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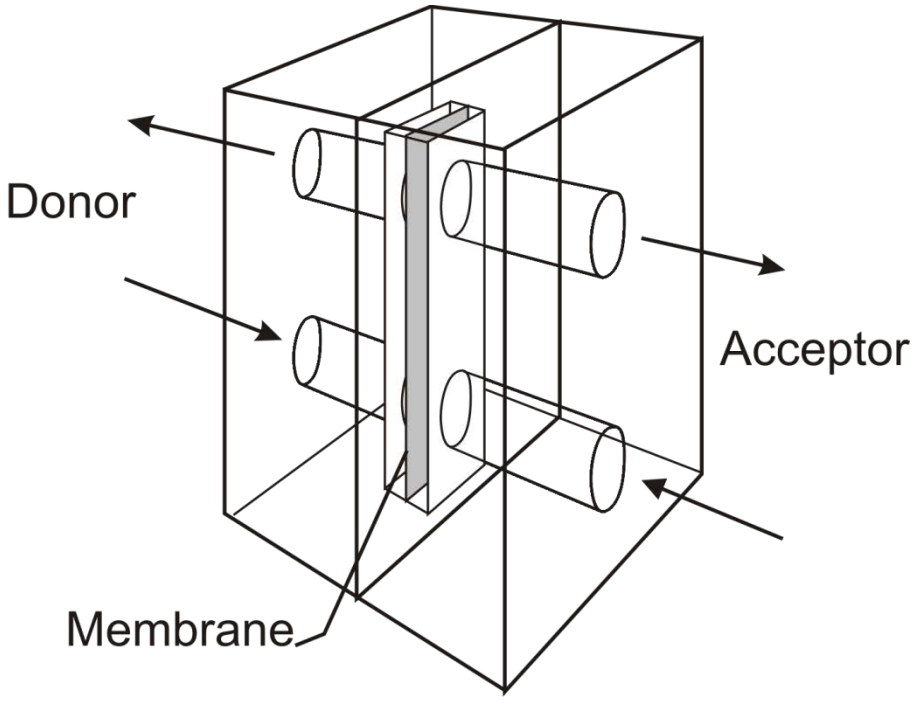
TRACE Analytics

User Manual
Bypass module



Technical Documentation Bypass module

December 2020 - Version 003 -

Important Note:
The data and information in this manual were compiled with the greatest of care. In spite of special care during creation of this document no warranty for an absolute accuracy can be given. If important information in this guidance are missed, if technical errors were found or if you would like to get more information about individual components, please notify us.
Please direct your inquiry directly to TRACE Analytics GmbH.

TRACE Analytics GmbH
Richard-Wagner-Straße 1
D-38106 Braunschweig
E-mail: info@trace.de
www.trace.de

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1 General Instructions

1.1 About this document

These instructions provide all the information necessary for operation of the bypass module. The instructions must be read, understood and used by all personnel using the bypass module.

- These instructions are part of the bypass module.
- Before working with the bypass module, read the instructions carefully and completely.
- Keep them in safe and easily accessible place near the bypass module site of installation.
- If the instructions are lost, request a replacement or download the latest instructions from our website.

Masculine or feminine forms are used to facilitate legibility in these instructions and always simultaneously denote the other gender as well.

1.2 Validity

These instructions apply to the bypass module in PEEK and stainless steel.

1.3 Target groups

The instructions are designed for the target group „User“, who is familiar with the operation of the bypass module and the associated working processes. The training takes place within the scope of start-up and is performed by TRACE Analytics GmbH or an authorized distributor.

1.4 Symbols used

The symbols used in the user manual are specifically intended to draw attention to the safety precautions! The symbol may not replace the text of the respective safety precaution. Therefore, the text must always be read completely!

Warning of potential consequential damage

1.5 Intended use

The bypass modules provide the perfect solution for sterile online sampling in connection with an online analyser e.g. TRACE C2 Control or BioPAT® Trace in bioreactors used in industrial and laboratory facilities.

The user must ensure that

- the bypass modules are used for its intended purpose only, see chapter 2 – product description.
- the bypass modules are used only when functional and in proper working order.
- the user manual is always kept legible and complete at the place of use.

1.6 Disposal

Packaging
The packaging is made of environmentally friendly materials that can be used as secondary raw materials. If the packaging is no longer needed, it can be disposed of by local waste disposal authorities.

Bypass module
The bypass module including accessories does not belong in your regular household waste as this equipment is manufactured from high-grade materials which can be recycled and reused.

1.7 Hazardous Materials

The bypass modules and accessories do not contain any hazardous materials that would necessitate special disposal measures.

Bypass modules contaminated with hazardous materials (NBC-contamination) will not be accepted for repair or disposal.

Decontamination Declaration
TRACE Analytics GmbH has a duty to protect its staff from hazardous substances. When returning the bypass modules, the sender must enclose a decontamination declaration as proof of compliance with the safety regulations governing the area of application for which they were used.

- This declaration must detail the microorganisms, cells and media that the bypass modules/components have come into contact with and the measures taken to disinfect and decontaminate it.
- The recipient must be able to read this decontamination declaration before opening the packaging.

The form of a decontamination declaration is on the website of TRACE Analytics at www.trace.de.

2 Product description

The bypass module is suitable for all types of cultivation. The application options depend on the reactor dimensions and the process conditions.

Figure 1: Bypass module a) stainless steel b) PEEK and c) single-use

The bypass module is an alternative to the dialysis probe. It is installed as a part of the perfusion tubing manifold outside of the bioreactor.

It is frequently used for perfusion cultures and in other cases where in-situ sampling with the dialysis or filtration probe is not possible.

The reusable bypass modules are made of stainless steel or PEEK and ensure a high level of sterility by the use of an extremely robust membrane. Alternatively, the single-use dialysis sampling module can be used.

The use of the bypass modules as a dialysis sampling system ensures analysis at constant volumes. The dialysis membrane is pre-prepared with appropriate sealing, can easily be installed in the bypass module and have to be replaced after every cultivation. The single-use unit has a preinstalled membrane and is replaced in its entirety after use.

If the bypass module is used to feed the sample from the bioreactor into an online analyser, then the analyte is transferred through a diffusion membrane into an internal pump-driven buffer stream and transported to the measuring cell.

3 Function

The following figure shows the principal function of the bypass module:

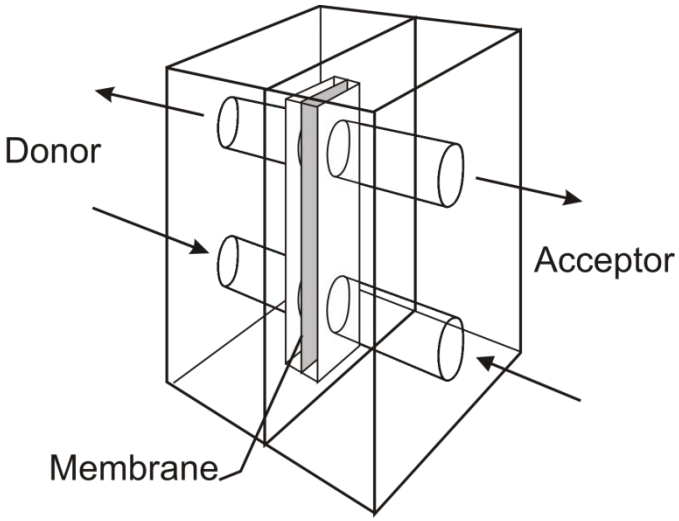


Figure 2: Principal function of the bypass module

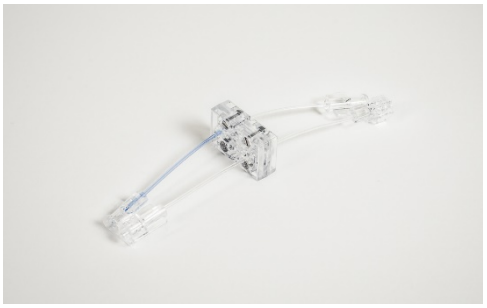
The dialysis membrane creates a sterile barrier between the two channels (donor/acceptor) and permits diffusion of the analyte into the acceptor stream.

The bypass module stainless steel consists of three individual blocks which can be easily fixed and sealed by Allen screws. It is used for larger volume flow rates of the donor stream.

Figure 3: Bypass module stainless steel

The bypass module PEEK consists of 2 individual blocks. It is used for online sampling in perfusion cell cultures for low volume flow rates of the donor stream.

Figure 4: Bypass module PEEK



The single-use dialysis sampling module is used for online sampling in perfusion cell cultures in single-use bioreactor setups. It provides the same features as the PEEK bypass module but as single-use format. The membrane and tubing are pre-mounted and fixed. The product is available non-sterile and sterile (gamma irradiated).

Figure 5: Single-use sampling module

For connection to the media line, the widely used LUER connection is available as standard. Other connectors are available on request.

4 Scope of delivery, consumables and spare parts

The bypass module including accessories is delivered in protective packaging.

- Please save this packaging; proper (return) shipping is only possible in the original packaging.
- Upon receipt, check the delivery for completeness and any possible damage that may have occurred in transit.
- Any transport damage must be reported within a week of delivery. Complaints made after this date will not be accepted.

4.1 Scope of delivery

The bypass module is delivered with 2 membranes, user manual and an installation kit.

Figure 6: Content of the installation kit bypass module

The following components are part of the installation kit (from left to right):

- Syringe 5 ml
- Adapter UNF-LUER male
- Adapter UNF-LUER female
- Allen key
- 2 O-rings (small)
- O-ring (large) – only for bypass module stainless steel
- Autoclave-loop

4.2 Order Information

4.2.1 Bypass modules

(Delivery with installation kit, 2 membranes and user manual)

Description	Order No.
Bypass module stainless steel, 3-part diffusion block with 2 barbed tubing adapter for I.D. 6 mm and I.D. 9 mm	860.202.001
Bypass module PEEK, 2-part diffusion block with 2 pump tubing adapter for tubing I.D. up to 2 mm	860.202.002

4.2.2 Membranes

Description	Order No.
Membranes (glucose/lactate) bypass module stainless steel/PEEK, 5 pcs, measuring range 0.5 - 40 g/l	860.211.050
Membranes (glucose/lactate/low) bypass module stainless steel/PEEK, 5 pcs, measuring range 0.1 – 5 g/l	860.211.046

4.2.3 Spare parts for the bypass modules

Description	Order No.
Installation kit for bypass module stainless steel	809.100.135
Installation kit for bypass module PEEK	809.100.136

4.2.4 Single-use modules

Description	Order No.
Single-use dialysis sampling unit for Glucose and Lactate monitoring. With LUER connectors for use with BioPAT TRACE or TRACE C2 tubing set, respectively. Individually packed in double pouch. Non-sterile.	860.500.100
Single-use dialysis sampling unit for Glucose and Lactate monitoring. With LUER connectors for use with BioPAT TRACE or TRACE C2 tubing set, respectively. Individually packed in double pouch. Gamma-irradiated, sterile.	860.500.200 on request

5 Installation

5.1 Bypass module stainless steel

The bypass module stainless steel is used for larger volume flow rates of the donor stream (media). It consists of three blocks which are fixed by Allen screws.

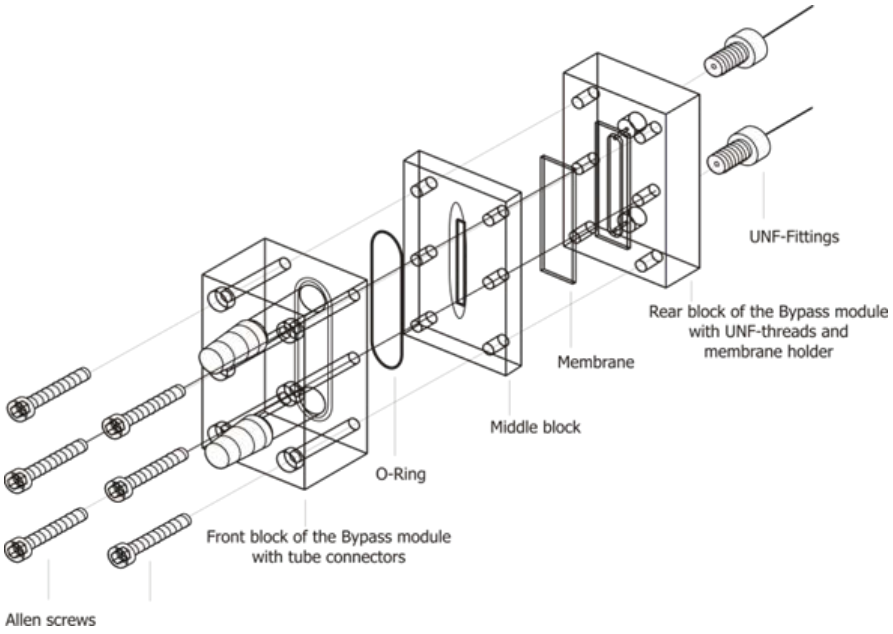
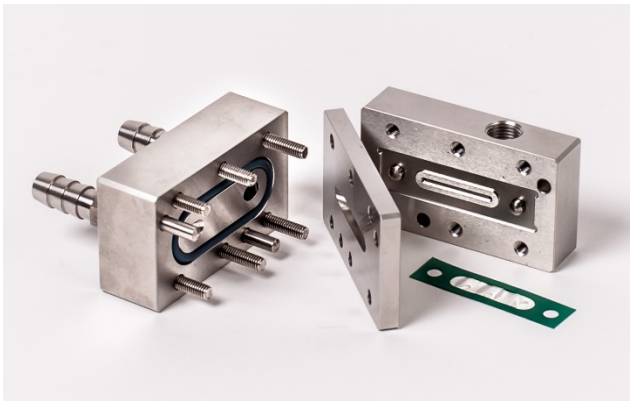


Figure 7: Configuration of the bypass module stainless steel

The front block and the middle block are forming the donor channel which connects the flowing stream of reactor medium with the dialysis membrane.
The membrane creates a sterile barrier and permits diffusion of the analyte into the acceptor stream.



A large o-ring is used for the sealing of the front and middle block.

The rear block serves as the acceptor-channel and fixes the dialysis membrane with the middle block.

Figure 8: Components of the bypass module stainless steel with standard membrane

2 barbed tubing adapters for tubing I.D. 6 mm or I.D. 9 mm are used for the connection with the perfusion tubes and UNF analytical fittings are used for the connection of the analyser manifold.

5.2 Bypass module PEEK

The bypass module PEEK is used for low volume flow rates especially for perfusion cell cultures. It consists of 2 individual blocks which are connected by Allen screws.

The front block (donor channel) connects the flowing stream of reactor medium with the dialysis membrane which creates a sterile barrier between the two channels and permits diffusion of the analyte into the acceptor stream.

Figure 9: Bypass module PEEK with dialysis membrane low

The rear block serves as the acceptor-channel and fixes the dialysis membrane with the front block.

The bypass module PEEK is prepared with 2 pump tubing adapters for tubing I.D. up to 2 mm and 2 o-rings for the additional sealing of the adapter.

5.3 Single-use dialysis sampling module

The single-use sampling module is an alternative to the PEEK bypass module and can be used for low volume flow rates especially for perfusion cell cultures. It also consists of 2 parts creating the donor and acceptor fluid path. All tubings are permanently fixed and have LUER connectors for easy integration in perfusion line and tubing set.

One side (donor channel) connects the flowing stream of reactor medium with the dialysis membrane which creates a sterile barrier between the two channels and permits diffusion of the analyte into the acceptor stream.

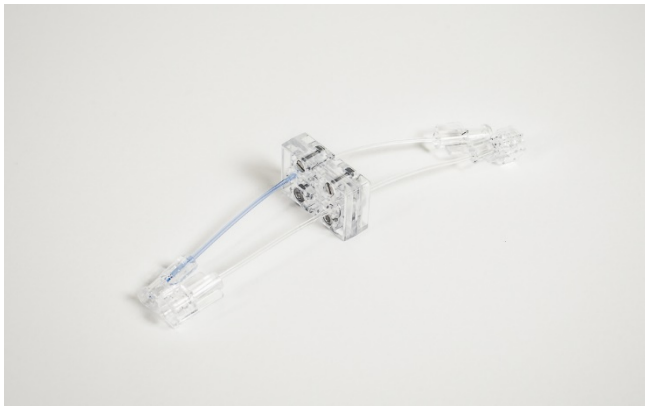


Figure 10: Single-use dialysis sampling module

The rear side serves as the acceptor-channel and fixes the dialysis membrane with the front side.

6 Getting started

6.1 Connecting the bypass module stainless steel

6.1.1 Mounting the dialysis membrane in the bypass module

Install a new membrane in the bypass module before every online measurement involving bioprocesses with sterile feeds, see figure 9. If this rule is not observed, a lack of sterility may jeopardize the entire cultivation process.

The new dialysis membrane must be placed correctly and the module parts must be tightened firmly with the screws, see figure 9.

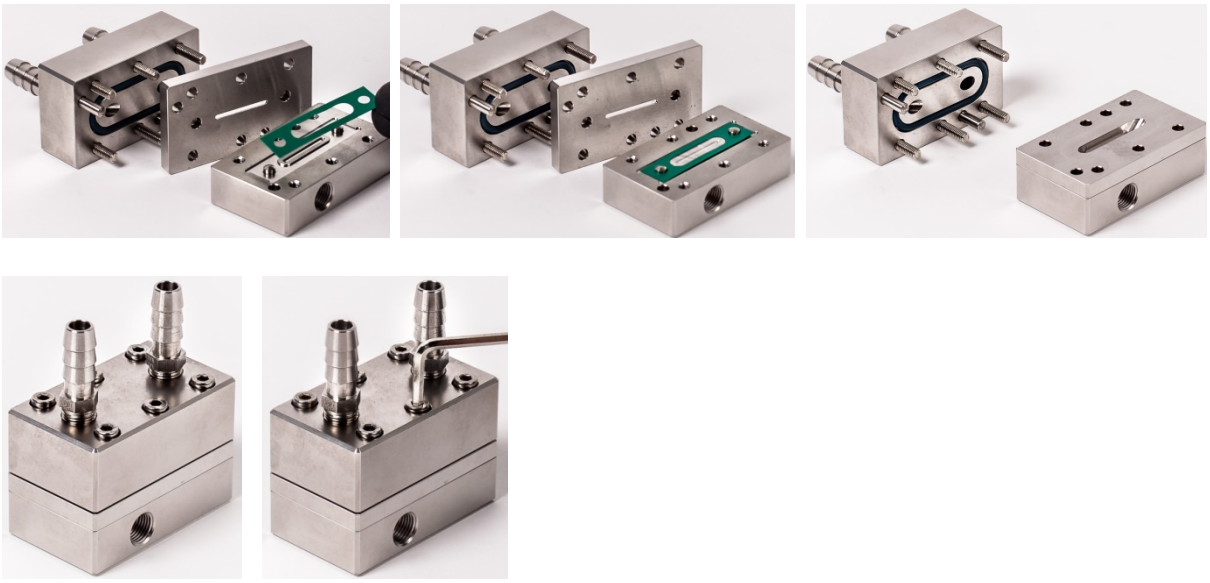


Figure 11: Inserting a new standard membrane in the bypass module stainless steel

⚠	Incorrect insertion of the membrane may result in leaks and jeopardize the sterility of the entire cultivation process. Pay particular attention to ensure that the membrane is seated correctly in the bypass module.

6.1.2 Sterilization of the bypass module

Connect the bypass module with the adapter „UNF to LUER“, see figure 12.

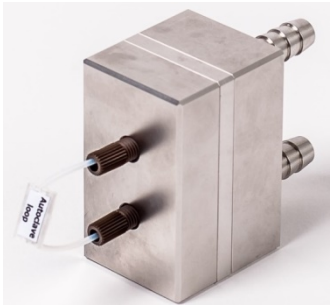



Figure 12,13: Filling the bypass module with buffer solution/Sealing the module prior to sterilization

a) Prior to sterilization, fill the bypass module with buffer solution using the single-use syringe and the UNF to LUER adapter. At the same time, the module can be checked for any leaks, see figure 12.
b) For sterilization, seal the bypass module with the “Autoclave-loop”, see figure 13. This will prevent one-sided overpressure from occurring at the membrane in the bypass module, which could damage the membrane.
c) Now sterilize the reactor, respectively the bypass tubing.
d) After sterilization: Reconnect the UNF to LUER adapter after cooling.
e) As before, fill the bypass module with buffer solution by using the single-use syringe and carefully check if it flows freely, see figure 12.
f) Now, the bypass module can be connected to the corresponding tubing set of the online analyser.

	Dry sterilization is not suitable because the membrane may be damaged.
	Steam sterilization at 1 bar and 121°C. Condition is that the membrane was installed correctly. During sterilization, the bypass module must be filled with buffer solution and closed with the "Autoclave-Loop" otherwise the membrane may be damaged.

6.1.3 Connecting the bypass module to the tubing set

The bypass module is connected to the online analyser through the dialysis tubing set. Insert the inlet at the bottom and the outlet at the top to allow any air bubbles to exit the bypass module easily. The labels on the tubing set show the flow direction, see figure 14.

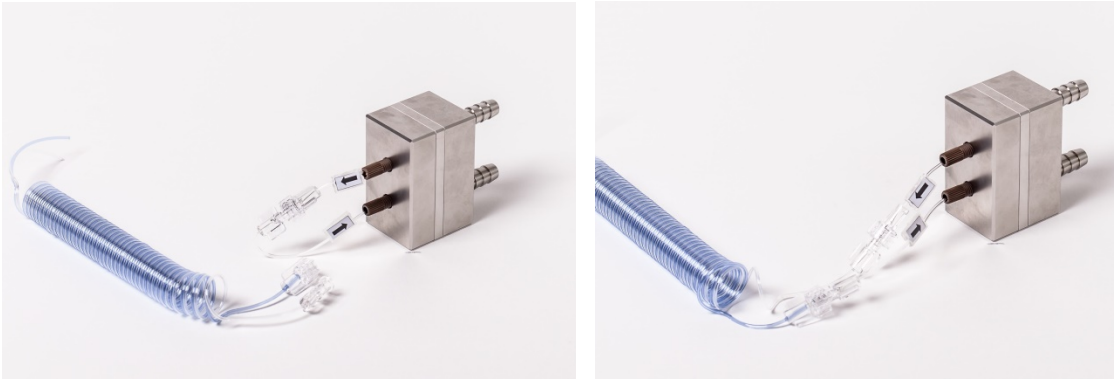


Figure 14: Connecting the bypass module stainless steel to the tubing set

When connecting the bypass module to the tubing set, care must be taken to ensure that as little air as possible is introduced into the tubing set in the form of small air bubbles, since these could be trapped in the measuring cell which could lead to fluctuating measurements.

Procedure:

- First, rinse the bypass module with buffer or distilled water.
- Then connect only the inlet line (arrow towards the bypass module) and leave the outlet line (arrow away from the bypass module) open.
- Then start the measurement. This triggers the purge and liquid and any remains of air escape from the output line of the bypass module.
- The second line of the tubing set is then connected and rinsed for a few minutes.

Basically, air bubbles in the tubing set are rinsed out over time. However, this process takes some time (e.g., during the priming process). If air bubbles are present in the measuring cell after the connection of the bypass module, it would be advantageous to operate the system with a maximum measuring frequency for a duration of approx. 30 minutes.

	If air bubbles are present in the measuring cell, under no circumstances should calibrations or referencing be carried out, as they may be faulty and consequently lead to incorrect results.

6.2 Connecting the bypass module PEEK

6.2.1 Mounting the dialysis membrane in the bypass module

Install a new membrane in the bypass module before every online measurement involving bioprocesses with sterile feeds, see figure 15. If this rule is not observed, a lack of sterility may jeopardize the entire cultivation process.

The new dialysis membrane must be placed correctly and the module parts must be tightened firmly with the screws, see figure 15.

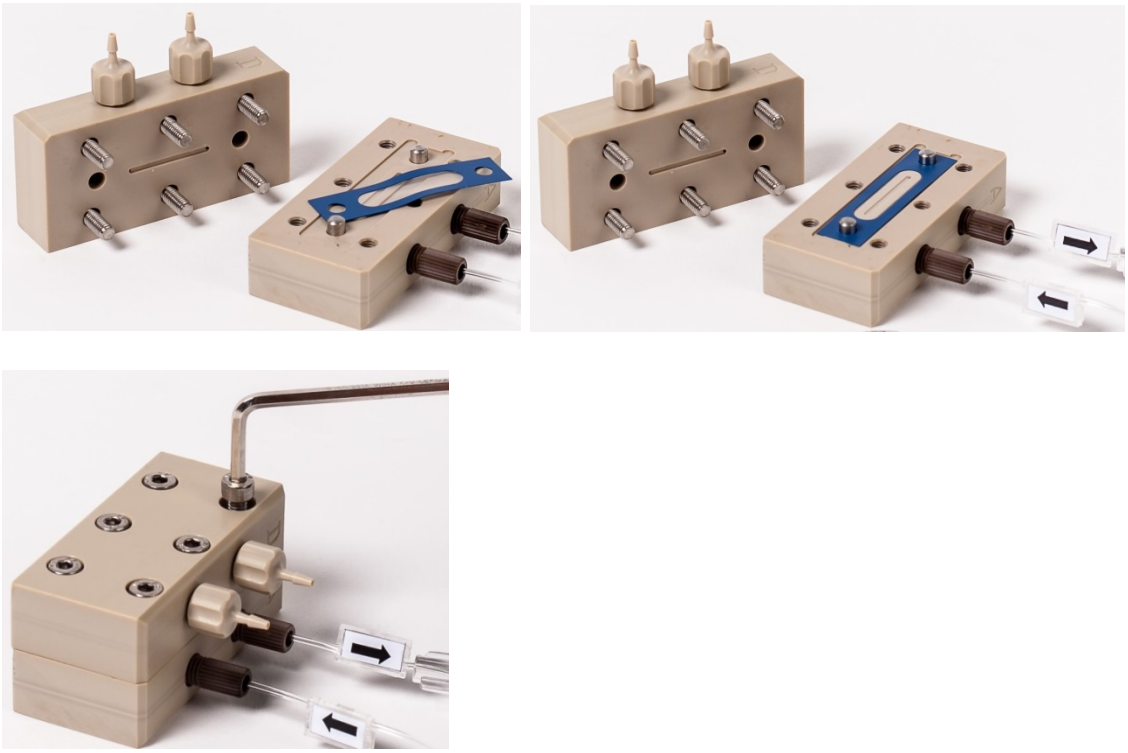


Figure 15: Inserting a new membrane for the lower measuring range in the bypass module PEEK

	Incorrect insertion of the membrane may result in leaks and jeopardize the sterility of the entire cultivation process. Pay particular attention to ensure that the membrane is seated correctly in the bypass module.

6.2.2 Sterilization of the bypass module

Connect the bypass module with the adapter „UNF to LUER“, see figure 16.

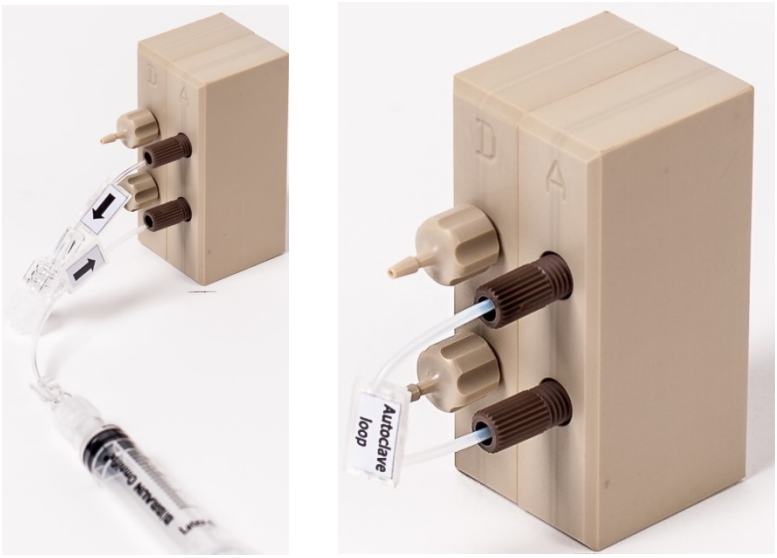


Figure 16,17: Filling the bypass module with buffer solution/Sealing the module prior to sterilization

a) Prior to sterilization, fill the bypass module with buffer solution using the single-use syringe and the UNF to LUER adapter. At the same time, the module can be checked for any leaks, see figure 16.
b) For sterilization, seal the bypass module with the “Autoclave-loop”, see figure 17. This will prevent one-sided overpressure from occurring at the membrane in the bypass module, which could damage the membrane.
c) Now sterilize the reactor, respectively the bypass tubing.
d) After sterilization: Reconnect the UNF to LUER adapter after cooling.
e) As before, fill the bypass module with buffer solution by using the single-use syringe and carefully check if it flows freely, see figure 16.
f) Now, the bypass module can be connected to the corresponding tubing set of the online analyser.

⚠	Dry sterilization is not suitable because the membrane may be damaged.
⚠	Steam sterilization at 1 bar and 120°C. Condition is that the membrane was installed correctly. During sterilization, the bypass module must be filled with buffer solution and closed with the "Autoclave-Loop" otherwise the membrane may be damaged.

6.2.3 Connecting the bypass module to the tubing set

The bypass module is connected to the online analyser through the dialysis tubing set. Insert the inlet at the bottom and the outlet at the top to allow any air bubbles to exit the bypass module easily. The labels on the tubing set show the flow direction, see figure 18.

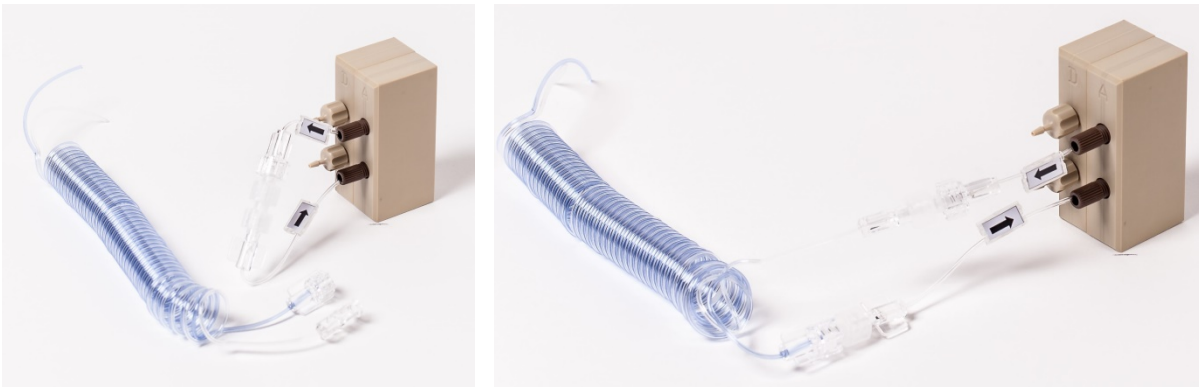


Figure 18: Connecting the bypass module PEEK to the tubing set

When connecting the bypass module to the tubing set, care must be taken to ensure that as little air as possible is introduced into the tubing set in the form of small air bubbles, since these could be trapped in the measuring cell which could lead to fluctuating measurements.

Procedure:

- First, rinse the bypass module with buffer or distilled water.
- Then connect only the inlet line (arrow towards the bypass module) and leave the outlet line (arrow away from the bypass module) open.
- Then start the measurement. This triggers the purge and liquid and any remains of air escape from the output line of the bypass module.
- The second line of the tubing set is then connected and rinsed for a few minutes.

Basically, air bubbles in the tubing set are rinsed out over time. However, this process takes some time (e.g., during the priming process). If air bubbles are present in the measuring cell after the connection of the bypass module, it would be advantageous to operate the system with a maximum measuring frequency for a duration of approx. 30 minutes.

	If air bubbles are present in the measuring cell, under no circumstances should calibrations or referencing be carried out, as they may be faulty and consequently lead to incorrect results.

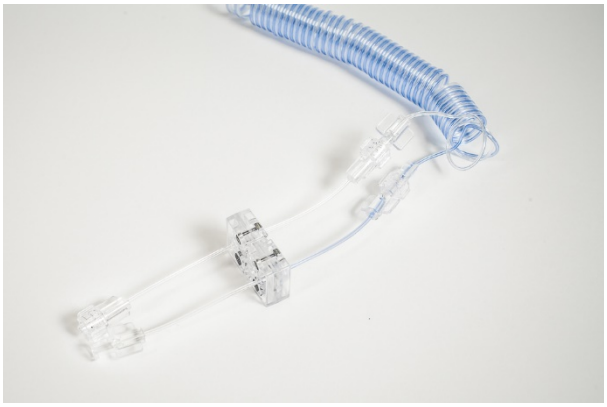
6.3 Cleaning the reusable bypass modules

a) Before removing the bypass module from the bioreactor-bypass, the tubing set is removed from the module by loosing the tube ends.
b) After harvesting the bioreactor or any dead autoclaving phase, remove the bypass module from the bioreactor. The subsequent cleaning of the bypass module and the adapter is carried out with a soft brush and water.
c) Check the gaskets on the bypass module to make sure that they are clean and seated properly.
d) Loosen the Allen screws at the top with the delivered Allen key; this allows the dialysis membrane to be removed from the bypass module.
e) Afterwards clean the parts with a soft brush and water.

6.4 Connecting the single-use sampling module

The single-use dialysis sampling module is delivered either non-sterile or pre-sterilized (gamma irradiated). The non-sterile version is to be integrated into the perfusion line by the bioreactor manufacturer prior to sterilisation of the overall setup. The pre-sterilized version can be connected to the bioreactor using a laminar flow cabinet.

6.4.1 Connecting the single-use module to the tubing set



The single-use module is connected to the TRACE analyser through the dialysis tubing set. Place the inlet at the bottom and the outlet at the top to allow any air bubbles to exit the bypass module easily. The blue tubing on the tubing set connects to the blue tubing on the single-use module, see figure 19.

Figure 19: Connecting the single-use sampling module to the tubing set

When connecting the module to the tubing set, care must be taken to ensure that as little air as possible is introduced into the tubing set in the form of small air bubbles, since these could be trapped in the measuring cell which could lead to fluctuating measurements.

Procedure:

- First, rinse the module with buffer or distilled water.
- Then connect only the inlet line (blue tubing) and leave the outlet line open.
- Then start the measurement. This triggers the purge and liquid and any remains of air escape from the output line of the module.
- The second line of the tubing set is then connected and rinsed for a few minutes.

Basically, air bubbles in the tubing set are rinsed out over time. However, this process takes some time (e.g., during the priming process). If air bubbles are present in the measuring cell after the connection of the single-use module, it would be advantageous to operate the system with a maximum measuring frequency for a duration of approx. 30 minutes.

	If air bubbles are present in the measuring cell, under no circumstances should calibrations or referencing be carried out, as they may be faulty and consequently lead to incorrect results.

7 Data sheet

Bypass module stainless steel	
Material	Stainless steel
Dimensions in mm (WxHxD)	35 x 60 x 40 (without tubing adapter)
Weight	625 g
Tubing adapter (donor-sided)	Barbed, I.D. 6mm or I.D. 9 mm
Flow max. (donor-sided)	1000 ml/min

Bypass module PEEK	
Material	PEEK
Dimensions in mm (WxHxD)	30 x 63 x 30 (without tubing adapter)
Weight	85 g
Tubing adapter (donor-sided)	Barbed, I.D. up to 2mm
Flow max. (donor-sided)	5 ml/min

Single-use module	
Material	Polycarbonate
Dimensions in mm (WxHxD)	10 x 32 x 18 (body)
Weight	11,5 g
Tubing adapters	LUER (male, female) on both sides
Tubing lenghts	4 x 60 mm
Flow max. (donor-sided)	5 ml/min

Table 1: Technical data sheet