特约评述

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工业酶创制：从高效改造到自主酶工程

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摘要：新酶创制是拓展酶催化工业应用的基础。其核心科学难题在于尚难以建立酶的序列、三维结构和催化机制与其在工业应用环境中的催化性能之间普适且可量化的映射关系。人工智能技术为解决这一问题提供了新路径：通过整合多模态数据、构效关系模型、计算设计工具、自动化工作流和高通量实验，构建可计算、可执行、可反馈的新酶创制研究范式，推动工业酶开发从高效改造向自主创制演进。“自主酶工程”是以应用目标为导向、由科研智能体在人类监督下组织计算与实验任务，依据过程数据和实验反馈进行多轮决策与迭代，并能在限定范围内自主调整研究路径的新酶创制范式。本文简要综述自主酶工程的科学与工程基础，重点介绍科研智能体在流程组织、科学假设生成、专业工具调用和长周期任务执行等方面的研发进展，据此提出“平台化—智能化—体系验证”的实现路径及自主性分级框架，并讨论可靠性、生物安全、权限控制和科研责任等治理问题，为自主酶工程技术研发、系统评价与应用部署提供指导。可以预见，随着科研智能体决策能力的提升和治理机制的完善，自主酶工程有望建立面向真实工业工况的设计、验证与反馈闭环，推动工业酶创制进入智能驱动的新研发范式。

关键词：酶创制；工业酶催化；人工智能；构效关系；科研智能体

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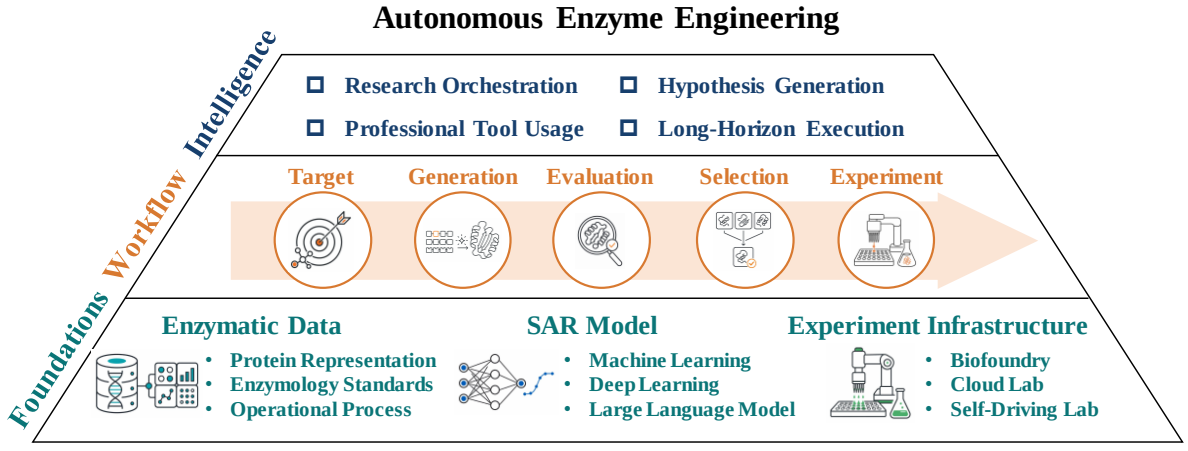
Industrial Enzyme Creation: From Efficient Modification to Autonomous Enzyme Engineering

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Abstract: The creation of novel enzymes is fundamental to expanding the industrial application of enzymatic catalysis. A pertinent scientific challenge, however, is the difficulty of establishing a generalizable and quantitative mapping between an enzyme's sequence, three-dimensional structure, and catalytic mechanism and its catalytic

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performance under industrial application conditions. Artificial intelligence (AI) offers an appealing approach to addressing this challenge by integrating multimodal data with sequence-structure-function modeling, computational design, automated workflows, and high-throughput experimentation. Together, these advances support a computable, executable, and feedback-driven paradigm for novel-enzyme creation, promoting the transition of industrial enzyme development from efficient modification toward autonomous creation. Autonomous enzyme engineering is an application-oriented paradigm for novel-enzyme creation in which scientific agents, under human supervision, coordinate computational and experimental tasks, make and iteratively update decisions across multiple rounds based on process data and experimental feedback, and autonomously adjust the research pathway within predefined bounds. This review briefly summarizes the scientific and engineering foundations of autonomous enzyme engineering, with particular emphasis on the standardization of enzymatic data, the development of sequence – activity-relation (SAR) models, and advances in automated and high-throughput experimentation. We then examine the typical workflows for novel-enzyme creation, including enzyme mining, enzyme engineering, and enzyme design, which constitute the major operational targets of autonomous enzyme engineering. We further review recent advances in scientific agents in terms of research workflow orchestration, scientific hypothesis generation, domain-specific tool use, and long-horizon task execution. Agents driven by large language models can operate across diverse research environments and coordinate multistep research workflows. Multi-agent architectures incorporating reflection and critique may facilitate the generation and evaluation of scientific hypotheses, while specialized computational tools can enhance agents' domain-specific capabilities by providing consistent and coherent analytical environments. Long-horizon execution remains challenging, however, particularly with respect to the stability and robustness of data-driven research systems and the establishment of reliable links between data, scientific hypotheses, and experimental validation. Finally, we propose a roadmap for autonomous enzyme engineering based on the coordinated development of digital platforms, intelligent agents, and system-level validation. The key governance issues, including reliability, biosafety, access control, and scientific accountability, are also discussed, thereby providing guidance for the responsible development, systematic evaluation, and practical deployment of autonomous enzyme engineering. It is anticipated that, with the continuous advancement of decision-making capabilities and governance mechanism of AI research agents, autonomous enzyme engineering will close the loop of design, validation, and feedback responding to application scenarios and open a new paradigm for industrial enzyme creation.



Keywords: enzyme creation; industrial enzyme catalysis; artificial intelligence; sequence – structure – function relationships; scientific agents

自然界丰富多彩的酶催化反应具有反应条件温和、反应速率高、选择性优等优势，为绿色生物制造提供了启发和催化剂资源[1-3]。创制能够在工业环境中高效催化非天然反应或具有改进性能的新酶是拓展绿色生物制造的前提[4, 5]。目前发展的新酶创制技术总体可以分为酶挖掘、酶改造和酶设计三大类[6]。酶挖掘是从自然环境、以及蛋白序列、结构或基因组数据库中筛选出可催化目标反应的酶[7-9]。酶改造是以具有催化活性的酶为起点，通过定向进化[10]、理性/半理性设计[11]等对其序列中的部分残基进行突变以优化其活性[12, 13]、稳定性[14, 15]、选择性[16, 17]或重塑底物谱[18]。酶设计可分为从头设计和再设计两大途径[19]：从头设计是基于催化机制对蛋白骨架[20-22]或活性位点[23]进行构建，创制出全新的人工酶；再设计则是在已知酶的基础上，对现有蛋白骨架[24, 25]进行序列设计，以改善催化活性[26]、可溶表达[27, 28]、稳定性[29]以及可进化性[30, 31]等。尽管酶创制技术不尽相同，但如何从高度组合化的序列空间中高效获得满足工业应用要求的新酶是研究者面临的共同挑战。

工业酶创制的根本困难在于酶的序列、三维结构、催化机制与其在工程环境中所体现的催化性能之间尚难以建立普适性的、可量化的映射关系[32-35]。例如，酶的催化活性不仅由活性位点残基决定，还受到底物进入与产物释放、构象动态、静电环境、溶剂和辅因子供给状态等多因素的共同调控[36-39]。酶能否被高效表达，不仅取决于宿主、载体和培养条件，而且还受到蛋白毒性、密码子偏好性、调控元件和翻译及分泌过程等因素影响[40]。这些问题都可能制约工业酶创制的成功率和研发周期。

近年来，机器学习和深度学习技术日益深入应用于工业酶创制过程（图 1），为酶设计和改造提供了高效工具[41-47]。机器学习模型依赖于显式构建的序列、结构和化学特征，并通过监督学习建立特征与酶功能及性质之间的映射[41]，应用于酶的分类[48]、催化残基识别[49]和酶-底物关系判

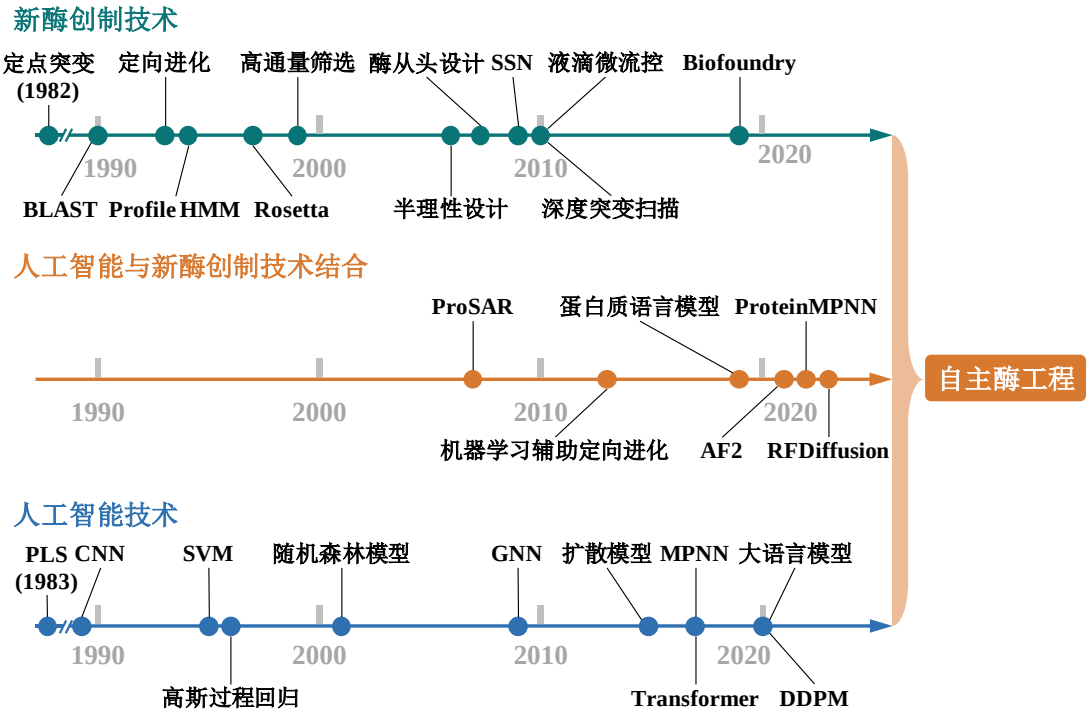


图 1　新酶创制技术与人工智能技术的协同演进

（BLAST—基于局部比对算法的搜索工具；HMM—隐马尔可夫模型；ProSAR—蛋白构效关系关联；SSN—序列相似性网络；AF2-AlphaFold2；PLS—偏最小二乘法；SVM—支持向量机；CNN—卷积神经网络；GNN—图神经网络；MPNN—消息传递神经网络；DDPM—去噪扩散概率模型）

Fig. 1　Co-evolution of novel-enzyme creation and Artificial Intelligence technology

断[50]等酶功能注释任务，并在酶改造过程中指导有利突变的选择[51-53]。随着酶学表征数据的不断积累，面向蛋白可溶性[54，55]、稳定性[56，57]和酶动力学性质[58，59]的通用预测工具也相继出现。上述进展建立起数据驱动新酶创制的工作范式，即从数据中学习构-效关系并指导酶分子设计的工作流程，但模型的构建仍然依赖人工特征选择，其建模酶催化中复杂相互作用的能力仍然有限，导致模型的泛化能力不足[60]。

深度学习模型能够以“端到端”的方式直接从数据中学习蛋白的多模态特征，降低对人工特征选择的依赖[61]。蛋白语言模型（Protein Language Model，PLM）通过自监督学习，对海量未标注的天然蛋白质序列建模其序列分布及其进化约束[62，63]，为酶挖掘[64，65]、性质预测[65，66]和生成式设计[67]提供可迁移的先验表征。AlphaFold 2基于注意力机制协同建模多序列比对信息与残基对关系，实现了蛋白质三维结构的低成本高精度预测[68，69]，为酶改造[70]、酶挖掘[71]和酶设计[72]提供了可靠的分子结构信息。当前深度学习技术正向着多模态融合[73，74]、全原子建模[75，76]和构象动态编码[77]方向推进，以更加精准地描述酶催化过程。尽管深度学习模型与工具日益丰富，但其选择和组合受到研究者自身的知识和经验“偏好”影响，因此迫切需要对新酶创制工作范式进行“进化”，以提高工业新酶的按需创制成功率。

智能体（Agent）的出现使得人工智能技术可以从更广泛的信息和数据处理层面参与科学研究过程[78]。智能体是指能够感知环境状态、围绕既定目标自主选择行动，并根据环境反馈持续调整决策的计算系统，即形成“感知—决策—行动”闭环[79]。大语言模型（Large language model，LLM）为智能体提供了通用性的语言理解、任务规划与人机交互层[80]。通过在模型外部构建包含角色与目标设定、状态管理、工具接口、执行控制和反馈处理的运行环境，LLM嵌入可持续迭代的决策流程，使其由生成回答的语言模型转变为能够执行任务的智能体[81]。科研智能体系统则进一步将自然语言规划、专业计算模型、可执行工具、实验反馈和人类监督相结合，在化学合成[82]、新材料制备[83]、生物医学[84]和机器学习研究[85]等领域初步实现了对于科学假设的自主探究。可以预见，在工业酶创制过程中应用智能体技术乃至实现自主酶工程，将会变革其研究范式并进而赋能生物制造。

本文首先分析自主酶工程的信息化基础，介绍新酶创制中酶挖掘、酶改造和酶设计的典型计算工作流；其次探讨实现自主酶工程所要解决的关键技术问题，概述科研智能体领域所发展的典型自主系统；最后分析自主酶工程的自主性等级划分与发展路径。

1 自主酶工程的信息化基础

生物信息学和化学信息学的发展与应用使得新酶创制成为一个可表示、可计算和可迭代的工程问题[86]，由此推进其向自主酶工程范式演进（图2）。其信息化基础包括研究对象和过程的标准化[87]、构效关系的模型化[88]以及实验通量的不断提升[89]，下文分别加以论述。

（1）研究对象的数据化和流程标准化为AI赋能新酶创制提供了数据流程入口。自主系统要求研究对象具有一致的语义表示[90]。新酶创制的研究对象，如酶序列、结构和反应等，已形成了相应的数据规范[91]。此外，酶学委员会编号（Enzyme Commission Number，EC）[92]和基因本体（Gene Ontology，GO）[93]分别为酶反应分类和功能注释提供了标准化体系。Rhea数据库[94]和EnzymeMap数据集[95]等对公开酶反应进行整理、校验和原子映射，为反应检索与数据驱动建模提供了高质量数据资源。在酶学数据层面，STRENDA规范[96]强调酶来源、反应条件、组分、操作模式、容器类型和混合条件、采样等报告要素的元数据要求；EnzymeML规范[97]将实验条件、时间序列、动力学模型和参数组织为机器可读、可交换的数据格式。从工作流程的角度，新酶创制过程可抽象为“设计—构建—测试—学习”（Design-Build-Test-Learn，DBTL）构成的循环[98]。

（2）构效关系建模及其计算工具的丰富性和多样性为AI赋能新酶创制提供了设计工具箱。目前酶创制相关数据库、算法和计算模型已达百种量级[43，60]，可对酶的序列、结构、残基位点、功

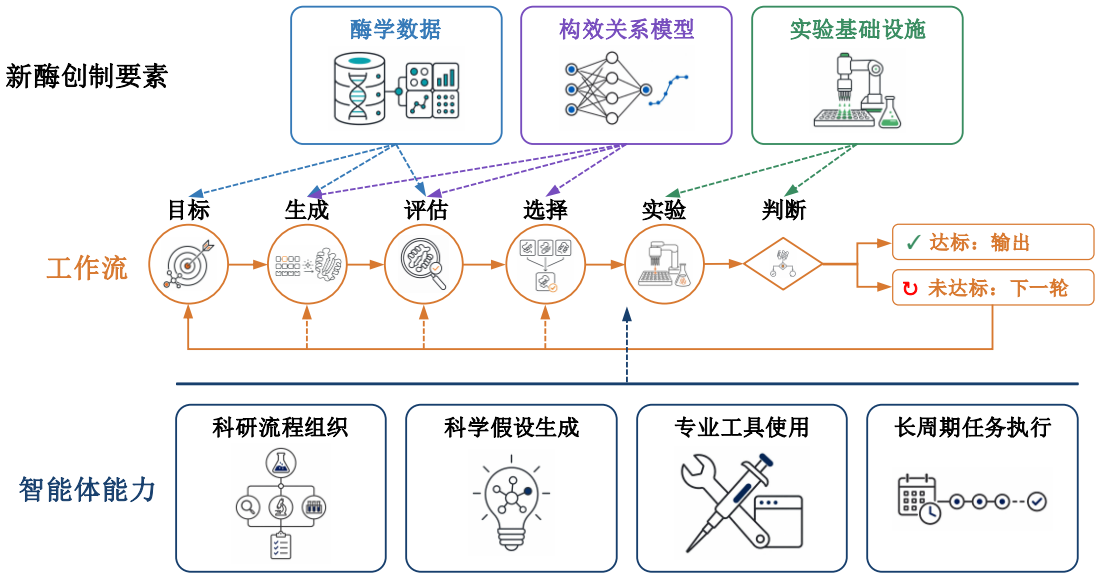


图 2　自主酶工程的基础要素、工作流对象及智能体能力

Fig. 2　Foundations, workflow objects and agent capabilities of autonomous enzyme engineering

能、性质和酶学数据等多种模态进行关联以用于新酶创制。此外，特定酶体系的构效知识大量散见于文献资料和数据库注释，对这些信息进行抽取和组织，可为工业酶创制决策提供更丰富的数据[99, 100]。基于多知识参考[101]、多模型集成[102]的共识评分策略已被应用于候选酶的挖掘与突变体筛选，并在部分体系中验证其提高了候选排序的稳健性。

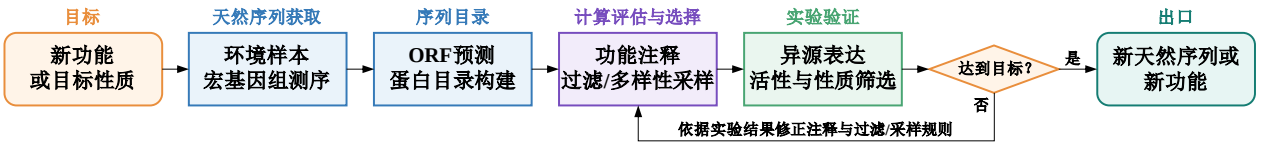
（3）自动化酶学实验设施为数据驱动的新酶创制提供了硬件支撑[103]。随着 DNA 合成与组装、微孔板检测、液滴筛选、细胞分选和高通量测序等技术及其装备的持续进步，实验平台已能够支持不同环节、不同规模的并行操作。液滴微流控和细胞分选系统适用于大规模单细胞或液滴事件筛选[104, 105]；微流控芯片可集成微量反应与检测[106, 107]；自动化移液工作站及工业级自动化实验平台则支持样品制备、构建和测定等流程的批量执行[108-112]。生物铸造厂和云实验室进一步通过标准化设备接口与实验协议，将分散的构建、测试环节封装为可调用的实验服务，为实验数据反馈计算决策并形成闭环提供基础设施[113]。

2　自主酶工程的研究单元：酶创制工作流

自主酶工程旨在将新酶创制中的专家决策逐步转化为智能体驱动的自主选择与迭代优化，其基础是将新酶创制过程形式化为机器可执行、可反馈的工作流。图 3 概括了目前所发展的酶挖掘、改造和酶设计的主要工作流，下面结合近期代表性研究分别加以评述。

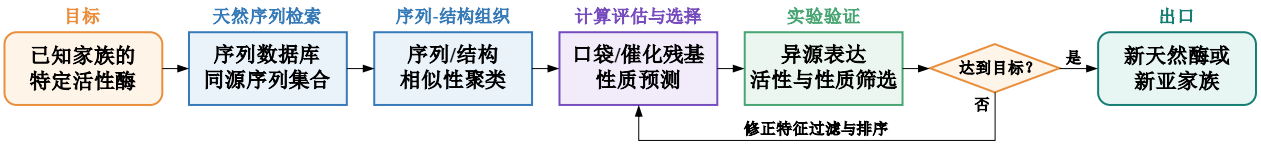
2.1　酶挖掘

基于基因组测序的酶挖掘［图 3(a)］：从环境中发现新酶是经典且有效的方法[8]。Tournier 等[114]从叶枝堆肥宏基因组来源的角质酶 LCC 出发，经蛋白质工程优化获得高效 PET 水解酶，实现了 PET 废料的高效解聚，并进一步制备出性能接近石化 PET 的再生材料。Santos 等[115]对长期覆盖甘蔗渣的土壤微生物群落进行宏基因组组装，从富含糖类活性酶基因的未培养基因组中筛选缺乏 CAZy 注释、但经远源同源性分析提示可能参与糖类代谢的蛋白，通过异源表达和底物活性筛选，发现了能够以氧化还原型外切机制裂解纤维素的铜依赖性酶，该酶在工业相关条件下提高了预处理木质纤维素的糖化效率，显示出在生物质转化中的应用潜力。针对于海洋宏基因组测序项目开发了全球海洋微生物组蛋白目录（GOPC）[116]，从中挖掘得到新型 CRISPR-Cas9 系统、多种抗菌肽以及具有嗜盐性质的 PET 降解酶。需要指出的是，基因组挖掘获得的候选酶通常仍需经过表达优化、



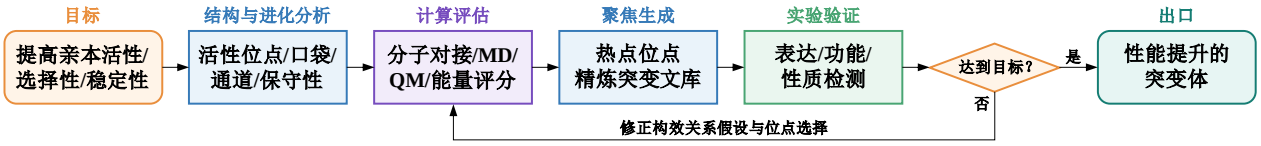
(a) 基于基因组测序的酶挖掘

(a) Enzyme mining based on genome sequencing



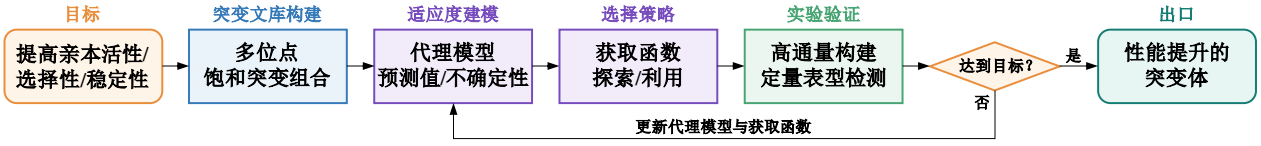
(b) 基于序列/结构特征的酶挖掘

(b) Enzyme mining based on sequence/structural features



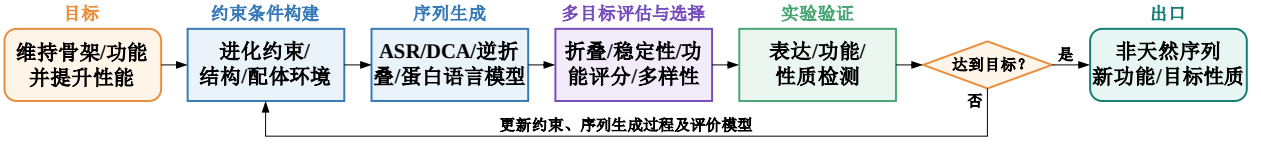
(c) 基于理性与半理性设计的酶改造

(c) Rational and semi-rational enzyme engineering



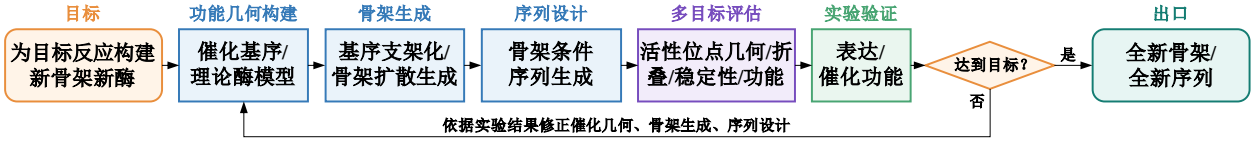
(d) 机器学习辅助的酶定向进化

(d) Machine Learning-assisted directed evolution of enzyme



(e) 基于进化与结构约束的酶的序列再设计

(e) Sequence redesign of enzyme based on evolutionary and structural constraints



(f) 从头酶设计

(f) *de novo* enzyme design

图3 新酶创制的典型工作流：酶挖掘、酶改造和酶设计

Fig. 3 Typical workflow for novel-enzyme creation: enzyme mining, enzyme engineering and enzyme design

(ORF—开放阅读框;MD—分子模拟;QM—量子化学计算;ASR—祖先序列重构;DCA—直接耦合分析)

酶改造、工艺适配和放大验证，才能实现从候选发现到工业应用的转化。

基于序列/结构特征的酶挖掘［图3(b)］：基于序列和结构特征的计算评估和选择可以提高酶挖

掘效率[117]。Damborsky等总结了计算筛选、酶构建和实验表征相结合的酶挖掘流程[118]，开发了酶挖掘平台EnzyMiner[119]，并在2.0版本[120]中引入了多个预测模型对酶的活性、溶解度、热稳定性进行评估以辅助酶筛选。Seo等[121]采用聚类采样和分层采样方法对聚酯酶-脂肪酶-角质酶家族进行系统探究，揭示了PET降解活性的广泛存在，并筛选得到在工业条件下具有良好表现的PET降解酶。Huang等[71]利用AlphaFold 2预测结构，通过基于TM-score的成对结构比对构建相似性矩阵，再进行层次聚类，据此识别不同的结构分支，并通过碱基编辑实验筛选具有目标活性的脱氨酶。Chen等[122]将Pythia-Pocket预测的催化口袋特征和Pythia预测的稳定性特征结合，应用于新型氨基甲酸酯酶的挖掘，用于工业聚氨酯的降解。Kipouros等[123]首先预测含cupin结构域的蛋白结构，再依据活性位点中两个组氨酸的空间构型识别潜在铁结合位点；与通常具有2His-1Asp/Glu配位基序的相关酶不同，Fe（II）/α-酮戊二酸依赖性自由基卤化酶的相应位置常由不参与金属配位的Gly/Ala占据，为卤离子结合留出配位位点。研究者据此筛选候选序列，并结合序列相似性网络和基因组邻域分析，最终经实验验证得到具有独特催化机制的自由基卤化酶。

2.2 酶改造

基于理性与半理性设计的酶改造［图3(c)］：Sun等[124]开发了Pythia模型，采用图神经网络基于蛋白结构进行自监督学习，可以用于预测突变后蛋白折叠自由能的变化；基于该模型构建的PythiaStudio平台[125]可以预测突变对蛋白质稳定性、蛋白质-蛋白质结合亲和力及配体结合口袋的影响。Roda等[126]开发了AsiteDesign设计方法，结合了基于蒙特卡洛的增强采样技术，用于在给定的结合口袋中引入新的催化残基，以创造新的催化活性或改变现有的催化活性。Gao等[127]应用HotSpot Wizard、分子对接、底物通道分析、多序列比对和分子动力学模拟和Funclib等多种工具以进行非特异性过氧化酶的发现和高效改造。Merlick等[128]开发了AI. zymes平台，集成ProteinMPNN、Rosetta、ESMFold、FieldTools等工具，用于改善酶催化相关的性质，如热稳定性、过渡态亲和力和局部电场等。

机器学习辅助的酶定向进化［图3(d)］：定向进化已形成若干具有明确工业应用价值的案例[129]。例如，经定向进化优化的多酶级联和化学-酶级联工艺，分别用于依斯拉韦[130]和恩利西肽[131]的合成。在此基础上，利用适应度数据训练模型，可进一步提高突变体选择与实验迭代的效率[42, 53]。Romero等[53]采用高斯过程回归基于之前轮次的数据建模预测酶的突变的适应度值，并同时给出预测不确定性以指导下一轮突变的开展；Wittmann等[132]的工作表明采取零样本预测策略构建信息丰富的训练集可以更有效地引导定向进化过程；Yang等[133]提出了主动学习引导的机器学习，并对于多种蛋白编码、模型、获取函数和不确定性量化方式进行了系统性评估。Jiang等[67]提出了EVOLVEpro模型，将蛋白语言模型和少量样本的主动学习结合，在微型CRISPR核酸酶等6个案例上实现了高效的酶进化。

2.3 酶设计

基于进化与结构约束的序列再设计［图3(e)］：序列再设计可在既有序列基础上进行较大幅度的调整，按其主要约束来源可分为三类：一是以进化信息为主要约束的方法，包括祖先序列重建[134, 135]，以及学习蛋白家族序列分布与残基共变规律的统计模型[136, 137]和深度学习模型，如ProGAN[138]等；二是以蛋白质三维结构为主要约束的逆折叠方法，包括ProteinMPNN[24]、ESM-IF[139]和ABACUS-T[140]等；三是以功能注释或多模态条件引导序列生成的方法，包括ProGen[141]和ESM-3[63]等。Sumida等[26]使用ProteinMPNN模型进行酶的再设计，通过保留功能上的重要位点和保守性位点，可以在维持酶活的同时大幅提高酶的可表达性和热稳定性；LigandMPNN模型[25]则可以显式引入小分子、金属等非蛋白原子作为蛋白生成的环境。Johnson等[142]构建了针对于蛋白生成模型的评估流程，引入了包括结构、序列等近20种指标，并在苹果酸脱氢酶（MDH）和铜

超氧化物歧化酶（CuSOD）上验证了这些指标的效果。Savage等[143]开发了引导式生成算法ProteinGuide，在序列生成过程中即引入性质评估模型来即时地对其进行引导，从而直接得到具有预期性质的目标蛋白，并在腺嘌呤碱基编辑器上验证了算法的效率。

从头酶设计［图3（f）］：Baker等开发了RFDiffusion模型[76, 144]，通过学习蛋白三维骨架的去噪过程，在功能基序和界面几何等约束下生成全新的蛋白质骨架，在蛋白水解酶[145]、丝氨酸水解酶[21]和Zn依赖型酮还原酶[146]等案例中验证了其方法的有效性，建立了“活性位点定义-骨架生成-序列设计”的从头酶设计流程。Braun等[147]提出了旋转异构体倒置片段查找器-扩散（Riff-Diff）策略，可以精确构建骨架-侧链片段、提高给定催化阵列的设计精度并且定制化设计结合口袋；实现了逆醛缩酶和催化Morita–Baylis–Hillman反应的酶（MBHases）的高精准度的设计。Listov等[22]构建了综合性的骨架生成、稳定性设计、活性位点-骨架匹配、多目标筛选和活性位点优化的完全计算从头设计策略，得到了与定向进化后的酶效果相当的Kemp消除酶。Degrado等[23, 148]采用在全新骨架上引入活性位点以及配体结合位点的策略，获得了可催化非天然金属卡宾反应的血红素酶。

3 自主酶工程智能体的能力与系统架构

酶挖掘、酶改造和酶设计工作流均需整合酶的序列、结构及实验数据，并在计算分析与实验验证之间反复迭代。现有科研智能体已能依托可执行、可反馈的研究环境组织部分计算与实验任务，根据中间结果选择后续行动，并在特定任务中形成反馈闭环[149, 150]。然而，在新酶创制中，候选酶或突变位点的选择、催化机制假设的提出、分析工具与实验方案的确定，以及根据实验结果调整新一轮目标等关键决策，仍主要依赖研究人员。为使智能体进一步参与这些决策，自主酶工程所依托的智能体系统需具备科研流程组织、科学假设生成、专业工具调用和长周期任务执行等能力。

科研智能体的系统架构仍在快速演进［图4］。下文讨论的系统主要应用于化学合成、药物发现等任务，尚未在新酶创制问题上进行验证，但其任务编排、假设生成、工具调用和跨轮次决策机制，可为自主酶工程智能体系统的构建提供借鉴。下面将围绕上述四项能力介绍相关技术的研究进展。

3.1 科研流程组织

在出现大语言模型驱动的智能体之前，机器人科学家（Robot Scientist）已展示目标驱动科研闭环的基本形态[90]。2004年King等[151]构建了酵母代谢知识的逻辑表示体系，遵循“假说-演绎”范式，通过溯因推断生成基因与酶反应之间的对应假说，演绎推导其可观测后果，并利用主动学习选择和执行实验，证明机器能够在预定义问题空间内自主完成假说检验。2009年出现的Adam系统[152]构建了科学实验本体，将研究假说、实验设计、操作、观测、分析、结论及元数据组织为包含10个层级和逾万个研究单元的逻辑结构，实现了科研过程的可追溯表示。其自动化硬件可连续完成菌株选择、培养及生长表型测定。这些工作确立了将推理、实验与反馈连接为可追溯闭环的自主科学发现范式，然而仍然依赖于形式化的知识表示。

大语言模型使得自然语言可以作为科研任务的统一表征与编排媒介。研究者以自然语言提出研究目标，而智能体将其转化为信息检索、计算分析、代码执行和实验操作，由此形成以自然语言驱动的科研全流程。2023年Boiko等[82]构建了GPT-4驱动的Coscientist［图4（a）］，该系统在预先限定的试剂和硬件空间内规划并执行了Suzuki-Miyaura和Sonogashira偶联反应，并在反应条件优化任务中表现出利用实验反馈调整后续决策的能力。该工作表明，大语言模型能够作为连接科研环节的通用语义与控制层。同期，ChemCrow[153]以“思考—执行—接受反馈—观察”的ReAct循环为控制框架，根据自然语言任务动态选择并调用18种化学专业工具［图4（b）］，覆盖信息检索、化学实体与结构转换、分子计算、价格与专利查询、

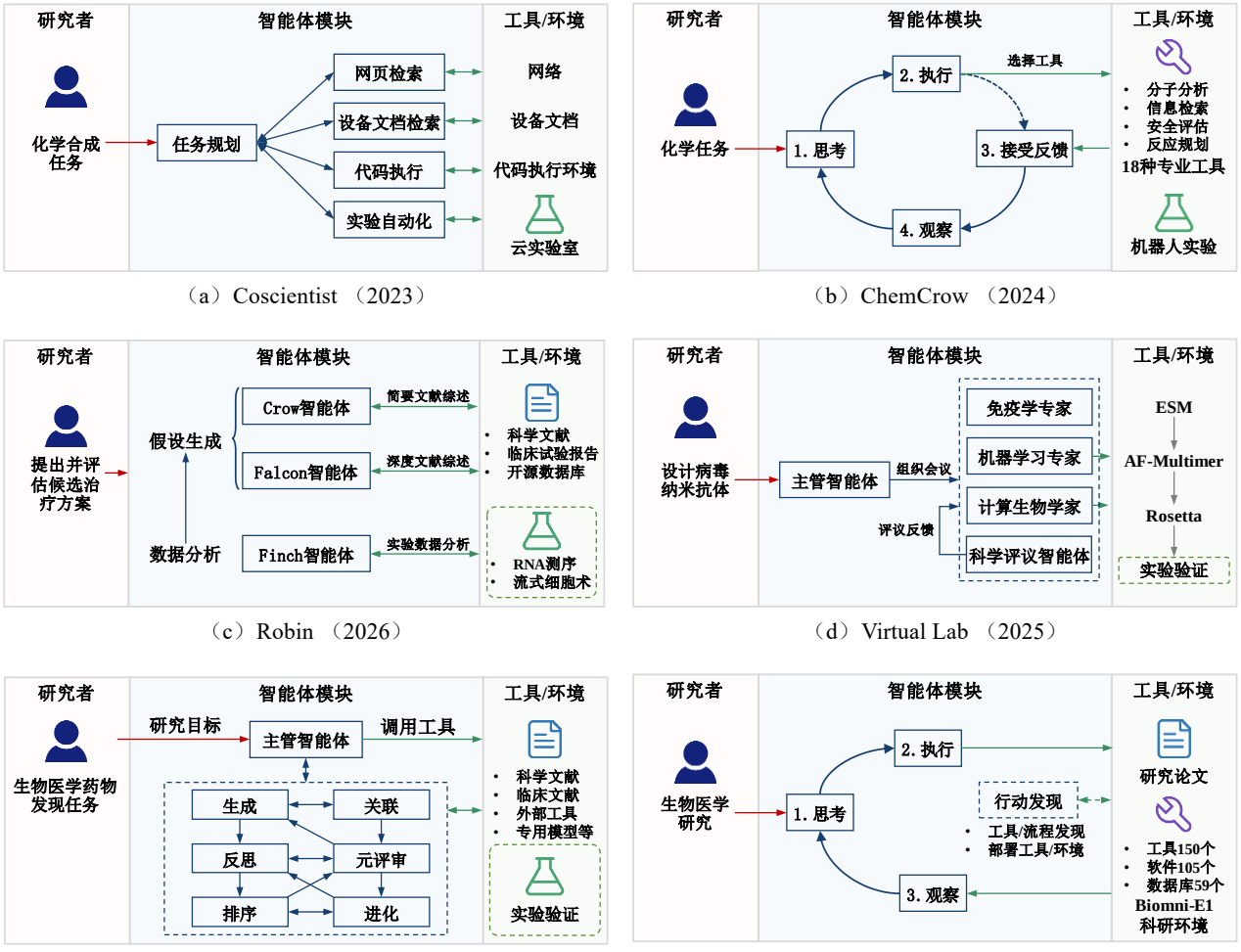


图 4　科研智能体的系统架构。六个系统分别展示了实验编排（Coscientist）、专业工具调用（ChemCrow）、证据整合（Robin）、角色协作（Virtual Lab）、假设生成与迭代（Co-scientist）以及通用科研工具环境（Biomni）等架构路径，为自主酶工程智能体设计提供参考。

Fig. 4　System architecture of scientific agents. The six systems exemplify distinct architectural pathways, including experimental orchestration (Coscientist), domain-specific tool use (ChemCrow), evidence integration (Robin), role-based collaboration (Virtual Lab), hypothesis generation and iteration (Co-Scientist), and a general-purpose scientific tool environment (Biomni), providing design insights for autonomous enzyme engineering agents.

安全评估、反应预测、逆合成规划及机器人实验等环节。专家评估显示，ChemCrow在化学事实正确性和任务完成度方面优于未接入工具的GPT-4，表明自然语言规划器能够将开放式化学任务转化为可执行、可验证的专业工具链。近期，Shao等[154]构建了基于高通量分子模拟的酶工程平台MutexaGPT，可以以自然语言描述改造要求，平台通过对话形式补全必要信息，将要求转成物理计算方案，再调用高通量分子模拟，返回具体突变建议和计算依据。该平台在卤代烷甲基转移酶和双结构域淀粉酶的酶工程改造中进行了验证。

3.2　科学假设生成

大语言模型为基于推理的科学假设生成提供了技术支持[155]。通过检索增强生成（retrieval-augmented generation，RAG）[156]等方法，文献证据与实验数据可以被纳入假设生成过程。Ghareeb等[157]构建的多智能体系统Robin将文献分析、假设生成和实验数据分析连接为连续的工作流［图4

（c）]。其中，Crow和Falcon智能体分别负责初步文献汇集和深度文献综述，Finch智能体负责实验数据分析。在一次典型研究任务中，系统可在2小时内分析500余篇文献，并根据实验数据修正候选机制解释。

智能体可利用思维链（chain-of-thought，CoT）分解复杂问题并组织推理过程[158]，还可通过推理-行动框架（Reasoning and Acting，ReAct）将推理、行动和反馈更新组织为循环，以支持复杂任务求解[159]。然而，单智能体在长时程任务中仍容易受到早期判断、上下文信息利用不足和单一路径推理的限制[160，161]。多智能体协作可通过并行生成、交叉评议和候选竞争拓展假设搜索空间，并对候选假设进行相互校验[162]。

Swanson等[163]以新型SARS-Cov-2抗体的开发为例，展示了Virtual Lab按照科研角色组织多智能体协作的模式［图4（d）］。在研究者提出开发针对SARS-Cov-2新变体KP.3刺突蛋白的结合分子这一目标后，主管智能体组建由免疫学、机器学习和计算生物学等不同专业背景智能体组成的团队，通过集体会议开展多轮讨论，形成了以已知抗体为起点、通过突变提高其对KP.3刺突蛋白受体结合域结合能力的设计方案。随后，团队选择ESM、AlphaFold-Multimer和Rosetta，用于生成单点突变、预测复合物结构并评估结合能。在此过程中，科学评议智能体负责识别错误与遗漏，各个专业智能体则依据评议反馈完成代码和设计任务。研究者最终对系统设计的92个候选抗体进行实验验证，其中超过90%能够可溶表达，2个表现出新的或增强的结合信号。

Gottweis等[164]构建的结构化科学思考智能体Co-Scientist将假设生成、反思、排序、关联、优化和元评审分配给不同专业智能体［图4（e）］，通过持续竞争和迭代修订提高候选假设的新颖性、证据一致性与可行性。消融实验和专家评价表明，角色化协作及其专用提示策略能够提高系统性能和稳定性；通过在药物重定位、新靶点发现与抗菌素耐药性三类案例验证了所提出的科学方案的合理性。类似的角色分工也开始应用于蛋白质研究：Sparks[165]在关键研究阶段配置“生成—反思”智能体，VenusFactory2[166]以首席研究员、机器学习专家、计算生物学家和科学批评者协同执行长时程蛋白设计任务，ProtAgents[167]则通过规划、执行、评估和会话管理智能体协作将蛋白设计目标转化为候选序列。

3.3 专业工具调用

对于大语言模型处理蛋白序列任务的基准测试表明，其将蛋白序列作为自然语言进行理解、改造和生成的能力仍然有限[168-171]，而利用大语言模型生成可执行代码，并据此完成构效关系模型的“端到端”构建提供了一条间接路径[172，173]。专业工具的接入使智能体能够获得与大语言模型能力互补的领域智能[174-176]。Teneggi等[177]基于Rosetta蛋白设计环境开发了Agent Rosetta系统。为降低RosettaScripts中复杂XML语法带来的错误，将Rosetta工作模块封装为结构化接口，消融试验表明，结构化接口可将氨基酸组成约束生成的成功率由最高约70%提高至98.88%以上。Ouyang等[178]提出了面向计算蛋白质设计的智能体框架PDAgent，将自然语言需求转化为热稳定性、溶解性、pH、长度和二级结构等结构化约束，并调用多种蛋白设计工具，在天然蛋白支架附近迭代生成、筛选和评价突变。

Anthropic于2024年11月发布模型上下文协议（Model Context Protocol，MCP），规范AI应用与外部数据源、工具及服务之间的连接方式[179]；与MCP互补，技能（Skill）将特定任务所需的操作步骤、领域知识、工具配置和执行约束封装为可复用模块[180]。Xu等[181]开发了面向计算蛋白工程的智能体框架ProteinMCP，将38个模型/工具的接口封装为MCP服务器，覆盖了文献检索、序列与多序列比对、适应度建模、结构预测、蛋白设计、性质预测、分子动力学和数据库工具8种类型。复杂流程则被固化为包含目标、依赖MCP、参数和执行步骤的技能，从而减少重复提示并提高复用性。

更大规模的工具集成并形成统一工作环境有助于智能体参与科学研究。Huang等[84]构建了通用生物医学研究智能体平台Biomni，将统一科学行动空间、检索增强规划、代码执行和领域强化

学习整合为可扩展体系［图4(f)］。其行动发现智能体（action-discovery agent）从文献中抽取研究任务、软件、数据库、AI模型和实验协议，经专家验证后构建了包含150个专用生物工具、105个软件包及59个数据库的Biomni-E1。基于该环境，智能体Biomni-A1能够进行资源检索、研究规划和工具调用，并在单细胞注释、罕见病诊断和基因组规模因果分析（GWAS）基因识别任务中提高了执行效率。然而，在完备工具和环境的基础上，智能体能否根据研究目标和中间结果动态地选择工具、设定参数并调整执行路径，仍然是需要验证的问题[182]。

3.4 长周期任务执行

智能体依靠上下文管理和外部记忆维持跨轮次状态[183]。长上下文训练、位置编码扩展和推理优化不断提升大语言模型处理长序列信息的能力[184]。在此基础上，科研智能体通过持续接收和分析新数据，更新科学假设、研究状态和后续计划，从而可以由一次性工具调用扩展支持长周期任务执行[185]。

Mitchener等[186]开发了长周期数据驱动科研智能体Kosmos，以结构化世界模型协调数据分析和文献检索。系统将每轮产生的分析脚本、统计结果、文献证据和候选发现压缩写入世界模型，并据此规划后续任务。典型运行包含约166个数据分析和36项文献综述，生成约42,000行代码、检索约1,500篇全文，并在最长约12小时的独立研究后形成3–4份可追溯至代码或原始文献的研究报告。独立专家支持其102项声明中的79.4%；其中，数据分析和文献陈述的准确率分别为85.5%和82.1%，但综合证据解释的准确率仅为57.9%。这些结果表明，结构化记忆与循环规划能够支持长时程计算研究，但综合多个来源证据的推断解释仍是主要瓶颈。

长时程自主运行首先要求智能体能够从数据中形成可靠结论。现有蛋白工程DBTL系统通常依据预先定义的适应度指标更新代理模型并选择下一轮候选[98]，适合目标明确的优化任务。然而，开放式研究还要求系统判断目标是否合理，并在证据变化时调整研究重点，例如由改善蛋白质稳定性转向提高目标反应活性。为此，还需评价智能体能否正确分析真实数据，对比不同实验要素以识别科学规律，并据此修订假设和目标[187, 188]。

在实验执行层面，智能体与自动化平台结合后，可根据真实测量结果开展多轮优化[189]。SAMPLE将主动学习与机器人实验连接，用于优化糖苷水解酶的耐热性[109]；自主酶工程平台进一步连接蛋白质语言模型、低样本学习与自动化实验，在多轮DBTL循环中优化卤化物甲基转移酶的底物偏好和植酸酶的中性pH活性[190]。然而，现有新酶创制应用仍依赖于可量化的目标和预先限定的动作空间，尚未体现对开放科学目标、机制假设和实验路线的自主修订能力。此外，长时程实验还面临步骤长、操作参数复杂、对照设置和安全约束等，任何局部遗漏都会导致整个实验批次失效[191]。

4 自主酶工程等级

自主酶工程的发展体现为AI决策边界随项目需求逐步扩展[192]。本文将其划分为A0—A5六个等级［图5］，其依据在于系统可支配的动作空间，包括可选择的策略、工具、参数以及计算和实验操作[89, 149]。随着自主性等级提升，智能体的决策范围由单项工具执行和固定流程，扩展至反馈优化、动态规划、实验闭环和科学假设修订；相应地，研究者关注的层次则由“如何执行”上移至“开展什么研究”以及“为何开展”。

实现更高水平的自主酶工程，可沿“平台化—智能化—体系验证”的路线协同推进[149]。平台化阶段应建设面向新酶创制的统一开发环境，以标准化的数据模型、项目状态表示和接口连接数据库、算法、模型及实验设备，并系统记录数据处理代码、参数配置、实验过程、设备状态、失败结果和探索轨迹，将研究过程及领域经验总结为语义明确、质量可控、可追溯和可复用的数字资源；智能化阶段应构建贯穿新酶创制全流程的科研智能体，使其能够理解研究目标、提出科学假设、制定研究方案、调用专业工具、分析实验数据，并依据反馈开展多轮决策与迭代；体系验

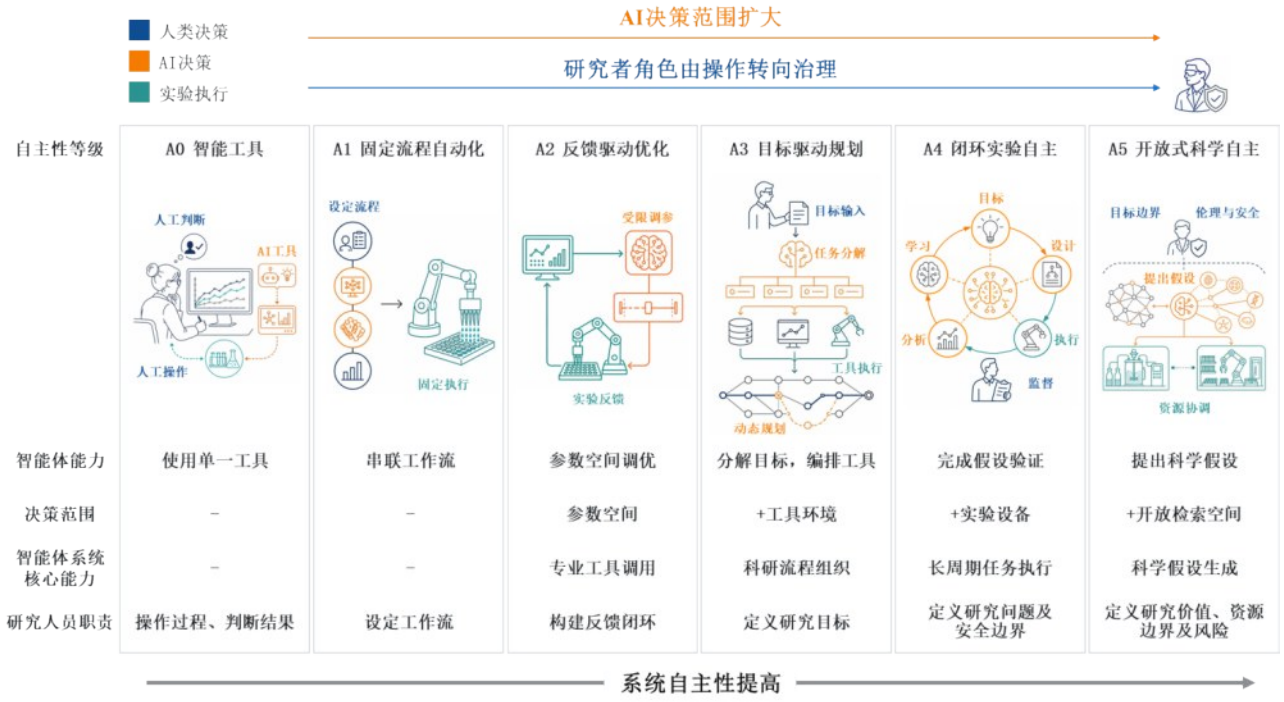


图5 自主酶工程的自主性等级。A0：使用单一工具完成指定任务；A1：按预设工作流自动执行任务；A2：根据结果反馈，在预设参数空间内优化后续决策；A3：围绕研发目标分解任务，并在授权工具集中选择工具、调整执行路径；A4：连接实验设备，在预设的操作与安全边界内实现“目标-设计-执行-分析-学习”闭环；A5：针对开放性科学问题提出假设，并自主选择工具开展研究

Fig. 5 Autonomy levels of autonomous enzyme engineering. A0: A single tool performs a specified task. A1: Tasks are executed automatically according to a predefined workflow. A2: Subsequent decisions are optimized within a predefined parameter space based on feedback. A3: The agent decomposes a research objective, selects from authorized tools, and adjusts the execution path. A4: Connected to experimental equipment, the agent operates a hypothesis-design-execution-analysis-learning loop within predefined operational and safety boundaries. A5: The agent formulates hypotheses for open-ended scientific questions and autonomously selects tools to investigate them

证阶段应针对真实酶创制任务建立分级基准，从静态任务和回顾性分析逐步拓展至前瞻性实验，综合评价科学正确性、任务完成率、实验收益、资源消耗、异常恢复和结果可重复性，并依据验证结果逐级开放更复杂、更开放和更长时程任务的自主执行权限。

自主性等级衡量完整系统在特定项目中的决策权限，而非模型性能或技术成熟度[193]。同一系统在不同任务、工具权限和实验条件下可能具有不同等级。更高自主性可以减少重复性人工决策及经验偏差，但也会扩大错误传播以及不可逆操作的风险，使得系统脆性提高[194]。因此，自主等级不应成为单向追求的性能指标，而应根据任务开放程度、实验风险、资源成本和验证证据进行选择[113]。对于边界明确或风险较高的任务，经过充分验证的较低等级系统可能更具实用价值。

不同的自主性等级对应着不同的治理要求，其控制强度应与任务本身的风险相称[195]。在A0智能工具和A1固定流程自动化阶段，研究人员应负责工具选择、流程配置、结果解释及后续决策；在A2反馈驱动的受限优化阶段，应将智能体的行动限制在预设的目标、文库、预算和质量标准内，并对关键轮次进行审核；在A3目标驱动的动态规划阶段，智能体虽可在授权工具集内调整研究路径，但高成本或高风险行动仍须经人工批准；在A4闭环实验自主阶段，鉴于智能体将连接真实实验设备并依据实验反馈执行多轮决策，还应强化设备接入授权、质量控制、异常停机和人工接管

机制；在A5开放式科学自主阶段，智能体可提出和修订科学假设、目标及研究策略，但涉及研究目标、资源使用或风险边界的重大变更仍需由人类审议，最终科研责任不能转移给智能体。

自主性的提升还需要受到科研价值、伦理规范与安全边界的约束。由于现有的大语言模型仍具有黑箱属性，存在软件越权和网络安全风险[196]；在酶设计等生物学任务中还涉及生物安全和双重用途伦理风险[197]；当智能体连接实验设备时，错误决策还可能转化为设备损坏、样品污染或人员伤害等物理风险。随着科研智能体更多地参与科学假设提出与知识生产，还需要进一步明确其使用披露、贡献认定和知识产权安排，并建立相应的科研治理规范[198]。

总结与展望

工业酶创制是支撑绿色生物制造发展的底层关键技术。随着生物数据积累与标准化、酶构效关系建模精度提升以及自动化实验技术持续进步，新酶创制正在呈现向自主酶工程演进的趋势。科研智能体为这一转变提供了新的技术载体。现有自主系统已能够在部分研究领域开展文献检索与综合、专业工具调用、数据分析和科学假设生成，并在目标明确的任务中连接自动化实验平台，实现多轮设计与优化。例如，生物医学研究智能体Biomni通过研究规划与工具调用，辅助研究者执行多类生物医学研究任务；物理计算驱动的酶工程平台MutexaGPT能够将自然语言描述的改造需求转化为高通量分子模拟任务，据此提出突变建议，并已在酶改造任务中得到初步验证；自主酶工程平台则结合蛋白质语言模型、低样本学习与自动化实验，通过多轮设计、构建、测试与学习循环，优化酶的底物偏好性和催化活性。这些进展表明，智能体能够将分散的数据、模型、工具和实验设备组织为连续的研究流程。然而，从执行预设任务到在开放环境中稳定开展科学发现，仍需解决科学推理、系统可靠性和实验闭环等一系列问题。

面向自主酶工程，科研智能体仍需重点发展四类能力。第一，准确理解研究目标与领域约束，将活性、选择性、稳定性、表达水平和工艺适配性等应用需求转化为可计算、可检验的科学问题的能力；第二，组织和动态调整研究流程，根据项目状态与中间结果选择工具、配置参数、分配资源，并在不同技术路线之间进行比较和切换的能力；第三，综合文献、数据库、计算预测和实验结果，形成可追溯的证据链和具有机制依据的科学解释的能力；第四，长周期任务运行，在多轮计算与实验反馈中保持目标和状态的一致性，并具备异常识别、结果校验、任务恢复与安全停止的能力。当前科研智能体在信息检索、代码生成和标准化工具调用方面进展较快，但其对专业知识和复杂约束的准确理解、跨来源证据综合、多工具动态编排、实验数据解释以及失败恢复能力仍缺乏充分、系统的验证。

在近期应用中，科研智能体更可能以分布式、模块化方式嵌入现有酶创制工作流。随着大语言模型、工具服务器和标准接口逐渐普及，可以在研究的具体环节部署智能体，并结合自身积累的数据、模型和实验条件进行定制。此类渐进式应用能够降低部署门槛，减少对既有科研流程的扰动，也有利于在边界明确的任务中积累可靠性证据。未来应在可靠性、安全性和可验证性的约束下，逐步扩大智能体的决策范围。通过持续完善数据资产、评价基准与基础设施建设，推动自主酶工程走向可持续应用的科学与工程实践。

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