High-throughput cryo-EM and cryo-ET workflows for automated sample preparation, screening and in situ structural biology

Challenges

Cryo-electron microscopy (cryo-EM) and cryo-electron tomography (cryo-ET) enable the study of macromolecules, cells and complex biological specimens in close-to-native states. However, producing high-quality samples and interpretable structural data remains a major bottleneck. Key challenges include:

- **Low throughput:** Extensive optimisation of buffers, grid supports, vitrification and imaging conditions is often required.
- **High operator dependency:** Sample preparation, imaging and data interpretation rely heavily on specialist expertise, limiting scalability and reproducibility.
- **Complex cryo-ET preparation:** Thick cells, organoids, tissues and small organisms require advanced workflows such as high-pressure freezing, FIB milling and lift-out.
- **Data analysis complexity:** Tomography generates large, computationally demanding datasets requiring specialist processing and interpretation.

Technology

The Mattei Team at EMBL develops automated methods and software for high-throughput cryo-EM sample preparation, screening and imaging. The platform combines specimen handling, condition screening, biochemical characterisation, controlled vitrification, automated microscopy and data management in a scalable workflow for cryo-EM and cryo-ET projects:

- **High-throughput cryo-EM sample preparation and screening:** Development of automated pipelines designed to address rate-limiting steps in cryo-EM projects, including sample preparation, screening and optimization.
- **Condition screening:** Assessment of sample stability across multiple buffer conditions.
- **Controlled vitrification:** Devices for efficient and reproducible cryo-grid preparation.
- **Automated imaging workflows:** Integration of imaging routines and software for large-scale cryo-EM screening.
- **Sample tracking and data management**: A planned dedicated data management system with secure web interface for project planning and real-time remote inspection of results.
- **Correlative in situ imaging:** Cryogenic light and electron microscopy workflows linking fluorescence signals with high-resolution structural information.

Internal EMBLEM Reference

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Applications

- **Cryo-EM workflow automation** for instrument vendors, sample-preparation technology developers and microscopy automation companies.
- **Sample preparation platforms** for cryo-grid preparation, vitrification and high-throughput condition screening.
- **Cryo-ET services and workflows** for cellular biology, virology, organoid biology, marine biology and native-context structural studies.
- **Data-management and remote-inspection tools** for cryo-EM facilities and distributed research infrastructure.

Intellectual Property

☒ Know-how based

☒ Copyright

Benefits

- **Higher throughput:** Designed to enable large-scale cryo-EM sample preparation and screening.
- **Reduced operator dependency:** The pipeline is intended to minimise the human factor and provide tracking throughout the process.
- **Improved reproducibility and robustness:** Development goals include optimising methods for in situ cellular tomography and high-throughput workflows.
- **Broad biological applicability:** Cryo-ET applications span cellular biology and virology, with potential for studies of virus replication, ribosomes in cellular context, parasites, marine specimens and other systems.

Keywords

cryo-EM; # cryo-ET; # high-throughput cryo-EM; # automated sample preparation; # vitrification; # cryo-CLEM

Commercial Opportunity

This technology offers a commercially attractive route to making cryo-EM and cryo-ET workflows faster, more reproducible and more scalable for pharmaceutical, biotechnology, microscopy-instrumentation and advanced imaging service markets. By reducing bottlenecks in sample preparation, screening and automation, the platform creates opportunities for partnerships.

Further Reading

[1] 10.1038/s41586-026-10530-7

[2] 10.1038/s41467-024-52911-4

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