Electronic Supplementary Material (ESI) for Lab on a Chip.


# Supplementary Information

# Assessing bioartificial organ function: the 3P model framework and its validation

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## 1.1. Selection of research papers

The sources of the research papers concerning in-vitro liver tissue culture are three well-known literature databases, namely PubMed, Scopus and Web of Science. Constructing a paper dataset includes three steps: roughly retrieving literature from online databases, finely selecting research papers by counting keywords frequency and finally screening the papers that cannot be standardized.

The three online databases provide advanced searches that can locate words in specific fields of the paper. For example, it can search results according to the title, the author, the abstract, the journal, etc. Moreover, users can make up multiple search fields to create a query expression. Therefore, we used such expressions to locate as many relevant papers as possible. Specifically, we defined three concepts “Liver”, “Organ-on-a-chip” and “3D culture”, then we searched corresponding papers using the combination of “Liver” and one of the other two concepts. Table S1 gives the detail which we used in the PubMed database. Note that “Mesh” denotes the Medical Subject Headings controlled vocabulary of biomedical terms which is used to describe the subject of journal articles in MEDLINE [1]. The “tw” is the abbreviation of “Text Words” that represents the words and numbers in the title, abstract, publication type, etc.

**Table S1.** Query expressions to search PubMed literature.

| Concepts | Query expressions |
|---|---|
| Liver | Liver[Mesh][tw] OR hepatocype*[tw] OR liver sinusoidal endothe*[tw] OR liver[tw]OR hepatic[tw] OR hepatocyte[tw] |
| Organ-on-a-chip | Body-on-a-chip*[tw] OR Human-on-a-chip[tw] OR organ on a chip* [tw] OR multi-organ-on-a-chip[tw] OR MOC[tw] OR Microfluidics[Mesh] OR Microfluidic*[tw] OR organ-on-a-chip*[tw]OR Microfluidic device[tw] OR Microphysiological systems[tw] OR microfluidic platform OR MPS[tw] OR MPSs[tw] OR microfabrication[tw] |
| 3D culture | organoid*[tw] OR three-dimensional (3D) culture model [tw] OR tissue engineering[tw] OR spheroid* OR three-dimensional (3D) cell culture models[tw] OR Cell Culture Techniques, Three Dimensional[Mesh] OR 3D culture[tw] OR 3D[tw] |

The query expressions helped us find 44176 research papers concerning in-vitro liver tissue culture. To obtain the research that involves liver synthesis function, we counted the word frequency of relevant keywords in the abstract to facilitate further selection. Specifically, we defined main keywords and secondary keywords which explain the secretion of albumin and urea and liver culture platform respectively. Then the word frequency is calculated based on the two types of keywords. Afterward, we chose the papers whose main and secondary keywords frequency are more than 3 and 2, which we believe such papers are quite relevant to our study. Table S2 shows the exact two types of keywords.

**Table S2.** Main and secondary keywords.

| Keyword Type | Keywords |
|---|---|

| | |
|---|---|
| Main keywords | function, functionality, metabolic response, albumin production, albumin secretion, production of albumin, secretion of albumin, urea secretion, secretion of urea, urea synthesis, synthesis of urea, statistical data, data, result |
| Secondary keywords | 3D culture, static culture, chip, microfluidic, spheroid, hepatocytes, hepatic, bioreactor, liver-on-a-chip |

The final selection is to filter the research that the secretion data cannot be standardized to a uniform unit. For the secretion level of albumin and urea, we determined a normalized format "μg/day/$10^6$ cells", and the research that adopted other units which cannot be converted to this format has been filtered. For example, the secretion level measured by "ng/mL" or "nM" in the scaffold-based papers [2, 3] has not been considered in this study. Additionally, as for the paper [4] that reported the secretion data in hours instead of days has also been filtered.

After the three steps of selection, we obtained the final paper dataset. The experimental data are derived from the selected research papers.

## 1.2. Prediction of functional secretion in a specific day

In this section, we tried to make predictions of a specific day that did not consider the number of days as a fitting parameter. In other words, we only adopted the experimental data which provides the secretion level on the third day as the modeling dataset. In doing so, we can eliminate the influence of the change of days to functional secretion. Table S3 and Table S4 respectively give the true and predicted results on the third day for 3D scaffold and 3D spheroid models. The column "Source" denotes the results are whether measured by the researchers (true) or predicted by the regression model (predicted).

**Table S3**. True and predicted urea on day 3 of 3D scaffold research.

| Source | Urea | Cell | Cell Seeding | Scaffold | Scaffold-1-Con | Pore Size | Diameter | Fabrication | … |
|---|---|---|---|---|---|---|---|---|---|
| true[5] | 0.03 | 8 | 4 | 10.11 | 5 | 11.7 | 15 | 1 | … |
| true[5] | 0.04 | 8.13 | 0.1 | 10.11 | 5 | 11.7 | 15 | 1 | … |
| predicted[6] | 104.23 | 9 | 1 | 18 | -1 | | 8 | 6 | … |
| predicted[6] | 104.23 | 9 | 1 | 18 | -1 | | 8 | 6 | … |
| predicted[7] | 28.7 | 10.11 | 0.8 | 13 | 5.9 | 462 | 5 | 5 | … |
| predicted[7] | 43.51 | 10 | 0.8 | 13 | 5.9 | 462 | 5 | 5 | … |
| true[8] | 25.97 | 10 | 0.2 | 10.11 | 15 | 25.6 | 15 | 1 | … |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| true[8] | 34.55 | 10.13 | 0.2 | 10.11 | 15 | 25.6 | 15 | 1 | … |
| true[8] | 38.96 | 10.1307 | 0.2 | 10.11 | 15 | 25.6 | 15 | 1 | … |
| true[9] | 327.78 | 8.23 | 3 | 19 | | 140 | 6 | | … |
| … | … | … | … | … | … | … | … | … | … |

**Table S4.** True and predicted albumin on day 3 of 3D spheroid research.

| Source | Albumin | Cell | Cell Seeding | Co-Cell Seeding | Spheroid-Dia | Tethered | Tethered Film | Modification | Flow Rate |
|---|---|---|---|---|---|---|---|---|---|
| predicted[6] | 1804.97 | 22 | 1 | -1 | 100 | 2 | -1 | -1 | 0 |
| predicted[10] | 1.14 | 8 | 0.6 | -1 | 200 | 2 | -1 | 8 | 800 |
| predicted[11] | 3.56 | 8 | 0.015 | -1 | | 2 | -1 | -1 | 0 |
| true[11] | 3.02 | 8 | 0.015 | -1 | | 2 | -1 | 4 | 0 |
| predicted[12] | 2674.05 | 19 | 80 | -1 | 109.5 | 2 | -1 | 6 | 50 |
| predicted[12] | 2650.2 | 19 | 0.025 | -1 | 109.5 | 2 | -1 | -1 | 0 |
| true[13] | 6.73 | 6 | 1 | -1 | | 2 | -1 | -1 | 0 |
| true[13] | 24.73 | 6.21 | 0.1 | 0.3 | | 2 | -1 | -1 | 0 |
| true[13] | 2.36 | 6 | 0.1 | -1 | | 2 | -1 | -1 | 0 |
| true[13] | 5.64 | 6.21 | 1 | 3 | | 2 | -1 | -1 | 0 |
| … | … | … | … | … | … | … | … | … | … |

The predicted results in the table are based on the regression model whose $R^2$ is greater than 0.8. Setting different fabrication parameters for each of the liver models can improve the accuracy of the regression model that aims to detect the fluctuation of functional secretion caused by small changes in these parameters. Ideally, given a set of fabrication parameters, the model would accurately predict albumin and urea secretion at day 3. Likewise, for the secretion of other specific days, the same method can be used to model and predict.

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