A Hybrid Control Model of Fractone-Dependent Morphogenesis

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Morphogenesis

What is **Morphogenesis**?

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- The biological process that gives a developing organism its shape.

Morphogenesis

What is **Morphogenesis**?

- The biological process that gives a developing organism its shape.
- Important Factors: DNA and the Extracellular Matrix

Extracellular Matrix

What is the **Extracellular Matrix**?

- Collection of molecules outside of cells (including basal lamina)
- Gives Structure
- Affects Behavior (communication, migration, differentiation)
- Has Growth Factors

Growth Factors

What is a **Growth Factor/Cytokine**?

- Chemical signal for cell
- Several families and types
- Signal many behaviors: Migration, Differentiation, Apoptosis, Mitosis
- Created by various cells

Growth Factors

What is a **Growth Factor/Cytokine**?

- Chemical signal for cell
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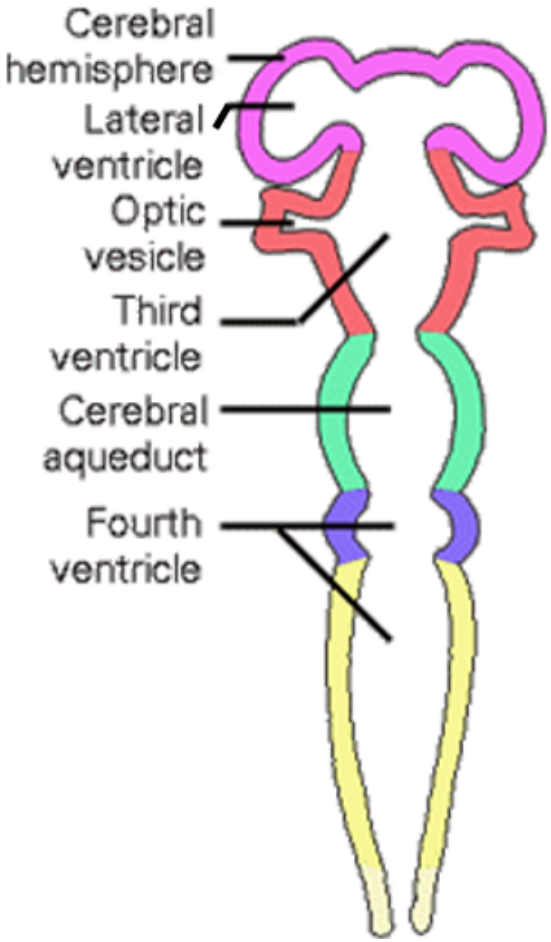
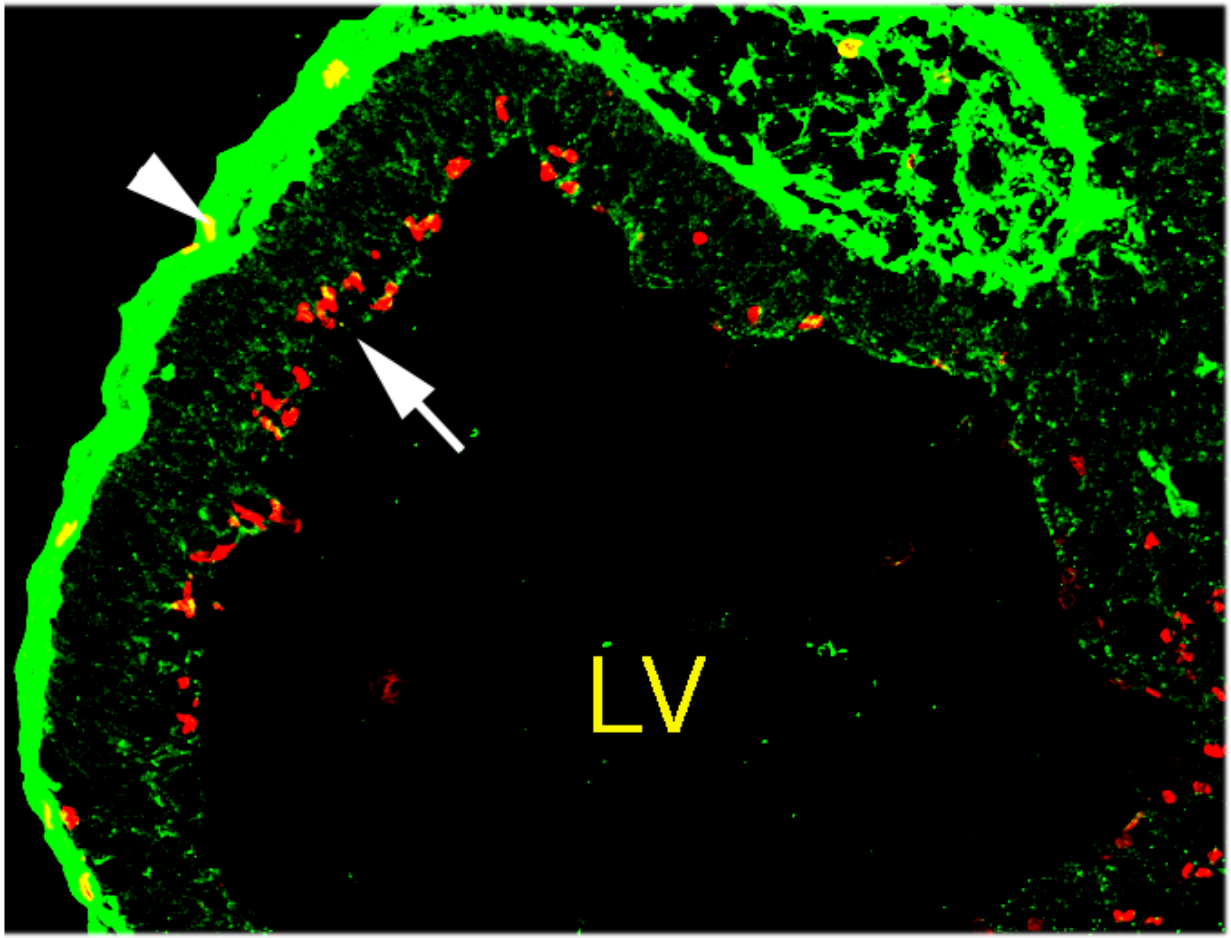
- Signal many behaviors: Migration, Differentiation, Apoptosis, Mitosis
- Created by various cells

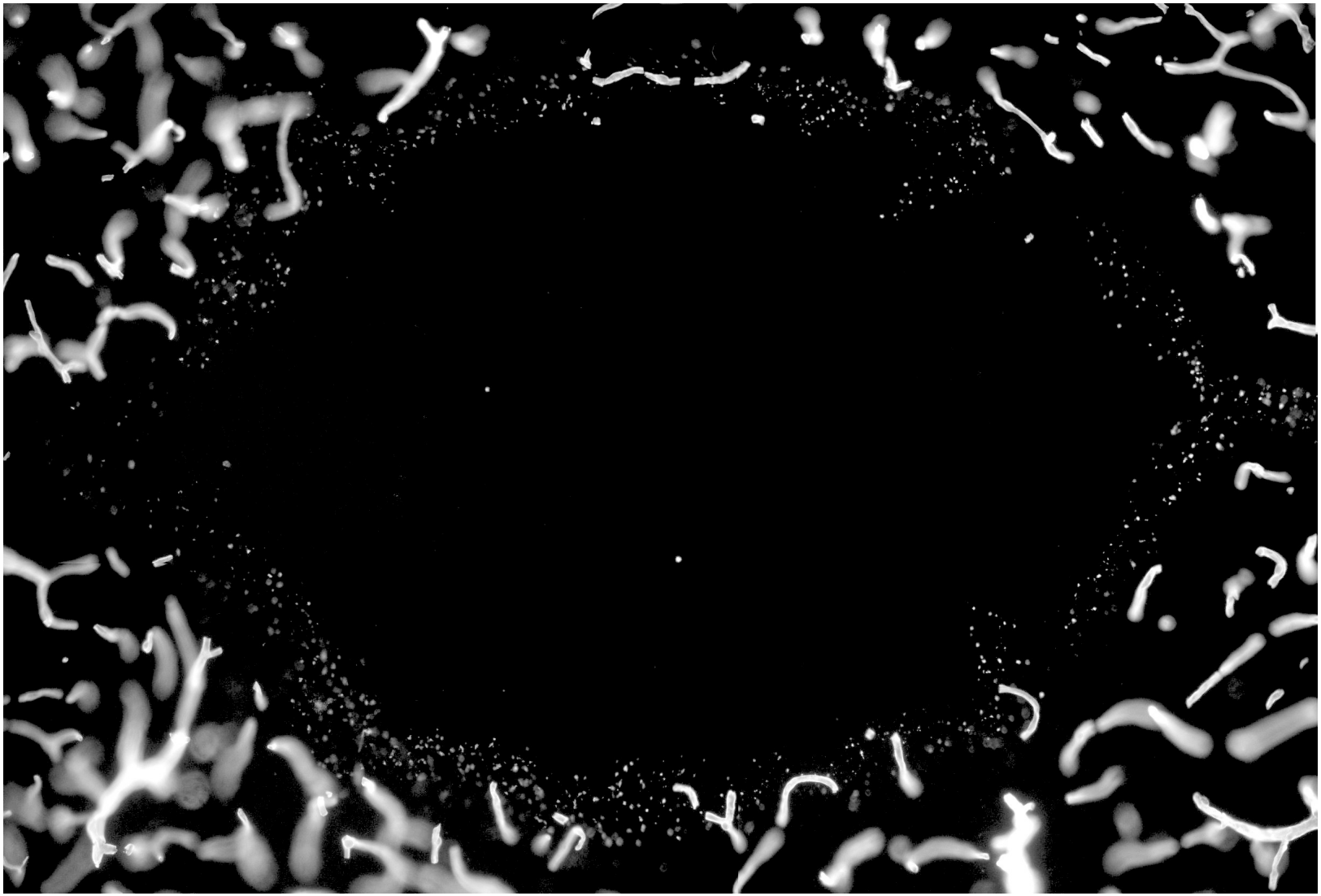
Examples from White Blood Cells and Cancer Cells

Lateral Ventricle



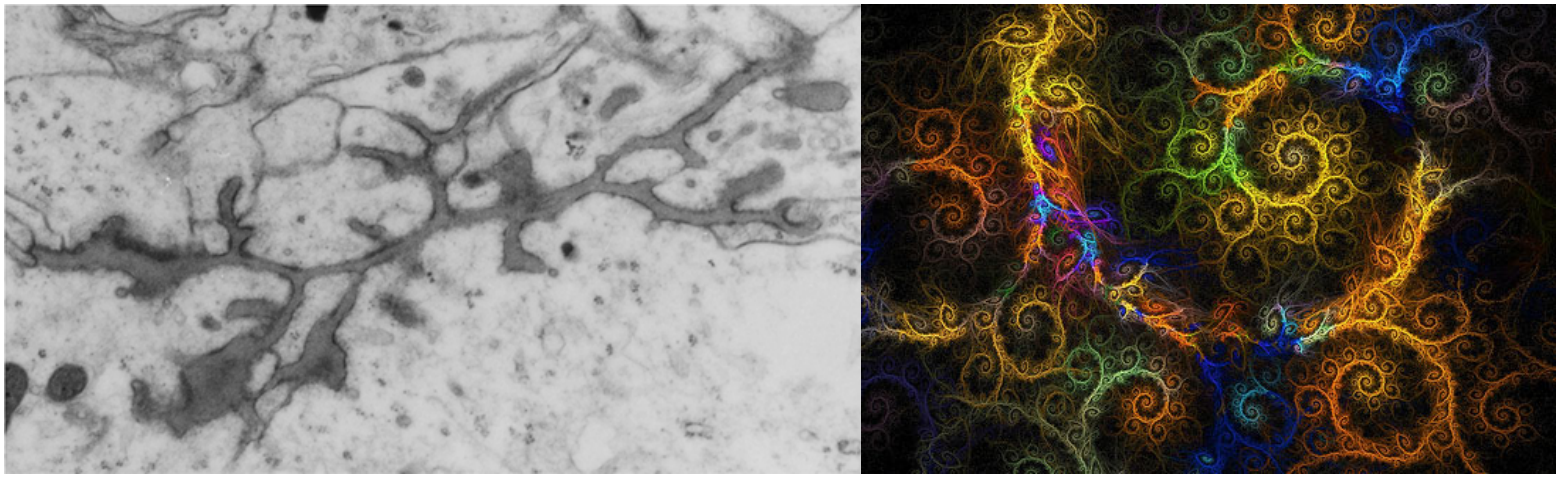


4th Ventricle

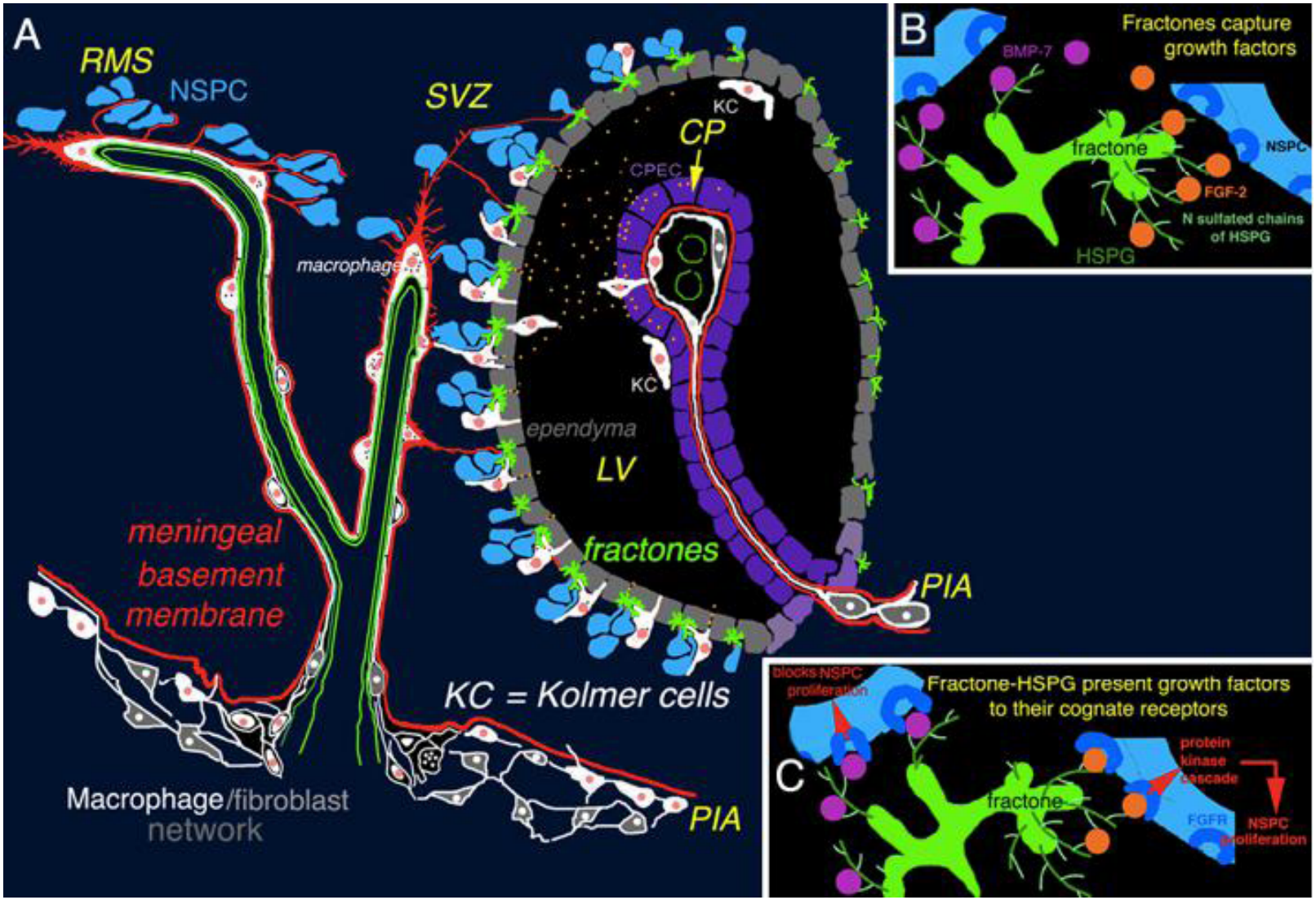


Fractones

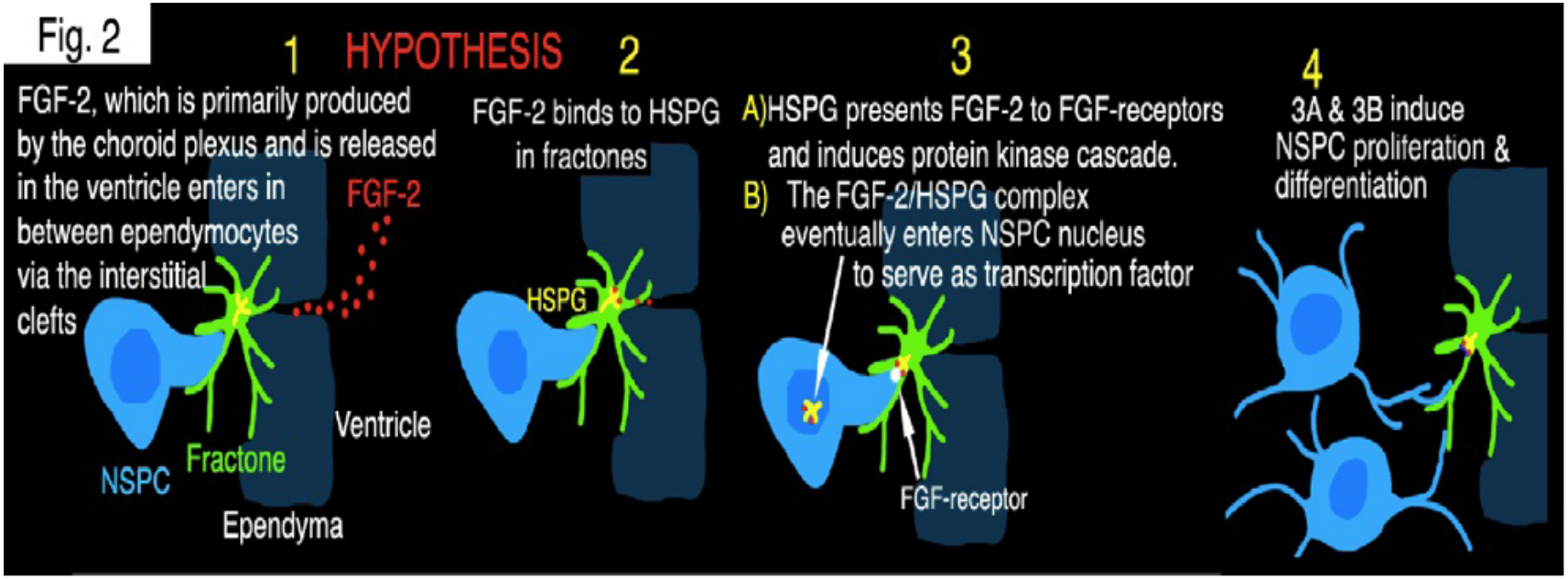
Basal lamina structures, termed **fractones**, directly contact neural stem cells, contact macrophage and fibroblast networks, and are associated with cell proliferation (creation)



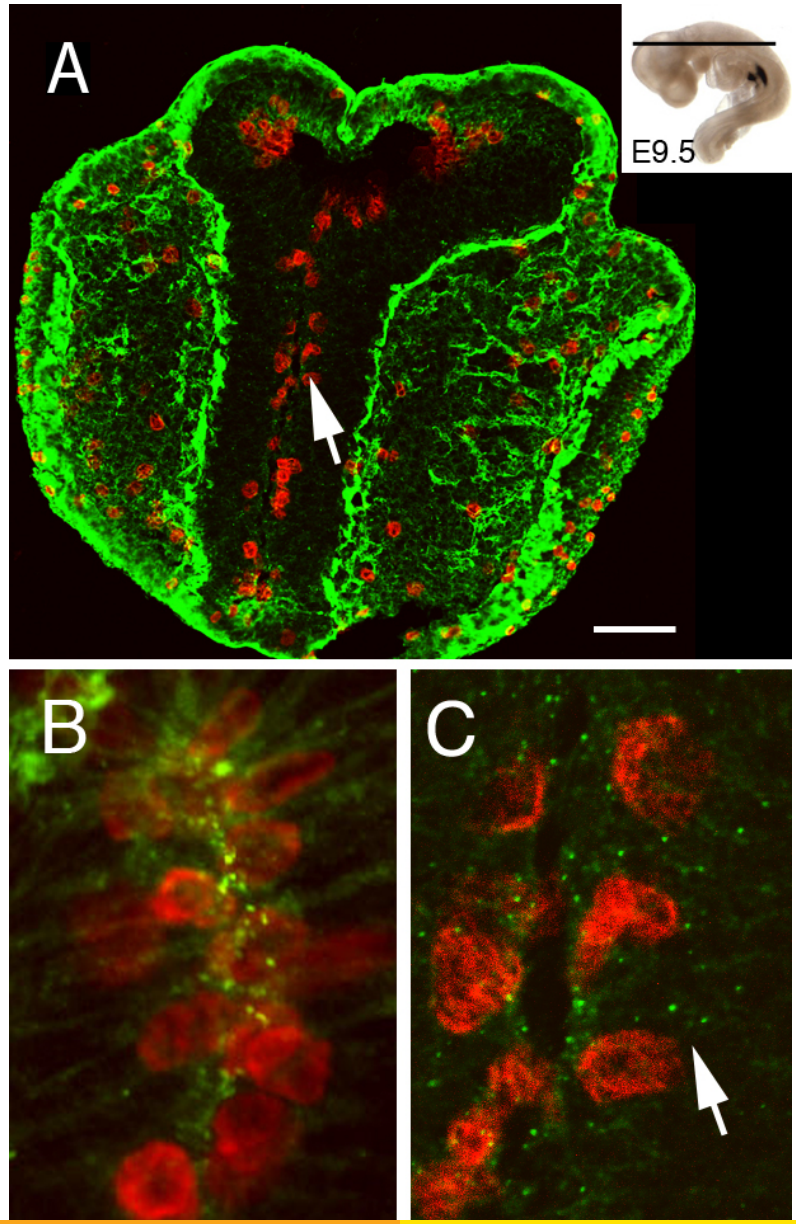
Hypothesized Function



Hypothesized Function

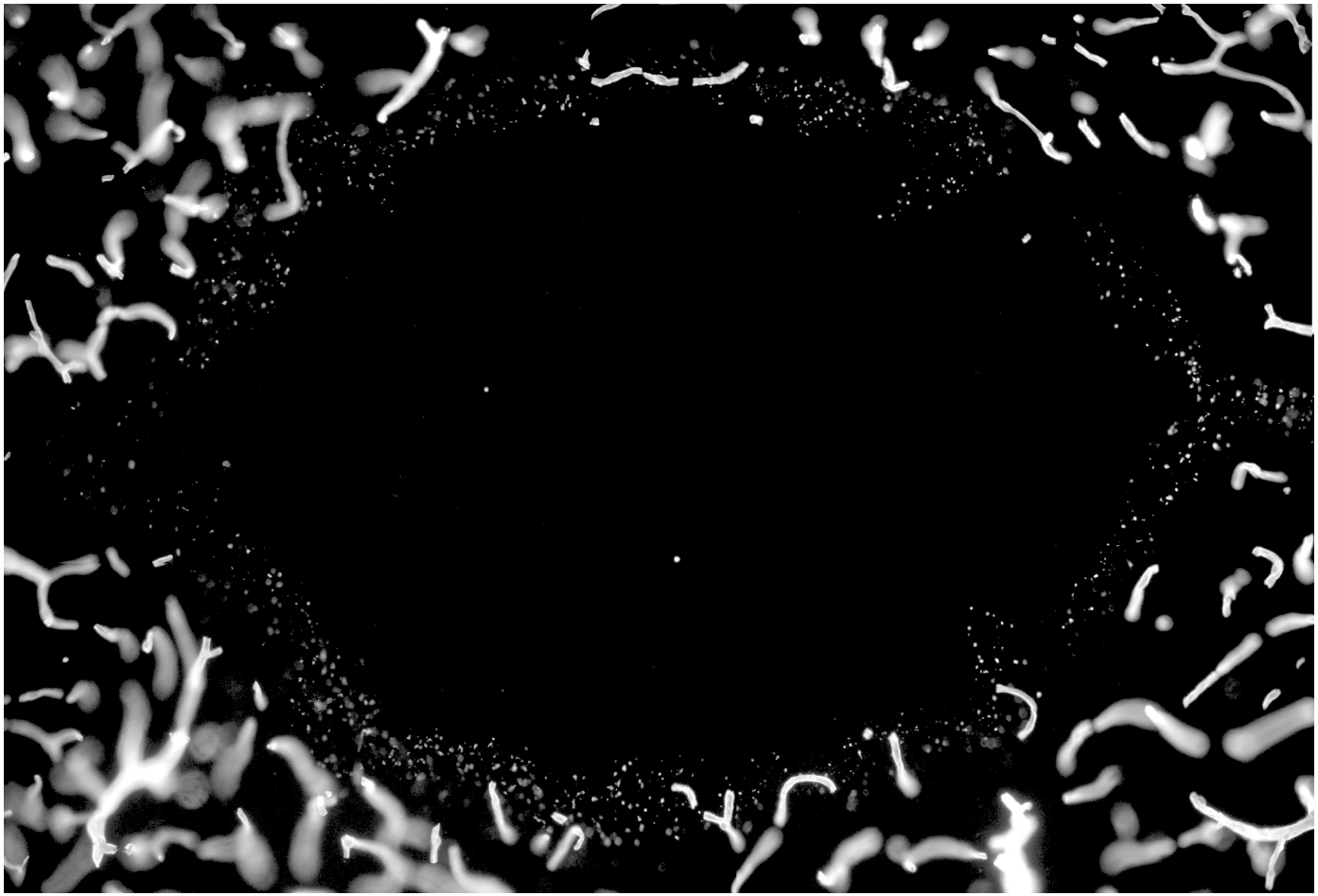


Embryonic Fractones

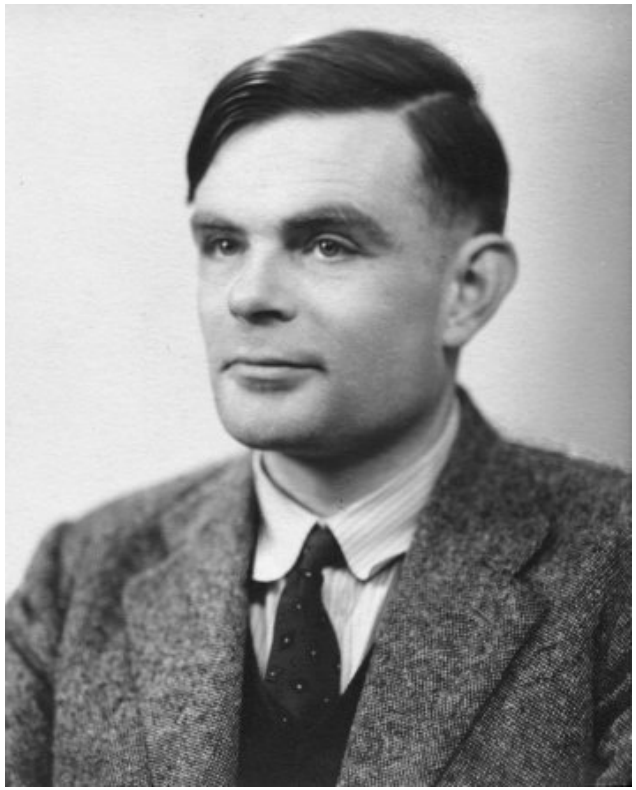


Biology

But testing the fractone hypothesis is hard...



Alan Turing



1912-1954

Reaction-Diffuion Model

The Chemical Basis of Morphogenesis, 1952

$$\left.\begin{aligned} \frac{dX_r}{dt} &= f(X_r, Y_r) + \mu(X_{r+1} - 2X_r + X_r - 1) \\ \frac{dY_r}{dt} &= g(X_r, Y_r) + \nu(Y_{r+1} - 2Y_r + Y_r - 1) \end{aligned}\right\} (r = 1, \ldots, N)$$

with $X_1 = X_{N+1}$ and $Y_1 = Y_{N+1}$

Reaction-Diffuion Model

Let $f(X_r, Y_r) = aX_r + bY_r$ and $g(X_r, Y_r) = cX_r + dY_r$

$$\left.\begin{aligned} \frac{dX_r}{dt} &= aX_r + bY_r + \mu(X_{r+1} - 2X_r + X_r - 1) \\ \frac{dY_r}{dt} &= cX_r + dY_r + \nu(Y_{r+1} - 2Y_r + Y_r - 1) \end{aligned}\right\} (r = 1, \ldots, N)$$

Reaction-Diffuion Model

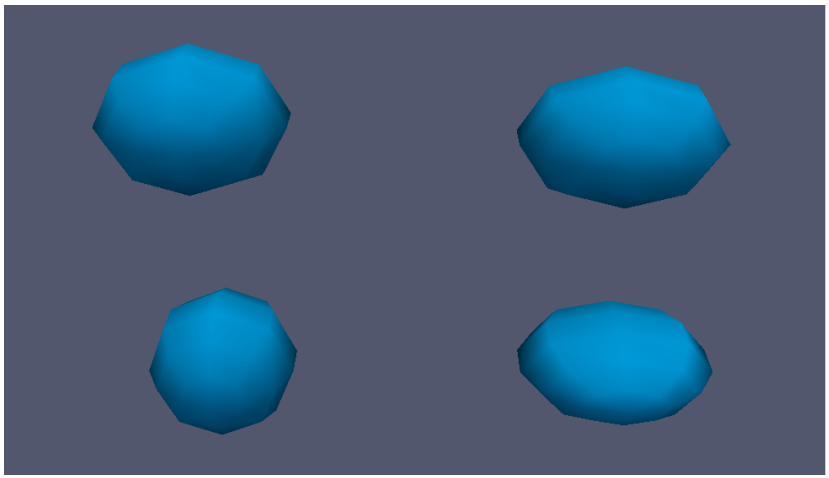
Recall heat equation: $\frac{\partial u}{\partial t} = \mu \frac{\partial^2 u}{\partial x^2}$

$$\left.\begin{aligned} \frac{\partial X}{\partial t} &= a(X-h) + b(Y-k) + \frac{\mu'}{\rho^2}\frac{\partial^2 X}{\partial \theta^2} \\ \frac{\partial Y}{\partial t} &= c(X-h) + d(Y-k) + \frac{\nu'}{\rho^2}\frac{\partial^2 Y}{\partial \theta^2} \end{aligned}\right\}$$

Cells

Definition

We define a *cell body* as an ellipsoid of fixed volume V and semi-axis lengths r_1, r_2, r_3, with $s \leq r_i \leq S$, $i \in \{1, 2, 3\}$, for constants $V, s, S \in \mathbb{R}$.



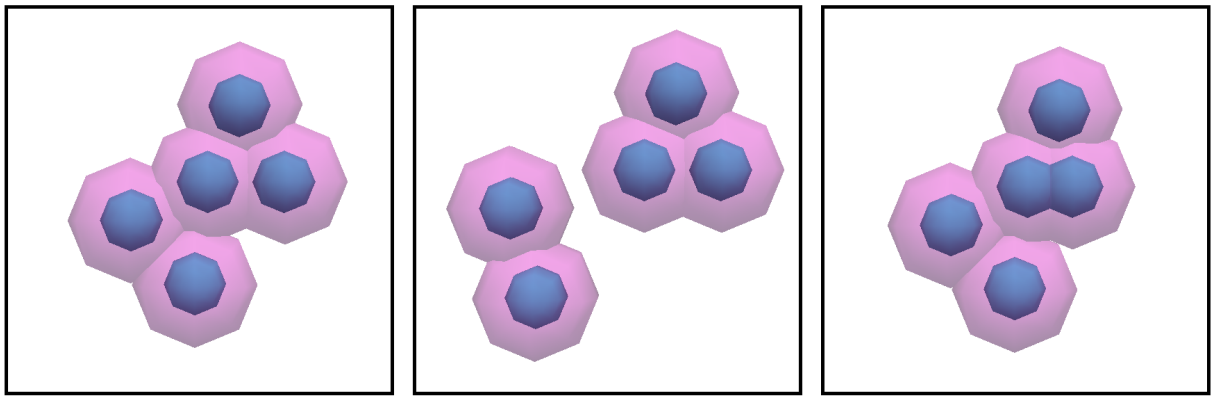
$$V = \frac{4}{3}\pi(4.5)^3,$$

$$s = 3,\ S = 6$$

Definition

We define a *cell time*, $t_c \in \mathbb{R}$, and pair it with a cell body, c_b, to define a *cell*, $c = \{c_b, t_c\}$.

Cells



Definition

Given $\epsilon \in \mathbb{R}$ and a set of cell bodies, $C = \{c_i\}$, for each cell body with semi-axis lengths r_{1i}, r_{2i}, r_{3i} we assign a concentric ellipsoid, $\hat{c}_i$, with semi-axis lengths $r_{1i} + \epsilon$, $r_{2i} + \epsilon$, and $r_{3i} + \epsilon$ respectively. Let $\hat{C} = \bigcup_i \hat{c}_i$. If $\hat{C}$ is a compact connected space and $c_i \cap c_j = \emptyset$, $\forall i, j,\ i \neq j$, then the configuration is *admissible*.

Fractones and Meninges and Growth Factors

Definition

We define the *meningeal cell* centered at $(x_0, y_0, z_0) \in A$ as

$$\overline{B_{\epsilon/2}(x_0, y_0, z_0)} = \Big\{(x, y, z) \in A | (x - x_0)^2 + (y - y_0)^2 + (z - z_0)^2 \leq \left(\frac{\epsilon}{2}\right)^2\Big\}$$

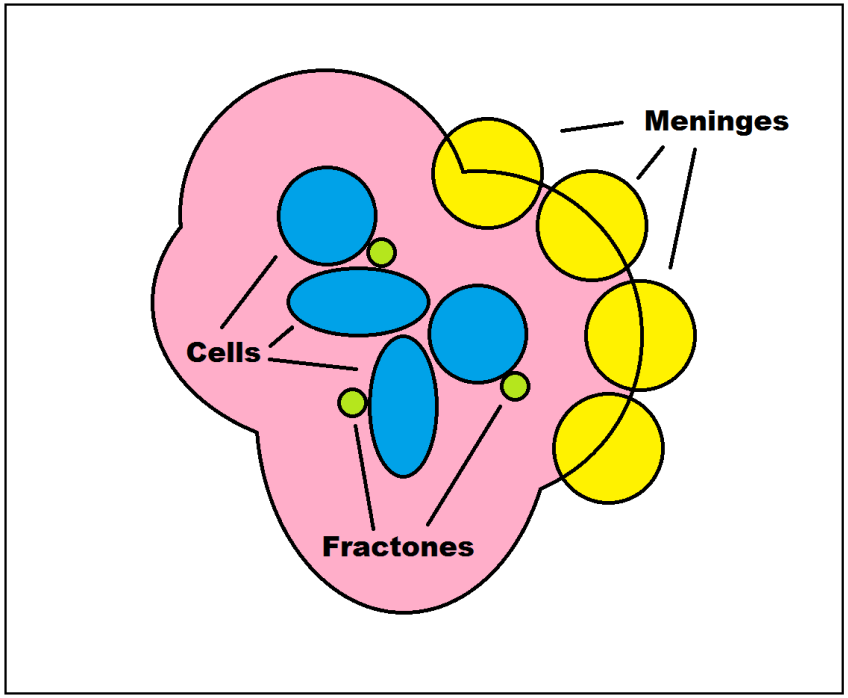
The center of meningeal cells are placed on the boundary of $\hat{C}$.

Fractones and Meninges and Growth Factors

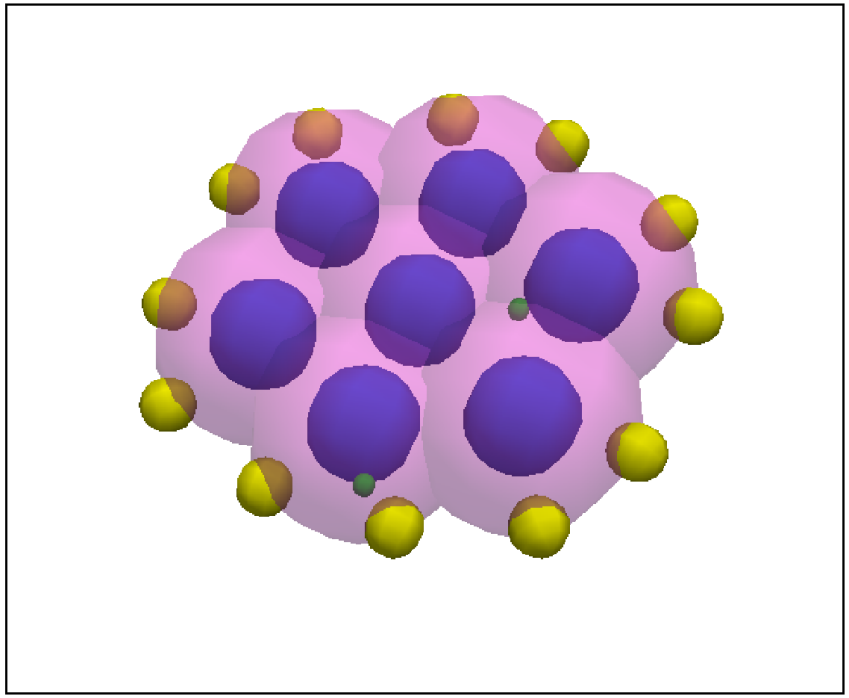
Definition

We define the *fractone* centered at $(x_0, y_0, z_0) \in A$ as $\overline{B_r(x_0, y_0, z_0)}$ where $r = \frac{1}{9}\sqrt[3]{\frac{3}{4\pi}V} = 0.5$. Given an admissible set of cells, C, a set of fractones, $\{f_q\}$, is *admissible* if every fractone is tangent to at least one cell body and $f_i \cap f_j = \emptyset$, $\forall i, j$, $i \neq j$.

Fractones and Meninges and Growth Factors



(a)



(b)

Two types of Growth Factors, Fractones, and Growth

Biological Structure

Definition

Given an admissible set of cells, C, and admissible meninges, C_m, we define the pair as a *cell mass*, $M = \{C, C_m\}$.

Definition

We define a *biological structure* as a triple, $\{M, F^+, F^-\}$, as a cell mass, M, paired with two admissible sets of fractones, F^+ and F^-, which represent the positive and negative fractones, respectively, in the system.

Hybrid Models

Hybrid Models

- Model continuous and discrete dynamics together
- Several model types exist
- Increasingly popular
- Limited number of results currently exist

Lin and Antsaklis. "Hybrid Dynamical Systems: An Introduction to Control and Verification". Foundations and trends in System and Control. Vol. 1 No. 1 (2014)

Reference

Notation and formulation of hybrid automata via:
J Lygeros, KH Johansson, SN Simic, SS Sastry, J Zhang. Dynamical properties of hybrid automata. *Automatic Control, IEEE Transactions*, 48(1):217, 2003.

Hybrid Automata Systems

$$H = (Q, X, f, Init, D, E, G, R)$$

Discrete State

Q: A finite set of discrete variables. By $\mathbf{Q}$, we denote the set of values these variables can take.

Continuous State

X: A finite set of continuous variables. We will always choose the continuous variables to be real-valued. We denote the set of valuations of n such variables $\mathbf{X} = \mathbb{R}^n$.

Continuous Dynamics

$f : \mathbf{Q} \times \mathbf{X} \to T\mathbf{X}$. The vector field describing the evolution of the continuous vector. Here $T\mathbf{X}$ denotes the tangent bundle of $\mathbf{X}$. We will assume for all $q \in \mathbf{Q}$ that $f(q, \cdot)$ is globally Lipschitz continuous.

Initial Conditions

$Init \subseteq \mathbf{Q} \times \mathbf{X}$. A set of initial continuous and discrete states. By $\mathbf{Q} \times \mathbf{X}$, we denote the set of valuations on $Q \times X$.

Domain

$D : \mathbf{Q} \to P(\mathbf{X})$. Here $P(\mathbf{X})$ denotes the set of all subsets of $\mathbf{X}$. D is a "domain". For $q \in \mathbf{Q}$, $D(q)$ is the subset of $\mathbf{X}$ in which the continuous evolution $\dot{x} = f(q, x)$ occurs.

Edges

$E \subseteq \mathbf{Q} \times \mathbf{Q}$ is the set of "edges". The edge $(q_i, q_j) \in \mathbf{Q} \times \mathbf{Q}$ represents the instantaneous change in discrete state from q_i to q_j.
Note: Not every pair of discrete states will be an edge.

Guard Conditions

$G : E \to P(\mathbf{X})$. The "guard conditions" for each edge - the subset of $\mathbf{X}$ which will cause a switch in the discrete state, along the given edge.

Reset Map

$R : E \times \mathbf{X} \to P(\mathbf{X})$. The "reset map" for each edge. When a discrete switch occurs along edge E, X may change, causing a discontinuous jump in the continuous dynamics.

Hybrid Time Trajectory

A *hybrid time trajectory*, τ, is a collection of intervals for continuous growth: $\tau = \{I_i\}_{i=0}^{N}$ such that:

- $I_i = [\tau_i, \tau_i']$ for all $i < N$
- if $N < \infty$, then either $I_N = [\tau_N, \tau_N']$, or $I_N = [\tau_N, \tau_N')$
- $\tau_i \leq \tau_i' = \tau_{i+1}$ for all i.

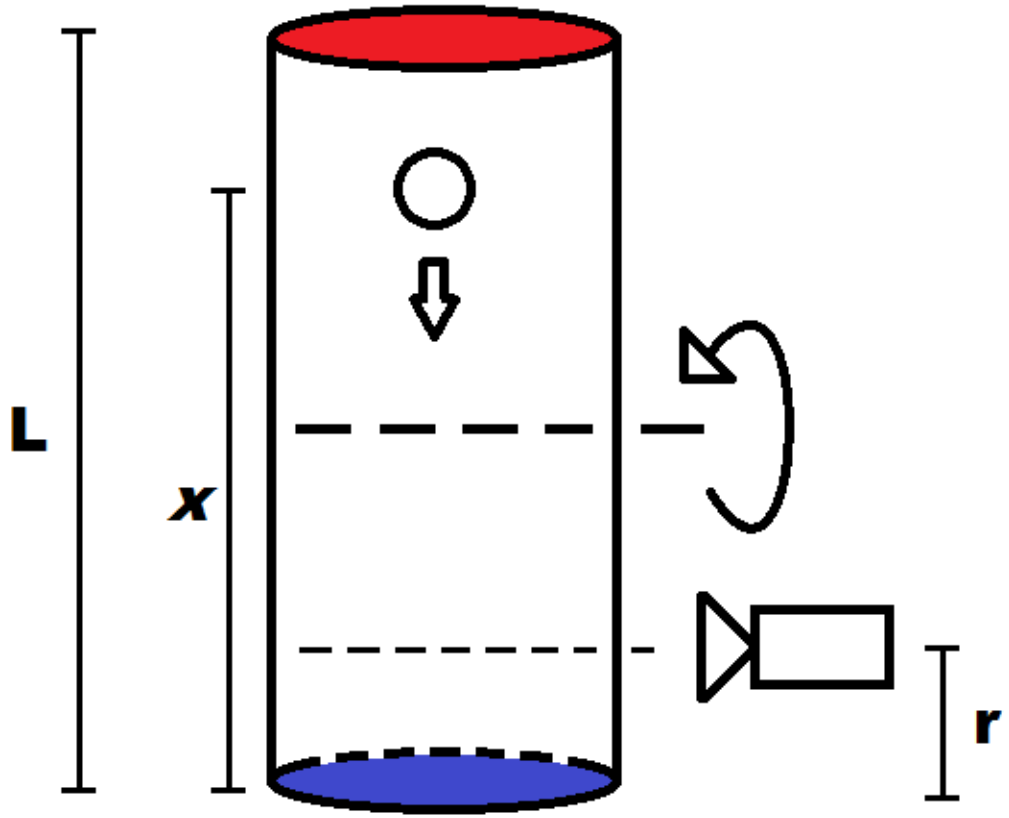
Define $\langle \tau \rangle = \{0, 1, \ldots, N\}$

An Execution

An *execution* of a hybrid automaton, H, is a collection $\chi = (\tau, \hat{q}, \hat{x})$, where τ is a hybrid time trajectory, $\hat{q} : \langle\tau\rangle \to \mathbf{Q}$, and $\hat{x} = \{\hat{x}^i(t) : i \in \langle\tau\rangle\}$ is a collection of differentiable maps $\hat{x}^i : I_i \to \mathbf{X}$, such that

- $(\hat{q}(0), \hat{x}^0(0)) \in Init$
- $\forall t \in [\tau_i, \tau_i'),\ \dot{\hat{x}}^i(t) = f\left(q(i), \hat{x}^i(t)\right)$ and $\hat{x}^i(t) \in D(\hat{q}(i))$
- $\forall i \in \langle\tau\rangle \setminus \{N\},\ e \equiv (\hat{q}(i), \hat{q}(i+1)) \in E$, and $\hat{x}^i(\tau_i') \in G(e)$, and $\hat{x}^{i+1}(\tau_{i+1}) \in R(e, \hat{x}^i(\tau_i'))$

Hybrid Automata Systems



Discrete State

Q: A finite set of discrete variables.

$$Q = \{q\}$$
$$\mathbf{Q} = \{\mathrm{RED}, \mathrm{BLUE}\}$$

Continuous State

X: A finite set of continuous variables.

Distance of the ball from the blue side.

$$X = \{x\}$$

$$\mathbf{X} = \mathbb{R}$$

Continuous Dynamics

$$f : \mathbf{Q} \times \mathbf{X} \to T\mathbf{X}.$$

$$f(\mathrm{RED}, x) = -\nu$$

$$f(\mathrm{BLUE}, x) = \nu$$

Initial Conditions

$$Init \subseteq \mathbf{Q} \times \mathbf{X}.$$

$$Init = \{(q, x) | q = \text{RED},\ x \in (r, L]\}$$

Domain

$$D : \mathbf{Q} \to P(\mathbf{X}).$$

$$D(\text{RED}) = \{x \in \mathbb{R} : x \geq r\}$$

$$D(\text{BLUE}) = \{x \in \mathbb{R} : x \leq L - r\}$$

Edges

$$E \subseteq \mathbf{Q} \times \mathbf{Q}$$

$$E = \{(\text{RED}, \text{BLUE}), (\text{BLUE}, \text{RED})\}$$

Guard Conditions

$$G : E \to P(\mathbf{X}).$$

$$G(\text{RED}, \text{BLUE}) = \{x \in \mathbb{R} : x = r\}$$

$$G(\text{BLUE}, \text{RED}) = \{x \in \mathbb{R} : x = L - r\}$$

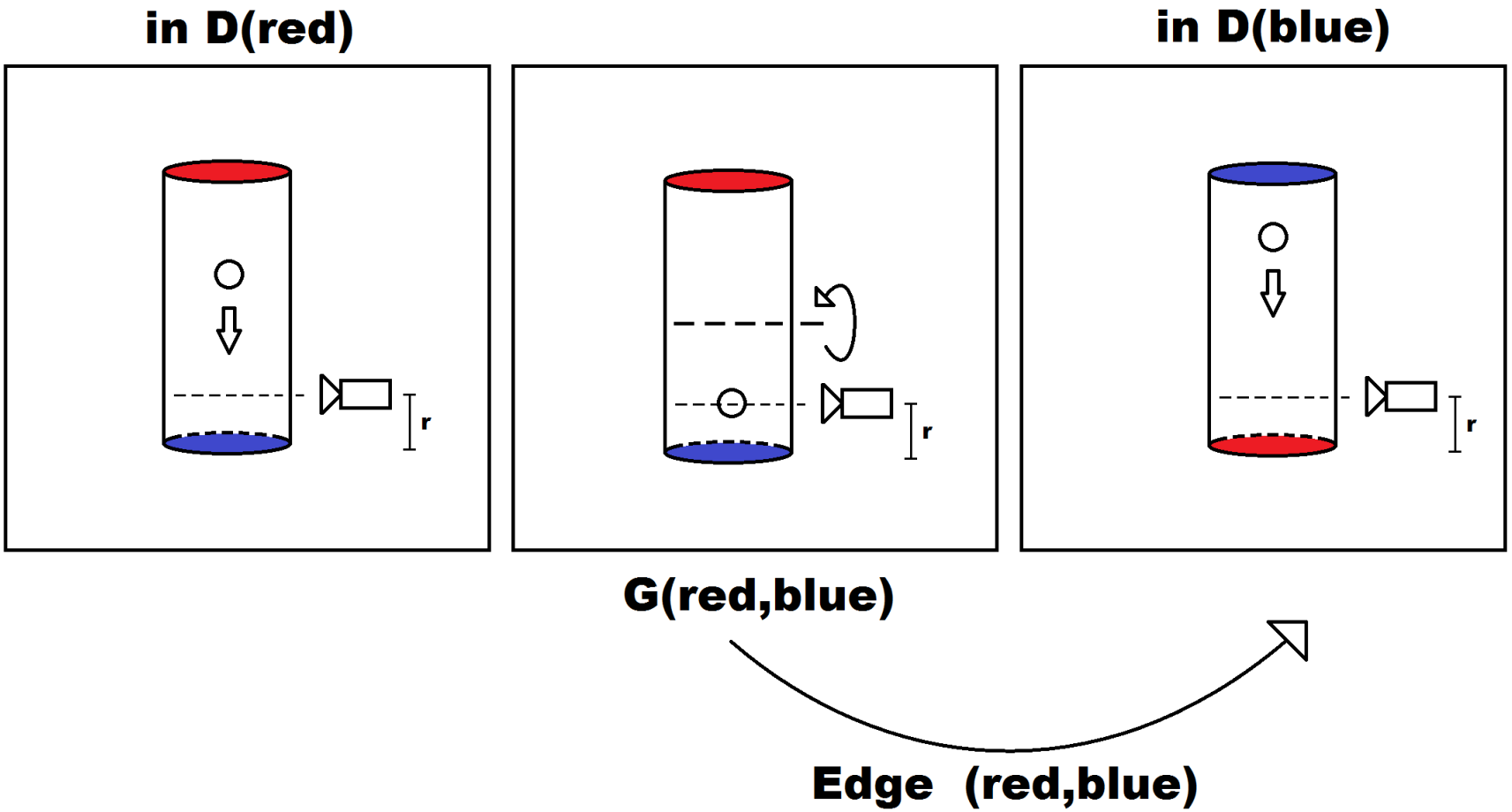
Reset Map

$$R : E \times \mathbf{X} \to P(\mathbf{X}).$$

$$R((\mathrm{RED}, \mathrm{BLUE}), X) = X$$

$$R((\mathrm{BLUE}, \mathrm{RED}), X) = X$$

Example



Our Model

- Q is the arrangment of cells, fractones, and meninges
- X is the distribution of growth factors in the system
- Continuous dynamics (f): Perturbed diffusion dependent on Q and X
- Edges (E): Define the rules of growth
- Growth conditions (G): Growth governed by growth factor capture and time
- Growth factor pushing (R): Growth causes physical pushing of growth factor

Changes to Hybrid Automata

1. Explicit time dependence (Timed Automata)
2. Control
3. Function space X

Continuous and Discrete Spaces

Q: A set of discrete variables
X: A set of continuous variables (but in our case, density functions and time)

Q: The set of all biological structures
X: A function space of all density functions

f, $Init$

Perturbed Diffusion

- The continuous dynamic $f(q, X)$ describes the diffusion of the growth factors
- Cells and meninges block diffusion
- Fractones act as sinks

Initial Conditions

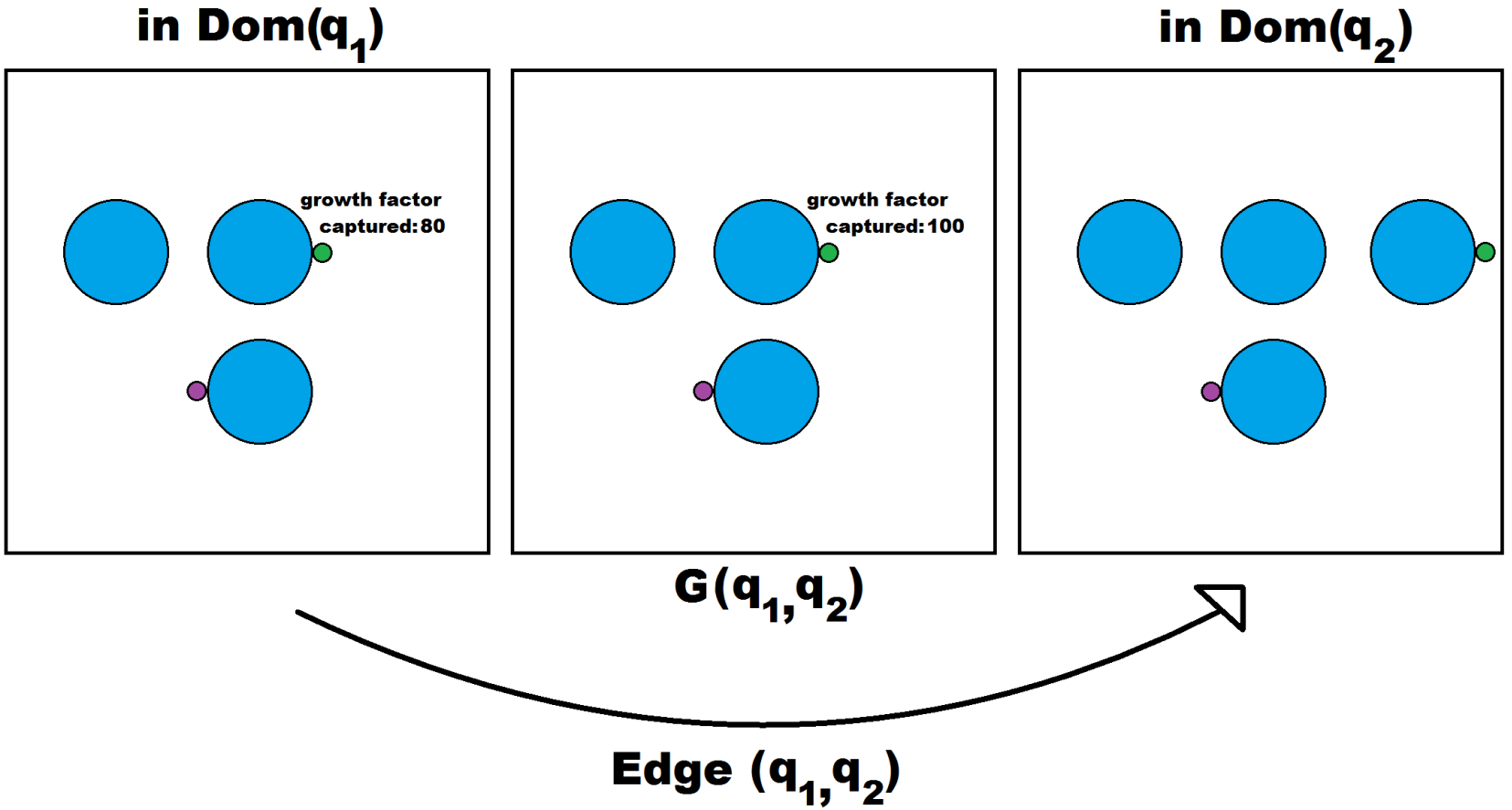
$$Init \subseteq \mathbf{Q} \times \mathbf{X}$$

Domains, Guards, and Edges

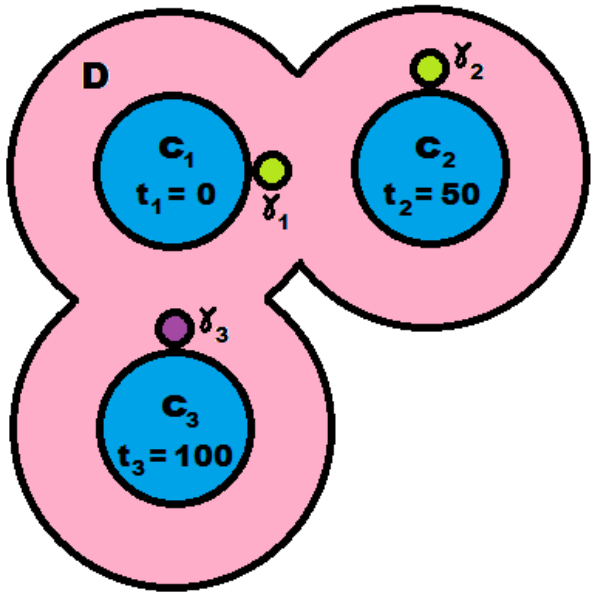
Discrete Dynamics

- $D : \mathbf{Q} \to P(\mathbf{X})$ - Domain, the continuous states allowed in each discrete state
- $E \subseteq \mathbf{Q} \times \mathbf{Q}$ - Edges, the allowed discrete changes
- $G : E \to P(\mathbf{X})$ - Guard conditions, the continuous states that cause a discrete change

Domains, Guards, and Edges



Domains, Guards, and Edges



$$G(e_1) = \Big\{ (X_1(x,t), X_2(x,t), T) \mid \int_{\gamma_1} (X_1(x,t) - X_2(x,t))\, dx \geq 100,$$

$$T \geq 360\}$$

Reset Map: GF Pushing

Reset Map

$$R : E \times \mathbf{X} \to P(\mathbf{X})$$

- Describes the change in the continuous state caused by a change in the discrete state.
- Can cause discontinuous jumps in the continuous state
- Represents the pushing of growth factors when cells move

Control

Control

- $u : A \times \mathbb{R} \to \{0, 1\}$
- Determines location of fractones
- f, G, and D are now dependent on u