

Keeping an “eye” on the experiment: computer vision for real-time monitoring and control

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General remarks

This supplementary information includes detailed information on the development and implementation of a generalized computer vision control system for automated monitoring and control of diverse chemical and non-chemical processes. All experiments were performed using existing resources in our lab. Unless otherwise mentioned, all chemicals were bought from conventional suppliers and used as received. The rationale behind decisions made in terms of chemicals and equipment used is explicitly stated in the following remarks. Code availability found in <https://gitlab.com/heingroup/heinsightv2> and *HeinSight2.0* model and data availability found in https://drive.google.com/drive/folders/1M1zpiaThiVlq9--AjoLQ_K6QHCKjoXjb.

Hardware

PC

The training and the experiment were run on two separate PCs, both with CUDA-compatible graphic cards:

	Training PC	Experiment PC
Graphic Card	NVIDIA GeForce RTX 3060	NVIDIA Quadro T2000
Processor	i5-11000	i7-9850H
Operating System	Microsoft Windows 11 Enterprise	Microsoft Windows 11 Pro
RAM	16 GB	32 GB
Hard drive	SSD	SSD
Camera	None	Razer Kiyos https://www.amazon.com/Razer-Kiyos-Streaming-Webcam-Built/dp/B075N1BYWB/ref=a

		sc_df_B075N1BYWB/?tag=h yprod- 20&linkCode=df0&hvadid=3 09807187084&hvpos=&hvne tw=g&hvrnd=15127172414 493030257&hvpone=&hvptw o=&hvqmt=&hvdev=c&hvdvc mdl=&hvlocint=&hvlocphy=9 003283&hvtargid=pla- 570671573005&th=1
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EasyMax and Webcam

All experiments were performed in a Mettler-Toledo EasyMax 102 Advanced Synthesis Workstation equipped with glass reactors (100 mL), mechanical overhead stirring, and a submersible thermocouple. For the solvent swap distillation experiments, Metter Toledo's pump. Temperature, stirring, and pump were controlled by Mettler Toledo software, iControl 6.0. The camera was placed flush against the viewfinder to the reaction vessel and anchored its position with a 3D printed enclosure (See CAD file in GitLab link and enclosure assembly instructions in the enclosure setup guide section). The webcam light was turned on to the lowest intensity and the backlight of the EasyMax was turned on in all experiments unless otherwise mentioned.

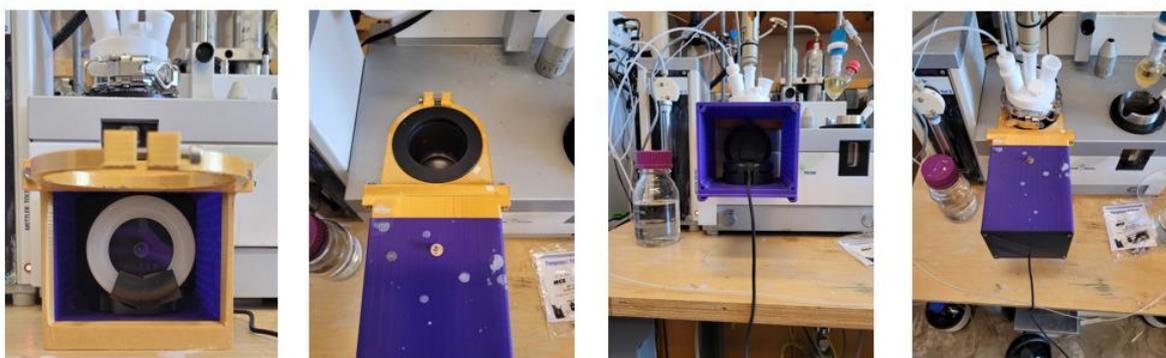


Figure S1. 3D printed enclosure.

Software

Software	Training PC version	Experiment PC version
Python version	3.8	3.8
Torch	1.13	1.13
CUDA Version	11.7	11.3
Excel	None	Excel 2019
iC Excel Plugin	None	iC DataShare1.1
PyCharm	None	CommunityEdition 11.0.7
VSCode	1.69	None
iControl	None	Version 6.1

An exact version for all used python modules can be found in the provided requirement.txt in our GitLab repository.

Model

Model choice

For the instance segmentation task, we utilized a model pre-trained on the COCO (Common Objects in Context) dataset from the detectron2 model zoo. Specifically, we selected the R101-FPN structure, which is a faster-RCNN-based model capable of performing instance segmentation. This model was then fine-tuned (transfer learning) to our data set.

Obtaining training data

823 images were collected for the training data. The process of obtaining the training data followed as is.

- 1) Auto-focus and white balance were disabled on the webcam and adjusted manually in the camera settings software.
- 2) OBS studio was turned on for camera capturing.
- 3) The experiment was designed and initiated in iControl software and recorded.
- 4) The resulting video was converted into images by taking a screenshot every minute. (This was done via a Python script)
- 5) The images were uploaded to the web version of SuperAnnotate for labeling.
- 6) The labeled images were downloaded together with the annotations in the form of a JSON file

Training Process:

The following hyperparameters were chosen inside the train.py file:

Parameter	Value
Learning rate	0.0025
Decay rate	None
Batch size	8
ROI samples per image	64

The obtained weights are saved and then transferred to the experimental PC via a USB-stick.

Running the application

- 1) Auto-focus and white balance were disabled on the webcam and adjusted manually in the camera settings software.
- 2) Both iC DataShare and the Excel sheet were opened and the Python script testModelNMSiCdataShareWebcamV2.1.py was executed from within PyCharm
- 3) In iControl configuration, iC DataShare was added as an additional link
- 4) The experiment design was placed in iControl

- 5) As the experiment was started, the iControl Excel Plugin was connected with the experiment to receive quantitative outputs from the CV code
- 6) Logitech Capture was used to monitor the iControl trends and CV model output
- 7) Once the experiment was halted, the Logitech Capture video record acts as a qualitative data of images recorded while the trends outputted from iControl represent the quantitative data collection ready for processing.

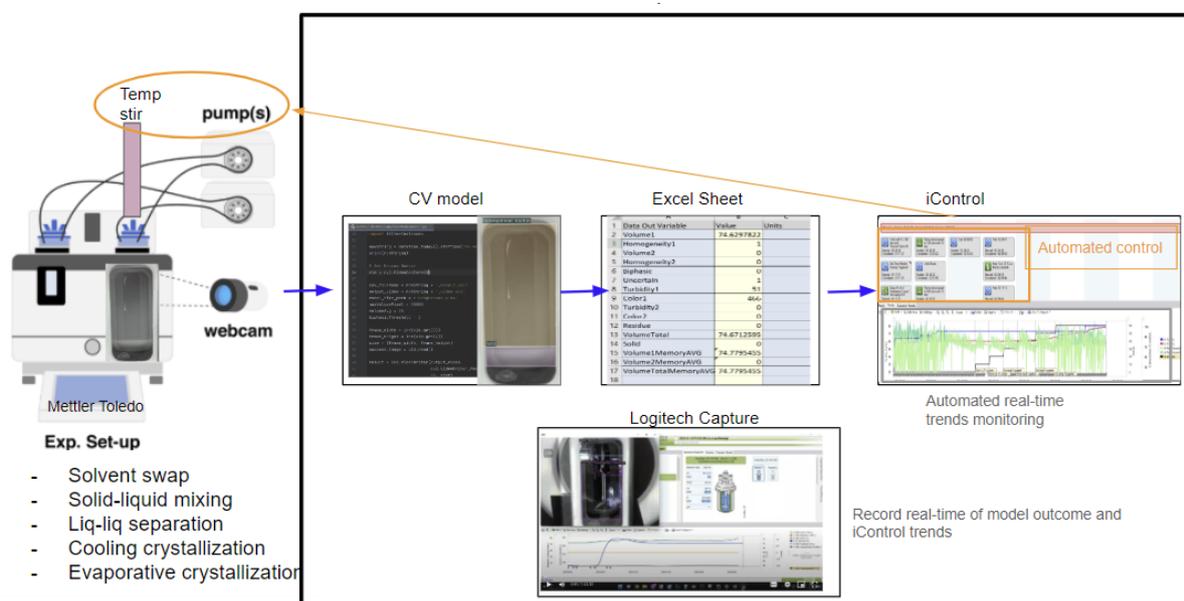


Figure S2. The interrelation among different modalities in our workflow.

Testing results

For testing purposes another 103 images were recorded (about 11% of the training data) and labelled by hand to represent the ground truth. These were then formatted and registered just like the training data (all steps follow exactly the same steps as the preparation of the training data). Resulting in the following APs (average precisions). With AP50 being the average precision computed at a 50% IoU (Intersection over Union). And AP is the overall measure of accuracy across a range of IoU thresholds of 0.50 to 0.95. AP of each class was also determined. The overall R-CNN/class accuracy was 0.97 and the R-CNN/ false negative scoring was 0.03.

	AP	AP50	AP75
Bounding Box	77.23	95.54	88.17
Mask	71.98	95.14	81.54

	Bounding box	Mask
Empty	74.23	70.03
Homogenous	84.69	83.43
Heterogenous	90.97	91.94
Residue	58.34	54.84
Solid	77.86	59.66

Post-Processing

Non-Maximum Suppression (NMS)

The raw output of the model occasionally presented multiple labels for the same region, particularly when distinguishing between the "solid" (located at the bottom) and the "residue" (above the liquid) classes. This confusion arose because both classes are formed by the same solid compound, thus having similar visual properties. To address this, a Non-Maximum Suppression (NMS) filter was implemented, ensuring that only the class with the highest confidence is displayed. NMS was also applied between different classes, such as Heterogeneous and Residue, as well as within the same class, such as between Homogeneous and Heterogeneous.

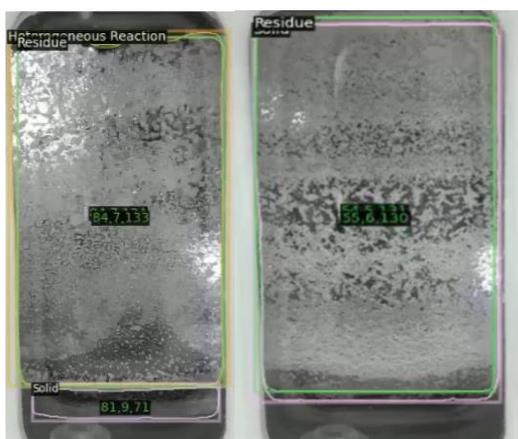


Figure S3. NMS applied among different classes.

Filtering the "Empty" Class

In the later stages of model development, the "liquid residue" class was merged with the "empty" class since they both indicate the presence of an air layer above the liquid level. Once the empty class is identified, it is filtered out and not included in the model's output. The data presented in the main text, which shows the "liquid residue," was

collected during the early stages of the model when it was not integrated with the empty class and thus represented in the final output.

Filtering the bottom of the EasyMax

Once solid was added as a class in the model, the model has fasly started classifying the bottom of EasyMax reactor as solid, as shown in Figure S4. This can be attributed to the bottom of EasyMax having similar visual properties as solid class. We decided to filter out the bottom region of the EasyMax from outputted value.



Figure S4. Images from early model development showing “solid” class at the bottom of EasyMax reactor.

Determination of Visual Outputs:

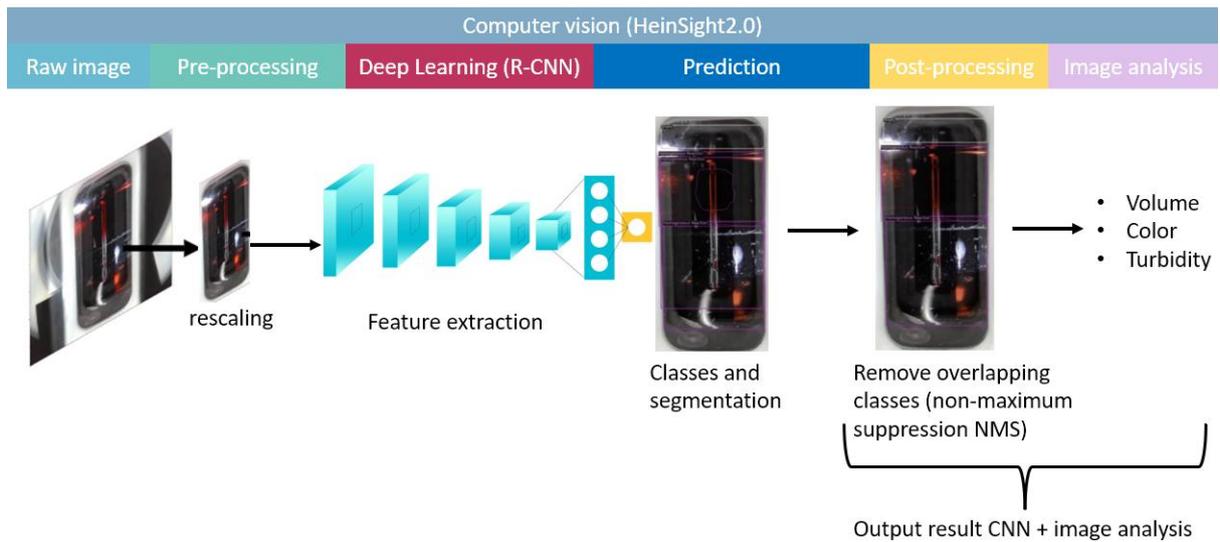
From the CNN (solid, Homogeneous, Heterogenous)

The class "Homogeneity" is divided into a binary classification (homogeneous or heterogeneous) by the CNN, utilizing bounding box classification. On the other hand, the "solid" and "residue" classes utilize segmentation techniques, with their values reflecting pixel-based counting

CV Calculations (Turbidity, Colour, Volume)

For all algorithmic calculations the image is first converted from an RGB (Red, Green, Blue) format into the HSV (Hue, Saturation, Value) format. From there the colour of each liquid layer and solid were determined individually by averaging the colour of all pixels in each mask. The continuous output 'Value' (0 to 255) of the HSV format was used as turbidity for each liquid layer, where lower readings represent a darker shade and higher ones a brighter one. The volume was calculated based on pixel counting.

An overall process of image analysis is outlined in the figure below.



Step-by-Step Guide to Using HeinSight2.0 with iControl

1) Camera Setup:

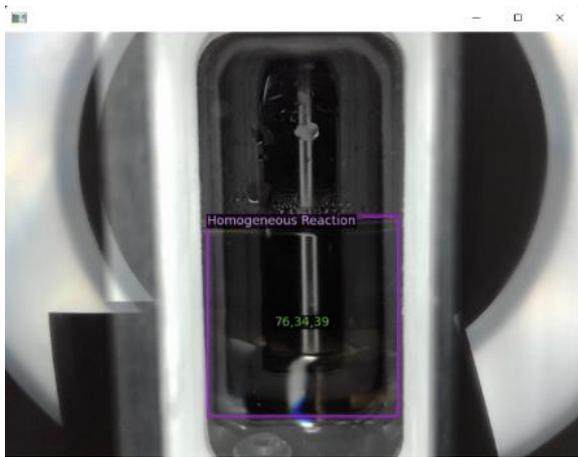
- Assemble the camera within the enclosure following the steps outlined in the “camera enclosure setup guide” section.
- Turn on the EasyMax 102 backlight and set the camera ring light to the lowest intensity.
- Disable autofocusing and manually adjust the camera focus using the camera settings software.



2) Installing HeinSight2.0:

- Download the repository from GitLab (<https://gitlab.com/heingroup/heinsightv2>) and the `heinsightv2_pretrained_model.zip` from https://drive.google.com/drive/folders/1M1zpiaThiVlq9--AjoLQ_K6QHCKjoXjb.

- b. Set up the Python environment by installing the required packages from the install.zip file and run the example_model_ic_link.py script.
- c. Ensure that the model path within example_model_ic_link.py is correctly linked to heinsight2_model.pth by moving the heinsight2_model.pth to the heinsightv2\models\ directory
- d. Run the code, and a visualizer will appear. Confirm that the correct camera is being captured. If not, change the webcam number.
Line 24: Camera_Index = (0)
- e. Upon successful execution, the visualizer should resemble the provided image.

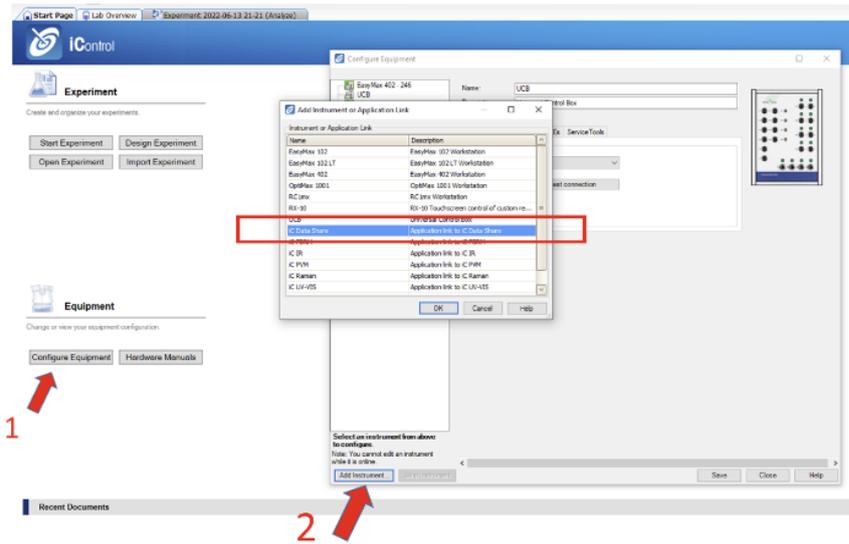


3) Connecting the Model with iControl via iC Data Share:

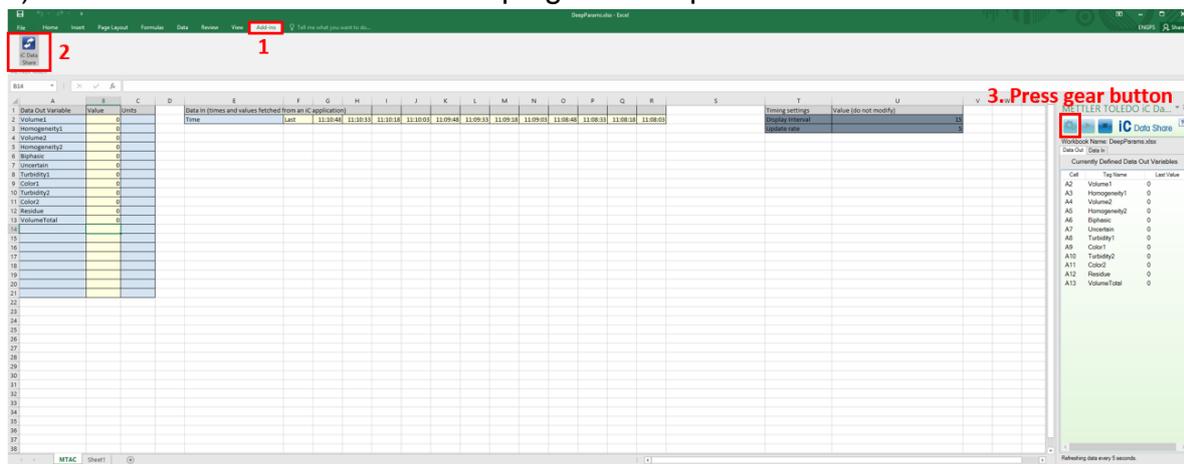
- a. Open the Excel sheet "DeepParams.xlsx" (found in the GitLab repository) and keep it open while running the code.

Data Out Variable	Value	Units
Volume1	0	
Homogeneity1	0	
Volume2	0	
Homogeneity2	0	
Biphasic	0	
Uncertain	0	
Turbidity1	0	
Color1	0	
Turbidity2	0	
Color2	0	
Residue	0	
Volume total	0	

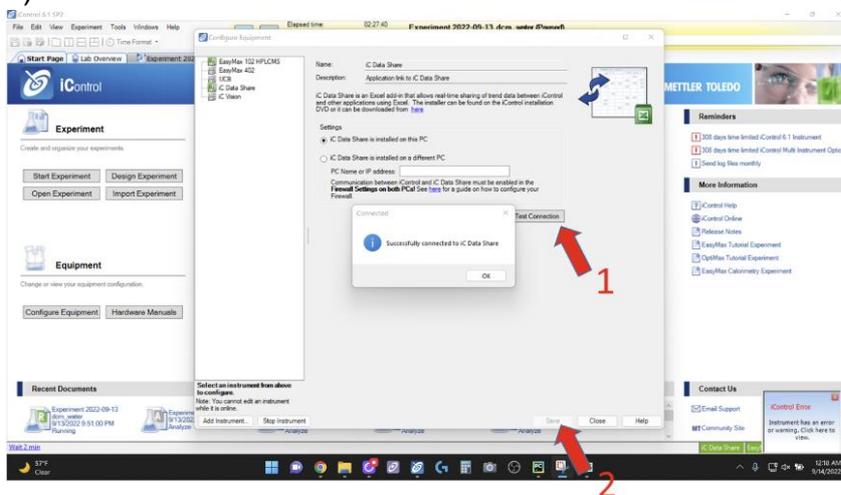
- b) Configure iC Data Share in iControl.



c) Enable the iC Data Share Excel plugin in DeepParams.xlsx.

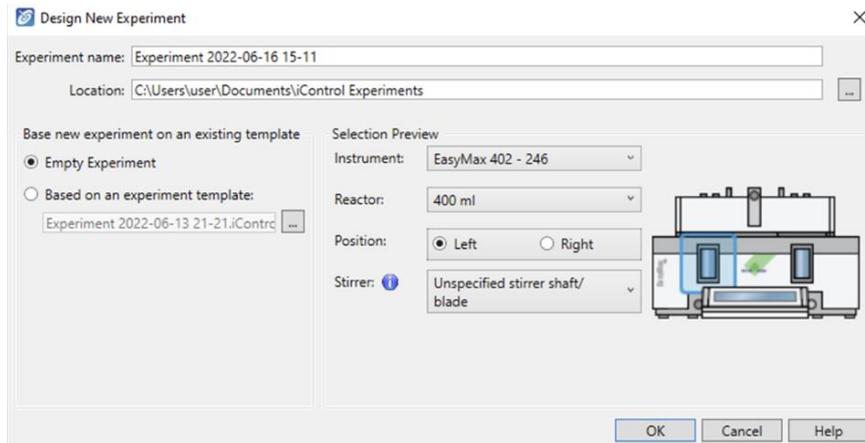


d) Test the connection in iControl to ensure it is successful.

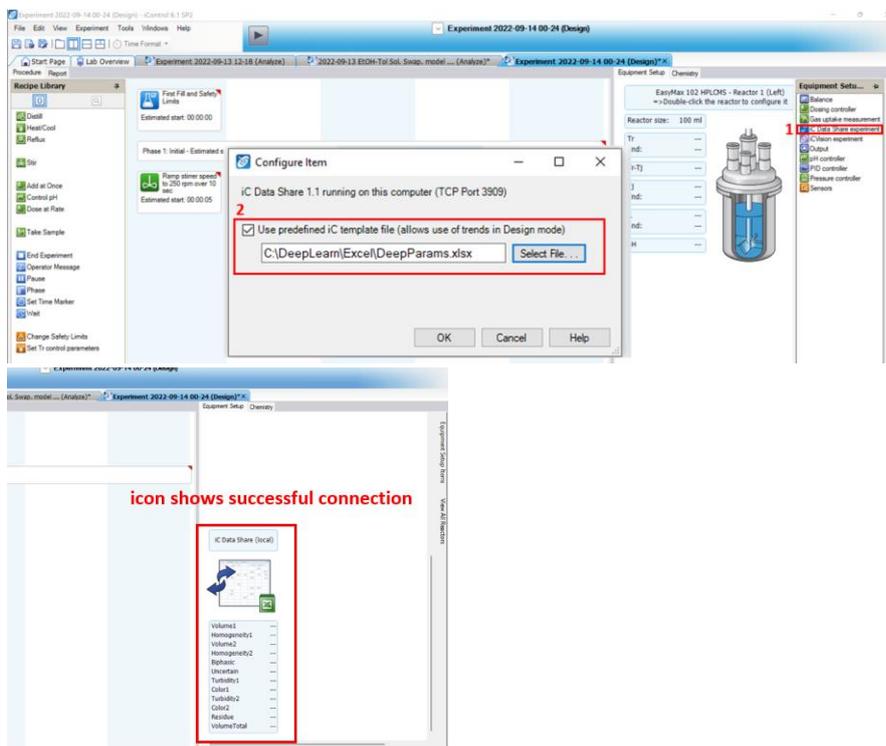


4) Setting up an experiment procedure

a. Create a new experiment in iControl



b. Connect the Excel sheet (DeepParams.xlsx) to the experiment and verify the successful connection.



c) Setup experimental procedure

Setup experimental design

Phase 1: Initial - Estimated start: 00:00:05

Wait until Volume > 60
Estimated start: 00:00:05

Can make experimental conditions dependent on visual cues monitored (feedback control)

Wait - Parameters

Caption: Wait until Volume > 60

Description: Wait until the following condition is met.

Comment:

Parameters

Wait: 10 min

Wait until the following condition is met.

Condition: Volume > 60

And: Volume > 2

OK Cancel Help

d) Run experiment.

EasyMax 402 - 246 - Reactor 1 (Left)
Controlling jacket temperature (Tj)

Reactor size: 400 ml

Tr: 25 °C
End: []
Tr-Tj: 0 K
Tj: 25 °C

EasyMax 402 - 246

Reactor 1 Reactor 2

Start Experiment Experiment 2022-06-...

Please consider the following warnings before starting the experiment.

IC Data Share experiment not ready to start.
Assure that IC Data Share is running on this computer.
Then click here to go to IC Data Share and prepare the experiment.

Start Experiment Don't Start Experiment

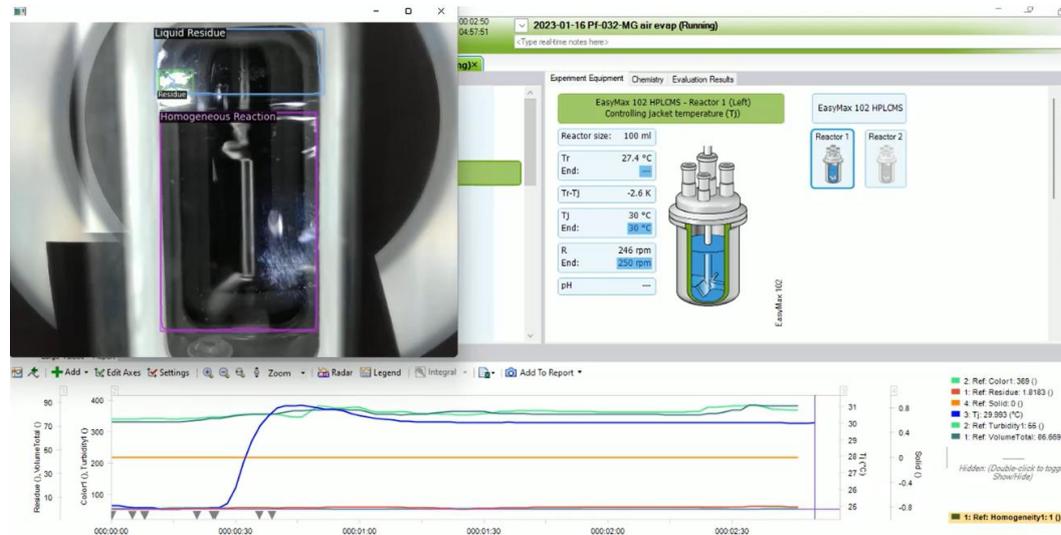
IC Data Share (local) Online

Warning! Click Here to Start Sharing Data between iControl and Excel File

Volume

5) Visualizing trends on iControl and analyzing videos with HeinSight2.0

Use Logitech Capture video for video screen recording.



Experimental Section:

Liquid-level: Solvent exchange distillation

Experimental workflow

Automated solvent exchange tests were conducted with HeinSight2.0 to swap the distilled solvent in the solution with a solvent possessing a higher boiling point. Mettler Toledo's iControl software and EasyMax102 were employed to manage temperature regulation, stir rate of the reaction vessel, and dosing pump behavior. The distilled solvent was guided through a distillation apparatus and accumulated in a round bottom flask, as depicted in Figure S5.

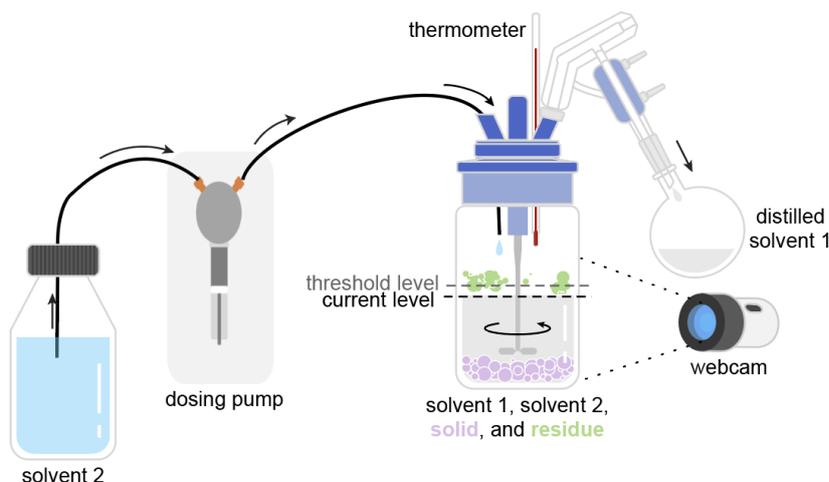


Figure S5. Diagram of solvent exchange set-up.

General procedure

1. An EasyMax102 device, equipped with a 100 mL reaction vessel, a 5-port lid, a temperature probe, and a mechanized stirrer, was arranged next to a short path distillation setup.
2. The required quantity of a solvent with a higher boiling point (referred to as Solvent 2 in Figure S5) was dispensed into a reservoir container, ensuring sufficient volume for completing the solvent replacement process.
3. Mettler Toledo's dosing pump was positioned between the EasyMax102 reactor and the reservoir container. Resistant tubing capable of withstanding chemical

reactions was connected from the reservoir, passing through the pump head, and leading into the lidded reaction container.

4. The camera was positioned adjacent to the viewing window of the reaction vessel and firmly affixed inside a 3D-printed housing.
5. The auto-focus and white balance settings were deactivated, and manual adjustments were made using the camera settings software.
6. A specified amount of a mixed-solvent solution was introduced into the reaction container. The vessel was sealed tightly, with the lid ports left open to accommodate the insertion of 1) the motorized stirrer, 2) the temperature probe, 3) a short path distillation apparatus, and 4) the tubing connected to the dosing pump. Septa were added when necessary to prevent any leakage.
7. A round-bottom flask of appropriate size was connected to the distillation apparatus and secured in place using a clamp and stand.
8. The temperature and stirring speed in the reaction container were adjusted using iControl. The temperature of the jacketed reactor was set slightly above the boiling point of the solvent with the lower boiling point (Solvent 1).
9. HeinSight2.0 was run and linked with iControl through iC Data Share.

https://community.autochem.mt.com/system/files/Release_Notes_iControl_RC1e_5.3.pdf)

10. An automated script was created in iControl to dispense Solvent 2 when the liquid level fell below a specific threshold.
11. The distillation process was allowed to continue until most of Solvent 1 had been replaced by Solvent 2.

Volume calibration

To account for the presence of a mechanical agitator within the reactor and the reliance on pixel number for volume calculation, calibration was necessary to align the model's volume readout with the actual volume, thus ensuring an accurate perception of the volume inside the reactor. To achieve this, different water volumes were manually introduced to the reactor, which included a mechanical agitator and a temperature probe, thereby mimicking real experimental conditions. The model's volume readout was recorded during this process. The tested volume range encompassed the viewing window of the EasyMax reactor (10 - 60 mL). The

relationship between the readout volume and the actual volume exhibited a linear correlation, as depicted in Figure S6.

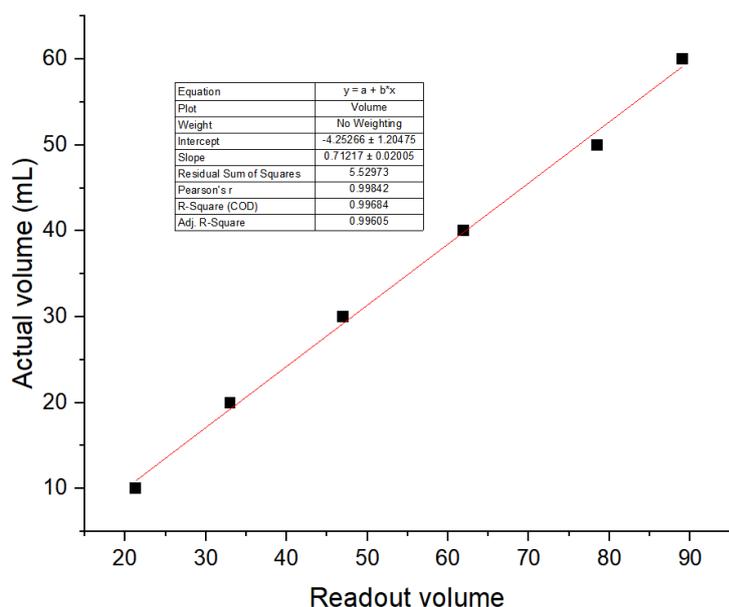


Figure S6. Calibration Curve - Linear Relationship between Readout Volume and Actual Volume in the EasyMax Reactor.

Experiments in solvent exchange distillation

Simple solvent exchange distillation

To refine HeinSight2.0's capability to monitor and regulate liquid levels, we initially focused on a straightforward solvent exchange scenario without additional visual complexities (such as solid residues on the reactor wall or solid precipitation from the solution). In this setup, a jacketed reactor contained a solution of Methanol (MeOH) heated slightly above its boiling point. When the total volume fell below a predetermined threshold, an automated process was triggered to introduce Toluene. This distillation process was repeated multiple times, ensuring the removal of the majority of MeOH.

Optimizing conditions

At higher mechanical agitation levels (>350 rpm), the liquid phase in the reactor generates swirling and vortex patterns. These patterns introduce challenges in accurately determining the true volume due to variations in local density and fluid height within the reactor. Moreover, these patterns cause visual complexities, leading

HeinSight2.0 to sometimes incorrectly classify a single agitated solution into multiple liquid layers (e.g., volume 1 and volume 2, as depicted in Figure S7). To address these concerns, solvent exchange experiments were conducted at elevated agitation values to ensure effective solution mixing. After each minute of high stirring, the stir rate was automatically reduced to lower than 350 rpm over a 10-second period, where the solution agitation no longer created a swirling pattern. At this stage, the model depicted the solution as a single volume layer, closely resembling the actual calibrated volume. The monitoring at the lower agitation value lasted for 30 seconds to ensure complete volume stabilization (volume total = volume 1). The volume was continuously monitored, but only when the stir rate reached 350 rpm or lower was it used to determine dosing action. Variations in liquid level monitoring were expected due to cycling between high and low agitation rates. However, since dosing action depended on the solvent being below a specific total volume threshold which is defined as (volume 1 + volume 2), the minimum total volume occurred when agitation stabilized. Therefore, the observed volume variation is due to changes in stir rate, not the model's monitoring precision.

The stir rate conditions were initially tested and optimized in a simple solvent exchange distillation process. However, these optimized conditions have also been applied to other solvent exchange experiments, such as slurry solvent exchange and constant volume antisolvent crystallization *via* solvent exchange distillation. The insights gained from the optimized conditions have guided the development of the control logic script used in solvent exchange distillation experiments.

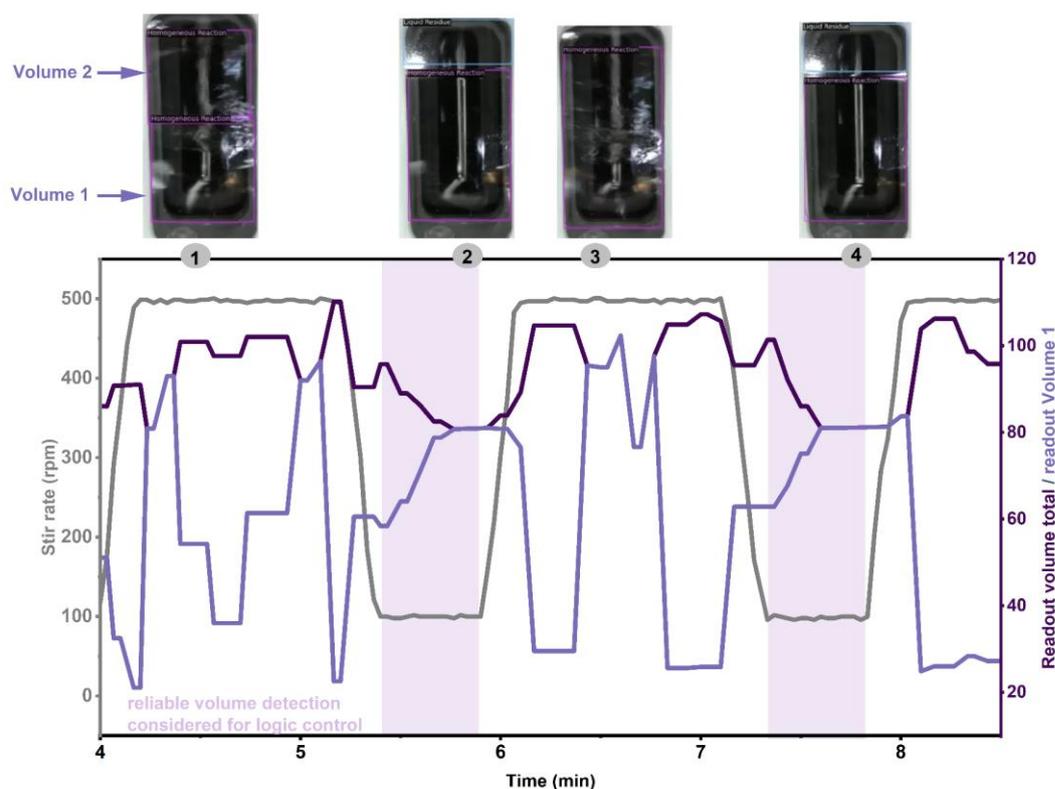


Figure S7. Simple solvent exchange. 1) 2 volume 3) incorrect volume. 2/4 decision action if any (correct volume).

Control logic

Automated solvent exchange control was performed using iControl software, following consistent logic regardless of the experiment type. Once initiated, the automated sequence followed these steps, with user-defined parameters (n , s , m , x , y , and z) set prior to each experiment:

1. Ramp stir to n rpm over s seconds.
2. Heat reactor vessel to $m^{\circ}\text{C}$ as fast as possible
3. Wait until stir rate $< x$ rpm and total volume $< y$ readout
4. Dose z mL of Solvent2 over 1 min
5. Repeat steps (3-4)

In parallel, another script was carried out to account for changes in the stir rate conditions to ensure accurate volume level detection. The following user-defined parameters (a , b , and c) were set prior to initiating the experiment.

1. Ramp stir to n rpm over s seconds
2. Wait for 1 min

3. Lower stir rate to x rpm (stir rate that is needed to ensure accurate depiction of total volume)
4. Wait for 30 seconds
5. Repeat steps (1-4)

The system cycled through this process for a specific number of cycles that were instructed by the user.

Materials and Parameters

Starting with an initial volume of 50 mL of Methanol (MeOH) in a jacketed reactor, which was heated to 69°C and subsequently raised to 78°C after 40 minutes, when the total volume dropped below 60 readout volume (38.48 mL actual volume), an automated process was initiated to dose 10 mL of Toluene over a duration of 1 minute. To ensure accurate volume representation, the stir rate was initially set at 500 rpm and lowered to 100 rpm for 30 seconds every minute. This distillation process was repeated six times to ensure the removal of the majority of MeOH.

Results and Discussion

The main objective of consistently keeping the liquid level above a designated threshold was successfully achieved during numerous dosing occurrences. Essential data for the process was extracted from the primary output (volume) and the secondary output (temperature). The distillation rate could be determined by analyzing the downward slope of the volume trend, which gradually decreased as the solution became enriched with the higher boiling point of Toluene. This observation was corroborated by an upward trend in temperature values. The model demonstrated adaptability to the non-linear dosing events that took place after the fourth dose.

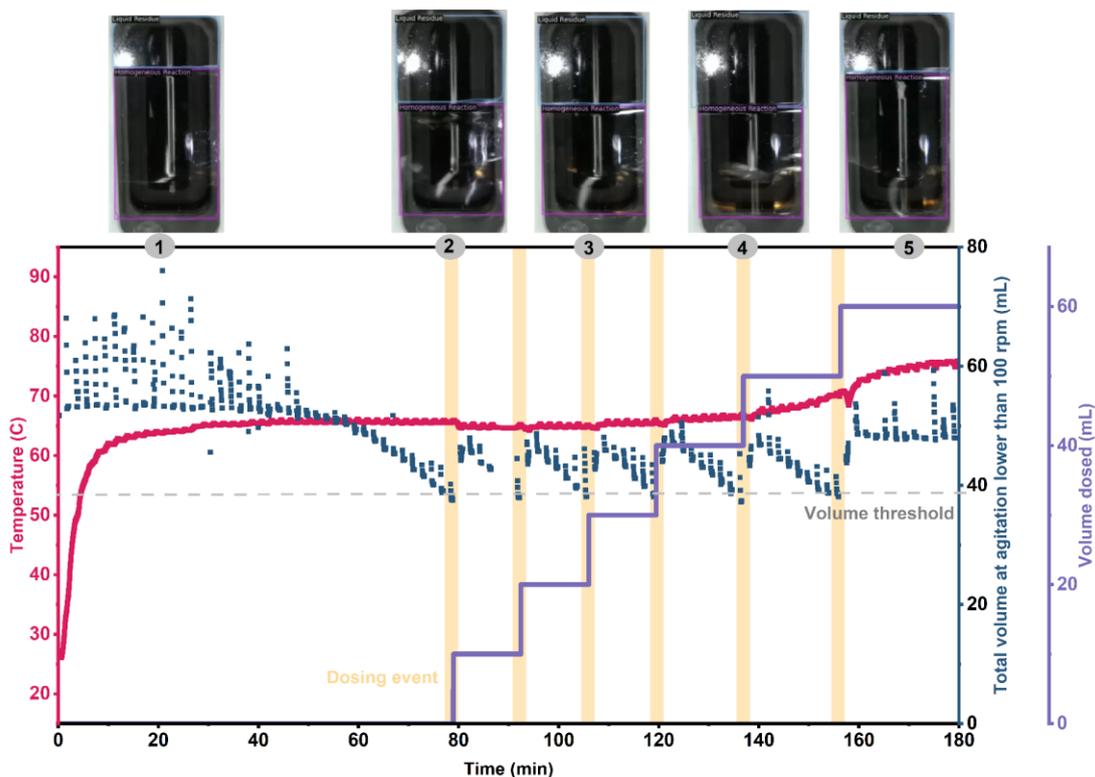


Figure S8. Simple solvent exchange distillation.

Slurry solvent exchange distillation

Materials and Parameters

1.00671 g of 3-(((ethylimino)methylene)amino)-N,N-dimethylpropan-1-amine hydrochloride (EDCI-HCl) was added to a 700 μ L triethylamine (TEA) solution in 50 mL acetone, creating a slurry in a 100 mL reactor. The jacketed reactor was heated above the boiling point of acetone, reaching 73°C. The reaction was stirred at 500 rpm. To ensure accurate volume detection, the stir rate was reduced to 300 rpm for 30 s every 1 min, with a drop rate of 10 s. When the stir rate reached 300 rpm and the total volume fell below 70 readout volume (45.60 mL), an automated dosing action of 10 mL of 2-Butanone in 1 min was performed. The control logic employed was the same as presented in Section 1.4.1.2. The process was repeated for 3 cycles. Unlike the optimized conditions in the simple solvent exchange, where the stir rate was dropped to 100 rpm, a stir rate of 300 rpm was used here to maintain a well-suspended slurry, requiring higher agitation levels.

Constant volume antisolvent crystallization *via* solvent exchange distillation

Materials and Parameters

Starting with a solution of 1.28 g of acetaminophen in 50 mL of acetonitrile (MeCN) in a 100 mL reactor heated above the boiling point of the solvent, 108°C, the system was dissolved and stirred at 500 rpm. To ensure accurate volume detection, the stir rate was periodically reduced to 100 rpm for 30 s every 1 min, with a drop rate of 10 s. When the stir rate reached 100 rpm and the total volume dropped below 60 readout volume (38.48 mL), an automated dosing action of 10 mL of toluene in 1 min was executed. Toluene was chosen given the low solubility of acetaminophen in the solvent, allowing for the determination of the MeCN/Toluene ratio required to achieve supersaturation in the solution. The control logic used followed the methodology described in Section 1.4.1.2

. This process was repeated for 6 cycles, leading to a complete transition from MeCN to toluene. At 124 min, the reactor temperature was raised to 112°C to facilitate solution evaporation.

Homogeneity and Turbidity (Crystallization)

Evaporative crystallization

Evaporative crystallization was conducted using an automated approach, where a stream of compressed air was directed towards the dissolved system. This airflow caused solvent evaporation, leading to supersaturation within the solution, as shown in Figure S9. The regulation of temperature and stir rate was handled by iControl, while HeinSight2.0 was responsible for monitoring and tracking changes in outputs such as volume, solid formation, residue presence, solution homogeneity, and turbidity.

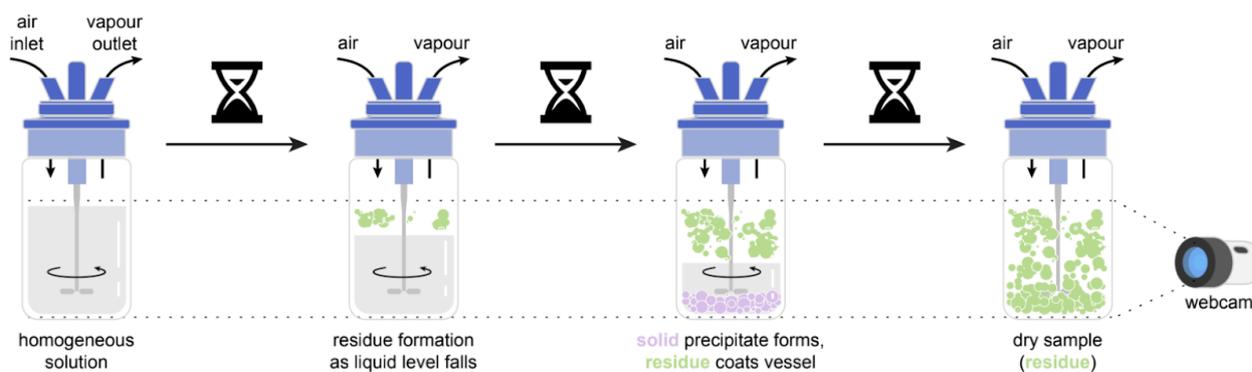


Figure S9. Illustration of evaporative crystallization setup.

Procedure, Parameters, and Materials

1. An EasyMax102 device was utilized for the experiment, featuring a 100 mL reaction vessel, a 5-port lid, a temperature probe, and a mechanized stirrer.
2. To enable visual monitoring, a camera was securely positioned beside the reaction vessel's viewing window within a 3D-printed housing.
3. The camera settings, including auto-focus and white balance, were deactivated, allowing manual adjustments through the camera setting software.
4. In the initial setup, 1.00421 g of acetaminophen was dissolved in 50 mL of MeCN and added to the reactor. The reaction vessel was tightly sealed, with certain lid ports left open to accommodate the insertion of the motorized stirrer, temperature probe, and an air compressor path. The remaining lid ports were left open to facilitate solvent evaporation.
5. Using iControl, the reactor temperature was set to 30°C, while the stirring speed was adjusted to 250 rpm within the reaction container.
6. The air purge in the reactor headspace was regulated to ensure a very low airflow.
7. HeinSight2.0 was then launched and connected to iControl via iC Data Share, facilitating seamless data integration and exchange
8. The experiment was automatically monitored overtime until the solvent fully evaporated.

Results and Discussion

HeinSight2.0 successfully determined the changes in liquid level caused by solvent evaporation and extracted key findings such as the rate of evaporation, volume

at the onset of nucleation, and time for complete dryness, as depicted in Figure 5 of the main text. To ensure the accuracy of the results, the experiment was repeated, yielding similar values for the initial rate of evaporation (0.75 mL/min compared to 0.77 mL/min in the first trial) and the volume at the onset of precipitation (30 mL compared to 29 mL in the first trial). This supports the estimation of the metastable limit for our system. However, the total time for full evaporation differed (55 min compared to 69 min in the first trial), likely due to minor variations in air flow rates between experiments, as shown in Figure S10. It is important to note that the actual volume is calibrated based on pixel-based measurements, resulting in an approximate +/-5 mL margin of error. This explains why the volume appears to go below zero.

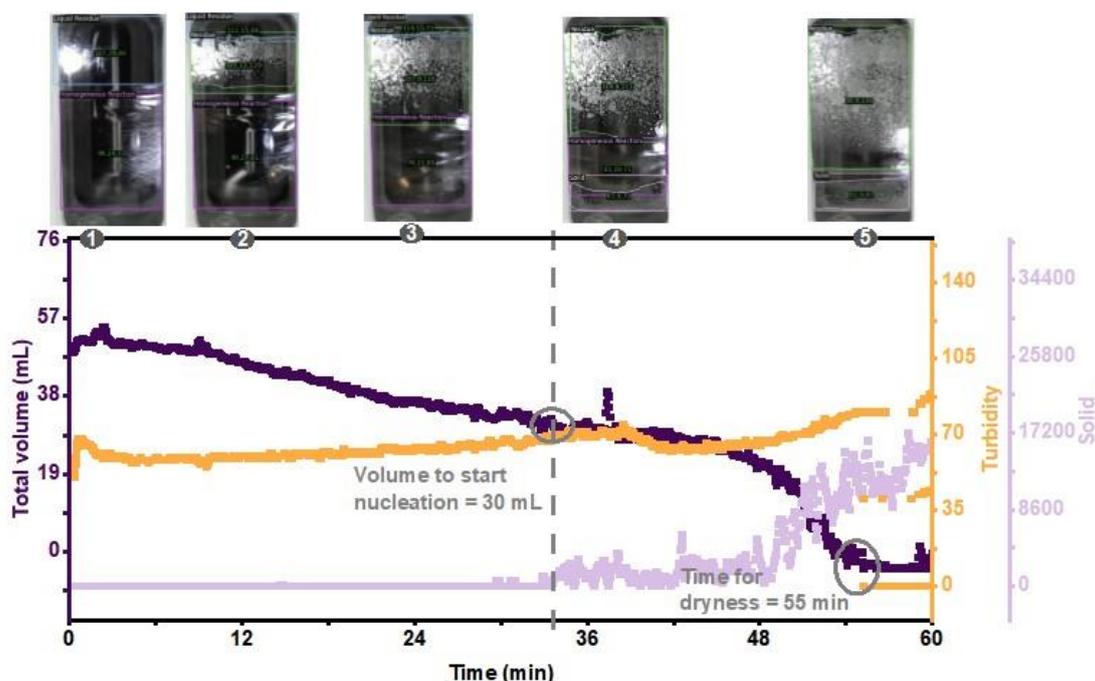


Figure S10. replicating evaporative crystallization.

Cooling Crystallization

Automated feedback control was utilized to conduct cooling crystallization, enabling temperature cycling in a solution of acetaminophen in MeCN for the purpose of determining nucleation and dissolution temperatures, as shown in Figure S11. The regulation of temperature and stir rate, as well as the monitoring and control of these outputs, was managed by iControl. Meanwhile, HeinSight2.0 monitored and tracked the changes in outputs like turbidity and homogeneity.

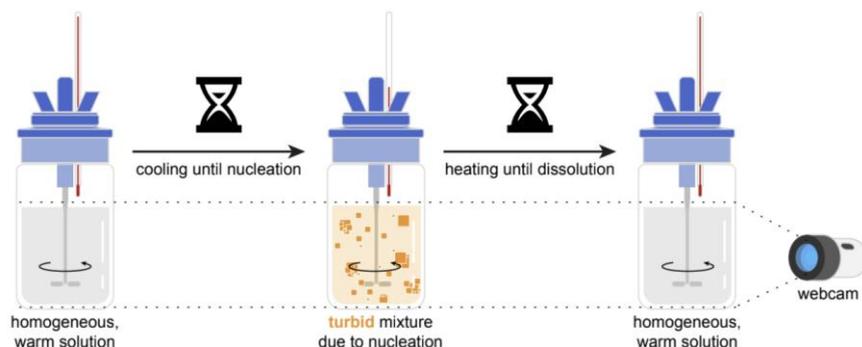


Figure S11. Illustration of cooling crystallization setup.

Procedure

1. An EasyMax102 instrument, featuring a 100 mL reaction vessel, a 5-port lid, a temperature probe, and a mechanized stirrer, was utilized.
2. A specific quantity of acetaminophen was placed into the reactor.
3. The camera was positioned adjacent to the viewing window of the reaction vessel and securely mounted inside a 3D-printed housing.
4. Auto-focus and white balance settings were disabled, and manual adjustments were made using the camera settings software.
5. A specific volume of MeCN was introduced into the reaction vessel, ensuring a tight seal with the lid ports open to accommodate the motorized stirrer and temperature probe. Septa were employed when necessary to prevent any leakage.
6. The solution was heated to 50°C to facilitate the dissolution of acetaminophen.
7. iControl was used to adjust the temperature and stirring speed in the reaction vessel. Automated temperature cycling between high and low temperatures was programmed.
12. HeinSight2.0 was operated and connected to iControl via iC Data Share

Materials, Parameters, and Logic Control

Starting with a 0.31 M acetaminophen solution, dissolved in 40 mL of MeCN at 50°C, the EasyMax jacket underwent controlled cooling at a consistent rate of 10 °C/min until the appearance of a heterogeneous solution, indicated by changes in homogeneity and turbidity. Following a 5-minute wait, the jacket was then heated at the same rate until dissolution occurred. Another 5-minute pause was observed before

repeating the cycle to confirm solubility and measure the metastable zone width (MSZW). The iControl logic executed the following sequence::

1. Ramp stir rate to 250 rpm.
2. Cool the reactor to 10°C at rate 10 °C/min. End if Homogeneity ≤ 0 (indicating heterogeneity) or if the reactor reaches 10°C.
3. Wait for 5 mins.
4. Heat the reactor to 50°C at rate 10 °C/min. End if Homogeneity ≥ 0 (indicating homogeneity) or if reactor reaches 50°C.
5. Wait for 5 mins.
6. Repeat steps 2-5.

Results and Discussion

The model successfully applied feedback looping to maintain temperature cycling of cooling crystallization. Once the nucleation/dissolution point was reached, the EasyMax system was instructed to maintain the jacketed temperature without any further temperature ramping. However, due to the high temperature ramping rate of 10°C/min, there was a temperature discrepancy between the jacketed temperature and the reactor temperature, as shown in Figure S12. As a result, the reactor temperature continued to heat/cool slightly beyond the point of dissolution/nucleation. This approach is advantageous since the CV system observes bulk properties, and microscopic changes may not have fully occurred at that stage. Therefore, surpassing the detected temperature ensures a complete transformation of the microscopic physical properties. The inflection point in the temperature trend occurred at 20 minutes resembled the time of the end of the waiting period. When the waiting period ends, iControl adjusted the experimental conditions to closely resemble the initial conditions before the waiting period. Hence, the observed inflection point during this period indicates the temperature stabilizing as the waiting period concludes.

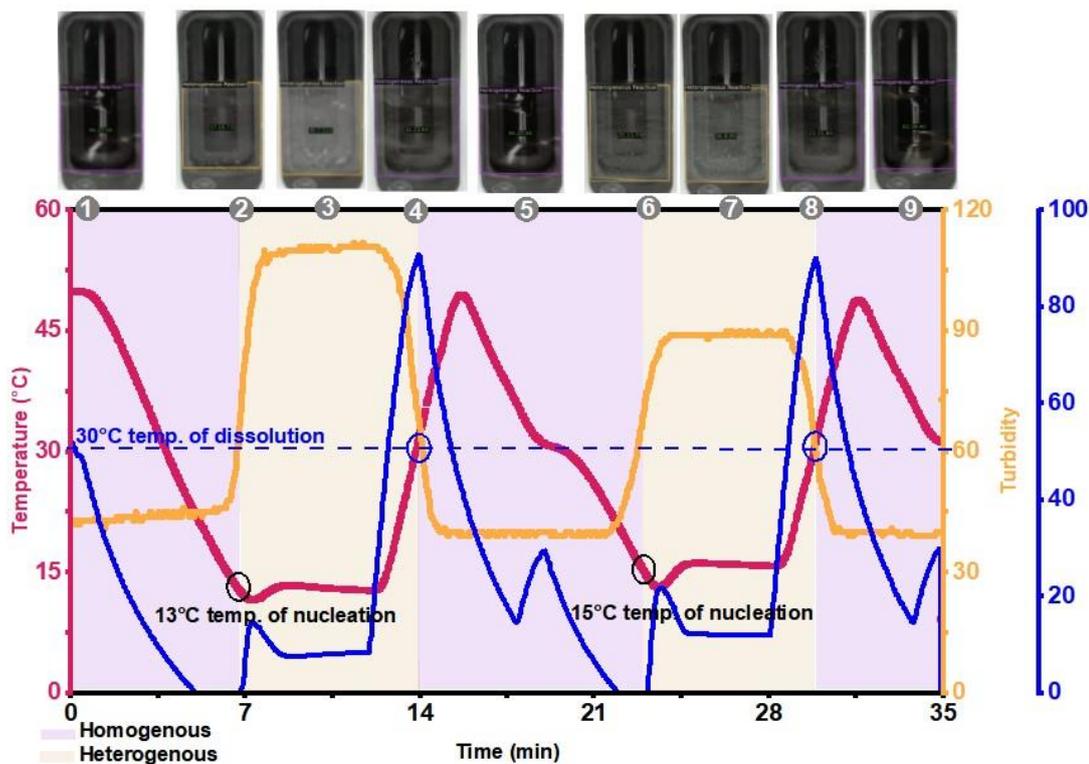


Figure S12. Feedback loop using real-time data to determine solubility and MSZW of acetaminophen in MeCN same graph as shown in main text Figure 3d with additional trends. The internal temperature of the reactor (red), and the jacketed temperature of the reactor (blue) are captured *via* the EasyMax temperature probe, while the turbidity (orange) and homogeneity (purple and yellow) are returned from the CV system.

To validate the capability of HeinSight2.0 in automated temperature cycling using visual cues, we repeated the experiment at a lower heating/cooling rate of 3 °C/min, as illustrated in Figure S13. We anticipated that if the system was accurate, the nucleation point would remain constant as it is a thermodynamic parameter, while the dissolution point would vary with the heating rate as it is a kinetic parameter. As expected, the clear point remained almost unchanged at 31°C, while the cloud point shifted to 21°C. This demonstrated the adaptability of HeinSight2.0 in providing dynamic feedback control in response to changing experimental conditions. We note that the absolute value for the resolved turbidity (orange) was not identical between both thermal cycle replicates, however this is partly expected. The numerical value for the reported turbidity is calculated based on the 2D cross section presented to the camera. This the relative luminance or perceive opacity of the turbid solution will

impact the returned absolute value. Thus, variation in some stochastic factors such as number of nucleation events and if material sticks to the reactor in the sight region of the camera will impact the absolute value. For the purpose of this control strategy the transition between turbidity states (low to high) through some threshold value is the what the workflow aims to extract. These transitions or relative changes are highly consistent between replicates and were used for future control strategies.

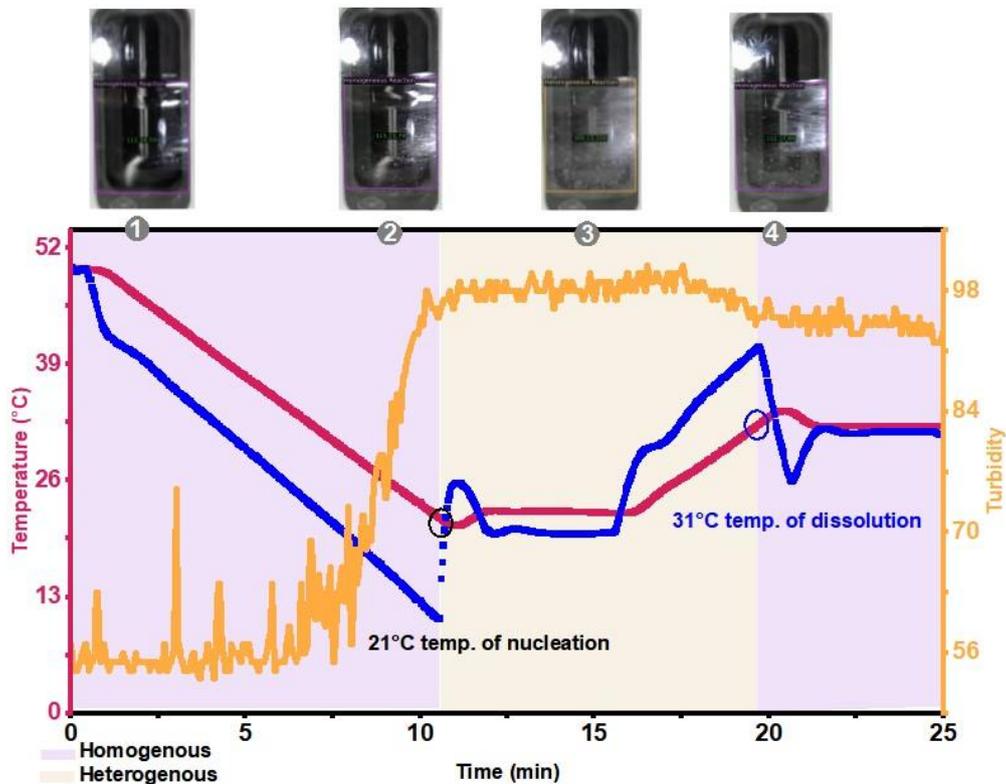


Figure S13. cooling crystallization at a lower heat/cool rate.

Solid and Turbidity: Solid-Liquid Mixing

During solid-liquid mixing, the stirring speed was controlled by iControl, while HeinSight2.0 monitored visual indicators such as solids, turbidity, homogeneity, and color.

Effective agitation

Commencing with a supersaturated solution, automated escalation of the stirring rate was employed to identify the minimum agitation speed required for the

complete suspension of the solid in the solution, indicated by the absence of solid and an increase in turbidity, as depicted in Figure S14.

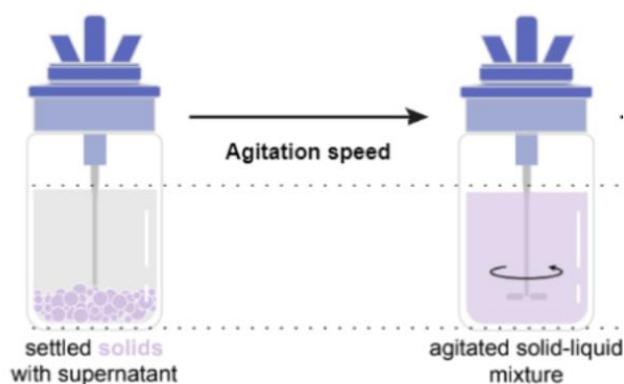


Figure S14. Illustration of effective agitation in solid-liquid mixing.

Procedure, Materials, and Parameters

1. An EasyMax102 device, equipped with a 100 mL reaction vessel, a 5-port lid, a temperature probe, and a mechanized stirrer, was employed.
2. A supersaturated solution containing 0.41 M acetaminophen in 50 mL of MeCN was prepared and introduced into the reactor, ensuring a tight seal with the lid ports left open to accommodate the motorized stirrer and temperature probe. When necessary, septa were used to prevent any leakage
3. The camera was positioned adjacent to the viewing window of the reaction vessel and securely mounted inside a 3D-printed housing.
4. Auto-focus and white balance settings were disabled, and manual adjustments were made using the camera settings software.
5. The solution was maintained at room temperature. Using iControl, the stir rate was programmed to increase by 20 rpm every three minutes, starting from 0 rpm and up to 300 rpm. The ramping of the stir rate took 10 seconds.
6. HeinSight2.0 was operated and connected to iControl via iC Data Share
7. The experiment was continuously monitored until the automated procedure was completed.

Results and Discussion

No solid suspension was observed below 160 rpm. From 160 rpm to 200 rpm, the onset of solid suspension became visible, as indicated by changes in turbidity, color, and homogeneity. Although the turbidity reached its peak at a stirring value of

200 rpm, solids were still present at the bottom of the flask until the stirring speed reached 220 rpm. This emphasizes the significance of examining multiple outputs.

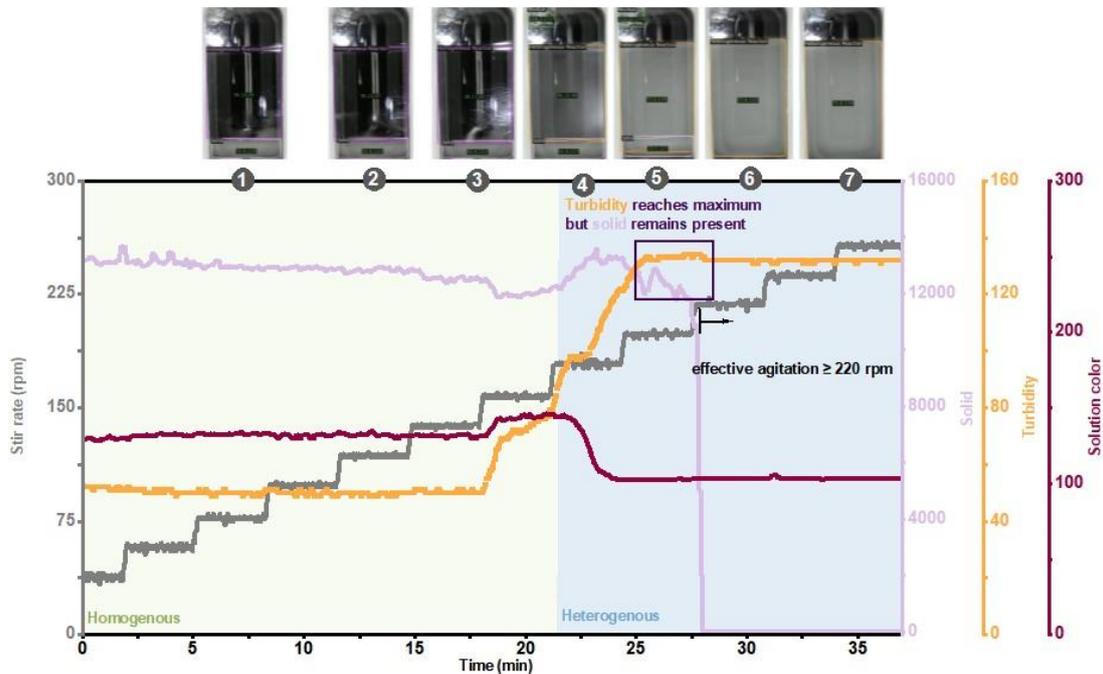


Figure S15. Results of effective agitation.

Settling Kinetics

Starting with a stirred supersaturated solution, the stir rate was halted to monitor the time for settling of solid to the bottom, indicated by the turbidity and solid trends, as shown in Figure S16.

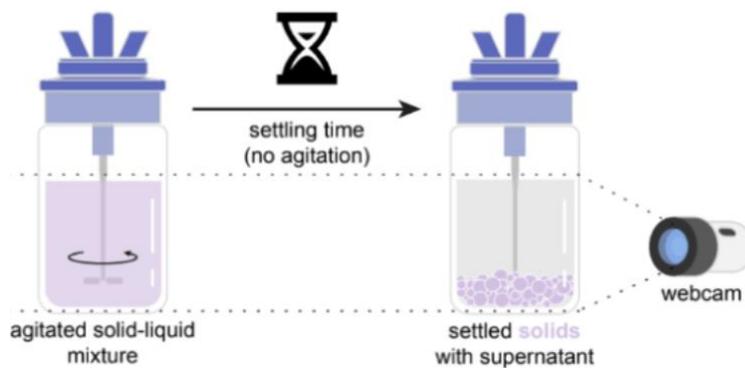


Figure S16. Illustration of settling kinetics of solid-liquid mixing.

Procedure, Materials, and Parameters

1. An EasyMax102 device, equipped with a 100 mL reaction vessel, a 5-port lid, a temperature probe, and a mechanized stirrer, was employed.
2. A supersaturated solution containing 0.48 M acetaminophen in 50 mL of MeCN was prepared and introduced into the reactor, ensuring a tight seal with the lid ports left open to accommodate the motorized stirrer and temperature probe. When necessary, septa were used to prevent any leakage
3. The camera was positioned adjacent to the viewing window of the reaction vessel and securely mounted inside a 3D-printed housing.
4. Auto-focus and white balance settings were disabled, and manual adjustments were made using the camera settings software.
5. The solution remained at room temperature. Through iControl, the stirring rate was set to well-agitated stir rate value for three minutes, followed by a 10-minute pause without stirring to observe the solid settling behaviour. This cycle was repeated for each stirring rate of 800, 600, and 400 rpm. The stir rate was increased and dropped in 10 s intervals.
6. HeinSight2.0 was operated and connected to iControl via iC Data Share
7. The experiment was continuously monitored until the automated procedure was completed.

Results and Discussion

The impact of different stir rates (800, 600, and 400 rpm) on the duration required for complete solid settling after agitation was examined. Consistent with expectations, a decrease in agitation speed resulted in a shorter settling time, as indicated by the turbidity trend. This observation was further supported by the solid and homogeneity trends, as shown in Figure S17.

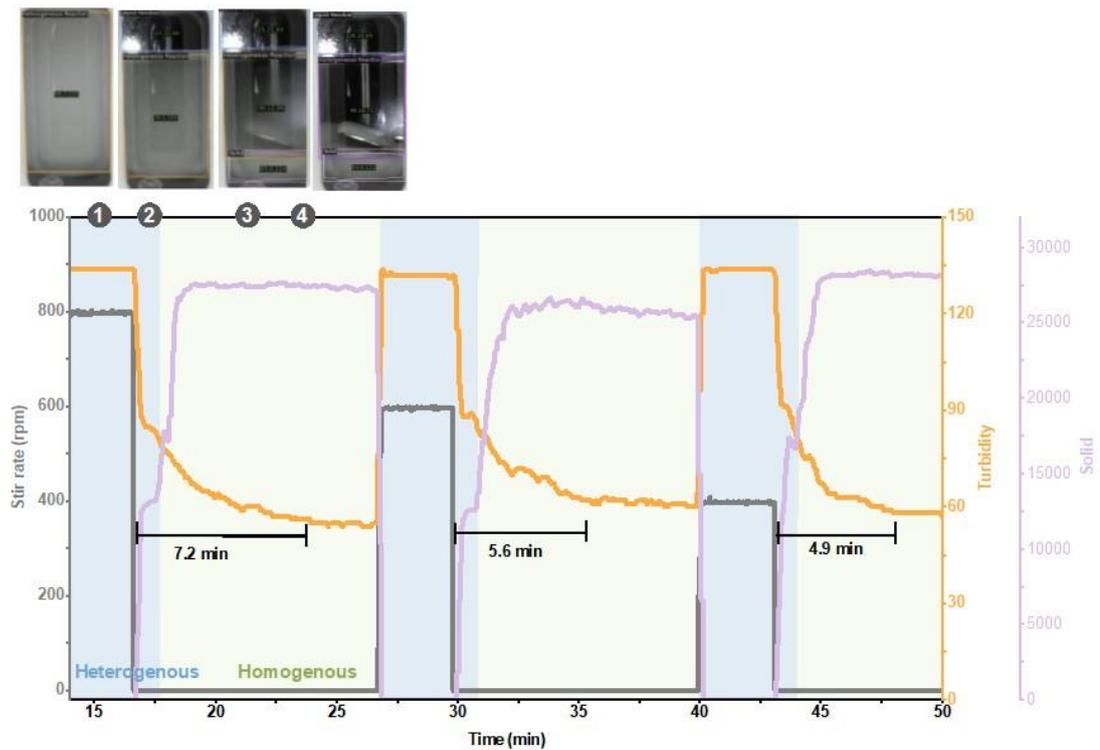


Figure S17. Results of settling kinetics.

Multiple-phase detection: liquid-liquid extraction

The temperature and stirring were controlled by iControl, while HeinSight2.0 provided the monitoring of outputs such as volume1 and volume2.

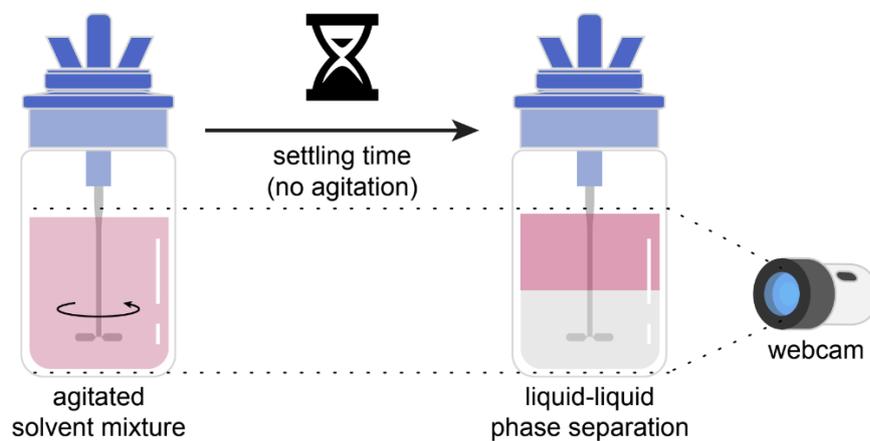


Figure S18. Illustration of liquid-liquid separation.

Simple liquid-liquid extraction

Automated liquid-liquid extraction of DCM and water was performed.

Procedure, Materials, Parameters

1. An EasyMax102 device, equipped with a 100 mL reaction vessel, a 5-port lid, a temperature probe, and a mechanized stirrer, was employed.
2. A mixture of immiscible liquids, comprising a specific volume of water (20 mL), brine (5 mL), and DCM (35 mL) containing citric acid was introduced into the reactor, ensuring a tight seal with the lid ports left open to accommodate the motorized stirrer and temperature probe. When necessary, septa were used to prevent any leakage
3. The camera was positioned adjacent to the viewing window of the reaction vessel and securely mounted inside a 3D-printed housing.
4. Auto-focus and white balance settings were disabled, and manual adjustments were made using the camera settings software.
5. The solution remained at room temperature. Using iControl, the stirring speed was set to 1000 rpm for a duration of three minutes, followed by a 5-minute period without stirring to allow for phase separation. The reduction in stir rate occurred over a 10-second interval.
6. HeinSight2.0 was operated and connected to iControl via iC Data Share.
7. The experiment was continuously monitored until the automated procedure was completed.

Results and Discussion

The impact of a stir rate of 1000 rpm on the duration for the mixture to achieve settling was examined. The settling time of 0.18 s was predominantly determined by analyzing the volume output for each phase, which was corroborated by secondary indicators such as color and turbidity, as depicted in Figure S19.

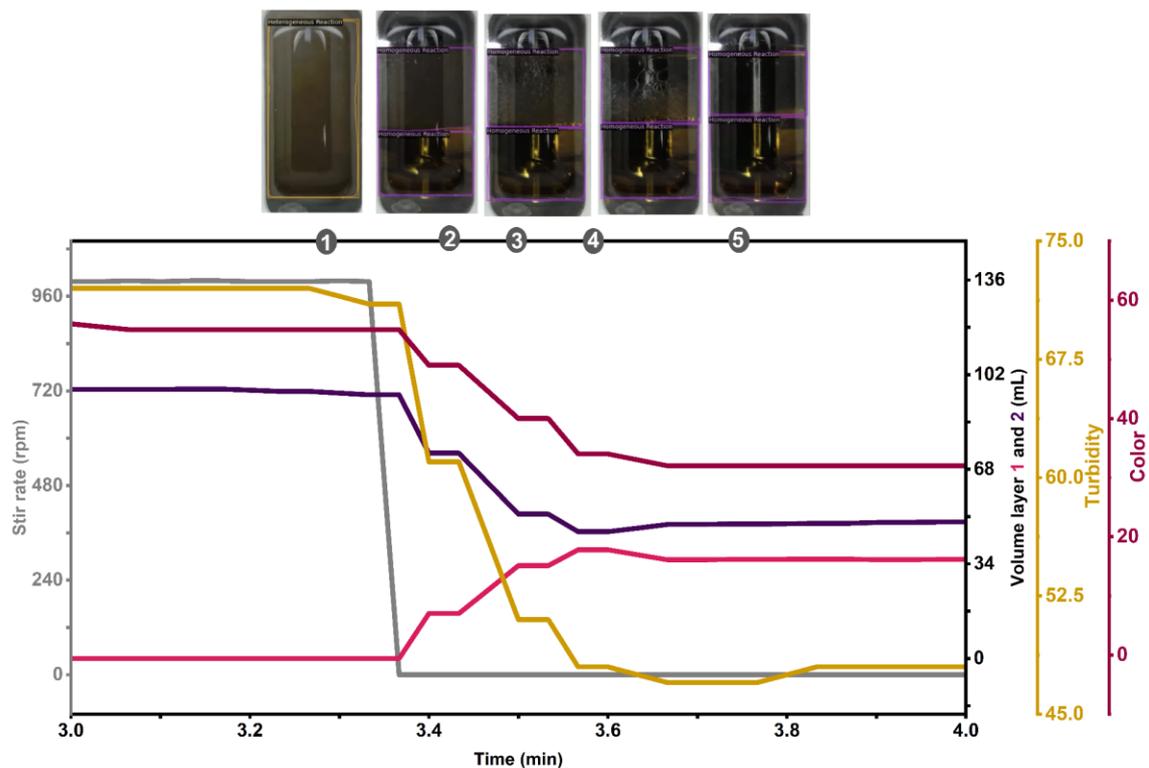
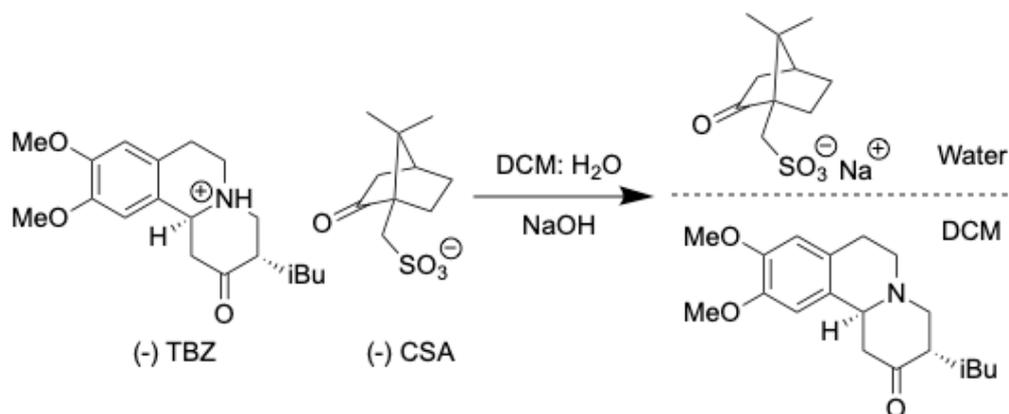


Figure S19. Results of liquid-liquid separation.

Liquid-Liquid Extraction of (-)TBZ(-)CSA

Automated liquid-liquid extraction of (-)TBZ(-)CSA in DCM and water was performed, as shown in Scheme S1.



Scheme S1. Separation of (-)TBZ(-)CSA in DCM and water.

Procedure, Materials, Parameters

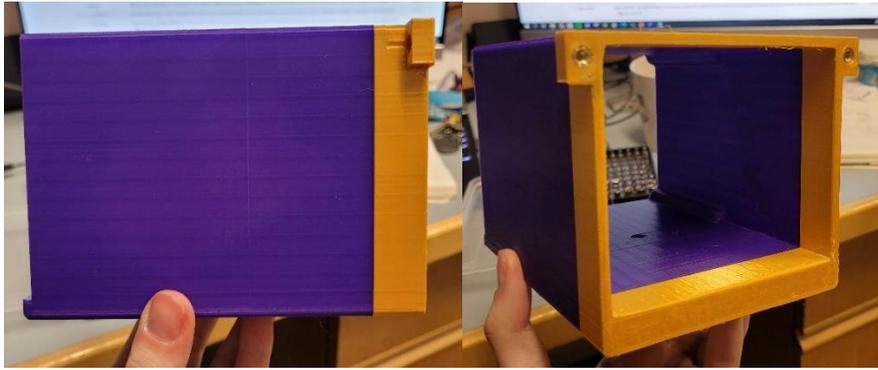
1. An EasyMax102 device, equipped with a 100 mL reaction vessel, a 5-port lid, a temperature probe, and a mechanized stirrer, was employed.
2. 1.557g of (-)TBZ(-)CSA was placed into the reactor followed by a minimum amount of DCM to create a homogenous solution. NaOH solution (0.5M) was added followed by water to give an equivalent volume to the organic later.
3. In the reactor, a tight seal with the lid ports left open to accommodate the motorized stirrer and temperature probe. When necessary, septa were used to prevent any leakage
4. The camera was positioned adjacent to the viewing window of the reaction vessel and securely mounted inside a 3D-printed housing.
5. Auto-focus and white balance settings were disabled, and manual adjustments were made using the camera settings software.
6. The solution was kept at room temperature. Employing iControl, the stir rate was initially set to a vigorous speed for 10 minutes to ensure thorough mixing. This was followed by a period of 30-60 minutes without stirring to facilitate phase separation. Various agitation speeds were tested, including 250, 350, 450, and 650 rpm. The decrease in stir rate was executed over a span of 10 seconds.
7. HeinSight2.0 was operated and connected to iControl via iC Data Share.
8. The experiment was continuously monitored until the automated procedure was completed.

Camera enclosure setup guide

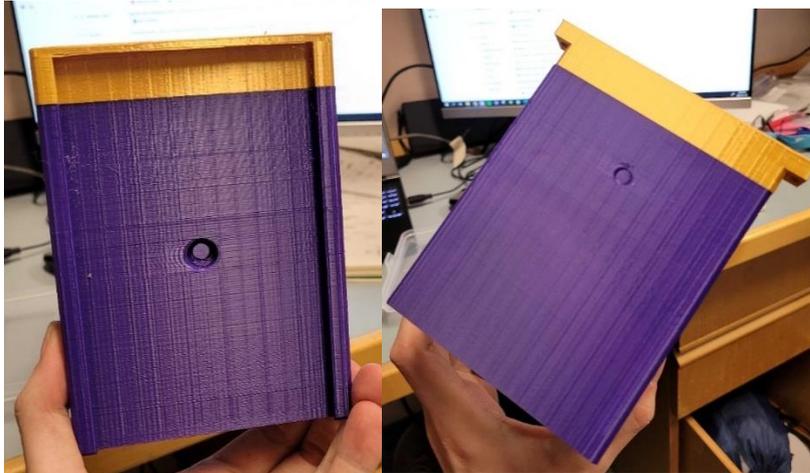
1. Print 4-part Enclosure STL Files from https://drive.google.com/drive/folders/1M1zpiaThiVlq9--AjoLQ_K6QHckjoXjb.

a. Everything can be PLA printed except for the clamp on the reactor, which needs to be made of nylon to withstand heating. Refer to the pictures below for views of the enclosure from all sides.

Side and front



Bottom (left photo) and top (right photo)



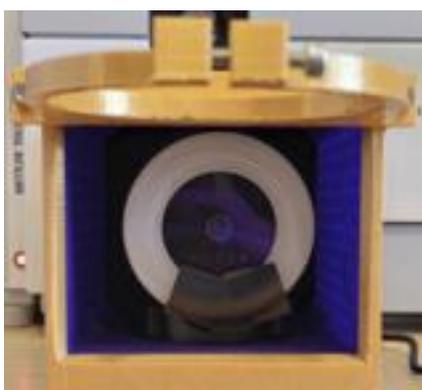
Back



2. Secure the camera in a fixed position.
 - a. Ensure that the camera joints are fully closed.



b. Tilt the second joint as far towards the front of the enclosure as it will go. Take the camera stopper and screw it into the top of the enclosure behind the camera. The side with the slant should face the front of the enclosure.



3. All heat-set screws are M4, except for the back plate, which uses M3. Assemble the enclosure using a soldering iron.



4. Clamp the enclosure to the EasyMax reactor.

