AI Detection Report for The Art of Mathematical Biology: a Foreword for th...

Sep 18, 2026 | 896 Words | Pangram 4.0

Summary

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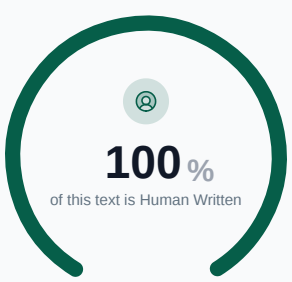

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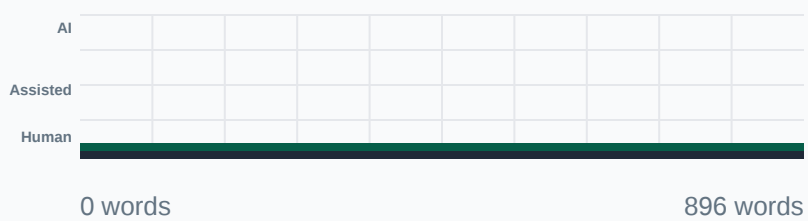

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The Art of Mathematical Biology: a Foreword for the Launch of BIOMATH We cannot debate that the advances made over the past 30 years in molecular biology, biochemistry and cell biology have dramatically changed biology and the biomedical sciences. Academic institutions and funding agencies increasingly recognize the interdisciplinary nature of biology and medicine, including the important role mathematical, statistical and computational modeling play in the analysis and interpretation of data and information. By and large, biologists and biomedical scientists appear to have more appreciation for mathematical biology research because they are increasingly attracted to discover new biological principles and mechanisms in collaboration with mathematicians. As a biomedical scientist active in the field of mathematical biology, I believe that the scope of mathematical biology includes providing novel biological insights that come from the mathematical formulation and analysis of biological problems. I fully recognized, however, that mathematical biology can also stimulate the development of new mathematics. There are excellent examples in the literature of mathematical biology research that have provided novel and important biological insights. Classical examples may be found in the work of Alan Turing [1] and of Alan Hodgkin and Andrew Huxley [2]. Much has changed since the publication of these papers. A mathematical biology research project is no longer guided by the independent spirit of one or two applied mathematicians working on a biological problem. Modern examples show that mathematical biology research is now a team science effort. How do we presently perform

mathematical biology research? An answer can be given by dividing the research process into the three steps of performing applied mathematics research [3]. The first step in performing mathematical biology research requires the formulation of the biological problem in mathematical terms. There is a widespread misunderstanding that this requires a proficiency and encyclopedic knowledge of biology. In reality it requires a good biological intuition and insight into the decision of which biological problems to attack. We need to learn to exercise excellent judgment in the formulation of the problem. This entails deciding what approximations to adopt in order to achieve a minimal model. The derivation of a minimal model, without losing the essential mechanisms of the problem, is an art form rather than a science. The mathematical biologist cannot master this art by working independently and as an isolated scientist. Biology is so complex that the knowledge, intuitions and insights now require interdisciplinary team work. The second step in performing mathematical biology research requires the solution of the mathematical model formulated. In mathematical biology, this now requires an extensive knowledge of mathematical, computational and statistical methods. The selection of the appropriate mathematical or computational technique will depend on the biological and physicochemical scales of the problem under consideration. The solution of most of the mathematical models requires the implementation of complex computational algorithms. Mathematical biologists need to investigate the model dynamics under biologically realistic parameter bounds. At the same time mathematical biologists need to investigate model sensitivity to parameters and initial conditions using statistical approaches and sensitivity analysis. Knowledge of mathematics, scientific computing and statistics is obviously necessary, but there is no person with an encyclopedic understanding of these methods. The isolated mathematician again will have limited chances of succeeding. The third step in performing mathematical biology research requires the interpretation of the mathematical model solutions and their empirical verification in experimental terms. This step serves as the culmination of the research, but it cannot be accomplished without the interdependence between the mathematical biologists and the experimentalists. Although it would be incorrect to say that all mathematical biology involves this third step (for example, the development of new mathematics and theory may not include this step), mathematical biology research must give priority of the empirical verification and evidence. Novel mathematical biology ideas, methods and techniques will need to show usefulness in the biological and biomedical sciences. In the context of the International Conferences on Mathematical Methods and Models in the Bioscience (BIOMATH 2011 and BIOMATH 2012), held in Sofia, Bulgaria, it is a great pleasure to see the steps of mathematical biology research effectively applied to investigate a wide range of problems in the biological and biomedical sciences. The BIOMATH conferences will serve to train and catalyze new research avenues for young scientists in Bulgaria, Eastern Europe and elsewhere. Mathematical biologists are now actively seeking collaboration with experimental biologists and the need for real application is being emphasized in mathematical biology research. There are tremendous opportunities for the new generation of mathematical biologists in interdisciplinary research. The Bulgarian Academy of Sciences is undertaking an exciting challenge with the new journal BIOMATH. They are launching BIOMATH to publish research being undertaken in the growing field of mathematical and computational biology. BIOMATH will strive to be a leader in the field, publishing new research articles, reviews and communications. The editorial team composed by Roumen Anguelov (University of Pretoria, South Africa), Svetoslav Markov (Bulgarian Academy of Sciences) and Nina Pesheva (Bulgarian Academy of Sciences) intends to appeal to a broad audience of researchers who draw on mathematics, statistics and computing, with the aim of providing insight into the life sciences. The Bulgarian Academy of Sciences and editorial

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team are launching BIOMATH with the determination to make it a success. I sincerely hope that you and your colleagues will enjoy reading the articles in this new journal and will submit your work for publication in BIOMATH.

AI Detection Report for Validity of the Michaelis–Menten equation– steady-...

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Summary

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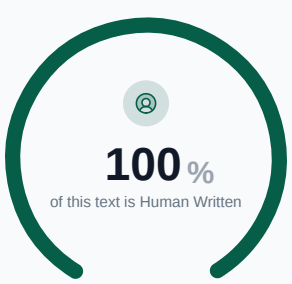

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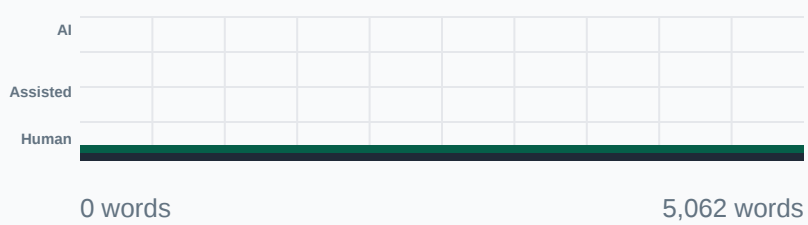

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Validity of the Michaelis–Menten equation– steady-state or reactant stationary assumption: that is the question The Michaelis–Menten equation is generally used to estimate the kinetic parameters, V and KM, when the steady-state assumption is valid. Following a brief overview of the derivation of the Michaelis–Menten equation for the single-enzyme, single-substrate reaction, a critical review of the criteria for validity of the steady-state assumption is presented. The application of the steady-state assumption makes the implicit assumption that there is an ini- tial transient during which the substrate concentration remains approxi- mately constant, equal to the initial substrate concentration, while the enzyme–substrate complex concentration builds up. This implicit assump- tion is known as the reactant stationary assumption. This review presents evidence showing that the reactant stationary assumption is distinct from and independent of the steady-state assumption. Contrary to the widely believed notion that the Michaelis–Menten equation can always be applied under the steady-state assumption, the reactant stationary assumption is truly the necessary condition for validity of the Michaelis–Menten equation to estimate kinetic parameters. Therefore, the application of the Michaelis– Menten equation only leads to accurate estimation of kinetic parameters when it is used under experimental conditions meeting the reactant station- ary assumption. The criterion for validity of the reactant stationary assump- tion does not require the restrictive condition of choosing a substrate concentration that is much higher than the enzyme concentration in initial rate

experiments. Keywords enzyme kinetics, initial rate experiments, limiting rate, Michaelis–Menten constant, rapid-equilibrium assumption, reactant stationary assumption, steady-state assumption Introduction The Michaelis–Menten equation is undoubtedly one of the most important mathematical expressions in bio- chemistry. It describes the initial rate of production formation (v0) for a family of enzyme-catalysed reac- tions in terms of two parameters: the limiting rate (V) and the Michaelis–Menten constant (KM) [1,2]. The initial velocity of the Michaelis–Menten equation is arectangular hyperbolic function of the initial substrate concentration (s0), which has the mathematical form: Vs0 v0 ¼ : ð1Þ KM þ s0 In the above expression, KM gives s0 at which v0 is half V, so if s0 = KM is substituted in Eqn (1), we obtainv0 ¼ 1 2 V. v0 is measured through initial rate experi- ments, which are performed by mixing the enzyme with a large excess of substrate. Under these condi- tions, the intermediate species builds up and achieves a pseudo-steady-state after an initial fast transient. After this point, v0 changes slowly and is typically monitored through accumulation of product with time [2,3]. At low s0, v0 increases linearly with s0. As s0 increases, the linear relationship breaks down and v0 increases less rapidly until it reaches the saturating value of V at high s0 (see Fig. 1). Initial rate experiments are simple to perform and analyse. They are also relatively free from complications such as back reaction and enzyme degradation. As a consequence, they are the most commonly used experimental assay in enzyme kinetics. The Michaelis–Menten equation was derived by Leo- nor Michaelis and Maud Menten in their seminal paper on enzyme kinetics which was published in the Biochem- ische Zeitschrift in 1913. In their paper, Michaelis and Menten measured the initial rates of the invertase reac- tion at different substrate concentrations. They showed that the Michaelis–Menten equation accurately describes the initial rates of the invertase reaction Michaelis and Menten are considered the founders of modern enzymology, because their initial rate experi- ments have served as a standard for most of the enzyme kinetics experiments over the last century [2,4]. The derivation of the Michaelis–Menten equation (Eqn 1) requires making some assumptions about the experimental conditions of the enzyme-catalysed reac- tions [5]. In most biochemistry textbooks, the Michael- is–Menten equation is derived using the steady-state assumption [4,6]. If the Michaelis–Menten equation is to be used to estimate KM and V, it is essential to know whether or not the steady-state assumption is valid in any given experimental assay for an enzyme- catalysed reaction. In this work, I review the foundations of the Micha- elis–Menten equation, examine the literature investigat- ing the validity of the steady-state assumption and provide general principles to derive criteria for the validity of the Michaelis–Menten equation to estimate the kinetic parameters in initial rate experiments. I argue that the strongest criterion to use the Michaelis– Menten equation for estimating KM and V in test tube experimental assays is not the steady-state assumption, but the reactant stationary assumption, which assumes that the substrate concentration does not change signif- icantly during the initial transient of the enzyme-cataly- sed reaction. I also show that the laboratory practice for initial rate experiments of choosing a substrate con- centration that is much higher than the enzyme concen- tration is unnecessarily restrictive for the validity of the reactant stationary assumption Derivation of the Michaelis–Menten equation In 1902, Henri [7,8] proposed the following reversible reaction mechanism between a substrate S and an enzyme E, giving the enzyme–substrate complex C, which irreversibly yields the product P: k1 S þ E k 1 C* k2 P þ E; ð2Þ where k1, k 1 and k2 are rate constants of the reaction. Henri derived an equation for the rate of product formation to explain the enzyme action, but he did not propose an experimental assay to study enzyme-catalysed reactions nor a protocol to estimate the rate constants of the reaction [4]. In addition, reac- tion mechanism (2) is a simplification, which assumes that the

overall enzyme-catalysed reaction is irrevers- ible and has only one intermediate complex. Despite these imperfections, modern textbooks present reaction mechanism (2) as the starting point for introducing and interpreting enzyme kinetics [2,3,9]. The difficulty of investigating the behaviour of the enzymatic reaction was largely resolved when Michael- is and Menten [10] showed that enzymes can be stud- ied by measuring v0 using Eqn (1) [4,5,11] under what it is currently known as the rapid-equilibrium assump- tion [3,12,13]. For this reason, Eqn (1) and reaction mechanism (2) are known, respectively, as the Micha- elis–Menten equation and reaction mechanism, although these authors clearly recognised Henri as the originator of both. Derivation of v0 by Brings and Haldane Currently, the mathematical protocol developed by Briggs and Haldane in 1925 [14] is considered the stan- dard approach to derive the Michaelis–Menten equation for reaction mechanism (2) using the steady-state assumption [2,4]. Briggs and Haldane [14] applied the law of mass action to determine the rate of c as follows: vC ¼ k1es ðk 1 þ k2Þc: ð3Þ They pointed out that C need not be in equilibrium with E and S, but within a very short time after starting the reaction, the rate of formation of C will almost balance its rate of destruction. Hence, C builds up to a pseudo- steady-state level, where its concentration is nearly constant. Thus, by making the steady-state assumption vC 0; ð4Þ reaction mechanism (2) has an enzyme conservation law e0 ¼ e þ c: ð5Þ Substituting e from the enzyme conservation law (Eqn 5) into Eqn (3), and applying the steady-state assumption (Eqn 4), we can solve c in terms of s, thus e0s c ¼ ; ð6Þ KM þ s where KM is the Michaelis–Menten constant, k 1 þ k2 KM ¼ : ð7Þ k1 In the second step of reaction mechanism (2), the enzyme catalysis takes place with a first-order rate constant, k2, known as the turnover number. The turn- over number represents the maximum number of sub- strate molecules converted to product per active site per unit time, or the number of times the enzyme is ‘turned over’ per unit time. In the second step, the rate of product concentration is defined by the law of mass action as vP ¼ k2c: ð8Þ From the enzyme conservation law (Eqn 5), c ≤ e0, and so, provided that the experimental condition is valid, e0 s0 1; ð9Þ then s0 ≫ c during the build-up of c. Therefore, during the initial transient of the reaction, the free substrate concentration can be approximated by s s0: ð10Þ Substituting Eqn (6) with Eqn (10) into vP as defined in Eqn (8), leads to: v0 ¼ Vs0 KM þ s0 ; ð11Þ with the limiting rate defined as V= k2e0. In fact, Eqn (11) is known as the Michaelis–Menten equation for the single-enzyme, single substrate catalysed reac- tion mechanism (2), even though it was derived using the Briggs and Haldane treatment. This recapitulation of the derivation of v0 using the Briggs and Haldane treatment provokes an important question: under what experimental conditions and range of rate constants is the steady-state assumption valid? To address this question, I present a historical review of literature investigating the validity of the steady-state assumption for the Michaelis–Menten reaction mechanism. A historical review of the validity of the steady-state assumption The validity of the steady-state assumption for the Michaelis–Menten reaction mechanism (2) was for- mally discussed for the first time in 1955 by Laidler [15] who suggested that a large ratio of s0 to e0 (equiv- alent to Eqn 9) is the main prerequisite for the validity of the assumption through a mathematical analysis. Ten years later, Hommes [16], Walter and Morales [17] and Walter [18] mapped the range of validity of the steady-state assumption for both the irreversible and reversible Michaelis–Menten reaction mechanisms using early analog computer simulations. They found notable shortcomings with the validity of the steady-

state assumption for cases with large reversible con- stants of the enzyme–substrate intermediates, such as k 1. In 1965, Wong [19] made an attempt to develop a continuous description of the initial transient and the steady-state phases of reaction mechanism (2), and concluded that the initial transient must be brief for the steady-state assumption to be applicable, which is achieved by increasing the s0/e0 ratio. In 1979, Stayton and Fromm [20] found the steady-state assumption to generally hold true for s0/e0 > 100 by exploring a wide range of rate constant values and initial reaction con- ditions using computer simulations. In 1980, Seshadri and Fritzsch [21,22] investigated the steady-state assumption for the Michaelis–Menten reaction mechanism (2) with reversible P formation using a scaling and simplification mathematical tech- nique known as singular perturbation analysis. To apply singular perturbation analysis, it is necessary to estimate the timescale of the initial transient and the steady-state period of the enzyme-catalysed reaction. In 1967, Heineken et al. [23] used singular perturba- tion analysis to implement the steady-state assumption in reaction mechanism (2) for the first time. Based on the findings of Laidler [15], Wong [19] and Stayton and Fromm [20], Heineken et al. [23] assumed that the ratio of e0 to s0 needed to be small (e0/s0 1) to apply the steady-state assumption. They also showed that the relative magnitude of k2 does not guarantee the validity of the steady-state assumption. In con- trast, Seshadri and Fritzsch [21,22] used a different criterion: e0 KM 1: ð12Þ Seshadri and Fritzsch [21] cited Reich and Sel'kov [24] as the source of their choice of criterion, but the latter authors provided no motivation for their choice. In addition, none of the above authors provide a biophysical rationale for selection of the timescale used to implement the singular perturbation analysis. Klonowski [25] provides a general discussion of timescales. However, the timescales selected to apply the steady-state assumption discussed by Klo- nowski were also introduced without motivation. It is worth noting that Klonowski found in the Russian literature that the steady-state assumption is valid when e0 s0, or when s0 KS and s0 K: ð13Þ In the above conditions, KS = k 1/k1 is defined as the equilibrium dissociation constant of C, and K= k2/k1 is the Van Slyke–Cullen constant [26]. Note that KM can be written as KM = KS + K. Using linear approximations and a modal analysis technique, Palsson and Lightfoot [27] and Palsson [28] derived Eqn (12) as the criterion for the validity of the steady-state assumption in 1984. In 1996, de la Selva et al. [29] obtained the same criterion by studying the slope of the rate of P formation versus S depletion at equilibrium using mathematical asymptotic analysis. One of the most rigorous analyses of the validity of the steady-state assumption for reaction mechanism (2) was performed by Schauer and Heinrich [30] in 1979. They investigated the numerical errors resulting from applying the steady-state assumption by studying the time-dependent change in s and c. They proposed three criteria to minimize the errors in the implementa- tion of the steady-state assumption. The first criterion is that the depletion of s must be small during the ini- tial transient of the enzyme-catalysed reaction. The second criterion is that the reaction timescale of C must be faster than the reaction timescale of S. The third criterion is that the instantaneous P formation rate must always be smaller than the limiting rate V under the steady-state assumption. Segel [6] and Slemrod [31] mathematically formal- ised the analysis of Schauer and Heinrich using a mathematical scaling and simplification technique, and obtained simpler formulae for the three criteria described above. They derived the following condi- tion: ; ð14Þ e0 KM þ s0 1 þ K KS 1 þ KM s0 for the validity of the steady-state assumption, i.e. vC 0. Interestingly, condition (14) is an extension of the conditions (9), (12) and (13). The domain for which the steady-state assumption is valid was extended by Borghans et al. [32] based on Segel's formulae and using a mathematical change of variables to study the total substrate concentration (the sum of s and c) rather than s. They proposed the following condition for the validity of the steady-state assump- tion: Ke0 ðKM þ e0 þ s0Þ2 1: ð15Þ Since the total substrate concentration cannot be depleted by the formation of c during the initial tran- sient, it is unfair to draw direct comparisons between condition (14) and the newly derived condition (15) for the total substrate concentration. In addition, the formulation using the total substrate concentration has a limited practical utility in estimating kinetic parame- ters, because the total substrate concentration cannot be measured experimentally in initial rate experiments. However, using this change of variable, analytical approximations have been derived to both estimate kinetic parameters using progress curves analysis [33,34] and investigate the dynamics of complex enzyme-catalysed reactions [35,36]. Conditions for the validity of the derivation of the Michaelis–Menten equation I have shown how the Michaelis–Menten equation can be derived by applying the steady-state assumption (the Briggs and Haldane derivation). This derivation implicitly assumes that s s0 while c builds up during the initial transient of the reaction. In 2008, this impli- cit condition was named the reactant stationary assumption by Hanson and Schnell [37], although it was originally defined computationally by Côme [38] in 1979. Over the last century, the majority of enzy- mologists did not consider the reactant stationary assumption to be an independent assumption from the steady-state assumption. If the steady-state assumption implicitly assumes s s0 during the initial transient of the reaction, is the reactant stationary assumption part of the steady-state assumption? The answer is no. In 2008, Hanson and Schnell [37] showed that the steady-state assumption can be valid without ensuring s s0 during the initial transient for reaction mechanism (2)

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Condition for the validity of the reactant stationary assumption I now focus on the validity condition of the reactant sta- tionary assumption for reaction mechanism (2). For the reactant stationary assumption to be valid, there must be a negligible decrease in s during the initial transient, tC. This decrease, which we denote by Ds, is certainly less than the product of tC and the maximal rate of s at the start of the reaction: vS j jt¼0 . This implies that Ds s0 ¼ tC vS j jt¼0 s0 Applying the law of mass action to the first elementary step (E + S ? C) of reaction mechanism (2) leads to vS j jt¼0¼ k1e0s0 j j. Using the definition of tC (Eqn 18), we can expand Eqn (22) to which is the criterion for validity of the reactant sta- tionary assumption. It is easy to see that, when Eqn (23) is valid, Eqn (21) must also be valid. Accord- ing to condition (23), the reactant stationary assump- tion can be valid for situations when e0=s0 1 as long as KM ≫ 1. Dividing the numerator and denominator of the left-hand side of Eqn (23) by KM, and rearrang- ing the condition to e0 KM 1 þ KM s0 ; ð24Þ it can be seen that the reactant stationary assumption is also valid when e0=s0 1 as long as e0 KM. Therefore, the reactant stationary assumption is a stronger condition than that required for the steady- state assumption, and is sufficient for the validity of the steady-state assumption. Is the Michaelis–Menten equation valid under the steady-state assumption or the reactant stationary assumption? Following the simpler formulae introduced by Segel [6] and Segel and Slemrod [31], it was found that condi- tion (23) ensures s s0 during the initial transient, but it also ensures vC 0 during the steady-state period. The regions of validity of the steady-state assumption and reactant stationary assumption are illustrated graphically in Fig. 2 by plotting conditions (21) and (23). In order to graphically represent the conditions, the threshold for ‘much smaller than unity’ was arbi- trarily set as equal to 0.1. Figure 2 shows the boundaries of the regions of validity of the steady-state assumption and the reactant stationary assumption in the e0/KM and s0/KM plane. The plane is divided into three regions: the upper region where the reactant stationary assump- tion and the steady-state assumption are both invalid, the middle region where the steady-state assumption is valid but the reactant stationary assumption is invalid, and the bottom region where both the reactant station- ary assumption and the steady-state assumption are valid. As e0 is increased or s0 is decreased, the reactant stationary assumption becomes invalid first, then the steady-state assumption also becomes invalid. Hanson and Schnell [37] investigated what would happen to the estimation of kinetic parameters when the Michaelis–Menten equation, derived using the Briggs–Haldane treatment (Eqn 11), is used in the Fig. 2. Limits of the validity of the steady-state assumption and reactant stationary assumption for the irreversible single-enzyme, single-substrate enzyme reaction mechanism (2). In the area labelled ‘RSA + SSA’, the reactant stationary assumption (RSA) and the steady-state assumption (SSA) are both valid, and the Michaelis– Menten equation (Eqn 11) can be used to estimate the kinetic parameters KM and V. In the area labelled ‘SSA’, the steady-state assumption is valid, but the reactant stationary assumption does not hold. Note that the criterion for the validity of the reactant stationary assumption is a sufficient condition for the validity of the steady- state assumption. However, if the reactant stationary assumption is not valid, the use of the Michaelis–Menten equation leads to inaccuracies of 10–1000-fold in the estimation of the kinetic parameters KM and V. In the top area, neither the steady-state assumption nor the reactant stationary assumption are valid. Parameters used for this figure are: KM = 1 lM and KS/K= 12.5. region where the steady-state assumption is valid, but the reactant stationary assumption is not. They found that the v0 for the single-enzyme, single-substrate reac- tion mechanism (2) may lead to widely inflated esti- mates of KM and V. The values can over-estimate the real KM and V values by as much as 10–1000-fold. This clearly indicates that the Michaelis–Menten equa- tion can only be used to accurately estimate kinetic parameters when the reactant stationary assumption is valid, i.e. when condition (23) is satisfied. It may be argued that the identification of the region of validity of the reactant stationary assumption has a limited significance for the practice of initial rate experiments, because these enzyme kinetics experi- ments are generally arranged such that s0 ≫ e0. Although the reactant stationary assumption is valid when s0 ≫ e0, this condition is unnecessarily restrictive, as shown in Fig. 3. As illustrated in the figure, and explained in the analysis in the previous sub-section, the Michaelis–Menten equation can be used even when s0 e0 , as long as e0 KM. If the reactant stationary assumption is not valid but the steady-state assumption holds, it is necessary Fig. 3. The condition s0 ≫ e0 is unnecessarily restrictive in initial rate experiments for the irreversible single-enzyme, single- substrate enzyme reaction mechanism (2). The Michaelis–Menten equation (Eqn 11) can be used to accurately estimate the kinetic parameters KM and V when the reactant stationary assumption (RSA) is valid. Note that in the area labelled ‘RSA + s0 ≫ e0’, both assumptions are valid, but the reactant stationary assumption is also valid in the region labelled ‘RSA’. When s0 e0 , the reactant stationary assumption is valid as long as KM ≫ 1 or e0 KM. In the top area, neither the condition s0 ≫ e0 nor the reactant stationary assumption are valid. The value of the Michaelis– Menten constant used in this figure is 1 lM. to make some corrections to rate equations and experi- mental assays. When considering the Briggs and Hal- dane treatment for reaction mechanism (2), if we do not adopt the reactant stationary assumption, we have to ignore the assumption that s s0 during the initial transient. Substituting Eqn (6) into vP =

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ists can relax the condition s0 ≫ e0 for the initial rate experiments of enzyme-catalysed reactions if the order of magnitude of KM is known a priori. This review also draws attention to the fact that the Michaelis–Menten equation, although widely believed to be valid under ‘steady-state kinetics’, is in reality truly valid under ‘reactant stationary kinetics’. Acknowledgements I am indebted to Marc R. Roussel (Department of Chemistry and Biochemistry, University of Lethbridge, Alberta, Canada) for calling my attention to the prob- lem of the reactant stationary approximation in enzyme kinetics a few years ago. I would also like to thank Mark Whidden, Allison Ho and Caroline Adams for carefully reading the manuscript. This work has been partially supported by the James S. McDonnell Founda- tion (Grant No. 220020223) under the 21st Century Sci- ence Initiative Studying Complex Systems Program.

AI Detection Report for Ten Simple Rules for a Computational Biologist's L...

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Summary

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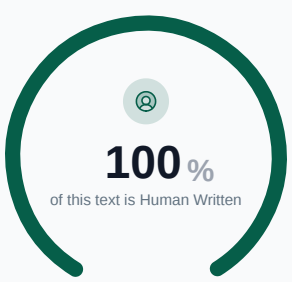

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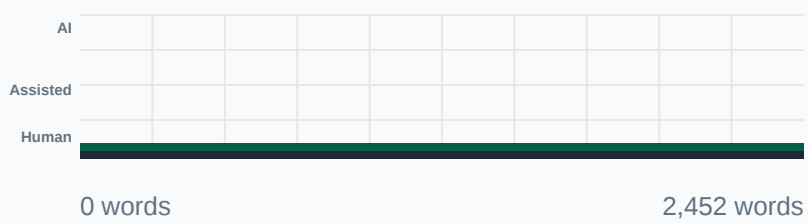

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Ten Simple Rules for a Computational Biologist's Laboratory Notebook One of the major hurdles I face as the head of a computational biology laboratory is convincing my research team—particularly those pursuing exclusively mathematical and computational modeling—that they need to keep a laboratory notebook. There seems to be a misconception in the computational biology community that a lab notebook is only useful for recording experimental protocols and their results. A lab notebook is much more than that. It is an orga- nizational tool and memory aid, which serves as the primary record of scientific research and activity for all scientists. It also serves as a legal record of ownership of the ideas and results obtained by a scientist. Here, I present the best practices (summarized as ten rules) for keeping a lab notebook in computational biology, for scientists pursuing exclusively"dry" research. Rule 1: Learn Your Institution's or Laboratory's Notebook Policy A lab notebook is an important tool for good record-keeping, research management, to protect intellectual property and prevent fraud [1]. Leading research institutions, research and devel- opment divisions in companies, and universities have comprehensive lab notebook policies, which research laboratories should implement. In the absence of an institutional policy, your research group should have a policy to explain to all team members the process for daily record-keeping and maintaining laboratory records. If your institution or laboratory does not have a standard policy, the following rules provide you with some guidelines for keeping a record of your scientific activities—a record that will likely be very

important for you, your research supervisor, or peers. Rule 2: Select the Right Medium for Your Lab Notebook There are three types of lab notebooks: the bound or stitched notebook, the loose-leaf or three-ring binder notebook, and the computer-based electronic notebook [1]. Each of these notebooks has its advantages and disadvantages [2]. You will need to select the right type of notebook for your research. Most computational biologists work on several projects at the same time. If you find it too complicated to keep all of your projects in a single lab notebook, you can maintain a lab notebook for each project. Alternatively, you can use a ring binder, in which each project is maintained behind a separate tab divider inside the binder. You also have the option of using an electronic lab notebook. The advantage of electronic notes is that they can be searched easily [3], and computer-generated figures can be quickly copied to the note- book. If you do not identify the right technology, it can be very time-consuming to make a pol- ished electronic notebook. Some laboratories [4] are writing lab notebooks using Microsoft Word, saving as“Web Page,” and automatically transfer the entries into a WordPress.com blog. Microsoft OneNote is a proprietary software option. If you write a lot of computer code and collect large datasets, the electronic notebook will be a better option for you because you can store and link your code and data to your electronic lab records [5]. Electronic lab note- books can also be shared and accessed easily online with collaborators and lab members [3,4]. However, if you have not identified the right technology for an electronic lab notebook, then you should organize your computer code and data in a safe medium (e.g., hard drive, CD-ROM, cloud storage, version-control databases, paper copies) [6] and record in your note- book where the code or data can be found. Rule 3: Make the Habit of Keeping the Lab Notebook in Your Desk You need to keep your lab notebook at hand, and write things down while you are working. If you rely on your recollection to remember a good idea, a suggestion during a meeting, or an important step in your data analysis or model simulation, you can find yourself in a situation where you no longer remember that critical thought. Furthermore, you will find that writing provides you the opportunity to reflect on these ideas as you put together a logical argument supporting your conjectures, results, or conclusions. Rule 4: Record All Scientific Activities in Your Lab Notebook There are scientists who believe that lab notebook records should be limited to wet or dry lab experimental entries. However, the intellectual activity of a theoretical scientist is not limited to experiments to test hypotheses. Thinking about the possible directions of your research and theorizing about how a system works is often how scientific breakthroughs are made. If you use paper pads or other assorted pieces of paper to write down your ideas or take notes during meetings and seminars, you may lose important items or waste too much time looking for ideas later. Recording your scientific activities will solve this problem. Scientists should record every experiment, every result, every research meeting, notes from seminars, research confer- ence calls, thoughts related to their research problem—all of these items go into their lab note- books. In a very real way, the lab notebook is a chronological log of everything scholarly a scientist does. Each lab notebook entry should be written immediately after the activity or work was performed. Rule 5: Every Entry Should Be Recorded with a Date, Subject, and Protocol The most logical organization of a lab notebook is chronological. Each entry should contain the date it was made and subject of the entry. If you make distinct sets of entries in the same day, you should separate them by using heading titles and leave sufficient space between the entries [1]. The titles of your entries are important. They should be short, sharp, and informa- tive, as you will use them to build a table of contents for your lab notebook. If you are using a paper lab notebook, you will need to write the date and time stamp and make your entries legi- ble, written in permanent ink and in a language accessible to everyone

in the laboratory. If you use an electronic lab notebook, the date and time stamps will be entered automatically for each new subject. You should also include a brief background for each entry [2]. It could be a short synopsis of your thought process that explains why this entry is important for your scientific work. You can support it with references published in the literature, ideas learned from a research talk, or a previous model developed by your laboratory. Then, record everything you do for this spe- cific entry. If you make a mistake in your paper lab notebook, put a thin line through the mistake and write the new information next to it [1]. Never erase or destroy an entry, because errors or mistakes are an important part of the scientific process. Rule 6: Keep a Record of How Every Result Was Produced The gold standard of science is reproducibility [7]. You need to keep a record of how every result was produced in your in silico experiments, statistical analyses, and mathematical or computational models. Noting the sequence of steps taken allows for a result or analysis to be reproduced. For every step in your model, analysis, or experiment, you should record every detail that will influence its execution [8]. This includes the preparation of your wet or dry experiment, preprocessing, execution with intermediate steps, analysis, and postprocessing of results [1,2]. You should also store the raw data for every figure. This will allow you to have the exact values for the visualization of your results. It will also give you the opportunity to redraw figures to improve their quality or ensure visual consistency for publication. If a result is obtained through a mathematical model, algorithm, or computer program, you need to include the equations and name and version of the algorithm or computer program, as well as the initial conditions and parameters used in the model. In many instances, a statistical or computational analysis creates intermediate data [9]. You should record intermediate results because they can reveal discrepancies with your final results, particularly if your analysis is time consuming or readily executable. At the same time, they can help you track any inconsis- tencies in your analysis or algorithms [8]. Electronic lab notebooks can be very convenient for storing data and linking to computer mathematical models, algorithms, and software stored in cloud mass storage systems. Rule 7: Use Version Control for Models, Algorithms, and Computer Code As a mathematical and computational biologist, you will be updating your models, algorithms, or computer programs frequently. You will also create scripts containing initial conditions and parameters to run analyses or simulations. Changes in your models, algorithms, programs, or scripts could drastically change your results. If you do not systematically archive changes, it will be very difficult or impossible to track the codes that you used to generate certain results [8,9]. Nowadays, there are version control systems to track the evolution of algorithms and computer programs or changes in scripts. Bitbucket, Git, Subversion, and Mercurial are among the most widely used version-control systems. You should use a standardized name system to identify changes. If you have a paper lab notebook, you should record the name and location of the scripts. Those using electronic lab notebooks can add links to each version of their scripts or programs. Rule 8: Keep a Lab Notebook That Can Serve As a Legal Record of Your Work The lab notebook serves as a legal record of ownership of ideas and results [10]. Lab notebooks can serve to determine authorship in scientific papers or rights for establishing copyright or patent rights. If you do not feel comfortable walking around with a notebook or having more than one lab notebook, you can still record all your notes in paper pads, but you should file

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them in a ring binder using the indexing system of a lab notebook. You can also use a tablet if you keep an electronic lab notebook. However, this is not generally advisable. At the moment, bound notebooks with numbered pages are the only legally recognized option to record and protect your work. Electronic records can be printed out on a regular basis and then bound to form a legally recognized laboratory notebook. If you keep a loose-leaf lab notebook, you should have a parallel hardbound notebook summarizing progress on your projects as a legal record of your work. For each lab notebook entry, clearly indicate who did what work and who was present for a discussion or in silico experiment; this is particularly important for collabora- tive projects. In addition, each entry should be signed by you and cosigned by a coworker or supervisor. Otherwise, the entry will not serve as a legally valid record. It is important to note that lab notebooks can be subpoenaed as evidence in cases of scien- tific misconduct by your institution or governmental funding agencies. According to educa- tional material provided by the Office of Research Integrity at the United States Department of Health and Human Services and the University of New Hampshire,“The integrity of research and scholarly activities depends on accurate, detailed, organized, complete, and accessible data” [11]. From the legal point of view, you keep a lab notebook to reflect your own scientific integrity and to give others the opportunity to corroborate the results of your research. If you keep an electronic lab notebook, you can make it open to the public. This will make your work more transparent to the scientific community, and it will give the opportunity for other scien- tists to learn more about your research, including the experiments and models that did not work out. Rule 9: Create a Table of Contents for Your Lab Notebook You should record the titles of all entries in your lab notebook in a table of contents as you fin- ish each entry or day. The idea of this index is to help you, your research supervisor, or some- one else find the record of your scientific work efficiently [1,2]. There are multiple formats for the table of contents. You should use the format agreed upon in your laboratory. It is generally advisable that each entry in the table of contents has the date the entry has been made, the sub- ject of your entry, and where in the lab notebook the entry can be found. To find information easily in your lab notebook, you should always start an event in a new page. Then, label the event accordingly ("Research Review with Dr. Williams," "Seminar by Dr. Murray," "Thoughts on Project X," etc.) and date it. Once you have done this, you can start taking notes and take as many pages as you need. If you have the standard paper lab notebook, the pages will be num- bered. Now you will be in the position to move forward with the critical step: create a table of contents on the first page of your notebook, where you will log the event and page number. If you do not have the standard lab notebook, you can put a page number at the top of each pair of pages counting by two. An advantage of electronic lab notebooks is that you do not need to worry about creating a table of contents because it will be done automatically for you. Rule 10: Protect Your Lab Notebook As your research activities are funded by or through your academic institution, your lab note- book does not belong to you; it belongs to your institution [1,10]. Your lab notebook is part of the scientific legacy of your laboratory. Therefore, you need to protect your lab notebook. Paper lab notebooks should not be taken home. When you leave the laboratory each day, you should leave your lab notebook in a location where your research supervisor can find it. Ideally, you should lock it in the same place every day. If your research institution or lab supervisor allows, you will be able to make copies of your lab notebook, but the original belongs to the institution that paid your salary and handled your research funds. Laboratories, research institutes, and universities have archival systems in operation to store lab notebooks. You might find this surprising, but lab notebooks generally end up in your uni- versity or research institution’s library. Maybe one day you will become a very important scien- tist, and your lab notebook will be shown in an exhibit, like Charles Darwin’s Notebook B, sketching the relationships between related species, or Albert Einstein’s notebook from 1928, elaborating how the Einstein field equations (a set of ten equations in his theory of general rela- tivity) can be extended to explain electricity and magnetism.

AI Detection Report for “Reproducible” Research in Mathematical Sciences R...

Sep 18, 2026 | 3,391 Words | Pangram 4.0

Summary

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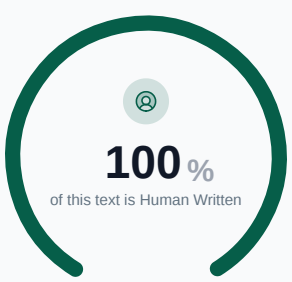
Authorship Breakdown



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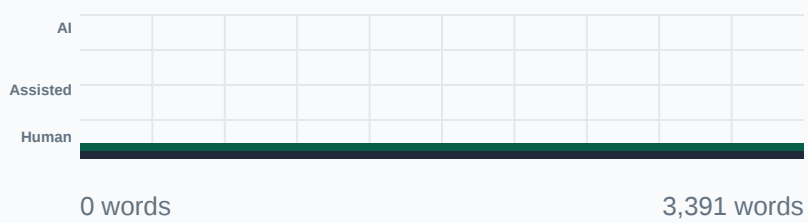
100 %	of the document	Human Written

Authorship Progression



Analyzed Text

Words that are underlined indicate AI phrases, while the numbers represent how frequently they are likely to appear in AI writing. These elements are not used to determine the results but are displayed separately as patterns commonly found in AI-generated text.

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“Reproducible” Research in Mathematical Sciences Requires Changes in our Peer Review Culture and Modernization of our Current Publication Approach Abstract The nature of scientific research in mathematical and computational biology allows editors and reviewers to evaluate the findings of a scientific paper. Replication of a research study should be the minimum standard for judging its scientific claims and considering it for publication. This requires changes in the current peer review practice and a strict adoption of a replication policy similar to those adopted in experimental fields such as organic synthesis. In the future, the culture of replication can be easily adopted by publishing papers through dynamic computational notebooks combining formatted text, equations, computer algebra and computer code. Keywords Reproducibility· Repeatability· Replicability· Editorial policies· Academic publishing 1 ScientistsareAwakeningtothe“Reproducibility”Crisis Repeatability, replicability and reproducibility are held as the gold standards for scientific research. As a consequence, the legitimacy of any research paper depends on the ability of other scientists to repeat, replicate or reproduce the results published in an article since the appearance of the first scientific journals—Journal des sçavans and Philosophical Transactions of the Royal Society—in 1665 (Kronick 1976; Shapin and Schaffer 1985). Over the last 15 years, there have been increasing concerns that many research findings published in influential peer-reviewed scientific journals cannot be replicated in the biomedical sciences (Hirschhorn et al. 2002; Ioannidis 2005; Prinz et al. 2011; Begley and Ellis 2012),

psychology (Bakker and Wicherts 2011; John et al. 2012; Pashler and Wagenmakers 2012; Van Bavel et al. 2016), sociology and economy (Bollen et al. 2015; Ioannidis et al. 2017) and computer science (Donoho et al. 2009). There are even expository articles arguing that the failure to “reproduce” also occurs in the mathematical sciences (Redish et al. 2018). In a recent survey by the journal Nature (Baker 2016), respondent scientists agreed that there is a reproducibility crisis. Although the survey results may not be representative of the scientific community, individual scholars confirmed their skepticism by trying—and often failing—to repeat, replicate or reproduce results. The “reproducibility” crisis has caused several academics, politicians and the public at large to call into question the reliability, value and trustworthiness of the scientific enterprise (Alberts et al. 2013; Macleod 2014; Van Bavel 2016; Wood and Randall 2016). The good news is that multiple studies show that there is no evidence that the failure to “reproduce” is the result of scientific misconduct (see Fanelli 2018 and reference therein). Less than 2% of scientists are fabricating or falsifying data (Shapiro and Charrow 1989; Steneck 2006; Fanelli 2009). Metaresearch studies suggest that the “reproducibility” crisis results from heterogeneous factors distributed across different areas of science that include bias in hypothesis testing (Fanelli 2010; Fanelli et al. 2017), poor experimental design, statistical problems (John et al. 2012; Button et al. 2013) and lack of standardization to report and share experimental protocols, results and data (Wicherts et al. 2006; Nature Editorial 2014; Stark 2018). 2 RecommendationsandPoliciesAdoptedinResponse tothe“Reproducibility”Crisis As a response to the “reproducibility” crisis, the scientific community is encourag- ing journals to maintain high standards to increase the likelihood of reproducibility, and journals are responding accordingly (McNutt 2014). In the biomedical sciences, new guidelines have been adopted requiring detailed experimental protocols, estab- lishing best practices for image-based data and statistical analysis (National Institutes of Health 2017). It has been recommended to modify the reward system in science by awarding scientists who aligned with best practices for reproducibility research (Ioannidis 2014). In the USA, federal funding agencies are now requiring training in rigor and reproducibility for scientists holding research grants. The National Insti- tutes of Health Office of Extramural Research revised grant application instructions and review criteria to enhance reproducibility of research findings by adopting a rigor and reproducibility guidance (Collins and Tabak 2014; National Institutes of Health 2018). Similar approaches are being adopted for the psychological, social and eco- nomic sciences (Munafò 2017). Most of the above reproducibility policies are geared toward the experimental biomedical sciences. However, mathematical and computational biology has not been ignored by the funding agencies and scientific community. In 2003, the US National Institutes of Health and National Science Foundation formed the Interagency Modeling and Analysis Group. This group provides an open forum of communication between funding agencies and scientists to discuss the development of new modeling and anal- ysis methods in the biomedical sciences.1 One of the working groups of Interagency Modeling and Analysis Group, the Model and Data Sharing Working Group, has been developing modeling standards, software and repositories of models and experimental data to facilitate model reproducibility and model sharing.2 Members of the Model and Data Sharing Working Group started to work on machine-readable description languages, such as Systems Biology Markup Language (SBML) (Hucka et al. 2003) and CellML (Lloyd et al. 2004), to encode mathematical models and facilitate their sharing and exchange. Simultaneously, model repositories, such as the CellML model repository (Lloyd et al. 2008), BioModels Database (Li et al. 2004; Chelliah et al. 2015) and JWS online (Olivier et al. 2004), were established to store and distribute these models encoded with SBML and CellML. More recently, funding agencies have been funding the development of

software tools to build reproducible dynamic mod- els that are reusable, like Virtual Cell (Loew and Schaff 2001), CompuCell3D (Swate et al. 2012) and Tellurium (Medley et al. 2018). In addition, scientific policy forums are recommending good practices for publish- ing scientific computing research (Stodden et al. 2016). These include making the raw data analyzed computationally available in the paper (Peng 2011; Stodden et al. 2013), adopting good laboratory notebook practices (Schnell 2015; Wilson et al. 2017) and making computer code and scripts openly available (Yale RoundTable Participants 2010; Stodden et al. 2012). 3 Havethe“Reproducibility”PoliciesbeenEffectiveinMathematical andComputationalBiology? The recommendations and policies available in the literature have been partially effec- tive. Standardization of mathematical models and computer code, and code sharing have not been straightforward because they are highly variable in many disciplines and subdisciplines (Renear et al. 2010). Despite this, the scientific communication has been improved in the mathematical and computational sciences because it is becoming a more common practice to share models and computer code with other researchers to make findings “reproducible” after publication (Stodden et al. 2013). Unfortunately, the effectiveness of model and code sharing has limited success in making scientific findings reproducible. An empirical study for articles published in Science shows that 44% of the authors respond to requests to share data and computer code after publi- cation. From those, it was only possible to “reproduce” the computational results of 26% of the papers (Stodden et al. 2018). Simultaneously, there are also challenges with the curation of mathematical and computational models in databases. Model repositories like BioModels have nearly twice as many non-curated models as curated models (fully “reproducible” models).3 Although the non-curated models could be “reproducible,” the open science movement and rapid growth of the model repositories are exceeding the capacity of database curators to verify the reproducibility of models. There are still numerous models that are not reproducible in databases, because they are not translatable into SBML or CellML formats. Some models are not “reproducible,” because errors were introduced into the model during the publication process, such as authors mistyping parameter values or equations in the publication, or publishers inevitably committing typesetting errors during the article production (Lloyd et al. 2008). In other instances, models are not “reproducible,” because they were not properly annotated following protocols, such as minimum information requested in the annotation of biochemical models (Novère et al. 2005). Given the limited success of the recommended policies by funding agency, scientific groups and some publishers, is there a best-practice solution to the “reproducibility” crisis in the mathematical and computational sciences? Here I argue that most of the current discussions of the “reproducibility” crisis overlook the essential role that the editorial and peer review process has played in confirming “reproducibility” of experimental findings in scientific fields like organic syntheses for nearly a century. The current discussions also overlook that the current form of the scientific paper dating from the 1600s is outdated (Sommers 2018) and needs to change to keep up with current technologies available in the mathematical and computational sciences. However, before I proceed, it is important to settle what is meant by the conceptual framework of “reproducibility” in the research enterprise. 4 HowcanweDefinetheR-WordsinMathematical andComputationalBiology? “Reproducibility” is an unsettled concept in most of the papers discussing it. The terms repeatability, replicability and reproducibility are used interchangeably in everyday

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language (Goodman et al. 2016). As a result, these R-terms are unfortunately used in nonstandard conceptual frameworks across the sciences. The definitions of the R-words, repeatability, replicability and reproducibility, vary between computer sci- entist subgroups (Association for Computing Machinery 2016; Rougier et al. 2017). They are also different between social, behavioral and economic sciences (Bollen et al. 2015), computational neuroscience (Crook 2013; Plesser 2018) and biomedical sciences (Goodman et al. 2016). The good news is that definition of the three R-words is well established in the experimental quantitative sciences, such as engineering, physics and chemistry. The International Union of Pure and Applied Chemistry has clear definitions in the IUPAC Compendium of Chemical Terminology, informally known as the Gold Book (Inter- national Union of Pure and Applied Chemistry 1997). The International Organization for Standardization (ISO 1994) describes the conditions necessary for repeatability, replicability and reproducibility under its International Standard ISO 5725-1, which were reiterated by the metrology community in its formal definition guides (Joint Committee for Guides in Metrology 2006). Inspired by the metrology community, the Association for Computing Machinery (2016) proposes a terminology in line with the experimental sciences. I am going to take the liberty of paraphrasing these definitions for the mathematical and computational biology community: Repeatability (Same team, same methodological setup): For experimental laboratory research, repeatability occurs when the measure- ment can be obtained with stated precision by the same team using the same measurement procedure, the same measuring system, under the same operating conditions, in the same location on multiple trials. For mathematical and com- putational biology research, this means that a researcher can reliably repeat their own mathematical analysis and numerical computation. Replicability (Different team, same methodological setup): For experimental laboratory research, replicability occurs when the measure- ment can be obtained with stated precision by a different team using the same measurement procedure, the same measuring system, under the same operating conditions, in the same or a different location on multiple trials. For mathemat- ical and computational biology research, this means that an independent group can obtain the same mathematical and computational results if they follow the methodology described in a published research paper, or reuse the same scripts and computer code. Reproducibility (Different team, different methodological setup): For experimental laboratory research, reproducibility occurs when the mea- surement can be obtained with stated precision by a different team, a different measuring system, in a different location on multiple trials. For mathematical and computational biology research, this means that an independent group can obtain the same mathematical and computational results using a methodology which they develop independently. Based on these definitions, failure to reproduce is a broader concept, which requires integrating potential conflicting observations, results and ideas into a coherent the- ory (Redish et al. 2018). However, repeatability and replicability are clearly the two minimum gold standards of science. Repeatability is a necessary, but not sufficient condition, to determine whether a novel research finding is ready to be submitted for publication, while replicability is the minimum standard by which any published scientific paper should be judged. If we establish a culture of replication, the scien- tific community will clear erroneous results and create a scientific community with a disciplined approach toward scientific discoveries (Peng 2011). 5 HowtoCreateaCultureofReplicationintheMathematical andComputationalBiologyCommunity? The culture of replication comes from multiple directions, but it must start in the journals through peer review practice. Journals are starting to implement replication policies, though the fraction is small. An empirical analysis of journals considering mathematical and computational models shows that 22% of the journals had a com-puter code sharing policy, and 38% had a data sharing policy as of 2012 (Stodden et al. 2013). The challenge is that these data and code sharing policies are having a limited impact in creating a replicability culture. For example, Biostatistics implemented a “reproducible” research policy (Peng 2009), where papers in the journals are kite- marked R if both data and code are made available in Supplementary Materials, and the Biostatistics Associate Editor for Reproducibility can use the data and code to replicate the results in the paper. Unfortunately, the “reproducibility” check is voluntarily, and only 4% of the paper received an “R” within the first 2 years of “reproducibility” policy implementation (Peng 2011). Since 2014, Nature journals require authors to provide a “Code Availability” statement indicating how code or algorithms could be accessed. However, peer reviewing code can be cumbersome. Nature Methods, Nature Biotechnology and Nature Machine Intelligence are now running a trial in partnership with Code Ocean to enable authors to share computer code and facilitate its peer review, while the manuscripts are under consideration for publication. Unfortunately, the trial is optional (Pastrana and Swaminathan 2018). A similar voluntary replication review process is available in ACM Transactions on Mathematical Software (Heroux 2015). The FEBS Journal, IET Systems Biology, Microbiology and Metabolomics are collaborating with JWS Online to replicate models to be published in the journals, but the model replication is limited to ordinary differential equation kinetic models of biochemical pathways (Snoep 2005). An empirical survey of 1576 scientists suggests that 70% of scientists have tried and failed to replicate another scientist’s findings (Baker 2016). I believe that most replication problems are

In the experimental methodological sciences, the publication model is evolving through Peer Reviewed Scientific Video Journal.5 Chemists are also starting to rou- tinely record experiments with video cameras to make research more accessible and “reproducible” (Björnmalm et al. 2016). Can we redesign the journal article in the mathematical sciences? Yes, we can. We already have the right tools in our computers, but they are not currently used to describe procedures and algorithms and share results in research papers. They are used as pedagogical tools to teach mathematical and computational modeling in the classroom. MapleSoft™ Maple Worksheets, Wolfram Mathematica Notebooks and MathWorks MATLAB® live scripts are interactive documents that combine scripts from those programs with formatted text, equations and images to visually explore and analyze problems in the classroom. These tools can be used to write, execute and test code in an interactive environment to describe and explain scientific findings dynamically. A scientific paper submitted in the form of a “computational notebook” will be easy to replicate during the peer review processes, because a referee can execute the model, while they are reading the paper. This is something that we cannot achieve with the PDF file, because it provides a static picture of research findings by “modeling a piece of paper.” Unfortunately, the proprietary nature of Maple, Mathematica and MATLAB will make them hard to adopt broadly as a publication tool. It is time to adopt open-source web-based applications that allows us to create and share our research with live computer code, equations, text and visualizations. In the same way that TeX and LaTeX revolutionized typesetting and publishing for mathematical and computational scientists, the Jupyter Project,6 through its Jupyter Notebook and JupyterLab, can be the modern solution to typeset and publish scien- tific papers in mathematical and computational sciences. The Jupyter Project supports the live execution of over 100 programming languages, including computer algebra algorithms and software, which are regularly used in mathematical and computational biology. Currently, Jupyter Notebooks are used as electronic notebooks, educational modeling laboratories and supplemental material to scientific articles. It is time to extend the current uses of Jupyter Notebooks for academic publishing. Jupyter Note- books allow us to typeset our research papers, share openly our computer codes and present dynamically our research (Sommers 2018). This proposal is highly ambitious and may be utopic on this point. It requires chang- ing the nature of science communication, which has relied on publishing research using paper (or an electronic paper-like form) for over 400 years. Mathematical and compu- tational scientists and academic publishers will need to be retrained to communicate research findings using web-based applications. The investment in the technology seems to be minimal as it is already available and accessible to many. However, the modernization of the publication technology will make mathematical and computa- tional research more open, transparent and replicable by making the scientific paper coming alive through the “computational notebooks.” Acknowledgements I am very grateful for the helpful insights provided by Rick Danheiser (Editor-in-Chief of Organic Syntheses and Massachusetts Institute of Technology, USA), Edmund Crampin (University of Melbourne, Australia) and Wylie Stroberg (University of Michigan). This work was partially supported through the educational programs funded by NIGMS (T32 GM008322) and NIDDK (R25 DK088752).

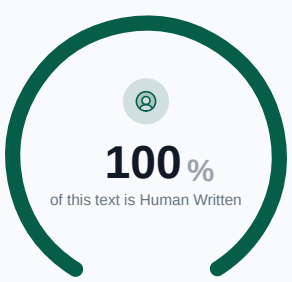
AI Detection Report for Have we come to the end of theoretical and mathema...

Sep 18, 2026 | 1,024 Words | Pangram 4.0

Summary

We believe that this entire text is human-written.

Authorship Breakdown



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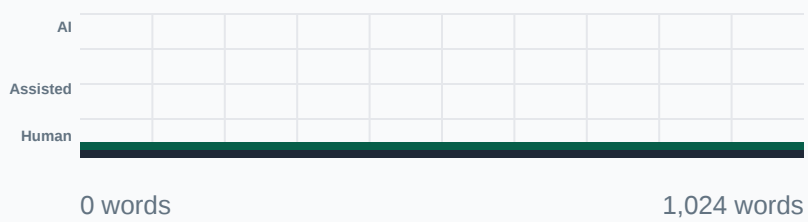
Authorship Progression



Analyzed Text

Words that are underlined indicate AI phrases, while the numbers represent how frequently they are likely to appear in AI writing. These elements are not used to determine the results but are displayed separately as patterns commonly found in AI-generated text.

Human Written | 1024 Words | High Confidence

Have we come to the end of theoretical and mathematical biology? We are living in the big data age. In our daily habits, we are increasingly relying on technology that uses algorithms to rapidly analyse data to improve our lives. These algorithms appear to be running our society (Sumpter, 2018). Futurists predict that we have reached a point in some key ar- eas of research where we are working with phenomena that re- quire levels of explanation that our human brains cannot handle. As a consequence, we need to move towards “Machine Science”. In this scientific enterprise, computers will become central to the ac- tual research work, and humans will become assistants rather than drivers of science. The machine will make predictions that no hu- man will be able to understand or articulate (Cowen, 2013). Puzzled by the predictive power of some algorithms, politicians, economists and science administrators are pressing and heavily in- vesting in data analytics. It is not surprising, as our societies are becoming more prosperous thanks to the technological advances and predictions made by machine “intelligence”. Data science is opening a window of opportunities for mathematical and com- puter scientists. In the life sciences, data comes in many forms (genome sequence, protein-protein interactions, medical histories) and is generated in massive amounts. Mathematicians are devel- oping statistical and computational tools in the form of algorithms to discover new patterns and structures in biological data sets. If data scientists are successful, there is a bonanza of knowledge in the biosciences. Does this mean that theoretical and mathematical biology are coming to an end? The

Pangram.

Human Written | 1024 Words | High Confidence

answer to this question is a resounding no. “Machine Sci- ence” is making very practical predictions or prediction-oriented decisions, and these will be geared for improving our lives in many areas. However, predictions are always a problem for scientists, particularly for mathematical and computational modelers. Predic- tion is what every mathematical and computational scientist strive to extract from their models, but the reality is that we are not very good at it. There is a good reason for the poor predictive value of models: the purpose of models – theoretical or mathematical – is to explain natural phenomena, not to predict them (Gunawardena, 2013). For this reason, the practice and understanding of science is not in for any major change. Our most important scientific results are understood from first principles by well-trained and intelligent scientists, like those who have been mentored by Professor Philip K Maini, FRS and are contributors to this special issue to celebrate his 60th birthday. Prof Maini has trained over 85 doctoral and postdoctoral stu- dents in theoretical and mathematical biology at the University of Oxford since 1990. His training philosophy uses critical rationalism (Popper, 1959), where he teaches young scientists how to face re- ality and how to understand it. He teaches how to conjecture an explanation about a biological phenomenon by using three critical steps of good applied mathematics research (Lin and Segel, 1988): 1 Formulating the biological problem in mathematical terms by using good biological intuition and insight. Prof Maini care- fully teaches his trainees how to exercise excellent judgement in the formation of the scientific problem by deriving a mini- mal model, without losing the essential biological mechanisms under investigation. This is an art form rather than a science. 2 Solving the mathematical model formulated by applying math- ematical analysis, and numerical techniques to understand the critical parameters and initial conditions driving and controlling the model dynamics. 3 Interpreting the mathematical model solution and analysis to reach the proper scientific conclusions for the biological prob- lem under investigation, and provide experiments to empiri- cally validate the model. The third and last step is critical for scientific progress. The- ory lays the roadmap from hypothesis to explanation. Models with testable assumptions set the agenda for what science was all about: you establish a theory, test it with a hypothesis, and if the hypothesis is valid, then you have explanation for a phenomenon. If model fail to explain our theories, we correct them by proposing new models. Because our models provide conjectural explanations, we cannot be certain that they are correct (Gunawardena, 2013). For this reason, there are always scientists testing theories against experimental observations. Using this approach, Prof Maini’s mathematical modelling of spatiotemporal processes in biology and medicine has led to sig- nificant scientific advances in mathematics, but also in biosciences. His work on biological pattern formation has led to detailed un- derstanding of the roles of noise, domain growth and gradients in pattern generation. He has generalised the concept of gradient in- formation and has proposed an experimentally consistent resolu- tion of the chemotactic wave paradox. He has developed multiscale models for wound healing and for vascular tumour growth. He has thereby elucidated the underlying mechanisms by which particu- lar growth factors reduce scar formation and has provided detailed insight into the design of combination cancer therapy. Prof Maini’s body of work is vast and includes more than 450 research publications in major scientific journals, with an h-index of 781 , which is unusually high for a theoretician, and he was re- cently adjudged a Highly Cited Researcher. His research has in- spired significant new mathematics, and new discoveries in biol- ogy. He has also received numerous honours and awards: a Royal Society Leverhulme Trust Senior Research Fellowship, Fellow of the Institute of Mathematics and its Applications, a Royal Society- Wolfson Merit Award, the Naylor Prize and Lectureship, Distin- guished Research Fellow at the African Institute for Mathemati- cal Sciences, Foreign

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Fellow of the Mexican Academy of Science, Fellow of the Society for Industrial and Applied Mathematics, Fel- low of the Society of Biology, Fellow of the Society of Biology, the Arthur T. Winfree Prize, and Fellow of the Royal Society. It is a great privilege to preface this special issue in honour of Prof Maini. He is a giant in science; like all great theoreticians he stands “pedes in terra ad sidera visus” (with the feet on the grounds and the eyes in the heavens). Those of us, who are not so tall, we honour him today!

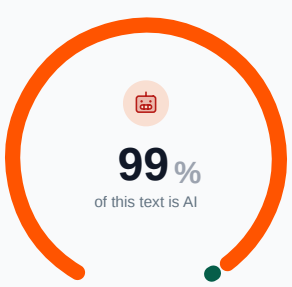
AI Detection Report for Who Wrote This? Turing, Total Variation, and the M...

Sep 18, 2026 | 6,234 Words | Pangram 4.0

Summary

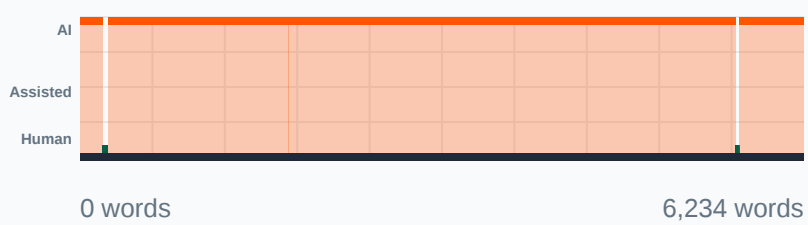
We believe this text is mainly AI, with some human-written content.

Authorship Breakdown



99 %	of the document	AI Generated
0 %	of the document	AI Assisted
1 %	of the document	Human Written

Authorship Progression



Analyzed Text

Words that are underlined indicate AI phrases, while the numbers represent how frequently they are likely to appear in AI writing. These elements are not used to determine the results but are displayed separately as patterns commonly found in AI-generated text.

AI | 177 Words | High Confidence

Who Wrote This? Turing, Total Variation, and the Mathematics of AI-Text Detection Abstract What can a finished text reveal about the process that produced it? Drawing on Turing’s imitation game and statistical decision theory, this article examines the limits of AI-text detection as an inference from a completed object to an unobserved history. For two known source distributions with equal prior probabilities, a standard identity gives the minimum average classification error as half their probability overlap. This overlap is one minus their total variation distance. Perfect detection therefore requires nonoverlapping distributions; useful discrimination does not. In practice, the problem is harder: human and machine writing form changing families of distributions, posterior probabilities depend on base rates, and “AI-written” becomes ambiguous when people and software contribute to the same text. Turing’s interrogator can ask another question; a detector restricted to finished prose cannot. Distinguishability, source attribution, authentication, and compliance are different inferential tasks. The paper’s own documented human–AI provenance shows what a production history can reveal that a binary label cannot.

Pangram.

Human Written | 43 Words | High Confidence

Keywords: AI-text detection, total variation, Bayesian inference, Turing test, authorship, provenance MSC Classification (2020): 62A01 (Primary) , 62B15 , 62C05 , 68T50 (Secondary) A suspiciously exact number Imagine the following scenario. An advanced undergraduate in a biology class submits an essay as a homework assignment.

AI | 1564 Words | High Confidence

The arguments are logical, the prose is fluent, the paragraphs orderly, perhaps a little too orderly. An instructor pastes the text into an artificial intelligence (AI) detector. A few seconds later, a number appears: 98% AI-generated. The number looks scientific. For a classroom assignment, though, that appearance can become an accusation remarkably quickly if the essay was supposed to be written without AI assistance. But what does the 98% actually measure? Is it meant to represent the probability that the essay was generated by AI? The probability that the student used AI at some point in producing it? The fraction of the text classified as AI-like? Or merely a model score transformed until it resembles a probability? More basically, what can the final arrangement of words tell us about the process that produced them? A 2023 experiment illustrates the difficulty. Weixin Liang and colleagues [2] tested seven widely used AI-text detectors on 91 English-language TOEFL essays written by non-native speakers. Every essay in the collection was human-written. Even so, the detectors produced an average false-positive rate of 61.3%. Eighteen essays were labeled AI-generated by every detector, and 89 were flagged by at least one. The researchers then asked ChatGPT to enrich the vocabulary of those same essays. After this intervention, the reported average false-positive rate fell from 61.3% to 11.6%. The irony is striking: introducing actual AI assistance made the essays appear more human to the detectors. These particular experimental results may not hold today. AI detection was still nascent in 2023, and both generative models and detectors have changed substantially since then. But the underlying inferential problem cannot be dismissed so easily. Given only a finished text of finite length, can we determine, with rigor, reproducibility, and robustness, whether it was written entirely by a human, generated by AI, or produced through some mixture of the two? A second problem lies behind the first. Classifying a text as more human-like or machine-like, attributing it to the process that produced it, and certifying that a particular person wrote it under particular conditions are related tasks, but they are not equivalent. They require different kinds of evidence, and confusing them can turn statistical resemblance into an accusation about a person. Alan Turing gives us a useful place to begin. Turing’s game, played backward In 1950, Turing opened his paper “Computing Machinery and Intelligence” [3] with the question “Can machines think?” He did not try to answer it directly. The meanings of machine and think, he argued, were too uncertain to support the inquiry in that form. Instead, he replaced the question with one stated in terms of observable behavior: the imitation game. Turing’s original game involved a man, a woman, and an interrogator communicating at a distance through written messages. He then asked what would happen if a machine took the place of one of the participants. Could the interrogator still make the correct identification? In the formulation that later became known as the Turing test, the essential idea is familiar: an interrogator exchanges messages with unseen respondents and tries to distinguish a machine from a human. The move is important. Turing set aside a disputed internal property—thinking— and replaced it with an experiment based on observable behavior. The interrogator need not decide what thinking is; she has to decide whether the evidence

available to her permits a reliable distinction. Bradford and Wollowski [4] later pushed this idea into explicitly mathematical territory by formalizing the Turing test as an interactive proof system and studying its limitations using ideas from probability and computational complexity. AI-text detection poses a related problem, but with a crucial change. There is no interlocutor. There is only a completed object: an essay, a report, a proof, this paper, perhaps a poem. From that fixed sequence of words, a detector tries to infer something about an unobserved source: human or machine? Shao, Uchendu, and Lee [5] use the phrase “reverse Turing test” for precisely the task of using a machine classifier to distinguish human-made from machine-made texts. But for our purposes there is a second reversal, and it matters mathematically. Turing’s interrogator participates in an interactive experiment. She can ask a question, observe the answer, choose another question in response, return to an earlier point, and probe whatever seems most informative. The evidence can be gathered adaptively. A detector examining a submitted essay cannot do this. The experiment, if we can call it one, is already over. The words have been chosen, their order is fixed, and no new observation can be requested from the process that produced them. The detector therefore faces a problem of reconstruction rather than interrogation. It observes an outcome and tries to infer a hidden history from the traces preserved in that outcome. This is an inverse problem: from a finite string of words, it attempts to reason backward toward the process that generated them. How much of that history can a finite string actually preserve? The overlap no detector can erase To set the stage, we boil the detection question down to its simplest form. The scenario will be unrealistic, but deliberately so: simplifying a problem is often the first step toward understanding what makes it difficult. For now, we ignore mixed human–AI authorship and suppose that every text comes from exactly one of two sources. Let X be the collection of all possible finite essays, and imagine two lotteries on that set. The human lottery assigns probability PH(x) to each possible text x; the AI lottery assigns probability PA(x). These are thoughtexperiment probabilities, not distributions that we could hope to estimate exactly in practice. We observe the essay, not the lottery that produced it, and must infer which source it came from. Now give the detector every possible advantage. Suppose that the two sources are equally likely in advance and that both distributions are known perfectly. After observing x, the optimal rule is immediate: choose human if PH(x) > PA(x), and AI if the inequality is reversed; ties may be broken arbitrarily. Even this ideal detector makes mistakes. At a given text x, the detector chooses the more likely source, so the error comes from the less likely one. With equal prior probabilities, the contribution of x to the average error is 1 2 min{PH(x), PA(x)}. Summing over all possible texts gives the smallest achievable error, 1 2 X x∈X min{PH(x), PA(x)}. The quantity inside the factor of one-half is the overlap between the two distributions. Total variation measures the complementary separation. Because min{a, b} = 1 2 (a + b − |a − b|) and each distribution sums to one, TV(PH, PA) = 1 2 X x∈X |PH(x) − PA(x)| = 1 − X x∈X min{PH(x), PA(x)}. Hence, with equal prior probabilities, the smallest average error of any detector is Rbest = 1 2 [1 − TV(PH, PA)] . (1) This identity is standard in statistical decision theory [6]. Here it gives us the central constraint: the overlap belongs to the statistical experiment, not to the ingenuity of the classifier. If total variation is zero, the two distributions are identical and no detector can do better than a coin toss. If it lies strictly between zero and one, classification may be useful, perhaps extremely useful, but some error remains unavoidable. Zero error requires TV(PH, PA) = 1. In the present discrete setting, this means that the two distributions have disjoint supports. In probabilistic terms, they are mutually singular. In plain language, perfect detection therefore requires separate worlds of writing: every text that can occur under one source must be impossible

AI | 1564 Words | High Confidence

under the other. If some text x has positive probability under both processes, then observing x cannot reveal its source with certainty. One might expect conventional phrases, standard transitions, or formulaic prose to contribute heavily to such overlap, but the mathematics itself does not tell us which texts occupy it. That is an empirical question. The identity says something more basic: wherever overlap exists, no cleverer classifier can recover information that the observation does not contain. We can visualize this idea by projecting the enormous discrete space X onto a one-dimensional evidence score. The natural ideal score is the log-likelihood ratio s(x) = log PA(x) PH(x) . Here we use the usual conventions that the score is +∞ when only the AI source assigns positive probability to x, and −∞ when only the human source does. Positive finite values favor the AI source; negative finite values favor the human source. Under our equal-prior assumption, the optimal decision boundary lies at s(x) = 0. Figure 1 shows the resulting overlap schematically. Figure 1 The overlap no detector can erase. The horizontal axis is the evidence score s(x),increasing from evidence favoring the human source to evidence favoring the AI source; the curves show its probability densities under the two sources in a Gaussian example. The shaded region is the overlap between these densities. Moving the decision threshold trades false positives against false negatives but cannot eliminate this overlap. With equal priors, the minimum average error is one-half of the overlap, as in Eq. (1). The exact log-likelihood ratio retains the information needed for the optimal binary decision; a cruder score may lose separation but cannot create it. Better algorithms still matter. More training data can bring an implemented detector closer to the optimal decision rule, and a better model may uncover information that a crude detector misses. But there is a ceiling. No algorithm can beat the error imposed by the statistical experiment itself.

AI | 1460 Words | High Confidence

Equation (1) does not say that detection must always fail. It describes the information available from a particular observation. Changing the observation therefore changes the experiment. A longer text, for example, may contain more evidence. If the longer observation includes everything contained in the shorter one, giving the detector the additional text cannot make the best possible classifier worse. The separation between the two sources, however, need not increase strictly, and Eq. (1) alone does not guarantee that the error will approach zero as more text is observed. That requires additional assumptions about how human and machine texts differ as more evidence is collected. Recent theory illustrates these two sides of the problem. Sadasivan and colleagues [7] connect optimal discrimination performance to total variation and show experimentally that paraphrasing can substantially reduce detectability. Chakraborty and colleagues [8] study the complementary question: when a distributional distinction persists, how much additional evidence—through multiple samples or longer sequences—is required to make reliable discrimination possible? There is no contradiction. One result emphasizes what happens when the two distributions are pushed closer together; the other studies what additional evidence can extract from a separation that remains. Detection therefore succeeds or fails relative to both the distributions being compared and the amount and structure of the evidence supplied to the detector. In practice, neither stays fixed for long. There is no canonical distribution of human writing The two-lottery picture is useful, but it hides much of the complexity of actual writing. There is no canonical, context-independent distribution PH of

AI | 1460 Words | High Confidence

human prose. A mathematician proving a lemma, a schoolchild writing under examination, a novelist revising the fifteenth version of a paragraph, and a scientist writing carefully in a second language are not plausibly samples from one stable statistical source. Add lawyers, journalists, doctors, businesspeople, theologians, and editors, and the simplification becomes harder to defend. Genre matters, as do subject, age, education, native language, editorial conventions, and individual writing habits. Nor is there a unique PA. Different AI models produce different distributions, and even the output of a particular model depends on its version, prompt, system instructions, sampling parameters, fine-tuning, retrieval context, translation, and subsequent revision. A more realistic formulation therefore replaces two fixed distributions with two families: PH $\in$ PH versus PA $\in$ PA. This changes the problem in an important way. It is no longer enough for one particular human distribution to be well separated from one particular AI distribution. A detector intended for general use must remain reliable across many different pairs drawn from these two families. This is where the Liang study becomes instructive. Liang and colleagues traced much of the disparity they observed to perplexity, a signal used directly or indirectly by several early AI-text detectors. Roughly speaking, perplexity measures how surprising a sequence of words appears to a particular language model. If the model assigns relatively high probability to the words that actually occur, the text has low perplexity; if the sequence repeatedly surprises the model, its perplexity is higher. If machine-generated prose tends to have lower perplexity than the human writing used for comparison, then low perplexity can become useful evidence for machine generation. But humans can also write predictable prose. Someone writing in a second language may rely on a narrower vocabulary or on familiar grammatical constructions. Technical disciplines may encourage standardized formulations. A careful writer may suppress precisely the lexical eccentricities that would make a language model more surprised. The statistical signal may therefore be real without its cause being unique. Liang and colleagues found that the TOEFL essays classified as AI-generated by all seven detectors had significantly lower perplexity. They then asked ChatGPT to enrich the vocabulary of the same essays. Perplexity increased, while the reported average false-positive rate fell sharply [2]. The intervention therefore increased actual AI involvement while moving the essays away from a feature on which the detectors appeared to rely. This does not mean that the detectors had no statistical basis. On the contrary, at least part of their behavior tracked a real statistical property of the text: predictability under a language model. The problem is that this property was not uniquely diagnostic of how the text had been produced. There is, however, an important counterpoint. Jiang and colleagues [9] assembled a large collection of Graduate Record Examination essays and developed detectors specifically for that setting using linguistic and perplexity-based features. They reported near-perfect discrimination between their human-written and ChatGPT-generated samples and found no evidence that their detectors disadvantaged non-native English writers. The two studies need not contradict one another. They describe different statistical experiments. Liang and colleagues evaluated widely available detectors on human essays drawn from particular existing collections. Jiang and colleagues constructed and evaluated detectors within a comparatively standardized assessment domain using data sampled for that purpose. The contrast illustrates a general problem of statistical generalization. A classifier can perform extremely well on the population and conditions for which it was developed yet deteriorate when the population, genre, model, prompt, or writing process changes. Validation results therefore belong not merely to an algorithm, but to an algorithm evaluated under a particular data-generating process. For a fixed pair PH and PA, the previous section asked how much the two distributions overlap. Once we admit families PH and PA, a harder question appears:

AI | 1460 Words | High Confidence

how close can some plausible human distribution come to some plausible AI distribution? Excellent separation for one pair tells us little about the pairs that were never tested. AI detection makes this problem especially difficult because the distributions themselves evolve. Models are updated or replaced. Prompting practices change. Human writers adapt to AI tools. Machine-generated passages are edited by people and may then be edited again by another model. What counted as the statistical distinction between “human” and “AI” in one setting may not be the same distinction a detector encounters later. The detector does not face two fixed targets. It faces two moving families.
What does 98% mean? Let us return to the AI-detector number on the instructor’s screen: 98% AI-generated. Most readers will naturally interpret this as a posterior probability, Pr(A | X = x) = 0.98 : given this particular essay, there is a 98% probability that it came from an AI source. Unfortunately, the percentage need not mean anything of the kind. It might be a transformed model score, a percentile relative to some reference collection, an estimated fraction of sentences judged AI-like, a similarity measure, or a quantity calibrated on a population quite different from the one now being tested. The percentage sign alone does not tell us which statistical object is being reported. Even if the human and machine likelihoods were known exactly, a posterior probability would still require one more ingredient: prior probabilities πA and πH for the two sources, assigned before the essay is examined. Bayes’ theorem gives Pr(A | x) = πAPA(x) πAPA(x) + πHPH(x) . (2) In the population-based example that follows, these prior probabilities encode the base rate: how common AI-generated essays are in the population under consideration before we inspect the particular essay. This matters because even a detector that distinguishes the two groups quite well can produce many false alarms if genuine AI-generated essays are rare. Before returning to a numerical score such as 98%, consider the simpler case in which an imaginary detector reports only a flag: positive or negative. Suppose that when an essay really is AI-generated, the detector flags it 95% of the time. This quantity, Pr(+ | A) = 0.95, is its sensitivity. Suppose also that when an essay really is human-written, the detector correctly leaves it unflagged 95% of the time. This quantity, Pr(− | H) = 0.95, is its specificity. Equivalently, its false-positive rate is 5%: Pr(+ | H) = 0.05. These numbers may sound excellent. But they do not yet answer the instructor’s question. They tell us how the detector behaves when the source is already known. The instructor faces the reverse problem: after seeing a positive result, how likely is it that the essay actually came from AI? Suppose the detector is used in a population where only 1% of essays are AI-generated. Imagine 10,000 essays from that population. About 100 would be AIgenerated. With 95% sensitivity, approximately 95 of those would be flagged. The remaining 9,900 essays would be human-written, and a false-positive rate of 5% would incorrectly flag about 495 of them. The detector would therefore produce approximately 95 + 495 = 590 positive results, of which only 95 would correspond to AI-generated essays. Thus Pr(A | +) ≈ 95 95 + 495 ≈ 0.16. Under these illustrative assumptions, the detector’s positive predictive value—the probability of AI generation after a positive result—would be only about 16%. Nothing about the detector has changed. Its sensitivity is still 95%, and its specificity is still 95%. What changed is the frequency of AI-generated essays in the population in which the detector is being used.

AI | 1574 Words | High Confidence

To see how strongly this matters, suppose instead that half of all essays are AIgenerated. Among 10,000 essays, there would then be 5,000 AI-generated and 5,000 human-written. The same detector would flag approximately 4,750 of the AI essays and falsely flag 250 of the human essays. Now Pr(A | +) = 4750 4750 + 250 = 0.95. The positive predictive value of the same detector has gone from about 16% to 95% simply because the population base rate has changed. This is the base-rate problem in its simplest form. Sensitivity tells us Pr(+ | A), the probability of a positive result assuming that the essay came from AI. What the instructor wants to know is Pr(A | +), the probability that the essay came from AI given that the detector returned a positive result. These conditional probabilities point in opposite directions. Bayes' theorem connects them, but it does not make them equal. Two decimal places do not make them the same quantity. This also exposes a practical difficulty with a number such as 98%. To interpret it as a posterior probability, we would need to know not only how the detector responds to human and AI text, but also what prevalence of AI-generated text was assumed or represented during its calibration. A detector calibrated in a collection containing equal numbers of human and AI texts need not produce calibrated posterior probabilities in a classroom where AI-generated submissions are much rarer—or much more common. Bayes' theorem also shows what certainty about a particular essay would demand. If both prior probabilities are positive, then Pr(A | x) = 1 requires PH(x) = 0 and PA(x) > 0. Within this simplified two-source model, the observed essay would have to be impossible under the modeled human distribution. It is not enough for the essay to be unusual for a human writer, unusually polished, low in perplexity, or even much more probable under the AI model. As long as PH(x) > 0, the posterior remains strictly below one. If both PH(x) and PA(x) are zero, the model has assigned zero probability to the observation and the posterior is undefined; that is a failure of the model, not certainty about the source. For ordinary prose, assigning probability zero to human production is an audacious claim. A large likelihood ratio can nevertheless constitute powerful evidence. It can move a reasonable prior probability far toward one source or the other. But evidence is not certainty, and a score displayed as a percentage does not acquire a probabilistic interpretation merely because it looks like one. Turing could ask another question The preceding sections have treated the essay as a fixed object. Once it has been submitted, the detector receives whatever information the text happens to contain and must work with that evidence alone. Socrates made the same complaint about written words: ask them a question and they say the same thing again [1]. Turing's imitation game suggests another possibility: change the experiment. Figure 2 contrasts passive inspection with an adaptive interrogation. Passive inspection completed essay x text-only classifier score or label the detector inherits a fixed experiment Interactive interrogation question q1 answer a1 next question q2(h1) answer a2 · · · later questions may depend on the history h1 = (q1, a1) Figure 2 Inspection and interrogation. In passive detection, a completed essay is passed to a classifier, which returns a label or score. In an interactive test, the interrogator chooses a question, observes an answer, and chooses the next question in light of the exchange so far. The detector inherits an experiment; the interrogator helps design one. In the imitation game, the interrogator is not restricted to inspecting a completed transcript. She can ask a question, observe the answer, and decide what to ask next. A surprising answer can be pursued. An inconsistency can be revisited. A line of questioning that proves uninformative can be abandoned. We can express this in the same probabilistic language used earlier. Let π denote a questioning strategy: a rule for choosing each new question from the exchange observed so far. Once the human and machine response mechanisms are fixed, a strategy π induces one distribution over complete transcripts when the respondent is human and another when the respondent is a machine: P π H and P π A. For any fixed strategy, the total-variation identity from Equation (1) still applies. With equal prior probabilities, the smallest possible classification error after that interrogation is Rbest(π) = 1 2 [1 − TV(P π H, P π A)] . But something has changed. The interrogator now has some control over the distributions themselves. Instead of accepting whatever evidence happens to be present in a finished essay, she can choose questions intended to make the two possible sources behave differently. In this abstraction, the best questioning strategy seeks sup π TV(P π H, P π A). Equivalently, the smallest achievable error becomes inf π Rbest(π) = 1 2 1 − sup π TV(P π H, P π A) . This is not Turing's notation. It is experimental design written in probabilistic form. Adaptivity can matter because the next observation need not be chosen in advance. A fixed questionnaire asks the same sequence regardless of the answers. An adaptive interrogator can make question k+1 depend on what happened in the first k exchanges. Among strategies with the same number of rounds and the same allowable questions, a nonadaptive strategy is available as a special case. Allowing adaptive questioning therefore cannot make the best possible experiment less informative; in favorable circumstances, it can make it substantially more so. What might this mean in the classroom? An instructor could ask why a particular example was chosen, request that an argument be restated in different terms, introduce an unexpected assumption, return to an earlier claim, ask where a quotation or factual assertion came from, or require the reasoning to survive a new example. An answer that raises a new question can itself determine what is asked next. A detector examining a completed essay cannot do this; its evidence was

AI | 702 Words | High Confidence

feature of that provenance. A document may, for example, have a compositional history such as human −→ AI −→ human −→ AI −→ final text. The final classification compresses this entire history into a single binary label— “human” or “AI.” Assigning the label does not resolve the ambiguity in the process; it merely hides that ambiguity inside the definition of the class. We can make the point slightly more formally. Let Z denote the complete, unobserved history by which a document was produced, and let X denote the finished text. A dataset labeled “AI” and “human” implicitly applies some rule Y = g(Z) that turns the complicated history Z into a binary label Y . A classifier then attempts to infer Y from X. Its accuracy can therefore be excellent even when the labeling rule g has little to do with the question its eventual user wants answered. Before asking for sensitivity, specificity, or accuracy, we should therefore ask a preliminary question: what exactly counted as “AI” in the training and validation data, and does that definition correspond to the decision now being made? Several distinct inferential tasks are easily conflated here. Turing’s question concerns distinguishability: can observable machine behavior be distinguished from human behavior? An AI-text detector is ordinarily used for attribution: given a completed text, which proposed source or production process better explains the observation? A university, publisher, court, or reader may instead require authentication: what evidence connects this particular work to this particular person? In many practical settings there is also a question of compliance: was the work produced under the conditions that were permitted? A student may unquestionably be the author of an essay and still have used prohibited assistance; conversely, a student may have used an allowed grammar tool without surrendering authorship of the work. These distinctions matter because a text’s source and production history are not directly observable in the finished text. We see the words, not the history that produced them. To move from “this passage has features associated with machine-generated text” to “this student used AI,” and then to “this student violated the rules,” is to make a succession of increasingly strong inferences: statistical resemblance −→ class-level source attribution −→ a claim about a particular person’s actions −→ a claim of noncompliance. The arrows are not logical implications. Each marks a separate inferential step requiring additional evidence or assumptions. Attribution is therefore an evidentiary commitment: a conclusion about an unobserved history, not a property read directly from prose. An AI detector may contribute evidence at the first one or two stages, depending on what it was trained and validated to distinguish. It cannot, from stylistic resemblance alone, establish a document’s complete history: human prose may resemble model output, and heavily AI-assisted prose may be revised until it resembles ordinary human writing. Watermarks and cryptographically signed provenance records illustrate two ways to change the experiment rather than escape Equation (1). A watermark modifies PA by embedding a detectable signal in machine-generated text; a signed provenance record augments the observation, so that the verifier receives evidence about the text’s production alongside the text itself [11, 12]. A valid signature does not by itself establish the truth or completeness of the recorded history. Neither method reconstructs a complete production history from unauthenticated prose alone. This suggests a different strategy when provenance genuinely matters. Rather than trying to reconstruct an entire writing process after the fact from stylistic traces, we can preserve evidence while the work is being produced. Draft histories, contemporaneous notes, source records, authenticated workspaces, supervised writing, and oral explanation are all imperfect, and some can be manipulated. But they observe aspects of the production process that disappear when the detector is handed only the final arrangement of words. Who wrote this? The paper you are reading makes the problem unusually literal. Its own provenance is mixed. I am a mathematical scientist whose work involves measurement in the chemical and life sciences. Questions about what an instrument, algorithm, or mathematical procedure actually measures—and under what assumptions its output can be interpreted—are therefore difficult for me to leave alone. After examining the outputs of AI-text detectors, I realized that it was far from clear what these systems were actually measuring. This paper began with that question.

Human Written | 43 Words | Medium Confidence

In September 2026, I asked OpenAI's GPT5.6 Pro whether an AI-written essay could ever be identified with certainty, and I suggested connecting the problem to Turing's imitation game and to the "reverse" Turing test posed by AI-text detection.

AI | 513 Words | High Confidence

GPT-5.6 Pro connected the question to binary hypothesis testing and statistical decision theory, proposed early structures and titles, identified candidate literature, and generated portions of early drafts. I chose the problem, journal, audience, and eventual direction of the argument. I decided which examples and results should remain central, including the decision to retain the Liang study while confronting it with important counterevidence. I checked the cited literature, rejected or corrected claims that I judged inaccurate, corrected mathematical and conceptual errors, and reorganized the argument. In revising the manuscript, I rewrote most sections and added substantial explanations. I occasionally asked GPT-5.6 Sol to provide language-editing assistance for sections I had rewritten. I created the figures and made the final decisions about the mathematics, interpretation, sources, organization, and wording. I take full responsibility for the resulting manuscript. Before submitting the manuscript for publication, I also asked GPT-5.6 Pro and Anthropic Claude Fable 5.1 to review it critically and identify issues that reviewers might raise. I evaluated the issues they identified and made corrections where I judged them warranted. Calling it "coauthored" would introduce a different confusion. Mathematical tools have long made substantive contributions without thereby becoming authors. Maple™ or another computer algebra system, for example, may carry out a complex and interactive symbolic calculation on which a perturbation analysis depends, while the mathematician chooses the problem, determines the calculation's relevance, interprets its output, and accepts responsibility for the resulting claim. The point is not that the software contributed nothing. It is that contribution and authorship are different roles. Generative AI can contribute more broadly—through language, structure, criticism, examples, or candidate ideas—but breadth of contribution does not by itself establish authorship. Scholarly authorship also carries accountability for claims, sources, errors, judgments, and the decision to publish; that accountability remains mine. A recent disciplinary statement articulates a closely related position. The Leiden Declaration on Artificial Intelligence and Mathematics calls for transparent disclosure of automated-tool use, assigns responsibility for correctness and citation to human authors, and does not treat automated systems as authors [13]. A provenance record therefore says something that a binary label cannot. The history of this manuscript is not human or AI. It is closer to human question −→ AI response −→ human judgment −→ AI criticism −→ human revision −→ · · · −→ final manuscript. That history is precisely the kind of object a text-only detector is being asked to reconstruct from the final prose. It may detect statistical traces associated with one stage of the process. It may even provide useful evidence about some possible histories. But the finished sequence of words does not contain a complete transcript of how the document was conceived, argued over, corrected, and made. The example also shows that mixed provenance need not imply mixed accountability: contributions can be distributed across people and tools, while responsibility for this manuscript remains mine. So who wrote this paper? The answer is available because its history has been recorded rather than inferred from its style. The title can therefore be answered, but not with one

AI | 513 Words | High Confidence

bit.

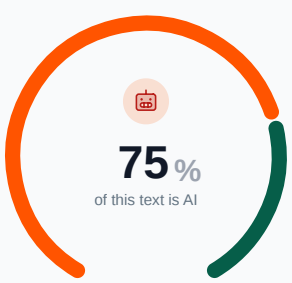
AI Detection Report for Spain’s Hit Film ‘Sundays’ Takes Religious Vocatio...

Sep 18, 2026 | 1,417 Words | Pangram 4.0

Summary

We believe that this text is a mix of AI and human-written content.

Authorship Breakdown



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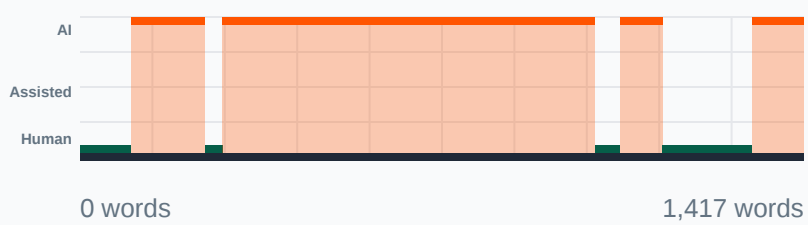
25 %	of the document	Human Written

Authorship Progression



Analyzed Text

Words that are underlined indicate AI phrases, while the numbers represent how frequently they are likely to appear in AI writing. These elements are not used to determine the results but are displayed separately as patterns commonly found in AI-generated text.

Human Written | 95 Words | High Confidence

Spain’s Hit Film ‘Sundays’ Takes Religious Vocation Mainstream In the award-winning Spanish film, an unbeliever’s camera provokes audiences to take seriously the possibility that God still calls. Warning: Minor spoilers ahead. That one of Spain’s most acclaimed recent films centers on a 17-year-old girl discerning cloistered religious life is remarkable. Alauda Ruiz de Azúa’s Sundays (Los Domingos in the original Spanish) swept the Goya Awards, Spain’s Oscars, taking “Best Film,” “Best Director” and “Best Original Screenplay,” after winning the top prize at the San Sebastián Film Festival.

AI | 146 Words | High Confidence

More than 650,000 Spaniards saw it in theaters before streaming, a notable feat for a religious-themed film in the largely secularized country. While Sundays’ success does not prove that Spain is returning to the Church, it does suggest something subtler. Modern audiences are still willing to be troubled by questions that secular culture often treats as settled — namely, those related to faith, family, obedience, freedom and the possibility that God still calls. Sundays is not a pious film. But neither is it an anti-clerical exposé. Its achievement

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AI | 146 Words | High Confidence

lies in refusing to lean towards one extreme or the other. When one considers that Ruiz de Azúa is an atheist, the film’s balance is even more impressive. As the director herself has said, her goal was neither to lecture nor to evangelize, but to present the phenomenon of religious vocation on its own terms.

Human Written | 34 Words | High Confidence

The Possibility of God The story centers on Ainara, played with luminous reserve by Blanca Soroa. A gifted teenager in the Basque country, she lives with her widowed father, Iñaki, and two younger sisters.

AI | 725 Words | High Confidence

Every week, the wider family gathers around her grandmother’s Sunday table. At the center of the family stands Aunt Maite, Iñaki's sister. The Church enters Ainara’s life chiefly through Father Txema, her spiritual director at school, and Mother Isabel, the prioress of the cloister she hopes to enter. When Ainara tells the family she wants to become a cloistered nun, Iñaki is bewildered but not hostile. In contrast, Maite is horrified. To her, Ainara’s vocational aspirations can only be the product of manipulation, immaturity, grief or escape. Maite’s response represents the perspective of many viewers who will search for the psychological key to explain the girl’s radical intention: the death of her mother, an absent father, a failed romance, or the influence of priests and nuns. The film gives us all these elements, and none should be dismissed. Ainara is wounded. She is young. She longs to be loved. She is not a plaster saint. But to reduce her vocation to her wounds is to miss the film’s openness to a more Catholic possibility. Faith rarely appears in a soul like lightning in a clear sky. Grace often works slowly, through practice: Sunday Mass, confession, prayer — the steady education of desire. While Sundays does not show us enough of Ainara’s sacramental history — one of the film’s limitations — it does give us traces. One scene is especially revealing. During a retreat, after staying up late talking with her friends, Ainara is faced with a choice the following morning. She could sleep in. Instead, she rises early, walks alone through the empty town in the first light of day, and enters the cloister church for morning prayer. She is the only layperson present with the nuns behind the grille of the enclosure — her first real sense of the hidden life drawing her. This is not decorative piety but evidence of a soul already under discipline — a faith cultivated through sacrifice. Before anyone applauds or condemns her, she is choosing to order her body and time toward God. Faith and Freedom The title of the film — Sundays — carries a double-edged meaning, according to Ruiz de Azúa. As the director has explained, Sunday is, for Catholics, the Lord’s Day, while for many families it is also the day of reunion, obligation and conflict. In the film, those two meanings collide: the family Sunday of meals, arguments and inherited wounds; and the ecclesial Sunday toward which Ainara’s life is being drawn. But the central conflict of Sundays is not simply between belief and unbelief. It is the tension between two accounts of freedom. For Ainara, freedom is receptive. It can answer a call because the One who calls is trustworthy. In Catholic tradition, a vow is not the negation of freedom but its consecration. One gives oneself not because life is empty but because love has become

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AI | 725 Words | High Confidence

sufficiently real to command everything. For Ainara's aunt Maite, freedom is possessive. It means keeping all options open and resisting any claim that limits self-determination. At first, her objections are understandable: Adults must protect minors from coercion and premature decisions. Authentic vocation requires discernment, freedom and the Church's careful confirmation. But Maite's concern hardens into control. She does not merely ask Ainara to wait; she mobilizes the family, presses friends and relatives into service, and even lies to the prioress in an effort to stop her niece from believing God is calling her. Ainara and Maite move in opposite directions. The girl whom others regard as captive becomes the character moving toward integration. The aunt who speaks most forcefully in the name of freedom becomes increasingly coercive. The ending makes this unmistakable. Maite does not simply fail to prevent Ainara's vocation. She expels her brother and his family from the grandmother's apartment. She removes Ainara and Iñaki from the will. Her marriage, corroded by her own coldness and self-absorption, strains toward breaking. She wins nothing and loses nearly everything. That is the film's most devastating irony. Maite believes the Church is taking Ainara away. Yet it is she who severs housing, inheritance, kinship and trust. The freedom she invoked against the convent becomes, in her hands, an instrument of her own dispossession. The Final Message Ruiz de Azúa's direction is exceptionally restrained.

Human Written | 50 Words | High Confidence

She does not caricature Maite as a secular monster — and, as remarkably, she does not caricature the Church. The nuns are serene and sincere; Father Txema listens patiently and never manipulates. Mother Isabel puts it in a line fit for any catechism: Faith is a gift, either received or not.

AI | 80 Words | High Confidence

Not every Catholic viewer will be reassured — some may fault the priest for accompanying without instructing, for instance — but crucially, the film never portrays a vocation as a product of manipulation. And in a culture that treats vocation as pathology, repression or propaganda, Sundays does something rarer. It does not merely permit the possibility that Ainara's call is real — it shows us where that call is sealed. After her grandmother's funeral, the decisive interior moment comes in prayer.

Human Written | 181 Words | High Confidence

The young woman prays St. Charles de Foucauld's "Prayer of Abandonment," repeating its words — "because you are my Father" — until she breaks into a cry of pain: "Please, say something. I can't go on." She collapses, and only afterward does the light come. Then she rises and embraces her own father. Her vocation crystallizes not under pressure but in surrender. The film then follows that "Yes" to its visible conclusion: Ainara prostrate on the chapel floor, in the habit,

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Human Written | 181 Words | High Confidence

passing into the enclosure as the withheld choral score finally swells. Sundays itself declines to say whether Ainara's call to the religious life is the result of grace or woundedness. But it refuses to explain the vocation away and rather lets her say "Yes" with her whole self. I will not pretend to have watched the film with the filmmaker's neutrality, however. That final ceremony moved me to tears — and to the eyes of faith, the scene reads as a soul arriving home. The success of Sundays does not mean that secular Spanish audiences have embraced Catholic doctrine.

AI | 106 Words | High Confidence

But it may mean they are no longer satisfied with a culture that explains faith only as a result of trauma or manipulation. The film asks them to sit, uncomfortably, with a different possibility. What looks like renunciation may be love. What looks like enclosure may be an opening. What looks like obedience may be the beginning of freedom. The scandal of Ainara's vocation is not that it has no explanation. It is that her reasons have been formed in a grammar many modern adults no longer speak. And perhaps the unexpected triumph of Sundays suggests that, even now, many are still willing to listen.

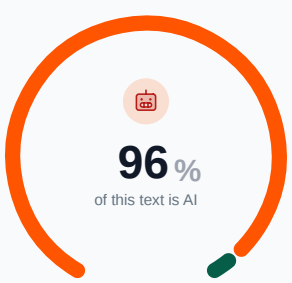
AI Detection Report for AI and the Worker: Rerum Novarum’s 135-Year-Old Warning

Sep 18, 2026 | 1,639 Words | Pangram 4.0

Summary

We believe this text is mainly AI, with some human-written content.

Authorship Breakdown



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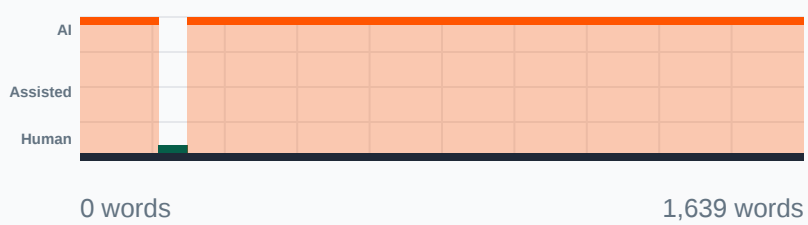
4 %	of the document	Human Written

Authorship Progression



Analyzed Text

Words that are underlined indicate AI phrases, while the numbers represent how frequently they are likely to appear in AI writing. These elements are not used to determine the results but are displayed separately as patterns commonly found in AI-generated text.

AI | 175 Words | High Confidence

AI and the Worker: Rerum Novarum’s 135-Year-Old Warning Pope Leo XIII's foundational encyclical prompts us to ask: Will AI amplify or replace human capacities? Every technological revolution arrives with its own apologetics. It promises efficiency, abundance, and relief from drudgery, and often delivers a measure of all three. What it does not deliver is the moral vocabulary required to govern it. Work changes faster than judgment. Power concentrates faster than law can restrain it. Households become vulnerable before anyone has counted the cost. This state of affairs describes the world into which Pope Leo XIII sent Rerum Novarum — “Of New Things” — on May 15, 1891. The encyclical described “the spirit of revolutionary change” that had passed from politics into economics. The “new things” were the industrial factory, the wage-labor contract, and a concentration of wealth that had disfigured the social fabric within a generation. In our own day, Rerum Novarum continues to provide a model for engaging the AI revolution, which risks outrunning the moral vocabulary needed to govern it.

Human Written | 65 Words | High Confidence

Given that Pope Leo XIV sees his ministry as a continuation of the tradition Leo XIII inaugurated 135 years ago this

Pangram.

Human Written | 65 Words | High Confidence

week, the anniversary of this foundational text of modern Catholic social teaching is an urgent invitation to reflect on AI in explicitly Leonine terms. Man Before the Machine Most readers likely remember Rerum Novarum as the encyclical that endorsed workers' associations and rejected socialism.

AI | 1399 Words | High Confidence

This is true. But a deeper, anthropological argument runs underneath those conclusions. Leo XIII's claim was that the human person, endowed with the capacity for reason, does not live by appetite alone. We plan, we provide, we assume responsibility across time. That is why private property matters: It is the stable material condition of foresight, household stewardship, and intergenerational provision. Work should give the worker access to that stability, not sever him from it. Property, on this account, is the durable form that labor's fruits take for the sake of the household. Family is where those fruits pass, in love, to those who did not earn them — and from the household's surplus, charity reaches the wider community. Strip these capacities away, or reduce them to transactional form, and you have not merely an economic problem but a wounded person. The 1891 crisis, as Leo diagnosed it, was that industrial modernity had replaced these capacities rather than amplified them. The worker had become, in his words, a "mere instrument for money-making," valued solely for his physical powers. The factory did not abolish the human; it displaced the human from the acts that make one human. Amplification or Replacement? Leo XIII was emphatically not a Luddite. He did not propose to dismantle industry. He simply insisted that any new technology be measured against the person it was meant to serve. Applied to AI, the question becomes: Does the tool amplify or replace human capacities? Does this new arrangement extend the worker's personal capacities, or absorb them? Does the tool advance her skill, or make it irrelevant? The distinction is mine, but it presses a recognizably Leonine concern. I have argued in these pages that this is precisely the question we must ask of AI in the classroom: Does the tool amplify the student's capacities — judgment, discernment, responsibility for truth — or replace them? An AI that drafts a student's essay while he remains incapable of defending his thesis has not educated him; it has produced on his behalf. The goal of education is not the production of essays but the formation of a person with a lively, responsible mind. The same test now applies beyond factories and schools: to offices, hospitals, courtrooms, firms, and increasingly the home itself. The technology is morally complex; it can amplify, and it can replace. The question is whether we will have the clarity and the courage to tell the difference. Application to AI Consider four areas where the test clarifies the stakes, with the family as the foundation beneath them all. First, judgment. Industrial machinery displaced the body's labor, but the worker still owned the judgment that ordered his work. AI threatens something the steam engine did not: displacement not only from an act, but from judgment about the act. Judgment is not merely the verdict that concludes thought. It is the operation by which a person frames a question, imagines alternatives, weighs what is at stake, and stands behind the answer. A workplace in which judgment is outsourced to a model leaves the professional, tradesman or technician with tasks to perform but not acts to own. Does the tool amplify the worker's skill or reduce her to just one cog in a mostly impersonal system? Second, the fruits of labor. Leo XIII argued that labor establishes a just claim to what it produces. Pius XI later clarified in Quadragesimo Anno that production involves the combined efforts of labor and capital, so the fruits

cannot be assigned to labor alone. But that still leaves a serious question when models are trained on the aggregated work of writers, coders, illustrators and analysts whose contributions may be unattributed and uncompensated. The magisterium has not given a final judgment; the tradition nonetheless tells us what must be weighed: Does the new tool amplify or reduce consent, attribution, compensation and the common good? Third, concentration. Leo XIII named, without apology, “a small number of very rich men” who had laid a yoke on the laboring masses. Our analogue is not hard to see: a handful of firms control the foundation models, computing power, and data on which contemporary AI depends. Markets and ownership are legitimate, but they must serve the common good, including the spiritual good of persons, not merely the material good. Does the tool amplify or reduce a just distribution of capital and power? Fourth, association. Leo XIII did not imagine the worker as a solitary contractor standing naked before power. He defended “workingmen’s associations”: communities of formation, mutual aid, and shared responsibility, not merely instruments of bargaining. That principle transfers directly to the AI economy. When hiring, evaluation, promotion and dismissal are mediated by opaque systems, workers need institutions that preserve contestability and human review: professional societies, faculty governance bodies, medical boards, and other mediating institutions through which judgment is formed and held accountable. Does the tool amplify or replace the particular human good of association? Association, for Leo XIII, is a natural right — and its purpose is not the pursuit of advantage against the employer, but the protection of the person against impersonal power of any kind. Preeminence of the Family Underlying the workplace is the family, which the Church consistently teaches is prior in nature and rights to the state; Leo XIII treated it as the deepest beneficiary of a just economy. A father worked so his children would not suffer want; a mother’s work anchored the household; inheritance carried labor’s fruits into the next generation. This was not sentimentality but social architecture — the foundation on which everything else rested. AI’s economic effects are now reaching that foundational level. The disruption is not confined within professions; the ability of people to make a livelihood and support their family, now and in future generations, is insecure. Leo XIII’s question about the just wage — whether work returns to the worker enough to sustain a household — is exactly the question an AI-era economy will have to answer. When stable careers fragment, when middle-class knowledge work becomes precarious, when young adults cannot project a future stable enough to marry and have children, the displacement is not merely individual. It is generational, and our evaluation of AI’s effects must take it into account. Continuing the Leonine Legacy The Catholic social tradition did not end with Rerum Novarum. St. John Paul II’s Laborem Exercens distinguished between the objective dimension of work — what is produced — and its subjective dimension: the person who works and is formed through working. The amplification-or-replacement question pays attention to this subjective meaning of work. Benedict XVI’s Caritas in Veritate likewise reminded us that technology is never merely technology: Every tool carries within it a conception of the human person and must be placed within a moral horizon, rather than permitted to become the horizon. Pope Leo XIV has already made the continuity explicit. In his May 10, 2025, address to the College of Cardinals, he explained that he chose the name Leo because the Church now faces another social and economic revolution, which poses “new challenges for the defense of human dignity, justice and labor.” In his June 2025 message on AI ethics, drawing on Antiqua et Nova, he insisted that access to data must not be confused with intelligence and that AI must be judged by integral human development. In a December 2025 address to labor consultants, he put the point in the simplest Leonine terms: Work must not revolve around capital, market laws or profit, but “the person, the family, and their well-being.” Leo XIII insisted that no purely

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AI | 1399 Words | High Confidence

procedural solution can reach the social question; only religion and morality can do that. The AI question cannot be addressed apart from religion and morality, either. Procedure alone, however efficient or well-informed, cannot produce what persons and institutions must become. The “new things” of any age must not determine the human ones. The person cannot be algorithmized away any more than she could be industrialized away. The Church’s call for discernment is constant, regardless of new technologies, because the person it defends does not change. What Leo XIV is saying fits within a framework that is 135 years old this week. Rerum Novarum remains the document most worth rereading as Leo XIV continues to develop the Church’s reflection on artificial intelligence.

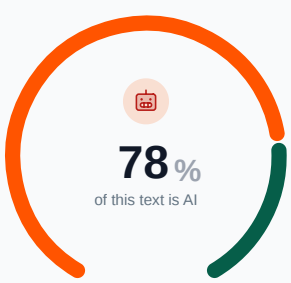
AI Detection Report for The Stairs of Reconciliation: A Mathematical Tourist in Graz

Sep 18, 2026 | 2,375 Words | Pangram 4.0

Summary

We believe that this text is a mix of AI and human-written content.

Authorship Breakdown



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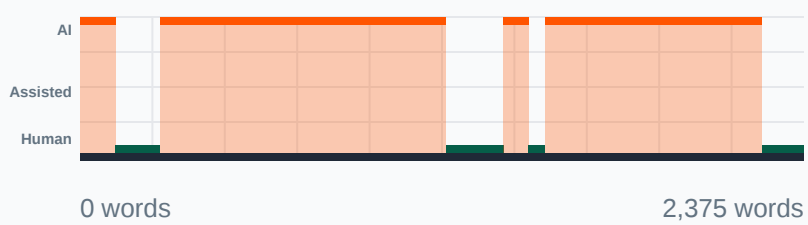

Analyzed Text

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AI | 108 Words | High Confidence

The Stairs of Reconciliation: A Mathematical Tourist in Graz Abstract Inside the Grazer Burg, two late-Gothic stone flights rise about distinct spindles, overlap, share several treads, and separate again. Their plan is governed not by a coaxial double helix but, to first approximation, by two intersecting circles. This elementary geometry yields a model of recurrent meeting and makes explicit the compatibility conditions that meeting requires. It also leads to a second object that geometers call a double spiral staircase— the helicoid—and to a useful distinction between resemblance and identity. The staircase becomes a meditation on how paths, models, and disciplines can meet without becoming the same.

Human Written | 136 Words | High Confidence

Keywords: mathematical tourism, spiral staircase, intersecting circles, helicoid, minimal surfaces, mathematical biology 1 An unplanned detour I had not come to Graz for a staircase. I had come for the 14th European Conference on Mathematical and Theoretical Biology, the joint meeting of the European Society for Mathematical and Theoretical Biology and the Society for Mathematical Biology, held at the University of Graz in July 2026 [1]. My

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Human Written | 136 Words | High Confidence

wife had spent part of the conference exploring the city. Knowing my susceptibility to geometric marvels, she led me, shortly Fig. 1 The Grazer Doppelwendeltreppe viewed from a reunion zone. Two flights rise about distinct spindles, share several treads in the middle, and divide again. Photograph © 2026 Mariana Schnell; used with permission before our departure, along Hofgasse, through the courtyard of the Grazer Burg, and into a narrow doorway.

AI | 950 Words | High Confidence

What waits inside is not a single spiral divided by a balustrade. It is a twin stair. Two flights rise about two different spindles, one turning clockwise and the other counter-clockwise. Between the spindles they approach, share several stone treads, and divide again. Higher up, the pattern recurs. The effect is Escherian not because the construction is impossible, but because it is exact: the eye keeps losing track of which stair is one and which is the other (Figure 1). The stair was completed around 1499–1500 during the building campaign of Emperor Maximilian I. Architectural descriptions call it a Zwillingswendeltreppe, a twin spiral staircase, and compare its horizontal plan with a figure eight [2]. Graz residents also call it the Vers¨ohnungsstiege, the stairs of reconciliation (locally also the Busserlstiege, the kissing staircase [3]): people who separate on the two flights meet again where the stone becomes common [4, 5]. Reconciliation is not the erasure of difference; it is the restoration of relation. The Latin reconciliare means to restore or bring together again. Its relation to concilium, an assembly or council, lends the metaphor of common counsel an apt resonance. 2 A model with two centres The first mathematical task is to identify the object being modelled. A tempting idealization places two oppositely handed helices on one cylinder about one axis. That construction is elegant, but it is not the Graz stair. The two flights have distinct centres. A model that suppresses tread width and replaces each flight by a smooth centreline should therefore begin with two circles. Let the spindle centres in plan be CL = (−a, 0), CR = (a, 0), let both idealized walking lines have radius R, and assume 0 < a < R. The two plan curves are (x + a)2 + y2 = R2, (x − a)2 + y2 = R2. (1) Subtracting the equations gives x = 0; substitution then gives the two intersection points P± = 0, ± p R2 − a2 . (2) Thus two meetings occur precisely when the circular plans overlap. The limiting cases are informative: if a = R the circles are tangent and there is one meeting; if a > R they are disjoint and there is none. Opposite circulation by itself does not force reconciliation. To add height, assume mirror symmetry, a common vertical rise rate p > 0, and a common vertical phase. One convenient parametrization is ΓL(t) = −a + Rcos t, Rsin t, pt , (3) ΓR(t) = a − Rcos t, Rsin t, pt . (4) The left flight turns counter-clockwise around CL. Relative to CR, the angular coordinate of the second is π−t, so the right flight turns clockwise as t increases. They have opposite handedness, but their reunion still depends on the additional assumptions of overlap, equal rise rate, and synchronized phase. Put α = arccos(a/R), b = p R2 − a2 = Rsin α. Equations (3) and (4) agree when cos t = a/R, hence ΓL(2πk ± α) = ΓR(2πk ± α) = 0, ±b, p(2πk ± α) , k ∈ Z. (5) Fig. 2 A symmetric two-centre plan model. The idealized flight centrelines are equal circles of radius R with centres CL and CR separated by 2a. For 0 < a < R they meet at P+ and P−. The shaded lens marks the overlap in which the real stair can form shared treads. This is a qualitative model, not a measured survey The vertical separations between consecutive meetings alternate between 2pα and 2p(π − α). They are equal only

Pangram.

AI | 950 Words | High Confidence

in the coaxial limiting case a = 0, for which α = π/2. The real staircase has finite-width, discrete stone treads, so the point intersections of the centreline model are thickened into short common zones. Without a measured plan and section, the equations should be read as a symmetric kinematic model, not as a dimensional reconstruction. A mathematical model earns its force by stating what has been idealized, which relations are structural, and which conclusions depend on chosen symmetries. Here the structural feature is not simply “two opposite spirals.” It is two overlapping circular systems whose vertical motions have been made compatible. 3 Geometry in the workshop The two-centre model is not merely imposed after the fact. Anatol Ginelli [2] compared the plan with a figure eight. A later architectural account says that the masons worked with compasses, brought two circles into overlap, and treated their common chord as an axis of symmetry [6]. The stone elements were cut with a constant rise ratio; in the overlap, the symmetry cut determined the joint angles and made the two flights assemblable as one construction. Much was resolved in a single cut: each tread was Fig. 3 Looking down into a reunion zone. The two radial tread systems are organised around distinct spindles and become common through a polygonal sequence of shared stones. Photograph © 2026 Santiago Schnell shaped in the workshop as one stone joining its bearing, its projecting winder, and its portion of the spindle, so that walking surface, support, and core rose together as one repeated element. A recent architectural-conservation study [5] likewise treats the stair as a twin, rather than merely doubled, system and analyses its historical, typological, and constructive logic. The photographs make the geometry legible. Looking down from above (Figure 3), one sees two radial fans organised around two spindles. Near the middle, neither fan can continue as though the other were absent. The treads become polygonal, align across the common zone, and then recover their separate curvatures. The abstract intersections P+ and P− are not points one could stand upon; masonry gives them area, thickness, and load-bearing form. This is enough for the present essay. A full structural account would require a surveyed geometry, material characterization, construction history, and an explicit load-path analysis.

Human Written | 218 Words | High Confidence

Fig. 4 A truncated helicoid. The thin straight rulings rotate as their height changes; the two boundary curves are shown solid and dashed. They are phase-shifted, same-winding curves about one axis. Away from a reunion zone, a smoothed single flight of the Graz stair is locally modelled by an annular strip of such a surface; the twin system is not one helicoid 4 Another double spiral staircase There is, however, a different mathematical object that geometers also call a “double spiral staircase”: the helicoid. For ȼ = 0, write H(u, v) = u cos v, u sin v, cv , u, v ∈ R. (6) For fixed v, the map u 7→ H(u, v) is a straight line. The helicoid is therefore a ruled surface: a horizontal line rotates at a constant rate while its height changes at a constant rate (Figure 4). The helicoid is a minimal surface. Indeed, Hu = (cos v, sin v, 0), Hv = (−u sin v, u cos v, c), so the first fundamental-form coefficients are E = 1, F = 0, and G = u2 + c2. A unit normal is proportional to (c sin v,−c cos v, u). The second fundamental-form coefficients are e = g = 0, f = −c √ u2 + c2 , so the mean curvature is H = eG − 2fF + gE 2(EG − F2) = 0.

Pangram.

AI | 85 Words | High Confidence

Thus the helicoid is stationary for the area functional. Its Gaussian curvature, by contrast, is K = eg − f2 EG − F2 = − c2 (u2 + c2)2 < 0, so the surface is saddle-shaped at every point: stationary for area, but nowhere flat. Only in the limit c → 0 does it degenerate to the plane. Vanishing mean curvature does not say that every compact piece is an area minimizer; stability and minimizing properties require additional hypotheses [7]; for an illustrated survey of minimal surface forms, see Almgren [8].

Human Written | 69 Words | High Confidence

Catalan [9] proved in 1842 that the plane and the helicoid are the only ruled minimal surfaces. Why is the helicoid called a double spiral staircase? Remove its axis and split it into the regions u > 0 and u < 0. On u = ρ > 0, the polar angle is θ = v and z = cθ. On u = −ρ < 0, the polar angle is θ = v + π, so z = c(θ − π).

AI | 693 Words | High Confidence

Both sheets satisfy dz/dθ = c. They spiral in the same angular–vertical sense and are separated by a phase of π; they do not form the oppositely handed, two-centre pair of the Graz stair. Colding and Minicozzi [10, 11] used precisely this double-staircase picture in their analysis of embedded minimal disks: informally, regions where curvature concentrates are modelled, after suitable rescaling, by two multi-valued sheets spiralling together around a common axis. Away from the reunion zones, however, a single smoothed flight has a natural helicoidal idealization. Replacing its discrete treads by continuously rotating radial segments gives an annular strip of a translated helicoid, rin ≤ u ≤ rout. The two flights require distinct axes and opposite signs of the pitch. This correspondence is local rather than global: in each reunion zone, the masonry departs from two independent helicoidal strips and resolves their overlap into common polygonal treads. The Graz stair is therefore neither one helicoid nor simply the union of two complete helicoids. The comparison is summarized in Table 1. The comparison with DNA is especially tempting to a mathematical biologist. Canonical B-DNA consists of two strands in a right-handed double helix about one axis [12]. Its strands are chemically antiparallel, but that is not the same as opposite geometric handedness. The distinction between the Graz stair, the helicoid, and DNA is a small example of a large scientific rule: analogy begins inquiry; it cannot replace identification. 5 Reconciliation by design Correcting the geometry changes the moral of the staircase, and improves it. Within the symmetric recurrent model above, reunion is secured by 0 < a < R, equal radii, equal rise rates, a synchronized phase, and a shared physical region in which an intersection can become a tread. Alter the separation, radii, rise rates, or phase, and the reunion may disappear. Reconciliation has to be made possible. I climbed the stair with more than a tourist’s interest in that proposition. I was trained first as a biologist and then took a doctorate in mathematics. I have spent my Table 1 Three constructions that are easily conflated. Their visual kinship is real, but their axes, handedness, and modes of connection differ working life since in the seam between them: biochemical phenomena and dynamical systems, measurements and models, experiments and the equations that would account for them. It has never felt like indecision. It has

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felt like standing on the landing. Mathematical biology is not biology decorated with equations, nor mathematics using organisms as convenient examples. Its two practices meet only when a common structure has been built: definitions refer to the same entities; units and scales are compatible; experiments render parameters identifiable; models preserve the biological meaning of their variables; and data are allowed to correct the equations just as equations discipline measurement. The living world and the language of numbers belong, in the end, in the same council. That, I think, is why the staircase would not let me go. Its flights remain distinct. Each keeps its own centre and its own direction. Yet the mason gave them overlapping ground, a matched ascent, and stones cut to bear both paths. The result is not an infinity trap but a repeated invitation: separate, meet, and separate again without pretending that difference has vanished. It is a good thing to be reminded of halfway up a tower, between sessions. 6 For the mathematical tourist The entrance to the Doppelwendeltreppe is at Hofgasse 15, inside the courtyard of the Grazer Burg. From Graz Cathedral, walk a short distance north along Hofgasse, enter the Burg courtyard, and look for the narrow doorway near the arch bearing the A.E.I.O.U. inscription. At the time of writing, admission is free; current opening hours should be checked on the official visitor page [4]. Acknowledgments I thank my wife, Mariana Schnell, for discovering the staircase, leading me to it, and sharing the photographic record of our visit. I also thank the organisers and participants of ECMTB 2026, and the leadership of the European Society for Mathematical and Theoretical Biology and the Society for Mathematical Biology, whose meeting supplied the occasion for this tourist visit.

Human Written | 116 Words | High Confidence

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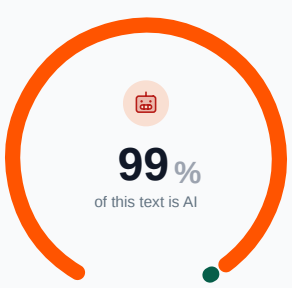
AI Detection Report for What Does Academic Freedom Look Like at a Catholic University?

Sep 18, 2026 | 4,579 Words | Pangram 4.0

Summary

We believe this text is mainly AI, with some human-written content.

Authorship Breakdown



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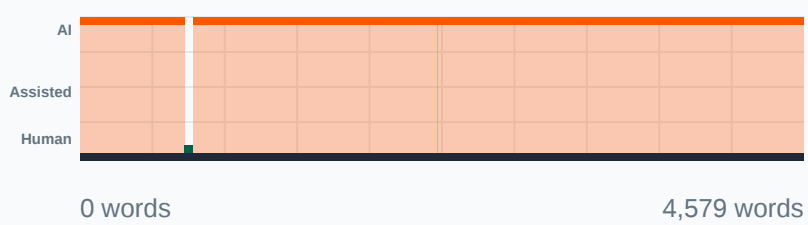
Authorship Progression



Analyzed Text

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AI | 645 Words | High Confidence

What Does Academic Freedom Look Like at a Catholic University? When a university advertises Catholic identity, it is making a promise to students and families: that faith and reason will be engaged seriously, that moral questions will be treated as real, that the human person’s complexity will not be assumed away. The controversy over the University of Notre Dame’s appointment of Susan Ostermann to direct the Liu Institute for Asia and Asian Studies has followed a familiar script: administrators emphasize scholarly credentials, the neutrality of an “administrative” role, and the norms of academic pluralism, while critics, the most prominent of whom are Catholic bishops, insist that senior leadership appointments are intrinsically expressive of institutional mission and therefore morally consequential. The dispute is often oversimplified as academic freedom versus Catholic identity. But the deeper problem is conceptual: both sides are liable—albeit in different ways—to treat “academic freedom” as a kind of indifference, a neutral zone in which commitments may be professed but cannot be allowed to govern. That conception cannot sustain any university, much less a Catholic one. What is needed is an older and more demanding account: freedom as a discipline ordered toward truth. Few phrases can reduce university professors to silence, but “academic freedom” is one of them. In the American context, it was codified by the American Association of University Professors (AAUP) in 1940, in a professional creed meant to protect the “free search for truth” from trustees, politicians, and other meddling powers. A generation later, Catholic leaders borrowed the language of autonomy to

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secure Catholic universities a place at the modern table in the 1967 Land O'Lakes Statement, insisting they needed genuine academic freedom even in the face of authority "external" to the academy. Then in 1990, Ex Corde Ecclesiae attempted to do what slogans cannot: hold together institutional autonomy and ecclesial identity, defining academic freedom within "the confines of truth and the common good." These three texts point to a single, unresolved question: is freedom a shield a university can wield against authoritative claims, or is it a condition of university culture that makes truth accessible at all? The conflict is thus framed as a contest between inquiry and authority, as though Catholic universities must choose one or the other. That framing is too thin to describe what is happening, and too weak to solve it. Every university already lives by a creed, whether it admits it or not, and those creeds shape what can be taught, funded, hired, and honored. The Catholic question is therefore not whether academic freedom will exist, but what kind of freedom will rule: freedom as indifference to truth, or freedom as pursuit of truth? A Catholic university can defend genuine academic freedom only by insisting that freedom is necessarily ordered toward truth and sustained by a shared form of life—not by pretending that its mission is an optional ornament. Even when reduced to a slogan, the AAUP's 1940 Statement ties academic freedom to the common good and to the search for truth, and it assumes institutions may articulate distinctive aims, provided they are disclosed candidly. Faculty members receive wide latitude in research and teaching, but within recognizable professional boundaries: one teaches one's subject, pursues truth by appropriate methods, respects students and colleagues as fellow rational agents. Even extramural speech is described as free yet morally freighted, because professors speak with a credibility that can easily become a weapon. The statement contains a line that many universities now live by in practice while pretending they do not: "Limitations of academic freedom because of religious or other aims of the institution should be clearly stated in writing at the time of the appointment." This sentence is controversial precisely because it is honest. All institutions have aims, and people deserve to know the terms of the community they are joining.

Human Written | 54 Words | High Confidence

Furthermore, it becomes impossible for an institution to achieve its aims when the mission is not known by the people who constitute it and carry out its work. But rather than increasing clarity about an institution's aims, the loudest proponents of "academic freedom" often seek to blot out any distinctive features or identities.

AI | 1544 Words | High Confidence

In this view, academic freedom is a generic expressive right—a solvent that dissolves curriculum into preference, hiring into faction, and administration into risk management. A committee proposes a coherent core; another insists that any shared requirement is coercion. But the university is not a collection of private platforms loosely sharing a payroll system. It is a common intellectual enterprise. A chemist is not oppressed by the constraints of evidence; a historian is not censored by the discipline's

insistence on sources; a mathematician is not coerced by the demand that proofs actually prove. These constraints are not external shackles. They are internal conditions of intellectual honesty. Once that is granted, the Catholic controversy looks less quixotic. Catholic universities are not introducing constraints into a previously constraint-free paradise. They are naming, in a particularly explicit way, commitments about reality they believe to be true: about the human person, about moral order, about the intelligibility of the world, about the possibility that revelation is not an enemy of reason, but its fulfillment. All universities ought to do the same, and the quality of a university depends at least in part on the truth of its foundational premises. In that light, the Land O'Lakes Statement becomes more than a historical talking point. It was an attempt to speak two languages at once. On one hand, it wanted Catholic universities to be "true universities" characterized by academic excellence, real research, and credibility in the wider world. On the other, it wanted Catholicism to be "perceptibly present and effectively operative." The problem was not the desire for excellence, and not even the desire for autonomy understood as freedom from improper interference. The problem was the definition of "authority" as external to the academic community. Once the Church is cast as an outside force, a Catholic university can easily begin to imagine itself as a secular institution that happens to have a religious sponsor. It is easy to see where such thinking leads. If the Church is "external," then Catholic identity becomes a brand rather than a source. The mission becomes a marketing line rather than a constitutive end. The bishop becomes a regulator to be managed rather than a shepherd with a stake in the university's project of forming souls. And once identity is reduced to branding, conflict is naturally treated as a public relations problem. Decisions are made to minimize reputational risk rather than to maximize truthfulness. In that environment, "academic freedom" is invoked less as a protection for inquiry than as a veto on the institution's own self-definition. "Academic freedom" becomes a bludgeon to crack on the head of any institution that dares stand out from its peers by claiming a distinctive identity. Ex Corde Ecclesiae, read against this backdrop, is best understood as an attempt to restore the grammar that Land O'Lakes strained to keep: autonomy is real, and Catholic identity is real, and neither survives if the other is reduced to theater. Ex Corde insists that a Catholic university needs institutional autonomy to do what universities do. It also insists that academic freedom is genuine and protected. But it adds the phrase that modern ears so often hear as an insult: academic freedom is exercised within the confines of truth and the common good. That is not a pious appendix. It is the hinge of the whole argument. The phrase forces a question the modern academy prefers to avoid. What is truth, and what is the good of a community that exists to seek it? If truth is merely what a guild happens to endorse this year, then freedom becomes a contest for power and prestige, and the winners can call that contest "open inquiry." But truth is not a prize. If truth is real, then the intellect is not a willful artist painting reality into existence, but a receptive power meant to be conformed to what really is. The common good of an intellectual community, then, is not simply the absence of conflict. It is the health of an intellectual ecology in which evidence can matter, arguments can persuade, and students can be initiated into disciplines bigger than any professor's ego. Freedom belongs to the university's ecology the way oxygen belongs to the body: not as a slogan, but a condition of life. Here the Catholic tradition offers an uncomfortable clarity. Freedom means very little when it has no object. Freedom reaches its maturity when it can choose what is truly good without being dragged there by force. That is not sentimental moralism; it is an anthropology—rooted in the Thomistic insight that the human intellect naturally yearns for truth and is capable of recognizing it when it is uncovered. A will that cannot move toward anything in particular

is not liberated; it is paralyzed. An intellect that cannot affirm anything as true is not brave; it is trapped in endless suspicion. The biblical claim that the truth will set you free therefore has an intellectual meaning as well as a moral one. Falsehood is a kind of captivity. The closer you come to truth, the freer you are. Neutrality or indifference toward truth, then, is not liberation but indeed its opposite. Once we see freedom this way, the Catholic argument about academic freedom stops sounding like a power struggle between religious and institutional leaders. It becomes an extension of what every discipline already knows: that constraints internal to truth are not enemies of inquiry, but its enabling conditions. The student who resents grammar will never write freely. The musician who despises scales will never improvise. The scientist who treats method as oppression will eventually treat results as propaganda. A university that teaches students to equate freedom with perpetual dissent is not forming free minds; it is forming minds incapable of assent. And a culture incapable of assent is a culture ripe for manipulation, because when nothing can be affirmed as true, only power can decide. This is the situation of most modern universities, which have long been confused about their purpose. The modern university often speaks as though neutrality is or ought to be the default. Yet such neutrality is always a lie. It carries assumptions about what counts as knowledge, what counts as a reason, which questions are “serious” and which are merely “private.” Those assumptions inevitably harden into taboos. They do not feel like coercion to those who share them, because they are breathed like air. But they shape hiring, promotion, and curriculum as surely as any religious mission statement. The difference is that a Catholic university, when it is honest, states its assumptions in public and invites people to enter freely. That honesty is not a threat to inquiry. It is a precondition of intellectual trust. The Catholic claim, properly stated, is that theology belongs in the university because reality is larger than what the natural sciences alone can measure. A Catholic university does not seek to replace chemistry with sermons. It exists to place chemistry, and everything else, inside a horizon in which questions of meaning, ends, and moral limits can be asked without embarrassment. If you forbid those questions in advance, you are not protecting freedom. You are imposing a metaphysics, presupposing many premises, while pretending you have none. Of course, a Catholic brand identity can be abused as an administrative weapon, deployed selectively to punish disfavored faculty, settle personal scores, or quiet inconvenient research. That danger is real. The remedy is not to empty the mission of its content, to make the Catholic identity thin and toothless, but rather to bind it to clear safeguards: transparency at hiring, disciplinary autonomy in evaluation, and persuasion rather than coercion in the university’s public witness. The first courtesy a Catholic university owes a scholar is to tell the truth about itself. If an institution claims a Catholic identity, it should say so plainly, early, and in writing—not as a wink and not as a trap. Candidates should know what the university is trying to be and what it expects of faculty as members of that community. A university that hires under ambiguity and then polices (sporadically, under pressure, as in Notre Dame’s case) is not defending mission. It is manufacturing scandal. But a university that invites people into a known way of life is honoring both freedom and truth. Equally essential is honest method. In each discipline, scholars should be judged by the canons of that discipline, by peers competent to evaluate the work, with due process and stable standards. That process protects inquiry from ideological meddling, whether the ideology comes from political fashion or from bureaucratic panic. At the same time, mission sets the horizon within which disciplines serve the university’s common good. It can ask, without violating the method, whether certain research and teaching are ordered toward human flourishing or toward its negation. The deepest mark of a Catholic institution is confidence that truth can

AI | 1544 Words | High Confidence

withstand examination. A Catholic university should not try to produce faith by force, because forced assent is not assent. It should embody its mission in practices that make genuine assent possible: serious liturgy, intellectual hospitality, public arguments that can be answered, and a willingness to engage objections without moralizing. Coercion is what institutions rely on when they no longer believe their own claims can persuade.

AI | 1284 Words | High Confidence

These safeguards help clarify a distinction that campus disputes often blur: the difference between inquiry and disagreement on one hand, and mission subversion on the other. Inquiry is the disciplined pursuit of understanding, open to evidence and argument. When inquiry leads to different conclusions, disagreement arises, but this can be honest and fruitful, especially when animated by a real desire to understand rather than to win. Mission subversion is different in kind: the deliberate use of institutional authority—curriculum committees, hiring pipelines, student formation structures—to turn the university against the very identity it advertises. A Catholic university can and should tolerate the first two. It cannot survive the third. These principles are clear enough in the abstract. The test is whether they can bear the weight of actual cases. Five objections are commonly raised against this account of academic freedom, and each deserves a careful answer. The first objection concerns the scholar who publishes work that contradicts the university's stated mission. Does academic freedom protect a political scientist at a Catholic university who publishes a peer-reviewed article supporting abortion? Or a moral theologian who argues in a scholarly journal that the Church is mistaken on a grave moral question? Here Catholic tradition itself distinguishes between what is definitively taught, what is authoritatively taught yet admits development, and what belongs to prudential application; justice requires that institutional expectations track that hierarchy rather than turning every contested question into a litmus test. Still, the governing answer depends on what happened at the front door. If the university stated its religious identity clearly at the time of appointment—as both the AAUP and Ex Corde require—then the scholar accepted those terms when she joined. A peer-reviewed article is not protected speech that the university must endure simply because it is scholarly in form. The form of the speech—whether it appears in a refereed journal or in an op-ed—may affect the proportionality of the university's response, but it does not determine whether the professor has a claim to academic freedom at that institution. The bounds within which the professor agreed to work upon joining a Catholic intellectual community answered that question before the article was written. There is, of course, a difference between scholarly and public speech that bears on the character of the university's response. A closely argued journal article deserves a closely argued reply; an op-ed campaign that leverages the university's prestige in a political fight implicates the institution's public witness in a way that scholarship alone does not. A Catholic university may rightly choose to respond to scholarly error with scholarly engagement—not as a concession that the error must be accommodated, but because that is how a university ordered to the logos conducts itself, and because confidence in truth prefers argument to administrative force. A university cannot govern interior assent; it can govern public acts that trade on its name, and it may decline to endorse agitation or dissent against moral truths essential to its own identity. The second objection concerns the difference between pedagogical engagement and institutional honor. A Catholic university can—and often

should—expose students to the strongest versions of arguments that challenge Catholic teaching. Inviting a prominent critic to address a class or debate on campus serves a legitimate educational purpose: it sharpens the student's capacity for honest engagement rather than sheltered ignorance. But there is a world of difference between inviting someone to make an argument and according that person institutional honors—an honorary degree, a named lecture, a commencement address. The first is a pedagogical act that can be framed explicitly as examination. The second is an act of institutional witness: it communicates whom the university honors, which lives are worthy of imitation, what moral vision it is willing to endorse. Honors are themselves a form of pedagogy: a university educates not only by what it permits to be argued, but by what it publicly praises as worthy of emulation. Academic freedom protects inquiry. It does not require institutional self-contradiction. The third objection is the most practically pressing, and it concerns a question the second does not reach. Honorary degrees and commencement addresses involve outsiders—people the university chooses to celebrate. But what about the university's own faculty? When a professor who has long enjoyed the protections of academic freedom is promoted into a leadership role, does that promotion remain a protected exercise of scholarly freedom, or does it become something else entirely? Even granting everything to the faculty member as a scholar, promotion to institutional leadership is a categorically different act. The distinction between the public use of reason and the use of reason in an office captures the point: the same person may have wide liberty as a scholar and real constraints as an officeholder. Leadership roles are not merely administrative. They are expressive. The more an office is outward-facing, formative, and holds sway over hiring, curriculum, and institutional partnerships, the more it functions as the university's public speech—and the less plausible it is to call it morally neutral. Prudence may counsel patience with a faculty member's strident public advocacy on matters directly contrary to the Church's teaching, especially in an institution that has long lived with internal pluralism. Reasonable people may disagree on that question. But it is another thing entirely to advance such a person into roles that, by their nature, speak on behalf of the university. Academic freedom may protect a professor from being fired for making arguments. It does not entitle anyone to be promoted into positions of institutional trust. This is why the Ostermann controversy is not a mere clash of preferences. The claim that the appointment is "administrative" and therefore neutral is a category mistake. Senior leadership appointments are never merely administrative. They shape the intellectual culture of a unit, influence hiring, set research priorities, and represent the institution to external partners. The person who directs an institute is not a clerk processing paperwork. She is the face and the mind of an institutional commitment. To pretend otherwise is to adopt the very posture of ambiguity that makes Catholic universities unintelligible to everyone—including themselves. This principle holds regardless of the university's past failures of candor. But the question remains: how did the controversy arise in the first place? The answer returns to the front door. If Notre Dame had done what both the AAUP and Ex Corde require—stated its horizon of religious truth claims plainly at the point of hiring, including the mission-significance of leadership offices—the question of whether this appointment violates academic freedom would never have arisen. The argument over whether a role is "administrative" is, at its core, an argument over what the institution thinks it itself is for. A university that has told the truth about itself does not need to debate that question, because the answer was given at the outset. When a university has not been transparent, justice requires that it acknowledge the failure honestly, afford due process to individuals hired without clear terms, and move forward with candor. But justice does not require, or indeed permit, indefinite deferral. This is not an argument for a

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cloister. A Catholic university benefits from the presence of non-Catholic scholars and students, and it should welcome them with real respect. Catholicism does not fear contact with other traditions, because it claims that truth is one and can be found wherever reality is honored. But welcome is not the same as surrender. A community can be hospitable without being incoherent. A Catholic university should ask of non-Catholic members what any moral community asks: that they respect the community's ends and not treat its identity as a target. In return, it owes them honesty, professional dignity, and a culture in which arguments can be made without caricature.

AI | 982 Words | High Confidence

A fourth objection extends the logic from persons to institutional infrastructure. When Notre Dame debated whether to filter pornographic content from its campus network, the objection was framed in the language of academic freedom: scholars must have unrestricted access to all materials, because the university cannot presume to judge what is relevant to research. But freedom ordered to truth is not indifference to content. A university's network, like its appointments, its curriculum, and its honors, is part of the moral ecology it offers to students and scholars. A Catholic university that has stated its commitment to human flourishing—as both Ex Corde and the transparency principle require—has already committed to an institutional environment that serves the pursuit of truth rather than one indifferent to what flows through it. The rare researcher who genuinely needs access to such materials for legitimate scholarly purposes can be accommodated through specific protocols, just as a chemistry department does not leave dangerous reagents on open shelves in the name of scientific freedom. The existence of a locked cabinet does not violate the chemist's freedom. It orders access to a legitimate purpose. A university that cannot say "this does not belong in our common space" has lost the capacity to say anything about what it is—and everyone knows that the vast majority of unfiltered use has nothing to do with research at all. The academic freedom claim, in this case, is not a defense of inquiry. It is a refusal to be a community for the formation of healthy young people. The student is the often-forgotten party in these debates, and that forgetfulness is itself a sign of institutional drift. Students do not come to a university merely to collect information. They come to be formed in habits of mind and heart that will govern their lives. When a university advertises Catholic identity, it is making a promise to students and families: that faith and reason will be engaged seriously, that moral questions will be treated as real, that the human person's complexity will not be assumed away. If the reality on campus is a quiet contempt for those promises, students learn a lesson more powerful than any syllabus. They learn that institutions do not mean what they say, and that ideals are mere marketing. That lesson is not liberation. It is a training in cynicism. An incoherent or opaque university ends up producing cynics rather than practitioners of free inquiry and respectful disagreement. A fifth objection runs deeper than any particular case. It holds that ecclesial authority has no place in the governance of a university—that the bishop, whatever his pastoral office, is unqualified to evaluate scholarly claims and his involvement necessarily compromises academic integrity. This objection has real force. A bishop who intervenes clumsily in matters of disciplinary method or scholarly evaluation inflicts real damage—not only to the university but to the Church's credibility as a friend of reason. But the objection mistakes the nature of

AI | 982 Words | High Confidence

the bishop’s role. The bishop belongs in the conversation not as a regulator of scholarship, but because the university acknowledges that its Catholic identity is not self-generated. It is received from a living community of faith, and it is answerable to that community in matters that touch the faith’s public witness. The bishop, in turn, should recognize that universities are not parish bulletin boards. They require his prudence and respect for disciplinary integrity. But they also require his presence. The university’s intellectual culture is forming the minds and souls of his flock, and that pastoral stake is not external to the university’s mission: it is part of it. When these relationships are healthy, academic freedom becomes easier to defend, not harder. Faculty members know what they have joined. Students know what they are being offered. Administrators do not need to improvise under pressure. The disagreements that remain will still be painful, because they are disputes about truth and loyalty and the formation of souls. But they will be honest fights, not theatrical ones. What, then, do the AAUP’s 1940 Statement, Land O’Lakes, and Ex Corde Ecclesiae look like when read together without an ideological lens? The first reminds us that academic freedom is a professional good ordered to truth and bounded by responsibilities. The second reminds us that Catholic universities need real autonomy to do real scholarship, and that Catholicism must be operative rather than ornamental. The third reminds us that autonomy without truth becomes self-devouring, because a university cannot survive as a university if it forgets or denies its own purpose. The task now is not to choose one text or another as a banner. It is to recover the unity they all struggled to articulate: freedom exists for truth, and universities exist to make that freedom livable. In the end, academic freedom cannot be reduced to a slogan or a rulebook, because it is a condition of corporate intellectual life. It can only exist in an institution brave enough to be what it claims to be, and humble enough to admit that truth is not its own invention. The most liberating thing a Catholic university can say is not “anything goes,” but “come and see.” It will have to say, without apology, that some truths are not negotiable because reality is not manmade. And it will have to say, with equal clarity, that no one is forced to submit, because coerced submission is not true membership at all. No university will do so perfectly. But the most important thing is not that it has arrived—it is that it has told the truth about what it is for, and has the courage to make an honest invitation: a life of the mind lived by whole persons oriented toward truth. It should be able to say, without theatrics and without coercion, “come and see a community in which reason is not embarrassed by faith and faith is not afraid of reason.”

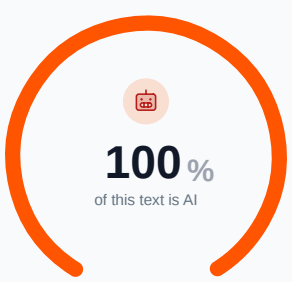
AI Detection Report for Repairing the Ruins: Why AI Can’t Replace Education

Sep 18, 2026 | 1,369 Words | Pangram 4.0

Summary

We believe that this entire text is AI.

Authorship Breakdown



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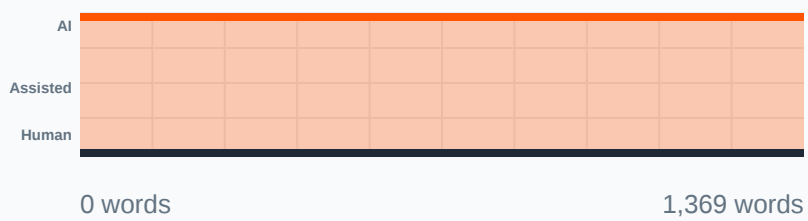
Authorship Progression



Analyzed Text

Words that are underlined indicate AI phrases, while the numbers represent how frequently they are likely to appear in AI writing. These elements are not used to determine the results but are displayed separately as patterns commonly found in AI-generated text.

AI | 1369 Words | High Confidence

Repairing the Ruins: Why AI Can’t Replace Education COMMENTARY: In an era when AI can write anything, authentic education must go beyond the mere production of words. “The end then of Learning,” wrote John Milton in 1644, “is to repair the ruines of our first Parents.” The image is hard to improve: education as repair, as recovery, as the restoration of capacities diminished by sin and neglect. Four centuries later, in the age of generative artificial intelligence (AI), that image has become urgent again — because we are now surrounded by a technology that offers to perform, on demand, much of what we had long assumed education required us to do ourselves. I came across Milton’s passage by chance while browsing a collection of the English writer’s works and opening it to his 1644 tract Of Education. Milton was not writing about algorithms. Yet he saw with unusual clarity the educational error that AI now magnifies: the confusion of language with learning. Language, he wrote, is “but the instrument conveying to us things useful to be known.” He warned against mistaking command of words for possession of the solid things those words are meant to disclose. He joined language to substance, sequence to maturation, and study to direct contact with reality — principles that four centuries have not made less urgent. No technology in recent memory has so enlarged the instrument. Large language models such as ChatGPT can summarize books, draft essays, organize research notes, translate passages, generate code, and imitate the prose that schools and universities have long taken as evidence of education. Used with discipline, they can be genuinely useful. A professor may use them

to prepare discussion questions. A researcher may use them to survey literature more quickly. An administrator may use them to accelerate routine writing. It would be foolish to deny their utility. But utility is not the same as education, and AI magnifies an older weakness. It tempts us to mistake verbal fluency for understanding itself. A student can submit polished prose without having really grappled with the question. A researcher can produce a competent summary without having seen the problem clearly. A professional can sound informed without having formed a judgment. The danger is not only dishonesty — it is substitution. For Catholic education, that substitution matters because learning is not the production of acceptable performances but the formation of a person capable of truth, judgment and responsibility. Milton saw a version of this in his own day. He criticized the practice of demanding “Themes, Verses and Orations” from young students before their minds had been formed by “long reading and observing.” He objected to asking for finished performances before the underlying powers had matured. Generative AI industrializes exactly that pedagogical mistake. It supplies finished language before the student has undergone the reading, questioning, hesitation and revision that make language meaningful. What Milton regarded as a mistake of sequence, AI turns into a system. This matters because education is not built from answers alone. Every answer worth teaching was once a response to a question someone genuinely asked. Students do not assimilate knowledge merely by receiving conclusions — they must be brought into the question. That is why the principal agent of education is the student. No one can learn in another’s place. A tool may assist instruction; it cannot do the learning for the student. The teacher’s role accordingly becomes more important in the age of AI, not less. A real teacher is not merely a distributor of content. A real teacher is an experienced guide in inquiry: someone who knows what the student has not yet seen, what distinctions must be made, what confusion needs exposing, and what question should come next. The best classroom is not a transfer of information from one container to another. It is a living act of thought. That is why seminar, disputation, laboratory, tutorial and serious conversation retain their force even when information itself becomes cheap. We tend to celebrate knowledge: facts accumulated, results confirmed, information stored. But as the biologist Stuart Firestein has argued, discovery begins not only with what we know but with a disciplined sense of what we do not yet understand. That frontier is where large language models reach their limit. They can reorganize the archive with astonishing fluency, but they cannot inhabit uncertainty, pose a genuinely new question, or take responsibility for truth. This clarifies why certain acts cannot be delegated to machines without ceasing to occur at all. Attending carefully to a text, weighing conflicting evidence, judging whether a conclusion is warranted, taking responsibility for what one claims — these are not ancillary tasks. They are the work by which a mind is formed. No machine can perform them in our place — not because machines lack processing power, but because these acts have no effect unless a person performs them. Their purpose is not to produce an output. It is to form the one who does them. Education worthy of the name has always understood this. Its end is not the delivery of content, however accurate. It is the formation of persons capable of judgment, attention and intellectual honesty. That formation requires a genuine encounter with difficulty — the friction of a hard text, the resistance of a problem that does not yield quickly, the discomfort of revising what one believed. It requires embodiment as much as intellect: reading slowly, speaking in one’s own voice, accepting the cost of standing behind one’s words. A person does not become capable of truth by managing information alone. Wisdom is formed in contact with reality, not in its simulation. The deepest challenge of AI in education is therefore not academic integrity, though that problem is real. It is whether we will allow our schools and universities to define learning as the production

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of acceptable outputs. If that is our standard, outsourcing will always look like efficiency. But if education is the formation of judgment, substitution becomes self-defeating. What should institutions do? The answer is neither panic nor blanket prohibition. It is pedagogical redesign. More writing done in class. More oral defense of arguments. More seminars organized around live questions rather than passive downloads of information. More laboratory and studio work in which students must explain not only what a result shows but what it does not. When students use AI, one reasonable requirement is transparency: disclose what was asked, what the system produced, what was kept, what was rejected, and why. The point is not surveillance. It is intellectual ownership — the habit of standing behind one's own thinking. Institutions should also reinvest in the teacher-scholar whose presence, judgment and intellectual seriousness cannot be automated. The same commitment belongs at home. A dinner table free of devices, conversation across generations, reading aloud together, and the habit of asking children not only what they think but why — these are small schools of freedom. They teach that education is not the production of impressive sentences. It is the formation of honest minds. The moment we are living through is, in this light, less a crisis than a clarification. AI has not created new educational problems; it has made old ones impossible to ignore. The habit of rewarding performance over understanding, fluency over depth, and polish over genuine engagement was already present in our institutions before the first language model was trained. AI simply industrializes and accelerates those habits until their emptiness becomes undeniable. That may be its most unexpected gift. If this disruption forces us to recover what education was always for — the formation of minds capable of real questions, careful judgment, and responsibility for truth — then the age of AI may prove, paradoxically, to be an age of educational renewal. Milton's deeper claim presses further. The end of learning is not merely competence or civic virtue, but to "know God aright, to love Him, to imitate Him, to be like Him." Education, in that view, participates in the restoration of what sin has obscured. No machine will ever repair those ruins. That restoration is finally God's work before it is ours; yet, aided by grace, we must still undertake the human labor of attention, judgment and love.

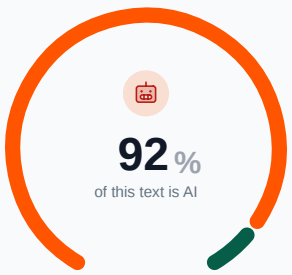
AI Detection Report for From Signals to Measurands: A Measurement-Science Roadmap for Reproducible Analytical Biochemistry

Sep 18, 2026 | 5,426 Words | Pangram 4.0

Summary

We believe this text is mainly AI, with some human-written content.

Authorship Breakdown



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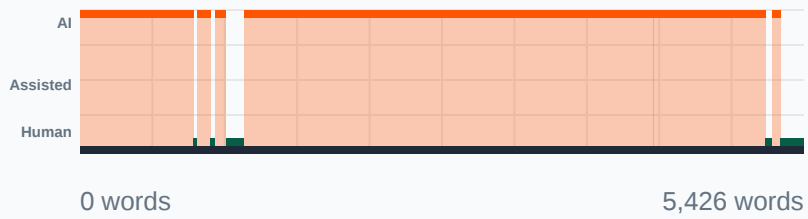

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From Signals to Measurands: A Measurement-Science Roadmap for Reproducible Analytical Biochemistry Abstract Analytical biochemistry often reports kinetic or binding constants as though they were observed di- rectly. Each result is instead inferred from an instrumental signal. Calibration establishes the scale, biochemical and observation models connect the signal to a target, and statistical analysis produces the estimate and its uncertainty. This Perspective treats reproducibility as the recovery of a speci ed mea- surand, with an uncertainty statement, through an auditable measurement chain. A Michaelis Menten substrate-depletion example provides the organizing case. Two progress-curve experiments generated with the same parameters and noise model both t well, yet only the design that samples substrate concentrations around the Michaelis constant yields a bounded interval for KM. In that design, uncer- tainty in active-site concentration dominates the uncertainty of kcat even though the curve t is precise. Ligand receptor binding shows parallel e ects of depletion, signal modeling, and parameter confounding. The framework connects established metrological and chemical-measurement concepts with enzymology reporting standards, machine-readable data formats, and modern identi ability analysis. It distinguishes repeatability, transfer to another laboratory, and agreement across independent measurement routes (or techniques), and explains what interlaboratory studies can reveal. The recommendations are prioritized as minimum practice, stronger support for parameter estimation, and reference-grade validation. The same logic applies whenever a biochemical quantity is

inferred from a measured signal. Keywords measurement science; measurand; enzyme kinetics; ligand binding; measurement uncertainty; identi ability; reproducibility Reproducibility begins with a measurement question A familiar problem in analytical biochemistry appears simple. A laboratory attempts to recover a published Michaelis constant, KM, for a well-studied enzyme. The protocol is followed carefully, the time courses are clean, and repeated runs give a stable estimate. Yet that estimate di ers from the published value by a factor of two. Before asking which laboratory is wrong, one must ask whether the two numbers refer to the same biochemical quantity and whether either experiment constrained it. An absorbance or binding trace does not arrive labeled KM, kcat, or KD. The reported quantity emerges only after the signal has been calibrated, related to a biochemical model, analyzed statistically, and assigned an uncertainty. The numerical result is therefore an inference from a measured signal to a speci ed measurand the quantity intended to be measured under stated conditions. What the instrument records and what the constant denotes are distinct objects: the trace is data, whereas the constant is a phenomenon inferred from it.1 5 This Perspective is addressed primarily to experimental analytical biochemists who infer quantitative results from instrumental signals. It should also be useful to measurement scientists and quantitative analysts concerned with comparison across experiments and laboratories. No prior training in metrology or identi ability analysis is assumed. Three problems are often grouped under the word reproducibility. An experiment can fail in execution because it was not performed as described. A report can fail in description because material information or tacit procedural knowledge is missing. A measurement can also fail in inference: the work was competently performed, yet the design or model did not support the claimed quantity. Reporting studies document the rst two problems, whereas identi ability studies show why the third can persist even when a tted curve looks satisfactory.6 10 These three failures call for di erent evidence, and the word reproducibility obscures the di erence. This Perspective therefore separates three checks that probe progressively more of the measurement: repeatability, transfer replication, and independent-method reproducibility. They are de ned in the section From repeatability to interlaboratory evidence and summarized in Table 3. The central claim is that reproducibility concerns the compatible recovery of a speci ed measurand, with uncertainty, after the experimental and inferential conditions have been made explicit. The contribution is integrative. It joins metrological de nitions to biochemical model validity, parameter identi ability, uncertainty evaluation, and reusable computational records.11 13 A Michaelis Menten substrate-depletion case study To make the problem concrete, consider the single-enzyme, single-substrate Michaelis Menten reaction mechanism with irreversible product formation, E + S k1 ⇌ k−1 ES kcat −−→ E + P. (1) For this reaction scheme, KS = k−1 k1 , K = kcat k1 , KM = k−1 + kcat k1 = KS + K. (2) Here KS is the dissociation constant of the enzyme substrate complex, K is the Van Slyke Cullen constant, and KM is the Michaelis constant. The Michaelis constant is not generally an equilibrium dissociation constant. It approaches KS only in the rapid-equilibrium, or slow-catalysis, limit kcat ≪ k−1.14 16 Under the usual quasi-steady-state reduction, with negligible substrate loss during the initial transient, substrate depletion is described by d[S] dt = − V [S] KM + [S] , V = kcat[E]0, (3) where [E]0 is the initial concentration of catalytically active enzyme sites.

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The corresponding progress curve is [S](t) = KMW0 [[S]0 KM exp ([S]0 − V t KM)] , (4) with W0 denoting the principal real branch of the Lambert W function.

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This is the Schnell Mendoza equation.17 20 In the worked example, substrate depletion is followed spectrophotometrically through A = εℓ[S]. Both experiments use KM = 50 µM, V = 0.20 µMs−1, the same absorption coe cient and path length, and the same additive absorbance-noise model. The initial substrate concentration is treated as a separately calibrated input obtained from an independent initial absorbance measurement on the same εℓ scale; it is not estimated from the rst noisy observation in the progress curve. Repeatability uncertainty in that separate initial measurement and uncertainty in the 1 cm path length are neglected in this illustrative in silico example.

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Design I begins at [S]0 = 10 µM (0.2KM), so the measured progress curve remains entirely below the Michaelis constant. Design II begins at [S]0 = 200 µM (4KM) and follows substrate depletion through concentrations on both sides of KM.

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Because the two designs deplete substrate on di erent timescales, Design I is sampled at 50 points over 1000 s and Design II at 60 points over 1800 s, each window spanning a comparable extent of depletion. Figure 1A shows the measured substrate concentrations and the tted progress curves. Three Design I concentration estimates are nonpositive because the additive absorbance noise exceeds the residual signal near depletion. They remain in the t and are shown as downward triangles at a declared plotting oor.

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Both ts have reduced χ2 values close to one. The di erence appears when KM is challenged directly. For each trial value of KM, V is re-estimated and the best conditional t is compared with the overall best t. The loss of t is summarized by the pro le deviance Dp(KM) = −2{ℓp(KM) − ℓmax}, (5) where ℓp(KM) is the maximized log-likelihood at xed KM. Under the usual likelihood-ratio regularity conditions, Dp = 3.84 is the nominal 95% threshold for one pro led parameter. Design II crosses that threshold on both sides of its optimum and gives a

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nite interval. Design I has no nite upper bound (Figure 1B). This conclusion is not inferred solely from the nite pro ling grid: in the limiting model [S](t) = [S]0 exp[−(V/KM)t] as KM → ∞, re-estimation of V/KM gives Dp(∞) = 1.68, below the nominal threshold.8,9 The reason can be seen directly from the rate law.

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When [S] ≪ KM throughout the observation window, d[S] dt ≈ − V KM [S]. (6) The substrate-depletion progress curve is then essentially exponential and determines the combination V/KM. At high substrate, the rate is close to V and carries little information about KM. Separate estimation requires observations near [S] ∼ KM, where the two parameters a ect the curve di erently. Figure 1C shows substratedepletion progress curves that begin in these di erent regimes, and Figure 1D shows the corresponding local sensitivities.16,21 Simulation-and-recovery con rms the pro le diagnosis. Across 400 synthetic data sets per design, the central 95% of recovered KM values extends from about 15 µM to the 10 mM search limit in Design I, whereas Design II recovers 48.6 51.3 µM. The point estimate for Design II is 49.5 µM, with a nominal 95% pro le interval of 48.4 50.5 µM. The failure of Design I is a property of the substrate regime rather than of sampling e ort. Given Design II's schedule, or four times the observations over the same window, or six times the observations over ve times the window, the pro le region for KM under Design I still spans between two and three orders of magnitude and remains open at the 10 mM limit of the pro led range in most replicates; the Supporting Information reports that comparison. The point estimates themselves illustrate the same di culty. Because V and KM have di erent units and poorly matched numerical scales in the chosen parameterization, the t is performed in log V and logKM from several starting points. The reported reference is the lowest residual sum of squares found by that bounded multistart procedure. For Design II this choice is immaterial. For Design I it is not: a t in the natural parameters stops about 0.05% above the best- t numerical minimum, but at a value of ˆKM some 13% away, while V/KM shifts by under 2%. When a point estimate is that sensitive to optimizer tolerance and the identi ed combination is not, the design, rather than the software, is what needs attention. A bounded kinetic parameter still requires a complete uncertainty evaluation. In Design II, the curve- t relative standard uncertainty of V is 0.4%. Converting V to kcat = V/[E]0 introduces the independently measured active-site concentration ([E]0 = 4.0 nM, established by titration of a nominal total of 5.0 nM), whose relative standard uncertainty is 8%, as well as a 2% absorbance-scale contribution. The combined standard uncertainty of kcat is therefore 8.3%. The absorption coe cient a ects KM and kcat but cancels from kcat/KM. The full likelihood, recovery study, and uncertainty budget the itemized list of the individual contributions to the uncertainty of a result, each with its magnitude and how it was evaluated are reported in the Supporting Information. A concise measurand declaration for Design II is set out in Box 2, in the section on recommendations; the complete computational and uncertainty record is in the Supporting Information. Figure 1: Substrate-depletion progress curves under di erent Michaelis Menten experimental designs. A Designs I and II use the same biochemical parameters and absorbance-noise model, and both tted curves describe the measured signal well. Three nonpositive Design I concentration estimates are retained in the t and shown by downward triangles at the plotting oor because the ordinate is logarithmic. B The pro le deviance Dp(KM) gives a bounded nominal 95% interval only for Design II; for Design I, the limiting

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value Dp(∞) = 1.68 remains below the 3.84 threshold, so no nite upper bound exists, although both designs constrain the combination V/KM. C Dimensionless progress curves beginning below, at, and above the Michaelis constant, the rst and last corresponding to Designs I and II, show which substrate regimes are traversed. D Local log sensitivities explain why low substrate chie y determines V/KM, high substrate chie y determines V , and concentrations near KM help separate the parameters. Table 1 sets the three contributions against the three reported quantities. The same tted curve underlies all three results, yet the dominant source of uncertainty di ers in each: calibration for KM, and activesite concentration for both kcat and kcat/KM. Because the progress-curve observations and the separately calibrated initial substrate concentration share one absorbance scale, the absorption coe cient rescales both together and cancels from the speci city constant. That removes one calibration contribution; it does not by itself make kcat/KM transferable, since active-site concentration, model validity, temperature, pH, and material state all remain. Table 1: Relative standard uncertainty budget for Design II. Type A components are standard uncertainties obtained from the tted covariance; the remaining components are evaluated from calibration and material characterization. uc is the combined standard uncertainty. The pro le regions reported earlier are interval diagnostics of identi ability and are not combined here. This case establishes two requirements that recur throughout the paper. The data must place useful bounds on the intended parameter, and the nal uncertainty must include important inputs outside the curve t. From signal to measurand The Michaelis Menten example can be generalized by distinguishing the intended quantity from the signal that is observed. A model connects them, and an analysis procedure produces the reported result. Box 1 de nes the terms used for that separation. The de nitions follow the International Vocabulary of Metrology (VIM) and the Guide to the Expression of Uncertainty in Measurement (GUM), with the technical report of the International Union of Pure and Applied Chemistry (IUPAC) providing a chemical interpretation. 1 3,5 A useful rst relation is q = h(θ, C), (7) where q is the intended biochemical quantity, θ contains the parameters that de ne it, and C speci es the biochemical context. Equation (7) is a measurand-de ning relation; it states what the quantity means but is not a complete measurement model. The context includes the molecular system and the conditions that can alter its behavior. For method m, let Ym(ti) denote the recorded signal. An observation equation can be written schematically as Ym(ti) = gm(x(ti; θ), ηm,Cm) + εm(ti), (8) where x(ti; θ) is the biochemical state, ηm contains method-speci c nuisance parameters, and Cm contains calibration information. A speci ed distribution or covariance structure for εm, together with the biochemical model for x, turns Eq. (8) into a statistical measurement model in the broad GUM-6 sense. The analysis procedure produces ˆqm = Am(Ym,Cm,Mbio,Mstat), (9) and the measurement result is reported as an estimate together with an uncertainty statement. The combined standard uncertainty uc(ˆqm) collects the contributions from every input; where an expanded uncertainty is wanted, U = k uc, and the coverage factor k and the intended coverage probability must be stated alongside it. The worked results below are reported as ˆq ± uc(ˆq). This hierarchy replaces the vague instruction to t the curve with a sequence of explicit decisions. The investigator de nes the target, states how the biochemical system produces the signal, speci es how variation is modeled, and then propagates the relevant sources of uncertainty. Table 2 summarizes the minimum record needed to make that sequence auditable. Figure 2 groups the same stages graphically. A protocol speci es the operations, whereas the measurement and observation models specify how the result is inferred. Repeating the protocol estimates variation conditional on the entire chain; it does not establish by itself that the chain reaches the intended measurand. Comparability also requires traceability of important inputs. In the

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progress-curve example, the molar absorption coe cient establishes the concentration scale and the active-site measurement establishes the scale for kcat. If those inputs are untraceable or incompletely characterized, repetition of the kinetic run cannot reveal the resulting common bias.1,2,22 Figure 2: The signal-to-measurand chain and three progressively stronger checks. The upper row separates the material and assay, measured signal, measurement model, and reported result. The lower row distinguishes local repeatability, transfer of the same procedure to another laboratory, and recovery of the same measurand by an independent measurement route (or technique). Existing standards and the contribution of this Perspective The measurement-science foundation already exists. The VIM establishes the vocabulary of the measurand, measurement result, and traceability. The GUM makes uncertainty part of the reported result, while GUM-6 explains how measurement models are developed and used. IUPAC and Eurachem translate those principles into chemical practice.1 3,5,22 Biochemistry has complementary infrastructure. The Standards for Reporting Enzymology Data, known as STRENDA, specify the minimum information that must accompany an enzyme-kinetic measurement for it to be interpretable, and STRENDA DB validates structured submissions against those requirements. 6,7,23 EnzymeML preserves reaction conditions and time courses in a machine-readable record, together with the associated models and tted parameters, while the System for the Analysis of Biochemical Pathways Reaction Kinetics (SABIO-RK) curates kinetic results and PEtab encodes parameter-estimation problems for systems biology.12,13,24,25 These e orts address di erent parts of the measurement. General metrology does not by itself determine whether a particular biochemical approximation is valid or whether a progress curve constrains KM. STRENDA improves experimental reporting, yet a complete STRENDA record need not contain an identi ability analysis or a full uncertainty budget for a model-derived parameter. EnzymeML and PEtab make data

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and models portable, but portability alone does not establish that the intended parameter was measured. The contribution of this Perspective is the linking architecture. It begins with a biochemical measurand and follows the complete chain from material and signal to model, inference, and uncertainty. It requires evidence both that the biochemical reduction is valid and that the experimental design constrains the intended parameter. It then places local repetition, transfer across laboratories, and agreement across independent routes (or techniques) within the same evidential framework. The prioritized recommendations later in the paper show how these requirements can be adopted without treating every routine assay as a reference measurement. Clinical enzymology demonstrates that such integration is feasible. The International Federation of Clinical Chemistry and Laboratory Medicine has developed primary reference procedures for catalytic activities at 37 ◦C. These procedures specify the measurand and the measurement equation, and document both the uncertainty budget and the calibration hierarchy.26 The same discipline can be extended beyond catalytic activity to kinetic and binding constants. The infrastructure required should remain proportional to the claim. Ligand receptor binding as a second case Consider reversible one-site binding, R + L kon ⇌ koff RL, KD = koff kon = [R][L] [RL] at equilibrium. (10) The reported dissociation constant depends on which free species and binding-competent material have been de ned, on whether equilibrium was reached, and on how the bound complex generated the recorded signal. A label or

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immobilized surface can therefore make the tted quantity method-speci c even when the curve is smooth and repeatable.27,28 The depletion-aware binding equation follows from mass balance. Writing c = [RL], so that [R] = [R]T−c and [L] = [L]T − c, substitution into Eq. (10) yields a quadratic in c whose physically admissible solution is the smaller root, [RL] = 1 2 { [R]T + [L]T + KD − √ ([R]T + [L]T + KD)2 − 4[R]T[L]T } , (11) because it satis es 0 ≤ [RL] ≤ min{[R]T, [L]T}. A uorescence experiment still requires an observation equation, for example Yi = Y0 + ΔY [RL]i [L]T,i + εi, (12) when the signal reports the fraction of labeled ligand bound. Here Y0 is the unbound baseline and ΔY is the response amplitude. Equation (12) becomes part of a statistical measurement model once the variation in εi is speci ed.3,27,28 In the illustration that follows, the labeled ligand is held at a xed total concentration and the receptor is titrated, as in a uorescence-anisotropy assay. Figure 3 shows two consequences. When total labeled ligand is not negligible, binding depletes free titrant and displaces the midpoint of the observed curve to [R]T,1/2 = KD + 1 2 [L]T, (13) so that a midpoint-based or simple-hyperbolic interpretation, which ignores mass balance, assigns an apparent half-saturation constant displaced by half the tracer concentration (Figure 3A). The displacement of the midpoint is exact; what an arbitrary least-squares hyperbola returns for a curve that is not a hyperbola depends on the tted range and weighting. The information about KD is also concentrated near the transition region. Low-concentration observations confound KD with the unknown amplitude, whereas saturated observations mainly de ne the plateau (Figure 3B). Kinetic binding presents the same separation problem. Under a pseudo- rst-order approximation the observed rate constant is kobs = kon[L]+koff, so association experiments at several ligand concentrations are needed to separate kon from koff. A single exponential at one concentration can t well while the microscopic constants remain weakly constrained.28,29 A complete binding report would rst identify the free receptor and ligand constructs and establish the binding-competent concentrations under stated chemical conditions. It would then give the mass-balance equation, the observation equation, and the error model. The concentration range should show that the transition was observed. The report should give an interval for KD, account for uncertainty from concentration and calibration, and state how labeling or immobilization might alter the result, treating depletion and linked equilibria explicitly where they are present. Figure 3: Ligand receptor binding illustrates depletion and parameter confounding. A Increasing the total labeled-ligand concentration displaces the midpoint of the binding curve to [R]T,1/2, even though the curve remains smooth and sigmoidal on a logarithmic titrant scale; the curves plotted are the exact mass-balance solution, which is not a hyperbola in [R]T. B For the low-depletion limiting curve f = u/(1 + u), with u = [R]T/KD, the panel shows the normalized magnitude 4|∂f/∂ lnKD|; the factor of four makes its maximum equal to one. Information about KD is greatest near the transition region, whereas observations far below or above it chie y determine a parameter combination or the response plateau. Does the experiment constrain the parameter? The form of variation is part of the measurement model. Constant-variance error may be reasonable on a raw absorbance scale and inappropriate after a nonlinear signal transformation. Drift, timing error, or repeated measurements from the same preparation can also create correlation. The estimator and its interval therefore cannot be interpreted apart from the observation scale and error structure. 2,22,30 Whichever likelihood L(θ) is adopted, the assumed variance structure enters it alongside the modelpredicted mean, so the estimator and its interval inherit that assumption; the Supporting Information gives the form used for the worked exemplar. Identi ability asks whether the speci ed experiment could have produced useful bounds on the parameter being reported. Structural identi ability addresses ideal, noise-free observations of the model. Practical identi ability

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addresses the experiment actually performed. Its assessment depends on the concentration range and sampling schedule, as well as on the noise and calibration. A parameter can satisfy the rst condition and remain unbounded in a particular experiment.8 10,31 A pro le likelihood provides an operational check. One parameter is xed at a sequence of values, the remaining parameters are re-estimated, and the best conditional ts are compared with the overall best t. Crossing the chosen threshold on both sides gives a nite interval; failure to cross in one direction shows that the data do not place a nite bound there. Sensitivity analysis identi es the observations that carry information, while simulation-and-recovery tests whether the proposed design can recover known values under realistic variation.8,9,32 Type A and Type B evaluations address the sources that contribute after the target has been identi ed. A standard uncertainty derived from a tted covariance is a Type A contribution; calibration, material characterization, and reference information contribute Type B components. A pro le-likelihood region is a di erent object. It is an interval diagnostic of what the data constrain, not a standard uncertainty, and it should not be combined with Type B inputs by root-sum-of-squares. Where the likelihood is markedly asymmetric the two will disagree, and the pro le region is the more faithful account of what the experiment supports. The combined uncertainty must re ect the inputs relevant to the declared measurand. When local propagation is unreliable, GUM Supplement 1 provides Monte Carlo propagation through the measurement model.2,22,33 Experimental design should follow the inverse question. Enzyme progress curves should sample the region around KM and characterize active enzyme separately. Binding experiments should cover the transition in the binding curve and quantify the binding-competent material. Replication is most useful when allocated to the sources that dominate the nal uncertainty. The corresponding local sensitivity and Fisher-information equations are provided in the Supporting Information.21,28 From repeatability to interlaboratory evidence Terminology di ers across communities, so the evidential distinctions should be stated explicitly. Repeatability asks whether the same team and apparatus produce compatible results under closely matched conditions. Transfer replication asks whether a speci ed procedure can be implemented in another competent laboratory. Independent-method reproducibility asks whether a di erent physical route (or technique) recovers the same measurand within uncertainty; in the notation of Eqs. (7) (9) it asks whether $\hat{q}_1$ and $\hat{q}_2$ are compatible when g_m, η_m, and C_m all di er, and it is therefore the strongest available test of the invariance of q to the route (or technique) by which it was obtained. ISO intermediate precision, which varies days, operators, or calibrations within one laboratory, lies between the rst two.1,34,35 Table 3 states what each check establishes and, equally important, what it cannot establish on its own. An interlaboratory study with a common material and procedure tests whether the method travels and whether the written record contains the knowledge needed to use it. Hierarchical designs can distinguish laboratory-level and material-level variation, including contributions from calibration and analysis. The observed spread can also be compared with the participants' uncertainty budgets. Dispersion that remains unexplained is often called dark uncertainty; it signals a missing or underestimated source that should be investigated.36 The design of the comparison determines the scienti c question. Holding the procedure xed tests transfer. Deliberately changing the measurement route (or technique) tests whether the measurand is stable to di erent observables and nuisance structures. The Yeast Systems Biology Network and STRENDA study

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illustrates the rst role by comparing enzyme activities under standardized, in-vivo-like conditions. 37 Independent routes (or techniques) provide a stronger test when their dominant errors di er. For example, a binding result obtained by calorimetry can be compared with a solution-phase optical method or a surface method, provided shared concentration standards and other common inputs are audited. Agreement then argues that the result survives changes in signal generation and analysis. Disagreement is also informative, indicating that the measurand was under-speci ed, that the material di ered, or that an approximation was invalid or a design uninformative.27,28,38,39 Prioritized recommendations for routine analytical biochemistry The evidential burden should rise with the claim. A screening quantity used to rank compounds does not require the same support as a constant interpreted within a speci ed molecular reaction mechanism or intended for reference use. Table 4 separates three levels of practice. The minimum level can be incorporated into an ordinary paper with a short measurand statement and a transparent analysis paragraph. The recommended level adds evidence that the chosen model and experimental range support the parameter. Reference-grade work requires infrastructure that most individual laboratories cannot supply alone, including comparison materials and coordinated studies. Adoption has real costs. Some laboratories lack metrological or statistical expertise, and active or bindingcompetent concentrations may be di cult to establish. Independent routes (or techniques) and interlaboratory studies also require resources. Proportional implementation keeps the framework practical: every study can declare its target, preserve the measured signal, state the model, and carry the relevant uncertainty into the reported result, with stronger evidence added as the claim warrants it. Box 2 shows what the recommended level looks like when written out for the worked case study. It is the concrete form of Table 2 and is short enough to sit in an ordinary methods section. Software can lower the entry barrier. PyEnzyme provides a high-level interface to the EnzymeML data model, and LMFIT o ers accessible nonlinear estimation and con dence- interval tools within the Scienti c Python ecosystem.40,41 The inferential convention still has to be reported, since packages di er in how they encode likelihoods and weighting, in the bounds they impose, and in the way they construct intervals. The explicit code for the worked example is supplied as a transparent reference implementation rather than an expectation that each laboratory reproduce the analysis from rst principles. A portable record makes that evidence reusable, and the FAIR principles that data be ndable, accessible, interoperable, and reusable set the standard it should meet.11 Such a record should preserve the assay description together with the raw signal and calibration, and the executable models and parameterestimation speci cation should travel with the diagnostics and the uncertainty budget. A persistent identi er and a record of the software environment then connect those objects to the reported measurand; deposition in an archive that mints such an identi er, rather than in a mutable code repository alone, is what makes the link durable. EnzymeML and PEtab already encode important parts of this structure. 12,13,25 Discussion and outlook The recommendations in this Perspective are intended to connect existing standards rather than replace them. IUPAC, the VIM, and the GUM provide the general grammar of measurement and uncertainty. STRENDA speci es the experimental information needed to interpret enzyme-kinetic data. EnzymeML and PEtab make data, models, and estimation problems exchangeable, while SABIO-RK supports curation and reuse. Each contribution is necessary, but each addresses a di erent layer of the measurement. The additional step developed here is evaluative. A biochemical constant is followed from the material and signal to its model-de ned target. Before that parameter is reported, the biochemical reduction and the information supplied by the design are both examined. Uncertainty from calibration and material characterization is then combined with t uncertainty. Finally, the claim is tested at an appropriate level: local repeatability, laboratory transfer, or agreement across independent routes (or techniques). This architecture turns terminology, reporting, and data exchange into a single signal-to-measurand work ow. The Michaelis Menten example shows why that connection matters. A valid reduced equation and a close t to the measured signal do not ensure that KM was separately determined, and a precise t does not account for uncertainty in active enzyme. Ligand receptor binding shows the same dependence on mass balance, observation equations, and experimental range. These are general features of analytical measurements that infer biochemical quantities from signals. The agenda that follows is practical rather than aspirational: the minimum level of Table 4 can be adopted immediately by any laboratory, and interlaboratory evidence and independent measurement routes (or techniques) are added as the consequence of the claim demands. Reproducibility is achieved when the meaning, information content, and uncertainty of the biochemical measurand remain explicit across that entire chain.

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Associated Content Supporting Information. Complete signal-to-measurand record for the worked Michaelis Menten exemplar, including measurement and observation models, likelihood and pro le-deviance de nitions, simulationand- recovery and sampling-schedule studies, uncertainty propagation, and computational diagnostics (PDF).

AI | 59 Words | High Confidence

Data Availability Statement No new experimental data were generated for this Perspective. The xed-seed synthetic observations used in the worked exemplar are deposited with the analysis code. Running run_all.py regenerates all manuscript gures and the values in Supporting Information Tables S1 S3 and S5 using seed 20240530; code/validate_schedules.py separately regenerates Table S4 using seed 20240531.

Human Written | 161 Words | High Confidence

The code is openly available at https://github.com/santiago-schnell/signals-to-measurands. All other claims rest on previously published literature listed in the References. Safety Statement No new experimental procedures, materials, or hazards are reported in this Perspective. Notes The author declares no competing nancial interest. Acknowledgments This work was supported in part by Dartmouth (New Hampshire, USA) and the Beilstein-Institut (Frankfurt am Main, Germany). I thank colleagues in the STRENDA Commission and the EnzymeML project, whose discussions at successive meetings prompted me to address the problems examined here, and the anonymous reviewers for comments that substantially improved the Perspective. During preparation and revision, I used OpenAI's ChatGPT to assist with language re nement, review of Python code and reproducibility documentation, and consistency checks across the manuscript, Supporting Information, and gures. I critically reviewed and veri ed all scienti c claims, equations, references, code, numerical results, and nal wording and accept full responsibility for the submitted content.

AI Detection Report for Reaction Acceleration: Reviving the Second Derivative in Chemical Kinetics

Sep 18, 2026 | 7,651 Words | Pangram 4.0

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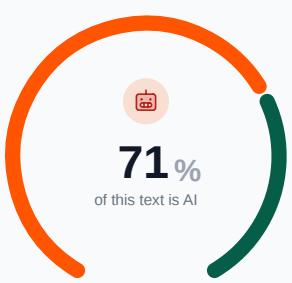

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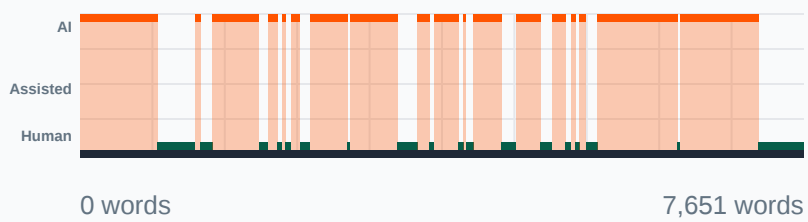

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Reaction Acceleration: Reviving the Second Derivative in Chemical Kinetics How do we know when a chemical reaction is speeding up, slowing down, or switching between kinetic regimes? The answer lies in the time derivative of the rate: reaction acceleration, v˙ = dv/dt = d2ξ/dt2. Although the thermodynamic foundation laid by Raw and Yourgrau has existed for seven decades, and although second-derivative landmarks are implicit throughout modern kinetics, no unified acceleration framework has been developed for the non-monotonic dynamics typical of systems chemistry. Here we develop such a framework. We (i) connect the Raw–Yourgrau singlereaction limit to network kinetics through matrix flux–force relations and the autonomous identity ¨c = J(c) f (c); (ii) derive closed-form acceleration landmarks for canonical mechanisms, including the Finke–Watzky two-step model; (iii) establish a sign-change taxonomy that makes explicit why the (+ → −) pattern is a constraint rather than a unique identifier; and (iv) benchmark a smoothing-plus-bootstrap workflow by quantifying bias, root-mean-square error, empirical coverage, and detection for noisy progress curves in an open-source Python implementation. Introduction Open any chemical kinetics textbook and you will find extensive treatment of reaction rates: the first time derivative of a progress variable (concentration or extent) with respect to time. Yet the time derivative of the rate (equivalently, the second derivative of the extent of reaction ξ(t) or the curvature of a concentrationtime trace) receives comparatively little explicit attention. This is puzzling. In classical mechanics, acceleration is fundamental: Newton’s second

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law relates force to acceleration, not velocity. In chemical kinetics, acceleration is rarely made explicit. Why? Throughout this article, reaction acceleration means the mathematical quantity v˙ or x¨, not the catalytic ‘rate acceleration’ ratio sometimes used to compare accelerated and uncatalyzed rates. The theoretical foundations for acceleration analysis were established seven decades ago. In 1956, C. J. G. Raw and W. Yourgrau published a brief but elegant paper in Nature that applied Prigogine’s irreversible thermodynamics to derive an explicit equation for reaction acceleration.[1] Their result connected the second time derivative of the extent of reaction to the rate at which chemical affinity changes during reaction progress. Yet this framework never entered mainstream kinetics pedagogy or practice. The curious situation is that second-derivative analysis already pervades modern kinetics; we simply do not recognize it as such. When a researcher observes a sigmoidal progress curve and identifies an inflection point, they are implicitly locating where the second derivative crosses zero. Autocatalysis is often recognized through this curvature pattern: the S-shaped curve reflects a transition from positive acceleration (reaction speeding up) to negative acceleration (reaction slowing down), although as we show below the same (+ → −) pattern is not uniquely diagnostic without complementary observables or perturbations. Derivative spectroscopy in process monitoring uses second derivatives to enhance spectral features. Oscillating reactions are characterized by their periodic acceleration reversals. These applications developed independently, each reinventing the wheel without reference to a unifying acceleration framework. Systems chemistry, with its focus on reaction networks, feedback loops, and emergent temporal behavior, stands to benefit most from explicit acceleration analysis. The reason is fundamental: systems chemistry deals with non-monotonic kinetics. In oscillating systems, autocatalytic cycles, and bistable networks, reaction rates rise and fall, speed up and slow down. Rate analysis tells us how fast; acceleration analysis tells us how the “how fast” is changing. When rates are non-monotonic, the second derivative becomes not merely useful but essential for characterizing system dynamics. Here we establish reaction acceleration as a unified analytical framework for systems chemistry and remove the practical and conceptual barriers that have kept it dormant. The four contributions are: 1. A thermodynamic-to-dynamical bridge from the Raw–Yourgrau single-extent near-equilibrium result to network kinetics. The bridge is made through the matrix flux–force form near equilibrium and, for autonomous kinetic models, through ¨c = J(c)f (c) (Eqs. 4 and (6) to (8)). 2. Closed-form acceleration expressions and landmarks for canonical mechanisms, including the Finke–Watzky two-step with existence conditions, landmark [B]∗ = Atot/2 − k1/(2k2), and crossing time t∗, as well as the Michaelis–Menten progress curve. 3. A sign-change taxonomy with explicit ambiguities. We identify cases where the (+→−) pattern is not unique to autocatalysis and give observation, perturbation, and model-comparison strategies for resolving it. 4. An operating-characteristic workflow pairing smoothing-spline differentiation with residual bootstrapping, and quantifying bias, root-mean-square error (RMSE), empirical coverage, and detection in an open-source Python package[2]. The article proceeds from thermodynamic origins to network generalization, to mechanism-specific derivations, observation-model effects, nonlinear dynamics, enzyme kinetics, and finally to the data-to-acceleration workflow and its operating characteristics.

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Thermodynamic Origins of Reaction Acceleration From Entropy Production to Reaction Acceleration The thermodynamic treatment of reaction acceleration begins with Prigogine's expression for entropy production in chemical reactions.[3] For a single reaction at constant temperature T, the rate of internal entropy production is: diS dt = A · v T where A is De Donder's chemical affinity,[4] defined as A = −(∂G/∂ξ)T,p, and v = dξ/dt is the reaction velocity expressed in terms of the extent of reaction ξ. The affinity represents the thermodynamic driving force for reaction: it is large and positive far from equilibrium, and zero at equilibrium. Differentiating Eq. 1 with respect to time yields: d2i S dt2 = 1 T (A˙v + Av˙) (2) where dots denote time derivatives. The two terms have clear physical meaning: A˙v captures how entropy production changes due to the evolving driving force, while Av˙ captures changes due to the evolving rate. The acceleration equation follows most directly from the near-equilibrium linear (Onsager) flux–force law v = LA, with a locally constant phenomenological coefficient L.[5] Differentiating and applying the chain rule ˙A = (∂A/∂ξ) v gives ˙ v = L ˙A = v A ∂A ∂ξ v = ∂ ∂ξ ln |A| A◦ p,T v2, which is the result of Raw and Yourgrau:[1] v˙ = ∂ ∂ξ ln |A| A◦ p,T · v2 (3) Here A◦ is an arbitrary fixed reference affinity introduced to make the logarithm dimensionless, and the expression is understood locally on a fixed-sign branch. Its derivative is independent of the value of A◦. Equation (3) connects the reaction acceleration v˙ = dv/dt = d2ξ/dt2 to the logarithmic derivative of affinity with respect to extent of reaction, multiplied by the square of the velocity. Within this same linear regime the two entropyproduction contributions in Eq. 2 coincide, A˙v = Av˙— both equal LA ˙A—a near-equilibrium symmetry noted by Prigogine.[3] It is therefore a restatement of the linear flux–force law rather than an independent premise, and the derivation above does not rely on it. Eq. 3 is a near-equilibrium statement, exact only insofar as L is constant and the flux remains proportional to the affinity. Readers unfamiliar with irreversible thermodynamics may proceed directly to the next section, where we derive equivalent results from kinetic rate laws without thermodynamic machinery. Physical Interpretation Near Equilibrium The physical meaning of Eq. 3 becomes clear when we consider how affinity changes during reaction progress (Figure 1). On the forward relaxation branch, A > 0 and v > 0. As equilibrium is approached, affinity decreases with extent, so [∂ ln(|A|/A◦)/∂ξ]p,T < 0, and Eq. 3 gives v˙ < 0.

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The reaction therefore decelerates as it exhausts its thermodynamic driving force. On the reverse branch, the same fixed-sign expression ln(|A|/A◦) applies locally; stable relaxation again gives an acceleration of opposite sign to the flux. The equation also quantifies the deceleration: it is proportional to v2 and to the local steepness of the affinity landscape.

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Raw and Yourgrau also established that accelerated chemical reactions, those with v⁄˙= 0, are always characterized by time-varying affinity. [6] Within the linear, locally constant-L

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Onsager regime used to derive (3), a constant affinity implies zero acceleration and hence a constant flux. An approximately constant affinity can be maintained, for example, in an open flow system with continuous reactant supply. From Single Reactions to Reaction Networks The Raw–Yourgrau relation (3) is derived for a system with a single reaction, parameterized by one extent ξ and one affinity A. A network has r reaction extents, an affinity vector A, and in the near-equilibrium Onsager regime a vector flux–force relation ˙ξ = LA, (4) where L is the phenomenological coefficient matrix. If L is locally constant, then differentiating gives ¨ξ = L ∂A ∂ξ ˙ξ = L ∂A ∂ξ LA.

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(5) This matrix form is the appropriate network analogue of the scalar Raw–Yourgrau construction. It also shows why a componentwise scalar extension is generally invalid: the cross-derivatives ∂Ai/∂ξj couple reaction channels, so the acceleration of a species need not be tied to a single affinity. At constant volume V , the species-level acceleration follows from the stoichiometry. With stoichiometric matrix ν = (νij), ¨ci = 1 V Xr j=1 νij ¨ξj . (6) If the system volume varies with time, additional terms obtained by differentiating 1/V (t) must be included. Thus the clean one-to-one connection between an affinity and the observed acceleration is lost. An observed sign change in ¨ci may reflect a balance among several fluxes, forces, and stoichiometric projections. For this reason, the practical definition of acceleration used throughout the rest of this article is dynamical. Given an autonomous kinetic model ˙c = f (c), the acceleration is the exact identity ¨c = J(c) f (c), (7) where J = ∂f/∂c is the Jacobian of the rate-law vector. For a driven or explicitly time-dependent kinetic model ˙c = f (c, t), the exact identity is instead ¨c = ∂f ∂t + Jc(c, t) f (c, t). (8) This distinction matters for flow reactors, dilution, feed protocols, temperature ramps, photochemical forcing, and other driven systems. The Raw–Yourgrau equation thus plays two roles in this article: a conceptual origin that explains why acceleration is physically meaningful near equilibrium, and a single-reaction limit of a broader kinetic description. All subsequent mechanismspecific derivations use (7) or its scalar chain-rule form directly rather than invoking affinity. Scope of Interpretive Limits Two notions of acceleration coexist. The thermodynamic statement (3) assumes a closed system at fixed T, p, local equilibrium, and a near-equilibrium (Onsager) regime in which the flux–force relation is approximately linear (v ≈ LA with locally constant L).[5] In that limit, A˙v = Av˙ and deceleration can be read directly from the affinity landscape. Most systemschemistry phenomena of interest (autocatalysis, oscillations, bistability) are far from equilibrium and may be non-autonomous. In these regimes (3) is best viewed as an interpretive limit rather than a general law, whereas (7) remains exact for autonomous models and (8) is the corresponding identity for explicitly driven models. Accordingly, acceleration landmarks are best treated as falsifiable constraints: they can rule out broad classes of mechanisms and highlight regime switching, but they rarely uniquely identify a network without complementary perturbations or observables. Acceleration Landmarks of Elementary Mechanisms Standard kinetics textbooks derive rate laws for elementary mechanisms but rarely present the corresponding acceleration expressions.[7] This is a significant gap: while rate laws describe how fast reactions proceed, acceleration expressions reveal how rates change: information that proves diagnostic for mechanism determination. The derivations are straightforward. For a onevariable rate

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law ˙ c = f(c), the acceleration follows from the chain rule: ¨c = df dc · ˙ c = f′(c) · f(c) (9) For multi-species networks the corresponding exact identity is (7); we use the scalar form here for textbook mechanisms.

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First-Order Reactions For an irreversible first-order reaction A B, the rate law is [A˙] = −k[A]. Differentiating: [A¨] = −k · [A˙] = −k · (−k[A]) = k2[A] (10) The acceleration is always positive. At first this seems paradoxical, because [A] is decreasing throughout the Figure 1. Thermodynamic relationships for a reversible reaction approaching equilibrium. (a) Affinity A decreases with extent of reaction ξ, reaching zero at equilibrium ξeq. The shaded area represents the corresponding Gibbs-energy decrease along the plotted relaxation branch. (b) The volumetric reaction rate v/V > 0 decays exponentially toward zero.

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(c) The volumetric acceleration v˙ /V < 0 throughout, indicating continuous deceleration as the thermodynamic driving force is exhausted. The numerical example uses V = 1 L, and the axis symbols v and v˙ are shorthand for the corresponding volumetric quantities. Thus the reaction proceeds forward while slowing down. reaction; the apparent contradiction is resolved by careful interpretation. Positive acceleration for a decreasing quantity means that the rate of decrease is itself decreasing: the reaction is decelerating, slowing its consumption of A as A becomes scarce. The concentration curve is concave up (bowl-shaped) throughout, with no inflection point.

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Second-Order Reactions For a second-order reaction 2A B with rate law [A˙] = −2k[A]2, applying the chain rule yields: [A¨] = −4k[A]·[A˙] = −4k[A]·(−2k[A]2) = 8k2[A]3 (11) Like first-order kinetics, the acceleration is always positive: the reaction decelerates monotonically with no inflection point.

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However, the cubic dependence on concentration has an important consequence: second-order reactions decelerate rapidly at high concentration but very slowly at low concentration. This explains the characteristic “fast start, long tail” shape of secondorder decay curves.

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Consecutive Reactions The consecutive reaction A k1 B k2 C provides the most instructive case for acceleration analysis, because the intermediate B exhibits a sign change in acceleration. The rate equation for B is [B˙] = k1[A] − k2[B]. Differentiating and substituting [A˙] = −k1[A]: [B¨] = k1 [A˙] − k2 [B˙] = k1(−k1[A]) − k2(k1[A] − k2[B]) = −k1(k1 + k2)[A] + k2 2[B] (12) This expression has two competing terms.

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The first, −k1(k1+k2)[A], is always negative and dominates early when A is abundant. The second, +k2 2[B], is always positive and grows as B accumulates. The acceleration changes sign when these terms balance. The key insight is that the inflection point follows the concentration maximum. Throughout the rising phase, B accumulates with negative acceleration (concave down): the rate is positive but decreasing. B reaches its maximum when the rate crosses zero. On the falling side, the acceleration eventually crosses zero and becomes positive (concave up) as B decays asymptotically toward zero.

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For the standard initial condition [B](0) = 0, the inflection occurs at exactly twice the maximum time, tinf = 2tmax. For k1≠ k2, tmax = ln(k1/k2)/(k1 − k2). In the equalrate limit k1 = k2 = k, [B](t) = A0kt e−kt, tmax = 1/k, and tinf = 2/k. Thus the ratio tinf/tmax = 2 is fixed under the stated initial condition, whereas the absolute times depend on both rate constants and their common timescale. The closed form is derived in the Supporting Information. Reversible Reactions For a reversible first-order reaction A k1 k−1 B, the acceleration takes a particularly elegant form: [A¨] = (k1 + k−1)2([A] − [A]eq) (13) The acceleration is directly proportional to the displacement from equilibrium.

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This result connects acceleration to the characteristic relaxation time τ = 1/(k1+ k−1): the system’s acceleration at any moment reflects how far it remains from its destination. Summary and Diagnostic Value Table 1 summarizes acceleration expressions for canonical kinetic cases, and Figure 2 illustrates the corresponding profiles. Two points deserve emphasis before we use sign changes as diagnostics. The sign change depends on the quantity being monitored. For a consecutive reaction A B C, the intermediate [B](t) shows (− → +), whereas the product [C](t) shows (+→−) because [C¨] = k2 [B˙] is positive while [B] rises and negative after [B] peaks. Monitoring different quantities yields different curvature landmarks for the same mechanism. The (+→−) pattern is not unique to autocatalysis. In addition to the consecutive-product case above, any derived observable linked to a kinetic species via a nonlinear (e.g., buffered equilibrium) transform can display the same acceleration pattern. We make this explicit in the

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Sign Change Ambiguity subsection below, immediately following the autocatalysis analysis. Acceleration of Observables versus Species Most kinetic experiments do not measure a concentration directly. They measure absorbance, fluorescence, pH, conductivity, scattering, calorimetric power, or a latent spectroscopic score. If the measured and calibrated observable is a linear function of concentrations, y = αTc + β, then ¨y = αT¨c and species-level acceleration relations carry over directly. If, however, y = g(c) is nonlinear, then ¨y = ∇g(c)T¨c + f (c)THg(c)f (c), (14) where Hg is the Hessian of the observation function. The second term is absent only for a linear calibration. It can create, suppress, or shift acceleration zero crossings even when the underlying species accelerations are monotone. Consequently, curvature landmarks are mechanistic only after the observation map has been calibrated or explicitly modeled. This is the central control on the sign-change taxonomy below. Diagnostics in Nonlinear Chemical Dynamics Autocatalysis: A Sign-Changing Landmark Autocatalytic reactions, in which a product catalyzes its own formation, are central to systems chemistry, appearing in contexts from the origin of life to selfreplicating materials.[8] These reactions produce characteristic sigmoidal concentration curves, and acceleration analysis reveals exactly why. Consider the minimal autocatalytic scheme A + B 2 B, where B catalyzes its own production from precursor A. With mass conservation [A] + [B] = Atot, the rate law becomes [B˙] = k(Atot−[B])[B], the logistic equation familiar from population biology.

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Differentiating yields the acceleration: [B¨] = k2[B](Atot − [B])(Atot − 2[B]) (15) The first two factors, [B] and (Atot − [B]), are always positive during the reaction.

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The third factor, (Atot − 2[B]), changes sign at [B] = Atot/2, where [A] = [B]. This is the half-pool point of the conserved A + B system; it equals 50% conversion of the initial A only in the zero-seed limit B0 → 0+. This gives rise to three distinct phases (Figure 3): 1. Lag phase ([B] < Atot/2): Acceleration is positive. The reaction speeds up as the autocatalyst B accumulates. The concentration curve is concave up. 2. Inflection point ([B] = Atot/2): Acceleration crosses zero. The rate reaches its maximum. This is the half-pool landmark and the internal rate maximum. 3. Saturation phase ([B] > Atot/2): Acceleration is negative. The reaction slows as substrate A is depleted. The concentration curve is concave down. Numerical example. For k = 1.5 M−1s−1, Atot = 1 M, and initial [B]0 = 0.02 M, the inflection occurs at t ≈ 2.6 s when [B] = [A] = 0.5 M. Because [A]0 = 0.98 M, the fraction of the initial A converted at the landmark is (0.98 − 0.50)/0.98 ≈ 0.4898, or approximately 49.0%. At this moment, the rate reaches its maximum value of vmax = k · 0.5 · 0.5 = 0.375 M/s. Before this point, the signed product rate is increasing; after, it is decreasing. The half-pool landmark is specific to the minimal A + B 2B scheme; the inflection location shifts predictably for extended mechanisms (see the Finke–Watzky discussion below). Diagnostic value. For the minimal autocatalytic scheme, the positive-to-negative sign change in [B¨] occurs at the internal maximum of [B˙]. This

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behavior distinguishes autocatalysis from first-order product formation, for which [B¨] < 0 throughout, and from a consecutive-intermediate curve, which shows the reverse direction (−→+). It does not, however, uniquely identify autocatalysis among all monitored observables: consecutive products and nonlinearly transformed readouts can also display (+ → −), so the sign change is best treated as a mechanistic constraint rather than a stand-alone verdict. If/then diagnostic. If, after smoothing and uncertainty quantification, the estimated acceleration of a monitored product-like species exhibits a robust positive-to-negative zero crossing together with a substantial early-time positive-acceleration window, then the progress curve is consistent with autocatalytic growth but is not uniquely diagnostic of it. The inference should therefore be tested against the alternative mechanisms discussed below by monitoring additional observables or by performing seeding, dilution, or inhibition experiments. If [B¨](t) remains nonpositive over the full course, autocatalysis of the monitored observable is not supported by curvature alone. Table 1. Acceleration expressions for canonical kinetic cases and the corresponding sign-change pattern of the monitored quantity. Sign changes depend on which quantity is monitored (reactant, intermediate, product, or derived observable); expressions differ by stoichiometry (e.g., for A B, [B¨] = −[A¨]). Several entries, including the consecutive-product and coupled-equilibrium cases, show that a (+→−) pattern is not unique to autocatalysis; see the Sign Change Ambiguity subsection. Rate constants follow the convention in which the stoichiometric coefficient appears explicitly in the rate law (e.g., [A˙] = −2k[A]2 for 2A B); folding the factor of two into k rescales the tabulated prefactors accordingly.

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Finke–Watzky Two-Step: Acceleration as a Quantitative Readout The minimal scheme A+B 2B assumes a nonzero seed of catalyst B at t = 0. Real autocatalytic systems typically include a slow initiation step that produces B from scratch, yielding the Finke–Watzky two-step model:[9] Nucleation: A k1 B, Autocatalytic growth: A + B k2 2B. With mass conservation [A] + [B] = Atot, the rate law becomes [B˙] = (k1 + k2[B])(Atot − [B]), (16) and the acceleration follows by direct differentiation: [B¨] = [B˙] · k2Atot − 2k2[B] − k1 . (17) The acceleration changes sign at [B]∗ = Atot 2 − k1 2k2 . (18) This is an internal positive-to-negative crossing only when B0 < [B]∗ < Atot. (19) For the unseeded case B0 = 0, this requires 0 < α < 1, where α = k1/(k2Atot). Otherwise, although [B](t) remains monotonically increasing, it may be concave down throughout the observed window, and the sigmoidal acceleration landmark need not exist. When the crossing exists, the inflection shifts to earlier times (lower conversions) as the nucleation rate k1 becomes non-negligible relative to the autocatalytic rate k2Atot (Figure 3). For a general initial seed B0, the crossing time is t∗ = 1 k1 + k2Atot lnR, (20) R = k2(Atot − B0) k1 + k2B0 . (21) For B0 = 0, R = α−1 and hence t∗ = (k1 + k2Atot)−1 ln(α−1). (22) As k1 → 0, the conversion landmark satisfies [B]∗ → Atot/2, recovering the minimal-autocatalysis half-pool landmark.

AI | 123 Words | High Confidence

For the unseeded case B0 = 0, however, the crossing time diverges in the same limit, t∗ → ∞, because initiation disappears. For finite k1, the position of the acceleration zero crossing therefore provides a direct, geometric readout of the mechanistic ratio k1/(k2Atot): a stronger claim than “autocatalysis is present” and one that can be tested against perturbations of Atot, seed level, or temperature. The Finke–Watzky framework has been applied directly to chemically realistic autocatalytic systems, most prominently transition-metal nanoparticle nucleation and growth.[9] Related initiation-plus-growth motifs also arise in other self-amplifying chemical and materials systems. The same qualitative initiation-andself- amplification motif is relevant to Soai’s asymmetric autocatalysis,[10] the prototypical chemical realization of self-amplifying enantiomeric excess.

Human Written | 47 Words | High Confidence

Recent in situ Figure 2. Acceleration landmarks as mechanistic constraints. Comparison of first-order (A B), consecutive (A B C), and autocatalytic (A + B 2 B) reactions. Top row: concentration profiles; blue, red, and gray denote [A], [B], and [C], respectively, where present. Middle row: rate profiles.

AI | 238 Words | High Confidence

Bottom row: acceleration profiles for the measured species (here [B](t)), with green shading indicating positive curvature (rate increasing) and orange shading indicating negative curvature (rate decreasing). The illustrative patterns differ: first-order reactions show only negative acceleration for product formation; consecutive reactions show a negative-to-positive transition for the intermediate; autocatalytic reactions show a positive-to-negative transition. Red dots mark inflection points where acceleration crosses zero. studies relate sigmoidal progress-curve features to transient catalytic intermediates and combine full kinetic profiles, intermediate measurements, and mechanistic simulations to discriminate among models.[11,12] Acceleration analysis is complementary to those efforts: the geometric landmarks [B]∗ and t∗ are observable-level quantities that do not presuppose a particular molecular mechanism, but they constrain which molecular mechanisms are admissible. Sign Change Ambiguity and the Monitored Quantity A (+→−) sign change in the acceleration of a measured observable is a canonical autocatalytic pattern, but it is not unique to autocatalysis. Two cases merit explicit discussion because they arise routinely in systemschemistry practice. Product of a consecutive reaction. For A k1 B k2 C, the intermediate [B](t) rises and then falls, and the product acceleration satisfies $[\ddot{C}] = k2\,[\dot{B}]$. While [B] increases, $[\ddot{C}] > 0$; after [B] peaks, $[\ddot{C}] < 0$. The product curve [C](t) is therefore sigmoidal with a (+→−) acceleration identical in direction to autocatalysis. Monitoring only the product cannot distinguish a two-step A B C sequence from genuine autocatalysis.

Human Written | 61 Words | High Confidence

Derived observables of coupled equilibria. The general observation formula (14) explains a second ambiguity. If a base is produced by a simple first-order reaction A B with [B˙] = k([A]0 − [B]), and one monitors [H+] via a buffered acid–base equilibrium [H+] = g([B]) with g a decreasing, nonlinear function, then [H¨+] = g′′([B])[B˙] 2 +g′([B])[B¨].

AI | 32 Words | High Confidence

This quantity can change sign depending on the curvature of g, even though the underlying reaction is monotonically decelerating. In practice, this matters for any experiment reading out a ki- Figure 3.

Human Written | 93 Words | High Confidence

Acceleration as a quantitative readout in the Finke–Watzky two-step model (A k1 B; A + B k2 2 B; Atot = 1 M, k2 = 1.5 M−1s−1, and B0 = 0). Colors encode three values of the dimensionless ratio k1/(k2Atot) (10−3, 10−2, and 10−1, corresponding to the curves from lightest to darkest red). (a) Product concentration [B](t): all traces are sigmoidal, but larger k1/(k2Atot) shortens the lag. Colored dots mark the acceleration zero crossing [B]∗ = Atot/2 − k1/(2k2); the dotted reference line is Atot/2.

AI | 284 Words | High Confidence

The bracket indicates the offset Atot/2 − [B]∗ = k1/(2k2) for the deepest-red case: the magnitude by which the inflection departs from the half-pool reference Atot/2—which equals 50% conversion here because B0 = 0—is the quantitative readout of the nucleation-to-growth ratio. (b) Rate d[B]/dt: the maximum rate moves to earlier times and, for fixed k2 and Atot, to higher maximum magnitude as k1/(k2Atot) grows. (c) Acceleration d2[B]/dt2: all three profiles show the characteristic (+→−) sign change, but the crossing time t∗ shifts systematically. Green and orange shading on the deepest-red trace indicate positive and negative curvature, respectively. netic variable through pH, fluorescence lifetime, spectral shifts, scattering, or activity coefficients. Practical resolution. Three strategies help resolve the ambiguity: (i) monitor multiple species simultaneously and check that their accelerations satisfy the stoichiometric and mass-balance relations implied by a single mechanism; (ii) exploit model-specific landmark relations under controlled perturbations: for minimal autocatalysis [B]∗ = Atot/2, whereas Finke–Watzky gives the offset Atot/2 − [B]∗ = k1/(2k2), so changing Atot, seed level, or temperature should shift the landmark predictably; and (iii) compare competing mechanisms against the full rate and curvature time series rather than relying on sign alone. Acceleration landmarks are strongest when deployed as one constraint among several. Oscillating Reactions: Periodic Acceleration Reversals In oscillating chemical systems, reaction acceleration takes on special significance because rates are inherently non-monotonic. Periodic reversals in

AI | 284 Words | High Confidence

acceleration sign provide reproducible kinetic phase landmarks within each oscillatory cycle. The Belousov-Zhabotinsky (BZ) reaction, the prototype of chemical oscillators, illustrates this principle.[13] We analyze it through the Oregonator model, a simplified three-variable representation that captures the essential dynamics.

Human Written | 151 Words | High Confidence

In the Oregonator, the dimensionless Ce4+-like oxidized-catalyst variable Z oscillates periodically. In the dimensionless form used here, ˙Z = X−Z, so the model-derived acceleration is ¨ Z = ˙X − ˙Z = fX(X, Y,Z) − fZ(X, Y,Z), (23) which is evaluated directly from the ordinary differential equations rather than by finite-difference differentiation of the simulated trajectory. The dimensionless equations, parameter values, initial condition, transient removal, plotted window, and zero-crossing rule used to generate Figure 4 are specified in the Supporting Information. The acceleration changes sign at characteristic points in each cycle (Figure 4): • Autocatalytic phase (¨ Z > 0): The system is dominated by HBrO2 chemistry. Ce3+ is oxidized to Ce4+ through an autocatalytic pathway, and the rate of Ce4+ production increases. • Inhibition phase (¨ Z < 0): Bromide ion (Br−) accumulates and inhibits the autocatalytic pathway. The rate of Ce4+ production decreases, and eventually Ce4+ is reduced back to Ce3+.

AI | 251 Words | High Confidence

Zero crossings of ¨ Z locate stationary points of the model rate ˙Z . This recasts rate-extremum location as a rootfinding problem and can be operationally convenient when model-derived derivatives are available; it is not inherently better conditioned when ¨ Z must itself be estimated from noisy observations. The crossing direction, + → − or − → +, distinguishes local maxima from local minima of the rate. These are kinetic phase landmarks rather than unique identifiers of molecular switching events. They are distinct from, and interleave with, the concentration extrema (the nullcline crossings ˙Z = 0, i.e. X = Z here); reporting the acceleration zero crossings, rate extrema, and nullcline crossings together partitions each cycle into its slow and fast segments. For limit-cycle oscillators generally, the acceleration vector describes the change in phase-space velocity; only its component normal to the trajectory determines geometric curvature. Stability itself is governed by Floquet multipliers rather than by a generic restoring-acceleration vector. The useful role of acceleration here is therefore operational: its zero crossings and extrema provide phase landmarks, and its magnitude peaks near the “corners” of relaxation oscillations where the system switches rapidly between slow and fast manifolds. If/then diagnostic. If the times at which the measured acceleration crosses zero recur at fixed phases from cycle to cycle (within experimental noise) and persist under moderate perturbations of initial conditions, then the dynamics are consistent with a stable limit cycle; if zero-crossing phases drift systematically or disappear, the oscillations are more likely transient, quasi-periodic, or noise-driven.

Human Written | 123 Words | High Confidence

Acceleration in Enzyme Kinetics Enzyme kinetics offers fertile ground for acceleration analysis, particularly in two contexts: extracting kinetic parameters from progress curves, and characterizing transient-state behavior before steady state is established. Michaelis–Menten Progress Curves Under quasi-steady-state conditions,[14] the rate of product formation follows the Michaelis–Menten equation: v = d[P] dt = Vmax[S] Km + [S] (24) As substrate is consumed ([S˙] = −v), the rate decreases monotonically. To find the acceleration, we apply the chain rule: [P¨] = dv d[S] · [S˙] = VmaxKm (Km + [S])2 · (−v) (25) Substituting the Michaelis–Menten expression for v: [P¨] = − V 2 maxKm[S] (Km + [S])3 (26) This acceleration is always negative: the rate of product formation decreases continuously as substrate is depleted.

AI | 148 Words | High Confidence

The product progress curve [P](t) is everywhere concave down, with no sign-changing inflection point. Nevertheless, acceleration analysis provides practical value. The magnitude of product acceleration, |[P¨]|, is not constant; it varies with substrate concentration and reaches a maximum when [S] = Km/2. This is an interior trajectory landmark only when [S]0 > Km/2; if [S]0 ≤ Km/2, the maximum of |[P¨]| over the observed trajectory occurs at the initial boundary, t = 0. Equivalently, when the interior landmark is traversed, the rate curve v(t) has a kinetic inflection point at this substrate concentration. This is a maximum-second-derivativemagnitude landmark, not a sign-changing inflection of the product progress curve [P](t). This yields a direct consistency check for determining Km: locate the time tacc at which |[P¨]| is largest, measure the substrate concentration [S]acc = [S](tacc), and compute Km = 2[S]acc.

Human Written | 58 Words | High Confidence

In 1985, Hasinoff proposed an early second-derivative method for estimating Km and Vmax from a single progress curve at one initial substrate concentration without following the reaction to completion.[15] Related identifiability and errorstructure issues in time-course fitting are analyzed by Stroberg and Schnell.[16] This construction is not a substitute for global progress-curve fitting.

AI | 44 Words | High Confidence

It is a curvature-based consistency check or starting estimate under the irreversible Michaelis–Menten model, and it requires a calibrated substrate/product relation, negligible reversibility, negligible product or substrate inhibition, no enzyme inactivation, and sufficient signal-to-noise for a second-derivative landmark.

Human Written | 56 Words | High Confidence

Numerical example. For an enzyme with Vmax = 10 μM/s and Km = 50 μM, the maximum-|[P¨]| landmark occurs when [S] = 25 μM. At this point, the acceleration magnitude reaches |[P¨]|max = (4/27)(V 2 max/Km) ≈ 0.296 μM/s2, so measuring [S]acc = 25 μM immediately yields Km = 50 μM. If/then diagnostic.

AI | 64 Words | Medium Confidence

If each progress curve begins at a sufficiently high substrate concentration to traverse the interior landmark, and the inferred Km = 2[S]acc is consistent across different [S]0 values and enzyme loadings, then the Michaelis–Menten model is selfconsistent for that dataset; if the inferred Km depends strongly on [S]0, additional effects (inhibition, inactivation, reversibility, or depletion of active enzyme) are implicated.

Human Written | 118 Words | High Confidence

Transient-State Kinetics Transient-state methods, which probe events before steady state is established, offer richer acceleration information.[17] Here, rates are explicitly time-dependent, and acceleration analysis directly reveals the underlying kinetic processes. Consider burst kinetics, commonly observed when product release is rate-limiting. The product concentration follows: [P](t) = A0(1 − e−kburstt) + Vsst (27) where A0 is the burst amplitude, kburst is the burst rate constant, and Vss is the steady-state velocity. The acceleration is: [P¨] = −A0k2 burste−kburstt (28) Within the idealized single-exponential burst model, this expression contains information about both parameters: kburst is obtained from the exponential decay Figure 4. Acceleration landmarks in the Oregonator model of the Belousov–Zhabotinsky reaction.

AI | 835 Words | High Confidence

(a) Phase-space limit cycle showing the HBrO2-like activator variable X versus the Ce4+-like oxidized-catalyst variable Z. Arrows indicate the direction of evolution; red dots mark model-derived acceleration zero crossings. (b) Time series of the scaled variable Z (solid blue) and model rate dZ/dt = X−Z (dashed red). (c) Model-derived acceleration d2Z/dt2 = fX − fZ. Green and orange shading indicate positive and negative acceleration, respectively. The red dots mark rate-extremum phase landmarks; they should not be interpreted as unique molecular switching events. rate, and A0 is then obtained from the initial acceleration magnitude, [P¨](0) = −A0k2 burst. Within this model, [P¨] → 0 asymptotically as the trace approaches its steady-rate regime. In experimental data, the transition should be defined operationally by |[P¨]| falling below a prespecified threshold that accounts for derivative-estimation uncertainty. A small estimated acceleration is not, by itself, proof that a more general mechanism has reached a true steady state. Acceleration analysis extends naturally to more complex enzyme mechanisms, including substrate inhibition and allosteric cooperativity, where curvature landmarks may carry information about inhibition

AI | 835 Words | High Confidence

constants and cooperativity coefficients. These extensions merit dedicated treatment elsewhere. From Data to Acceleration: Estimation and Uncertainty The Noise Amplification Problem The fundamental barrier to acceleration analysis is noise amplification. Differentiation acts as a high-pass filter: it amplifies high-frequency components (noise) relative to low-frequency components (signal). Second derivatives amplify noise even more severely. For data with measurement error σ, a naive finite-difference estimate of the second derivative has variance proportional to σ2/Δt4; the fourth power of the sampling interval makes this extremely sensitive to noise. Direct numerical differentiation of raw experimental data is therefore rarely practical. The solution is to smooth first, then differentiate: fit a smooth function to the data, then differentiate the smooth function analytically A Practical Workflow Recommended procedure: 1. Calibrate the observable. Convert raw signal (absorbance, fluorescence, etc.) to concentration using appropriate calibration. Apply baseline correction if needed. 2. Estimate noise level. From replicates, from highfrequency residuals, or from instrument specifications. This guides smoothing parameter selection. 3. Fit a smooth representation. Use smoothing splines (preferred for irregular sampling) or Savitzky–Golay filters (for uniform sampling). Select the smoothing strength from the data: we recommend a penalized spline[18] whose penalty is chosen by generalized cross-validation (GCV), which substantially reduced the systematic landmark bias of the fixed rule in the benchmark reported below (see Supporting Information). A transparent fallback is the fixed factor s ≈ nσ2 (n points), increased to ≈ 1.5–2 nσ2 for second-derivative (acceleration) stability; if used, it should be cross-checked with a sensitivity sweep, as it over-smooths and biases the landmark at higher noise. 4. Differentiate analytically. Compute dˆx/dt and d2ˆx/dt2 from the fitted function. Identify sign changes (inflection points) and extrema; for sigmoidal or single-peaked progress curves, take the inflection to be the acceleration zero crossing nearest the rate extremum rather than the first crossing, which can be displaced by noise-induced early sign changes; crossings within the first or last few samples are likewise excluded (by default the outermost 5% of the record at each end), as second derivatives are least reliable there (see Supporting Information). 5. Assess fit quality and quantify uncertainty. Check residuals for systematic patterns (which indicate over- or under-smoothing). Use bootstrap resampling to estimate confidence intervals for landmark times. Verify that landmarks are stable when smoothing parameters are varied by ±50%. Detailed algorithms, worked examples, and reference Python code are provided in the Supporting Information. The residual bootstrap used here assumes that residuals are approximately independent and homoscedastic after smoothing. For heteroscedastic errors, a wild or replicate-based bootstrap is preferable; for serially correlated errors, a block or model-based bootstrap should be used. Operating Characteristics on Synthetic Data To make the workflow falsifiable rather than merely procedural, we evaluated it on synthetic progress curves with known ground truth. The benchmark uses the canonical autocatalytic system A + B → 2B with k = 1.5 M−1s−1, Atot = 1 M, B0 = 0.02 M, and true inflection time t∗ = ln(49)/1.5 = 2.5945 s. For each relative noise level, 50 independent homoscedastic Gaussian realizations were sampled at n = 100 time points and analyzed with the rate-anchored positiveto- negative acceleration zero-crossing detector. On identical data we compare two smoothing pipelines: the recommended data-driven penalty selected by generalized cross-validation (GCV), and, as a cautionary baseline, the fixed rule s = 2nσ2. Residual-bootstrap intervals used 300 resamples per realization. Figure 5 reports the operating characteristics. Both pipelines detected the landmark in all 50 realizations at every noise level; they differ sharply in accuracy. The fixed rule carries a systematic smoothing bias in the landmark time (−0.11, −0.15, −0.08, and +0.06 s at 0.5%, 1%, 2%, and 5% relative noise), and because each nominal 95% interval is

AI | 835 Words | High Confidence

centered on that biased estimate, empirical coverage is 68%, 84%, 100%, and 74%, respectively.

Human Written | 27 Words | Medium Confidence

The GCV pipeline selects the smoothing strength from each data set; its bias remains within ±0.03 s, and empirical coverage is 100%, 100%, 98%, and 100%.

AI | 781 Words | High Confidence

With 50 realizations per level, these observed proportions are compatible with nominal 95% coverage given the Wilson Monte Carlo intervals shown in Figure 5, although they indicate slight overcoverage for GCV in this benchmark. Reading coverage alongside interval width, tabulated in the Supporting Information, clarifies the result: the fixed rule's coverage fluctuations arise from the combination of smoothing bias and smoothing-dependent interval width rather than from detection failure. No residual-bootstrap interval corrects smoothing bias; GCV substantially reduced that bias here. At 5% noise, the heavily oversmoothed fixed rule had lower RMSE (0.08 versus 0.22 s) because its variance reduction outweighed its bias, although its empirical interval coverage remained only 74%. At the relative-noise levels σ/signal range ≤ 2% examined here, GCV was consistently less biased and had better-calibrated coverage; its RMSE was lower at 0.5% and 1% and essentially equal to that of the fixed rule at 2%. These percentages are illustrative operating characteristics rather than universal constants. This benchmark converts acceleration analysis from a curveshape heuristic into a benchmarked estimator with explicit failure modes. Robustness Checks Acceleration-based diagnostics are powerful but not infallible. The following checks help ensure reliable results: Data quality issues: • Undersampling: Sparse data can miss genuine inflection points or create spurious ones. For oscillatory systems, ≳ 10 points per period is only a bare minimum; acceleration landmarks usually require 20–30 points per period, and denser sampling near fast relaxation transitions. • Boundary derivatives: Second derivatives are least reliable near the first and last few sampling points. Landmark calls close to the experimental boundaries should be treated as provisional unless early- or latetime sampling is dense and independently validated. • Instrument artifacts: Dead time, mixing delays, and baseline drift can create artificial curvature; treat early-time data with caution and, when possible, validate with replicate traces. Analysis issues: • Smoothing sensitivity: If landmark positions shift substantially under order-one changes in smoothing parameters, the landmarks may not be reliable. • Non-identifiability: Different mechanisms can produce similar acceleration patterns; use acceleration as one constraint among several, not as definitive proof. When these checks are satisfied, acceleration landmarks are more likely to be robust and reproducible. Summary and Outlook Reaction acceleration reframes kinetics in terms of curvature: the time derivative of the rate (or, more generally, the second derivative of an observable) highlights when reaction systems switch regimes. Here we (i) revisited the thermodynamic origin of acceleration in affinity-driven relaxation, (ii) extended the framework from single reactions to autonomous networks via ¨c = J(c)f (c), (iii) derived explicit acceleration Figure 5. Operating characteristics of

AI | 781 Words | High Confidence

acceleration-landmark recovery for the canonical autocatalytic benchmark (t∗ = 2.5945 s, n = 100 points). Two smoothing pipelines are overlaid on identical data: the recommended GCV-penalized spline (filled circles, solid) and the cautionary fixed rule s = 2nσ2 (open squares, dashed). Each point summarizes 50 noise realizations; bootstrap intervals used 300 residual resamples per realization. (a) Bias in the estimated crossing time: the GCV pipeline stays near zero whereas the fixed rule shows a systematic bias. (b) RMSE: the fixed rule attains a lower RMSE only at the highest noise, where it over-smooths and trades bias for variance. (c) Empirical coverage of nominal 95% bootstrap intervals (dashed line, 95%); GCV produced 98–100% empirical coverage in this benchmark, compatible with nominal coverage within the reported Wilson Monte Carlo intervals, whereas fixed-rule coverage was less stable. (d) Detection rate. Vertical bars in panels (c) and (d) show Wilson 95% Monte Carlo intervals for the binomial coverage and detection proportions. Detection is robust for both pipelines; the fixed rule's coverage deficit reflects smoother-induced bias, which the data-driven GCV penalty substantially reduced in this benchmark. expressions for canonical mechanisms while clarifying the sign-change taxonomy and its mechanistic ambiguities, and (iv) established and benchmarked a practical smoothing-and-bootstrap workflow for extracting acceleration landmarks with uncertainty from noisy data. The framework is therefore both conceptual and operational: the remaining task is to make such diagnostics routine in experimental and computational kinetics. Why Now? Three developments make acceleration analysis particularly timely. Modern instruments (stopped-flow spectrometers, rapid-quench apparatus, continuous monitoring systems) provide the time resolution and signalto- noise ratios that meaningful second-derivative analysis requires. Computational methods for robust derivative estimation, including smoothing splines, local polynomial filters, and resampling-based uncertainty quantification, now address the noise-amplification barrier that historically limited practical application. And systems chemistry, with its focus on non-monotonic kinetics in oscillating, autocatalytic, and networked systems, provides exactly the scientific questions that acceleration analysis is suited to answer. Promising Directions To make these opportunities operational, we phrase them as falsifiable if/then diagnostics.

Human Written | 433 Words | High Confidence

Autocatalysis screening. If a product-like progress curve [B](t) shows a robust positive-to-negative zero crossing in d2[B]/dt2 together with a sustained earlytime positive-acceleration window, then it can be flagged as a candidate autocatalytic trace in complex mixtures (e.g., unexpected autocatalysis in organic synthesis or self-replicating species in prebiotic experiments) and prioritized for complementary tests such as multi-observable monitoring, seeding, dilution, or inhibition. Oscillator characterization. If zero-crossings of the acceleration d2Z/dt2 recur with low cycle-to-cycle jitter, then they provide objective phase markers for quantitatively comparing oscillator waveforms across chemical implementations and for designing/analyzing coupled oscillator networks with specified entrainment and synchronization behavior. Reaction network inference. If multiple mechanisms fit concentration–time data comparably well, then retaining only those that also reproduce the observed ordering, timing, and sign pattern of acceler-ation landmarks provides additional, complementary constraints that can improve experimental mechanism discrimination and computational inference of reaction networks from time-series data. Software integration. If kinetics platforms such as COPASI,[19] DynaFit,[20] or KinTek

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Explorer[21] expose acceleration observables (e.g., v˙ and d2ci/dt2) together with built-in landmark extraction and uncertainty estimates, then acceleration-based diagnostics can become routine outputs for automated mechanism screening and model validation. Closing Thought The Raw–Yourgrau equation is 70 years old, yet the framework it established remains largely dormant. The mathematical relationships are straightforward; the diagnostic value is clear; the barrier has been awareness, not difficulty. The second derivative has been hiding in plain sight, implicit in every sigmoidal progress curve, every oscillation, every enzyme progress trace. Systems chemistry, with its inherent focus on dynamic behavior and emergent phenomena, is the natural home for its revival. We hope this article serves as an invitation to make the implicit explicit, and to put reaction acceleration to work. Acknowledgements The author acknowledges support from Dartmouth. Conflict of Interest The author declares no conflict of interest. Data Availability Statement The data and code that support the findings of this study are available in the Supporting Information and in the open-source reaction-acceleration repository (version 0.5.1). Supporting Information Supporting Information is available and includes: (i) detailed derivations with all intermediate steps; (ii) numerical differentiation methods and smoothing parameter selection; (iii) bootstrap uncertainty quantification; (iv) an operating-characteristic benchmarking framework for assessing acceleration analysis pipelines; and (v) documented Python code for implementing these methods. The Python code for the algorithms and examples presented in this paper is available in the reaction-acceleration repository. Keywords: reaction kinetics • chemical acceleration • irreversible thermodynamics • autocatalysis • enzyme kinetics

AI Detection Report for Universities are fighting AI cheating. But there’s a deeper problem.

Sep 18, 2026 | 845 Words | Pangram 4.0

Summary

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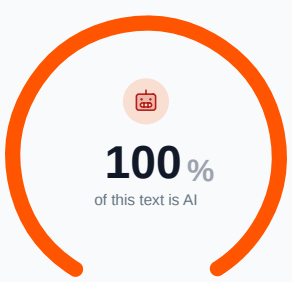

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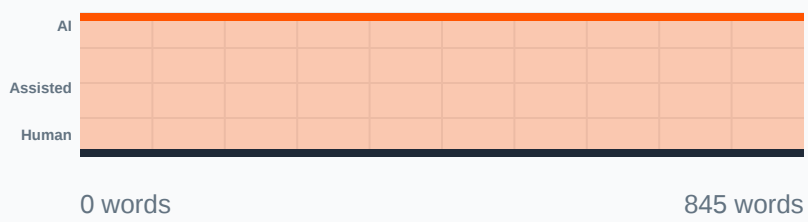

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Universities are fighting AI cheating. But there’s a deeper problem. A degree should distinguish what students can do independently from what they can accomplish with AI. Colleges are reviving proctored exams, blue books and oral assessments as they try to determine whether students are learning or merely using artificial intelligence to generate finished work. This fall, the University of Chicago Law School will pilot a general prohibition, with limited exceptions, on electronic devices in core first-year classes. Such measures can deter cheating and help professors see what students can do without AI. Other universities should watch the results closely. In many courses, finished work once served as useful, if imperfect, evidence of learning. A well-written essay was not proof of independent effort, but it usually reflected reading, reasoning and revision. Generative AI has weakened that inference. Students can now produce proficient prose without performing much of the intellectual work the prose appears to represent. As a university provost, I initially viewed generative AI chiefly as an academic-integrity problem, requiring clear rules about permitted use and ways to identify violations. My scientific work concerns measurement, which led me to a more basic question: What capability does the submitted work actually reveal? Universities need to define that capability before choosing how to assess it. Universities should assess independent competence (what a student can recall, reason through and explain without delegating the task) separately from AI-assisted performance. Today’s graduates will need both. A strong result using AI does not show what the student can do

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independently. Early evidence shows that how AI is used in instruction matters. In a randomized study of 120 undergraduates, students given unrestricted ChatGPT access while studying scored lower on a surprise retention test given 45 days later than those who had studied conventionally. On the other hand, a separate randomized trial in undergraduate physics found that a purpose-built AI tutor produced greater immediate learning gains than an active-learning class. These studies examined different settings and outcomes, so they do not yield a simple verdict on AI. The practical lesson is to use AI for questions, feedback and extra practice, rather than to supply a finished answer before a student has attempted the reasoning behind it. Assessment conditions must match the claim attached to the result. A take-home essay completed with unrestricted AI may show that a student can ask useful questions, check sources and improve machine-generated prose. It does not, by itself, show whether the student could explain the subject or construct an argument without AI. A degree loses meaning if universities treat those skill sets as interchangeable. The problem continues after graduation. Junior lawyers learn by checking citations and comparing contracts under a senior lawyer’s supervision. Analysts reconcile inconsistent records; research assistants clean data and investigate anomalous results. Such tasks are attractive candidates for automation because employers see their immediate output more readily than their formative value. As entry-level work changes, universities may need to provide more supervised professional practice through clinics, research apprenticeships and project courses. Otherwise, firms could gain current productivity while shrinking the pool of future experts. Universities need more than a return to blue books. At Dartmouth, where the term “artificial intelligence” was coined 70 years ago, some first-year seminars ask students to compare their own summaries of an assigned essay with an AI-generated version, identify inaccuracies and defend their judgments aloud. Foundational courses should include work done without outside assistance, with appropriate accommodations, so that baseline competence can be observed. Later assignments can require AI and ask students to verify its claims, identify its errors and defend their conclusions. An oral examination tests whether a student understands an argument; an outline, draft and revision show how it developed; solving a problem or explaining code aloud exposes the reasoning behind the answer. Each assessment should state what assistance is permitted and what capability is being evaluated. Universities should identify which degree requirements provide evidence of independent mastery and which evaluate intelligent use of AI. This approach does not require preserving needless difficulty. AI can turn lecture audio into captions, generate additional practice problems and provide preliminary feedback on a draft essay. The tasks worth protecting are those that develop recall, explanation, revision and judgment. Working through a calculation or proof without AI, or defending an argument orally, reveals whether a student understands the work well enough to supervise a machine. A degree is a public claim as well as a private benefit. Employers, patients, clients and citizens rely on it as evidence that its holder can exercise judgment. Self-government also depends on citizens who can distinguish a sound argument from a fluent approximation. Universities therefore need to show that graduates can use AI intelligently, recognize when its answer is wrong or incomplete and decide when a task should not be delegated. Generative AI makes polished work easy to produce. Universities must now devise credible ways to observe the capacities behind it. The value of a degree will depend increasingly on whether they succeed.