Tissue modeling

Multi-scale modeling of multicellular systems

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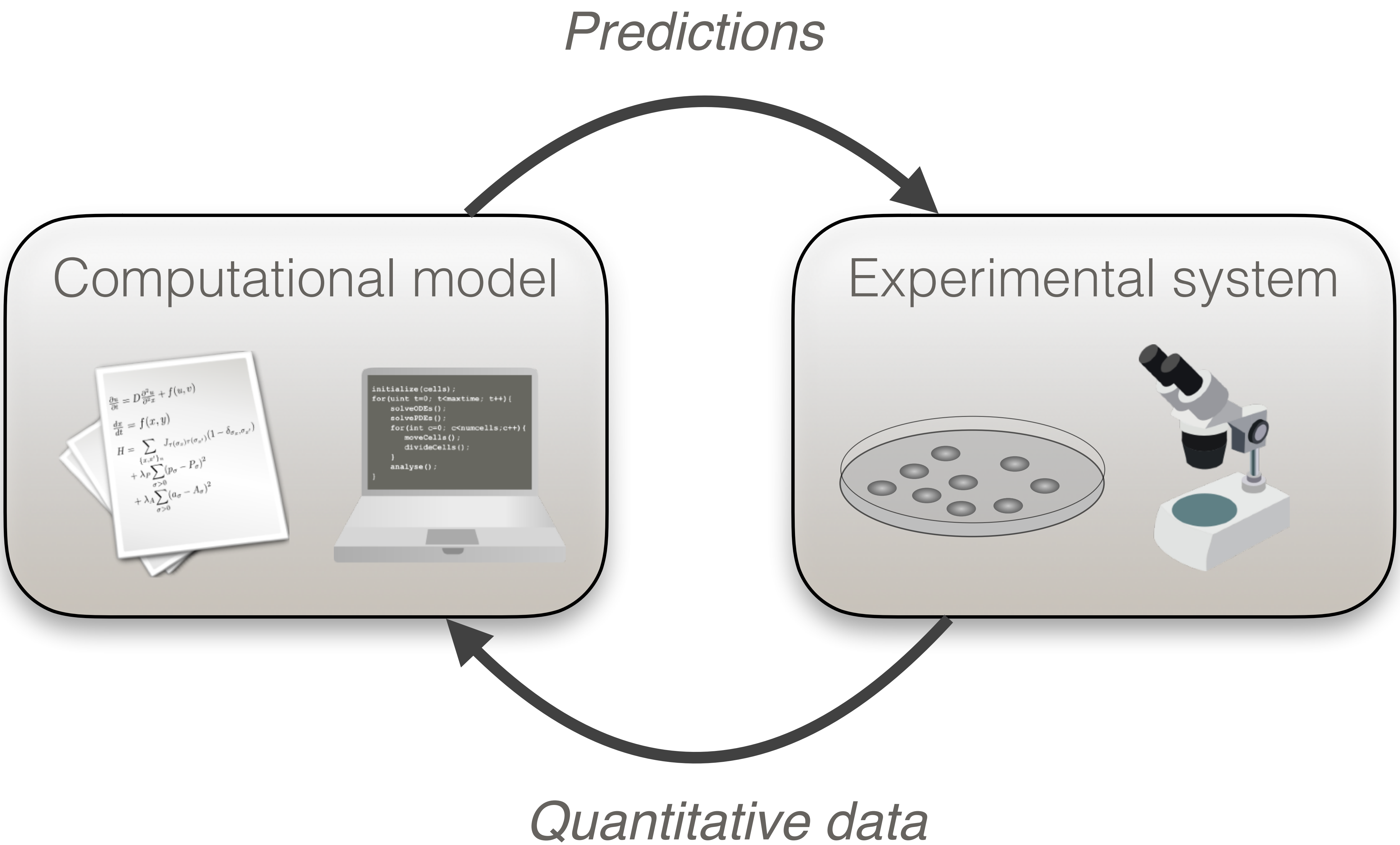
"Carl Gustav Carus" Faculty of Medicine
TU Dresden

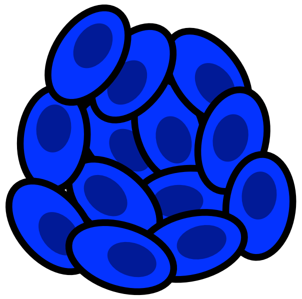
Systems Biology workshop, HZI Braunschweig, 2017

Systems biology cycle



Systems biology

Tissue



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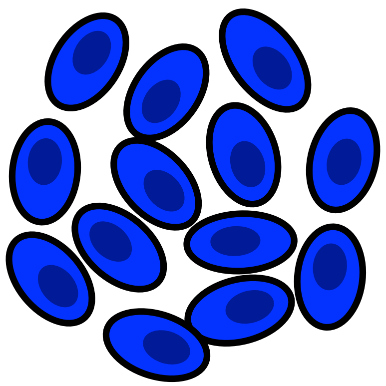

Systems biology

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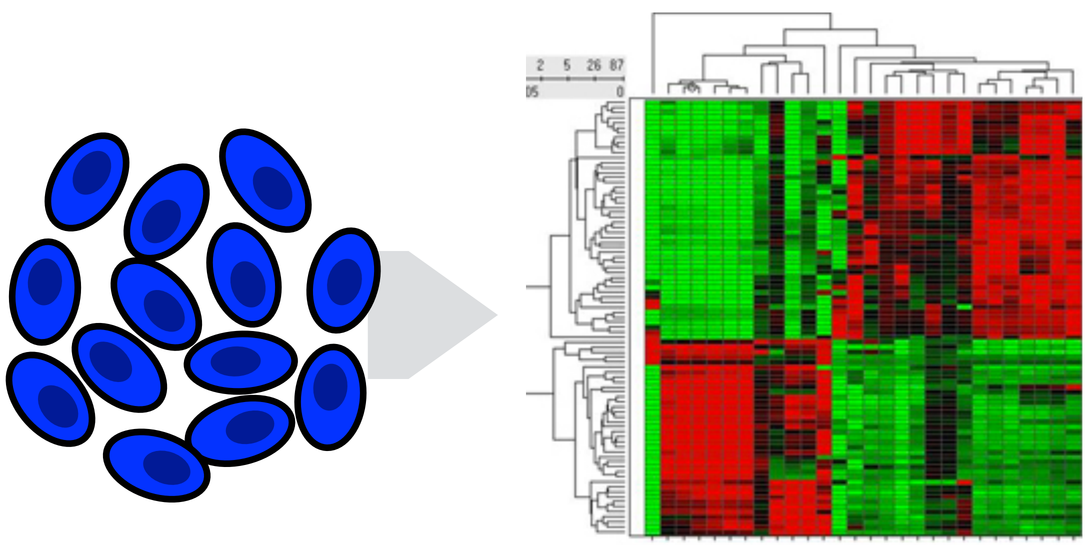

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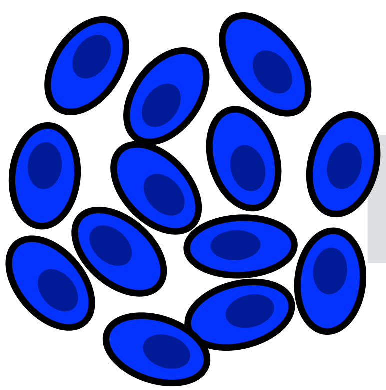

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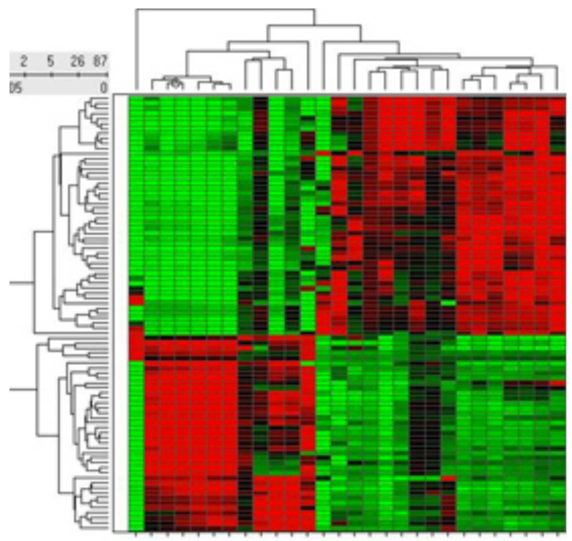
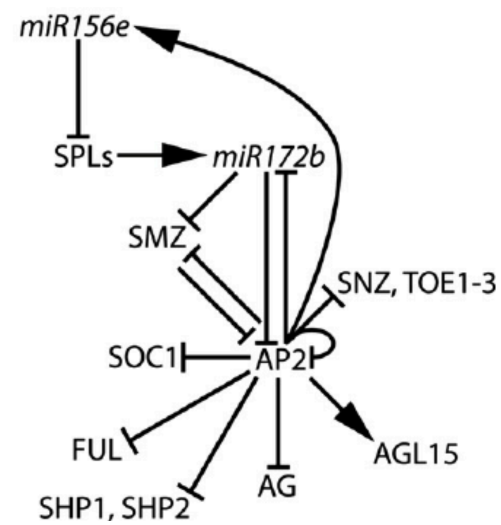


Intracellular network



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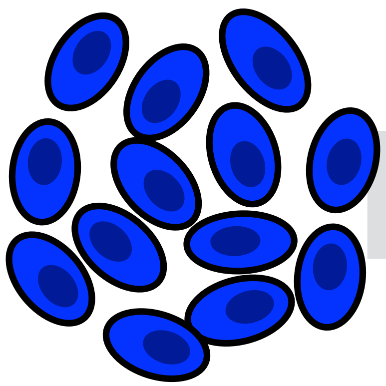

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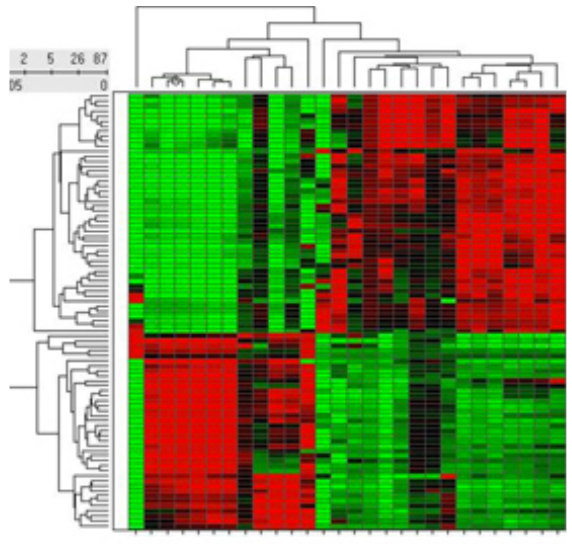

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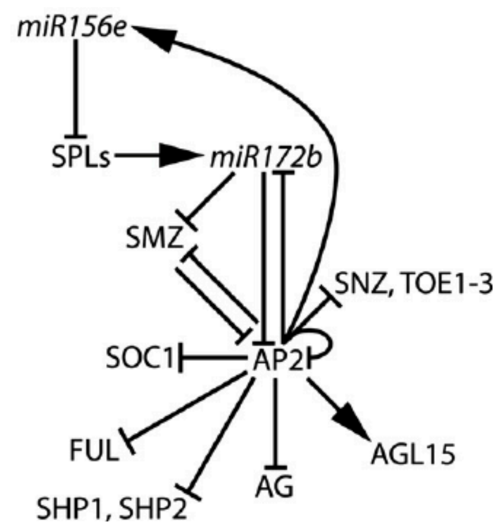
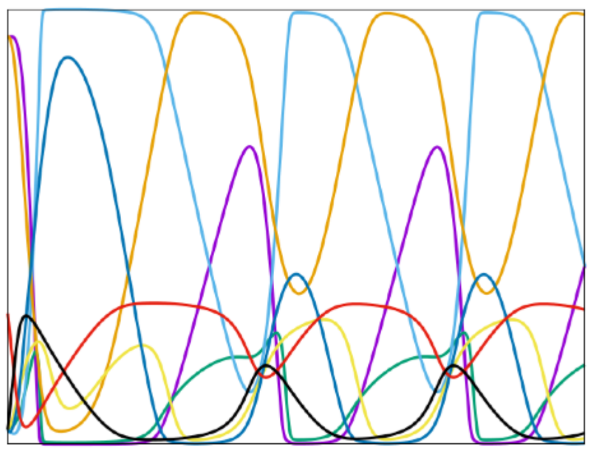
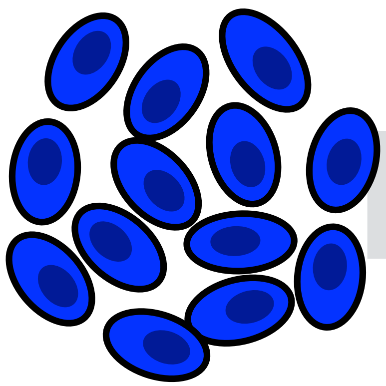


Dynamic simulation



Multicellular Systems biology

Tissue



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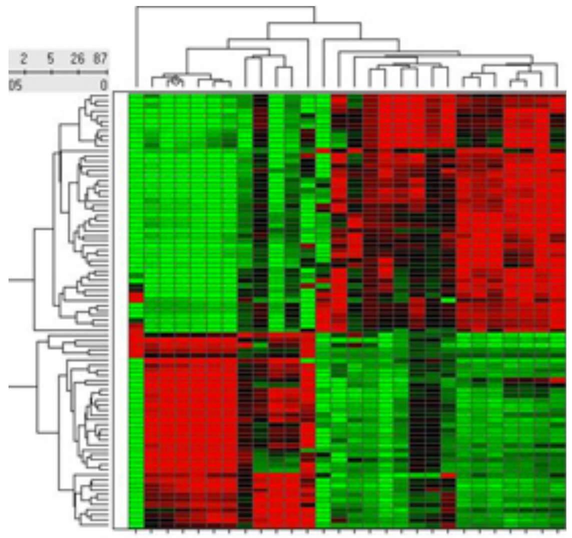

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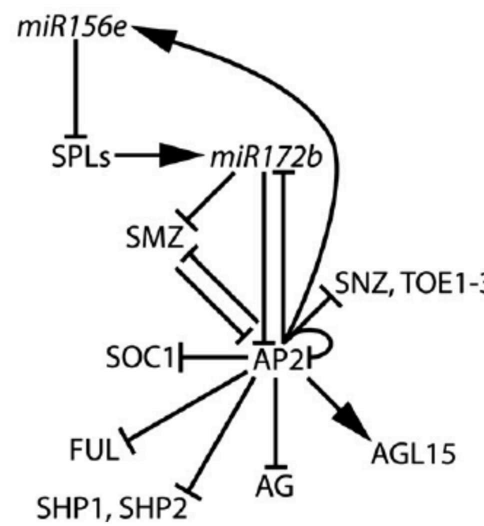

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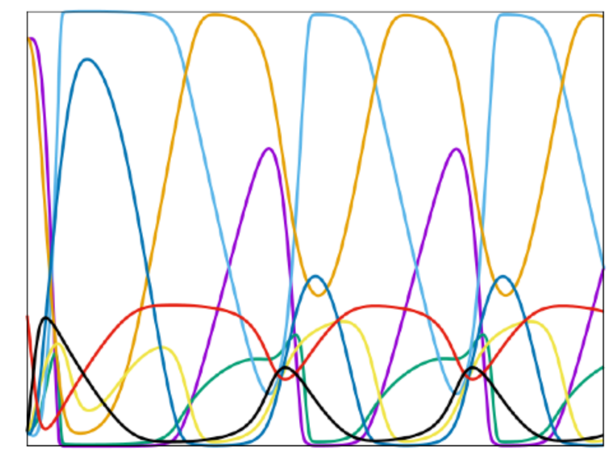

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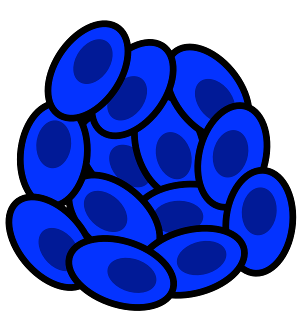

From SysBio to Multicellular SysBio

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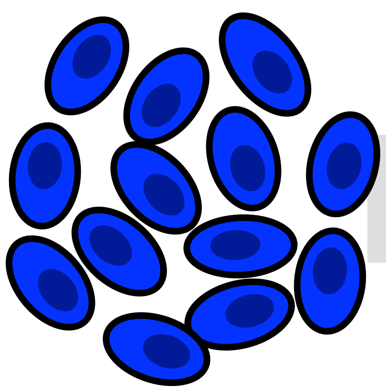

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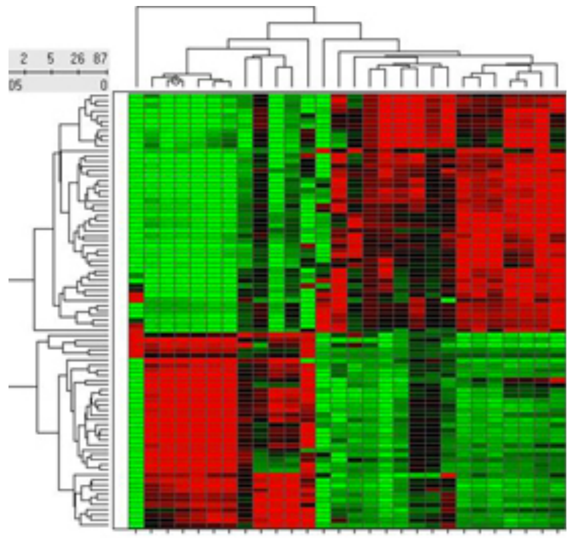

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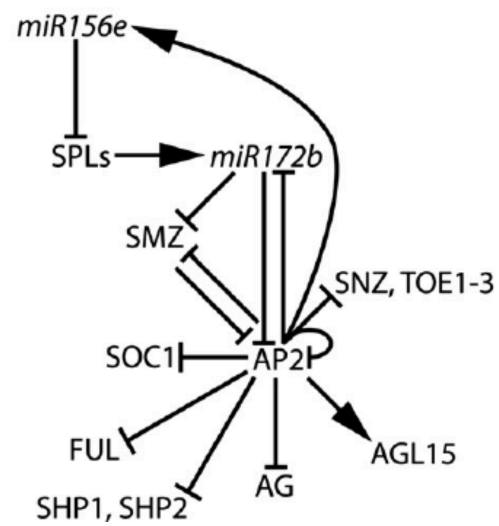

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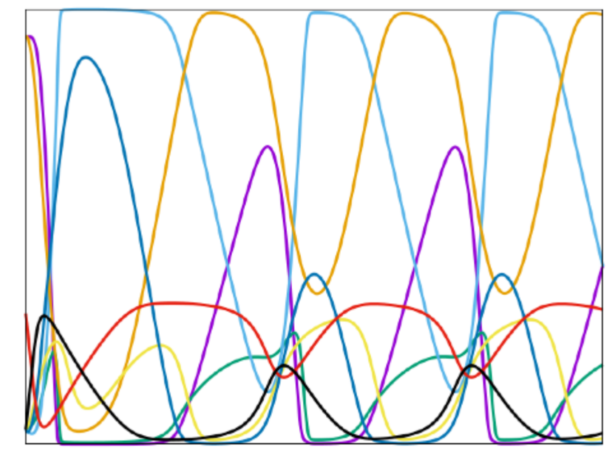

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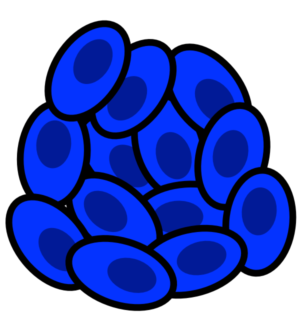

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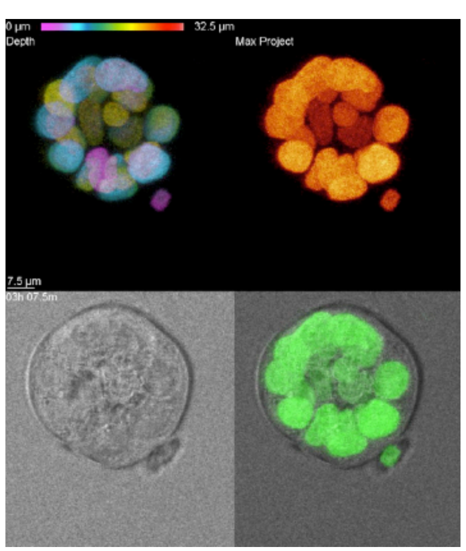

Drost et al, 2015

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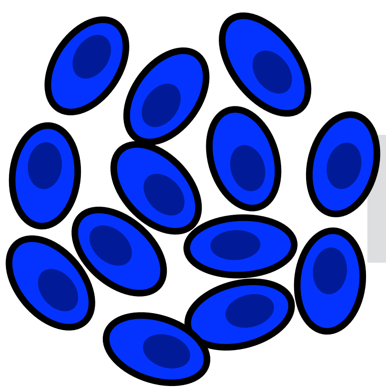

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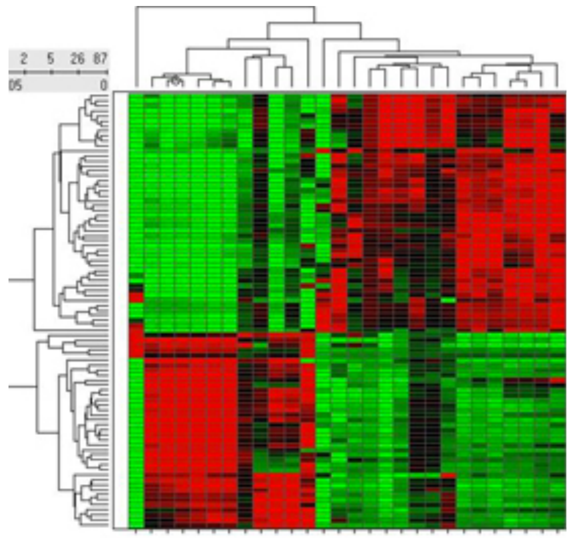

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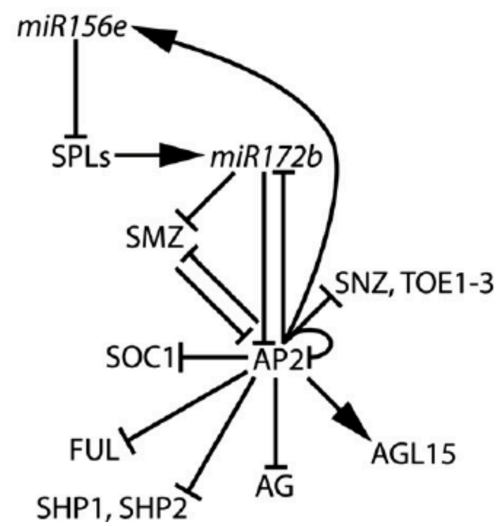

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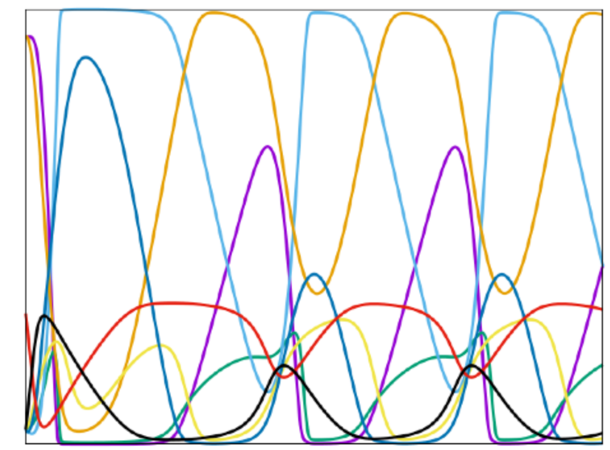

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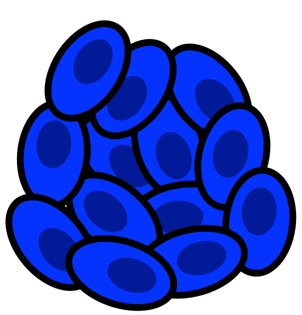

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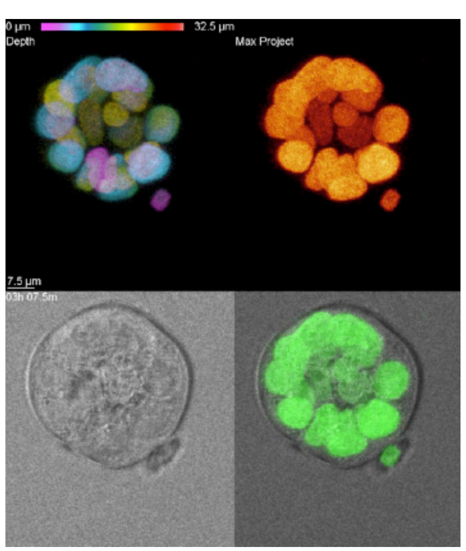

Drost et al, 2015

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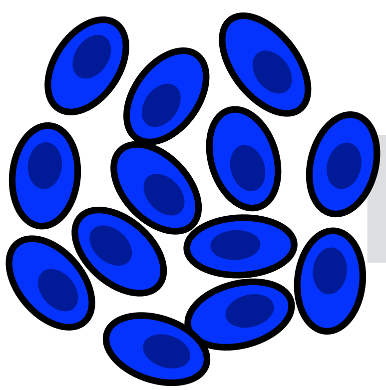

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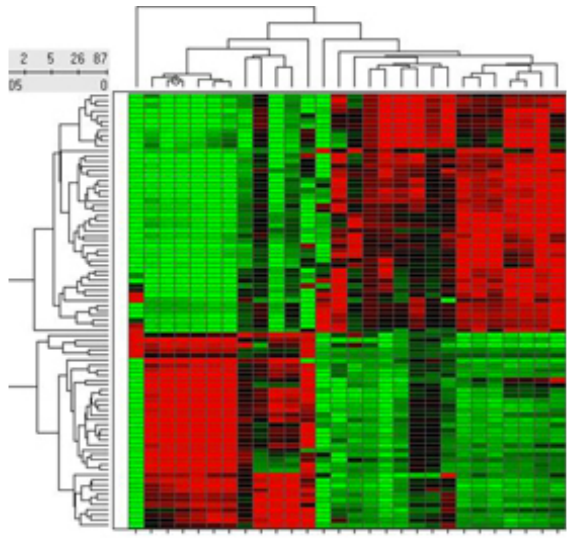

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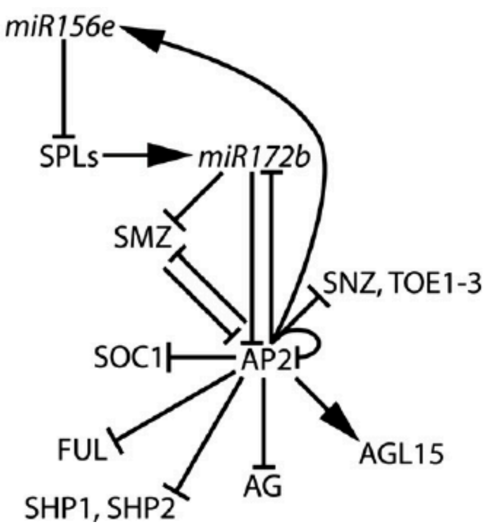

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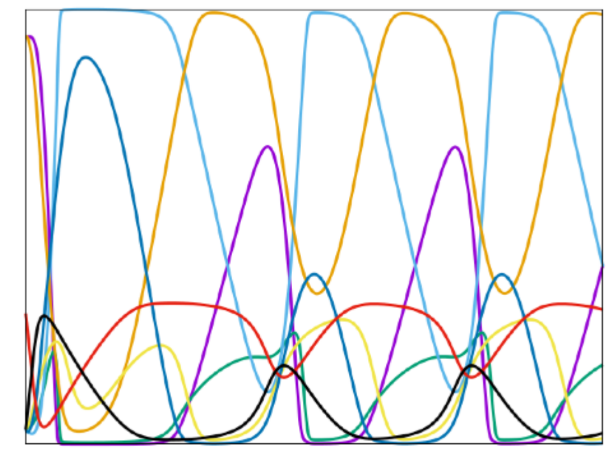

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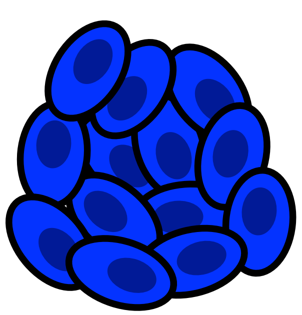

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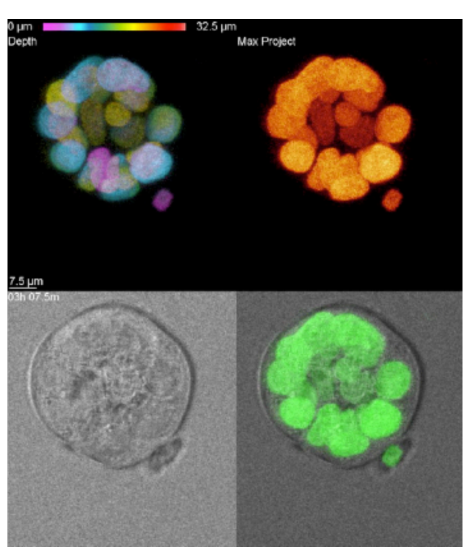
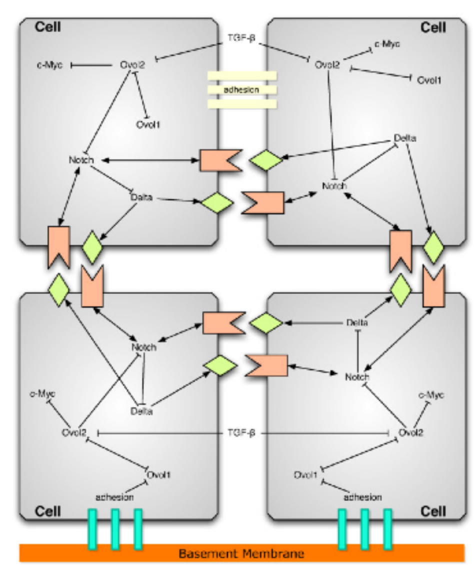


Drost et al, 2015

Intercellular network



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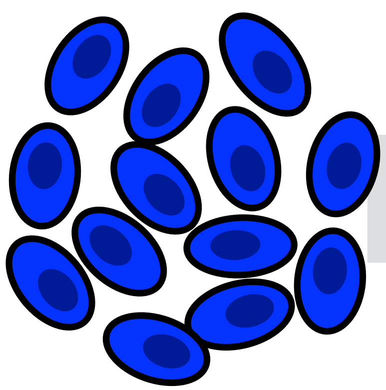

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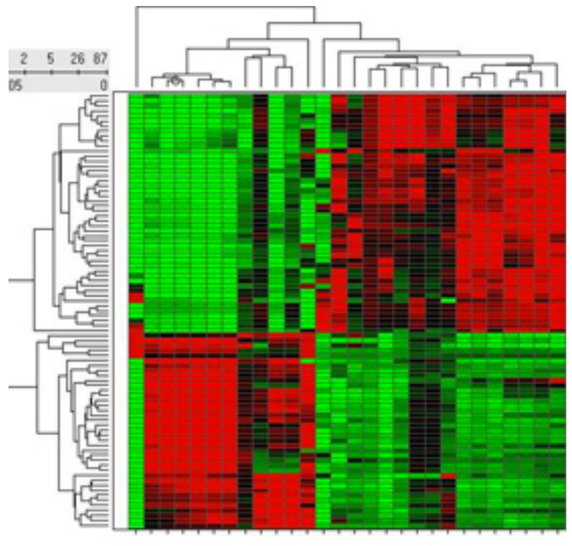

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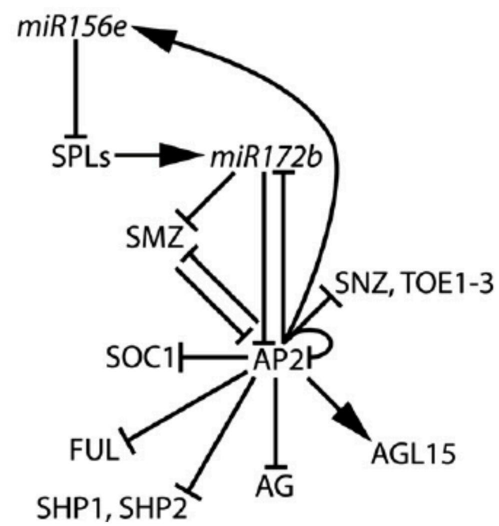

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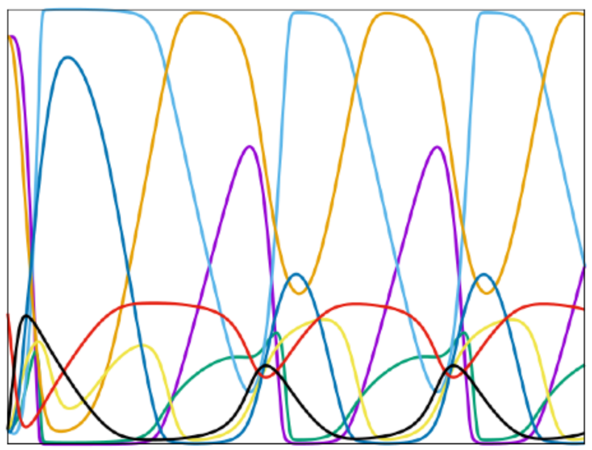

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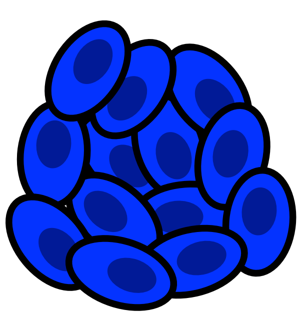

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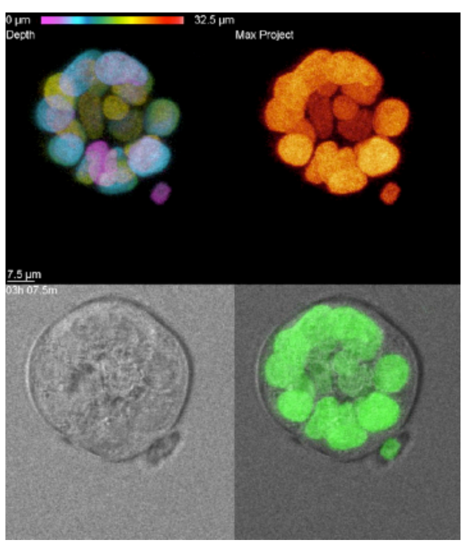

Drost et al, 2015

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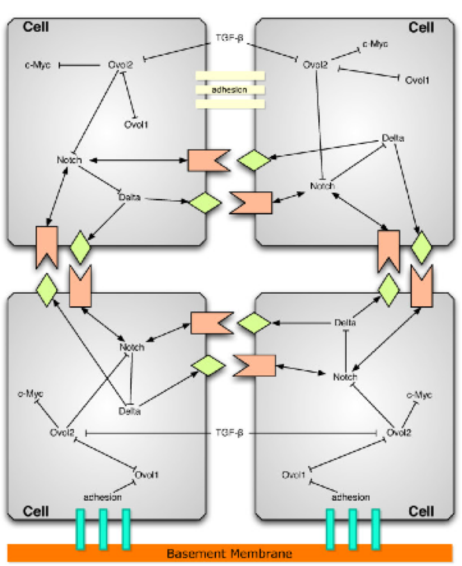

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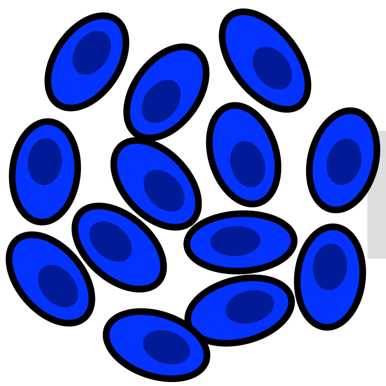

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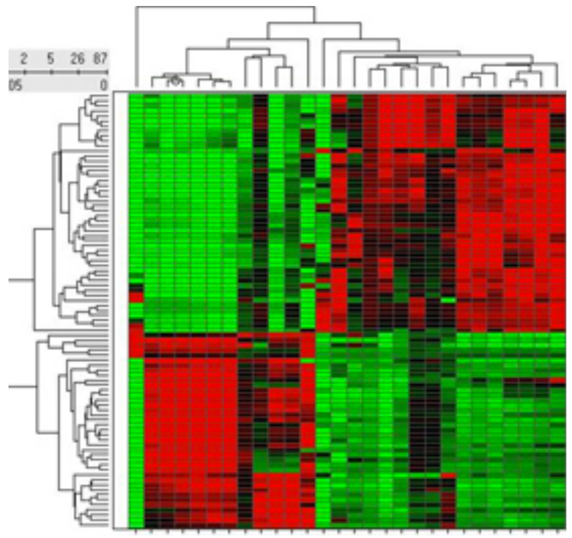

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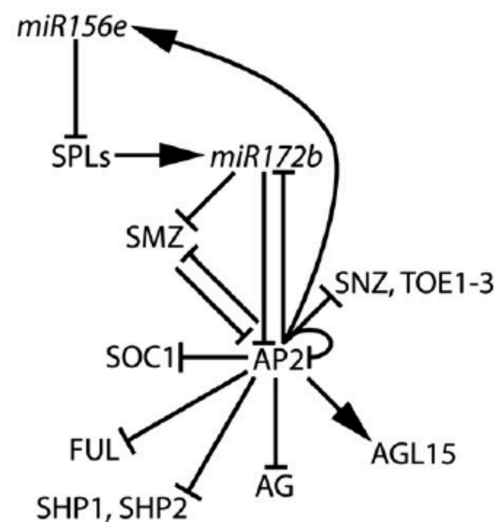

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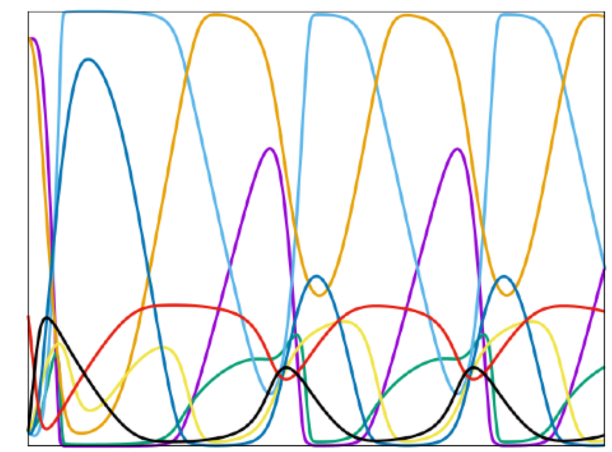

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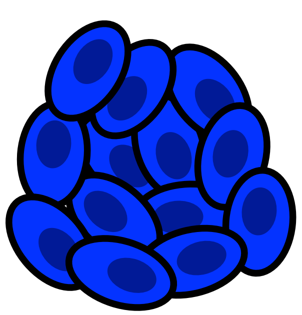

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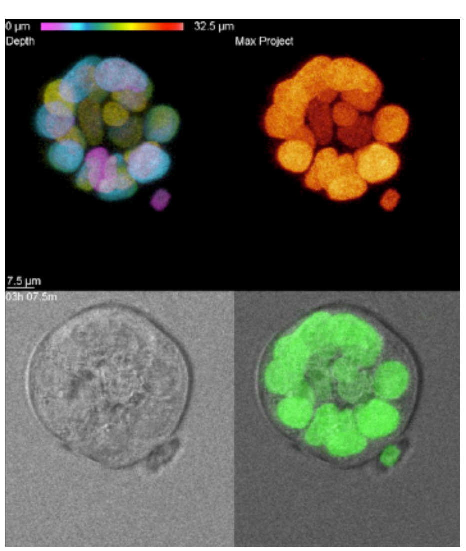
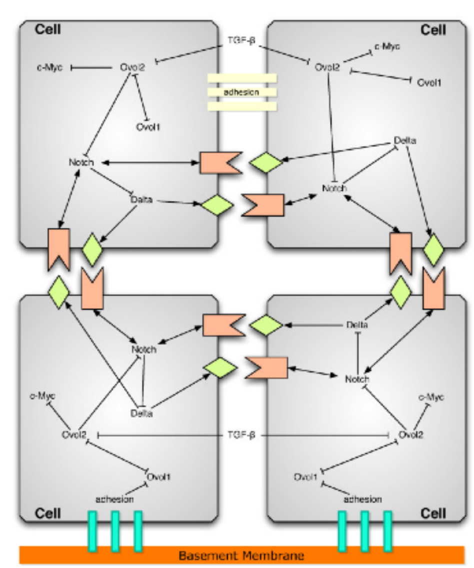
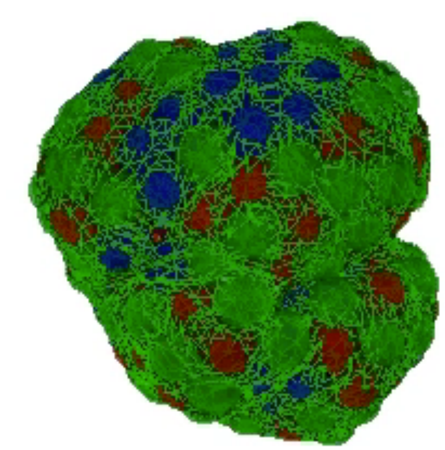


Drost et al, 2015

Intercellular network



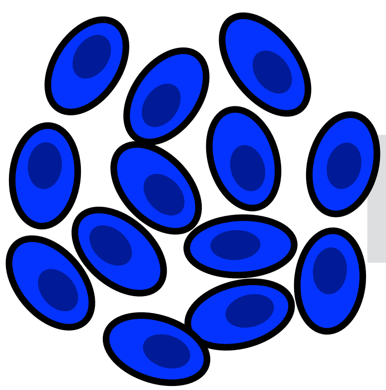
Multicellular simulation



Buske et al., 2012

From SysBio to Multicellular SysBio

Tissue



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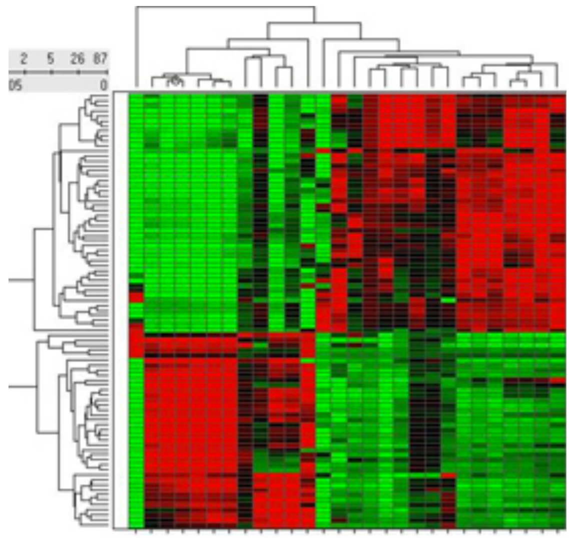
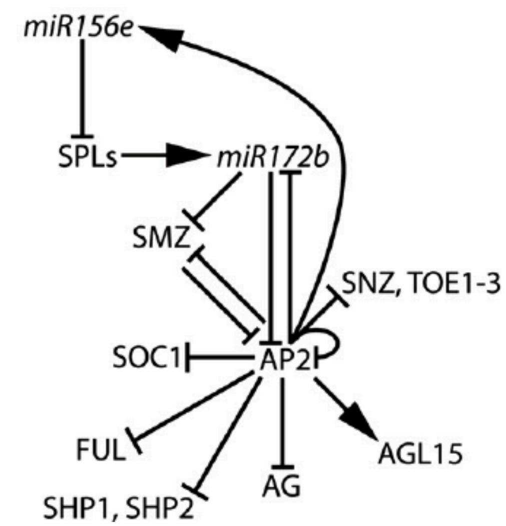
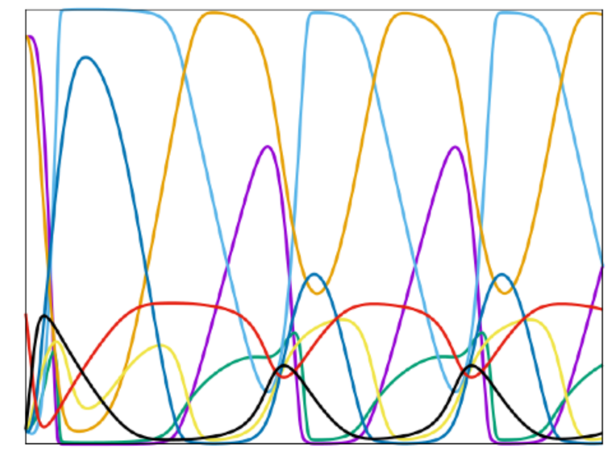


Intracellular network



Dynamic simulation



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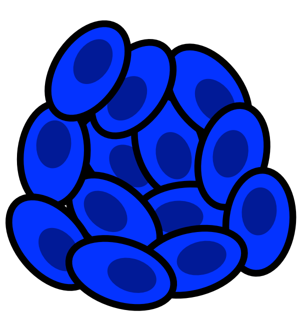

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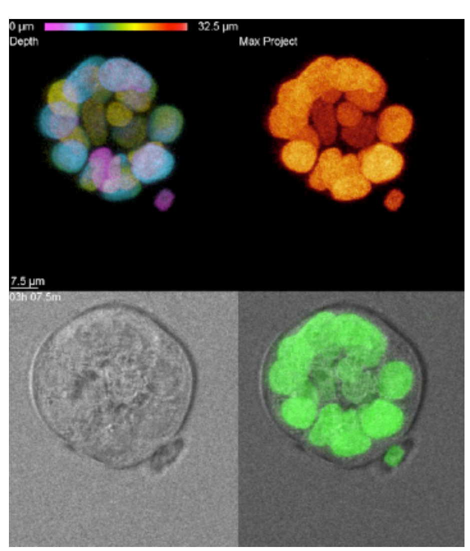
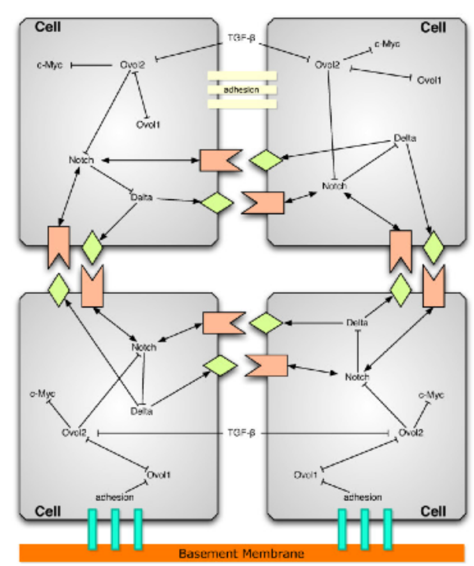
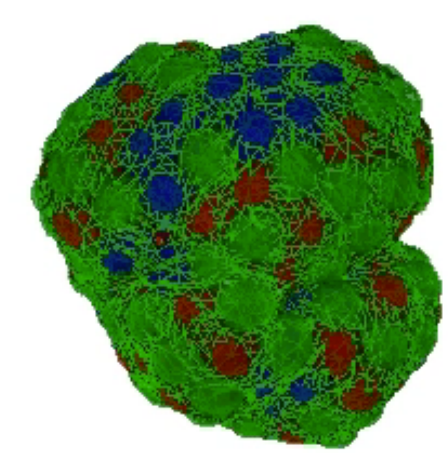


Drost et al, 2015

Intercellular network

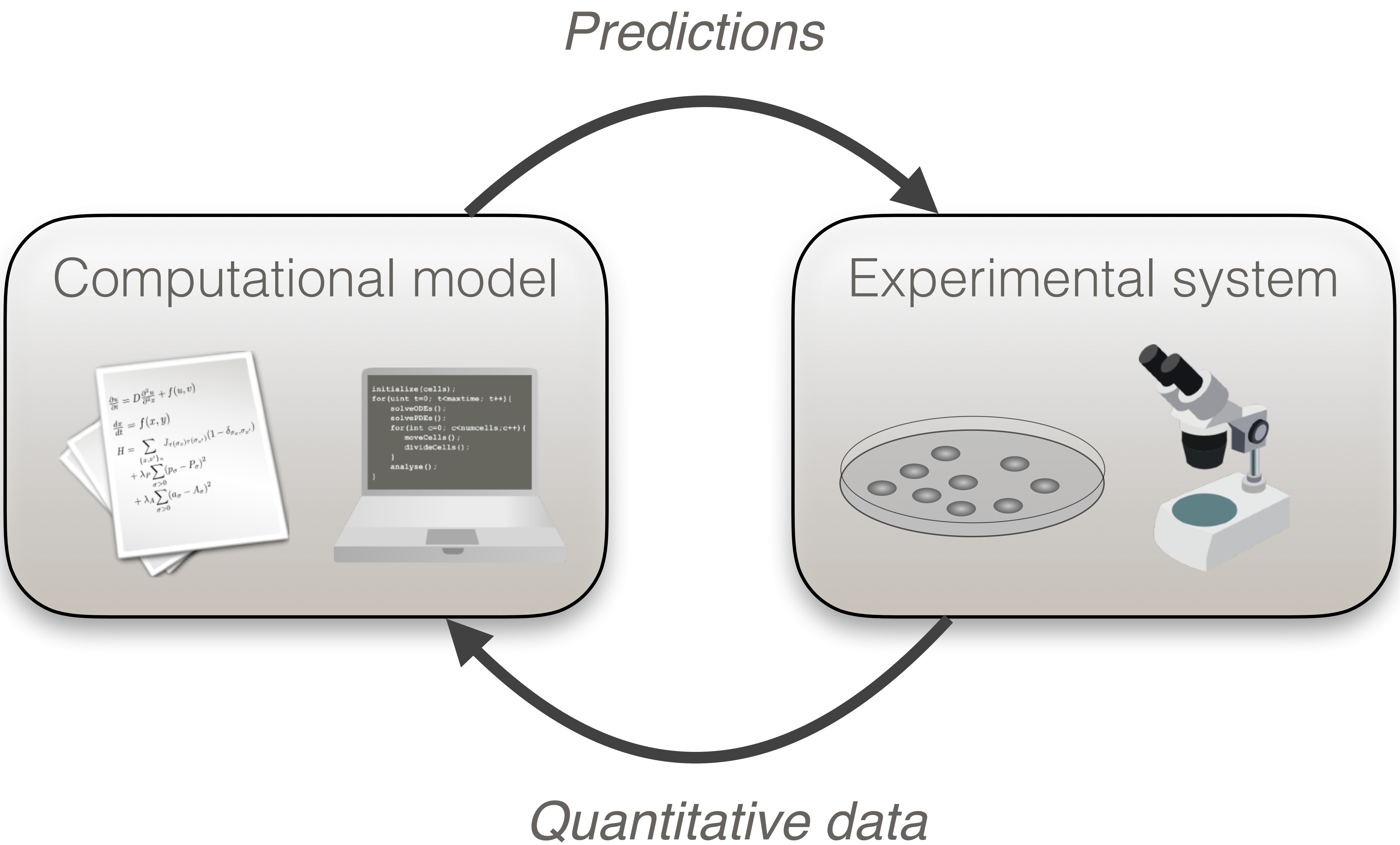


Multicellular simulation



Buske et al., 2012

Systems biology cycle



Content

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  - Platform for multi-scale multicellular modeling

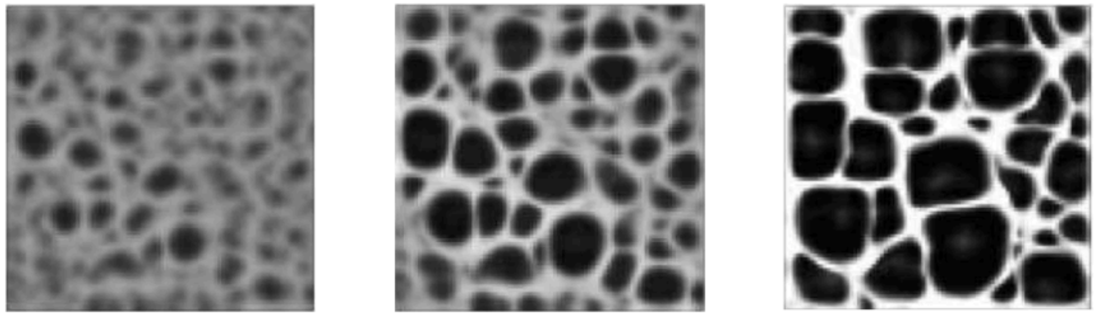
Doe et al., 2017.

Modeling approaches

for tissue modeling

Tissue modeling: continuous approach

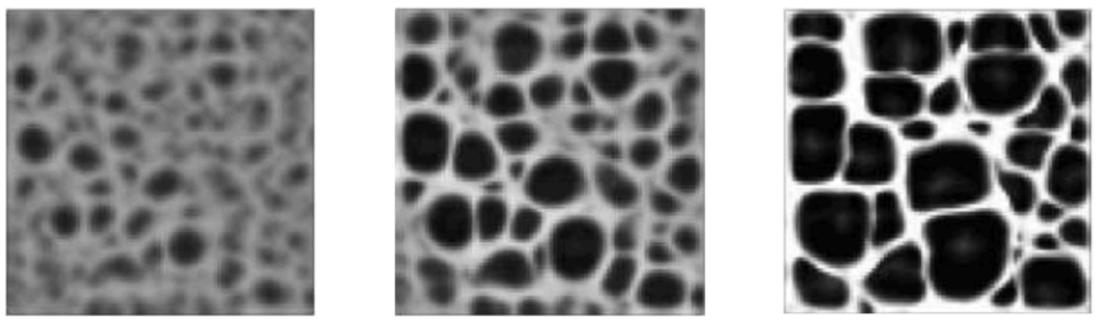
Vascular patterning



Manoussaki et al., 1996

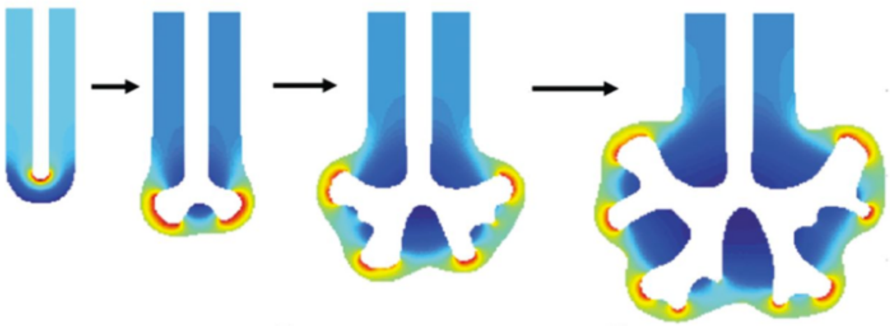
Tissue modeling: continuous approach

Vascular patterning



Manoussaki et al., 1996

Branching morphogenesis



Iber et al., 2013

Tissue modeling: continuous approach

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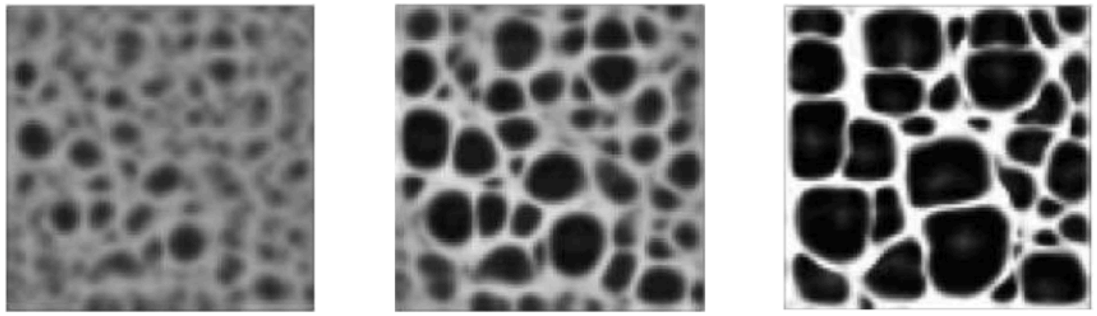

Manoussaki et al., 1996

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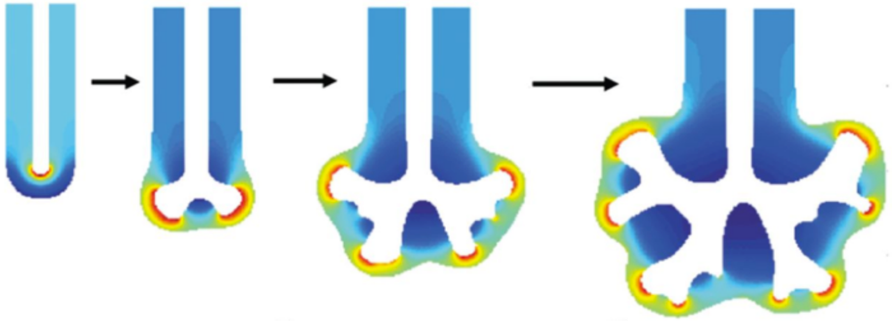
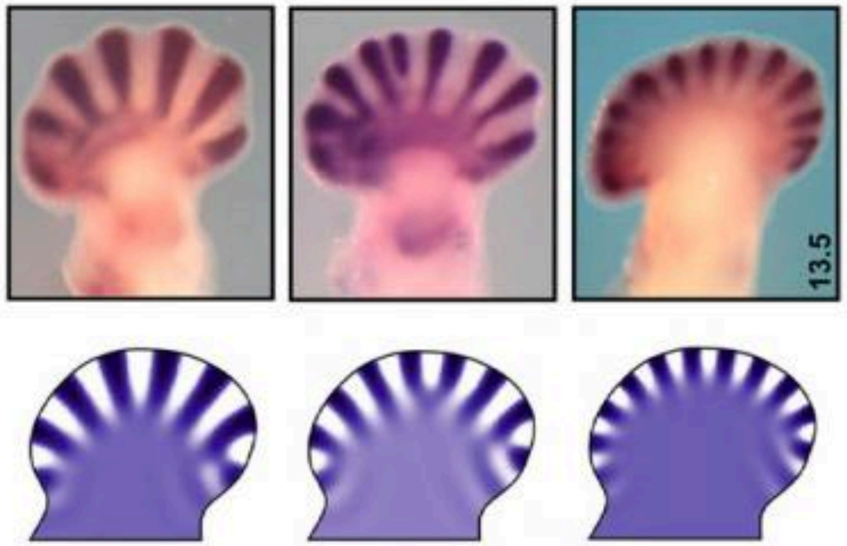


Iber et al., 2013

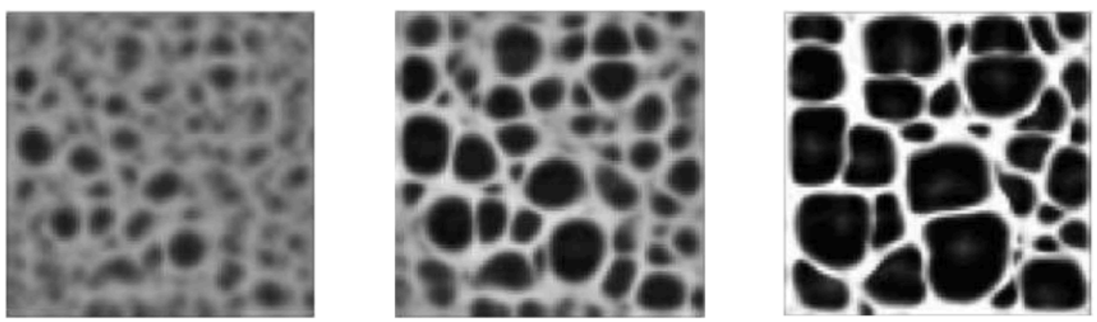
Limb morphogenesis



Sheth et al., 2012

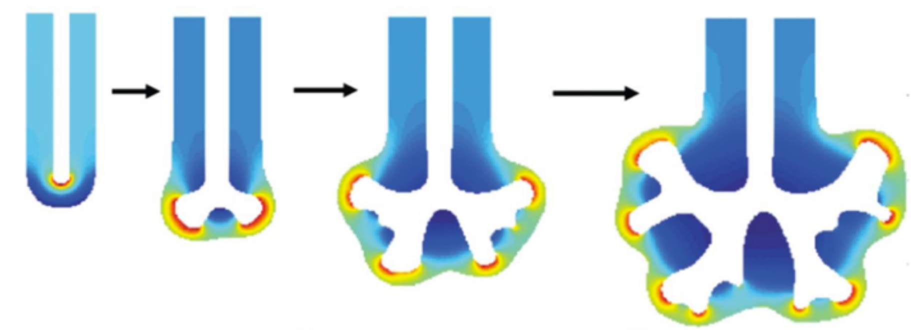
Tissue modeling: continuous approach

Vascular patterning



Manoussaki et al., 1996

Branching morphogenesis



Iber et al., 2013

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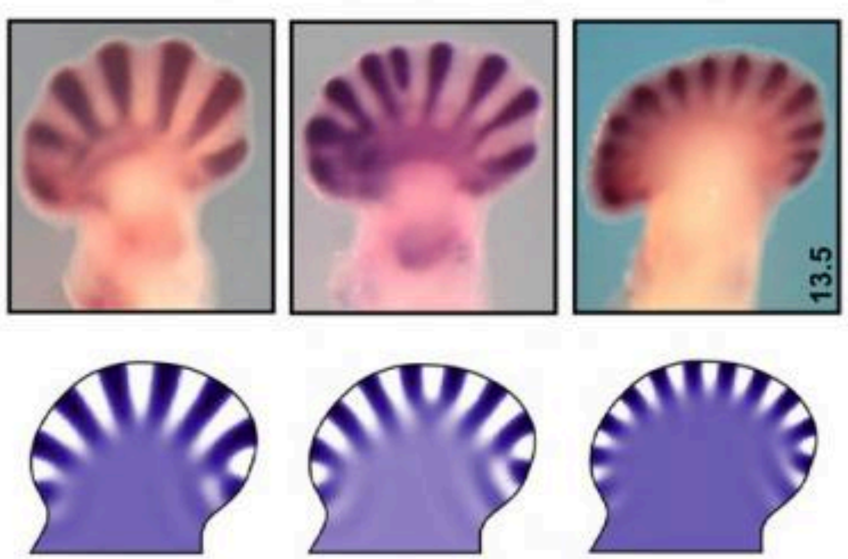
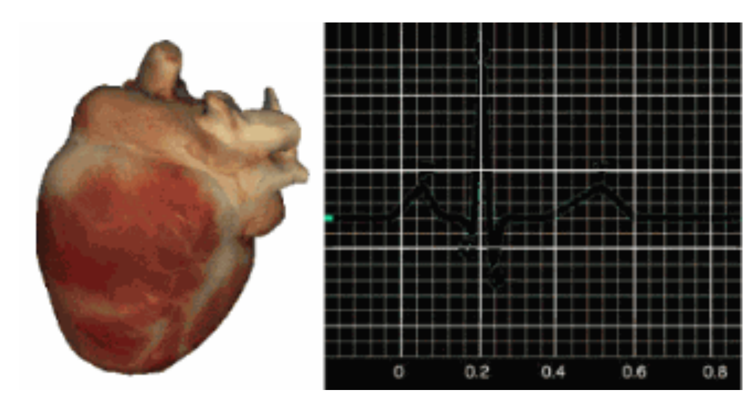


Sheth et al., 2012

Cardiac physiology



Fenton et al., 2008

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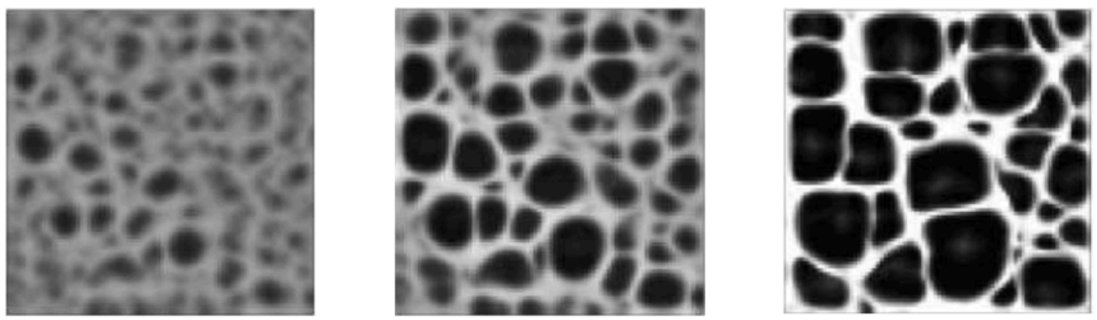
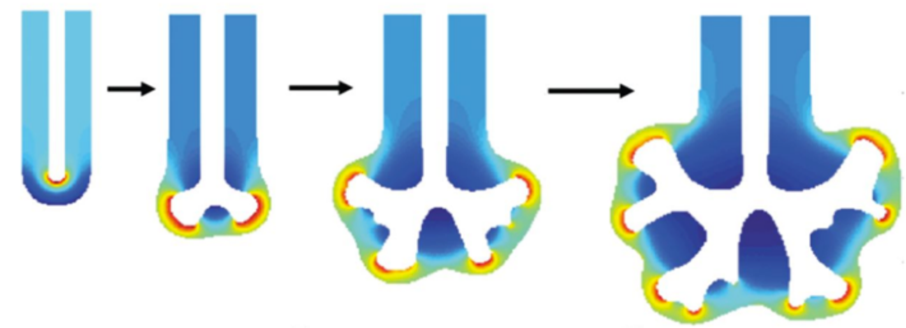


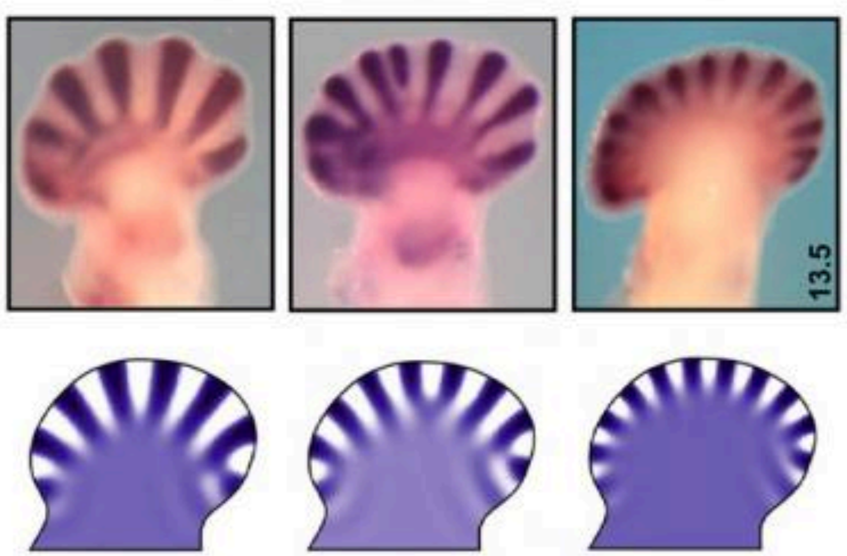
Manoussaki et al., 1996

Branching morphogenesis



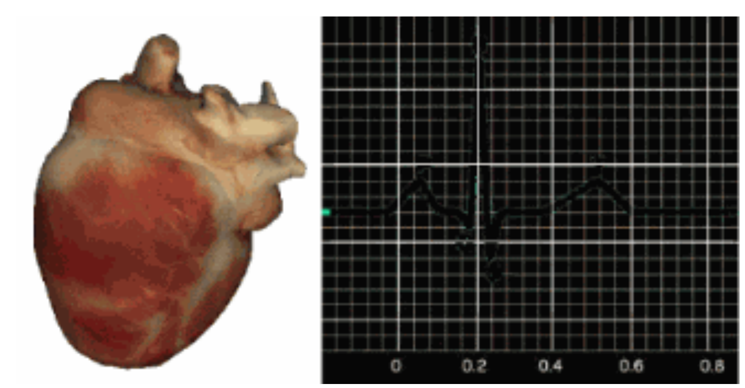
Iber et al., 2013

Limb morphogenesis



Sheth et al., 2012

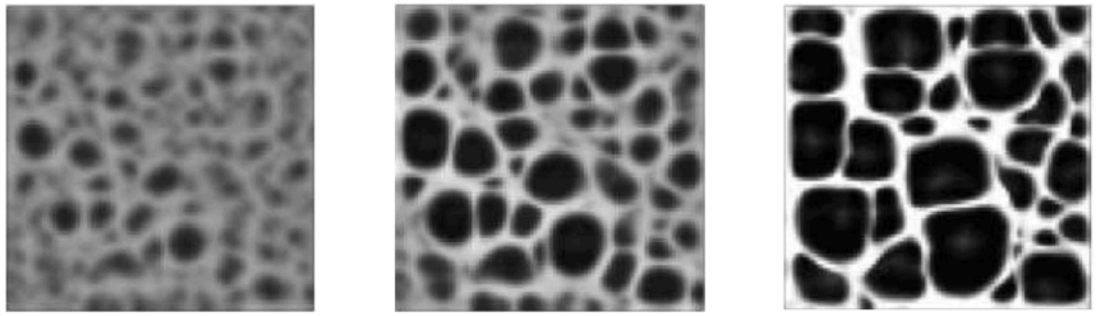
Cardiac physiology



Fenton et al., 2008

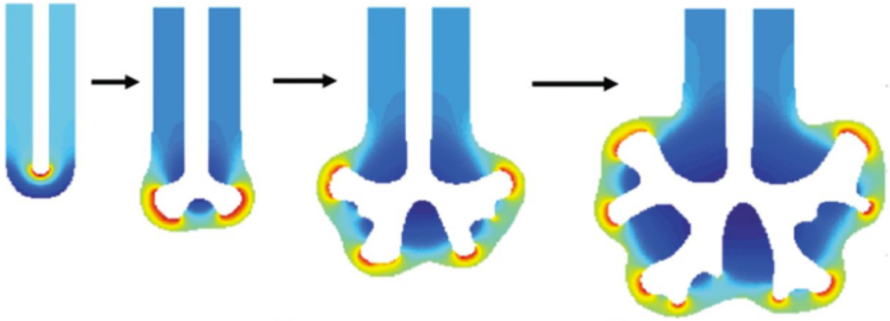
Tissue modeling: continuous approach

Vascular patterning



Manoussaki et al., 1996

Branching morphogenesis



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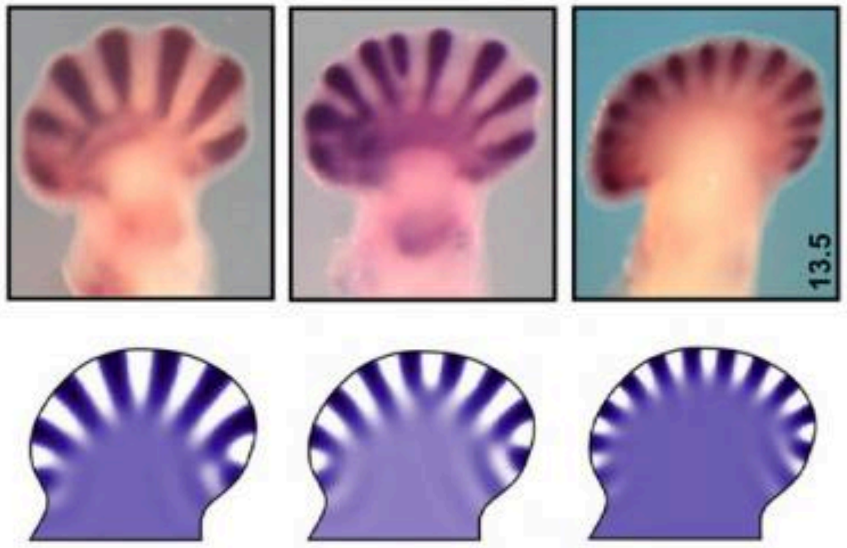
Limb morphogenesis



Sheth et al., 2012

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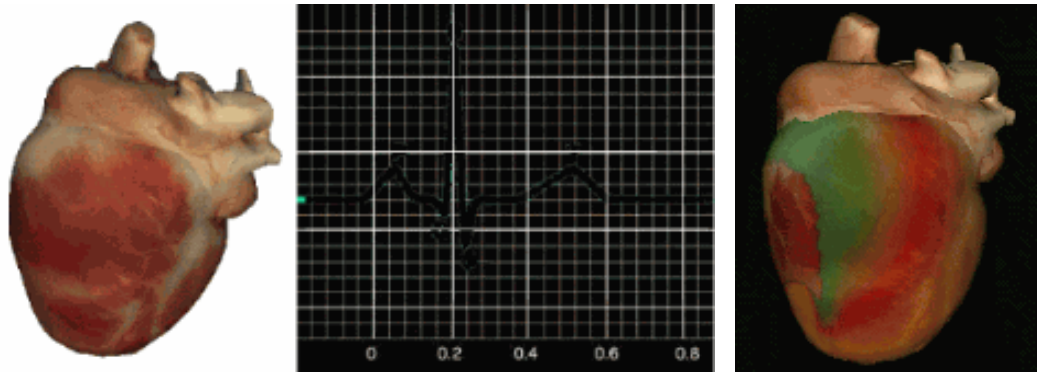

Fenton et al., 2008

Tissue modeling: discrete approach

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- Tissue organization
  - spatial structure

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- Cellular behavior
  - cell motility
  - cell division
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  - intracellular processes
  - extracellular gradients

Tissue modeling: discrete approach

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Cell-based modeling

- Tissue organization
  - spatial structure
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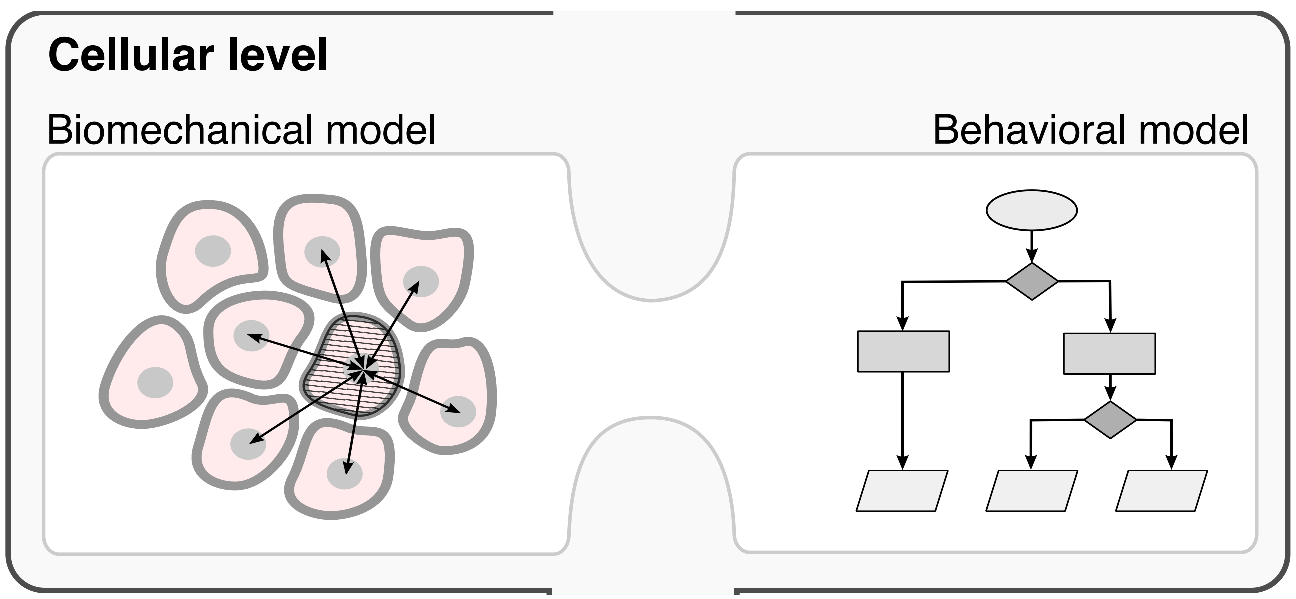

de Back, 2015.

Multi-scale cell-based modeling

- Tissue organization
  - spatial structure

- Cellular behavior
  - cell motility
  - cell division
  - cell adhesion
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  - etc.

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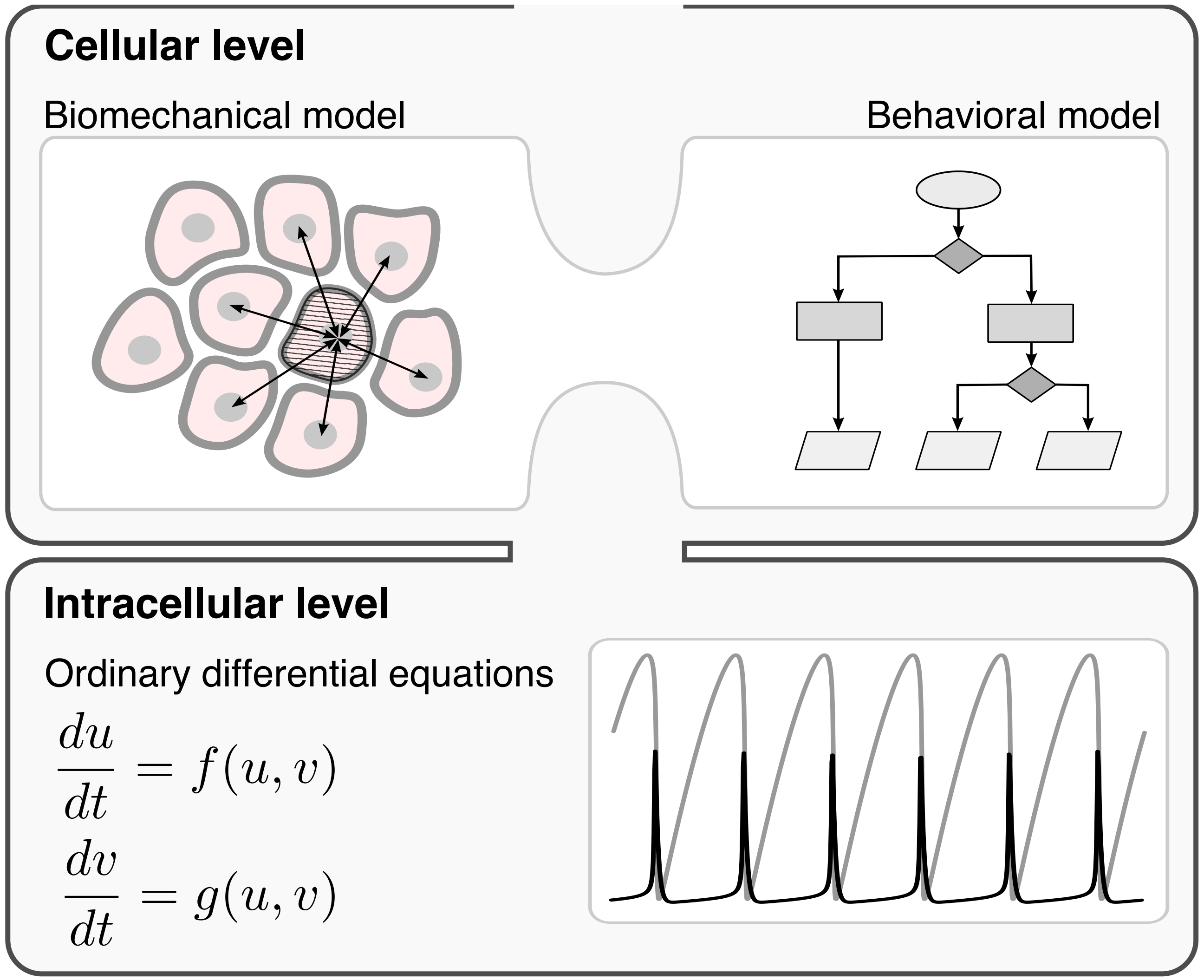

de Back, 2015.

Multi-scale cell-based modeling

- Tissue organization
  - spatial structure
- Cellular behavior
  - cell motility
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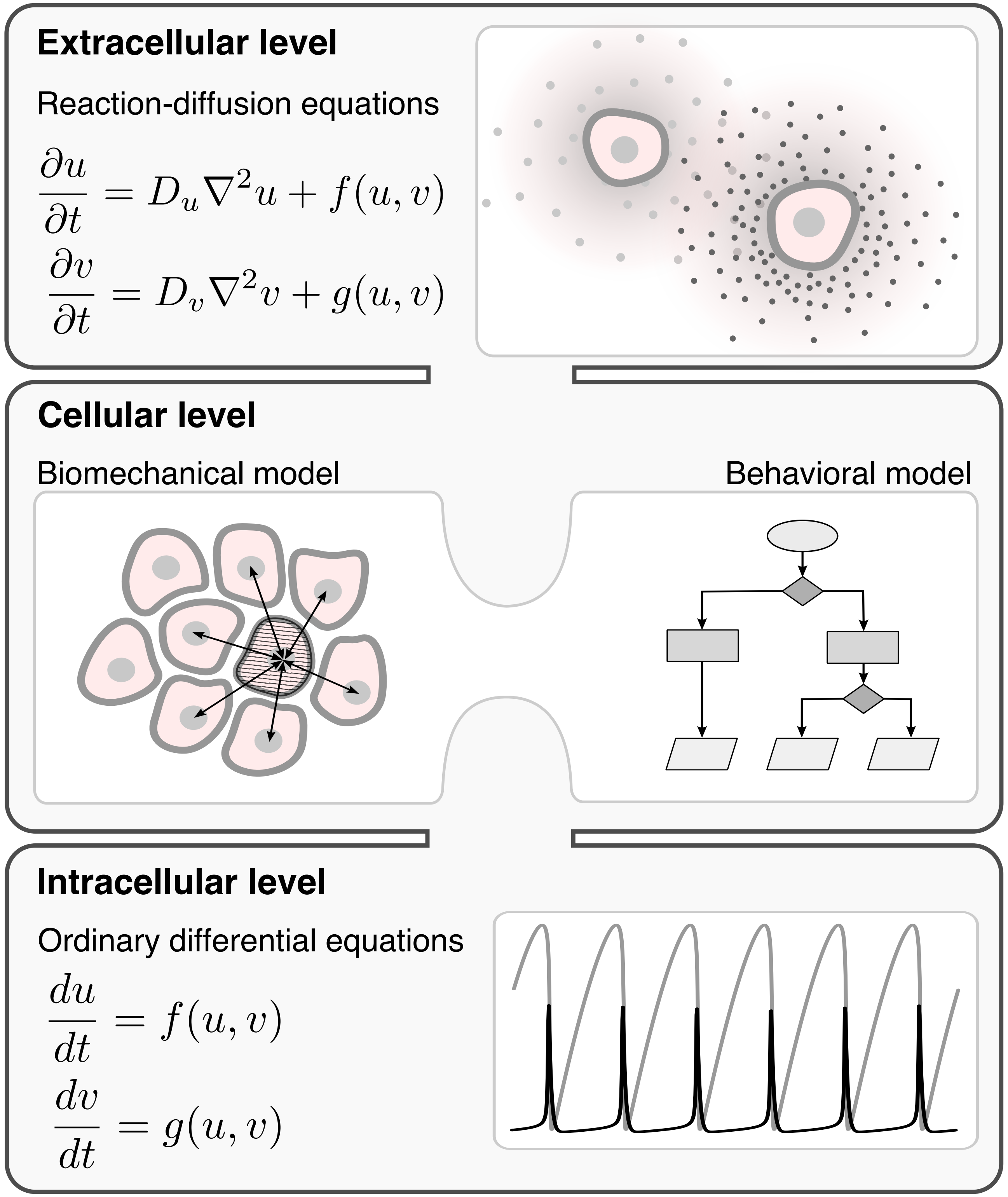

de Back, 2015.

Middle-out multi-scale cell-based modeling

- Tissue organization
  - spatial structure
- Cellular behavior
  - cell motility
  - cell division
  - cell adhesion
  - cell shape
  - etc.
- Small population size
  - stochasticity
- Multi-scale coupling
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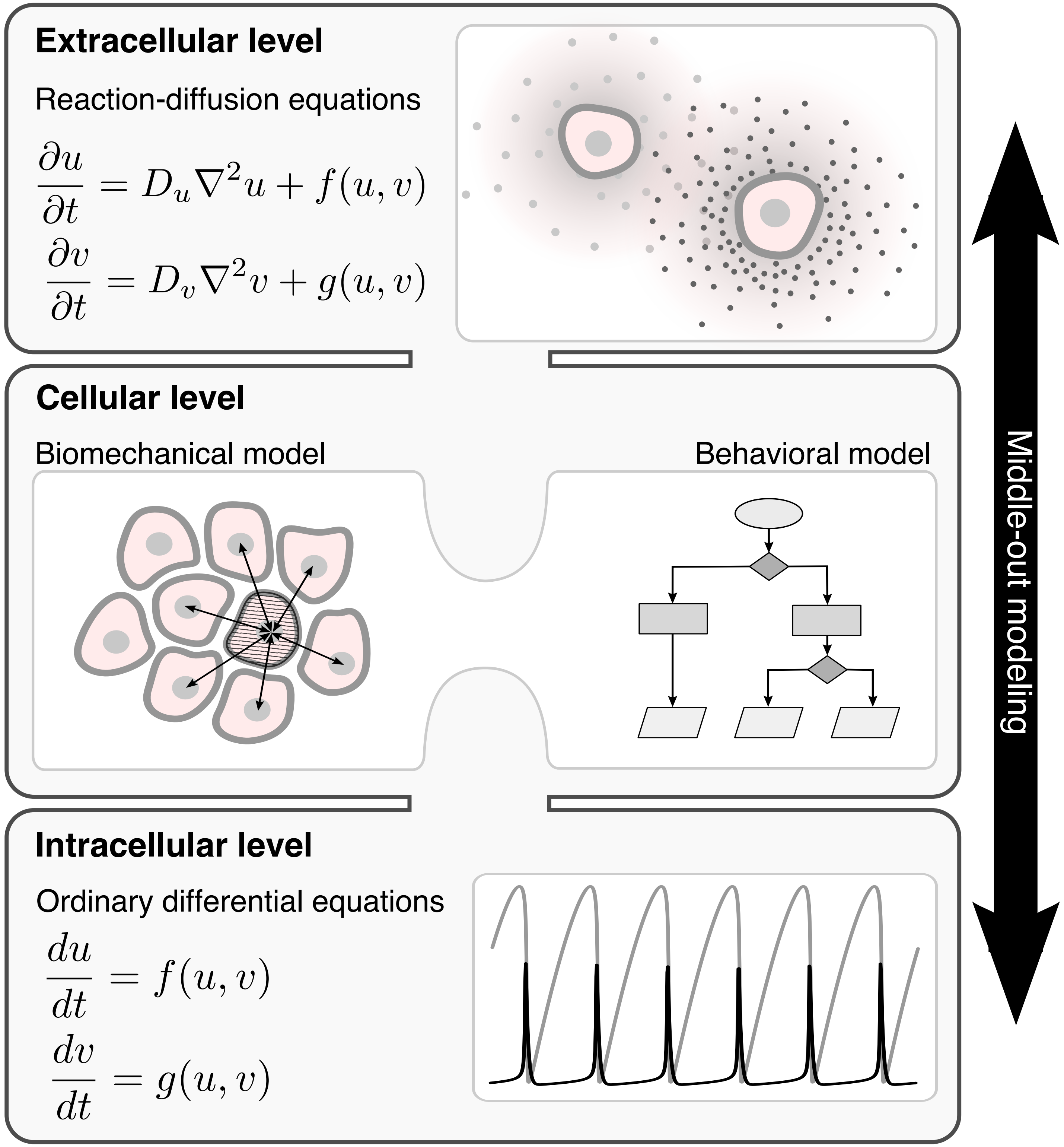
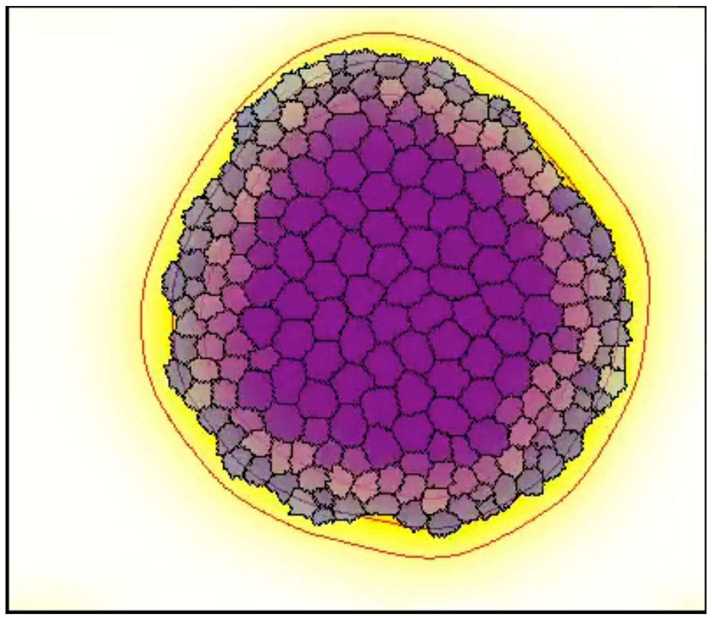
  - extracellular gradients



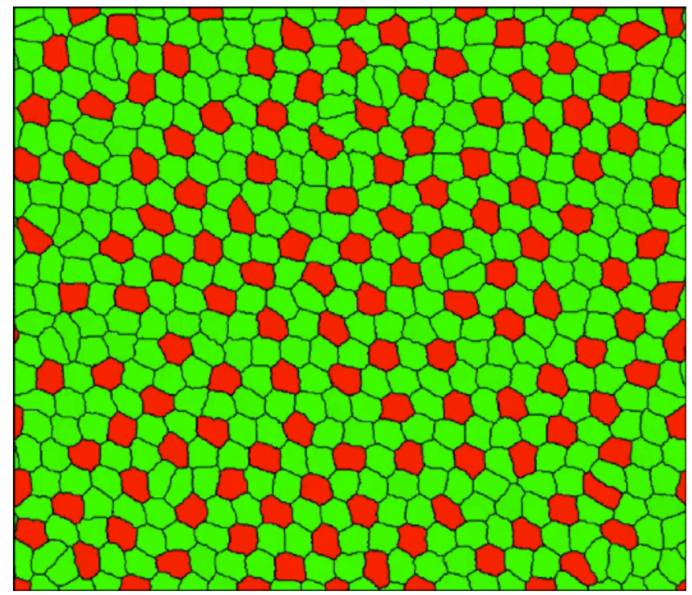
de Back, 2015.

Some examples….

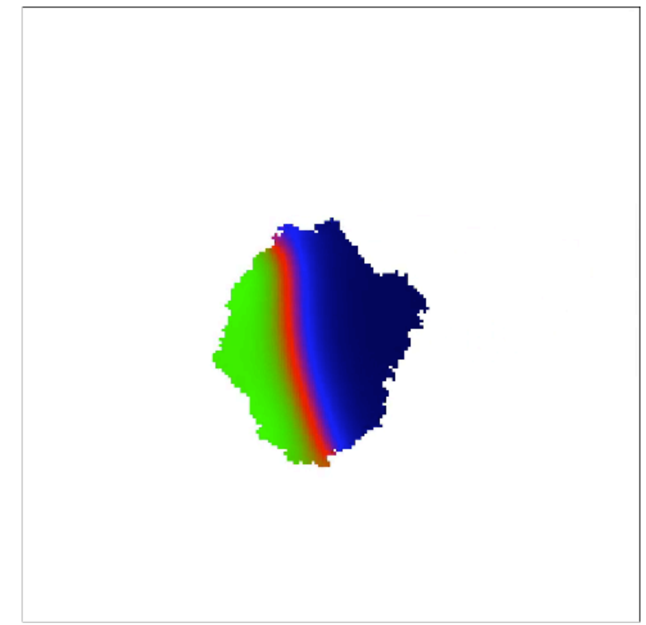
Tissue growth



Lateral inhibition

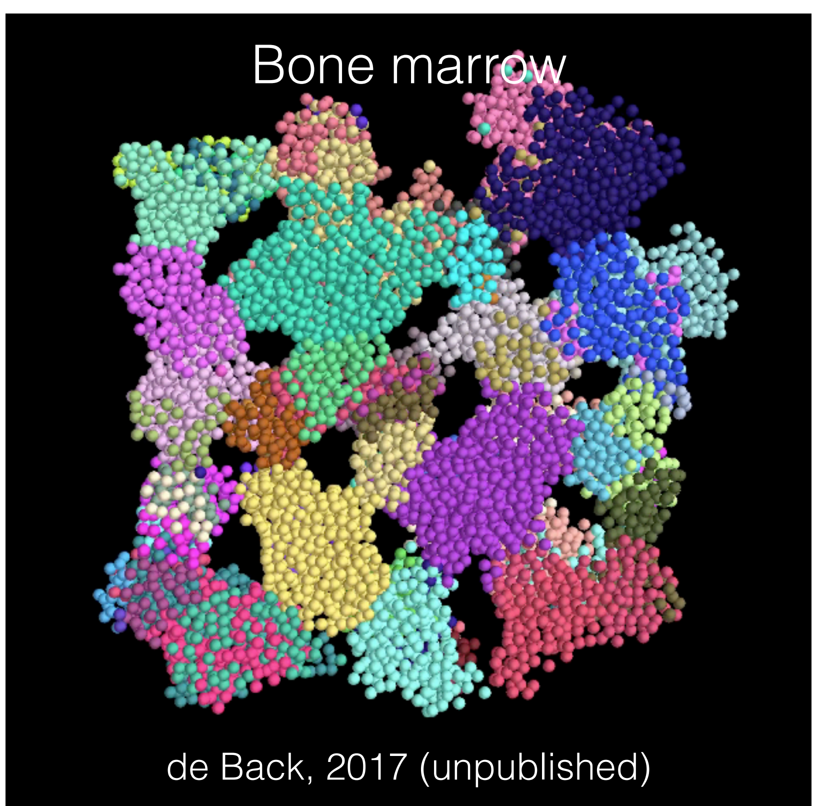


Single cell migration



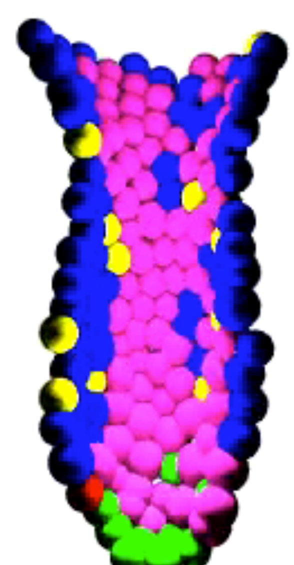
After Maree et al., 2012

Bone marrow



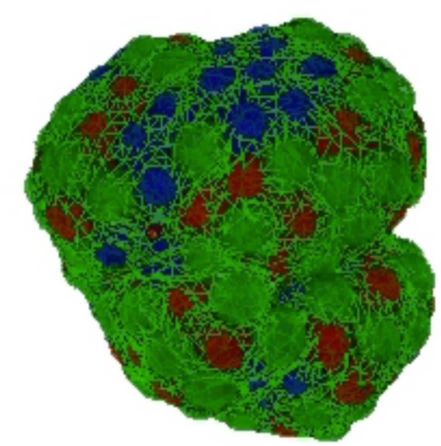
de Back, 2017 (unpublished)

Intestinal crypt



Buske et al., 2011

Organoid



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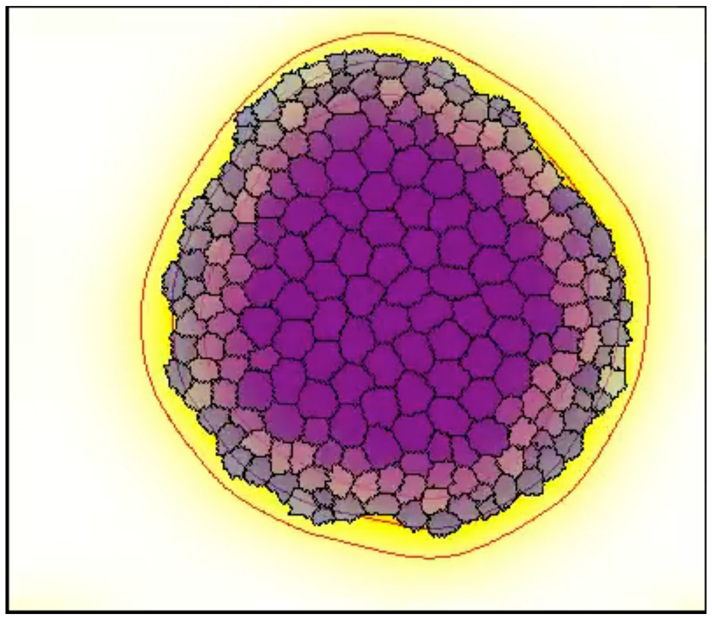
Some examples….

Tissue growth



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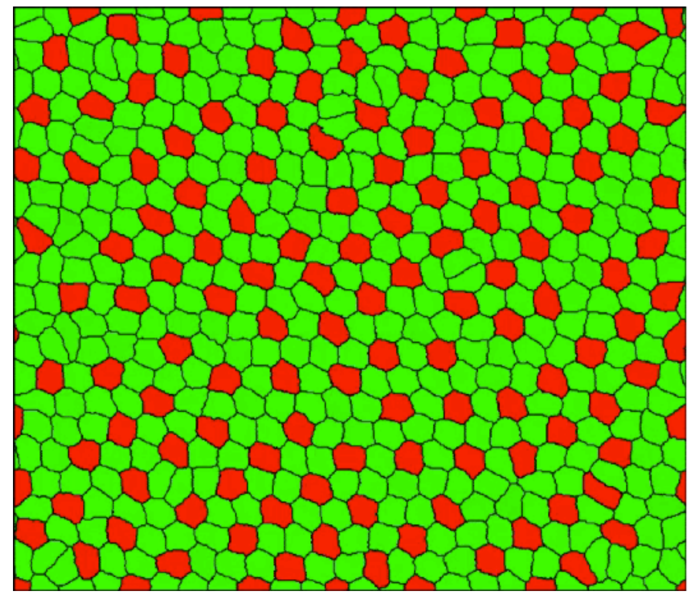

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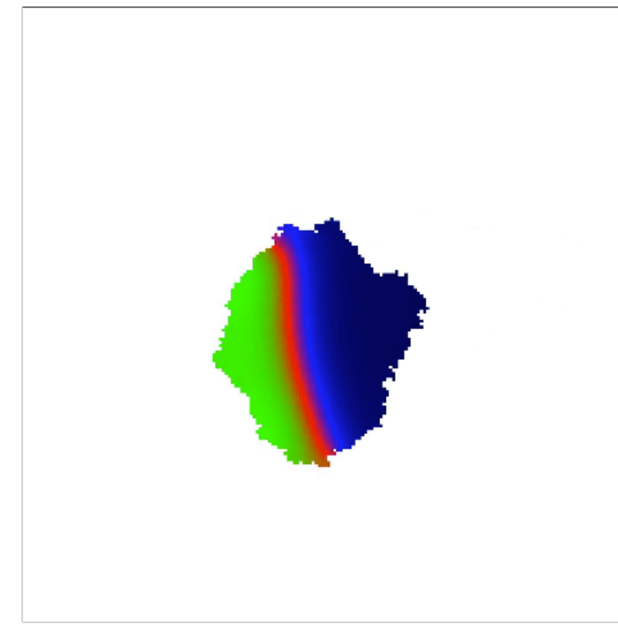

After Maree et al., 2012

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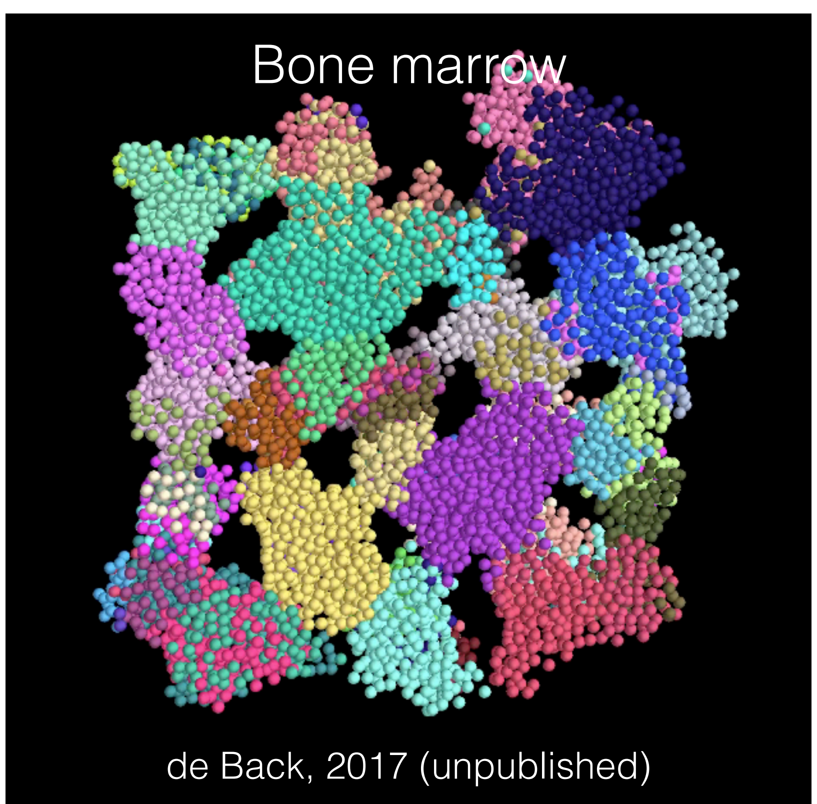

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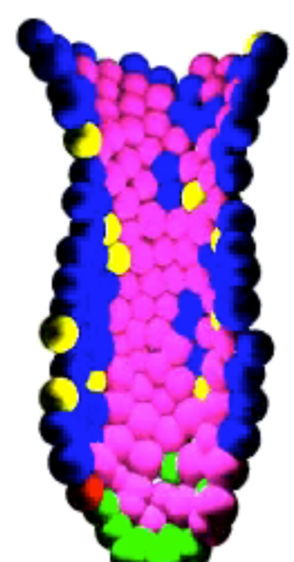

Buske et al., 2011

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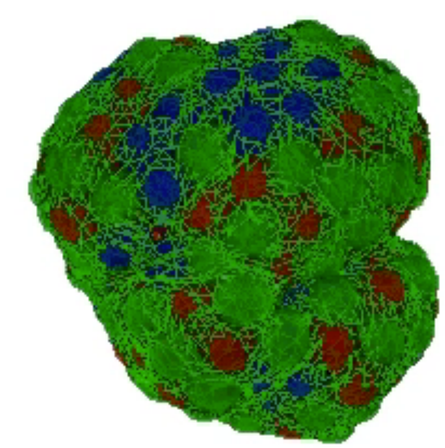

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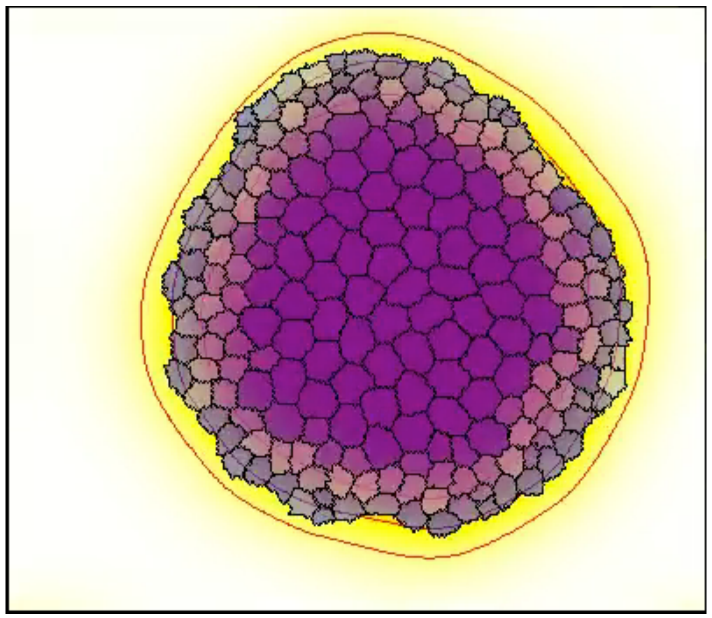

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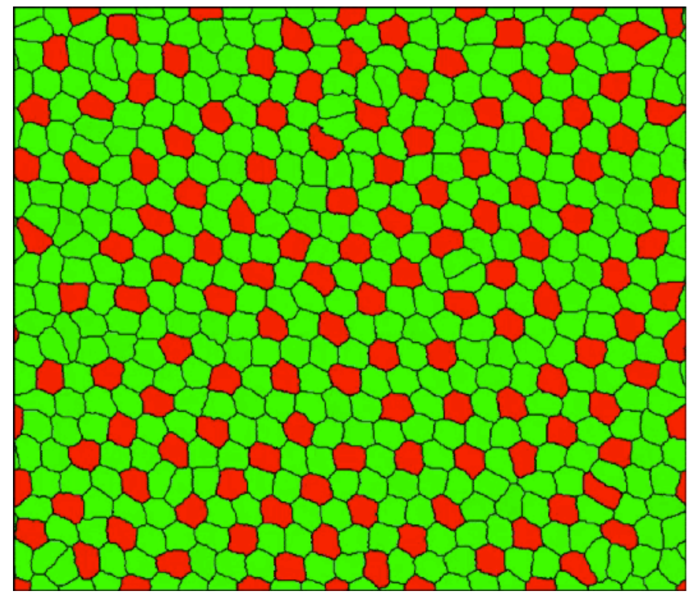

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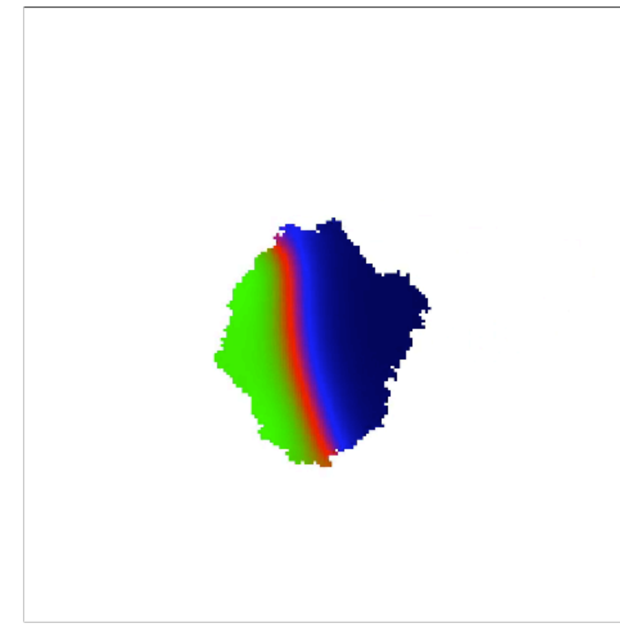

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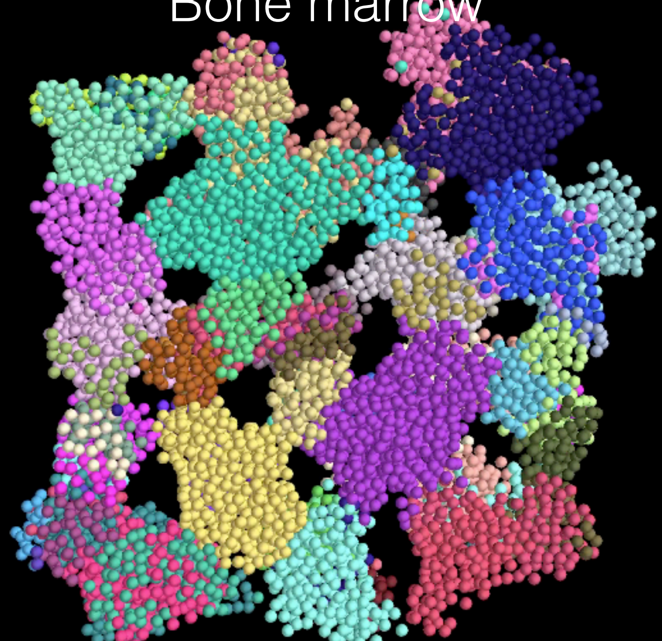

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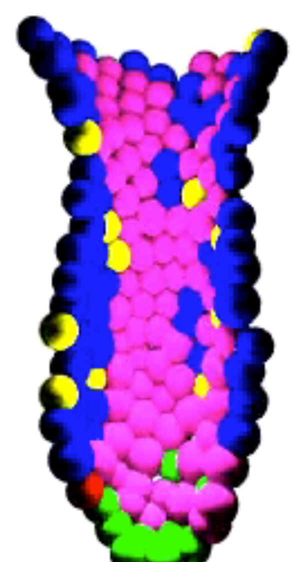

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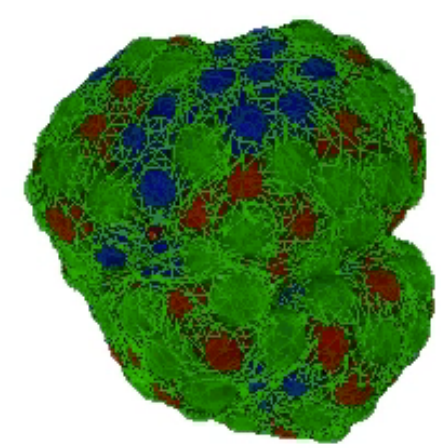
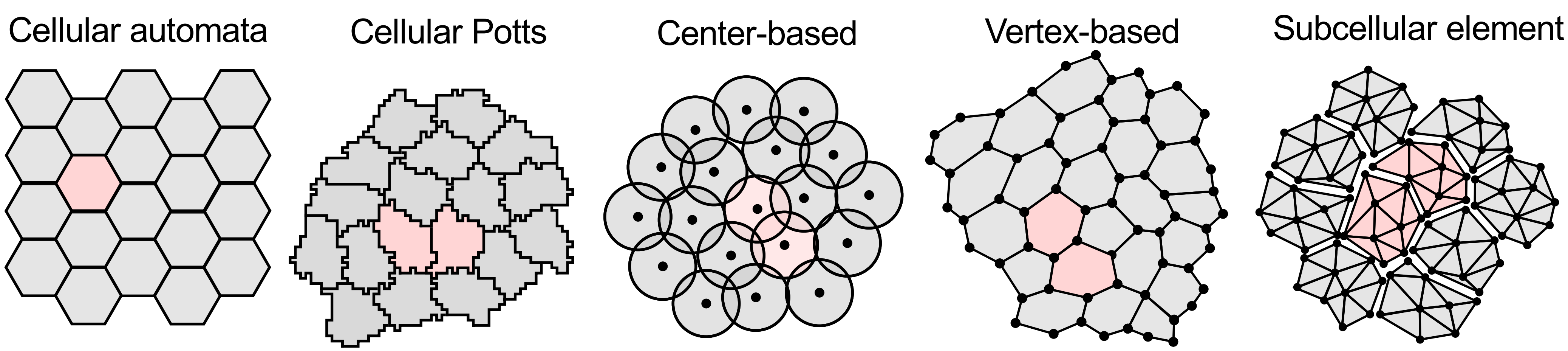


Buske et al., 2012

Computational methods

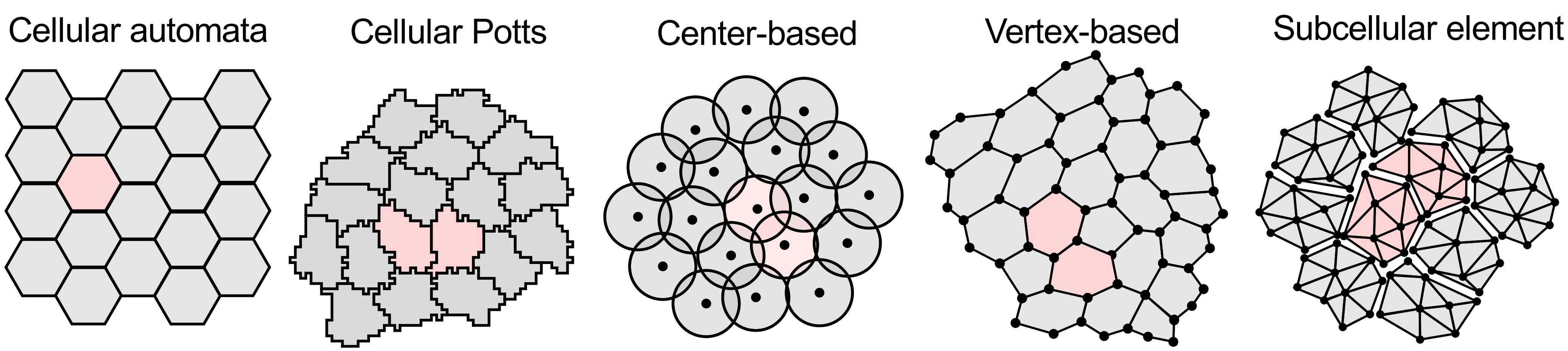
for cell-based modeling

Different cell-based modeling approaches



de Back, 2015.

Different cell-based modeling approaches



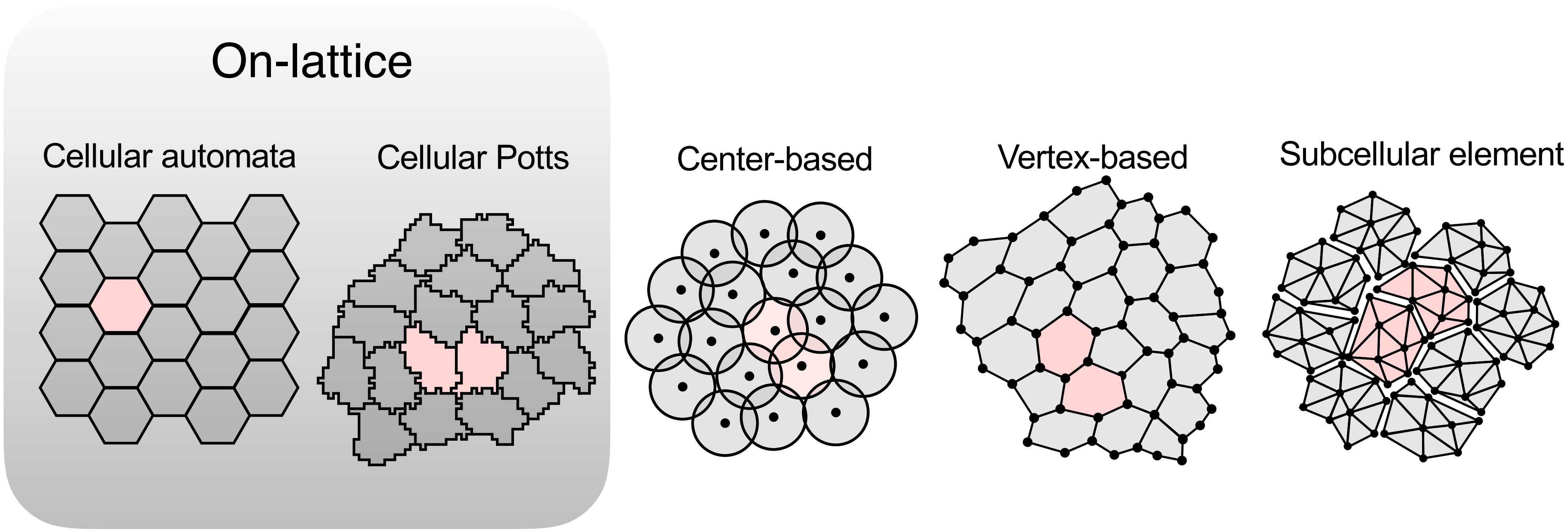
How are cell spatially represented?

On-lattice

Off-lattice

de Back, 2015.

Different cell-based modeling approaches



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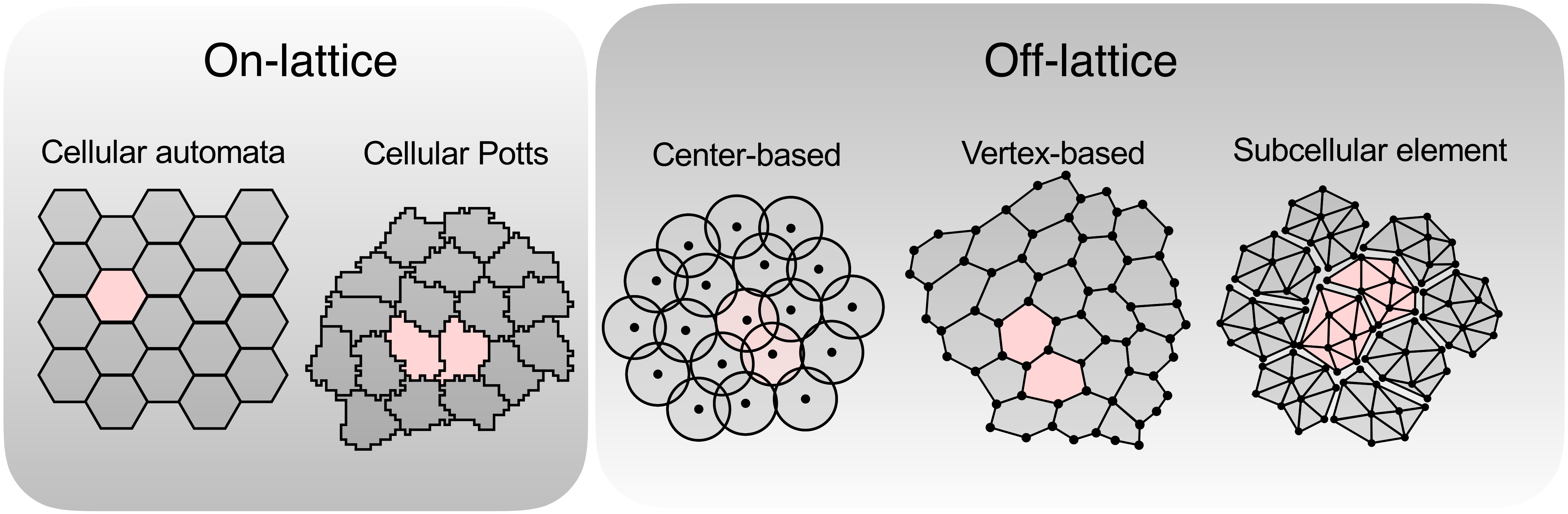

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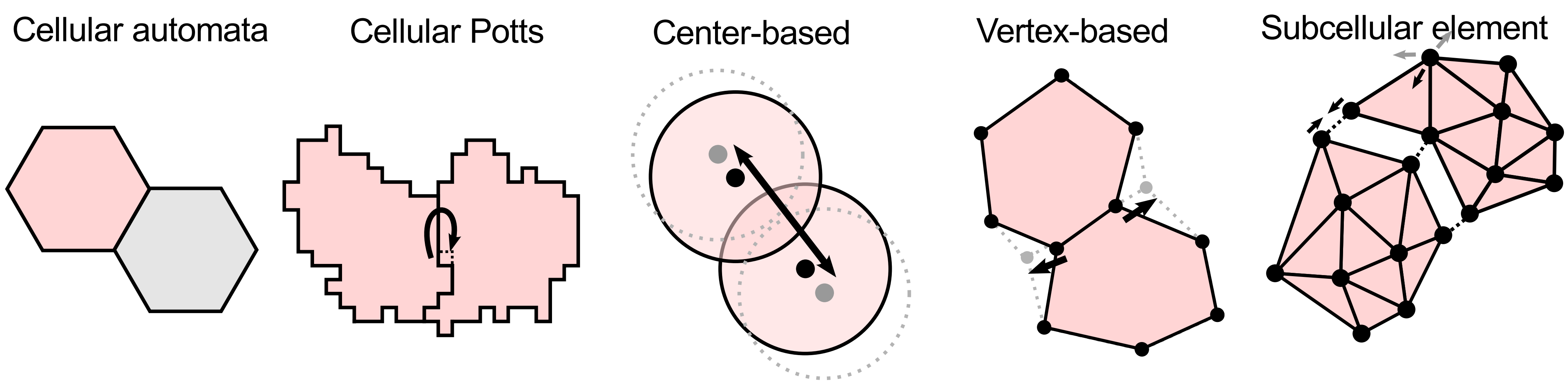


How is cell motility modelled?

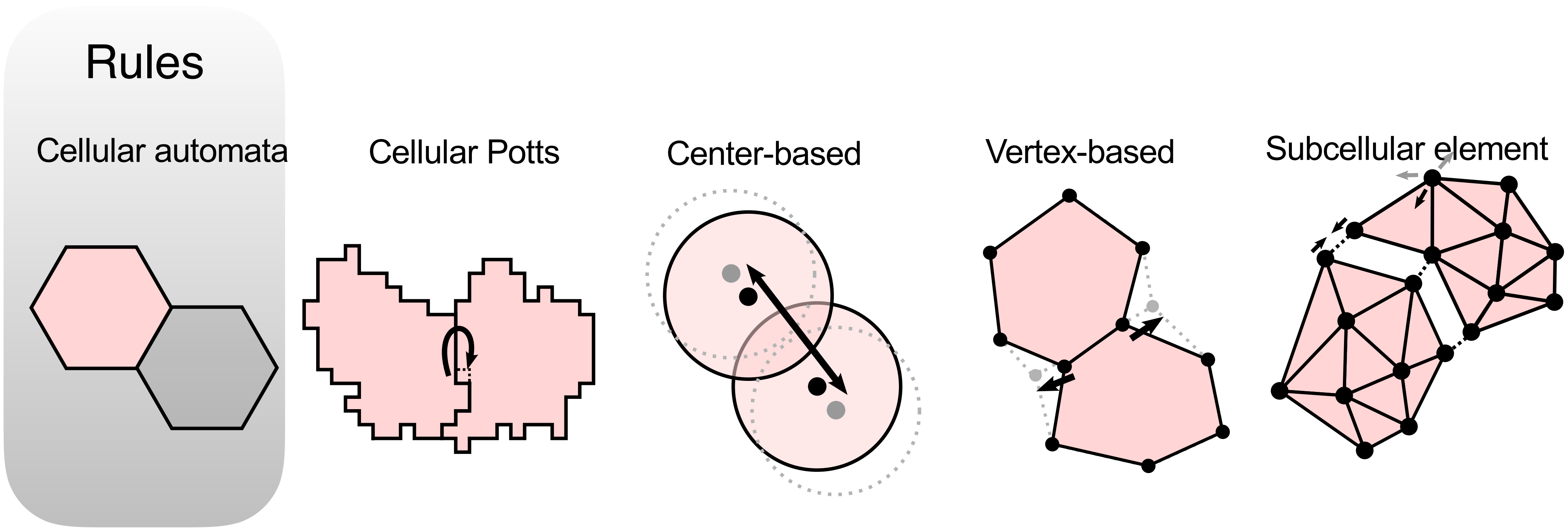
Rule-based

Energy-based

Force-based

de Back, 2015.

Different cell-based modeling approaches



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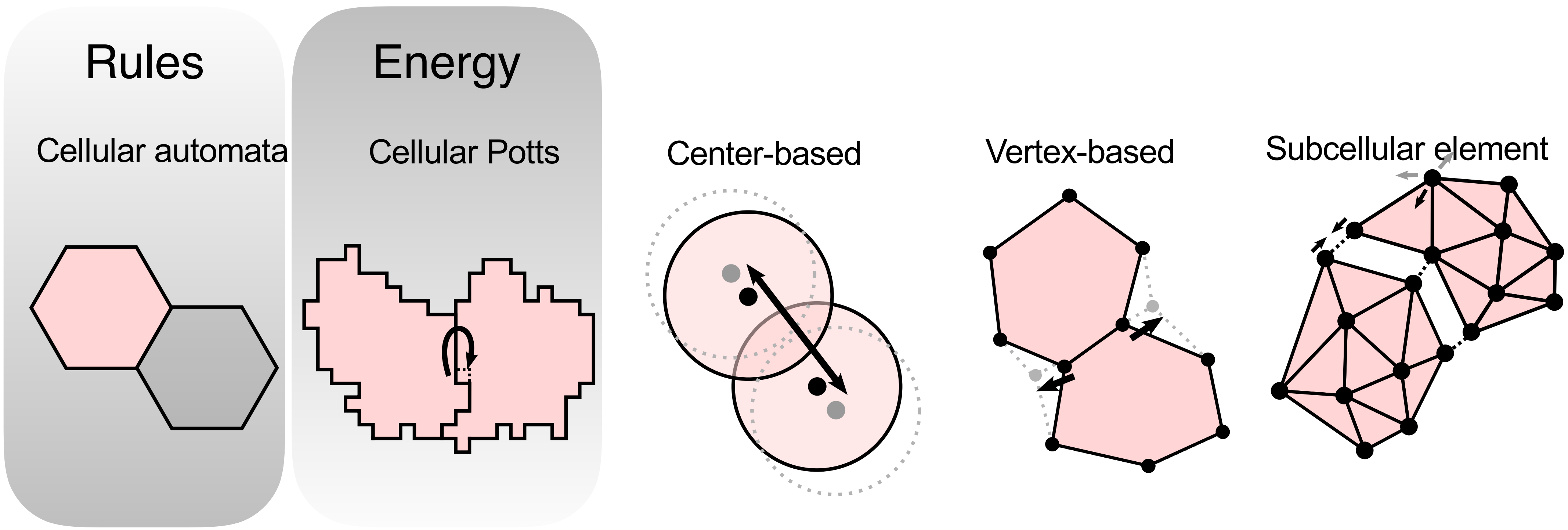

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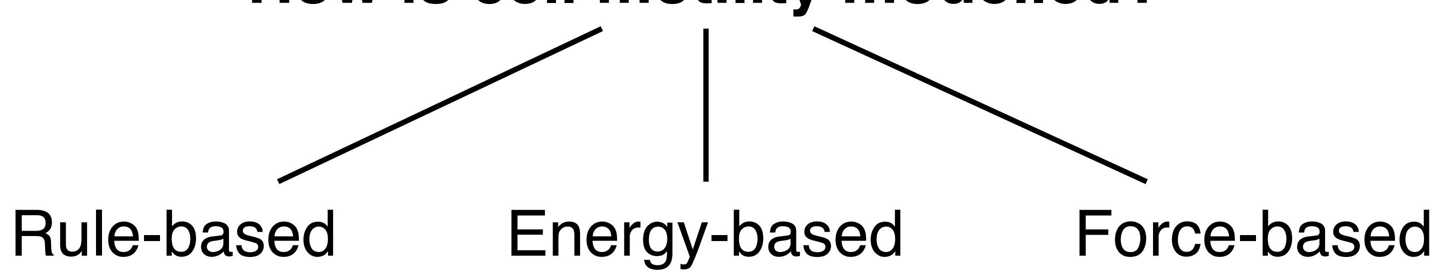

de Back, 2015.

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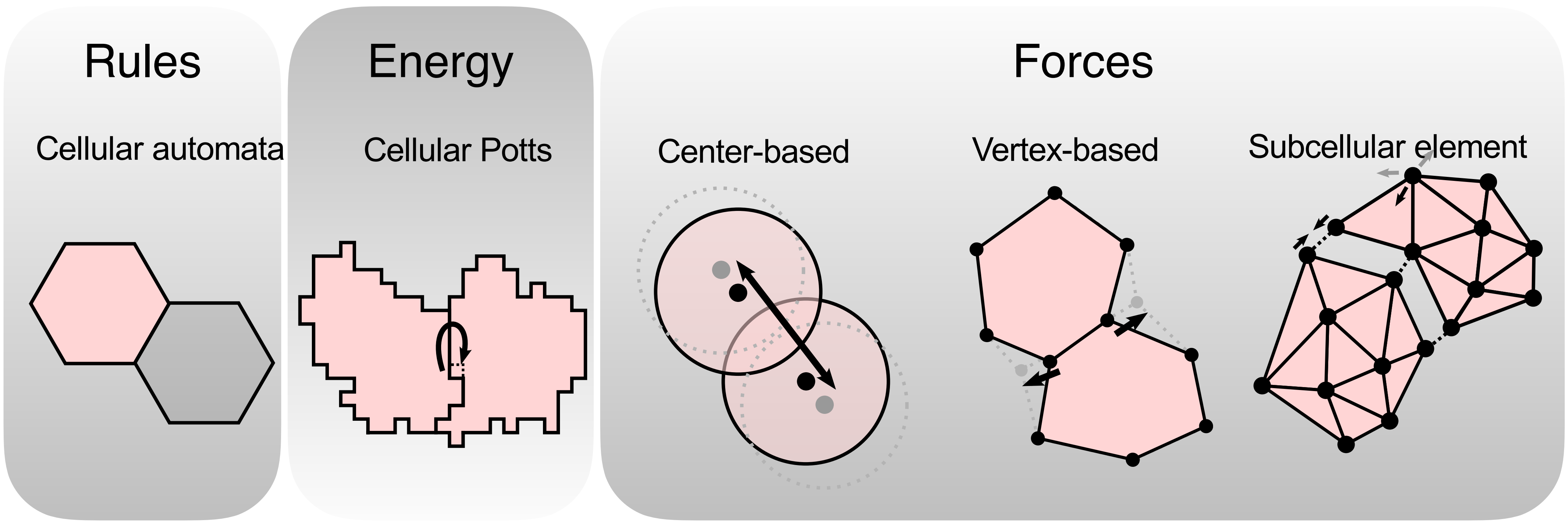

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de Back, 2015.

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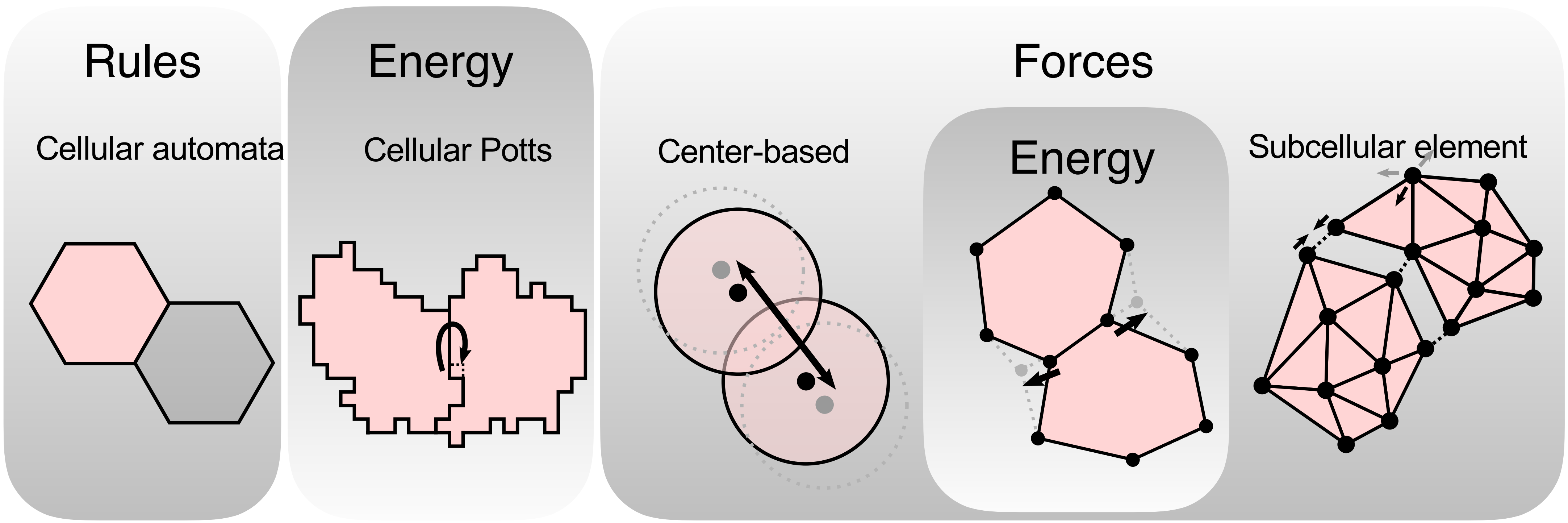


How is cell motility modelled?

Rule-based   Energy-based   Force-based

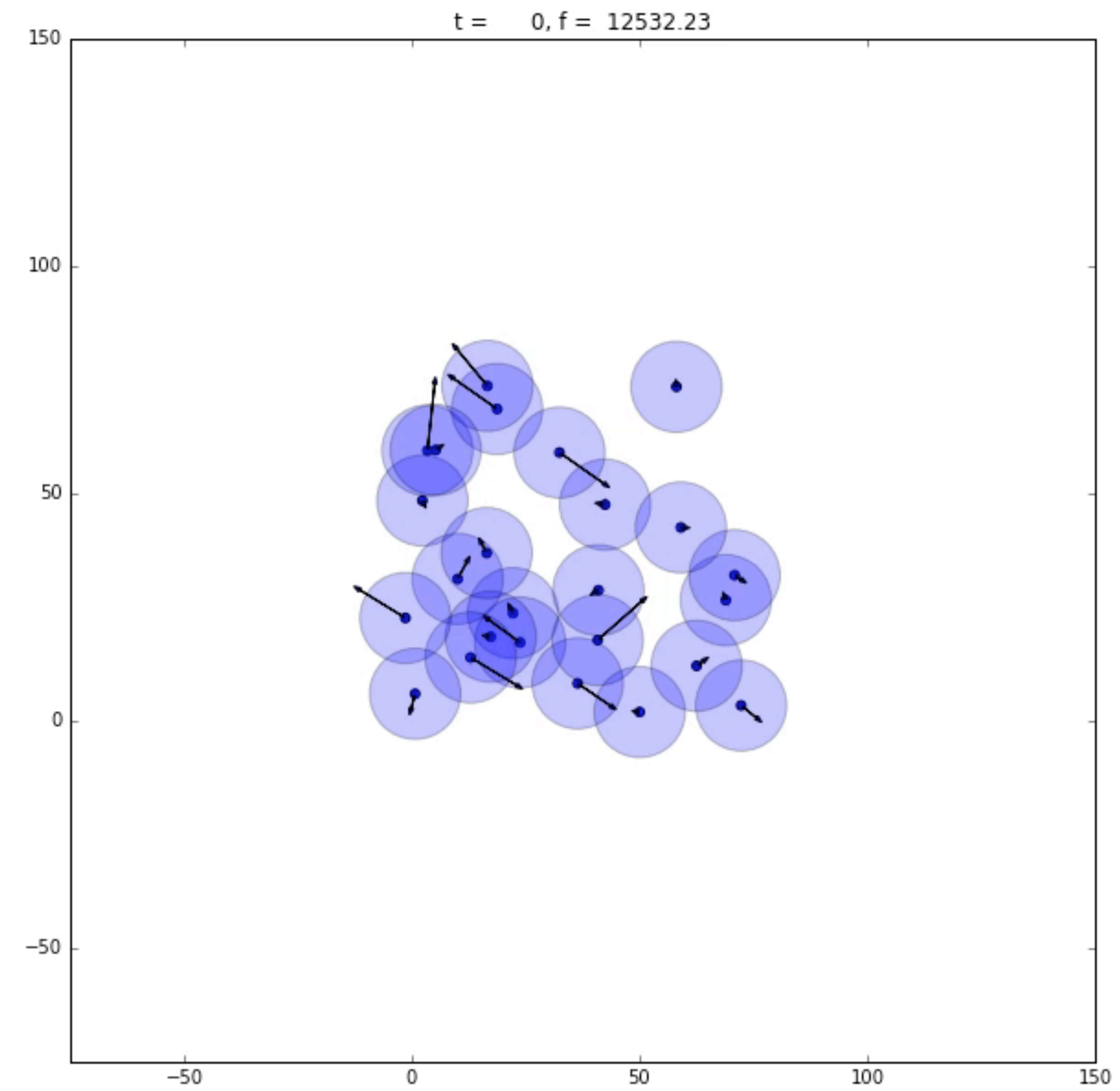
de Back, 2015.

Center-based model

Overlapping spheres

Center based model

- Cell represented as a circles (or spheres)
- Movement controlled by forces
- Interaction between cells:
  - *Adhesion* when close
  - *Repulsion* when too close
  - *No interaction* when too far



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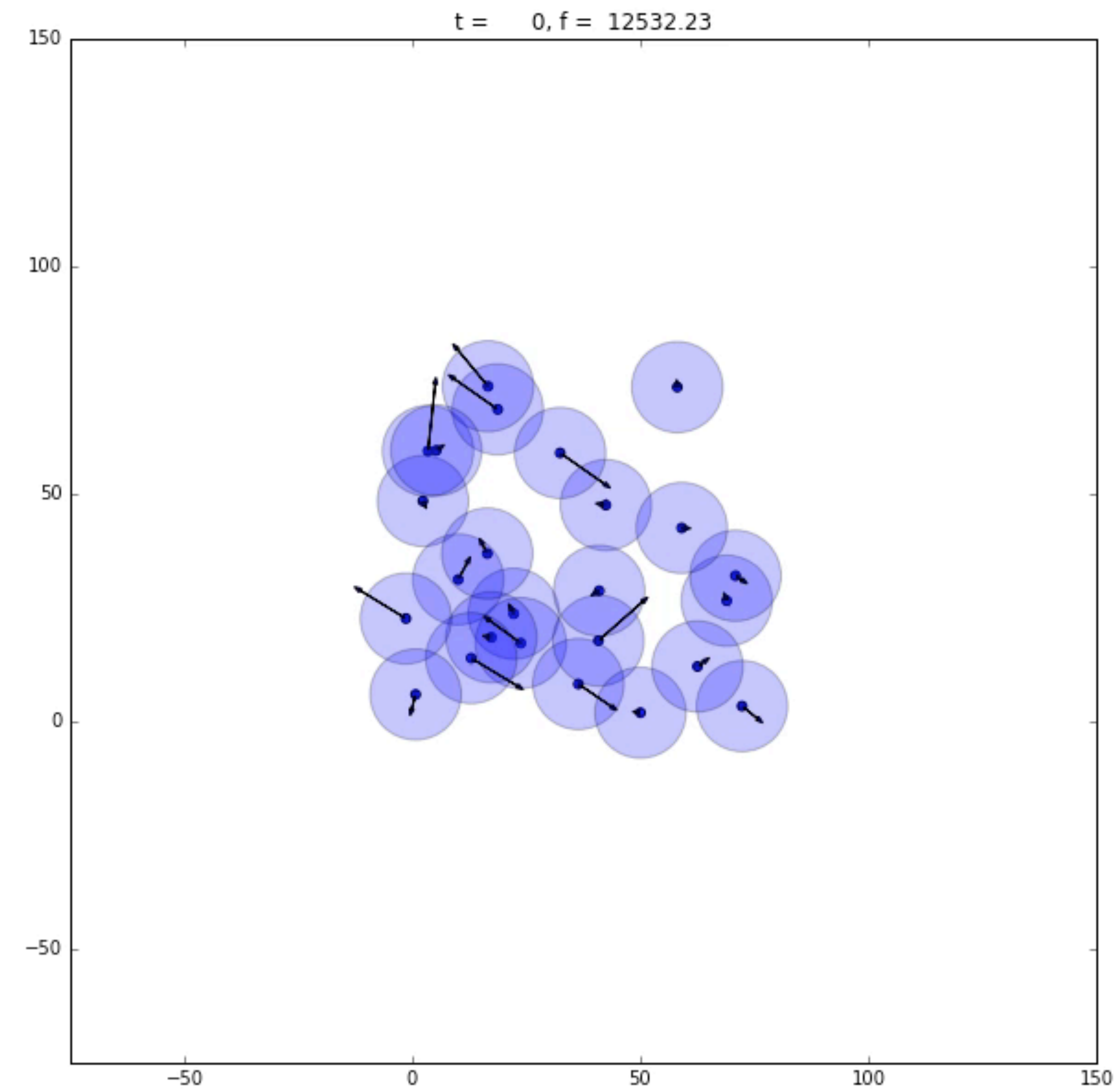


Center based model - cells

Cell represented as a circles or spheres

Set of cells:

$$\mathbf{r}_1, \mathbf{r}_2, \ldots, \mathbf{r}_{Ncells}$$

Interaction radius

$$r_{max}$$

Vector from cell i to cell j

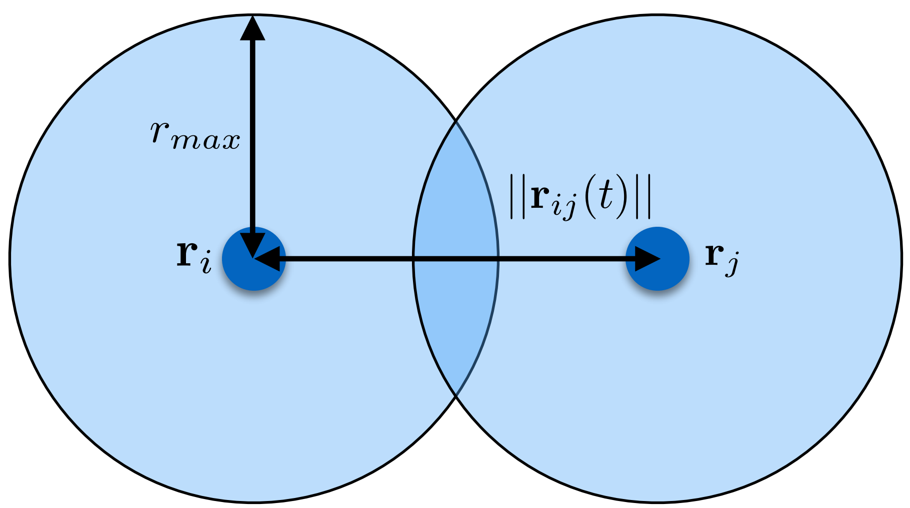
$$\mathbf{r}_{ij}(t) = \mathbf{r}_j(t) - \mathbf{r}_i(t)$$

Distance from cell i to cell j

$$||\mathbf{r}_{ij}(t)||$$

Natural separation

$$s_{ij}(t)$$



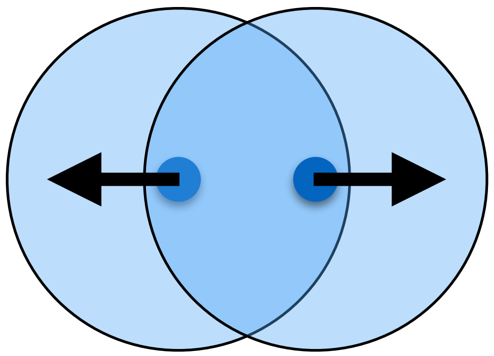
Center based model - forces

Forces on a cell:

- volume exclusion
- adhesion

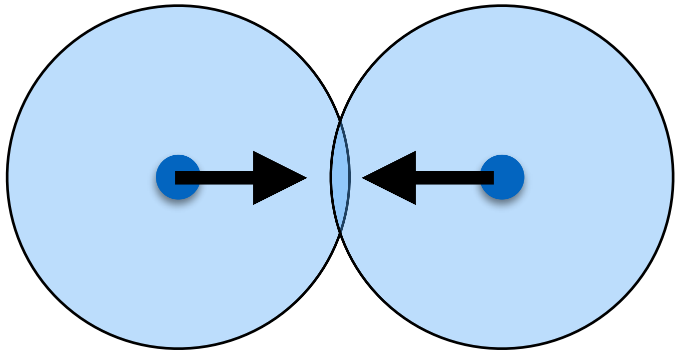
Repulsion

$$||\mathbf{r}_{ij}(t)|| < s_{ij}(t)$$



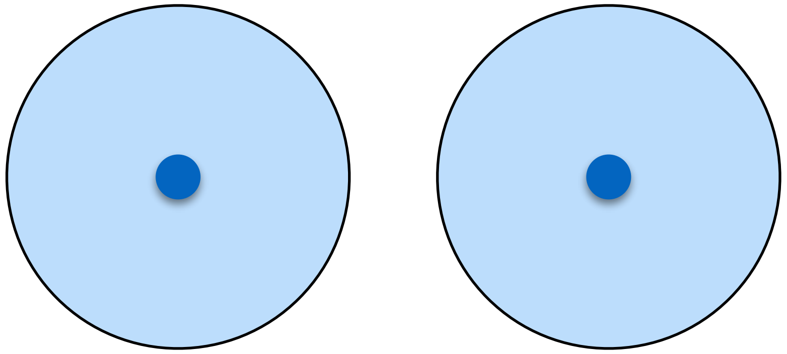
Attraction

$$s_{ij}(t) \leq ||\mathbf{r}_{ij}(t)|| \leq r_{max}$$



No interaction

$$||\mathbf{r}_{ij}(t)|| > r_{max}$$

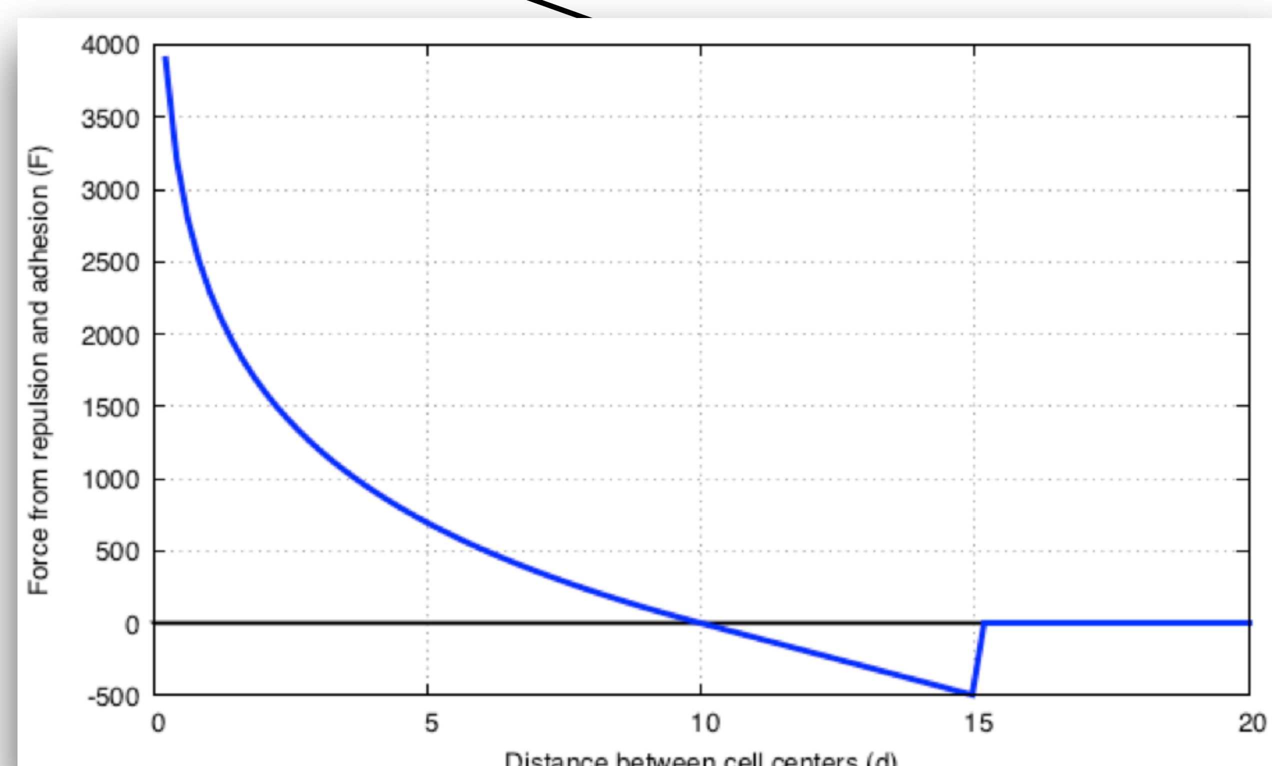


Center based model - forces

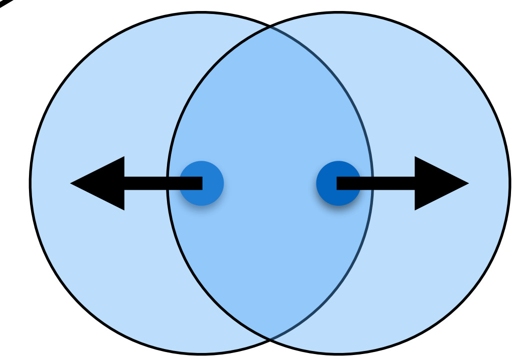
Forces on a cell:

- volume exclusion
- adhesion

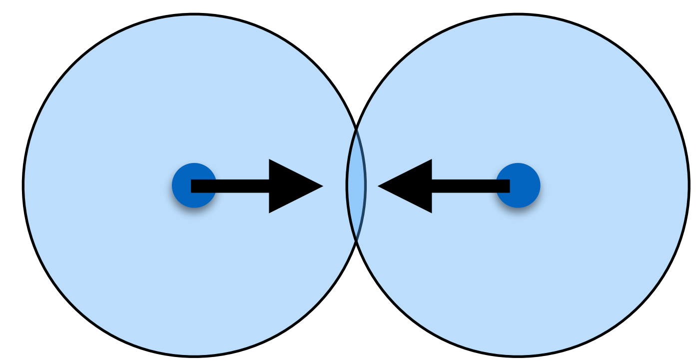
$$\mathbf{F}_{ij}(t) = \begin{cases} \mu_{ij} s_{ij}(t) \hat{\mathbf{r}}_{ij}(t) log(1 + \frac{||\mathbf{r}_{ij}(t)|| - s_{ij}(t)}{s_{ij}(t)}), \\ \mu_{ij}(||\mathbf{r}_{ij}(t)|| - s_{ij}) \hat{\mathbf{r}}_{ij}(t) exp(-k_c \frac{||\mathbf{r}_{ij}(t)|| - s_{ij}(t)}{s_{ij}(t)})), \\ 0, \end{cases}$$



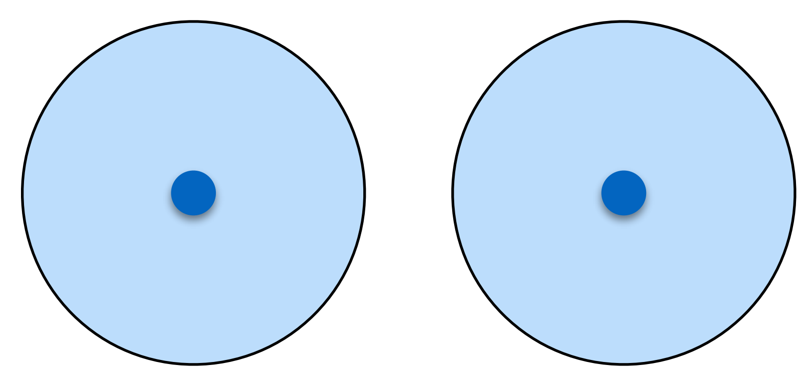
Repulsion



Attraction

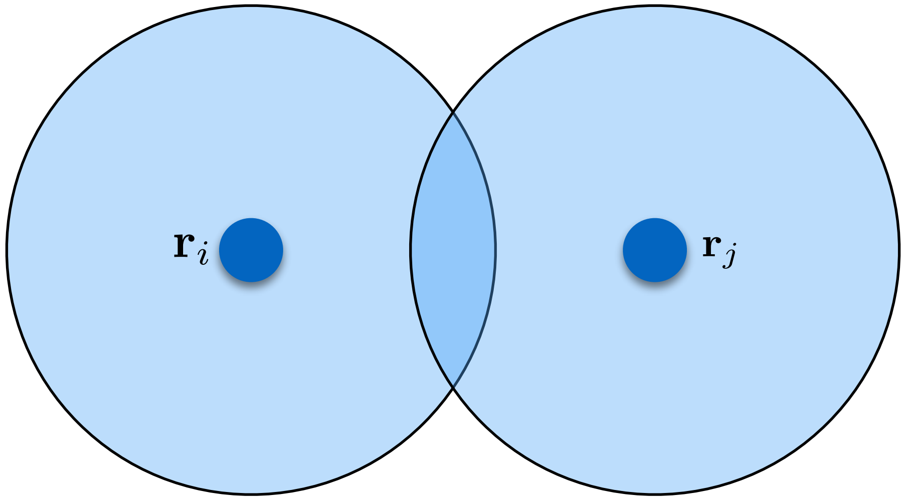


No interaction



Center based model - motility

Cell represented as a circles or spheres



Update positions according to linear ODEs:

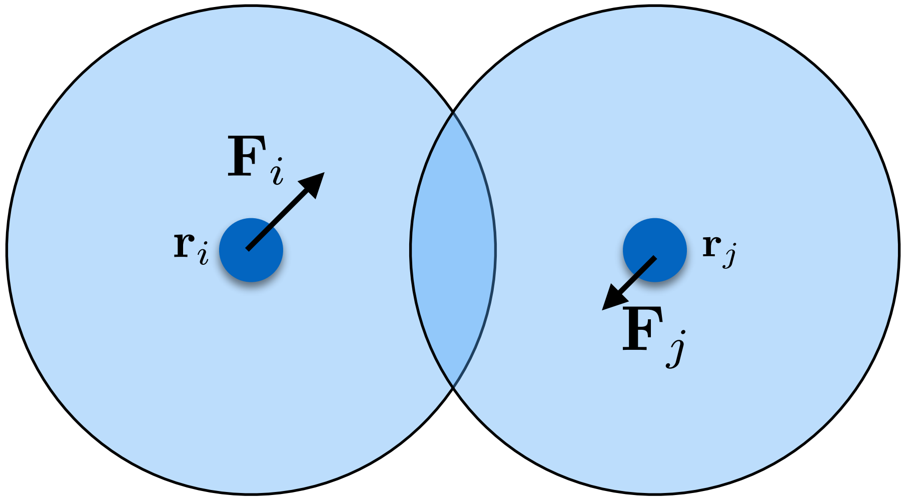
$$\eta \frac{d\mathbf{r}_i}{dt} = \mathbf{F}_i(t) = \sum_{j \in \mathcal{N}_i(t)} \mathbf{F}_{ij}(t)$$

Discretized in time:

$$\mathbf{r}_i(t + \Delta t) = \mathbf{r}_i + \frac{\Delta t}{\eta} \sum_{j \in \mathcal{N}_i(t)} \mathbf{F}_{ij}(t)$$

Center based model - motility

Cell represented as a circles or spheres



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Center based model - motility

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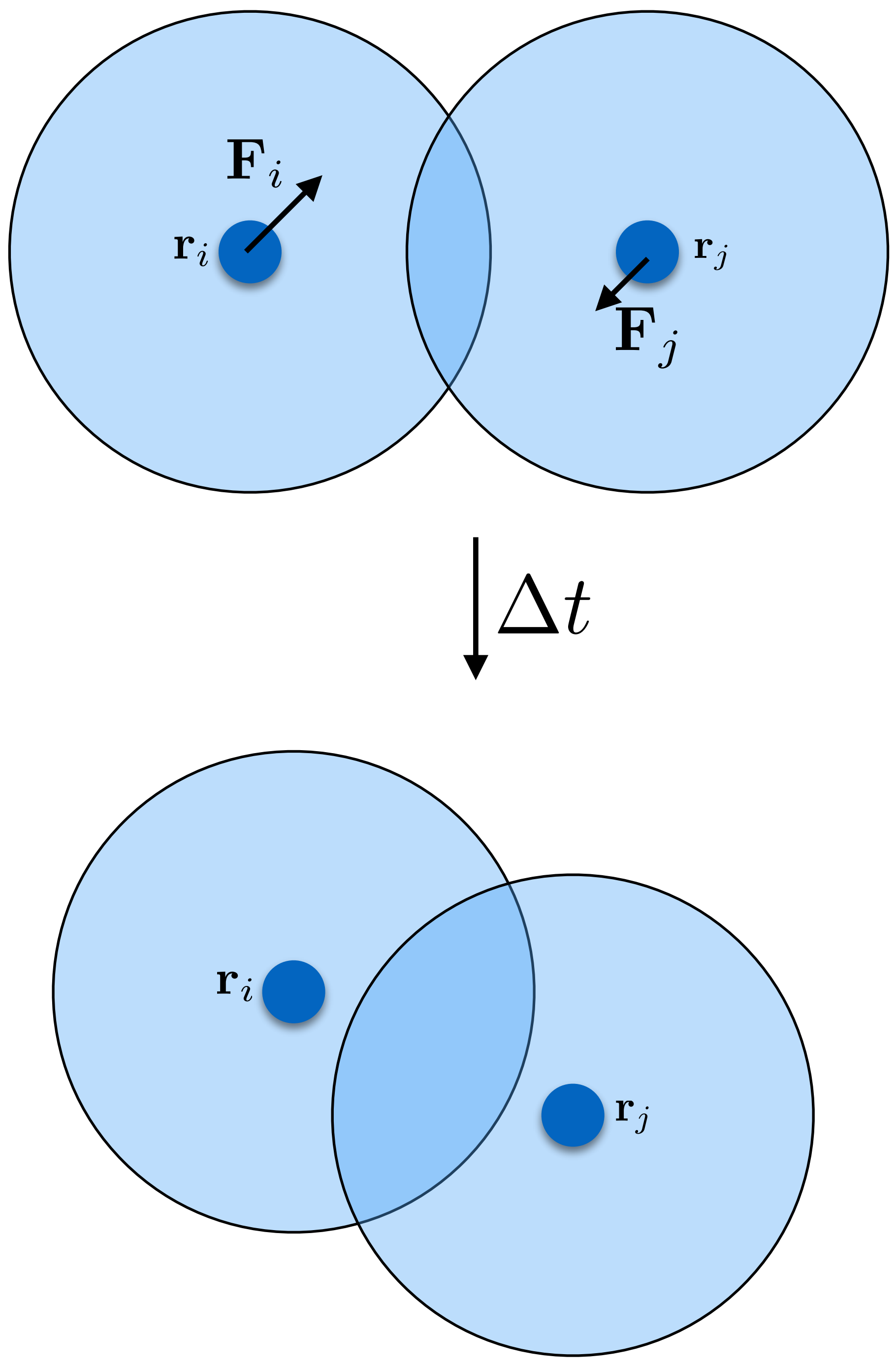
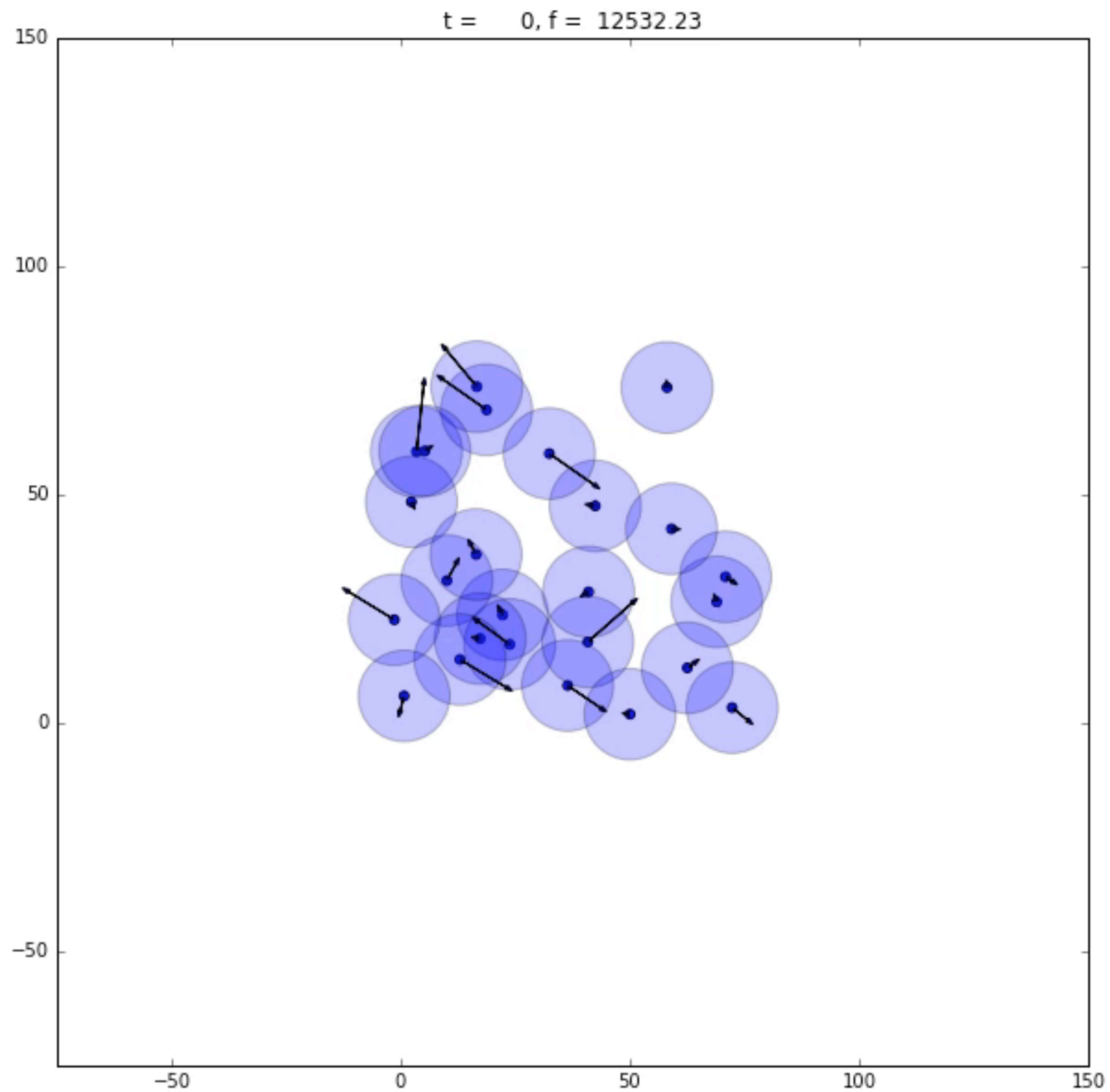
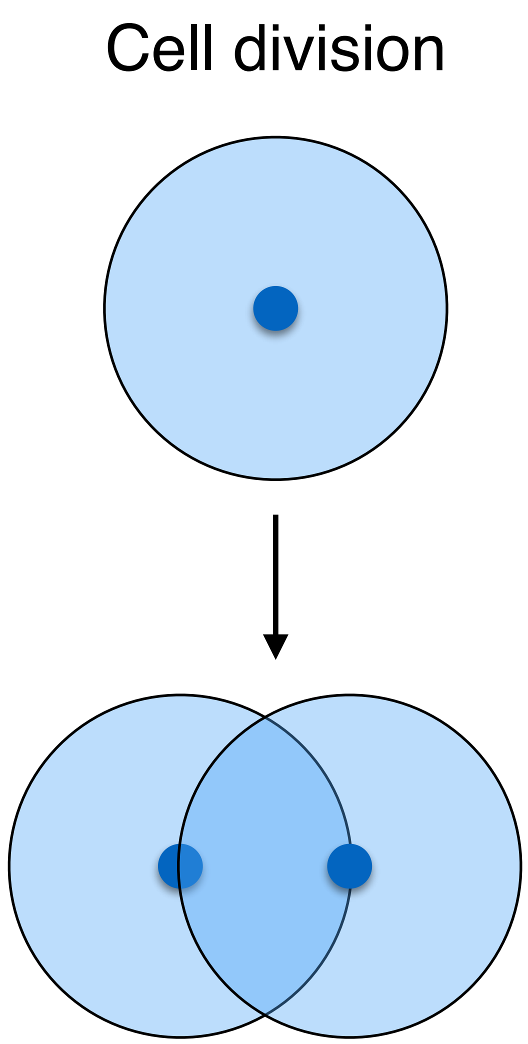


Center based model





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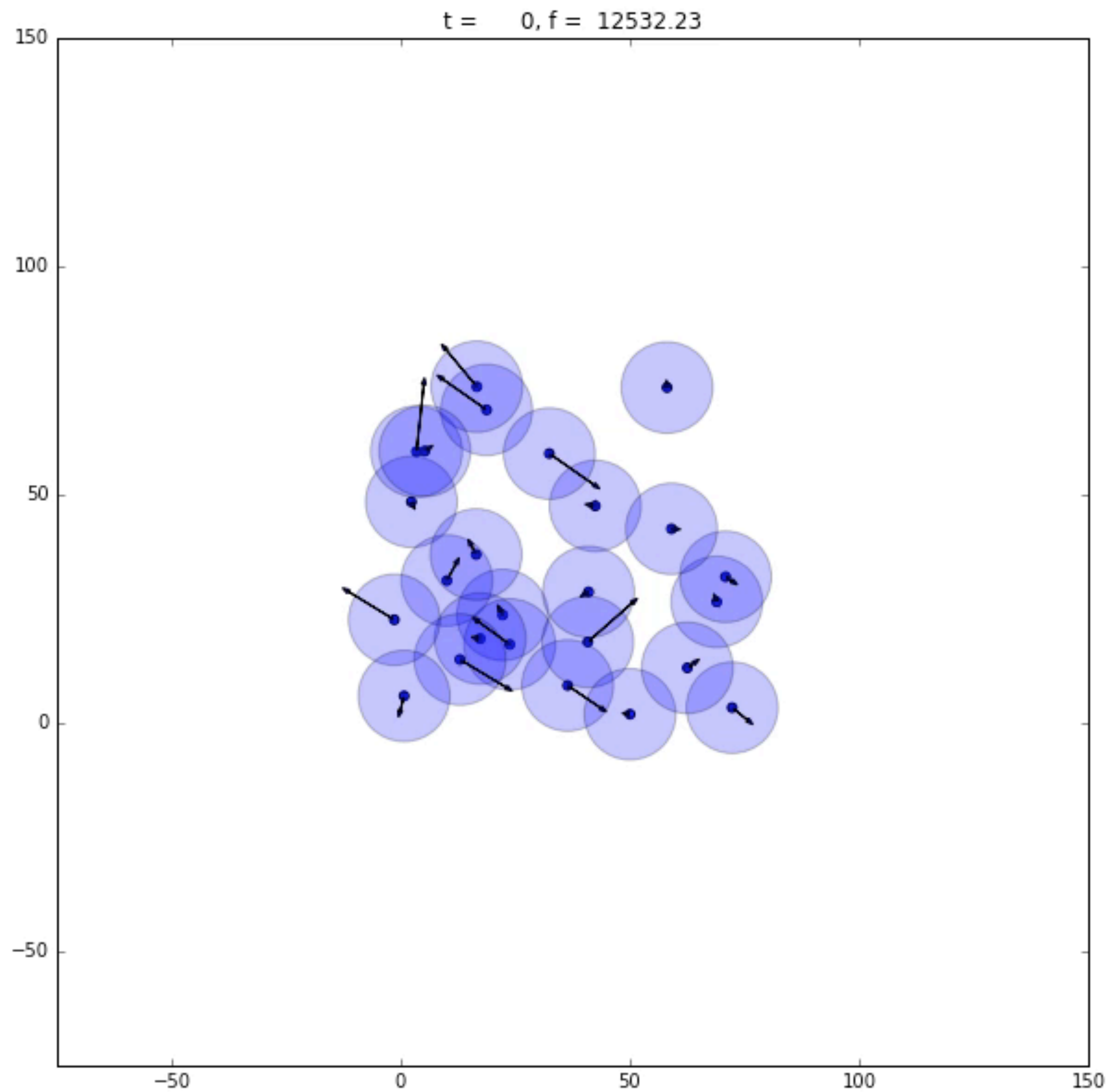
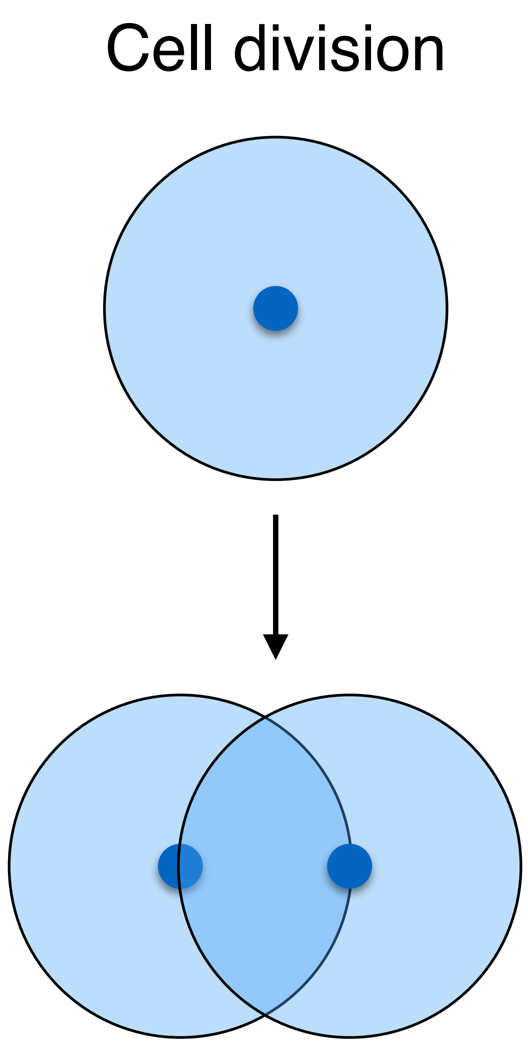
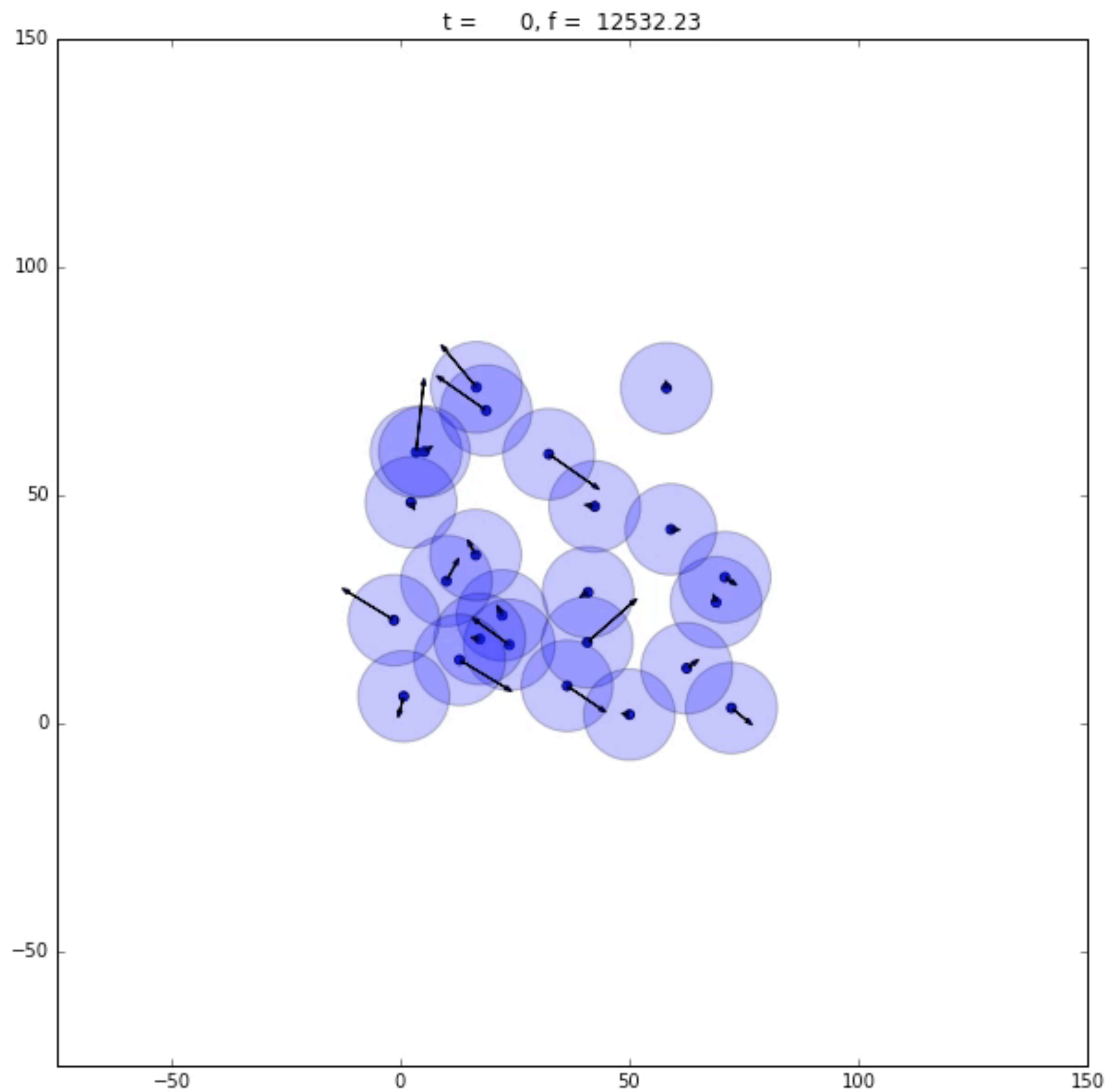
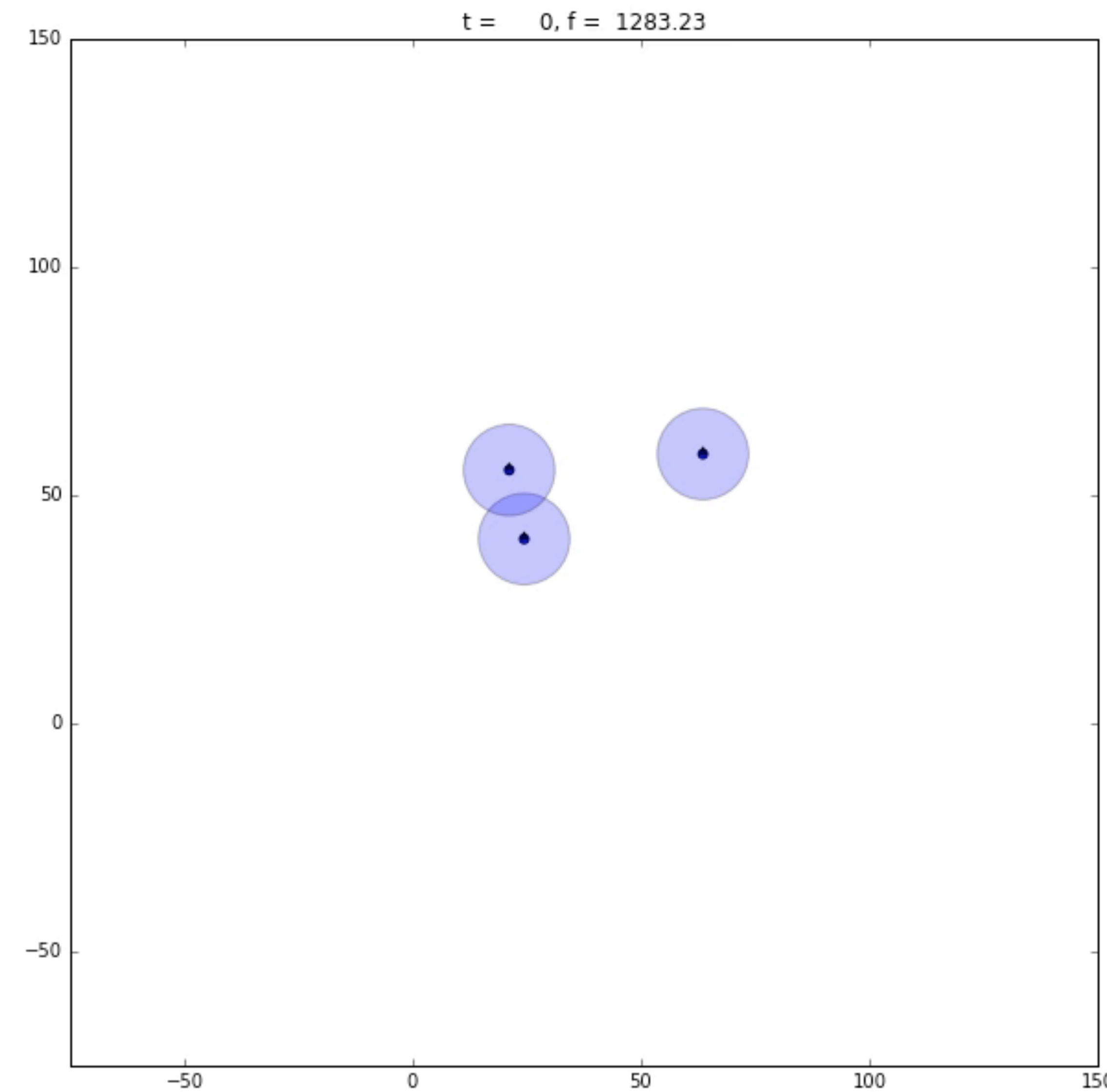




Center based model - cell division





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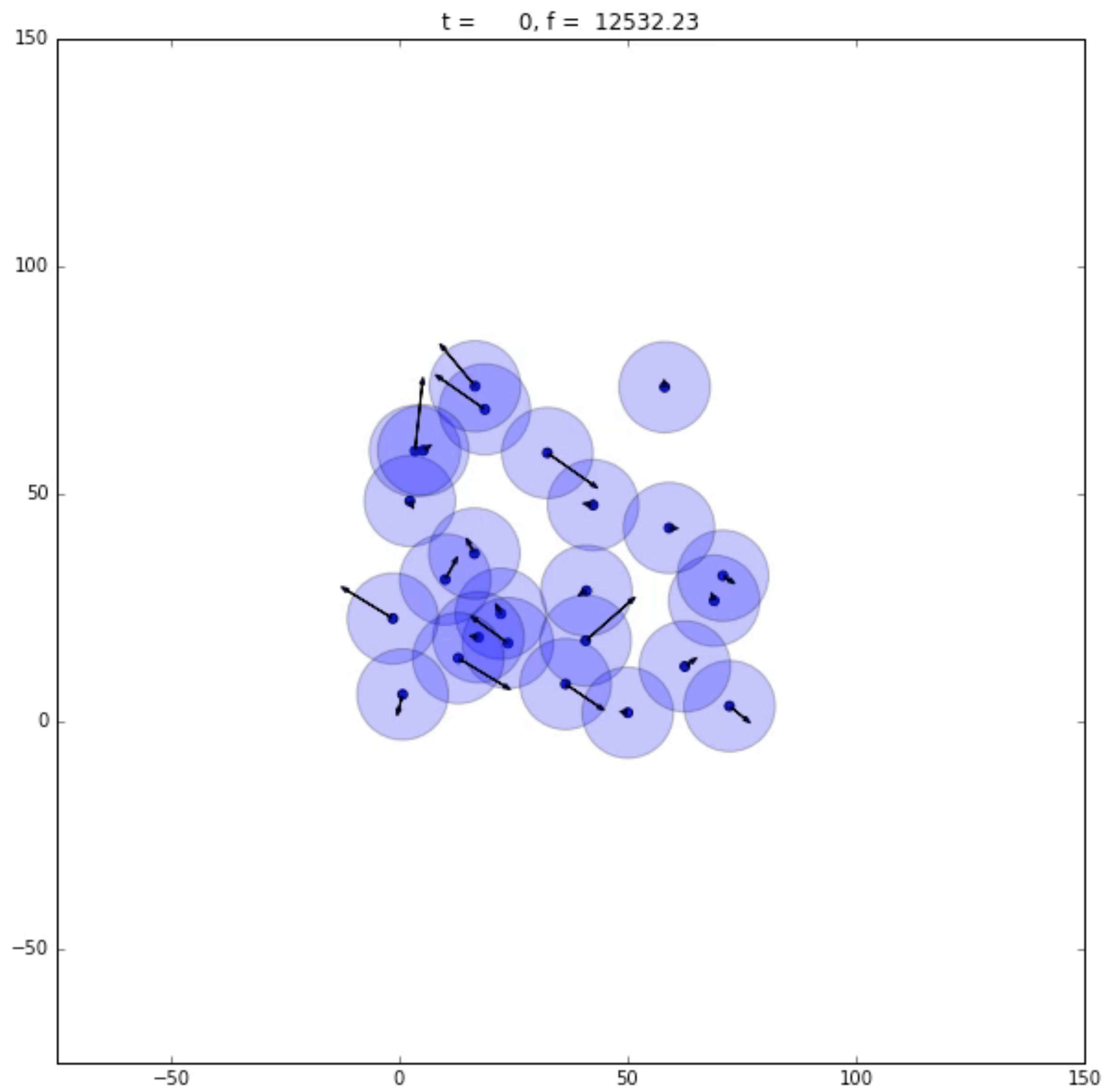
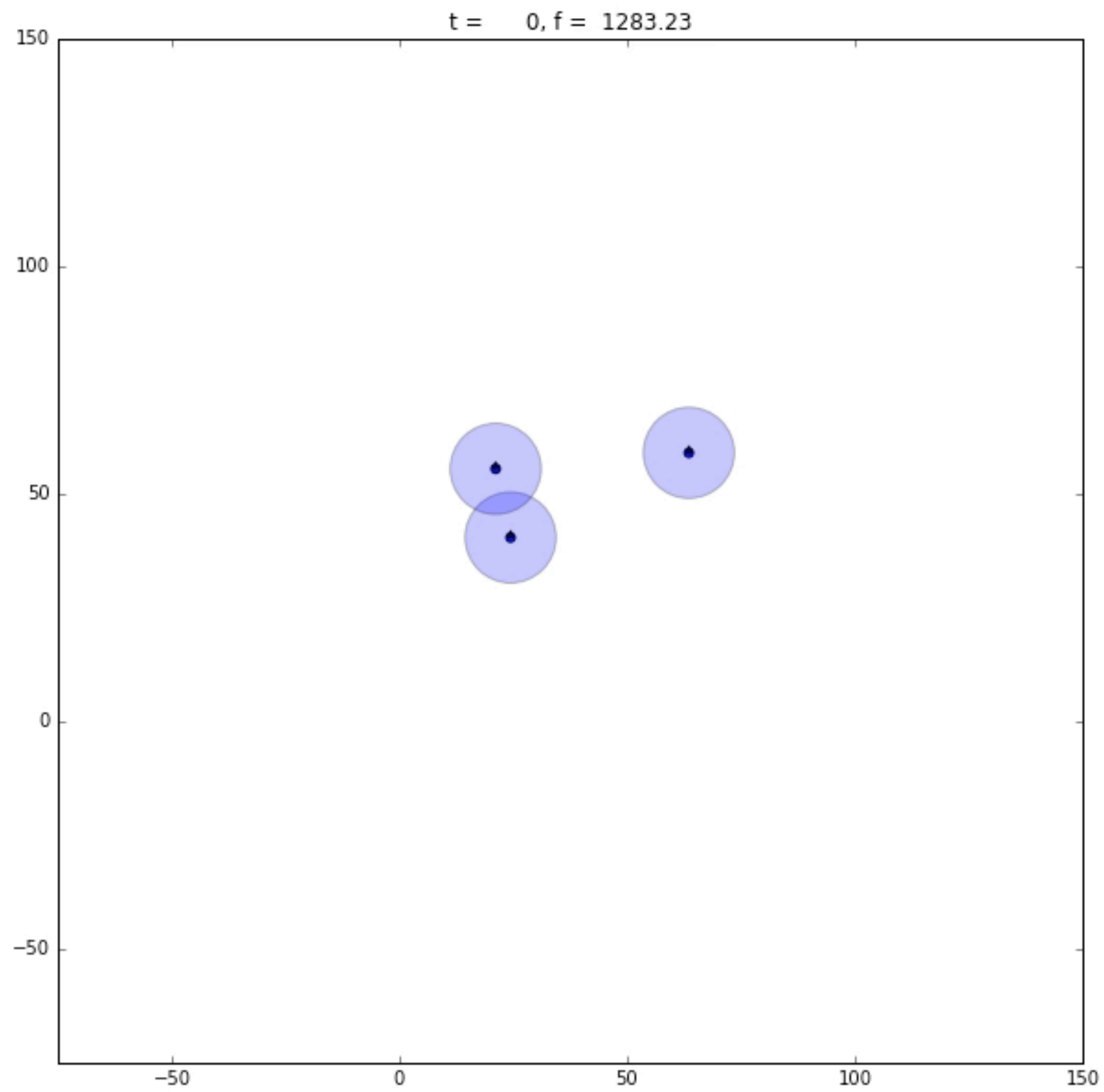


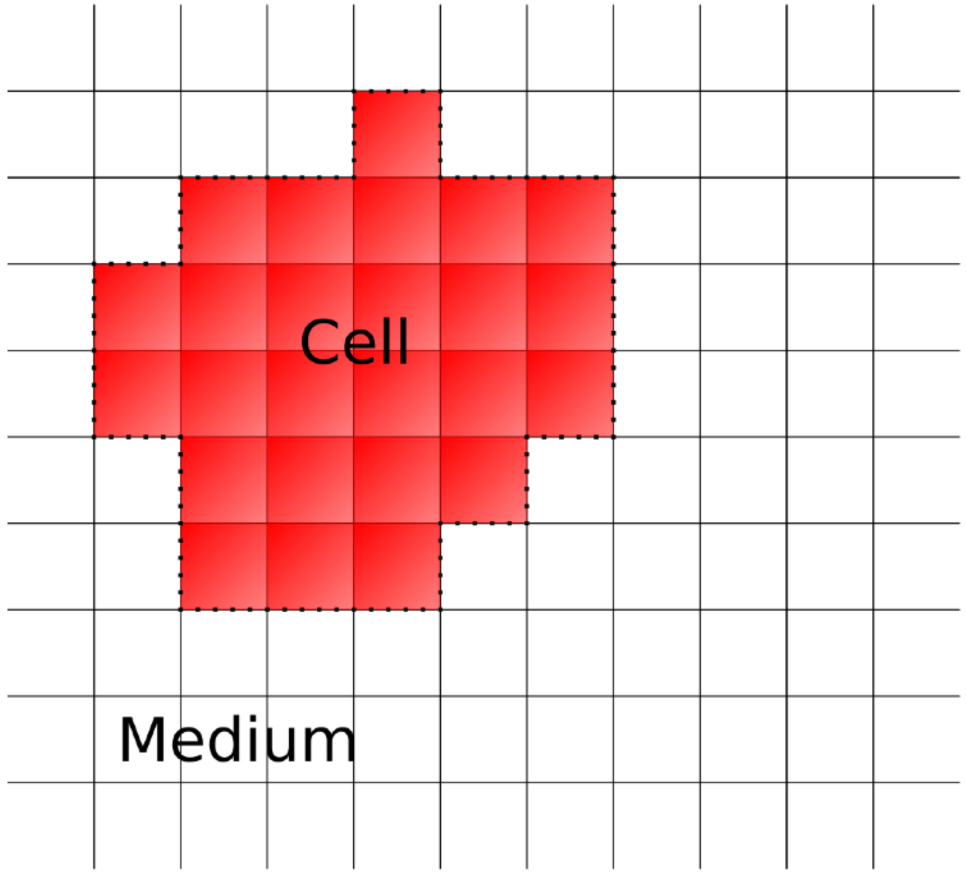


Cellular Potts model

Cellular Potts model - cell size

Cell represented as a lattice domain

$$H = \sum_{\sigma > 0} (a_\sigma - A_\sigma)^2$$

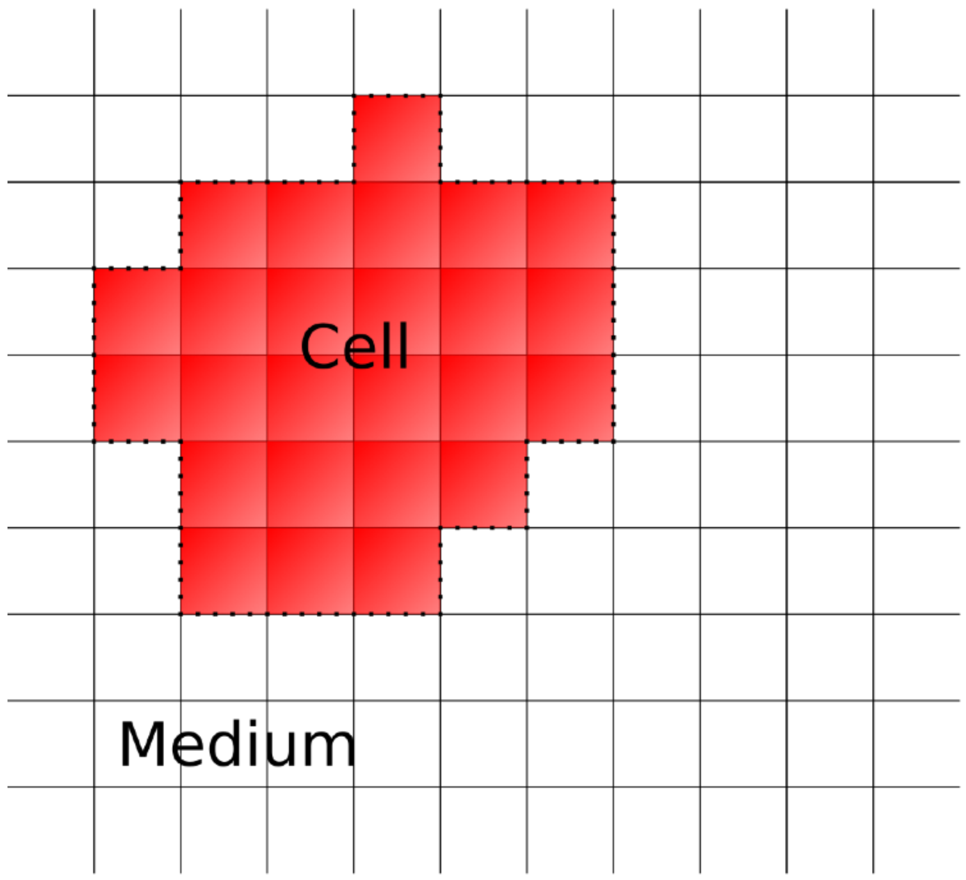


Cellular Potts model - cell size

Cell represented as a lattice domain

energy

$$H = \sum_{\sigma > 0} (a_\sigma - A_\sigma)^2$$



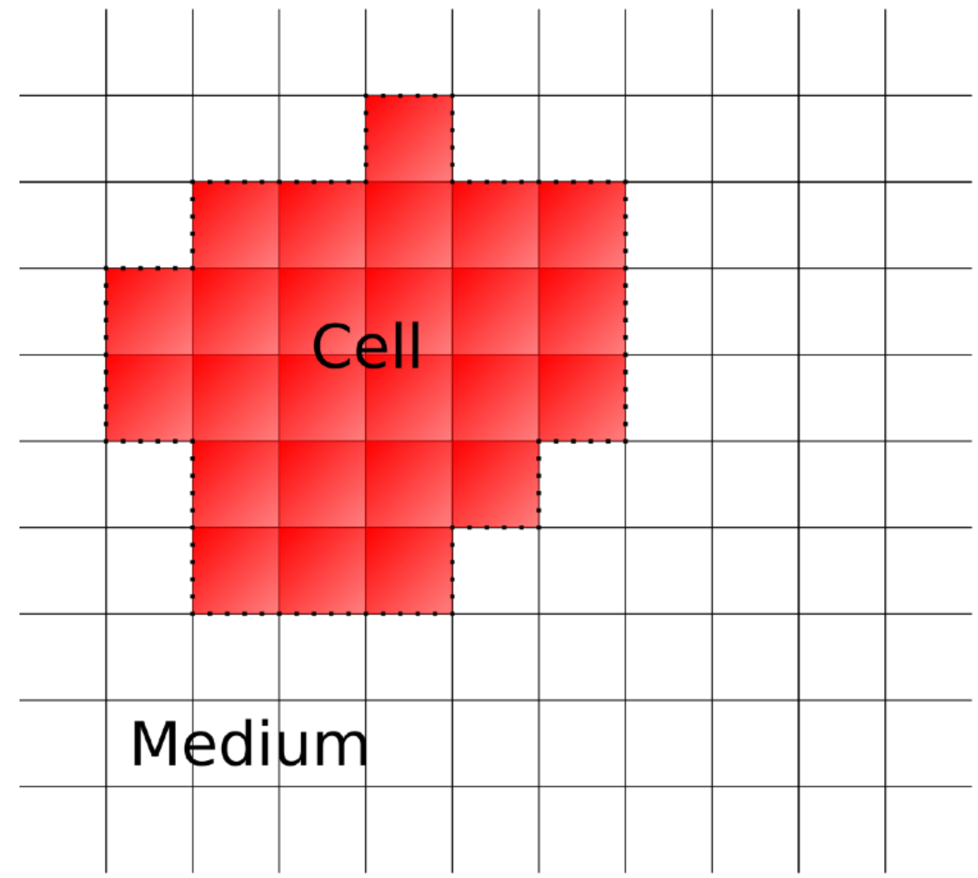
Cellular Potts model - cell size

Cell represented as a lattice domain

energy

$$H = \sum_{\sigma>0} (a_\sigma - A_\sigma)^2$$

sum over cells



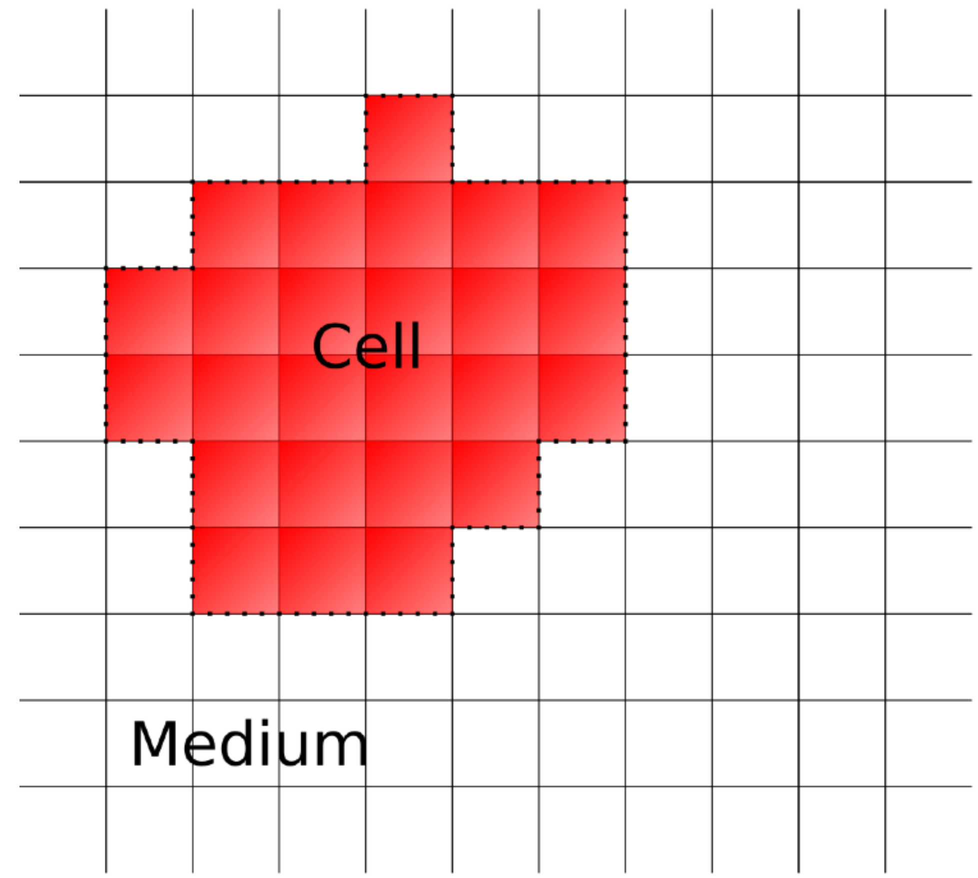
Cellular Potts model - cell size

Cell represented as a lattice domain

energy actual area

$$H = \sum_{\sigma>0} (a_\sigma - A_\sigma)^2$$

sum over cells



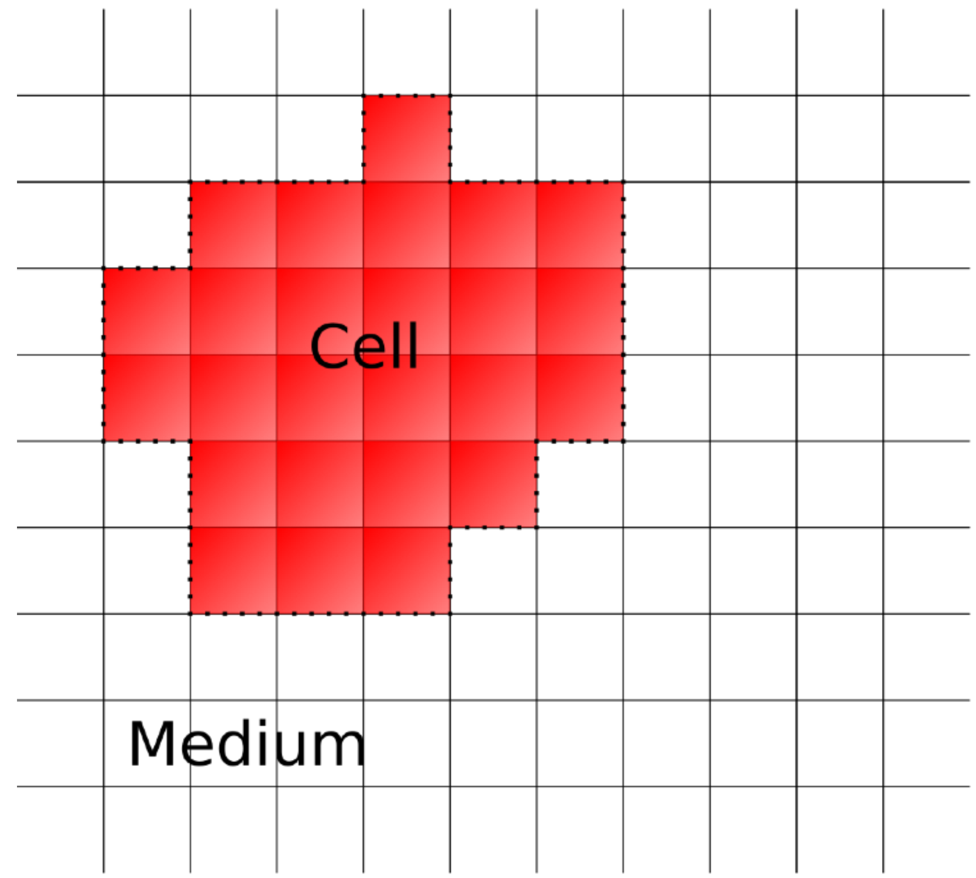
Cellular Potts model - cell size

Cell represented as a lattice domain

energy actual area

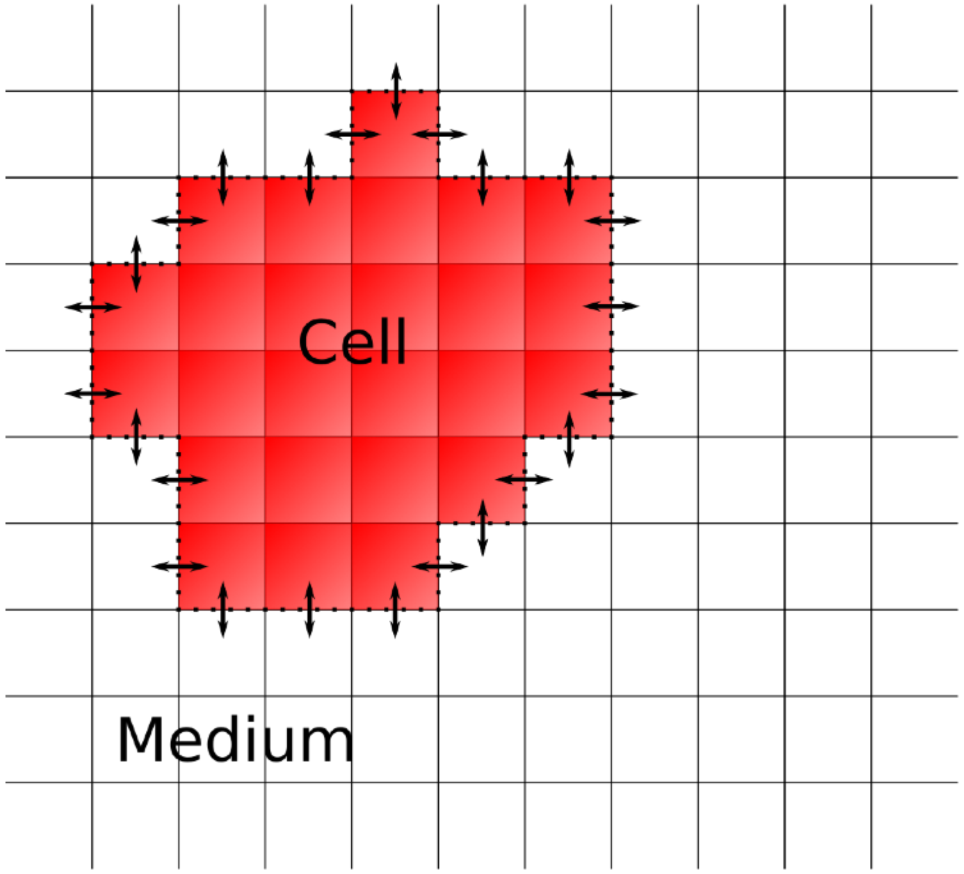
$$H = \sum_{\sigma>0}(a_\sigma - A_\sigma)^2$$

sum over cells target area



Cellular Potts model - contact energy

$$H = \sum_{interfaces} J_{x,y}(1 - \delta_{x,y})$$



Cellular Potts model - contact energy

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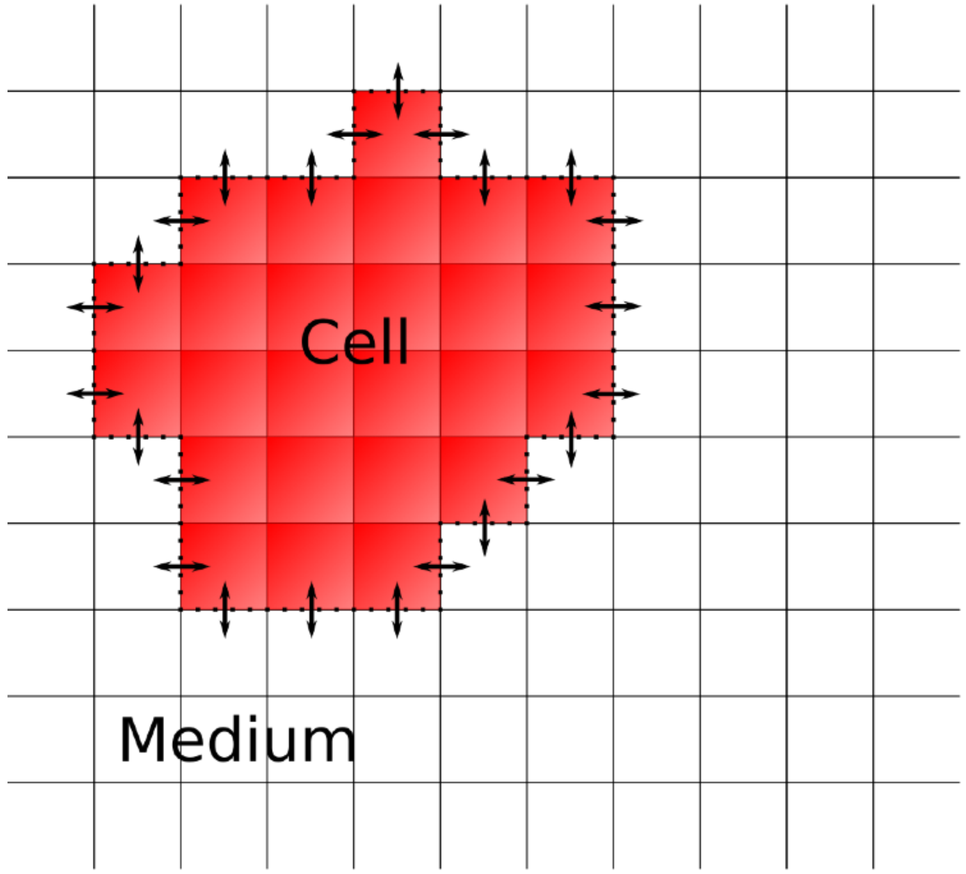
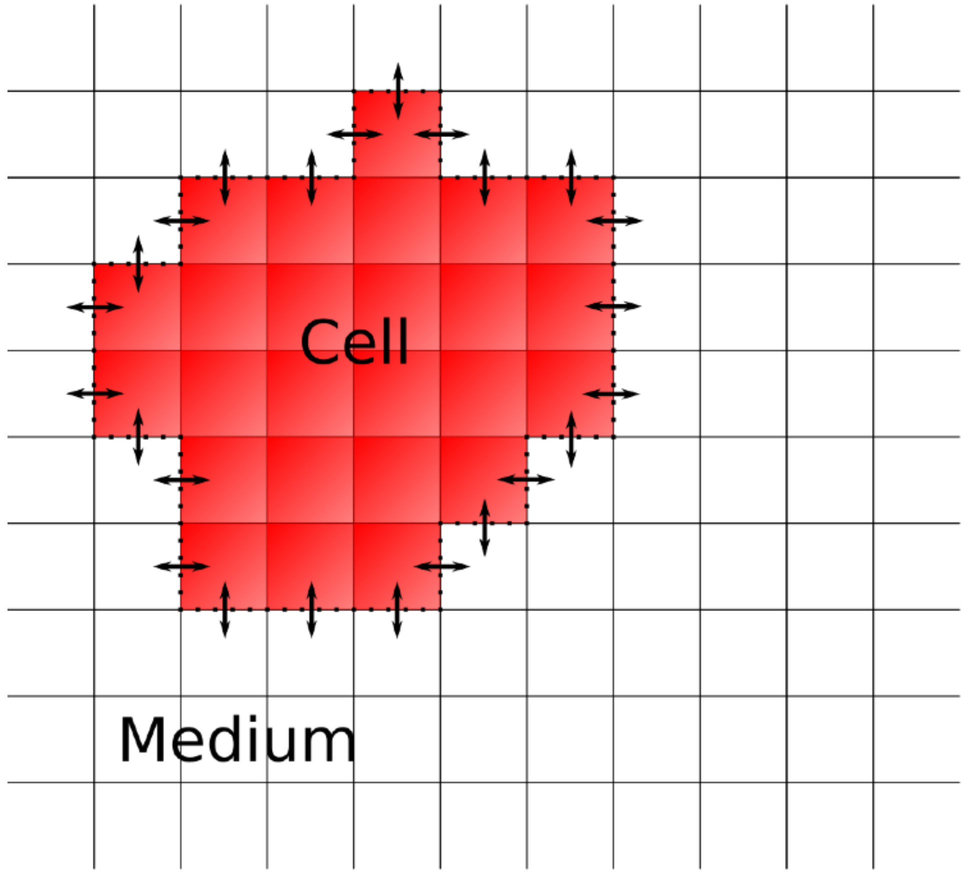


Cellular Potts model - contact energy

energy

$$H = \sum_{interfaces} J_{x,y}(1 - \delta_{x,y})$$

sum over interfaces



Cellular Potts model - contact energy

energy

contact energy

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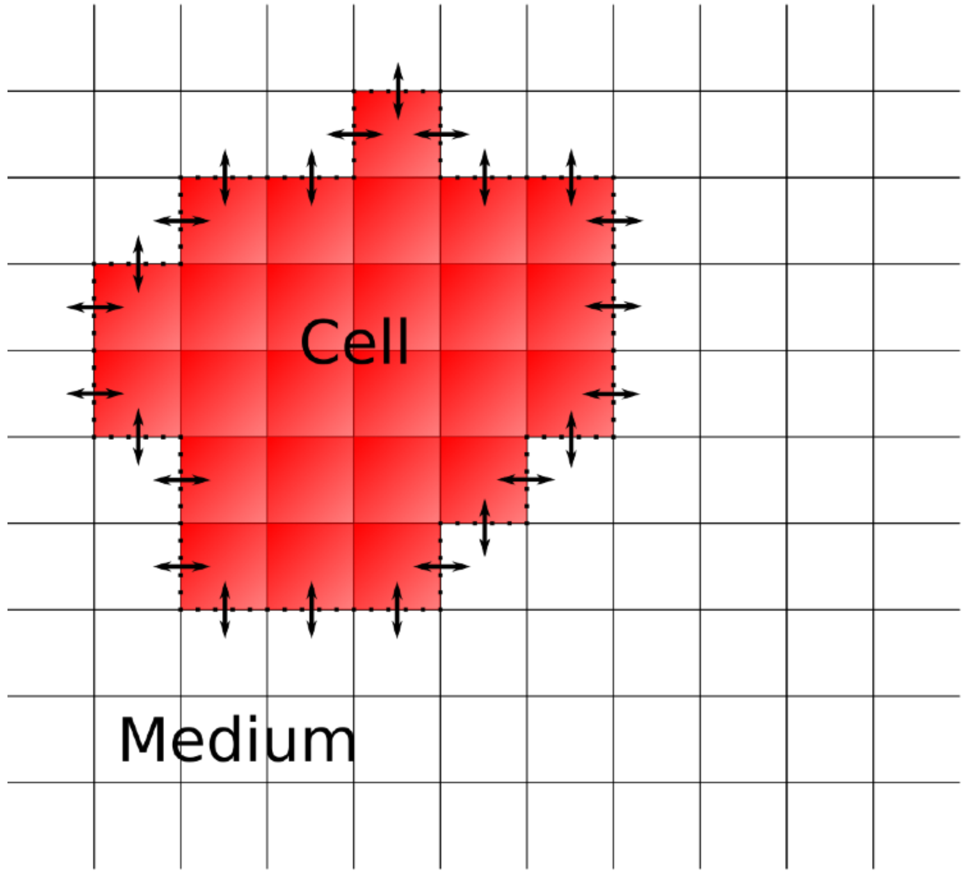
sum over interfaces

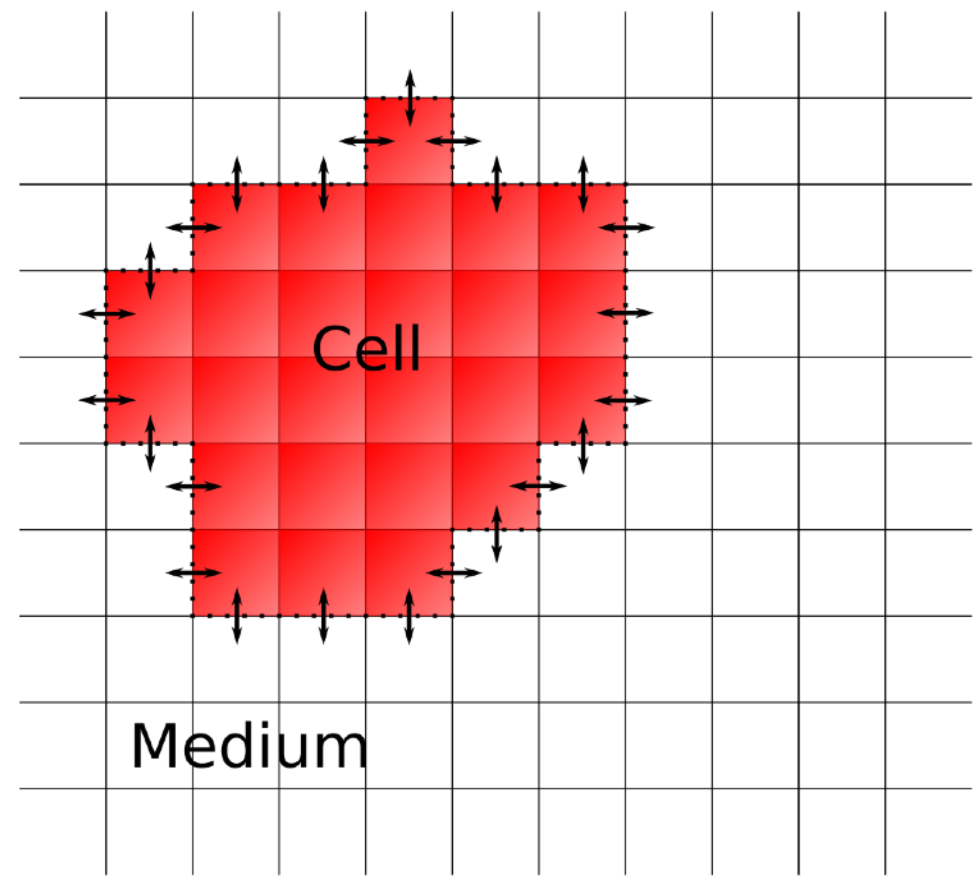


Cellular Potts model - contact energy

energy contact energy

$$H = \sum_{interfaces} J_{x,y}(1 - \delta_{x,y})$$

sum over interfaces between domains



Cellular Potts model - contact energy

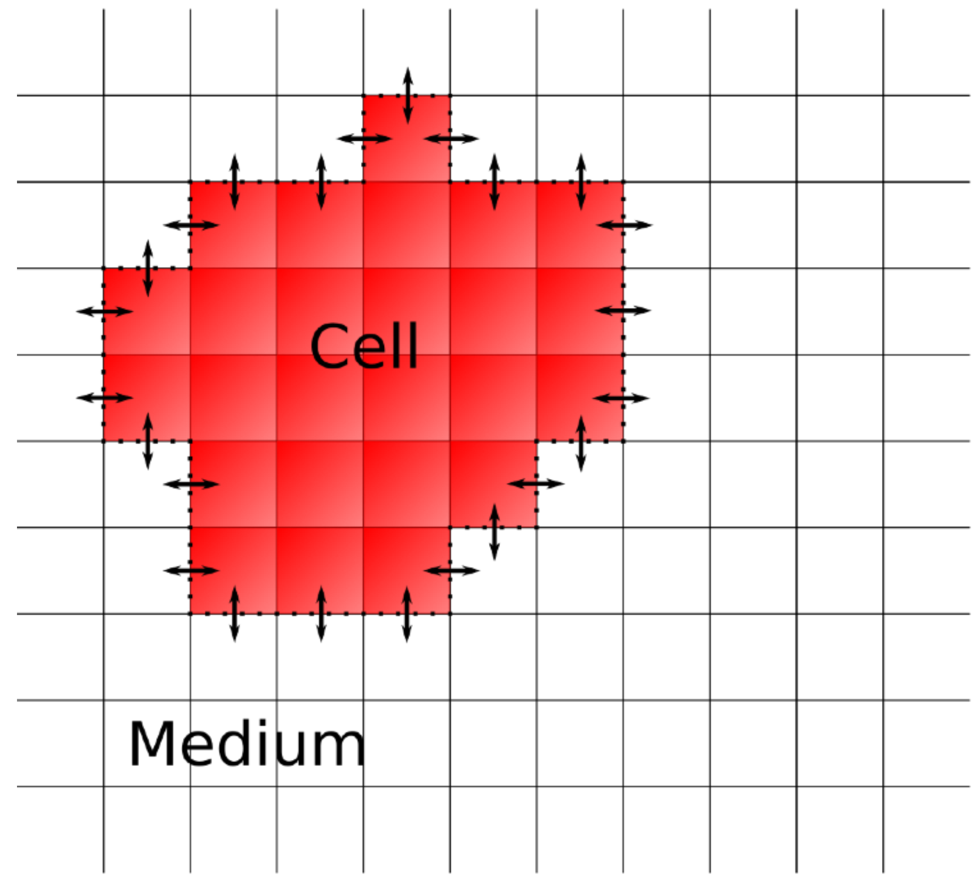
energy

contact energy

$$H = \sum_{interfaces} J_{x,y}(1 - \delta_{x,y})$$

sum over interfaces

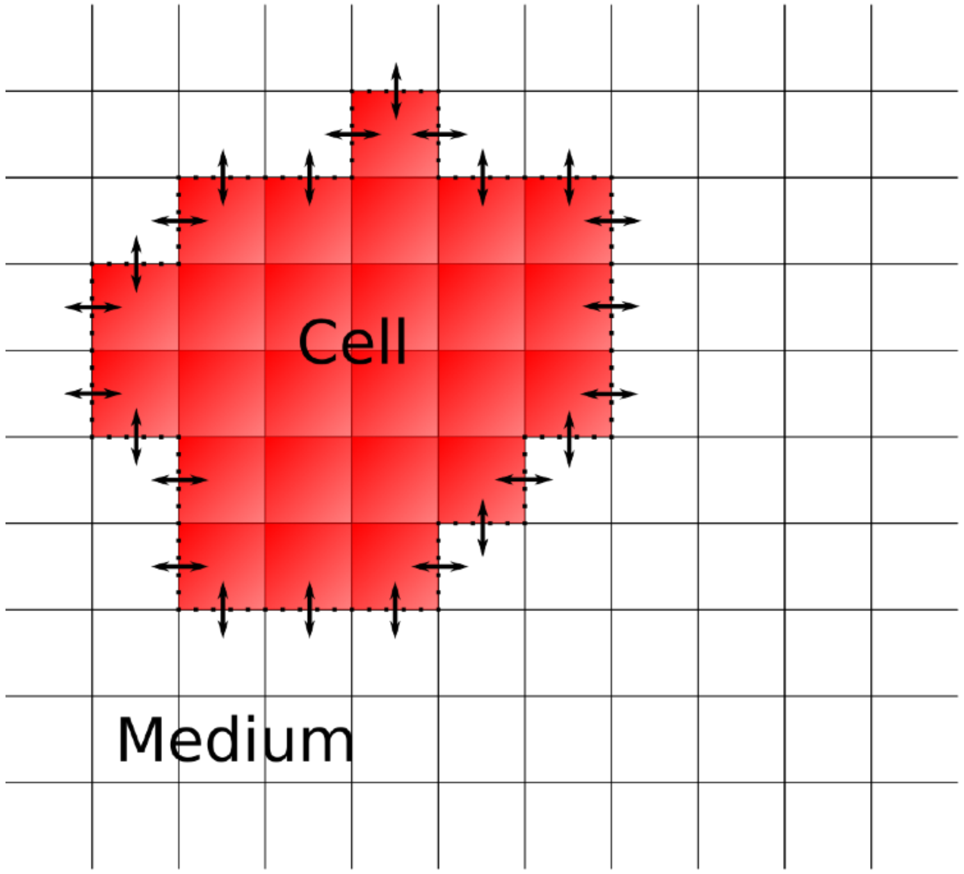
between domains



Contact	Cell	Medium
Cell	J_{CC}	J_{CM}
Medium	J_{CM}	—

Cellular Potts model - energy function

$$H = \sum_{interfaces} J_{x,y}(1 - \delta_{x,y}) + \sum_{cells} \lambda_A (a_\sigma - A_\sigma)^2$$



Cellular Potts model - energy function

energy

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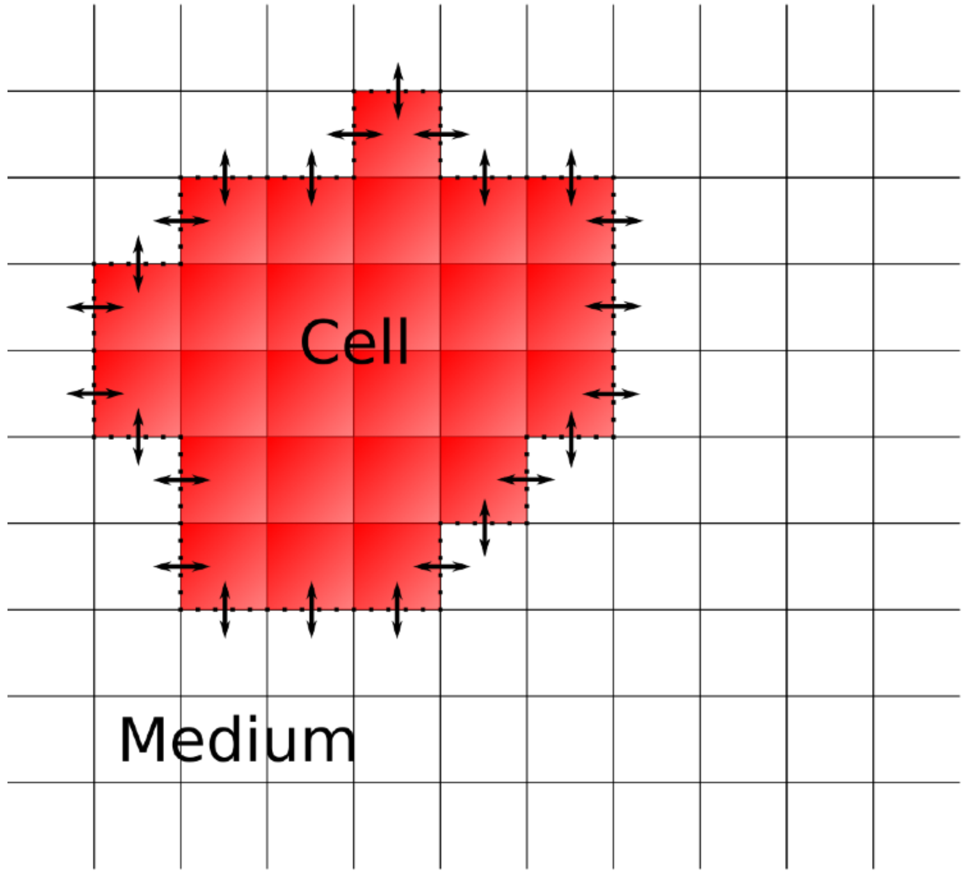
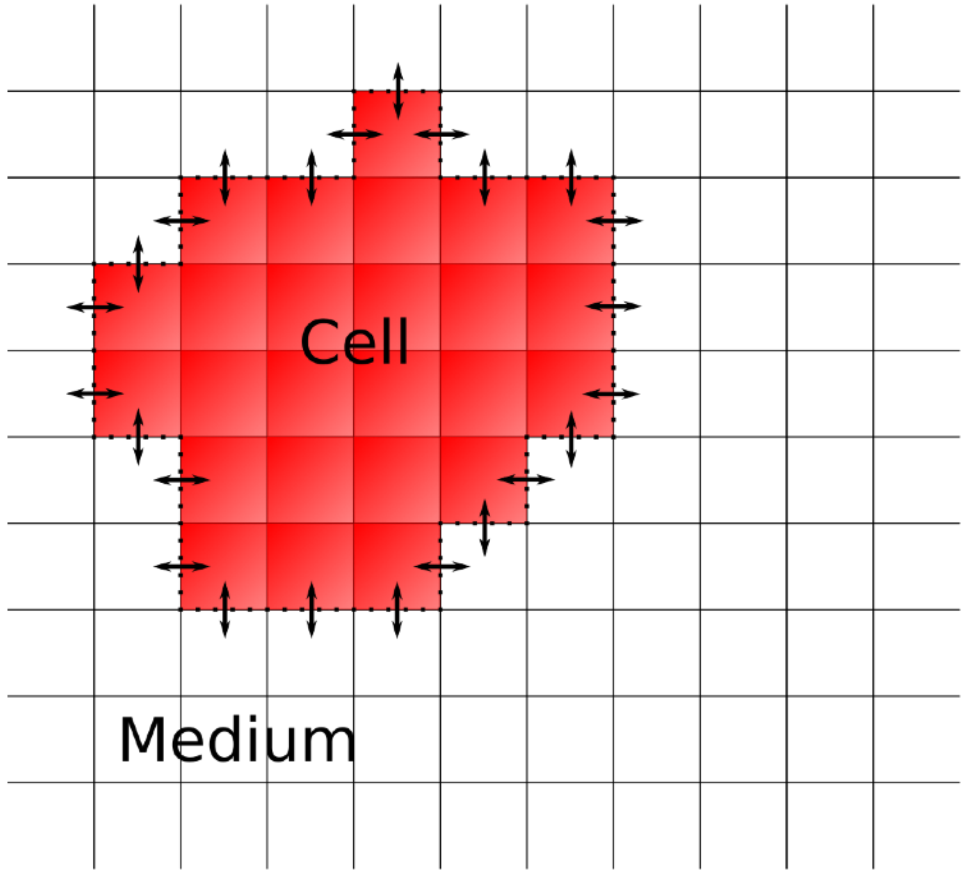


Cellular Potts model - energy function

energy

adhesion

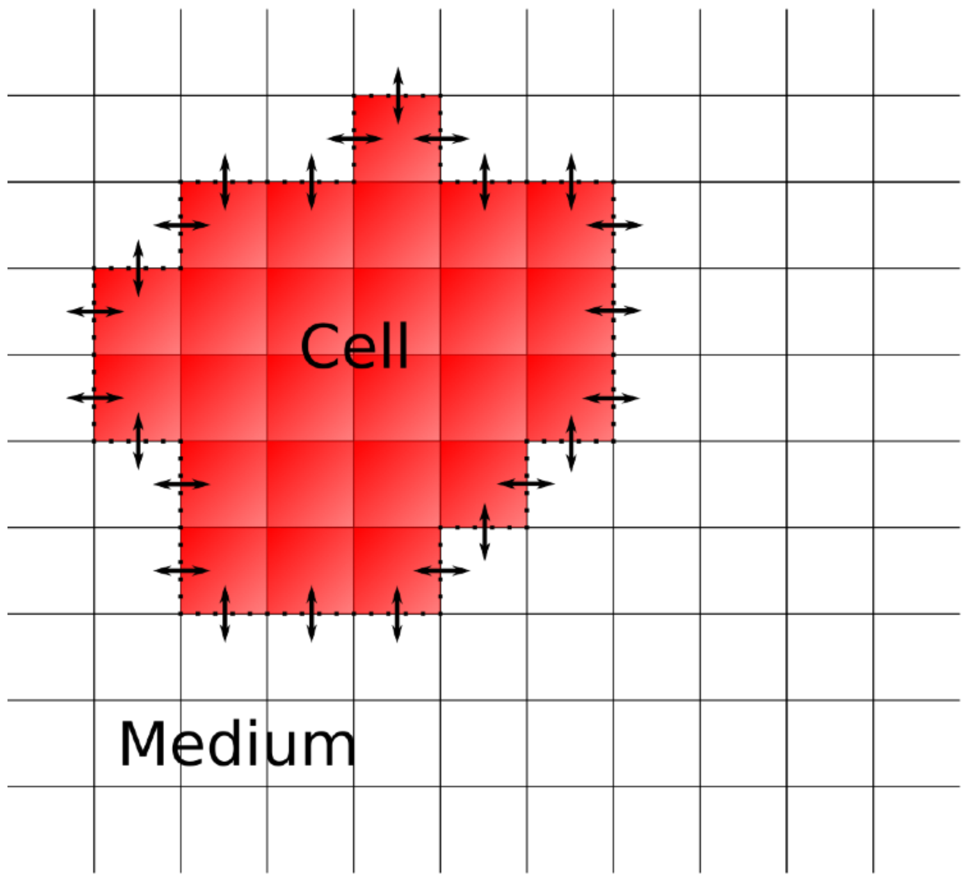
$$H = \sum_{interfaces} J_{x,y}(1 - \delta_{x,y}) + \sum_{cells} \lambda_A (a_\sigma - A_\sigma)^2$$



Cellular Potts model - energy function

energy — adhesion — area constraint

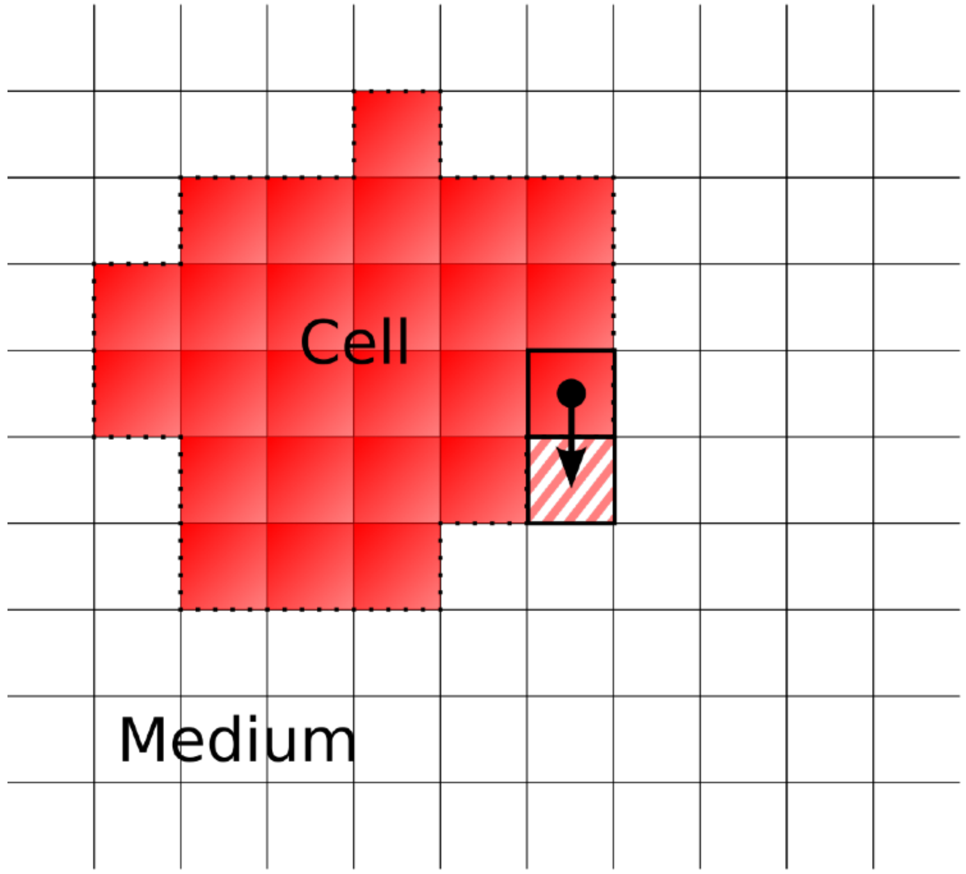
$$H = \sum_{interfaces} J_{x,y}(1-\delta_{x,y}) + \sum_{cells} \lambda_A (a_\sigma - A_\sigma)^2$$



Cellular Potts model - dynamics

Stochastic minimization of energy

Modified Metropolis algorithm:



Cellular Potts model - dynamics

Stochastic minimization of energy

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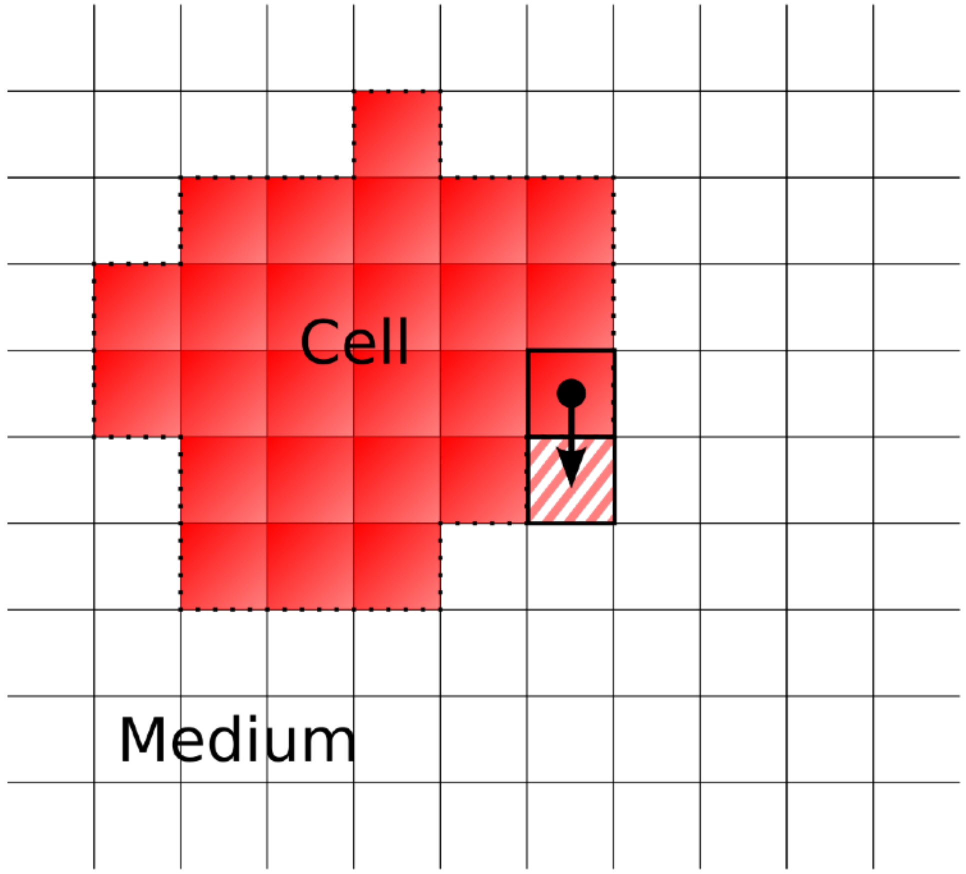
- Pick a random node

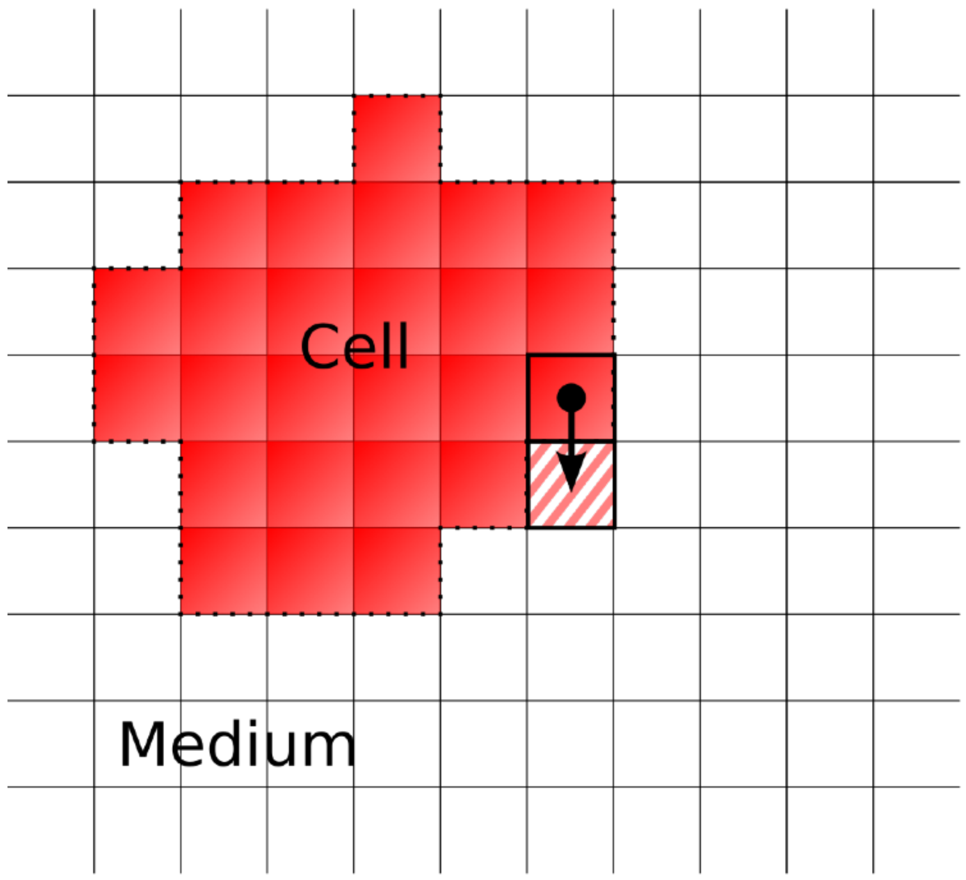


Cellular Potts model - dynamics

Stochastic minimization of energy

Modified Metropolis algorithm:

- Pick a random node
- Pick a second random node in neighborhood



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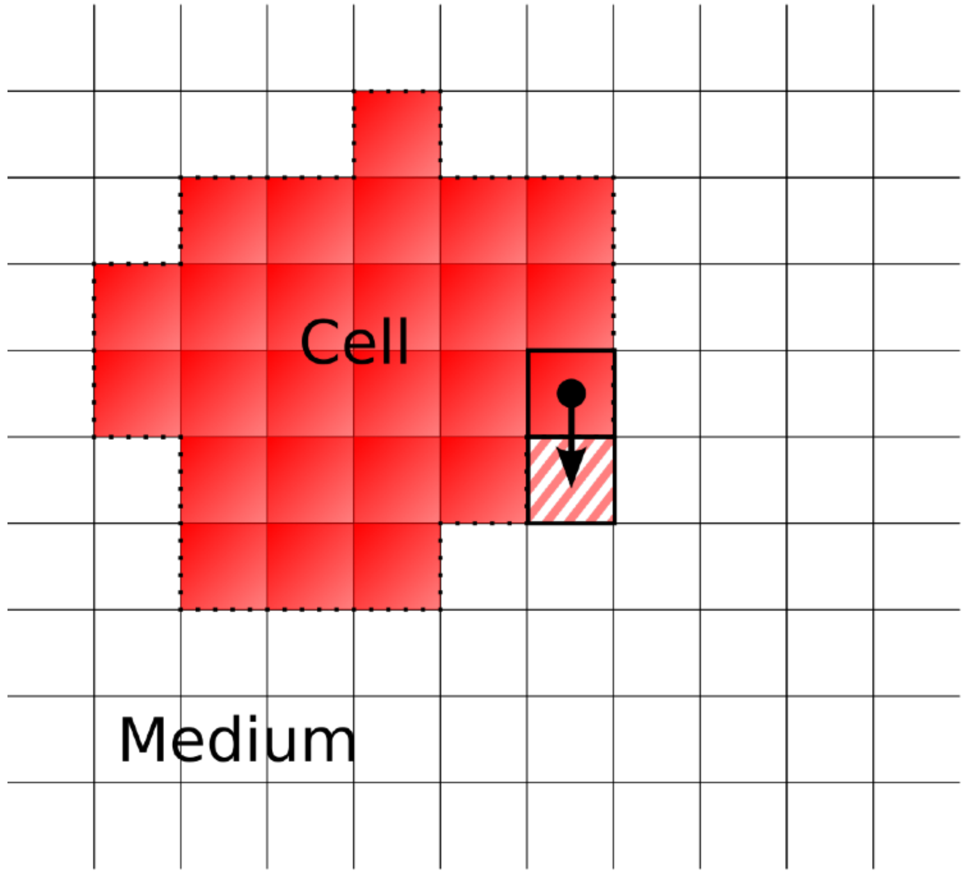

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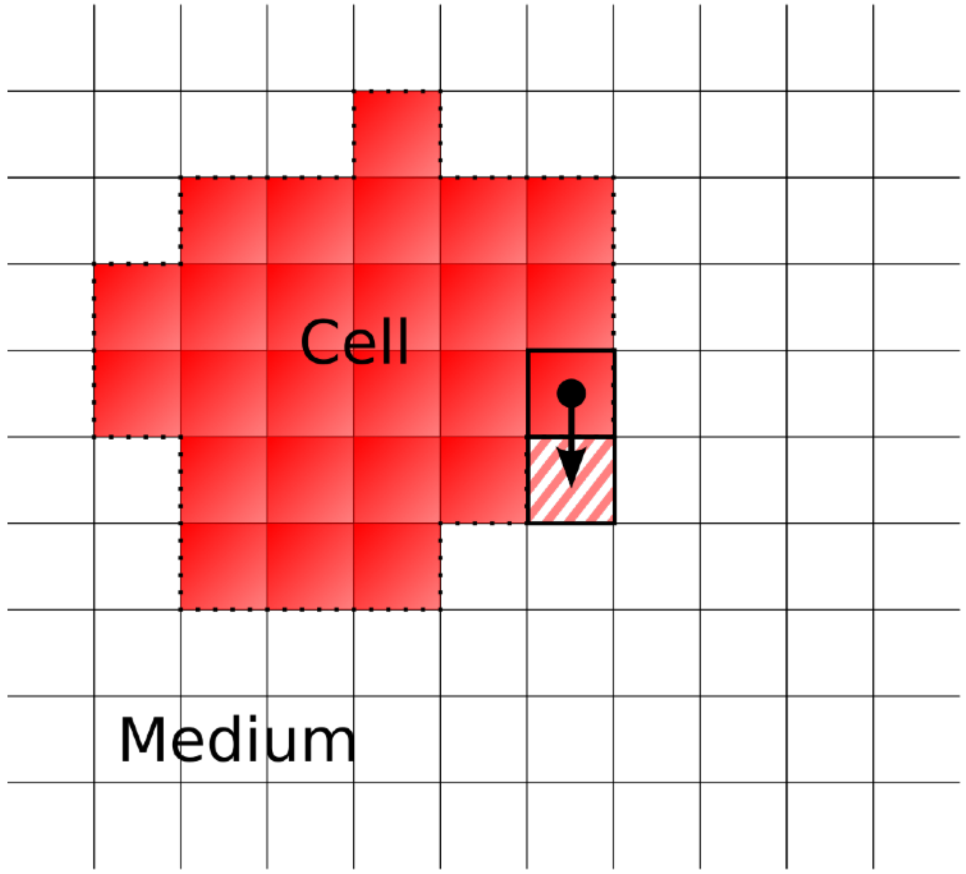

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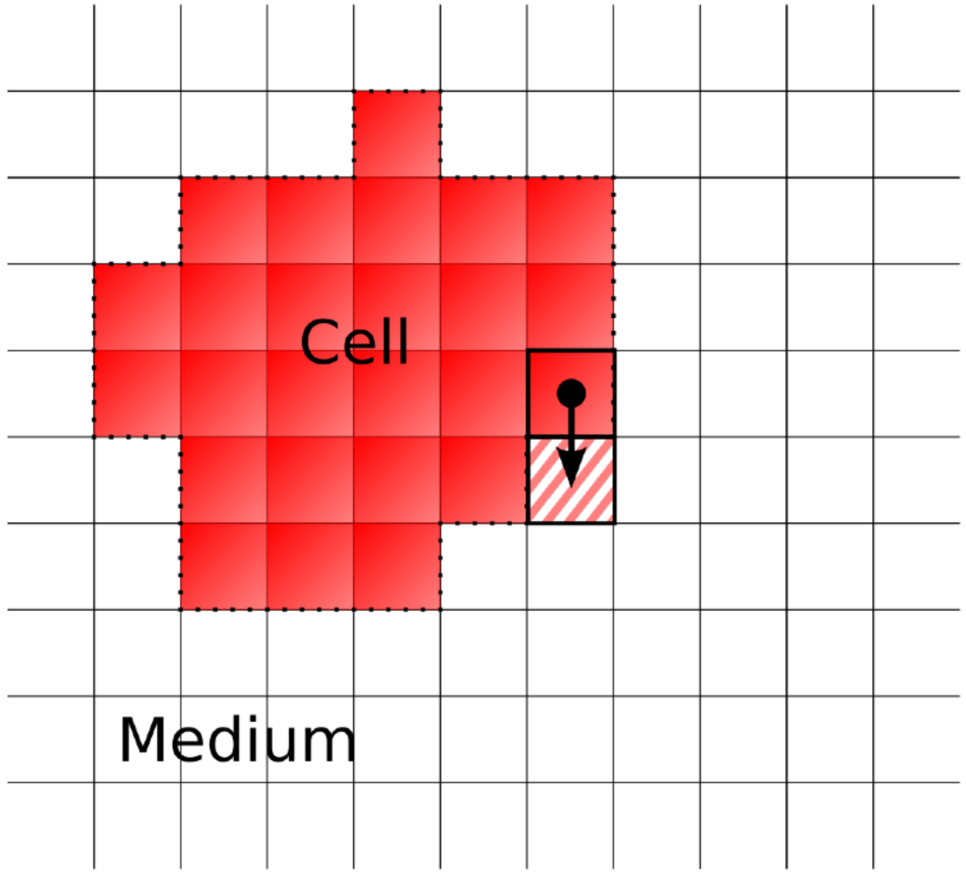

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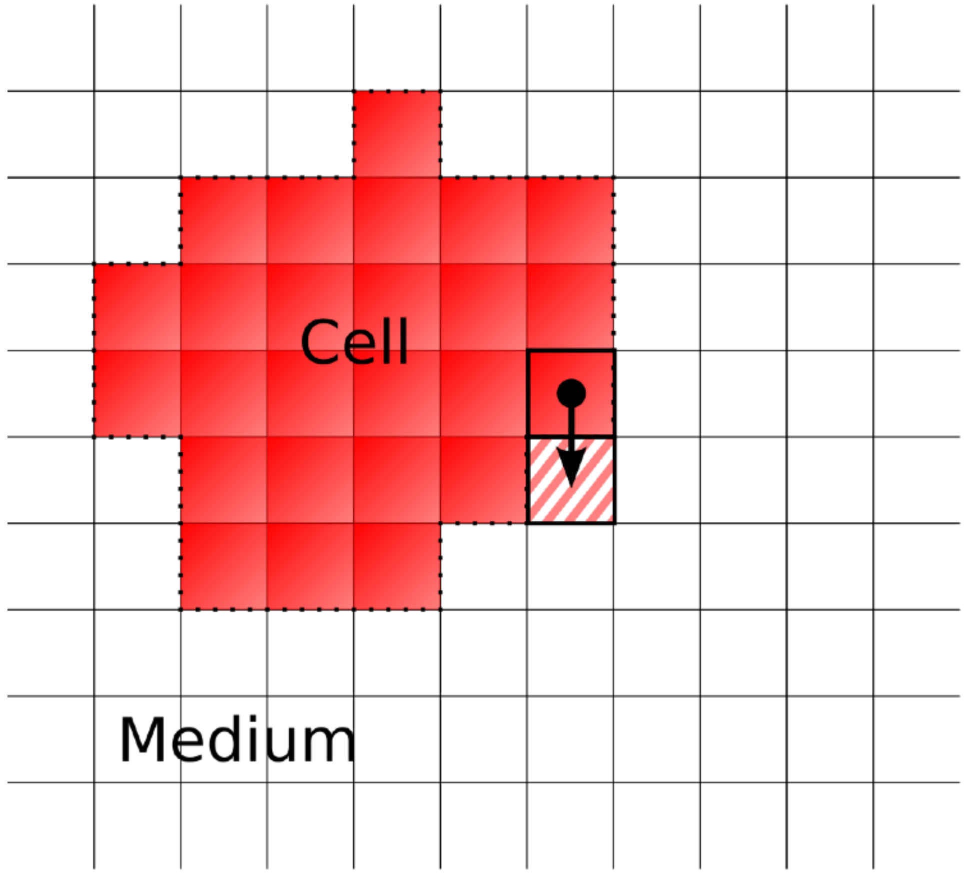

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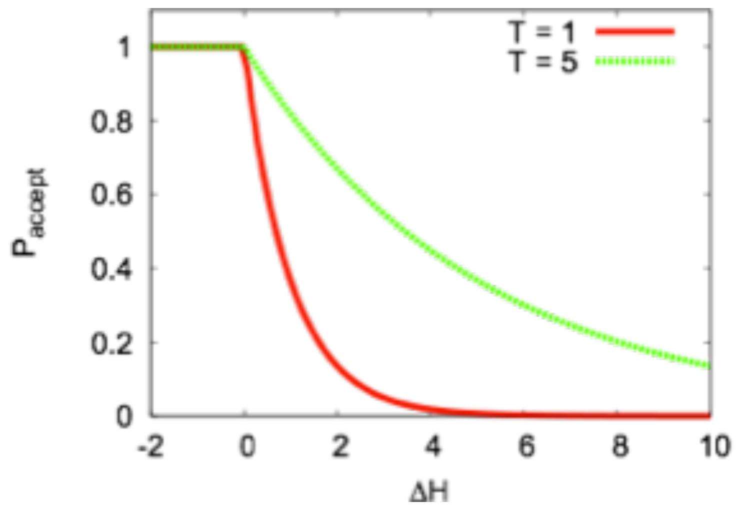

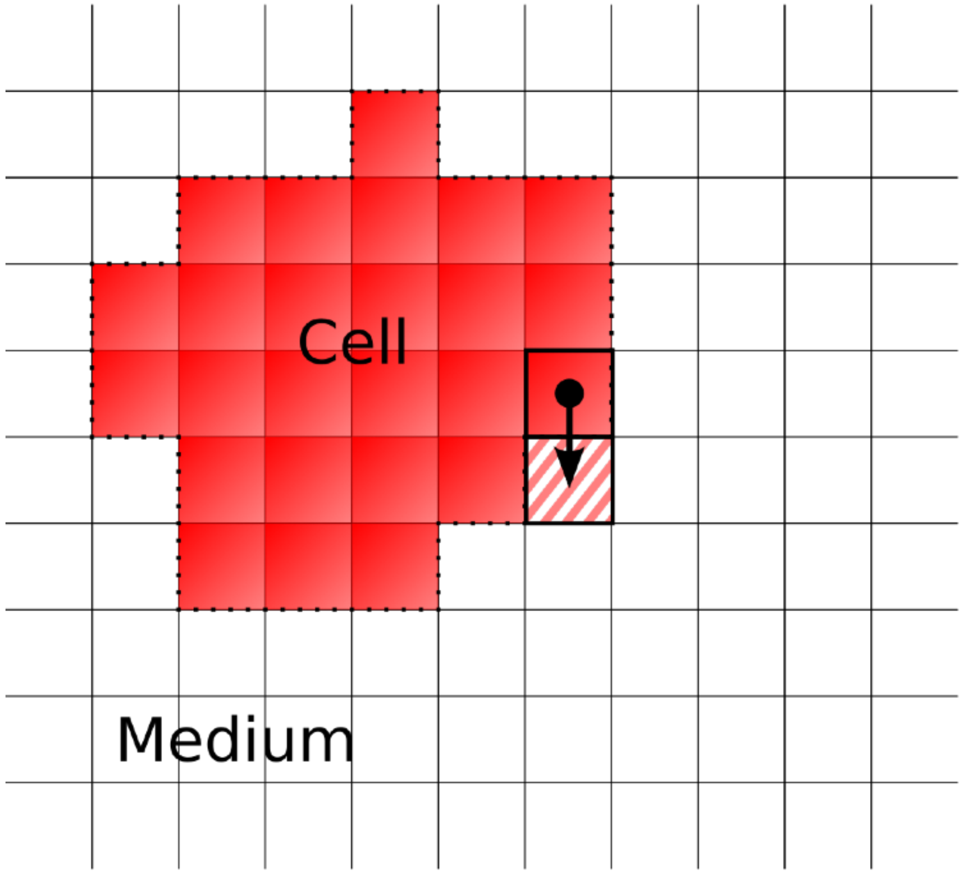

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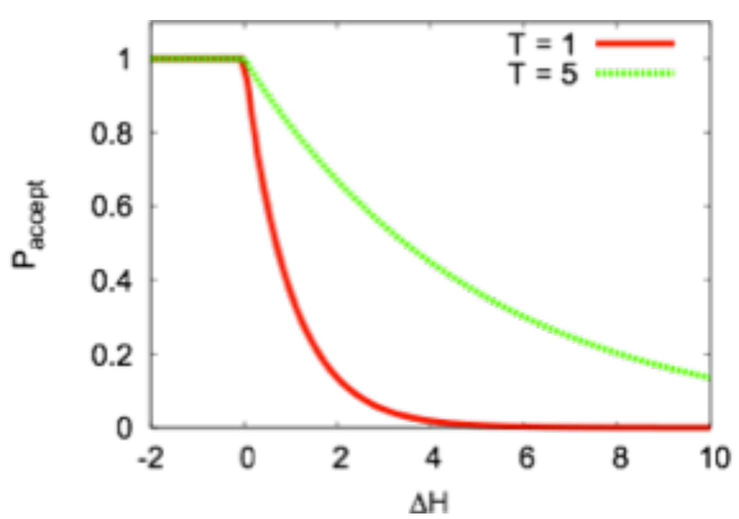

Cellular Potts model

Energy function (Hamiltonian):

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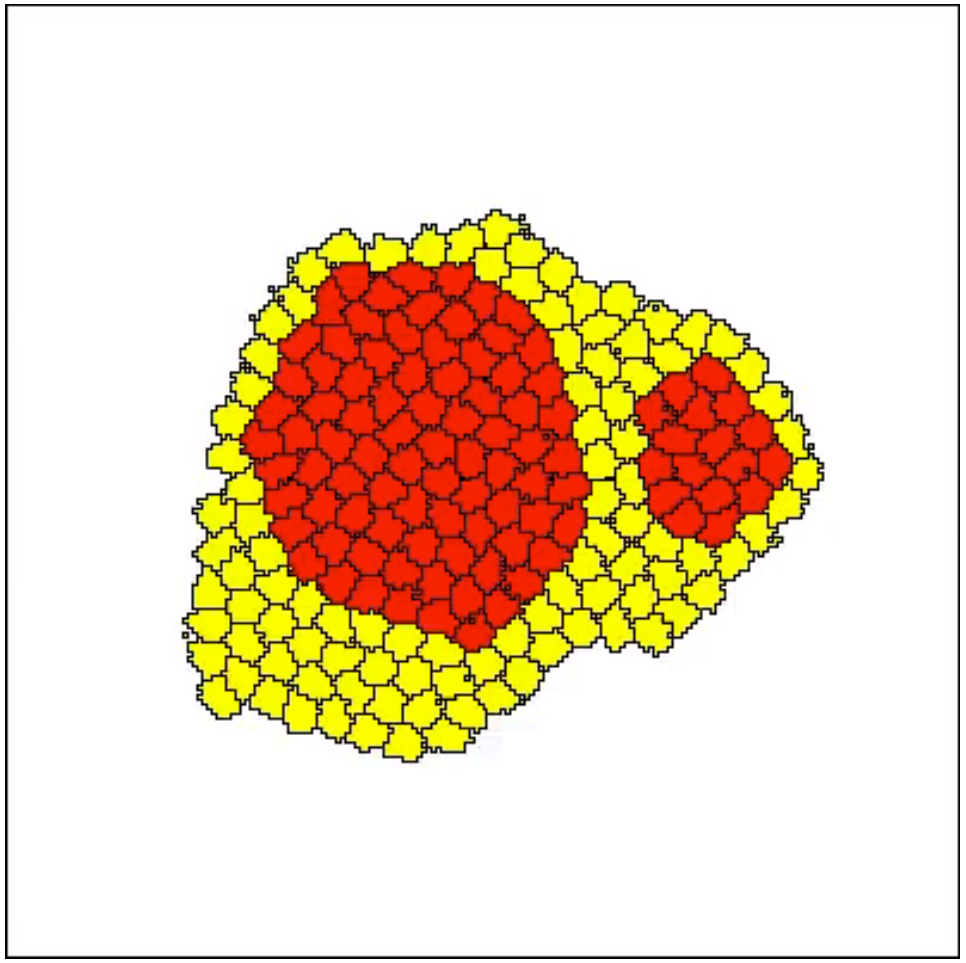

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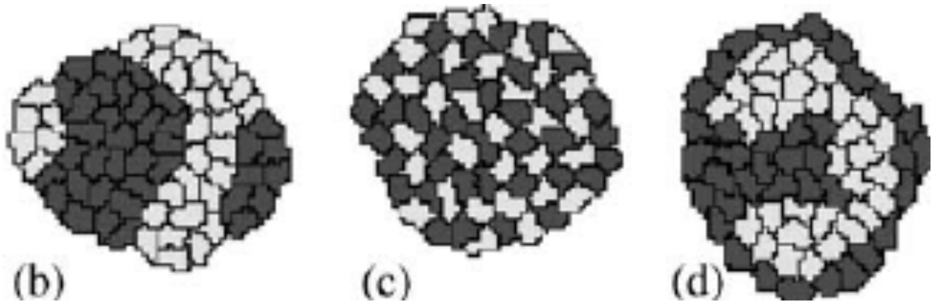

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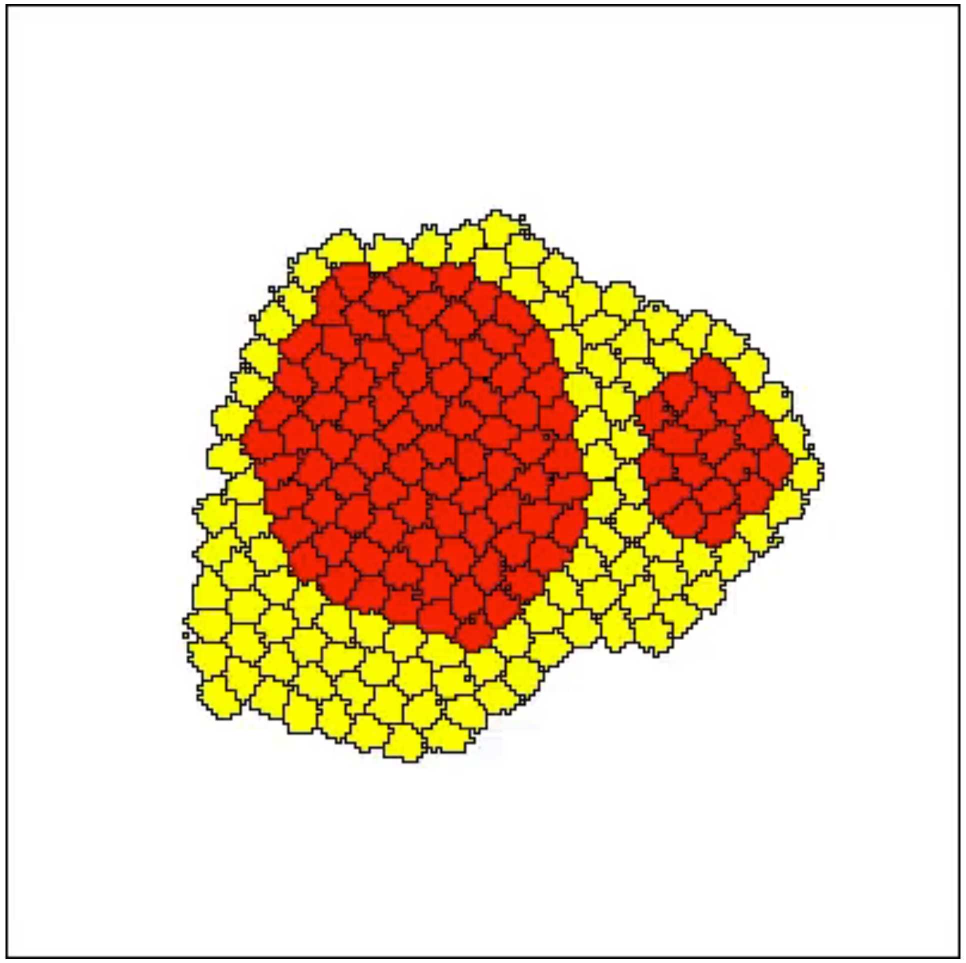

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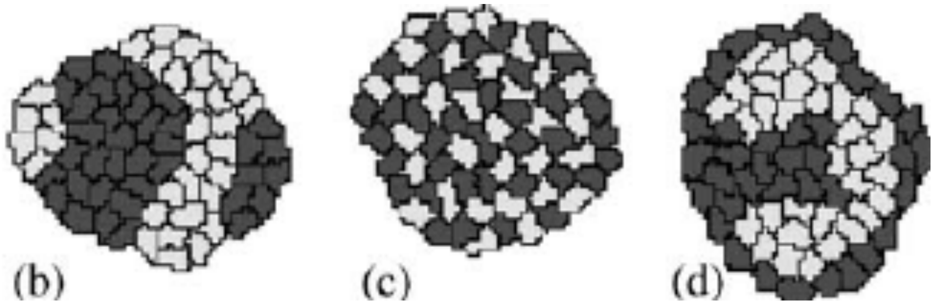
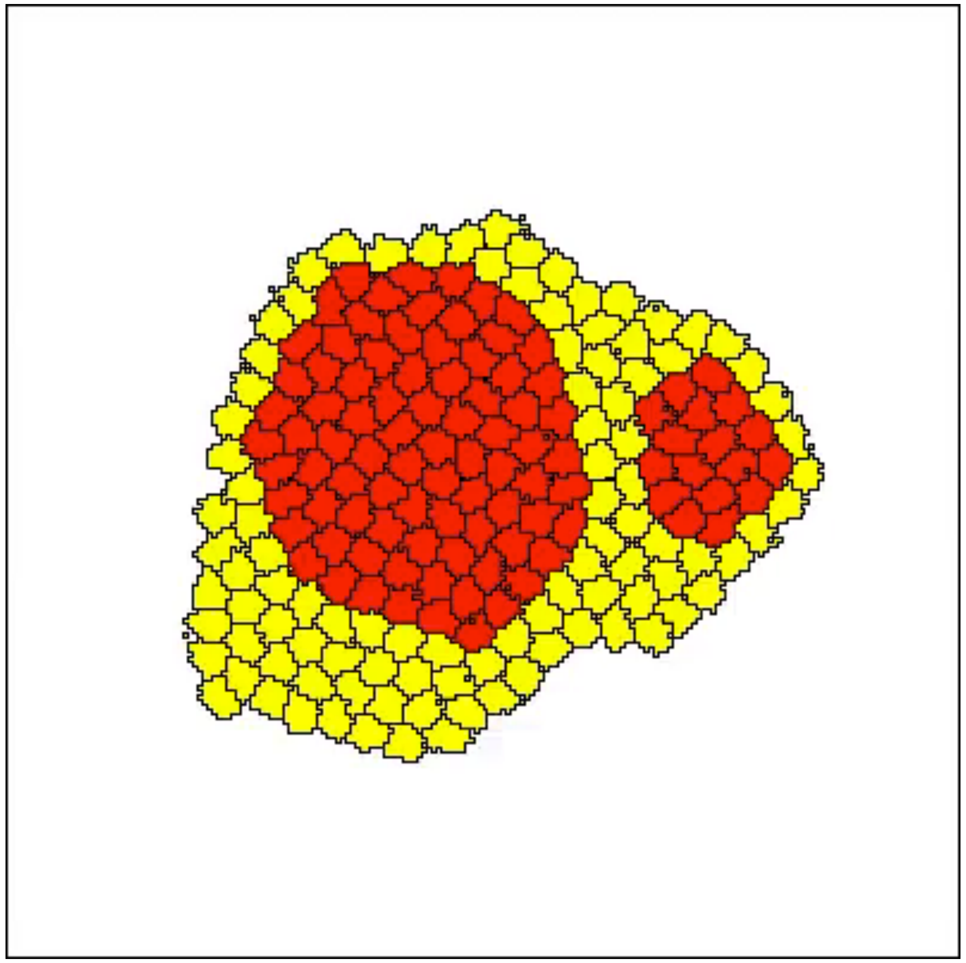


Cellular Potts model

Energy function (Hamiltonian):

energy

$$H = \sum_{interfaces} J_{x,y}(1-\delta_{x,y}) + \sum_{cells} \lambda_A (a_\sigma - A_\sigma)^2$$



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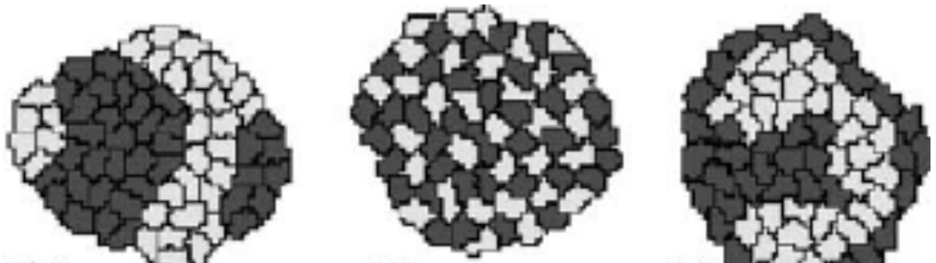

(b) (c) (d)

Cellular Potts model

Energy function (Hamiltonian):

energy adhesion

$$H = \sum_{interfaces} J_{x,y}(1-\delta_{x,y}) + \sum_{cells} \lambda_A (a_\sigma - A_\sigma)^2$$

Energy minimization:

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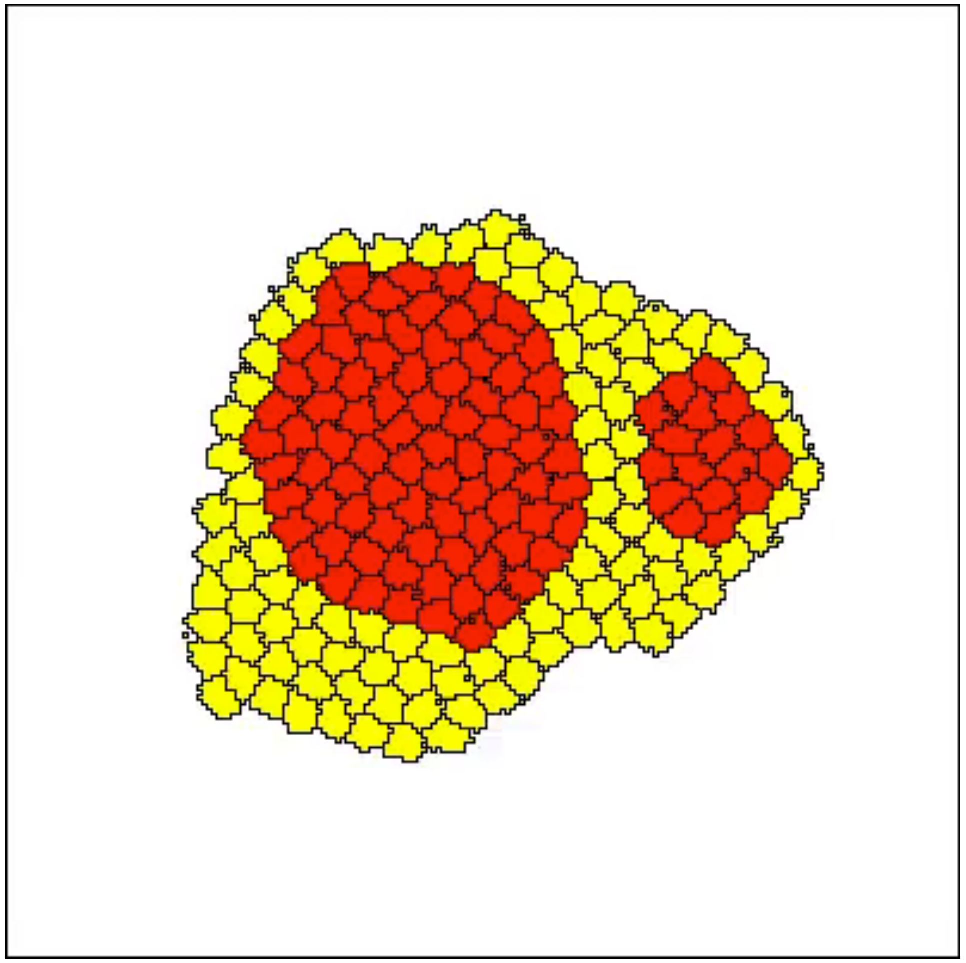

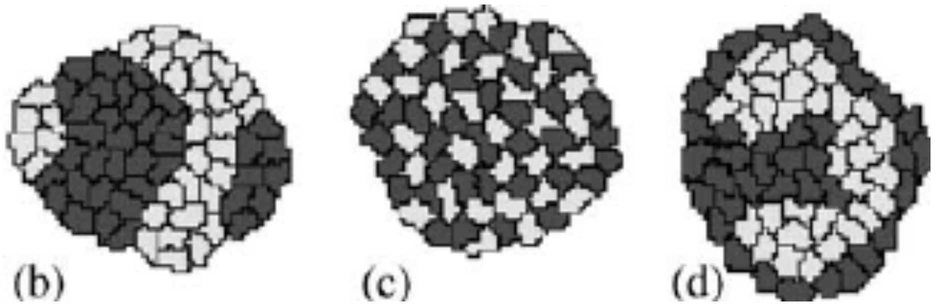

Cellular Potts model

Energy function (Hamiltonian):

$$\underbrace{H}_{\text{energy}} = \underbrace{\sum_{interfaces} J_{x,y}(1-\delta_{x,y})}_{\text{adhesion}} + \underbrace{\sum_{cells} \lambda_A (a_\sigma - A_\sigma)^2}_{\text{area constraint}}$$

Energy minimization:

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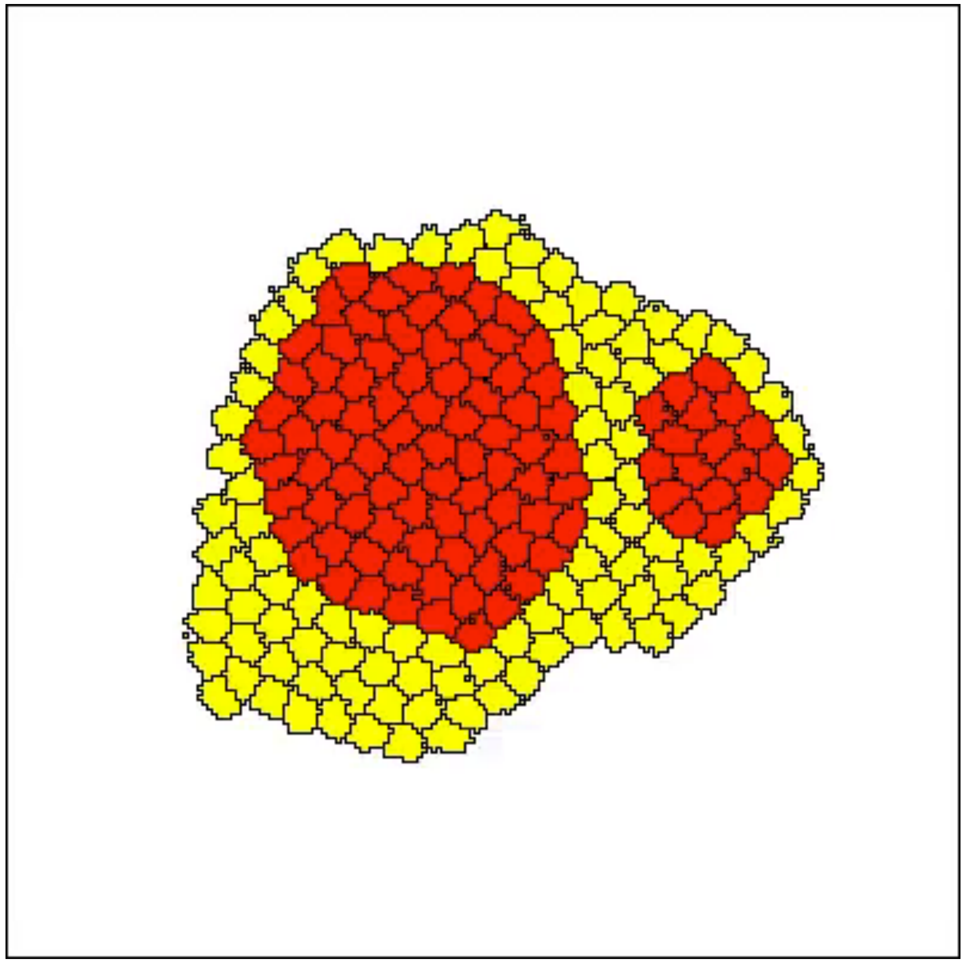

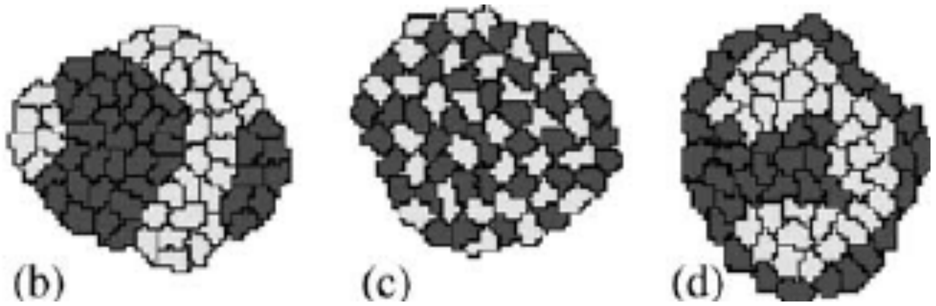

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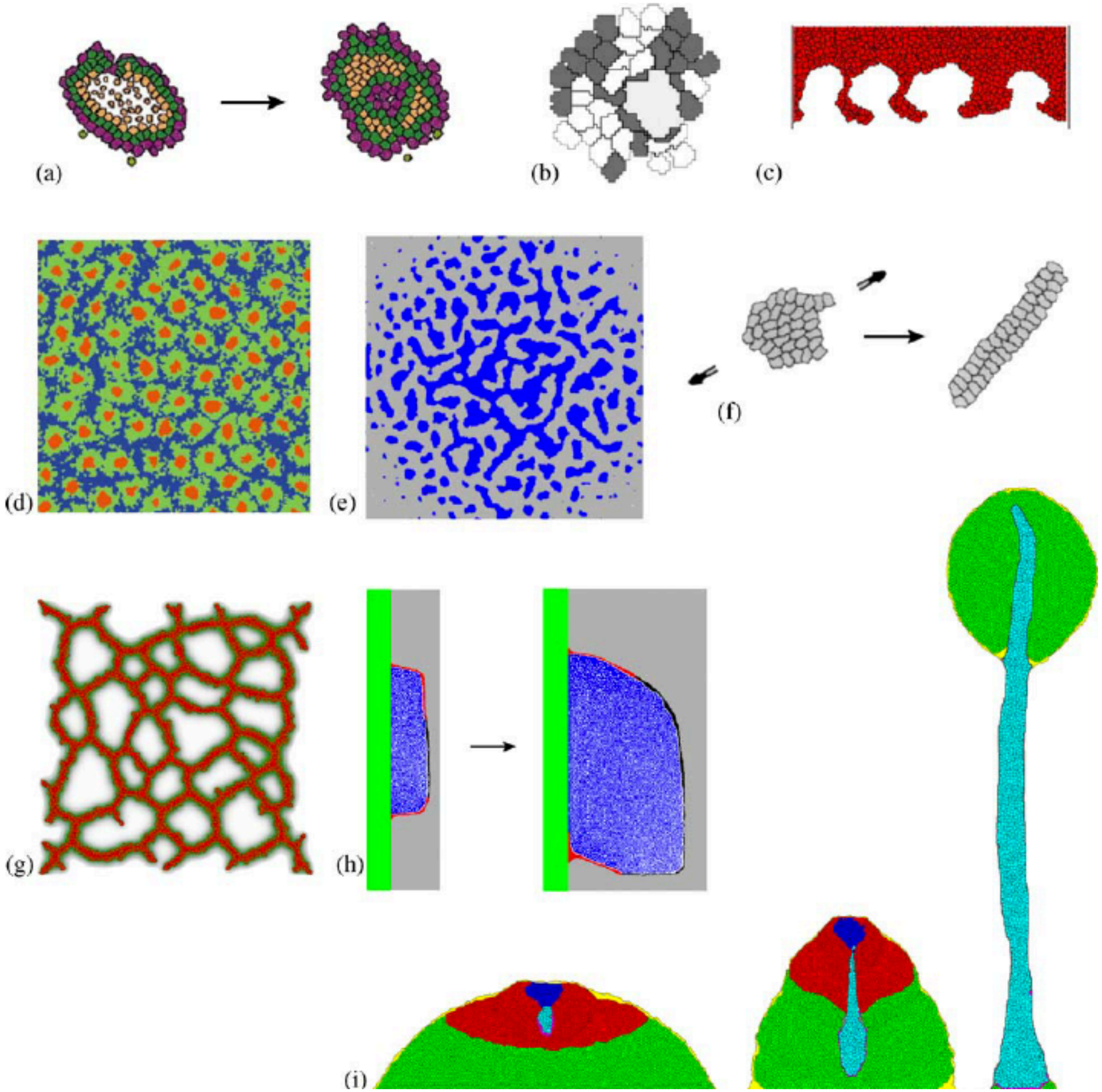
Cellular Potts model

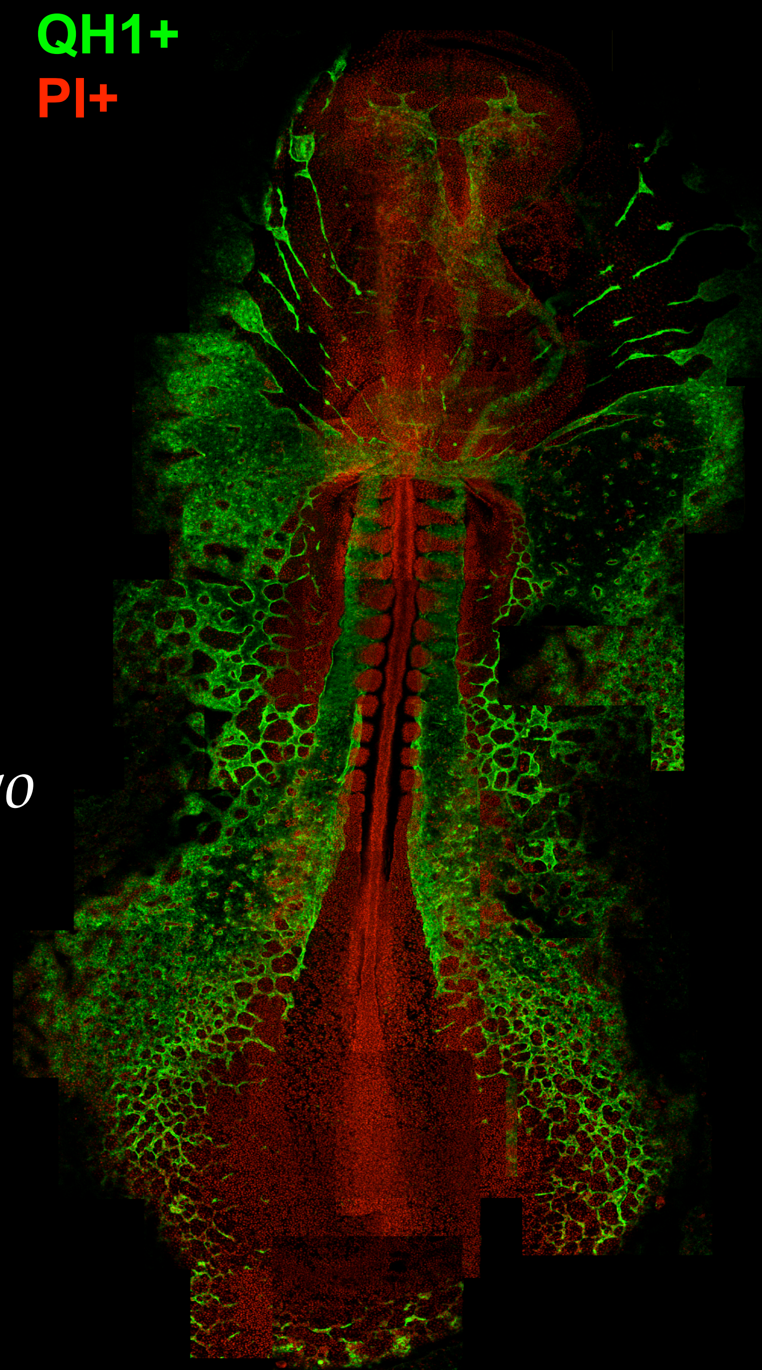


Merks, R.M. and Glazier, J.A., 2005. *A cell-centered approach to developmental biology.* Physica A. 352(1), pp.113-130.

Vascular patterning

Example study

How do cells
form a blood vessel network?

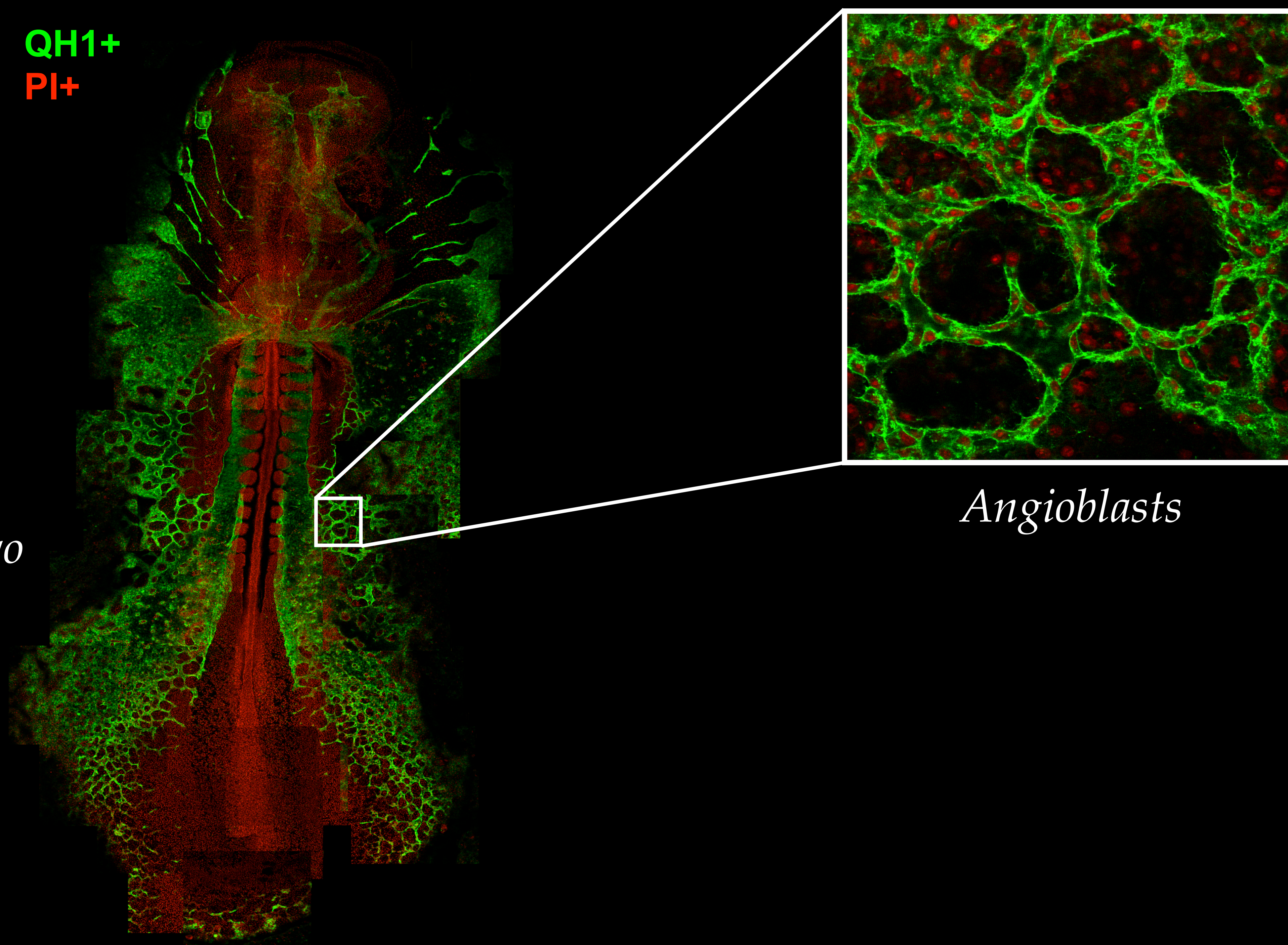


Quail embryo
HH stage 11

Perez-Pomares lab, Malaga

How do cells form a blood vessel network?

Quail embryo
HH stage 11

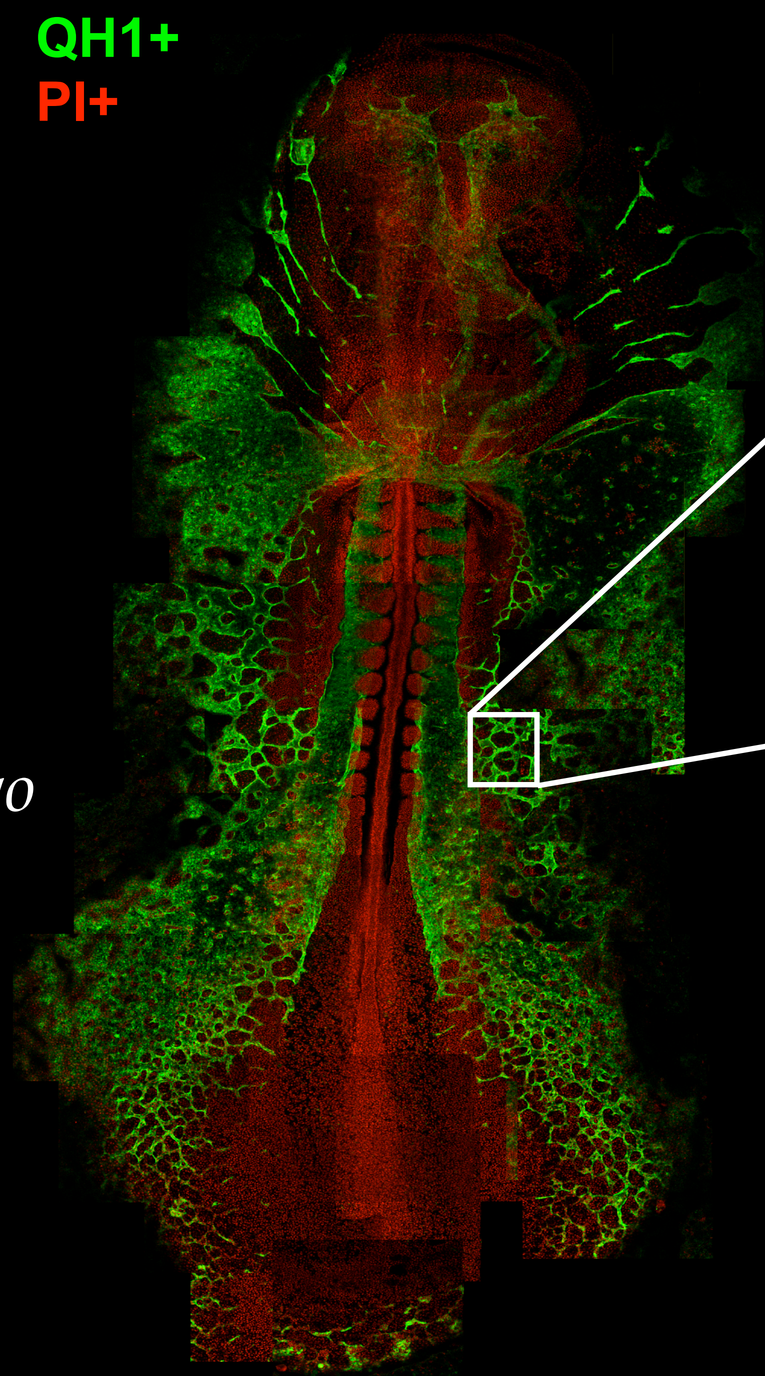


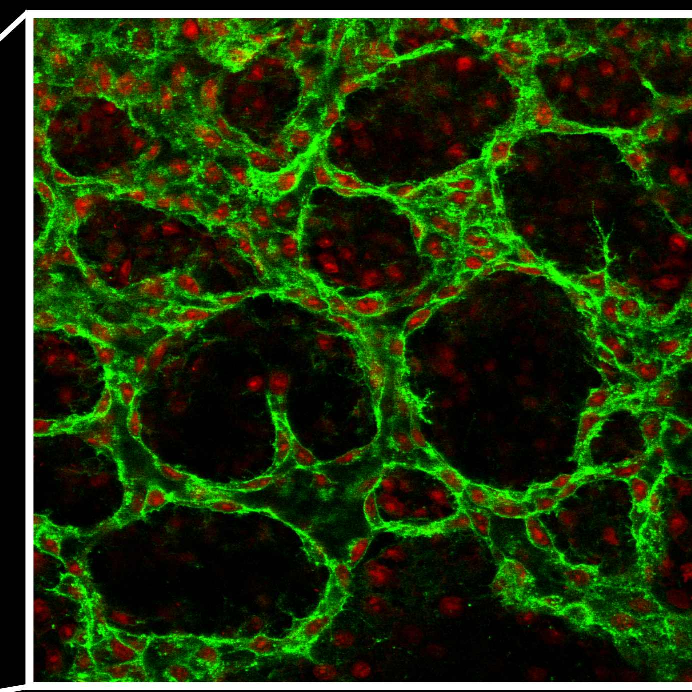
Angioblasts

Perez-Pomares lab, Malaga

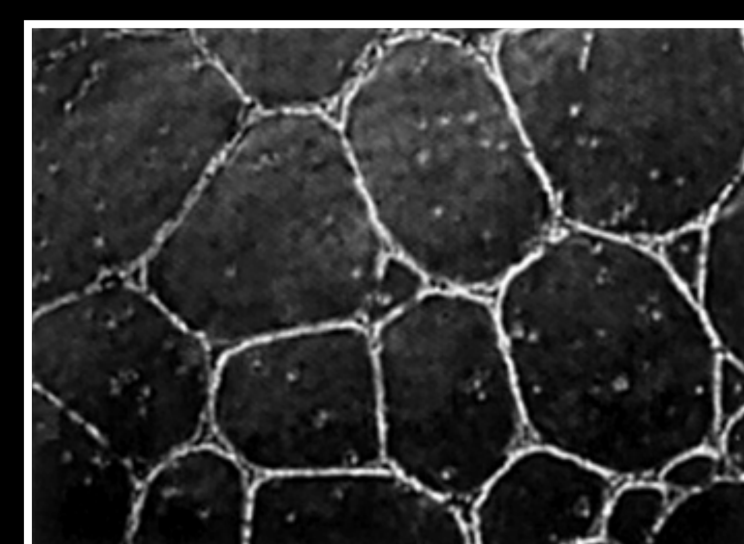
How do cells form a blood vessel network?

Quail embryo
HH stage 11





Angioblasts



HUVEC in Matrigel

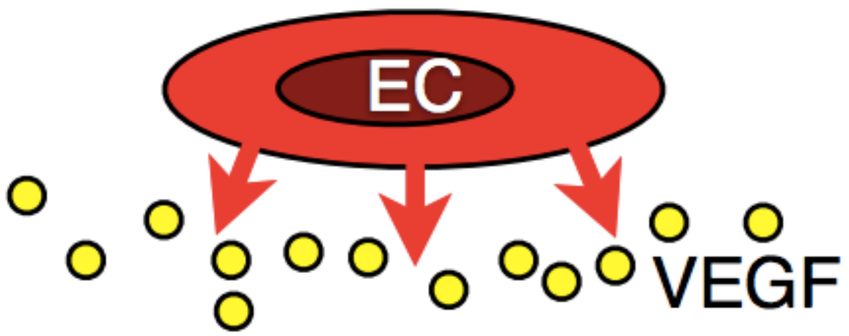
Perez-Pomares lab, Malaga

Wang et al., 2003

Chemotaxis model of vascular network formation

Autocrine chemotaxis model

VEGF = Vascular endothelial growth factor



- Angioblasts produce VEGF
- Angioblasts migrate towards VEGF

Chemotaxis model of vascular network formation

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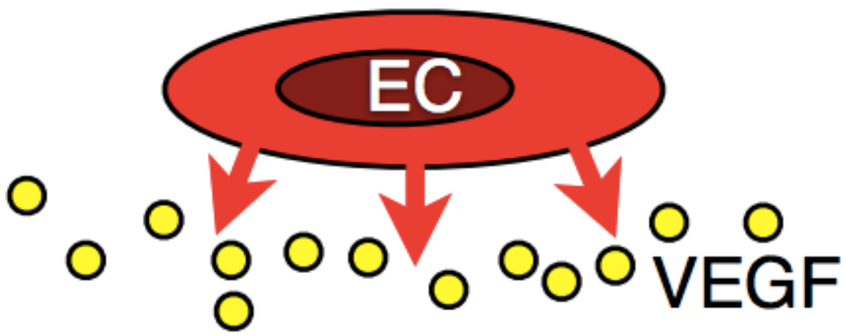

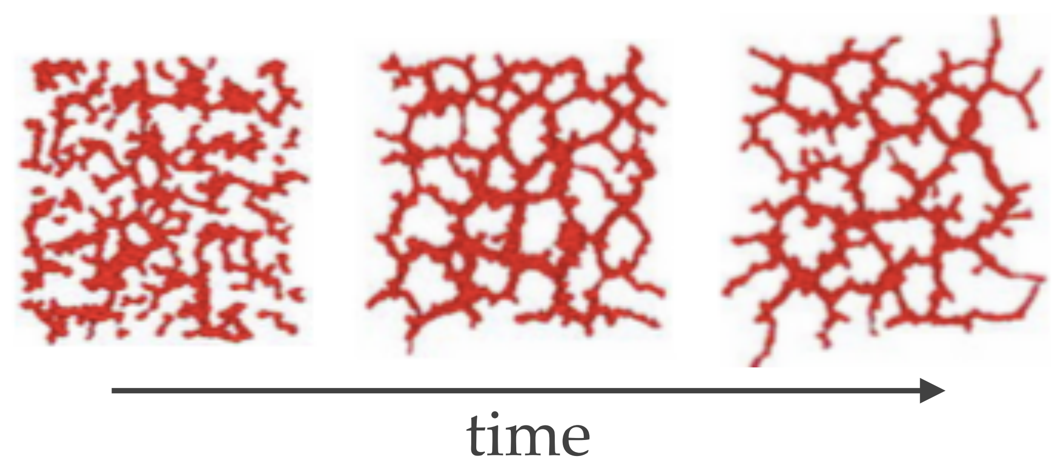

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Merks et al., 2008

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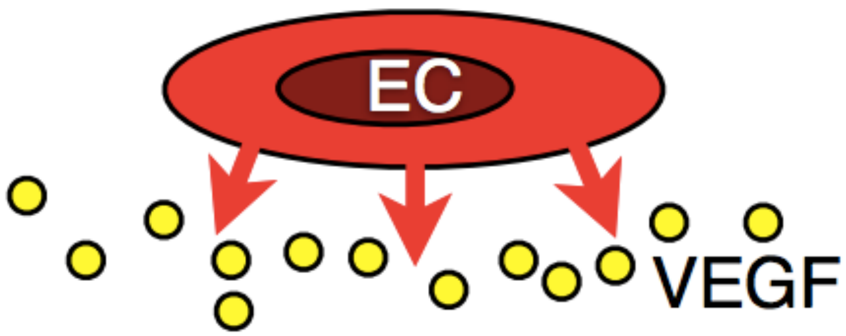

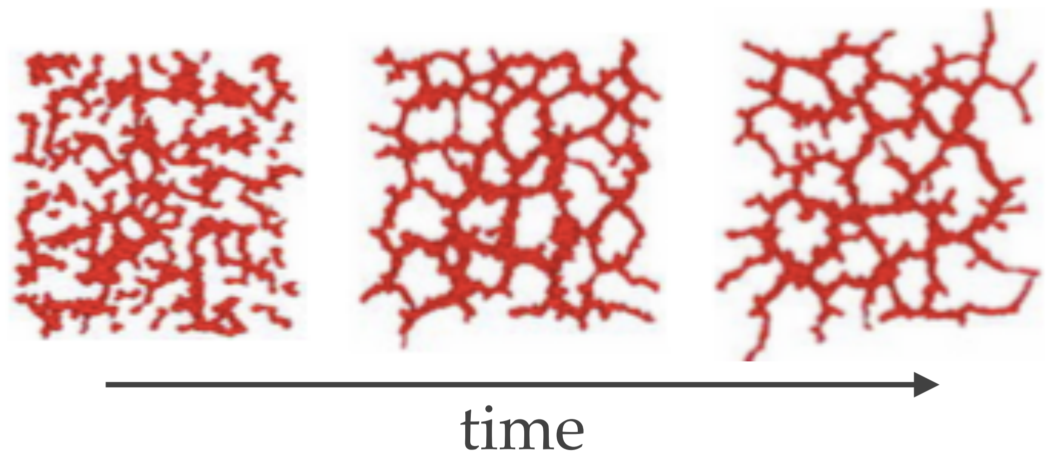

- Angioblasts produce VEGF
- Angioblasts migrate towards VEGF

However:

- Little evidence for VEGF production
- Unrealistically low diffusion rate

Merks et al., 2008

Chemotaxis model of vascular network formation

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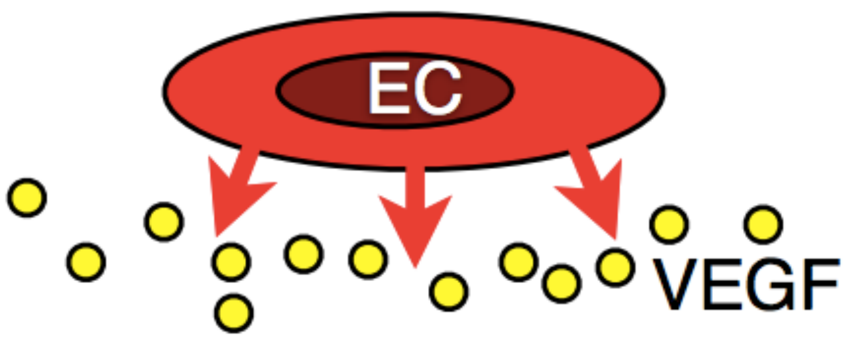


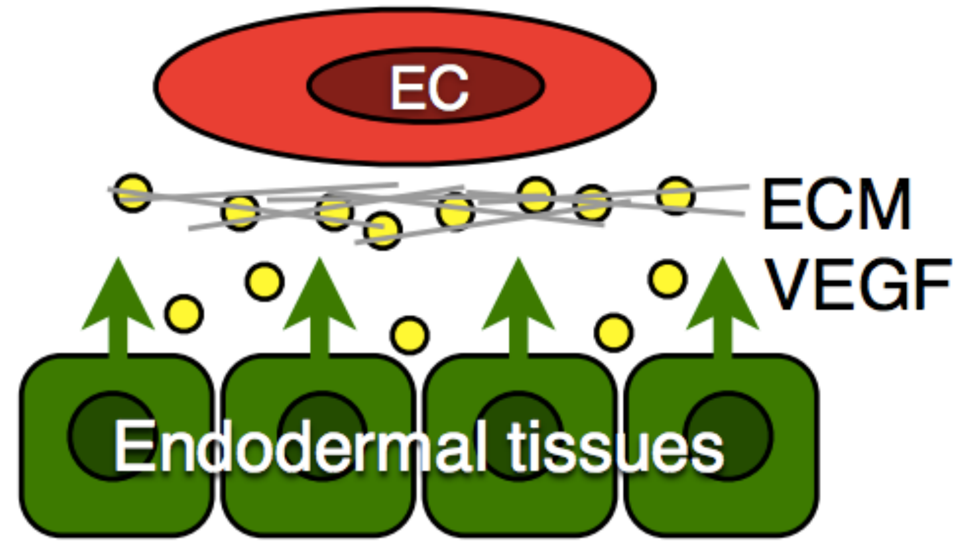
- Angioblasts produce VEGF
- Angioblasts migrate towards VEGF

However:

- Little evidence for VEGF production
- Unrealistically low diffusion rate

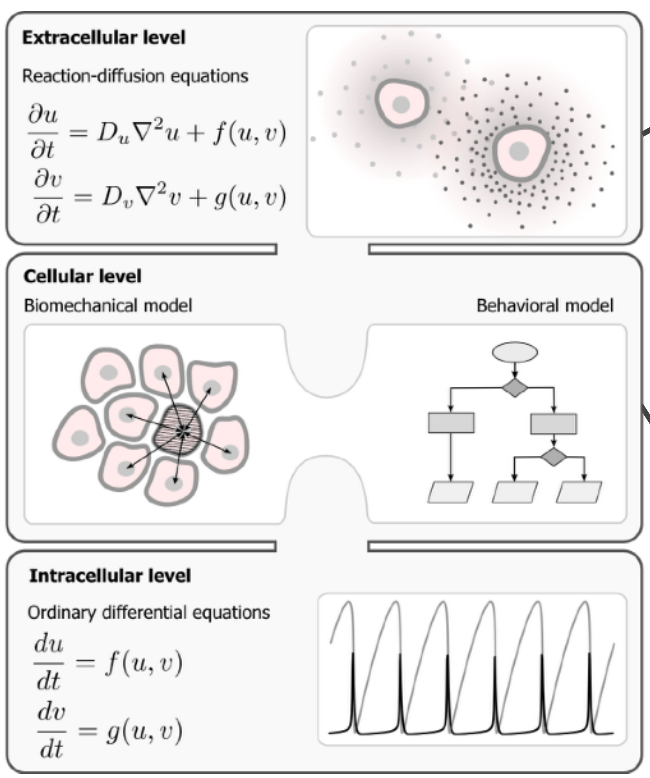
Paracrine chemotaxis model

ECM = Extra-cellular matrix



- Endoderm produces VEGF
- Angioblasts modify ECM
- VEGF binds to modified ECM
- Angioblasts migrate to bound VEGF

Modeling approach



Extracellular level

Spatiotemporal dynamics of VEGF

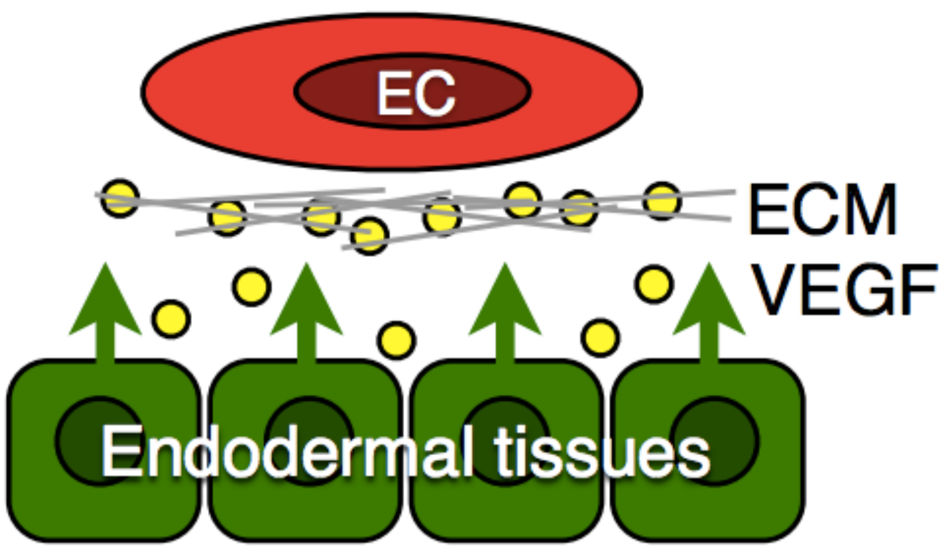
Cellular level

Chemotactic behavior of angioblasts

Spatiotemporal dynamics of VEGF

Reaction-diffusion model

$$\mathrm{VEGF} + \mathrm{ECM} \rightarrow \mathrm{VEGF_b}$$

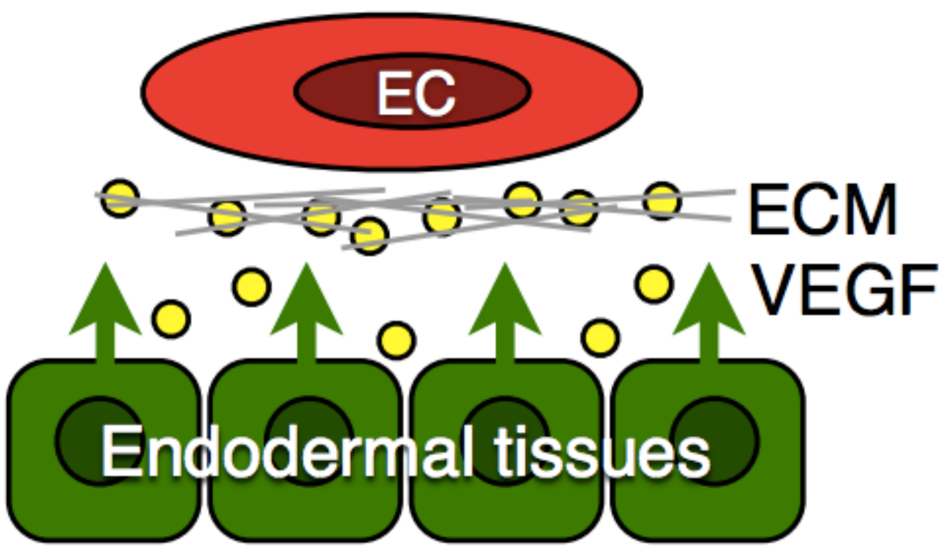


$$\begin{array}{lrcl}
\mathrm{VEGF_s} & \dfrac{\partial u}{\partial t} & = & D\Delta u + \gamma_1 - f(u,v) - \delta u \\
\mathrm{ECM} & \dfrac{\partial v}{\partial t} & = & \gamma_2 \delta_{\sigma_{x,0}} - f(u,v) \\
\mathrm{VEGF_b} & \dfrac{\partial w}{\partial t} & = & f(u,v)
\end{array}$$

Spatiotemporal dynamics of VEGF

Reaction-diffusion model

$$\mathrm{VEGF} + \mathrm{ECM} \rightarrow \mathrm{VEGF_b}$$



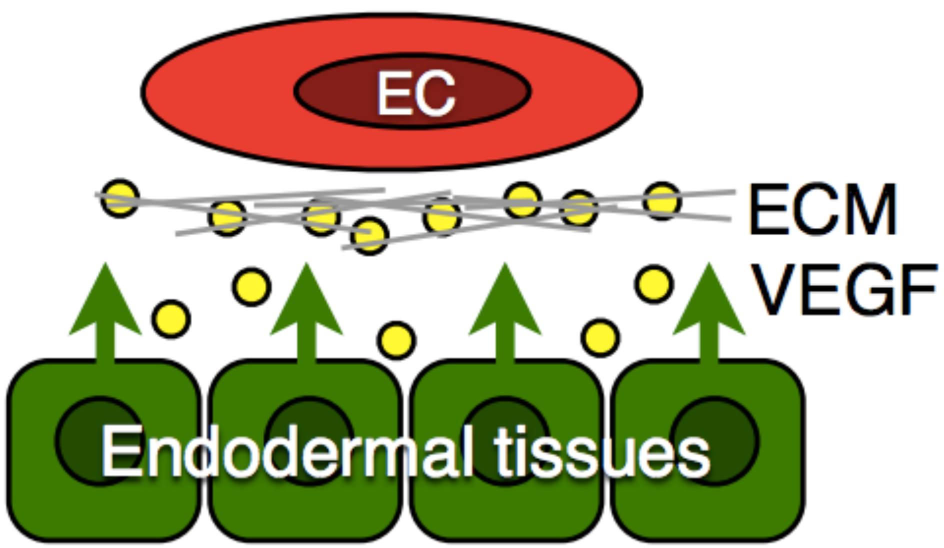
Diffusion

$$
\begin{aligned}
\mathrm{VEGF_s} \quad \frac{\partial u}{\partial t} &= \boxed{D\triangle u} + \gamma_1 - f(u,v) - \delta u \\
\mathrm{ECM} \quad \frac{\partial v}{\partial t} &= \gamma_2 \delta_{\sigma_{x,0}} - f(u,v) \\
\mathrm{VEGF_b} \quad \frac{\partial w}{\partial t} &= f(u,v)
\end{aligned}
$$

Spatiotemporal dynamics of VEGF

Reaction-diffusion model

$$\mathrm{VEGF} + \mathrm{ECM} \rightarrow \mathrm{VEGF_b}$$

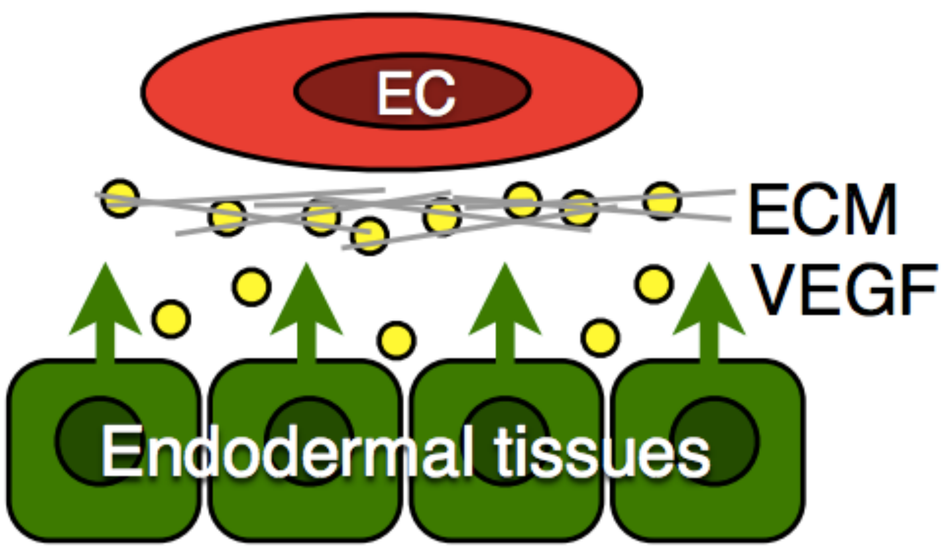


$$\begin{aligned}
\mathrm{VEGF_s} \quad \frac{\partial u}{\partial t} &= \overbrace{\boxed{D\triangle u}}^{\text{Diffusion}} + \overbrace{\boxed{\gamma_1}}^{\text{VEGF production by endoderm}} - f(u,v) - \delta u \\
\mathrm{ECM} \quad \frac{\partial v}{\partial t} &= \gamma_2 \delta_{\sigma_{x,0}} - f(u,v) \\
\mathrm{VEGF_b} \quad \frac{\partial w}{\partial t} &= f(u,v)
\end{aligned}$$

Spatiotemporal dynamics of VEGF

Reaction-diffusion model

$$\text{VEGF} + \text{ECM} \rightarrow \text{VEGF}_b$$



Diffusion

VEGF production by endoderm

Decay

$$\text{VEGF}_s \quad \frac{\partial u}{\partial t} = \boxed{D\Delta u} + \boxed{\gamma_1} - f(u,v) - \boxed{\delta u}$$

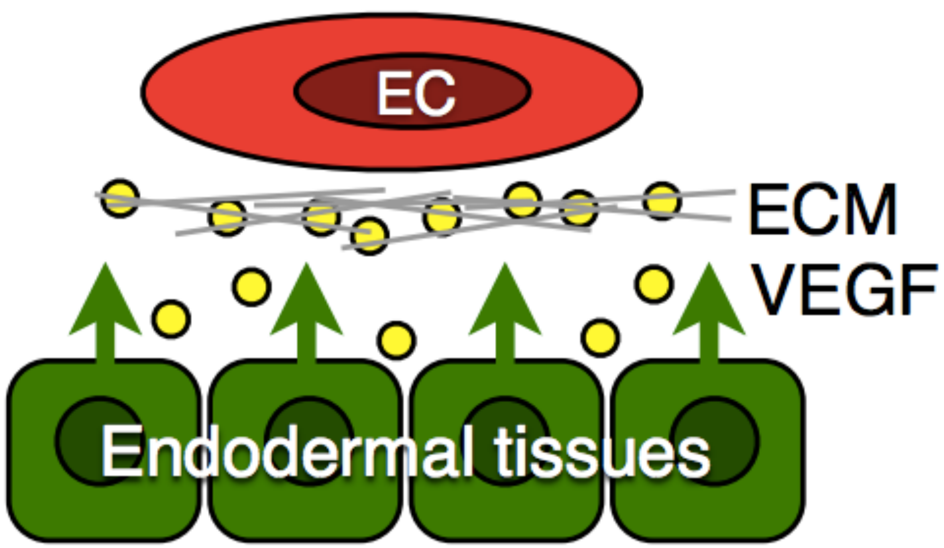
$$\text{ECM} \quad \frac{\partial v}{\partial t} = \gamma_2 \delta_{\sigma_{x,0}} - f(u,v)$$

$$\text{VEGF}_b \quad \frac{\partial w}{\partial t} = f(u,v)$$

Spatiotemporal dynamics of VEGF

Reaction-diffusion model

$$\mathrm{VEGF} + \mathrm{ECM} \rightarrow \mathrm{VEGF_b}$$



Diffusion

VEGF production by endoderm

Decay

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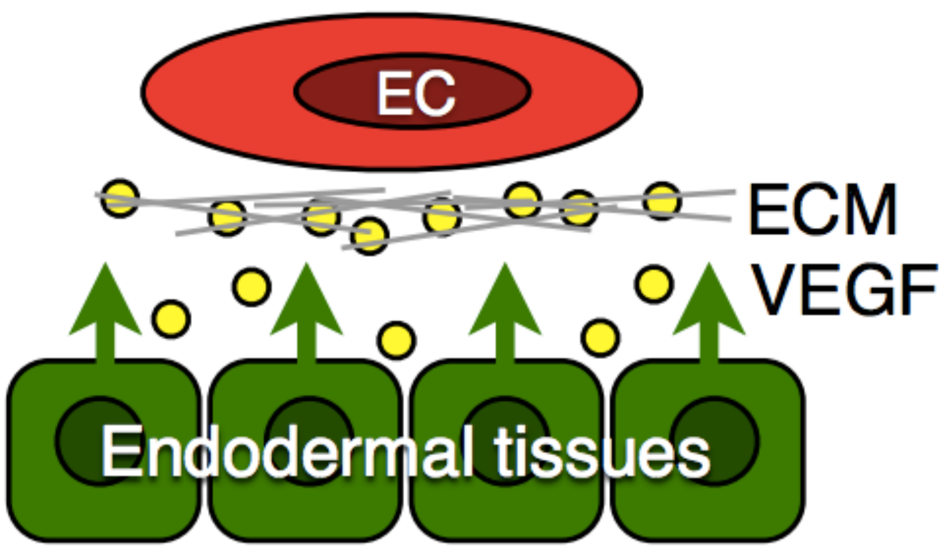
$$\mathrm{VEGF_b} \quad \frac{\partial w}{\partial t} = \boxed{f(u,v)}$$

Binding of VEGF to ECM

Spatiotemporal dynamics of VEGF

Reaction-diffusion model

$$\mathrm{VEGF} + \mathrm{ECM} \rightarrow \mathrm{VEGF_b}$$



Diffusion

VEGF production by endoderm

Decay

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$$\mathrm{VEGF_b} \quad \frac{\partial w}{\partial t} = \boxed{f(u,v)}$$

$$f(u,v) = \boxed{\alpha u v}$$

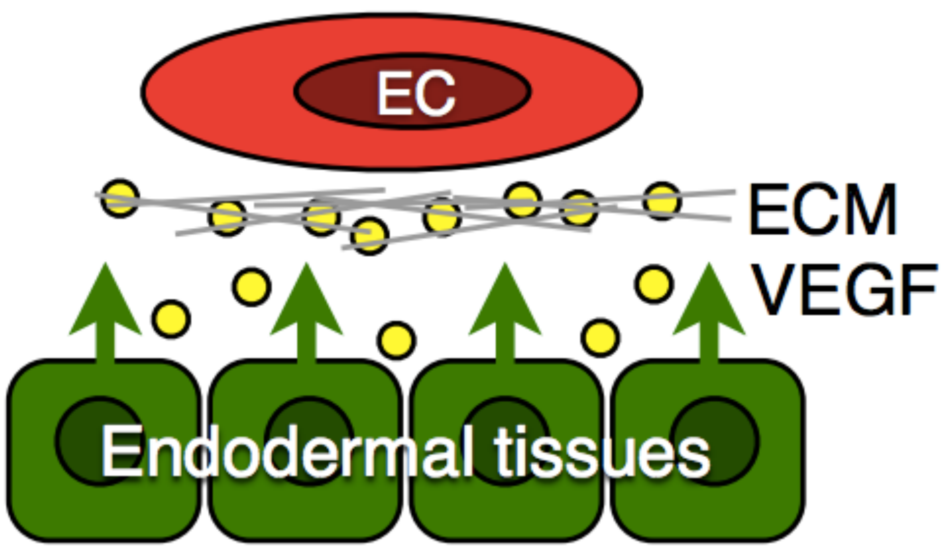
Binding of VEGF to ECM

Mass action kinetics

Spatiotemporal dynamics of VEGF

Reaction-diffusion model

$$\mathrm{VEGF} + \mathrm{ECM} \rightarrow \mathrm{VEGF_b}$$



Diffusion

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$$f(u,v) = \boxed{\alpha u v}$$

Binding of VEGF to ECM

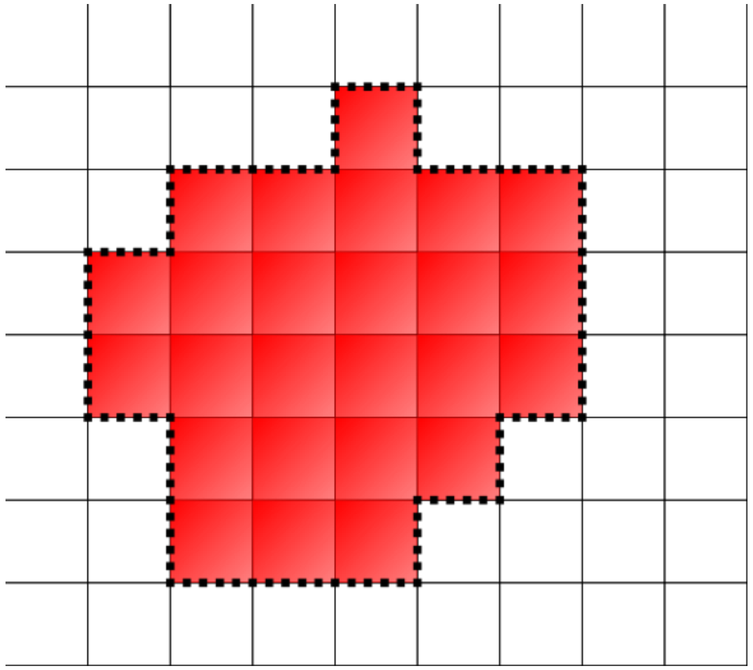
Mass action kinetics

Cell-dependent ECM modification

Chemotaxis of angioblasts
Cellular Potts model

Energy function

$$H = \sum_{\sigma > 0} \left(\lambda_a (a_\sigma - A)^2 + \lambda_p p_\sigma \right)$$



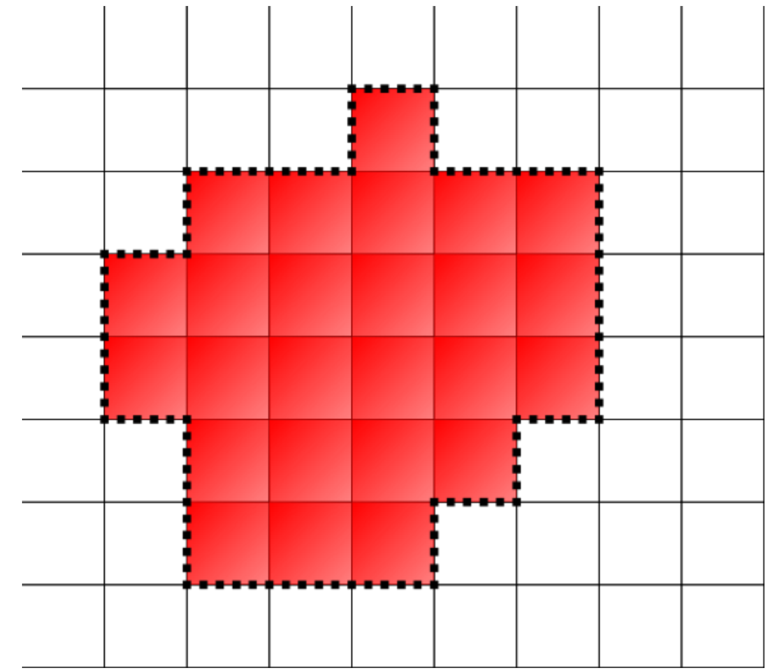
Chemotaxis of angioblasts
Cellular Potts model

Energy function

$$H = \sum_{\sigma > 0} (\lambda_a (a_\sigma - A)^2 + \lambda_p p_\sigma)$$

Number of

Target number of



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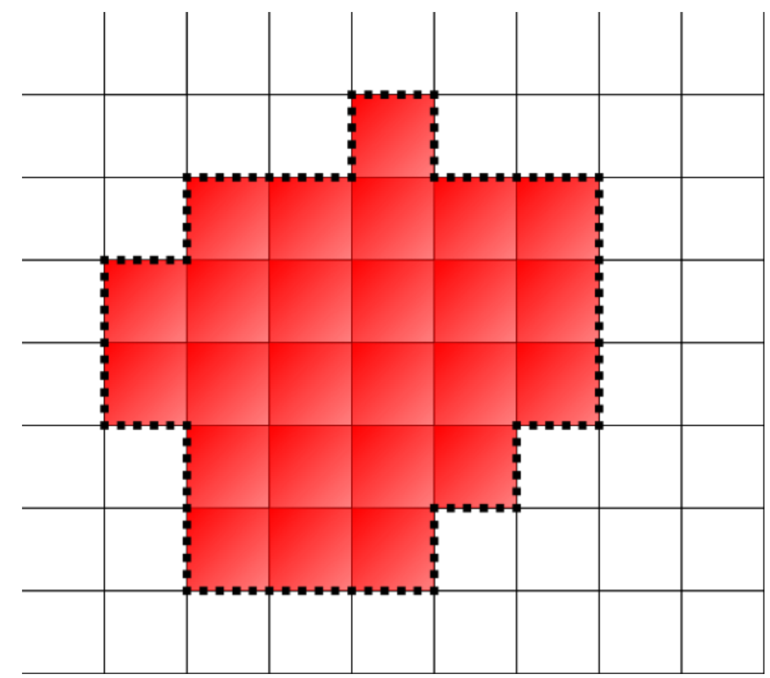

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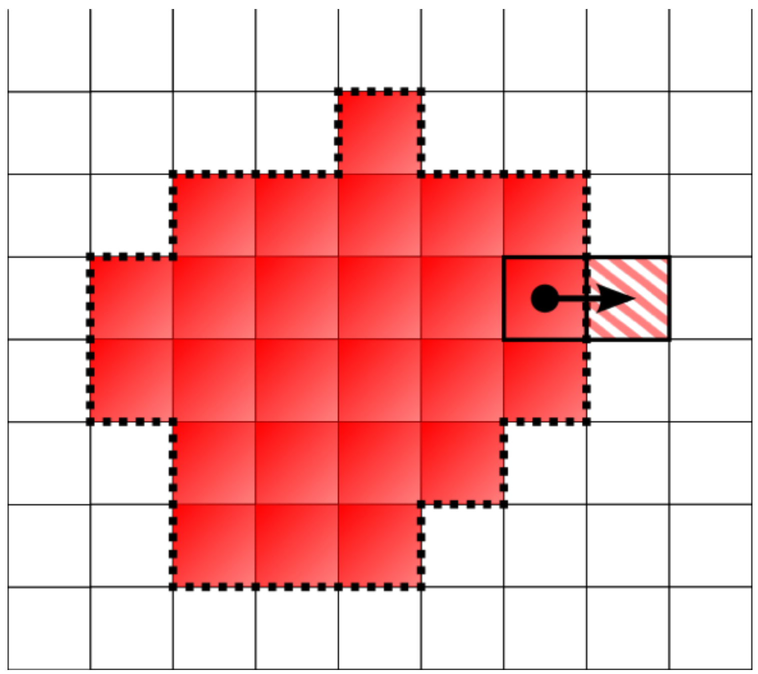


Chemotaxis of angioblasts

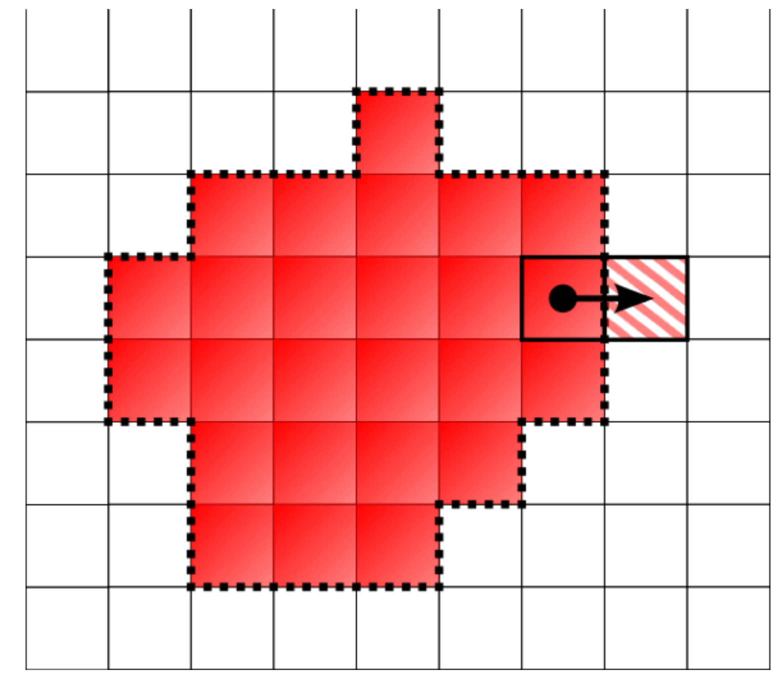
Cellular Potts model

Energy function

$$H = \sum_{\sigma>0} \Big(\lambda_a \big(\underbrace{a_\sigma}_{\text{Number of}} - \underbrace{A}_{\text{Target number of}}\big)^2 + \lambda_p \overbrace{p_\sigma}^{\text{Number of}}\Big)$$

Metropolis kinetics

$$P(\Delta H) = \begin{cases} 1 & \text{if } \Delta H < 0 \\ e^{\frac{-(\Delta H)}{T}} & \text{otherwise} \end{cases}$$



Chemotaxis of angioblasts

Cellular Potts model

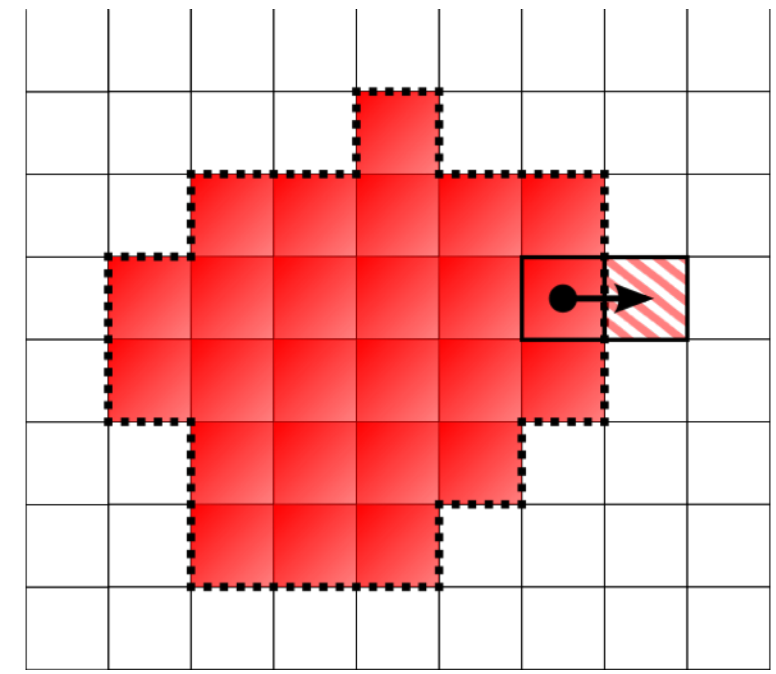
Energy function

Number of

$$H = \sum_{\sigma>0} \left(\lambda_a (a_\sigma - A)^2 + \lambda_p p_\sigma\right)$$

Number of

Target number of

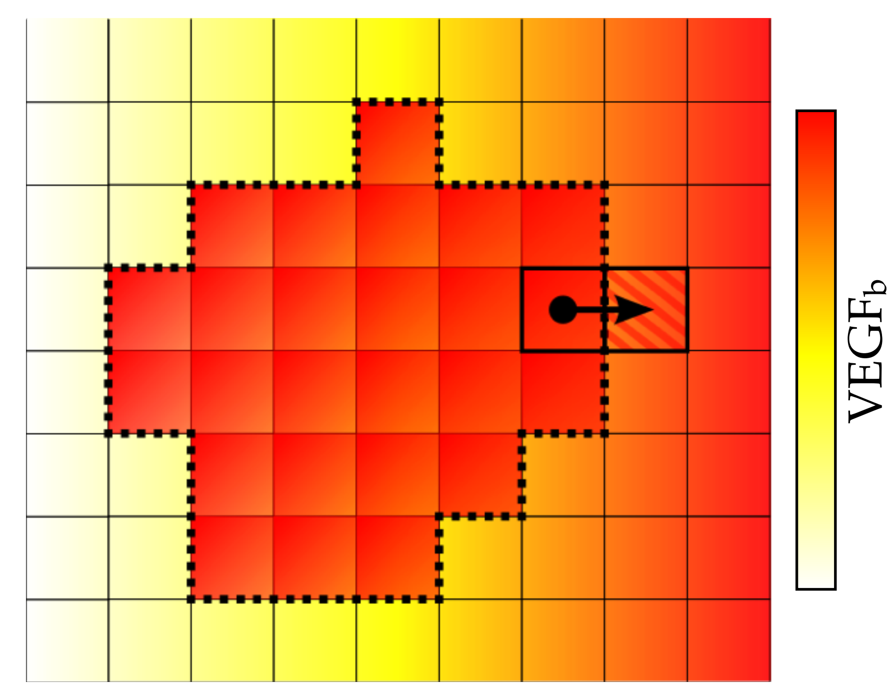


Metropolis kinetics

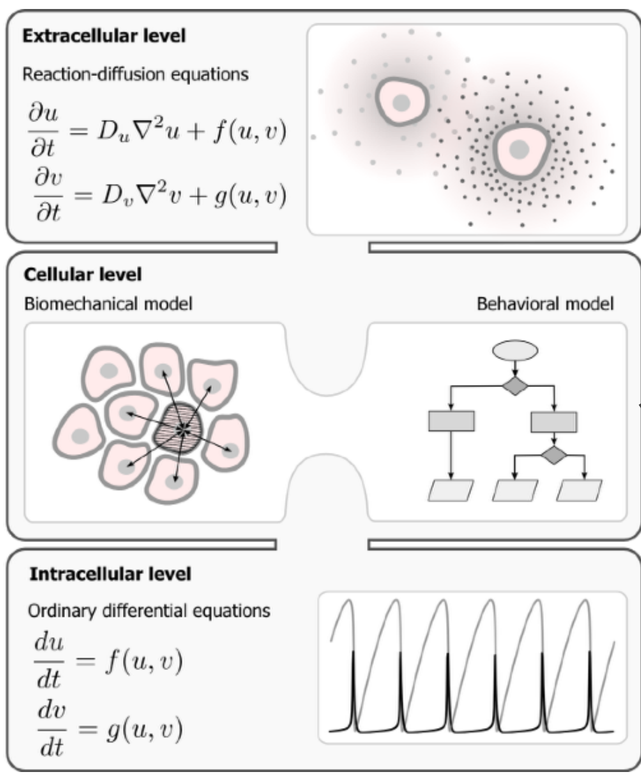
$$P(\Delta H) = \begin{cases} 1 & \text{if } \Delta H < 0 \\ e^{\frac{-(\Delta H)}{T}} & \text{otherwise} \end{cases}$$

Chemotaxis

$$\Delta H_{chemotaxis} = \Delta H - \mu_b\left(w(x_{target}) - w(x_{source})\right)$$



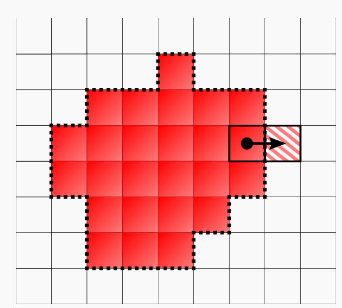
Multi-scale coupling



Extracellular level

$$\begin{aligned}
\frac{\partial u}{\partial t} &= D\triangle u + \gamma_1 - f(u,v) - \delta u \\
\frac{\partial v}{\partial t} &= \gamma_2 \delta_{\sigma_{x,0}} - f(u,v) \\
\frac{\partial w}{\partial t} &= f(u,v)
\end{aligned}$$

Cellular level

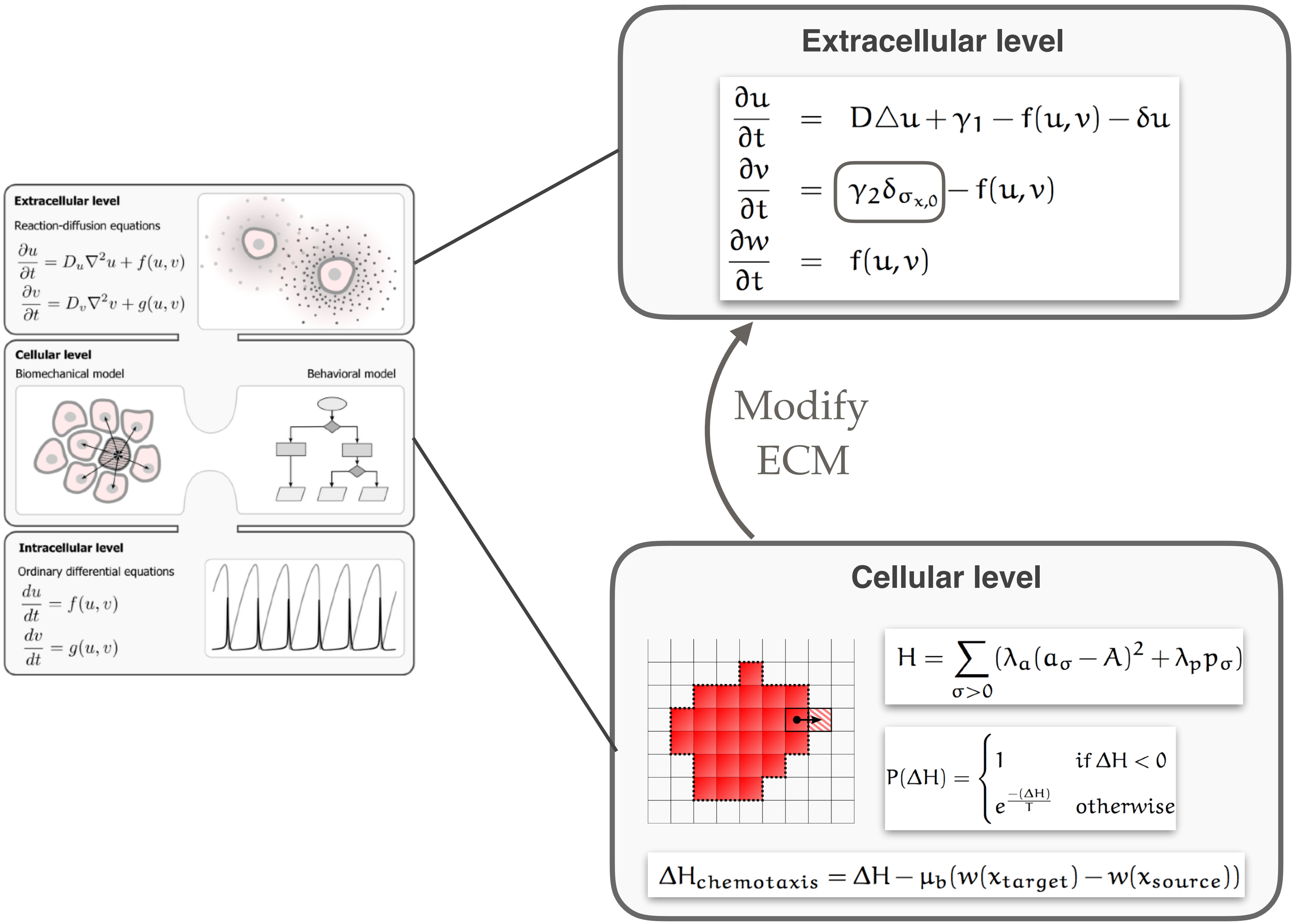


$$H = \sum_{\sigma>0} (\lambda_a (a_\sigma - A)^2 + \lambda_p p_\sigma)$$

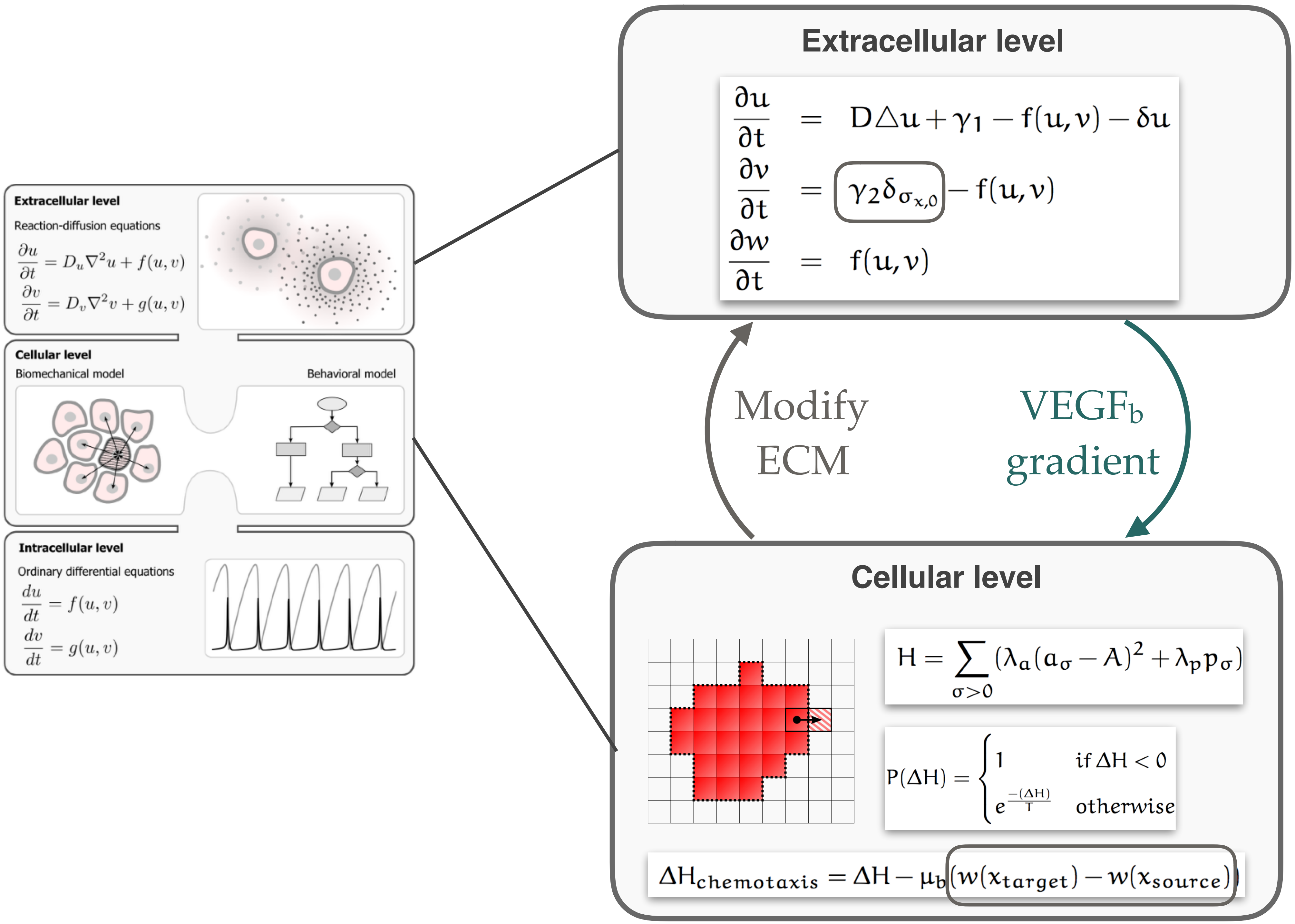
$$P(\Delta H) = \begin{cases} 1 & \text{if } \Delta H < 0 \\ e^{\frac{-(\Delta H)}{T}} & \text{otherwise} \end{cases}$$

$$\Delta H_{chemotaxis} = \Delta H - \mu_b (w(x_{target}) - w(x_{source}))$$

Multi-scale coupling

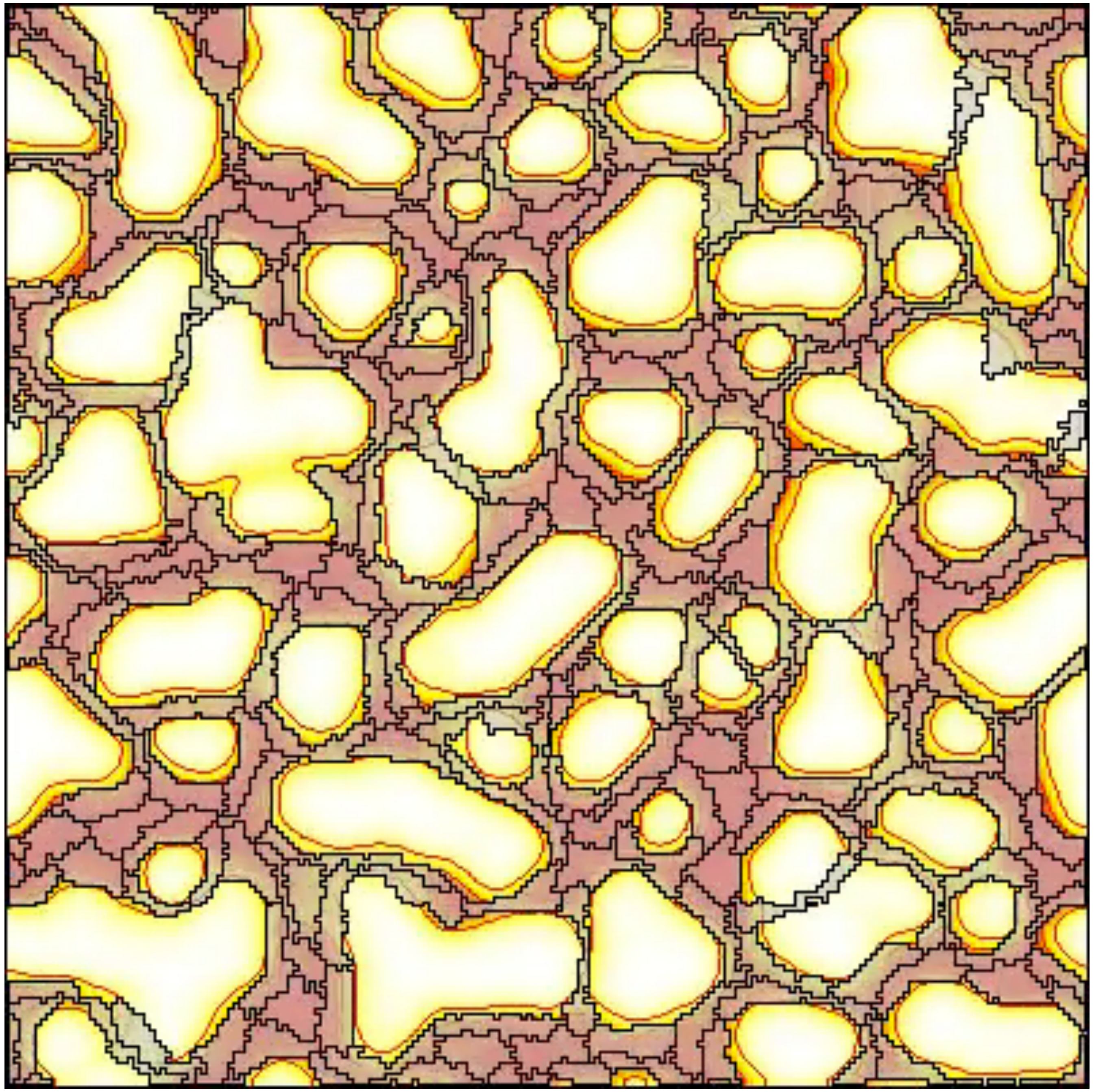


Multi-scale coupling



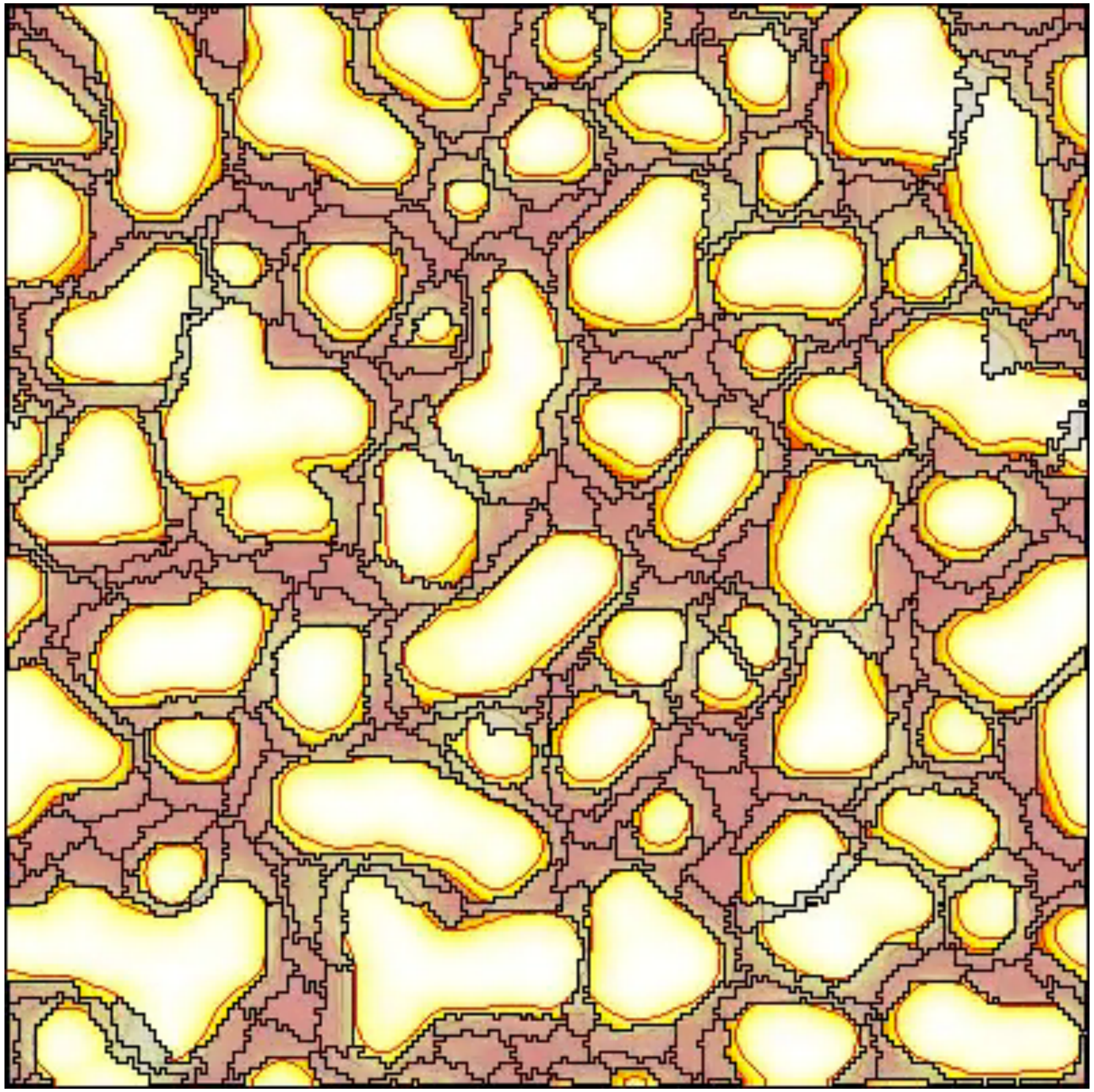
Results

Network formation and morphometric comparison



Results

Network formation and morphometric comparison



Results

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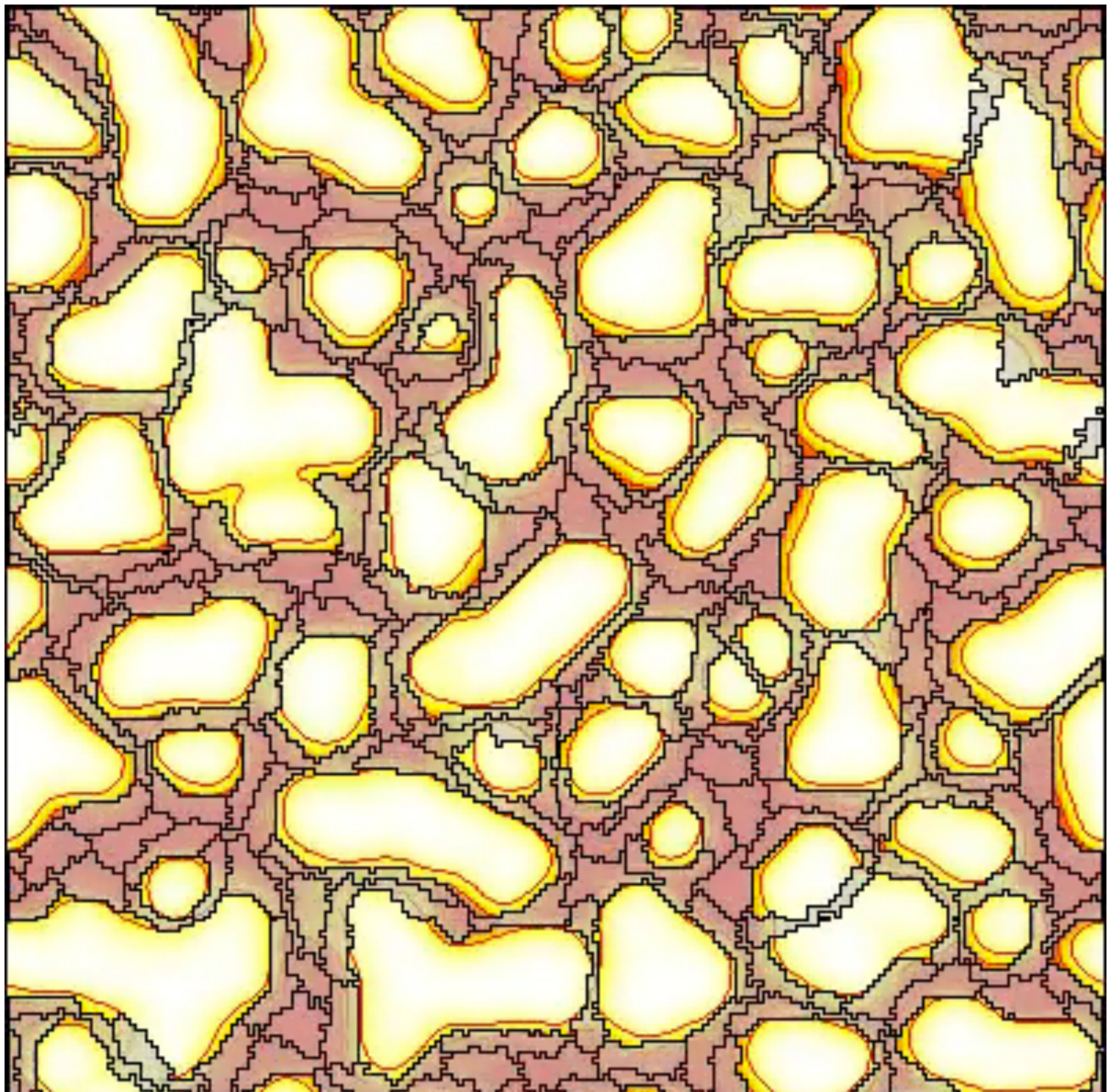
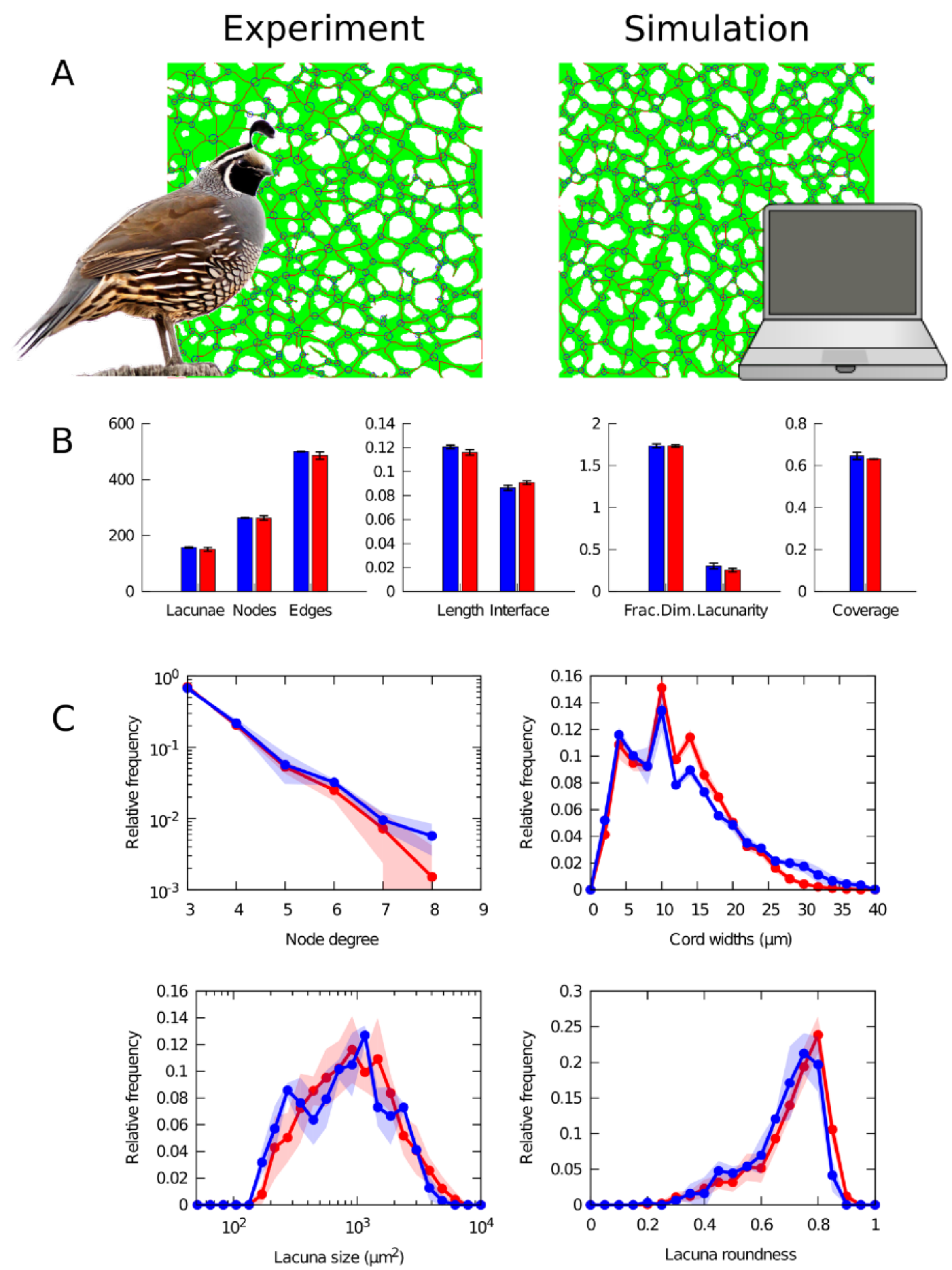


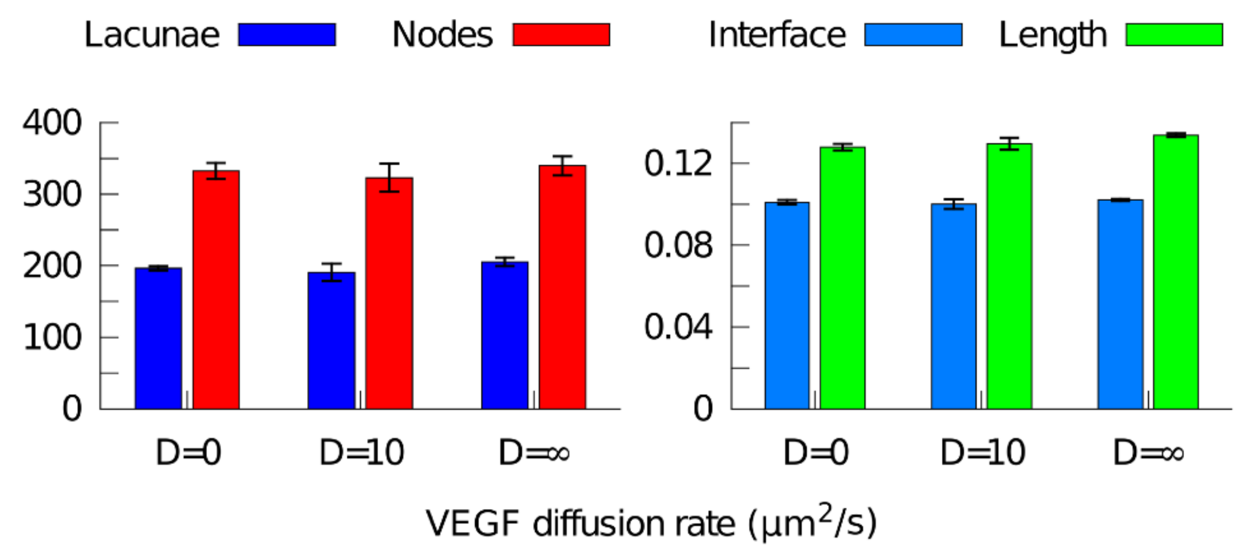


Results

Dynamics of network formation

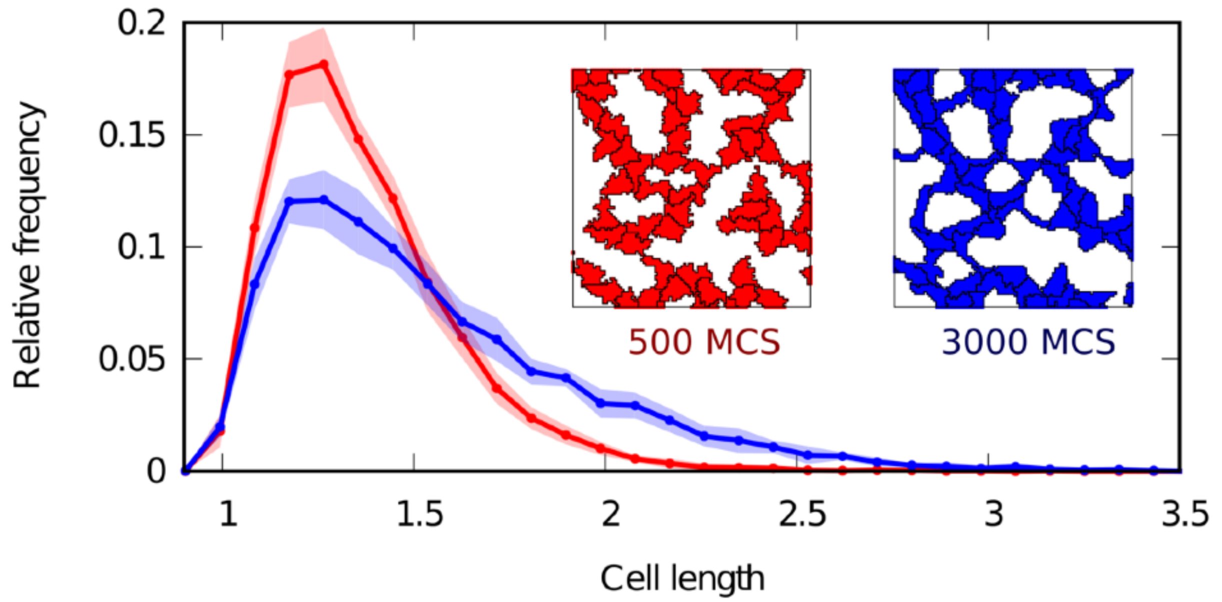
- Sensitivity analysis

  Network formation independent of diffusion coefficient

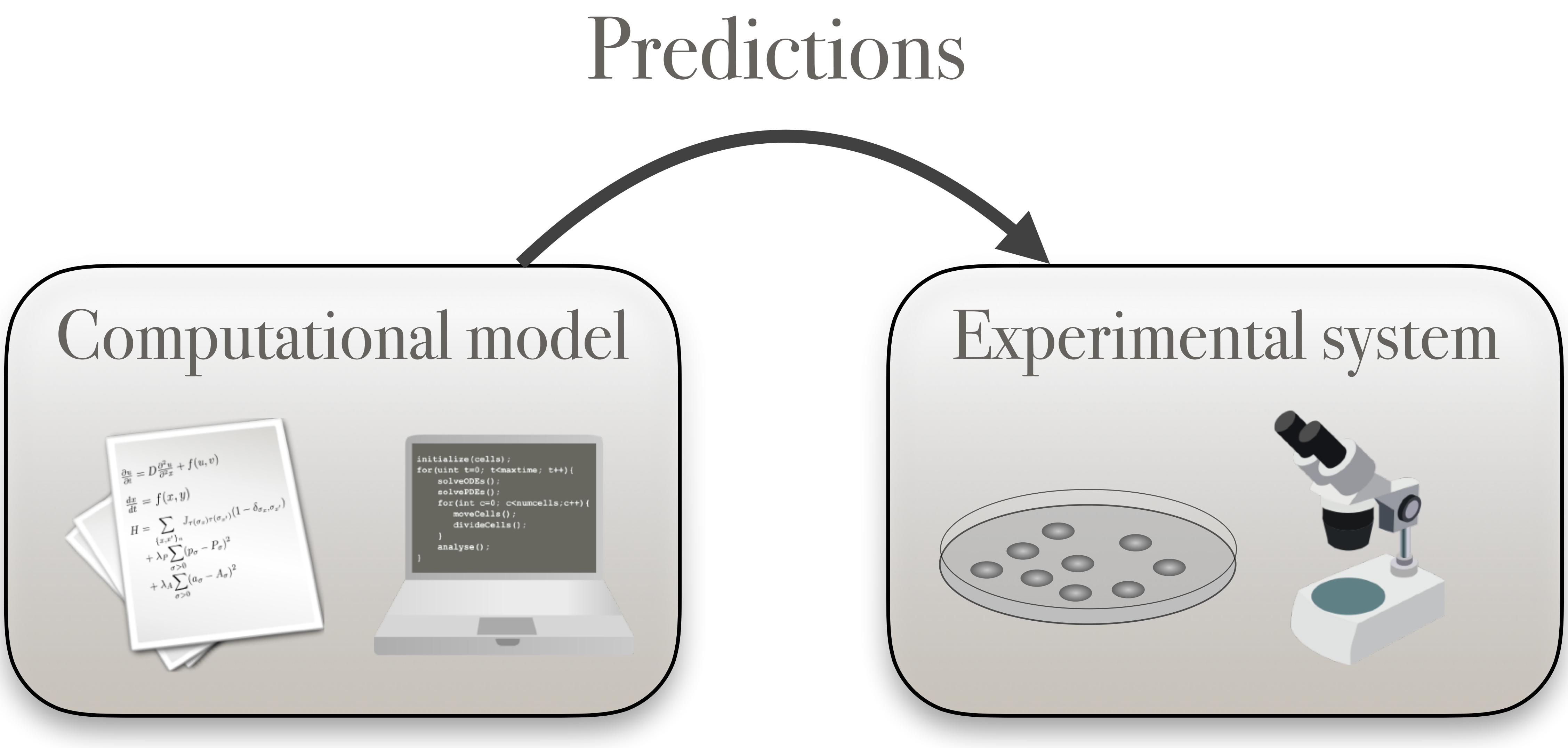


- Cell elongation

  Emergent effect rather than cause



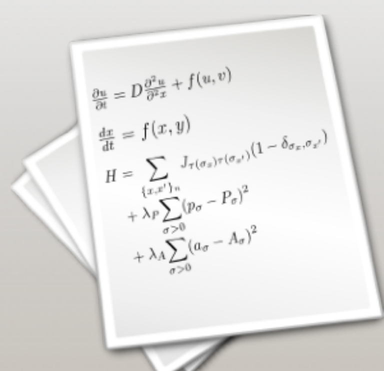
Systems biology

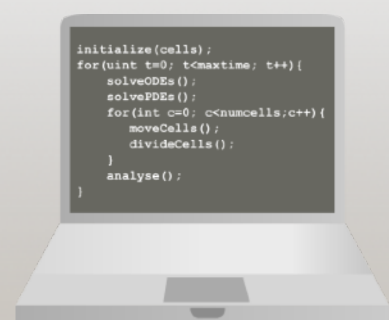


Systems biology

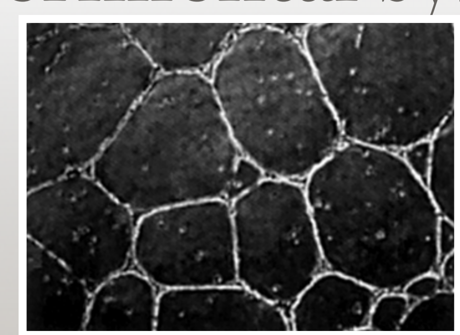
Predictions

Computational model





Experimental system



HUVEC in Matrigel

Prof. Takashi Miura
Kyushu University
Fukuoka, Japan

Dr. Alvaro Köhn-Luque
Complutense University,
Madrid, Spain

Absorption of VEGF

Prediction: VEGF should be absorbed near HUVECs

HUVEC = Human Umbilical Vein Endothelial Cell

Absorption of VEGF

Prediction: VEGF should be absorbed near HUVECs

HUVEC = Human Umbilical Vein Endothelial Cell

Experiment:

Add fluorescent $VEGF_{165}$ after normal network formation

Absorption of VEGF

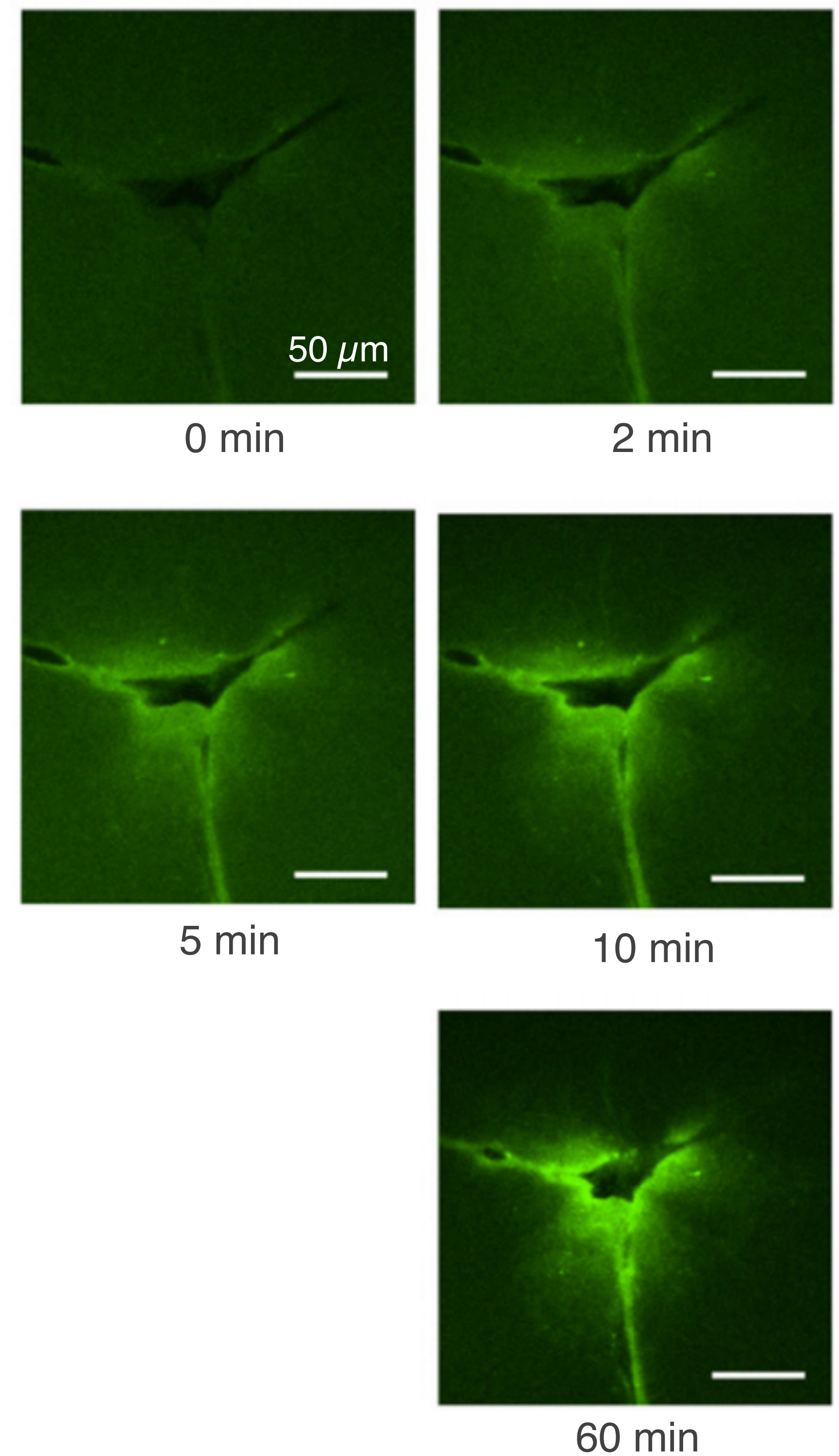
Prediction: VEGF should be absorbed near HUVECs

HUVEC = Human Umbilical Vein Endothelial Cell

Experiment:

Add fluorescent VEGF$_{165}$ after normal network formation

Result: Fluorescent VEGF accumulates near HUVECs



VEGF dynamics

Prediction: Near HUVECs, VEGF is bound rather than diffusing

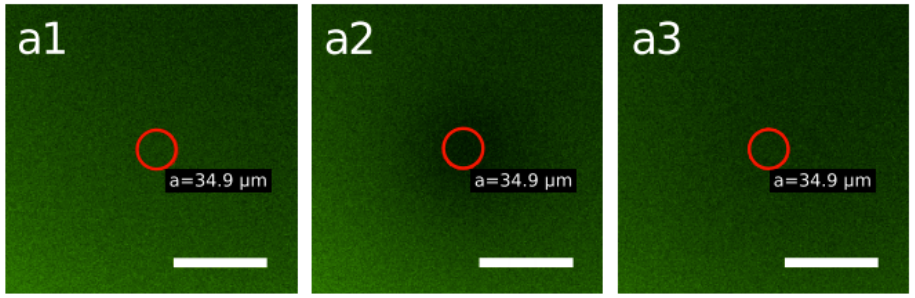
HUVEC = Human Umbilical Vein Endothelial Cell

VEGF dynamics

Prediction: Near HUVECs, VEGF is bound rather than diffusing

HUVEC = Human Umbilical Vein Endothelial Cell

Experiment: FRAP: Fluorescent recovery after photobleaching



Before bleach After bleach 20 sec

VEGF dynamics

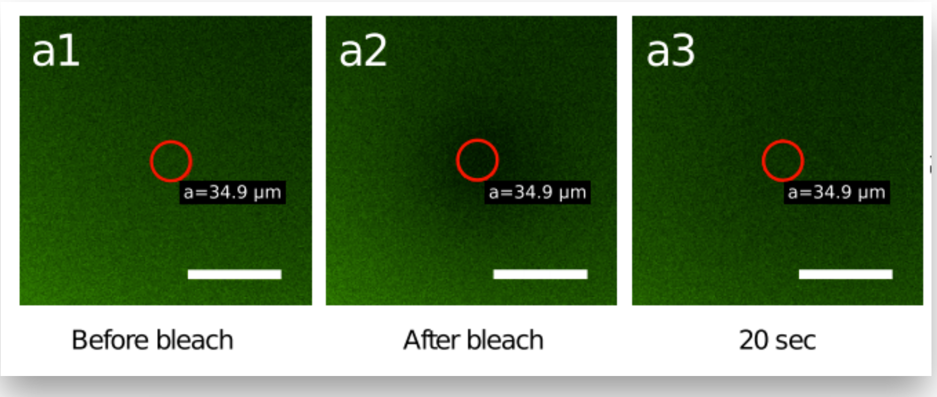
Prediction: Near HUVECs, VEGF is bound rather than diffusing

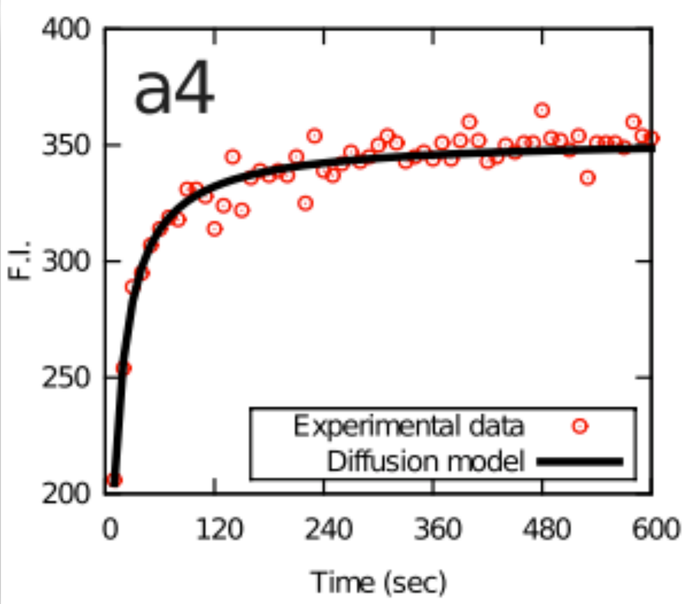
HUVEC = Human Umbilical Vein Endothelial Cell

Experiment: FRAP: Fluorescent recovery after photobleaching

Result: In **absence** of cells: Consistent with diffusion

$$\mathrm{frap}(t) = F_\infty \exp\left(-\frac{2}{1 + 8Dt/a^2}\right)$$





Jacobson et al., 1976

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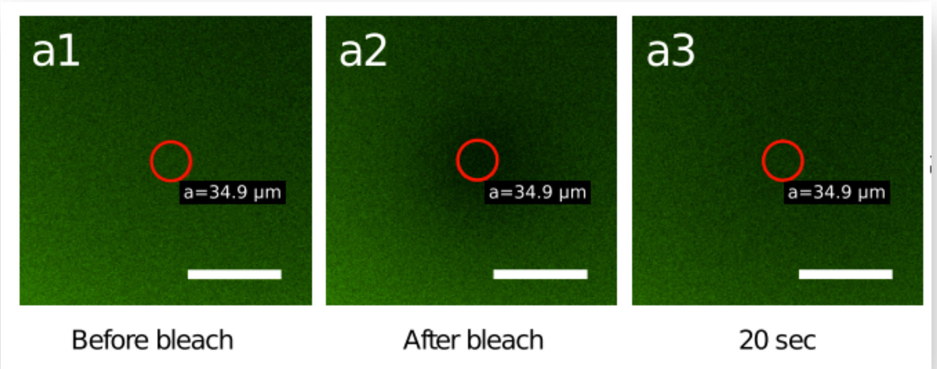
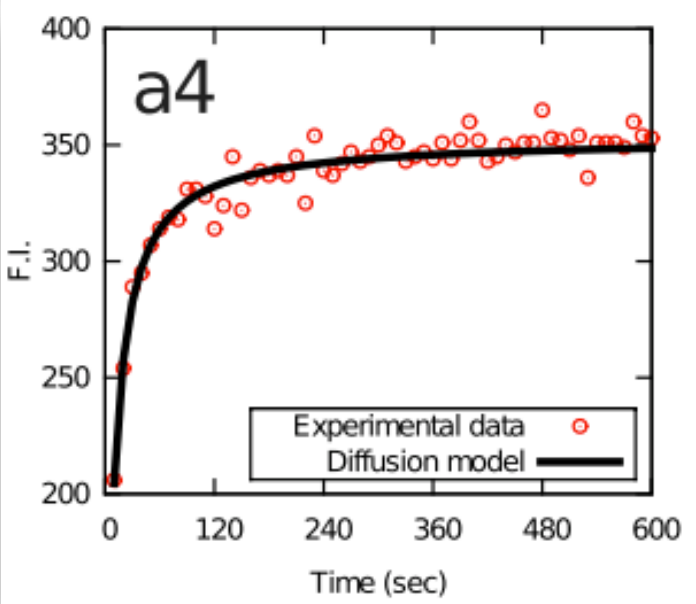


$$\mathrm{frap}(t) = F_\infty \exp\left(-\frac{2}{1+8Dt/a^2}\right)$$

$$D \approx 5.87 \times 10^{-7} \mathrm{cm}^2/\mathrm{s}$$



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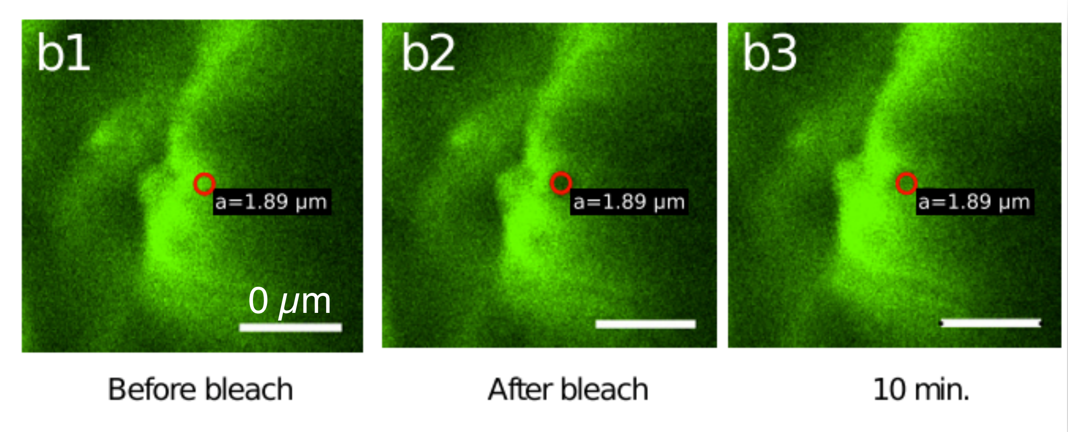
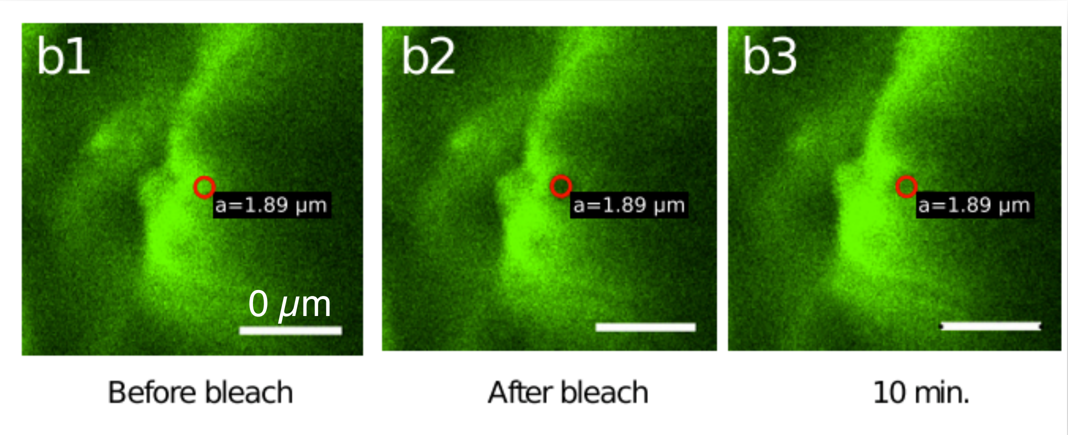


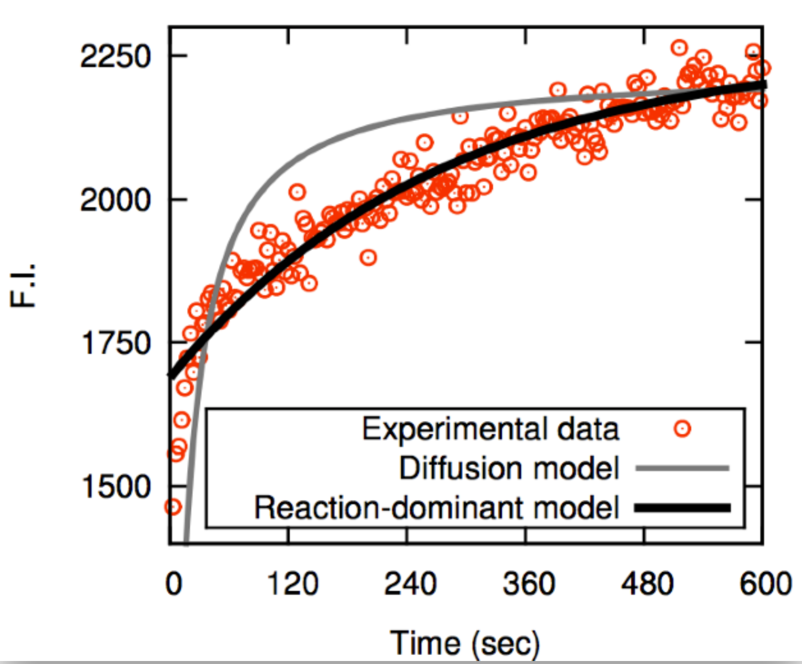
VEGF dynamics

Prediction: Near HUVECs, VEGF is bound rather than diffusing

Result:

Near cells: **Inconsistent** with diffusion





VEGF dynamics

Prediction: Near HUVECs, VEGF is bound rather than diffusing

Result:

Near cells: **Inconsistent** with diffusion

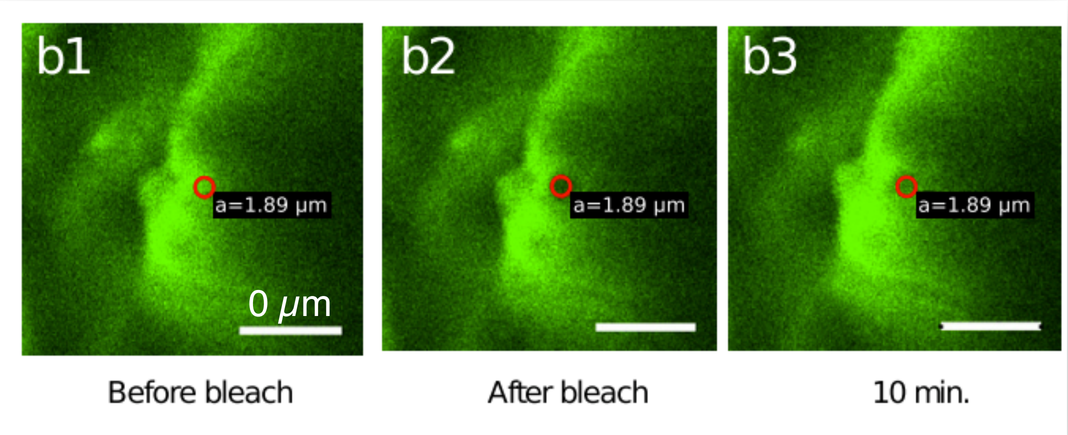
Consistent with **reaction-dominant** model

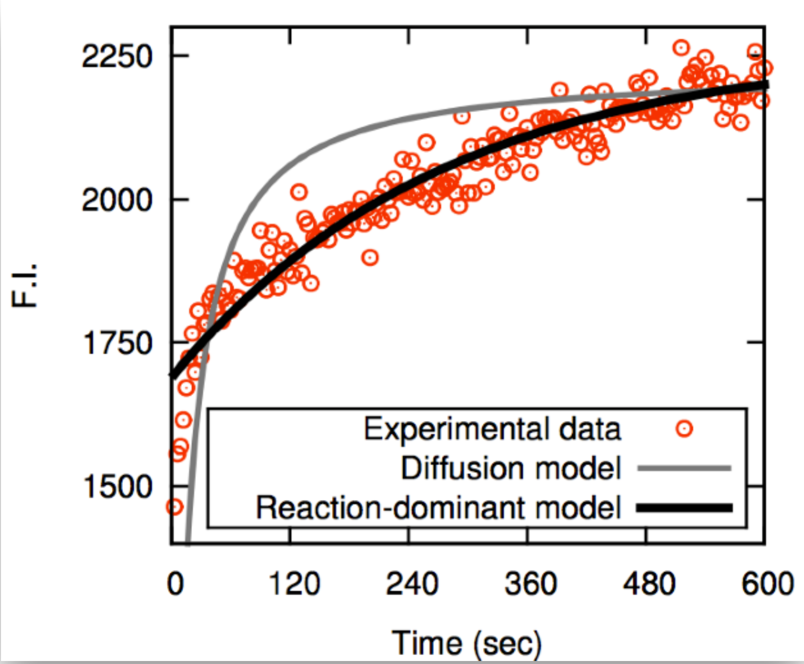
$$\mathrm{frap}(t) = u(t) + b(t) = 1 - \frac{k_{on}^*}{k_{on}^* + k_{off}} e^{-k_{off} t}$$

$$k_{on}^* \approx 1.5 \times 10^{-3} s^{-1}$$

$$k_{off} \approx 3.6 \times 10^{-3} s^{-1}$$

$$k_{on} = \frac{k_{off}}{K_d} = 3.6 \times 10^4 M^{-1} s^{-1}$$





Quantitative modeling

Parameter	Estimate	Method
	PDE	
D	$5.87 \cdot 10\ \mu m^2 s^{-1}$	FRAP
k_{on}	$8.57 \cdot 10^{-7}\ ng\ ml^{-1} s^{-1}$	FRAP
k_{off}	$3.6 \cdot 10^{-3}\ s^{-1}$	FRAP
ϵ	$2.67 \cdot 10^{-6}\ s^{-1}$	ELISA
γ	$0.5 - 2.0\ ng\ ml^{-1} s^{-1}$	Estimated in this study
	CPM	
A	$300\ \mu m^2$	Measured in this study
λ_a	0.5 a.u. μm^{-2}	[102,252] rescaled
λ_p	1.6 a.u. μm^{-1}	[102,252] rescaled
μ	$40 - 140$ a.u. $ng^{-1} ml$	Calibration using data from [262]
	Initial condition	
u_0	$1.5\ ng\ ml^{-1}$	ELISA
s_0	$0.0\ ng\ ml^{-1}$	Assumed in this study
b_0	$0.0\ ng\ ml^{-1}$	Assumed in this study

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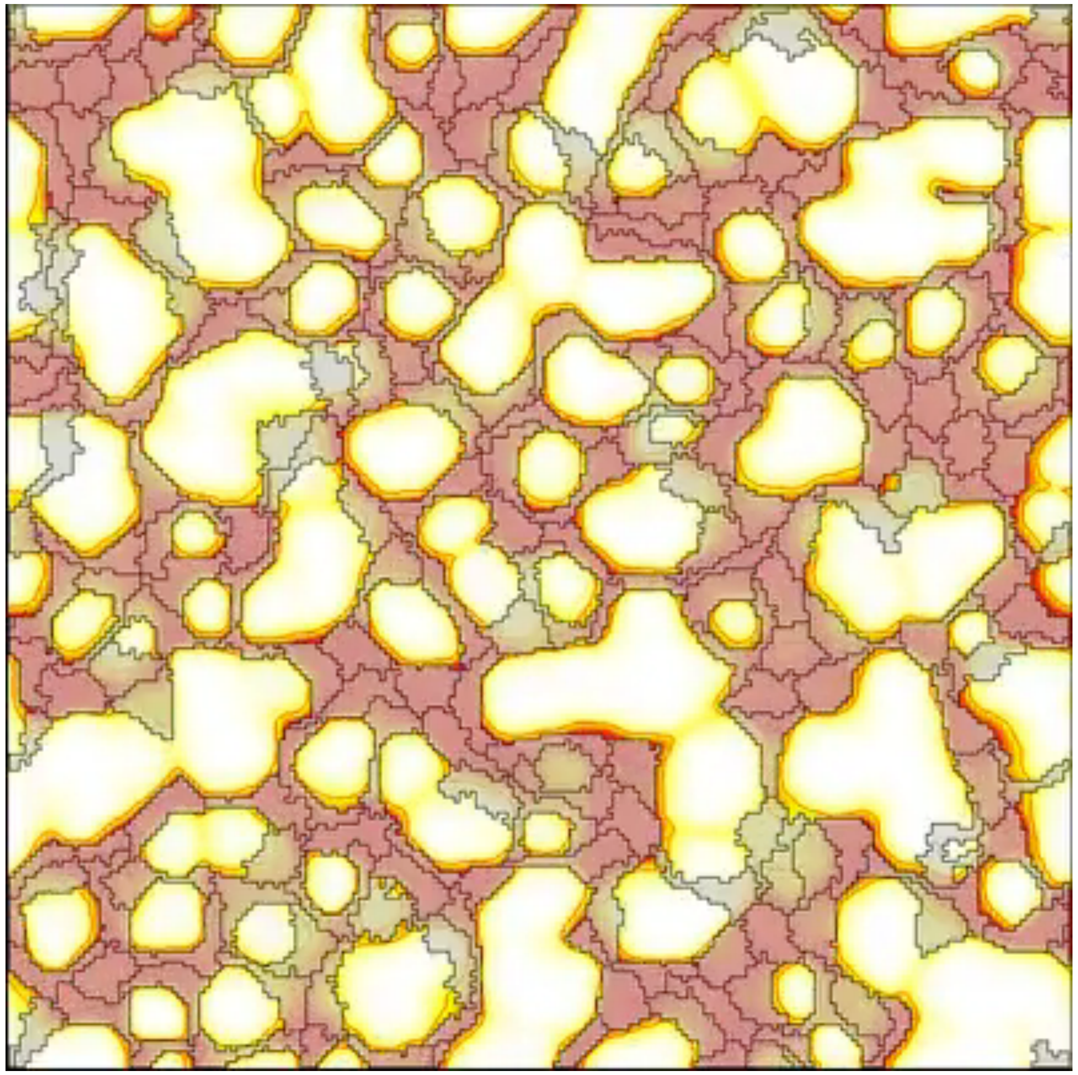
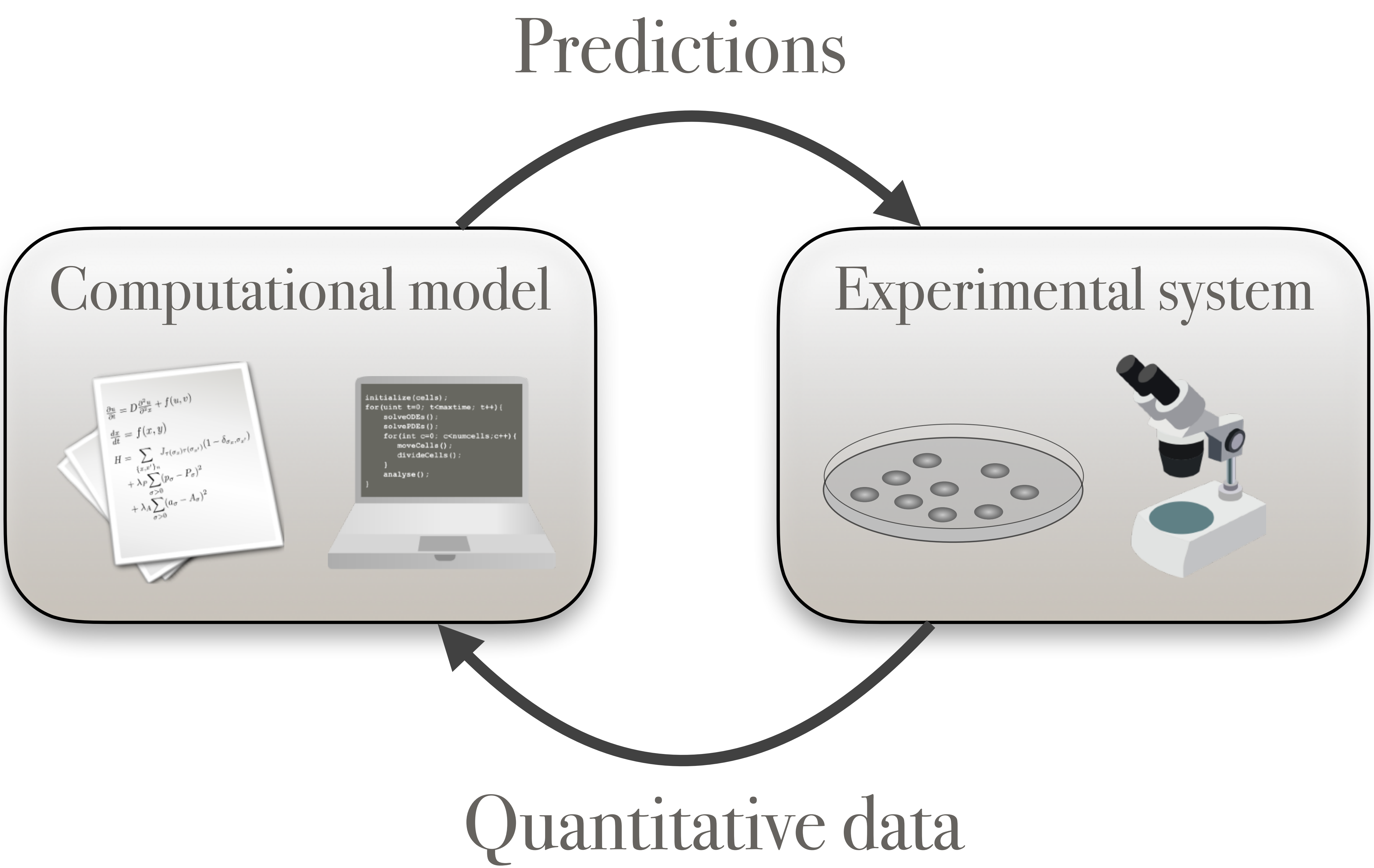


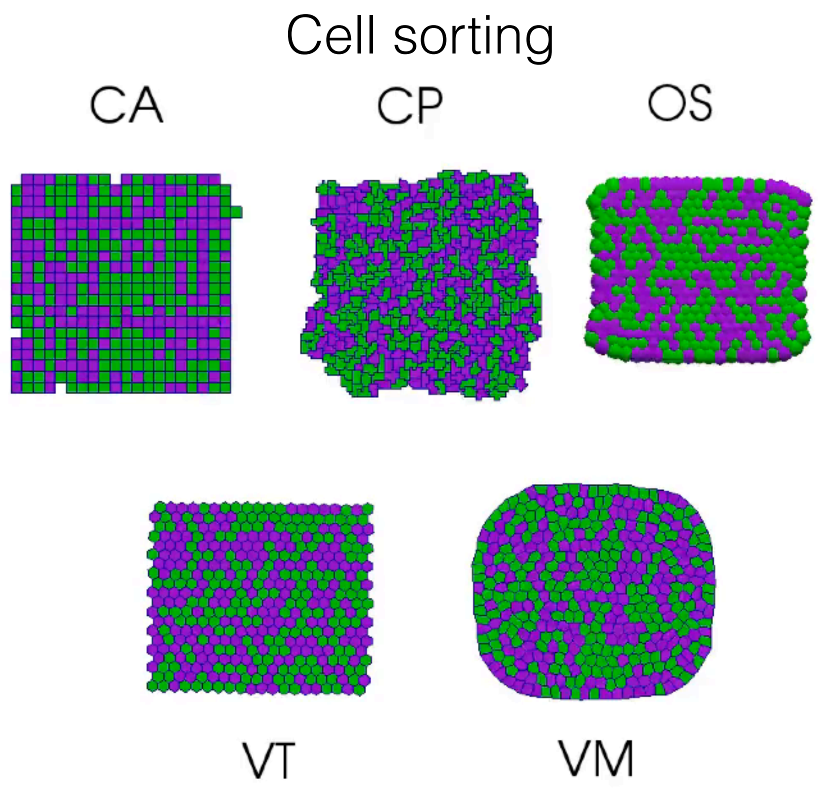
Systems biology cycle



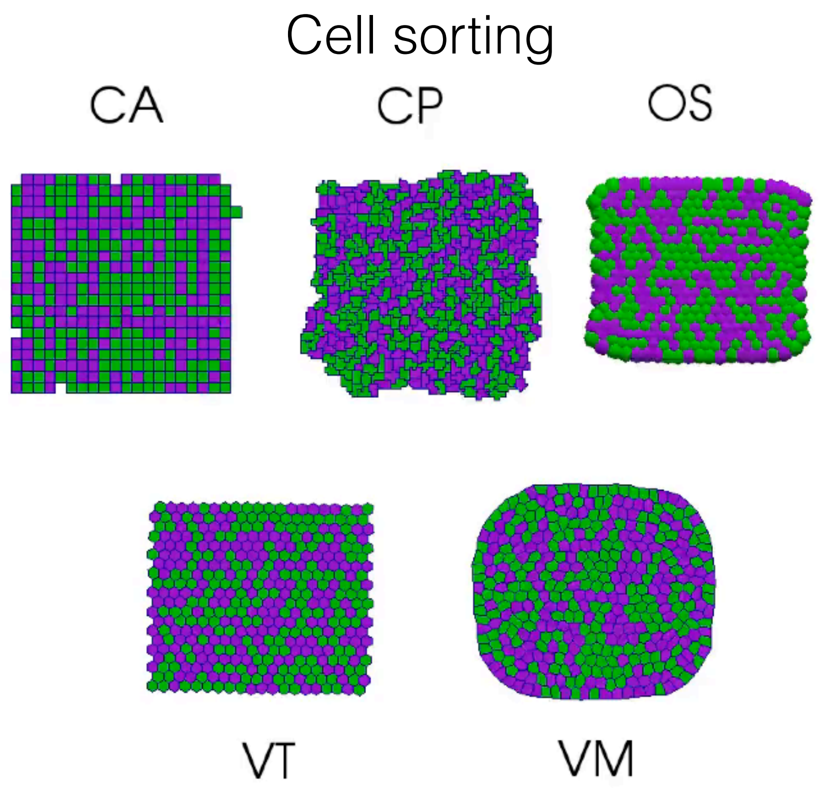
Comparing cell-based models

Osborne et al. 2017

Comparison based on case studies



Comparison based on case studies



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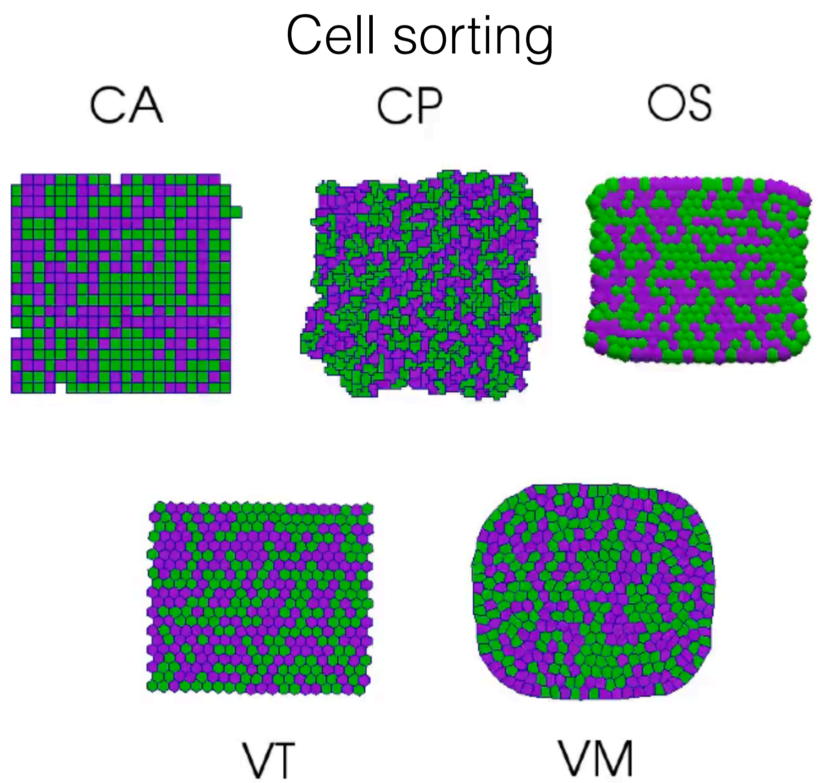
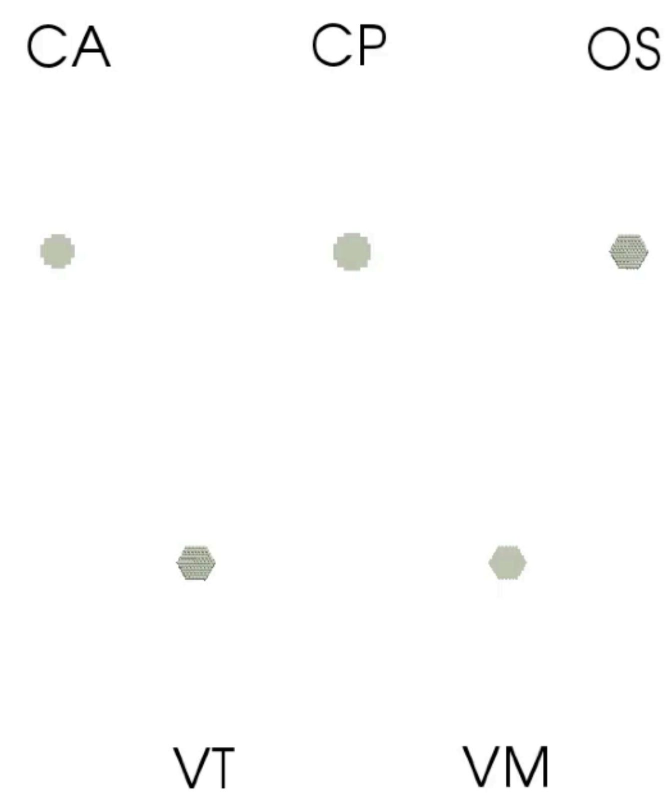
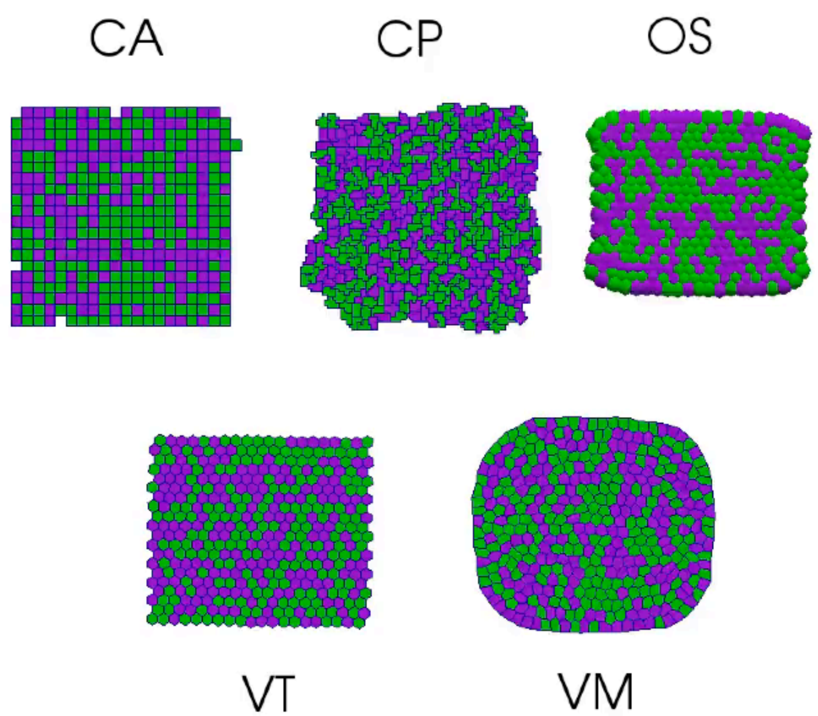


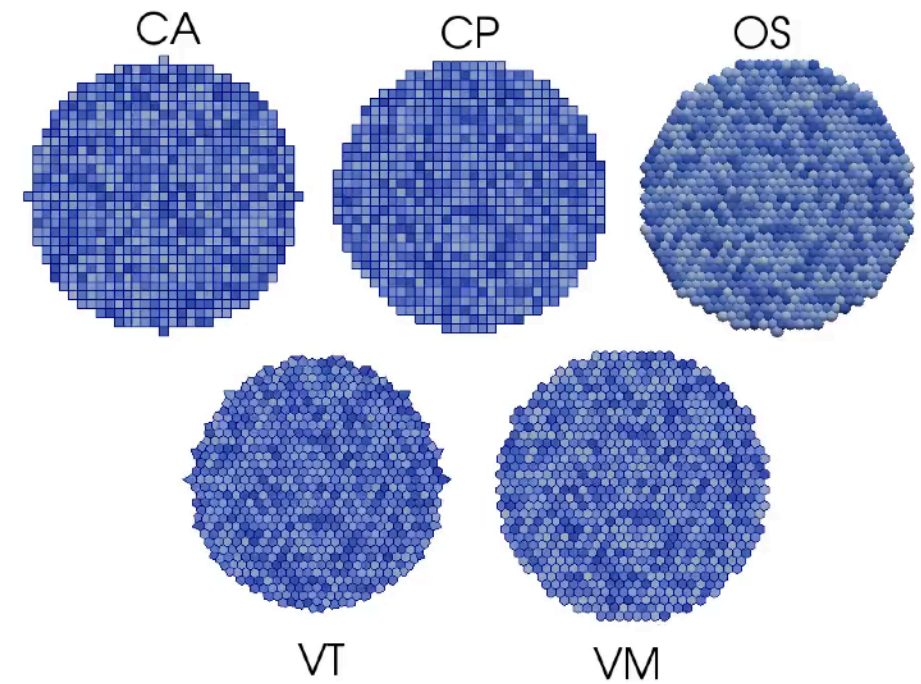


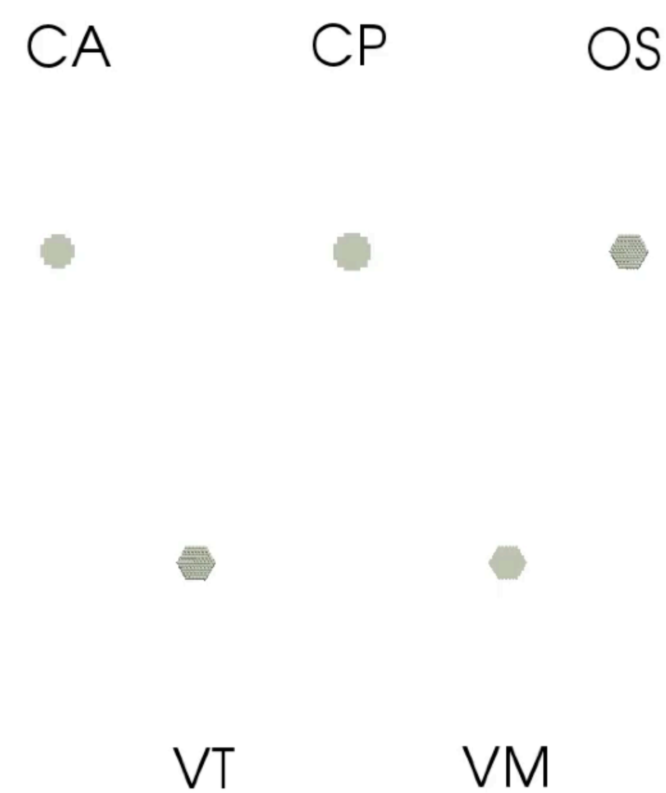
Comparison based on case studies

Cell sorting



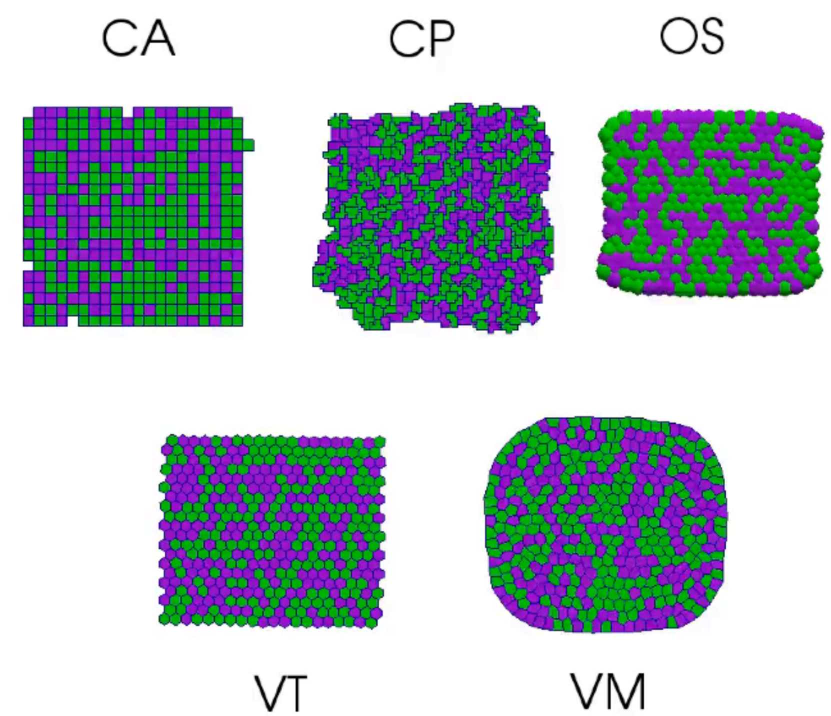
Short-range signaling



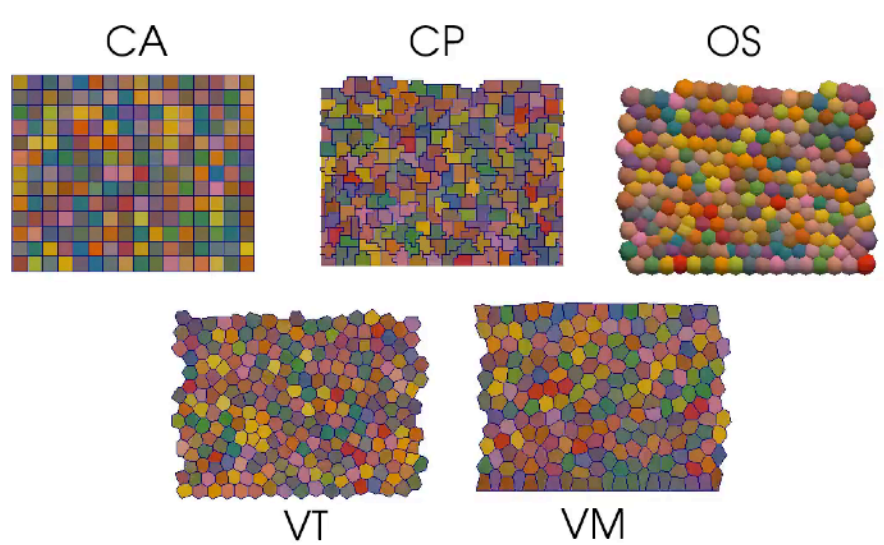


Comparison based on case studies

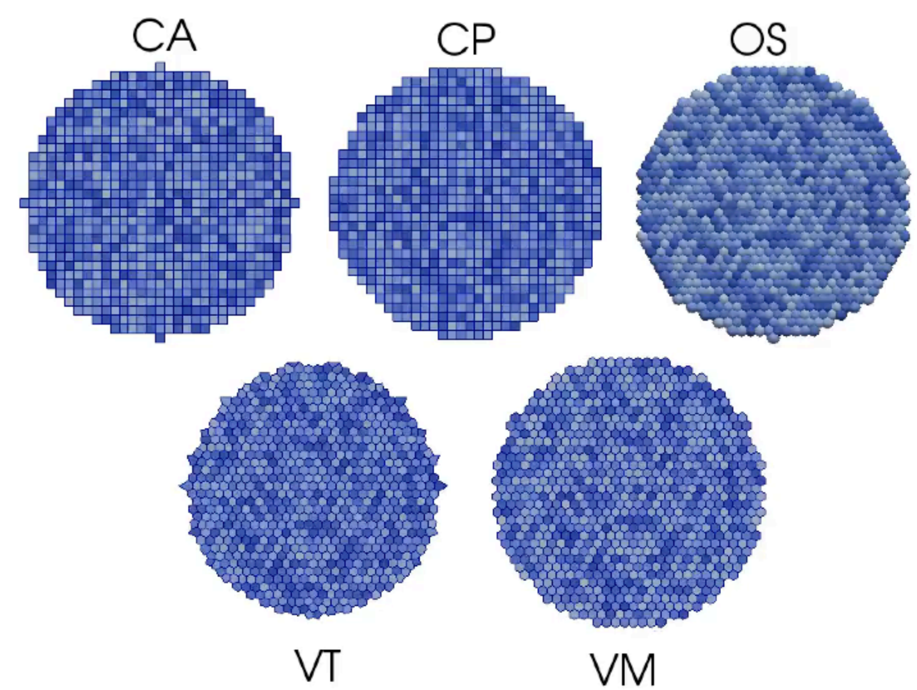
Cell sorting

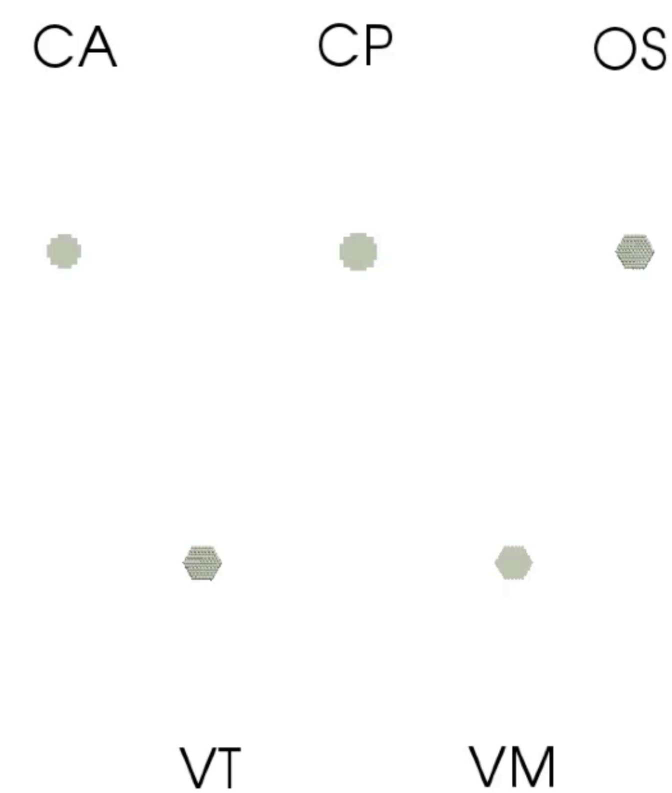


Proliferation



Short-range signaling





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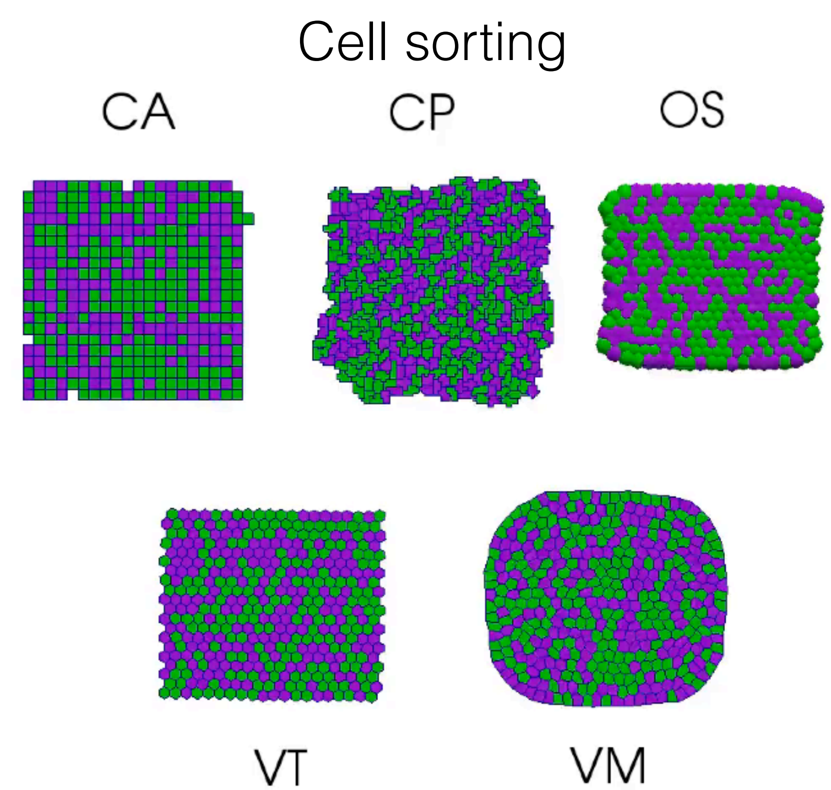
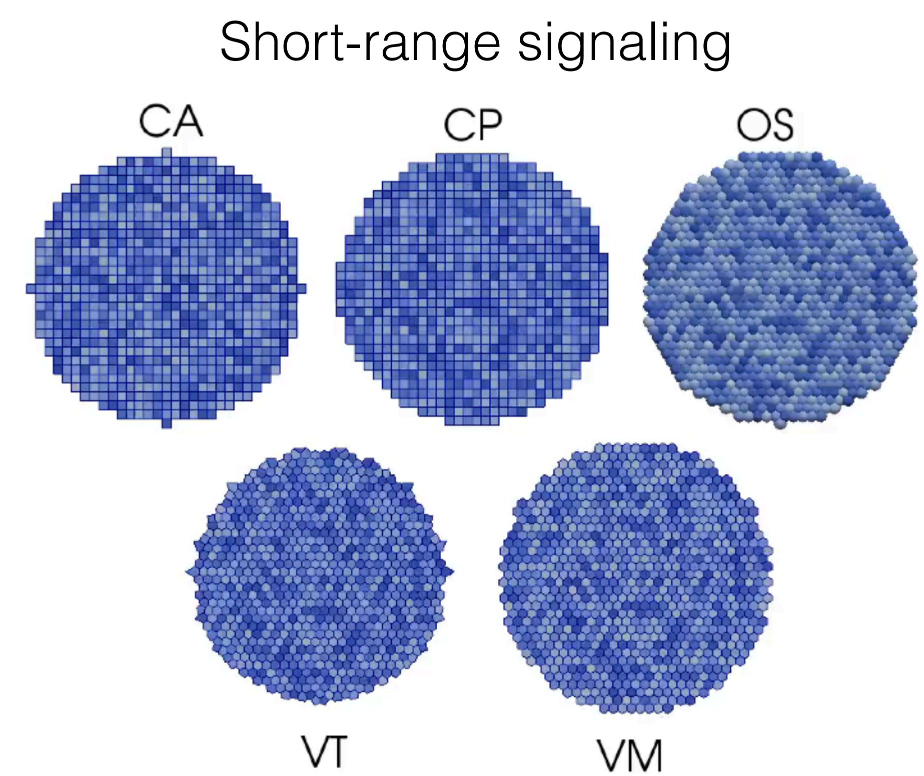
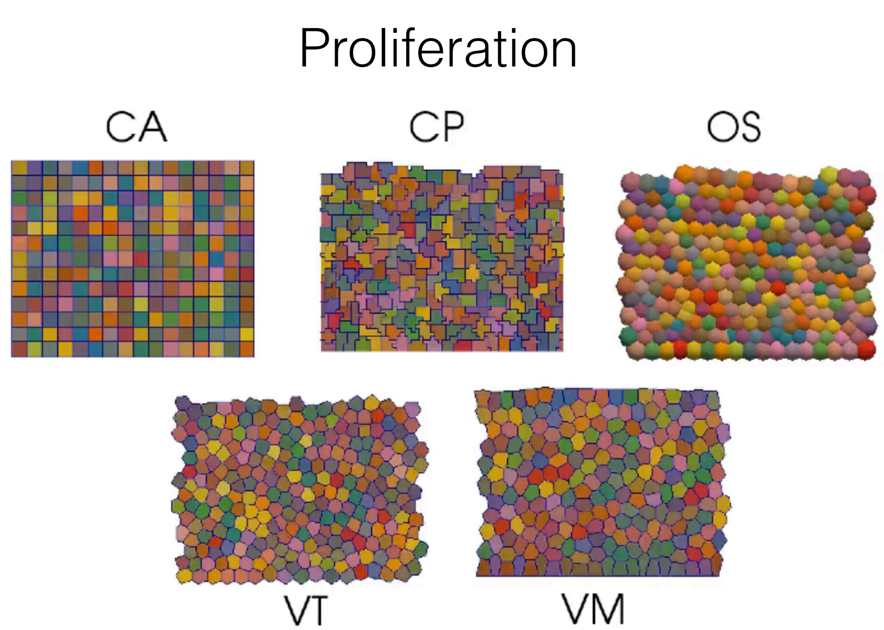
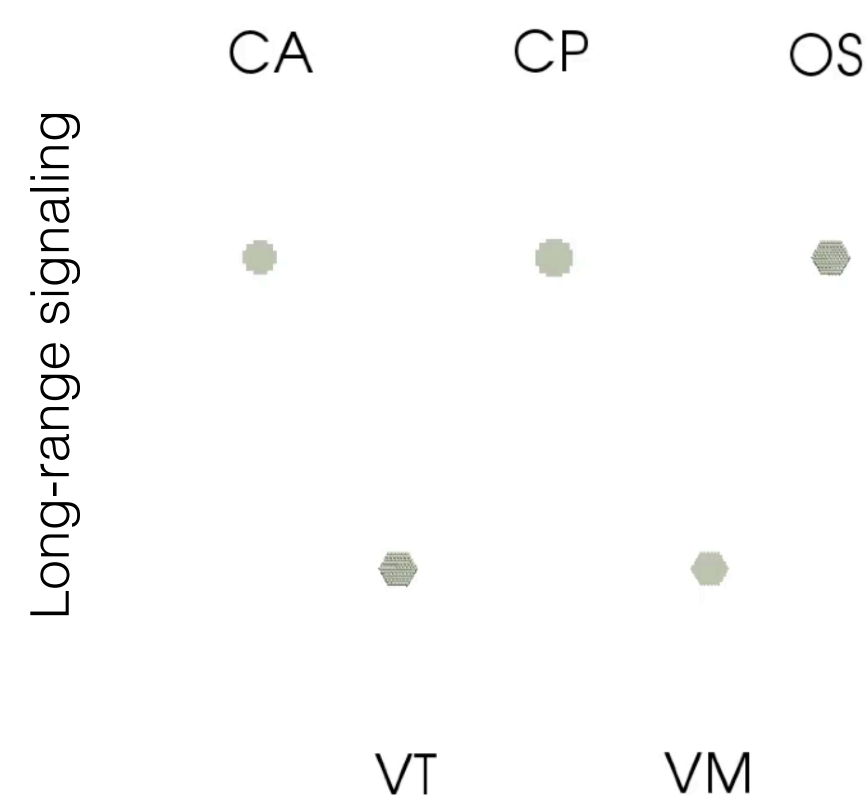






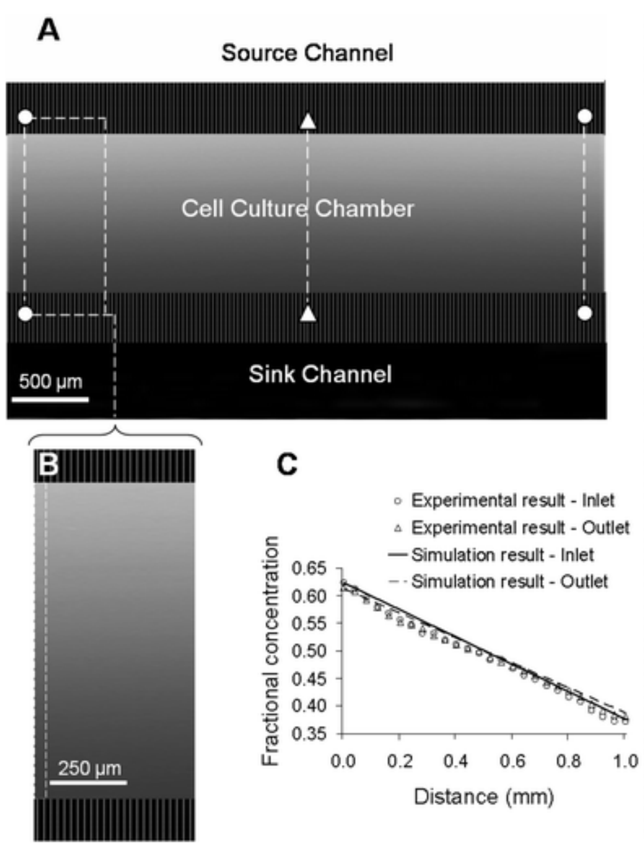


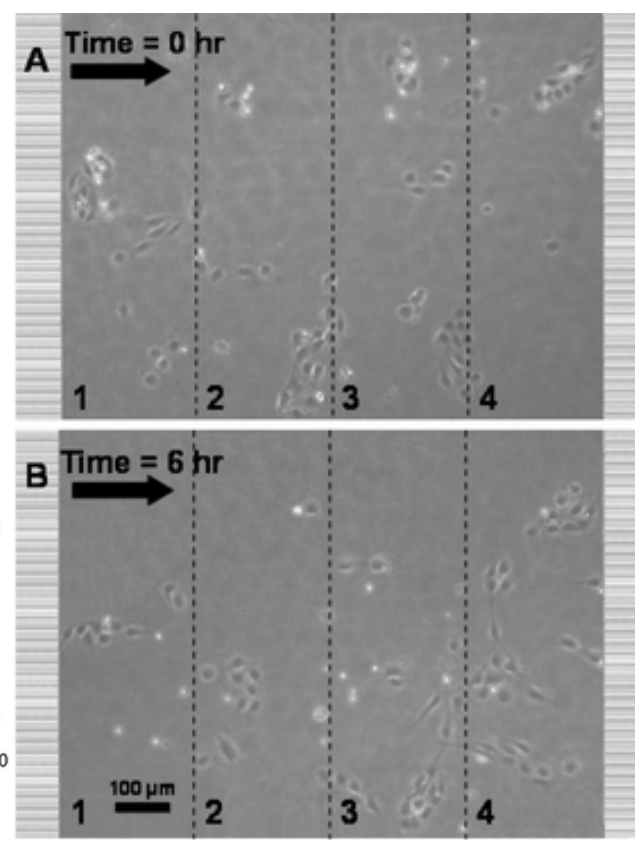
Fitting to experimental data

Approximate Bayesian Computation

Estimating chemotactic sensitivit

- Experiment
  - Microfluidic device
  - Stable VEGF gradient
  - Measure cell movement





Shamloo et al., 2008

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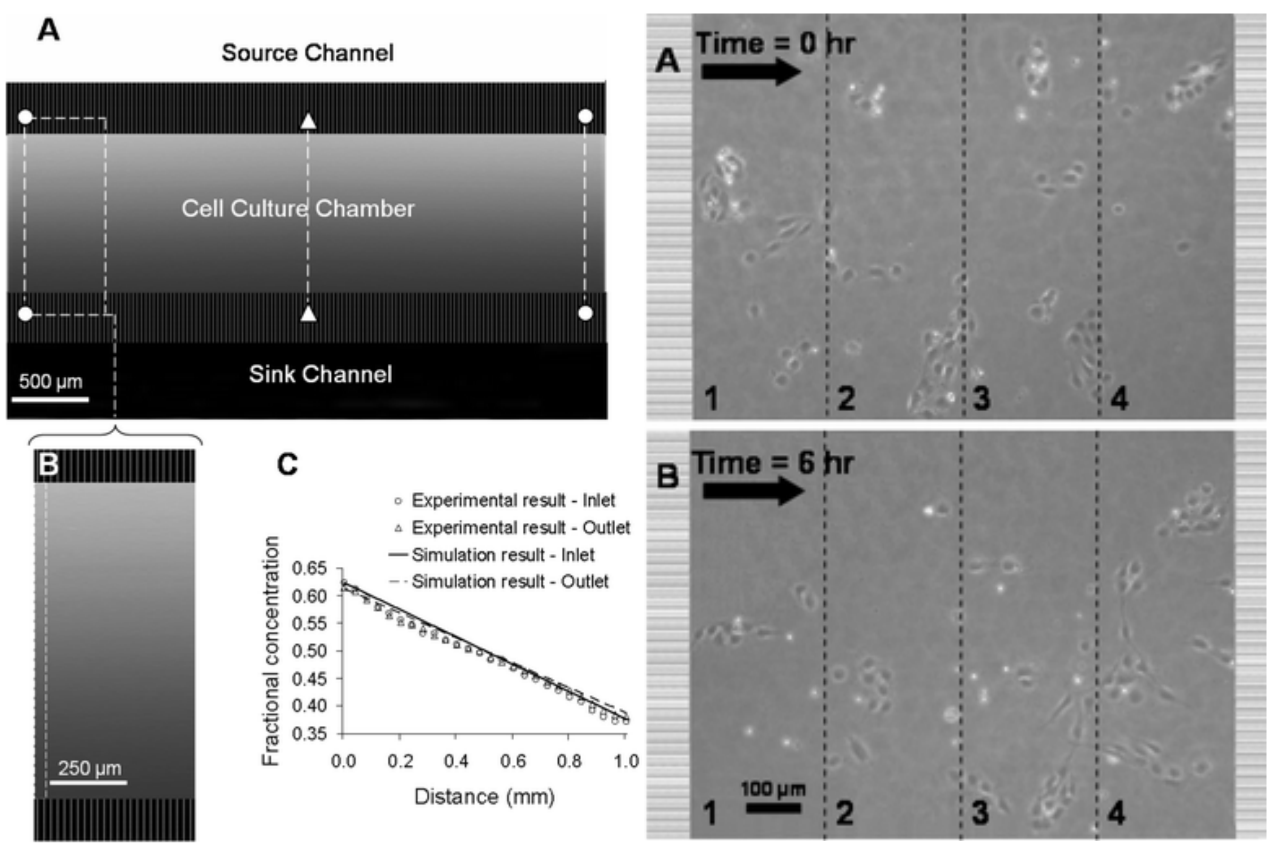
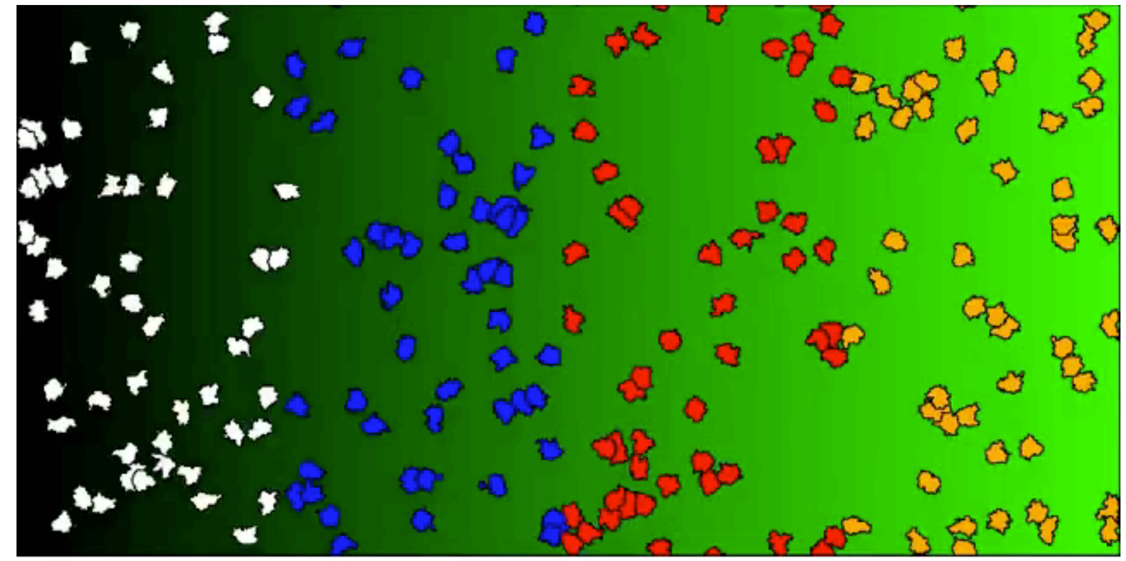
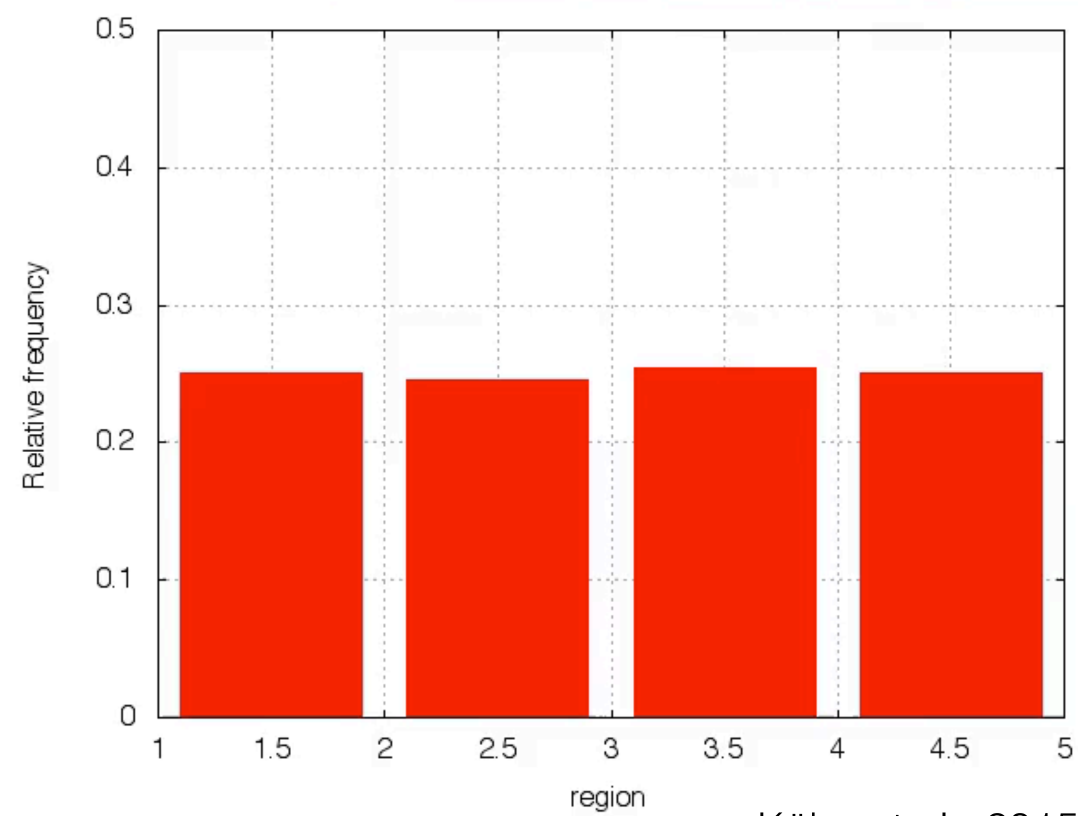


Shamloo et al., 2008





Köhn et al., 2015

Estimating chemotactic sensitivit

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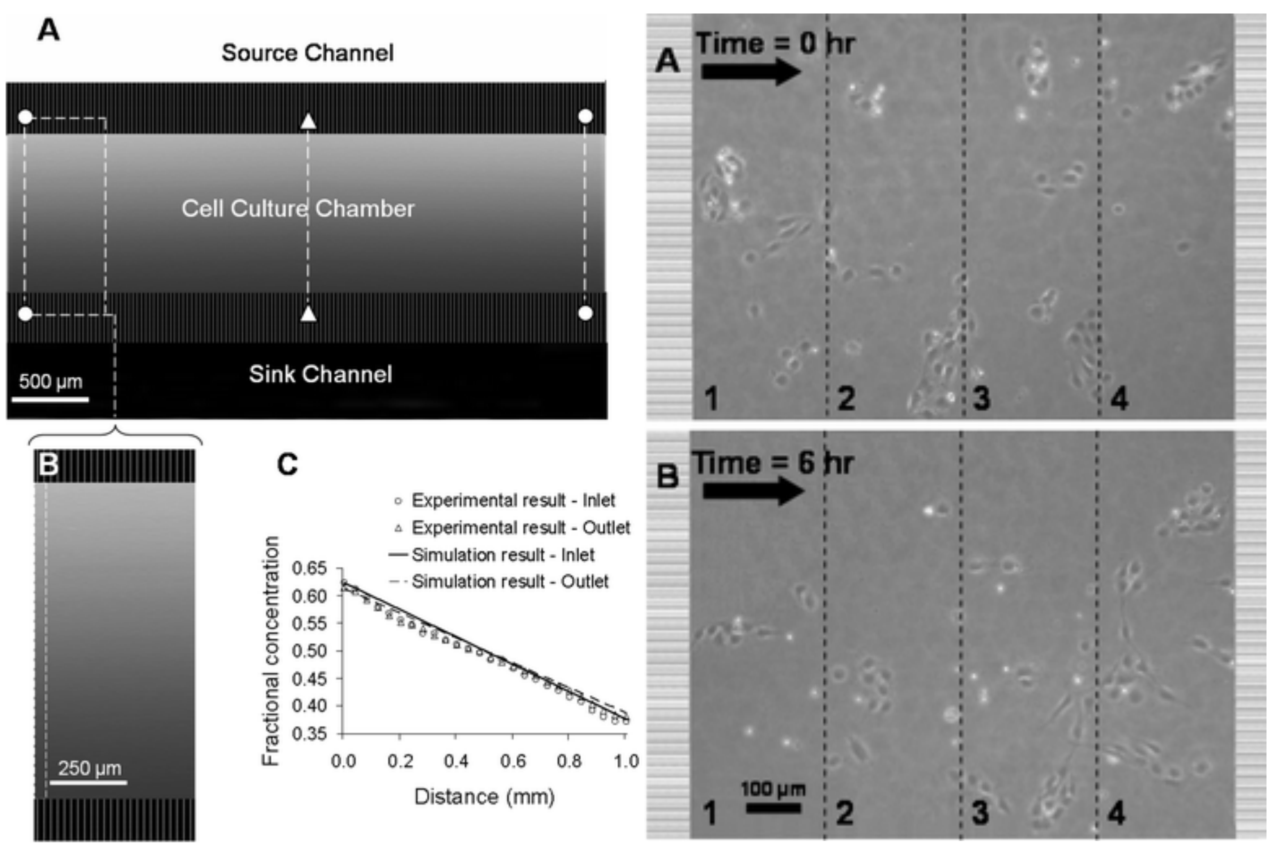
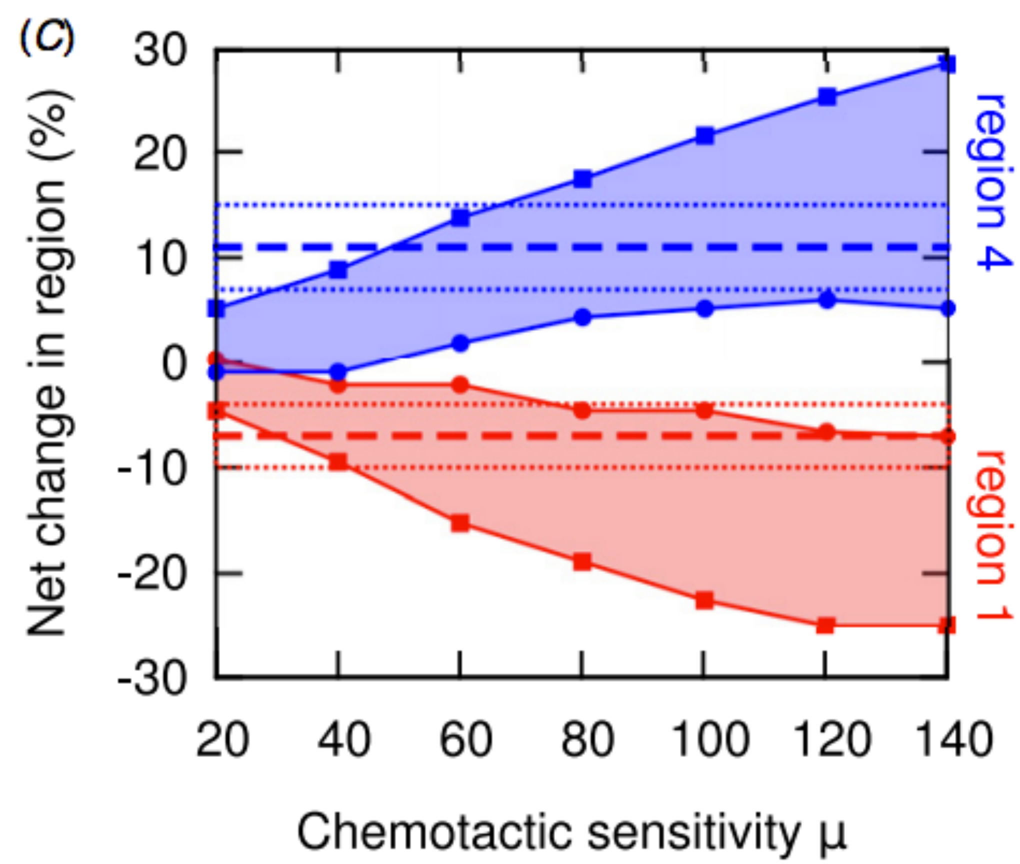


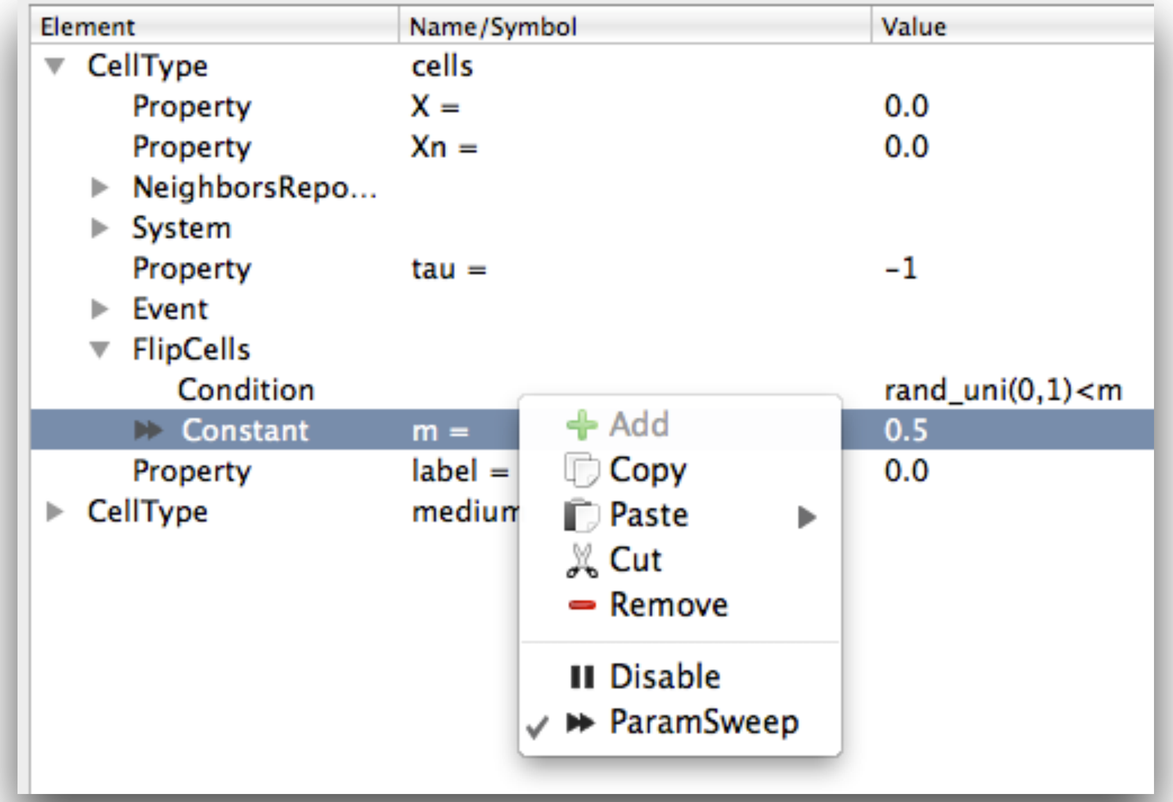
Shamloo et al., 2008

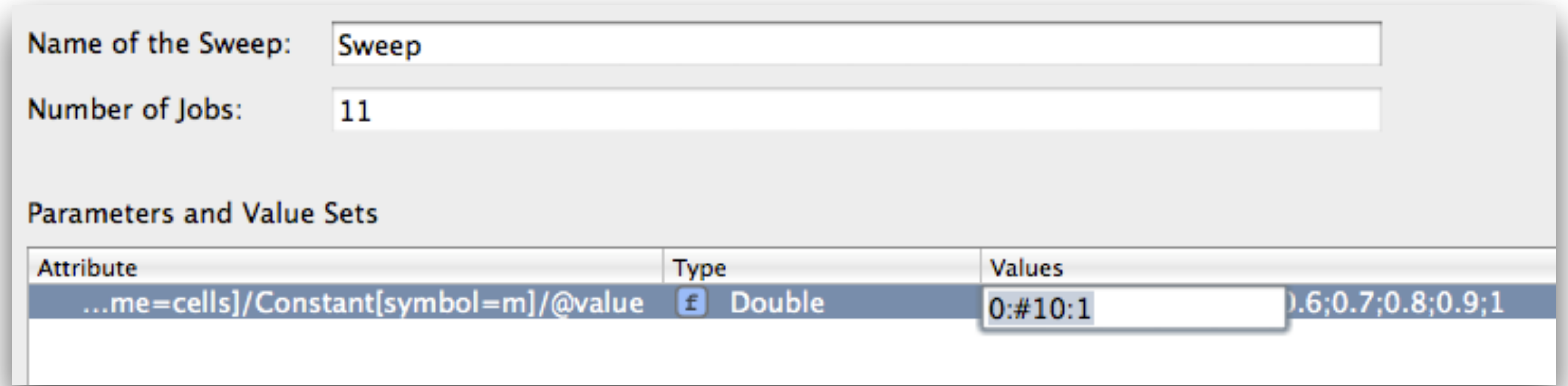


Köhn et al., 2015

Parameter sweep in Morpheus

- "Brute force" grid search
  - explore parameter space
  - with fixed intervals





Approximate Bayesian Computation

- Likelihood-free method
  - for complex models for which an analytic likelihood function cannot be written down
  - approximate posterior distribution by sampling

$$\text{posterior} = \frac{\text{likelihood} \times \text{prior}}{\text{marginal likelihood}}$$

- Requirements
  - Summary statistic
  - Distance measure
  - Tolerance (error)
  - Patience

Approximate Bayesian Computation

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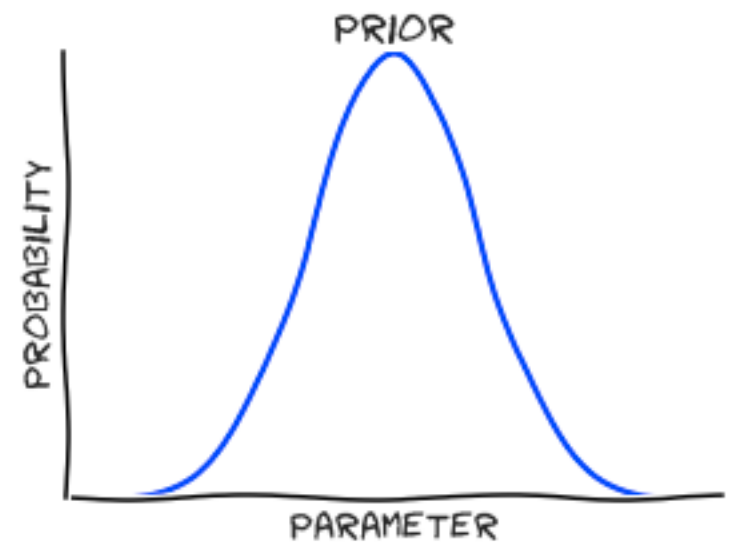
  - Patience

Bayes Rule:

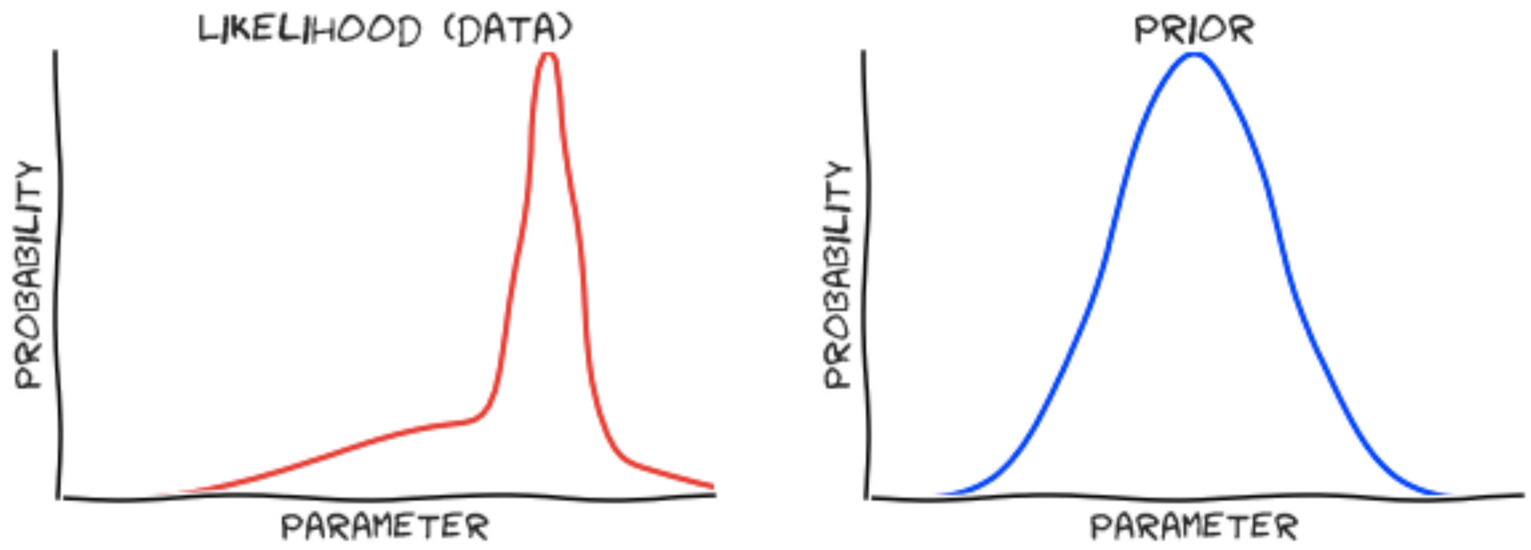
$$p(\theta_s|x) = \frac{p(x|\theta_s) \times p(\theta_s)}{p(x)}$$

$$\boxed{\text{posterior} = \frac{\text{likelihood} \times \text{prior}}{\text{marginal likelihood}}}$$

BAYESIAN INFERENCE



BAYESIAN INFERENCE



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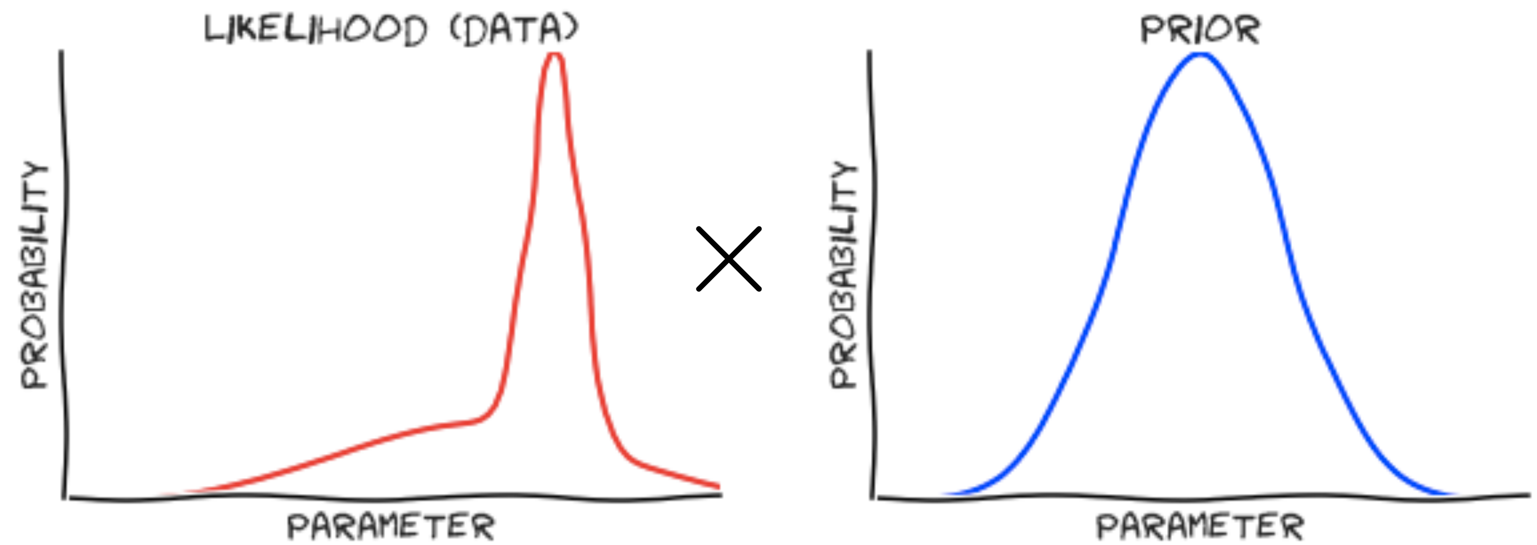

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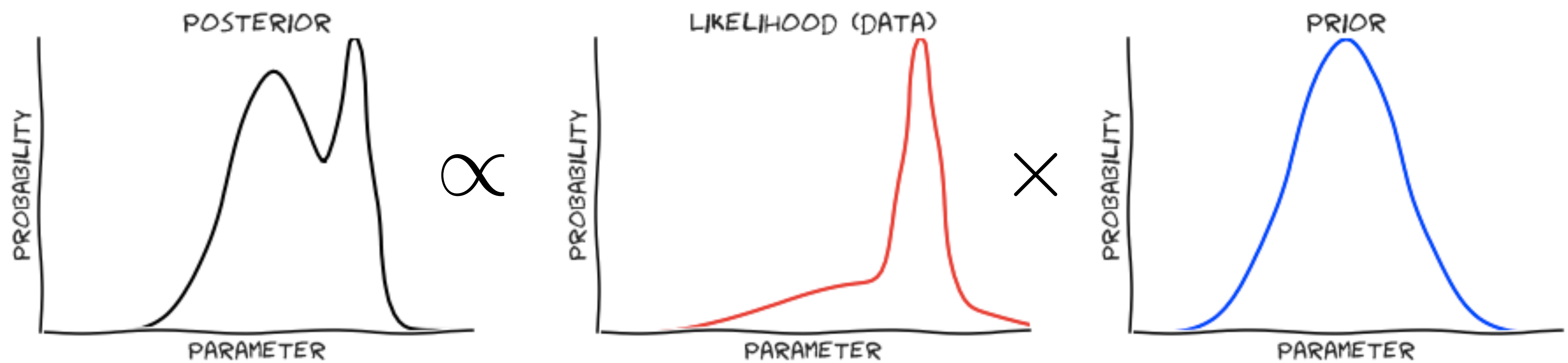

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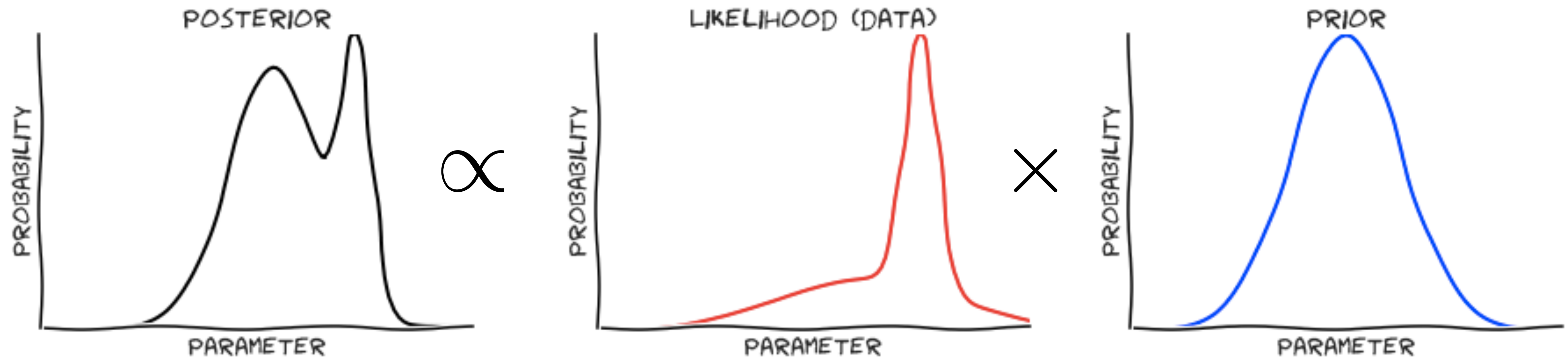
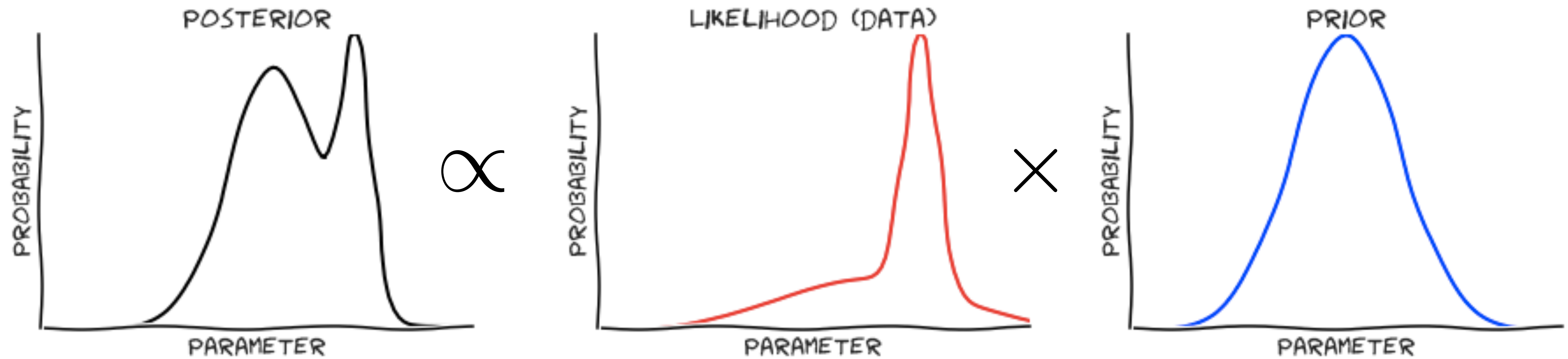


"TODAY'S POSTERIOR IS TOMORROW'S PRIOR" (LINDLEY, 1970)

BAYESIAN INFERENCE



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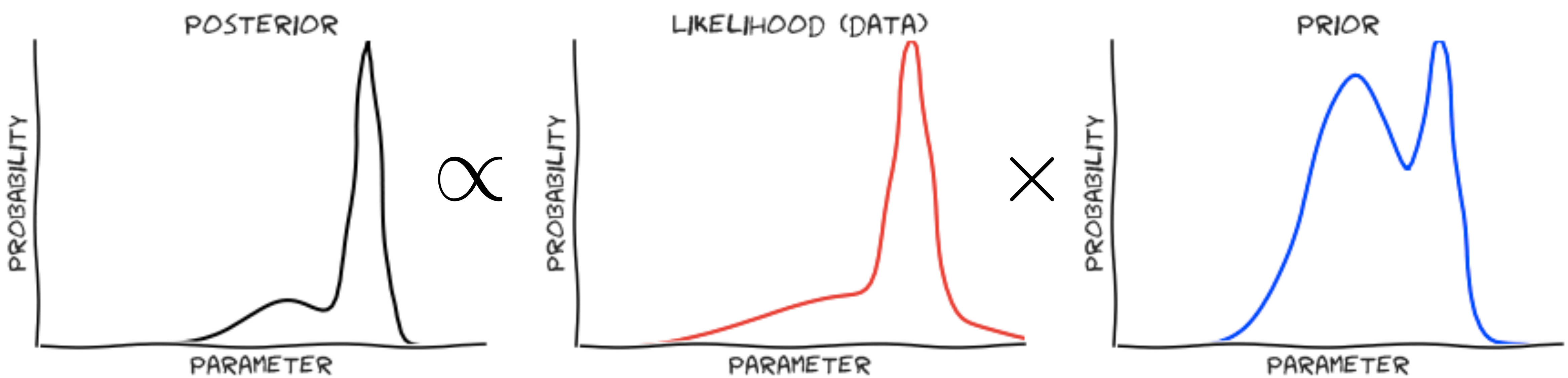
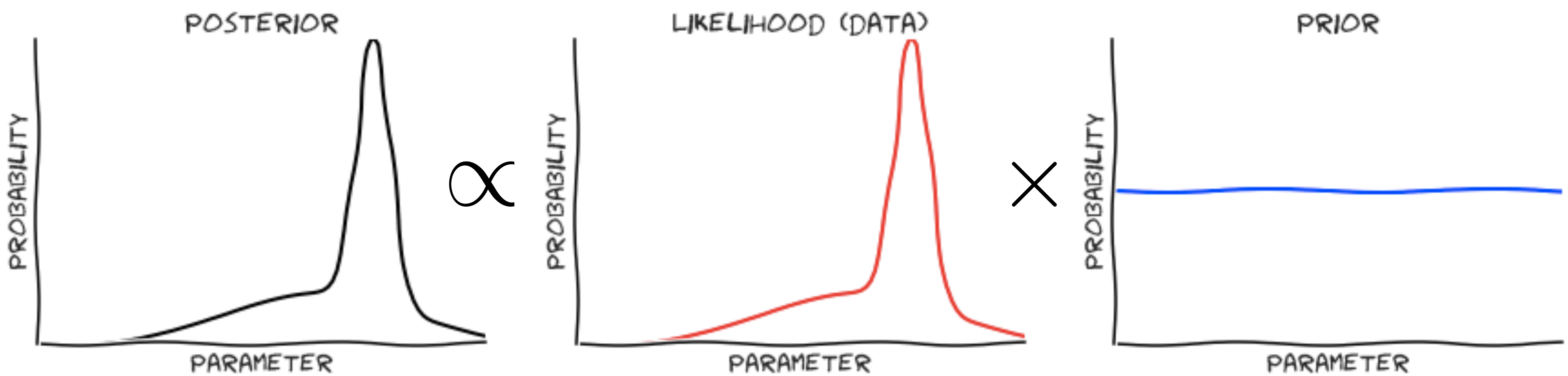
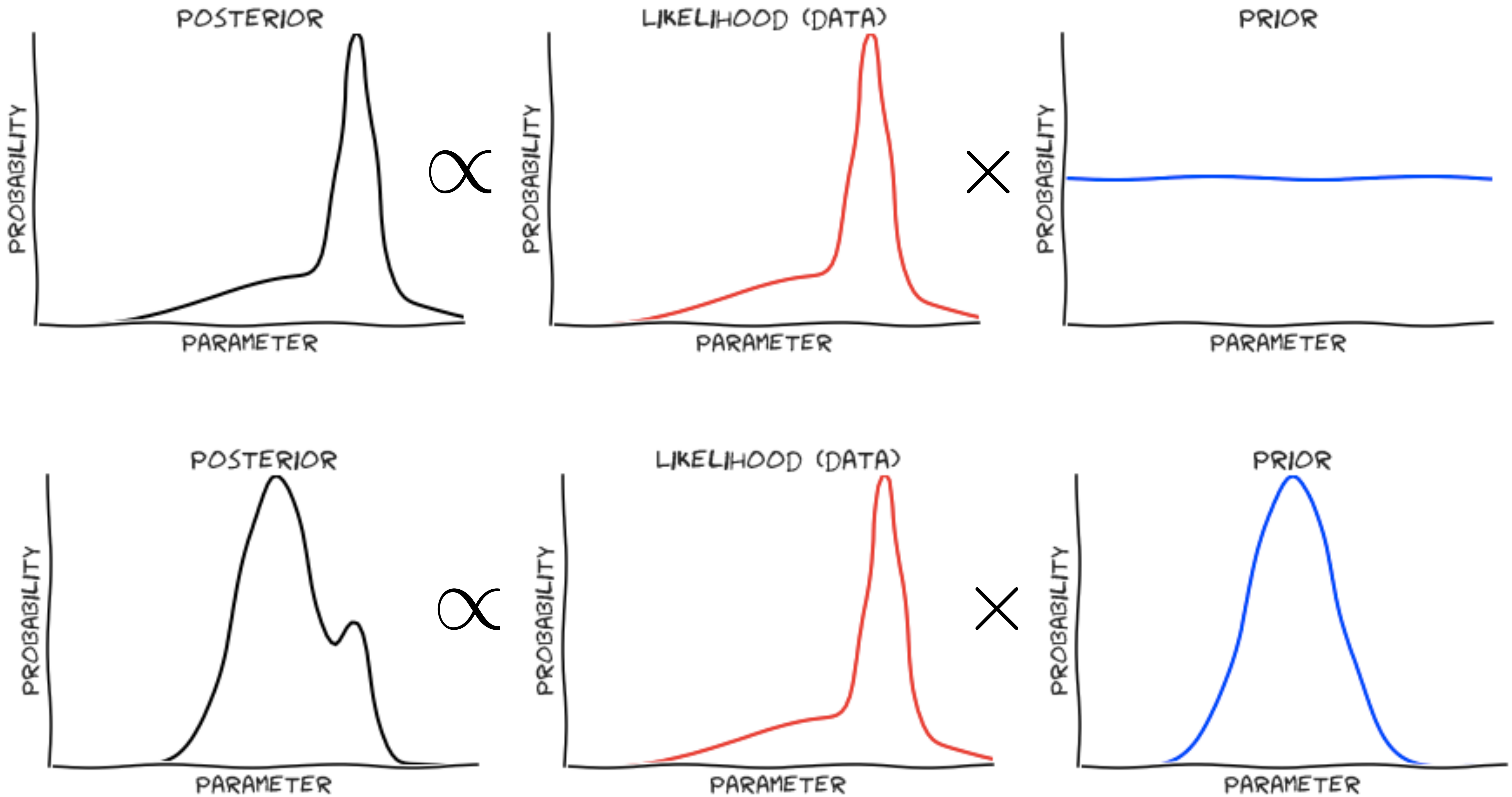


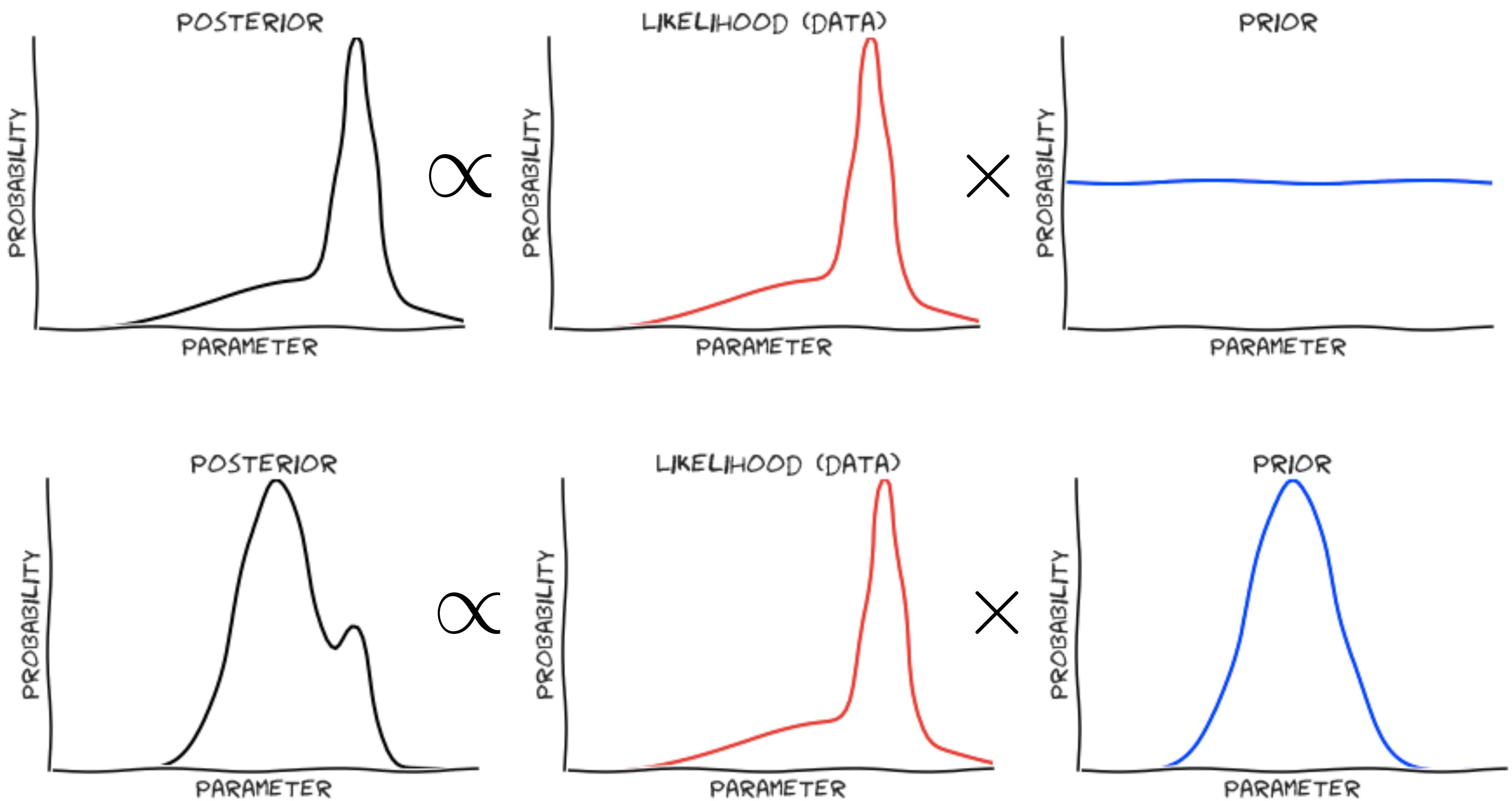
WEAK AND STRONG PRIORS



WEAK AND STRONG PRIORS

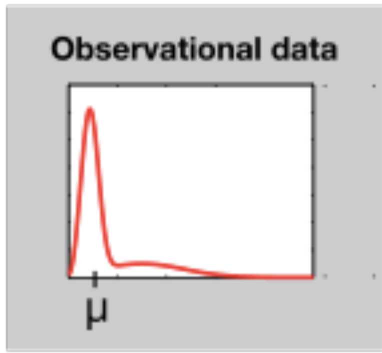


WEAK AND STRONG PRIORS

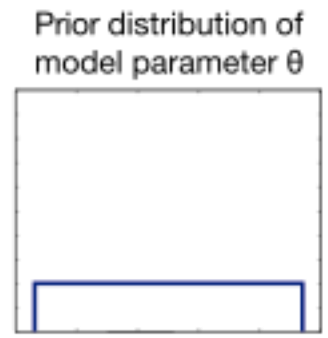


"EXTRA-ORDINARY CLAIMS REQUIRE EXTRA-ORDINARY EVIDENCE"
(CARL SAGAN)

ABC – STEP1 – DEFINE PRIOR & SUMMARY STATISTIC

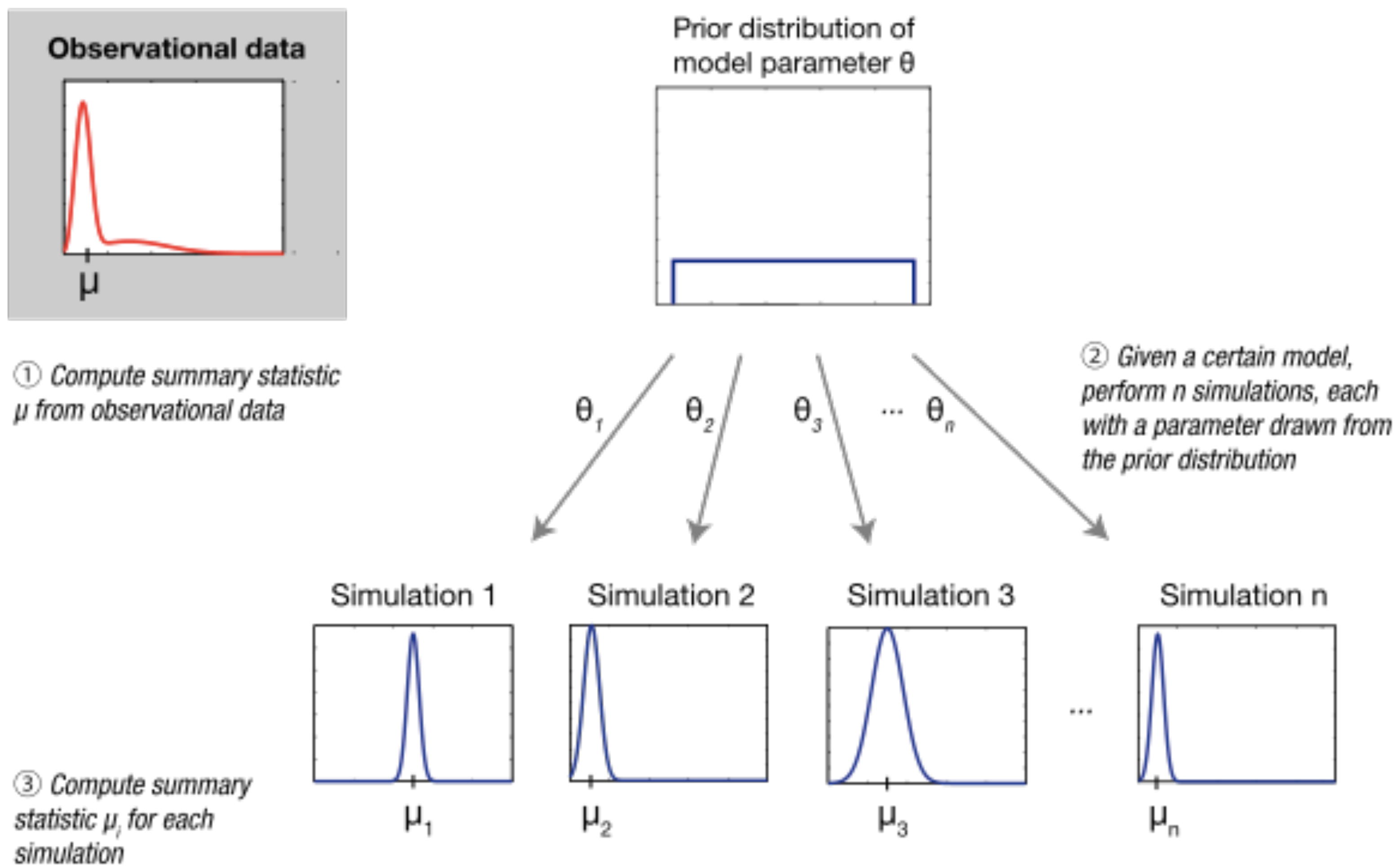


① *Compute summary statistic μ from observational data*



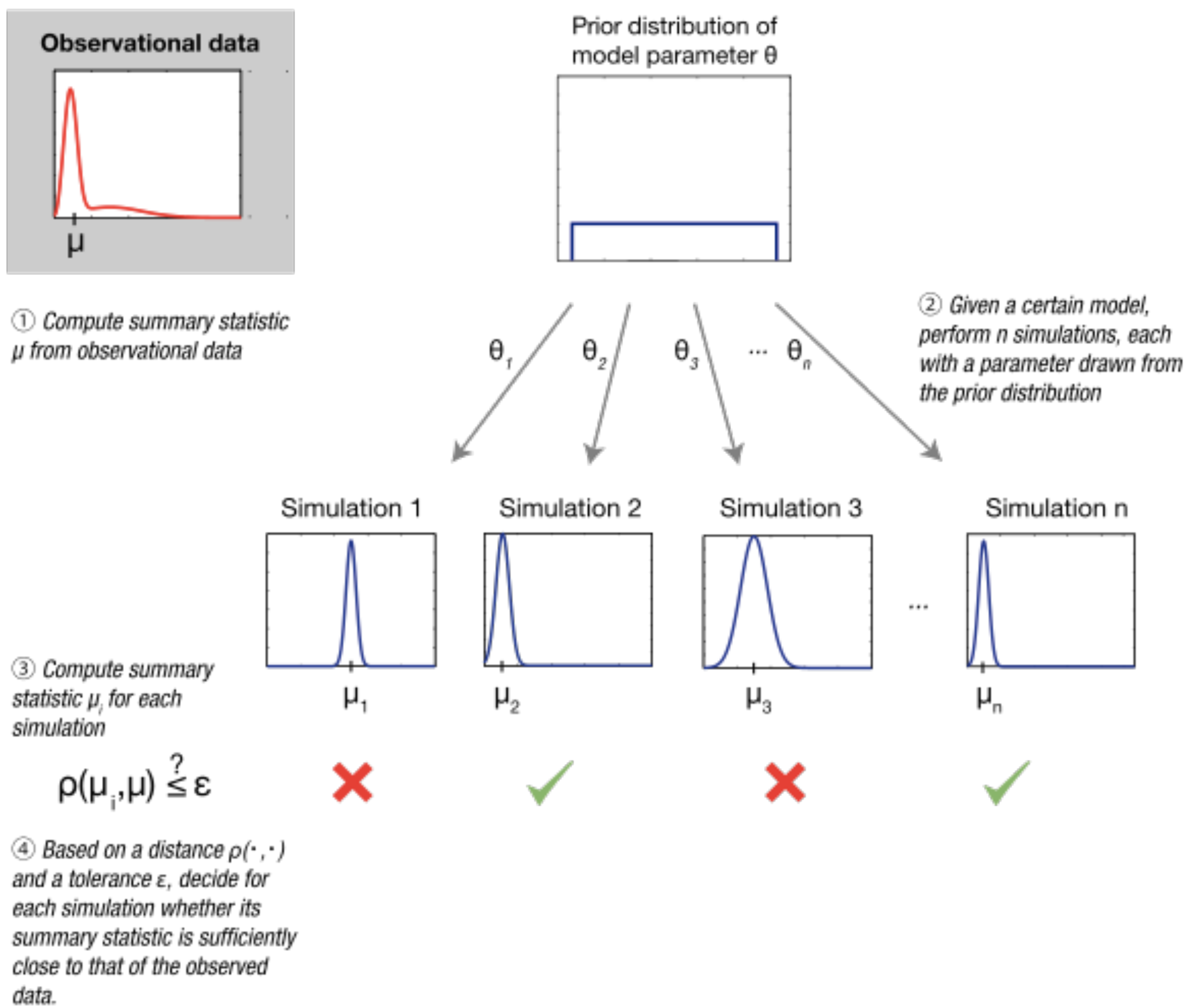
Wikipedia

ABC – STEP 2 – SAMPLE FROM PRIOR & RUN SIMULATIONS



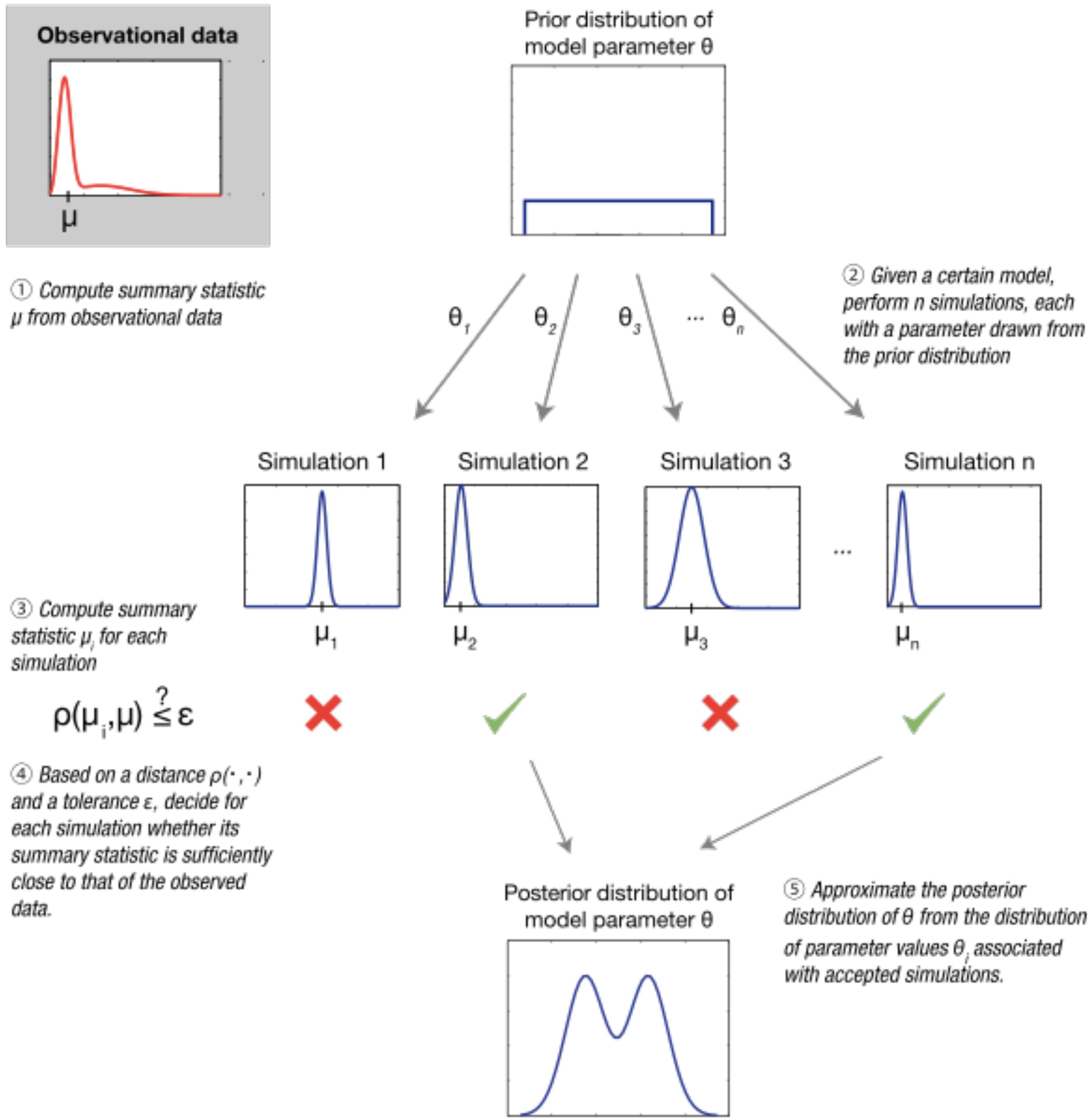
Wikipedia

ABC – STEP 3 – ACCEPT / REJECT MODELS



Wikipedia

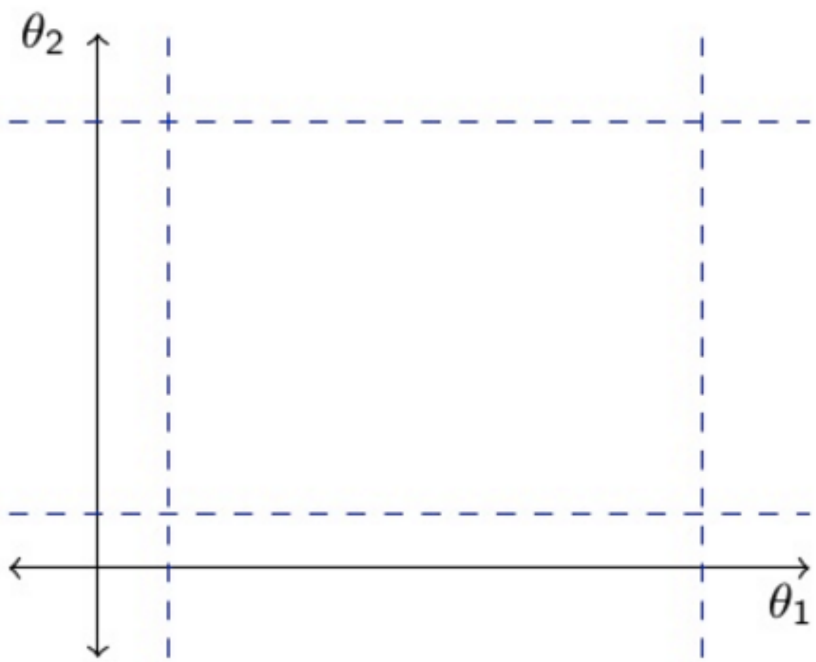
ABC – STEP 4 – APPROXIMATE POSTERIOR DISTRIBUTION



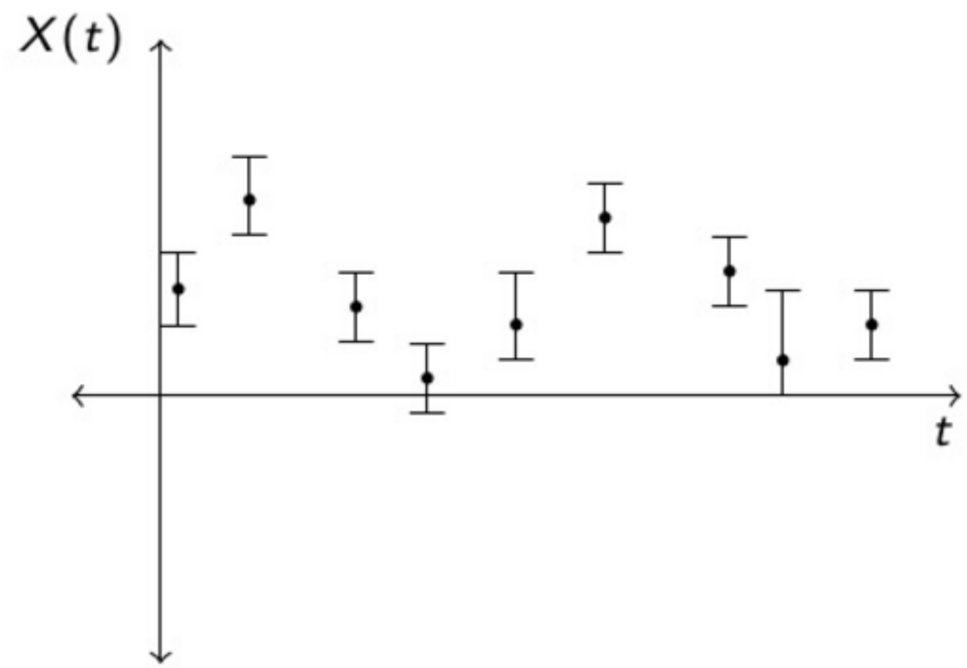
Wikipedia

Approximate Bayesian Computation

Model



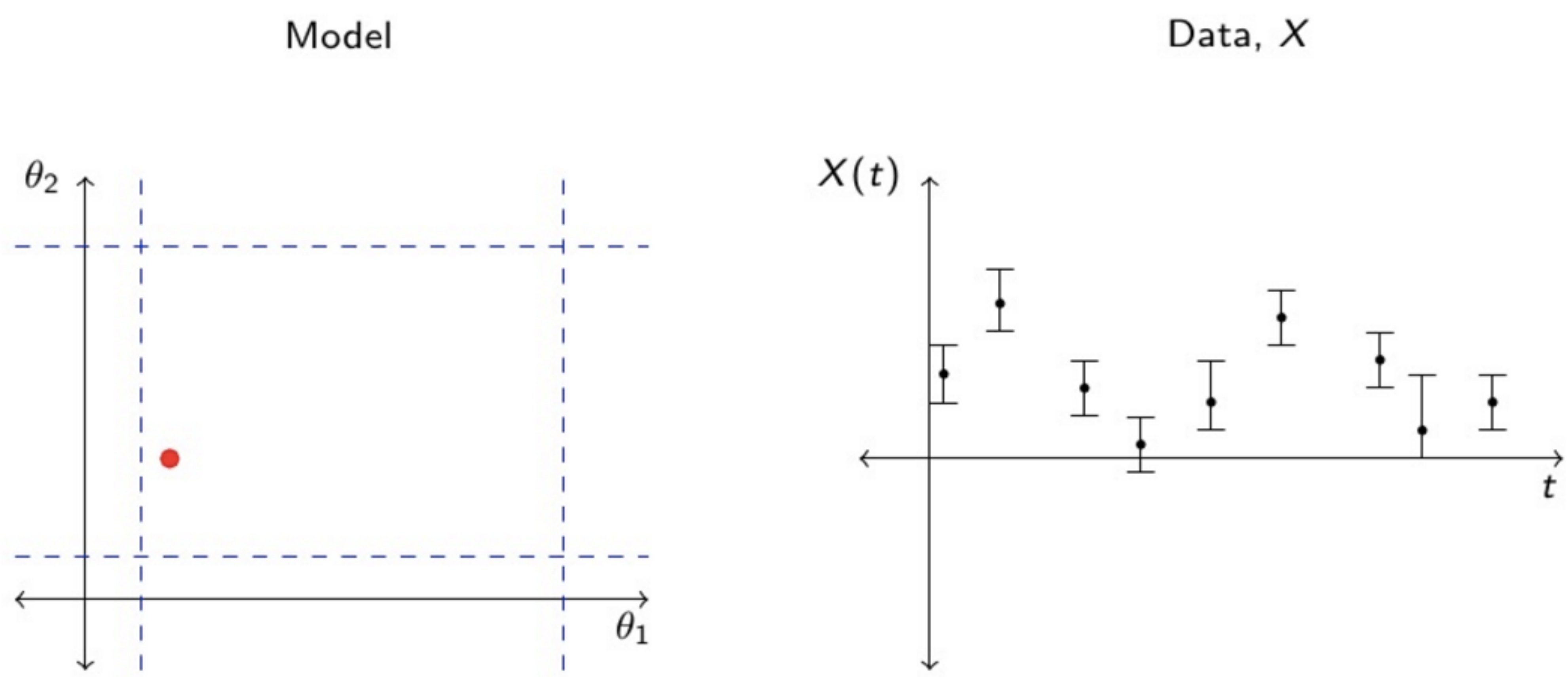
Data, X



Imperial College London

C. Barnes, ABC-SysBio, SlideShare

Approximate Bayesian Computation



C. Barnes, ABC-SysBio, SlideShare

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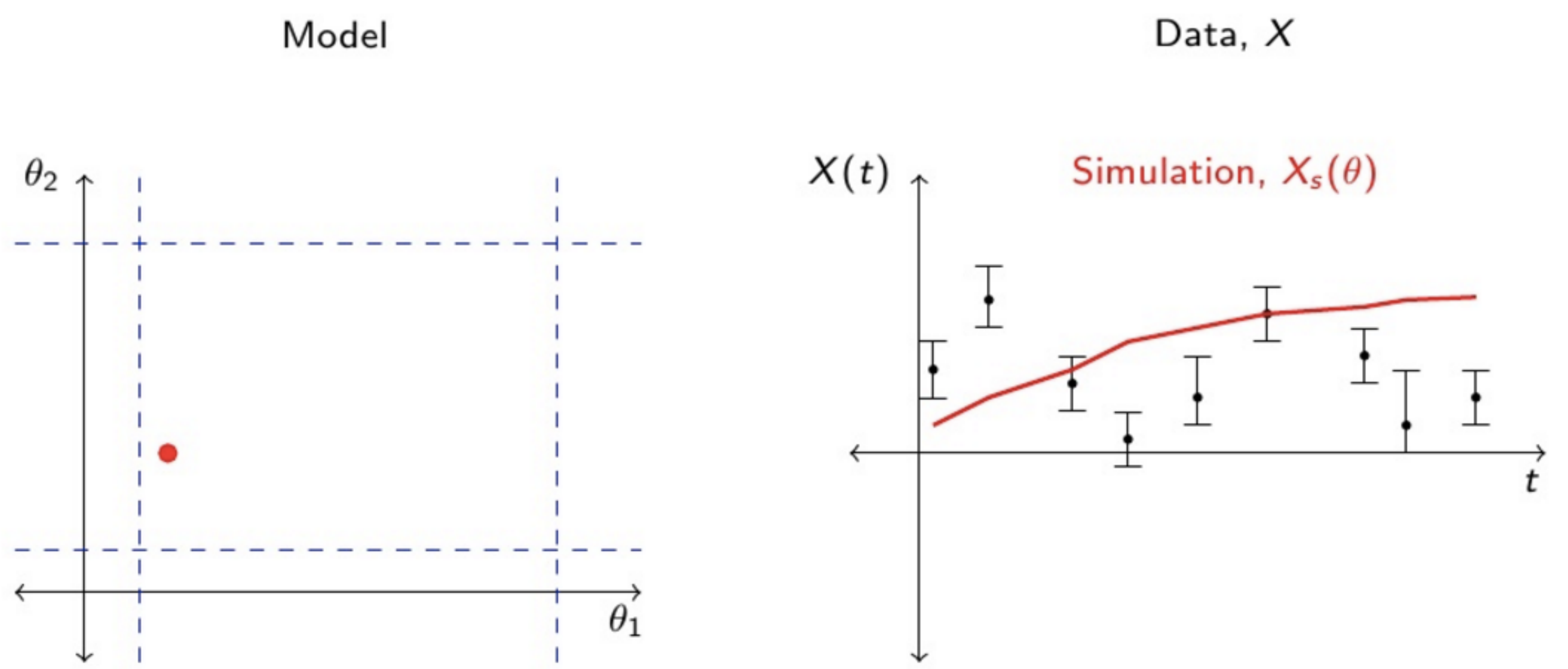

C. Barnes, ABC-SysBio, SlideShare

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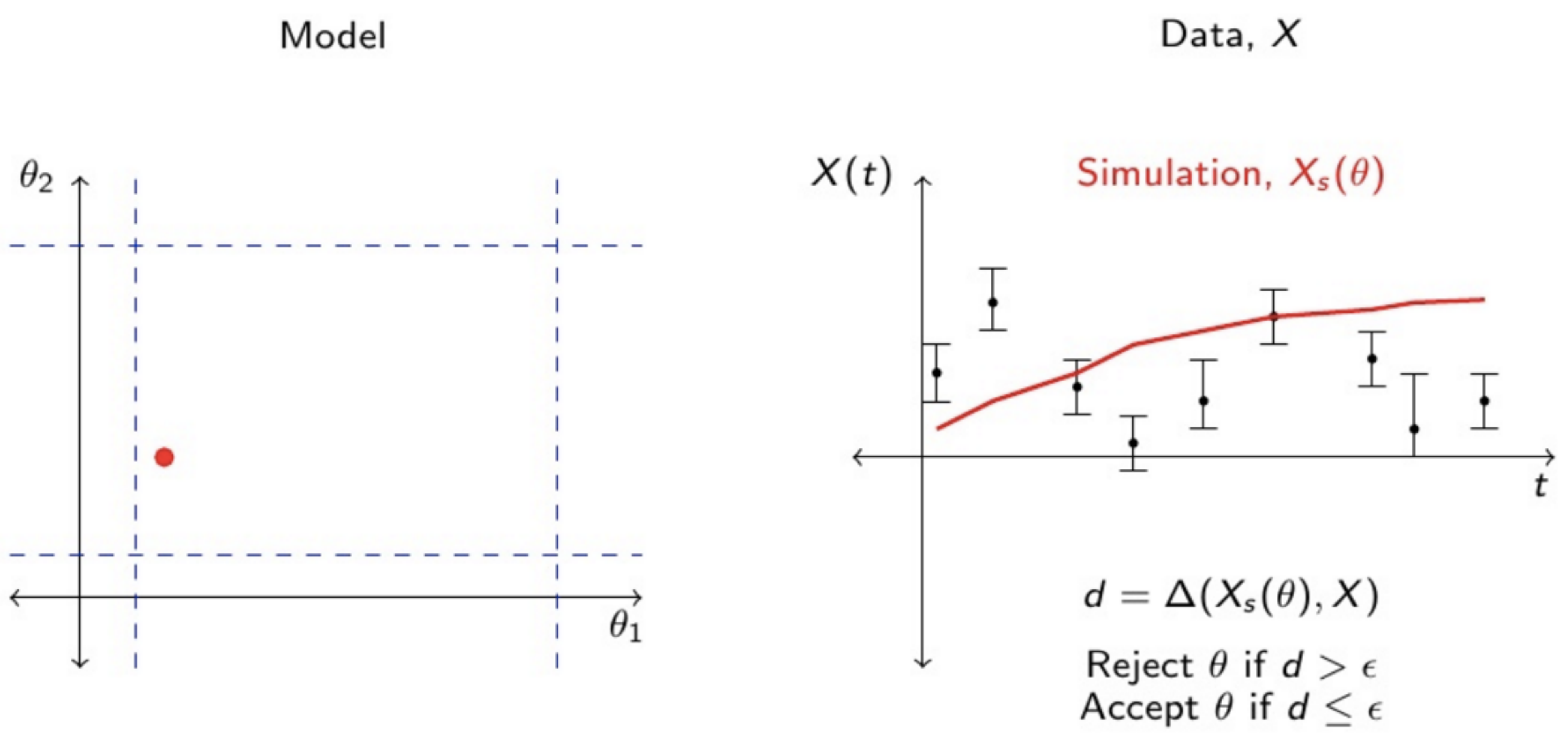

C. Barnes, ABC-SysBio, SlideShare

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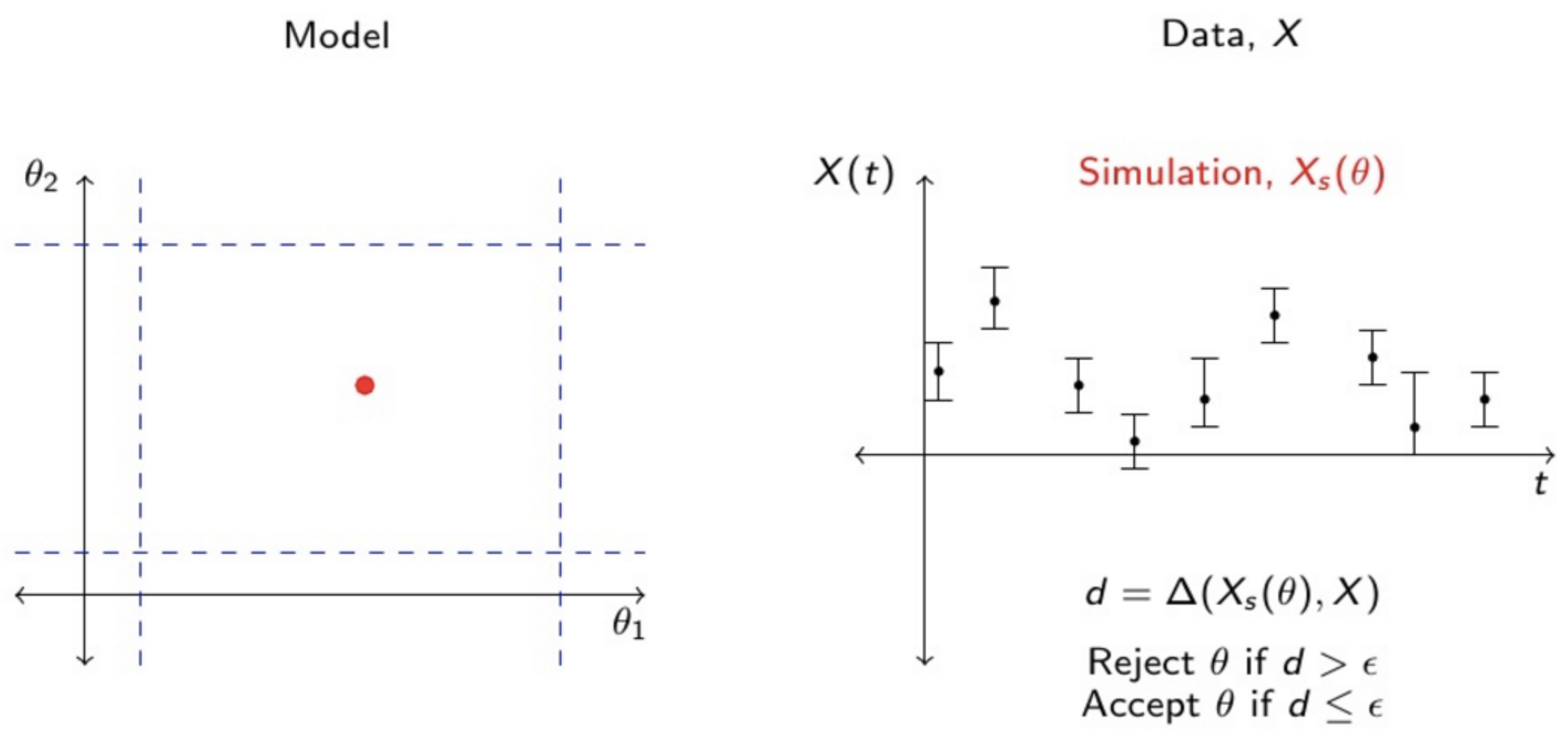

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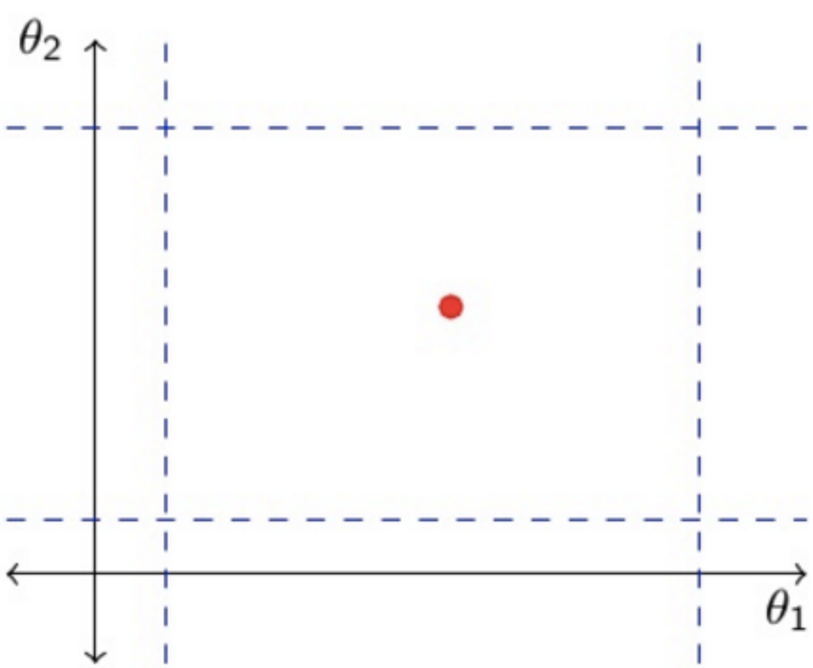
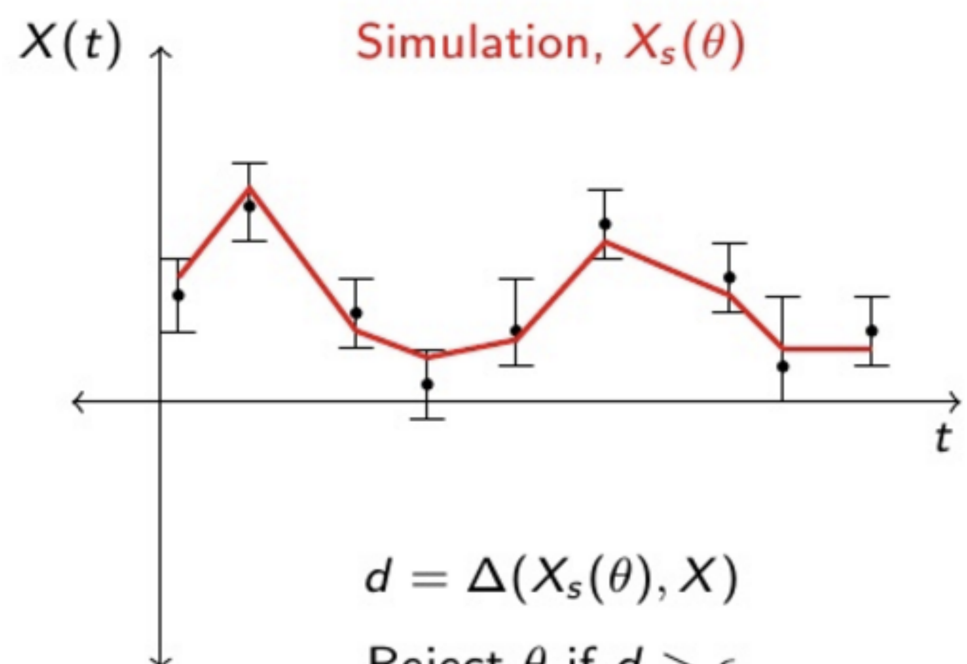
Approximate Bayesian Computation

Model



Data, X

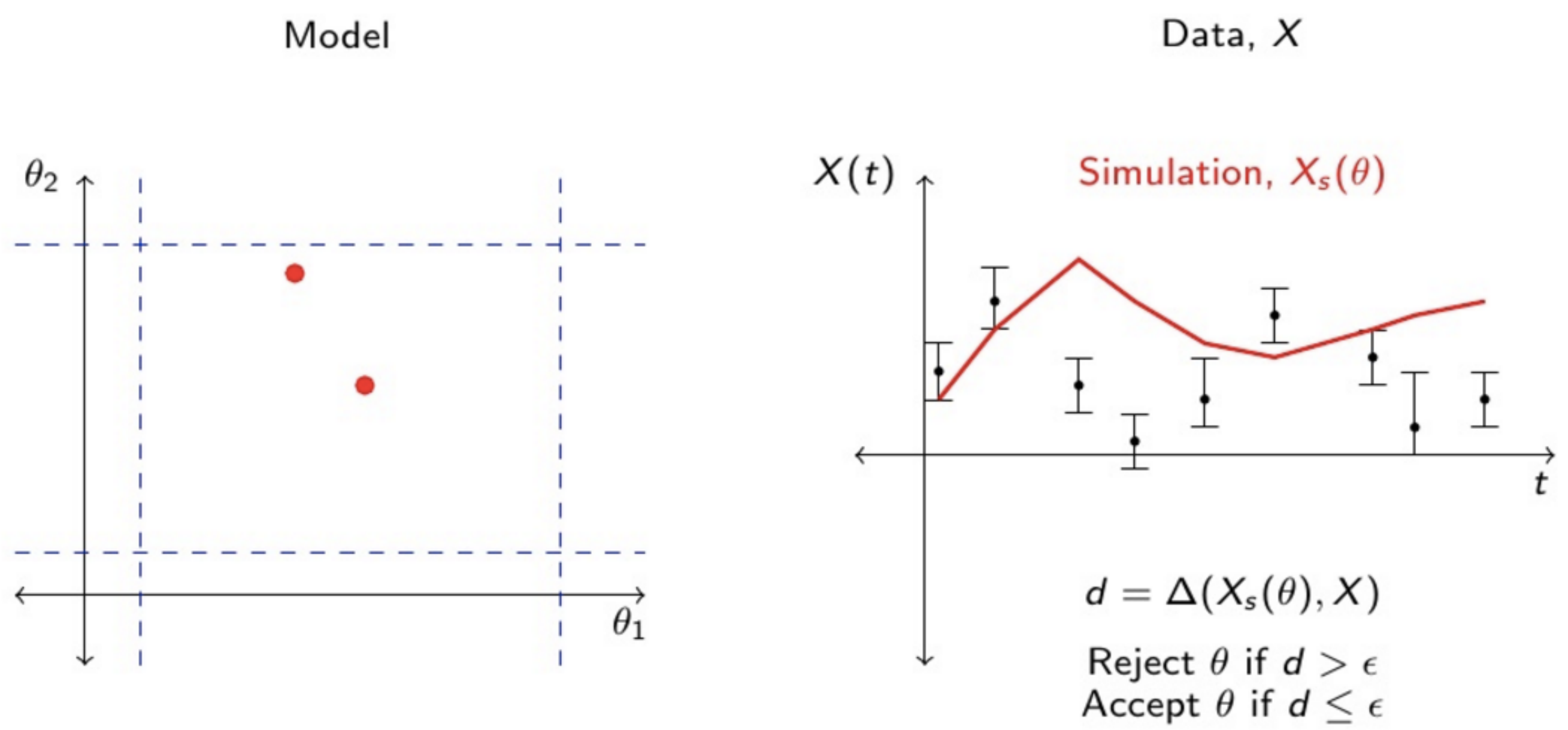


$$d = \Delta(X_s(\theta), X)$$

Reject θ if $d > \epsilon$
Accept θ if $d \leq \epsilon$

C. Barnes, ABC-SysBio, SlideShare

Approximate Bayesian Computation



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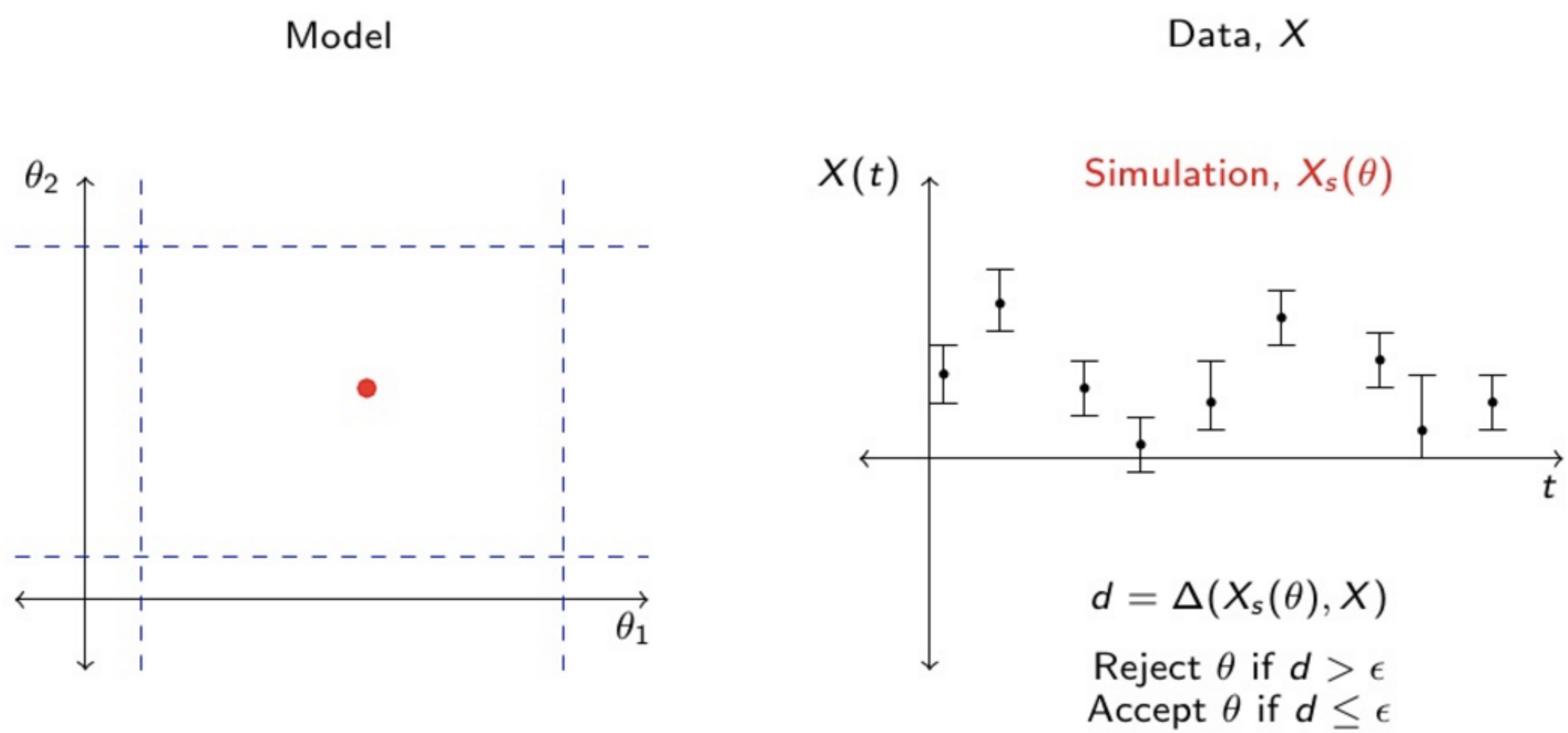

C. Barnes, ABC-SysBio, SlideShare

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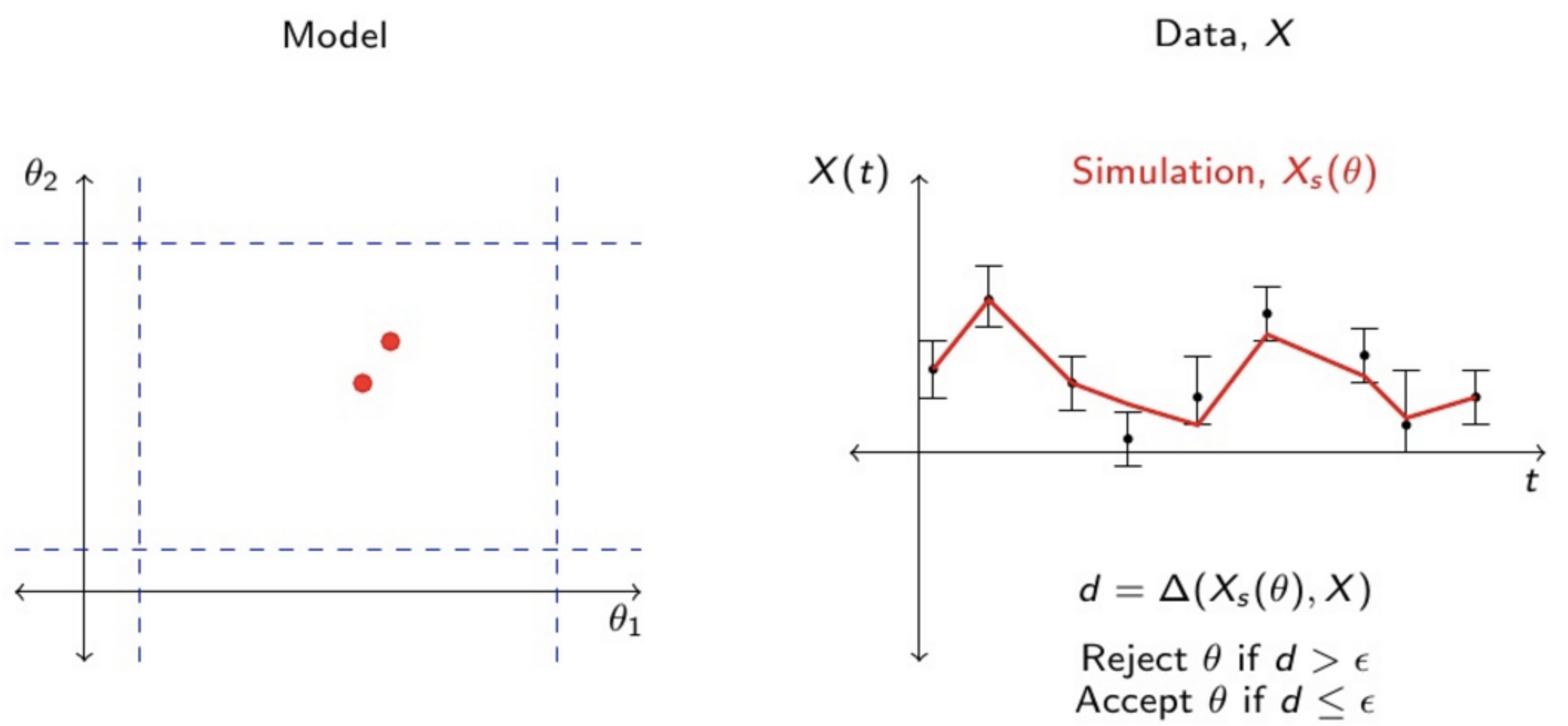
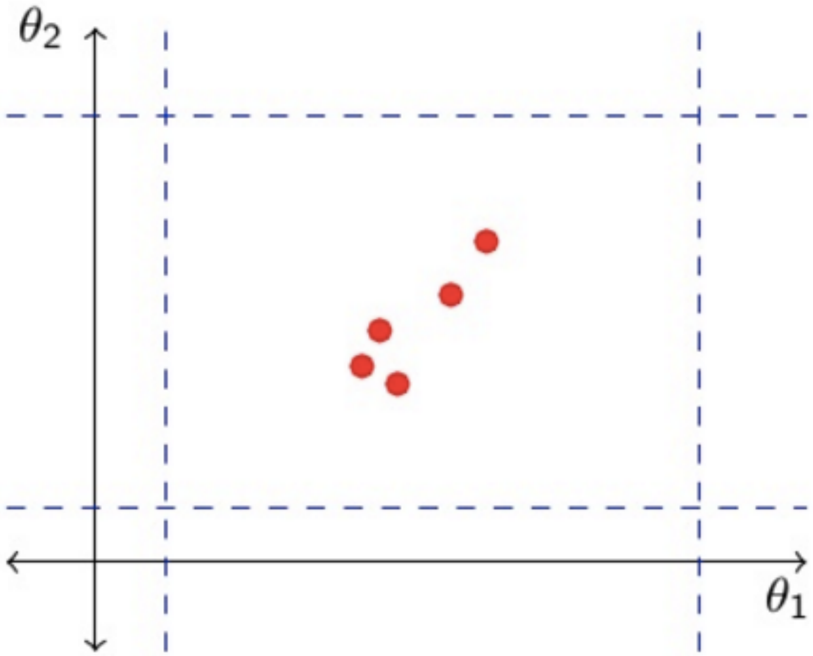


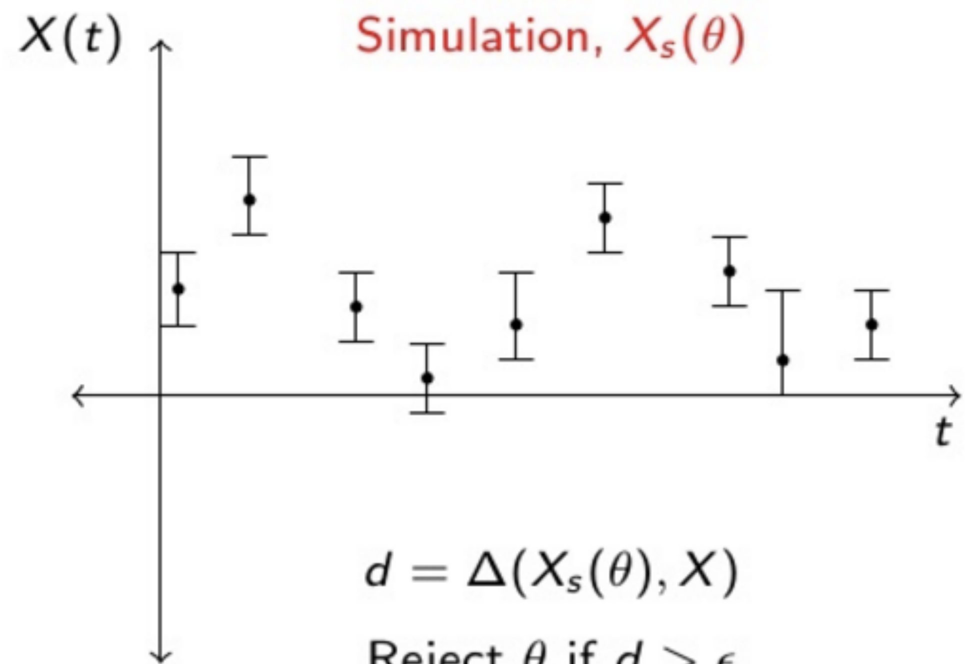
C. Barnes, ABC-SysBio, SlideShare

Approximate Bayesian Computation

Model



Data, X



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C. Barnes, ABC-SysBio, SlideShare

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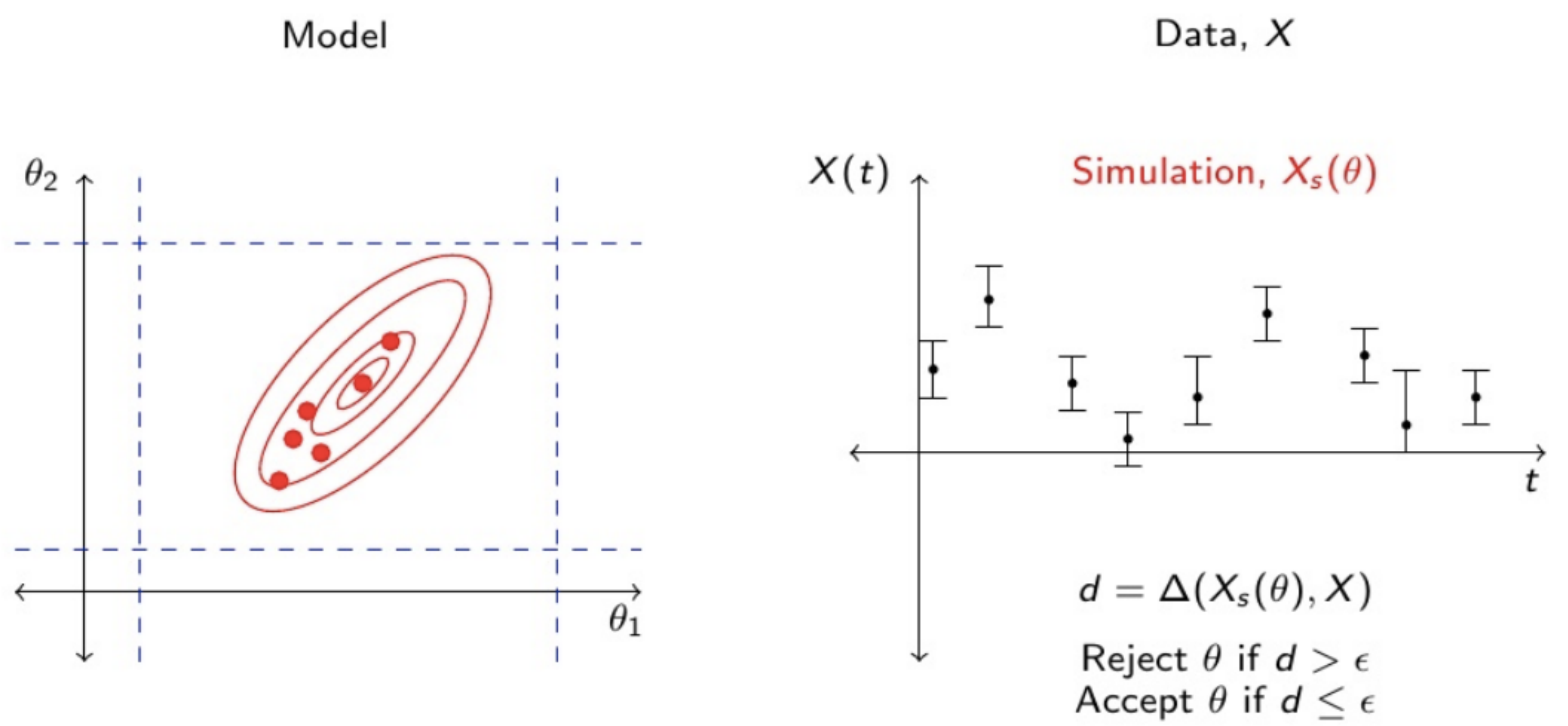
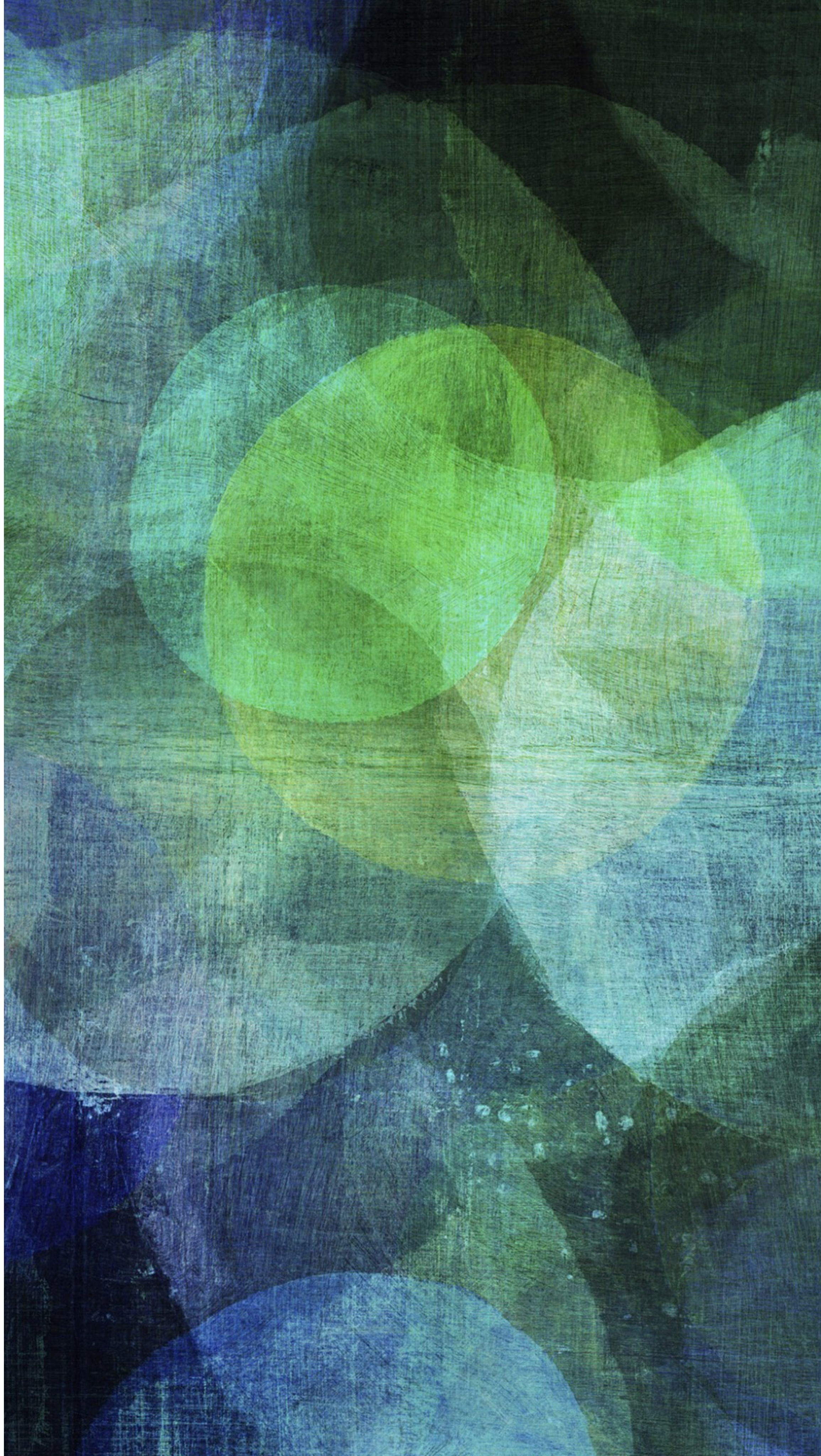
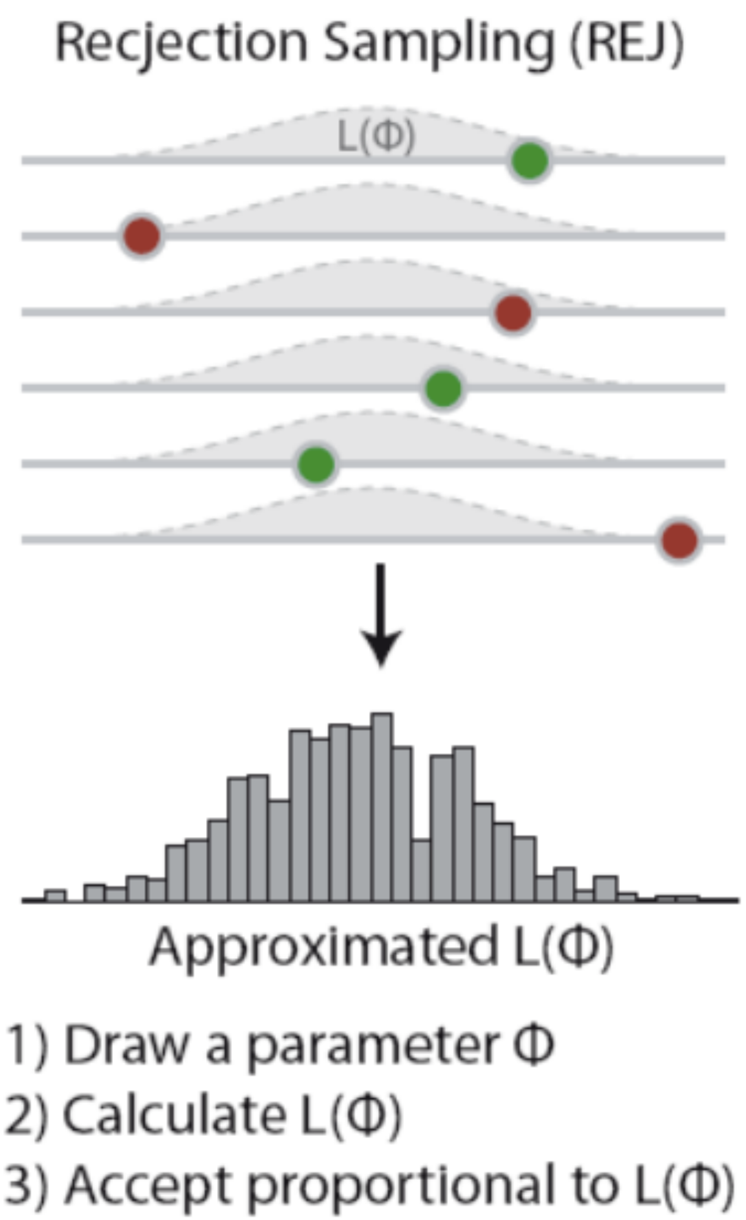


C. Barnes, ABC-SysBio, SlideShare

ABC
ALGORITHMS



REJECTION SAMPLING

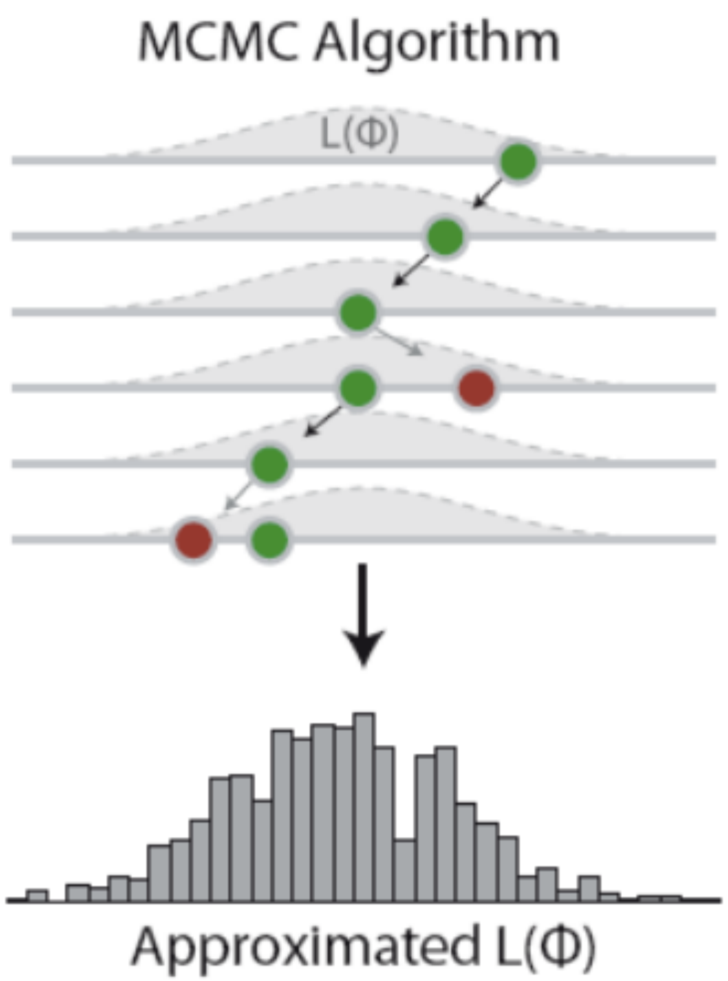


Algorithm 2 ABC-REJ (Tavare *et al.* 1997; Fu & Li 1997)

1: Define metric $d(S, S')$
2: Calculate S_{obs} from the data
3: **repeat**
4: Sample parameter ϕ from prior
5: Obtain simulated value S_{sim} from $M(\phi)$
6: Accept when $d(S_{sim}, S_{obs}) < \epsilon$
7: **until** Convergence criteria met

Hartig et al., Ecol Letters, 2011

MARKOV CHAIN MONTE CARLO (MCMC)



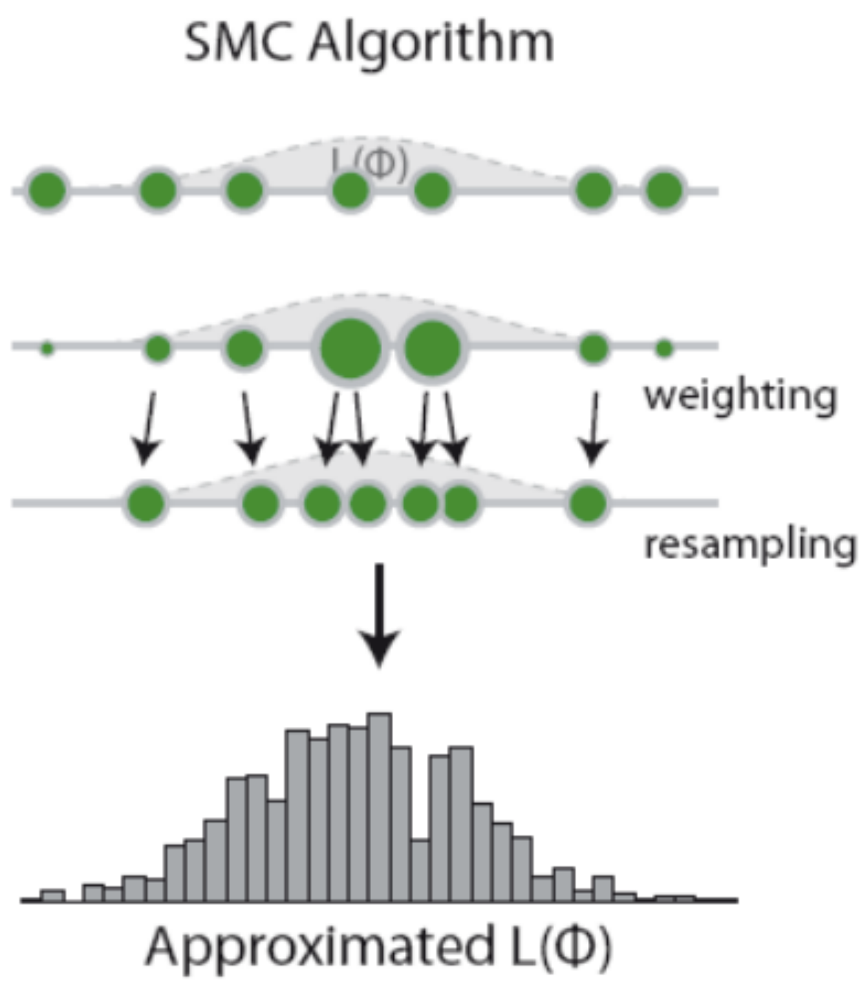
1) Draw new parameter Φ′ close to the old Φ
2) Calculate L(Φ′)
3) Jump proportional to L(Φ′)/L(Φ)

Algorithm 3 ABC-MCMC (Marjoram *et al.* 2003)

Define metric $d(S, S')$
Calculate S_{obs} from the data
Draw / choose initial ϕ
repeat
  Propose new ϕ according to proposal function $q(\phi \rightarrow \phi')$
  Obtain simulated value S_{sim} from $M(\phi')$
  if $d(S_{sim}, S_{obs}) < \epsilon$ **then**
    Jump to ϕ' with probability $\frac{p(\phi')q(\phi' \rightarrow \phi)}{p(\phi)q(\phi \rightarrow \phi')}$
  else
    Stay at ϕ
  end if
until Convergence criteria met

Hartig et al., Ecol Letters, 2011

SEQUENTIAL MONTE CARLO (SMC) A.K.A. PARTICLE FILTERING



1) Last set of parameters $\{\Phi_i\}$
2) Assign weight ω_i proportional to $L(\Phi_i)$
3) Draw new $\{\Phi_i\}$ based on the ω_i

Algorithm 4 ABC-SMC (Sisson *et al.* 2009; Beaumont *et al.* 2009)

Define metric $d(S, S')$
Set start acceptance distance $\epsilon_{t=0}$
repeat
    repeat
        if t = 0 **then**
            Sample particle ϕ_i^0 from initial distribution $\mu(\phi)$
            Set $\omega_i^0 = p(\phi)/\mu(\phi)$
        else
            Pick ϕ_i^t from the ϕ_j^{t-1} with prob ω_j^{t-1}
            Perturb ϕ_i^t by Kernel $K(\phi, \phi')$
            Set $\omega_i^t = p(\phi)/\sum_{j=1}^{N} \omega_j^{t-1} K(\phi_i^t, \phi_j^{t-1})$
        end if
        if $d(M(\phi_i^t), S) < \epsilon_t$ **then**
            Accept ϕ_i^t for the next generation
        end if
    until N particles sampled
    Optional: update ϵ_t and $K(\phi, \phi')$
until Convergence criteria met

Hartig et al., Ecol Letters, 2011