

New experimental evidence unlocks a puzzle in vascular tissue engineering

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Blood vessels can form complex network-like structures and each structure is unique. The metaphorical photo is courtesy of the AIRO trampoline park. Image credit: Grzegorz Krzyzewski. Credit: Source: IPC PAS, Grzegorz Krzyzewski

Angiogenesis is a process of forming hierarchical vascular networks in

living tissues. Its complexity makes the controlled generation of blood vessels in laboratory conditions a highly challenging task.

A promising approach to the engineering of vascular structures relies on the use of microstructured biomaterials which may help guide angiogenesis and which, as such, have been extensively studied worldwide—in particular in view of the treatment of vascular diseases.

Recently, scientists at the Institute of Physical Chemistry of the Polish Academy of Sciences have successfully unlocked a puzzle in vascular tissue engineering, providing important experimental evidence towards understanding and controlling of the sprouting angiogenesis in vitro. The study is [published](#) in the journal *APL Bioengineering*.

Angiogenesis is a complex process that involves the formation of new blood vessels from the pre-existing ones via a process of vessel division and sprouting. Angiogenesis can occur in any part of the body and is so complex that its control and/or mimicking in a laboratory setting has become one of the central challenges of bioengineering.

Full understanding and controlling of the formation of vascular networks could help manage a wide range of diseases, ranging from regeneration of blood vessels that have been damaged by trauma to the treatment of metastatic cancer, making controlled angiogenesis a holy grail of regenerative medicine.

Following this lead, researchers at the Institute of Physical Chemistry of the Polish Academy of Sciences (ICP PAS) conducted a series of experiments on the evolution of the sprouting capillary networks using fibrin gels as the supporting tissue-like material and established possible general dynamical principles governing the sprouting angiogenesis.

Before this breakthrough research, the study of the evolution of the

sprouting microvascular networks has been largely based on the analysis of a single, or at most several time points in the culture. Though this approach was sufficient to estimate the overall trends in growth, it never allowed to decipher the different stages of the microvascular evolution in vitro.

To uncover the possible rules governing the angiogenic dynamics, many and diverse theoretical approaches at various levels of complexity have been proposed. Unfortunately, a direct comparison of the theoretical predictions with the experiments has been limited due to the scarcity of the time-resolved [experimental data](#), hence most [theoretical studies](#) relied only on a qualitative comparison of the late-time morphologies.

This puzzle has been recently solved with new experiments and custom-developed automated image analysis tools by a team of researchers from IPC PAS and their collaborators from Institute of Theoretical Physics of University of Warsaw. In their work, the researchers demonstrated the possibility of extracting detailed statistical–topological features of sprouting microvascular networks.

One of the goals of the project was the development of more reliable and reproducible angiogenesis-based drug testing assays as well as new strategies for vascular tissue engineering. How does it work?

Researchers isolated sprouting microvascular networks and monitored their growth day-by-day for 14 days under well-controlled culture conditions. They recorded a range of morphometric parameters such as the overall length of the sprouts, their area, as well as the statistical distributions of the lengths of individual branches or the branching angles.

Based on microscopic images collected from multiple parallel experiments, large-scale [statistical analysis](#) was performed. At the same

time, the observations were focused on the dynamics of the vascular network formation to determine the characteristic features of the angiogenic growth processes. The goal was to understand the complexity of the early stages of angiogenesis which include the formation of sprouts and their bifurcations followed by the formation of interconnections, etc.

Dr. Rojek, the first author of this work says, "We think our work is unique since we build our model of the formation and evolution of sprouting vascular networks on large amount of biological data.

"Up to now, most conclusions and rules have been provided by mathematical modeling, which is a very powerful tool but often suffers from oversimplifications and fails to reproduce the actual biological systems. This underlines how important is the close collaboration between experimentalists and theoreticians."

The authors developed new image-analysis protocols that allowed them to determine the abovementioned parameters in an automated manner.

"Our software, written in Python programming language, is optimized for the processing of a large amount of data from multiple experiments. It provides a solid background in terms of implementation and offers fast computation time.

"The time-resolved data spanning the whole lifetime of the networks, allowed us to propose basic rules governing the topological development of the sprouting microvasculatures," adds Ph.D. candidate Antoni Wrzos and prof. Szymczak who led the development of the data-analysis software.

Scientists performed studies via day-by-day tracking of the evolution of sprouting networks with the use of Python programming language to

deliver the details of the topology of the networks including the branching angles and their distributions. Presented studies resulted in a broad library of data on the typical network formation stages.

In particular, those stages included (i) an initial inactive stage when the cells proliferated without forming sprouts, (ii) a rapid growth stage in which sprouts elongated and branched, and (iii) a final maturation stage in which the rate of growth slowed down. Analyzes also delivered data on the growth differences in different media indicating the impact of the added vascular endothelial growth factor on the behavior of cultured cells.

The most important effect of the "enriched" media was the earlier sprouting and the increase in the number of branches, whereas of the linear rate of growth of branches remained independent of the added growth factor. The statistical morphometric analysis performed by researchers from IPC PAS additionally revealed that the branching angles fluctuated around an average value which, quite surprisingly, appeared close to the "magic" value of 72 degrees characteristic of the so-called Laplacian growth models, the latter typically applied to describe growth of crystals or the dissolution of fractured rocks.

The analogy suggests that—just as in the Laplacian models—the advancing tips of the sprouts may tend to follow the local gradients of the growth factor concentration.

"Collectively, our results, due to their high statistical relevance, may serve, e.g., as a benchmark for predictive models. Future studies could potentially provide for better understanding of how the external cues affect vascularization in biomaterials with embedded endothelial seeds and help to optimize tissue repair strategies, e.g., via proper design of the prevascularized wound dressings," remarks Dr. Guzowski.

As the angiogenesis is a complex process that depends on many factors, in this work researchers delivered findings that can be useful in the understanding of angiogenesis in vitro, e.g., during the drug testing assays as well as in tissue engineering. The presented work can be a step towards faster and more effective testing of new drugs and the development of personalized medical treatments.

Based on the numerical analyses, proposed studies have a potential for enhancement of the outcomes of high-throughput screening studies. The authors point out the importance of the development of data libraries as one of the most critical steps in identification of potential drug candidates as well as in future applications in bioengineering. Besides the scientific aspect of the demonstrated studies, the authors emphasize the importance of interdisciplinarity in research.

More information: Katarzyna O. Rojek et al, Long-term day-by-day tracking of microvascular networks sprouting in fibrin gels: From detailed morphological analyses to general growth rules, *APL Bioengineering* (2024). [DOI: 10.1063/5.0180703](https://doi.org/10.1063/5.0180703)

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