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Mathematical Modelling of Lymphangiogenesis

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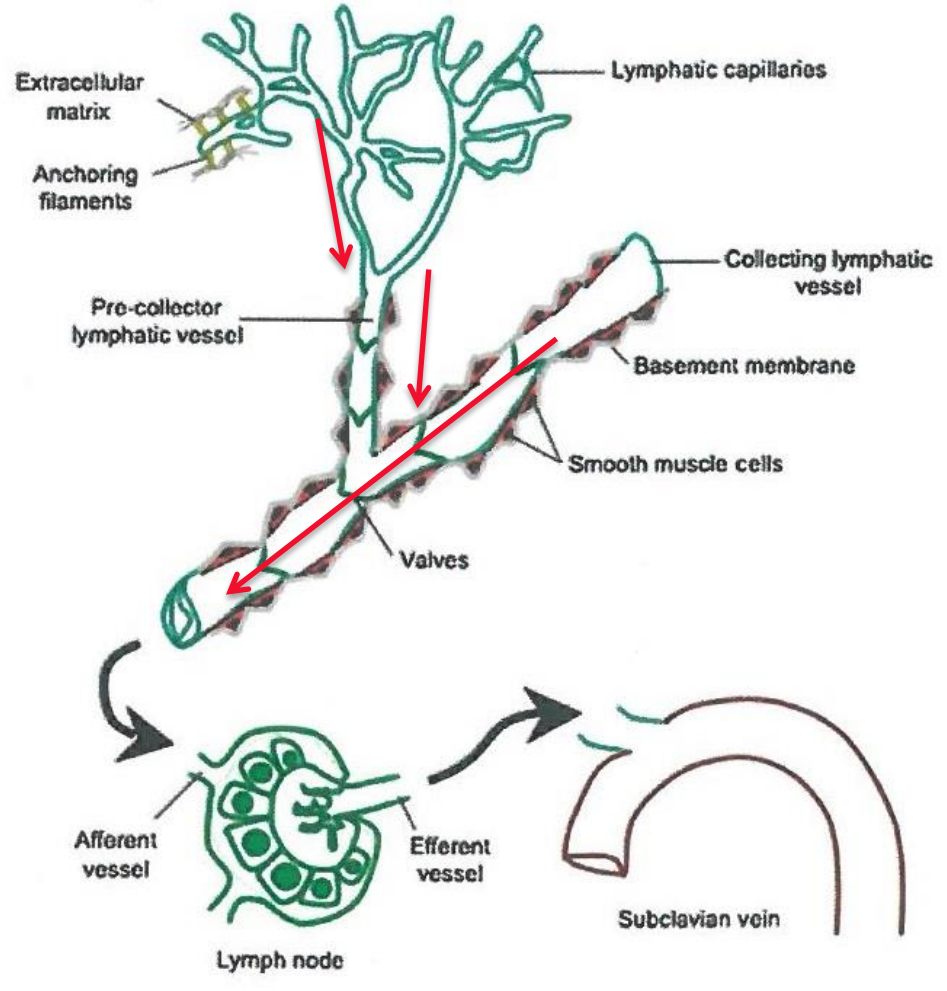
Structure and functions



Maby-El Hajjami and Petrova (2008)

In health

1. Draining:
   - Excess fluid.
   - Dietary fat.
2. Immune responses.

Malfunctioning

- Lymphoedema: Swelling in tissues.

Cancer

- Tumour metastasis.
- Similar mechanisms to embryonic lymphatic growth.

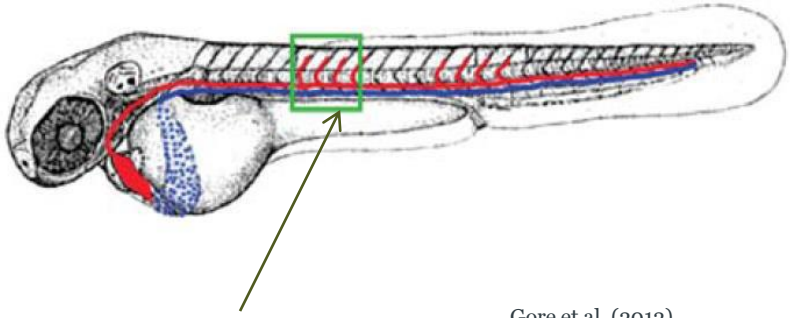
- Zebrafish

a) Small size and simple anatomy.

b) Rapid development.

c) Transparent embryo *ex utero*.

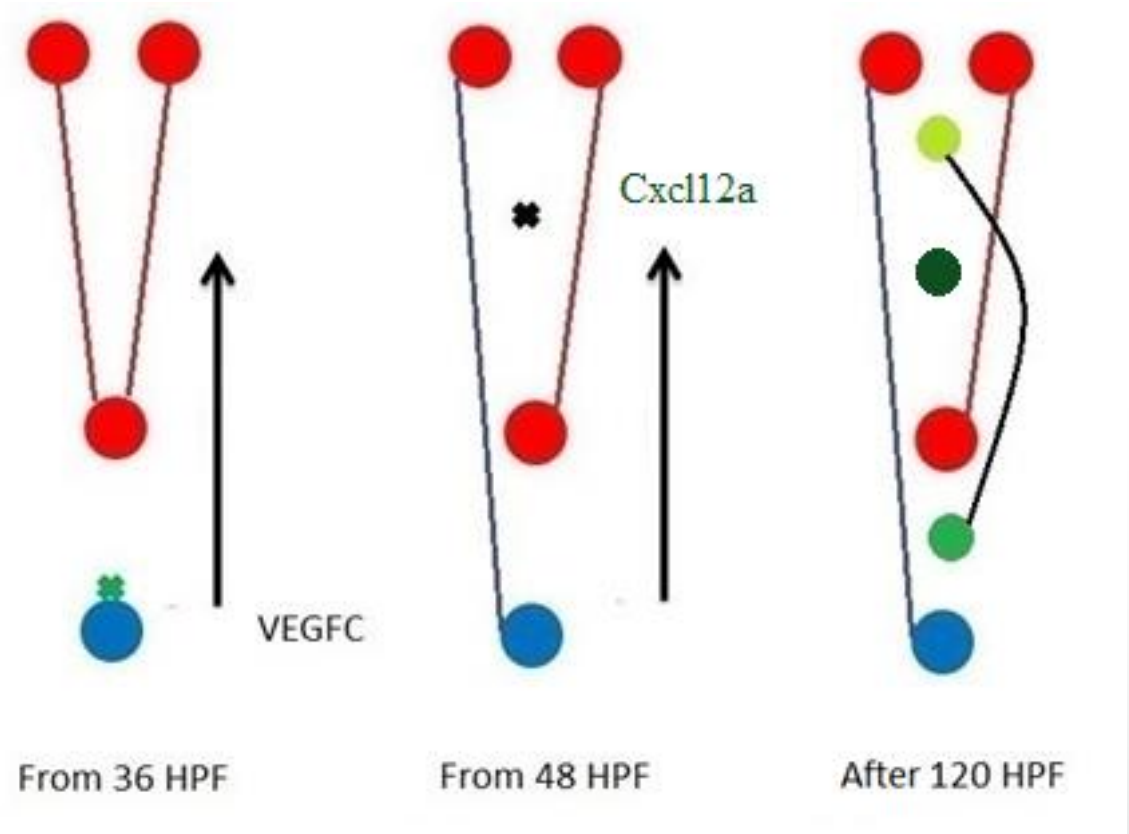
d) Mutant lines.



Gore et al. (2012)

- Developmental mechanisms are usually conserved across vertebrates.
- Consider a cross section of the zebrafish's trunk.

Major Developmental Steps



Red vessels: arteries.
Blue vessel: vein.
Green vessels: lymphatic vessels.
Cross: lymphatic progenitor cell.

Questions:

1. Why does the cell migrate from the vein to the horizontal myoseptum?
2. What causes it to differentiate *en route*?
3. What induces the maturation of the lymphatic vessels?

Exit the vein. Into the horizontal myoseptum. Spreading out.

VEGFC = vascular endothelial growth factor C.

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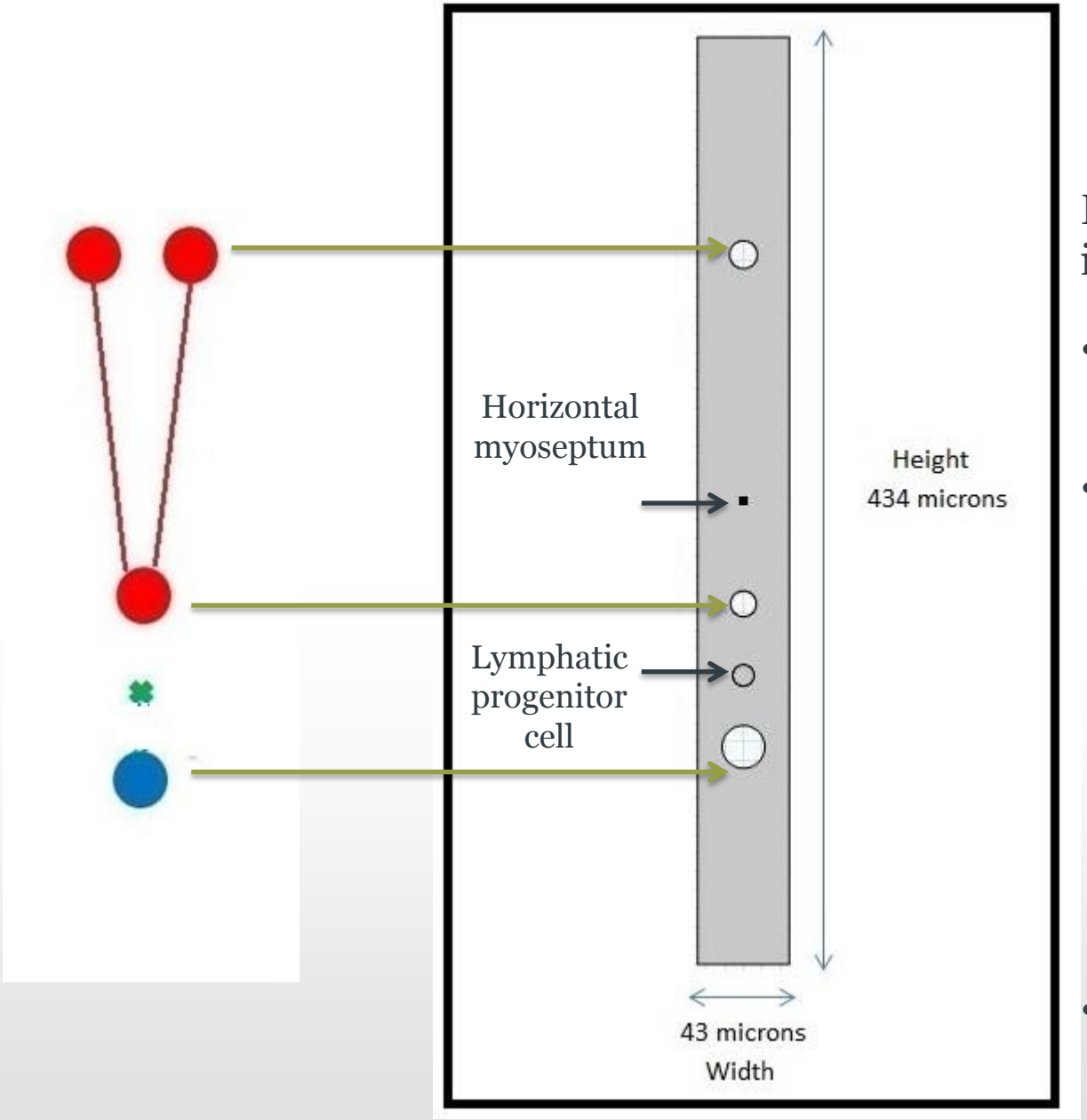
Hypothesis (questions 1 and 2)

- Known: VEGFC is a growth factor for lymphatic progenitor cells, i.e. survival, growth, and migration.
- Hypothesis:

1. Morphogen: its gradient patterns gene expression; 3-fold over 30 microns.
2. Chemotactic factor: it guides cell migration by attraction or repulsion.



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Box of collagen I with an interstitial flow through it:

- The blood vessels have different pressures.
- Brinkman's equation:

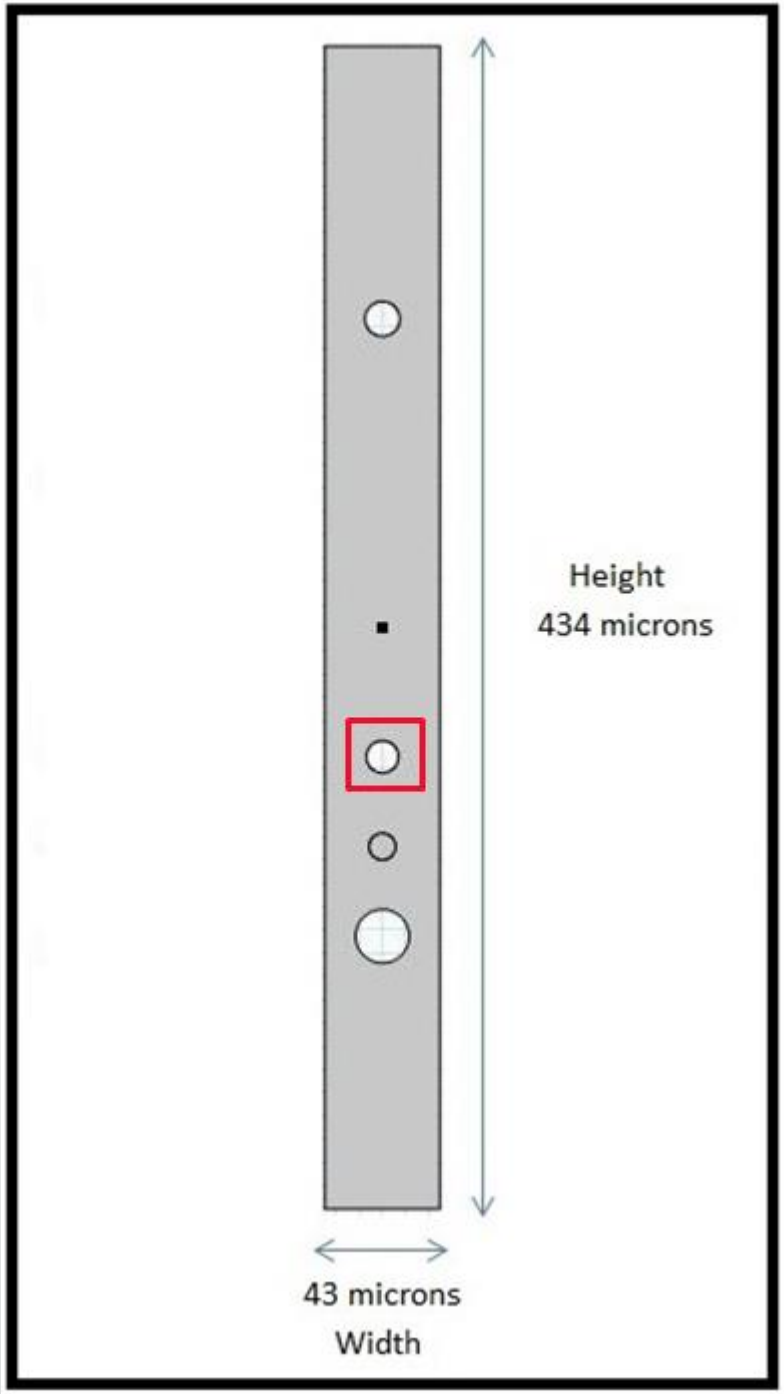
$$\nabla P = -\frac{\mu}{\kappa}\boldsymbol{u} + \mu\nabla^2\boldsymbol{u}$$

Darcy's law: Extracellular matrix.

Stokes' law: Channels of fluid in the matrix.

- Conservation of mass:

$$\nabla \cdot \boldsymbol{u} = 0$$



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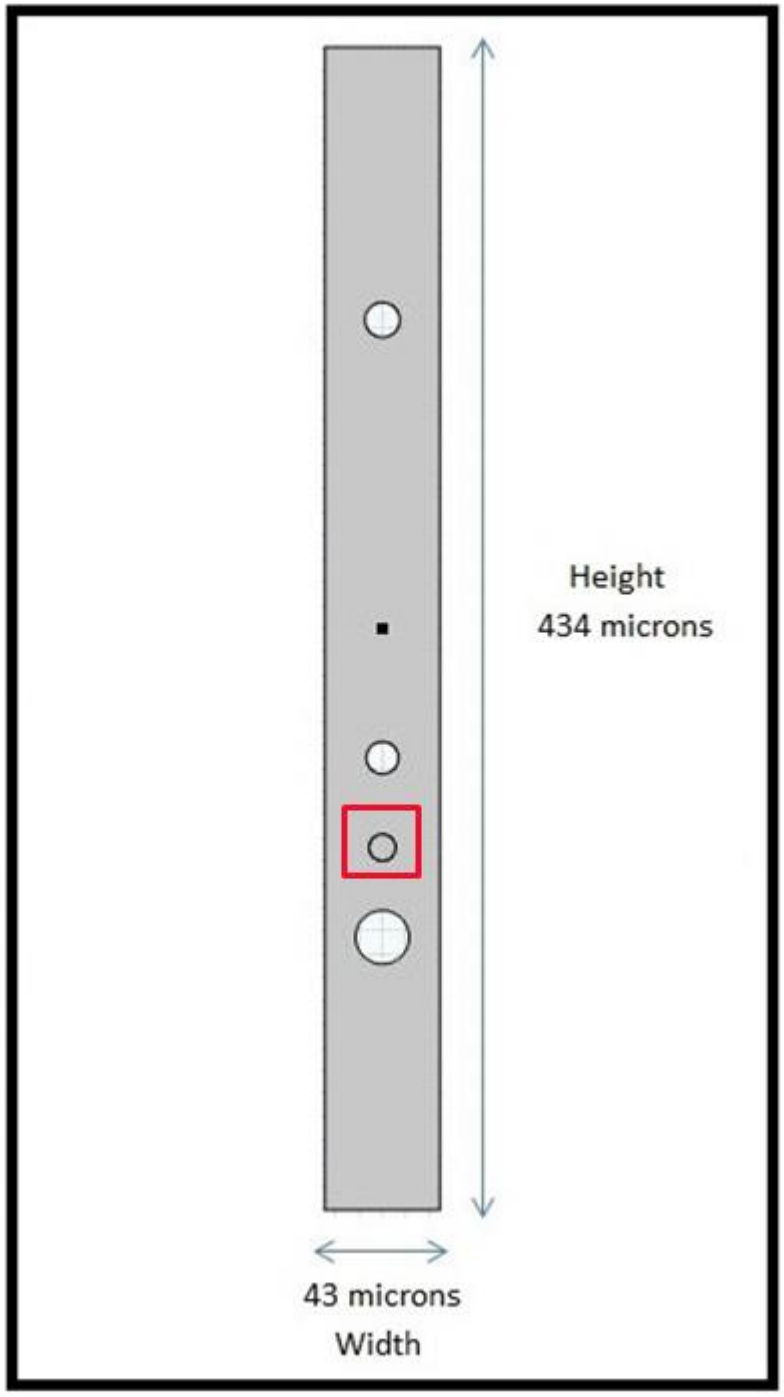
Reactive transport of VEGFC:

- The dorsal aorta (in the red box) releases VEGFC into the interstitial space.
- VEGFC binds to collagen I reversibly.
- Equation for VEGFC:

$$\frac{\partial C_i}{\partial t} = \boldsymbol{\nabla} \cdot (D_i^{eff} \boldsymbol{\nabla} (\frac{C_i}{\omega}) - \boldsymbol{u} C_i) + R_i^{IS}$$

- Equation for free and VEGFC-bound collagen I:

$$\frac{\partial C_i}{\partial t} = R_i^{IS}$$



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Intracellular production of MMP2:

- 4-step mechanism.
- proMMP2 and TIMP2 are mobile.

$$\frac{\partial C_i}{\partial t} = D_i^{\infty} \nabla^2 C_i + R_i^{LEC}$$

- MT1-MMP is an immobile receptor.

$$\frac{\partial C_i}{\partial t} = R_i^{LEC}$$

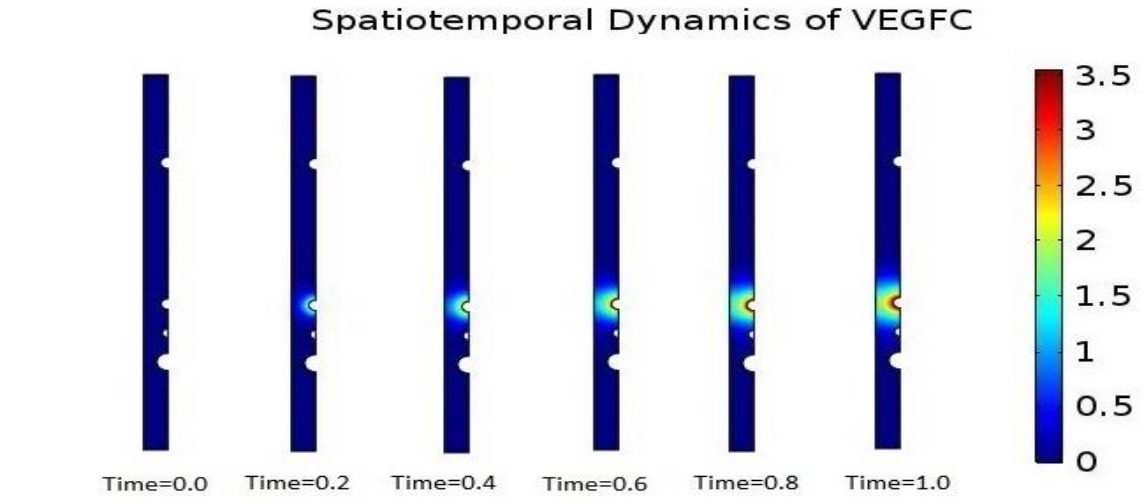
Interstitial space:

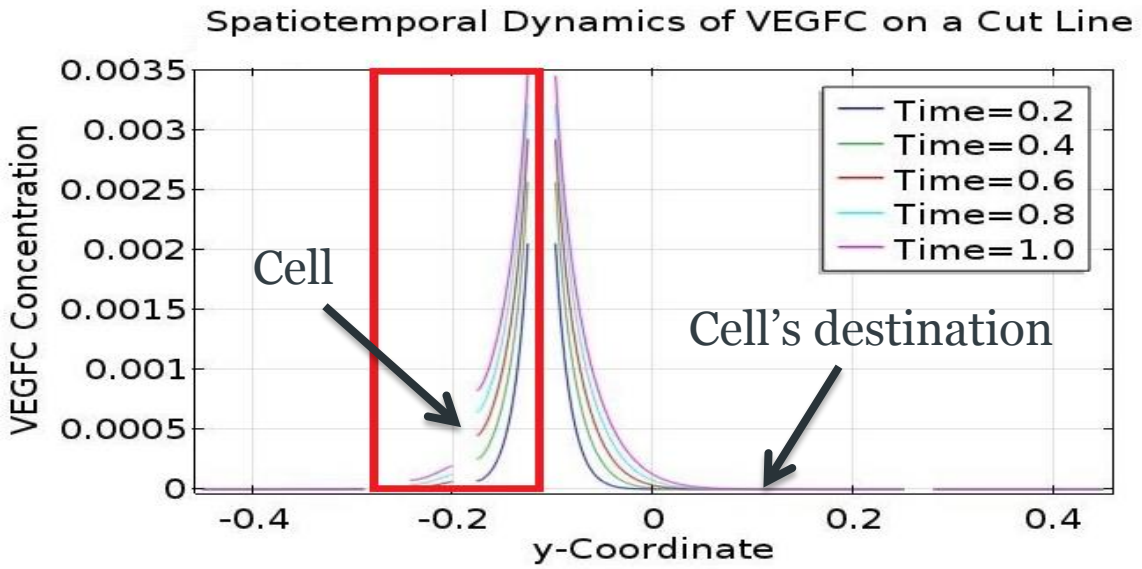
- MMP2 degrades collagen I.

$$\frac{\partial C_i}{\partial t} = \nabla \cdot (D_i^{eff} \nabla (\frac{C_i}{\omega}) - \boldsymbol{u} C_i) + R_i^{IS}$$

Parametrisation, nondimensionalisation, finite element method.

Scenario 1: Diffusion dominates over convection (Péclet number)





Red box:

- 7-fold VEGFC concentration gradient.
- Viable morphogen gradient.

Symmetry around the peak:

- Inconsistent direction.
- Not a chemotactic factor.

Numerical experiment:

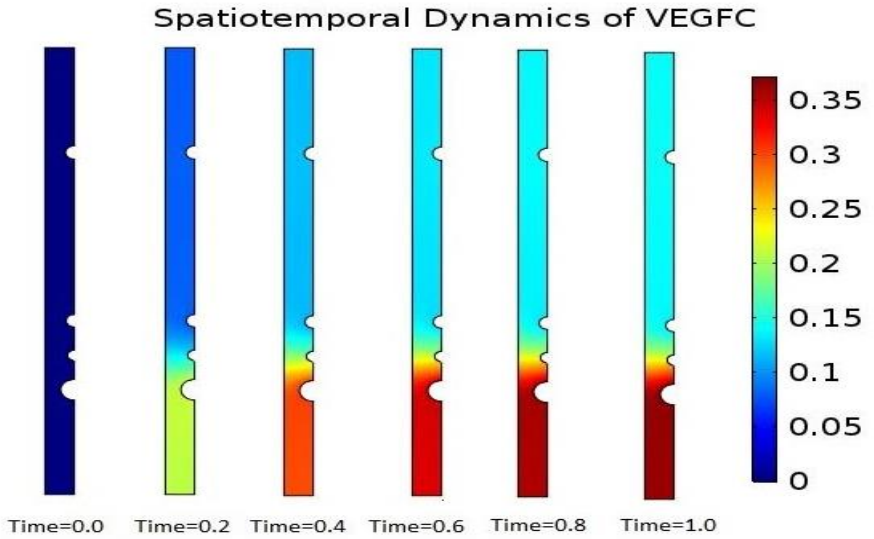
- VEGFC-collagen I binding off.
- The gradient flattens out.

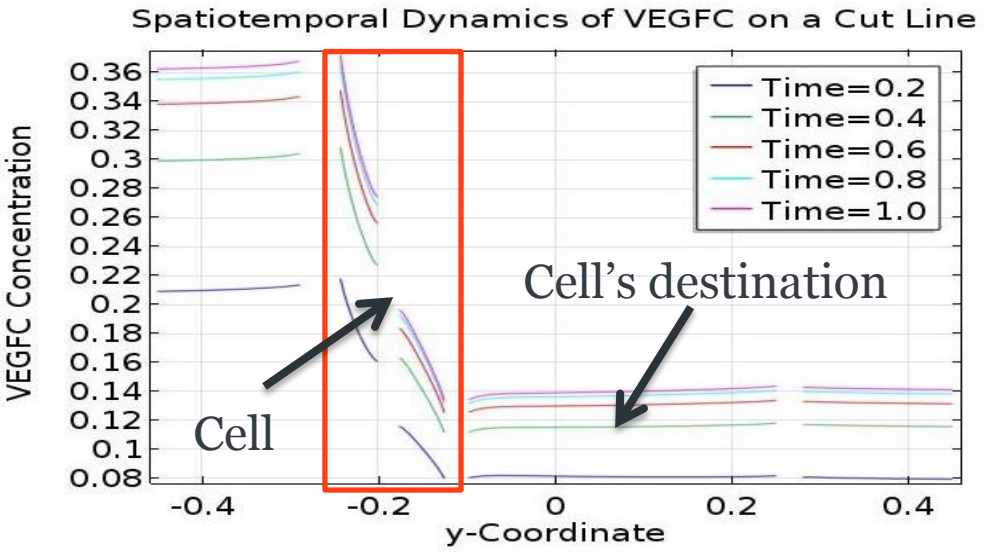
Scenario 2: Less collagen I (10 %), convection is dominant.

Assumption: other extracellular matrix proteins are produced to sequester VEGFC.

VEGFC behaves as in scenario 1 because the matrix protects it from the interstitial flow.

Scenario 3: Same as scenario 2, but VEGFC-collagen I binding is off. An asymmetric, steeper pressure field





Red box:

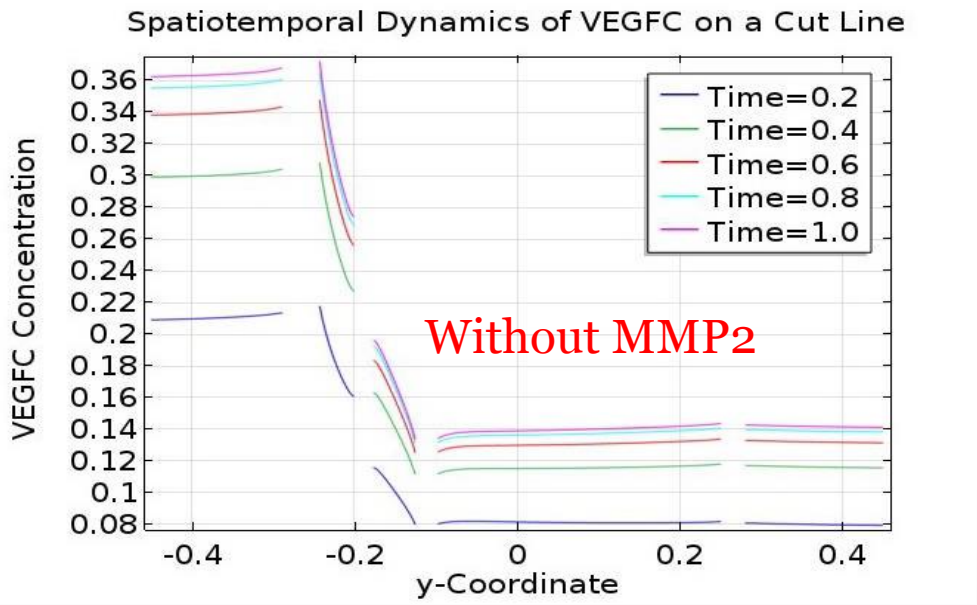
- 3-fold VEGFC concentration gradient. Morphogen, yes.
- Consistently decreasing; chemotaxis by repulsion.
- The embryo is likely to have a pulsating, chaotic pressure field.
- Pressure field is the key: steepness and direction.

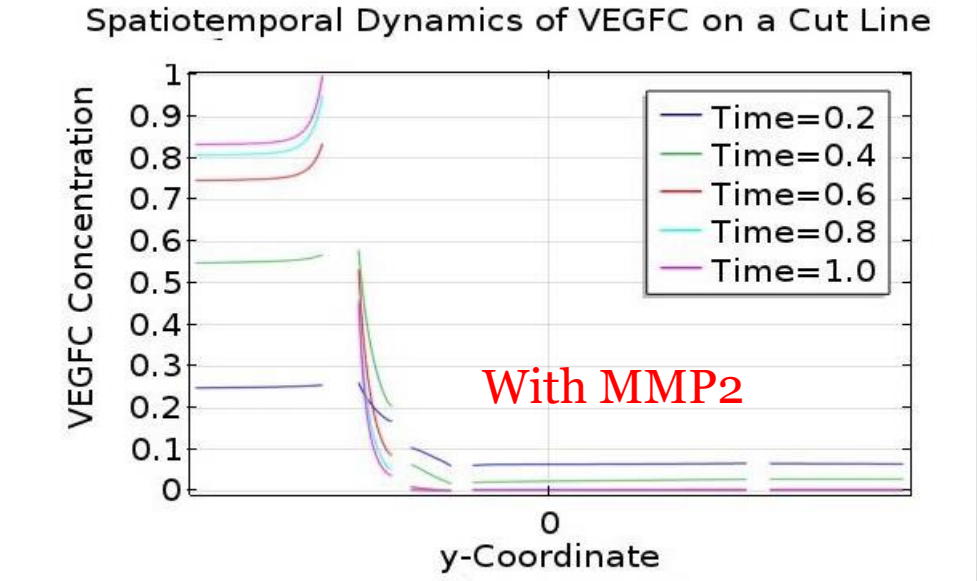
VEGFC needs MMP2.

MMP2 degrades collagen I to control which scenario VEGFC is in, thus patterning VEGFC.

In scenario 3, MMP2 enhances VEGFC's powers.

Scenario 3





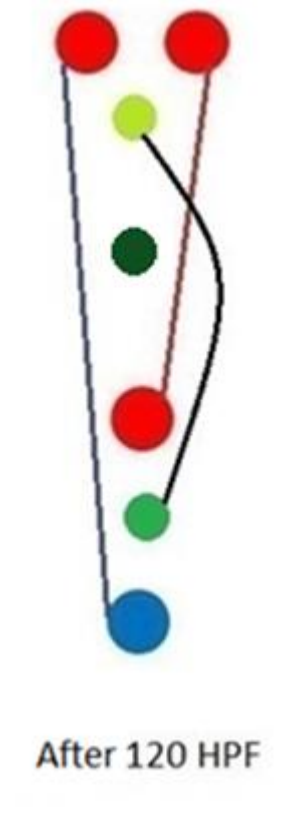
Recap: convection is dominant and VEGFC-collagen I binding is off.

Positive feedback loop:

- MMP2 accumulates in the direction of the interstitial flow.
- The flow increases further in that direction.
- VEGFC goes with the flow.

The VEGFC gradient is 3 times steeper because of MMP2.

Question 3: once in place (>120 HPF), how do the lymphatic ducts mature?



Notable features:

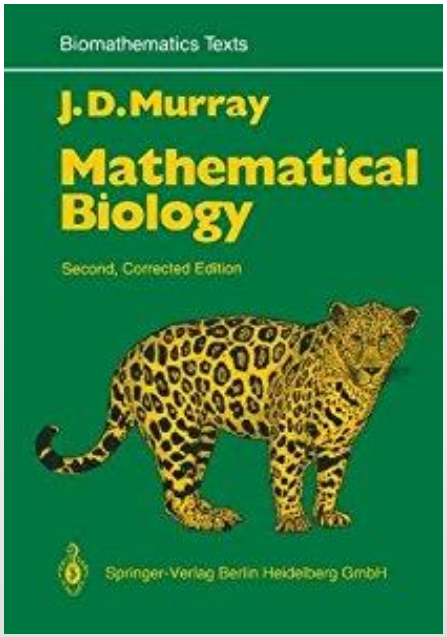
- Cell migration is over: VEGFC and MMP2 production uniform.
- More collagen I: no interstitial flow.
- Homogeneous steady state (HSS).

Hypothesis:

- Noises to the HSS can break its symmetry.
- Resulting VEGFC pattern can induce the 3 lymphatics' maturation.

Turing's mechanism:

At a homogeneous steady state, when 2 or more species diffuse at different rates and react nonlinearly, selected noise components may grow into a heterogeneous pattern.



$$f(x) = \sum_{n=0}^{\infty} a_n \cos(nx) + b_n \sin(nx)$$

The function f(x) represents noises to the HSS.

Each term in the infinite sum is a noise component with a unique wavelength.

Turing pattern analysis

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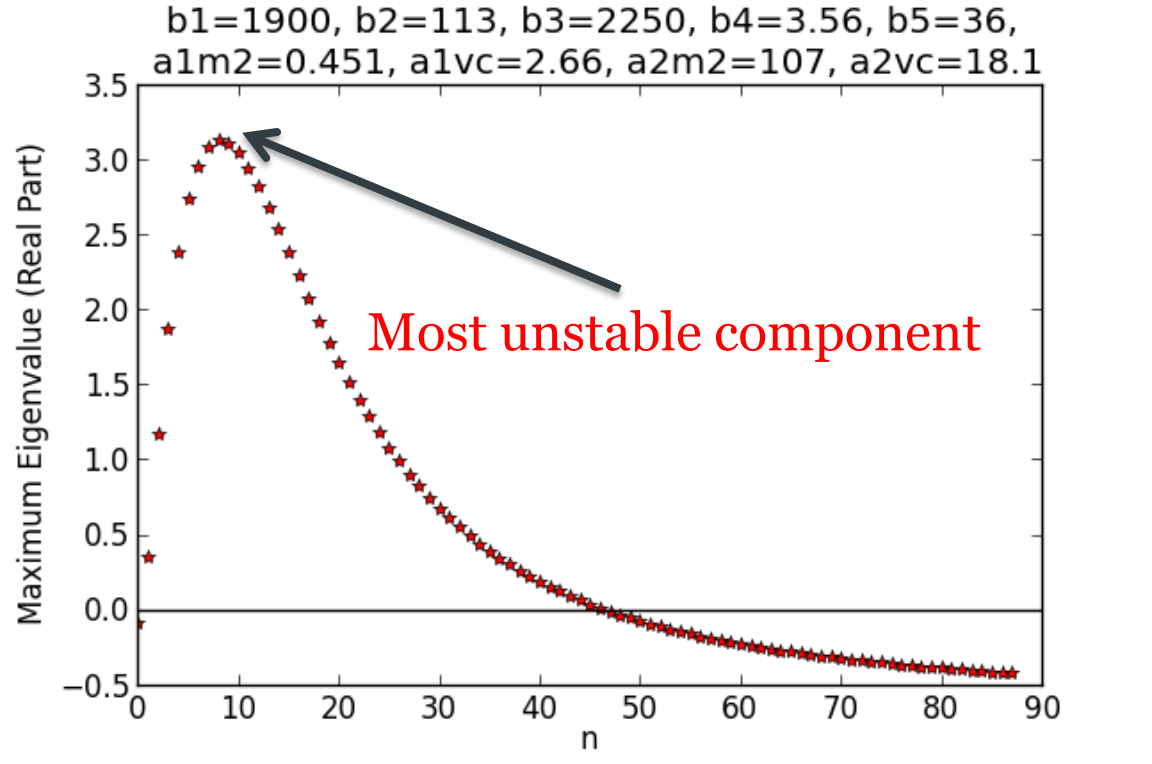
Prerequisites:

- Homogeneous steady state (HSS) is physical.
- HSS is unstable to selected noise components.
- 1 of the unstable components must grow faster than the rest.

Linear stability analysis (skipped); dispersion relation:

- It tells you how unstable each noise component is.

Example of dispersion relation



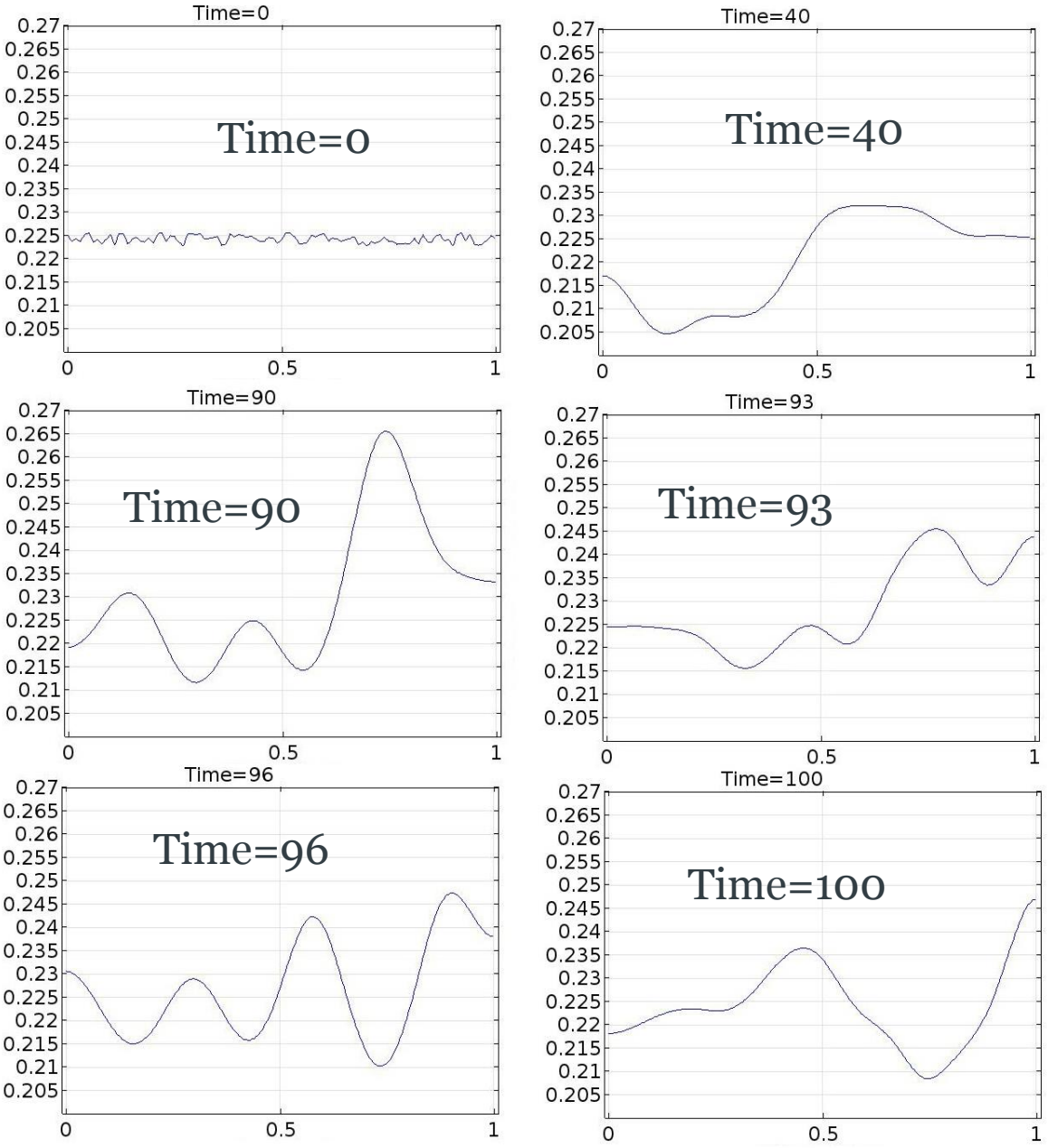
n <= 2: the wavelength is bigger than the trunk.

n >= 87: the wavelength is smaller than an LEC.

Turing pattern analysis

- Simplify the model: 2 PDEs, 2 ODEs.
- Consider ~2 million points in the parametric space.
- Turing's mechanism works at 94 points.
- Pick 1 and simulate the VEGFC dynamics.

VEGFC pattern



VEGFC concentration profiles in 1 spatial dimension.

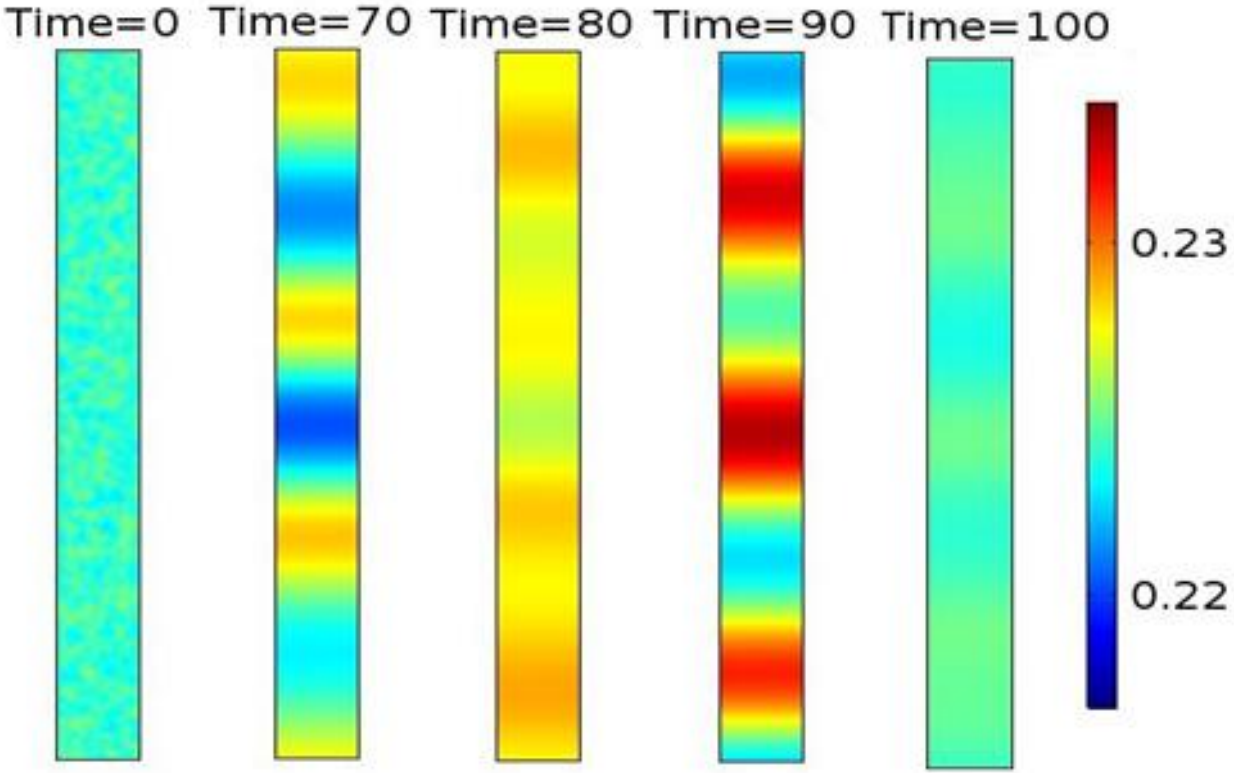
Dimensionless concentration, space, and time.

Most noise components decay; concentration range widens.

Oscillations: 3 peaks appear and disappear. Wavelength: 0.333, as predicted by the dispersion relation.

Similar results in 2 dimensions.

VEGFC pattern



Periodic boundary conditions.

More regular pattern.

Embryo not periodic.

Versatile patterning mechanism.

Q1. Is VEGFC a chemotactic factor?

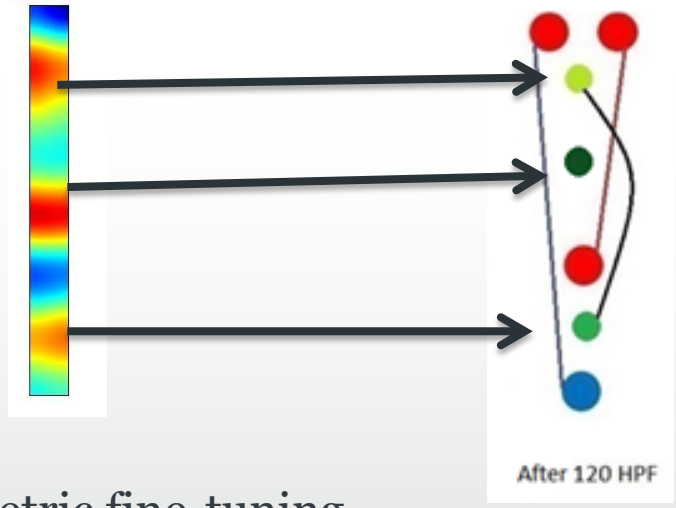
- Only possible under stringent conditions: convection dominates, VEGFC-collagen I binding off, steep and asymmetric pressure field.
- Unlikely.

Q2. Is VEGFC a morphogen?

- Developmental mechanisms were shaped by evolution; not accidental.
- It is positioned like a morphogen in many scenarios.
- Very likely.
- MMP2 is indispensable; MMP2 patterns VEGFC.

Q3. What guides the lymphatics' maturation?

- Potential mechanism: Turing patterns of VEGFC.



- Parametric fine-tuning.

Future work

- Circumstantial evidence; experimental validation please.
- Demonstrated mechanisms can pattern other molecules.
- More realistic geometry, more extracellular matrix proteins, and cell migration.

Acknowledgements

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