Medical Xpress

# New mathematical models describe diffusion and metabolism dynamics in 3D tissues, stem cell-derived organoids

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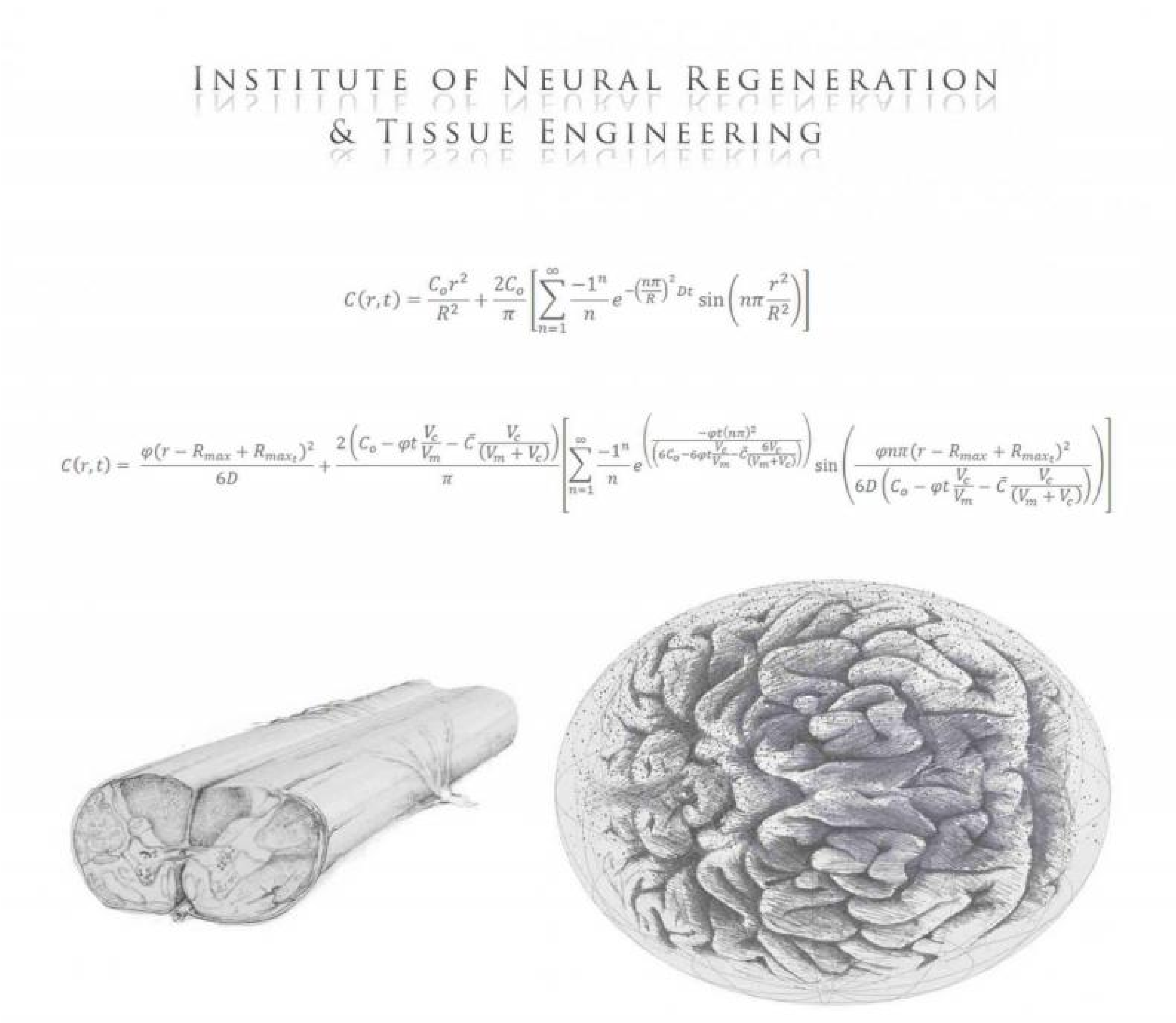


Models for 3-D neural tissue constructs are shown, which will provide new tools and insights into tissue development, disease modeling, and regenerative medicine. Credit: Richard McMurtrey / Institute of Neural Regeneration & Tissue Engineering

New research has shed light on the complex interactions of stem cell function and molecular diffusion in neural tissue, which may explain many phenomena from stem cell differentiation to the formation of the cortex of the brain. While researching new methods of reconstructing 3D neural tissue and neural pathways in the brain and spinal cord, Dr. Richard McMurtrey devised new mathematical approaches for understanding the concentration of nutrients within the 3D tissue constructs and how this could affect tissue growth.

Stem cells have very unique behaviors and responses to specific concentrations of many molecular factors, meaning that it is important to understand the complex dynamics of nutrient signaling, diffusion, and metabolism in 3D tissues. Many 3D tissues have been constructed with the hope of replicating "mini-organs" from a patient's own stem cells, including "mini-brains" or cerebral organoids that can be used to study neurological diseases or which may one day be directly transplanted into damaged tissues of a patient. The ability to guide and direct stem cell development and function to the desired effect in the organoids is therefore an essential aspect of this research.

"I first stumbled upon these ideas when trying to figure out how to obtain exact nutrient concentrations in some 3D tissues I had designed that were composed of neural stem cells," said Dr. McMurtrey. "The mathematics involved has always fascinated me, but I was surprised that answering my questions was a lot more difficult than I thought it would be. I felt like I kept going down a rabbit hole trying to find solutions, and eventually I figured out the mathematics that could answer my questions.

I think these ideas really help us understand the role of diffusion in brain function and neural development better than ever before. But of course there is also much more to still learn."

During human development, stem cells near the center of the developing brain will migrate outwardly and form the neurons in the cortex on the outer rim of the brain, the region where thoughts are formed and processed. The mathematical work described in the paper describes growth limitations imposed by diffusion and metabolism and also suggests an underlying physical basis for the phenomenon of neural migration to a dense external cortical layer. Once the neurons are programmed to migrate to the outer surface, the cortex can then become more convoluted or wrinkled to create more extensive neural networks.

One of the unique aspects of these physical models involved implementing features of cell metabolism in the equations, and the work enables any researcher to adapt the models to their specific cell types as well as to their specific tissue shape and architecture. Even though the mathematics involved in deriving these equations is complex, one of the advantages of these models is that researchers only need to have a working knowledge of algebra to use them. The modeling of many physical phenomena generally requires specialized skills in computational programming, but this work sought to provide what are called analytic or explicit solutions, which simply allow the parameters to be inserted into the formulas and the solutions to be determined.

Dr. McMurtrey's research currently focuses on reconstructing brain and spinal cord structures and pathways using synthetic 3-dimensional neural tissue made with stem cells, biomaterials, and nanotechnology, and he hopes to use the models to design enhanced artificial tissue implants that could be used clinically to repair sites of tissue damage. These engineered tissue constructs can also be used for studying models of development and disease under controlled conditions or for conditioning cells to enhance survival after implantation into the body. "Many physicists and mathematicians have studied medicine, like Fick or Helmholtz, or wondered in awe at the complex function of the brain, like Einstein or Feynman," Dr. McMurtrey stated. "I wanted to be a physicist growing up, but I happened to end up in medicine, though I still marvel at the underlying physics that can both govern a vast universe and yet also make all neural function possible. I think we will see that, just as with all other systems in the universe, we cannot fully understand a system as complex as the brain until we understand the mathematics governing many fundamental components of that system, whether that is the complexity of neural networks, the dynamics of cell signaling and gene expression networks, the Hodgkin-Huxley-like electrical activity of neuronal membranes, or the biomechanics of developing tissues. Ultimately I believe that physics and engineering have a lot to contribute to solving problems in the human body that the medical field as of yet cannot solve."

**More information:** Richard J. McMurtrey. Analytic Models of Oxygen and Nutrient Diffusion, Metabolism Dynamics, and Architecture Optimization in Three-Dimensional Tissue Constructs with Applications and Insights in Cerebral Organoids, *Tissue Engineering Part C: Methods* (2015). DOI: 10.1089/ten.TEC.2015.0375

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