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# Multiple Molecular Explanations for the Same Cellular Phenotype: An Identifiability Framework for Distinguishing Mechanistic Equivalence from Causal Specificity in Computational Biology

**Daniel Okoro*, Grace Okafor**

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## Abstract

A cellular phenotype rarely identifies its molecular cause uniquely. Regulatory redundancy, resource competition, compensatory interactions, alternative network configurations, and incomplete measurement can allow distinct molecular states to generate observations that are difficult or impossible to distinguish under a given assay. This creates an identifiability problem that is deeper than ordinary uncertainty in parameter estimation: the scientific question is whether competing molecular explanations are distinguishable at all from the available observations and, if not, what additional evidence could separate them. This article develops a non-empirical methodological framework for analyzing that problem in computational biology. It distinguishes mechanistic equivalence, defined relative to specified observables and experimental conditions, from structural and practical identifiability in mathematical network models, and then links these concepts to perturbation-based causal discrimination. The framework treats model fit, predictive accuracy, perturbational responsiveness, and causal specificity as different evidentiary achievements rather than interchangeable indicators of mechanistic truth. Evidence from single-cell perturbation studies, gene-regulatory-network inference, multimodal profiling, dynamic-model calibration, and identifiability analysis shows that additional measurements can narrow an explanation space without necessarily producing a unique causal account. The central implication is that causal specificity should be claimed only when competing explanations generate discriminably different predictions under explicitly defined observations or interventions and those differences survive relevant measurement, model, and biological-context limitations. Where such discrimination fails, mechanistic equivalence should be retained rather than resolved by model complexity or interpretive preference.

**Daniel Okoro***
Department of Biochemistry, University of Malawi, Zomba, Malawi.

**Grace Okafor**
Department of Molecular Biology, University of Malawi, Zomba, Malawi.

***E-mail:** daniel.okoro@unima.ac.mw

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## Introduction

Computational models increasingly connect molecular measurements to regulatory structure, pathway activity, and cellular phenotype, but successful reproduction of an observed state does not imply that the underlying molecular explanation has been uniquely determined. In dynamic biological models, even well-fitting parameterizations can remain weakly identifiable when observations are incomplete, noisy, or censored, so apparently precise model behavior may coexist with broad uncertainty about the parameter combinations that generated it (Porthiyas *et al.*, 2024). At the causal level, the problem is more demanding because an association or predictive relationship must be distinguished from a claim that a particular molecular route is responsible for the observed phenotype. Causal machine-learning approaches in single-cell genomics therefore depend on assumptions about interventions, confounding, measurement and transport across experimental conditions (Tejada-Lapuerta *et al.*, 2025).

Large-scale perturbation experiments partly change this evidentiary situation. Genome-scale Perturb-seq demonstrates that direct genetic interventions can produce information-rich genotype–phenotype maps at single-cell resolution, providing contrasts that are unavailable from passive observation alone (Replogle *et al.*, 2022; Tejada-Lapuerta *et al.*, 2025). Yet perturbation does not make interpretation automatic. A transcriptional response after gene disruption may reflect the targeted relation, downstream adaptation, feedback, compensatory regulation, or properties of the assay and cellular context. Intervention thus increases the possibility of discrimination without guaranteeing a uniquely identified molecular mechanism.

The same distinction applies to computational prediction. Network-inference methods can generate experimentally testable hypotheses about regulatory control, and in-silico perturbations have been used to nominate factors whose subsequent manipulation changes cell identity in the predicted direction (Kamimoto *et al.*, 2023). Nevertheless, predictive sophistication is not a substitute for discriminatory evidence. Recent benchmarking

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has shown that deep-learning models for perturbation-effect prediction do not necessarily outperform simpler linear baselines under evaluated conditions (Ahlmann-Eltze *et al.*, 2025). Moreover, harmonized analysis of dozens of single-cell perturbation datasets reveals extensive differences in perturbation type, assay, cell context and effect structure across studies (Peidli *et al.*, 2024). A mechanism that appears discriminable in one dataset may therefore remain unresolved in another.

This article addresses the inferential space between observing a phenotype and assigning a specific molecular cause. Its central claim is conditional: distinct molecular explanations should be treated as mechanistically equivalent whenever they remain indistinguishable with respect to a defined set of observations, experimental conditions and model assumptions. Causal specificity is warranted only after additional evidence separates the competing explanations in a manner that cannot be accounted for by the relevant alternatives. The following sections distinguish biological phenotypic underdetermination from formal structural and practical identifiability, and then prepare the basis for evaluating how perturbations and model discrimination can reduce, or fail to reduce, an initially non-unique explanation space.

## Materials and Methods

*Mechanistic Equivalence and the Problem of Phenotypic Underdetermination*

Phenotypic underdetermination arises when the mapping from molecular state to measured cellular outcome is many-to-one. The relevant molecular alternatives need not be minor parameter variations within one mechanism. Resource competition in synthetic biochemical circuits illustrates how interactions mediated through shared cellular resources can produce system-level phenotypes that differ from the behavior expected when circuit components are considered independently (Al-Radhawi *et al.*, 2023). Consequently, an observed output can be compatible with more than one internal allocation or regulatory state. Such cases motivate a restricted definition of mechanistic equivalence: two explanations are equivalent only with respect to the observables and conditions under which they cannot currently be separated. They need not be biochemically identical.

A related form of underdetermination appears in gene-regulatory-network reconstruction. Benchmarking of network-inference algorithms using single-cell transcriptomic data has shown that different computational approaches recover regulatory structure with substantially different performance and that incomplete ground truth complicates evaluation (Pratapa *et al.*, 2020). Transfer-learning approaches can nonetheless learn representations that contain biologically useful information about regulatory relationships and perturbational responses (Theodoris *et al.*, 2023). These results support a distinction between usefulness and uniqueness. A representation can predict a phenotype or regulatory response without demonstrating that the network encoded by the model is the only molecular organization capable of producing it.

This distinction becomes particularly important as models integrate increasingly rich data. Foundation models trained on large single-cell corpora can capture gene-context relationships that support perturbation and network-related tasks (Theodoris *et al.*, 2023; Cui *et al.*, 2024). Single-cell multiome approaches can further constrain regulatory inference by combining expression, chromatin accessibility and external atlas information (Yuan & Duren, 2025). In parallel, computational analyses show that network topology itself affects the distribution and informativeness of gene-perturbation effects (Aguirre *et al.*, 2025). Additional modalities and priors therefore reduce some ambiguities, but increased information should be described as constraining an explanation set rather than automatically collapsing it to one mechanism.

The resulting analytical distinction is summarized below.

**Table 1** summarizes molecular and inferential configurations that generate or resolve mechanistic equivalence.

**Table 1.** Molecular and inferential configurations that generate or resolve mechanistic equivalence

| Biological or inferential configuration | What remains observationally indistinguishable | Principal source of underdetermination | Evidence capable of increasing discrimination | Interpretation permitted |
|---|---|---|---|---|
| **Resource-coupled network states** | Different internal allocations producing a similar measured output | Shared limiting resources and indirect coupling | Orthogonal measurements of resource use, component activity or state-dependent response | Equivalent only at the measured output level |
| **Alternative regulatory-network reconstructions** | Competing edge structures compatible with the same expression snapshot | Partial observability and algorithm-dependent inference | Independent perturbation, temporal measurements or additional molecular modalities | Multiple candidate regulatory explanations remain |
| **Learned latent representations** | Different internal representations yielding comparable predictive performance | Prediction does not uniquely specify biological structure | Mechanistically targeted intervention or external network validation | Predictive equivalence without causal equivalence |
| **Network-topology-dependent response states** | Distinct structures generating overlapping perturbation phenotypes | Compensation, hierarchy, modularity and downstream convergence | Perturbations chosen to generate divergent | Conditional mechanistic discrimination |

| | | | | |
|---|---|---|---|---|
| | | | candidate-specific predictions | |
| **Genetic-interaction states** | Different single or combinatorial perturbations entering related phenotype regions | Nonlinear interaction and convergence of downstream programs | Higher-dimensional molecular readouts and factorial perturbation | Shared phenotype does not establish shared mechanism |
| **Multimodal but phenotypically convergent states** | Similar global outcomes with distinct RNA, protein or pathway-level changes | Compression of several biological levels into one endpoint | Joint transcriptomic, proteomic and intervention evidence | Orthogonal mechanisms can be distinguished despite endpoint similarity |
| **Matched-target chemical and genetic perturbations** | Mechanistically related interventions that do not map cleanly by morphology | Off-target activity, assay sensitivity and incomplete phenotype capture | Target-proximal readouts, orthogonal assays and context-matched validation | Morphological similarity or dissimilarity alone is insufficient |

High-dimensional perturbation experiments make the many-to-one structure of phenotype generation more visible. Combinatorial CRISPR screens have revealed organized manifolds of genetic interactions in which different perturbations produce related cellular states while retaining distinguishable interaction structure (Norman *et al.*, 2019). Multimodal Perturb-CITE-seq provides a complementary example: simultaneous perturbational, transcriptomic and protein measurements in cancer immune-evasion models separated mechanisms that could not be reduced to a single resistance pathway (Frangieh *et al.*, 2021). These studies show why phenotypic convergence should not be confused with mechanistic identity. Distinct molecular routes can enter nearby or apparently similar endpoint states while remaining separable when the experiment interrogates the appropriate intermediate levels.

The converse is also important: interventions believed to act on related targets do not always produce readily recognizable phenotypic matches. Large-scale paired chemical and genetic morphological profiling has demonstrated that known mechanistic relationships can be difficult to recover from image-derived phenotypes alone (Chandrasekaran *et al.*, 2024). Thus, failure to observe phenotypic equivalence does not prove mechanistic difference, just as apparent equivalence does not prove mechanistic sameness. Both conclusions depend on the measurement surface through which the biological system is observed.

This creates a useful representation of the problem: distinct molecular configurations may remain separated internally while converging at a limited observation surface, and additional measurements may either reveal their separation or leave them unresolved.

**Figure 1** summarizes phenotypic convergence across molecularly distinct network regimes.

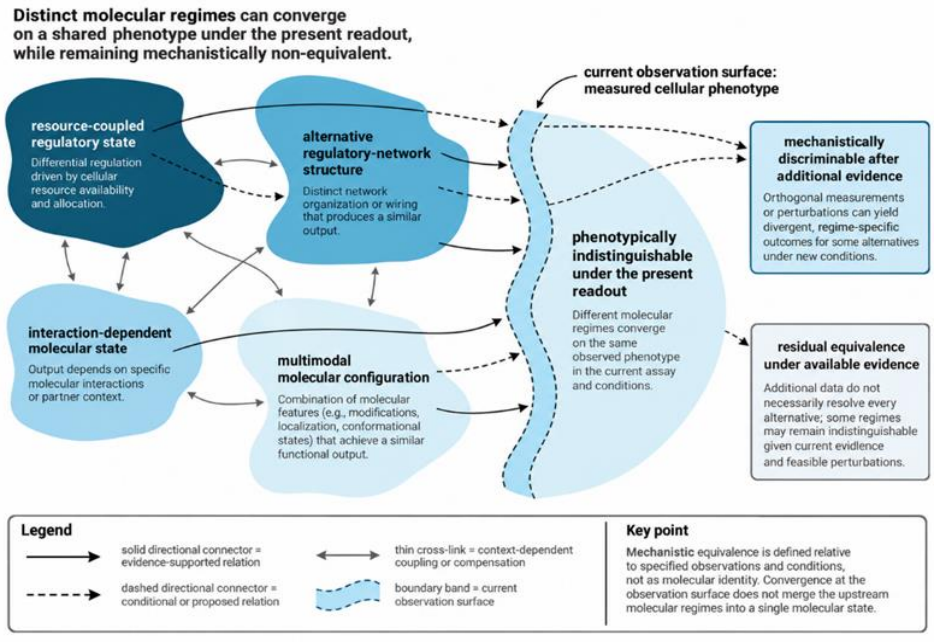



**Figure 1.** Phenotypic convergence across molecularly distinct network regimes

Phenotypic underdetermination therefore has at least two origins. Biology itself may contain redundancy, compensation, interaction and multiple routes to related endpoints; measurement may then compress those differences further. The methodological

consequence is that mechanistic equivalence cannot be adjudicated solely by asking whether two models reproduce the same phenotype. It requires asking whether their differences are observable in principle and, if they are, whether the available data are sufficiently informative to recover them. That question leads directly to structural and practical identifiability.

*Structural and Practical Identifiability in Molecular Network Models*

Structural and practical identifiability formalize different reasons why a model may fail to yield a unique explanation. Structural identifiability concerns whether parameters can, in principle, be uniquely determined from ideal, noise-free observations of specified model outputs. Practical identifiability concerns whether the available finite and noisy data actually constrain those parameters with useful precision (Wieland *et al.*, 2021). For the present argument, these concepts provide a disciplined way to separate two situations that may look similar empirically. One explanation may be non-unique because the model structure itself permits indistinguishable parameterizations; another may be distinguishable in principle but insufficiently resolved by the current experiment.

Structural analysis is consequently a property of the specified model–observation relationship rather than of goodness of fit. Scaling-based methods can identify parameter transformations that preserve model outputs and thereby reveal classes of structural non-identifiability (Castro & de Boer, 2020). Such tests, however, have defined domains of validity. Analyses of their limitations show that simple scaling procedures can miss non-identifiability produced by transformations outside the assumed class (Castro & de Boer, 2021). Passing a single diagnostic therefore should not be interpreted as proof that a biological mechanism is uniquely recoverable.

Practical identifiability introduces experimental design into the problem. Dynamic-model calibration protocols emphasize that optimization, uncertainty assessment and identifiability analysis must be considered together because a numerically satisfactory fit can coexist with poorly constrained parameters (Villaverde *et al.*, 2022). More recent computational work demonstrates how information-based analysis, regularization and experimental-design strategies can identify observations that improve practical recoverability in biological models (Wang & Hao, 2025). In the language of competing molecular explanations, this means that the evidentiary value of a measurement depends not simply on how much data are collected but on whether the measurement distinguishes predictions made by the candidates under consideration.

The computational infrastructure needed to perform these analyses has become increasingly mature. pyPESTO provides modular optimization and uncertainty-analysis methods for parameter-estimation problems (Schälte *et al.*, 2023), whereas PEtab formalizes interoperable definitions of models, parameters, observables and experimental conditions so that estimation problems can be reproduced across software environments (Schmiester *et al.*, 2021). AMICI provides scalable forward and adjoint sensitivity computation for large ordinary-differential-equation models (Fröhlich *et al.*, 2021). These developments improve reproducibility and computational tractability, but they do not change the logical status of the model. An optimization procedure can locate a best-supported parameter set within a specified model without demonstrating that the model is the only plausible molecular explanation of the data.

Model flexibility can make the distinction still sharper. Hybrid neural ordinary differential equations can represent incompletely specified biological dynamics, but increased functional flexibility also creates opportunities for unknown components to trade off against parameters intended to retain mechanistic meaning. Explicit identifiability analysis in such models has shown that apparently successful fitting can coexist with compromised recovery of mechanistic parameters (Giampiccolo *et al.*, 2024). At the opposite end of the scale, computational advances have made parameter estimation feasible for very large biochemical reaction networks (Fröhlich *et al.*, 2017). Scalability is scientifically valuable, but solving a larger optimization problem does not by itself establish uniqueness of the recovered biological explanation.

These considerations imply that identifiability should be assessed at more than one inferential layer. A parameter may be practically recoverable within a specified model while the model itself remains one member of a larger class of molecular explanations. Conversely, competing models may be structurally distinguishable in principle while the available experiment fails to generate observations with sufficient resolution to separate them. The methodological task is therefore not simply to label a model identifiable or non-identifiable. It is to specify what is being identified, relative to which observations, under which model assumptions, and at what biological scale.

For competing molecular explanations, the most consequential transition occurs when this diagnosis becomes prospective. Once an equivalence class has been identified, the next question is whether a new measurement, perturbation or experimental condition can force the candidates to make different observable predictions. Structural identifiability establishes whether separation is possible under the model and observation scheme; practical identifiability establishes whether the attainable data can support that separation. Neither alone demonstrates causal specificity. Causal specificity requires a further step in which competing explanations are confronted with interventions or observations that were chosen because their predicted consequences diverge.

*Distinguishing Causal Specificity through Perturbation and Model Discrimination*

Perturbation can convert an observational equivalence problem into a discrimination problem only when competing explanations predict different consequences. Models such as CPA, GEARS and PerturbNet show that cellular responses to previously unmeasured chemical or genetic perturbations can be predicted from learned structure (Lotfollahi *et al.*, 2023; Roohani *et al.*, 2024; Yu *et al.*, 2025). Their scientific value for identifiability lies in prospectively ranking interventions that should separate candidates. Predictive success alone, however, does not identify the causal mechanism.

Controlled simulation offers a complementary strategy. GRouNdGAN uses an explicit gene-regulatory structure to generate causal single-cell simulations and in-silico knockouts (Zinati *et al.*, 2024). Such systems can ask whether candidate mechanisms would remain observationally equivalent after a proposed intervention, but the encoded causal graph is an assumption of the simulation rather than an independently discovered truth. Experimental validation of network-derived perturbation predictions, as demonstrated in cell-identity studies, is therefore essential when causal interpretation is intended (Kamimoto *et al.*, 2023).

The evidentiary standard becomes stronger when intervention is combined with orthogonal measurement. Causal single-cell analysis requires assumptions about intervention, confounding and transport across contexts (Tejada-Lapuerta *et al.*, 2025). Multimodal Perturb-CITE-seq illustrates how RNA, protein and perturbational evidence can distinguish mechanistically different routes associated with a related endpoint (Frangieh *et al.*, 2021). Causal specificity is therefore best understood as a comparative claim: one explanation gains support because a discriminating intervention produces the outcome it predicts while credible rivals fail under the same conditions.

Model complexity cannot substitute for this comparison. Deep perturbation predictors may fail to outperform simple baselines under some benchmarks (Ahlmann-Eltze *et al.*, 2025), while morphology may fail to recover known chemical–genetic relationships even when perturbations have related targets (Chandrasekaran *et al.*, 2024). A useful discriminator must therefore produce candidate-specific differences at a measurement scale capable of resolving them.

**Figure 2** summarizes experimental separability of competing molecular explanations across an identifiability boundary.

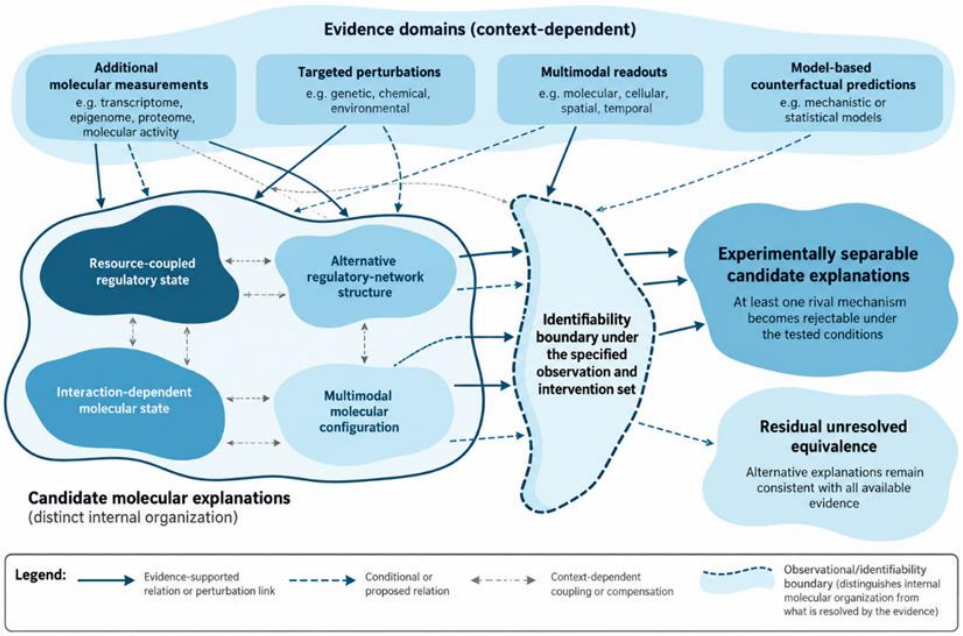



**Figure 2.** Experimental separability of competing molecular explanations across an identifiability boundary

Perturbation informativeness remains context dependent. Genome-scale Perturb-seq demonstrates how broad intervention can expose otherwise hidden genotype–phenotype structure (Replogle *et al.*, 2022). Cross-dataset analyses show that perturbation effects vary with assay and biological context (Peidli *et al.*, 2024). Network topology can also change which perturbations are informative (Aguirre *et al.*, 2025). The practical objective is therefore to select observations that maximize disagreement among plausible explanations while preserving the biological context in which the causal claim will be made.

*An Identifiability Framework for Competing Molecular Explanations*

The proposed framework begins by declaring the candidate explanations, the observable phenotype, and the level at which uniqueness is being claimed. Structural and practical identifiability should then be evaluated separately (Wieland *et al.*, 2021). Where experimental design can improve recoverability, the relevant question is whether an added observation reduces ambiguity among the specified candidates rather than merely tightening uncertainty within one model (Wang & Hao, 2025).

Mechanistic equivalence is retained when different explanations remain observationally indistinguishable under the current evidence. Resource-coupled circuits provide one example of how distinct internal interactions can yield similar system-level outputs (Al-Radhawi *et al.*, 2023), while network-structure analyses show that different architectures alter the distribution of perturbation effects (Aguirre *et al.*, 2025). Equivalence should therefore be stated relative to a defined phenotype, assay and condition.

A candidate measurement or intervention becomes discriminating only when rival explanations predict observably different outcomes. Explicit problem specification helps make those contrasts reproducible (Schmiester *et al.*, 2021), and predictive perturbation models can nominate prospective tests (Lotfollahi *et al.*, 2023). Such predictions do not count as causal confirmation until the resulting observations are obtained and compared with the alternatives.

Causal specificity is consequently bounded rather than absolute. Causal-learning theory emphasizes assumptions and unmeasured confounding (Tejada-Lapuerta *et al.*, 2025), while causal simulation shows how much discrimination depends on the structure supplied to the model (Zinati *et al.*, 2024). The strongest defensible conclusion is that one explanation is more specifically supported than named rivals under stated observations, interventions and biological conditions.

## Results and Discussion

*Interpretive Boundaries and Implications for Computational Biology*

A central implication is that predictive sophistication and causal discrimination should be reported separately. Benchmark evidence shows that complex perturbation models do not automatically improve prediction over simpler alternatives (Ahlmann-Eltze *et al.*, 2025), and GRN inference performance remains dependent on assumptions, datasets and available ground truth (Pratapa *et al.*, 2020). Computational complexity is therefore not an evidentiary substitute for a discriminating experiment.

Transfer across contexts introduces another boundary. Harmonized perturbation datasets retain substantial biological and technical heterogeneity (Peidli *et al.*, 2024), while multiome-based network inference can depend on external atlas information and priors (Yuan & Duren, 2025). An observation that separates mechanisms in one cell type, assay or state may fail to do so elsewhere, so identifiability should be re-evaluated in the target context.

Model structure can also mimic or conceal practical uncertainty. Simple structural-identifiability tests have documented blind spots (Castro & de Boer, 2021), and flexible hybrid neural models can permit unknown components to trade off against mechanistic parameters (Giampiccolo *et al.*, 2024). Ambiguity should therefore not be assigned automatically to noise or insufficient sample size when the model class itself may permit alternative explanations.

Finally, generalization to unseen perturbations remains distinct from causal specificity. GEARS demonstrates predictive capacity for novel multigene perturbations (Roohani *et al.*, 2024). PerturbNet similarly predicts distributions of responses to previously unseen perturbations (Yu *et al.*, 2025). GRouNdGAN provides a different capability by generating controlled simulations conditioned on an explicit regulatory structure (Zinati *et al.*, 2024). These methods are most informative when used to design tests that expose disagreement among mechanisms. When plausible alternatives survive the available observations, computational biology should preserve that uncertainty rather than convert predictive adequacy into an unwarranted causal claim.

## Conclusion

The same cellular phenotype can support multiple molecular explanations because biological systems contain redundancy, compensation and alternative network routes, while assays observe only part of that internal structure. The appropriate response is not to select the most elaborate or best-fitting explanation by default. Mechanistic equivalence should be retained until competing accounts generate separable predictions under relevant observations or perturbations. Structural identifiability establishes whether separation is possible in principle; practical identifiability asks whether attainable data can support it; causal specificity requires successful discrimination among credible rivals.

Failure to discriminate is itself interpretable: it identifies the current observation–intervention set as insufficient for stronger causal attribution. Progress therefore consists not merely in improving fit, but in designing evidence that changes which explanations remain scientifically defensible. The framework thus treats unresolved alternatives as an informative scientific state rather than a defect to be hidden by model complexity.

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