Networking Chemical Robots Using Twitter for #RealTimeChem

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The development of the internet of things has led to an explosion in the number of networked devices capable of control and computing. However, whilst common place in remote sensing, these approaches have not impacted chemistry due to difficulty in developing hardware and software systems flexible and varied enough for experimental data collection. Herein we present a simple and affordable (<$500) chemistry capable robot built with a standard set of hardware and software protocols that can be networked to coordinate many chemical experiments in real time, such that the different chemical reactions can be distributed over many sites simultaneously. We demonstrate how multiple chemical processes can be done with two internet connected robots collaboratively, exploring a set of azo-coupling reactions in a fraction of time needed for a single robot, as well as encoding and decoding information into a network of oscillating BZ reactions transferring a message between two different locations using chemical reactions. The system can also be used to assess the reproducibility of chemical reactions and discover new reaction outcomes using game playing to explore a list of reaction conditions not accessible when the robots instead take it in turn to each a pre-define reaction from a list.

The digitisation of everyday life through the computer and internet revolution[1] has led to systems that allow error-correction, distributed 'multi-core' working[2], and gamification of task-based work [3-4]. Thus digitization has led to an explosion in cooperativity driven by common standards and protocols which means that tasks centrally managed can be distributed over many sites, yet this approach has yet to impact the field of chemistry[4-5]. However, the automation of chemical reactions has been an expanding field in the last decade including flow chemistry, peptide and nucleic acid synthesis[6]. These robotic systems are specialised and expensive ($50-500K) so the adoption of such automation in chemistry has been limited. This is because using robots to do chemistry is hard due to

the bespoke nature of many chemical operations reactions resulting from a lack of standards [7-8]. We hypothesised that the connection of robots capable of doing chemical reactions in real-time by the internet could lead to new approaches to explore many chemical reactions, assess reproducibility, and control complex chemical reactions in real time. Conceptually we started by imagining a chemical-cloud whereby the code to control a number of identical robots could be held remotely or distributed all the robots. By sharing a common hardware, list of chemical reactions, and code the robots could collaborate by doing common chemical tasks simultaneously but decentralised over several laboratories in different locations, see **Figure 1**.
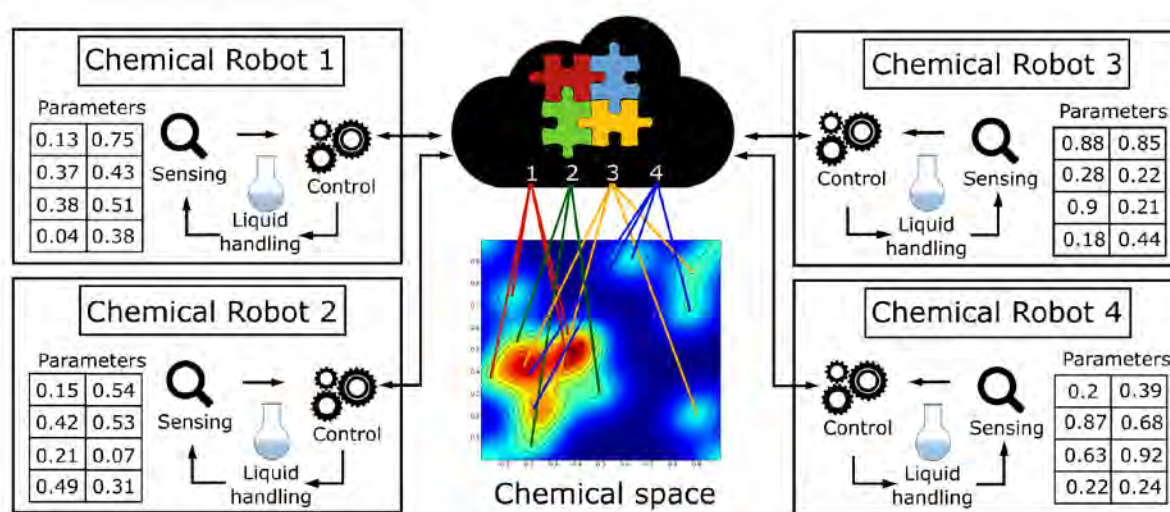

Figure 1: Schematic describing the concept of real-time networked chemical robots. Here four physically separated units (ChemPUs) are connected to a cloud via the internet. They receive the reactions parameters from the cloud in order to explore a chemical space in an optimized way, when the reactions are done the analysis results are returned and shared trough the cloud.

Similar to the world of distributed and cloud computing our concept can act as a cluster system to explore large chemical spaces[9] by distributing the workload across the robots connected to the network. Our aim is that the results can be easily reproduced anywhere and anytime by a similar machine, greatly increasing the reliability of chemical research allowing instantaneous validation of new procedures and discoveries [10]. To investigate this concept, we designed a system around a low power single board pcDuino3 computer running the Linux Ubuntu operating system, see SI. We then

built a software platform, using Python, to control the robot and the sensor system. The liquid handling system comprises a number of peristaltic pumps connected to a driver board and the sensor array is a single web cam connected to the pcDuino3 via USB. Both the hardware and the software are modular and can be easily upgraded to include other chemical effectors and sensors. By using a common software base, it is possible to tailor the system for a particular chemical problem combining the three main parts of the robot with related external libraries (See SI). Communication is achieved via a network (Wi-Fi or ethernet) connection so the robot can broadcast its state and communicate with the other units. As a proof of concept all communication has been conducted through the Twitter platform or by a bespoken server system. The data collected is analysed locally on each board and sent as plain and readable text to the Twitter account or server. In this way the posts are then acquired and can be processed by any other board on the network. For the work presented in this manuscript a total of six identical robots have been built. The reactions are performed in a flask with magnetic stirring, each is washed and reused for each experiment.

The principle of multi-threaded networking of individual chemical robots can be showed by considering simulations of the relevant strategies using an agent-based modelling approach, see **Figure 2**. Here each agent represents a chemical robot as an entity that does all the possible reactions until the goal is achieved. Different strategies can be used by the agents: in the random strategy, the most basic, each robot has no memory of the reactions attempted. In contrast an approach where the robot has memory of the previous reactions increases the probability of finding the goal in the next move, and when the number of robots is increased, and they can see the history of all the previous moves, all the robots can work together collaboratively solving the problem most quickly, see **Figure 2a**. This shows that as the number of robots increases the number of experiments each robot has to do decreases with the best efficiency when the collaborative approach is adopted. **Figure 2b** explains how the collaborative approach wins by showing how much less space has to be searched by each robot as the number of robots increase.
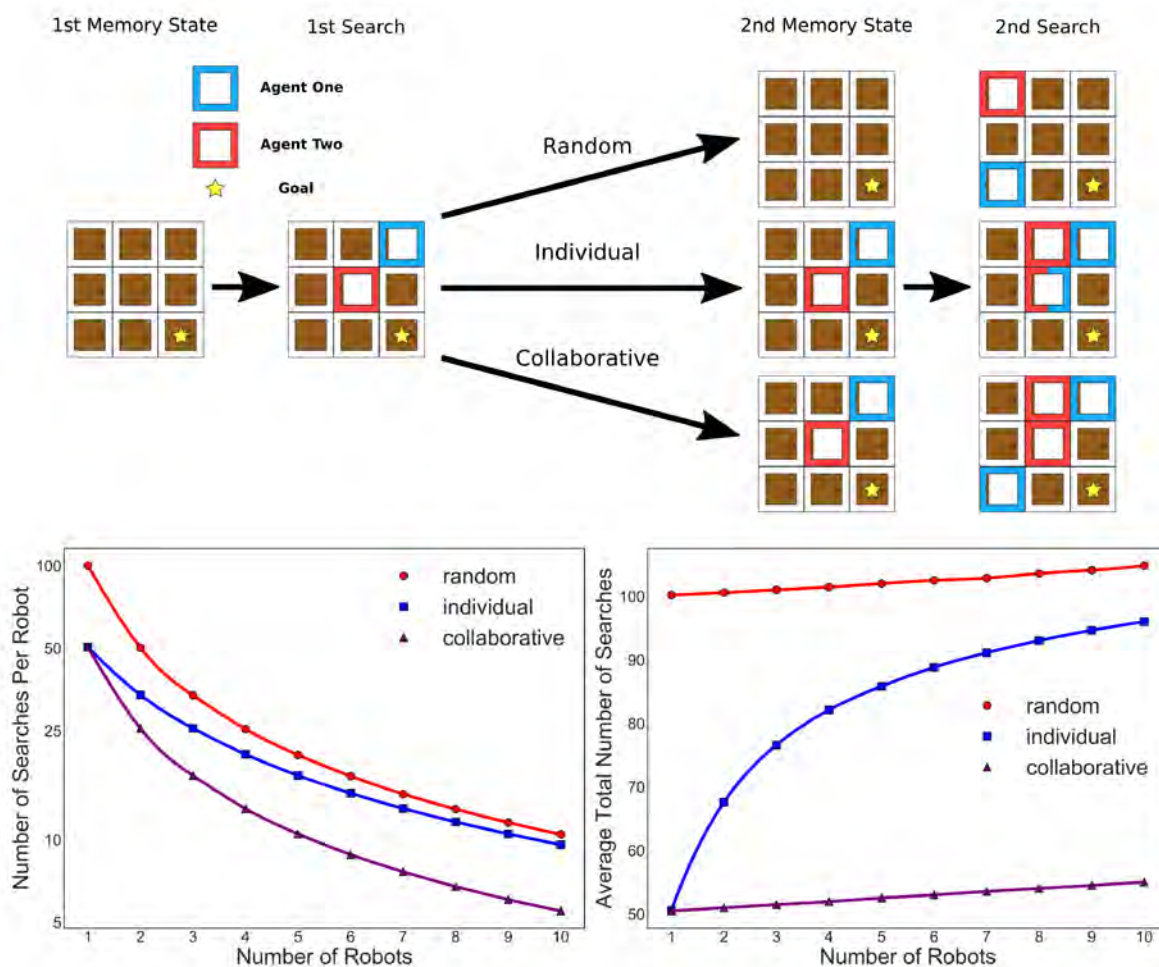
Figure 2: Agent based simulations. The top half shows the scheme of the simulated search with the three different strategies. In the bottom half the plot on the left shows the average number of searches needed under each strategy as a function of the number of robots. The plot on the right shows the search efficiency in terms of the total number of searches that are needed on average.

For many chemical searchers, the brute force exploration of many different combinations of reagents and concentrations is a powerful way to optimize a reaction, or to discover new reactivity. In recent years most of this workload can be automated in the laboratory, but the individual work-sites are isolated from each other. We envisaged that by networking two or more robots capable of doing a given set of reactions, it would allow the robots to collaborate with each other, even if they are physically separated over a range of different sites anywhere in the world. To realise this practically in the laboratory we deployed our robots to explore a reaction grid forming a range of dye colourants looking for a set of specific colours[11]. They did this by mixing 2 different reagents together in a

clean sample vial and the results of each reaction were automatically recorded with a webcam, analyzed and shared in real time using Twitter. By reading each other's Twitter feed the robots were able to collaboratively search the space and reduce the total number of experiments required to reach the goal of exploring colour space.
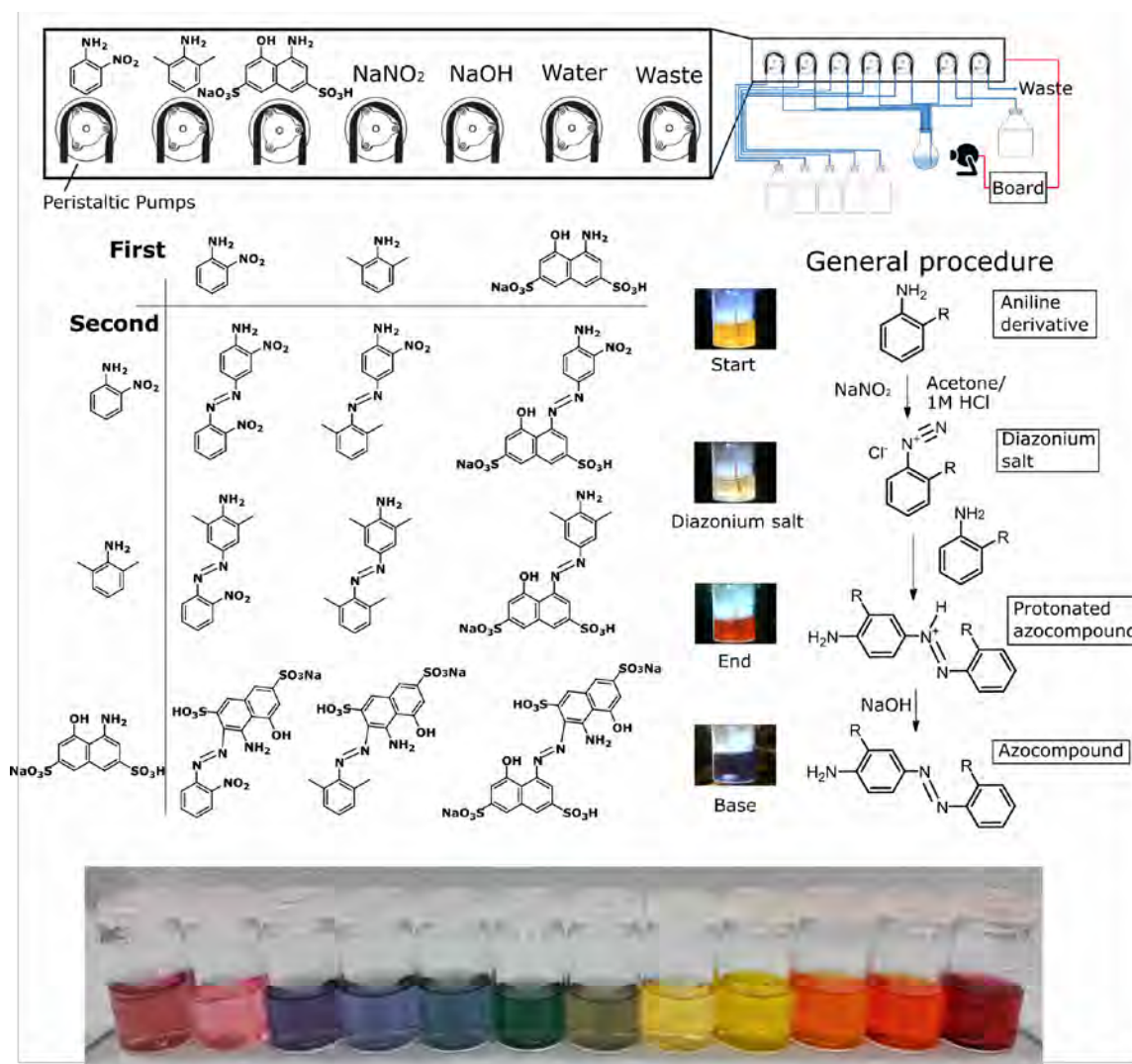

Figure 3. Three aniline derivatives were mixed in different order with sodium nitrite in an azo-coupling reaction (general procedure on right-hand side). In the top part the system connections with the reagents are showed. The starting materials were chosen purposely to be used both as first and second reagent. The addition of a basic solution to the product and a set of reagent ratios lead to a large variety of colours (bottom part).

During the chosen reaction two aniline derivatives are mixed with sodium nitrate in an azo-coupling reaction. After ca. 30 minutes the synthesis of the azo compound can be confirmed by a colour change and the colour of the solution is recorded and analysed in real time. To cover the largest number of

distinct colours using the least number of starting materials three aniline-derivative were selected: o-nitro-aniline, 2-6-dimethyl-aniline and sodium 4-amino-5-hydroxy-2,7-napthalenedisulfonate hydrate. Each starting material could be used both as a first component (to synthesize the diazonium salt with the amine group) or as the second component (for the substitution on the benzene ring). The nine molecules obtained from the grid (left-hand side of **Figure 3**) were expanded further by using 13 different ratios for each reaction, obtaining 117 possible combinations. Due to the chemistry involved some of the molecules synthesized acted as pH indicators, therefore a fixed amount of base was added after each reaction to check for a colour change. Overall, the time for each reaction including cleaning and dispensing was around 40 minutes, and during each experimental cycle the algorithm was designed to select a random reaction and share the chosen parameters via Twitter or the server. Next, the system then performs the selected reaction and saves four representative images of the reaction which are analyzed locally and shared online, see **Figure 4**.
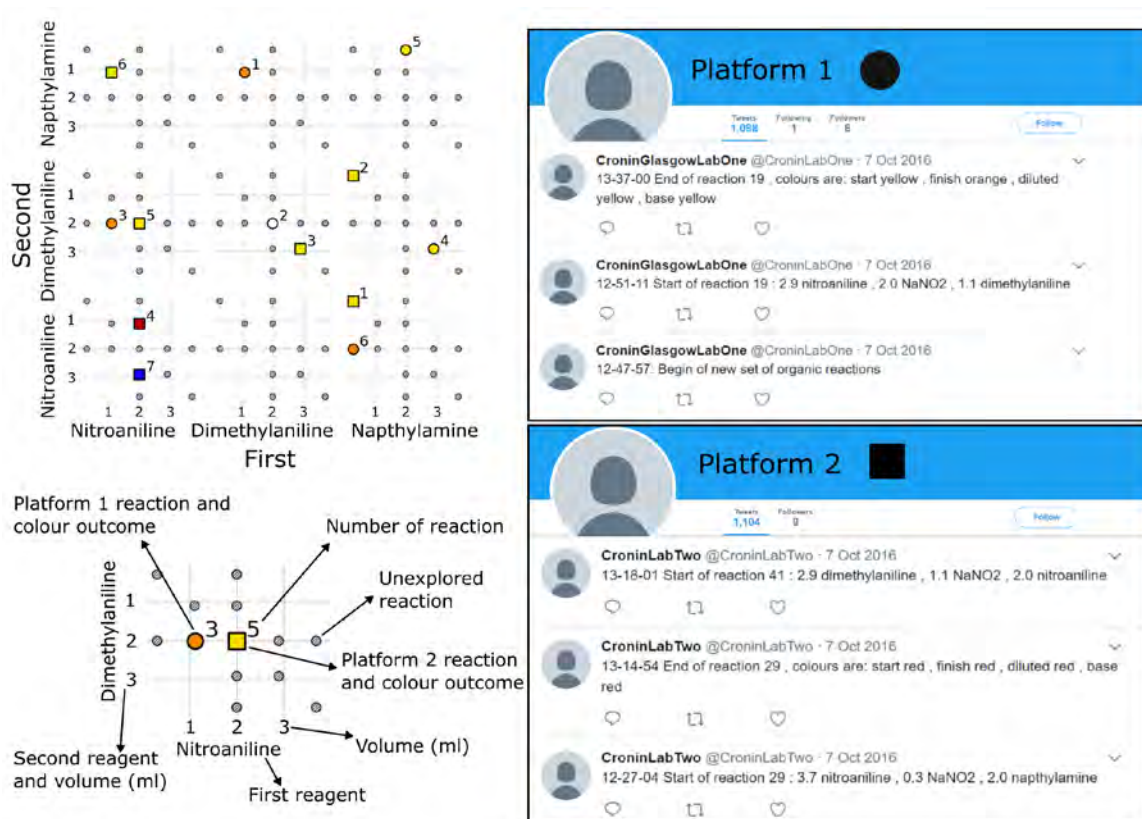

Figure 4: Example of the organic space exploration managed by two collaborating units (squares and circles). In the right hand side the Twitter accounts used for real-time data sharing.

A parallel background process checks the other robots every 5 minutes for Tweets and updates the database with the results respectively. This allows both boards to have the same data stored in their internal databases, avoiding doing the same reaction twice. The search has been successfully run several times, and this shows that the average number of reactions to find the rare blue colored one is halved. Also, during the exploration of the full grid, some unexpected colours were observed e.g. green and pink, which are rare to associated with azo-dye motifs.

To explore the real-time aspect of the networked chemical robots, we investigated a chemical oscillator based on the Belousov–Zhabotinsky reaction (BZ reaction)[12], whereby the system two physically separated oscillators have been synchronised in real time[13-14]. The reaction consists of the oxidation of malonic acid by potassium bromate, catalysed by a metal-complex in acidic aqueous solution. Initially the robots begin the reactions at different starting points and, through image analysis, data sharing and chemical adjustments, they can use the synchronisation algorithm to reach identical oscillation periods. By ensuring constant stirring, the oscillations show stable dynamics via the webcam, and the period is recorded and calculated on-board the robot with a real-time image analysis algorithm. Different strategies to achieve a control over the oscillation period have been reported in the literature, either by using the ratio of starting materials, the stirring speed or the temperature. Here we modulate the oscillation period in real time while the reaction is already running by using small additions of starting materials. To do this, potassium bromate and water were selected respectively to increase and decrease the oscillation period through a series of controlled additions where two functions were used to predict the behaviour of the reaction, see **Figure 5**.
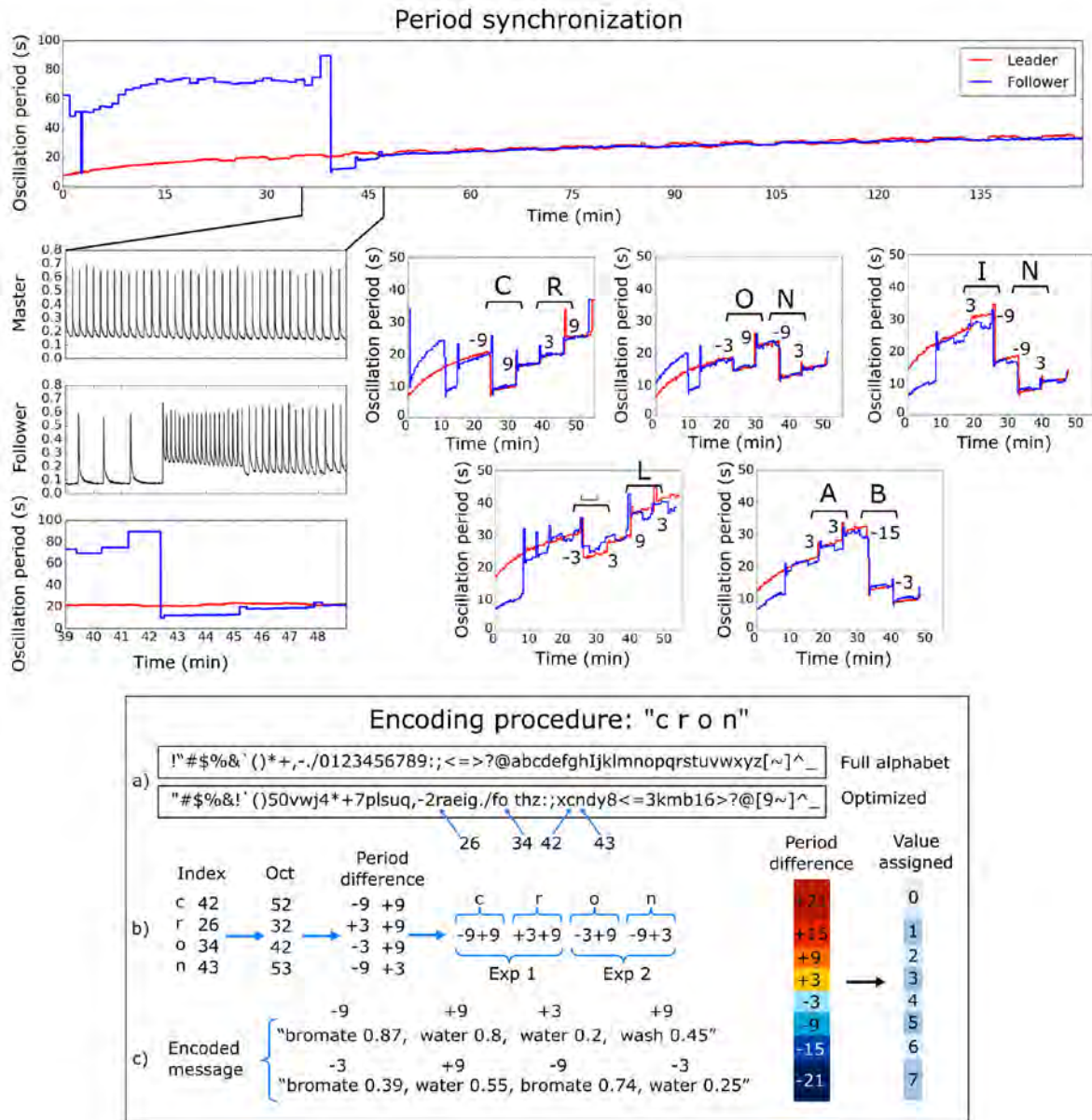
Figure 5: BZ reaction synchronization achieved by two units acting as Leader and Follower. In the bottom an example of encoding procedure for the word "cron". On the right real data of encoding/decoding of "cronin lab"

While one board acted as the 'Leader', simply sharing its period every 4 minutes, the other acted as a 'Follower', trying to synchronize its own period with the one of the Leader. Within a few iterations, and by applying the empirical functions, the two periods have successfully been synchronized in real time with an uncertainty of 2 seconds. To explore this, the periods of both platforms were recorded for 90 minutes showing that the reactions kept oscillating at the same frequency. To demonstrate the reliability of the platform we managed to send a message between two oscillating systems by

encoding it into a change in frequency. The message is split into individual characters and each is converted into a number using an optimized alphabet (**Figure 5-a**). The number is converted into octal numerical system (base-8 numbers), the digits of obtained octal are expressed using the degree of modulation of the reaction frequency by using the threshold table (**Figure 5-b**). The experiment starts with two separate systems oscillating with different periods. When synchronization is achieved the Leader adds the material to change its frequency by the difference associated with the message, then sends the amount added to the Follower (**Figure 5-c**). The Follower adds this amount and measures the value of the new frequency. The new frequency should be the same for both systems and the difference is the encoded message. In **Figure 5** the details of the encoded message for the partial word "cron" is showed as an example, however the amount of material to obtain the period difference depends on the current period of the reaction and is calculated in real-time during the encoding/decoding. Therefore, the encoded message is not a direct translation but depends on Leader's reaction period and can be successfully decoded only if the Follower's reaction is oscillating at the same speed. Since a single experiment can hold up to 4 additions in a reliable way it is possible to send two characters for each BZ reaction before proceeding to the automatic clean cycle. However, a program to perform a series of reactions and send a message of any length have been written and used to successfully encode/decode "cronin lab".

To collaboratively search chemical space for the evaluation of the reproducibility[15] of a complex cluster based upon a known tungsten polyoxometallate cluster[16] was chosen. Firstly, we set out to establish values of reagent stoichiometry and pH that would produce crystals of the compound within 2 hours, monitored by a webcam. The reaction conditions meeting this criterion were repeated to determine the reproducibility of the process. Full automation of the synthesis, reaction recording, and crystal recognition was achieved using the platform described above combined with image analysis machine learning software. A grid of 120 reactions was split into 8 series of 15, each of which was explored collaboratively between two platforms. To start each series, the Leader selects at random a reaction from the list of 15 shared between it and the Follower and informs the network. The Follower repeats this step with the remaining 14 reaction options and the process continues until the series has

been completed. In real-time the network is informed with feedback about each reaction result i.e. observing precipitation or the formation of crystals or not. Reagents are added to the reaction vial in sequence and the resulting solution is stirred for 10 minutes. Following transfer of the reaction solution to a recording vial, suspended over a webcam, the reaction is recorded for 2 hours. A machine learning crystal recognition method was developed by training a model from previous reactions and deployed during the 2-hour recording period. Many both clear and crystalized reaction images from previous experiments were compiled into a database to train this model. The grid of 120 reactions was completed 3 times between the two collaborating platforms revealing 13 conditions in the space that produced crystals at least once, see **Figure 6**.
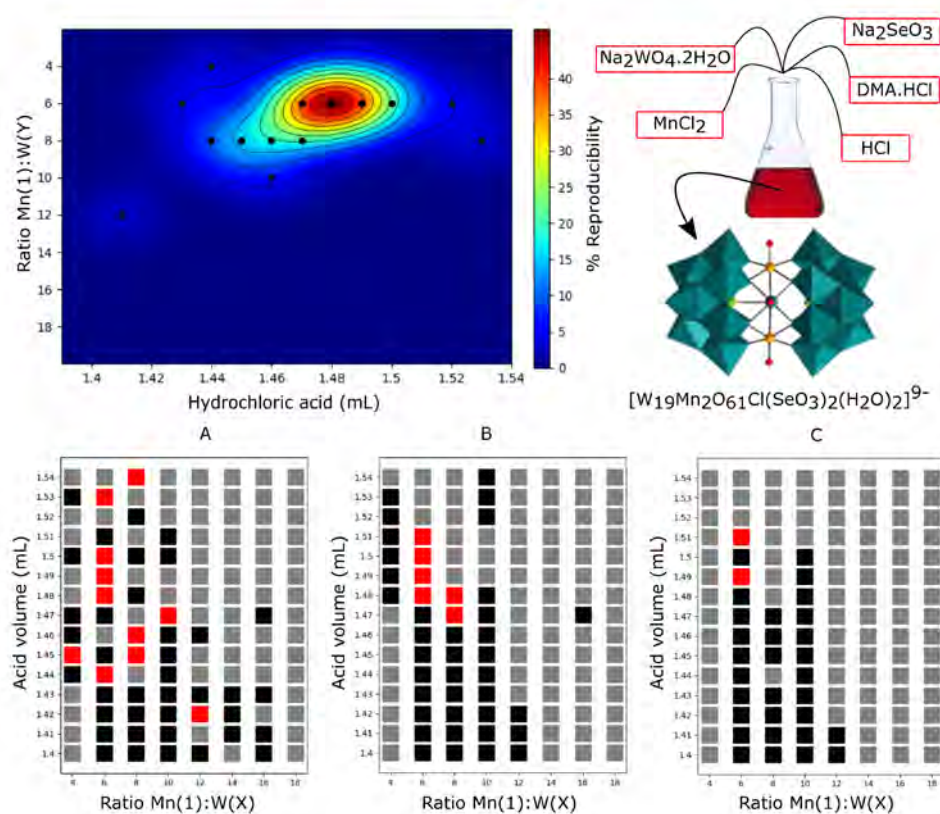
Figure 6. Bottom, three automated grid search results of reaction space (red = crystals, grey = precipitate, black = no crystals). Top left, heat map of % reproducibility of each conditions that produced crystals at least once. Top right, one-pot synthesis of the $W_{19}Mn_2Se_2$ polyoxometalate cluster with accompanying structure.

Each of these reaction conditions were repeated until a consistent average percentage of reproducibility emerged. If the reaction reached 15 failed experiments in a row it was abandoned as being too stochastic. Of the 13 reaction conditions to have produced crystals at least once 7 never again produced crystals. The remaining 6 showed percentages of reproducibility of between 11.8-50 % with the optimum reaction conditions being a Mn:W ratio of 1:6 using 1.49 mL of 2.32M HCl.

Normally in chemistry, the process to design experiments into a grid is a very well known and defined process. Using the process of collaboration shown here, we showed how the chemical robots could effectively collaborate by covering more reactions at the same time, by avoiding duplications and sharing the outcomes. We wondered if we could adapt this by allowing the robots to play a game, and then, rather than just doing the reactions as specified, allow them to change the reaction parameters (cleaning, concentration, time) in an effort to develop a strategy to win the game. This is because we linked the outcome of the chemical reactions, in this case which colour the solution changed to, and how often that particular colour was observed, to which move the robot could make on the board game. The game selected for this was Hex[17], a very simple strategy board game played by two players on a grid of hexagons traditionally shaped as a 11 x 11 rhombus. In the normal game players select a hexagon on the grid and attempt to join one side with the opposite side with a linked set of hexagons (see the middle of **Figure 7**). In our game the players are each a chemical robot, each with an identical list of chemical reactions that can be done. For the first move, a player randomly selects a reaction from their grid and performs the reaction. The chosen reaction space consisted of the same three aniline derivatives described in **figure 3**, and the move each robot can make is determined by the colour of the reaction that each robot performs. The game logic is based on the rarity of the reaction result; if a new/rare colour has been found, the optimal move is allowed however if the result has been seen many times, a sub-optimal or random move is allowed on the game board. Once the winner of the first game has emerged, the losing robot is allowed to change strategy by changing the variables associated with a given reaction, thereby attempting to find more new/rare colours to allow a better move. In this case the reaction space (possible combinations of same three aniline compounds) is increased for the loser, in the hope of finding new results see **Figure 7**. The platforms communicate

via a shared server that updates the live game board and optimal movements are determined by a Hex game algorithm using Monte-Carlo simulations.
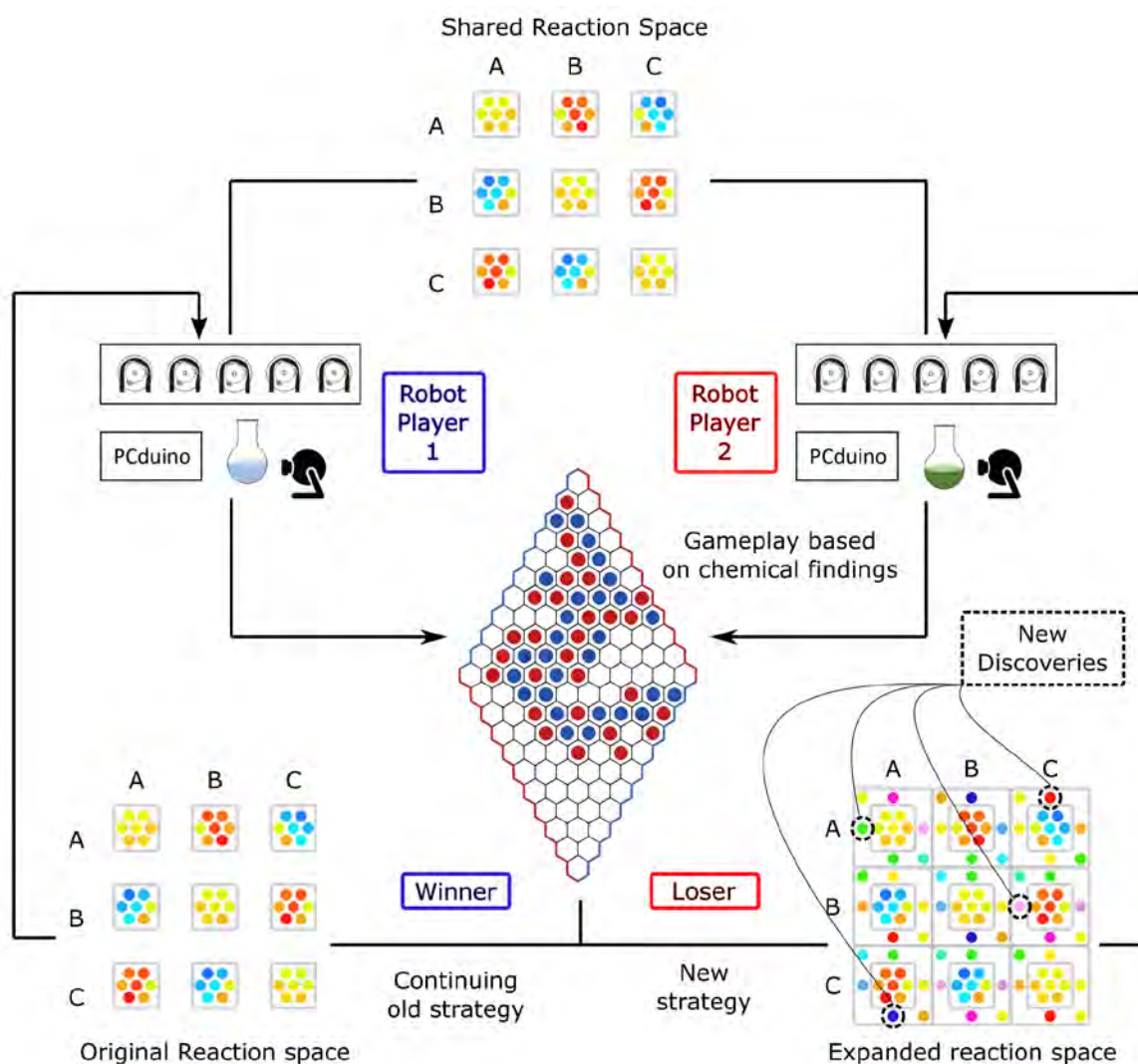

Figure 7. Schematic of Player 1 vs Player 2 in a series of Hex games. Strategies change once the initial game winner has emerged.

A typical game sequence can see between 2-5 games completed between two players before the reaction space is complete. **Figure 8** shows a typical sequence of 4 complete games (5th remained incomplete) in which the losing strategy, over time, produces significantly more unique discoveries then a continued search of the original reaction space. By presenting the goal of victory in a game of hex to these platforms and allowing changes to be made in search strategy toward that goal after suffering loss, we have shown the potential for new chemical discovery outside the realm of laborious

sequential search methods between networked robotic platforms. This development in the strategy results after feedback from the robot playing the game, the move allowed as a function of the game, and then the result of the game allowing the robot to change the strategy to discover new / rare colours.
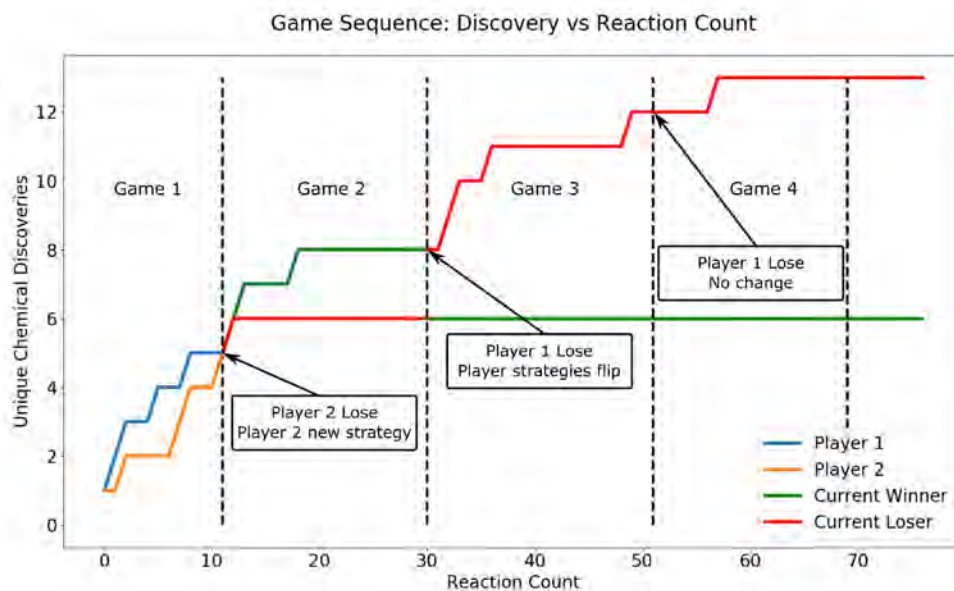
Figure 8. Discoveries over time of a four Hex game sequence between two automated platforms. This shows that a losing robot can adopt a new strategy and therefore discover new / rare colours more quickly than the previous winner.

We have presented a network of robots capable of autonomously performing chemical reactions, analysing them and using the internet to communicate data. The system was designed to be purposely as simple as possible; nevertheless, it was capable to manage three completely different chemical processes, all involving collaborative approaches based on data sharing. A combinatorial grid of organic molecules has been explored in half the time looking for a specific result, showing the advantages of multiple units. By using the real-time communication, the periods of two oscillating reactions have been precisely controlled and used to encode and decode information. Two units performed and reproduced POM syntheses under varied conditions in order to assess the

reproducibility percentages of different parameters. Finally, we showed that chemical robots who could only choose the 'moves' or reactions to perform as a function of the state of a game are able to make more discoveries compared to the screening approach. We imagine that an expansion in automated systems inside chemistry laboratories, where robots will be used to repeat standard procedures, will allow chemists more time to do more challenging experiments. A network of such robots in distant labs would be easily scalable and might become a worldwide system with thousands of units connected. This would exponentially increase the productivity and reliability of research.

Author Contributions LC conceived the idea, designed the project and coordinated the efforts of the research team with AH. The robot was built by DC, DS, AH, GAC, and the software developed by AC, SS, and GK. DC and DS contributed equally to the work with DC doing the dye and BZ work whilst DS did the POM and game work. LC co-wrote the paper with input from all the authors.

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Networking Chemical Robots Using Twitter for #RealTimeChem

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Contents

1. Robot design and concept:

The robot computational core is a pcDuino3 running Linux Ubuntu operating system that executes homebuilt code in python to control a number of pumps and a webcam. Access to internet is achieved via a wired ethernet or WiFi connection. For everyday use the board was connected also to a monitor, mouse and keyboard. Liquid handling is performed by a set of peristaltic pumps, the pumps are turned on for duration of the required addition time. The pumps are connected through tygon® tubing with the reagents and the reaction flask. Generally 5 pumps are dedicated to adding the reagents, one adds water for washing and the last one is used to empty the reaction flask. Data is aquired with a USB webcam able to record images and video from the reactions. The reactions are performed in a standard 14ml glass vial. It is magnetically stirred with a home built stirrer using a small fan. The robot has been designed to be as simple and affordable as possible. Therefore it can be assembled in just few hours.
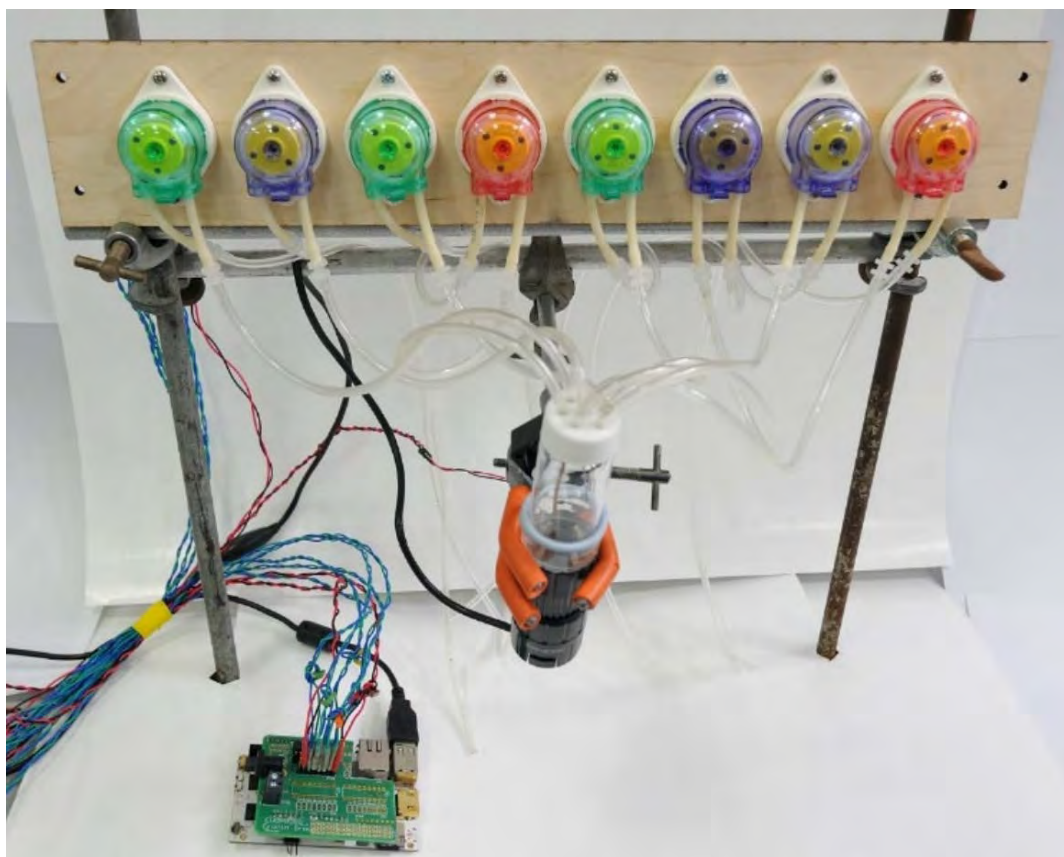

Figure 1: Photograph of the Robot. A unit is made of a set of peristaltic pumps for liquid handling (top), a webcam for reaction analysis (center, under the vial), and a pcDuino board for electronic control (bottom left).
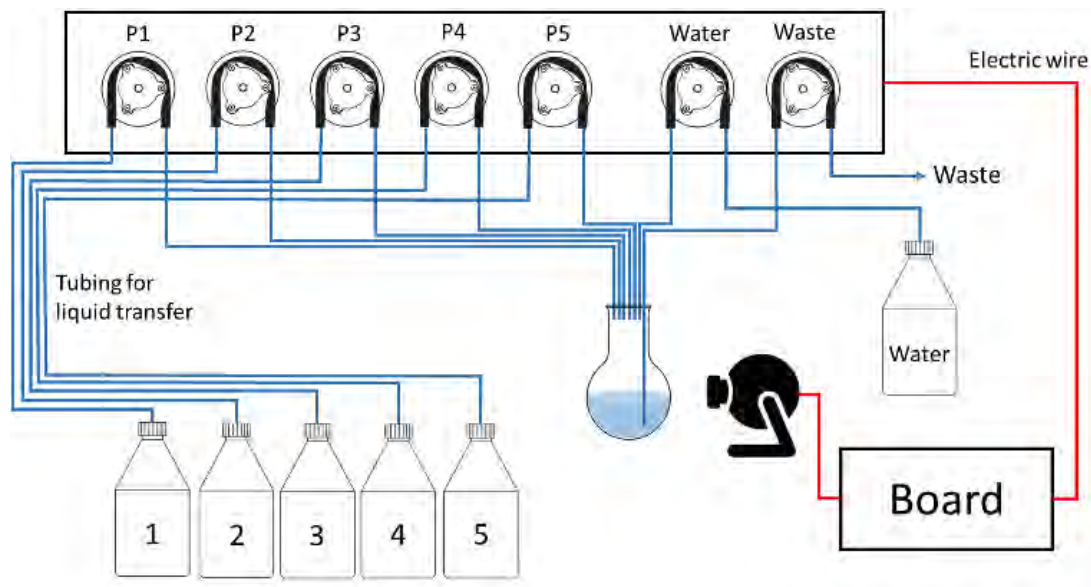
Figure 2: Schematic representation of the electric (red) and liquid transfer tubing (blue) connections of the system.
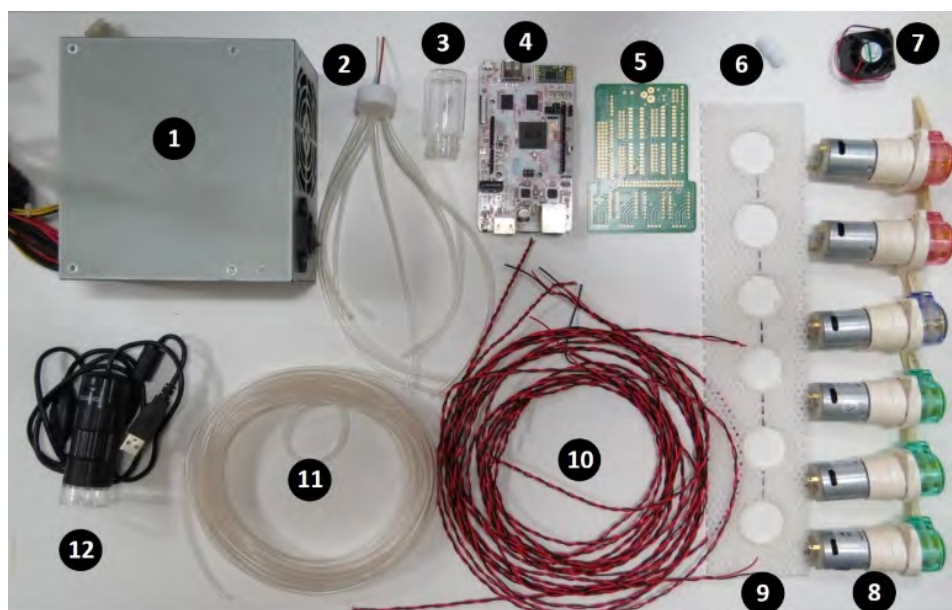

Figure 3: Robot required parts; **1)** Power supply (12V,5V), **2)** vial cap with tubing, **3)** a glass vial, **4)** pcDuino board, **5)** costum designed pumps driver board, **6)** magnetic stirrer bar; **7)** small dc fan, **8)** peristaltic pumps, **9)** pumps holder panel, **10)** electrical wiring, **11)** Tygon® tubing, **12)** USB webcam

1.1 Peristaltic pumps

The control over the solutions was performed using a set of peristaltic pumps. The pump is driven by a 12V DC and it is connected to the driver board mounted on pcDuino. In this work, we used the model KFS-HB2B06M, where M is either R,B,G,P which refer to pump colour (Red,Blue,Green,Purple). The pumps are designed to have a flow rate of 4ml/min towards a single

direction. Since a loss in precision over time was observed the pumps were recalibrated every week and after any manteinance operations.

1.2 pcDuino board

The robot runs on a pcDuino3, it is powered by a 5V (2A) power supply fed through a micro USB cable. This board features the following:

- CPU: AllWinner A20 SoC 1GHz ARM Cortex A7 Dual Core
- GPU: OpenGL ES2.0, Open VG 1.1 Mali 400 Dual core
- 1GB DRAM, Onboard Storage: 4GB Flash memory, microSD card slot (supports up to 32GB)
- Arduino style Peripheral headers
- HDMI Video output
- SATA socket, IR receiver, LVDS LCD interface and MIPI camera interface
- Audio out: 3.5 mm Analog Audio and I2S Stereo Digital Audio
- USB interface
- RJ45 Ethernet Connection 10M/100Mbps and Wi-Fi module

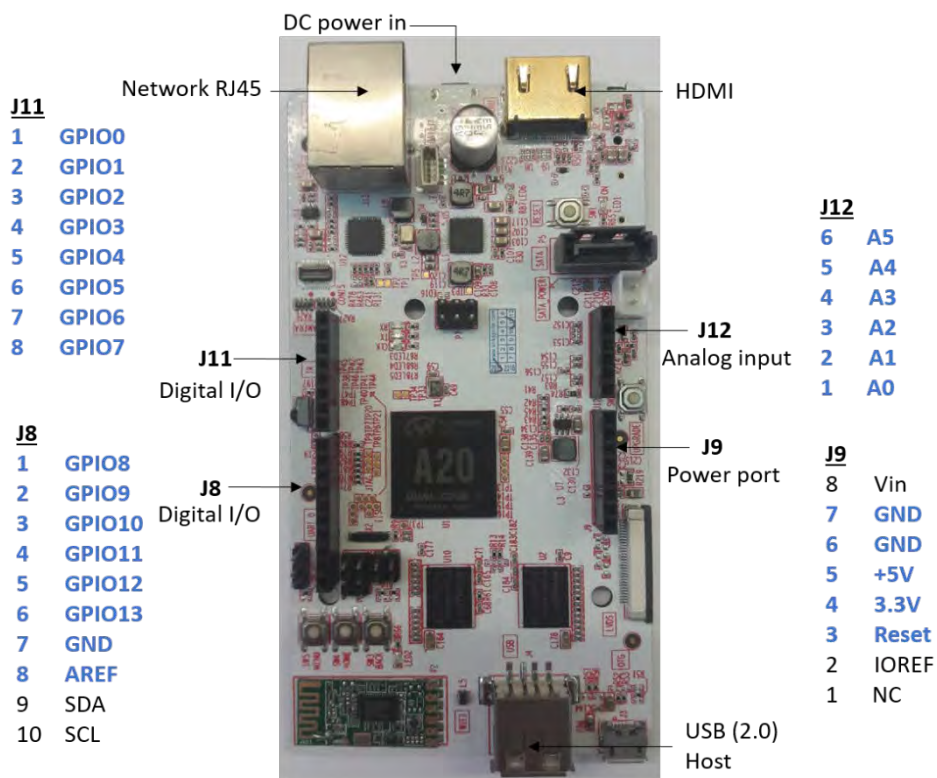API interfaces such as UART, 6xADC, 2xPWM, 14xGPIO, 1xI^{2}C, 1xSPI

Figure 4: pcDuino3 board with all the system peripherals and pinouts.

1.3 Power supply unit

The robot is powered by a 5V (2A) DC power source. However, the Peristaltic pumps are driven by a 12V (1A) DC source. In this work, a 500W ATX power supply unit was used.

1.4 Software

The pcDuino3 runs with the Ubuntu operating system. The platform is controlled by a dedicated program written in python. Due to specific experiments each project part has been completed by using a dedicated program. However, the low-level software is the same and is composed by three main parts with respective external libraries:

Pump control: This is based on gpio[2], a common library to control the pins of the pcDuino, and therefore operate the pumps. Since there is no feedback from the pumps a code converts the amount of solution required into a time interval used to run the pump. This time interval is derived from a calibration process where the flow rate of each pump is tested, verified and saved as a variable.

Webcam control: This is based on the opencv library[3]. The webcam is accessed by the computer and provides images and videos of the reaction. Further image/video analysis will be discussed in the respective project sections.

Network management: This uses the twython[4] library and controls the networked part of the platforms. It allows the platform to update its state by sending a tweet on its account and scan other accounts for synchronization and collaboration.

General Software	Peristaltic pumps control and calibration	Webcam control Frame/video acquisition	Network management (write/read)
Support library:	gpio	opencv	twython
Organic	-Reagent mixing -Dilution -Cleaning cycle	-Frame saving -Color detection -"Color difference" calculation	-Shared chemical space exploration
Physical	-Reagent mixing -Real-time additions -Cleaning cycle	-Real time video processing -Oscillation period calculation -Blue pixel count saving	-Oscillation period synchronization -Message Encoding
Inorganic	-Reagent mixing -Mixture transfer to crystallization flask -Cleaning cycle	-Video recording -Crystals/precipitate detection	-Chemical space exploration -Reproducibility assessment

Figure 5: Description of the software in a table. At the top the common and lower layer code is reported. Based on that we developed specific programs for each project. They will be discussed in the relative sections.

Coordinator: The software core of each project section is a "coordinator" program. It manages all the experiment components: physical reactions, image analysis, network synchronization and search algorithm.

Software to run the system will be at https://github.com/croningp/NetworkedChemistryPlatform

2. Part I – Organic

2.1 Stock solutions

o-nitro-aniline: 0.01M in acetone/HCl 1.7 M 1:1

2-6-dimethyl-aniline: 0.01M in acetone/HCl 1.7 M 1:1

Na 4-amino-5-hydroxy-2, 7 napthalenedisulfonate hydrate: 0.01M in acetone/HCl 1.7 M 1:1

Sodium nitrate: 0.01M in water

Sodium hydroxide: 0.5M in water

2.2 Experiment protocol

The reaction selected to explore the co-operative exploration of a grid of reactions was the an azo-coupling reaction. The starting materials include two aniline derivatives and sodium nitrate. During each reaction the first aniline derivative (**1**) is mixed with sodium nitrate (**2**) to form the relative diazonium salt (**3**). After 2 minutes the second aniline derivative (**4**) is added to the solution. After a period between 1 and 60 minutes the synthesis of the azo compound (**5**) is observed with a colour change. The reaction is an electrophilic aromatic substitution reaction where the aryldiazonium cation is the electrophile and the benzene ring of the second aniline is the nucleophile (Scheme 1) [5].
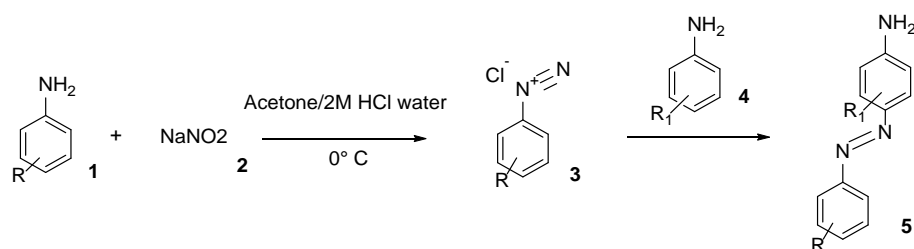
Scheme 1. Description of the azo-coupling reaction.

In order to cover the largest variety of colours with the least amount of starting materials three aniline-derivative were selected: o-nitro-aniline (**6**), 2-6-dimethyl-aniline (**7**) and sodium 4-amino-5-hydroxy-2, 7 napthalenedisulfonate hydrate (**8**). Each starting material can be used both as first component (to synthetize the diazonium salt using amine group) or second component (for the

substitution on the benzene ring). As a result, a 3x3 reaction grid could be performed, obtaining several colours (**Figure 6**).
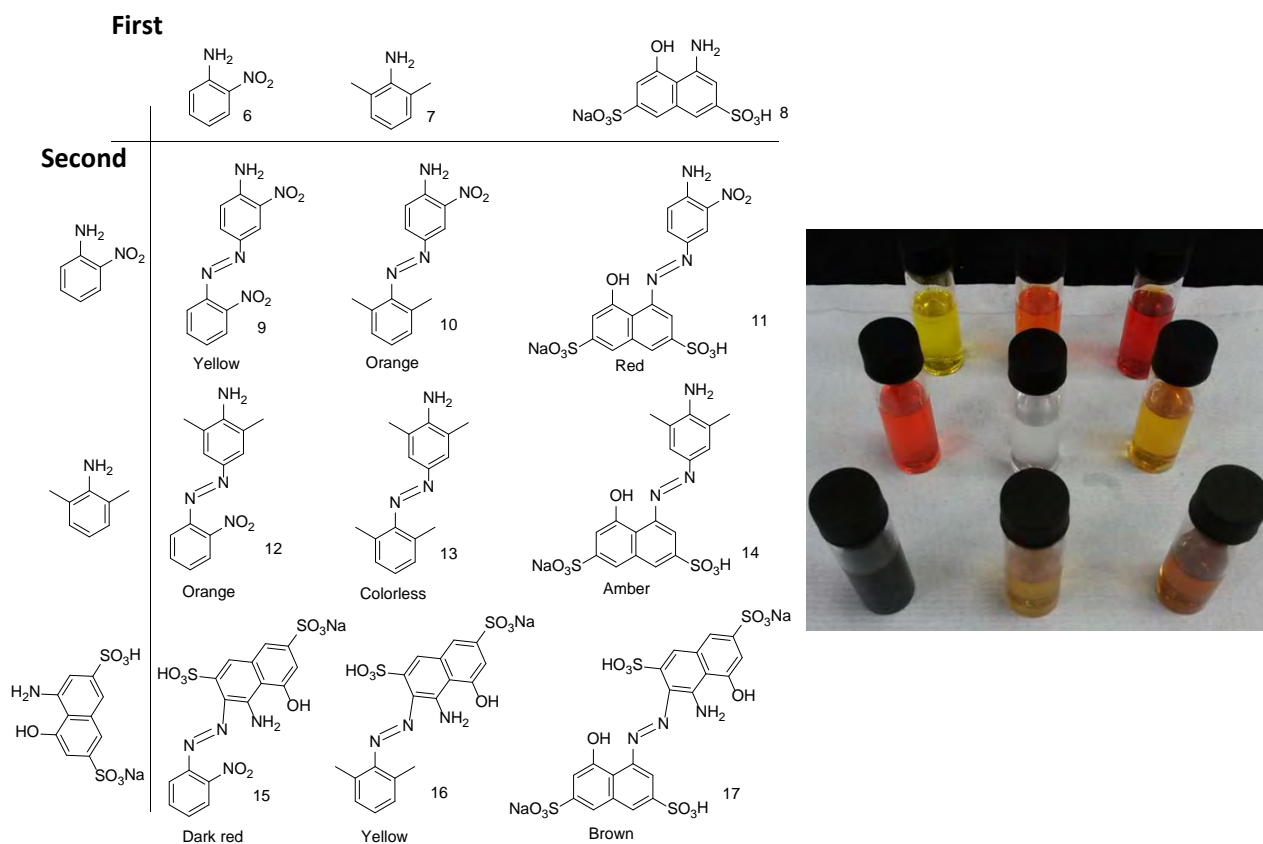

Figure 6: The nine possible products obtained with different order of addiction and relative bench preparation.

Each reaction has been further expanded using different reagents ratios. 5 possible volume ratios (0.3, 1.1, 2.0, 2.9, 3.7 ml) were chosen, each reaction is expanded using all combination of these ratio for the three components, maintaining total volume 6ml: [0.3, 3.7, 2][1.1, 2.9, 2][2.9, 1.1, 2][3.7, 0.3, 2][0.3, 2, 3.7][1.1, 2, 2.9][2.9, 2, 1.1][3.7, 2, 0.3][2, 0.3, 3.7][2, 1.1, 2.9][2, 2.9, 1.1][2, 3.7, 0.3][2, 2, 2]
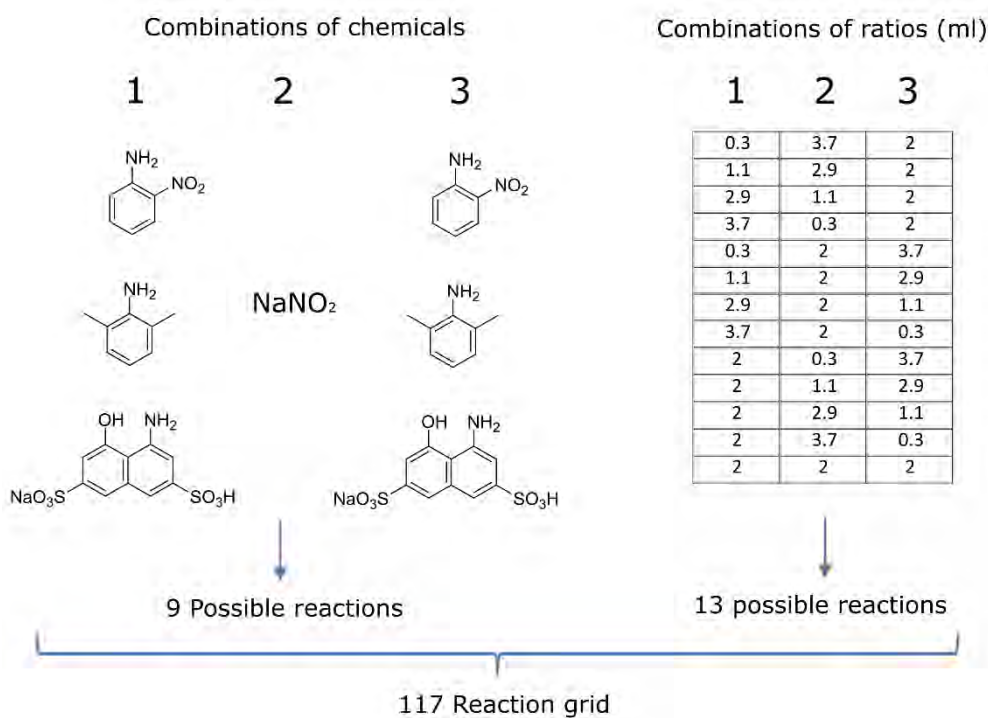
Scheme 2: Structure of the expanded chemical space as a combination of reagents and ratios.

9 possible reactions of the first grid have been expanded with 13 possible reagents ratio, obtaining a 117 reactions space (**Scheme 2**). Since some of the products are useful as pH indicators a further expansion of the 'colour space' can be obtained by adding a basic solution after the reaction is completed.

Figure 7: Example of colours obtained in the expanded grid

2.3 Image analysis

For the colour determination, the image frames recorded are converted into hsv colour domain. To allow the calibration of each colour, they have to be associated to a specific hsv range value. In each experiment a region of interest is analyzed and the pixel values are compared with the color ranges.

The colour with the highest pixel count is considered the solution colour (red, orange, yellow, blue, colourless, black). Individual colour counts are saved and stored in a csv file for post processing.
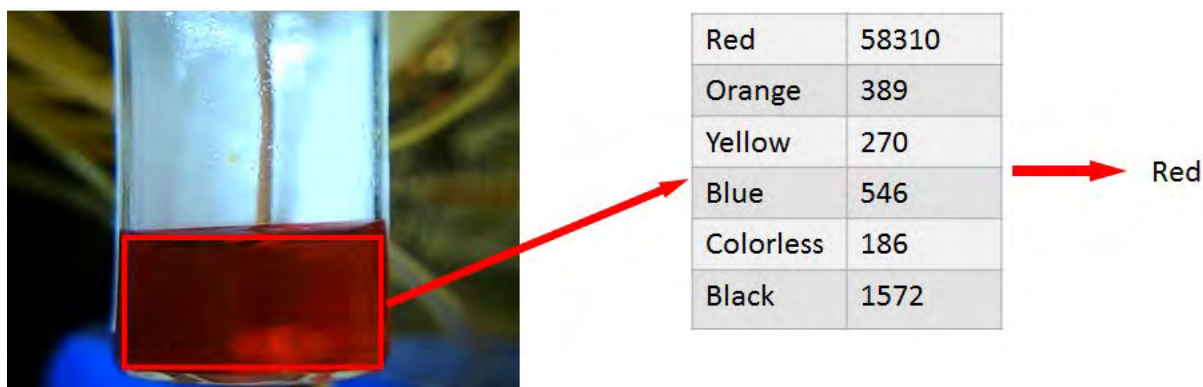

Red	58310
Orange	389
Yellow	270
Blue	546
Colorless	186
Black	1572

→ Red

Figure 8: Example of frame recorded with the webcam, from a region of interest the pixel count is extracted. The solution colour corresponds to the highest value

2.4 Full grid scan

The 117 reactions grid has been fully explored with two platforms in 88 hours using a simple program. The board starts by adding the first aniline derivate and the sodium nitrate in the flask. After waiting 2 minutes for the diazonium salt synthesis it adds the second aniline and wait 30 minutes. When the reaction is concluded the solution is diluted and a base is added.

During each reaction the board records 4 frames:

- "start": at reaction's beginning, right after reagents mixing.
- "finish": at reaction's end, after 30 minutes.
- "diluted": at reaction's dilution, 5ml out of 6 are removed and replaced with water.
- "base": after NaOH solution is added.
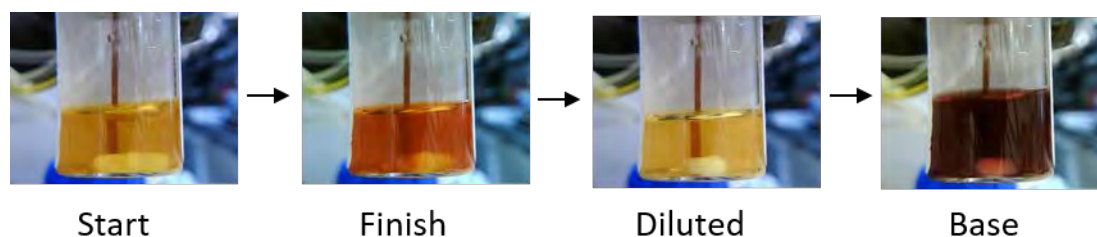

Start → Finish → Diluted → Base

Figure 9: Example of 4 key moments recorded during a reaction.

Image frames have been analysed with the colour detection and plotted in order to visualize the colour distribution.
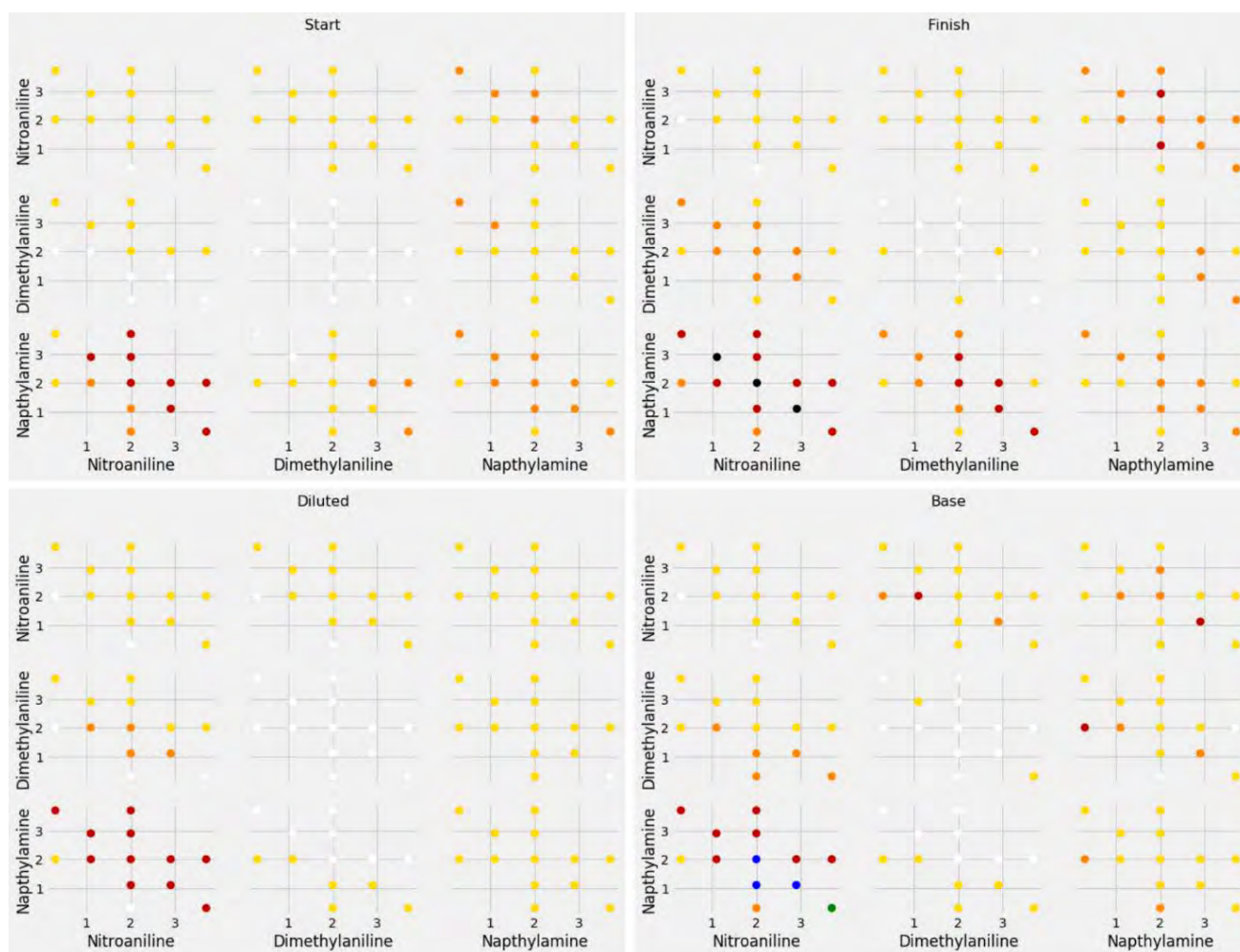
Figure 10: Four colour plots showing the full 117 reaction grid. Each plot shows a specific reaction moment. X axis corresponds to the aniline derivate used as first, Y axis to the one used as second. Subplots show 13 combination of ratios, the colour of the point corresponds to the solution colour extracted with the webcam.

2.6 Collaborative algorithm

Two identical and physically separated platforms have been used to explore the 117 reaction grid. They run the same algorithm and the aim was to find a blue reaction using a random search, sharing the results in real time using Twitter to reduce total time. The algorithm starts by selecting a random reaction and sending a Tweet with the reaction parameters. The system then performs the selected reaction and saves 4 frames. These are analyzed on board, the database is updated and an "end" Tweet with the results is sent. If a blue reaction is not present in the database the board will restart with a new random reaction, otherwise it will send a "stop" Tweet and stop. A separated thread in the background checks every 5 minutes the other board's Tweets and update the database with those reactions result (**Figure 11**). In this way both boards will avoid performing the same reaction twice.
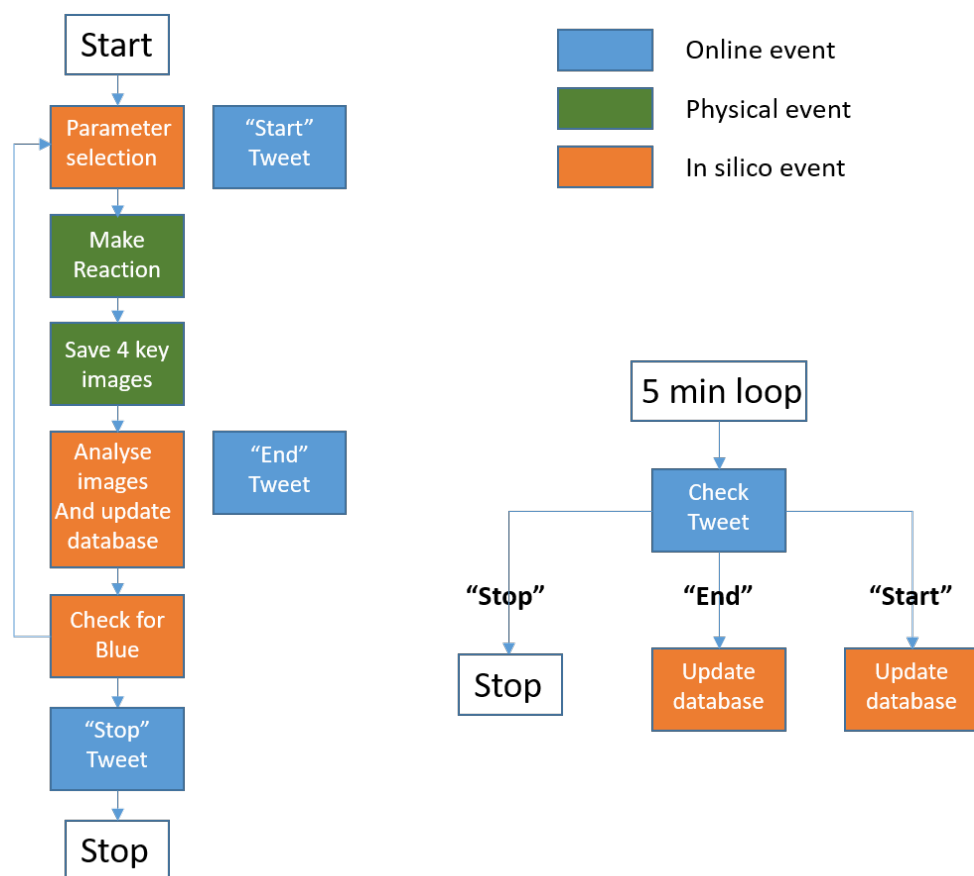
Figure 11: schematic structure of the collaborative algorithm run by two identical platforms. It has a main thread (left) that manages the reaction making, data saving/analyzing and result sharing. The second thread (right) checks every 5 minutes the other board results and updates the database.
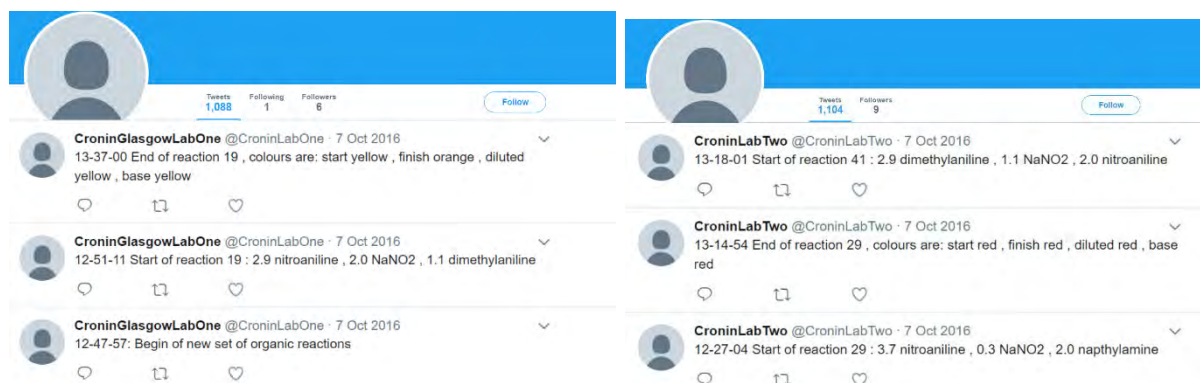

Figure 12: Example of two boards sharing results in real time using two real Twitter accounts.

This script has been used to look for a blue reaction out of 117 total combinations. After 14 sequences blue has been found on average after 15.1 reactions. The theoretical number of reactions necessary for two platforms sharing results looking for 3 blue reactions out of 117 is 19.5.

3. Part II – Physical

3.1 Reaction parameters and recording

Stock solutions:	Standard receipt:
1M malonic acid in water	0.88ml of ferroin solution.
0.5M potassium bromate in 1M sulfuric acid	1.25ml of sulfuric acid solution.
1M sulfuric acid in water	1.67ml of malonic acid solution.
10^{-3}M ferroin solution in water	1.8ml of potassium bromate solution

The reaction consists of the oxidation of malonic acid by bromate, catalysed by metal ions or metallo-complexes in acidic aqueous solution [6-7]. The oscillations are visible as blue/red colour change thanks to the ferroin, that acts both as catalyst and indicator.
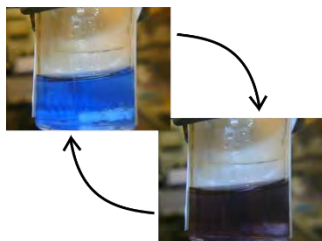

Figure 13: BZ oscillation of the solution. The color change is caused by the ferroin redox indicator.

During each experiment the webcam data stream is analyzed by the pcDuino in order to extract the oscillation period and make real time decisions. The count of blue pixels is also saved in a .csv file on the board for post processing. Due to the limited computational power of the pcDuino for real time analysis the frame rate is set on 3 fps, it is considered an acceptable speed since each BZ oscillation lasts for about 2-3 seconds.
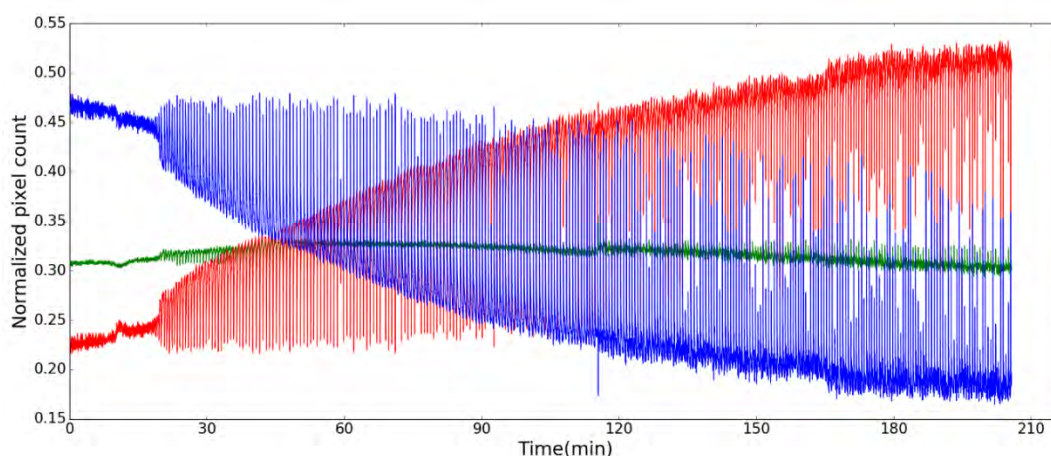

Figure 14: Normalized pixel counts vs time. Green pixels are approximately constant for the whole reaction. Oscillations start around 20 minutes. Until the end of the reaction (200 minutes, 3.3 hours) it oscillates around 540 times.

3.2 Plot the oscillations

In order to observe the oscillation period behaviour over time a script for data processing was created and the output demonstrated in Figure 15.
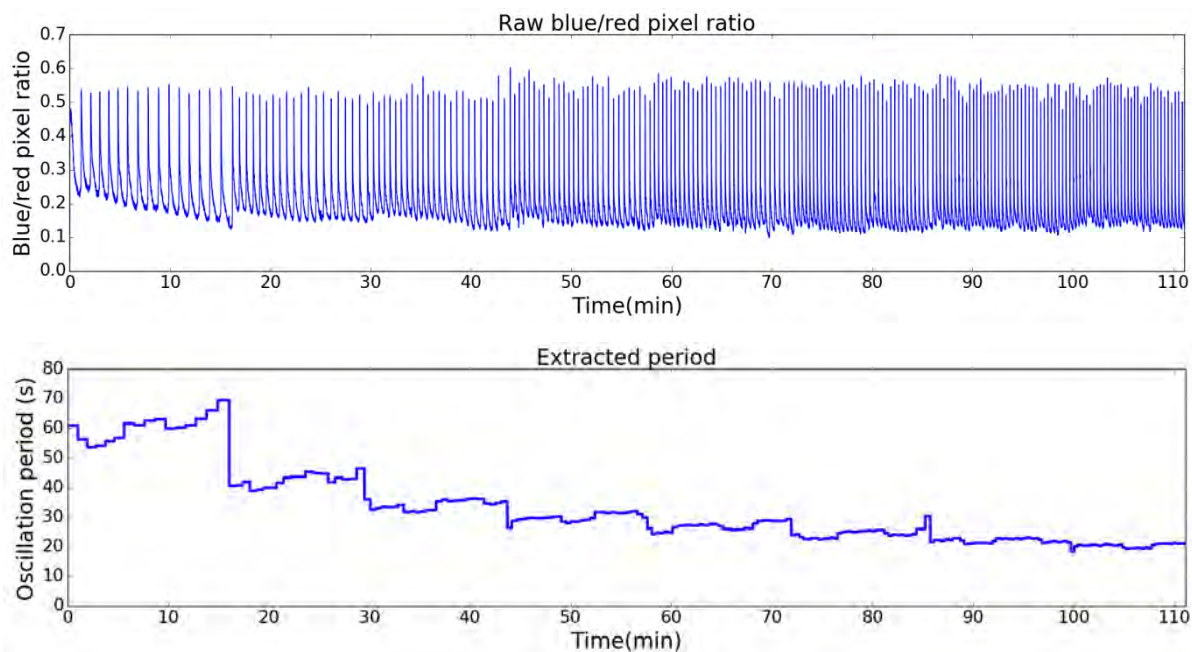

Figure 15: Raw data (top) of blue\red pixel ratio on an oscillating BZ reaction recorded with the webcam. (bottom) same data after the period extraction processing.

3.3 Predicting the chemical influence on oscillation period.

In order to predict the behaviour of the oscillation period when small amounts of water and potassium bromate are added we monitored several reactions while constant and regular additions were made. By processing the results, it has been possible to obtain two functions that correlate the amount of material added with the oscillation period change, within a reasonable time window and error, see Figures 16 and 17).
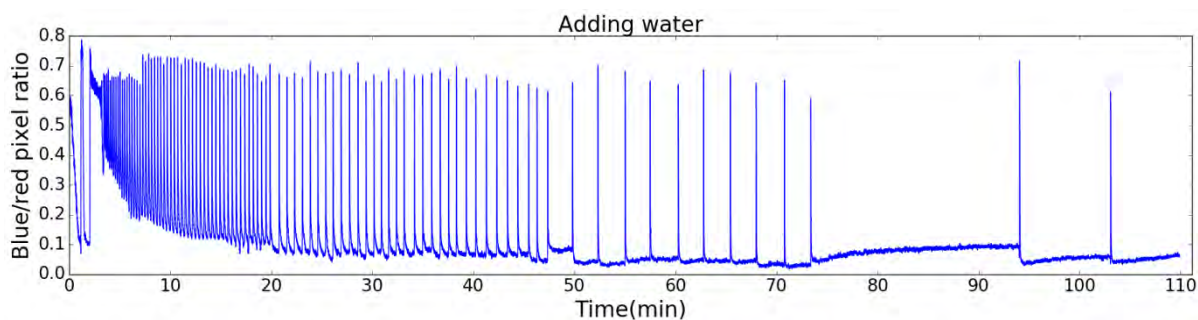
Water additions – slower period

Figure 16: Example of water additions to an oscillating BZ reaction causing slower periods. After 20 minutes from reagents mixing 1 ml of water is added. This is repeated at 48 and 73 minutes.
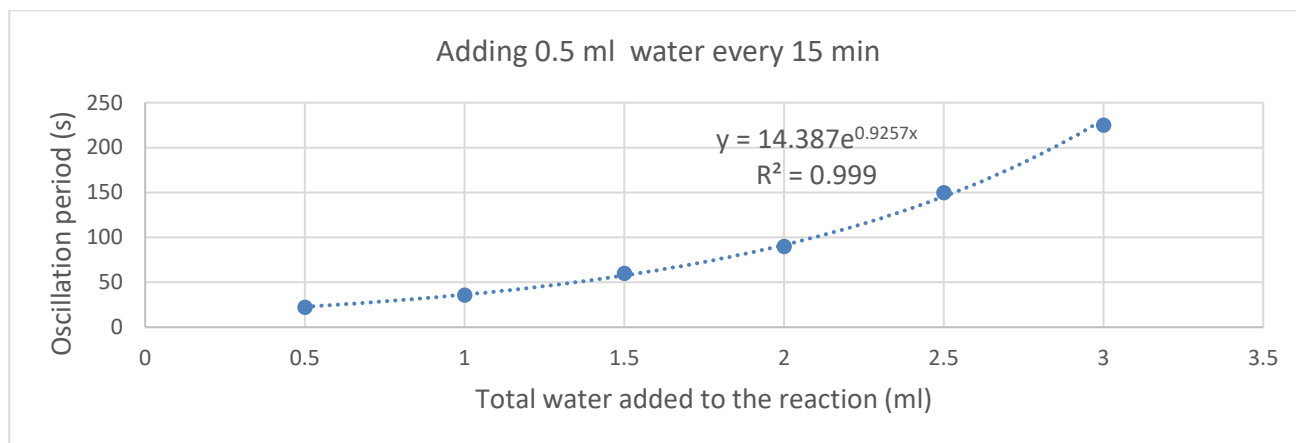
Figure 17: 0.5ml of water are added every 15 minutes to an oscillating BZ reaction. The graph shows the extracted oscillation period and its dependence to the amount of water added.

Shape of the curve is: $period = k * e^{amount}$ (equation 1)

Reversed form: $amount = \ln\left(\frac{goal\ period}{k}\right)$ (equation 2)

It will give an estimate of water *amount* to add in order to reach a specific *period*. Since it is referred to the reaction start, for real-time additions we need to consider also the current period:

$amount = \ln\left(\frac{goal\ period}{k}\right) - \ln\left(\frac{current\ period}{k}\right)$ (equation 3)

It easy to see that the empirical constant k is irrelevant, the function used to predict water additions is:

$amount = \ln(goal\ period) - \ln(current\ period)$ (equation 4)

When bromate is added there is a faster period, see Figure 18 and 19.
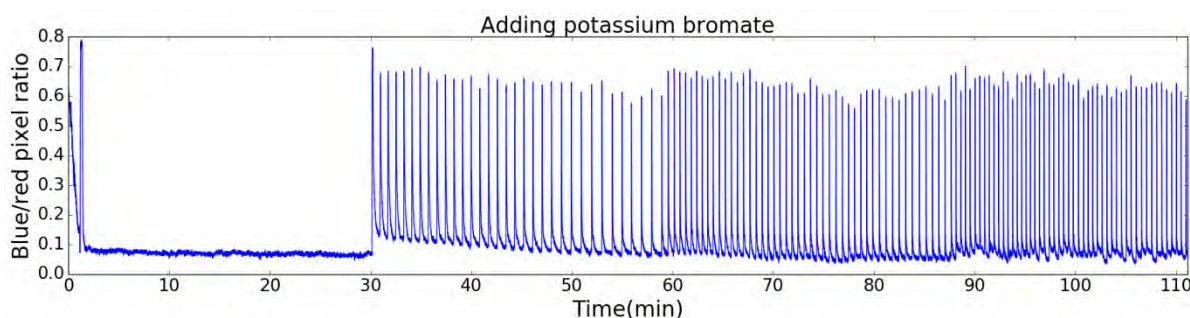

Figure 18: Example of potassium bromate additions to an oscillating BZ reaction resulting in faster periods. After 30 minutes from reagents mixing 1 ml of potassium bromate is added. This is repeated at 60 and 90 minutes.
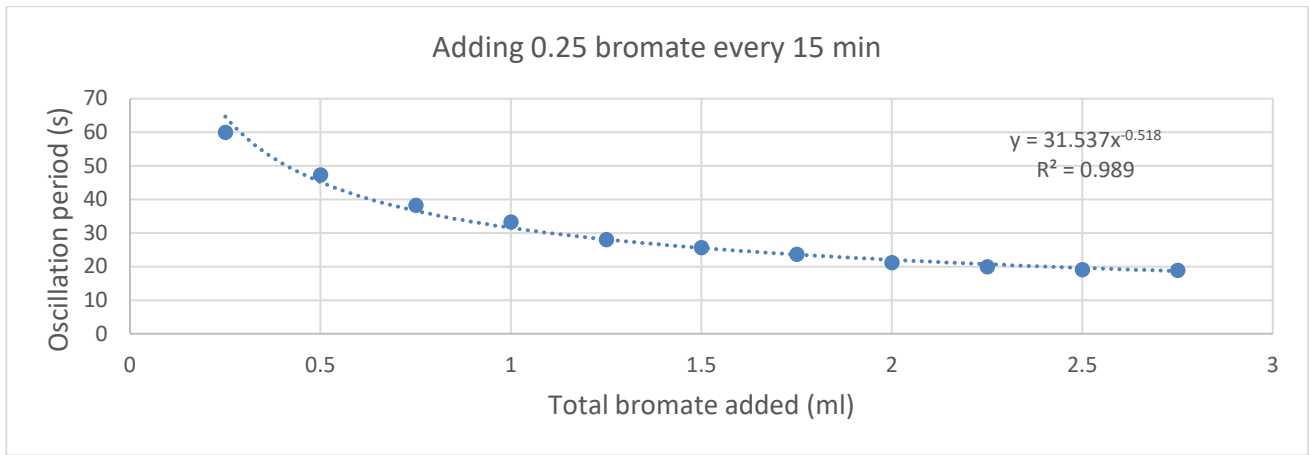
Figure 19: 0.25ml of potassium bromate are added every 15 minutes to an oscillating BZ reaction. The graph shows the extracted oscillation period and its dependence to the amount of potassium bromate added.

By using the data obtained in multiple addition tests we obtained the first empirical function

$$amount = \frac{num\ value}{current\ period^2 - goal\ period^2} \text{ (equation 5)}$$

Since the *numerical value* is not constant but depends on the period difference, a series of real additions at different periods have been used in order to obtain this correlation (**Figure 20**).
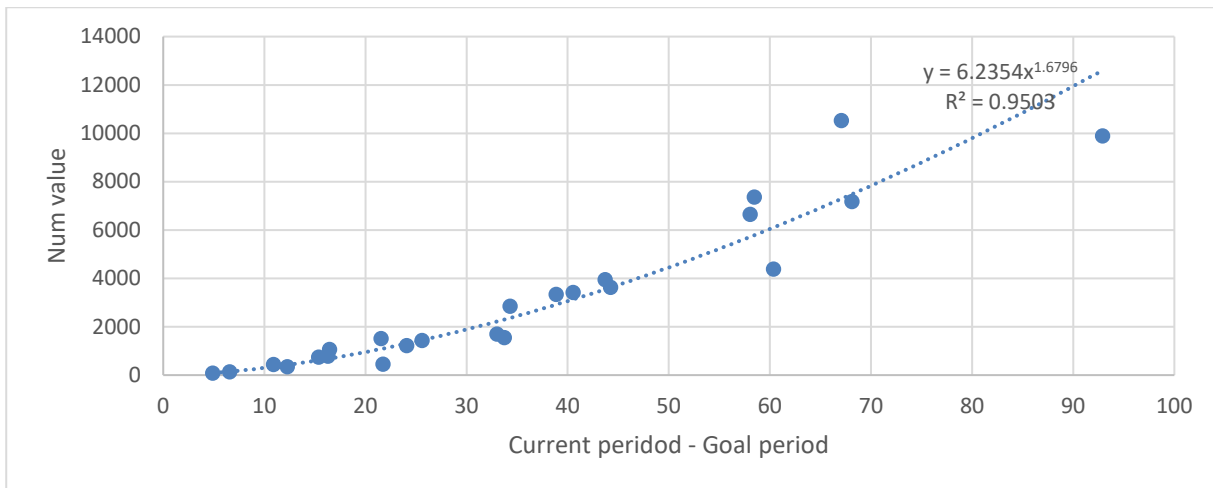
Figure 20: A series of real additions have been performed recording amount of material added and observed start/end periods. The *numerical values* calculated from this data and equation 5 are plotted vs the period difference and a new dependence is found.

By replacing the *numerical value* with the dependence to the period difference we obtained the final empirical function for bromate additions:

$$amount = \frac{6.2356(current\ period - goal\ period)^{1.67}}{current\ period^2 - goal\ period^2} \text{ (equation 6)}$$

3.5 Period synchronization

Figure 21: Scheme of the algorithms used to synchronize two BZ reactions. Both robots start their reactions and then enter a 4 minutes loop. The leader checks its period and broadcasts it, the Follower tries to match its period to the leader one.
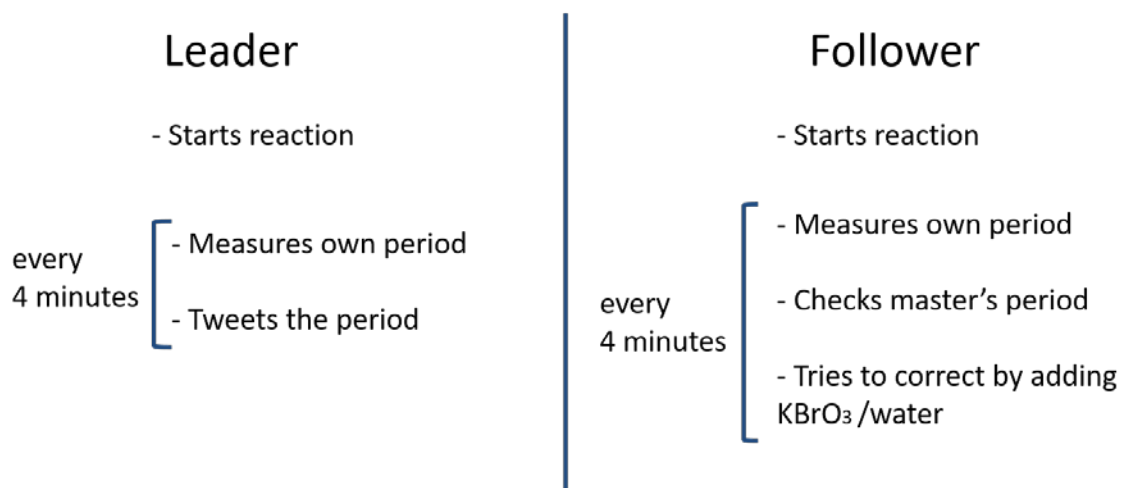
By using real time additions of water and potassium bromate two BZ reaction have been successfully synchronized in real time using Twitter according to the approach shown in Figure 21. In Figure 22 is it possible to observe the two boards starting with different oscillation periods: around 20 seconds the Leader (red line) and around 65 second the Follower (blue line). As soon as the reaction starts to oscillate the Leader board begins to extract its own oscillation period through the webcam and tweet it every 4 minutes.

After 40 minutes the Follower starts to monitor its own period in the same way and to check the Leader's period. By using the empirical functions, the algorithm makes an estimation of the amount of starting material to add in order to synchronize its period with the Leader's one. Within few iterations the two periods are synchronized with an uncertainty of 2 seconds. The period of both platforms are recorded for the next hour and half showing that the reactions keep oscillating at the same frequency.
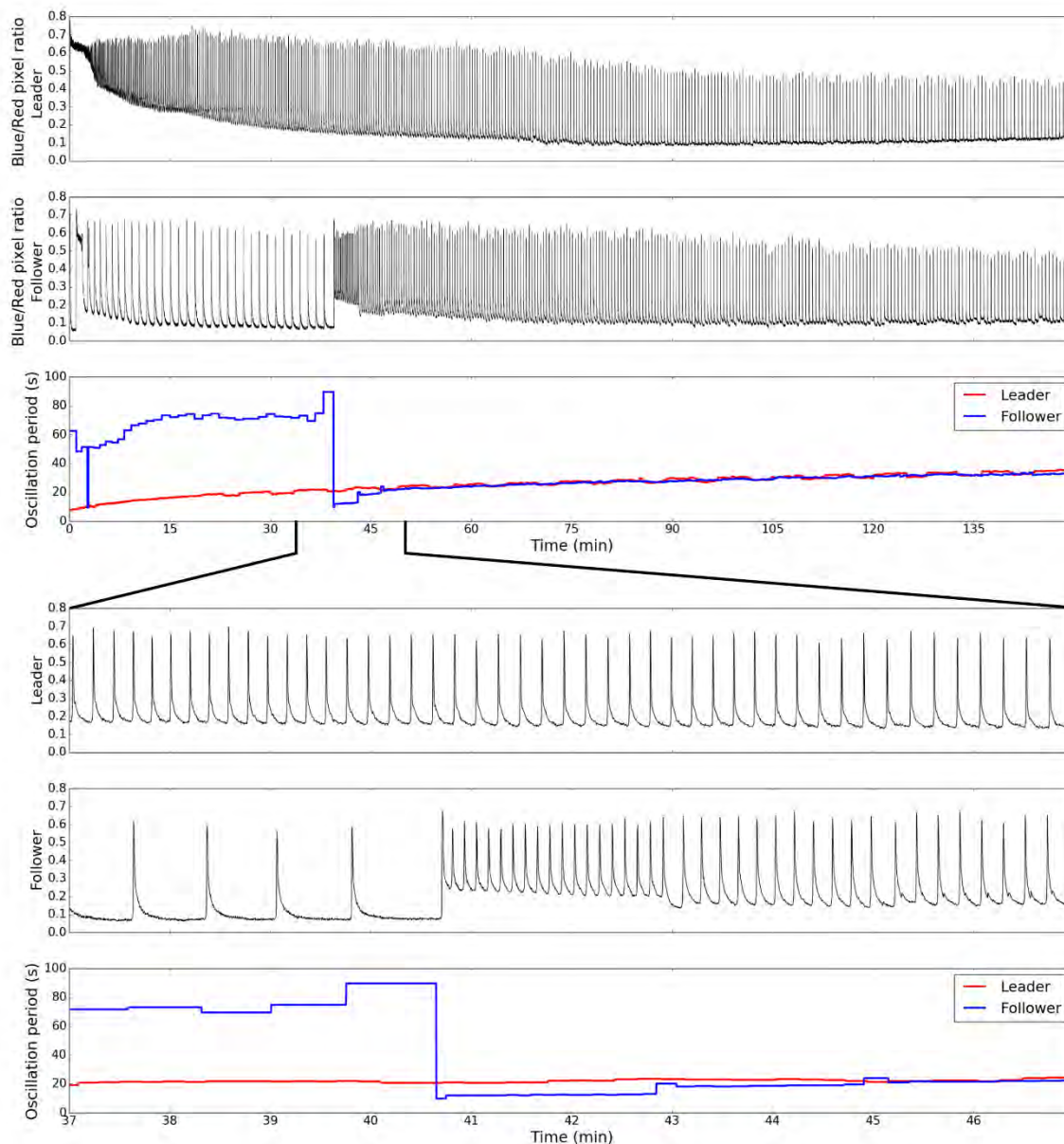
Figure 22: Oscillations of two parallel reactions. After 40 minutes the follower starts the synchronization procedure and manages to get to the same period of the leader with 3 additions.

3.6 Message encoding

The experiment starts with two separate systems oscillating with different periods. After 10 minutes the Follower synchronized its frequency with the Leader. When synchronization is achieved the Leader adds the material to change its frequency by a determined "difference", then sends the amount to the Follower. The Follower adds this amount and checks the new frequency. The new frequency should be the same for both systems and the difference obtained is the encoded message. It is important to highlight that the period difference is static value that contains the encoded message while the information shared between the robots (the amount of material to add) is variable and depends on the current oscillation period.

Procedure for message encoding

The message is split into individual characters and each is converted into a number using an optimized alphabet, from 0 to 63, see Figures 23 and 24. The number is converted into octal numerical system (base-8 numbers), the obtained octal is expressed using the degree of modulation of the reaction frequency. To represent an octal base there are 8 thresholds for oscillation period: 21, 15, 9, 3, -3, -9, -15, -21 seconds. A single experiment can hold 4 additions, each corresponding to one octal number, in a reliable way. This means that it is possible to send two characters for each BZ reaction before needing to clean the reaction vessel and start a new one. A program to perform a series of reactions and send a message of any length have been made.
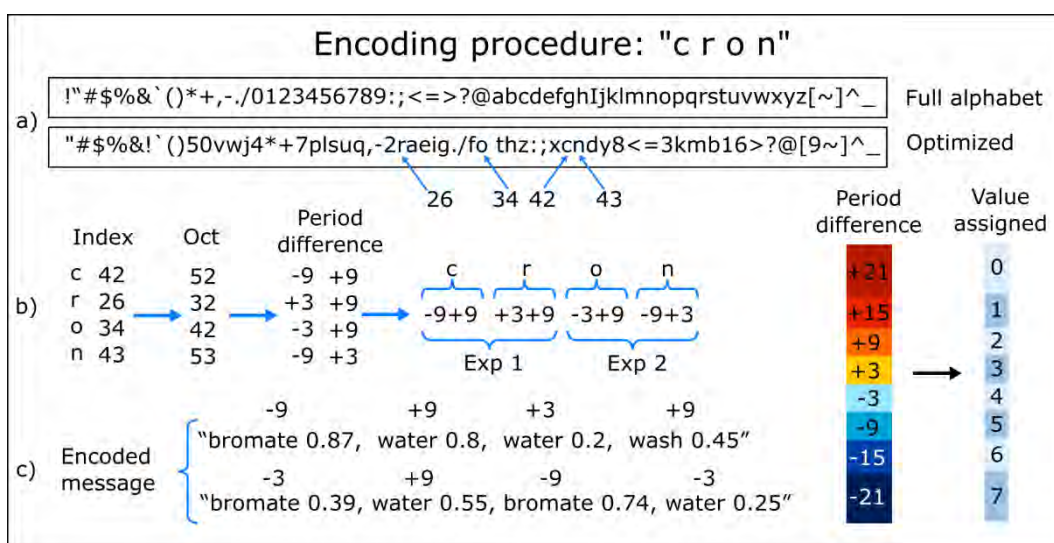
Figure 23: Encoding of the word "cron". **a)** Each character is converted into the relative number using the optimized alphabet. **b)** These Numbers are converted first into octal and then into a frequency change by using the threshold table. **c)** final encoded message, each character is represented by two reagent additions. The amounts are reported as an example since real amounts are dynamic and are calculated in real time by monitoring the oscillation frequency.

Figure 24: Real data for the message "cronin lab".

4. Part III – Inorganic

Several reaction series of varying W/Se:Mn ratios were preformed collaboratively by two platforms communicating in real-time over Twitter. Within each series 15 reactions of varying pH were used to determin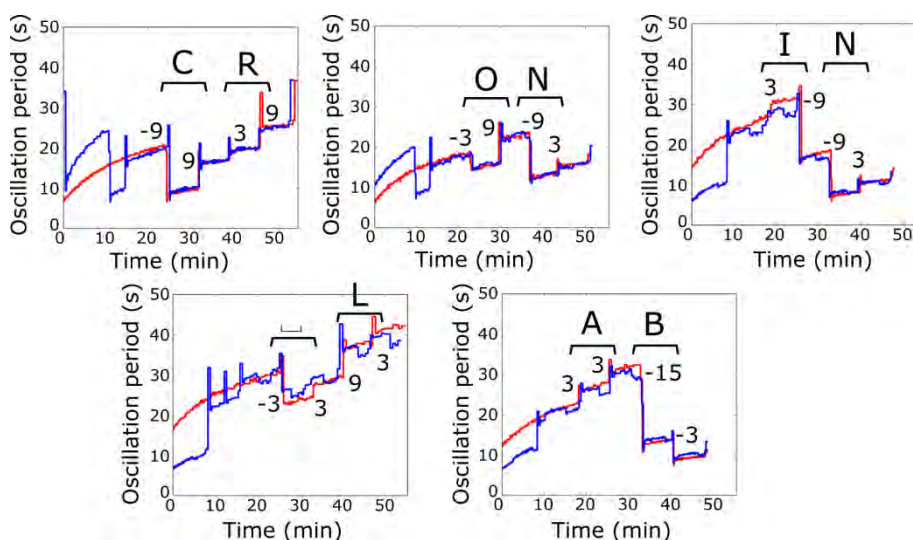e the ideal conditions for producing crystals within a 2-hour window and later to repeat these conditions to assess the reproducibility of the chemistry. Peristaltic pumps supply volumes of stock solutions to a reaction vial. Following 10 minutes of stirring at room temperature the reaction solutions are transferred to recording vials, suspended over a webcam, again using a peristaltic pump. Reactions are recorded and analysed in real-time for crystal formation and results are stored on a local network. Once complete both reaction and recording vials are extensively cleaned with an automated cycle for the process to begin again.

Image analysis techniques were developed to allow for full automation of reaction monitoring. A large database of images was gathered for both clear and crystalized reaction solutions in order to train a model used for crystal recognition in real-time via a HD webcam. A frame of the reaction solution is taken every 8 seconds and analysed for the presence of crystals using this model. Once a specific threshold of frames containing crystals has been met the program determines the reaction a success and updates the network. If no crystals have been observed after 2 hours the platform starts a cleaning cycle and continues with the remaining reactions. Further image processing of the early reaction solutions using colour analysis (Hue) is deployed to identify precipitated reactions. Precipitation of this reaction occurs most often within the first few minutes of the reaction recording. After 5 minutes of reaction recording a frame is analysed using this method. A mask is applied to isolate the reaction solution, a colour conversion from RBG to HSV (Hue, Saturation, Value) is applied and largest representative Hue value is returned. A Hue value above 160 in all cases seen have been precipitates. This method is highly reliable and saves a great deal of time running the platform long term. Simple python commands are used to perform and report on the reactions to a network.

4.1 Synthesis

Stock solutions used:
- Na$_2$WO$_4$.2H$_2$O (75g), Na$_2$SeO$_3$ (6g), DMA.HCl (30g) in 450 mL
- MnCl$_2$.4H$_2$O (9.36g) in 450 mL
- 2.32M HCl (57.1 mL conc made to 300 mL)

The polyoxometallate chosen for this study was previously reported within our group and can be seen below in Fig. 1. Formula: $[W_{19}M_2O_{61}Cl(SeO_3)_2(H_2O)_2]^{9-}$.

4.2 Stage one- Collaboratively explore a chemical space

At each stage of synthesis and analysis both platforms update shared network files for the other to read and proceed accordingly. For example, when one platform selects a reaction volume at random to explore, the other will acknowledge it and remove it from its own series before continuing with its own choice. Conditions that have produced crystals are stored by both platforms for repetition later. The flow diagram in Figure 25 describes the collaborative process between two platforms, the leader and follower:
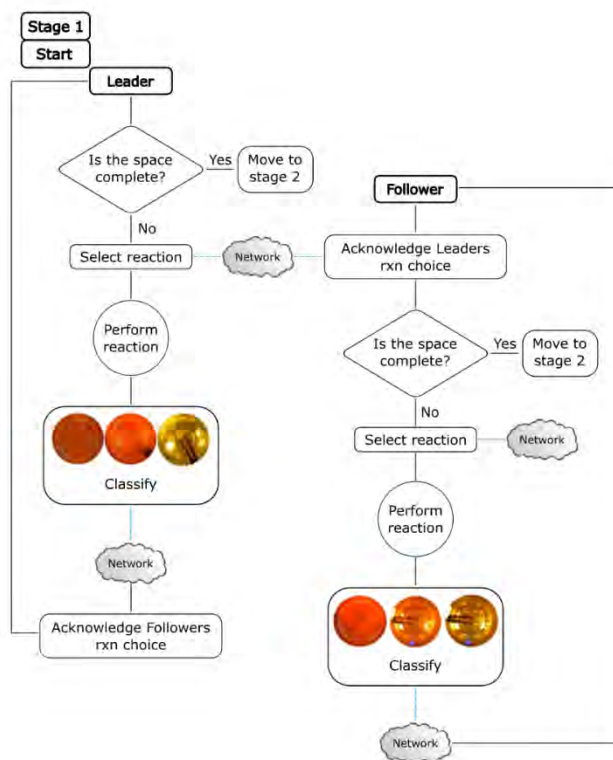

Figure 25: First stage of the algorithm for collaborative chemical space exploration. Different parameters are tested by two systems sharing the workload.

4.3 Stage two- Repetition of Successful conditions

The successful reactions conditions from the collaborative stage are compiled and repeated in order to establish the reporducibility of the chemistry/crystallization. One set of conditions is choosen and both platforms perform repeat reactions. Once enough data has been collected to establish an average percentage of reproducibility of obtaining crystals is complete and the next set of reaction conditions are begun, see Figures 26 and 27.

Seen below is the outline of stage 2, Assessment of the reproducibilty of crystal producing reaction conditions.
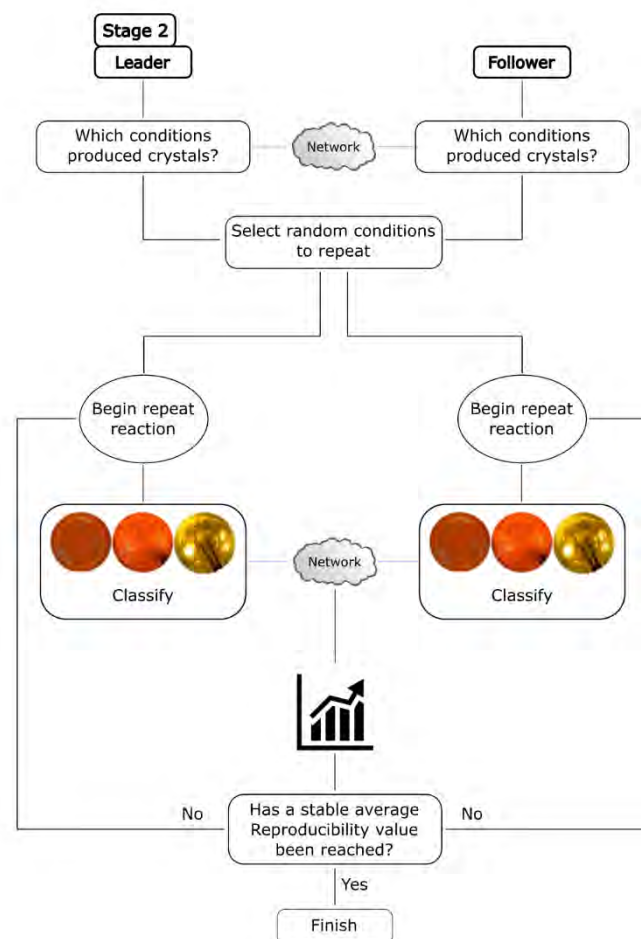
Figure 26: Stage 2, the crystal yielding reactions are repeated to assess their reproducibility.

Below is included a timeline diagram of a single example of one such reaction cycle using a 1:6 W:Mn ratio. Constant communication between platforms + image recognition of precipitated reactions allowed for completion time of 20 hours 57 minutes.
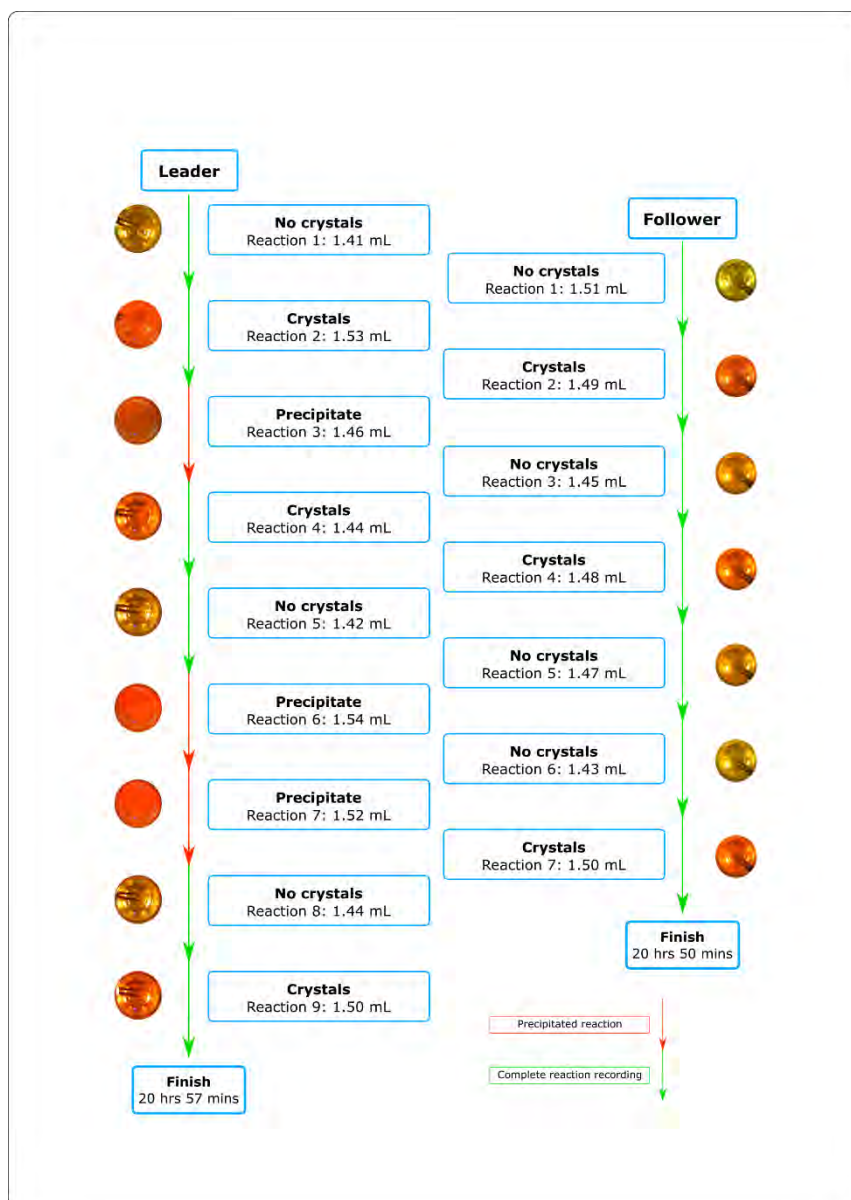
Figure 27: Timeline of workload sharing between two platforms.

4.4 Reproducibility of crystallization

The stochastic nature of synthesis and crystallization in inorganic chemistry is a significant contributing factor to the growing crisis of reproducibility. The crystallizing conditions found during the collaborative chemical space search were repeated on both platforms as many times as were needed to quantify the percentage of reproducibility of these two processes. For the example shown above two of the five crystallizing conditions using 1.43 and 1.53 mL of acid never again produced crystals during repeat experiments. However acid volumes 1.48, 1.49 and 1.50 mL revealed reproducibility of between 37.5-50%.

Shown below are accumulating averages of all three volumes, each requiring over 25 repeat experiments to produce consistent results.

4.5 Grid search of reaction conditions

8 reaction series each with varying Mn:W ratio were performed collaboratively by the two platforms by the methods detailed above (see table 4.1). Each reaction series varied in acid volume from 1.4-1.54mL HCl (approximately between pH 3-6.5) and each reaction was monitored by web cam for crystal formation within 2 hours of reaction completion. The full grid was repeated 3 times to more thoroughly explore the space. The results of each grid can be seen in below as 2D colour maps, see Figure 28.

Ratio Mn:W	Acid Volume mL														
1:4	1.4	1.41	1.42	1.43	1.44	1.45	1.46	1.47	1.48	1.49	1.5	1.51	1.52	1.53	1.54
1:6	1.4	1.41	1.42	1.43	1.44	1.45	1.46	1.47	1.48	1.49	1.5	1.51	1.52	1.53	1.54
1:8	1.4	1.41	1.42	1.43	1.44	1.45	1.46	1.47	1.48	1.49	1.5	1.51	1.52	1.53	1.54
1:10	1.4	1.41	1.42	1.43	1.44	1.45	1.46	1.47	1.48	1.49	1.5	1.51	1.52	1.53	1.54
1:12	1.4	1.41	1.42	1.43	1.44	1.45	1.46	1.47	1.48	1.49	1.5	1.51	1.52	1.53	1.54
1:14	1.4	1.41	1.42	1.43	1.44	1.45	1.46	1.47	1.48	1.49	1.5	1.51	1.52	1.53	1.54
1:16	1.4	1.41	1.42	1.43	1.44	1.45	1.46	1.47	1.48	1.49	1.5	1.51	1.52	1.53	1.54
1:18	1.4	1.41	1.42	1.43	1.44	1.45	1.46	1.47	1.48	1.49	1.5	1.51	1.52	1.53	1.54

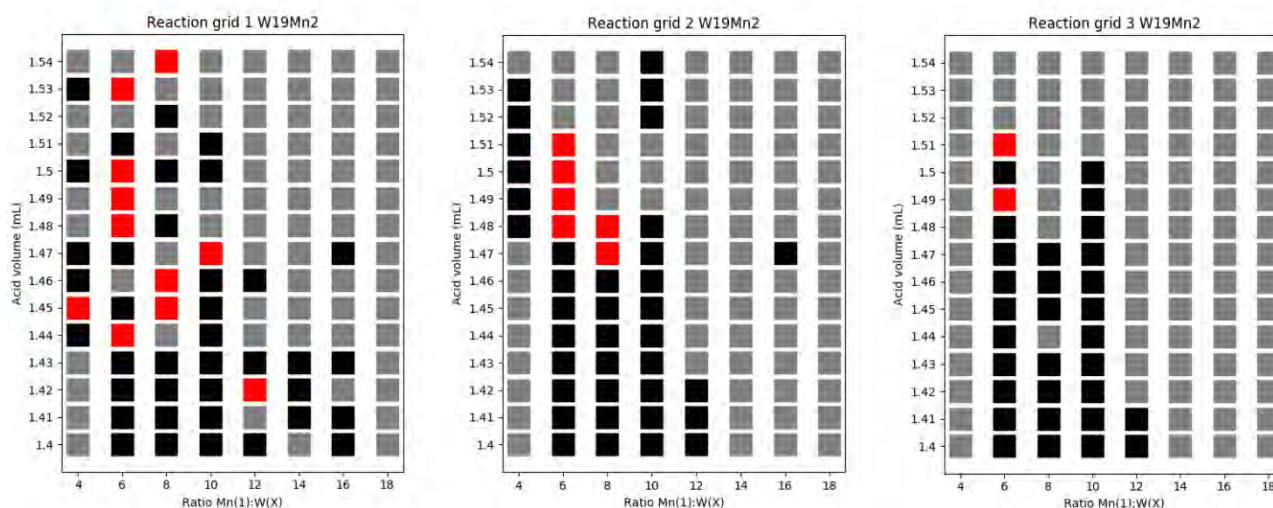**Table 4.1**: 120 Reaction grid of W:Mn to HCl

Figure 28: Results of 3 repetitions of the full grid. Red squares correspond to the production of crystals, grey to precipitate and black to a clear solution.

Each of the conditions marked in red produced crystals at least once during these automated runs, all were repeated to assess the likelihood of growing crystals again. After 15 repeat reactions if no

crystals had been produced the reaction was abandoned and the next set of conditions were started. A significant number of these crystalizing conditions never again produced crystals. Others varied from 10-50% in frequency of crystal formation across up to 48 reactions (See table 4.2). Shown below is a 3D representation of the likelihood of crystal formation for all conditions of the chemical space and the top 6 conditions for crystal formation without 2 hours, see Figure 29.
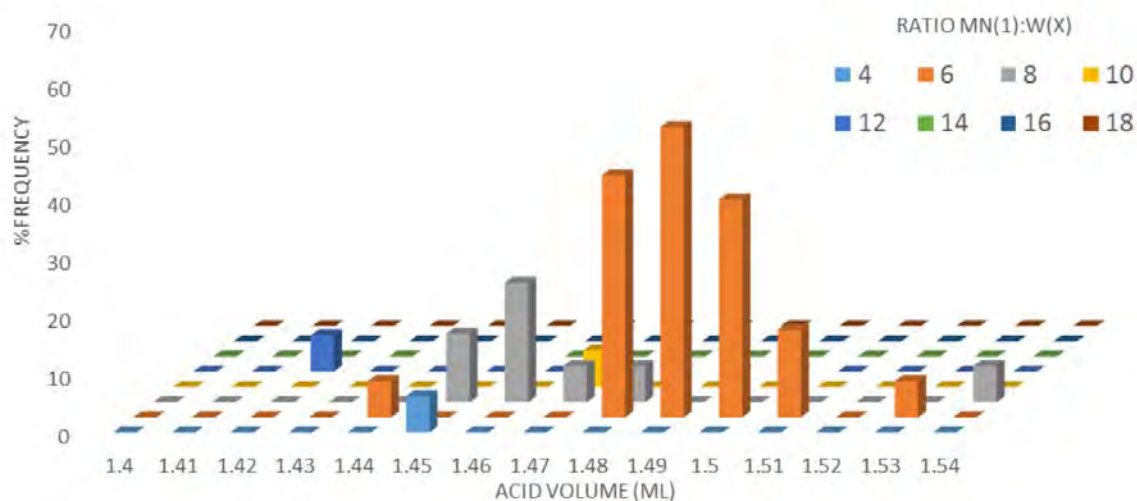

Figure 29: Further investigation of the crystal yielding reactions. They are repeated multiple times to assess the frequency of crystal formation.

Ratio Mn:W	Total volume mL	Acid volume mL	Reproducibility %
1:6	10.38	1.49	50
1:6	10.37	1.48	41.7
1:6	10.39	1.5	37.5
1:8	9.35	1.46	20.6
1:6	10.4	1.51	15
1:8	9.34	1.45	11.8

Table 4.2: Reaction conditions that produced the best reproducibility of successful crystal formation within 2 hours in descending order

5. Agent based simulation

To demonstrate the importance of information sharing between chemical robots we first developed computer simulations of the relevant strategies, see Figure 1. Each simulated chemical robot performs

experiments randomly until the target experiment is conducted. The simulations are performed over three different approaches. The random strategy is the most basic, where the robots have no memory of the reactions they have conducted previously. As an example, if we take a space the size of 10 locations, the robot might randomly decide to look at location number 7 first, if the goal isn't there than it will choose another location to search. When making the decision this second time the robot does not remember that it had tried location 7 already without success and so is as likely to pick that location again as any other. The second strategy is called the individual strategy. In this case the robots remember their past. Thus for the example case above after trying location 7 the robot would not check it again. However, using this strategy one robot still acts independently as there is no information sharing between the robots. The final strategy is collaborative. Each of the robots knows its own and all the actions of all other robots. It is this pooling of information that makes the collaborative strategy the most favourable. Figure 30 shows the search efficiency as the average total number of searches that are performed before the goal was reached. For all cases the average number of experiments that need to be performed is the highest for the random strategy, better for the individual strategy and lowest for the collaborative. In the case of a single robot the collaborative strategy reduces to the individual. From that point as the number of robots increases the advantage of the collaborative strategy becomes more pronounced as the individual strategy becomes less advantageous. The individual strategy is useful with a small number of robots but has diminishing returns with increasing numbers of agents. An increase of one robot from one to two yields a 50% improvement while an increase from two robots to three yields a lower improvement of 33.3% and so on. The simulations show that the collaboration strategy is by far the most efficient and that as the number of available robots increases the benefit of using collaboration increases as well. Figure 1b shows that for all strategies, the total number of searches that had to be conducted decreases. With the y axis logarithmic, the constant slopes show that the improvement in searching is exponential. The individual strategy will always be better than the random one, no matter the number of agents, yet by a narrowing margin. As expected all strategies improve with an increase in the number of robots yet the collaborative strategy is superior to both the random and individual strategy under any conditions.
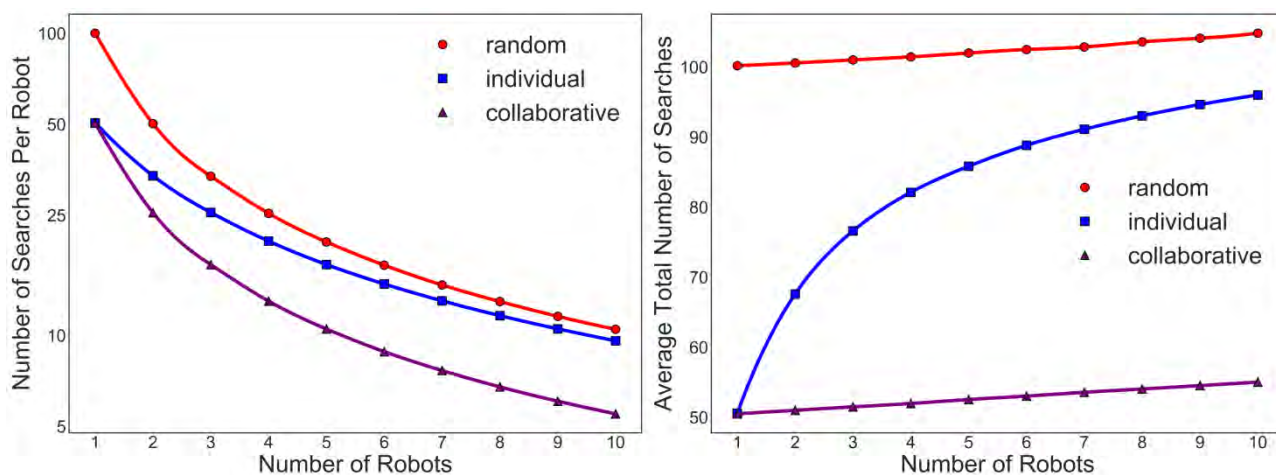
Figure 30: Agent based simulations. On the left the number of searches for the three different strategies as a function of the number of agents conducting the search. The y axis is logarithmic. On the right the average number of searches that need to be perform in total for three different strategies with increasing numbers of agents.

6. Game

6.1 General Overview

Two automated platforms were tasked with playing a game of Hex. New/rare reaction results allowed the player to use the optimum movement (determined algorithmically described later) with uncommon/common results allowing only for sub-optimal/random movements. Losing games trigger a change in strategy for the losing platform, in this case an expansion of the reaction grid the player was allowed to explore. The idea being to show that a game outcome could drive a player to either change or maintain its current strategy in the hope of making more chemical discoveries in future. The chemistry chosen for this project was the same seen in the Organic section (page S8) and results were gathered and analyzed via web-cam.

6.2 Decision Making

The goal for players in a Hex game is to connect one side of the board with the opposite side using a continuous line of that player's color. The game cannot end in a draw. From a randomly assigned first board position or the current state of the board the optimal movement was calculated using Monte-Carlo simulations with the goal of completing the game. Once an optimal movement has been calculated, the results of the chemistry determine if the player may use it. Color rarity vs move selection allowance is determined by the following:

- Unique/Rare colors observed up to 4 times   Optimal movement
- Uncommon Colors observed between 5 and 7 times   Sub-optimal movement
- Common Colors observed more than 7 times   Random movement

Sub-optimal movements were defined as a position beside, above or below the optimal and was selected based on availability.

6.3 Communication Between Platforms

In order to keep both players in sync with one another, a remote server was developed to handle all communications between the platforms. Each platform selects a reaction and processes the information through image analysis and the decision-making algorithm as described previously. The selected move is then sent to the remote server from the platform for processing. All logic for the game, such as updating board movements, is handled by the server. Once an iteration of the game has been completed, the server broadcasts a message to all connected clients detailing who has won the game. The players then adjust their strategies accordingly.

The reasoning behind developing a remote server system for this task was a separation of concerns. By separating the game logic from the platforms, as opposed to each platform having its own representation of the game, we minimize the risk of each platform falling out of sync with one another leading to inaccurate results. We also prevent potential race conditions with platforms attempting to access a single file at the same time. A single server with file access eliminates this risk. The design of the server allows for multiple concurrent connections and data processing which opens the possibility of increasing the number networked platforms working towards a common goal.

6.4 Strategy

Both players begin the first game in the sequence by selecting reactions from an identical chemical space (Fig 31 center). Once the loser of the first game has been established, that player is allowed to access a new strategy/expanded grid (Fig 31 right) whilst the winner continues with the original. Each strategy/chemical space consists of 9 grids small grids of two aniline derivatives labelled A, B and C (Fig 31 left). The change of the reaction space from the original to the expanded is achieved by adding two extra values of reagent volume to each of these 9 smaller grids. The stock solutions and experimental protocol are identical to those described in the Organic section (page 8).
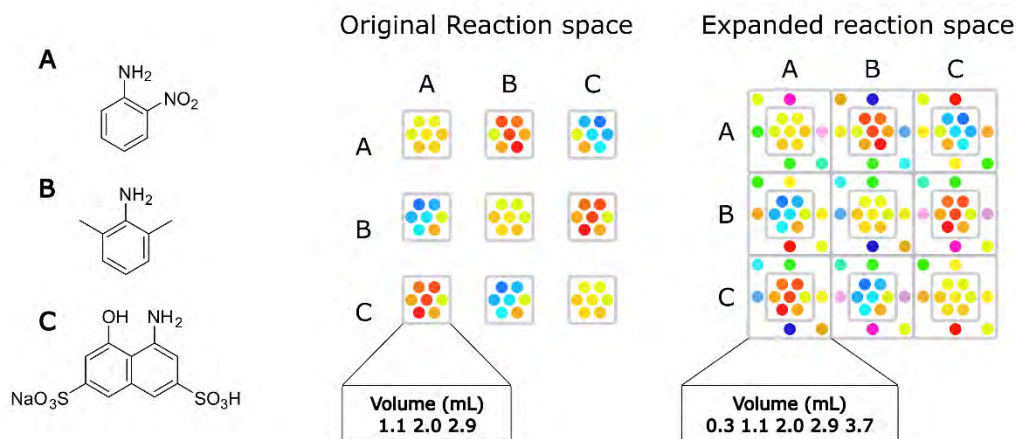
Figure 31: Aniline derivatives (left) A- o-nitro-aniline, B- 2-6-dimethyl-aniline, C- 4-amino-5-hydroxy-2, 7 napthalenedisulfonate hydrate. Shared original reaction space (Centre), Expanded reaction space (right).

Given that the game sequence proceeds one platform after another the original reaction space restricts the total reaction number to 81 for each player (9 grids of 3x3 reagent volumes). A typical game sequence can consist of between 2-5 completed games. Seen below in Figure 32 is a game sequence showing 4 complete games (5th game was incomplete) in which the losing strategy was adopted by player 2 after game 1. Against the logical expectation the losing strategy, whilst allowing player 2 to win game 2, did not result in many new unique discoveries. However, when player 1 adopted the losing strategy after game 2, its unique discovery count increased significantly, but did not result in a victory for the remained of the total game sequence. This can be explained simply by the fact a game is still based on probability and a new advantageous strategy will work most, but not all of the time.
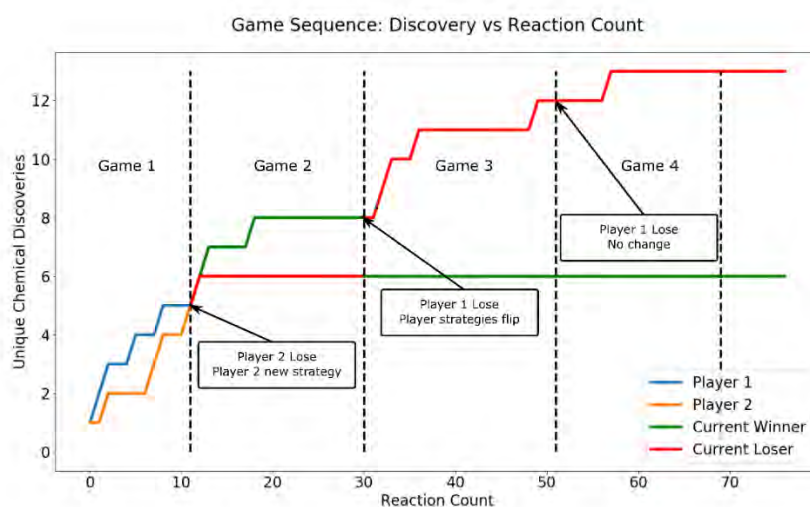

Figure 32: A 4 game sequence showing adoption of a new strategy allows, over time, for an increased number chemical discoveries.

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