Modeling the Growth of Kidney Organoids subject to optogenetically-induced BMP4

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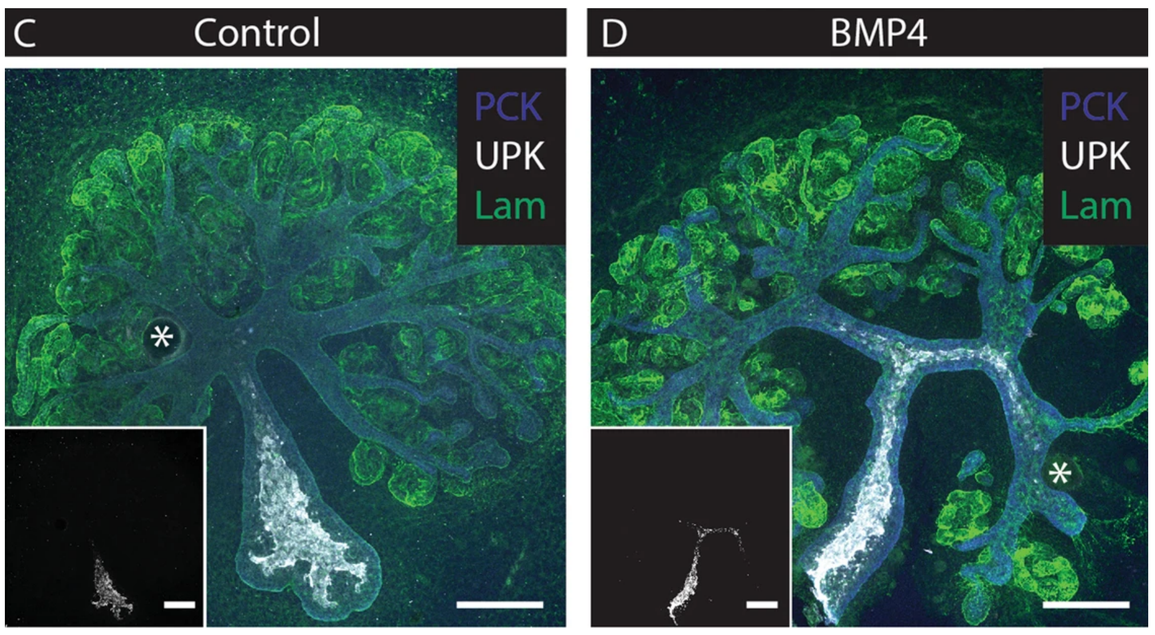
The CyGenTiG project combines optogenetic and control methods to study self-organization and pattern formation. We propose an experimental setup comprised of two cell-types to study effects of BMP4 on kidney morphogenesis and how to control emerging properties of the tissue. For up-front exploration, we developed an agent-based model with the aim to qualitatively depict the system.

BMP4 in Kidney Morphogenesis

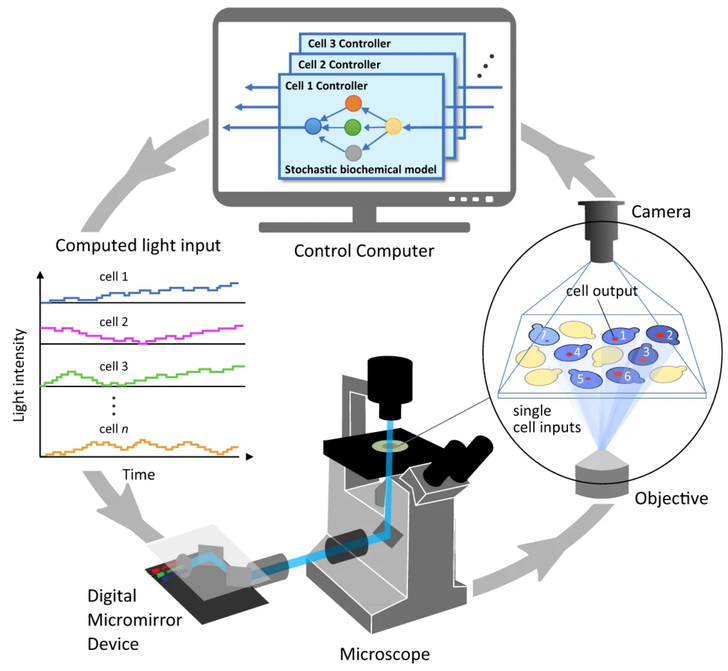
- BMP4 promotes ureter duct formation and inhibits branching
- Improves realism of kidney organoids



Mills, Christopher G., Melanie L. Lawrence, David A. D. Munro, Mona Elhendawi, John J. Mullins, and Jamie A. Davies. 2017. Asymmetric BMP4 Signalling Improves the Realism of Kidney Organoids. Scientific Reports. Springer Science and Business Media LLC. https://doi.org/10.1038/s41598-017-14809-8

Optogenetic Control

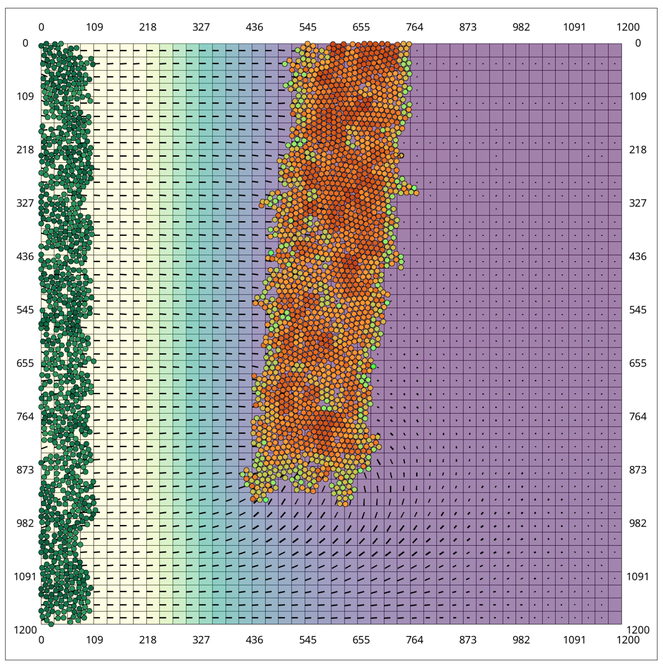
- DMD (Digital Micromirror Device) can target individual cells
- Closed loop control with input of (global) readout
- Dynamic setpoint realization of system property



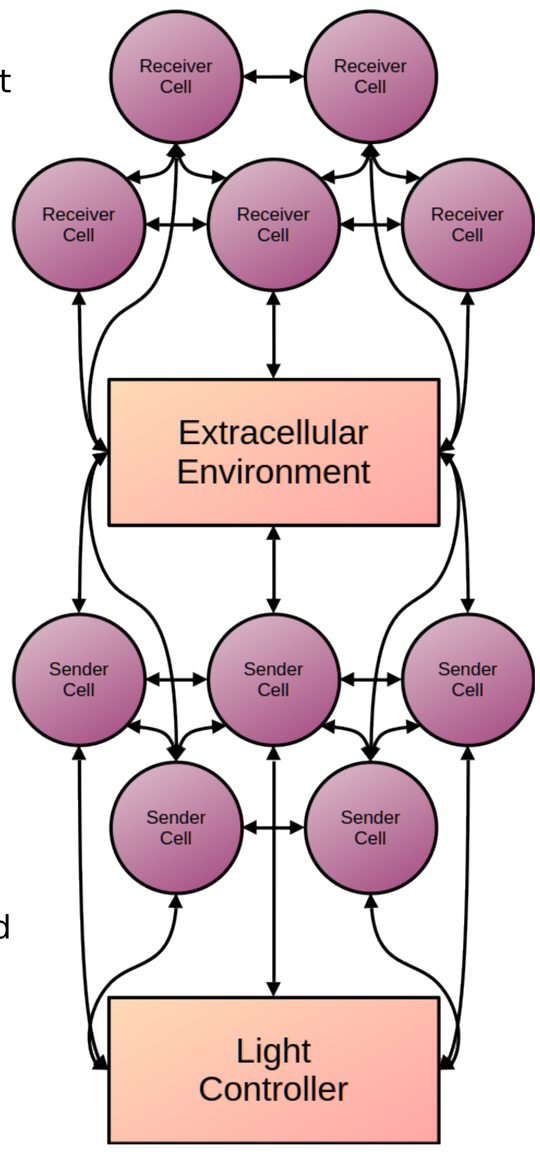
Kumar, Sant, Marc Rullan, and Mustafa Khammash. 2021. Rapid Prototyping and Design of Cybergenetic Single-Cell Controllers. Nature Communications. Springer Science and Business Media LLC. https://doi.org/10.1038/s41467-021-25754-6

Computational Model

- Effective, behaviour-driven agent-based model
- Only local rules, not global (excl. light controller)
- Focus on ureter duct

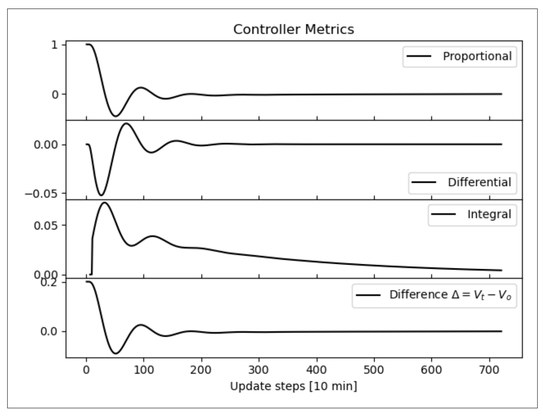


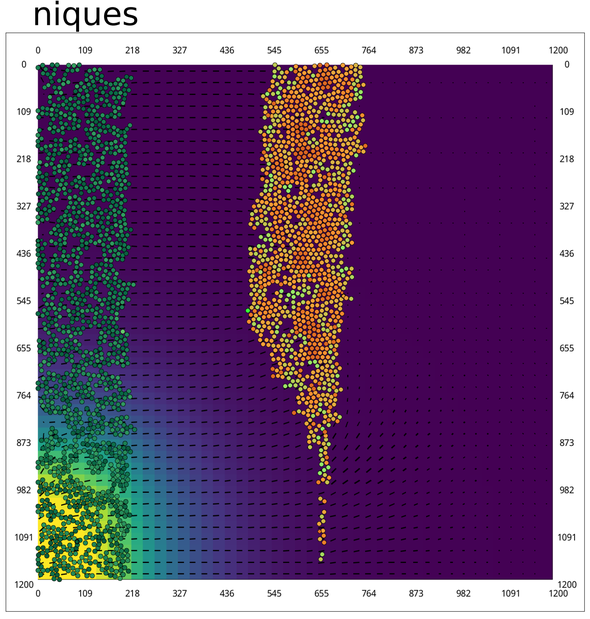
- Two cell-types: sender and receiver
  - Sender-cells release BMP4 (induced by light exposure)
  - Receiver-cells take up BMP4
- Secretion + Diffusion of BMP4
- Resource-restricted proliferation
- Differentiation of epithelial cells



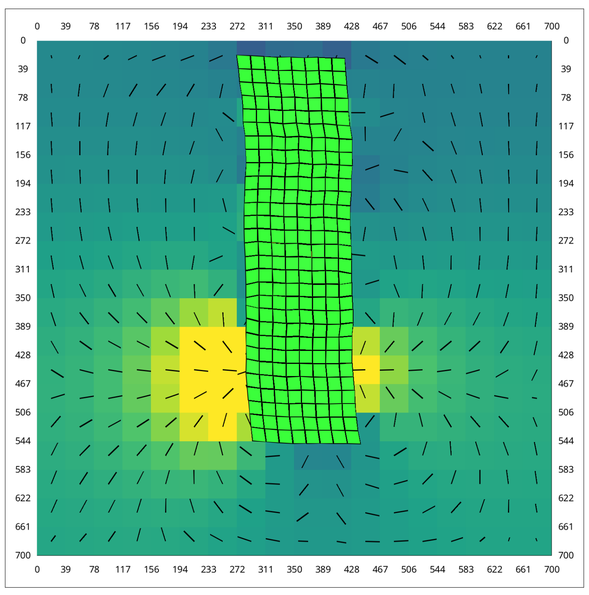
Preliminary Results

- Explore different spatial configurations
- Closed-loop control of
  - Cell-density
  - Intracellular morphogen
- Spatially directed morphogen variation only possible with temporal variation
- Different cell-representation techniques





Controlling cell-density indirectly via secretion



A vertex-like cell-representation with free agents

Further Model Extensions

- Implement realistic optogenetic modules and reaction of sender-cells to light exposure
- Expand scope of relevant reaction dynamics and differentiation effects
- Branching and nephrogenesis

Research Questions

- Which spatial configuration creates the most realistic pattern?
- Find the number of relevant quantifiable systems parameters.
- Can we control other morphogenetic modules?
- Is it possible to target individual sections of the organoid?
- Can we predict and quantify how BMP4 affects branching in nephrogenesis?

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[2]University of Edinburgh, [3]ETH Zürich