

Prototype implementation of an assembly system for tissue engineered constructs

M. REISCHMANN, R. MERZ, L. SCHULTZ, L. E. WEISS

In the course of the research described in this paper a prototype assembly system for the automated fabrication of customized, biodegradable bone implants for tissue engineering applications has been developed. This work is part of a collaborative effort between the Handling Laboratory (hLab) of Fachhochschule Vorarlberg and the Bone Tissue Engineering Center (BETC) of Carnegie Mellon University. Bone implants are built up using thin layers of highly porous, biodegradable polymer scaffold materials. These layers can be seeded with cells prior to assembly. The main focus of this work is robotic handling of the prefabricated polymer layers. Additional components that are addressed include the cutting of contoured polymer layers from sheetstock and the assembly of the 2 1/2 dimensional layers to form 3D bone implants. Cutting tests have been performed to assess different cutting technologies. Assembly tests with mechanical connectors and fibrin adhesive have also been conducted. These components are integrated within a robot cell to demonstrate overall system feasibility.

Keywords: tissue engineering; robotics; artificial bone implants

Implementation eines Prototyp-Systems für den Aufbau von künstlichem Knochengewebe. In der hier beschriebenen Forschungsarbeit wurde ein Prototyp-System für die automatische Herstellung von maßgefertigten, biologisch abbaubaren Knochenimplantaten für Anwendungen im Bereich des Tissue Engineering entwickelt. Diese Arbeiten sind Teil eines Gemeinschaftsprojekts zwischen dem Handlinglabor (hLab) der Fachhochschule Vorarlberg und dem Bone Tissue Engineering Center (BTEC) der Carnegie Mellon University. Die Grundstruktur der Knochenimplantate wird aus dünnen Schichten eines hochporösen, biologisch abbaubaren Kunststoffmaterials gebildet. Vor dem Zusammenbau können die Schichten mit Zellen durchsetzt werden. Der Schwerpunkt der Arbeit liegt im Bereich der robotischen Handhabung der hochporösen Kunststoffschichten. Weitere Gebiete, die behandelt werden, sind das Ausschneiden von Kunststoffsubstraten aus dem vorgefertigten Grundmaterial und das Verbinden der einzelnen, zweieinhalbdimensionalen Schichten zum dreidimensionalen Implantat. Zur Belegung der Durchführbarkeit des Ausschneidens der Substrate wurden Schneideversuche mit verschiedenen Verfahren durchgeführt. Versuche zum Verbinden der einzelnen Schichten wurden mit mechanischen Verbindern und einem auf Fibrin basierenden Klebstoff durchgeführt. Zur Demonstration der allgemeinen Machbarkeit wurde das Gesamtkonzept in einer Roboterzelle implementiert.

Schlüsselwörter: Tissue Engineering; Robotik; künstliche Knochenimplantate

1. Background

A multidisciplinary research group at Carnegie Mellon University (CMU) is developing a method to fabricate bone substitutes for reconstruction of diseased or damaged bone based on tissue engineering methods (Weiss, 2007). The bone implants are constructed of highly porous biodegradable scaffold materials. The scaffold material is seeded with cells (e.g., bone cells or stem cells harvested from the bone marrow), or growth factors, or both. Once implanted into the patient, the scaffold material degrades and is replaced with healthy bone by host tissue in growth. The main benefit of manufactured bone material is to provide an off-the-shelf alternative to autografts and allografts.

The Bone Tissue Engineering Center (BTEC) at CMU is developing a process to incrementally build up substitute bone materials from polymers. The process permits selectively seeding of the polymer layers with cells and/or growth factors during the build up cycle (Fig. 1). This method is based on the idea of Solid Freeform Fabrication (SFF).

For this newly developed SFF-process for bone implants a CAD model of the three-dimensional structure of the implant is sliced into layers with an approximate thickness of 0.5 mm - 1.0 mm. Every layer is cut from a sheet of scaffold material and is seeded with cells or growth factors or both. The individual layers are stacked on top of each other and connected with biodegradable connectors.

REISCHMANN, Martin, Dipl.-Ing. (FH), Absolvent der FH-Vorarlberg, Studiengang Technisches Produktionsmanagement, Höchststraße 73, A-6850 Dornbirn und Entwicklungsingenieur, Leica Geosystems AG, Heinrich-Wild-Strasse, CH-9435 Heerbrugg.
MERZ, Robert, Prof. (FH) Dipl.-Ing. Dr., FH-Vorarlberg, Wissenspool Technik, Höchststraße 73, A-6850 Dornbirn. SCHULTZ, Lawrence, Senior Research Engineer, WEISS, Lee E., PhD, Principal Research Scientist, Carnegie Mellon University, The Robotics Institute, 5000 Forbes Ave., 15213 Pittsburgh, PA, USA. (e-mail: martin.reischmann@leica-geosystems.com)

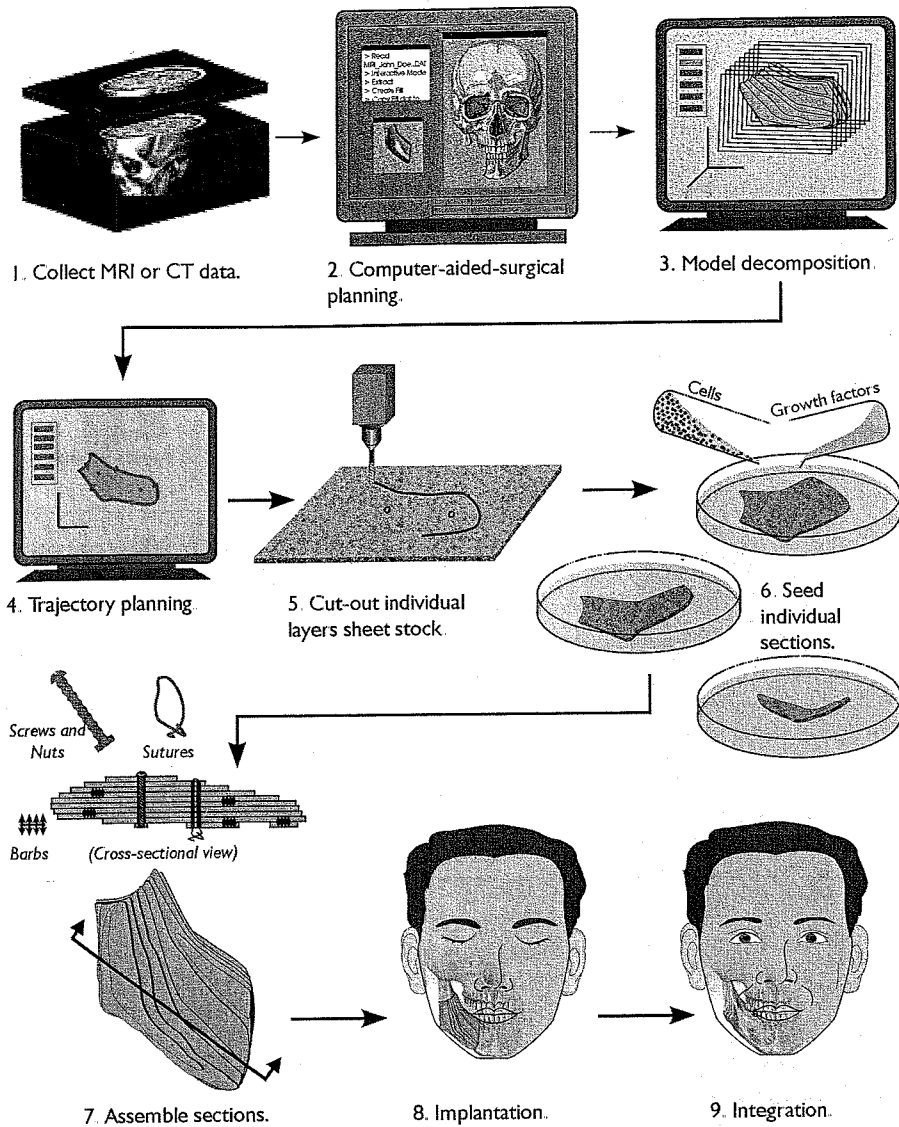


Fig. 1. Incremental build-up of tissue engineered bone substitutes

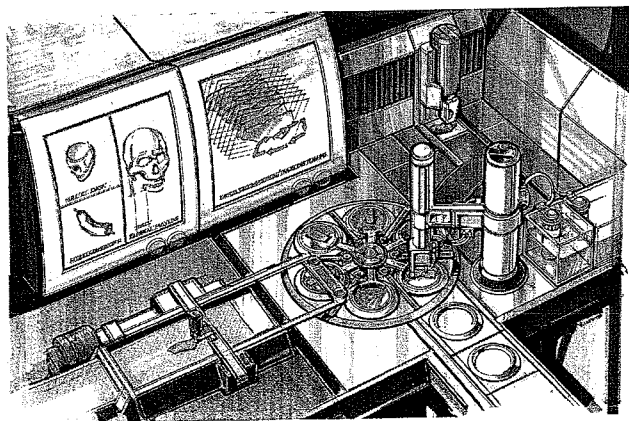


Fig. 2. Vision of a CAD/CAM aided bioreactor

One goal of BTEC is to develop a robot-based CAD/CAM bioreactor (Fig. 2) to grow larger customized bone implants *in vitro*. As part of this effort, a project to develop and implement the main components of a prototype Assembly System for Tis-

sue Engineered Constructs (ASTECC) was carried out by the Handling Laboratory (hLab) of Fachhochschule Vorarlberg. The goal of this project, which is described in this paper, was the development and implementation of a robot cell which can automatically build three dimensional bone implants based on the method for layered manufacturing of tissue which is currently developed by CMU.

2. Overview of the Assembly System for Tissue Engineered Constructs (ASTECC)

The Assembly System for Tissue Engineered Constructs (ASTECC) was the first attempt to realize the vision of the engineers at Bone Tissue Engineering Center (BTECC) which is a robot based CAD/CAM bioreactor (depicted in Fig. 2). A concept for the steps 5 to 7 of the engineering paradigm shown in Fig. 1 was proposed and implemented in the Handling Laboratory (hLab) of Fachhochschule Vorarlberg (Reischmann, 2001).

The robot cell developed by FH-Vorarlberg (Fig. 3) consists of three stations. The stations are used to cut the substrate material (Fig. 1, step 5), to seed the substrate layers with cells and/or growth factors (Fig. 1, step 6) and to assemble the substrate layers (Fig. 1, step 7). The process steps were developed under

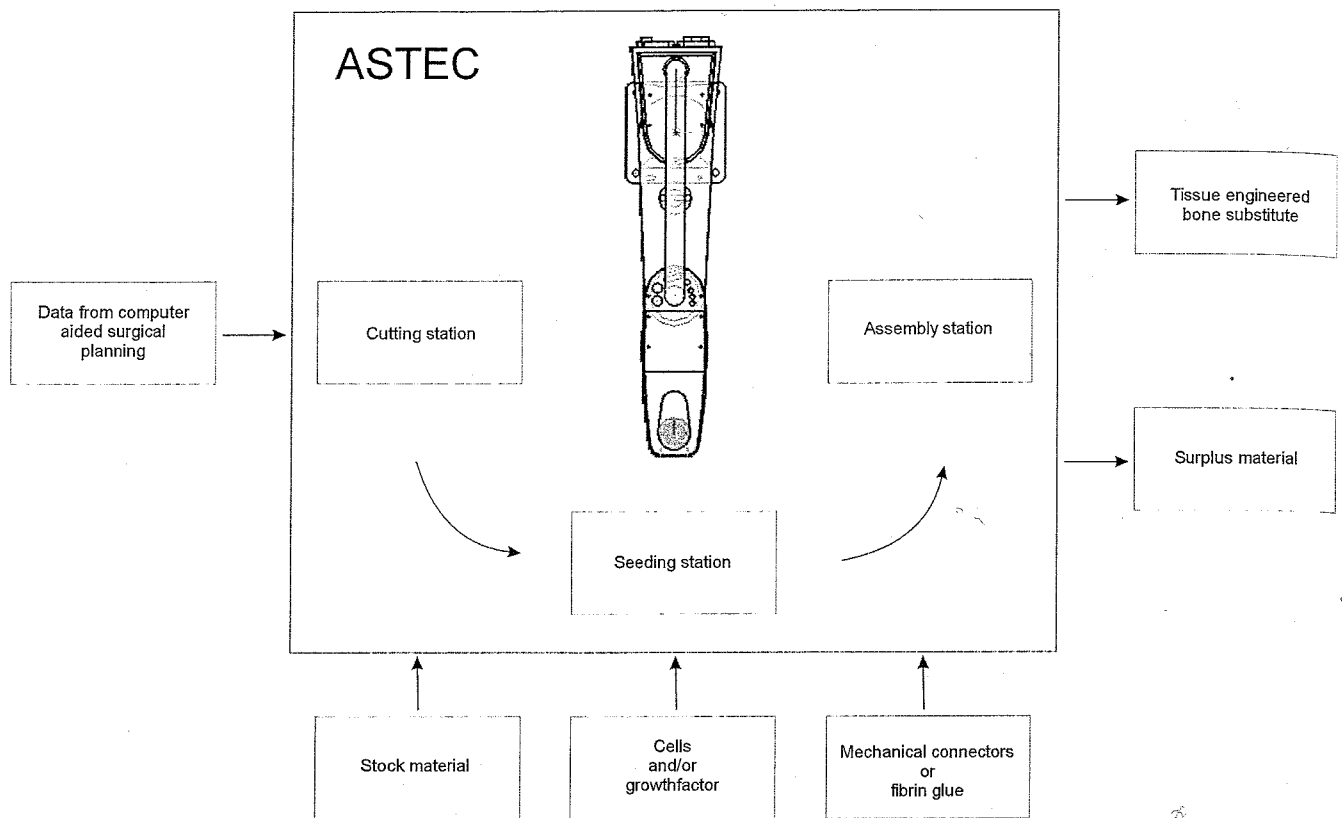


Fig. 3. General concept of the ASTEC-robotic cell

consideration of a maximum flexibility concerning the substrate shape (the physiological size limitation is $12 \times 12 \times 12 \text{ mm}^3$), minimum cell killing during the process and the feasibility to set up the process in a sterile environment.

Raw materials for the production of the implant are 0.5 mm – 1.0 mm thick, highly porous, biodegradable polymer sheets. The polymer sheets are produced using a solvent-casting procedure followed by a particulate-leaching technique. In the cutting station all layers (substrates), which are necessary to create the implant, are cut from the polymer sheets. The cutting paths are controlled by the data of the 3D computer model of the implant (Fig. 1, step 5). As part of the study cutting technologies such as water jet cutting and laser cutting were evaluated. After performing several tests water jet cutting was selected as the appropriate cutting technology and a set of suitable parameters was developed.

After cutting, the substrates are seeded with cells and/or growth factor (Fig. 1, step 6). Therefore, a station has been developed which consists of a tank to take up the cell/growth factor solution, a needle matrix used for fixation of the substrates and a stripper-plate to strip the substrates from the needle matrix.

To move each single substrate from station to station a special robot end-effector (Fig. 4) has been developed. The end-effector is capable of reliable gripping and manipulating the substrates in dry and soaked condition. To grip a substrate two 0.3 mm thick needles, which are positioned in a crosswise style, are used. This enables the end-effector to grip very small substrates. During the development of the end-effector special attention was given to minimize cell killing and the deformation of the substrate during the gripping and manipulation procedure. Therefore, a weight compensation unit was developed. In addition, an analog inductive sensor is used to measure the thickness of the substrates during the manipulation procedure to allow compensation of deviations in the substrate thickness.

After seeding the substrates with cells and/or growth factor the individual layers are assembled to form the desired implant in the third station of the robot cell (Fig. 1, step 7). Special biodegradable pins were developed to connect the individual layers. The pins are mechanically forced into the layers. Because this method causes a substantial amount of unseeded material throughout the implant the feasibility of using commercially available fibrin adhesive to connect the layers has been investigated. The results of the tests look very promising, thus further investigations concerning all biological aspects of fibrin adhesive connection of the substrates are currently performed at the BTEC.

After the assembly of all substrates the implant can be taken from the robot cell and directly implanted into the human body.

3. Details of ASTEC

3.1 Robot end-effector

The robot end-effector consists of three different units. These are the gripper with crossed needles, a weight compensation unit (WCU) which is used to adjust the contact force on the substrate and to measure the thickness of the layers, and a robot interface. The WCU and the gripper are described in depth in the following subchapters. For the robot interface a commercially available tool exchange system has been used, so no further explanations are given.

The principle task of the WCU (Fig. 5) is to compensate the weight of the gripper and thereby control the pressure, which is applied onto the substrate. An additional task of the WCU is to measure the thickness of the substrate to determine deviations of the layer thickness. The WCU has a linear motion range of 3 mm, which enables it to measure a wide distribution of layer thicknesses. To achieve weight compensation the pressure in a pneumatic low friction cylinder is adjusted to the pressure at

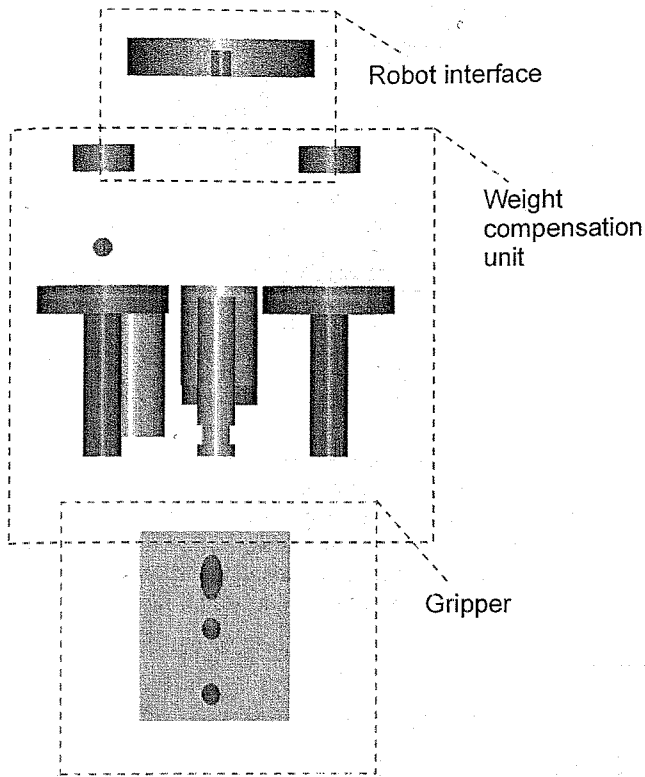


Fig. 4. Robot end-effector

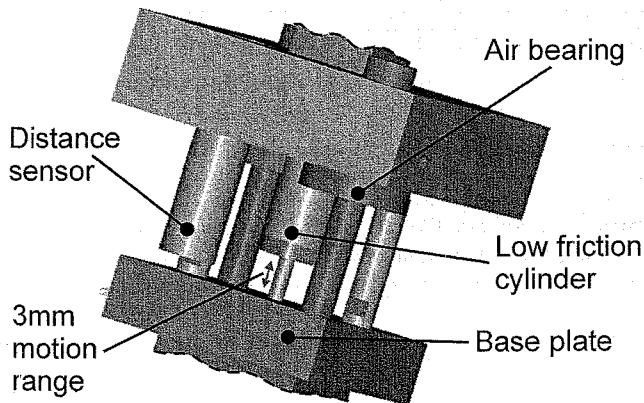


Fig. 5. Weight compensation unit

which the force produced by the cylinder is equal to the weight of the gripper.

To minimize the friction during the movement of the WCU the pneumatic cylinder is designed as low friction cylinder. Further, there are two air bearings implemented in the WCU to guide the movement of the WCU with a minimum of friction loss.

An electrically adjustable proportional pressure regulator controls the pressure in the low friction cylinder. The input voltage of the pressure regulator is directly proportional to the output pressure. The weight compensation pressure (p_{comp}) is determined manually by iterations. By varying the voltage, pressure respectively, around p_{comp} the contact force that is applied on the substrate can be varied. Hence, the weight of the gripper can be compensated and the contact force on the substrate can be controlled. This procedure minimizes cell killing and the deformation of the substrates.

An inductive, analogue distance sensor is used to measure the distance to the base plate of the WCU. The measured distance is used to determine the thickness of the substrate in order to detect deviations of the layer thickness. This is necessary since deviations in the layer thickness can be as large as 10% and will lead to an inaccurate 3D bone substitute when used without compensation (see Fig. 6).

The concept of the needle gripper with crossed needles (Fig. 7) has been designed to have a maximum of flexibility concerning the substrate size and to minimize cell killing by minimizing the area of the substrate which is influenced by the gripper. Two 0.3 mm thick commercially available acupuncture needles, which were glued to two micro pneumatic cylinders, are used to pierce into the scaffold material. The micro pneumatic cylinders are mounted into bushings. The bushings are necessary to take up the clamping force applied by headless screws which are required to hold the needle assemblies in place. The position of the needle assembly is manually adjusted during calibration of the end-effector.

3.2 3D model correction algorithm

As shown in Fig. 6, deviations of the layer thickness, if not detected and compensated, lead to an inaccurate 3D structure. Thus, it is necessary to measure the thickness of the layers and if necessary change the number of layers which are necessary to build up the 3D model during the assembly procedure. If the number of layers has to be changed the cutting trajectories for the layers have to be adapted as well.

A schematic build up sequence is depicted in Fig. 8. The correction mechanism is highlighted in red. Variables are highlighted in blue. The program language used to describe the al-

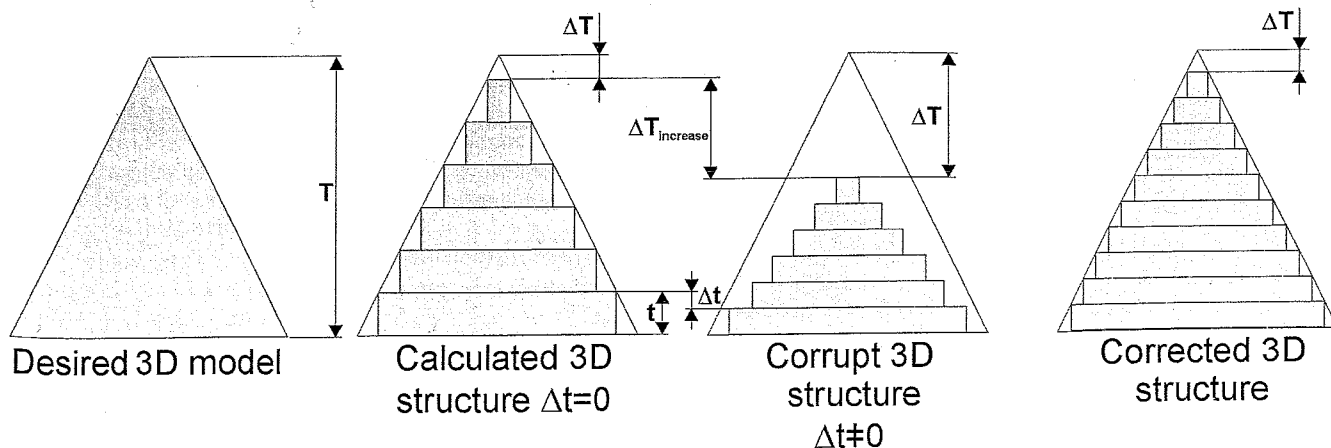


Fig. 6. 3D model correction

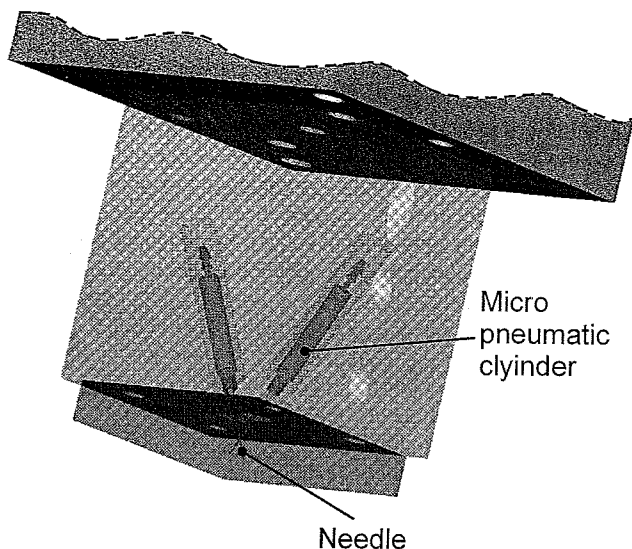


Fig. 7. Gripper

and not eliminated totally. The reason for this is that until deviation of the layer thickness is detected (after the seed procedure) a number of layers have already been cut & placed in the seeding stations.

4. Results

As part of BTEC's effort to develop a CAD/CAM bioreactor prototype robot cell for constructing tissue engineered bone implants has been developed and implemented at the hLab Fachhochschule Vorarlberg. The robot cell is based on a manufacturing method for layered build-up of tissue, which is currently under development at CMU.

The successful prototype implementation at hLab shows the feasibility for automating BTEC's layered tissue engineering concept. A suitable method for cutting the cross-sectional layers from sheet material has been developed. A station to seed and substitute bone material with seed cells and growth factors has been developed and tested. A gripper has been designed for the robot to handle dry and wet skeleton materials. The gripper includes a weight compensation unit, a control mechanism to regulate the contact pressure and a system to measure the

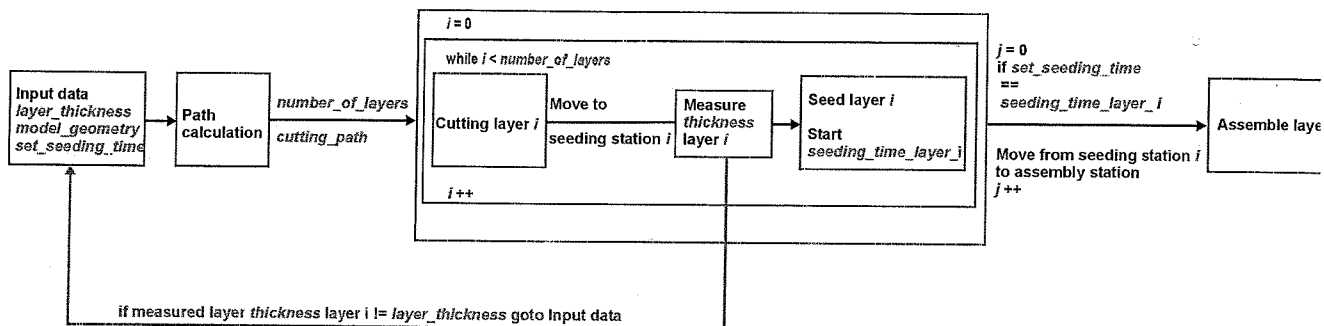


Fig. 8. Correction algorithm

The algorithm is fictive and has to be converted into a common program language to be implemented. The correction algorithm enables the system to detect deviations of the layer thickness during the handling of the first substrate from the cutting station to the seeding station. As a result the height failure caused by the deviation can be compensated totally. As an extension of the correction algorithm it would be possible to detect additional deviations of the handled substrates after the seeding procedure. These deviations could be caused by swelling of the substrate during seeding. This again would require the correction of the number of layers and the cutting paths. In this case, the height failure caused by the deviation can only be minimized

layer thickness and the height of the growing implant. Further, a method to compensate inaccuracies in the thickness of individual layers has been developed and implemented to ensure the correct height of the artificial implant. Several samples of both implants have been manufactured by the prototype system.

References

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