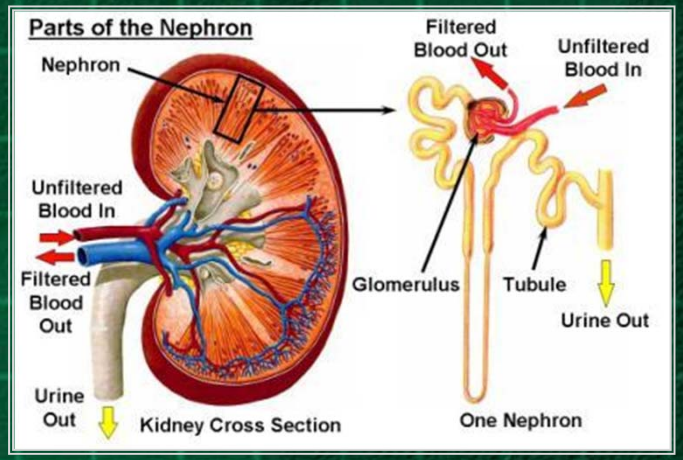
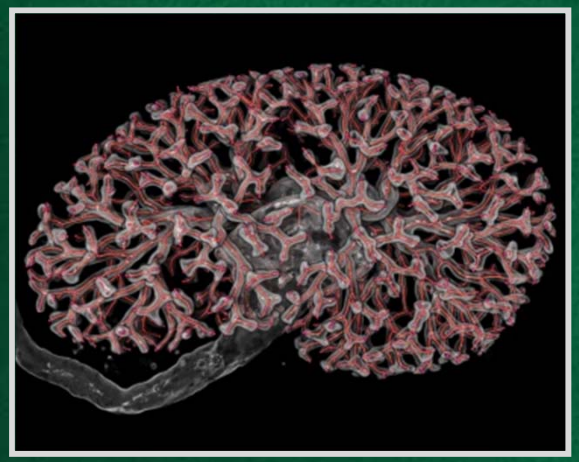
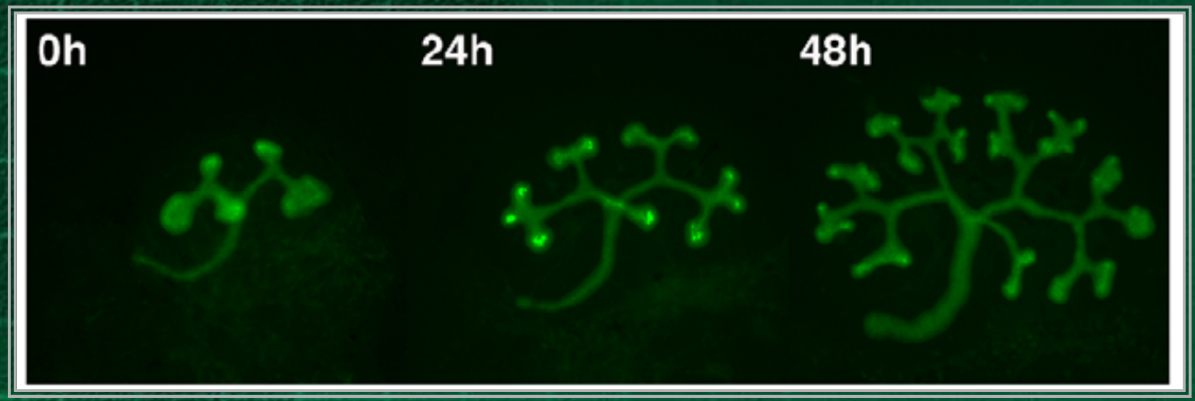
Mathematical model of Kidney Morphogenesis.







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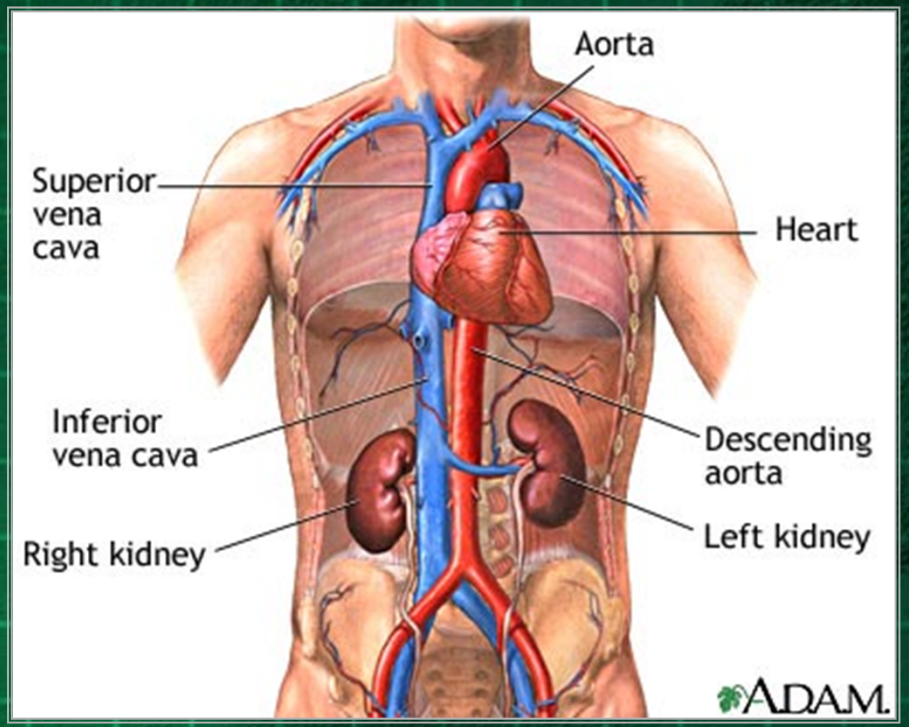
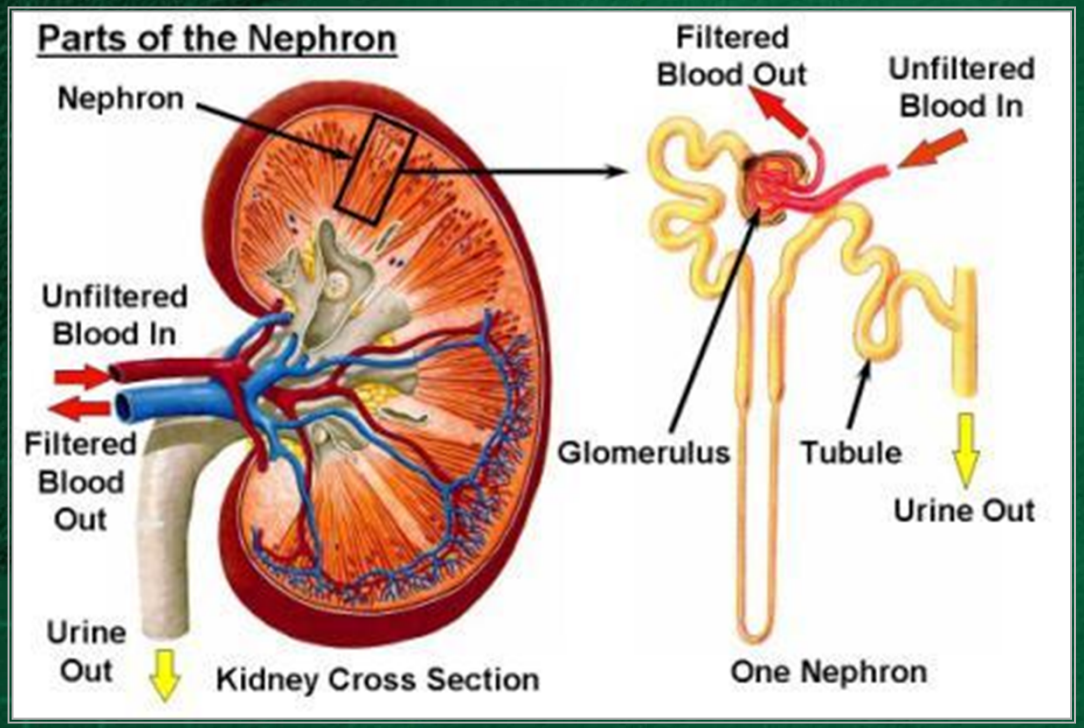
Jul 2015

Kidney

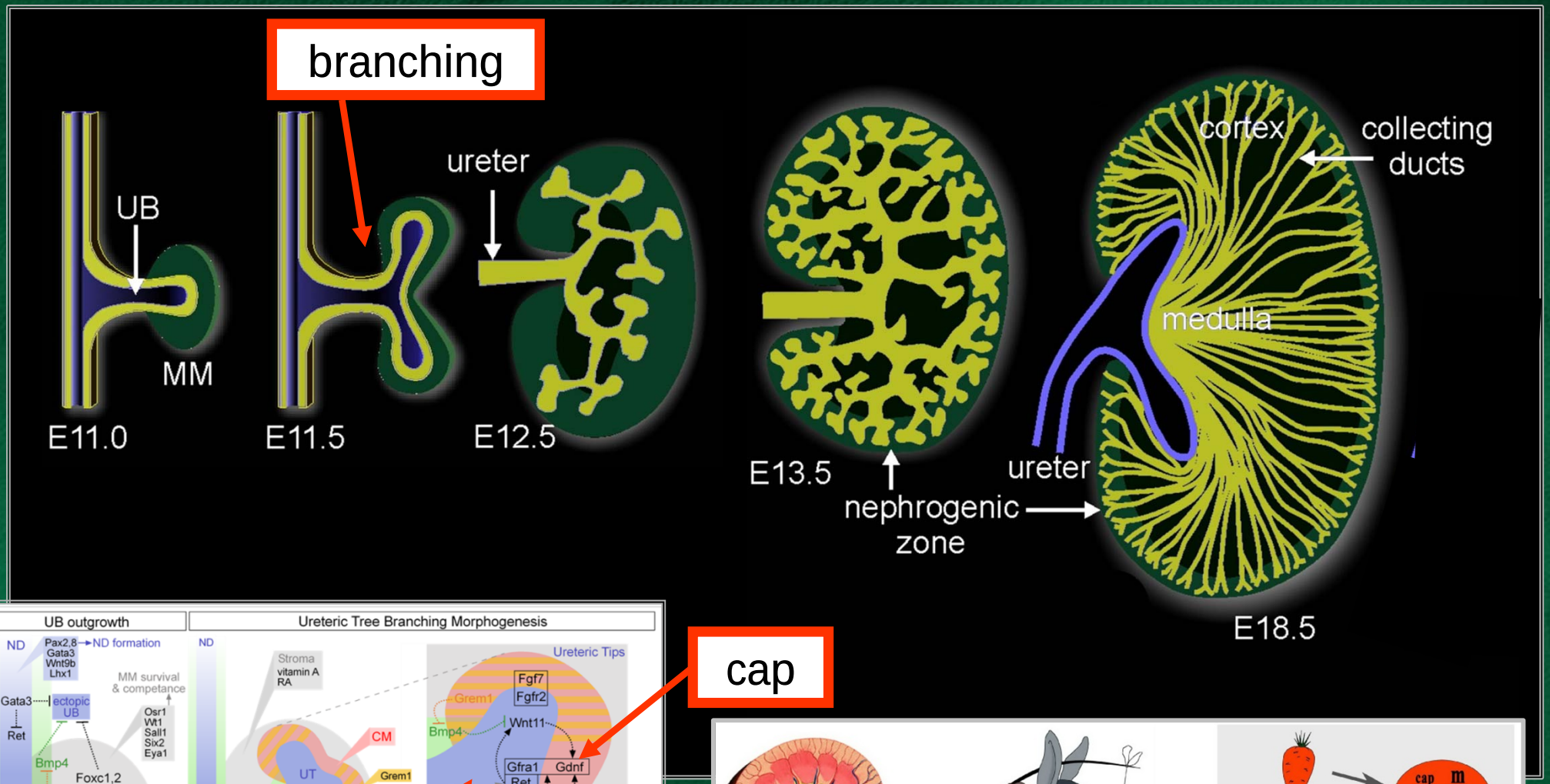


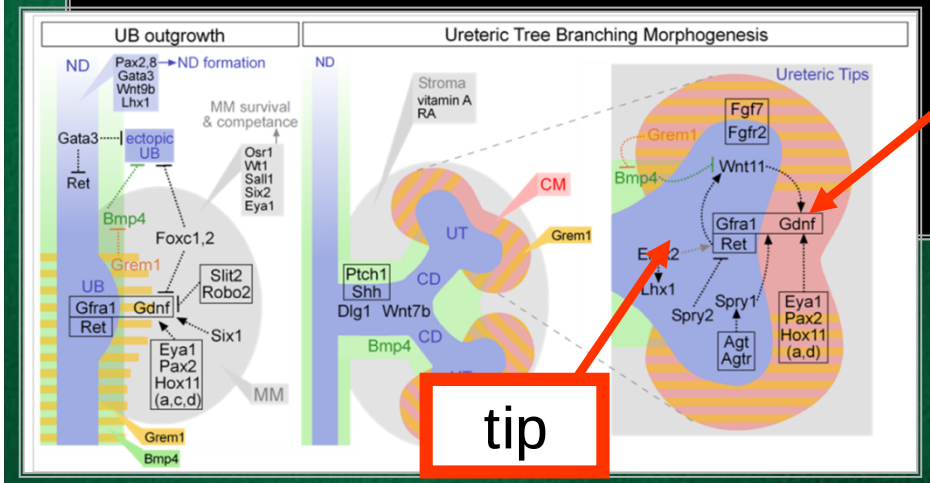


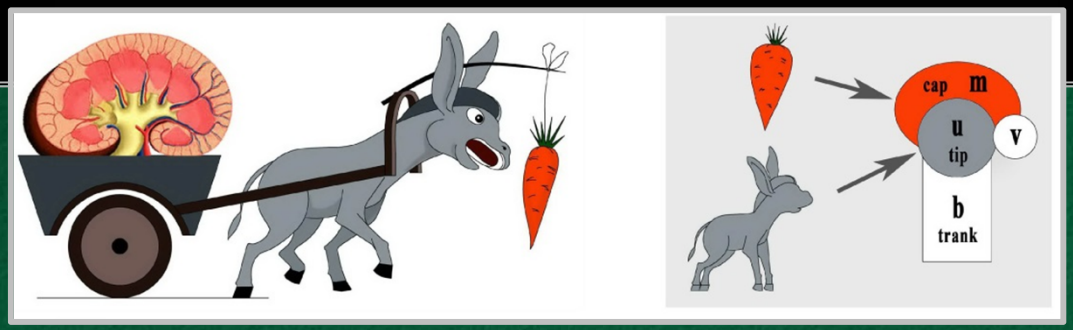
unckidneycenter.org

Mammalian kidneys are vital organs that filter wastes such as urea from the blood and excrete them, with water, as urine.

Branching morphogenesis drives kidney development

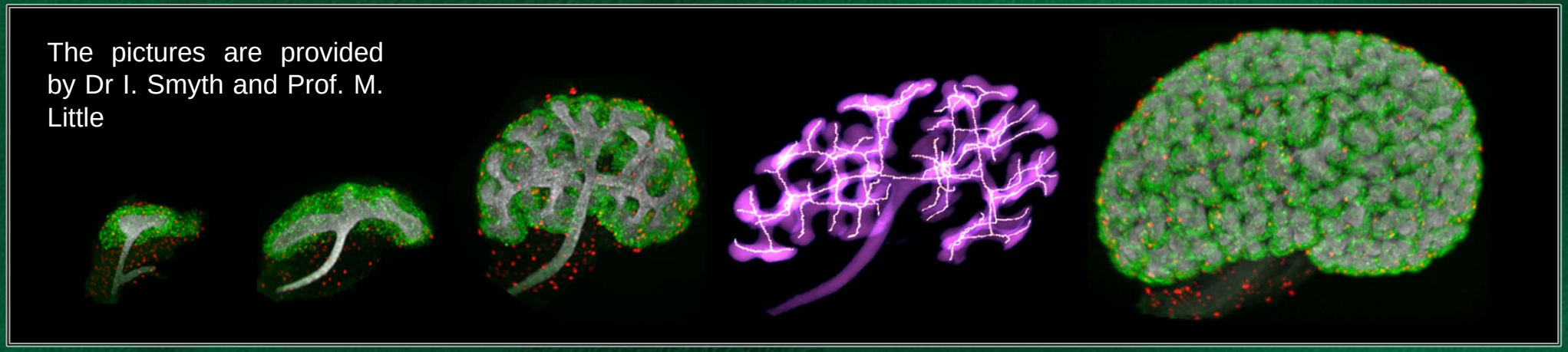


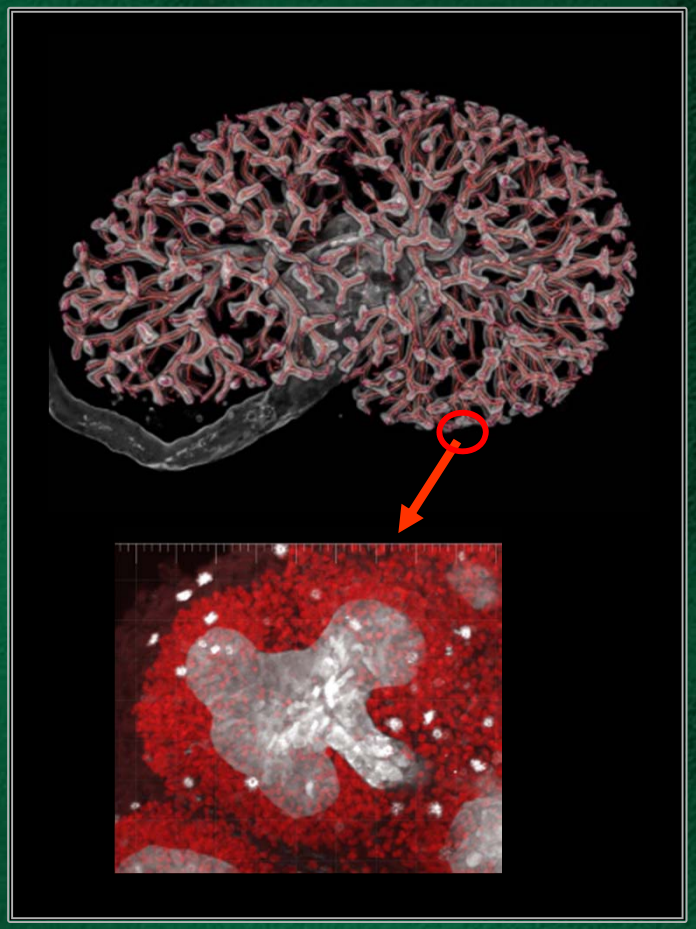




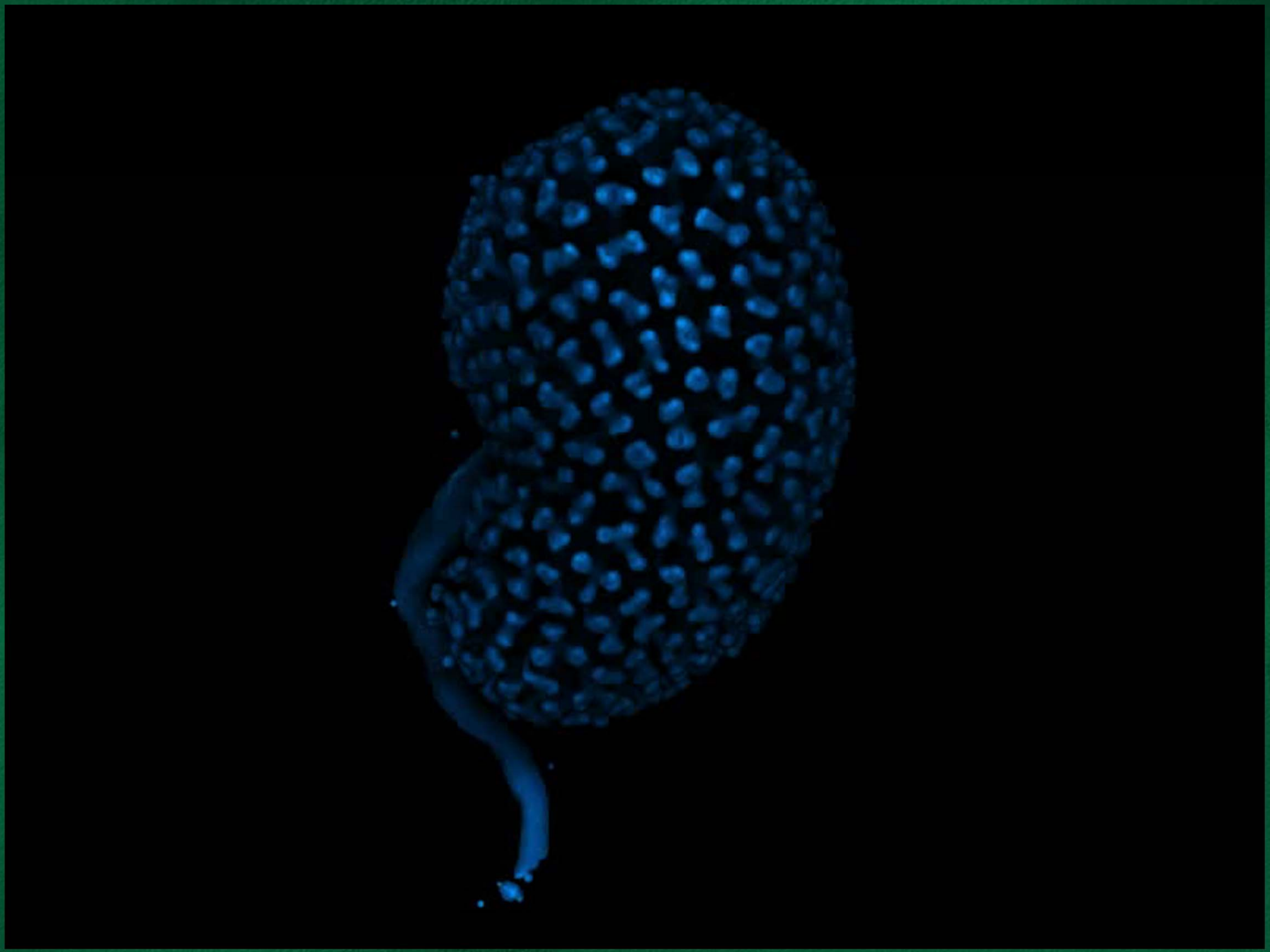
Kidney morphogenesis observations

The pictures are provided by Dr I. Smyth and Prof. M. Little



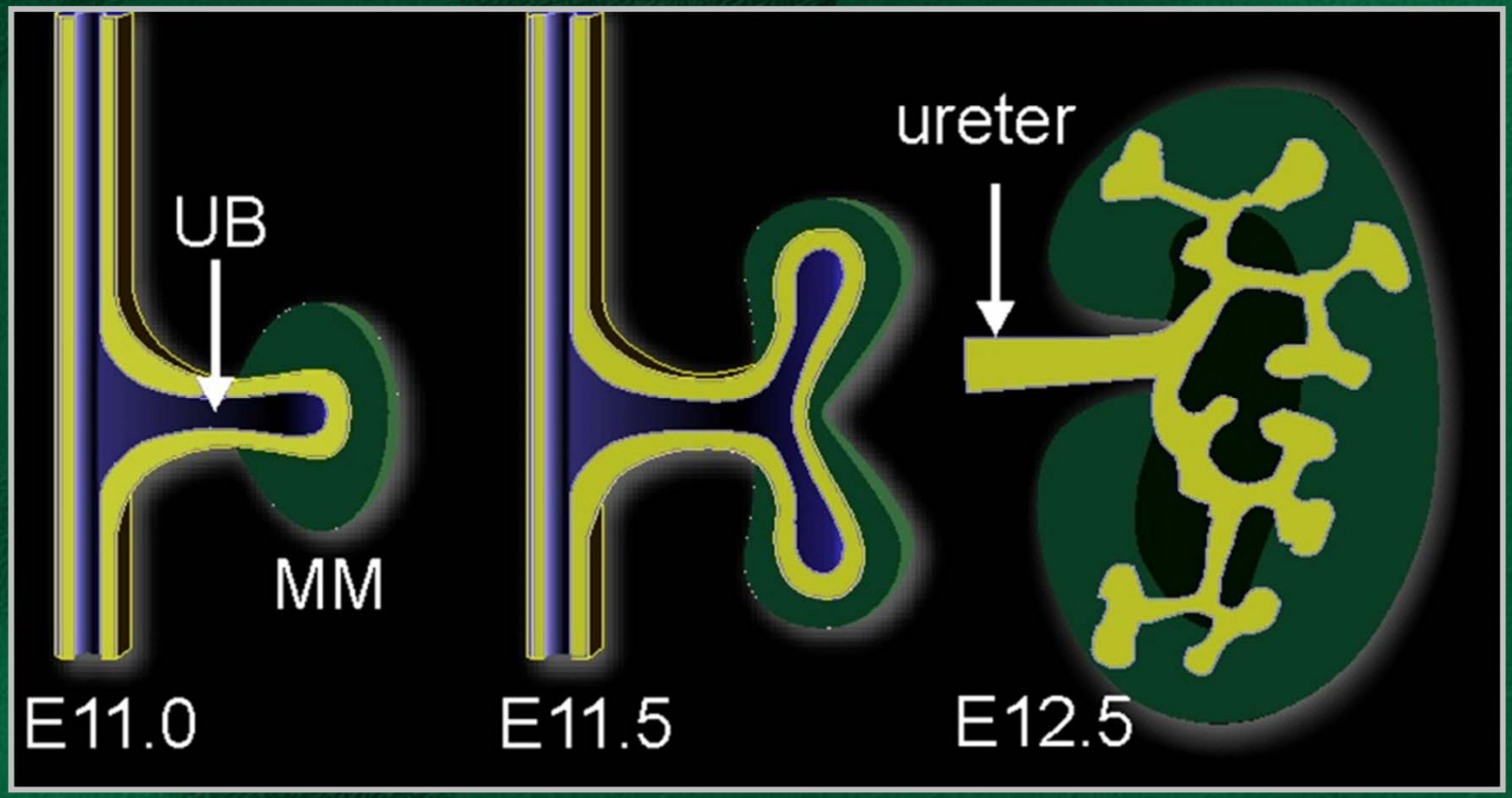


Recently, new experimental tools were developed and a big amount of data can now be available.

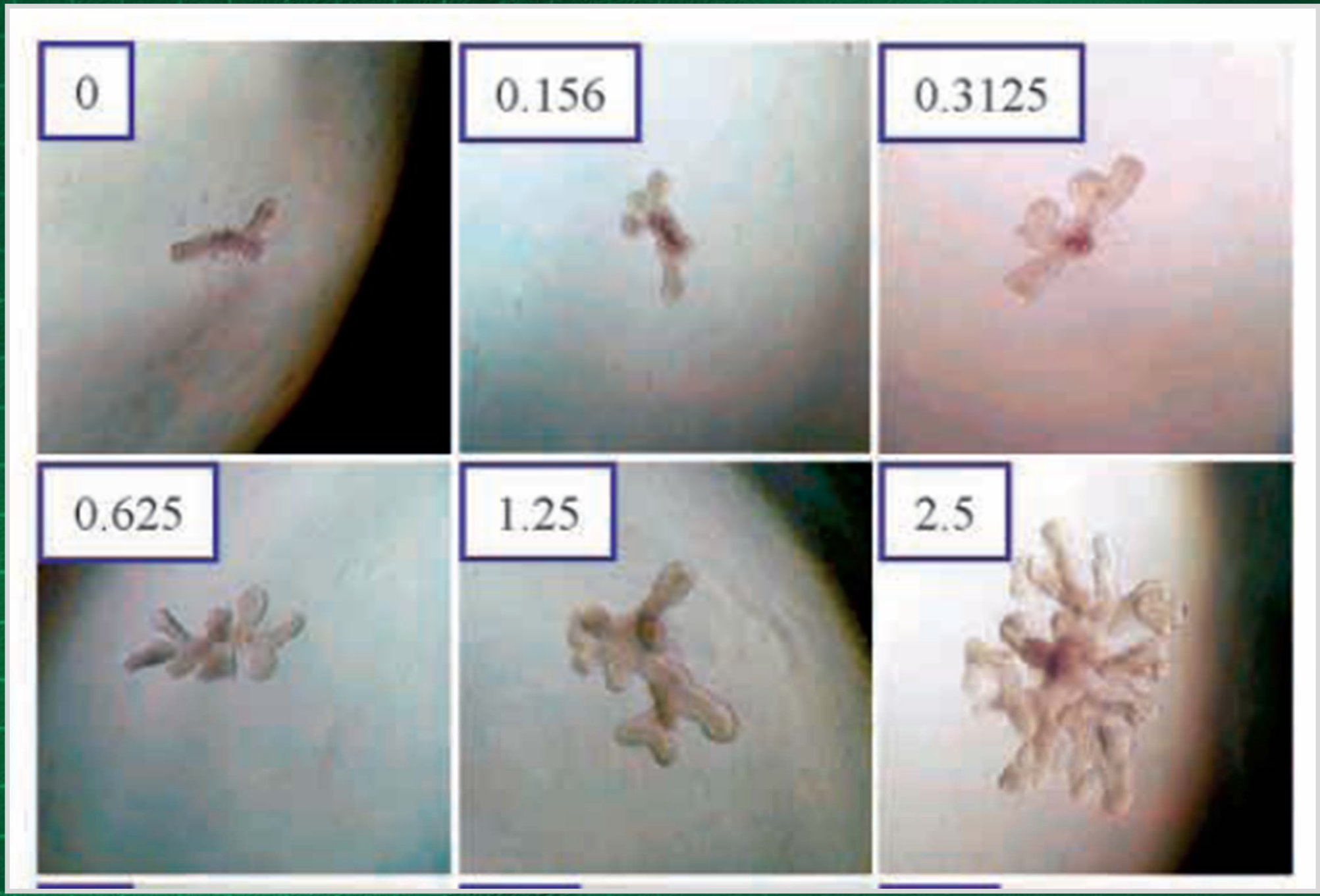


Question

Why does the branching occur?

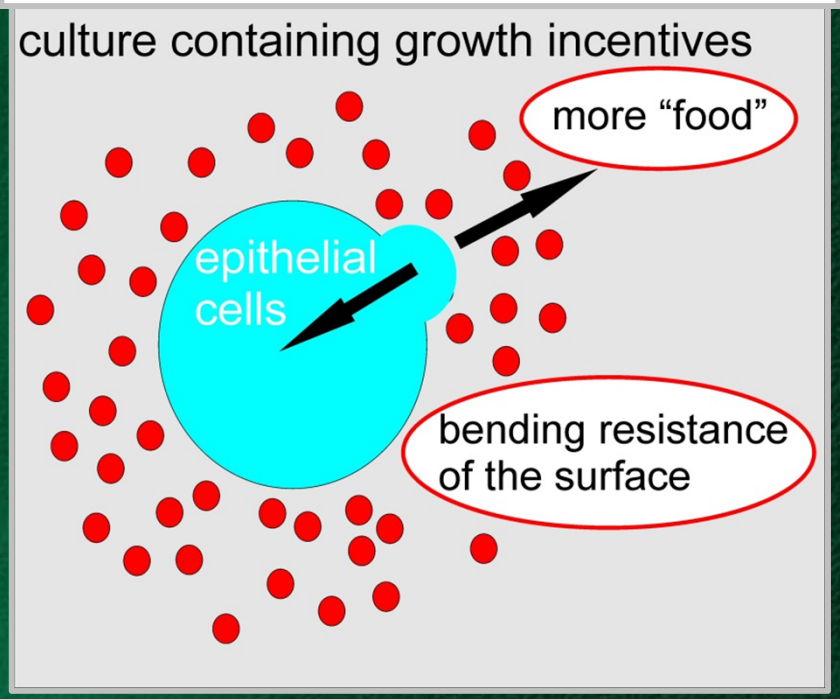


Kidney Development In vitro



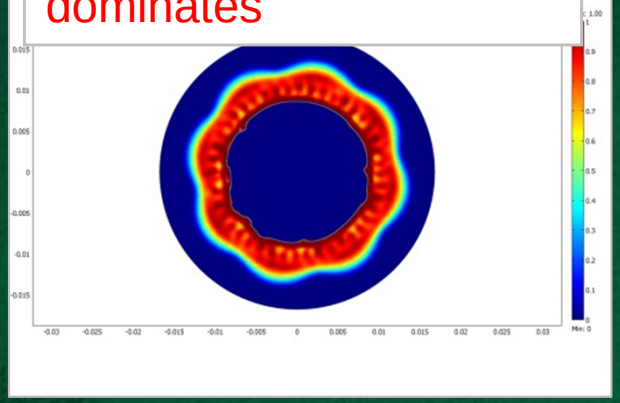
Kidney branching mechanism

Bending resistance vs Growth

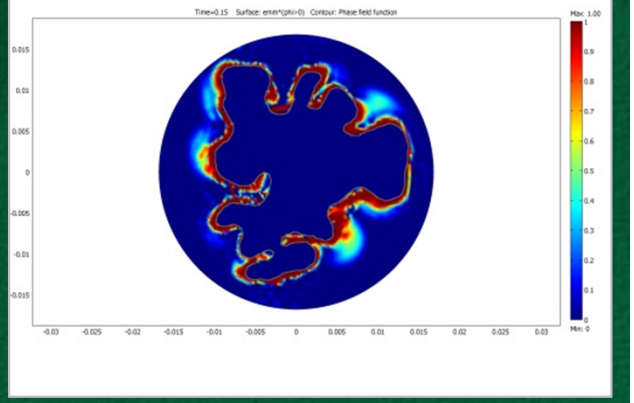


We will show that branching is driven by the following mechanism: tip cells tends to move further from the smooth tip surface as they get more GDNF and, as a result, have higher proliferation and chemotactic attraction.

Bending resistance dominates



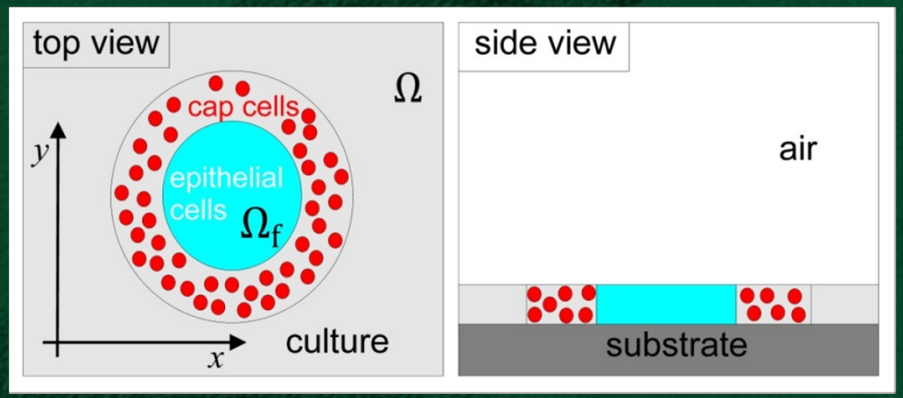
Growth dominates

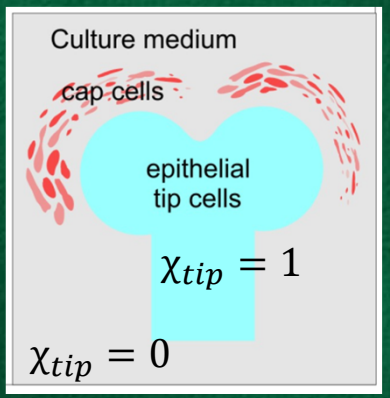


Model formulation

Mathematical Model (multiphase flows)

Tip cells: We model the epithelial tip cells and the culture medium as continuous mediums (incompressible Newtonian fluids). Proliferation, Viscosity and Chemotaxis are defined by GDNF concentration, *c*: if *c* is low, tip cells do not move and do not proliferate.





u - velocity

viscosity

chemotaxis

$$\rho \frac{\partial \boldsymbol{u}}{\partial t} + (\mathbf{u}\nabla)\mathbf{u} = \nabla[-p\mathbf{I} + \mu(\nabla\mathbf{u} + (\nabla\mathbf{u})^T) + \chi_{tip}F_{chem} + \delta(\partial\Omega_f)F_{surf\_ten}$$

elasticity of the epithelial boundary

$$\nabla\mathbf{u} = \chi s(c)$$

cell proliferation

Mathematical Model P2

We suppose that the concentration of the GDNF (nutrient), c, is governed by the convection-diffusion equations; *c* can also go throw the tip cells.

c – nutrient concentration:

Diffusion

degradation

$$\frac{\partial c}{\partial t} = D_c \Delta c - k_c(c)\chi_{tip} - \delta_c c$$

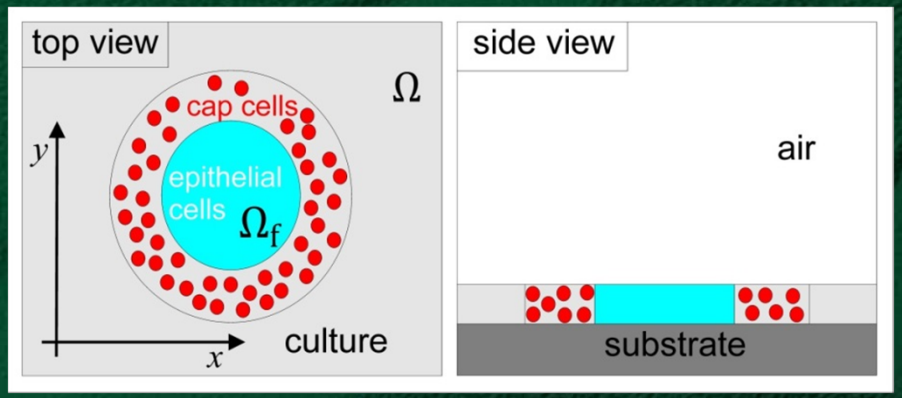
Changes of c with time

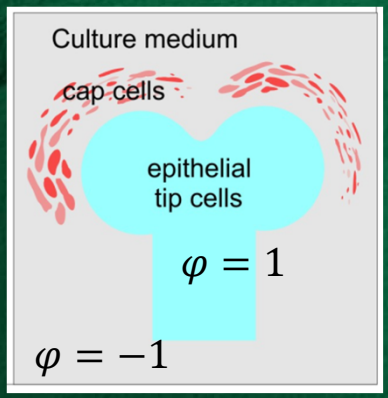
Collection by tip cells

Mathematically, the problem is very similar to an evaporative droplet heated (condensated) in a gas.

Mathematical Model P3

The problem was solved numerically using Phase Field Method





phase field variable

mobility

mixing energy density

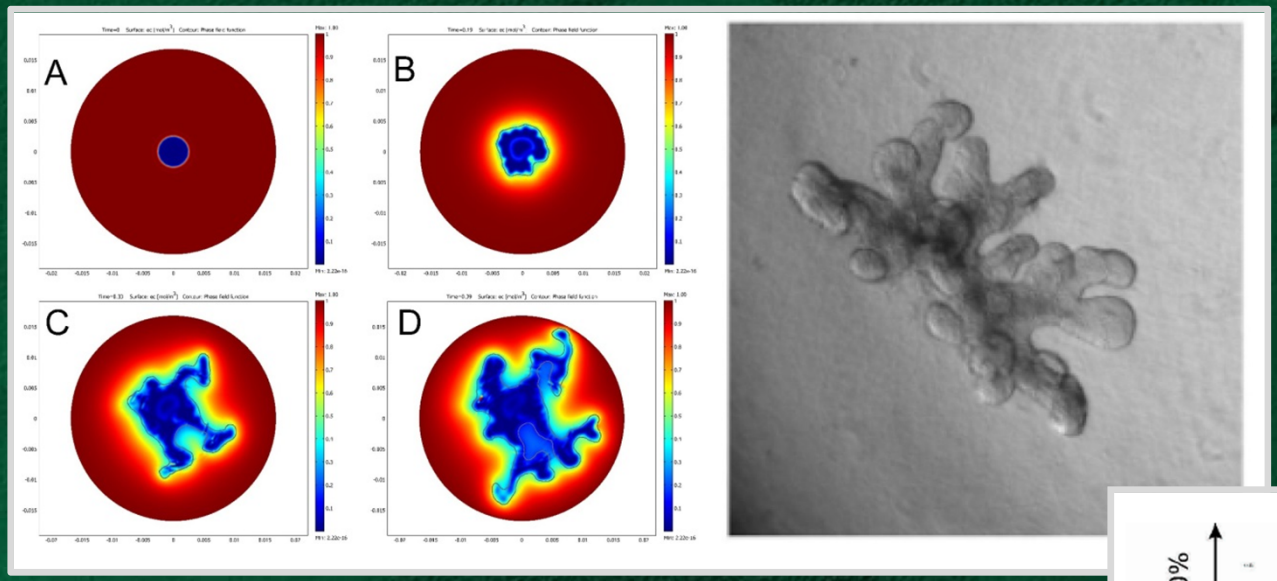
$$\frac{\partial \boldsymbol{\varphi}}{\partial t} + (\mathbf{u}\nabla)\boldsymbol{\varphi} = \nabla \frac{\gamma\lambda}{\varepsilon^2} \nabla \psi$$

$$\psi = -\nabla\varepsilon^2\nabla\boldsymbol{\varphi} + (\boldsymbol{\varphi}^2 - 1)\,\boldsymbol{\varphi}$$

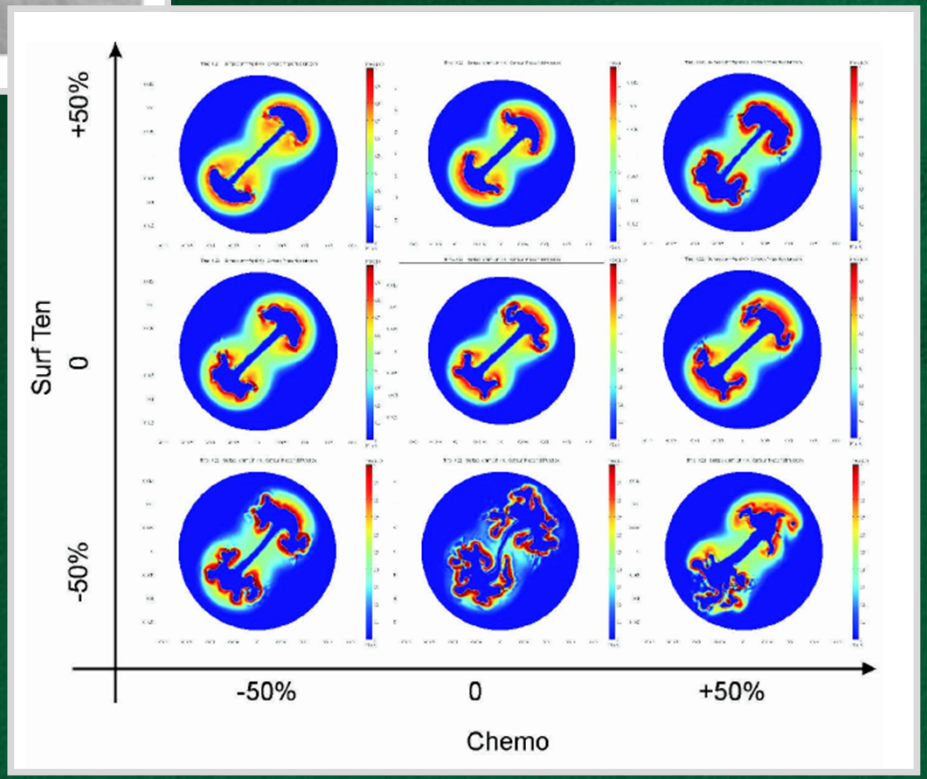
thickness of the interface

Results

Branching of the kidney explant (gray curve is the boundary of the epithelial explant):

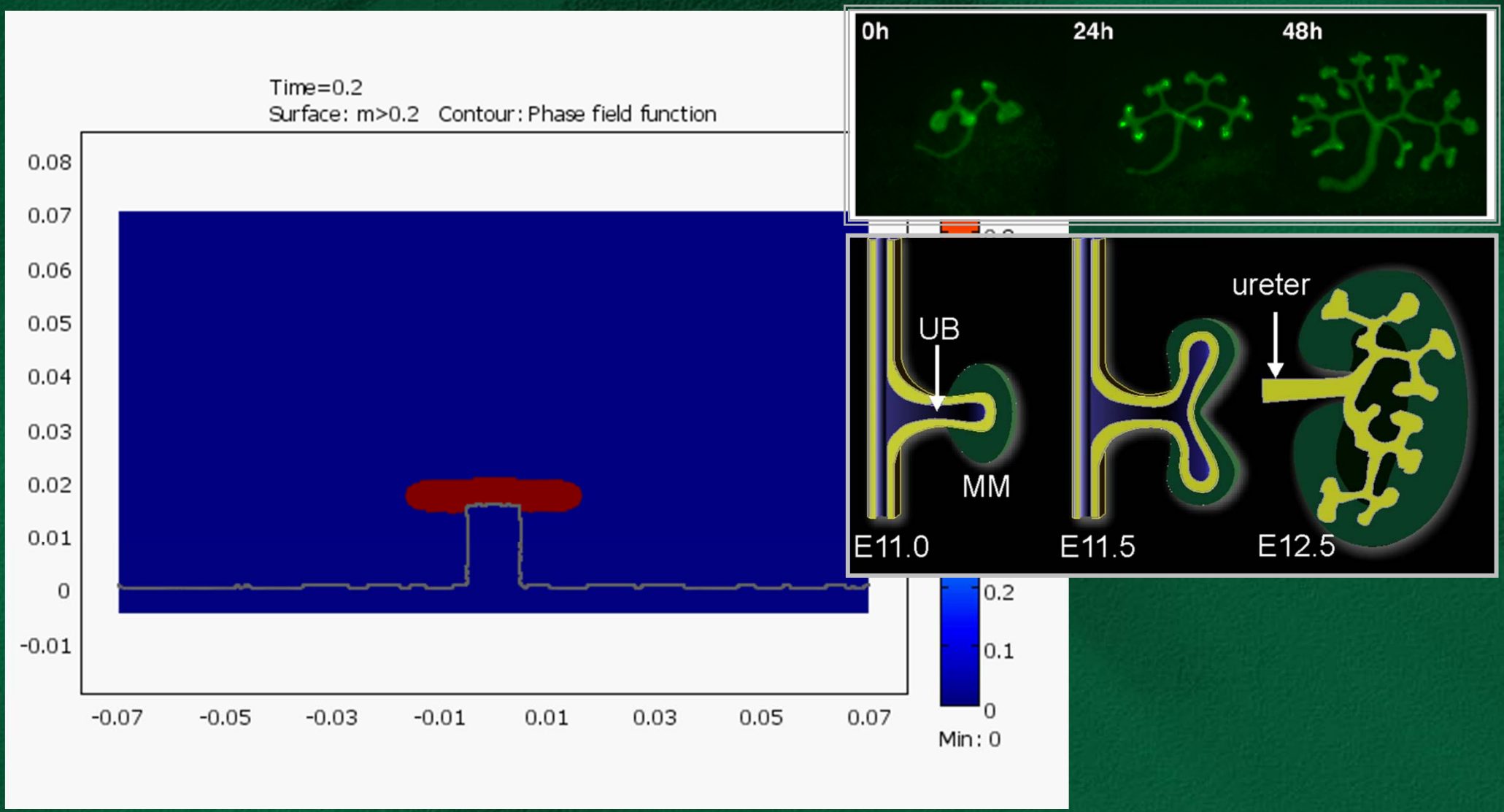


Our team included three laboratories that provided us experimental data collected from developing mouse kidneys. These data were analysed using statistical methods and helped me to build and validate the mathematical model. Later, model predictions were used to formulate new hypotheses and design new experiments.



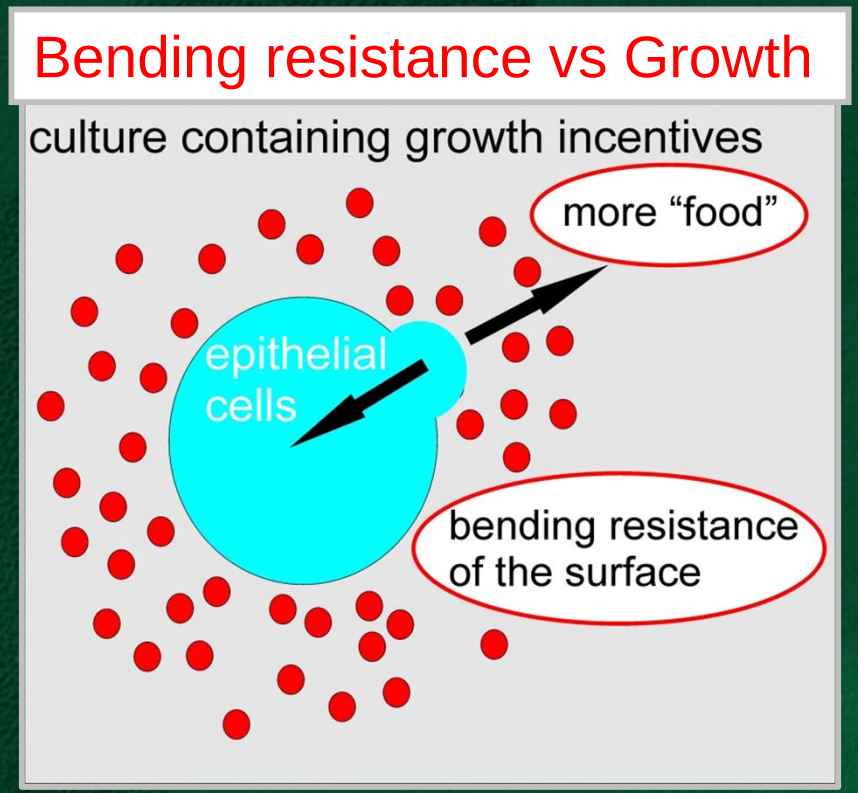
Results

Branching of the Bud (gray curve is the boundary of the epithelial explant):



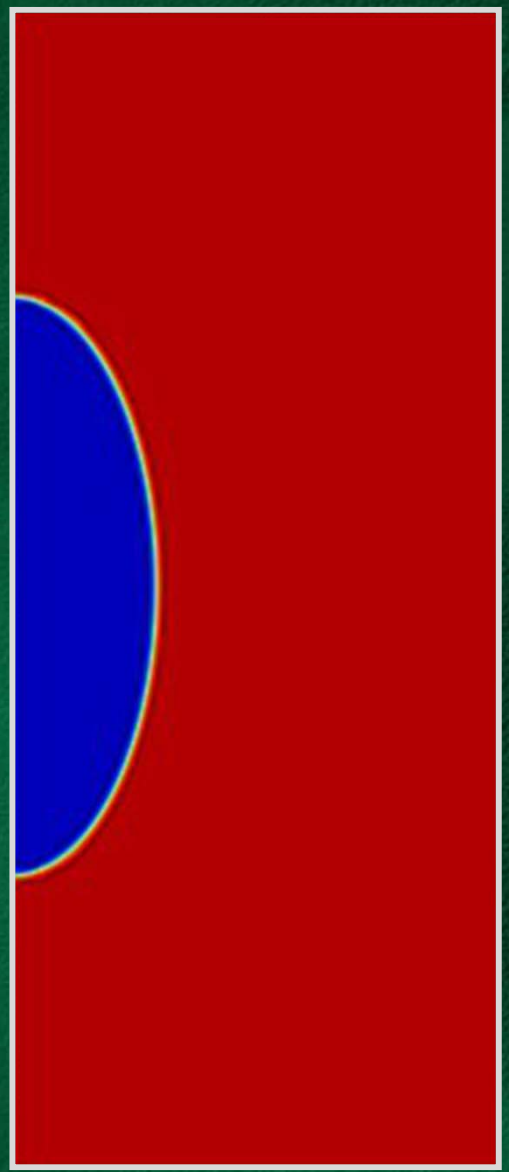
Conclusion

- We showed a mechanism that can drive kidney branching



Multiphase flows and sprays

Dynamics of evaporating drop



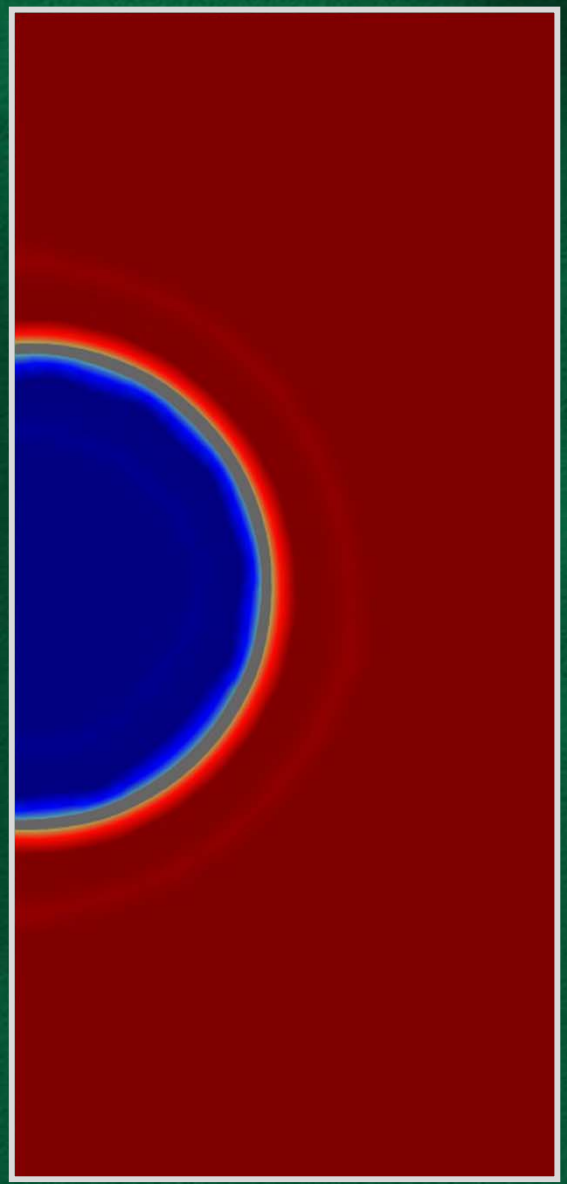
Surface tension

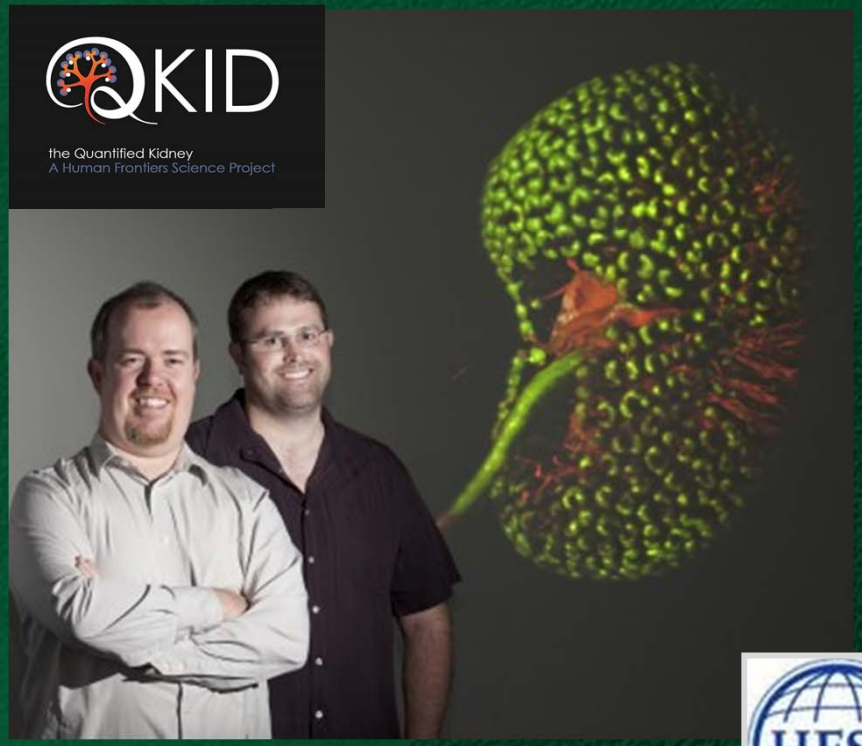
Moving boundary

Evaporation/Growth

Temperature/Growth factor

Growing Kidney





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