Operating Instruction & Manual
Harmonia thermal control unit

Cronus-PCS

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Version 1.3

IMPORTANT

At any time:

- Harmonia MUST operate with heating elements of same voltage as the mains supply voltage. Do NOT mix 110 and 230 VAC!!!
- Harmonia MUST be connected to wall power INCLUDING perfect ground.
- Electrical-Heating-Blanket (EHB) MUST be mounted tight around a vessel INCLUDING the liquid to be heated – which at least cover the inner side of the vessel well above the EHB.
- Heating-Support-Foot (HSF) MUST have the OD 3 x 100 mm thermocouple installed in the HSF body hole.
- thermocouple MUST be mounted in the vessel INCLUDING the liquid in order to be submerged.
- Don’t mix up A and B channels thermocouple and heaters.
- Keep Harmonia out of contact with any liquid.
- Keep the HSF out of contact with any liquid.

Contents

1.0 - Concept overview

Harmonia is a **dual channel** electrical heating controller for temperature regulation for **endothermic** reactions primarily in cultivation of mammalian cell applications with from 0.5 to 50 litre VV / thermal mass. Harmonia can work in stand-alone setup or chained with other Cronus-PCS components. Harmonia offer unique Adaptive tuning for optimum PID algorithm.

Harmonia is designed and manufactured by www.cronus-pcs.com

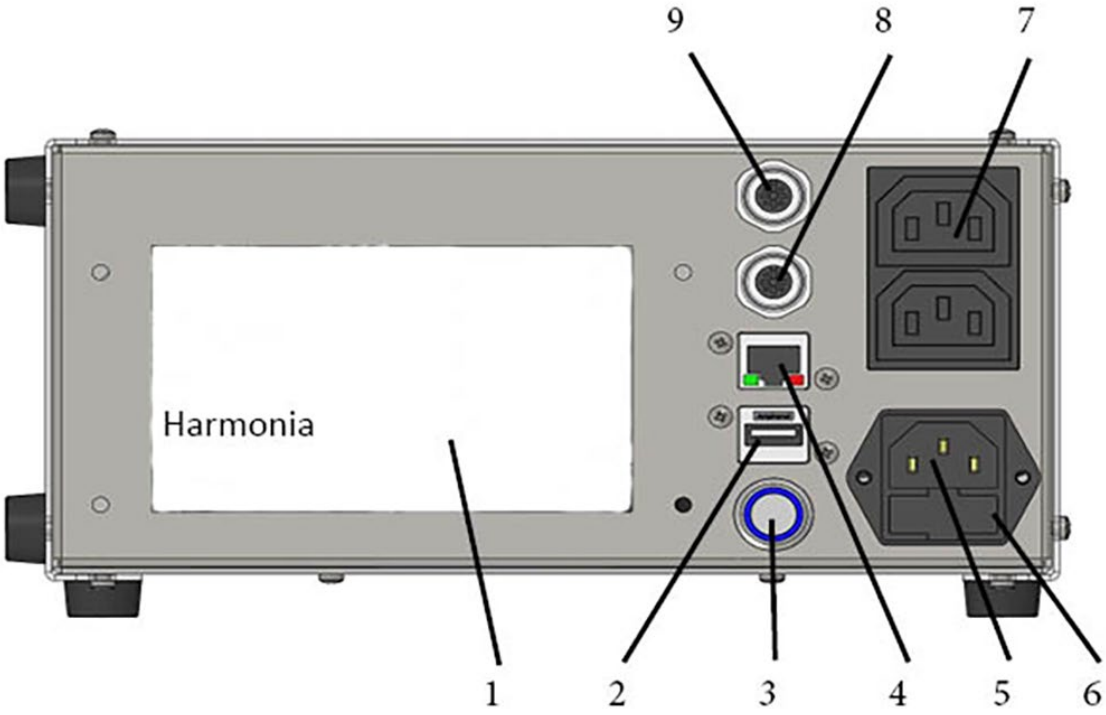
1.1 - Product purpose

The scope of the Harmonia product is:

- Thermal control of two Single-Use-Bioreactors (SUB) in parallel.
- The PID control receives the actual process temperature from a thermo couple mounted inside (the non-invasive thermo well) each of the two targets.
- The temperature is regulated by adjusting the electrical energy being added from exposing the heating supply to electrical power converted to heat.

2.0 - Device Overview

Harmonia is a product from www.Cronus-PCS.com housed in a Hephaestus U2 cabinet.



The front panel is equipped with:

1. TFT 5” colour display
2. USB socket for Wi-Fi access or USB memory for datalogging files
3. Button main power breaker
4. RJ45 socket for Local-Are-Network (LAN) connection

5. Single VAC power inlet, IEC standard male with ground, max 10 amp
6. Fuse tray, 10 amp, 5x20 mm
7. Dual VAC controlled power outlet, IEC female socket with ground, Channel A and Channel B
8. Pt100 / Pt1000 sensor input via 4 leg M12 RKF socket – channel B
9. Pt100 / Pt1000 sensor input via 4 leg M12 RKF socket – channel A

2.1 – Harmonia internal design

Important components inside Harmonia are:

- Micro-processor transmitter converting the Pt100 / Pt1000 sensor span of ÷20 - +150°C to a linear signal (class C sensor is sufficient).
- Each channel facilitating 110 - 230 VAC supply span with a Crydom 12 amp Solid-State-Relay (SSD) breaker generating very little self-heating offering unlimited lifetime.

2.2 – Requirement

The unit must be properly installed according to the liquid diagram.

2.3 Specification

When connection to a suitable supply of power the spec is:

External sensor	Dual Pt100 or Pt1000
Power breaker	SSR 10 amp each channel
GUI	5” TFT display
Computer power	900 MHz quad-core ARM Cortex-A7 CPU running Linux with Code-Sys PLC software
USB socket	for Wi-Fi and data download
RJ45socket	for IP/TCP via LAN - ModBus and OPS
Power supply	230 VAC, max 2,000 watt
Noise level, dBa	<45
Duty cycle	100%
Orientation	any
Operating conditions	10°C to 50°C, <80% relative humidity, non condensing
Lifetime, estimated, hours	>50,000
MTBM (mean time before maintenance)	10,000
Cabinet size and material	U2 – AISI304
Weight, kilo	3.5

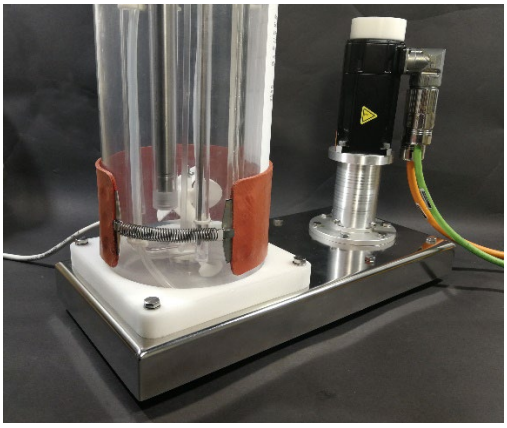
3. Heating design

Harmonia facilitate and depend on heating elements kept in good maintenance standard.

3.1 Electrical-Heating-Blanket and handling

Construction of flexible heating element - made up of a nickel-chrome or nickel-copper alloy heating wire wound in a spiral around a slender fibre glass core. This heating element is then placed between two layers of woven fibre glass impregnated with silicon elastomer. This

material is an excellent electrical insulator (approx. 12 kV/mm), a good conductor of heat ($7x10^{-4}$ W/cm/K) and flexible. It can withstand continuous temperatures of around 200°C. The fibre glass weave endows the assembly with good mechanical resistance, while allowing it to remain very flexible.



Heating blankets for dimension illustration on left, small one mounted on 3.2L vessel right.

Important procedure to follow before Power-On:

1. Finished filling the SUB with media, mounted on the MST or with HPD drive, all the hoses, etc.
2. Mount the heating blanket to the SUB and do **NOT** connect the plug to Harmonia IEC female socket.
3. Mount Pt100 sensor via appropriate cables to Harmonia - without the use of tools!
4. Mount Pt100 sensor by insertion inside **the media filled** SUB, SUF, SUM
5. Connection heating blanket plug to Harmonia socket

General precautions:

- Heating blanket should be mounted tight with full contact to the SUB circumference
- Thermocouple, Pt100 sensor mounted in the well with some ml glycerine oil for better thermal contact and connected to M12-RKF socket.
- Media has been added to a sufficient height / volume covering **ALL of** the heating blanket.
- Agitation has started.

Blankets and info available from https://cronus-pcs.com/products/accessories/heating-blankets/

During operation check daily that the heating blanket is mounted properly and dry.

Whenever there is contact with splashing water or media, interrupt heating operations, remove the heating blanket from the culture vessel, clean and dry it thoroughly.

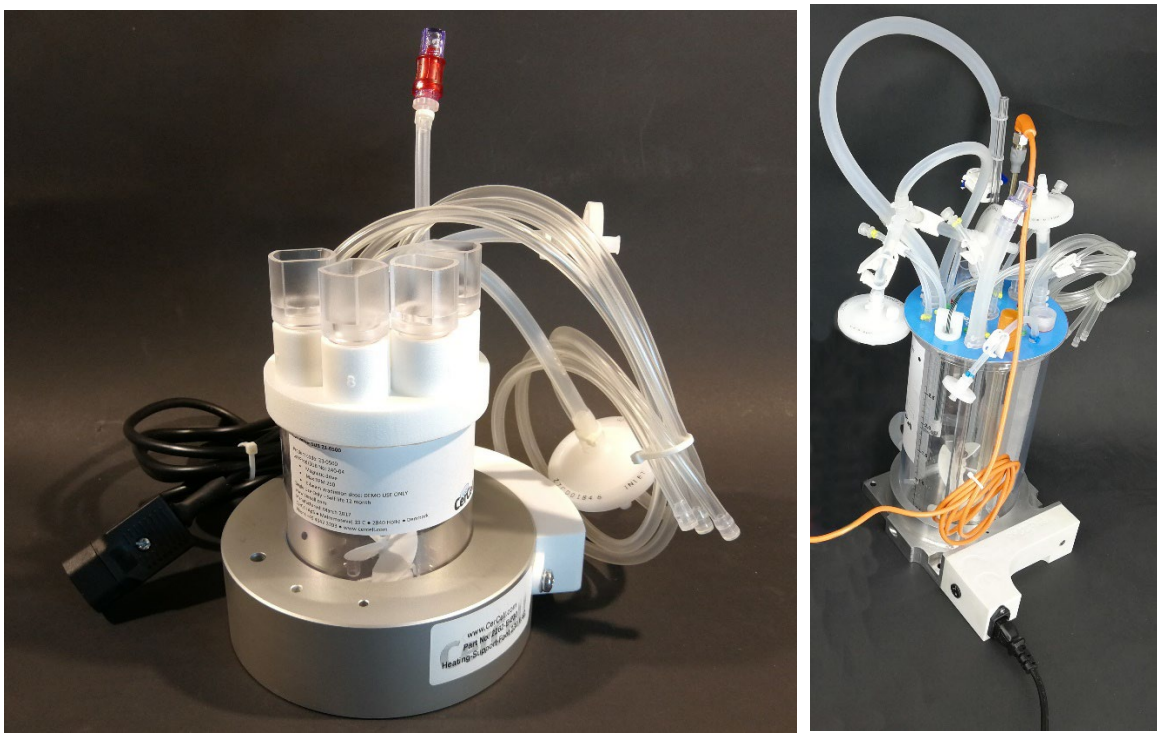
3.2 Heating-Support-Foot and handling

The Heating-Support-Foot (HSF) is an aluminum construction allowing the Magnetic-Stirrer-Table (MST) to insure very stable support, superior agitation and thermal control, and ease

of use. The MST isolates and protects the light weight 500 ml and 3,200 ml (SUB, SUF, SUM) from the often large and heavy servo motor.

The HSF integrates dual heating elements allowing user to select either 110-120 VAC or 220-230 VAC supply by rotating a switch. Response time for electrical heating is a 20 degrees Celsius lift in around 30 minutes. So, if you start at 18°C it takes 30 - 40 minutes to reach 37°C including 1 liter media.

Be sure the voltage selection for the 3,200 / large HSF is the same as the supply voltage!!!! Check black rotating selected on the white body.



Small HSF for 500 ml SUB at left and the large 3,200 ml HSF at right. Note holes for thermocouple.

3.3 Description of functionality

When the process requires energy input (for cultivation) to increase or keep SUB, SUF, SUM temperature stable the SSD opens sequentially for the electrical heating elements.

- Precision when correctly tuned PID is better than 0.1°C
- The program is based on self-tuning functionality which learn and improves accuracy over time.
- Thermal correction is based on Proportional, Integral, and Derivative control loop.

4. Start-up

The scope of the product is to thermally control two bioreactors.

Requirement

The system must be properly installed and connected in accordance with the specifications and previous information. Operator must also have gained familiarity with the Safety Instructions to be found separately on www.cronus-pcs.com/support/Safety_Instruction .

Make in particular sure that the 110 or 230 VAC wall plugs have a ground connection fully functional.

Harmonia is factory pre-programmed to operate at 37.5 °C and will seek to obtain this temperature whenever powered up. Changing the set point required simple programming of the unit.

4.1 Quick instruction

It takes approximately 1 min after power-on before the regulator is up running.

Sound bibs heard repeatably indicates that the internal battery isn't fully charged, after a while it will stop automatically.

Harmonia can operate in three modes manual PID mode or Adaptive. In PID mode the user manual specifies the PID constant and the offset. In Adaptive mode the user shall just specify the set point and press start, but it requires that the temperature in the reactor is lower than 4.5°C from the setpoint to begin with. The last mode is also adaptive but for a small reactor of 250-500ml.

For PID mode the regulator is controlled by three constants **P, I, D** seen by pressing PID on the touch screen.

If e(t) is the difference between the set point and the measured temperature the **duty_cycle** is determined by this formula:

$$\text{duty\_cycle} = P\left(e(t) + \frac{1}{I}\int e(t) + D\frac{de(t)}{dt}\right)$$

I and D are specified in seconds.

Every time a dialog window is closed for one of the constant or for the set point the Integral is reset. But an offset can be specified so the regulator does not have to build up the integral part again.

In adaptive mode when the reactor temperature is lower than 4.5 °C from the setpoint the regulator will first try to determine the room temperature roughly. It will take 3 minutes.

Next it will heat up the reactor with a duty cycle of 100% until the reactor's temperature has increased with 3 degrees.

Next it will wait until the temperature drops which can take some time if MST is used.

Based on the observations above the regulator will heat up the reactor with 100% duty cycle to a safe temperature where a PID will take over. When the calculation has taken place, the new constants can be seen pressing ADA.

The constants for this PID regulator are determined and calculated by the above observations. The constants cannot manually be changed.

For MST two HSF can be used, a small one for up to 500 ml a bigger one for up to 3.2 liter. It takes longer time for the 3200 HSF to reach the set point (hours) which is the reason why **I** is very big in order to make the integral part small. But if **I** is to big the **duty-cycle** will not

be big enough when the temperature closes in on the set point. The result can be that the temperature suddenly drops for a while until the Integral part takes over.

If the temperature is closer to the setpoint or above, the regulator will enable a PID regulator with the last used PID constants. **Therefor the regulator might not work properly if the reactor is preheated in ADA mode.** The last used constants can be seen by pressing ADA

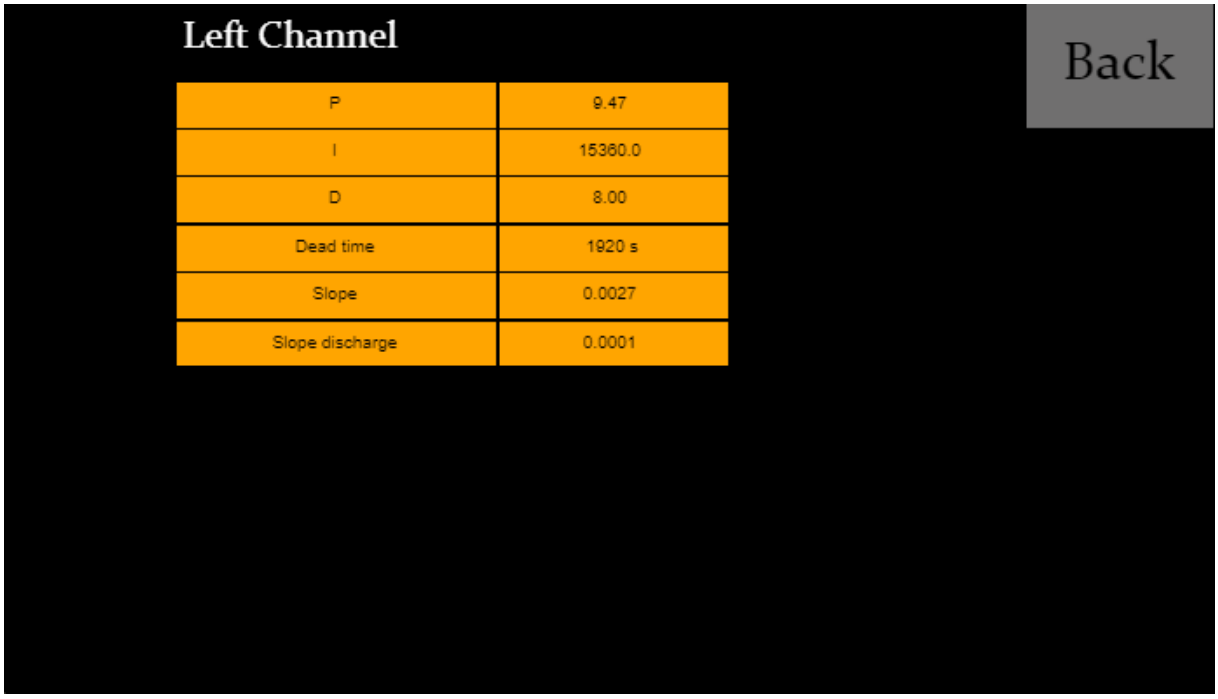


Figure 1 Constants to be used in adaptive mode for left channel.

To help the user for PID mode (not adaptive mode) some predefined settings have been made. Can be seen and selected by pressing SET. These predefined constants have been found through experiments with 37ºC as set point:

- 500 ml Vessel Volume (VV) tested with 200 ml Working Volume (WV) arranged in Heating-Support-Foot (HSF) on Magnetic-Stirrer-Table (MST)
- 3,200 ml Vessel Volume (VV) tested with 2,000 ml Working Volume (WV) arranged in Heating-Support-Foot (HSF) on Magnetic-Stirrer-Table (MST)
- 30 L (VV) arranged with Electrical-Heating-Blanket blanket

The constant can be modified and saved for future use. The constants can be seen on Figure 2 Stored values for PID mode

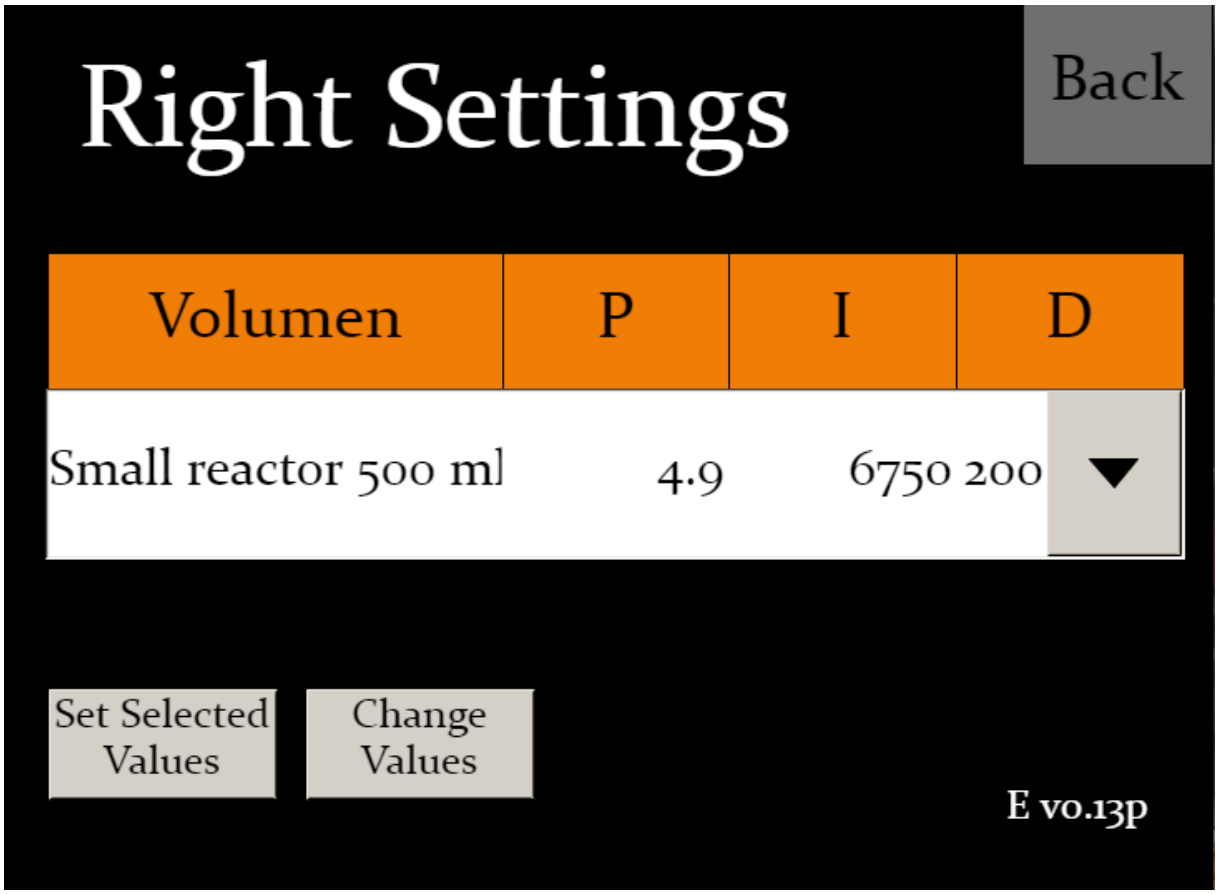


Figure 2 Stored values for PID mode

During turn off or power loss the controller will not immediately turn off it will take 16-60s depending on the model. That gives the user the option to restore power without the PID regulator losing its integral state.

4.2 – Harmonia GUI instructions

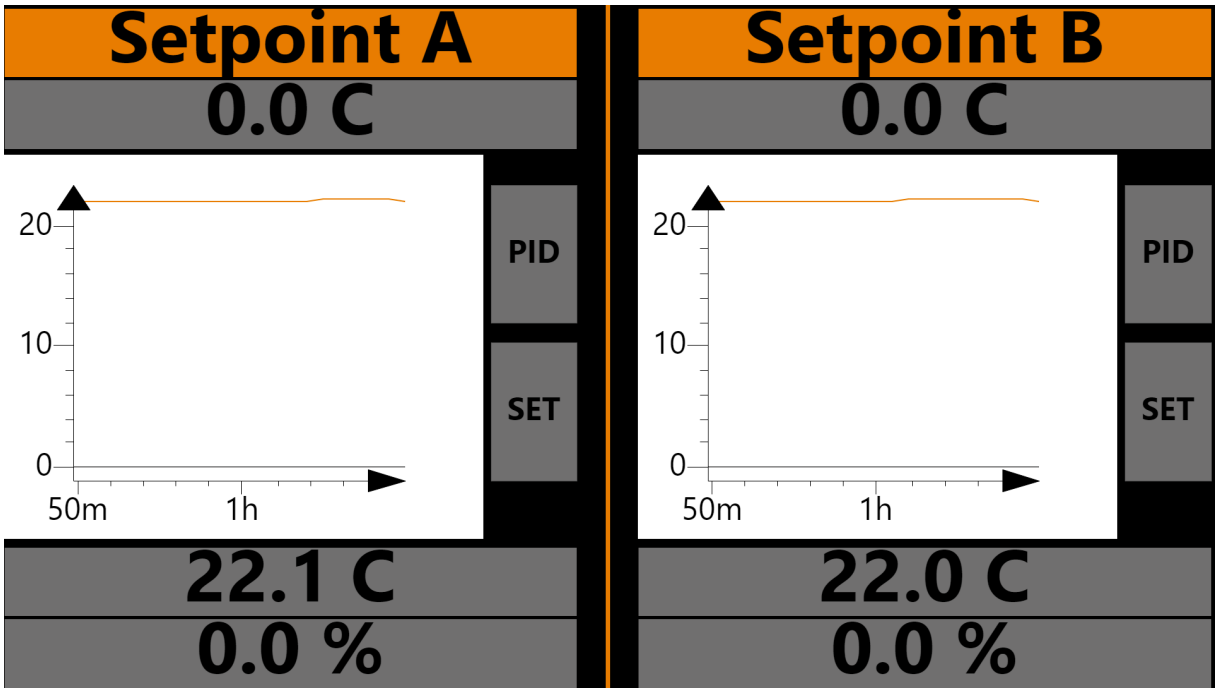
4.2.1 – Harmonia Cable setup

The first thing you must insure before operating the Harmonia unit is that the setup is correct. All the cables are connected to the right places, have a look on the following pictures to get an idea of how it could look like.

How to correctly connect the cables and sensors into Harmonia.

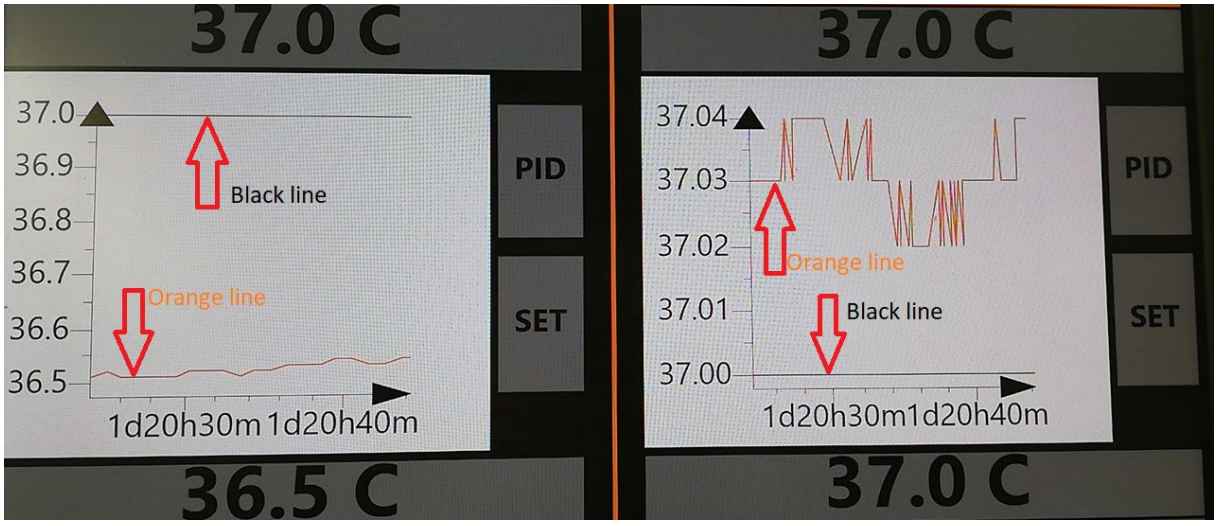
4.2.2 – Harmonia Main GUI

The Harmonia Main GUI is a split screen A (left) and B (Right).



Harmonia Main GUI show on top the two set point value temperatures.

On the picture below you can see, the dynamic temperature diagram where the orange line is the actual temperature and the black line is the setpoint it wants to reach. Left side on its way to 37.0 C and right side being 0.04 C from the setpoint.



Illustrated how a run could look like with the dynamic's diagrams.

The bottom of the Harmonia Main GUI shows the measured values in Celsius and the duty cycle in % of power applied.

Channel A and B with actual temperatures and duty cycles.

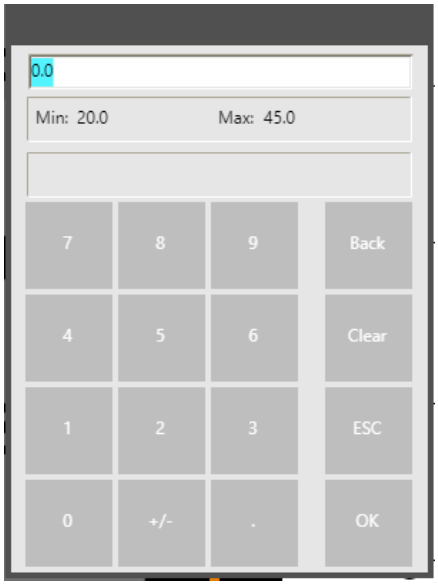
On Harmonia Main GUI there you have 3 options:

1 select – change the setpoint

Change the setpoint to what you wish the temperature of your liquid should be by pressing the grey area under setpoint where the wished temperature will be shown:

Set point button.

Then a numpad will pop-up:



Numpad to set desired values.

The numpad will show minimum and maximum value. You must be in the shown range to set a new value. The **Back** button will erase one character, the **Clear** button will clear all the characters, the **ESC** (Escape) button will close the

numpad without any changes. The **OK** button will set the new values and close the numpad if the new values is between the minimum and maximum.

2 select – go to PID manual set value by pressing the PID button

PID button.

Any of the 3 PID parameters are fully accessible and free to program typically according to requirement of the thermal mass of your system (PID = Proportional, Integral and Derivative influence).
But only set the PID parameters yourself if you have knowledge about it.

3 select – go to SET where you can select preinstalled PID or Adaptive PID values by pressing the SET button.

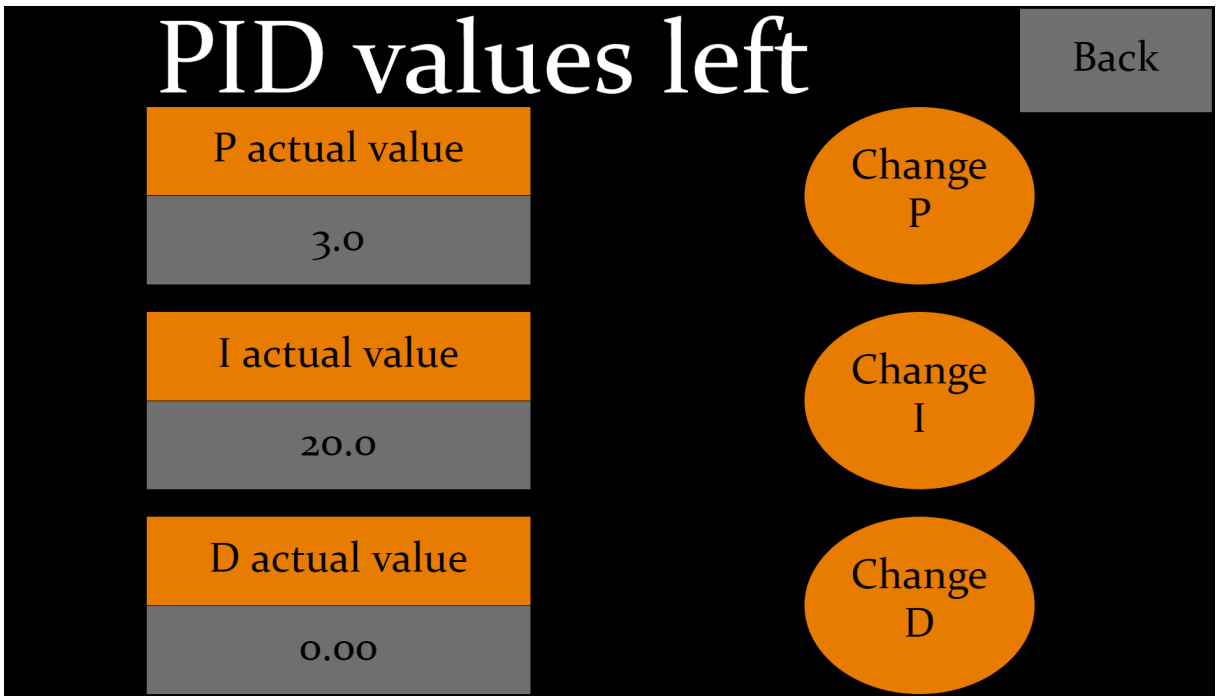
SET button.

4 Select – to start/stop the process you need to press on Setpoint A or Setpoint B and it will turn green when on and orange when off.

4.2.3 – Harmonia PID GUI, left and right

The P, I and D control values to the heating elements can be controlled manually, by going to the Harmonia PID GUI. It requires some knowledge about PID control to reach any benefits doing that.

You can set the PID values can be manual selected for both channel A / left and channel B / right.



Harmonia PID GUI can be both left and right.

1 – To change a value fx P, go press the Change P button:

Change value button.

A numpad will show and then you can change the value.

2 – After you have changed the values you want press the Back button to go back to Harmonia Main GUI.

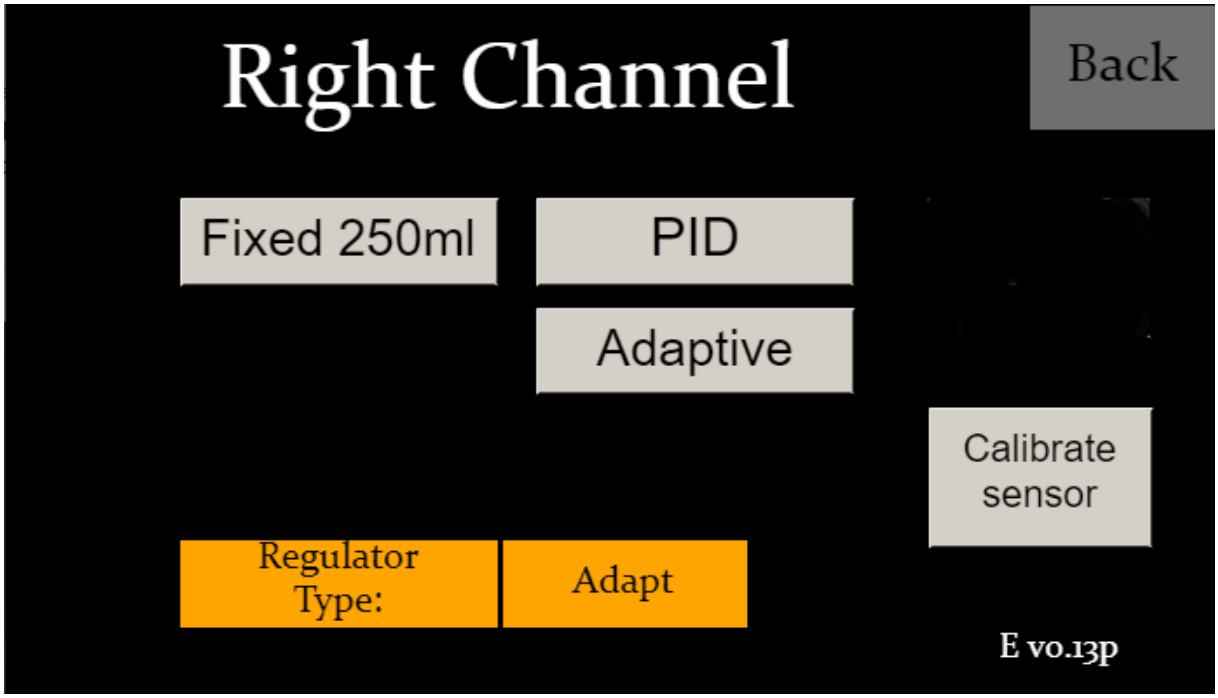
4.2.4 – Harmonia SET GUI, left and right

The SET GUI you can do 3 things beside calibrating the sensor.

1: The first opportunities are what we recommend to use is to press Adaptive so the regulator type shows Adapt, then Harmonia will automatically find the best PID values for your vessel taking some values in consideration as e.g., room temperature, it will after you press start take some minutes for Harmonia to make these calculations but will result in the most precisely result.

2: The second option we only recommend using if you use a 250 ml vessel, because Harmonia have some trouble calculate any values for that small amount of liquid and vessel, then we recommend using the preinstalled PID values by pressing Fixed 250ml.

3: Pres PID to go to SET, PID GUI and you can choose 3 preinstalled PID values for 500 ml, 3.2 L and 30 L but we still recommend using Adaptive on these sizes of vessels.

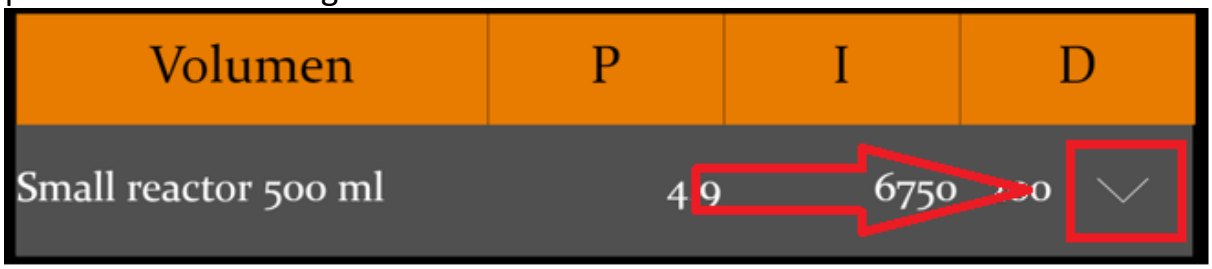


4.2.5 – Harmonia SET, PID GUI, left and right

The SET GUI lets you pick pre-set of PID values these values are not ideal but estimated from a worst-case scenario with an offset value of 0 % where the temperature is low compared to the set point. In a real scenario you would heat up the reactor with 100% (Set offset to 100%) until you are 1°C from the set point and then stop. Then ender some more ideal PID constant and an reasonable offset and then start again. The predefined values can be seen in Figure 2 Stored values for PID mode

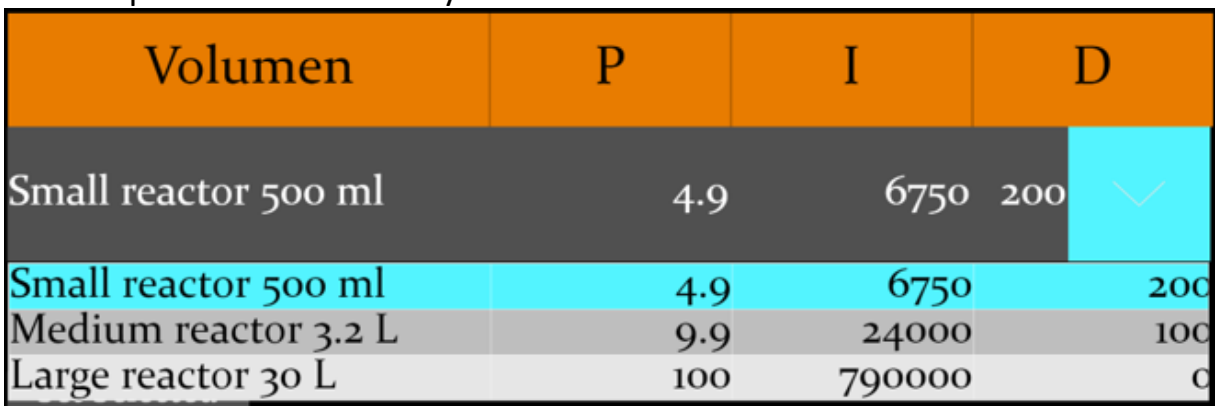
Harmonia SET, PID GUI can be both left and right.

1 – to pick one of the recommended pre-set PID constellation you need to press the arrow on right side:



Selection bar to determined PID values according to vessel size.

2 – And press the vessel size you use:



Selection bar to determined PID values according to vessel size.

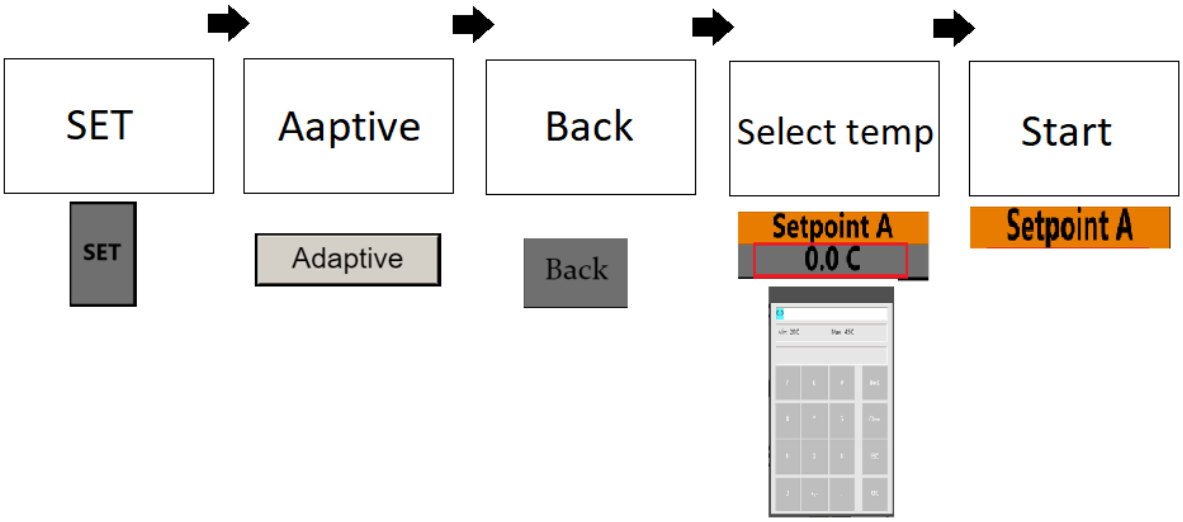
3 – When you have selected the reactor you use and thereby the PID combination it is important that you press, Set Selected Values button, otherwise the values not be upgraded, changed:

Set Selected Values button.

4- Go back to Harmonia Main GUI by pressing the Back button.

4.2.5 – Harmonia Quick start on GUI

This is far the most commonly way to operate Harmonia:



5. Communication

- Internal 5” touch sensitive TFT display hooked on the Apollon PLC
- External connection to PC, PADs or smart-Phones via Wi-Fi for programming and info from the built-in webserver
- USB port for USB adapter with software upgrades / Wi-Fi connection
- RJ45 port for LAN, ModBus, OPC via IP/TCP and for firmware upgrades and data acquisition

5.1 - Operation principles

Assuming a correct assembly of all systems, connections, etc. according to your Fluid Diagram – check all connections are tight.

5.2 - Wi-Fi connection

When Perseus is equipped with the NetGear Wi-Fi access point the Apache webhost will be accessible from a browser. Go into “Settings”/ Wi-FI

NETWORKS" and check if you can see Harmonia and select. Return to a browser and write anything in the address line for access to Apollon.

Harmonia can be controlled via an USB Wi-Fi dongle: SSID: harmoniaXX-cronus

Phrase: cronus-harmonia

5.3 – LAN IP/TCP connection

Check present development status on https://cronus-pcs.com/support/

5.4 – Software upgrade

Check out www.cronus-pcs.com/support/communication/software-upgrade

5.5 – Power supply

CE marked Harmonia operate on AC voltages ranging from 110 and 230 VAC.

6. Safety precautions

Various components require individual attention. Operator must also have gained familiarity with the Safety Instructions to be found separately on www.cronus-pcs.com/support/Safety_Instruction .

6.1 Heating elements

Danger for electrical shock is highly likely if heating blanket is damaged!
Heating blanket and wiring should be porous, folded, kinked or chipped. The silicone foil should not be discoloured. This is a sign of short circuiting due to broken heating coils or a defective power cord.

Malfunction and dangerous operating states can occur if damage was overlooked during the pre-use check.

- If so, switch out the heating blanket and discontinue its use.

Inappropriate cleaning agents or procedures may cause damage. Do not use any cleaning agents or solvents that can corrode the power supply, silicone foil or silicone foam and make them porous.

- Do not use any hard and / or sharp objects to remove stubborn soiling.

Danger for electrical shock is highly likely if cables, sockets, connectors for both heating blankets and heating rods is damaged!

6.2 Documentation

Harmonia functionality must be checked on a regular basis and data of such testing kept recorded.

6.3 Declaration of Conformity

CE

CE Declaration of Conformity

Company: Cronus-PCS A/S

Company address:
Noerrelundvej 10
DK-2730 Herlev - Denmark
www.cronus-pcs.com

We hereby declare that based on the design, construction and product placed on the market, the product designated below fulfils the relevant fundamental safety requirements and health regulations specified by the pertinent EC Directive.

The declaration shall become legally invalid if any modifications are made to the product, which have not been certified by Cronus-PCS.

Designation of the product: Harmonia - p/n 3110

Relevant directives of the EC:

- 2006/42/EC Machinery
- 2004/108/EC Electromagnetic Compatibility
- 2006/95/EC Electrical equipment designed for use within certain voltage limits
- 97/23/EC Pressure Equipment

Date of signature: 2020-04-20

Function of Signature
Per Stobbe
CEO and Director of R&D