Kinematic analysis of a parallel mechanism for automated imaging of an Organ-on-a-Chip culture system

Kinematische Analyse eines Parallelmechanismus zur automatisierten Bildgebung von Organ-on-a-Chip Kulturen

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Short Summary

Organ-on-a-Chip approach makes it possible to produce vascularized organoids for pre-clinical drug studies using incubators and rockers. Automation of organoids generation is desirable to reduce human resources and increase reproducibility. However, automation requires information such as the growth status of the organoids to be recorded directly within the incubator. Hereby, avoiding regular incubator opening by including an autonomous planar parallel robotic imaging system will prevent disturbing the organoids' growth. To avoid rotations of the miniature microscope while inspecting the different organoids-on-a-chip in the constrained incubator space, the parallel robot is constrained to two translational DoFs. Here, we present the kinematic design of the robot that fulfils the workspace requirements and space constraints inside the incubator.

Introduction

Organs are defined as a collection of tissues that structurally form a functional unit specialized to perform a particular function. Organoids are in vitro miniaturized and simplified model systems of organs which self-organize into complex structures [1]. Organoids have proven to be accurate human model systems (HMS) for in vitro pharmaceutical research [2, 3, 4]. Successful synthesis of full or partial human organs for regenerative medicine is still in it's early phase of research [5]. Several approaches exist to synthesize organoids, including the organ-on-a-chip (OoaC) approach, in which cells self-assemble in a gel using microchannels engraved into a chip for nutrition placed in a chamber designed to maintain a constant temperature, high humidity and atmosphere: an incubator [6]. This approach is commonly used for pharmaceutical studies and research, such as at F. Hoffmann-La Roche (Basel, Switzerland, https://www.roche.com) [7]. For synthesis, the organoids require a cell culture medium. When a culture fluid is continuously moved through a microchannel, the system is said to be under perfusion. Under perfusion, organoids might form blood vessels. Organoid blood vessels structure is called vasculature. Several start-ups in the OoaC field are commercializing standardized OoaC plates compatible with perfusion for vascularized organoids (Mimetas, Netherlands; AIMbiotech, Singapore). The majority of OoaC in pharmaceutical research are placed on a rocking system to automatically actuate the perfusion feeding organoid lumens by transferring culture medium from a reservoir to another using hydrostatic pressure. Synthesis of vascularised organoids with OoaC and a perfusion rocker has proven to be reliable, however, the workflow steps are mostly manual, time-consuming, and commercial solutions for automation are not performing medium exchange, imaging capabilities on the rocker, imaging capabilities in the incubator. Many points, such as the regular medium exchange and the imaging of organoids during the culture, remain burning topics of research. Imaging of the organoids using microscopes is used for human visual inspection of the organoid growth and health at certain time points during the synthesis. In situ imaging inside the incubator on the rocker would be beneficial since organoid perfusion would neither need to be stopped nor would organoids have to be taken out of the incubator risking contamination and abrupt temperature changes. Imaging of organoids during perfusion on a perfusion rocker is currently not possible for rocker-actuated hydrostatic pressure OoaC because the OoaC orientation is changing constantly. A constant microscope orientation from the organoid is important to image organoids in a similar orientation, simplifying the human image readability and computer analysis. Furthermore, successful automation of organoid culture synthesis requires measurement and feedback on information such as cell adherence completion after plating, organogenesis, tube formation completion, or angiogenesis. To overcome the current shortcomings in vasculature of OoaC, we propose introducing a parallel mechanism consisting of two parts: a parallel manipulator (Fig. 1, black) combined with an additional parallel linkage mechanism (Fig. 1, green), both attached directly to the OoaC support or the incubator frame. A miniature microscope is mounted on the parallel manipulator's end-effector. The parallel manipulator allows to move the microscope in 2 translational degrees of freedom (DoF) above the plate and the additional parallel linkage mechanism ensures a constant orientation of the microscope during imaging of the organoids. Parallel mechanisms appeared to be the best choice because of their high accuracy and rigidity [8]. Furthermore, the actuators of the parallel manipulator can be fixed to the base, which minimizes the footprint of the mechanism's moving parts.
In this paper, we present the kinematics of the robot (Fig. 1). The available space for the robot inside the incubator is limited to a depth (y) of 155 mm, a width (x) of 280 mm and a height (z) of 200 mm (red in Fig.2). The robot should move the microscope between stacked OoaC plates inside the incubator. This operational workspace is therefore smaller than the available space in side the incubator and has a depth (y) of 115 mm, a width (x) of 147 mm and a height (z) of 19 mm (Fig. 2, green) to image an area of depth (y) of 75 mm and a width (x) of 117 mm (Fig. 2, blue) called the imaging workspace.

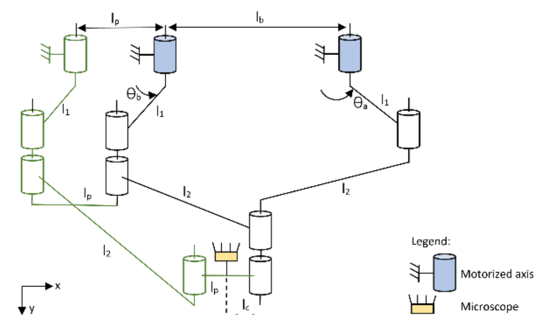

Figure 1 CAD schematics of the joints. In black, the parallel manipulator mechanism, in green the parallel linkage mechanism.

Additionally, the microscope orientation should be passively actuated to stay constant when the robotic arm is actuated.

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Also, the microscope's position accuracy should be below 400 µm in x-direction and below 400 µm in y-direction.

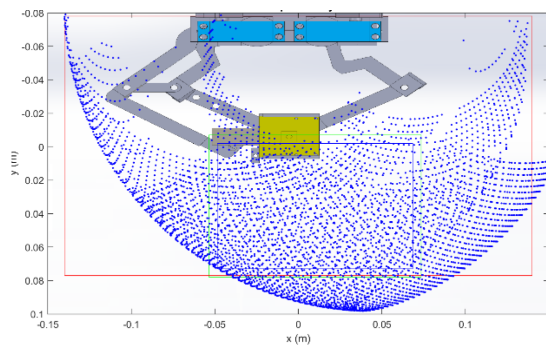

Figure 2 Example of the workspace coverage in relation to the desired imaging workspace for a given set of robot parameters {l_1, l_2 and l_b} in Matlab Simscape.

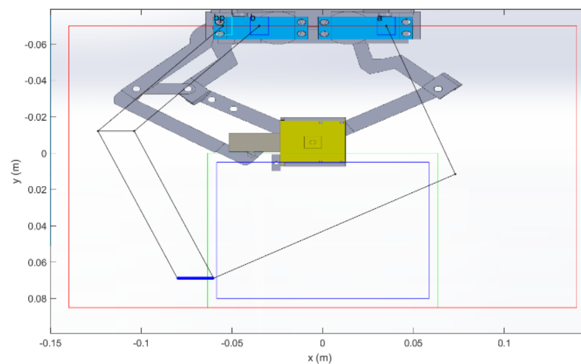

Figure 3 Example of visualisation of all links' position and orientation within the allowed workspace footprint in red for one specific robot input parameter sets {l1, l2 and lb} and one ϑ_a and ϑ_b possiblity.

Materials and methods

The additional parallel linkage mechanism (Fig. 1, green) is maintaining the end-effector's orientation. The length of the link l_p is chosen arbitrarily at 20 mm.

We used Matlab and Simscape to find all possibilities for the robot's arm link lengths and verify the constant end-effector orientation to doublecheck the lengths of the additional parallel linkage mechanism, i.e. robot synthesis. The joint positions were computed using the *KinematicsSolver* from Simscape for a multibody model. The link lengths l_1, l_2 and l_b are iteratively edited to respect the following conditions 1) the microscope should access all the imaging workspace 2) the robotic arm should stay inside the workspace footprint.

The kinematic solver is computing joint positions for each parameter by moving actuated joint angles θ_a and θ_b from 1 to 179 degrees over 100 points for each angle. The solver might find different possible solutions for different robotic arm configuration. Therefore initial parameters from other angles than θ_a and θ_b are provided to the solver to avoid that the solver is ccomputing joint positions for another configuration.

Different robot parameter sets {l_1, l_2, and l_b} are provided to the kinematic solver for given values of {l_p and l_c}.

If the solver finds a solution, end-effector positions are visualized in Matlab in a first drawing (Fig. 2) and all robotic arm links are visualized in Matlab in a second drawing (Fig. 3). A visual inspection is performed to verify that 1) the imaging workspace is covered by simulated end-effector points on the first drawing 2) joint positions are within the allowed footprint workspace 3) no regime change is happening 4) no singularity is visible on the second drawing.

Results

The robot synthesis resulted in different feasible robot parameter sets {l_1, l_2, and l_b}. The visualization of the achievable workspace of one parameter set is shown by discrete end-effector points that are achieved by changing the motor angles θ_a and θ_b in discrete steps (Fig. 2). The visual inspection of these end-effector positions verified that the robot can reach the targeted operational workspace as required (Fig. 2). The robot synthesis demonstrates that with link lengths l_1 = 90 mm, l_2 = 92 mm, and l_b = 70 mm define a feasible set of parameters because the resulting robotic arm design can access the desired imaging workspace within the allowed operational workspace. The constraints given by the operational workspace and the desired imaging workspace entail that the kinematics is close to singularities in the corners of the imaging workspace.

For different robot parameter sets {l_1, l_2, and l_b}, the visualization shows a constant orientation of the microscope supporting link of length l_p (Fig. 3). The simulation results confirmed that the orientation of the robotic arm's end-effector is constant for all the calculated end-effector positions.

Discussion

Parallel manipulators have been extensively studied due to their advantages in terms of accuracy and stiffness. In this abstract, we add an additional passive parallel linkage mechanism that is linked to the planar parallel kinematics structure to generate a pure translational end-effector motion. This allows the robot to keep the rotation of a microscope on the end-effector constant.

The robot synthesis in order to find the robot parameters {l_1, l_2, and l_b} for given values of {l_p and l_c} for covering a desired imaging workspace while remaining within the bounds of the operational workspace has been achieved using the *KinematicsSolver* from Simscape.

The mechanism is close to singularities when accessing imaging workspace corners thus 1) singularity analysis should be implemented in the control system and calibration routine to ensure that no singularity occurs during operation or 2) an alternative mechanism should be studied that prevents getting close to singularities for the given requirements.

Finally, robot synthesis revealed a parameter set for a potential design and visualized the achievable workspace by a cloud of discrete points.

Acknowledgments

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[1] Moritz. Hofer and Matthias P. Lutolf, "Engineering organoids", Nature Reviews Materials, pp. 402--420, feb 2021.
[2] T. Takebe, K. Sekine, M. Enomura, H. Koike, M. Kimura, T. Ogaeri, R.-R. Zhang, Y. Ueno, Y.-W. Zheng, N. Koike, S. Aoyama, Y. Adachi, and H. Taniguchi, "Vascularized and functional human liver from an ipsc-derived organ bud transplant," Nature, pp. 481–484, jul 2013.
[3] C. Quint, M. Arief, A. Muto, A. Dardik, and L. E. Niklason, "Allogeneic human tissue-engineered blood vessel," Journal of vascular surgery, pp. 790–798, 2012.
[4] M. Nikolaev, O. Mitrofanova, N. Broguiere, S. Geraldo, D. Dutta, Y. Tabata, B. Elci, N. Brandenberg, I. Kolotuev, N. Gjorevski, H. Clevers, and M. P. Lutolf, "Homeostatic mini-intestines through scaffold-guided organoid morphogenesis," Nature, p. 574–578, sep 2020.
[5] C.-H. Wassmer, F. Lebreton, K. Bellofatto, D. Bosco, T. Berney, and E. Berishvili, "Generation of insulin-secreting organoids: a step toward engineering and transplanting the bioartificial pancreas," Transplant International, vol. 33, no. 12, pp. 1577–1588, 2020.
[6] Encyclopedia of Biomedical Engineering. Elsevier Science and Techn., Sept. 2018.
[7] N. Gjorevski, B. Avignon, R. Gerard, L. Cabon, A. B. Roth, M. Bscheider, and A. Moisan, "Neutrophilic infiltration in organ-on-a-chip model of tissue inflammation," Lab on a chip, vol. 20, pp. 3365–3374, 2020.
[8] J.-P. Merlet, "Parallel Robots", Second Edition, 2006.

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