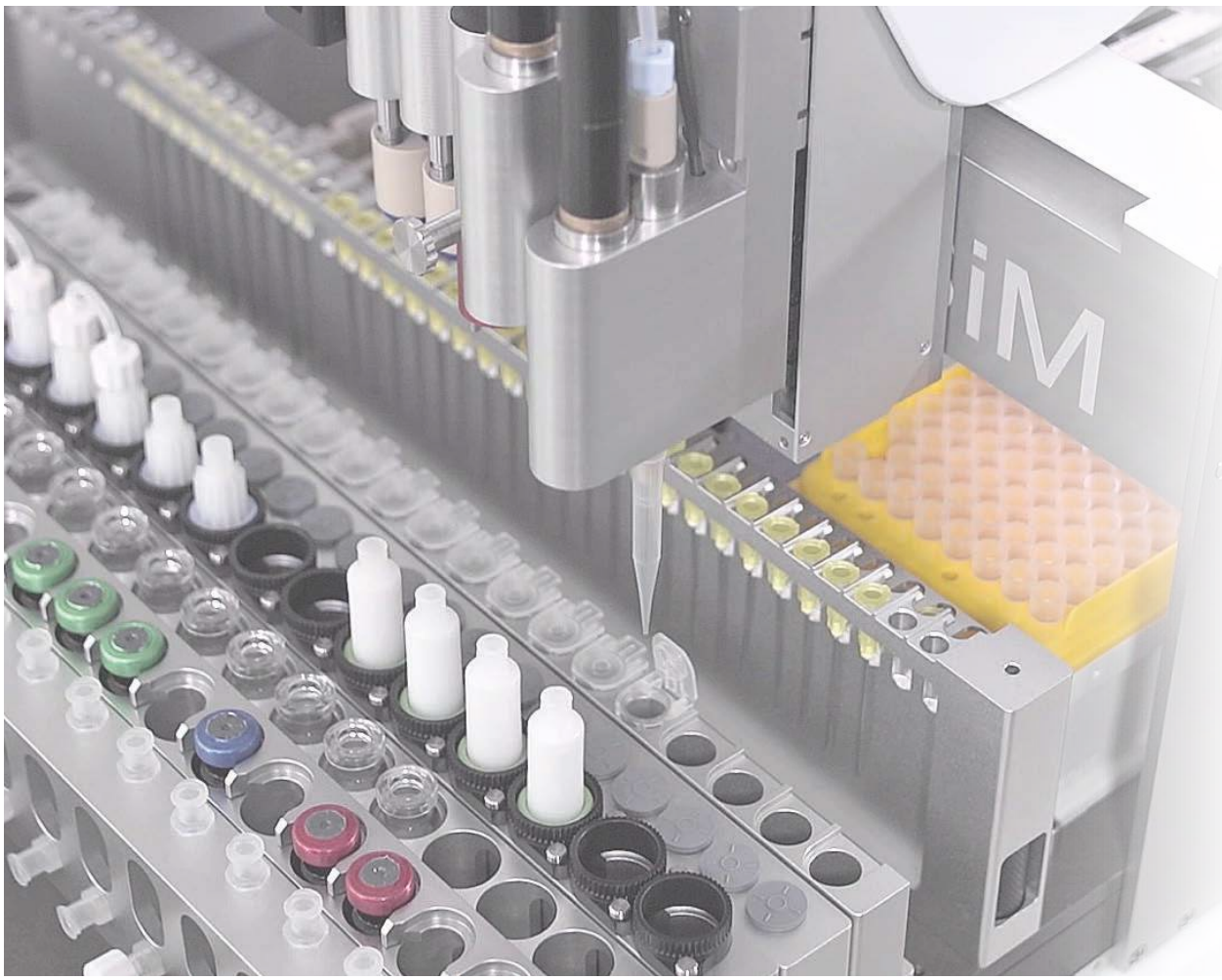
BioSyntheSizer

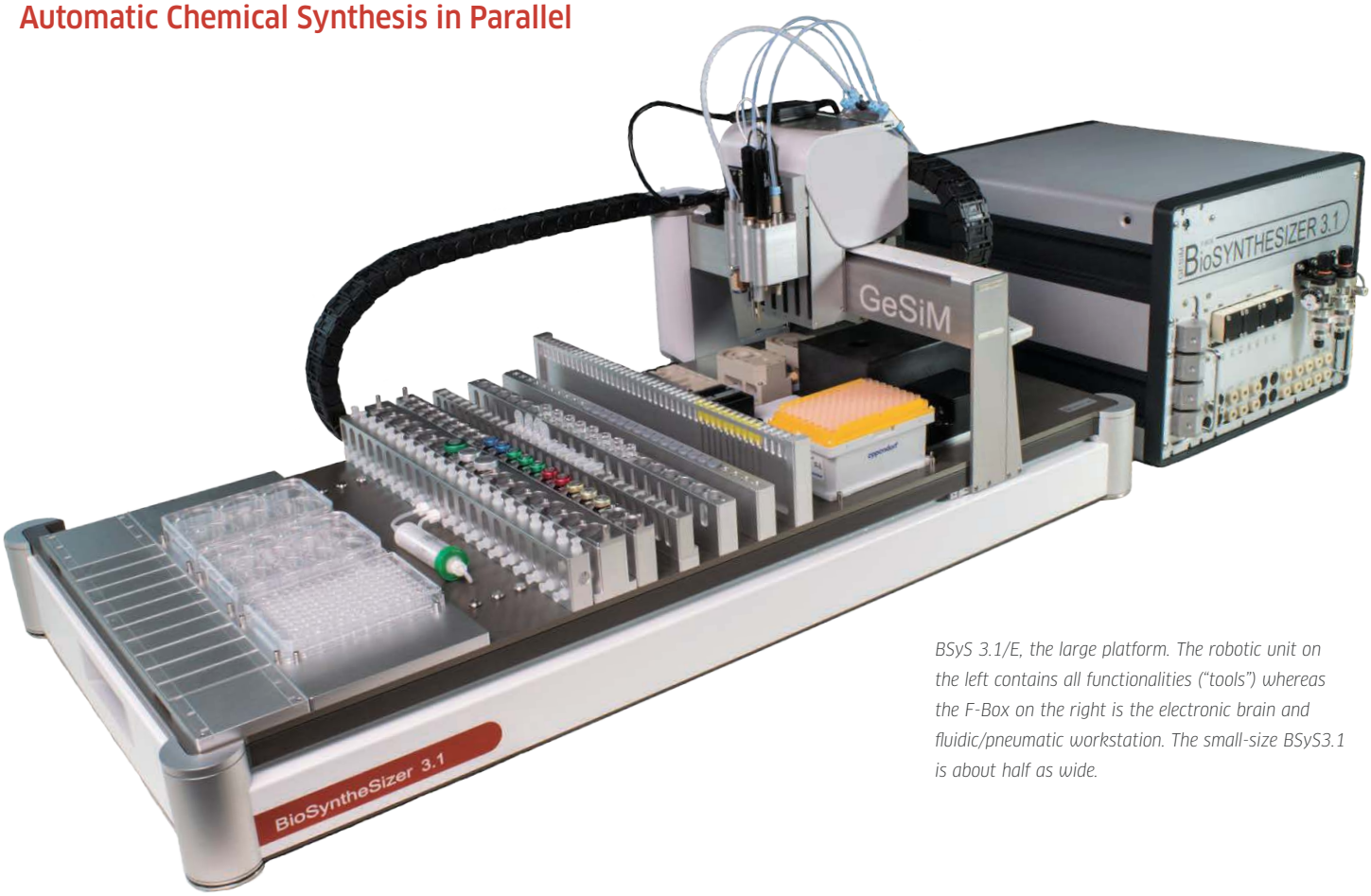
Multi-Synthesis Liquid Handling Robot



GESIM

CHEMICAL SYNTHESIS

The GeSiM BioSyntheSizer 3.1 and 5.1 – Automatic Chemical Synthesis in Parallel



BSyS 3.1/E, the large platform. The robotic unit on the left contains all functionalities ("tools") whereas the F-Box on the right is the electronic brain and fluidic/pneumatic workstation. The small-size BSyS3.1 is about half as wide.

The BSyS – A dream come true in chemical synthesis

The GeSiM BioSyntheSizer or short **BSyS** stands for the synthesis of biologicals and chemicals in a modular and flexible liquid handler of rather small footprint. Its goal is to synthesize not only one or two chemicals without supervision, but also other compounds using different protocols – at the same time!

For this we invented a novel multi-tool head featuring up to seven independent Z-drives, on which a variety of tools can be mounted. Not only tools shown here in any combination (for pipetting, tube/vial gripping, powder transfer etc.), but also those that turn the BSyS into a 3D bioprinter or a microcontact printer: e.g. pneumatic extruders, optical systems, stamping tools or even microfluidic components (separate brochures). Not to mention tools yet to be invented.

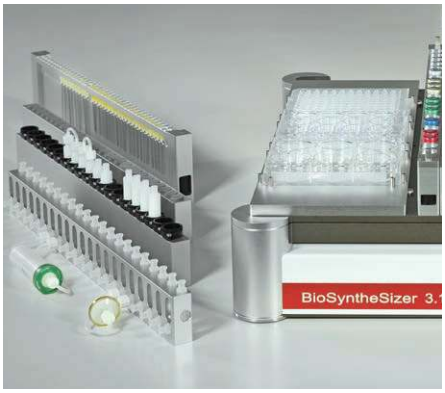
The work deck holds stations for tip washing, tip alignment, tip tests and septum removal, plus tools such as self-filling containers for solvents and a heatable reactor chamber. Easy-to-mount racks for disposable plastic pipette tips or Luer-Lock needles are also arranged there.

The BSyS comes in different flavours

The standard instrument (BSyS3.1) has a small platform and tooth belt drives. The larger belt-driven instrument (BS3.1/E) has more space for slides, microtitre plates, vials etc. We also offer a production platform with fast linear motors, the **BSyS5.1**. This machine is available with small and large (BSyS5.1/E) platform. Please inquire for all the options.

Remember, the BSyS is not just another ordinary liquid handler! It will become your ideal companion for any small-scale synthesis project, including peptide synthesis and combinatorial chemistry, and is the perfect OEM lab automation platform.

But if you like, you can certainly use it as a simple pipetting robot.



Racks removed from the robotic unit and replaced with holders for microtitre plates. Holders for slides exist, too.

Tools on the work plate – Of functions and holders

Holders for various storage and reactor vessels, such as crimp vials, Eppendorf tubes or cartridges are mounted on the work deck. The racks can be slid out with ease and replaced by others – including holders for glass slides and microtitre plates. Holders can be heated or cooled, if required. The picture on the right shows only a fraction of what is possible; customization is our business.

A rack containing tubes with Luer nozzles also exists. These tubes can be connected with filters or columns for reaction, extraction or purification, or with other vials or systems for inspection such as an HPLC or a cuvette/spectrophotometer. The conical pipetting nozzles, which can be washed from the inside, can pick up solutions and push them through a column.

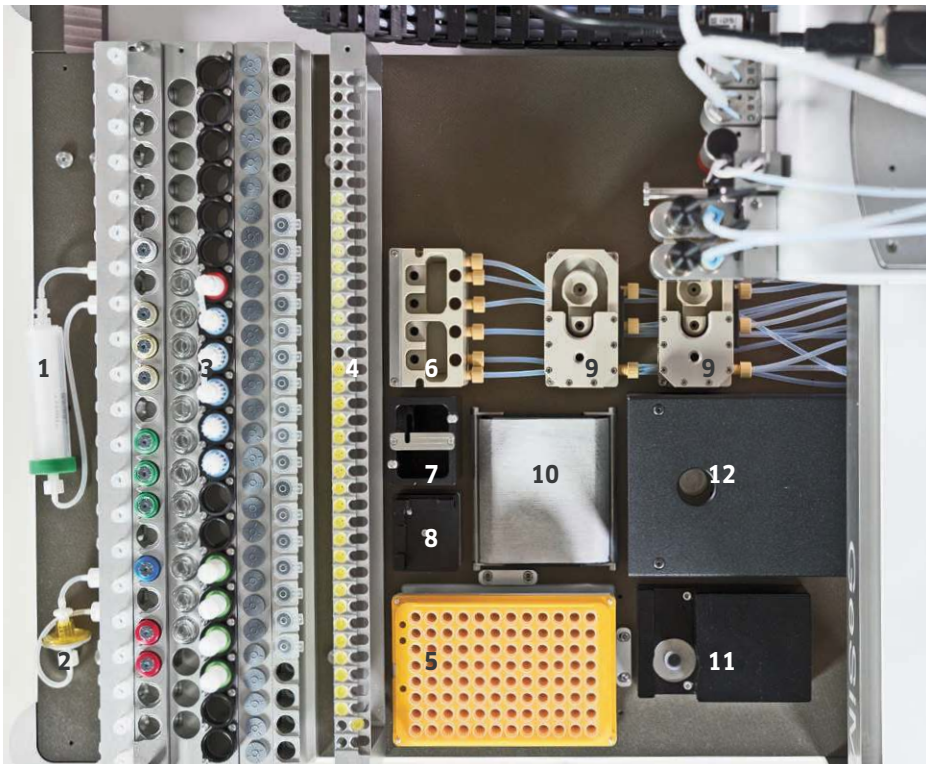
Disposable pipetting tips, either plastic tips or needles that penetrate septa, can be placed in their holders and are automatically taken and ejected by the respective nozzles on the head (see below).

Ready-to-use "kit plates" that combine all items necessary for a synthesis in one rack (filled and empty reservoirs, vials, tubes, solid-phase extraction and other cartridges, etc.) are another option. They are built to order, so please inquire if you require them to develop synthesis kits.

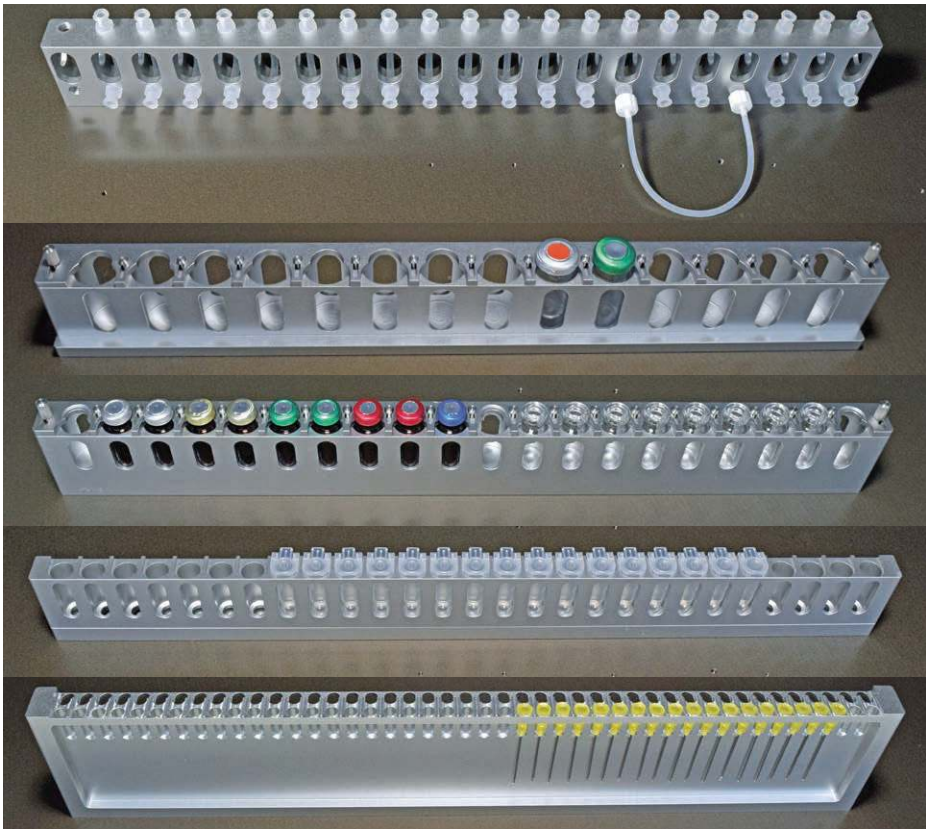
Permanently mounted on the work deck are solvent reservoirs that are automatically refilled, tip wash stations with water or solvents plus a dry station, a photosensor-based XYZ alignment tool for dispensing tips, a septum remover, and a stroboscope for the automatic check of the function of a piezo pipette, to name a few.

The heart of the BioSyntheSizer is the **reactor**: a heatable chamber with quick temperature ramps for vials in which chemical reactions can take place at elevated temperature and, if a cap is mounted, also at higher pressure. If you use the 3-lumen pipette, "azeotropic drying" is possible.

More tools will be added in the future. We await your suggestions.



Typical objects on the work plate: (1) purification column; (2) sterile filter; (3) racks for tube adapters, closed/open crimp vials, reactor columns, septum vials, FlipTubes; (4) needle holder, (5) single-use pipette tips; (6) automatically replenished solvent reservoirs; (7) septum remover; (8) tip alignment station; (9) two wash stations for piezo tips; (10) piezo drying station; (11) stroboscope for piezo pipette check; (12) heated reactor chamber



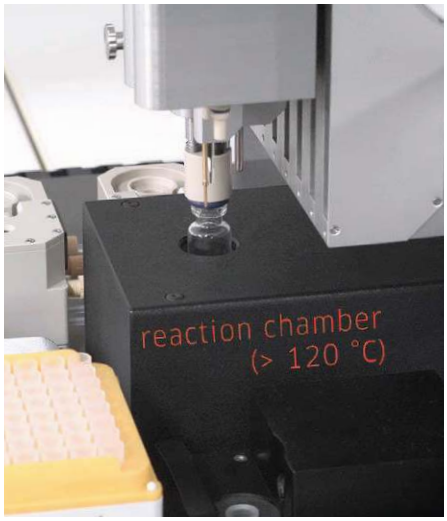
Some available racks: for tube adapters to connect nozzles to tubes/columns etc., for crimp vials (two sizes), for "FlipTubes" for which an opening/closing tool exists, and for Luer-type needles. Most standard containers and cartridges can be used, or special holders can be added later.

Tool Head Configuration

Print head tools – A multitude of options

The tool head is probably the most important part of the machine. It can feature numerous functions in arbitrary order – optical devices (object cameras, holders for UV fibres, nozzles/ejectors for standard pipette tips (which can also pick up Luer needles), different dispensers for the non-contact transfer of tiny volumes (GeSiM piezoelectric picolitre dispensers and third-party dispensers with e.g. solenoid valves).

Invented for chemical synthesis is the **3-lumen pipette** whose tubes can be filled with fluids and gases. When it operates with solvent, inert gas and vacuum, it can be used for azeotropic drying of solutes, especially in the heatable reactor, by flushing a vial with solvent and gas and simultaneously removing the azeotrope of solvent and water. The vacuum of the 3-lumen pipette is also used for gripping open vials, e.g. to carry them to the reactor chamber.



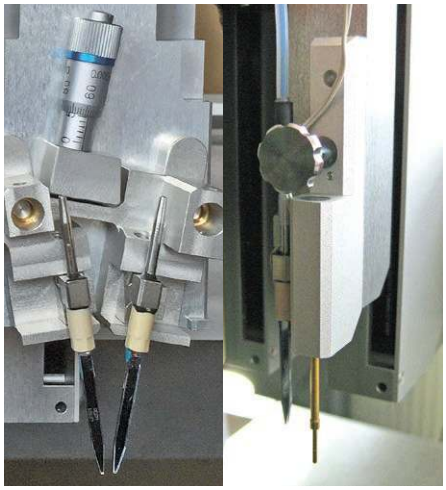
3-lumen pipette/gripper moving a vial into the heated reactor chamber.

Piezo dispensers, which are valveless, can eject droplets down to about 60 picolitres (pl). Bulk liquid handling (sample uptake from a microtitre well, washing) is done by a syringe pump. A stroboscope flashing at the same frequency as the tip is used for function control.

A GeSiM specialty is the **twin piezo dispenser** whose two tips can be swivelled after sample uptake so that two drops are mixed in flight, e.g. to initiate a chemical reaction.

Example of a fully equipped pipetting head with (1) camera, (2+3) gripper/3-lumen pipette (one tool!), (4) FlipTube opener, (5) piezo tip + Z-sensor on one Z-axis, (6+7) nozzles for single-use needles and tips

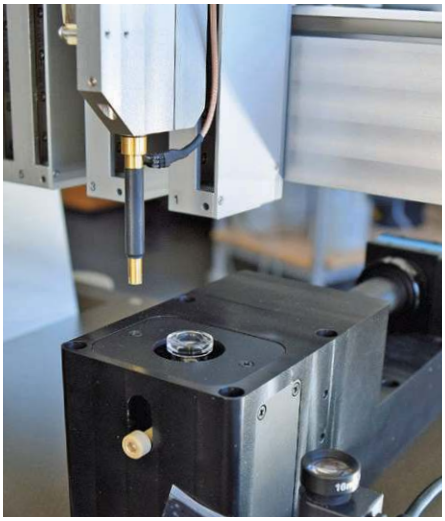
Quite useful is the mechanical **Z-sensor** to measure substrate height profiles, also in wells. Together with the tip measurement this leads to an effortless alignment of tips with objects (e.g. vials) and with one another, e.g. if 3D printing is required. It is normally mounted on the same Z-axis as the piezo tip; the Z-sensor must be removed when printing.



Twin tip pipetting device (left), swivelled. Teflon tubes to piezo dispensers are missing. On the right, an (old) Z-sensor, side by side with a single piezo tip.

A special you hardly find anywhere else is the **powder dispenser** for very small amounts of solids, designed by GeSiM. It operates pneumatically by sucking a fixed amount of beads into a cavity and transfer it to a vial. Transfer is optimized by shaking the support on which powder is loaded. Depending on the size of the cavity, the powder dispenser can operate down to a **single bead**.

Not shown is the new **pH titration pipette** (Tit-Pip) with glass electrode for automatic stepwise pH adjustment in liquids.



Micro-powder dispenser above a piezo-actuated powder reservoir. Two control cameras inspect the loading from the side and from below. Depending on the tip structure, different amounts ob beads can be transferred.

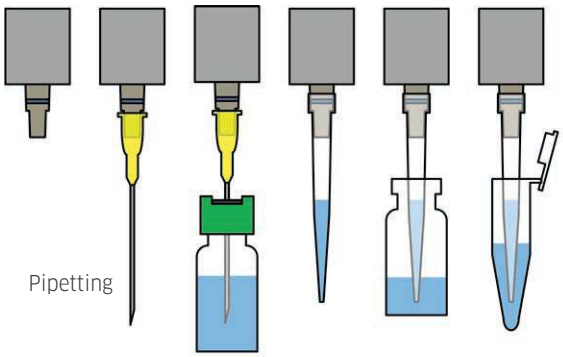
→

*Schematic drawings of many BSyS functions, GeSiM inventions are marked by * (not all tools are shown):*

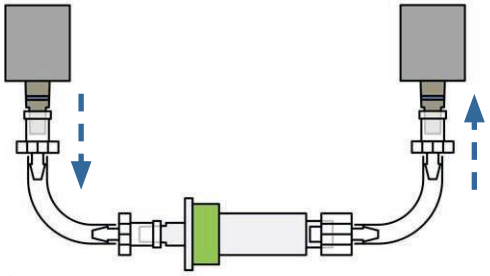
- *Nozzles/ejectors are used for both disposable plastic tips and Luer-size needle injectors. Two nozzles can operate independently or in concert, e.g. to pump fluid through filters or columns. Nozzles can be washed.*
- *Piezo dispensers can operate alone (standard) or as twin dispenser. Sample uptake and washing is done by a connected syringe pump.*
- *Typically the 3-lumen pipette is used with solvent, inert gas and vacuum for azeotropic drying of solutes. Its second function is gripping.*
- *Overpressure in the reactor is produced by heating (≥ 120 °C) a sealed vial and is not measured.*
- *The GeSiM powder dispenser can reliably transfer a single particle (see photo). The powder bed can be shaken for better transfer.*
- *Finally there is a tool for automatic opening and closing "FlipTube" microcentrifuge tubes.*

Nozzles for disposable tips + needles

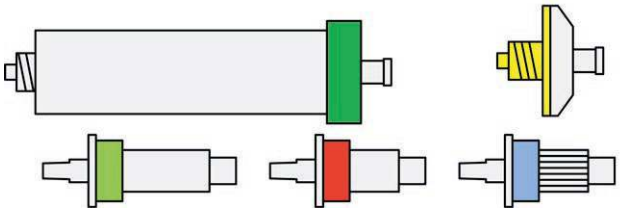
Single channel



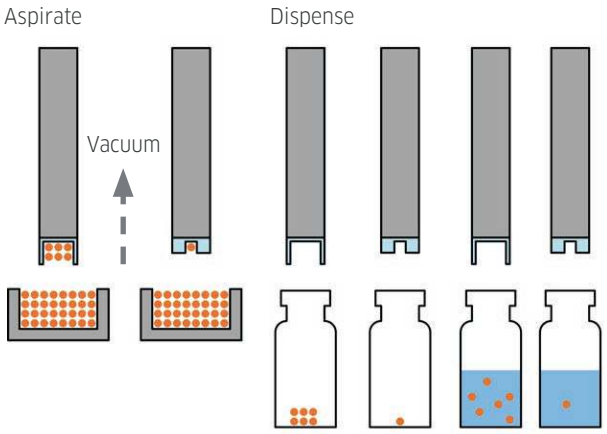
Double channel



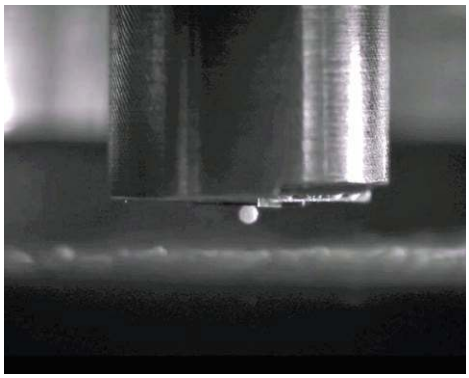
Various columns



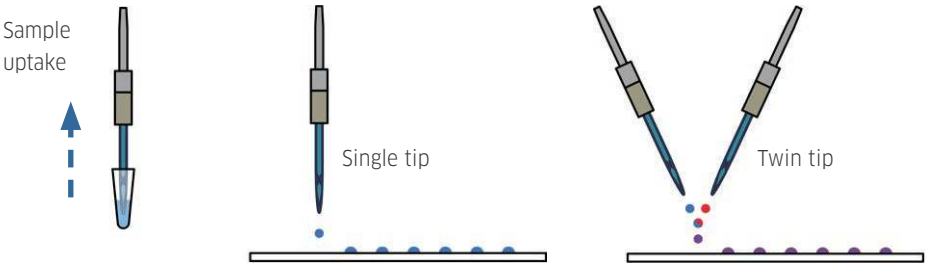
Powder microdispenser *



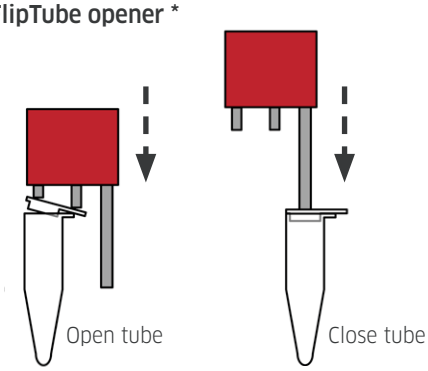
Powder dispenser: transfer of a single bead



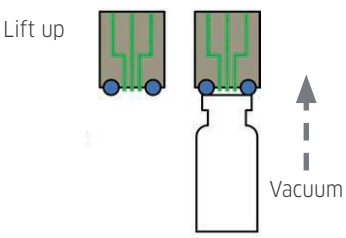
Piezo dispenser *



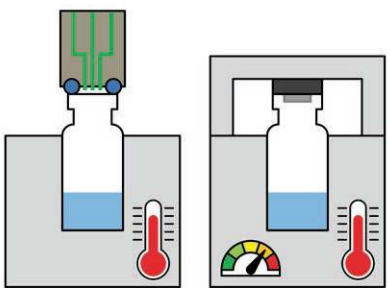
FlipTube opener *



Gripper / 3-lumen pipette *



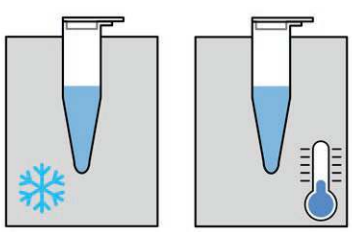
Reactor (heated)



Place in reactor / azeotropic drying

Heat with septum to generate pressure

Temperature block



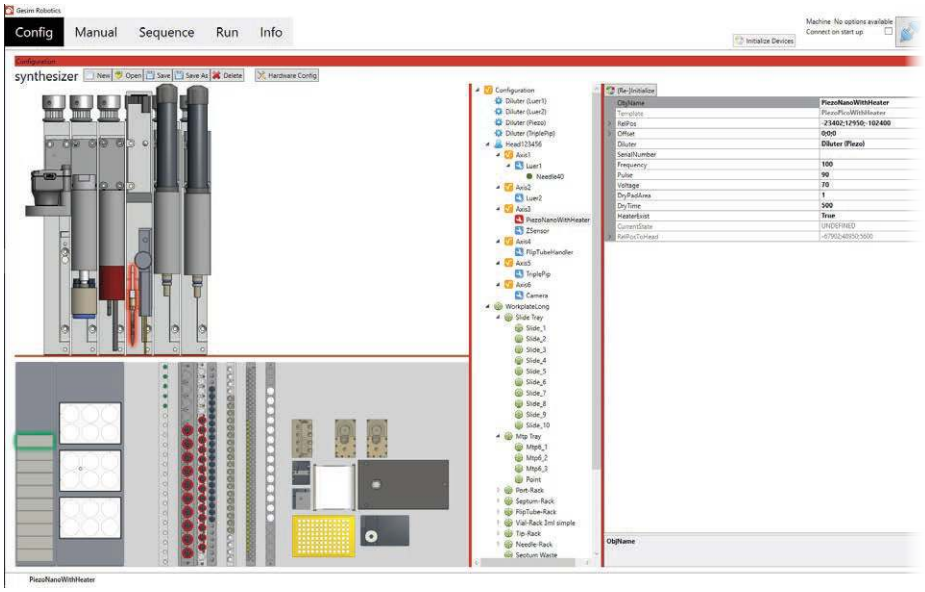
Freezing / cooling / heating

Software, Two-Level Instruments

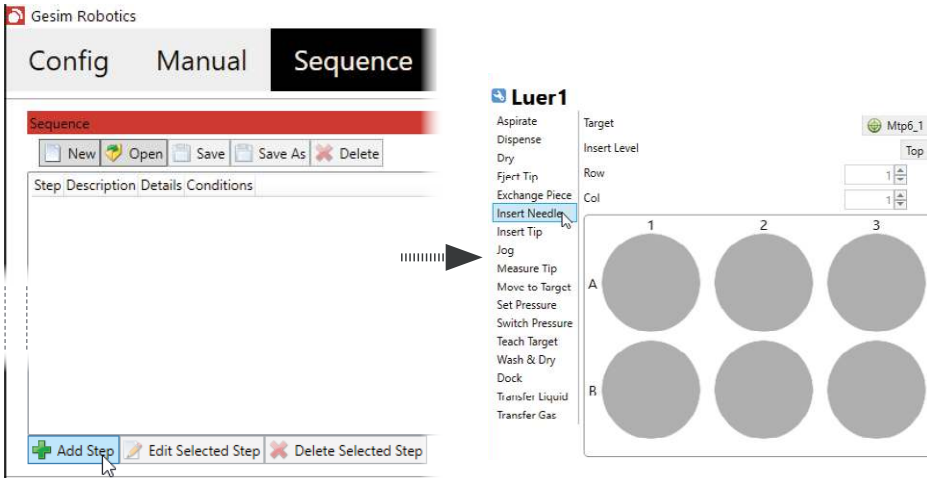
Clear and easy control software

We have created an easy, consistent graphical user interface that is identical for all GeSiM robotics instruments. It consists of several pages:

- Configuration: hierarchical definition of objects in a “tree view”, starting from a parent object, (diluter, tool head or work plate). For each object, a pre-defined parameter set (“template”) with supported parent and child objects, upper and lower bounds and allowed actions exists.
- Manual: interactive head movement using the keyboard, pressure regulation, fluidic control (tube filling, washing) etc.
- Sequence: define a list of instructions for automatic synthesis, e.g. sample uptake and release, tip washing, heating etc.
- Run: execute a previously defined sequence (start/pause/stop), with status information



Software, configuration page active. On the left, the configurations of head and work plate are shown. The middle and right panels show the hierarchy of objects and the parameters for a selected object. Panels can be resized. Here the piezo tip is selected (red outline on head, red label in hierarchical view, template shown on the right).



How to define a sequence of events: first add a new step by selecting the tool (Luer1) from the hierarchical view of objects. On the right, select a step (Insert Needle) and the right work plate object (Mtp6) from lists and drop-down menus, and define into which well a Luer-size needle is inserted.

- Info: Information on software, manufacturer and hardware, keyboard short-cuts; also data export/import and error log

A pre-configured Windows computer tested with your system is provided for each instrument. In most cases, users need not install software on their own; F-Box updates will be installed remotely.

To make things as easy as possible, **templates** containing all the necessary data are provided only for those tools that are mounted in your instrument. If you add tools later, the necessary templates come with them.

Instruments with linear motors

The **BS5.1**, is a larger, more robust and even more flexible **24/7 production platform** featuring fast linear drives. A safety enclosure is mandatory for operation and available from GeSiM.

As required, certain functions can be placed on a second level. Typically these are optical devices such as collimator/fluorescent microscope to monitor processes in the upper (fluidic) level.

Please visit our homepage frequently to receive the latest news on this system.

A two-level BSyS5.1/E (B-LAB) for automatic “organ-on-chip” cell culture with liquid and cell handling on the upper and a fluorescence microscope on the lower level

Synthesis of radiopharmaceuticals, the first application

The machine is the result of a joint project funded by the German research ministry (BMBF) that was aimed at the synthesis of radiochemicals used in positron emission tomography (PET), a popular tool for research and diagnosis.

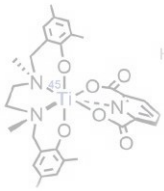
It has been shown that the synthesis of [^{18}F]-fluorodeoxyglucose (FDG) is feasible, especially because the small BSyS platform fits in a normal hot cell. Other than that, its size is scalable and the synthesis protocol freely definable:

- Robotic stage with multi-tool head for up to seven different tools
- Needle reservoirs
- Heatable reactor chamber (> 120 °C)
- Flow-through tube microreactor (Luer connectors)
- On the small platform a maximum of eight "kit plates" featuring reactors, vials, and solid-phase extraction (SPE) cartridges can be placed and run in parallel without manual interaction.
- A versatile yet easy to use graphical programme interface is used for simple system configuration and rapid development of new chemical synthesis strategies.
- Note: syntheses with [^{18}F] (FDG, FLT, FMISO, NaF, FES, FET, peptides) and [^{68}Ga] (peptides) can be run on the system, but users must develop and optimise their own strategy. At present no protocol exists that is working out of the box.

Small BSyS prototype with eight "kit plates" (containing septum vials, reactors, tubes, SPE columns etc.) and a needle holder, arranged as in a standard hot cell (W x D x H: 100 cm x 80 cm x 100 cm)

Example: titanium-containing antineoplastic agents

Research groups from Roskilde and Copenhagen, Denmark, use the BSyS to develop, among others, Ti-containing cytotoxic compounds without cisplatin cross-resistance. To monitor their biodistribution, the radioactive ^{45}Ti nuclide is used for synthesis, and the animals are analysed by PET imaging.



Another example: synthesis of biocompatible hydrogels

A synthesis strategy pursued at the Leibniz Institute for Polymer Research Dresden starts with the conjugation of polyethylene glycol (PEG) with cysteine-containing peptides such that the conjugate contains a terminal thiol group. At the same time, heparin is coupled with reactive groups, all in an automated way.

The PEG-peptide-thiol polymer is then linked to the heparin via a sulphur bridge, and other components (cells, adhesive peptides) are added. Star-PEG hydrogels are possible.

Other examples are the production of microcrystalline hydrogel strands via extrusion, combinatorial chemistry, peptide synthesis, …

The F-Box, the electronic brain of the instrument and also central control station for pressure, vacuum and liquids, plus bottles with liquid level control and four syringe pumps for dispensers

General technical specifications and location requirements

- Scalable size (small and large width), modular and flexible design
- Work plate:
  - Easy-to-mount holders/racks for slides, microtitre plates (MTPs), microcentrifuge tubes, septum vials, Luer-Lock needles, disposable pipette tips etc.
  - Racks with ports to e.g. HPLC or cuvette
  - Special kit plates (made to order)
  - Wash/dry stations, also for solvents
  - Tip alignment station, stroboscope, etc.
  - Heatable reactor chamber: temperature ramps to at least 120 °C, pressure up to 800 kPa (8 bar)
  - Flow-through tube microreactor (Luer)
- Multi-Z head with up to seven independently controlled Z-drives, more than one tool per drive possible
- Head tools:
  - Camera for image processing
  - Microcentrifuge "FlipTube" handler (snap-cap opening/closing)
  - Piezo dispenser for pl drops
  - Solenoid valve nl dispenser
  - Connectors for disposable tips *and* Luer cartridges (with ejector)
  - Vacuum gripper with 3-lumen pipette (for fluid/N_2/vacuum, works in 3 ml septum vials, e.g. for azeotropic drying)
  - UV lamp
  - Z-height sensor, etc.
- Specials: pneumatic powder dispenser (for µg quantities, GeSiM design) and powder storage; pipette with pH sensor for automatic pH adjustment
- Tools from the BioScaffolder and µCP instruments (e.g. extruders) are available
- Prepared for inert gas such as N_2
- Windows computer with control software to define all tools and synthesis steps
- Expandable; more features (e.g. plasma pen) to come in the future

The system needs a safety enclosure and also a certain lab infrastructure (temperature, power, compressed air, inert gas, vacuum, and certain connectors) for all of this. Please discuss the details with us before placing an order.

This flyer shows only a fraction of what is possible. Please review our other brochures or contact us if you have a specific problem in mind. We are keen on making tests or developing new hard/software to make your dreams come true.

2019

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