Hybrid modeling and parameter inference reveal branching constraints for kidney morphogenesis

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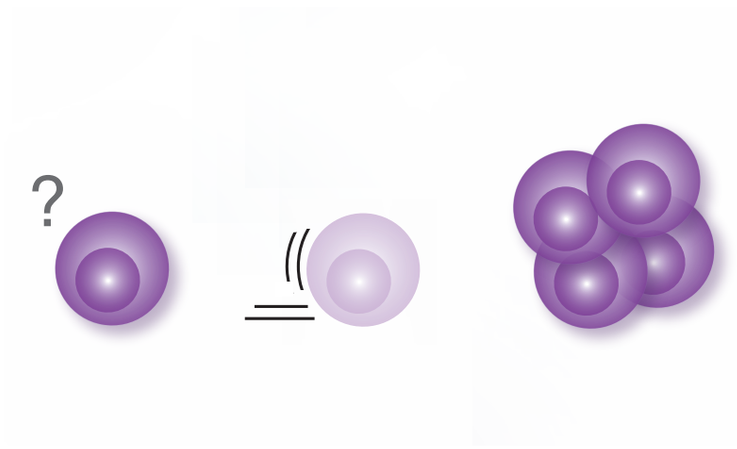
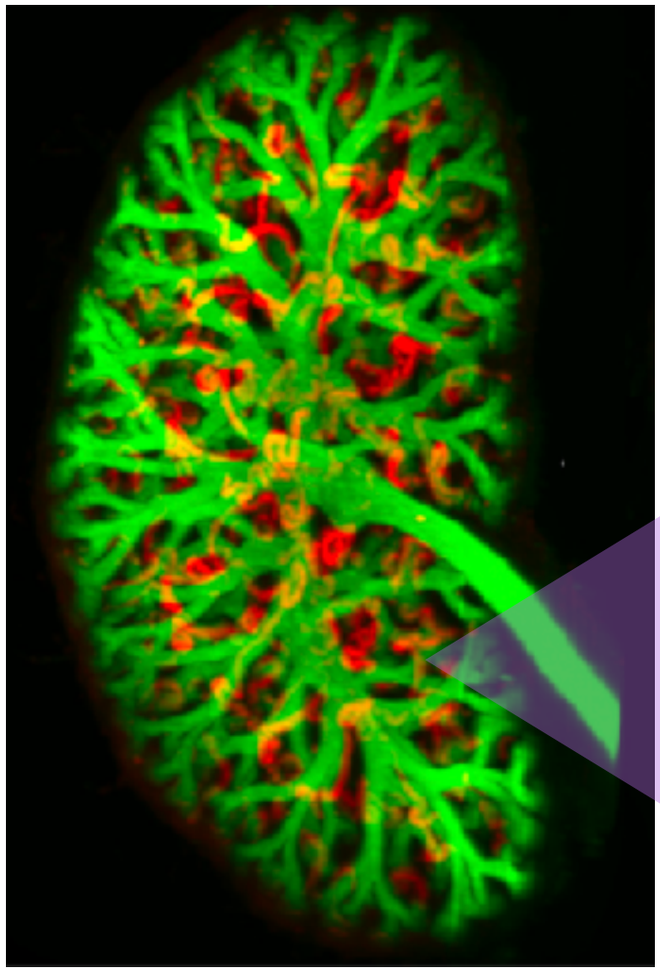


Overview

- Multiscale biological systems
- A hybrid model of kidney branching morphogenesis
- Comparison with data & summary statistics
- Parameter inference via **approximate** approximate Bayesian computation
- Identification of key parameters controlling kidney development
- Summary & Outlook

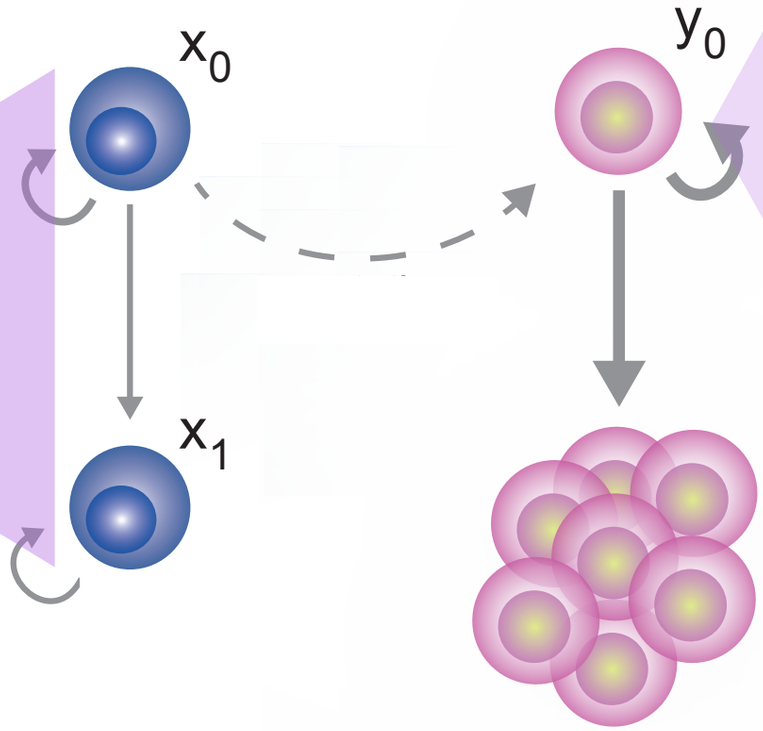
Epithelial tissue branching morphogenesis is a complex and multiscale process

Tissue growth and regeneration

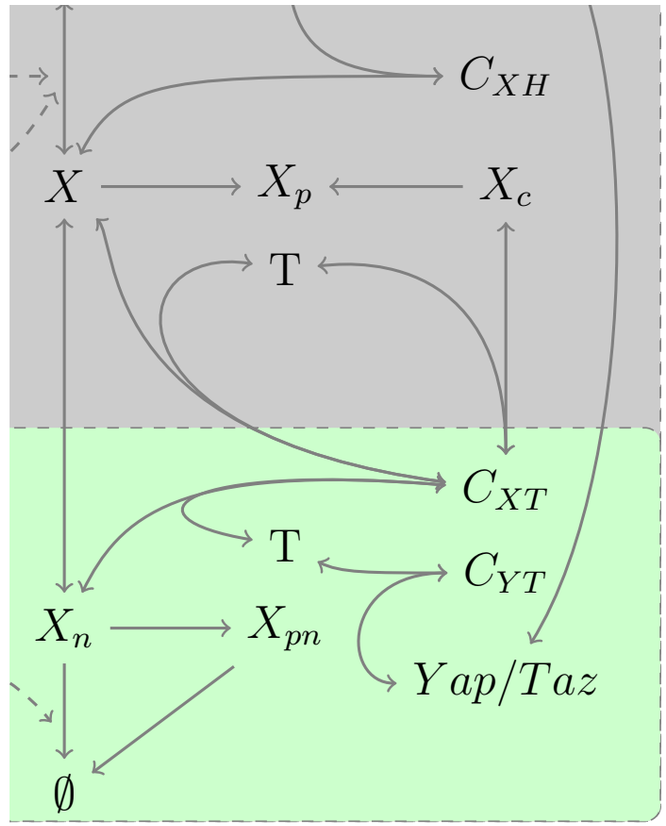


Short et al. (2018), *eLife*

Cell division, differentiation, migration, feedback, lineage interactions



Molecular signaling networks

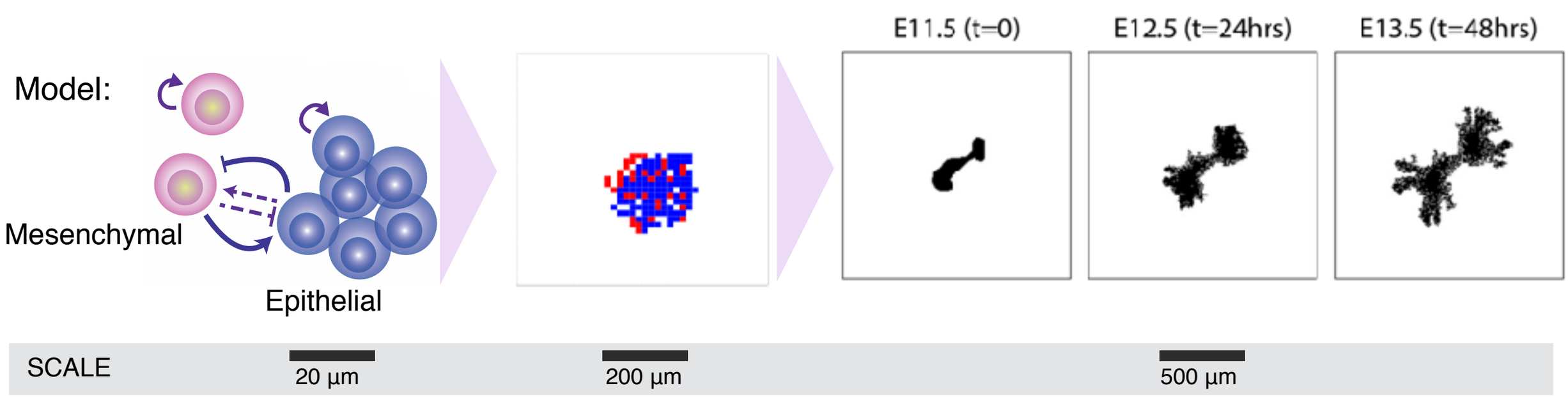


A hybrid model for kidney epithelial branching morphogenesis

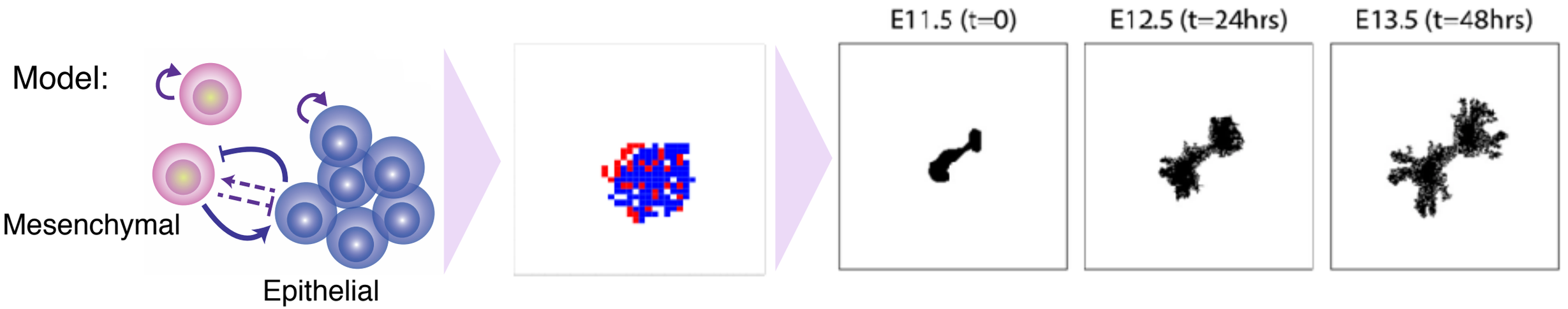
Questions

- How is branching initiated in the nephric duct?
- How do mesenchymal signals regulate branching?
- What are the affects of spatial heterogeneity?

Approach: couple cell-based interactions (division, migration) with continuous morphogen fields to describe the growth of the tissue



A hybrid model for kidney epithelial branching morphogenesis



Mesenchymal-epithelial interactions mediated by GDNF (G)

$$\frac{\partial G}{\partial t} = D_G \nabla^2 G - \Phi_G \quad \text{where} \quad \Phi_G = \begin{cases} K_G G(x,y,t) & \text{for E} \\ 0 & \text{o.w.} \end{cases}$$

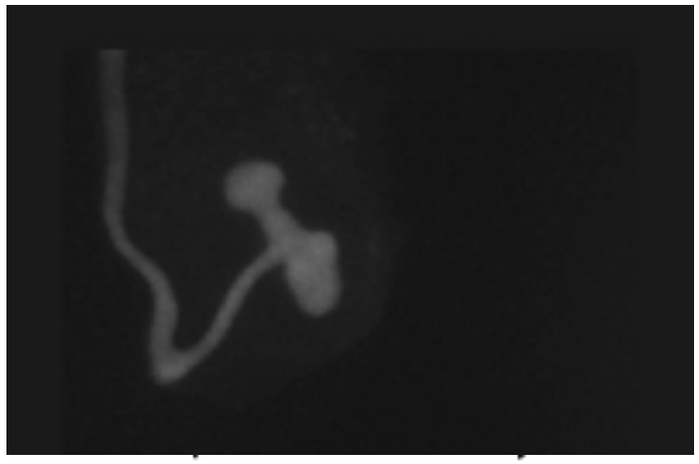
Cellular automaton (CA) defines epithelial cell growth (p_{cd}) and cell migration into neighboring grid cells, occurring with probability p_i

$$p_{cd} = \Phi(c_1 + c_2 g(\eta_x, \eta_y, t)) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{c_1 + c_2 g(\eta_x, \eta_y, t)} e^{-\frac{\tau^2}{2}} \, d\tau$$

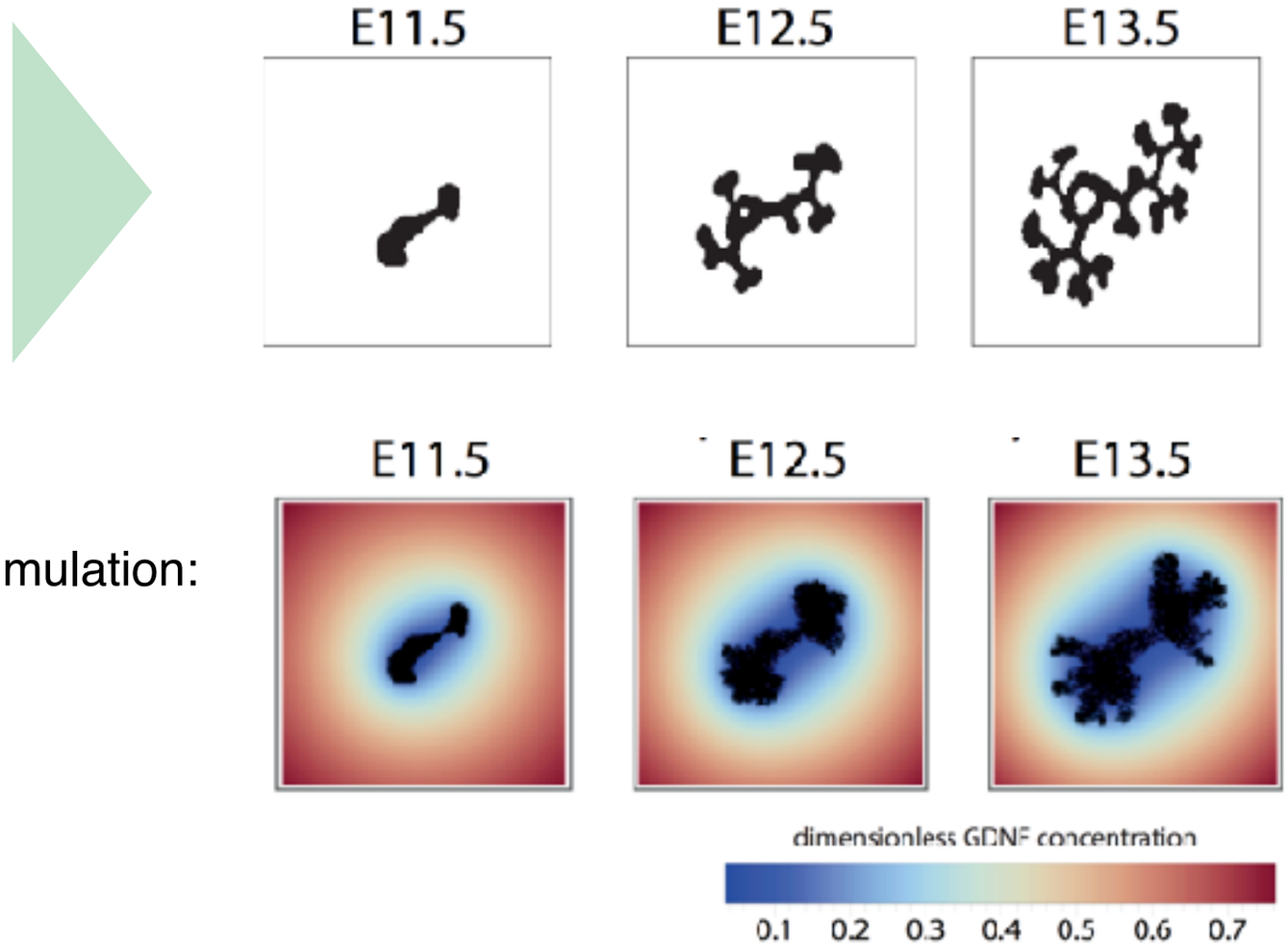
$$p_i = \frac{exp(\beta_a g_i)}{\sum_{j=1}^{K} exp(\beta_a g_j)}$$

Summary statistics for data-model comparison

Data:

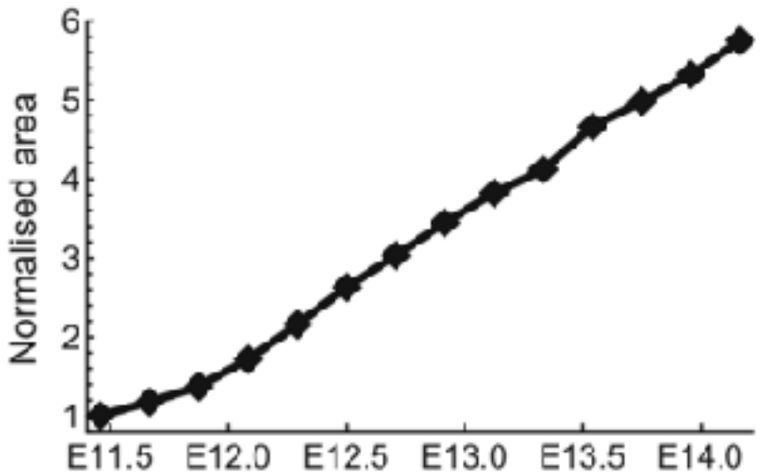


Watanabe & Costantini

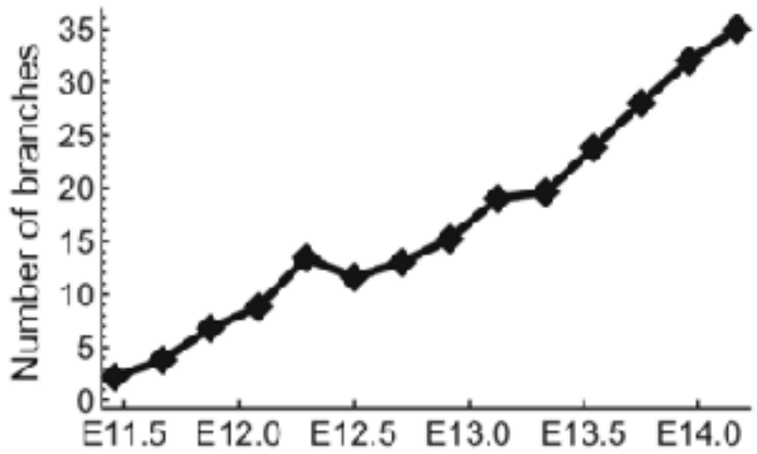


Summary statistics

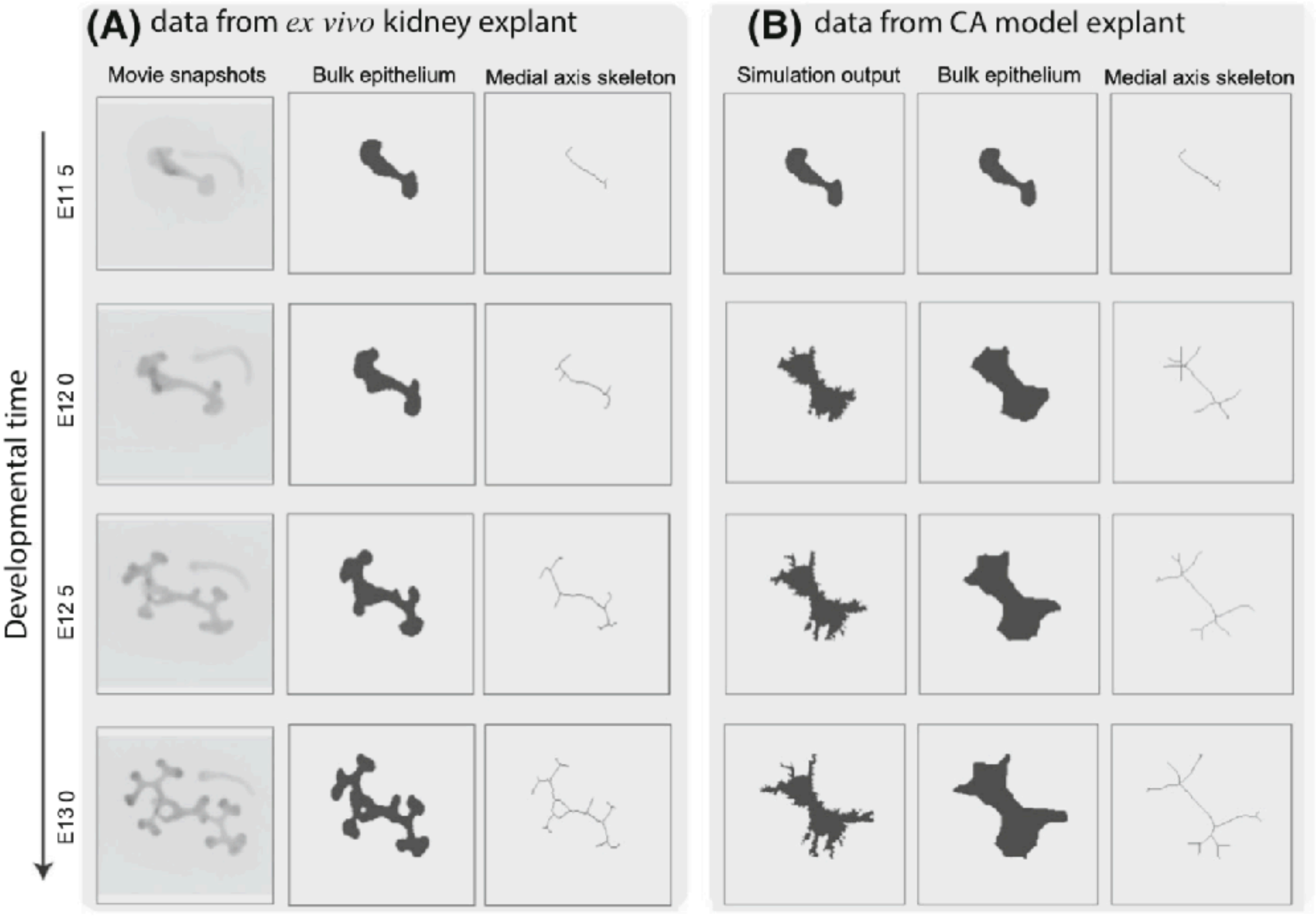
1. Epithelial area



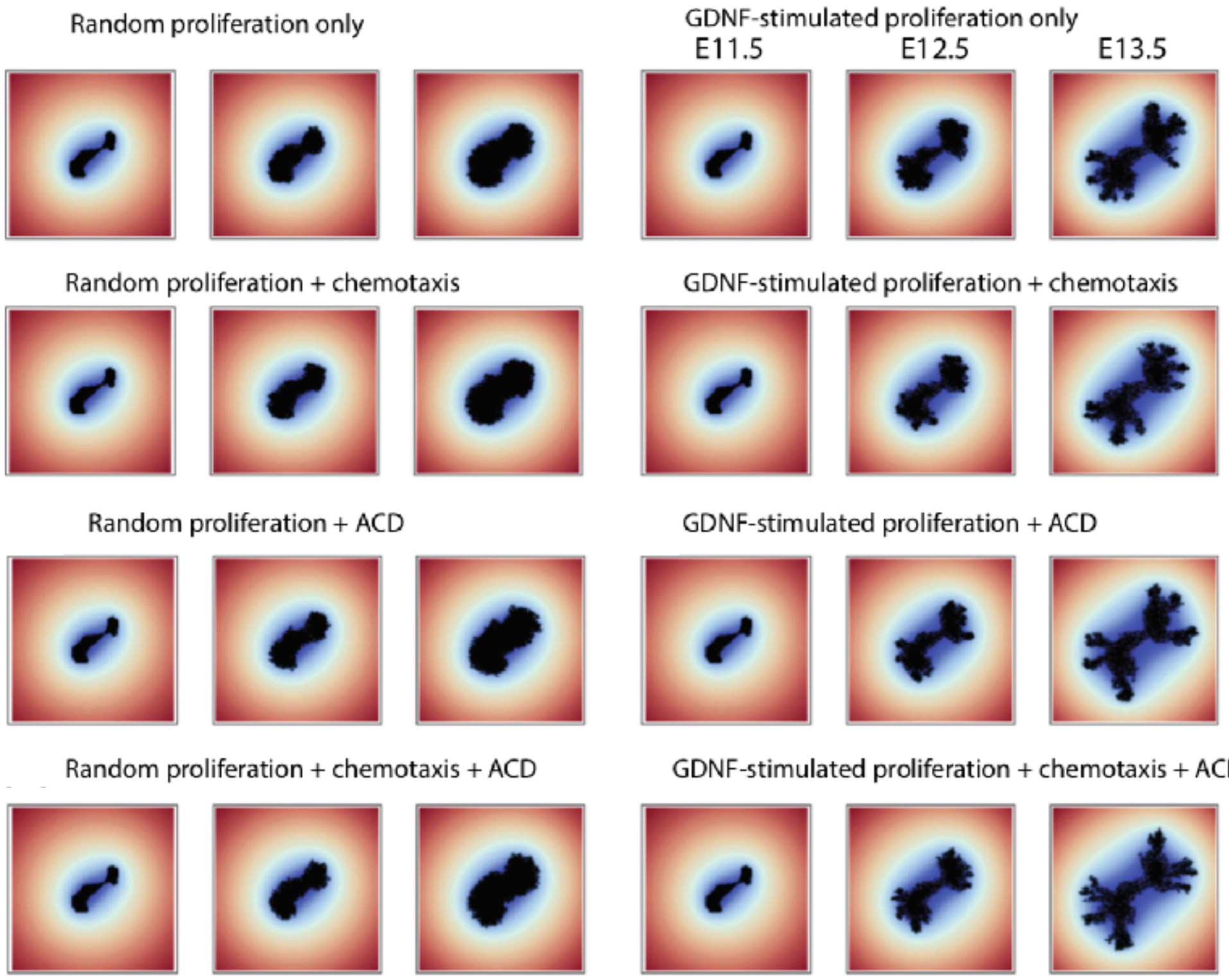
2. Number of branches (medial axis skeleton)



Summary statistics for data-model comparison: medial axis skeleton



Topological model exploration: necessary conditions for branching



AABC: **Approximate** approximate Bayesian computation

- Simulation time of this model (and typically of ABMs) is prohibitive for inference by ABC
- Approach: replace the mechanistic model with a statistical model parameterized via an intermediate distribution (from ABC)

Algorithm

1. ABC-Rejection: simulate the full model and, for θ_i, accept datasets $\mathbf{x}_i = (x_{1i}, x_{2i}), i \in (1, 2, ..., m)$ where m is the number of parameter sets

2. Sample a new parameter set θ^* from the prior, and calculate its weight according to an Epanechnikov kernel:

$$\omega_i = \frac{3}{4}\frac{1}{(\theta^* - \theta_{(k+1)})}\left[1 - \left\|\frac{\theta^* - \theta_i}{\theta^* - \theta_{(k+1)}}\right\|^2\right]\mathbb{1}_{\{\|\theta^* - \theta_i\| < \|\theta^* - \theta_{(k+1)}\|\}}$$

   where the indicator function selects the *k* shortest distances from θ^*

3. Draw a sample $\phi \sim Dir(\omega)$

4. Simulate a new dataset $\mathbf{x}^*$ by resampling from $\mathbf{x}_i$ with probabilities set by ϕ

5. Calculate distance, and accept iff $||\mathbf{s}_i^* - \mathbf{s}_0|| < \epsilon$

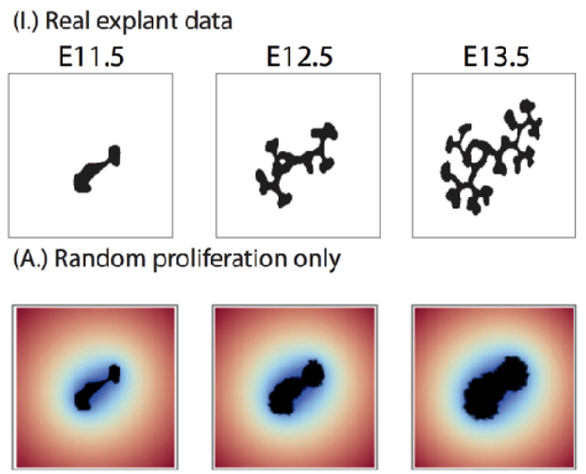
6. Repeat until convergence in the approximate posterior is reached

Buzbas and Rosenberg (2015), *Theor Pop Biol*

AABC parameters sufficient to induce branching

Priors chosen for the parameters:

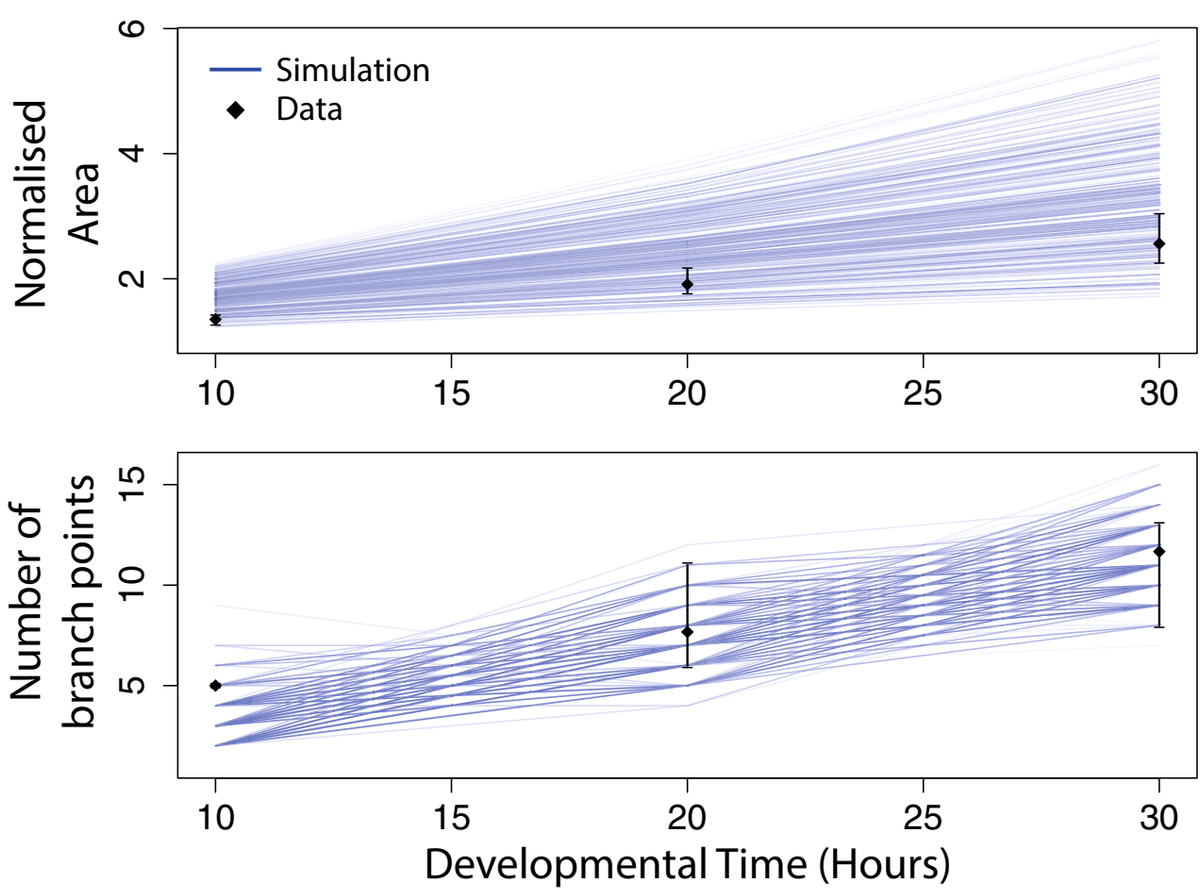
- $\{c_1, c_2\}$ determine the sensitivity of proliferation to GDNF level
- $\{p_{move}\}$ probability of cell migration



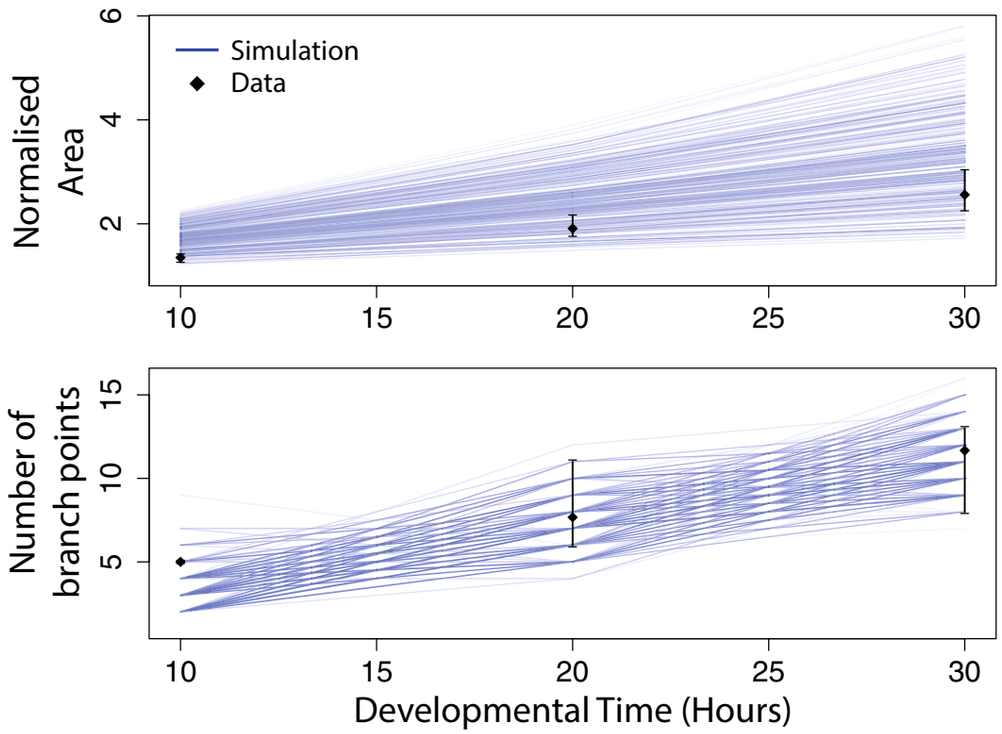
Intermediate distribution (ABC) → AABC posterior (estimate of the ABC posterior)

$$P(\theta|d(s_i^*, s_0) < \epsilon)$$

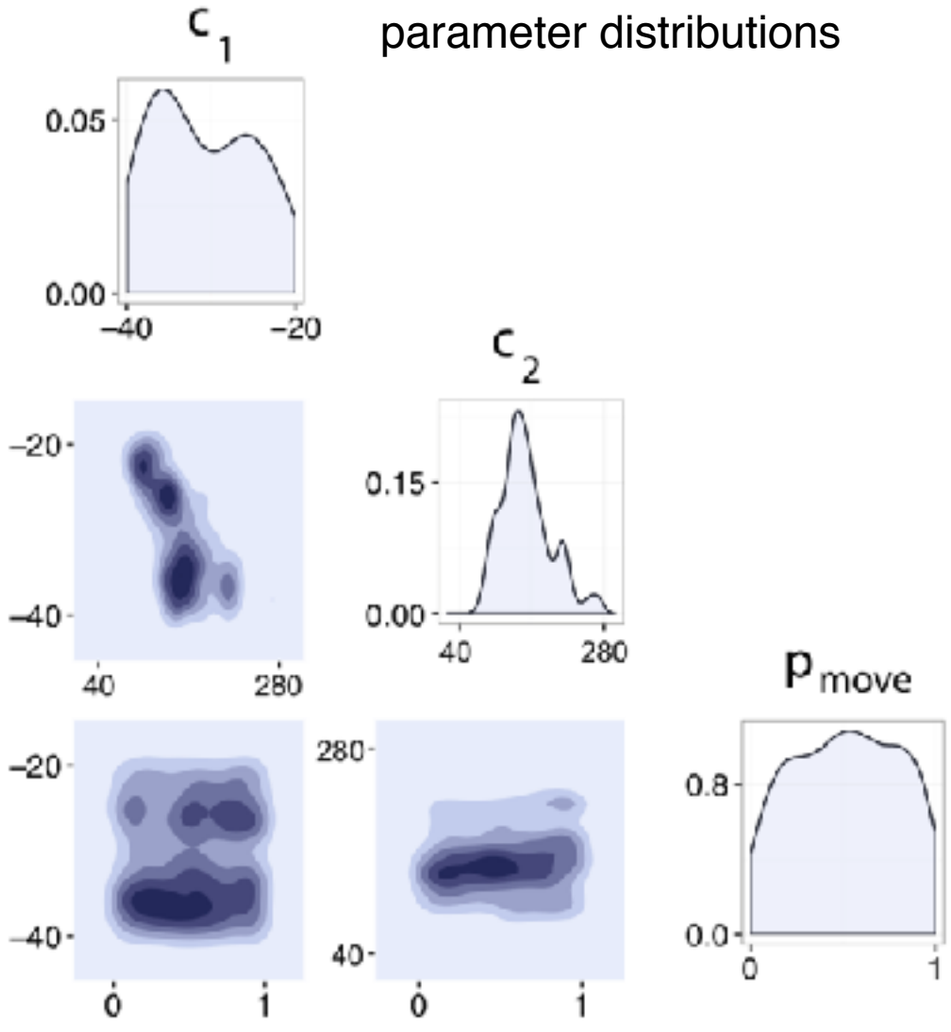
Simulations with parameters sampled from the posterior:



AABC identifies parameters sufficient to induce branching



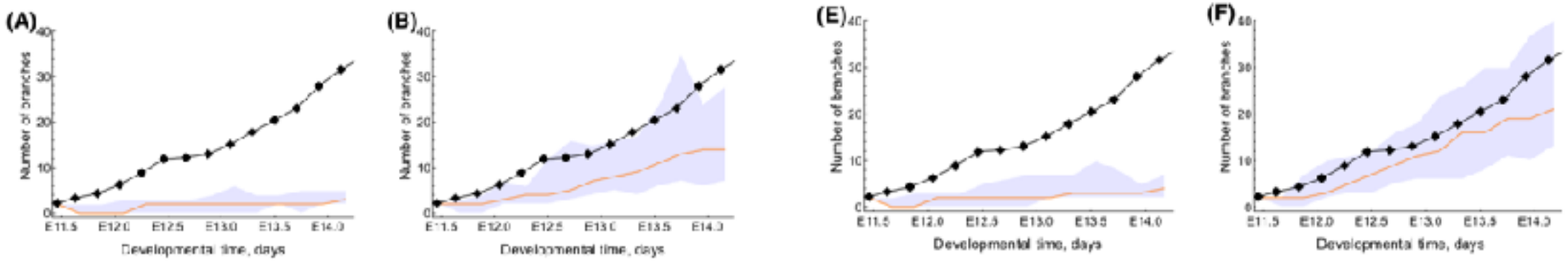
Joint density marginal parameter distributions



- Branching is most sensitive to GDNF-sensitivity parameter c_2
- Branching is robust to the migration probability
- c_2 and c_2 are closely correlated

Fine-tuned growth sensitivity to GDNF is crucial for branching

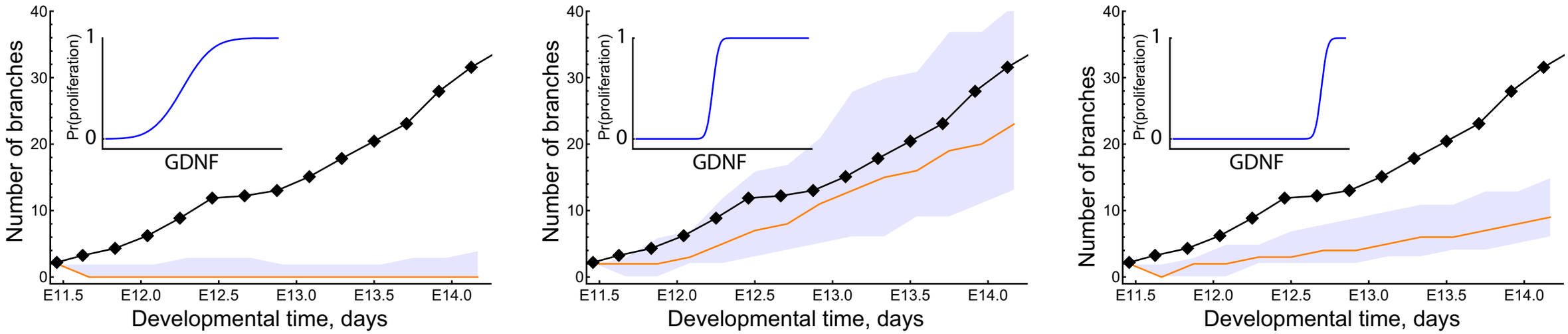
GDNF switching behavior:



Gradual switch

Sharp switch
mid-threshold

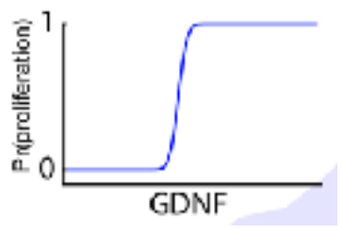
High threshold



Lambert*, MacLean* et al. (2018), *J Math Biol*

Summary

- Multiscale/hybrid/individual cell-based models can be too expensive for ABC
- AABC provides an alternative in such cases
- Applied to kidney development the model is successful at fitting explant epithelial data describing branching morphogenesis
- We identify a GDNF-controlled sharp switching mechanism as a sufficient mechanism for branching



Open Questions and Challenges

- Better summary statistics?
- How to deal with large parameter spaces? What criteria can be used to give sufficient number of ABC samples?
- Dealing with parameters across multiple scales? Not always straightforward to rescale model

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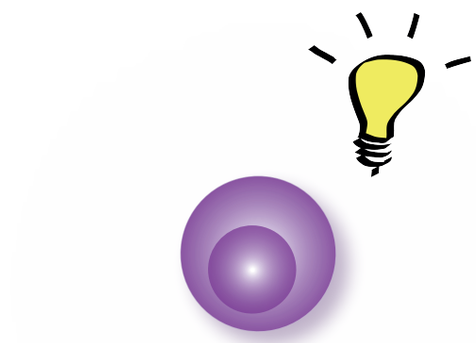

Thank you

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HFSP
NIH National Institutes of Health
CCBS Center for Complex Biological Systems