

3D-BIOPLOTTER Reseller Package

Index

- Principle of the 3D-Bioplotter (purpose, key features)
- Low Temp, High Temp, UV Head
- Parking Positions, default packages, multi-material
- Differences between Series, available upgrades
- Typical customer questions, typical reseller questions
- Conference strategies, sales processes, checklists
- What type of customers to contact
- Comparison with competitors

Supplied materials for resellers during workshop

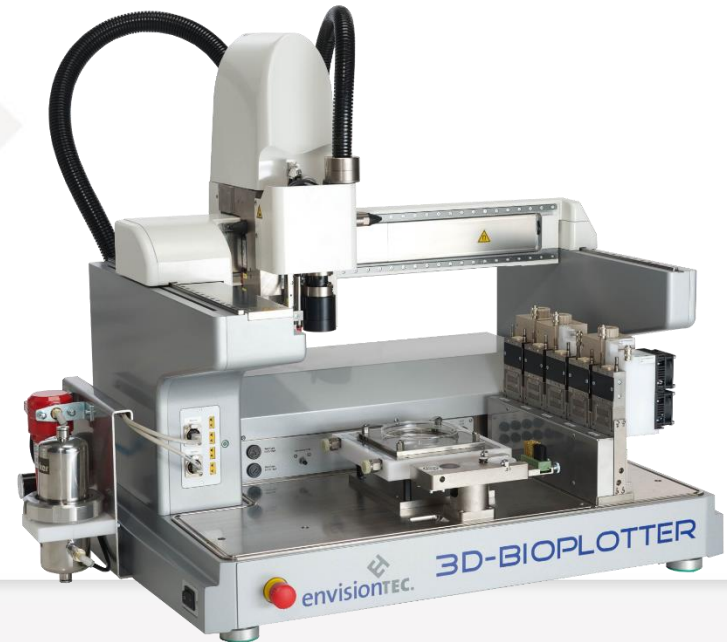
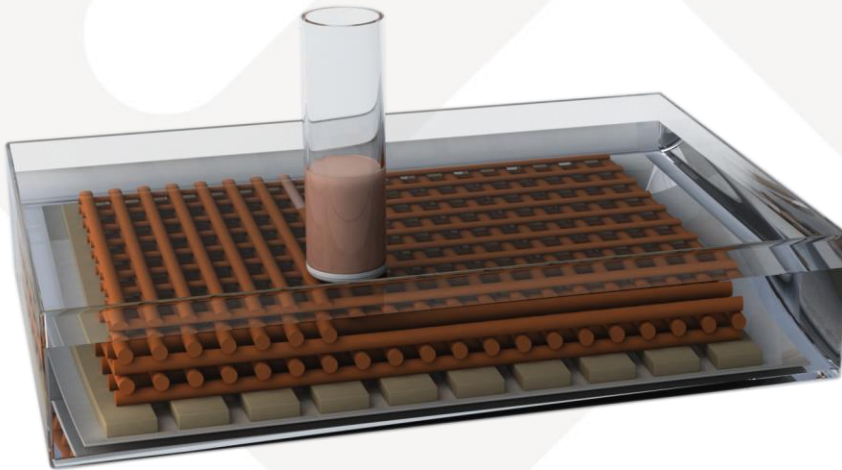
- Reseller presentation (this one) as PDF
- Reseller-Customer presentation as PDF
 - PPT available for translation, but translated PDF must be submitted to Envisiontec for approval
- English Pamphlet as PDF
 - PPT available for translation, but translated PDF must be submitted to Envisiontec for approval
- Customer questionnaire as DOCX
- 4 sample parts
- 1 piece of tubing for compressed air

What is the 3D-BIOPLOTTER

- A 3D printer that can process a large number of biomaterials into scaffolds for biomedical applications
- Extrusion based system with multi-material capability
- Open system for customer materials, not locked to any EnvisionTEC materials
- Developed at the Freiburg University in Germany in 2001
- Currently in the 4th generation since December 2009

Principle of 3D-BIOPLOTTER

Intuitive, easy to understand process: a liquid is dispensed from a syringe using air pressure, while moving the syringe in all three dimensions



Definition of a scaffold

Scaffolds are defined as three-dimension porous solid biomaterials designed to perform some or all of the following functions:

1. Promote cell-biomaterial interactions, cell adhesion, and ECM deposition,
2. permit sufficient transport of gases, nutrients, and regulatory factors to allow cell survival, proliferation, and differentiation,
3. biodegrade at a controllable rate that approximates the rate of tissue regeneration under the culture conditions of interest, and
4. provoke a minimal degree of inflammation or toxicity in vivo.

R. Langer and D. A. Tirrell, "Designing materials for biology and medicine," Nature, vol. 428, no. 6982, pp. 487–492, 2004.

Purpose of the 3D-Bioplotter

To fabrication temporary, bio-resorbable scaffolds for bone or soft tissue regeneration.

While these scaffolds dissolve in the body, the defective area should heal.

In the end, the patient has his own bone / soft tissue again.

Types of scaffolds

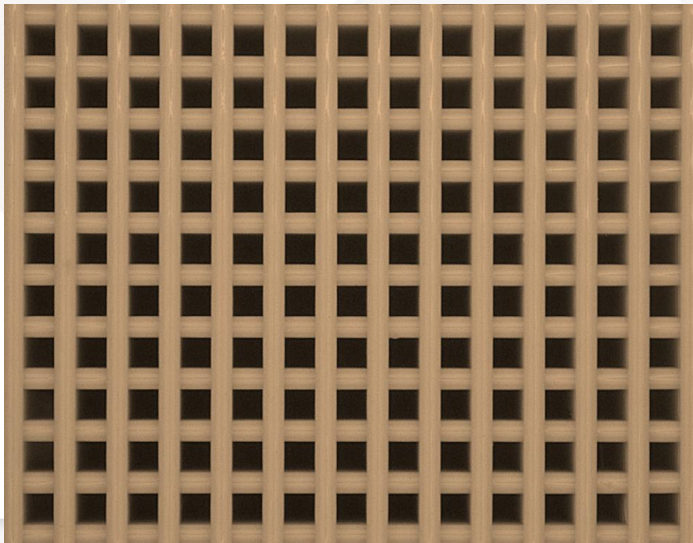
- Hard Tissue
 - Bone
- Soft Tissue
 - Cartilage
 - Trachea (throat)
 - Meniscus (knee, elbow)
 - Ears
 - Nose
 - Skin grafts
 - Heart valves, arteries
 - Internal organs



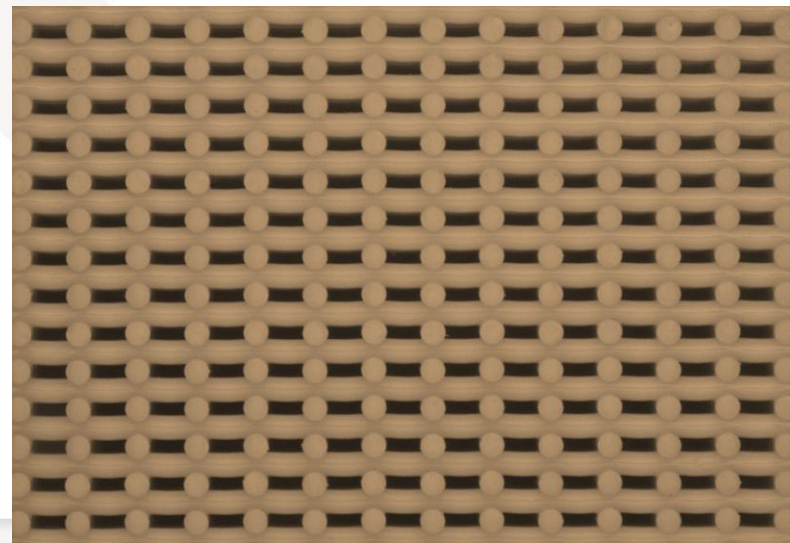
Interconnecting porosity of scaffolds

Necessary to allow the flow of nutrient media to cells inside the scaffold: speed up regeneration through cell growth inside and outside the scaffolds

Top view



Vertical cut through the object

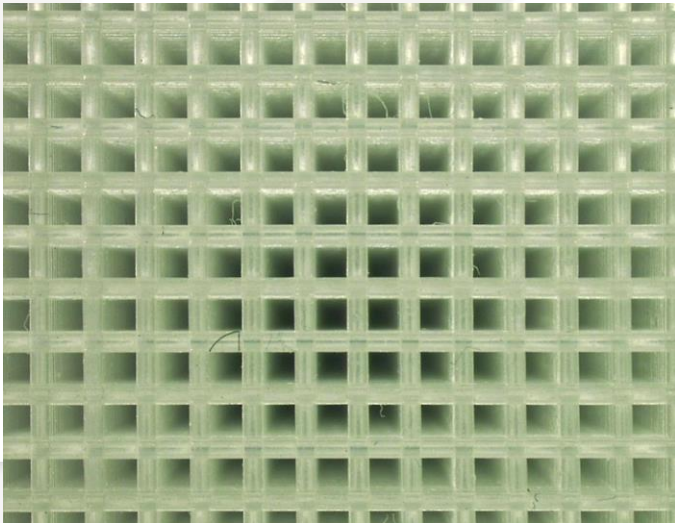


Control of the pore size and shape

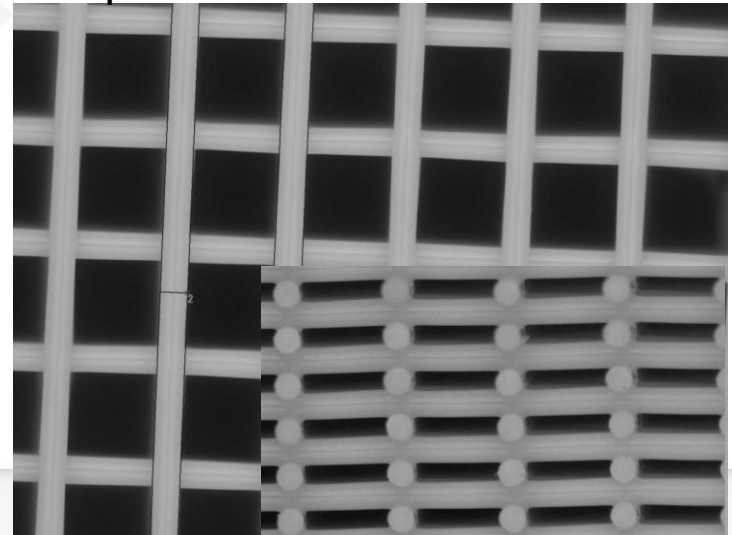
Minimum strand diameter 0.1mm, controlled through the size of the used needle tip

Minimum pore size required for cells: 400 μ m – 800 μ m pores

400 μ m strand size



250 μ m strand size



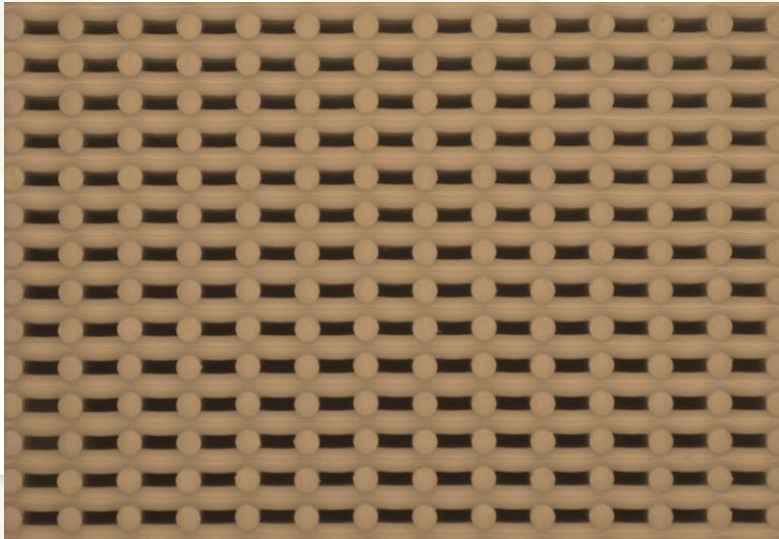
Pattern controls:

Change in angle from layer to layer: 0.1° steps

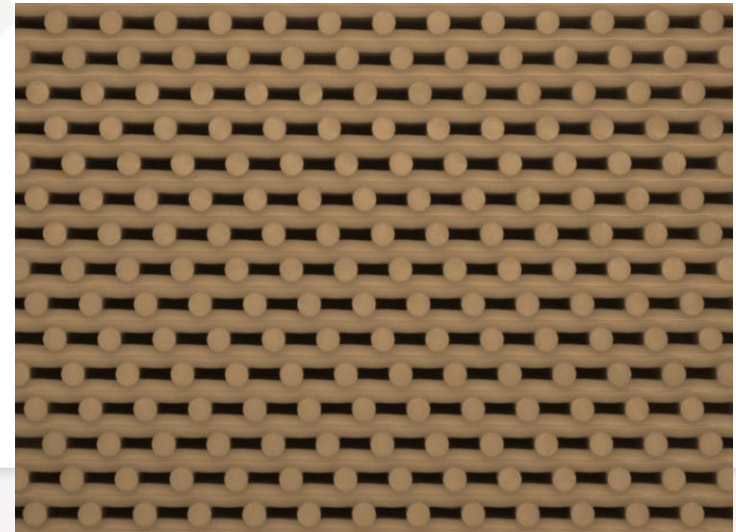
Distance from one strand to the parallel one: $10\mu\text{m}$ steps

Strand shift for improved cell adhesion: $10\mu\text{m}$ steps

Without shift

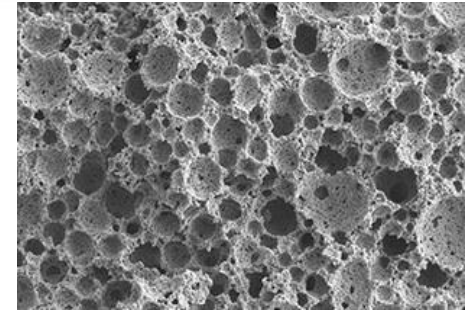


With shift



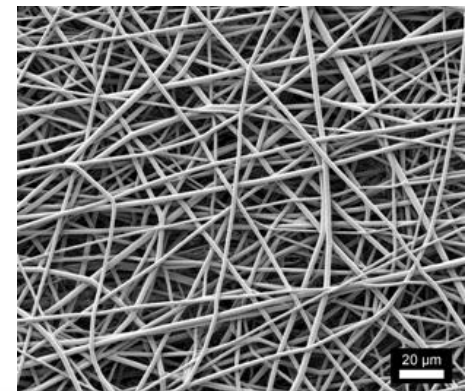
Other methods of building scaffolds

- Freeze drying
- Foaming
- Salt leaching
 - Very chaotic porosity, from nano to macro
- Casting
 - Limited interconnecting porosity
- Electrospinning
 - Non reproducible, irregular patterns
 - Very small fibers = very long build time



Foam scaffold

Electrospun scaffold



Key features of the 3D-BIOPLOTTER

Unsurpassed large choice of materials

Ceramic/Metal Pastes	Thermoplasts
Hydroxyapatite	PCL
Titanium	PLLA
Tricalcium Phosphate	PLGA
Sintering	Phase Transition

Hydrogels			
Agar	Soy	Alginate	Chitosan
Gelatin	Hyaluronic Acid	Fibrin	Collagen
Phase Transition	2 Component System	Precipitation	

Other Materials			
Polyurethane	Silicone	Acrylates	Graphene
Phase Transition	RTV 1	UV Curing	Evaporation

High Temp head + cartridge

- 30°C to 250°C
- Reusable stainless steel cartridge and needle tips



Bone Regeneration
Drug Release

PCL

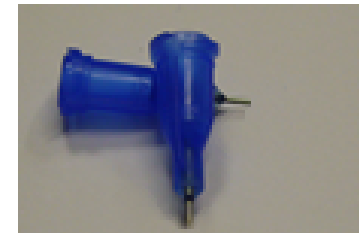
PLGA

PLLA

Low Temp head + cartridge

All other materials

- 0°C to 70°C (dependent on room temperature)
- Disposable polypropylene cartridges and needle tips



UV curing head

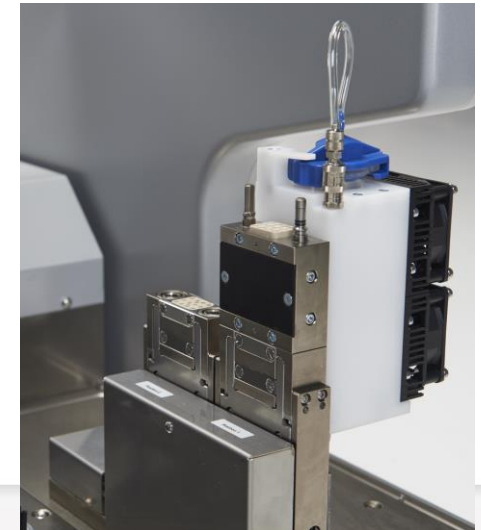
UV curable
materials
(acrylates)

- Powerful UV source at 365 nm (most commonly used)
- No other wavelengths currently available
- Apertures available for wide/thin beams and filters
- Not a dispensing head, only UV source:
 - Print Layer 1
 - Change to UV head
 - Cure Layer 1
 - Change to print head
 - Print Layer 2
 - etc



Tool Changing System

- 5 parking positions on the Manufacturer Series
- 2 parking positions on the Developer Series
 - Available upgrade to max 3 parking positions



Heads included in the default package

- 5 parking positions on the Manufacturer Series
 - 1x Low Temperature Head
 - 1x High Temperature Head
 - 3x empty parking positions
- 2 parking positions on the Developer Series
 - 1x Low Temperature Head
 - 1x empty parking position
- All head types usable on both machines, any configuration possible.
- Changes to default package possible upon request

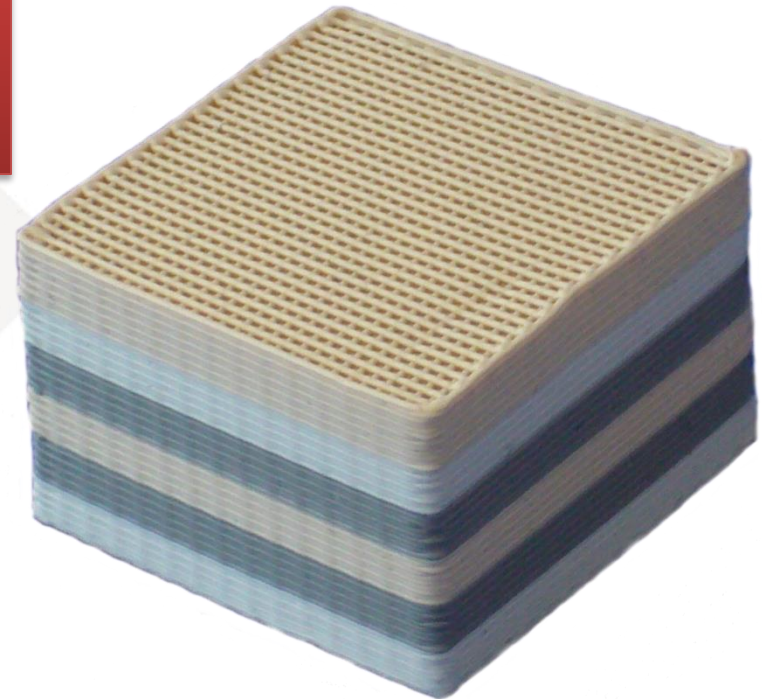
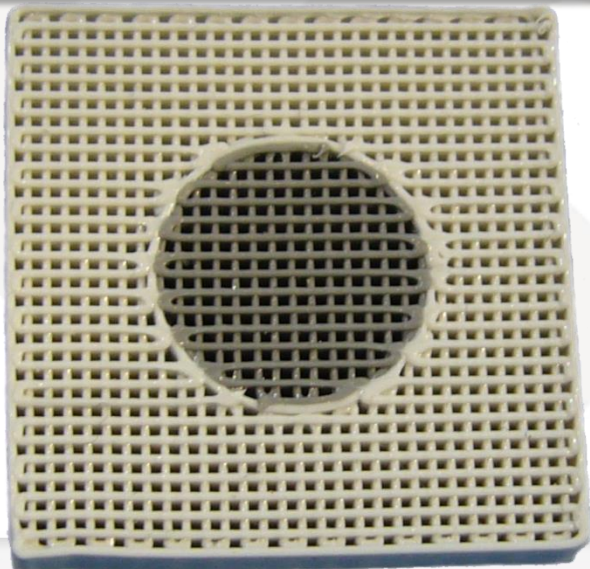
Other Temperature controls

- Platform can be temperature controlled (Manufacturer Series only) between -10°C and 80°C using external chiller
 - Cool to freeze materials in place (example: chocolate)
 - Low heat for higher cell survivability (body temperature)
 - High heat to evaporate solvents
 - High heat to avoid curling in polymer melts ($\sim 50\text{-}60^{\circ}\text{C}$ for PLLA)
- UV Head (maintain stable temperature = stable light source)

Multi-Material Capability

Up to 5 materials per object
(Manufacturer), or up to 2/3 (Developer)

Individual material deposits and needles
= no contamination



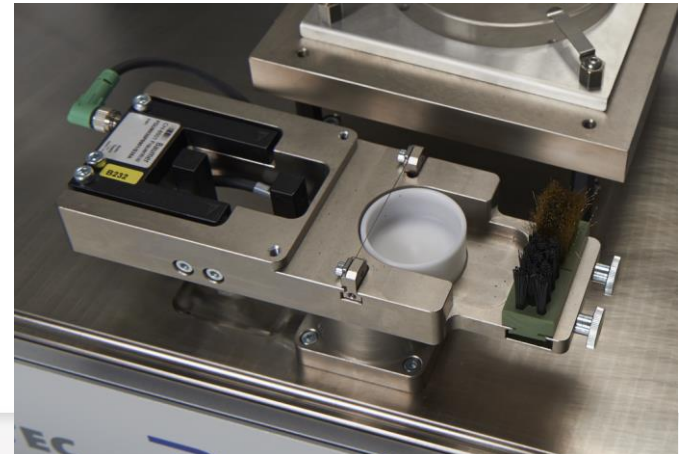
Differences between Series



MANUFACTURER	DEVELOPER
5 parking positions	2 parking positions
2 heads in default package	1 head in default package
Sterile Filter	-
Heatable Platform	RT Platform
Camera	-
4 Plugs for thermocouples	-

Calibration Processes

MANUFACTURER	DEVELOPER
<ol style="list-style-type: none"> 1. Press Z-Sensor (Z) 2. Clean 3. Place dot on grey/black plate 4. Take picture 5. Software analyses dot position (XY) 	<ol style="list-style-type: none"> 1. Move needle through X sensor (X) 2. Move needle through Y sensor (Y) 3. Center on XY sensors 4. Move up (Z) 5. (clean tip and repeat)



Major Upgrades / Attachments

MANUFACTURER	DEVELOPER
	1 parking position (max 3 total)
	Sterile Filter
Low Temperature Head (max 5 total)	
High Temperature Head (max 5 total)	
UV Head (max 1 total)	
Air Compressor (silent, max 7 bar)	
Laminar Flow Hood (Class II, Type A)	

Surrounding equipment

- Pre: Incubators
- Post: Bioreactors
- Post: Sintering ovens
- Post: Freeze dryers

Document “Setting up a Tissue Engineering Lab” available upon request for “new research groups”.

Pricing, delivery times, installation dates

- Contact our sales team
 - Björn Stickdorn (bjoern.stickdorn@envisiontec.de)
 - Mandy Berger (mandy.berger@envisiontec.de)
 - Pricing on machines, consumables, accessories
 - Delivery time of machine (usually 14 weeks after PO)
 - Installation dates (should be discussed shortly after PO; or before PO if part of the contract)

Support (Hardware, Software, Technical)

- Contact our support team
 - Krystian Koziarski (support@enviontec.de)
 - Available Monday-Friday, 9:00 to 17:00 German Time Zone
 - Remote support over Teamviewer solves 90% of the issues
 - Instructions sent to user or reseller (depending on complexity) if hardware needs to be checked or replaced
 - Only on rare occasions is a service visit by an Envisiontec technician necessary

Typical questions: Why “bio” plotter

- We use “BIO” materials (either bio-compatible or actually natural materials found in the body)
- The main application of the machine is “BIO” medical
 - Fabrication of implants
 - Research in Tissue Engineering
 - Research of biosensors
 - Etc.

Typical Questions: Type of dispensing system

- We only have time/pressure based systems
 - Syringe with liquid material
 - Apply pressure on the top, material comes out of the bottom
 - Like pressing a tube of toothpaste, then moving it in all three dimensions to build an object
 - Easy to clean, sterilize and exchange cartridges
 - Very little dead volume (~1ml)

Typical questions: Why no ink jet

- Ink jet is impossible to sterilize (we asked, washing with alcohol is not enough for hospitals / FDA).
- Ink jet is faster in printing individual dots, but much slower to build 3D object
- Can't build interconnecting porosity without support material because you're dispensing dots, not lines
- Cells don't survive the process well because of the "crash" against the platform

Typical questions: How to ensure sterility

- The machine can be sold with laminar flow biosafety cabinet (or customer can try to find one that fits)
- Materials only touch the following:
 - Cartridges + plungers (can be autoclaved)
 - Needle tips (can be autoclaved)
 - Platform attachments, like petri dishes or well plates (can be autoclaved or otherwise sterilized before use)
- Additionally, compressed air passes through a sterile filter before going into the machine (Manufacturer Series or Developer + Upgrade).

Typical questions: Why so expensive?

- Not locked to ET Materials, customers can use their own
- Medical grade materials can be used without contamination
- Sterile processing possible (with laminar flow)
- Cell printing possible
- Multi-Material capabilities
 - Join soft and hard tissue in one print job
 - Co-cultivation of different cell typed in specific positions
- Production level machine
 - High reproducibility of parts
 - Text logs after each print job for ISO / GMP documentation
 - Photographic logs available for Manufacturer Series

Typical questions: Which range of viscosities can it use

- There is no fixed range for minimum or maximum
 - Very low viscous materials have to solidify quickly
 - Very high viscous materials need a lot of pressure to dispense
- If a material is too viscous to process using a specific needle tip size, customers can use wider needle tips
 - Available in sizes 100 μm to 1.2mm
 - Still able to process, but lose resolution

Typical questions: How to print ceramics/metals

- Mix a fine powder or ceramic/metal with a binder into a viscous paste (similar to toothpaste)
- Sieve the paste
- Print the paste into a soft, fragile 3D object
- Freeze-dry the 3D object
- Sinter the 3D object at $>1000^{\circ}\text{C}$
 - The binder is removed
 - The particles melt together to a strong, pure ceramic/metal part

Typical questions: What is the resolution

- Directly dependent on needle tip size / material viscosity
- Smallest needle tip in our portfolio: 100 μm
- Per company policy, no sale of 100 μm tip in first 3 months
- Complex processing, materials must be specially adapted to print at this level: low viscosity but quick solidification
- There are sub-100 μm Luer Lock needle tips available
- Customers are free to use other needle tip vendors, does not affect warranty.
- Cells are 10-20 μm diameter. At sub 100 μm , cell death may occur due to pressure and shear stress during printing.

Typical questions: When is the 5th gen available

- Current generation is very well designed, very stable
- Customers are very happy with current design
- Continuous development of the software not only to fix bugs, but provide more functionality
- Modular head design of Developer and Manufacturer Series allow for new head types to be designed and added to old and new machines

= New functionality using the same machine + new attachment

Typical questions: Can I video job using built-in camera

- The camera is not looking to the needle tip, but is parallel to it
- Process:
 - Print layer 1
 - Take picture of layer
 - Print layer 2...
- This means, after 1 hour of printing, there are about 100 pictures to look through, takes about 1-2 minutes
- If a video was made, user would need to watch 1 hour of video to see if there are defects inside



Camera

Needle Tip

Typical questions: What are typical running costs

- Customers require power, compressed air, materials and some consumables
- First three are responsibility of the customer
- Typical consumables are:
 - Cartridges
 - Needle tips
 - Plungers (Low Temp only)
- For Low Temp head, consumables are single use
- For High Temp head, these can be recycled for use next day (place in solvent bath overnight)

Typical questions: Required Maintenance

- Customers are provided with preventive maintenance training
- Axes are mostly maintenance free, some lubrication required after one year typically
- Materials don't touch the heads, so no cleaning / maintenance of heads necessary during regular use
- Service kit available, recommended once per year, containing:
 - Lubricant for XY axes
 - Grease for Z axis
 - Cleaning cloth
 - Cleaning fluid
 - 2 brushes of each type (plastic, metal)
 - Tubing + adapter for High Temp head
 - Cooling / heating fluid for chiller (Manufacturer Series only)

Typical questions: Any hidden costs

- Costs for the machine will be included in the quotation
- But:
 - Quotations may not contain taxes
 - Quotations may not include shipping costs
 - Quotations may not include travel expenses for training personell
- Software licenses are for perpetual for that version and 1 PC, but may include a activation cost every 6 months

Typical questions: What materials does ET provide

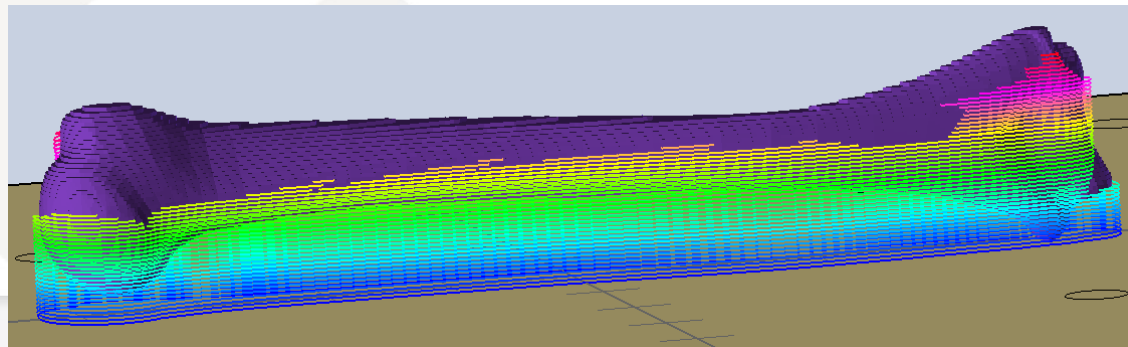
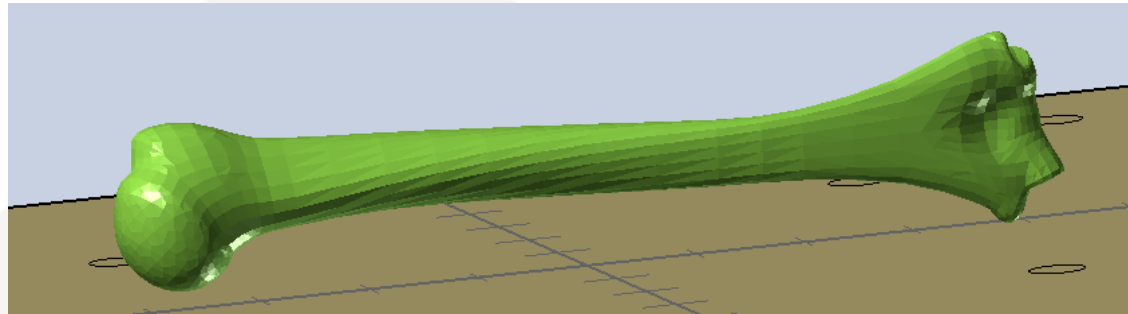
- With the machine, Envisiontec will provide demo materials for testing the corresponding heads + training
 - Silicone (Low Temperature)
 - Sugar based support material (High Temperature)
- Official sales materials at the moment are:
 - High Temp support material, sugar based
 - Low Temp support material, cellulose based
 - PCL, 45kDa, research grade

Typical questions: Why would a customer need ET materials

- When using their own materials, customers must spend time choosing appropriate materials / compositions / mixtures, etc.
- Then, customers must spend time finding process parameters to correctly dispense materials, which may take days to complete
- ET materials come with full instructions for immediate use, so great savings in time if their main purpose is the final part, not material research.

Typical questions: Why would a customer need support materials

- Complex, organic shapes require support structures



Typical questions: Can the materials include solvents

- When using the Low Temperature Head, materials may include solvents that do not affect PE or PP.
- The use of the plunger is mandatory when using solvents, to ensure gases do not flow back into the 3D-Biplotter
- This is why solvent materials can't be used with the High Temperature Head: no plungers available

Typical questions: Can I get a copy of the manual

- Manuals are only supplied to customers during the installation of the machine, no exceptions.
- A physical and a digital copy of the manual is supplied during the installation
- Resellers are allowed to copy the PDF for their private use during the installation, but are expressly forbidden to forward it to other customers or put it online

Typical questions: Can I get some screenshots

- Partial screenshots are provided only in very exceptional cases
- We prefer customers to visit us at Envisiontec or during a conference/show, where we not only show screenshots, but can display workflow, ease of use, etc
- Reference customers can be provided upon request for visit to see machine in use by other customers and get their feedback/opinion

Typical questions: How can the customer be sure his STL/material works

- This is the most typical question
- Check the literature pages for the material
- Send us the STL file / material description, we'll let you know
- If customer requests it, we can test the STL file / material at our office in Germany. 1-2 samples will be created
- This applies post-sales as well: customers are welcome to contact us if they have difficulties with the machines

Typical questions: How long is the warranty

- The regular warranty of the machine is 1 year, starting from the installation date by an Envisiontec technician
- We have extensions (AMC) available, which can be purchased with the machine or just before the previous warranty / AMC ends
- Warranty or AMC do not include a service visit
- If customer wants to buy AMC after warranty / AMC ends, a paid visit by a technician is required first to ensure there are no current defects

Typical questions: Are software updates for free

- During warranty or AMC, all software updates are for free
- After warranty / AMC:
 - Bug-fixing updates will be for free
 - Major updates including new features may have a cost
 - Software updates required to use new purchased hardware are for free (example, new head requires software update = free when customer purchases new head)

Reseller questions: Can we show the machine at customer site

- Unfortunately, no.
- Large, heavy machine with table, compressor, etc necessary
- Expensive to ship + handling customs
- A technician from Envisiontec would need to accompany the machine to customer site, install, show, pack it again
- We prefer customers visit us or meet us at shows/conferences

Reseller questions: Can we show the machine at conference / show X?

- Possibly, but typically not during the same year.
- Show budget planning at Envisiontec in October for following year
- Feel free to send us show information including:
 - Expected number of participants (>300)
 - Date and location
 - Main topics (biofabrication, regenerative medicine, 3D printing...)
 - Possible competitors exhibiting at the show
- Decisions made case by case

Reseller questions: Used / old machine for sale?

- We neither have used nor previous generation machines for sale.
- Our customers typically use the machine for years non-stop
- No customer has yet returned a 3D-Bioplotter to Envisiontec permanently

Typical questions: How long installation & training

- The 3D-Bioplotter package includes 3 day installation and training
 - Day 1 – only installation, make sure machine is 100%
 - Day 2 + 3 – Training in Software, Hardware, testing using supplied demo material
- Some customers want to test their shapes/materials while we're on site
 - Optional day 4 – Testing customer STL / materials while our technician is on site helping

Typical questions: Safety precautions / features

- Because of magnetic linear motors, people with pacemakers must stay 0.5 m away from a 3D-Bioplotter
- Motors have force feedback and will stop if they recognize something on the way
- 2x Hard Drives in the industrial PC running in RAID 1 (automatic backup of all files)
- Automatic backup of config files every 3 days

Conference Strategies / Face to Face discussions

- What is the main material being used?
- Can we print it?
- What is the solidification process?
- Are any additives used (ceramic powders, growth factors, cells, etc)?
- What parts should be built?
- Are self-made machines being used or manual work?
- Can we sell them a machine?

Booth Strategies

- Customers will not stay long at a booth if not engaged
- Just giving out brochures without discussion is not sufficient
- Have parts on the booth and have customers touch them. Most are surprised we can do soft (silicone)
- After a few seconds on the booth, ask about materials they wish to print and compare to our list
- Ask about type of parts they wish to print (bone, skin, ...)

What to do with special requests

- Delivery times
 - Ask us if shorter/longer deliver times are possible before the PO
- Installation dates
 - Ask us if a specific date can be met before or shortly after PO
- Sales terms
 - We do have some flexibility, for example payment after delivery
 - Ask us (must be accepted case by case)
- Hardware/software
 - Hardware/software development will be discussed directly with the customer regarding feasibility and cost

Reseller vs. Distributor

- Distributor is responsible for sample fabrication, sales, import, installation, maintenance, technical support
- Reseller is responsible for sales and import. Everything else is handled by Envisiontec. Smaller commission, but much less work and almost no responsibility.
- Bioplotter customers have very technical questions beyond 3D printing: cell-material interaction, for example
- We will only start consideration of upgrading reseller to distributor after the sale of 5 machines, plus one demo machine at distributor site

Reseller vs. Distributor

- Percentage of machine price, none on consumables
- May be called upon to help repair the machine, if necessary
- Reseller doesn't need to have machine on site
- Distributor **MUST** have demo machine (large investment)

- No country exclusivity, but customer reservations
- Reseller / Distributor must sell Bioplotter as exclusive bioprinter

Reseller reservation process

- To avoid resellers spending their time fighting against each other, we do customer reservations
- Contact us (Björn) regarding intent to contact new customer, we'll let you know if someone is already in contact with them.
- If another reseller contacts this customer, let us know, we'll tell that reseller to back off.
- Reservation hold for a maximum 1 year, extensions will be handled case by case

First contact processes

- Send “thank you” email, CC Envisiontec Germany
- Customer is reserved to reseller
- A few days later, an Envisiontec technician will ask customer if all technical questions have been answered, CC reseller
- Customer may request reseller to visit, test of materials/STL (free of charge for small quantities), etc
- Customer may ask for quotation for grant application

PO processes

- Customer informs reseller that money is available for purchase
- Site preparation visit, discussion of exact materials/applications
- Reseller informs Envisiontec of upcoming sale
- Discussion on (if requested by customer):
 - Delivery times
 - Sales Terms
- Envisiontec technician may contact customer to ensure configuration is correct, no parts missing
- Customer places PO
- Reseller should ask customer, when installation would be ok based on discussed delivery times + shipping/customs delay

Site preparation visit + discussion of details

- Use checklist for
 - Room conditions (temperature, humidity, size)
 - Electrical conditions (type, number of power sockets available)
 - Compressed air available (type, max pressure, adapter)
- Discussion of details
 - Which materials to be used?
 - Cells to be used during printing process?
 - Which parts for which specific application to be printed?

Site preparation checklist – page 1

- Stable table / Envisiontec BSC / Own BSC
- Work surface 120 x 75 cm or larger
- Elevators / doors will fit palette
- 1m above palette for unpacking
- Temperature controlled room / small temp deviations
- Temp: 18 – 30°C, optimal 18-22°C
- Humidity: 10-90% non-condensing, optimal 45-60 %

Site preparation checklist – page 2

- 3x power sockets, 110-220V, 50/60Hz, 16 A each
- Power supply fluctuations? Require UPS?
- Electrical socket type _____
- Compressed air supply 6-10 bar (85 - 145 psi)
- Adapter for 3D-Bioplotter compressed air tubing (5mm inner, 8mm outer diameter)
- Ethernet ports close by / WiFi available for support?
- Hotel close to installation site for Envisiontec personnel

Installation processes

- Machine is delivered to customer site and left unopened
- Envisiontec technician opens the box, makes short inventory and installs / calibrates / tests the 3D-Bioplotter
- Checklist is filled, copy available upon request
- 2/3 days of customer training, reseller attends to understand technology; learn 1st level support; translate
- Signing of acceptance protocol. Either
 - Envisiontec – Reseller / Reseller – customer
 - Envisiontec – Customer; copy to Reseller

Post-sales processes

- Typically, customers don't contact us for a few weeks sales (testing period)
- First questions may be about things seen during training and then forgotten, or very specific material questions
- Reseller should contact customer after a few weeks/months to ask if customer requires:
 - Consumables
 - Technical advice
 - Material recommendations

What type of academic customers to contact

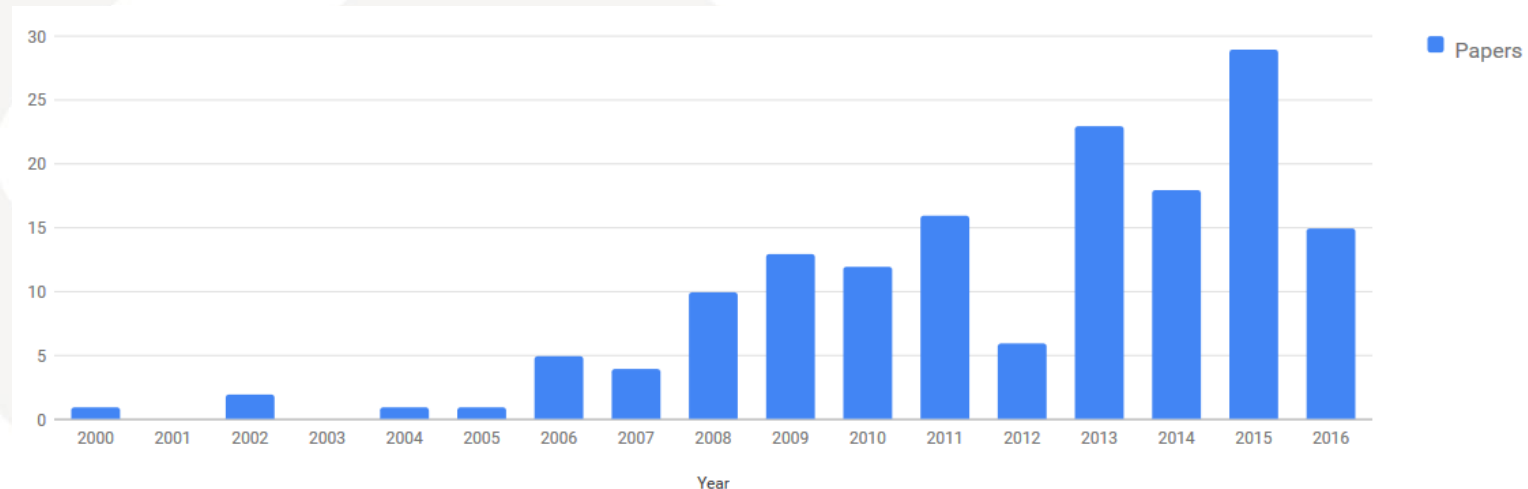
- Institutes, research hospitals or groups researching:
 - Biofabrication
 - Regenerative Medicine
 - Tissue Engineering
 - Cell Printing
 - Organ Printing

What type of industry customers to contact

- Industry customers
 - Veterinary hospitals or clinics
 - Hospitals
- interested in
- Scaffold fabrication
 - Implant fabrication using 3D printing
 - Drug testing using 3D printed tissue samples
 - Drug release testing
 - Animal / human clinical trials using 3D printed parts

3D-BIOPLOTTER research papers

Large list of published work using 3D-Bioplotter (>150)
 = customers starts from high level, not from zero



Full list of 3D-Bioplotter papers available at:
www.envisiontec.com/3d-bioplotter-research-papers/

3D-Bioplotter vs RegenHu Discovery

3D-Bioplotter	RegenHu Discovery
Standard, all machines alike	Custom made, all machines unique
Comparable results to previous works	Non-comparable results
Modular design, change configuration as required by current work	Fixed design, can't change configuration
Max volume 150 x 150 x 140mm	Max volume 130 X 90 X 60mm
Fixed printing platform, low vibrations	Moving platform, part vibrates/shakes
All inputs through software	Pressure, temperature hardware set
Change High Temp material in seconds	Must clean complete High Temp head before changing: minutes to hours
Platform Temperature Control	No temperature control of platform

Bioplotter vs Regenovo

3D-Bioplotter	Regenovo
Standard, all machines alike	Bad Chinese copy of 3D-Bioplotter
Comparable results to previous works	3 major machine versions in only a few years; nothing to compare to; future issues with software development and spare parts
Automatic head exchange	Manual head exchange
All inputs through software	Temperature set over hardware
Temperature control in Z-axis and parking positions	Temperature control only in Z-axis
Fixed printing platform, low vibrations	Moving platform, part vibrates/shakes
>150 papers by customers worldwide	1 main user in China (developer)

Bioplotter vs Gesim Bioscaffolder 3.1

3D-Bioplotter	Bioscaffolder 3.1
Standard, all machines alike	Only a few machines with customers
Comparable results to previous works	Customers quickly re-design the machine to make it work as required, making all machines unique
Low Temp, High Temp and UV Head	Only Low Temp Heads
Excellent reproducibility, accuracy	Badly formed objects on brochures
All inputs through software	External control box for pressure
Max volume 150 x 150 x 140mm	Max volume 100 x 346 x 40mm
User friendly software, specially in multi-material design	Limited, unfriendly software. STL only available since 2015, simple patterns

Bioplotter vs nScript

3D-Bioplotter	nScript
Standard, all machines alike	Custom made, all machines unique
Comparable results to previous works	Non-comparable results
Modular design, change configuration as required by current work	Fixed design, can't change configuration
Change Low Temp material in seconds	Must clean complete Low Temp head before changing: minutes to hours
Automatic needle tip calibration	Manual needle tip calibration
Max number of heads: 5	Max number of heads: 1
User friendly software, specially in multi-material design	Limited, unfriendly software. Can't open STL files