

Coupling Mechanistic Lyophilization Models with a Multi-Agent AI Interrogation Engine for Autonomous Process Discovery

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“Before bed, you give DAEMON a research question. By morning, it’s run thousands of in-silico experiments and delivered interpretable recipe recommendations for your next lab run.”

1 BACKGROUND AND MOTIVATION

- Lyophilization development is a multi-variable decision problem.
- For mRNA-LNP products, both recipe and formulation can affect final CQAs.
- In this study, the mechanistic model exposes a 20-input search space.
- Useful discovery requires more than running simulations; it requires choosing informative next experiments.
- DAEMON combines mechanistic simulation with multi-agent reasoning to support and automate that discovery process.

Table 1. Comparison table of this work vs. traditional solutions.

Approach	Physics-based	Adaptive search	Interpretable hypotheses	Evidence trail
Classical DOE	No	No	Limited	Moderate
Mechanistic simulation	Yes	No	Limited	Moderate
Black-box optimization	Optional	Yes	Low	Low
AI system w/o mechanistic simulation	No	No	Moderate	No
AI system w/ mechanistic simulation [This Work]	Yes	Yes	Yes	Yes

2 OBJECTIVE

- Automate lyophilization process discovery using a team of AI agents with access to a mechanistic model.
- Identify recipe-formulation relationships linked to key CQAs.
- Generate evidence-backed recipe recommendations.
- Allow the user to set the goal (a.k.a. research question) and constraints, then review results and analysis during and after the session.

3 DAEMON SYSTEM OVERVIEW

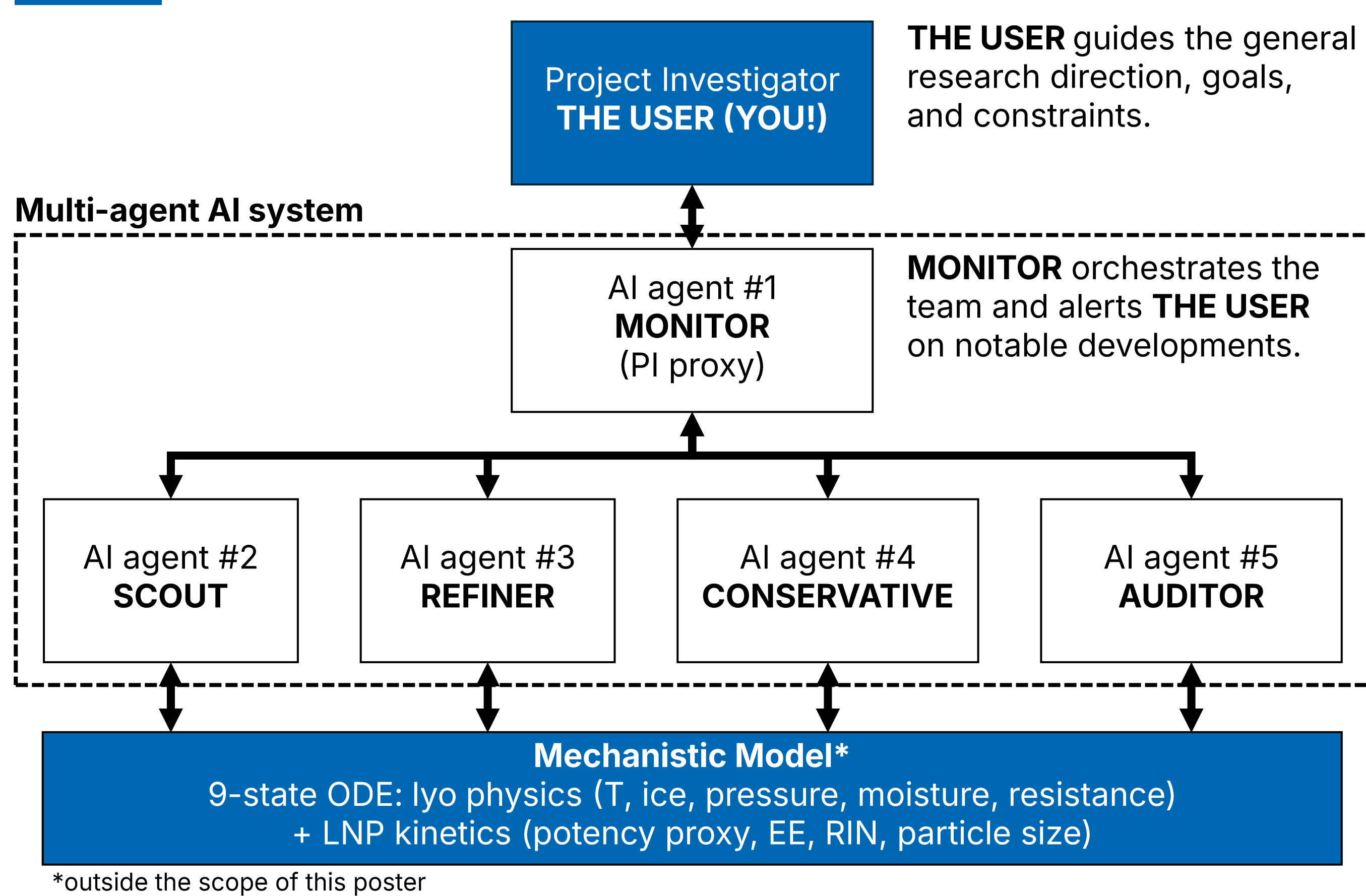


Figure 1. DAEMON system architecture.

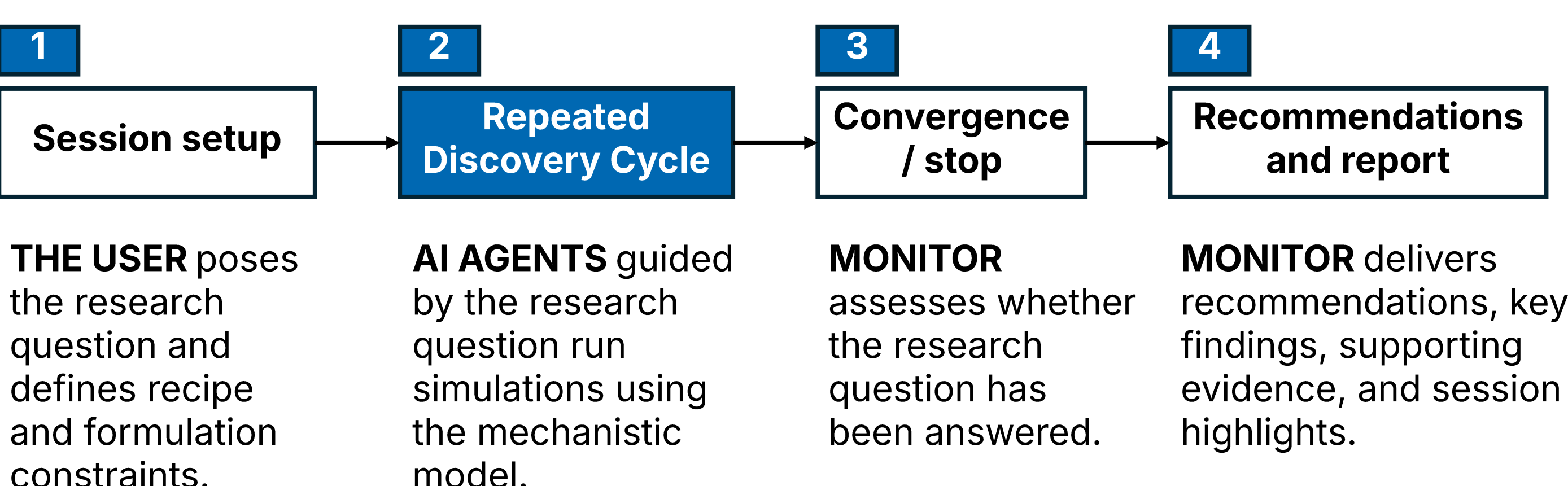
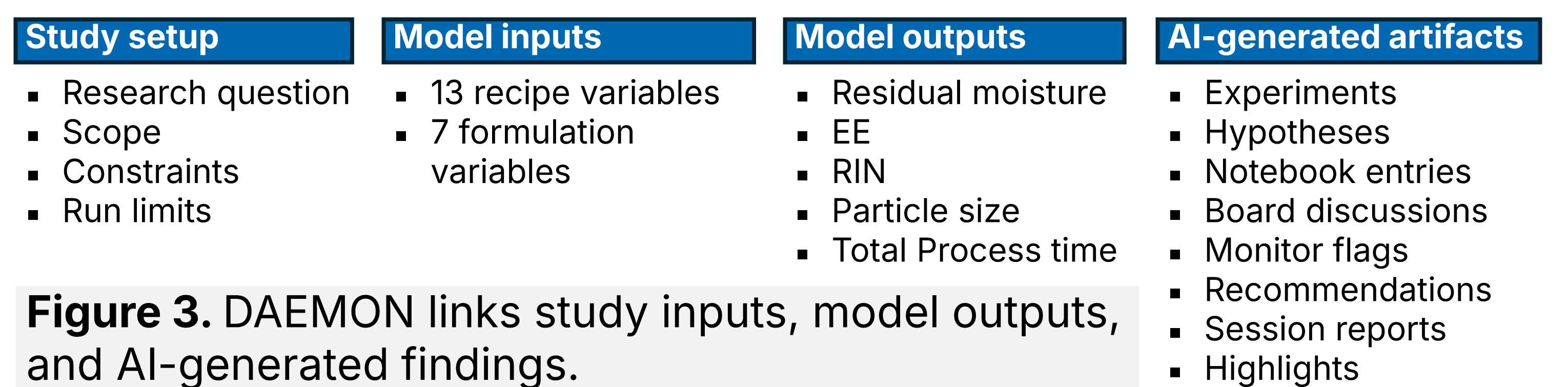


Figure 2. Automated discovery process.

GLOSSARY

- **DAEMON:** Discovery Agents Exploring Mechanistic ODE Networks, a multi-agent framework for model-driven scientific discovery.
- **Mechanistic Model:** A first-principles process model used to simulate how controllable inputs affect system behavior and CQAs.
- **Multi-agent AI interrogation Engine:** A coordinated set of AI agents that interrogate the model through iterative experiment proposal, interpretation, and discussion.
- **Autonomous Process Discovery:** The use of automated reasoning and simulation to identify candidate operating conditions and scientific insights from a defined search space.

4 STUDY SETUP AND METHODS



5 CASE STUDY AND HIGHLIGHTS

TRACEABILITY SESSION_ID: S_fe1881b2 / Status: converged / Created: 2026-03-14T17:59:21.112896+00:00 / Completed: 2026-03-14T18:21:39.257529+00:00 / Total cycles: 5 / Total experiments: 57

Research Question: Which recipe and formulation factors reduce residual moisture below 4% while maintaining EE above 90% and RIN above 7? 9 fixed, 3 restricted (buffer_ph, ionic_strength_mm, sd_pressure_mtorr), and 8 free/optimizeable parameters.

Which recipe and formulation factors reduce resi... **RUNNING** CYCLE 4 43 EXPERIMENTS 15M 13S **Pause** **Stop** **New Session**

RESEARCH QUESTION

STUDY SETUP

AGENTS (3)

HYPOTHESES EXPERIMENTS RECOMMENDATION BOARD NOTEBOOKS QUESTIONS ACTIVITY LOG

AI Active Supported Retired

STATEMENT	CONFIDENCE	EVIDENCE	STATUS
Increasing secondary drying shelf temperature (sd_shelf_temp_c) above 30°C significantly reduces residual moisture below the 4% target, provided that primary drying conditions are sufficiently robust.	93%	+12 / -0	SUPPORTED
Primary drying pressure above 300 mTorr significantly slows moisture removal, preventing the achievement of <4% residual moisture within standard process times, identifying the operational limit for throughput.	92%	+11 / -0	SUPPORTED
Secondary drying shelf temperatures above 40°C are required to consistently drive residual moisture below 1% without compromising LNP stability (EE > 90%, RIN > 7), identifying the efficiency-stability boundary.	92%	+11 / -0	SUPPORTED
Increasing Secondary Drying (SD) shelf temperature within the 30C-60C range serves as a critical threshold to drive residual moisture below 1% without compromising EE or RIN, directly addressing the primary drying efficiency ...	90%	+8 / -0	SUPPORTED
Primary drying shelf temperatures below -40°C significantly increase process time without providing proportional benefits to residual moisture reduction, defining the lower efficiency boundary for the process.	83%	+4 / -0	ACTIVE
There exists a synergistic threshold between protectant_conc_pct (>15%) and sd_shelf_temp_c (>40°C) that enables achieving <4% residual moisture while simultaneously protecting LNP integrity (EE > 90%, RIN > 7), defining th...	83%	+4 / -0	ACTIVE
Protectant concentrations (protectant_conc_pct) at or above 15% are required to maintain EE above 90% and RIN above 7 during aggressive dehydration cycles, ensuring formulation stability against process stress.	83%	+4 / -0	ACTIVE
Secondary drying pressure below 60 mTorr is a critical threshold for achieving <1% residual moisture within reasonable process times, serving as an operational limit for high-efficiency dehydration.	87%	+1 / -0	ACTIVE
Protectant concentrations above 20% are essential to counteract the LNP structural damage (monitored via Particle_Size_nm) observed during high-temperature secondary drying cycles (>45°C), ensuring the formulation remain...	87%	+1 / -0	ACTIVE

Type a command (stop, pause, flag, suggest, question) or message... **Send**

Figure 4. DAEMON web GUI Hypotheses tab sorted by confidence*.

*Confidence in certain hypotheses are voted on every discovery cycle by the AI agents based on supporting and contradicting evidence from their mechanistic simulation runs.

Excerpt from DAEMON Session Report (Session_ID: S_fe1881b2) Optimal Lyophilization Parameters (n=50 successful experiments):

- **Secondary drying temp:** 40–50°C (>40°C needed for <1% moisture; >50°C causes particle growth)
- **Primary drying pressure:** <300 mTorr (higher pressures impede moisture removal)
- **Protectant concentration:** ≥15% (buffers LNP integrity under thermal stress)
- **SD hold time:** Up to 2500 min (diminishing returns beyond)

Boundaries:

Primary drying shelf <-40°C is inefficient. SD >50°C compromises EE/RIN. Lipid-mRNA ratio × protectant interaction at the 15% threshold needs further validation.

RECOMMENDED CANDIDATE
E_1f6b2311 Cycle 3 Agent conservative 08:11:07 8.340

PARAMETER	VALUE	PARAMETER	VALUE
Freeze Temp (°C)	-40	Protectant Conc. (%)	20
Freeze Hold Time (min)	40	Buffer pH	6.5
SD Shelf Temp (°C)	40	Ionic Strength (mM)	25
SD Hold Time (min)	2800	Lipid:mRNA ratio	20
Primary Drying Pressure (mTorr)	300	Primary Drying Temp (°C)	40
Secondary Drying Pressure (mTorr)	300	Secondary Drying Temp (°C)	40
Primary Drying Time (min)	2000	Secondary Drying Time (min)	2000
Secondary Drying Time (min)	2000	Primary Drying Temp (°C)	40

Session must be running to send commands **Send**

Recommended Candidate (Exp_ID: E_1f6b2311)

- **Freezing:** -40°C (ramp 60 min), hold 180 min
- **PD:** -15°C (ramp 105 min), 100 mTorr (ramp 20 min), hold 3000 min
- **SD:** 40°C, hold 2800 min (fixed)
- **Formulation:** Protectant conc. 20%, Buffer pH 6.5, Lipid mRNA ratio 20, Ionic strength 25 mM

5 CONCLUSION & FUTURE WORK

Conclusion

- DAEMON combines multi-agent AI and mechanistic modeling to generate interpretable lyophilization recommendations faster.

Limitations and Future Work

- The model is not yet experimentally calibrated, so results are directional. Current LLM selection favors speed and cost.
- Benchmark LLMs, calibrate the model, give AI agents access to classical DOE/statistical tools, and validate recommendations experimentally.