

Crystallization for Manufacturing in Microgravity; Are We There Yet?

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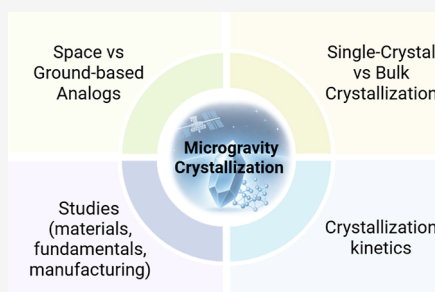


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ABSTRACT: Crystallization in microgravity has been extensively investigated because of its potential to enhance crystal quality compared to terrestrial conditions. While early efforts were primarily directed toward single-crystal growth for structural studies, increasing attention is now being given to its relevance for manufacturing in low-Earth orbit (LEO) and future in-space manufacturing (ISM). This review provides a structured and systematic analysis of the literature on microgravity crystallization by examining the materials studied, distinguishing between single-crystal and bulk crystal regimes, and evaluating the experimental methodologies used to investigate crystallization kinetics. Emphasis is placed on the current platforms. By adopting a manufacturing perspective, this work identifies key challenges and outlines directions for advancing microgravity crystallization toward scalable and controlled processes for manufacturing under microgravity. To date, the current body of literature remains fragmented and insufficiently aligned with process engineering and manufacturing considerations, including restricted in situ monitoring, a lack of standardization, and limited comparability across studies.



1. INTRODUCTION

Crystallization plays a key role in many processes occurring both in nature and in manufacturing.¹ It is a controlled process that enables the isolation, purification, and stabilization of materials while modulating their physicochemical properties.^{1–3} Reliable and reproducible control over the solid-state of crystalline materials is therefore essential for both industrial applications and research and development (R&D) across diverse sectors, including (bio)pharmaceuticals,^{1–3} semiconductors, food and nutrients, personal care, and materials science.^{1–3} The production of crystals of the desired solid form control and quality remains a significant challenge. Protein crystallization exemplifies these difficulties, as many biomolecules are inherently difficult to crystallize or tend to form poorly ordered structures.^{4–6}

Therefore, since the 1970s, microgravity has been explored as a distinctive environment for crystallization.⁷ In the absence of buoyancy-driven convection and sedimentation, diffusive transport dominates the mass transfer. Under these quiescent conditions, crystallization yields typically well-ordered crystals with enhanced mosaicity, structural quality, and uniformity compared to those grown under terrestrial gravity,^{6–9} highlighting the potential of microgravity for both fundamental studies and industrial applications. The first microgravity crystallization experiments were conducted onboard the Skylab mission in 1973.¹⁰ Subsequent studies aboard the MIR space station and on various Space Shuttle missions from the mid-1980s through the 1990s provided fundamental insights into crystal growth mechanisms under microgravity.¹¹ Since then, the research has continued aboard the International Space

Station (ISS) (Figure 1). These studies laid the foundation for potential industrial applications in, e.g., pharmaceuticals, electronics, and materials science.^{4,12–15}

While the early crystallization efforts in microgravity focused primarily on fundamental understanding and single-crystal growth for structural elucidation studies, current research is increasingly oriented toward industrial applications,⁴ establishing the foundation for in-space manufacturing (ISM).^{16,17} As spaceflights are projected to extend beyond low-Earth orbit (LEO), e.g., to the Moon and Mars, long-duration missions face strict limits on mass and volume of materials that can be brought on the mission.^{16–18} Shelf life and structural stability of these materials during long duration missions may also be impacted as exposure to radiation,¹⁹ temperature fluctuations, and microgravity can compromise stability. For example, most drugs in the ISS medical kit possess shelf lives shorter than the expected mission duration (>3 years), leaving only a small fraction of those prestocked medications effective.¹⁹ These limitations of materials for and during deep space missions coupled with the impracticality of resupply from Earth, underscores the need for ISM, including e.g., medicine. For instance, ISM enables the production of materials, tools, advanced materials, and pharmaceuticals in space, thereby

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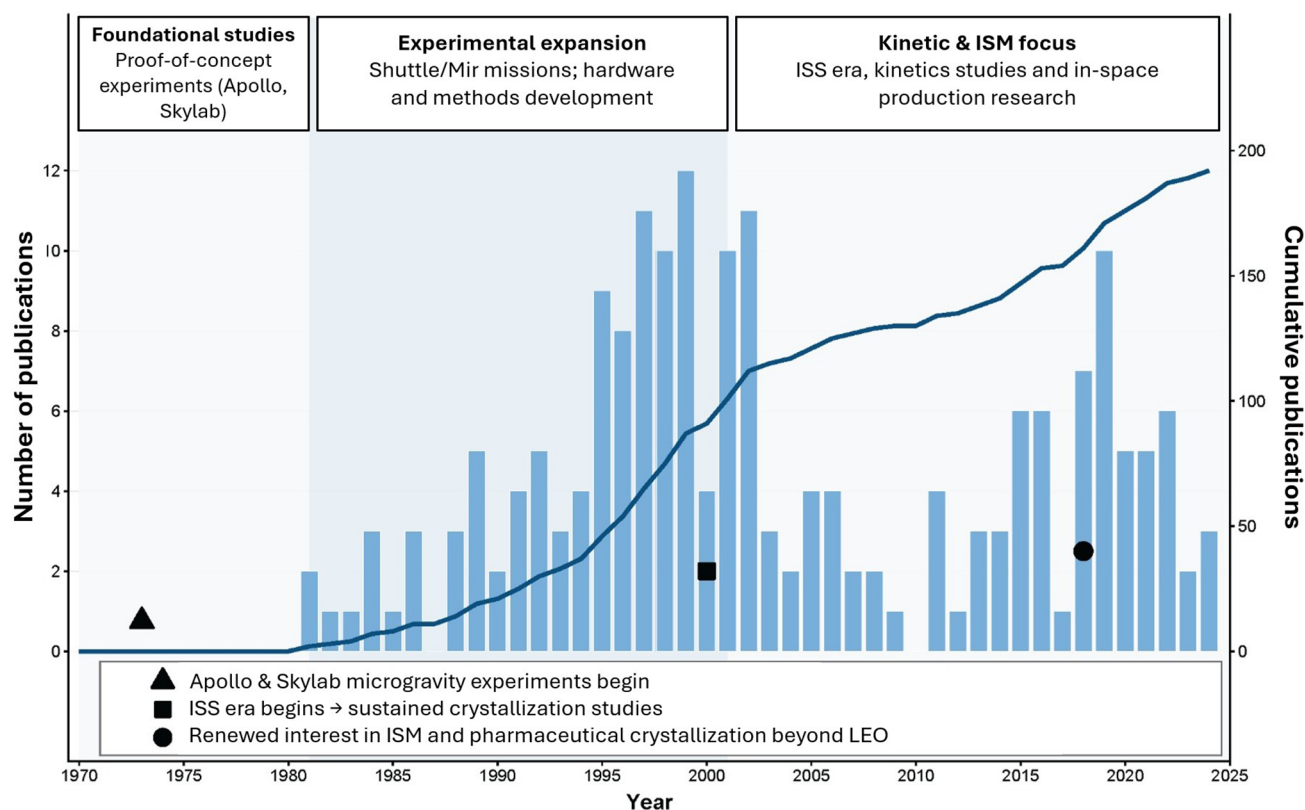


Figure 1. Publications and citations related to microgravity crystallization from 1981–2024. Shaded regions denote key stages in the evolution of the field, from early spaceflight proof-of-concept studies (1970–1980), through hardware and method development mostly focused on protein crystallization (1981–2000), to modern investigations of kinetics and toward in-space manufacturing (ISM) applications (2000–2024). The detailed methodology used for data collection and classification is provided in the [Supporting Information](#).

decreasing the reliance on Earth-based logistics, reduces mission costs, and increases operational flexibility, while contributing to the overall health and safety of the crew.^{20,21} Within ISM, crystallization emerges as a key manufacturing capability that will be required to ensure reliable pathways to produce stable, easy-to-store materials with the desired solid-state structure at the point-of-use.^{4,22}

Beyond its relevance to deep space missions, microgravity crystallization has yielded numerous beneficial insights for terrestrial manufacturing (e.g., novel drug formulations),⁴ a prelude to LEO. Recent private sector developments in next generation spacecrafts and reusable launch systems have spurred a new era of space technology exploration,^{16,23} which serves as a stepping stone to ISM.²⁴ The increasing interest is evident by a growing body of literature on crystallization related research in microgravity reported between 1970s and 2024. [Figure 1](#) summarized the number of microgravity crystallization studies (total 189 publications).^{4,8,9,11,15,23,25–201}

Despite over four decades of crystallization research in microgravity, the understanding of crystal growth kinetics under reduced gravity is scattered.^{9,102} Particularly, there is a dearth of literature on bulk crystallization, which is critical for ISM as it enables us to manufacture larger quantities of materials with an ideally uniform population of crystals. As a note, much of the early data in the 1970s was never published and often confined to internal reports.⁹ Since the 1980s, studies have indicated that microgravity conditions can fundamentally enhance material properties, yet materials often behave very differently in microgravity than on Earth,

making consistent replication difficult.²⁰² In addition, differences in experimental protocols, analytical techniques, and the fragmented or proprietary nature of the data available have made cross-study comparisons difficult.⁹ Bridging these knowledge gaps is therefore crucial to developing potential crystallization strategies for ISM, which require a comprehensive understanding of kinetics, morphology, and crystal quality beyond single crystals toward bulk systems.

Unlike prior reviews that primarily summarize experimental outcomes or examine microgravity crystallization from a structural or materials science perspective, this work attempts to evaluate the field through the lens of manufacturing feasibility. It consolidates the currently scattered literature with emphasis on kinetics, morphology, and crystal quality, while establishing a structured framework that links microgravity crystallization research to process engineering and industrial deployment. For detailed discussions about the mechanistic differences between crystallization under microgravity and on Earth, the interested reader is referred to existing reviews.^{7,66,203}

To facilitate this discussion, [Section 2](#) details the definition for manufacturing. [Section 3](#) focuses on the materials studied. [Section 4](#) contrasts single-crystal and bulk crystallization regimes, while [Section 5](#) discusses crystallization kinetics and methods utilized. [Section 6](#) highlights ground-based microgravity analogues. Finally, [Sections 7](#) and [8](#) offer future perspectives and concluding remarks, respectively.

2. CONCEPTS AND DEFINITIONS

To establish a unifying baseline for this review article, the authors feel the need to define the term manufacturing.

- Manufacturing is defined as the application of physical and chemical processes to modify the geometry, properties, and/or appearance of a given starting material, including recycled materials to produce products of higher value.²⁰⁴ Broadly speaking, this includes producing individual crystals with higher quality used in pharmaceuticals, semiconductors, and other industrial applications. However, in the traditional sense, manufacturing typically involves a sequence of unit operations designed to transform raw materials into a desired final or commercial state, representing the outcome of a complete manufacturing process.²⁰⁴ This increase in value encompasses not only economic benefits but also societal advantages, such as improved health and quality of life provided by formulated pharmaceutical products.^{4,204} Moreover, manufacturing requires not just the establishment of the quality and performance attributes of the product but also their approval by a regulatory agency based on a process model or structure for effective quality management (quality system).
- In-space manufacturing (ISM) is assumed to take place outside of the Earth's atmosphere to leverage the unique conditions of microgravity or the need during deep space missions.²⁰⁵ Thus, similar to manufacturing on Earth of e.g., pharmaceuticals, ISM needs to rely on careful process design, automation, and quality control to achieve consistent, reliable, and scalable production in a challenging environment under current good manufacturing practice (cGMP).²⁰⁵
- Low-Earth orbit (LEO) manufacturing refers to the production or processing of materials and products in facilities located in altitudes of about 160–2000 km above Earth (e.g., the ISS or commercial space stations),²⁰⁵ while ISM encompasses the broader set of manufacturing in space.

By defining these terms, this review establishes a framework allowing us to interpret the existing microgravity crystallization literature (Figure 1). Here, it needs to be stated that to the best of the authors' knowledge, all reported literature (Figure 1) remains within the process-development domain and does not constitute manufacturing. To date, microgravity is leveraged as a platform for fundamental and proof-of-concept crystallization studies aimed at understanding and improving material quality, uniformity, and functionality to be employed in terrestrial applications. Thus, all studies are primarily of exploratory nature, representing R&D or trial-and-error studies rather than ISM, as defined above.²⁰⁴

3. MATERIALS INVESTIGATED IN MICROGRAVITY

Crystallization studies in microgravity have been reported across a diverse range of materials, from water/ice⁶³ and simple small molecules to complex proteins, colloids,¹¹² and semiconductors⁵² (Figure 2). A detailed list of materials and publications is provided in Sections S2 and S3 of the Supporting Information.

From total 146 materials studied in 189 publications, proteins and enzymes dominate the microgravity crystallization studies by far, accounting for ~ 70% of reported experiments

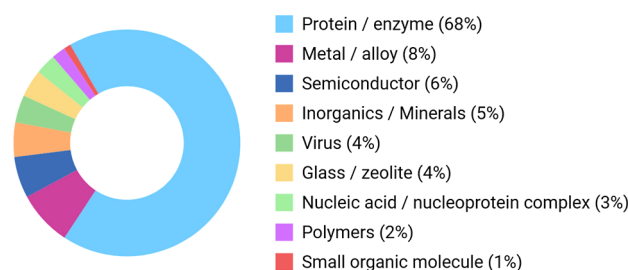


Figure 2. Distribution of 146 materials examined across 189 microgravity publications (Figure 1), organized into major categories. Details are provided in Table S1.

(Figure 2). This prevalence reflects the historical emphasis on biologically and structurally relevant macromolecules, where microgravity offered clear advantages for producing highly ordered crystals for diffraction-based analysis.^{9,57} While advances in structural biology techniques, such as cryo-EM, NMR, and MicroED, have reduced the exclusive reliance on crystallization for structure determination,^{144,206} they have not diminished interest in crystallization under microgravity.

In contrast to proteins and enzymes, other materials relevant to industrial crystallization are comparatively underrepresented. Semiconductors (6%), metals and alloys (8%), inorganics and minerals (5%),¹⁸⁴ viruses (4%), glass and zeolites (4%),¹⁹⁵ nucleic acids and nucleoprotein complexes (3%), polymers (2%), and small organic molecules (1%) are studied far less frequently. Combined, these categories account for only ~30% of the reported studies (Figure 2). This imbalance highlights an important limitation in the current knowledge base, as most microgravity crystallization research has historically focused on improving crystal quality^{9,88,102} rather than understanding crystallization processes relevant to scalable manufacturing.^{23,140}

Nevertheless, recent years have seen a gradual shift in the focus. Microgravity crystallization studies continue to grow, increasingly emphasizing process understanding, formulation, and manufacturing sciences. This shift is reflected in expanding research efforts in LEO, including studies on therapeutic proteins aimed at improving manufacturability on Earth (e.g., pembrolizumab/Keytruda),^{4,98} as well as investigations into advanced materials such as optical and ZBLAN fluoride glasses.^{192,194} It should be stated that for glasses, efforts are generally focused on inhibiting crystallization by elucidating the underlying crystallization mechanisms.

4. CRYSTALLIZATION REGIMES

Beyond the analysis of the type of materials studied in microgravity, it is also insightful to consider under what regime these materials were crystallized. Identifying the crystallization regime of the studies, hints at the purpose and thus, possible application toward ISM. The literature identified (Figure 1) can be grouped into two regimes of crystallization experiments:

- Single-crystal crystallization involves the growth of isolated crystals, ideally one but typically a few per experiment. Although essential, primarily for structural characterization of material or fundamental studies, this approach, typically, does not represent manufacturing-relevant crystallization.
- Bulk crystallization produces many crystals simultaneously, ideally generating a homogeneous population with measurable critical quality attributes (e.g., size,

distribution, morphology) and high yield, which is essential for informing crystallization processes. Thus, a system that could be enacted to manufacture different amounts of materials with equivalent results (scalable), if all other requirements are met.²⁰⁷ This definition of bulk crystallization technically constitutes the beginning of manufacturing, thus ISM strategies. Experiments were defined as bulk in this review when the crystallization conditions promoted the formation of multiple crystals, yielding a crystal population within the experimental setups (e.g., vials,⁴ microfluidic devices,⁶⁷ etc.).

The identification of these two groups of documented crystallization results reveals differences in the experimental focus and practical relevance of the 146 materials studied in 189 publications in microgravity crystallization (Figure 1). Of these publications, 159 studies reported on single-crystal experiments and 80 on bulk crystallization experiments, per the definitions established in this Review above. Importantly, the total number of materials and studies does not directly correspond to the number of publications. A single publication may investigate multiple materials and studies, and not all publications report specific materials, with some focusing instead on experimental setups, methodologies, or instrumentation.

Examining these two data sets side by side highlights clear differences in both the types of materials chosen and their relevance to specific applications (Figure 3). A detailed list of materials summarized in Figure 3 is provided in Table S3.

Generally, reported single-crystal experiments are dominated by well-characterized model proteins 76%, with lysozyme representing 33% of all studies, followed by insulin (4.85%) and a small group including canavalin, catalase,^{59,65} cytochrome c, PfGST, and ribonuclease (~2.9% each), while most

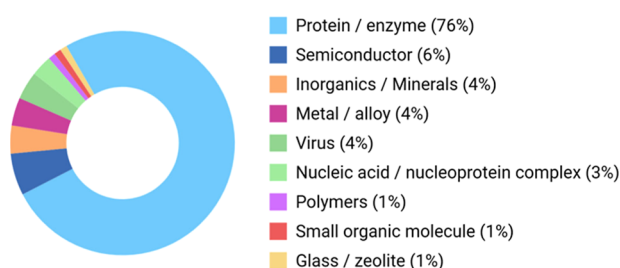
other proteins individually represent ~2% or less. A smaller fraction of studies focuses on semiconductors (7%, e.g., germanium). Other material categories represent ≤3%.

All of these studies typically involve small, isolated systems chosen for their sensitivity to transport phenomena, making them ideal for probing fundamental crystallization mechanisms such as defect formation, impurity rejection, diffusion-limited assembly, and growth kinetics. For instance, the latter is often related to growth rates of certain faces to study fundamentals and normally not used to describe the overall growth of crystals in a manufacturing sense.

In contrast, bulk crystallization studies encompass a broader and more heterogeneous range of materials, though model proteins still dominate in terms of frequency (53%). Here, lysozyme represents the most frequently reported material, accounting for ~12% of bulk studies, reflecting its continued use as a benchmark system for crystallization behavior. A second tier of materials, including glucose isomerase, thaumatin, ZBLAN-type glasses, and selected metal or alloy systems such as silver–germanium, each contribute between ~2–5% of the reported material classes (Figure 3). The predominance of simple, well-characterized proteins (e.g., lysozyme and glucose isomerase), reflects their ease of crystallization and wealth of existing data, making them ideal for fundamental crystallization experiments to validate methodologies (e.g., optical and video microscopy, optical interferometry), equipment (e.g., Diffusion-Controlled Apparatus for Microgravity,⁵⁷ Protein Crystallization Apparatus for Microgravity,⁸ capillary counter-diffusion platforms,⁶⁰ etc.), and to establish reproducible crystallization frameworks. However, it needs to be stated that the number of reviewed articles on bulk crystallization (Figure 3) providing quantitative information on the actual yields of the process is very limited despite its importance for assessing ISM efficiency.

Beyond these model systems and fundamental studies, research is progressing toward more complex and industrially relevant bulk crystallization. For example, in recent years, biomolecules such as monoclonal antibodies⁴ were studied to enable direct assessment of microgravity-enabled benefits for formulations, stability, and solid-state processing in LEO. These results may be utilized for future ISM scenarios.^{4,178} To date, only a few microgravity studies qualify as true bulk crystallization and premature ISM, such as Keytruda,⁴ the production of L-histidine crystals,⁶⁷ and the crystallization of ZBLAN conducted on the ISS.²⁰⁸ Material classes such as ZBLAN are of particular interest due to their exceptional optical properties and their potential use in high-performance fiber optics.^{192,194} On earth, the production of ZBLAN fibers is challenging because gravity-driven convection and crystallization introduce defects that degrade optical performance. Under microgravity, reduced convective mass transfer rates slow nucleation and crystal growth, minimizing defects and enabling more uniform, higher-quality fibers.²⁰⁹ These factors make LEO an interesting environment for their potential manufacture as the microgravity environment allows to suppress nucleation and crystallization (undesired for ZBLAN fibers). Consequently, ZBLAN represents a compelling example of a material whose production might directly benefit from processing in the LEO. Collectively, these studies illustrate how the bulk crystallization landscape is slowly evolving, starting from accessible, reproducible model proteins and gradually incorporating materials with higher strategic and

Single-Crystal Studies (n= 159)



Bulk Crystallization Studies (n= 80)

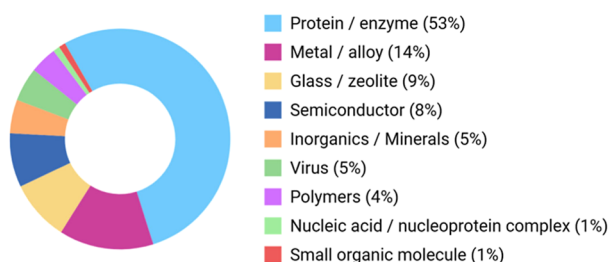


Figure 3. Distribution of 146 materials examined across 189 microgravity publications (Figure 1), separated by single-crystal and bulk crystallization experiments, and grouped by major material classes as defined in Section 3.

Table 1. Summary of Experimental Techniques Used in 189 Microgravity Crystallization Publications (Figure 1)^a

technique	studies (n)			focus	materials / applications	references
	total number	growth kinetics	induction time			
Optical & video microscopy	13	12	4	Single crystals	Proteins (e.g., lysozyme, <i>P. falciparum</i> GST); visualizing crystal formation and orientation	58,63,69,73,75,79, 85,93,93,100,111,145,193
Optical interferometry (Michelson, Mach-Zehnder, Fabry-Pérot)	5	5	1	Single crystals	Proteins, optical glasses; nanometer-scale crystal face advancement	55,63,81–83
Light scattering (dynamic, Bragg)	4	4	3	Bulk	Colloids, metallic systems; nucleation and front propagation	42,127,137,164
Thermal analysis	1	1	0	Bulk	Metals, alloys; nucleation undercooling, solute redistribution	182
X-ray diffraction / EDX	2	2	1	Single crystals	Proteins, crystals post-flight; lattice uniformity, structural quality	62,182

^aFor each technique, the total number of studies (n) and the number reporting growth kinetics and induction time are shown based on direct counting of the literature reviewed. The predominant experimental focus (single-crystal or bulk) and representative materials or applications are included.

industrial value, setting the stage for innovative applications in both LEO operations and future ISM ventures.^{140,191}

5. KINETICS STUDIES IN MICROGRAVITY

Despite the documented advances in microgravity crystallization (Figure 1), significant knowledge gaps persist in terms of the kinetic studies. Mathematical models describing crystallization kinetics in microgravity have been reported,^{76,91,171} yet they are predominantly theoretical and were not included in this analysis of experimental kinetic data. Of the 189 publications reviewed (Figure 1), only 25 reported kinetic data. Of these, 18 focused on single-crystal experiments and 7 on bulk crystallization, with just 19 providing direct comparisons between microgravity and earth-based outcomes, enabling scientifically rigorous conclusions.

All other publications focused mostly on fundamental insights under diffusion-limited conditions, including defect formation and impurity rejection,^{9,48,133} hardware descriptions, mission reports, or mere analyses without extractable kinetic measurements. This limit of available information leaves critical questions about nucleation, growth, and reproducibility at scale, needed for ISM largely unresolved. Addressing these knowledge gaps is essential to developing ISM of, e.g., bulk pharmaceuticals, advanced materials, and other high-value products in larger quantities with uniform properties across the crystal population.

Studying bulk crystallization kinetics in microgravity presents unique challenges, primarily due to the limited opportunities for measuring the kinetics of crystal populations. Unlike Earth-based experiments, where a wide range of offline and in situ analytical techniques are available, microgravity studies are constrained by the restricted environment, resources/hardware available, crew time, and experimental complexity.^{70,146} As a result, the range of methods applied in microgravity crystallization studies is comparatively limited

with a strong reliance on direct observation techniques, including optical and video microscopy (Table 1).

Optical and video microscopy ($n = 13$) allows continuous or time-lapse visualization of crystal formation and orientation, which can be utilized to measure nucleation induction times and anisotropic crystal growth for specific crystal faces, as demonstrated (e.g., for lysozyme crystals) aboard the ISS.⁸³ When combined with optical spectroscopy (e.g., time-resolved reflection spectroscopy or laser confocal differential interference contrast microscopy,⁷⁵ these approaches provide additional insight into crystallization processes. They enable tracking of the temporal evolution of molecular or colloidal arrangements^{42,164} from a disordered solution to a well-defined crystalline lattice. This allows for a more detailed analysis of nucleation and growth dynamics beyond microscopy alone.

For higher spatial precision, laser confocal differential interference contrast microscopy ($n = 1$)⁹³ allows three-dimensional mapping of crystal surfaces at nanometer-scale resolution. This technique captures subtle variations in growth rates and surface topology. Similarly, optical interferometry ($n = 5$), including Michelson,^{81,83} Mach-Zehnder,⁸² and Fabry-Pérot⁶³ configurations has been used for lysozyme and ice crystals to provide quantitative measurements of crystal face advancements (growth kinetic) and concentration fields.

Other complementary methods include light scattering techniques ($n = 4$), such as dynamic and Bragg scattering, which monitor nucleation and front propagation through changes in scattered light, revealing altered nucleation, supercooling, and solute redistribution in metallic systems processed under microgravity. Specifically, light scattering techniques were used to track crystallization kinetics and ordering in colloidal (e.g., polystyrene and silica spheres)^{42,137,164} and mineral systems.^{64,127}

Thermal analysis ($n = 1$) was applied to metallic alloys (e.g., Ag-Ge)¹⁸² to evaluate nucleation supercooling, solidification behavior, and solute redistribution under microgravity

conditions. In addition to experimental techniques employed in microgravity, postflight characterization on Earth using X-ray-based techniques growth ($n = 2$) (e.g., X-ray diffraction and EDX)^{62,182} are commonly used to evaluate crystal structural quality, polymorphism, lattice uniformity, and solute segregation, providing indirect benchmarks of microgravity effects on crystal. However, these analyses may be affected by sample handling, storage (in suspension or dried solids), and rugged re-entry conditions,^{70,187} which can alter the as-grown crystal properties, e.g., of thermodynamically metastable solid forms.^{1,210,211} For instance, these approaches have been applied to systems such as calcium phosphate crystals and Ag–Ge alloys,^{62,182} where postgrowth analysis enabled determination of phase composition, lattice structure, and microstructural differences relative to Earth-grown counterparts.

While Table 1 summarizes the feasibility of measuring growth kinetics in situ under diffusion-dominated transport in microgravity, it also highlights the limitations of predominantly microscopy-based approaches. While they are well suited to track crystal growth of typically single crystals or individual crystal faces, these kinetics are not representative for bulk crystallization studies,¹ essential for controlling crystallization pathways toward ISM. Thus, the transferability to manufacturing settings lacks.

6. GROUND-BASED ALTERNATIVES

Studies have reported that microgravity environments provide advantages for the crystallization of a wide range of materials. However, performing experiments in space remains costly, logistically complex, and difficult to scale or repeat. These challenges are further compounded by the inherently high cost and limited accessibility of space-based experimentation. The financial and logistical burden associated with orbital platforms, combined with restricted flight opportunities and fixed hardware configurations, severely reduce the ability to perform iterative studies or systematically explore process parameters. As a result, experimental campaigns are often constrained to a small number of predefined conditions, reducing the flexibility and slowing process development.

To overcome these limitations, whether crystallization or other research applications, a variety of ground-based platforms have been developed to simulate key aspects of the space environment or probe gravity-related effects. These analogue platforms can be broadly categorized into three groups: (i) microgravity or quasi-microgravity systems (e.g., spaceflight platforms, random positioning machines (RPMs), clinostats, rotating wall vessels, and magnetic or acoustic levitation systems), which aim to eliminate or average the gravity vector;^{75,90,100} (ii) variable- or fractional-gravity systems (e.g., centrifuge-assisted platforms and reduced-gravity aircraft campaigns),²¹² which enable controlled modulation of gravitational acceleration across different G-levels; and (iii) hyper-gravity systems (e.g., large-diameter centrifuges), which expose samples to gravitational accelerations exceeding 1 g.

Based on the literature research conducted in this review (Figure 1), only 4 studies were identified using systems such as magnetic levitation,^{90,100} microfluidic convection-free platforms,^{75,85} or parabolic flight experiments.⁴² It is important to note that studies based on simulated microgravity using ground-based systems fall outside the scope of this review. Moreover, the search strategy for this review (detailed in Section S1) was centered on microgravity-related terminology

in space and not designed to capture the full breadth of ground-based analogue research.⁹⁵ Consequently, relevant studies may be underrepresented in this Review. Readers interested in these terrestrial platforms are referred to dedicated literature.²¹³

While these ground-based alternatives cannot fully reproduce the $\sim 10^{-6}$ g microgravity conditions, they nonetheless provide cost-effective and accessible experimental environments. As such, they may play a critical role in enabling systematic crystallization studies, facilitating process optimization, and allowing direct comparison across gravity regimes. Importantly, beyond serving as valuable prescreening tools prior to spaceflight experiments, these systems may also function as practical manufacturing platforms on Earth by enabling material production under microgravity-simulated conditions.

7. FUTURE PERSPECTIVES

To date, most microgravity crystallization studies have focused on the single-crystal growth of well-characterized model proteins, most notably lysozyme, primarily to investigate fundamental growth mechanisms and enhance structural resolution. In contrast, relatively few studies have addressed systematically bulk crystallization and its kinetics, both of which are essential for process development and manufacturing. This imbalance underscores that microgravity crystallization in the context of LEO and ISM is in its infant stage.

A central barrier lies in the lack of standardization and comparability. Differences in hardware, protocols, and analytical methods, combined with the absence of coordinated space–ground experimental frameworks, make it difficult to isolate the true effects of microgravity and extract generalizable trends.¹¹⁵ For instance, from the 25 publications reporting kinetic studies only $\sim 76\%$ included terrestrial controls (Table 1). Inconsistencies across experimental designs continue to limit reproducibility and cross-study interpretation. More critically, current experiments provide limited insight into crystallization kinetics beyond specific crystal faces measured using single crystals.^{55,83} Most studies rely on end-point characterization due to the lack of real-time monitoring, precise control of supersaturation, and in situ analytical tools. As a result, key questions regarding nucleation pathways, process dynamics, and population behavior remain unresolved. This lack of real time process analytical technology (PAT),²¹⁴ kinetic understanding, and control represents a major bottleneck but is essential for advanced manufacturing²⁰⁷ advocated by regulatory entities,²¹⁵ and thus for any ambitions toward ISM.

Given the inherent challenges with spaceflight-based²¹⁶ experiments, ground-based microgravity analogues may provide a more accessible and cost-effective alternative for experimental development.^{75,90} Platforms such as magnetic levitation, microfluidic convection-free platforms,⁸⁵ or RPMs²¹⁷ may enable systematic studies under controlled conditions and over extended time scales. Although they cannot fully reproduce orbital microgravity (e.g., radiation, vibration, atmospheric composition, thermal fluctuations, etc.), they may play a critical role in enabling early stage optimization and mechanistic investigation prior to spaceflight experiments.

Advancing microgravity crystallization toward practical implementation will depend on bridging the gap between fundamental studies and process engineering. Future efforts

toward manufacturing in microgravity should prioritize kinetic understanding, bulk system behavior, and standardized, multiplatform experimentation and analytical instrumentation, including PAT.^{1–3,207} Specifically, crystallizers designed for microgravity will be essential, because traditional crystallizers used on Earth cannot be translated to space due to fundamental differences in the requirements, e.g., design (no gravity, no headspace^{218,219}), hydrodynamics, mass transfer. Only by aligning experimental approaches with the needs for equipment and scalable manufacturing²⁰⁷ will it be feasible to realize the full potential of crystallization in microgravity. This assessment is also pending regulatory guidance and an exploitable infrastructure for manufacturers, a discussion beyond the scope of this review.

8. CONCLUSION

While decades of research have demonstrated that microgravity can influence crystal morphology and defect formation, the experimental landscape remains poorly aligned with the requirements of manufacturing-oriented crystallization. As a result, critical gaps persist in the process design, scalability, and productivity assessment. This misalignment largely stems from the historical focus of the field on fundamental, small-scale studies, often centered on single-crystal growth under highly controlled conditions. While these investigations have been essential for uncovering underlying mechanisms, they provide limited insight into bulk crystallization behavior, process dynamics, and scale-up strategies required for manufacturing applications. The field appears to be transitioning from exploratory fundamental studies toward more application-driven investigations. However, realizing the full potential of crystallization for low-Earth orbit (LEO) manufacturing or future in-space manufacturing (ISM) will require systematic kinetic studies, standardized experimental methodologies and equipment,¹⁴⁶ and quantitative evaluation of crystallization performance under microgravity conditions in real time. In addition, this transition will also require enabling infrastructure for manufacturers and regulatory frameworks.²²⁰ Addressing these gaps will be essential to move from proof-of-concept experiments toward robust and scalable crystallization processes for the manufacture of materials with superior properties.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.cgd.6c00807>.

Details regarding literature search strategy and comprehensive list of materials and publications (PDF)

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Notes

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■ LIST OF ABBREVIATIONS

cGMP	current good manufacturing practice
cryo-EM	cryogenic electron microscopy
EDX	energy-dispersive X-ray spectroscopy
GST	glutathione S-transferase
ISM	in-space manufacturing
ISS	International Space Station
LEO	low earth orbit
MicroED	microcrystal electron diffraction
MIR	Mir space station
NMR	nuclear magnetic resonance
PfGST	<i>Plasmodium falciparum</i> glutathione S-transferase
R&D	Research and development
RPM	Random positioning machine

XRD	X-ray diffraction
ZBLAN	Zirconium fluoride–barium fluoride–lanthanum fluoride–aluminum fluoride–sodium fluoride

REFERENCES

- (1) *Handbook of Industrial Crystallization*, 3rd ed.; Myerson, A. S., Erdemir, D., Lee, A. Y., Eds.; Cambridge University Press, 2019.
- (2) Beckmann, W. Chapter 2: Mechanisms of Crystallization. In *Crystallization: Basic Concepts and Industrial Applications*; Wiley-VCH Verlag GmbH & Co. KGaA, 2013.
- (3) Stelzer, T. C.; Lakerveld, R. Crystallization. In *Kirk-Othmer Encyclopedia of Chemical Technology*; John Wiley & Sons, Inc., 2026; <https://doi.org/10.1002/0471238961.0318251918152119.a01.pub4>.
- (4) Reichert, P.; Prosise, W.; Fischmann, T. O.; Scapin, G.; Narasimhan, C.; Spinale, A.; Polniak, R.; Yang, X.; Walsh, E.; Patel, D.; Benjamin, W.; Welch, J.; Simmons, D.; Strickland, C. Pembrolizumab Microgravity Crystallization Experimentation. *npj Microgravity* **2019**, *5* (1), 28.
- (5) Li, H.; Li, Y.; Jiao, J.; Lin, C. Recent Research Progress on Crystallization Strategies for Difficult-to-Crystallize Organic Molecules. *Results Chem.* **2023**, *5*, 100859.
- (6) Timofeev, V.; Samygina, V. Protein Crystallography: Achievements and Challenges. *Crystals* **2023**, *13* (1), 71.
- (7) Jackson, K.; Brewer, F.; Wilkinson, A.; Williams, A.; Whiteside, B.; Wright, H.; Harper, L.; Wilson, A. M. Microgravity Crystal Formation. *Crystals* **2024**, *14*, 12.
- (8) Carter, D. C.; Wright, B.; Miller, T.; Chapman, J.; Twigg, P.; Keeling, K.; Moody, K.; White, M.; Click, J.; Ruble, J. R.; Ho, J. X.; Adcock-Downey, L.; Dowling, T.; Chang, C. H.; Ala, P.; Rose, J.; Wang, B. C.; Declercq, J.-P.; Evrard, C.; Rosenberg, J.; Wery, J.-P.; Clawson, D.; Wardell, M.; Stallings, W.; Stevens, A. P. A Multi-User Facility-Based Protein Crystallization Apparatus for Microgravity. *J. Cryst. Growth* **1999**, *196* (2–4), 610–622.
- (9) McPherson, A.; DeLucas, L. J. Microgravity Protein Crystallization. *npj Microgravity* **2015**, *1*, 15010.
- (10) Yue, J.; Voltmer, F. Influence of Gravity-Free Solidification on Solute Microsegregation. *J. Cryst. Growth* **1975**, *29* (3), 329–341.
- (11) Littke, W.; John, C. Materials: Protein Single Crystal Growth under Microgravity. *Science* **1984**, *225* (4658), 203.
- (12) Yamada, M.; Kihira, K.; Iwata, M.; Takahashi, S.; Inaka, K.; Tanaka, H.; Yoshizaki, I. Protein Crystallization in Space and Its Contribution to Drug Development. In *Handbook of Space Pharmaceuticals*; Pathak, Y., Araújo Dos Santos, M., Zea, L., Eds.; Springer International Publishing: Cham, 2021; pp 1–26.
- (13) Strong, R. K.; Stoddard, B. L.; Arrott, A.; Farber, G. K. Long Duration Growth of Protein Crystals in Microgravity Aboard the MIR Space Station. *J. Cryst. Growth* **1992**, *119* (3–4), 200–214.
- (14) DeLucas, L. J.; Smith, C.; Carter, D. C.; Twigg, P.; He, X.-M.; Snyder, R. S.; Weber, P.; Schloss, J.; Einspahr, H.; Clancy, L.; McPherson, A.; Koszelak, S.; Vandonselaar, M. M.; Prasad, L.; Wilson Quail, J.; Delbaere, L.; Bugg, C. E. Protein Crystal Growth Aboard the U.S. Space Shuttle Flights STS-31 and STS-32. *Adv. Space Res.* **1992**, *12* (1), 393–400.
- (15) DeLucas, L.; Smith, C.; Smith, H. W.; Vijay-Kumar, S.; Senadhi, S. E.; Ealick, S. E.; Carter, D. C.; Snyder, R. S.; Weber, P. C.; Salame, F. R.; et al. Protein Crystal Growth in Microgravity. *Science* **1989**, *246* (4930), 651–654.
- (16) Jose, S. A.; Jackson, J.; Foster, J.; Silva, T.; Markham, E.; Menezes, P. L. In-Space Manufacturing: Technologies, Challenges, and Future Horizons. *J. Manuf. Mater. Process.* **2025**, *9* (3), 84.
- (17) Salotti, J.-M.; Heidmann, R.; Suhir, E. *Crew Size Impact on the Design, Risks and Cost of a Human Mission to Mars*; IEEE, 2014; pp 1–9.
- (18) Yu, J.; Zhang, W.; Yang, S.; Zhang, Y.; Hui, X.; Zhong, H.; Yan, M.; Yu, Y. Recent Advances and Future Prospects of Space Materials Science. *Rev. Mater. Res.* **2025**, *1* (2), 100065.
- (19) Blue, R. S.; Bayuse, T. M.; Daniels, V. R.; Wotring, V. E.; Suresh, R.; Mulcahy, R. A.; Antonsen, E. L. Supplying a Pharmacy for NASA Exploration Spaceflight: Challenges and Current Understanding. *npj Microgravity* **2019**, *5* (1), 14.
- (20) Du, B.; Daniels, V. R.; Vaksman, Z.; Boyd, J. L.; Crady, C.; Putcha, L. Evaluation of Physical and Chemical Changes in Pharmaceuticals Flown on Space Missions. *AAPS J.* **2011**, *13*, 299–308.
- (21) McNulty, M. J.; Berliner, A. J.; Negulescu, P. G.; McKee, L.; Hart, O.; Yates, K.; Arkin, A. P.; Nandi, S.; McDonald, K. A. Evaluating the Cost of Pharmaceutical Purification for a Long-Duration Space Exploration Medical Foundry. *Front. Microbiol.* **2021**, *12*, 700863.
- (22) Seoane-Viaño, I.; Ong, J. J.; Basit, A. W.; Goyanes, A. To Infinity and beyond: Strategies for Fabricating Medicines in Outer Space. *Int. J. Pharm. X* **2022**, *4*, 100121.
- (23) Snell, E. H.; Helliwell, J. R. Microgravity as an Environment for Macromolecular Crystallization – an Outlook in the Era of Space Stations and Commercial Space Flight. *Crystallogr. Rev.* **2021**, *27* (1), 3–46.
- (24) NASA Strategic Plan - NASA. <https://www.nasa.gov/ocfo/strategic-plan/> (accessed May 18, 2026).
- (25) Pan, J.-S.; Niu, X.-T.; Gui, L.-L.; Zhou, Y.-C.; Bi, R.-C. Crystallization under Microgravity of Acidic Phospholipase A2 from Venom of Agkistrodon Halys Pallas. *J. Cryst. Growth* **1996**, *168* (1–4), 227–232.
- (26) Stagno, J.; Lee, Y.-T.; Chen, J.; Ding, J.; Yu, P.; Yefanov, O.; White, T.; Barty, A.; Sierra, R.; Spence, J.; Chapman, H.; Wang, Y.-X. Microgravity Crystallization for Improving Uniformity and Homogeneity of Crystals for Time-Resolved Diffusive Mixing XFEL Experiments. *Acta Crystallogr. Sect. Found. Adv.* **2021**, *77* (a1), a246.
- (27) Regel, L. L.; Shumayev, O. V.; Vidensky, I. V.; Safonova, I. M.; Vedernikov, A.; Komarov, V. F.; Ivanov, A. I.; Suleiman, S. Experiments on Crystallization of Semiconductor Materials, Eutectic Alloys and Crystal Growth from Water Solution in Microgravity. *Acta Astronaut.* **1990**, *21* (5), 331–348.
- (28) Desre, P. J.; Joud, J. C. Surface Tension Temperature Coefficient of Liquid Alloys and Definition of a “Zero Marangoni Number Alloy” for Crystallisation Experiments in Microgravity Environment. *Acta Astronaut.* **1981**, *8* (5–6), 407–415.
- (29) Eposito, L.; Sica, F.; Sorrentino, G.; Berisio, R.; Carotenuto, L.; Giordano, A.; Raia, C. A.; Rossi, M.; Lamzin, V. S.; Wilson, K. S.; Zagari, A. Protein Crystal Growth in the Advanced Protein Crystallization Facility on the Lms Mission: A Comparison of *Sulfolobus Solfataricus* Alcohol Dehydrogenase Crystals Grown on the Ground and in Microgravity. *Acta Crystallogr.* **1998**, *D54*, 386–390.
- (30) Yagi-Utsumi, M.; Yanaka, S.; Song, C.; Satoh, T.; Yamazaki, C.; Kasahara, H.; Shimazu, T.; Murata, K.; Kato, K. Characterization of Amyloid β Fibril Formation under Microgravity Conditions. *npj Microgravity* **2020**, *6* (1), 17.
- (31) Di Renzo, F.; Fajula, F.; Espiau, P.; Nicolle, M.-A.; Dutartre, R. The Influence of Microgravity on Zeolite Crystallization. *Zeolites* **1994**, *14* (4), 256–261.
- (32) Wardell, M. R.; Skinner, R.; Carter, D. C.; Twigg, P. D.; Abrahams, J.-P. Improved Diffraction of Antithrombin Crystals Grown in Microgravity. *Acta Crystallogr. D Biol. Crystallogr.* **1997**, *53* (5), 622–625.
- (33) Carruthers, C. W., Jr.; Gerdt, C.; Johnson, M. D.; Webb, P. A. Microfluidic, High Throughput Protein Crystal Growth Method for Microgravity. *PLoS One* **2013**, *8* (11), No. e82298.
- (34) Tanaka, H.; Umehara, T.; Inaka, K.; Takahashi, S.; Shibata, R.; Bessho, Y.; Sato, M.; Sugiyama, S.; Fusatomi, E.; Terada, T.; Shirouzu, M.; Sano, S.; Motohara, M.; Kobayashi, T.; Tanaka, T.; Tanaka, A.; Yokoyama, S. Crystallization of the Archaeal Transcription Termination Factor NusA: A Significant Decrease in Twinning under Microgravity Conditions. *Acta Crystallogr. Sect. F Struct. Biol. Cryst. Commun.* **2007**, *63* (2), 69–73.
- (35) Higashiura, A.; Kurakane, T.; Matsuda, M.; Suzuki, M.; Fujiwara, K.; Inaka, K.; Sato, M.; Kobayashi, T.; Tanaka, T.; Tanaka, H.; Nakagawa, A. 1P-002 Crystallization in Microgravity Conditions

and High-Resolution X-Ray Crystallography of Bovine H-Protein of the Glycine Cleavage System (Protein:Structure, The 47th Annual Meeting of the Biophysical Society of Japan). *Seibutsu Butsuri* **2009**, 49 (supplement), S63.

(36) Zegers, I.; Carotenuto, L.; Evrard, C.; Garcia-Ruiz, J.; De Gieter, P.; Gonzales-Ramires, L.; Istasse, E.; Legros, J.-C.; Martial, J.; Minetti, C.; Otolara, F.; Queeckers, P.; Schockaert, C.; VandeWeerd, C.; Willaert, R.; Wyns, L.; Yourassowsky, C.; Dubois, F. Counter-diffusion Protein Crystallisation in Microgravity and Its Observation with PromISS (Protein Microscope for the International Space Station). *Microgravity Sci. Technol.* **2006**, 18 (3–4), 165–169.

(37) Galazka, R. R.; Warminiński, T.; Bak, J.; Auleytnner, J.; Dietl, T.; Okhotin, A. S.; Borovikova, R. P.; Zubritskij, I. A. Directional Crystallization of CdHgTe in Microgravity Conditions. *J. Cryst. Growth* **1981**, 53 (2), 297–308.

(38) Stelian, C.; Duffar, T. Numerical Modeling of CdTe Crystallization from Te Solution under Terrestrial and Microgravity Conditions. *J. Cryst. Growth* **2014**, 400, 67–75.

(39) Day, J.; McPherson, A. Macromolecular Crystal Growth Experiments on International Microgravity Laboratory-1. *Protein Sci.* **1992**, 1 (10), 1254–1268.

(40) Koszelak, S.; Day, J.; Leja, C.; Cudney, R.; McPherson, A. Protein and Virus Crystal Growth on International Microgravity Laboratory-2. *Biophys. J.* **1995**, 69 (1), 13–19.

(41) Dubova, K. M.; Dubovskii, P. V.; Utkin, Y. N.; Samygina, V. R. Effect of Microgravity on the Crystallization of Cardiotoxin from the Venom of Spectacled Cobra *Naja Naja*. *Crystallogr. Rep.* **2023**, 68, 900–904.

(42) Okubo, T.; Tsuchida, A.; Takahashi, S.; Taguchi, K.; Ishikawa, M. Kinetics of Colloidal Alloy Crystallization of Binary Mixtures of Monodispersed Polystyrene and/or Colloidal Silica Spheres Having Different Sizes and Densities in Microgravity Using Aircraft. *Colloid Polym. Sci.* **2000**, 278 (3), 202–210.

(43) Ilyukhin, V. V.; Iskhakova, L. D.; Komarov, V. F.; Melikhov, I. V.; Prokofjev, M. A.; Trunov, V. K.; Vedernikov, A. A. Peculiarities of Crystallization Process in the Solution under Microgravity (ERDE-NET Experiment). *Acta Astronaut.* **1984**, 11 (10–11), 651–658.

(44) Samsonenko, A. A.; Artiukhova, N. A.; Letyagin, G. A.; Kiryutin, A. S.; Zhukov, I. V.; Veber, S. L. Microgravity-like Crystallization of Paramagnetic Species in Strong Magnetic Fields. *Int. J. Mol. Sci.* **2024**, 25 (10), 5110.

(45) Erdmann, V. A.; Lippmann, C.; Betzel, C.; Dauter, Z.; Wilson, K.; Hilgenfeld, R.; Hoven, J.; Liesum, A.; Saenger, W.; Muller-Fahrnow, A.; Hinrichs, W.; Duvel, M.; Schulz, D. E.; Muller, C. W.; Wittmann, H. G.; Yonath, A.; Weber, G.; Stegen, K.; Plaas-Link, A. Crystallization of Proteins under Microgravity. *FEBS Lett.* **1989**, 259 (1), 194–198.

(46) Okuda-Shimazaki, J.; Yoshida, H.; Lee, I.; Kojima, K.; Suzuki, N.; Tsugawa, W.; Yamada, M.; Inaka, K.; Tanaka, H.; Sode, K. Microgravity Environment Grown Crystal Structure Information Based Engineering of Direct Electron Transfer Type Glucose Dehydrogenase. *Commun. Biol.* **2022**, 5, 1334.

(47) Schönlein, M.; Plank, J. Influence of PCE Kind and Dosage on Ettringite Crystallization Performed under Terrestrial and Microgravity Conditions. *J. Am. Ceram. Soc.* **2018**, 101 (8), 3575–3584.

(48) Otolara, F.; Novella, M. L.; Gavira, J. A.; Thomas, B. R.; Garcia Ruiz, J. M. Experimental Evidence for the Stability of the Depletion Zone around a Growing Protein Crystal under Microgravity. *Acta Crystallogr.* **2001**, 57, 412–417.

(49) Savitsky, E. M.; Torchinova, R. S.; Turanov, S. A. Influence of Crystallization in Microgravity Conditions on the Structure and Magnetic Properties of Gd₃Co and (Gd_{0.2}Tb_{0.8})₃Co Compounds. *Acta Astronaut.* **1984**, 11 (3–4), 185–188.

(50) Nakata, J.; Kuratani, N.; Tomozawa, H.; Nishimura, Y.; Yokogawa, N.; Inagawa, I. Seedless Crystallization of Levitated Ge and GaSb Spherical Melts under Microgravity. *Jpn. J. Appl. Phys., Part 1* **1998**, 37, 11396.

(51) Shul'pina, I. L.; Prokhorov, I. A. Results of the Experiments on the Crystallization of a Ge-Si-Sb Solid Solution under the Conditions

of Microgravity on the Soyuz-Apollo Spacecraft. *Phys. Solid State* **2019**, 61, 541.

(52) Wiedemeier, H.; Trivedi, S. B.; Zhong, X.-R.; Whiteside, R. C. Crystal Growth and Transport Rates of the GeSe - Xenon System under Microgravity Conditions. *J. Electrochem. Soc.* **1986**, 133 (5), 1015–1021.

(53) Zemskov, V. S.; Belokurova, I. N.; Vasilina, B. S.; Mavrin, O. I. Crystallization of Germanium-Silicon Solid Solution from the Vapour Phase in Microgravity Conditions. *Adv. Space Res.* **1983**, 3 (5), 191–194.

(54) Avduyevsky, V. S.; Grishin, S. D.; Lescov, L. V. Some Physical Aspects of Unidirectional Crystallization in Microgravity. *Acta Astronaut.* **1982**, 9 (9), 583–588.

(55) Furukawa, Y.; Nagashima, K.; Nakatsubo, S.; Yoshizaki, I.; Tamaru, H.; Shimaoka, T.; Sone, T.; Yokoyama, E.; Zepeda, S.; Terasawa, T.; Asakawa, H.; Murata, K.; Sazaki, G. Oscillations and Accelerations of Ice Crystal Growth Rates in Microgravity in Presence of Antifreeze Glycoprotein Impurity in Supercooled Water. *Sci. Rep.* **2017**, 7, 43157.

(56) Tanaka, H.; Tsurumura, T.; Aritake, K.; Furubayashi, N.; Takahashi, S.; Yamanaka, M.; Hirota, E.; Sano, S.; Sato, M.; Kobayashi, T.; Tanaka, T.; Inaka, K.; Urade, Y. Improvement in the Quality of Hematopoietic Prostaglandin D Synthase Crystals in a Microgravity Environment. *J. Synchrotron Radiat.* **2011**, 18 (1), 88–91.

(57) Carter, D. C.; Wright, B. S.; Miller, T. Y.; Chapman, J.; Twigg, P.; Keeling, K. M.; Moody, K.; White, M.; Click, J.; Ruble, J. R.; Ho, J. X.; Adcock-Downey, L.; Bunick, G. J.; Harp, J. M. Diffusion-Controlled Crystallization Apparatus for Microgravity (DCAM): Flight and Ground-Based Applications. *J. Cryst. Growth* **1999**, 196, 602–609.

(58) Martirosyan, A.; DeLucas, L. J.; Schmidt, C.; Perbandt, M.; McCombs, D.; Cox, M.; Radka, C.; Betzel, C. Effect of Macromolecular Mass Transport in Microgravity Protein Crystallization. *Gravitational Space Res.* **2019**, 7 (1), 33.

(59) Long, M. M. *Large Scale Crystallization of Protein Pharmaceuticals in Microgravity via Temperature Change*; NASA, 1992.

(60) Lutz, W. E.; Azadmanesh, J.; Lovelace, J. E.; Kolar, C.; Coates, L.; Weiss, K. L.; Borgstahl, G. E. O. Perfect Crystals: Microgravity Capillary Counterdiffusion Crystallization of Human Manganese Superoxide Dismutase for Neutron Crystallography. *npj Microgravity* **2023**, 9, 39.

(61) Gioia, M.; Michaletti, A.; Scimeca, M.; Marini, M.; Tarantino, U.; Zolla, L.; Coletta, M. Simulated Microgravity Induces a Cellular Regression of the Mature Phenotype in Human Primary Osteoblasts. *Cell Death Discov* **2018**, 4 (1), 59.

(62) Madsen, H.; Christensson, F.; Polyak, L. E.; Suvorova, E. I.; Kliya, M. O.; Chernov, A. A. Calcium Phosphate Crystallization under Terrestrial and Microgravity Conditions. *J. Cryst. Growth* **1995**, 152, 191.

(63) Yokoyama, E.; Yoshizaki, I.; Shimaoka, T.; Sone, T.; Kiyota, T.; Furukawa, Y. Measurements of Growth Rates of an Ice Crystal from Supercooled Heavy Water under Microgravity Conditions: Basal Face Growth Rate and Tip Velocity of a Dendrite. *J. Phys. Chem. B* **2011**, 115 (27), 8739.

(64) Tsuchida, A.; Taguchi, K.; Takyō, E.; Yoshimi, H.; Kiriya, S.; Okubo, T.; Ishikawa, M. Microgravity Experiments on Colloidal Crystallization of Silica Spheres in the Presence of Sodium Chloride. *Colloid Polym. Sci.* **2000**, 278, 872–877.

(65) Long, M. M.; DeLucas, L. J.; Smith, C.; Moore, K.; Harrington, M. D.; Pillion, D. J.; Bishop, S. P.; Rosenblum, W. M.; Naumann, R. J.; Chait, A.; Prah, J.; Bugg, C. E. Protein Crystal Growth in Microgravity-Temperature Induced Large Scale Crystallization of Insulin. *Microgravity Sci. Technol.* **1994**, 7 (2), 196–202.

(66) Wright, H.; Williams, A.; Wilkinson, A.; Harper, L.; Savin, K.; Wilson, A. M. An Analysis of Publicly Available Microgravity Crystallization Data: Emergent Themes Across Crystal Types. *Cryst. Growth Des.* **2022**, 22 (12), 6849–6851.

- (67) Zhang, Y.; Cheng, J.; Glick, Y.; Samburski, G.; Chen, J.; Yang, C. Antisolvent Crystallization of L-Histidine in Micro-Channel Reactor under Microgravity. *Microgravity Sci. Technol.* **2020**, *32* (1), 27–33.
- (68) Goldberg, B. E. Microgravity Crystallization of Macromolecules: An Interim Report and Proposal for Continued Research. *NASA Technol. Pap.* **1986**.
- (69) Bray, T. L.; Kim, L. J.; Askew, R. P.; Harrington, M. D.; Rosenblum, W. M.; Wilson, W. W.; DeLucas, L. J. New Crystallization Systems Envisioned for Microgravity Studies. *J. Appl. Crystallogr.* **1998**, *31*, 515–522.
- (70) Cassanto, J. M.; Ziserman, H. I.; Chapman, D. K.; Korszun, Z. R.; Todd, P. Simulation of Launch and Re-Entry Acceleration Profiles for Testing of Shuttle and Unmanned Microgravity Research Payloads. *Adv. Space Res.* **1988**, *8* (12), 141–146.
- (71) Dong, J.; Boggen, T. J.; Chayen, N. E.; Raftery, J.; Bi, R. C.; Helliwell, J. R. Bound-Solvent Structures for Microgravity-, Ground Control-, Gel- and Microbatch-Grown Hen Egg-White Lysozyme Crystals at 1.8 Å Resolution. *Acta Crystallogr.* **1999**, *55* (Pt 4), 745–752.
- (72) Hirschler, J.; Fontecilla-Camps, J. C. Contaminant Effects on Protein Crystal Morphology in Different Growth Environments. *Acta Crystallogr.* **1996**, *52*, 806–812.
- (73) Judge, R. A.; Whitaker, A. F. *Delta L: An Apparatus for Measuring Macromolecular Crystal Growth Rates in Microgravity*; NASA Tech. Rep. 2001. <https://ntrs.nasa.gov/citations/20020022709>.
- (74) Jun, D.; Yaoping, W.; Qing, H.; Ruchang, B. Structural Study on Hen Egg-White Lysozyme Crystals Grown in Gravity and Microgravity. *Sci China C Life Sci.* **1998**, *41* (3), 238–244.
- (75) Maeki, M.; Yamazaki, S.; Takeda, R.; Ishida, A.; Tani, H.; Tokeshi, M. Real-Time Measurement of Protein Crystal Growth Rates within the Microfluidic Device to Understand the Microspace Effect. *ACS Omega* **2020**, *5* (28), 17199–17206.
- (76) Maxwell, D. L. A. *Finite Element Simulation of Crystallization from Solution in Microgravity*, Masters Thesis; University of Tennessee, Knoxville, 1996. https://voljournals.utk.edu/cgi/viewcontent.cgi?article=12570&context=utk_gradthes.
- (77) Niimura, N.; Kurihara, K.; Ataka, M. Dissolution Rate of Hen Egg-White Lysozyme Crystal under Microgravity. *Biol. Sci. Space* **2001**, *15* (Suppl), S176.
- (78) Otálora, F.; Capelle, B.; Ducruix, A.; Garcia Ruiz, J. M. Mosaic Spread Characterization of Microgravity-Grown Tetragonal Lysozyme Single Crystals. *Acta Crystallogr.* **1999**, *55*, 644–649.
- (79) Riès-Kautt, M.; Broutin, I.; Ducruix, A.; Shepard, W.; Kahn, R.; Chayen, N. E.; Blow, D. M.; Paal, K.; Littke, W.; Lorber, B.; Théobald-Dietrich, A.; Giegé, R. Crystallogensis Studies in Microgravity with the Advanced Protein Crystallization Facility on SpaceHab-01. *J. Cryst. Growth* **1997**, *181* (1–2), 79–96.
- (80) Strelov, V. I.; Zakharov, B. G.; Bezbakh, I. Zh.; Safronov, V. V.; Chernyshev, B. V.; Dutyshev, I. N. Implementation of Temperature-Controlled Method of Protein Crystallization in Microgravity. *Crystallogr. Rep.* **2018**, *63* (1), 149–153.
- (81) Suzuki, Y.; Tsukamoto, K.; Yoshizaki, I.; Miura, H.; Fujiwara, T. First Direct Observation of Impurity Effects on the Growth Rate of Tetragonal Lysozyme Crystals under Microgravity as Measured by Interferometry. *Cryst. Growth Des.* **2015**, *15* (10), 4787–4794.
- (82) Vekilov, P. G. Protein Crystal Growth—Microgravity Aspects. *Adv. Space Res.* **1999**, *24*, 1231.
- (83) Yoshizaki, I.; Tsukamoto, K.; Yamazaki, T.; Murayama, K.; Oshi, K.; Fukuyama, S.; Shimaoka, T.; Suzuki, Y.; Tachibana, M. Growth Rate Measurements of Lysozyme Crystals under Microgravity Conditions by Laser Interferometry. *Rev. Sci. Instrum.* **2013**, *84* (10), 103707.
- (84) Yoshizaki, I.; Nakamura, H.; Fukuyama, S.; Komatsu, H.; Yoda, S. Scientific Approach to the Optimization of Protein Crystallization Conditions for Microgravity Experiments. *Ann. N.Y. Acad. Sci.* **2004**, *1027*, 28–47.
- (85) Yu, Y.; Li, K.; Lin, H.; Li, J. The Study of the Mechanism of Protein Crystallization in Space by Using Microchannel to Simulate Microgravity Environment. *Crystals* **2018**, *8*, 400.
- (86) Zhen-He, Z.; Lin, L.; Chao-Rong, L.; Pei-Wen, G. Stability of Crystal Growth Face and Dissolution Face in Crystallization from Solution under Microgravity. *Commun. Theor. Phys.* **2002**, *37* (1), 117–124.
- (87) Baskakova, S. S.; Kovalyov, S. I.; Kramarenko, V. A.; Zadorozhnaya, L. A.; Lyasnikova, M. S.; Dymshits, Y. M.; Shishkov, V. A.; Egorov, A. V.; Dolgin, A. M.; Voloshin, A. E.; Kovalchuk, M. V. New Scientific Equipment for Protein Crystallization in Microgravity, Belka, and Its Approbation on the Bion-m No. 1 Spacecraft. *Crystallogr. Rep.* **2015**, *60*, 148–154.
- (88) Chayen, N. E.; Helliwell, J. R. Microgravity Protein Crystallization - Are We Reaping the Full Benefit of Outer Space? *Ann. N.Y. Acad. Sci.* **2002**, *974*, 591–597.
- (89) Carotenuto, L.; Cartwright, J. H. E.; Castagnolo, D.; Garcia Ruiz, J. M.; Otálora, F. Theory and Simulation of Buoyancy-Driven Convection around Growing Protein Crystals in Microgravity. *Microgravity Sci. Technol.* **2002**, *13* (3), 14–21.
- (90) Wakayama, N. I.; Yin, D. C.; Harata, K.; Kiyoshi, T.; Fujiwara, M.; Tanimoto, Y. Macromolecular Crystallization in Microgravity Generated by a Superconducting Magnet. *Ann. N.Y. Acad. Sci.* **2006**, *1077* (1), 184–193.
- (91) Annunziata, O.; Albright, J. G. Mathematical Model for Diffusion of a Protein and a Precipitant about a Growing Protein Crystal in Microgravity. *Ann. N.Y. Acad. Sci.* **2002**, *974*, 610–623.
- (92) Stoddard, B. L.; Farber, G. K.; Strong, R. K. The Facts and Fancy of Microgravity Protein Crystallization. *Biotechnol. Genet. Eng. Rev.* **1993**, *11* (1), 57–78.
- (93) Martirosyan, A.; Falke, S.; McCombs, D.; Cox, M.; Radka, C. D.; Knop, J.; Betzel, C.; DeLucas, L. J. Tracing Transport of Protein Aggregates in Microgravity versus Unit Gravity Crystallization. *npj Microgravity* **2022**, *8*, 4.
- (94) Mazzoni, S.; Cerbino, R.; Vailati, A.; Giglio, M. Fluctuations in Diffusion Processes in Microgravity. *Ann. N.Y. Acad. Sci.* **2006**, *1077*, 351–364.
- (95) Snell, E. H.; Helliwell, J. R. Macromolecular Crystallization in Microgravity. *Rep. Prog. Phys.* **2005**, *68* (4), 799–853.
- (96) Miele, A. E.; Federici, L.; Sciarra, G.; Draghi, F.; Brunori, M.; Vallone, B. Analysis of the Effect of Microgravity on Protein Crystal Quality: The Case of a Myoglobin Triple Mutant. *Acta Crystallogr.* **2003**, *59*, 982–988.
- (97) Ahari, H.; Bedard, R. L.; Bowes, C. L.; Coombs, N.; Dag, O.; Jiang, T.; Ozin, G. A.; Petrov, S.; Sokolov, I.; Verma, A.; Vovk, G.; Young, D. Effect of Microgravity on the Crystallization of a Self-Assembling Layered Material. *Nature* **1997**, *388*, 857–860.
- (98) Amseleem, S.; Kogan, D.; Loboda, O.; Levy, A.; Feuchtwanger, Y.; Balvi, D. Monoclonal Antibodies from Space: Improved Crystallization under Microgravity during Manufacturing in Orbit. *J. Explor. Res. Pharmacol.* **2024**, *9* (2), 96–105.
- (99) Alvarado, U. R.; DeWitt, C. R.; Shultz, B. B.; Ramsland, P. A.; Edmundson, A. B. Crystallization of a Human Bence-Jones Protein in Microgravity Using Vapor Diffusion in Capillaries. *J. Cryst. Growth* **2001**, *223* (3), 407–414.
- (100) Nakamura, A.; Ohtsuka, J.; Kashiwagi, T.; Numoto, N.; Hirota, N.; Ode, T.; Okada, H.; Nagata, K.; Kiyohara, M.; Suzuki, E.; Kita, A.; Wada, H.; Tanokura, M. In-Situ and Real-Time Growth Observation of High-Quality Protein Crystals under Quasi-Microgravity on Earth. *Sci. Rep.* **2016**, *6*, 22127.
- (101) Inaka, K.; Takahashi, S.; Aritake, K.; Tsurumura, T.; Furubayashi, N.; Yan, B.; Hirota, E.; Sano, S.; Sato, M.; Kobayashi, T.; Yoshimura, Y.; Tanaka, H.; Urade, Y. High-Quality Protein Crystal Growth of Mouse Lipocalin-Type Prostaglandin d Synthase in Microgravity. *Cryst. Growth Des.* **2011**, *11* (6), 2107–2111.
- (102) Judge, R. A.; Snell, E. H.; van der Woerd, M. J. Extracting Trends from Two Decades of Microgravity Macromolecular Crystallization History. *Acta Crystallogr.* **2005**, *D61*, 763–771.

- (103) Owens, G. E.; New, D. M.; Olvera, A. I.; Manzella, J. A.; Macon, B. L.; Dunn, J. C.; Cooper, D. A.; Rouleau, R. L.; Connor, D. S.; Bjorkman, P. J. Comparative Analysis of Anti-Polyglutamine Fab Crystals Grown on Earth and in Microgravity. *Acta Crystallogr.* **2016**, *72*, 762–771.
- (104) Aibara, S.; Suzuki, A.; Shibata, K.; Yamane, T. Influences of Microgravity on Protein Crystal Growth. *Biol. Sci. Space.* **1998**, *12* (3), 286–287.
- (105) Aibara, S.; Shibata, K.; Morita, Y. Protein Crystallization in Microgravity. *Biol. Sci. Space* **1997**, *11* (4), 339–345.
- (106) Dong, J.; Pan, J.; Wang, Y.; Bi, R. Studies on the Solvent Structure in Protein Crystals Grown in Microgravity. *Space Med. Med. Eng.* **1998**, *11* (1), 26–29.
- (107) Akporiaye, D. E.; Stöcker, M.; Junggreen, H. Results of the Crystallisation of Zeolite Molecular Sieves under Microgravity Conditions during the Eureca-1 Mission. *Adv. Space Res.* **1995**, *16* (8), 55–58.
- (108) Bi, R. C.; Gui, L. L.; Wang, Y. P.; Chen, S. Z.; Han, Q.; Hu, Y. L.; Shen, F. L.; Niu, X. T.; Hua, Z. Q. Protein Crystal Growth in Microgravity. *Sci. China* **1994**, *37* (10), 1185–1191.
- (109) Braddock, M. From Target Identification to Drug Development in Space: Using the Microgravity Assist. *Curr. Drug Discovery Technol.* **2020**, *17* (1), 45–56.
- (110) Chayen, N. E. Microgravity Protein Crystallisation Aboard the Photon Satellite. *J. Cryst. Growth* **1995**, *153* (3–4), 175–179.
- (111) Chayen, N. E.; Snell, E. H.; Helliwell, J. R.; Zagalsky, P. F. Ccd Video Observation of Microgravity Crystallization: Apocrustacyanin c-1. *J. Cryst. Growth* **1997**, *171* (1–2), 219–225.
- (112) Cheng, Z.; Zhu, J.; Russel, W. B.; Meyer, W. V.; Chaikin, P. M. Colloidal Hard-Sphere Crystallization Kinetics in Microgravity and Normal Gravity. *Appl. Opt.* **2001**, *40* (24), 4146–4151.
- (113) Drago, V.; Mueser, T.; Schall, C. Toledo Crystallization Box: Microgravity Crystallization of Perdeuterated s. Typhimurium Tryptophan Synthase for Neutron Diffraction. *Acta Crystallogr.* **2020**, *76*, a135.
- (114) Engle, M. Protein Crystal Growth in Microgravity. *Biomed. Sci. Instrum.* **1993**, *29*, 71–76.
- (115) Garcia-Ruiz, J. M. On the Sensitivity of Protein Crystallization Due to the Quality of the Microgravity Environment. *Microgravity Sci. Technol.* **1998**, *11* (2), 74–77.
- (116) Gonzalez-DeWhitt, K.; Spinale, A. Lessons Learned from Using the Mitegen in Situ-1 (Tm) Crystallization Plate for Microgravity Protein Crystallization. *Acta Crystallogr.* **2020**, *76* (a1), a89.
- (117) Gonzalez-DeWhitt, K. R. Measure and Might of the Mitegen in Situ-1TM Crystallization Plate for Microgravity Protein Crystal Growth. *Acta Crystallogr.* **2018**, *A74*, a2.
- (118) González-Ramírez, L. A.; Van Driessche, A. E. S.; Melero-García, E.; Gavira, J. A.; García-Ruiz, J. M. Crystallization in Gels and Microgravity: A Comparative Study. *Acta Crystallogr. A* **2011**, *67* (a1), C89.
- (119) Holemans, J.; Cassanto, J. M.; Müller, T. W.; Cassanto, V. A.; Rose, A.; Luttes, M.; Morrison, D.; Todd, P.; Stewart, R.; Korszun, R. Z.; Deardorff, G. The BIMDA Shuttle Flight Mission: A Low Cost Microgravity Payload. *Microgravity Q* **1991**, *1* (4), 235–247.
- (120) Hoyer, J. R.; Piezyrsky, R. A.; Liu, H.; Whitson, P. A. Effects of Microgravity on Urinary Osteopontin. *J. Am. Soc. Nephrol.* **1999**, *10* (Suppl14), S389–S393.
- (121) Ilyin, E. A.; Oganov, V. S. Microgravity and Musculoskeletal System of Mammals. *Adv. Space Res.* **1989**, *9* (11), 11–19.
- (122) Imura, T.; Nakagawa, K.; Kawahara, Y.; Yuge, L. Stem Cell Culture in Microgravity and Its Application in Cell-Based Therapy. *Stem Cells Dev.* **2018**, *27* (18), 1298–1302.
- (123) Pechkova, E.; Bragazzi, N.; Bozdaganyan, M.; Belmonte, L.; Nicolini, C. A Review of the Strategies for Obtaining High-Quality Crystals Utilizing Nanotechnologies and Microgravity. *Crit. Rev. Eukaryot. Gene Expr.* **2014**, *24*, 325–339.
- (124) Judge, R. A.; Snell, E. H.; Kephart, R.; vanderWoerd, M.; Curreri, P. A. Decades of Data: Extracting Trends from Microgravity Crystallization History; 20020051105; NASA: Marshall Spaceflight Center, 2002. <https://ntrs.nasa.gov/citations/20020051105>.
- (125) Kim, G. T. Application of Diffusion-Limited Theory to the Crystal Growth Rate of Zinc Selenide in Microgravity Environments. **2005**.
- (126) Krausepenhaar, R.; Rypniewski, W.; Kalkura, N.; Moore, K.; DeLucas, L.; Stoeva, S.; Mikhailov, A.; Voelter, W.; Betzel, C. Crystallisation under Microgravity of Mistletoe Lectin i from Viscum Album with Adenine Monophosphate and the Crystal Structure at 1.9 Å Resolution. *Acta Crystallogr.* **2002**, *58*, 1704–1707.
- (127) Liu, X. Y. Effect of Microgravity on Ca Mineral Crystallization and Implications for Osteoporosis in Space. *Appl. Phys. Lett.* **2001**, *79* (21), 3539–3541.
- (128) Cook, M. E.; Croxdale, J. L.; Tibbitts, T. W.; Goins, G.; Brown, C. S.; Wheeler, R. M. Development and Growth of Potato Tubers in Microgravity. *Adv. Space Res.* **1998**, *21* (8–9), 1103–1110.
- (129) Lorber, B. The Crystallization of Biological Macromolecules under Microgravity: A Way to More Accurate Three-Dimensional Structures? *Biochimica Biochimica et Biophysica Acta* **2002**, *1599* (1–2), 1–8.
- (130) Maes, D.; Decanniere, K.; Zegers, I.; Vanhee, C.; Sleutel, M.; Willaert, R.; Van De Weerd, C.; Martial, J.; Declercq, J.-P.; Evard, C.; Otolara, F.; Garcia Ruiz, J. M. Protein Crystallisation under Microgravity Conditions: What Did We Learn on TIM Crystallisation from the Soyuz Missions? *Brem. Microgravity Sci. Technol.* **2007**, *XIX* (5/6), 90–94.
- (131) McPherson, A. Effects of a Microgravity Environment on the Crystallization of Biological Macromolecules. *Microgravity Sci. Technol.* **1993**, *6* (2), 101–109.
- (132) McPherson, A. Recent Advances in the Microgravity Crystallization of Biological Macromolecules. *Trends Biotechnol.* **1997**, *15* (6), 197–200.
- (133) McPherson, A.; Malkin, A. J.; Kuznetsov, Y. G.; Koszelak, S.; Wells, M.; Jenkins, G. D.; Howard, J. F.; Lawson, G. The Effects of Microgravity on Protein Crystallization: Evidence for Concentration Gradients around Growing Crystals. *J. Cryst. Growth* **1999**, *196* (2–4), 572–586.
- (134) Nedukha, E. M. Possible Mechanisms of Plant Cell Wall Changes at Microgravity. *Adv. Space Res.* **1996**, *17* (6–7), 37–45.
- (135) Ng, J. D.; Lorber, B.; Giege, R.; Koszelak, S.; Day, J.; Greenwood, A.; McPherson, A. Comparative Analysis of Thaumatin Crystals Grown on Earth and in Microgravity. *Acta Astronaut.* **1997**, *53*, 724–733.
- (136) Nunes, C. R.; Roedersheimer, M. T.; Simske, S. J.; Luttes, M. W. Effect of Microgravity, Temperature, and Concentration on Fibrin and Collagen Assembly. *Microgravity Sci. Technol.* **1995**, *8* (2), 125–130.
- (137) Okubo, T.; Tsuchida, A.; Okuda, T.; Fujitsuna, K.; Ishikawa, M.; Morita, T.; Tada, T. Kinetic Analyses of Colloidal Crystallization in Microgravity Aircraft Experiments. *Colloids Surf. Physicochem. Eng. Asp.* **1999**, *153*, 515.
- (138) Owen, R. B.; Zozulya, A. A.; Benoit, M. R.; Klaus, D. M. Microgravity Materials and Life Sciences Research Applications of Digital Holography. *Appl. Opt.* **2002**, *41* (19), 3927–3935.
- (139) Schall, C.; Obouji, E.; Mueser, T. The Toledo Crystallization Box: A Capillary Diffusion Apparatus for Microgravity Protein Crystallization Experiments. *Acta Crystallogr. Found. Adv.* **2019**, *75* (a1), A121.
- (140) Scott, T. J.; Vonortas, N. S. Microgravity Protein Crystallization for Drug Development: A Bold Example of Public Sector Entrepreneurship. *J. Technol. Transfer* **2021**, *46* (5), 1442–1461.
- (141) Sidorov, V. S.; Zakharov, B. G.; Serebryakov, Yu. A.; Pereverzev, A. V.; Nagaev, E. M.; Strelou, V. An Updated Facility for Crystal Growth with Modeling of the Conditions of Crystallization in Microgravity. *Instrum. Exp. Technol.* **1999**, *42* (2), 279–283.
- (142) Snell, E. H.; Weisgerber, S.; Helliwell, J. R.; Weckert, E.; Hölzer, K.; Schroer, K. Improvements in Lysozyme Protein Crystal

- Perfection through Microgravity Growth. *Acta Crystallogr. D Biol. Crystallogr.* **1995**, *51* (6), 1099–1102.
- (143) Snell, E. H.; Cassetta, A.; Helliwell, J. R.; Boggon, T. J.; Chayen, N. E.; Weckert, E.; Holzer, K.; Schroer, K.; Gordon, E. J.; Zagalsky, P. F. Partial Improvement of Crystal Quality for Microgravity-Grown Apocrustacyanin C1. *Acta Crystallogr. D Biol. Crystallogr.* **1997**, *53* (3), 231–239.
- (144) Borgstahl, G. E. O.; Vahedi-Faridi, A.; Lovelace, J.; Bellamy, H. D.; Snell, E. H. A Test of Macromolecular Crystallization in Microgravity: Large Well Ordered Insulin Crystals. *Acta Crystallogr. D Biol. Crystallogr.* **2001**, *57* (8), 1204–1207.
- (145) Snell, E. H.; Boggon, T. J.; Helliwell, J. R.; Moskowitz, M. E.; Nadarajah, A. CCD Video Observation of Microgravity Crystallization of Lysozyme and Correlation with Accelerometer Data. *Acta Crystallogr. D Biol. Crystallogr.* **1997**, *53* (6), 747–755.
- (146) Snyder, R. S.; Fuhrmann, K.; Walter, H. U. Protein Crystallization Facilities for Microgravity Experiments. *J. Cryst. Growth* **1991**, *110* (1–2), 333–338.
- (147) Stagno, J. R.; Yu, P.; Spinale, A.; Todd, P. W.; Giulianotti, M.; Wang, Y.-X. Effects of Microgravity Crystallization on a Ligand-Induced RNA Crystal Phase Transition. *Acta Crystallogr. Sect. Found. Adv.* **2019**, *75* (a1), a128.
- (148) Stoddard, B. L.; Strong, R. K.; Farber, G. K.; Arrott, A.; Petsko, G. A. Design of Apparatus and Experiments to Determine the Effect of Microgravity on the Crystallization of Biological Macromolecules Using the MIR Spacestation. *J. Cryst. Growth* **1991**, *110* (1–2), 312–316.
- (149) Takahashi, S.; Tanaka, H.; Sato, M.; Inaka, K.; Yan, B.; Yamanaka, M.; Furubayashi, N.; Sano, S.; Kobayashi, T.; Nakagawa, A.; Tanaka, T. Protein Crystallization Strategy in Microgravity. *Acta Crystallogr. A* **2008**, *64* (a1), C581–C582.
- (150) Tanokura, M.; Nakamura, A. ISBP-02 Protein Crystallization under Microgravity Conditions (ISBP The Development of New Crystallization Methods for Bio-Macromolecular Crystallography, Symposium, The 52nd Annual Meeting of the Biophysical Society of Japan (BSJ2014)). *Seibutsu Butsuri* **2014**, *54*, S121.
- (151) Tatarchenko, V. A.; Brantov, S. K.; Leskov, L. V.; Levto, V. L.; Agafonov, M. S. Experimental Results of the Crystallization of Indium by the Stepanov Method in Conditions of Microgravitation. *Bull. Acad. Sci. USSR Phys. Ser.* **1985**, *49*, 79.
- (152) Vaney, M. C.; Maignan, S.; Riès-Kautt, M.; Ducruix, A. High-Resolution Structure (1.33 Å) of a HEW Lysozyme Tetragonal Crystal Grown in the APCF Apparatus. Data and Structural Comparison with a Crystal Grown under Microgravity from SpaceHab-01 Mission. *Acta Crystallogr. D Biol. Crystallogr.* **1996**, *52* (3), 505–517.
- (153) Wagner, G. Bacteriorhodopsin Crystal Growth under Microgravity—Results of IML-1 and Spacehab-1 Experiments. *ESA J.* **1994**, *18* (1), 25–32.
- (154) Wang, W.; Hu, W. R. Concentration Distribution in Crystallization from Solution under Microgravity. *J. Cryst. Growth* **1996**, *160* (3–4), 398–405.
- (155) Wang, Y. P.; Han, Y.; Pan, J. S.; Wang, K. Y.; Bi, R. C. Protein Crystal Growth in Microgravity Using a Liquid/Liquid Diffusion Method. *Microgravity Sci. Technol.* **1996**, *9* (4), 281–283.
- (156) Zhu, D.-W.; Zhou, M.; Mao, Y.; Labrie, F.; Lin, S.-X. Crystallization of Human Estrogenic 17 β -Hydroxysteroid Dehydrogenase under Microgravity. *J. Cryst. Growth* **1995**, *156* (1–2), 108–111.
- (157) Zhen-He, Z.; Yong, H.; Pei-Wen, G.; Yu-De, Y. Yu-De. Effects of Interface Kinetics and Anisotropy on the Stability of the Growing Crystal Face and Dissolution Face during Crystallization from Solution under Microgravity. *Chin. Phys.* **2004**, *13* (12), 1982–1991.
- (158) Wilke, S. K.; Al-Rubkhi, A.; Koyama, C.; Ishikawa, T.; Oda, H.; Topper, B.; Tsekrekas, E. M.; Möncke, D.; Alderman, O. L. G.; Menon, V.; Rafferty, J.; Clark, E.; Kastengren, A. L.; Benmore, C. J.; Ilavsky, J.; Neufeind, J.; Kohara, S.; SanSoucie, M.; Phillips, B.; Weber, R. Microgravity Effects on Nonequilibrium Melt Processing of Neodymium Titanate: Thermophysical Properties, Atomic Structure, Glass Formation and Crystallization. *npj Microgravity* **2024**, *10* (1), 26.
- (159) Barta, C.; Trnka, J.; Triska, A.; Ryšavá, N.; Kuhl, R.; Röstel, R.; Schultze, D. A New Module for the Csk-1 Crystallizer: Thermographic Dta Probe for the Study of Metastable Phase Equilibria under Microgravity Conditions. *Adv. Space Res.* **1988**, *12* (8), 137–140.
- (160) Durachenko, A. M.; Regal, L. L. Crystallization of Metal Alloys in Microgravity and Uniform Compression Conditions. *Acta Astronaut.* **1986**, *13* (11–12), 651–654.
- (161) Drago, V. N. *Microgravity Crystallization and Neutron Diffraction of PLP-dependent Enzymes*, Ph.D. Dissertation; The University of Toledo: Toledo, OH, 2022.
- (162) Drago, V. N.; Devos, J. M.; Blakeley, M. P.; Forsyth, V. T.; Kovalevsky, A. Y.; Schall, C. A.; Mueser, T. C. Microgravity Crystallization of Perdeuterated Tryptophan Synthase for Neutron Diffraction. *npj Microgravity* **2022**, *8* (1), 13.
- (163) Zhu, J.; Li, M.; Rogers, R.; Meyer, W.; Ottewill, R. H.; Russel, W. B.; Chaikin, P. M.; STS-73 Space Shuttle Crew. Crystallization of Hard-Sphere Colloids in Microgravity. *Nature* **1997**, *387* (6636), 883–885.
- (164) Cheng, Z.; Chaikin, P. M.; Zhu, J.; Russel, W. B.; Meyer, W. V. Crystallization Kinetics of Hard Spheres in Microgravity in the Coexistence Regime: Interactions between Growing Crystallites. *Phys. Rev. Lett.* **2001**, *88* (1), 015501.
- (165) Cook, M. E.; Croxdale, J. G. Ultrastructure of Potato Tubers Formed in Microgravity under Controlled Environmental Conditions. *J. Exp. Bot.* **2003**, *54* (390), 2157–2164.
- (166) Nakae, S.; Shionyu, M.; Ogawa, T.; Shirai, T. Crystallization of Pearl Biomineralization Protein in Microgravity Environments. *Int. J. Microgravity Sci. Appl.* **2019**, *36* (1), 360105.
- (167) Berisio, R.; Vitagliano, L.; Sorrentino, G.; Carotenuto, L.; Piccolo, C.; Mazzarella, L.; Zagari, A. Effects of Microgravity on the Crystal Quality of a Collagen-like Polypeptide. *Acta Crystallogr.* **2000**, *56* (1), 55–61.
- (168) Sato, M.; Tanaka, H.; Inaka, K.; Sano, S.; Shinozaki, S.; Takahashi, S.; Yamanaka, M.; Hirota, E.; Yan, B.; Kobayashi, T.; Tanaka, T. Protein Crystallization under Microgravity in JAXA New-GCF Project. *Acta Crystallogr. A* **2008**, *64* (a1), C582.
- (169) Quirk, S.; Lieberman, R. L. Improved Resolution Crystal Structure of *Acanthamoeba* Actophorin Reveals Structural Plasticity Not Induced by Microgravity. *Acta Crystallogr. Sect. F Struct. Biol. Commun.* **2021**, *77* (12), 452–458.
- (170) Chayen, N. E.; Gordon, E. J.; Zagalsky, P. F. Crystallization of Apocrustacyanin C-1 on the International Microgravity Laboratory (Iml-2) Mission. *Acta Crystallogr.* **1996**, *52* (1), 156–159.
- (171) Tanaka, H.; Sasaki, S.; Takahashi, S.; Inaka, K.; Wada, Y.; Yamada, M.; Ohta, K.; Miyoshi, H.; Kobayashi, T.; Kamigaichi, S. Numerical Model of Protein Crystal Growth in a Diffusive Field Such as the Microgravity Environment. *J. Synchrotron Radiat.* **2013**, *20*, 1003–1009.
- (172) Henning, C.; Frank, J.; Laubender, G.; Fromme, P. Crystallization of Membrane Protein Under Microgravity; 34th COSPAR Scientific Assembly, 2002.
- (173) Asano, K.; Fujita, S.; Senda, T.; Mitsui, Y. Crystal Growth of Ribonuclease s under Microgravity. *J. Cryst. Growth* **1992**, *122* (1–4), 323–329.
- (174) Achari, A.; Roeber, D. F.; Barnes, C. L.; Kundrot, C. E.; Stinson, T. N. *Equilibrium Kinetics Studies and Crystallization Aboard the International Space Station (Iss) Using the Protein Crystallization Apparatus for Microgravity (Pcam)*, 2002. <https://ntrs.nasa.gov/citations/20020067783>.
- (175) Sieker, L. C. Microdialysis Crystallization Chamber. *J. Cryst. Growth* **1988**, *90* (1–3), 349–357.
- (176) Khurshid, S.; Chayen, N. E. Upside-down Protein Crystallization - Designing Microbatch Experiments for Microgravity. *Ann. N.Y. Acad. Sci.* **2006**, *1077*, 208–213.
- (177) Trakhanov, S. D.; Grebenko, A. I.; Shirokov, V. A.; Gudkov, A. V.; Egorov, A. V.; Barmin, I. N.; Vainstein, B. K.; Spirin, A. S.

- Crystallization of Protein and Ribosomal Particles in Microgravity. *J. Cryst. Growth* **1991**, *110* (1–2), 317–321.
- (178) Amselem, S. Remote Controlled Autonomous Microgravity Lab Platforms for Drug Research in Space. *Pharm. Res.* **2019**, *36* (12), 183.
- (179) Boyko, K. M.; Timofeev, V. I.; Samygina, V. R.; Kuranova, I. P.; Popov, V. O.; Kovalchuk, M. V. Protein Crystallization under Microgravity Conditions. Analysis of the Results of Russian Experiments Performed on the International Space Station in 2005–2015. *Crystallogr. Rep.* **2016**, *61*, 718–729.
- (180) Popov, A.; Kostadinov, I.; Mateev, M.; Regel, L.; Baturin, N. The Influence of the Front of Crystallization upon the Phase Content in RbAg₄I₅ Bulk Crystals Grown in Microgravity. *Solid State Ion* **1992**, *57* (3–4), 211–215.
- (181) Vojtěch, D.; Holeček, S.; Barta, C.; Barta, C.; Görler, G. P.; Otto, G.; Wittmann, K. Crystallization of Silver–Germanium Alloys under Microgravity I. Eutectic Crystallization in Hypoeutectic Alloy. *Cryst. Res. Technol.* **1997**, *32* (7), 973–981.
- (182) Vojtěch, D.; Barta, C.; Barta, C.; Görler, G. P.; Otto, G. Non-Equilibrium Primary Crystallization in Silver–Germanium Alloy under Microgravity Conditions. *Mater. Sci. Technol.* **1999**, *15* (11), 1266–1272.
- (183) Wang, W.; Hu, W. R. Effects of the Orientation of Microgravity on the Concentration Distribution in Crystallization from Solution. *Adv. Space Res.* **1998**, *22* (8), 1261–1264.
- (184) Fontana, P.; Pettit, D.; Cristoforetti, S. Sodium Chloride Crystallization from Thin Liquid Sheets, Thick Layers, and Sessile Drops in Microgravity. *J. Cryst. Growth* **2015**, *428*, 80–85.
- (185) Abd Rahman, R. N. Z. R.; Mohamad Ali, M. S.; Sugiyama, S.; Leow, A.; Inoue, T.; Basri, M.; Salleh, A.; Matsumura, H. A Comparative Analysis of Microgravity and Earth Grown Thermostable T1 Lipase Crystals Using HDPCG Apparatus. *Protein Pept. Lett.* **2015**, *22* (2), 173–179.
- (186) Lorenz, S.; Perbandt, M.; Lippmann, C.; Moore, K.; DeLucas, L. J.; Betzel, C.; Erdmann, V. A. Crystallization of Engineered Thermus Flavus Ss Rna under Earth and Microgravity Conditions. *Acta Crystallogr.* **2000**, *56*, 498–500.
- (187) Lorber, B.; Sauter, C.; Robert, M. C.; Capelle, B.; Giegé, R. Crystallization within Agarose Gel in Microgravity Improves the Quality of Thaumatin Crystals. *Acta Crystallogr.* **1999**, *55*, 1491–1494.
- (188) Liu, Y.; Wan-chun, C.; Pei-wen Interface Shape and Concentration Distribution in Crystallization from Solution under Microgravity. *Acta Phys. Sin.*, *8*(12), 881.
- (189) Safonova, T. N.; Mordkovich, N. N.; Polyakov, K. M.; Manuvera, V. A.; Veiko, V. P.; Popov, V. O. Crystallization of Uridine Phosphorylase from *Shewanella Oneidensis* MR-1 in the Laboratory and under Microgravity and Preliminary X-Ray Diffraction Analysis. *Acta Crystallogr. Sect. F Struct. Biol. Cryst. Commun.* **2012**, *68* (11), 1387–1389.
- (190) Eistrikh-Heller, P. A.; Rubinsky, S. V.; Samygina, V. R.; Gabdulkhakov, A. G.; Kovalchuk, M. V.; Mironov, A. S.; Lashkov, A. A. Crystallization in Microgravity and the Atomic-Resolution Structure of Uridine Phosphorylase from *Vibrio Cholerae*. *Crystallogr. Rep.* **2021**, *66*, 777–785.
- (191) Vonortas, N. S. *Protein Crystallization for Drug Development: A Prospective Empirical Appraisal of Economic Effects of ISS Microgravity*; Final Report; NASA, 2015; p 31. https://www.ige.unicamp.br/wp-content/uploads/sites/51/2015/07/Report-NASA_Modeling-Drug-Development-and-Protein-Crystals_2015.pdf (accessed 2026–05–14).
- (192) Varma, S.; Prasad, S. E.; Ahmad, A.; Wheat, T. A. Effect of Microgravity on Crystallization in Heavy Metal Fluoride Glasses Processed on the CSAR-I Sounding Rocket. *J. Mater. Sci.* **2001**, *36* (8), 2027–2035.
- (193) Torres, A.; Barr, R. The Development of a Heated-Stage Optical Microscope for ZBLAN Microgravity Crystallization Studies. *Microgravity Sci. Technol.* **2016**, *28* (4), 367–380.
- (194) Torres, A.; Ganley, J.; Maji, A. Experimental and Analytical Techniques for Studying ZBLAN Crystallization in Microgravity. *Exp. Technol.* **2016**, *40* (2), 501–512.
- (195) Song, H.; Illegbusi, O. J.; Sacco, A. Kinetics of Zeolite NaA Crystallization in Microgravity. *Mater. Lett.* **2005**, *59*, 2668.
- (196) Cazzaniga, A.; Maier, J. A. M.; Castiglioni, S. Impact of Simulated Microgravity on Human Bone Stem Cells: New Hints for Space Medicine. *Biochem. Biophys. Res. Commun.* **2016**, *473* (1), 181–186.
- (197) Zhang, H.; Kamotani, Y.; Ostrach, S. Zeolite Crystallization Process Modeling and Comparison with Microgravity Flight Results. *J. Spacecr. Rockets* **1995**, *32* (1), 110–116.
- (198) Sano, T.; Mizukami, F.; Kawamura, M.; Takaya, H.; Mouri, T.; Inaoka, W.; Toida, Y.; Watanabe, M.; Toyoda, K. Crystallization of ZSM-5 Zeolite under Microgravity. *Zeolites* **1992**, *12* (7), 801–805.
- (199) Aibara, S. Crystallization of Wheat γ -Gliadin under a Microgravity Environment Using Space Station MIR. *J. Cryst. Growth* **1995**, *155* (3–4), 247–253.
- (200) Schlagheck, R. A.; Trach, B. L. Microgravity Research Results and Experiences from the NASA/MIR Space Station Program. *Acta Astronaut.* **2003**, *53* (12), 983–996.
- (201) Zhu, Z.; Ge, P.; Chong-Ru, H.; Chen, D.; Li, C. Stable Shape of Crystal Growth Face in Crystallization from Solution under Microgravity. *J. Cryst. Growth* **2001**, *13* (12), 1009–1063.
- (202) McPherson, A.; Malkin, A.; Kuznetsov, Y. The Science of Macromolecular Crystallization. *Structure* **1995**, *3* (8), 759–768.
- (203) Timofeev, V. I.; Ivanovsky, A. S.; Marchenkova, M. A.; Rakitina, T. V.; Kuranova, I. P. Growth of Protein Crystals in Microgravity: History and Present Status. *Crystallogr. Rev.* **2024**, *30* (4), 236–260.
- (204) Groover, M. *Fundamentals of Modern Manufacturing Materials Processes and Systems*, 4th ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 2010.
- (205) *Space Manufacturing and Resources: Earth and Planetary Exploration Applications*, 1st ed.; Hessel, V., Stoudemire, J., Miyamoto, H., Fisk, I. D., Eds.; Wiley, 2022.
- (206) Eistrikh-Heller, P. A.; Rubinsky, S. V.; Samygina, V. R.; Gabdulkhakov, A. G.; Kovalchuk, M. V.; Mironov, A. S.; Lashkov, A. A. Erratum to: Crystallization in Microgravity and the Atomic-Resolution Structure of Uridine Phosphorylase from *Vibrio Cholerae*. *Crystallogr. Rep.* **2021**, *66* (7), 1333.
- (207) Románach, R. J.; Stelzer, T.; Sanchez, E.; Muzzio, F. Advanced Pharmaceutical Manufacturing: A Functional Definition. *J. Adv. Manuf. Process.* **2023**, *5* (2), No. e10150.
- (208) Optical Fiber Production - NASA. <https://www.nasa.gov/missions/station/iss-research/optical-fiber-production/> (accessed May 18, 2026).
- (209) Torres, A.; Ganley, J.; Maji, A. Understanding the Role of Gravity in the Crystallization Suppression of ZBLAN Glass. *J. Mater. Sci.* **2014**, *49* (22), 7770–7781.
- (210) Hernández Espinell, J. R.; Toro, V.; Yao, X.; Yu, L.; López-Mejías, V.; Stelzer, T. Solvent-Mediated Polymorphic Transformations in Molten Polymers: The Account of Acetaminophen. *Mol. Pharmaceutics* **2022**, *19* (7), 2183–2190.
- (211) *Crystallization: Basic Concepts and Industrial Applications*, 1st ed.; Beckmann, W., Ed.; Wiley, 2013.
- (212) Manzano, A.; Herranz, R.; den Toom, L. A.; te Slaa, S.; Borst, G.; Visser, M.; Javier Medina, F.; van, L.; Novel, J. J. W. A. Moon and Mars, Partial Gravity Simulation Paradigms and Their Effects on the Balance between Cell Growth and Cell Proliferation during Early Plant Development. *npj Microgravity* **2018**, *4*(9).
- (213) Yuan, J.; Zhang, S.; Xu, Y.; He, C.; Cai, Z.; Wang, Z.; Chen, Q. Microgravity and Cancer Cells: From Molecular Mechanisms to Therapeutic Strategies. *Cell Death Discov* **2026**, *12* (1), 9.
- (214) Fontalvo Gómez, M.; Johnson Restrepo, B.; Stelzer, T.; Románach, R. J. Process Analytical Chemistry and Nondestructive Analytical Methods: The Green Chemistry Approach for Reaction Monitoring, Control, and Analysis. In *Handbook of Green Chemistry*; Anastas, P. T., Ed.; Wiley, 2019; pp 257–288.

(215) U.S. Department of Health and Human Services; Food and Drug Administration; Center for Drug Evaluation and Research (CDER); Center for Veterinary Medicine (CVM); Office of Regulatory Affairs (ORA). *Guidance for Industry PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*, 2024.

(216) van Loon, J. J. W. A. Some History and Use of the Random Positioning Machine, RPM, in Gravity Related Research. *Adv. Space Res.* **2007**, 39 (7), 1161–1165.

(217) Wadhwa, A.; Bruun, L.; Petersen, J. C. G.; Petersen, L. G. Guidelines for Use of the Random Positioning Machine as a Reduced-Gravity Analog. *Sci. Rep.* **2026**, 16 (1), 10012.

(218) Albertazzi, J.; Pandit, A. V.; Aprile, G.; Pons Royo, M. D. C.; Busini, V.; Rota, R.; Myerson, A. S.; Stelzer, T. Computational Fluid Dynamic Study in a Multistage Small-Scale Tower Crystallizer. *Ind. Eng. Chem. Res.* **2026**, 65 (6), 3474–3486.

(219) Aprile, G.; Pandit, A. V.; Albertazzi, J.; Vetter, T.; Viano, R.; Milani, L.; Adamo, A.; Myerson, A. S.; Stelzer, T. Residence Time Distribution Characterization and Proof-of-Concept of a Novel Stacked 7-Stage Continuous Crystallizer Cascade with Diaphragm-Driven Slurry Transfer. *Ind. Eng. Chem. Res.* **2024**, 63 (42), 18199–18211.

(220) U.S. Food and Drug Administration. Emerging Technology Program (ETP). <https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/emerging-technology-program-etp>.