectiveness against lymphomas. A recent review of 360 clinical trials of CAR-T cell therapy for non-Hodgkin lymphoma found that relapse remained relatively common with CD19-targeted therapies, particularly with first-generation treatments [12]. Researchers have therefore explored "armored" CD19 CAR T cells designed to enhance therapeutic activity. In a clinical study involving 21 patients with refractory lymphoma, for whom previous CD19 CAR treatments had failed, an intervention involving a new CD19 CAR that secretes IL18 saw partial activation in 81% of participants and complete activation in 52%. In this patient population, the CAR treatment was found to be actively working in the cells for a median response time of 9.6 months [13]. The need to modify CD19 to support full remission in refractory cases highlights the newness of CAR-T cell therapy as a treatment, but the fact that scientists have been able to successfully engineer armored versions points to the long-term flexibility and promise of the treatment.

Treatment Side Effects and Challenges

Despite the novelty of the treatment, many patients experience significant side effects. The most common side effects are cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome (ICANS) [2]. CRS results from the influx of proteins that stimulate the immune system (called cytokines) during treatment, which can lead to symptoms as mild as aches and a fever to severe symptoms like hypertension or organ failure [14]. As a result of these complications, the FDA produced another treatment, humanized anti-IL6 receptor antibody tocilizumab, for use alongside CAR-T cell therapies, hoping to limit the likelihood that patients would develop CRS. Another common side effect, also linked to the release of cytokines, is ICANS, which can cause brain inflammation, prompting confusion, excessive sleepiness, and impaired speech, though these side effects can generally be treated with steroids [1].

Aside from these side effects, this therapy is not always accessible to those who need it. Many people who suffer from cancer severe enough to warrant this treatment struggle to access it due to financial or geographical constraints. The price of this treatment is exceptionally high, with the implantation and creation of the cells alone costing from 373,000 to 475,000. This price does not include the cost of treatment itself, inpatient stays, food, or travel [15]. Currently, there are also only a limited number of treatment sites, with less than four percent of U.S. health centers authorized to provide CAR-T cell therapy. A third of patients receiving treatment live more than two hours away from these facilities [16]. The number of treatment centers is a major source of disparity, particularly due to the higher number of centers in the Northeast and the more limited facilities in the South, even though disease prevalence tends to be higher in the South [17]. Nevertheless, growing recognition of these disparities provides an opportunity to expand treatment centers, reduce costs, and ensure that the benefits of CAR-T cell therapy reach a broader and more diverse population.

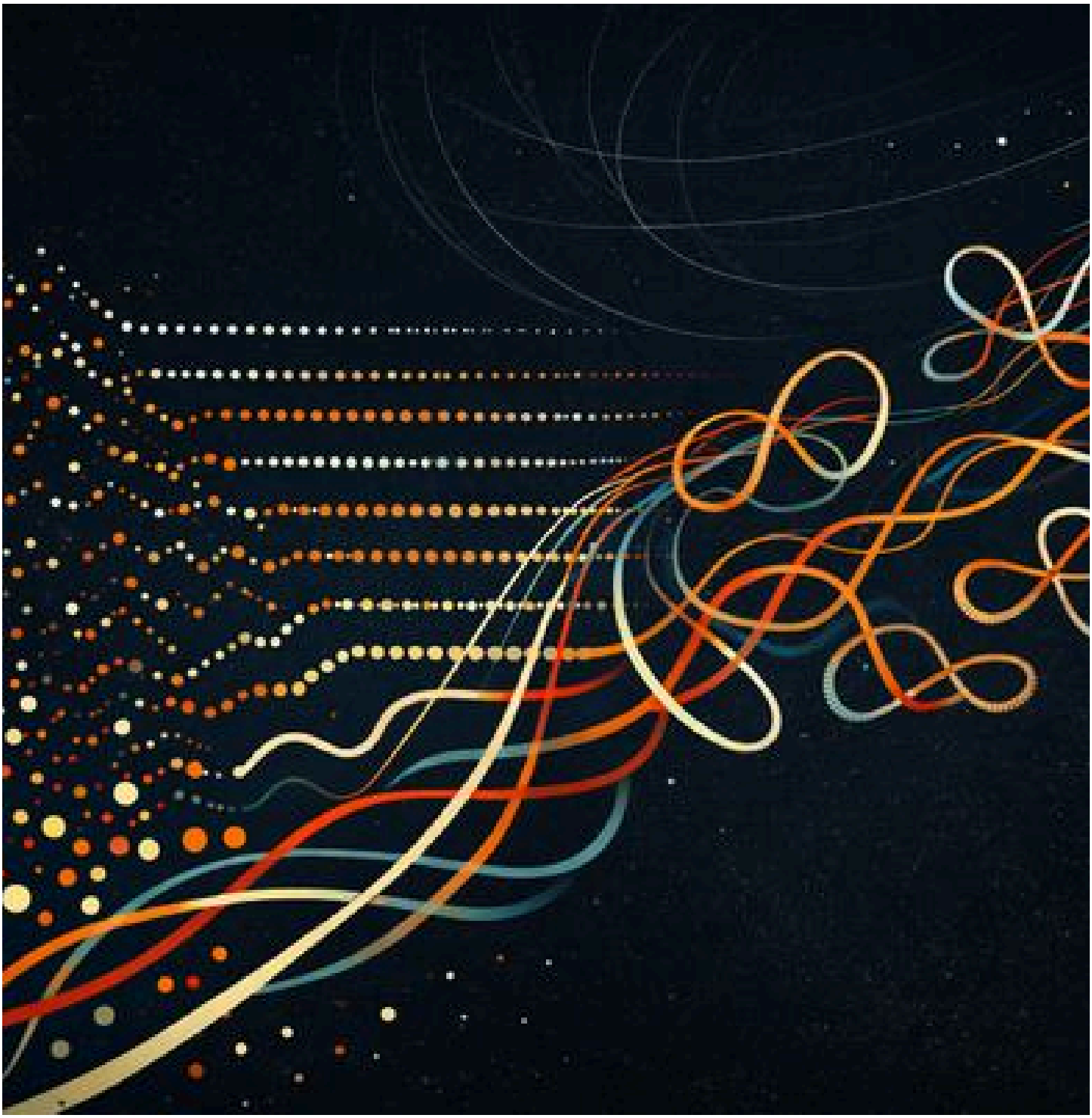
CONCLUSION

Over the past decade, CAR-T cell treatment has established itself as a first-line treatment for patients with persistent cancers for whom other treatment methods, such as chemotherapy, have been ineffective. Most CAR-T cell therapies work by taking the patient's own immune cells and engineering them to target antigens that are heavily expressed in the cancer. This approach has seen widespread success in patients with leukemias and lymphomas, particularly when the CAR targets the CD19 antigen. Even in cases where CD19-based treatment fails, scientists have been able to modify the CAR that targets CD19 so that it secretes IL-18, representing the adaptability of the CAR in the face of increasingly challenging cancers. Though there is room for improvement in making CAR-T cell therapy more widely available and tolerable, the potential in this highly personalized treatment is undeniable, pointing to the need for further research on effective targets in other cancers.

LOOP QUANTUM GRAVITY VS STRING THEORY:

THE QUEST FOR A UNITED THEORY OF EVERYTHING.

BY GIANLUCCA GRASSI



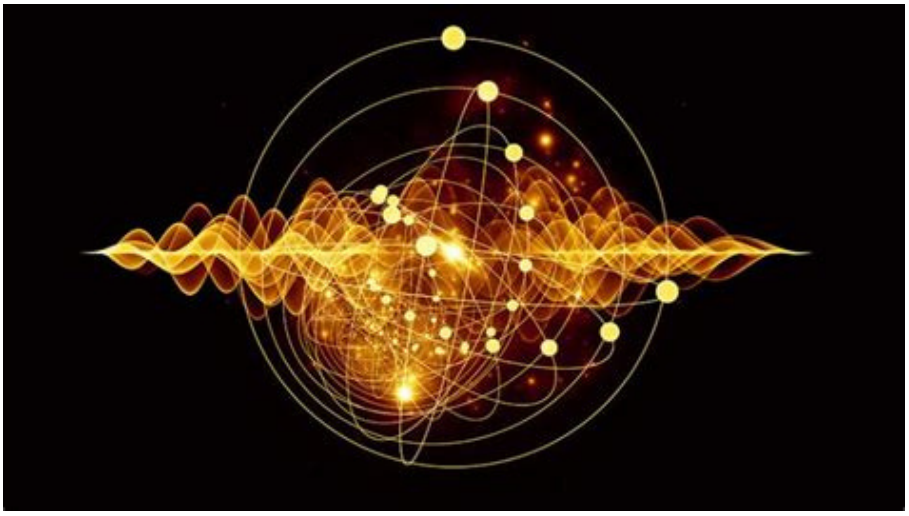
INTRODUCTION

Fifty years ago, the Standard Model of Particle Physics was completed, and to this day is perhaps the most successful theory in all of science. Capable of predicting the effects of three forces (electromagnetism, responsible for affecting charged particles; the strong force, responsible for holding together the building blocks of matter called quarks; and the weak force, responsible for decay), the Standard Model reduces these forces to particles called bosons that carry them. However, there is a force omitted from the model: gravity.

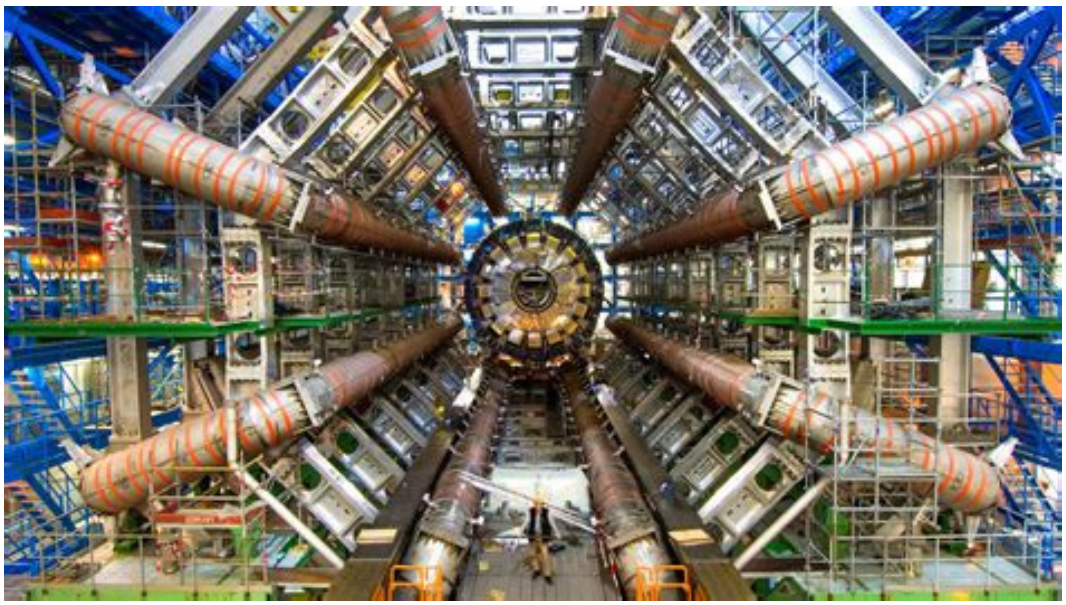
THE FORCE LEFT OUT

Gravity is described well by Einstein's general theory of relativity which describes our reality as being four dimensional, comprised of the three spatial dimensions and time. In the theory, mass warps and curves spacetime around it and this is the gravity we experience: curvature of spacetime is described by equations generated for curved surfaces. Interestingly, this means that time is slower in more curved areas of spacetime (areas nearest a large mass). The issue is that Einstein's theory doesn't play nice with a second theory, quantum mechanics which is what the Standard Model is built off.

Quantum mechanics describes the behaviour of atomic and subatomic particles, where they can exhibit characteristics of a wave or a particle, depending on what is being observed. It also describes energy in discrete packets called quanta, for instance photons, the quanta of light. Additionally, Heisenberg's Uncertainty Principle states that the velocity and position of a particle cannot be recorded simultaneously with perfect accuracy, resulting in particles dissolving into "clouds of probability" wherein the particle can exist in all states of probability until we observe it, at which point the cloud collapses and the probabilities converge on the fixed point. As great as this all sounds, quantum mechanics treats time as separate to other physical quantities which contradicts general relativity. Also, if you consider a hydrogen atom with its singular electron, quantum mechanics claims that the electron is in many locations at once. On the other hand, the electron has mass so must curve space time due to general relativity. But where exactly is this curvature? Therein lies another contradiction.



The leading contender in the race for a theory of everything is string theory. This transforms the fundamental particles into vibrating strings, capable of reproducing the behaviour of said particles. The mathematics of the theory lends itself to a boson that carries the force of gravity called a graviton. This result is important as it unites quantum mechanics and general relativity. However, string theory is not without its weaknesses: the strings require nine spatial dimensions to oscillate in whereas we only know about three. Scientists reconcile this with the claim that the extra six dimensions are very small and so do not affect us. Additionally, string theory requires supersymmetry which is the idea that every fundamental particle has a shadow equivalent. The Large Hadron Collider smashes together billions of particles every second to form new particles however they have never observed these shadow particles which is a serious thorn in the side of supersymmetry.



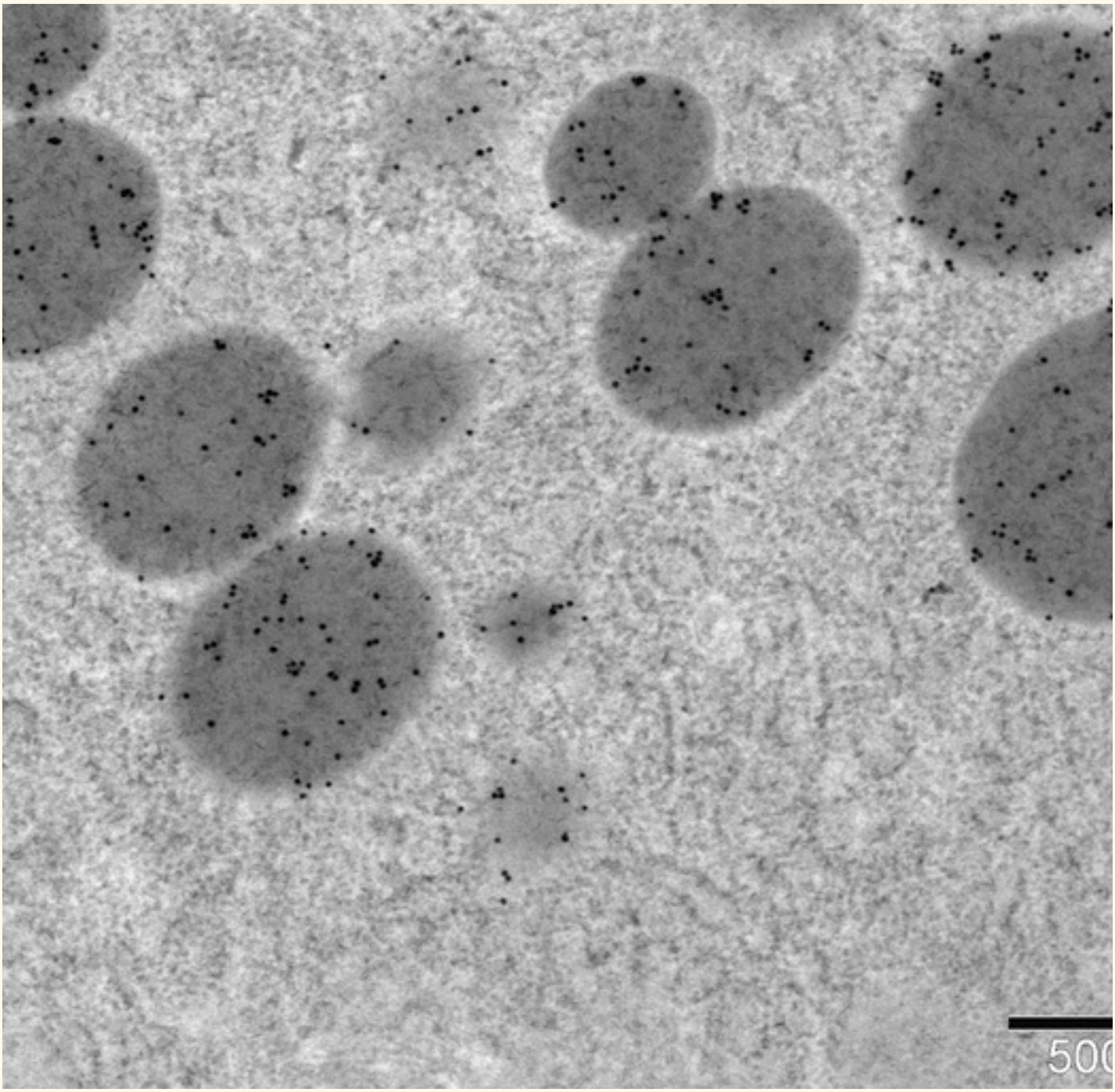
Large Hadron Colider, CERN, ZURICH

String theory does have a contender in the form of Loop Quantum Gravity. This theory takes a different approach in that it quantises the regions of spacetimes into nodes of spatial quanta. This means there is a minimum length called the Planck Length and a minimum area and volume to boot. These minimum lengths are joined by loops which is where the theory gets its name. It claims that the spinfoam formed by all the loops gets distorted by mass and this is the gravity that we experience. Because time is also quantised in this model, the time we experience is similarly a series of discrete loops, implying that there must be a minimum time. As idyllic as these strange spinfoam structures may seem, the theory also predicts that photons with higher energy should be slower than photons with lower energy. This effect ought to be small but observable, yet no such observations have been made.

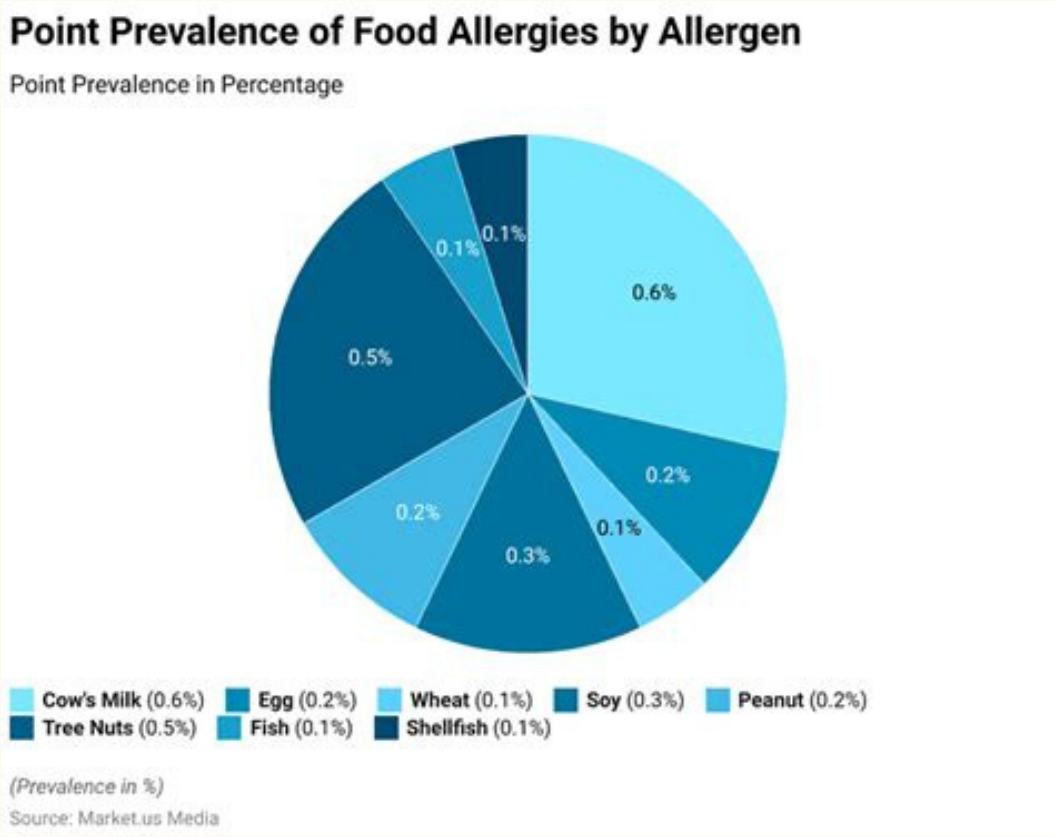
To conclude, the frontrunners in the race for a theory of everything are string theory and Loop Quantum Gravity, with their main strengths lying in uniting quantum mechanics and general relativity. However, both have prominent flaws stopping them from being fully accepted. In my opinion, string theory is more plausible as loop quantum gravity has observable consequences which we have not yet seen. Alternatively, there are scientists working on a combined solution, merging string theory and loop quantum gravity which could pick up traction. Ultimately, a theory uniting general relativity and quantum mechanics is predicted to be the greatest scientific achievement of the coming generation and these theories (even if they turn out to be false) showcase the abstract thinking of modern science to bring us closer and closer to the equations of reality.

THE BIOLOGY OF ALLERGENS: HOW THEY IMPACT THE BODY

BY Jhovanny Quintero Brand



According to the Center for Disease Control (2026), approximately one in three U.S. adults and children has an allergy, whether seasonal or food-based. Allergens are substances that are responsible for triggering an immune response in people who have some kind of sensitivity. There are many common allergens, such as pollen, dust mites, animal dander, and certain foods. Although these substances are generally harmless to most people, the immune system of an individual who is allergic may mistake them as threats to the body, causing the body to respond by attacking them. This response can cause various symptoms, which can range from mild things such as sneezing and itching to vastly more severe life threatening reactions. Understanding the biology of said allergens and how they work requires being able to examine how exactly the immune system identifies allergens. They can also be useful for determining which cells and chemicals are participating in allergic reactions and how these processes affect different parts of the body (National Library of Medicine, 2019).



The development of an allergic reaction can happen gradually, and it often begins with a process which is called sensitization.

This is a process that sees the immune system recognizing an allergen and, in response, producing something called immunoglobulin E (IgE), an antibody that is associated with allergic responses. These antibodies attach to the receptors that are on immune cells, which are called mast cells and basophils. During an exposure, the allergen can bind to the IgE antibodies, which causes these cells to activate and in response it triggers a release of inflammatory chemicals (Stone et al., 2010). A chemical that is released during this process is called histamine. Histamine is one of the chemicals that are released during a reaction, and it is responsible for contributing to the itching, swelling, and increased mucus production that someone may experience during a reaction; it is also responsible for the widening blood vessels. These effects help explain why allergic individuals may experience symptoms such as watery eyes, a runny nose, skin irritation, or congestion. Mast cells also are responsible for releasing other inflammatory mediators that also contribute to both immediate symptoms and longer lasting inflammation. According to Galli and Tsai (2012), IgE antibodies and mast cells play important roles in acute allergic reaction as well as chronic allergic conditions one of which is asthma.

Allergens are capable of affecting several of the body's systems, depending on how and when a person comes across the allergen and how their immune system responds to it. When someone who is allergic is exposed to allergens such as pollen or animal dander, inhalation can cause inflammation in the nose and airways. Symptoms from this exposure may include things such as sneezing, congestion, coughing, and wheezing. In some individuals, allergic inflammation contributes to asthma, which is when the airways tissue becomes narrow and irritated due to allergens over time (Galli & Tsai, 2012). The skin is another area of the body which is commonly affected by allergies. The release of inflammatory chemicals in response to allergens can cause symptoms itching, redness, swelling, and hives on a person's skin. These symptoms occur because immune activity affects the tissues and blood vessels in the skin. Allergic reactions can also affect a person's digestive system when food proteins trigger an immune reaction. This can cause symptoms such as abdominal pain, vomiting, and other digestive issues in affected individuals. Food related allergies involve several immune pathways rather than having just one unchanging pathway. Azouz and Rothenberg (2019) explain that gastrointestinal allergic disease can involve disruptions in immune tolerance, type 2 immune responses, and changes in the protective lining of the digestive tract. However, it is very important to know that not every food allergy operates through the same mechanism. Some reactions involve IgE antibodies while others involve different kinds of immune processes. This is a demonstration that allergies are biologically complex, rather than being just one uniform condition.

Although many allergic reactions are and remain relatively mild, some can become incredibly severe. Anaphylaxis, which is caused by allergens, is a serious systemic allergic reaction that can affect multiple organs. It can cause difficulties breathing, swelling, gastrointestinal symptoms, and a dangerous drop in blood pressure. t

hese effects can occur when inflammatory mediators produce widespread changes throughout the body of an individual. Because anaphylaxis can progress so rapidly, it requires immediate emergency medical attention, which is why many people with allergies carry Epinephrine (National Library of Medicine, 2019). The severity of an allergic reaction widely varies between individuals and different circumstances. Many things such as genetic factors, environmental exposures, and the type of allergen can all influence a person's allergic reactions. Scientists also continue to investigate how all these factors affect immune regulation and why some people develop allergies while others do not.

Overall, there are several common allergens that tend to affect people in different ways depending on their biological sensitivities, genetics, and environment. Because allergic reactions are medical emergencies, it is important to take these responses seriously and know how to react if one were to occur. While Epinephrine (Epi-Pens) can be effective and life-saving, many people still require emergency treatment within a narrow window of time. Understanding the biology of allergens is important because recognizing how these triggers interact with immune cells and inflammatory responses can be essential in promoting positive health outcomes.

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