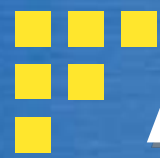


Turing structures, 0-diffusion sets, applications in morphogenesis

J. Demongeot

UGA/IUF

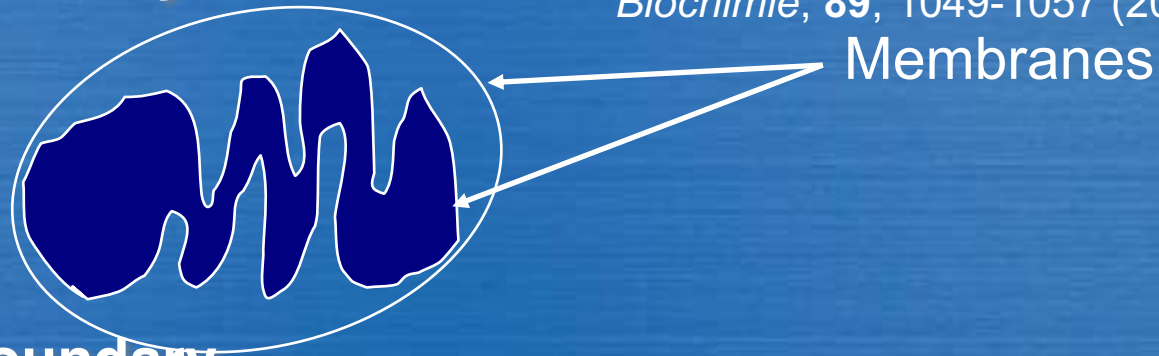


Anatomo-functional dilemma

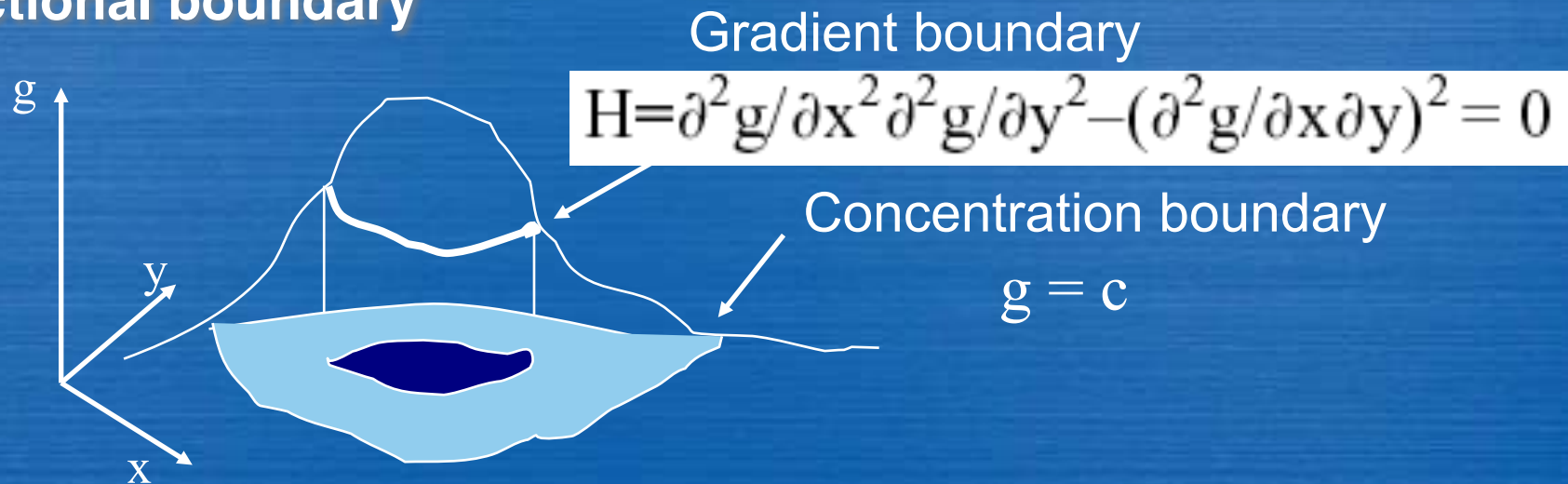
JD, N. GLADE, O. HANSEN & A. MOREIRA

An open issue: the inner mitochondrial membrane as a free boundary problem.
Biochimie, **89**, 1049-1057 (2007).

- **Anatomic boundary**



- **Fonctional boundary**





Cell boundary functions

Transportation (active & passive carriers)

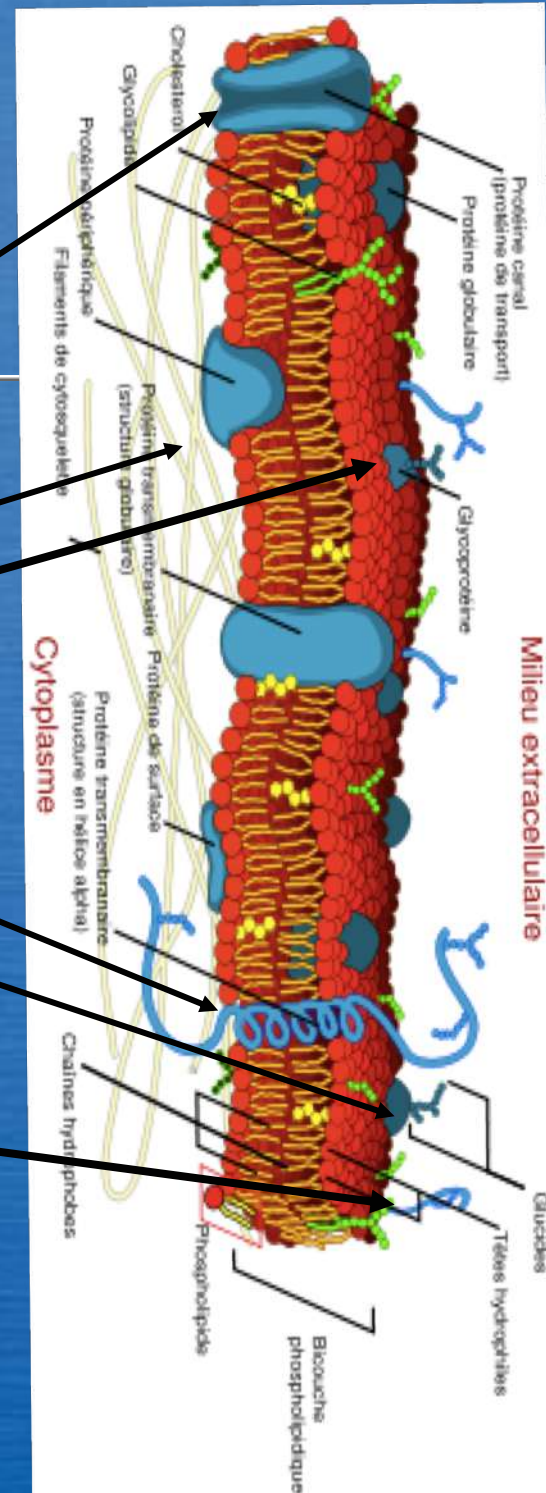
Structure (cytoskeleton & extra-cellular matrix)

Signalling (active & inactive receptors)

Information (inhibitors & activators)

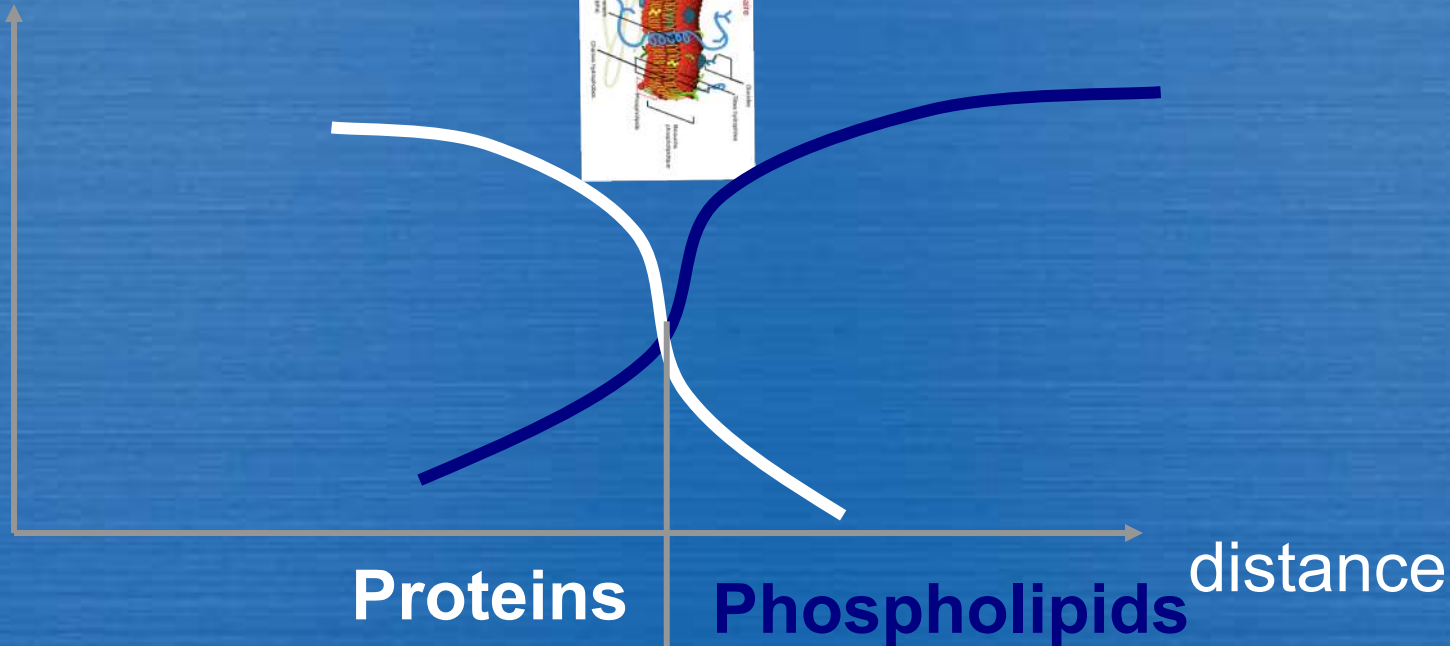
Homeostasis (thermo & baroregulation)

Protection (immunoactive & epidermopassive)



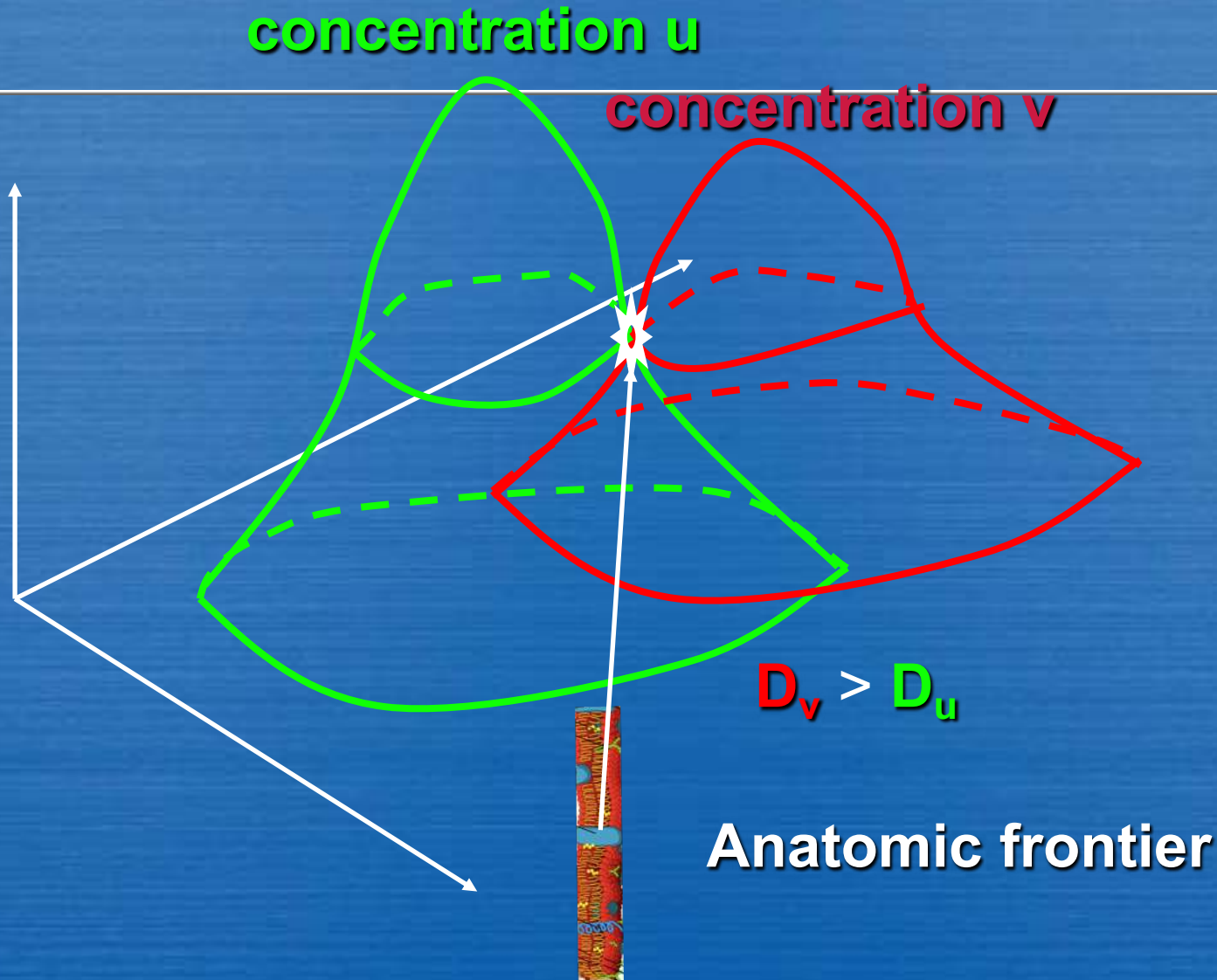
Proteo-Phospho-Lipid interface

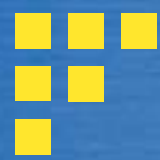
concentration



Proteophospholipidic membrane

Gradient boundaries





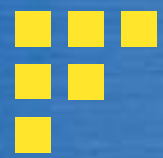
Mean Gaussian curvature

$$K = \frac{f''_{xx} f''_{yy} - f''_{xy}^2}{(1 + f'^2_x + f'^2_y)^2}$$

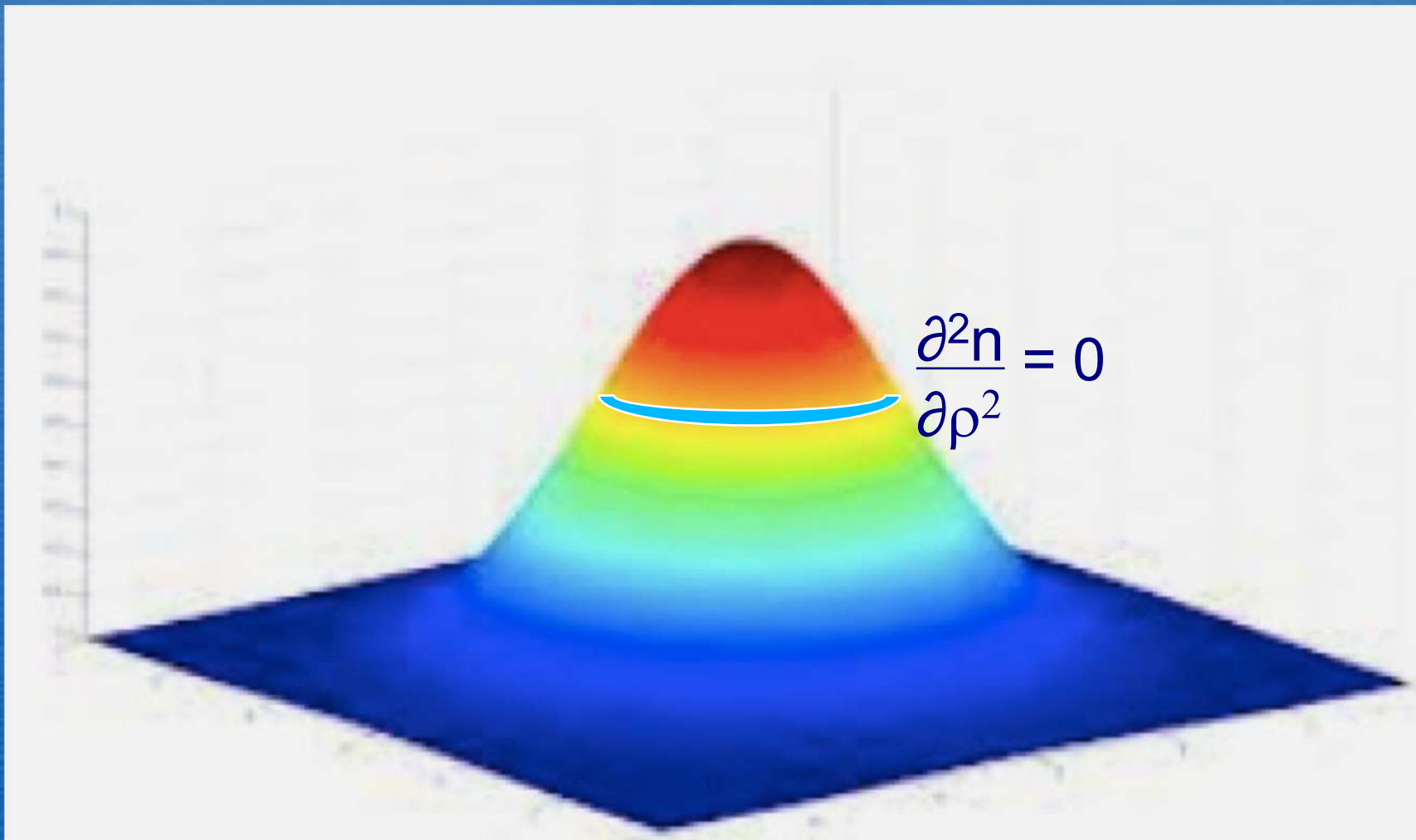


Link with diffusion

- If the diffusion and reaction are isotropic, Turing structures have a revolution symmetry and the zero-diffusion sets are exactly the min Gaussian curvature sets of the surface representing the substrate concentration.

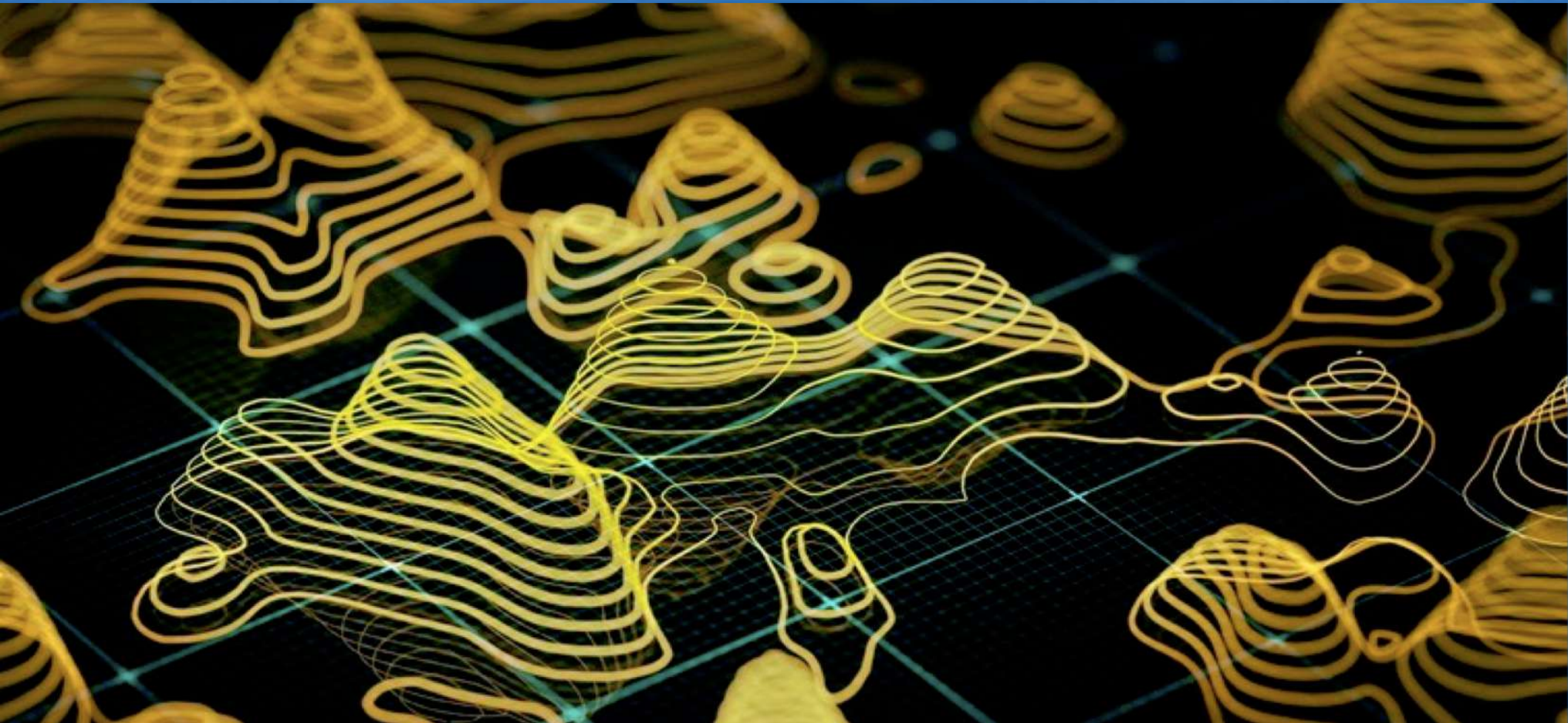


Revolution symmetric peak





Not revolution symmetric peak



Heat equation

J. FOURIER 1808-1822

Mémoire sur la propagation de la Chaleur dans les corps solides, Nouveau Bulletin des sciences Société Philomathique de Paris, 6, 112-116 (1808)

NOUVEAU BULLETIN DES SCIENCES, PAR LA SOCIÉTÉ PHILOMATHIQUE.

PARIS. Mars 1808.

L'abonnement est de 14 fr. pour les départements, franc de port; et de 15 francs chez BERNARD, éditeur des Annales de Chimie, quai des Augustins, n°. 25.

HISTOIRE NATURELLE. MINÉRALOGIE.

Mémoire sur la réunion de la Pycnite avec la Topaze;
par M. HAÛY.

La substance à laquelle M. Haüy a donné le nom de pycnite étoit connue anciennement sous celui de *schorl blanc prismatique d'Altenberg*. M. Werner la regarde comme une variété de l'émeraude de Sibérie, à laquelle il a conservé la dénomination de béril, et il donne à la pycnite celle de *schorlartiger beril*. La plupart des autres minéralogistes étrangers ont fait du même minéral une espèce particulière qu'ils ont appelée *stangenstein*. M. Haüy n'ayant eu jusqu'alors entre les mains que des groupes de cristaux prismatiques de ce minéral, déformés par des stries longitudinales, n'avoit pu déterminer exactement la figure et les dimensions de ses molécules. Seulement, il avoit présumé que sa forme primitive étoit le prisme hexaèdre régulier. Mais en ayant acquis récemment un morceau dont la cristallisation étoit un prisme hexaèdre qui avoit en faisant mouvoir à la lumière la vu un joint naturel d'un éclat d'autres joints beaucoup plus foibles ceux qu'il a reconnus depuis environ du prisme faisoient entre eux deux 118°, et les positions des facettes de décroissement dépendantes de ces fragments qui approchoient

SOCIÉTÉ PHILOM.

N°. 6.

ΔX

Ces résultats conformes à ceux des observations qui ont été faites sur les lieux aussi par M. Roussille-Champseru et par M. Larrey, et qui ont été communiquées à l'Institut de France, paroissent devoir fixer enfin l'opinion des savans sur cette singulière affection.

La plique, ainsi ramenée à ses causes et réduite à ses effets, doit cesser d'être considérée comme une maladie, et elle doit rentrer dans le domaine de la police médicale et l'hygiène. Il est donc permis d'espérer que les Polonais rendus, par les événemens qui viennent de changer leur état politique, à l'exercice des droits et des devoirs de la société, se hâteront, en devenant plus éclairés, de faire disparaître de leur pays une affection que désormais on ne pourroit plus attribuer à leur climat, mais bien à leurs habitudes, à leurs préjugés.

D.

MATHÉMATIQUES.

Mémoire sur la propagation de la Chaleur dans les corps solides; par M. FOURIER.

INSTIT. NAT.

21 Déc. 1807.

L'AUTEUR de ce Mémoire s'est proposé de soumettre la théorie de la chaleur à l'analyse mathématique, et de vérifier, par l'expérience, les résultats du calcul. Pour exposer l'état de la question, supposons une barre de métal cylindrique et d'une longueur indéfinie, plongée par une de ses extrémités, dans un fluide entretenu à une température constante : la chaleur se répandra successivement dans la barre; et



■ ■ ■ ■ ■ Diffusion: Key Points

- Substances diffuse according to their concentration gradient; within a system, different substances in the medium will each diffuse at different rates according to their individual gradients.
- After a substance has diffused completely through a space, removing its concentration gradient, molecules will still move around in the space, but there will be no net movement of the number of molecules from one area to another, a state known as dynamic equilibrium.
- Several factors affect the rate of diffusion of a solute including mass of the solute, temperature of the environment, solvent density and distance traveled.



Minimal mean free path & maximal time exit from the 0-diffusion set

- If two substances share the same zero-diffusion set, then the location at which they remain together and react the most is this common set.

Reaction-diffusion

$$F(X) + D\Delta X = X_t$$

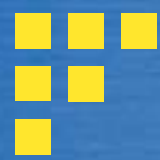
Logistic

Allosteric

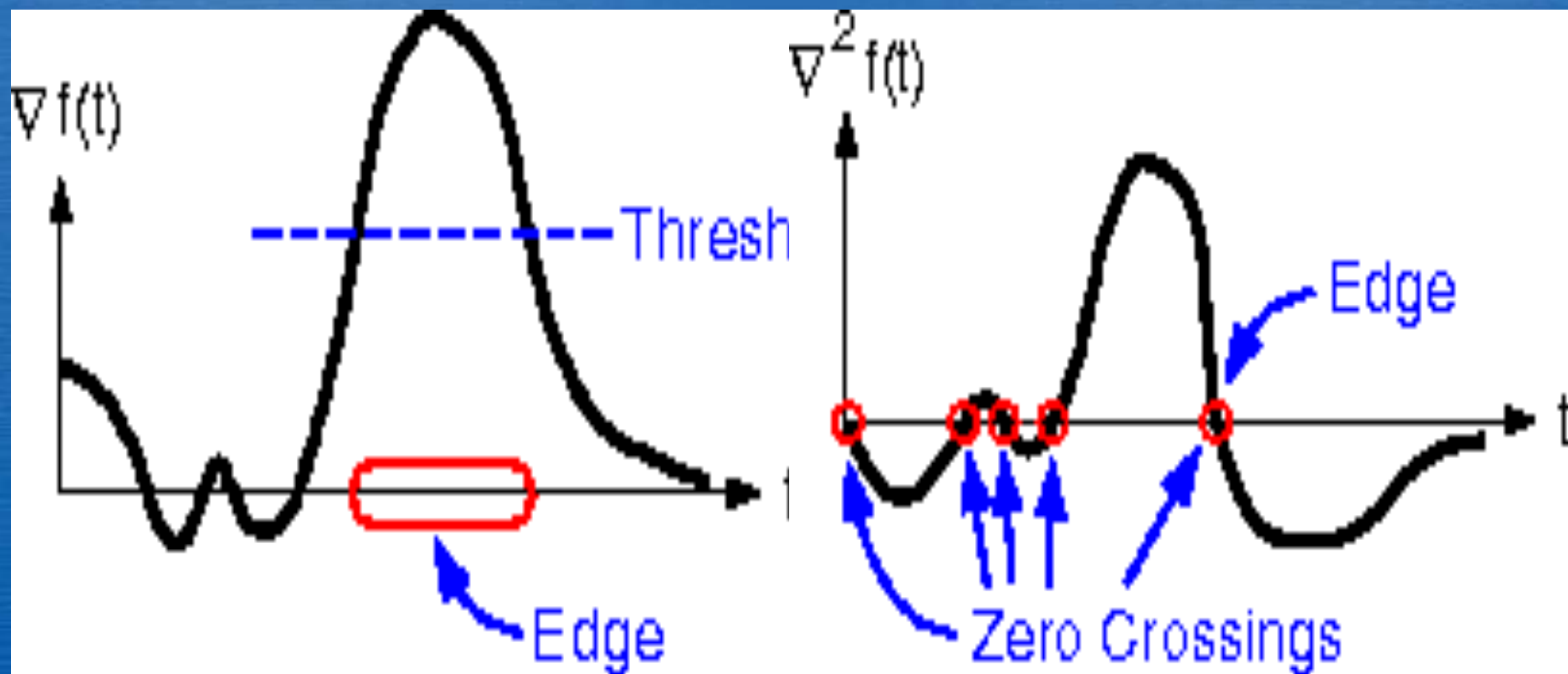
Hill

Michaelis-Menten

Fitzhugh-Nagumo



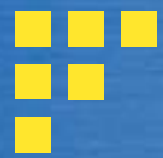
Laplacian Edge Detection





Recent references

- Rueda-Contreras, M.D., Gallen, A.F., Romero-Arias, J.R. *et al.* On Gaussian curvature and membrane fission. *Sci Rep* **11**, 9562 (2021).
- Penič, S. *et al.* Budding and fission of membrane vesicles: A mini review. *Front. Phys.* **8**, 342 (2020).
- Barrio, R., Alarcon, T. & Hernandez-Machado, A. The dynamics of shapes of vesicle membranes with time dependent spontaneous curvature. *PLoS ONE* **15**, e0227562 (2020).
- Fonda, P., Al-Izzi, S. C., Giomi, L. & Turner, M. S. Measuring gaussian rigidity using curved substrates. *Phys. Rev. Lett.* **125**, 188002 (2020).
- Dharmavaram, S., She, S. B., Lázaro, G., Hagan, M. F. & Bruinsma, R. Gaussian curvature and the budding kinetics of enveloped viruses. *PLoS Comput. Biol.* **15**, e1006602 (2019).



Example 1

Gastrulation

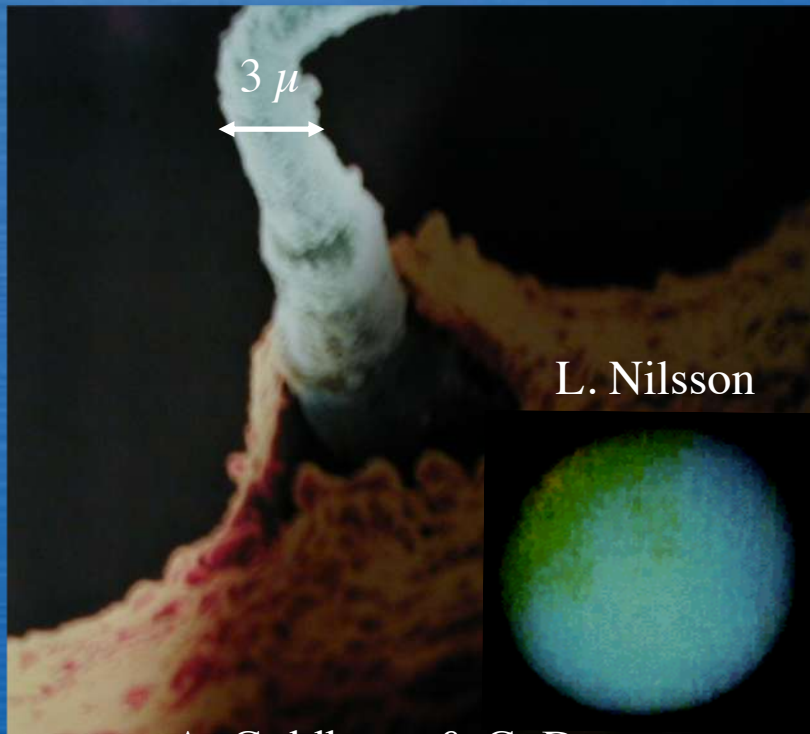


L. Forest

«Tous les curieux ont vu
de ces animalcules

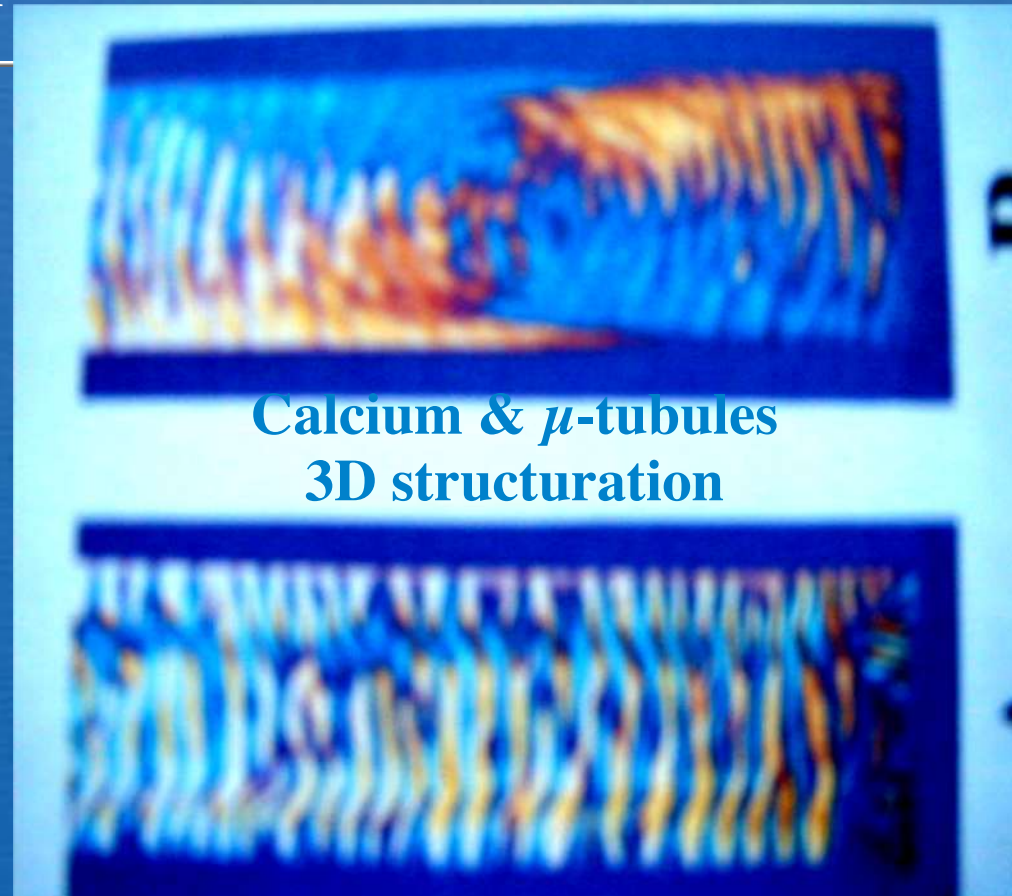
*le plus adroit s'insinuer dans l'œuf
que lui fournit la femme»*

In L'homme plus que machine



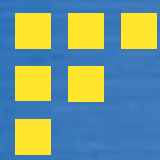
A. Goldbeter & G. Dupont
PNAS 85 (1988)

La Mettrie 1748

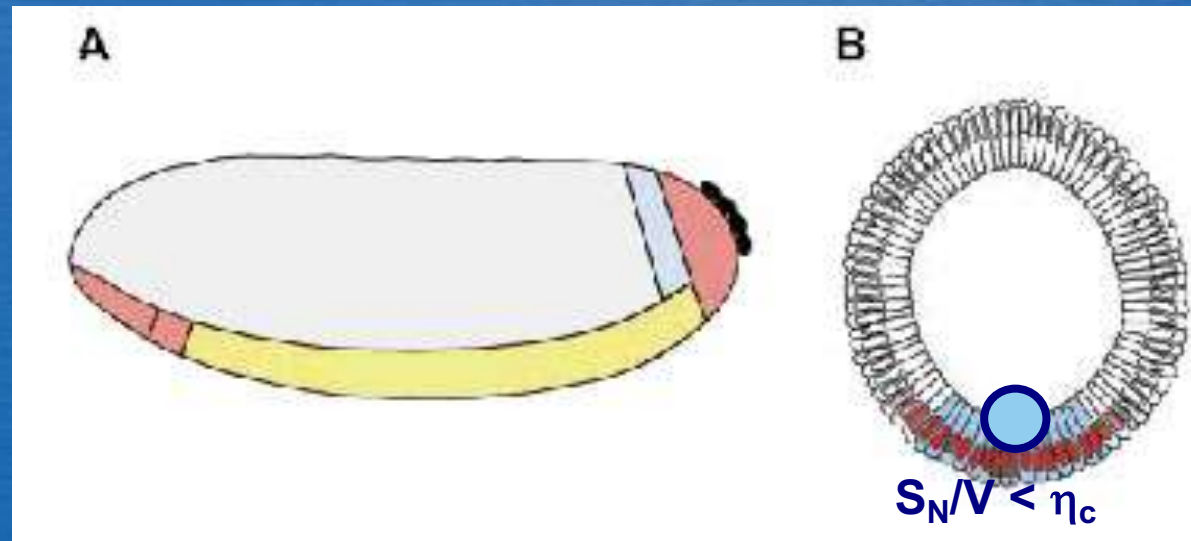
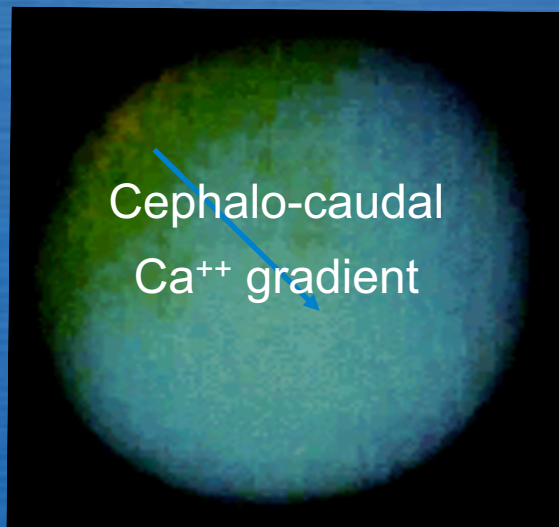


Calcium & μ -tubules
3D structuration

J. Tabony, N. Glade & JD
BMC Cell Biology 5 (2003)



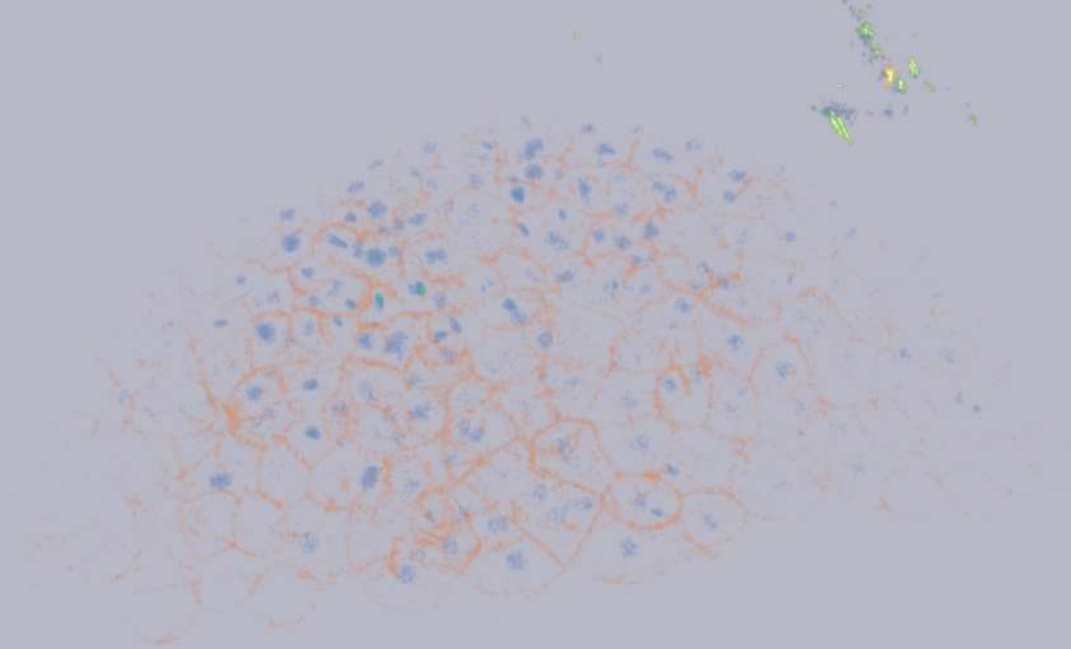
Embryonic life

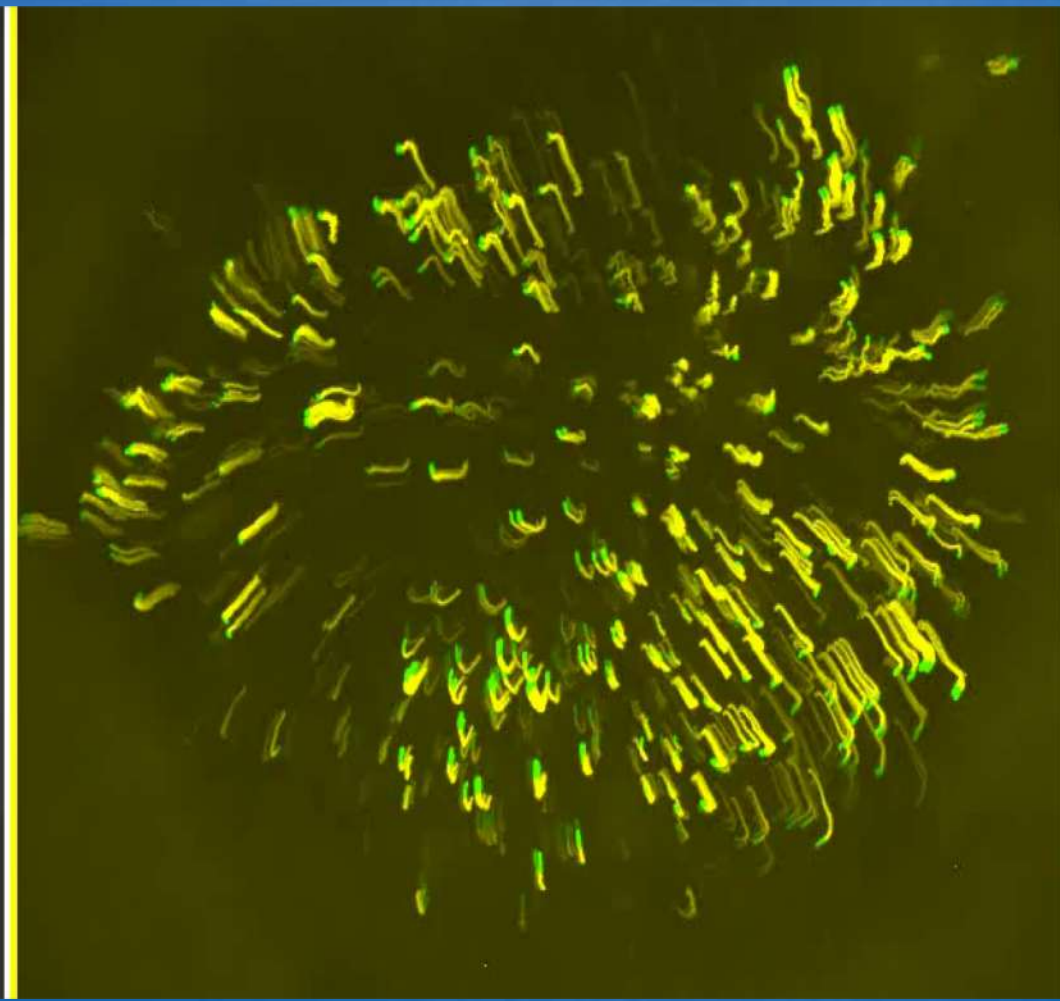
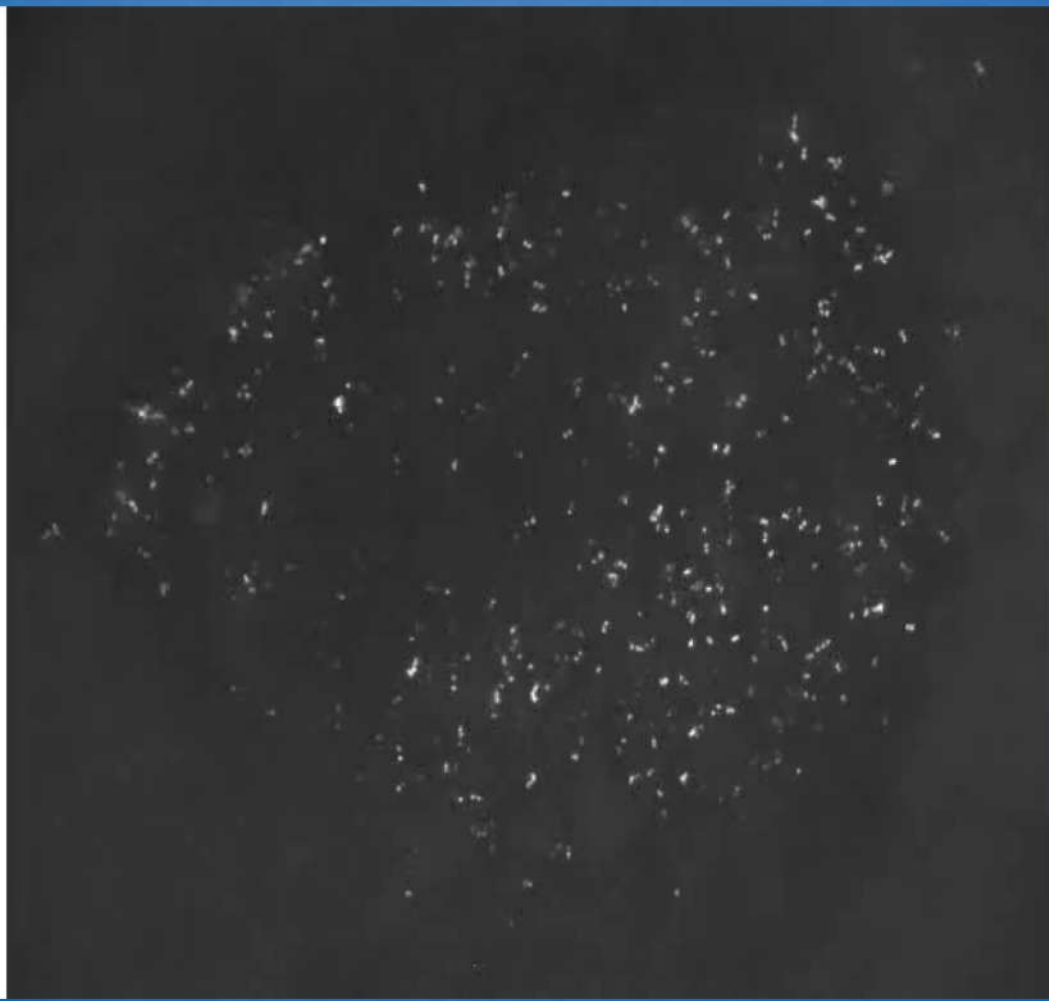


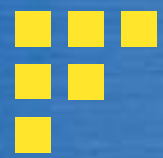
Spheric symmetry breaking

Revolution symmetry breaking

Drosophila melanogaster

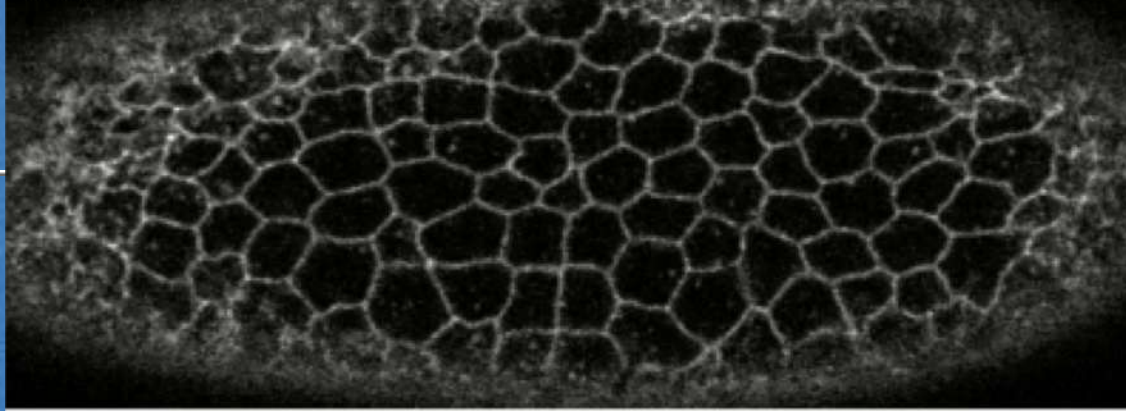




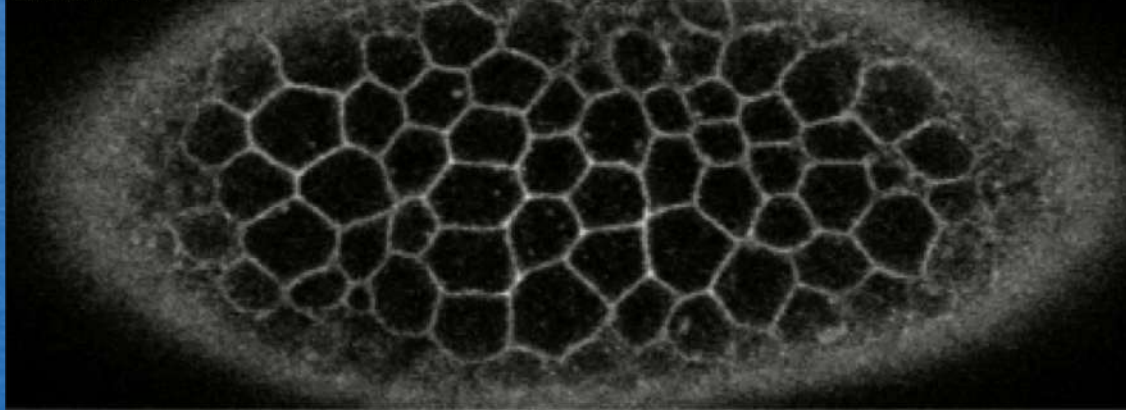


Gastrulation

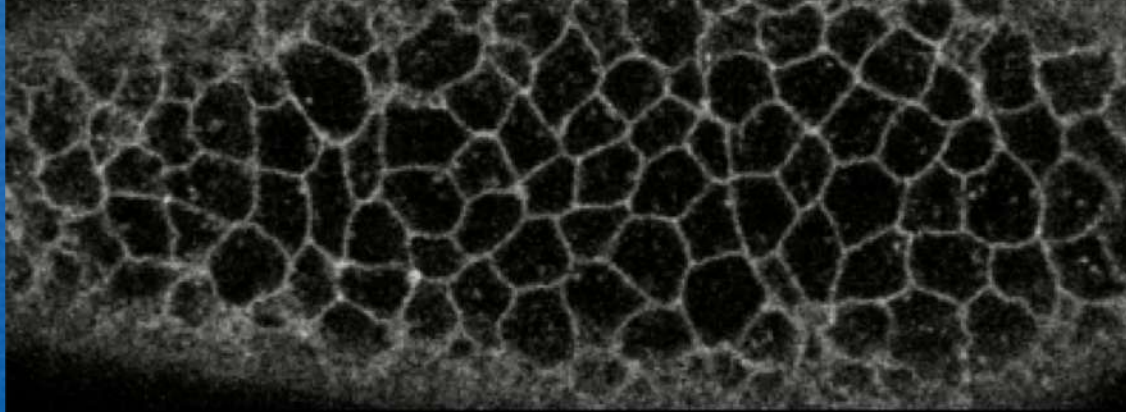
Control RNAi

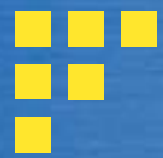


snailRNAi

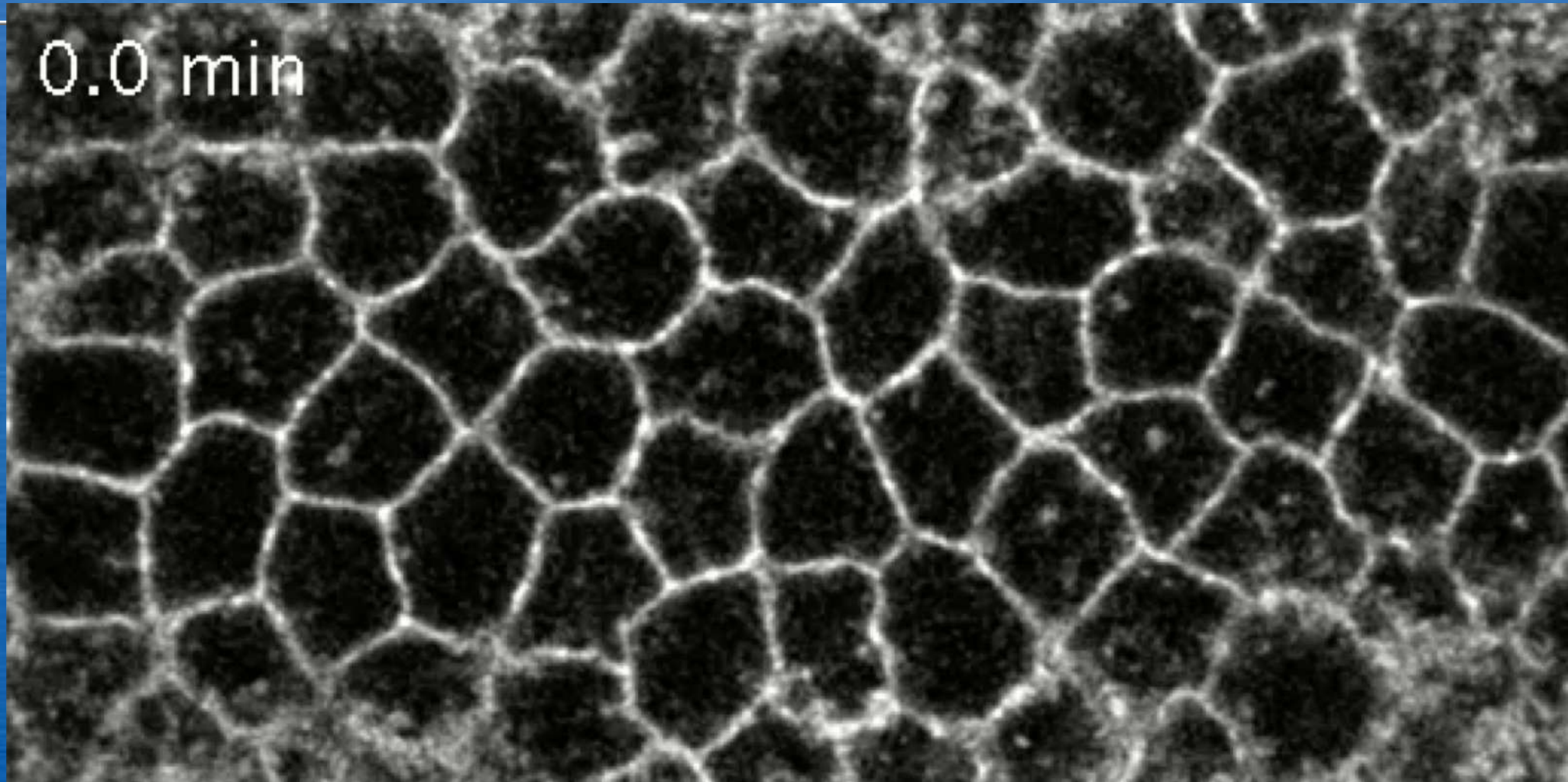


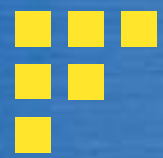
twistRNAi



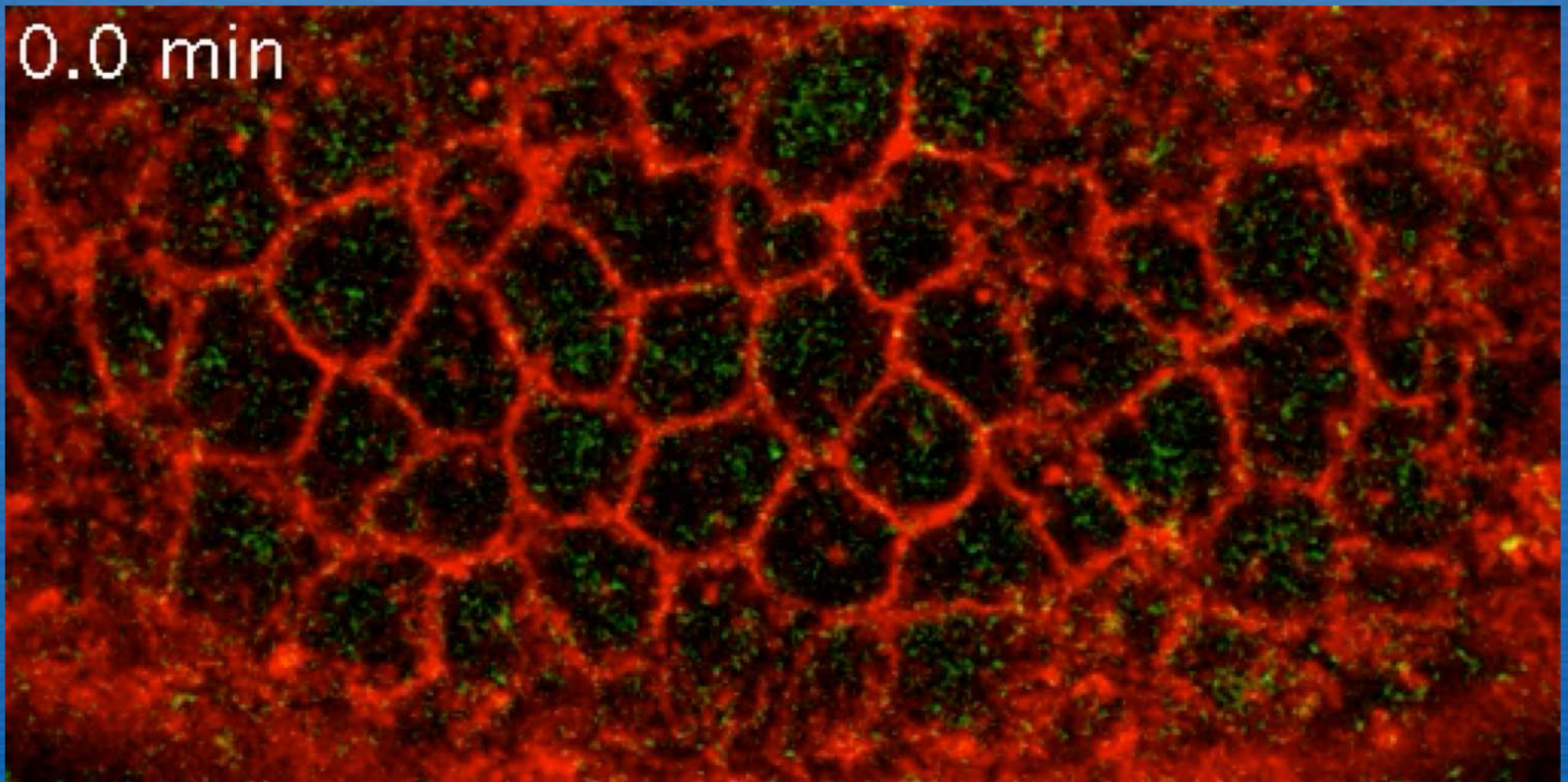


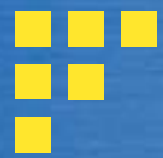
Gastrulation



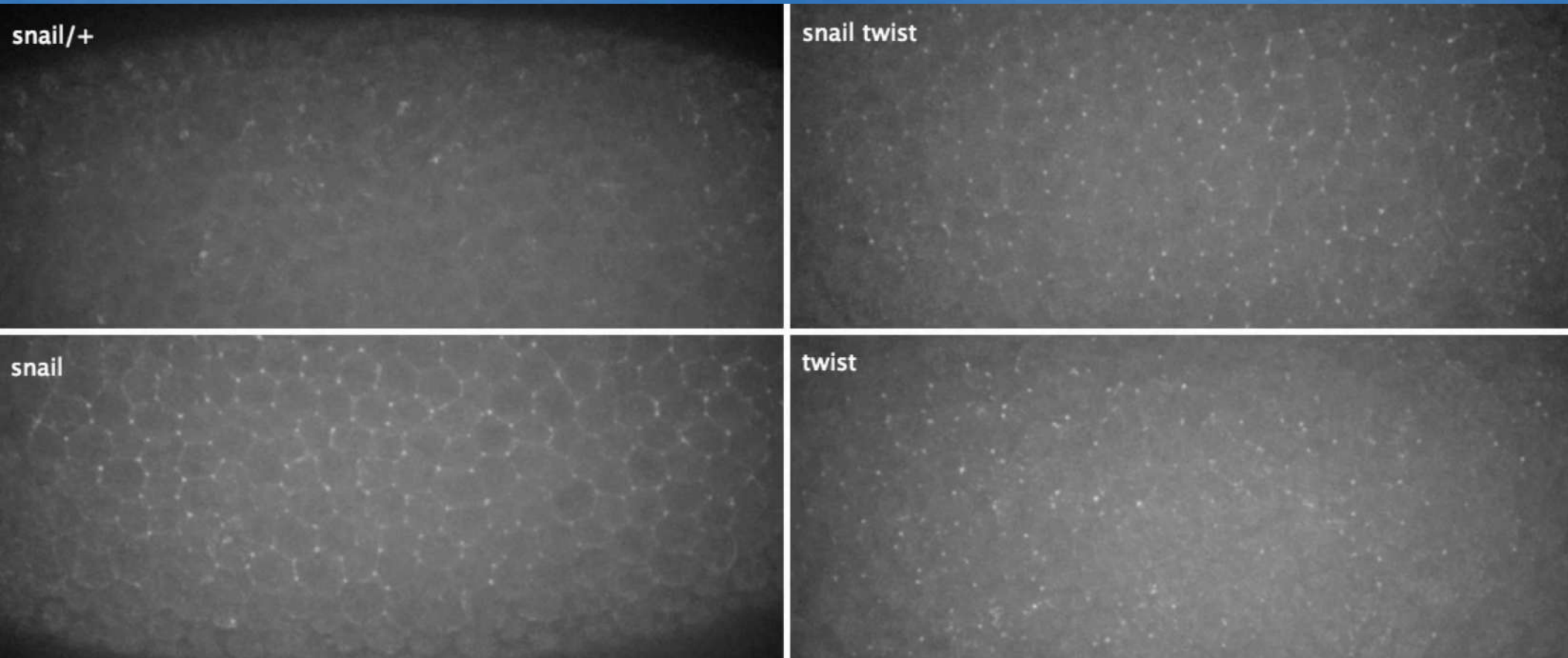


Gastrulation

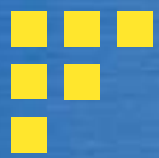




Gastrulation

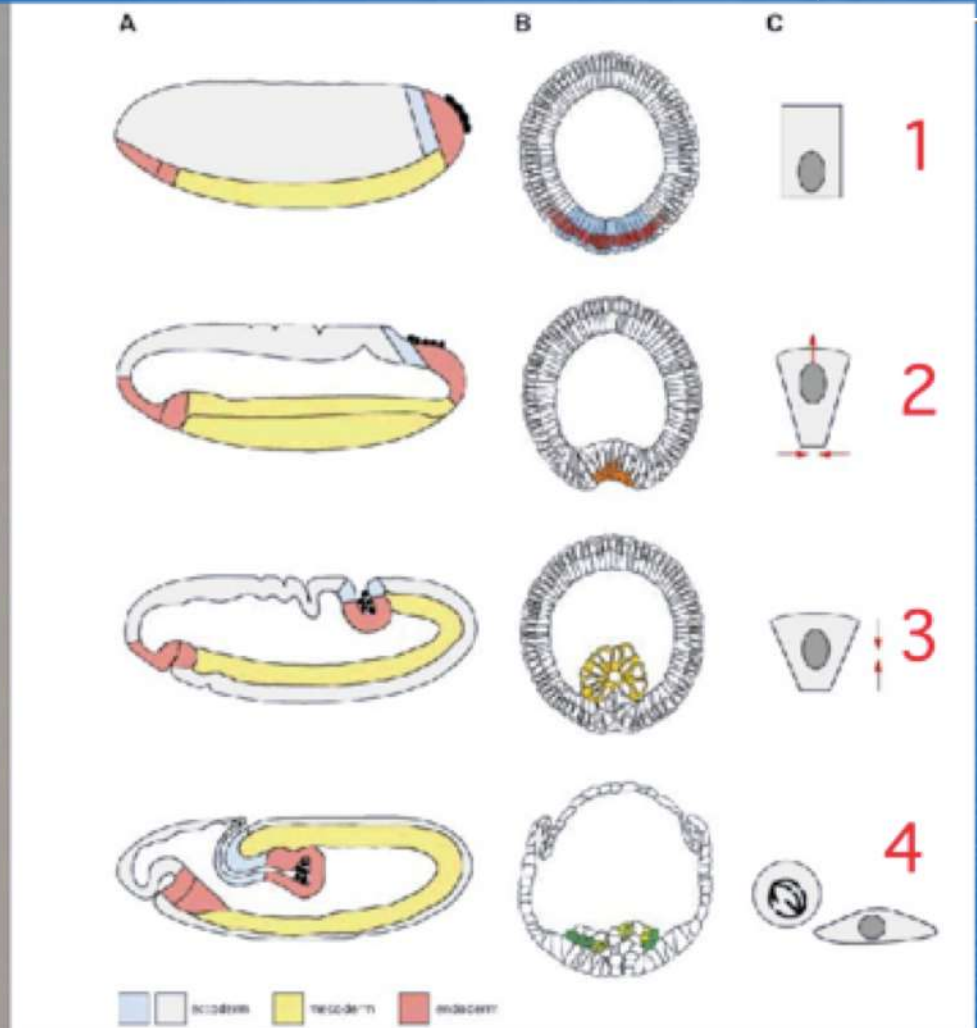
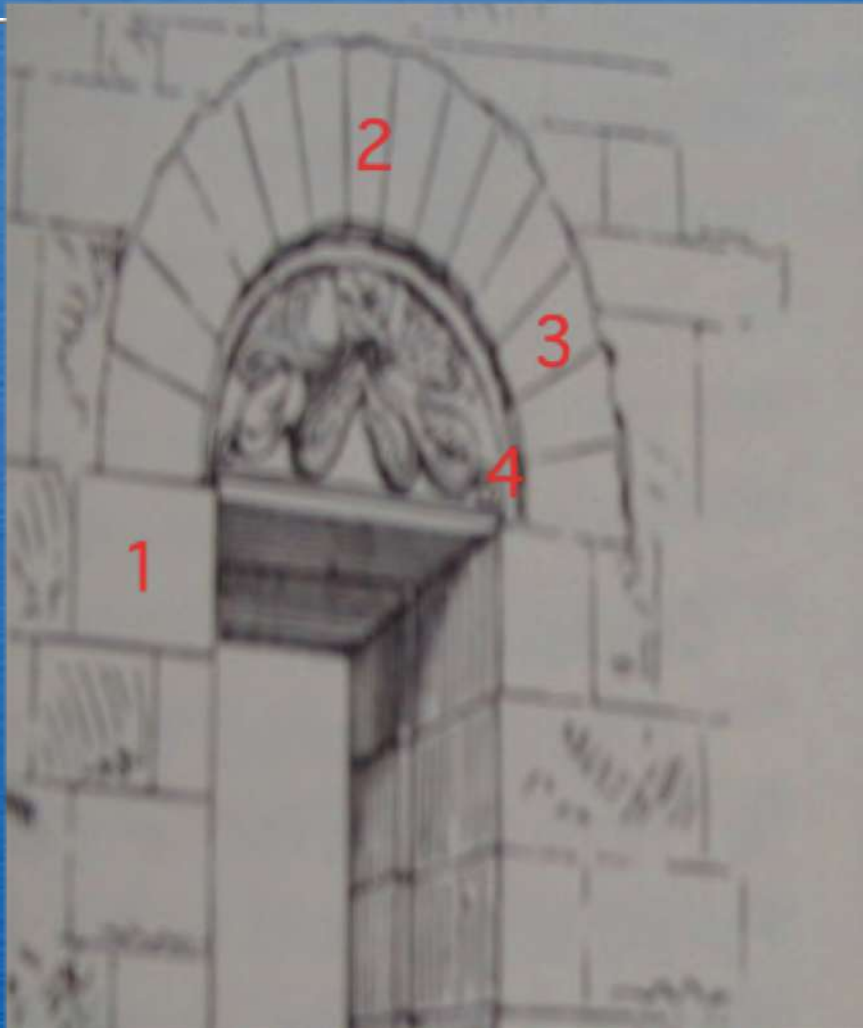


E. Wieschaus



Gastrulation

Bottle cell
differentiation
↓



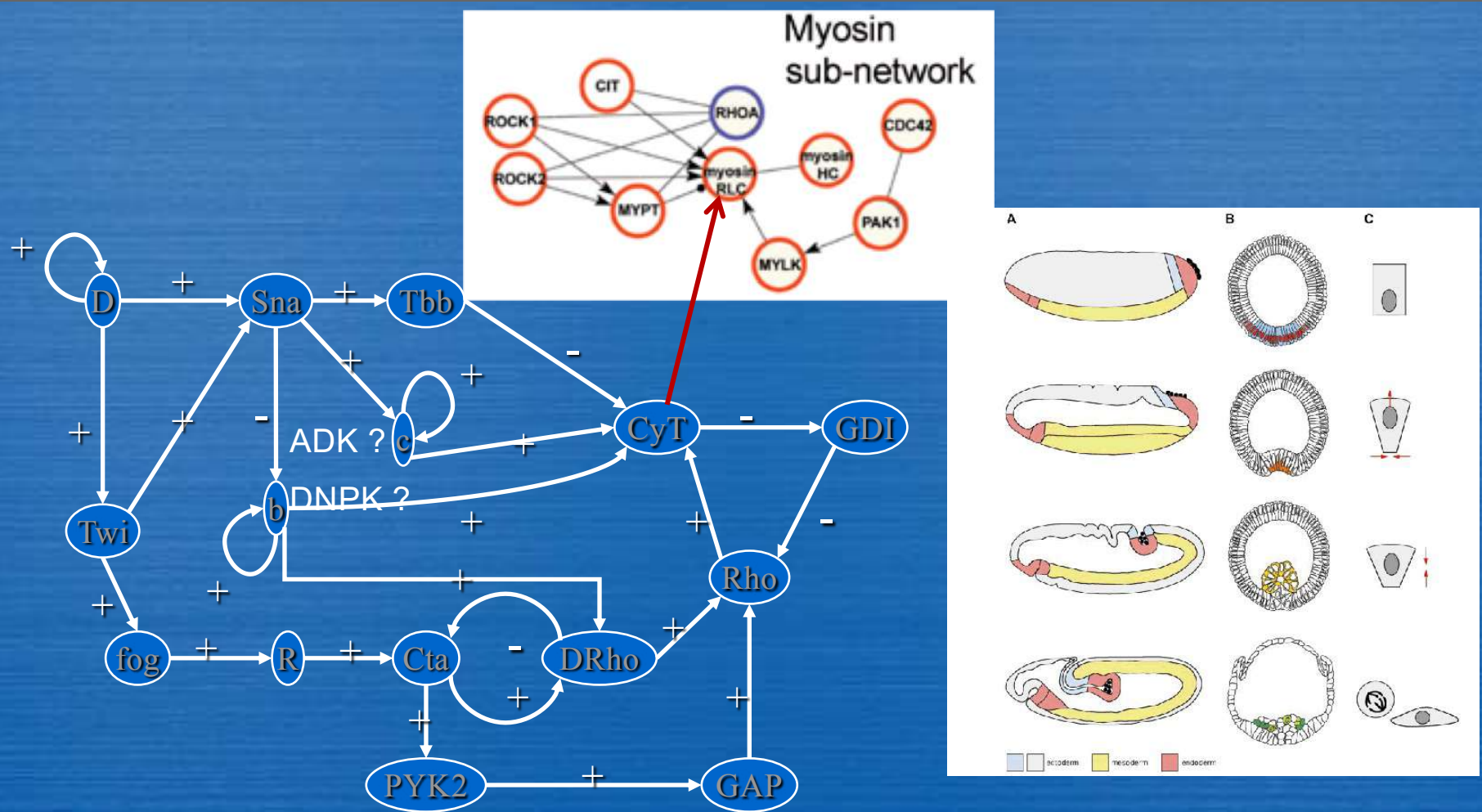
M. Leptin, EMBO J (2000)

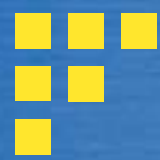
Rouen 22

Regulatory network for cell shape changes during *Drosophila* ventral furrow formation





JD, F. Thuderoz, T.P. Baum, F. Berger & O. Cohen, CR Biologies (2003)

J. Aracena, M.González, A. Zuñiga, M. Méndez.& V. Cambiazo, JTB (2006)





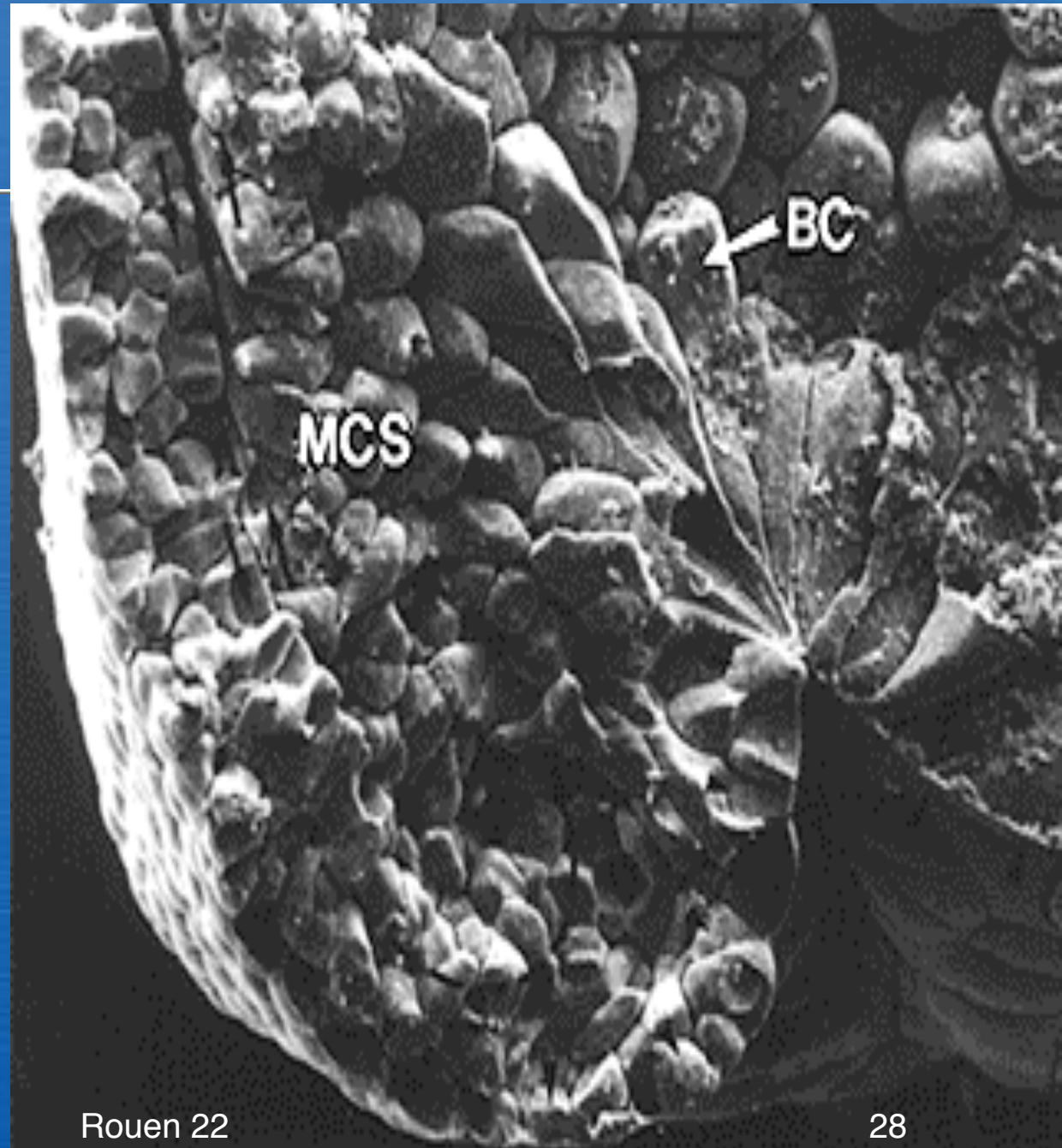
Gene activation

Ph.	D	Twl	Sna	fog	Cta	R	DRho	Rho	Gap	CyT	GDI	Tbb	Pyk2
	0	0	0	0	0	0	1	0	0	0	1	1	0
	1	1	1	1	1	1	1	1	1	1	0	0	1
	1	1	1	1	1	1	1	1	1	1	0	0	1
	1	1	1	1	1	1	1	1	1	1	0	0	1

Bottle cell

Amniotic feeding

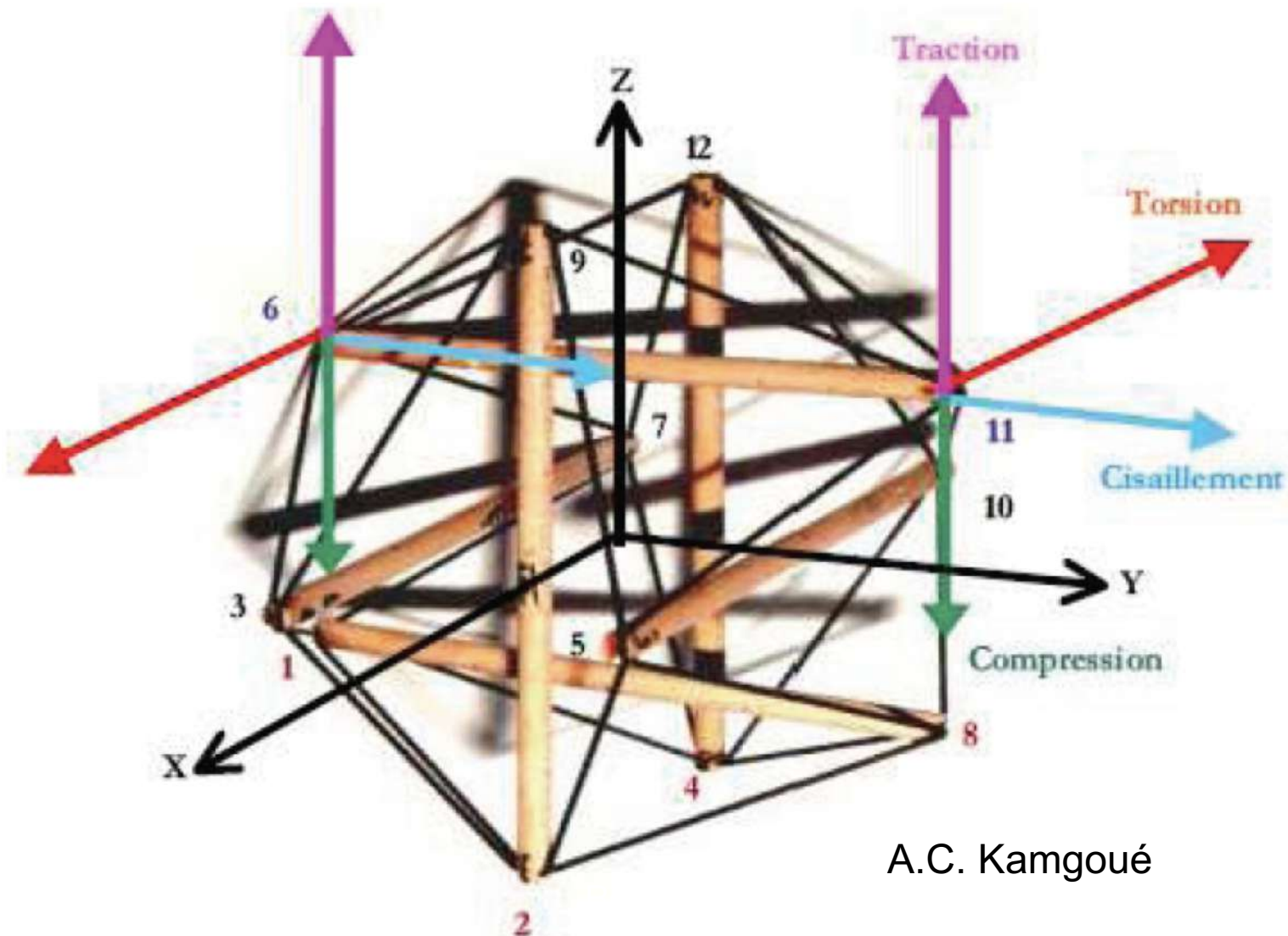
10/07/2022



Rouen 22

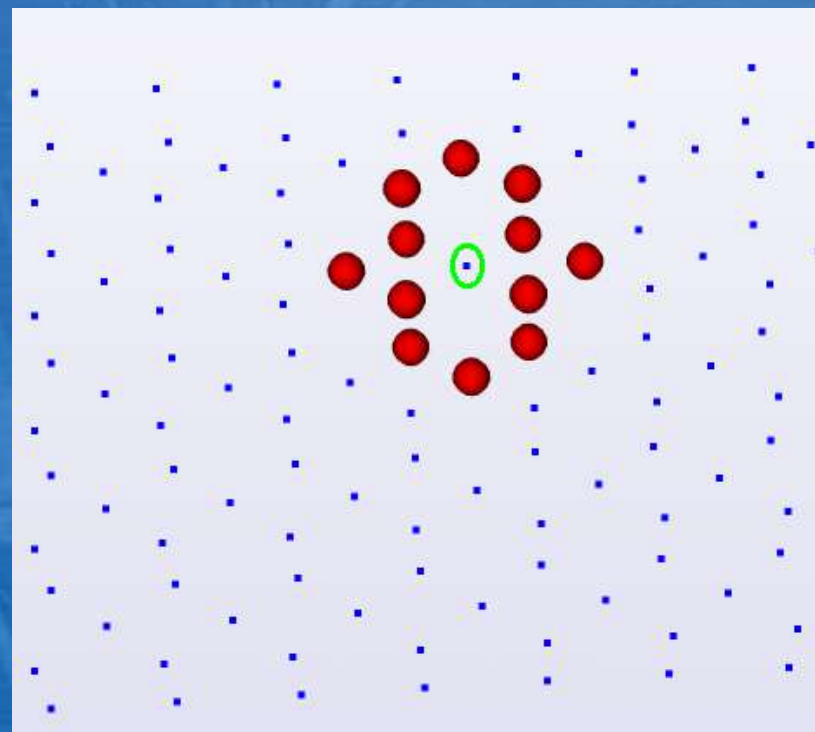
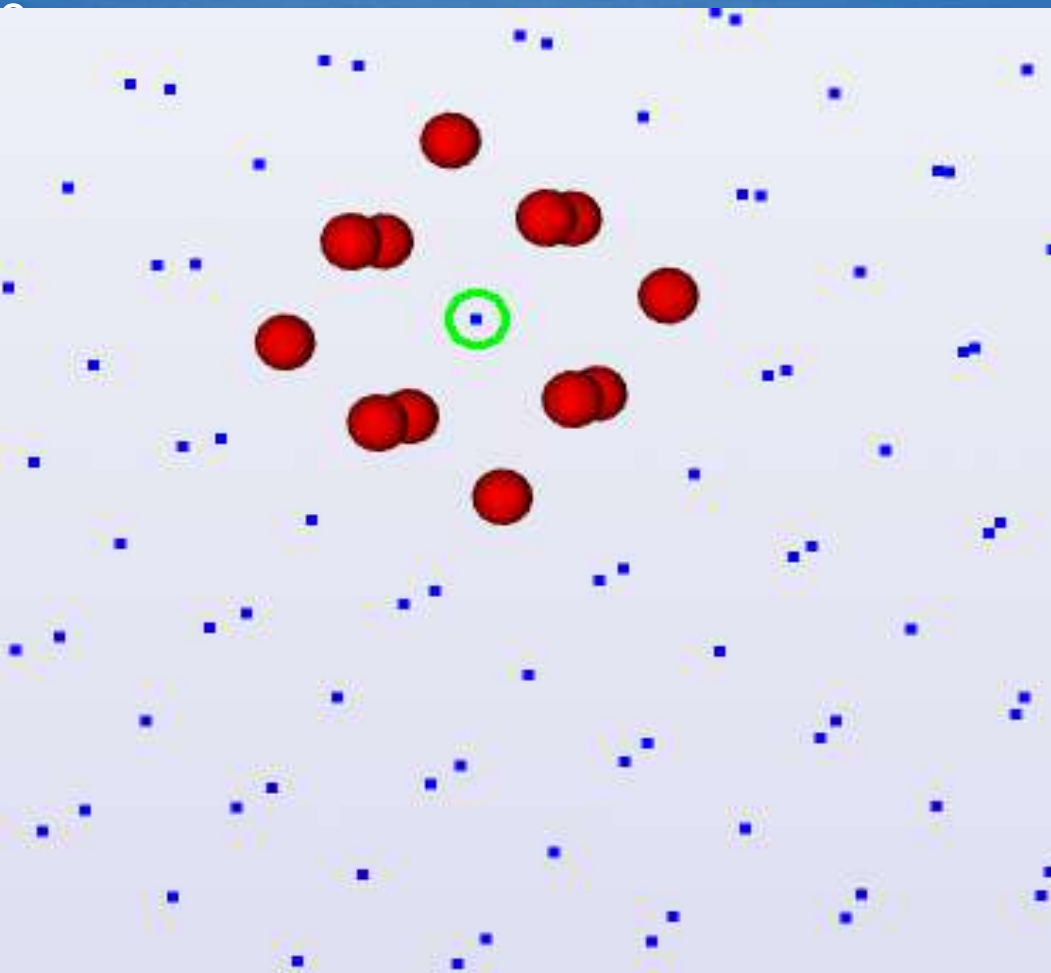
28

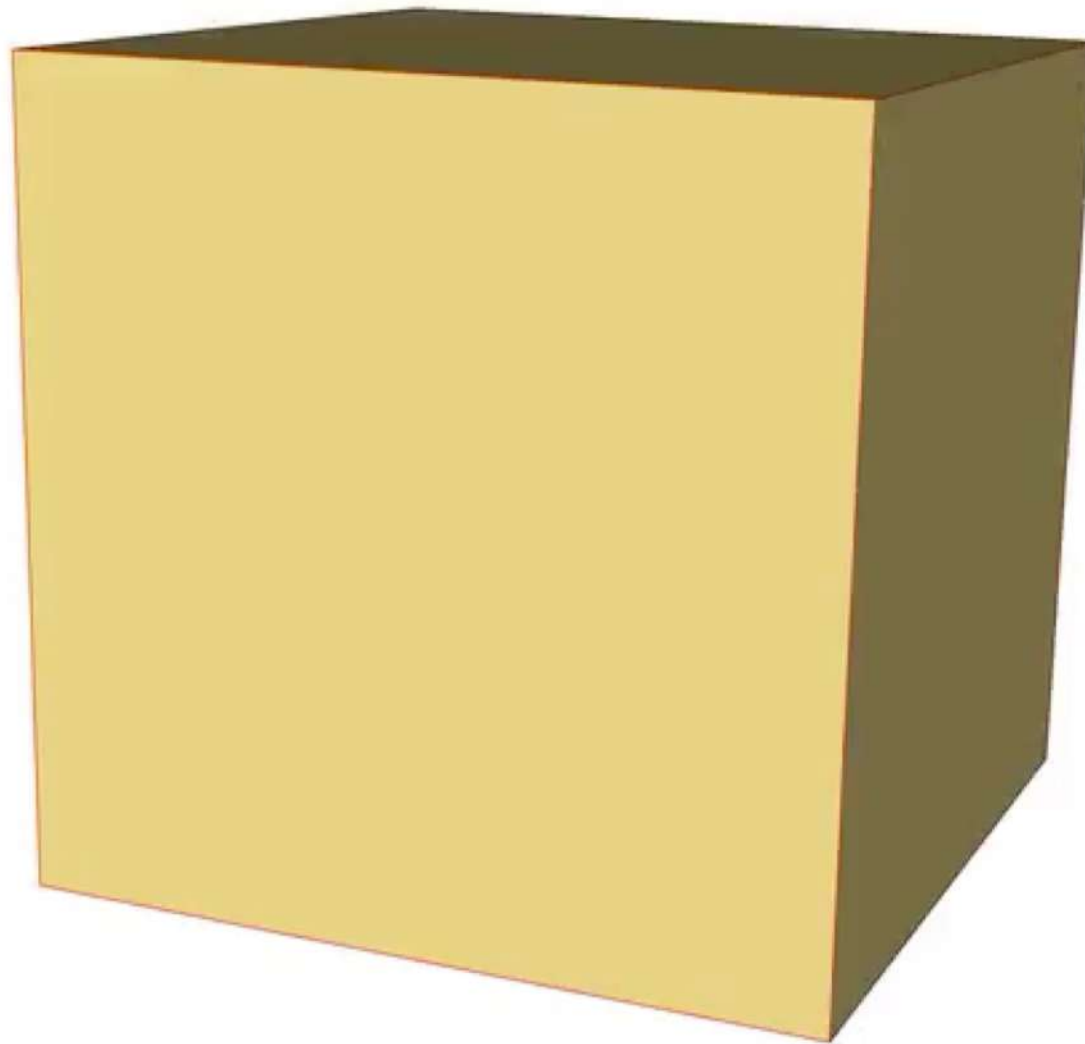
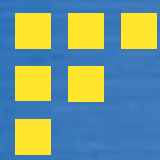
Cytoskeleton complexity



A.C. Kamgoué

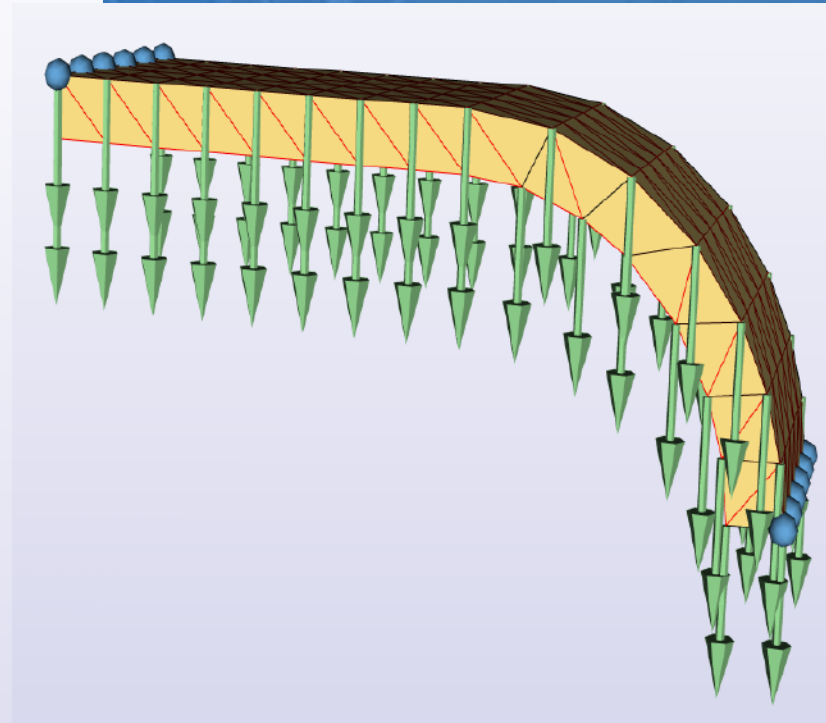
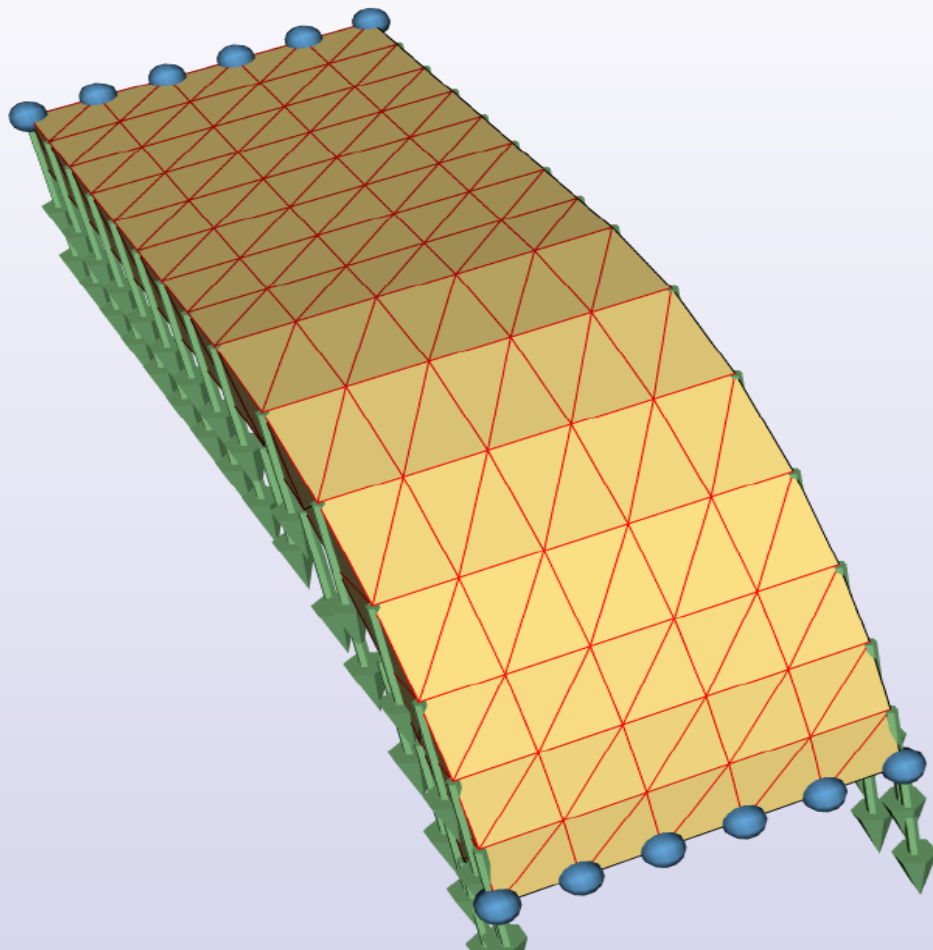
Presentation of the structure



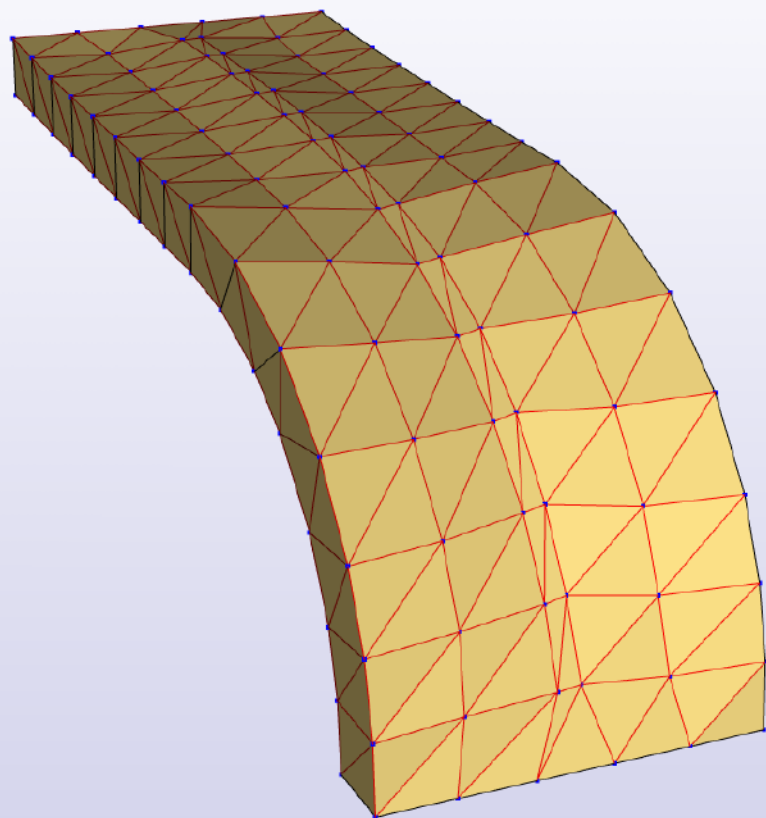


Comix / imp
(c) TMC - MAG

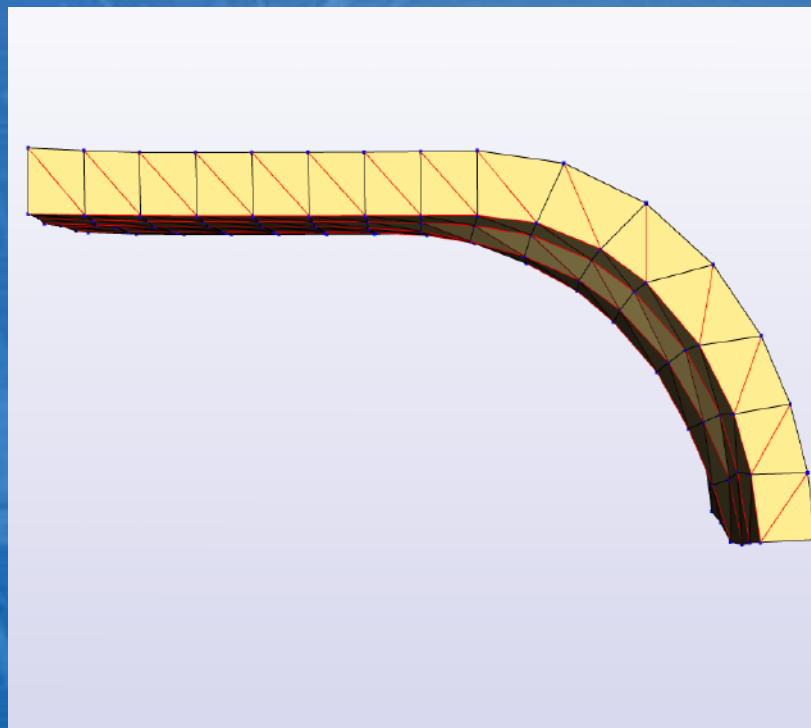
Screenshots from the simulation



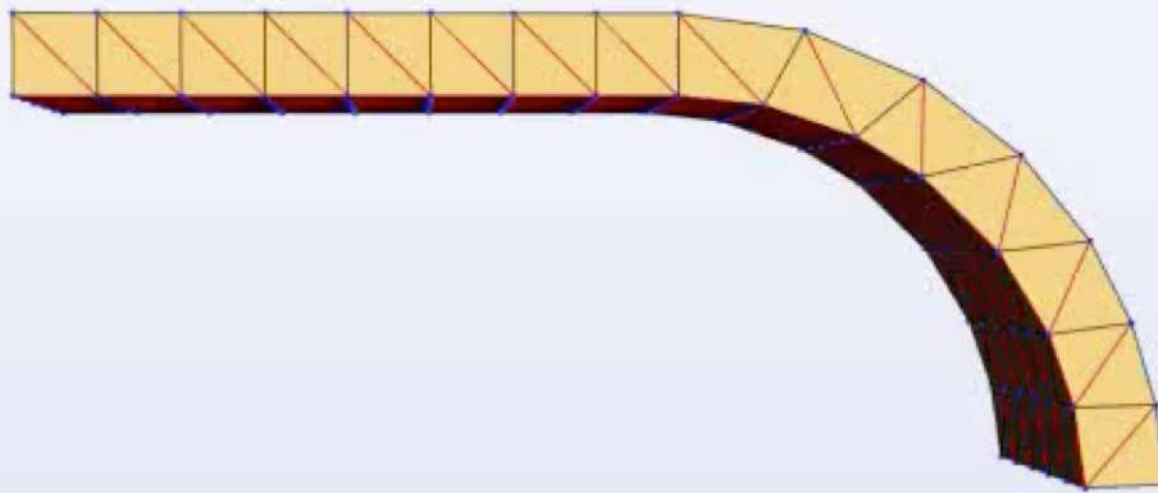
Screenshots from the simulation

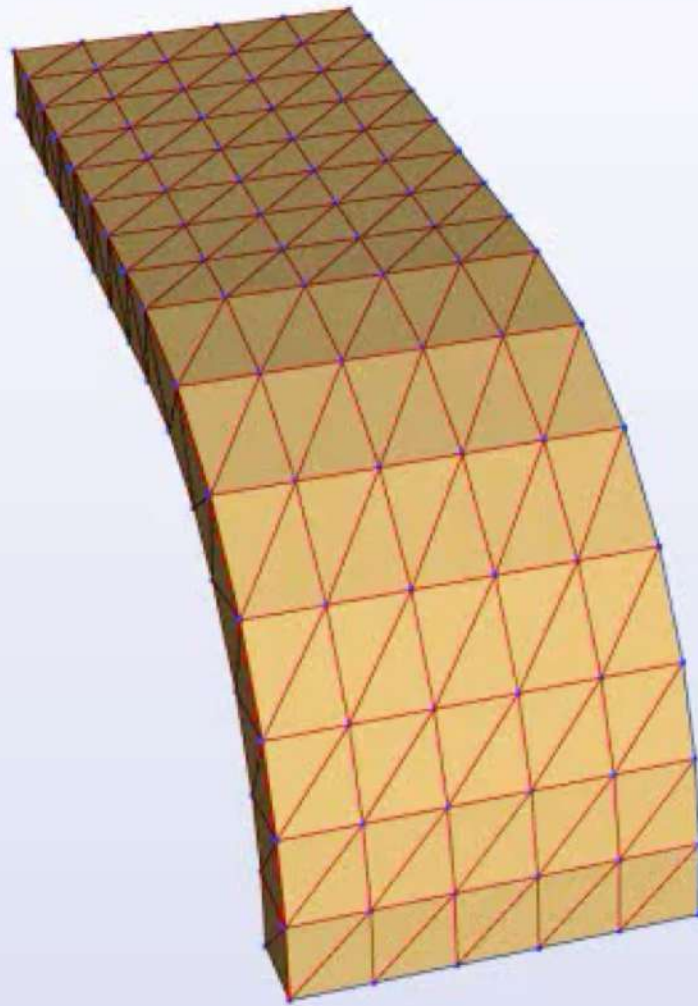


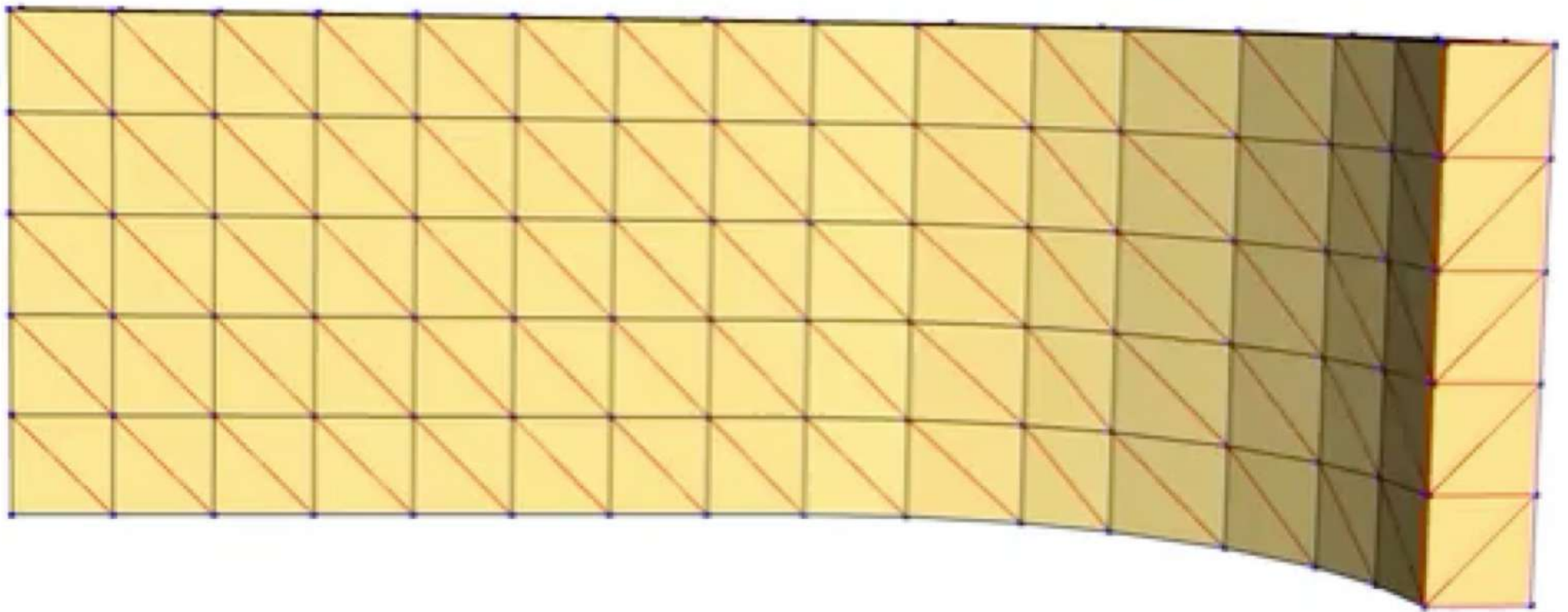
ComiTK / imp
(c) TIMC - IMAG

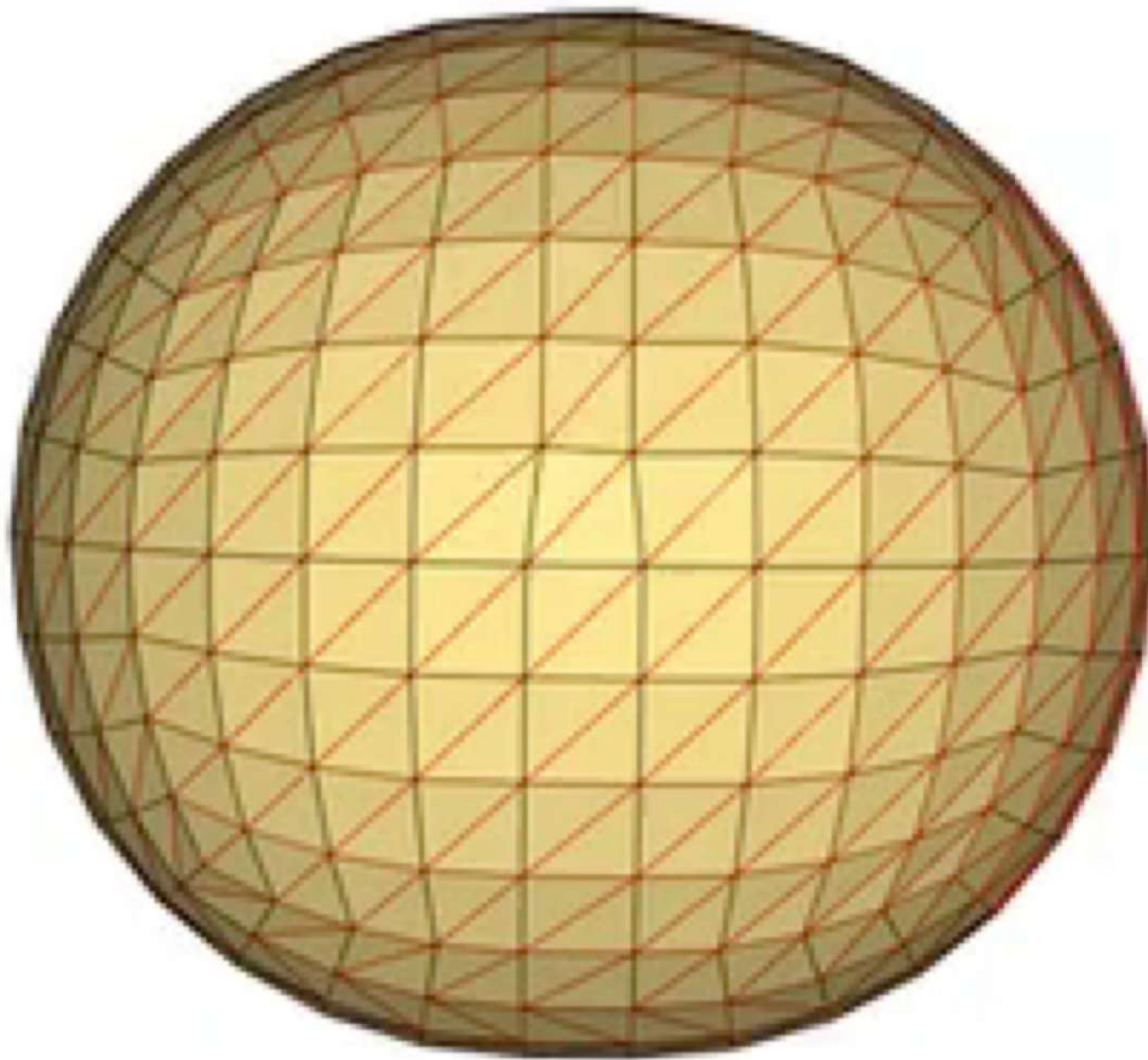


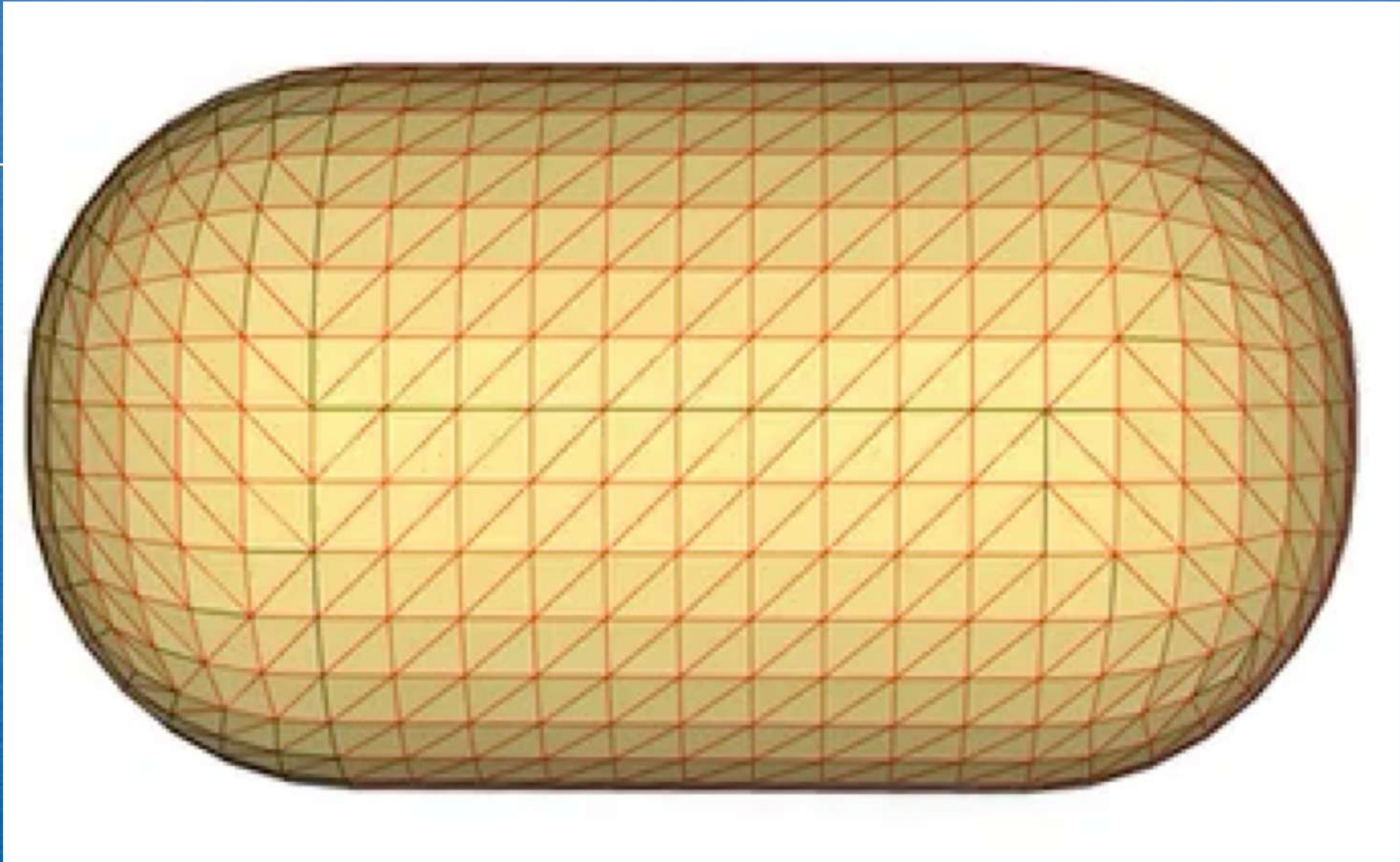
Simulation after 150 time-steps

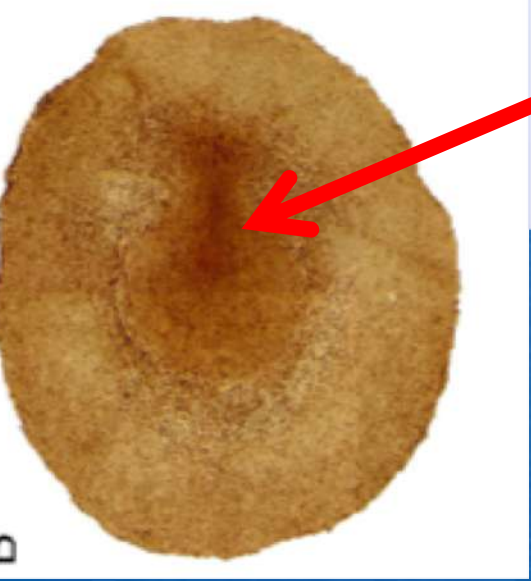
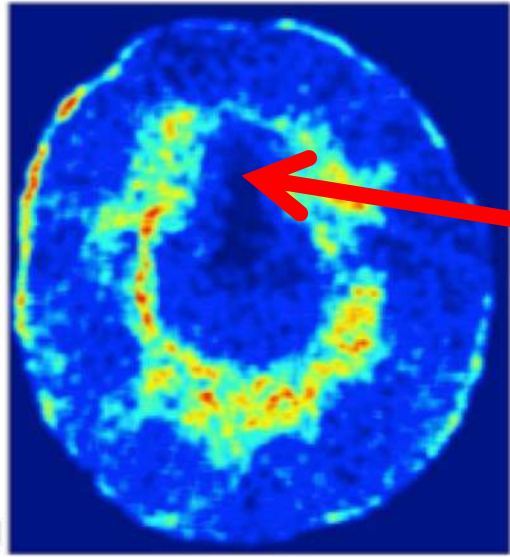
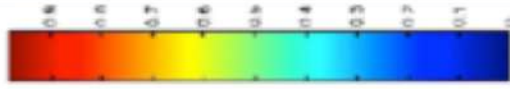
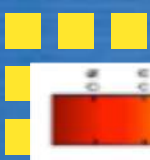




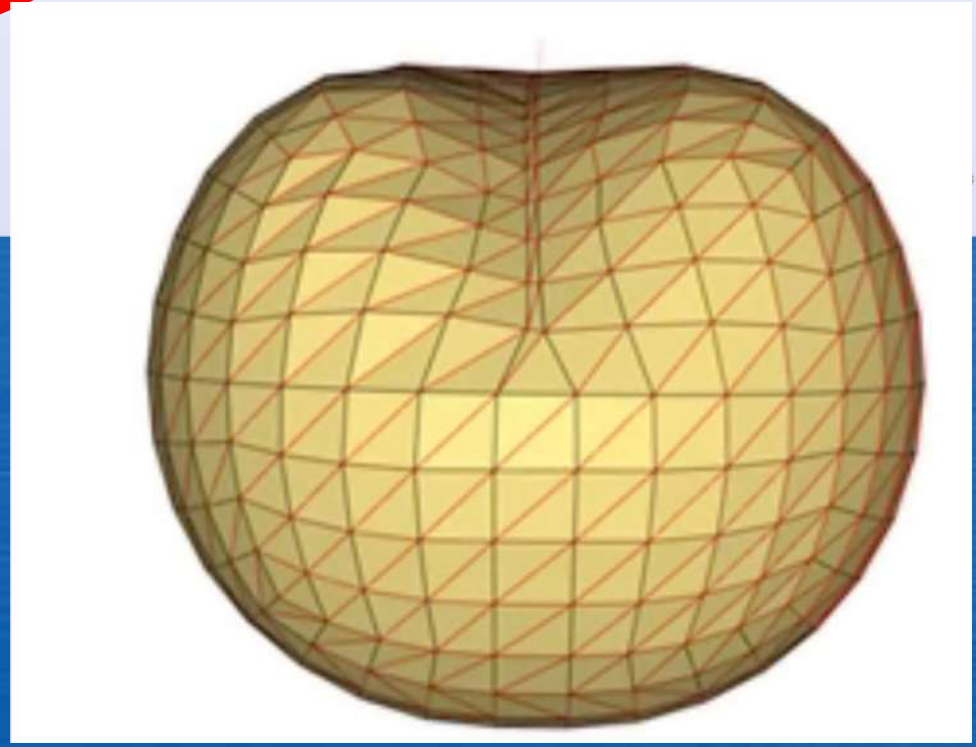
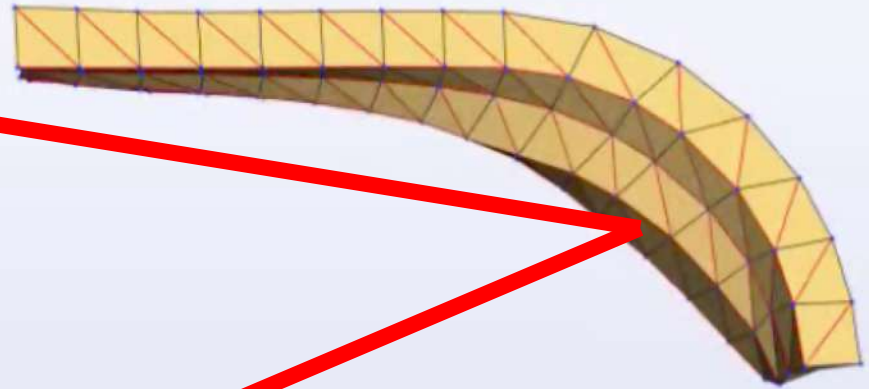






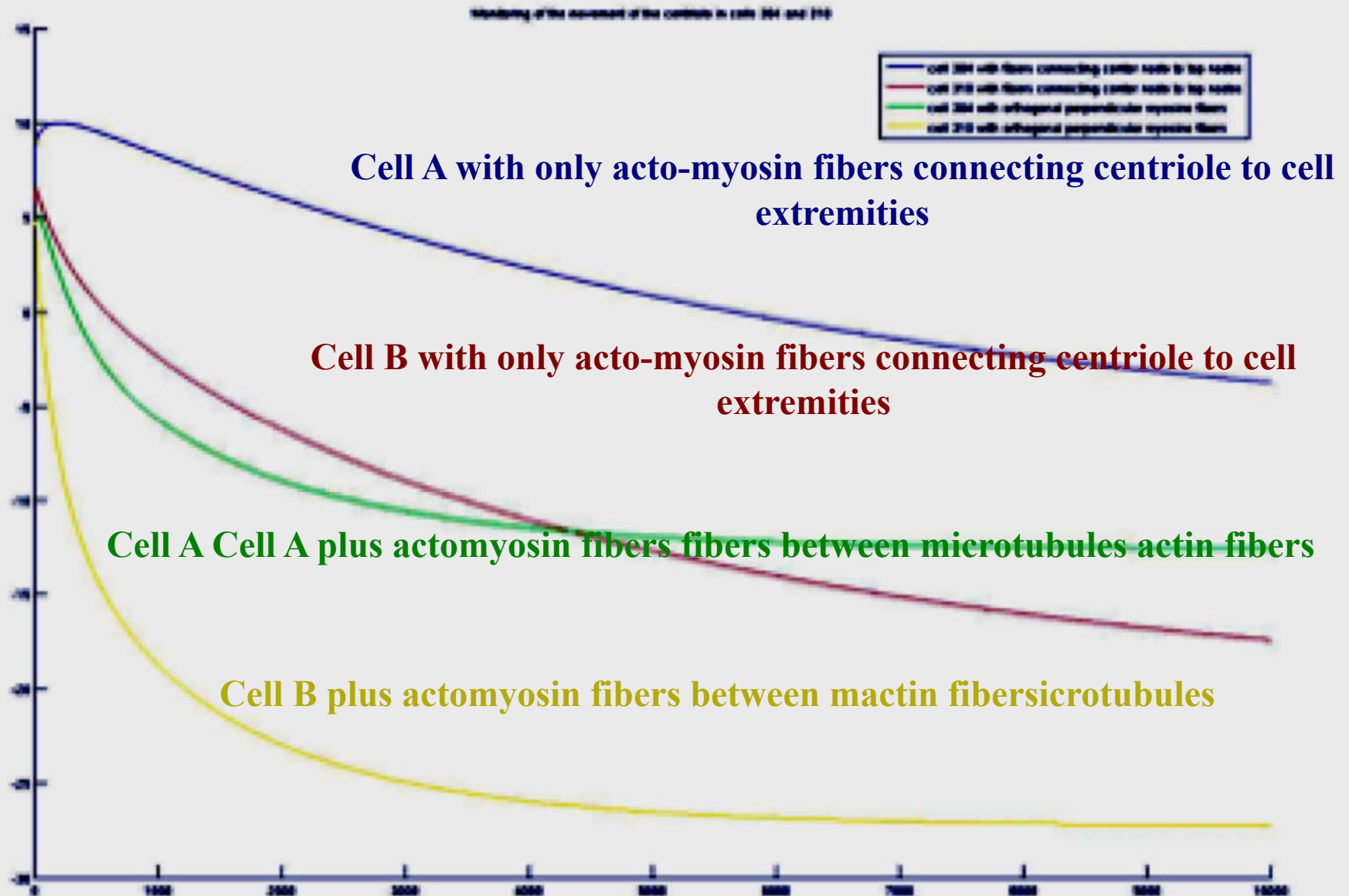


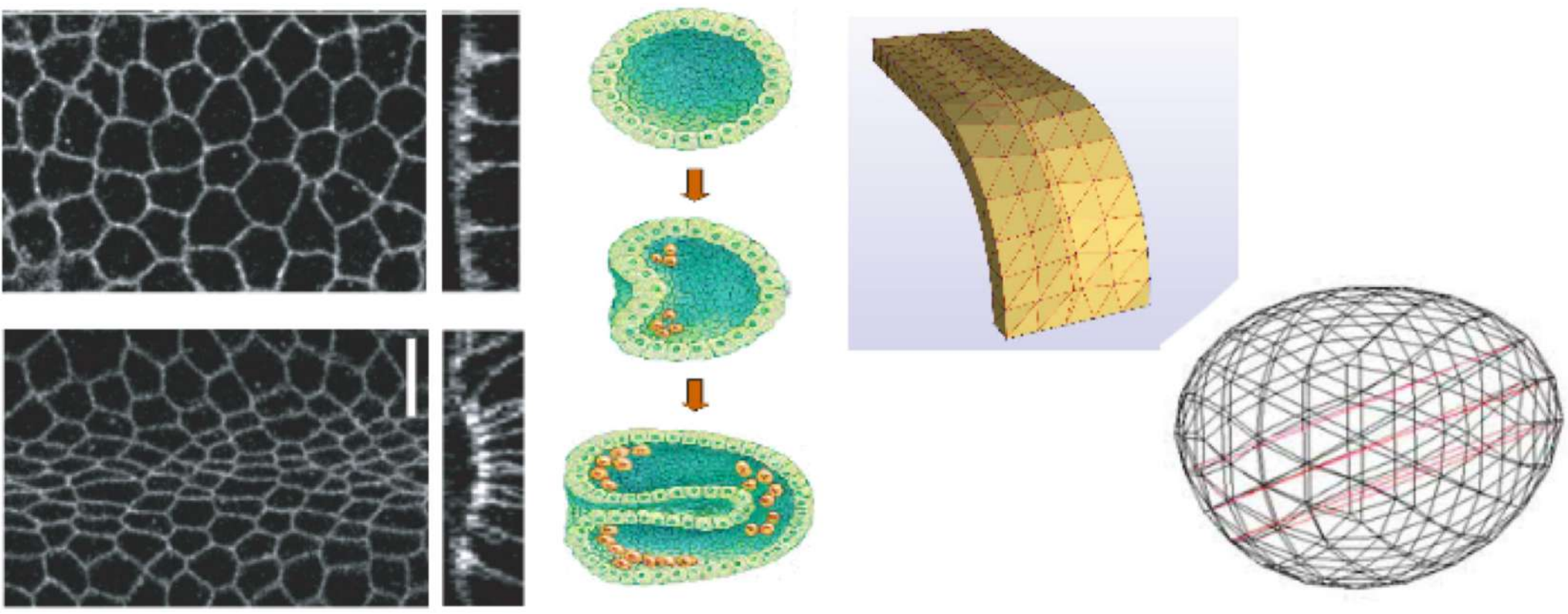
proliferation



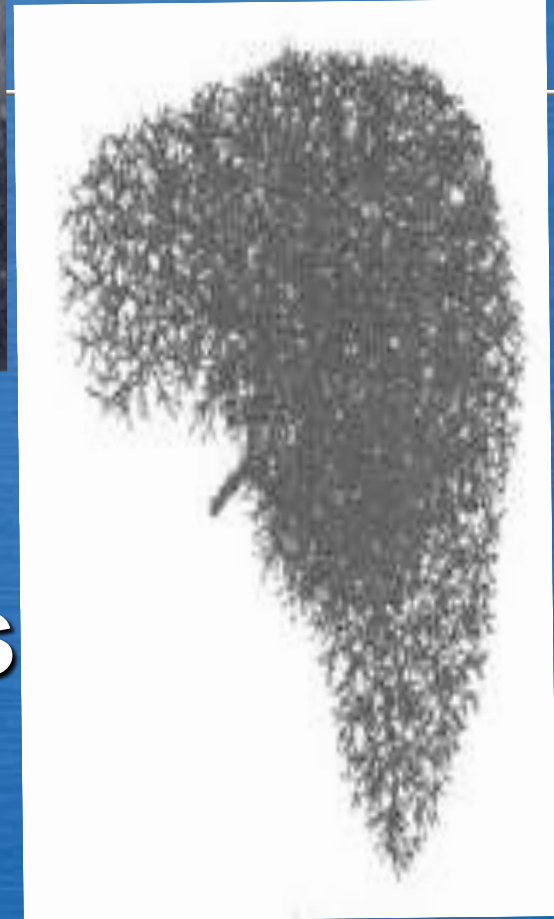
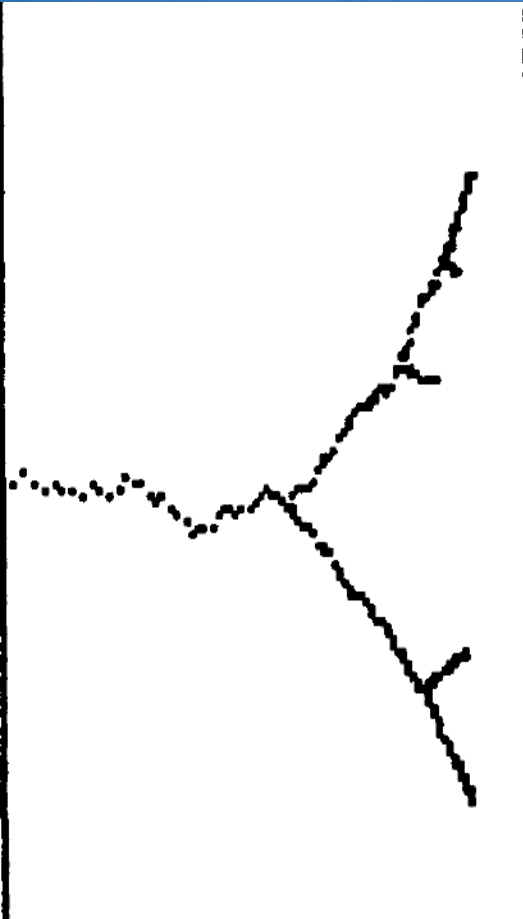
Surface/Volume ratio

Surface/Volume Ratio





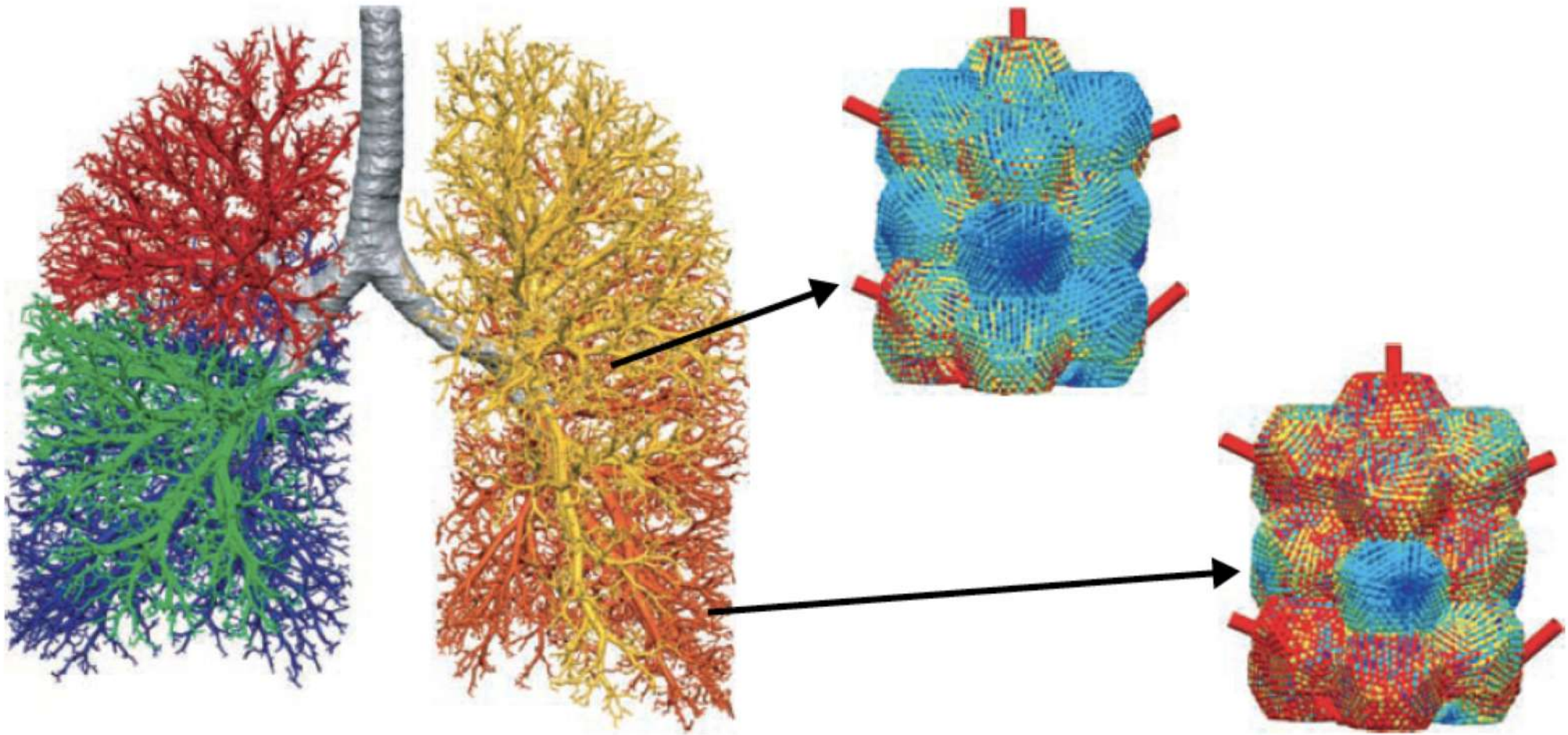
A. Lontos, E. Promayon, JD



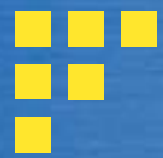
Draining territories

Y.L. Kergosien, *Acta Biotheoretica*,
38, 243-255 (1990)

JD, J. Bezy-Wendling, J. Mattes, P. Haigron,
N. Glade, J.L. Coatrieux, *Proc. of the
IEEE Society*, 91, 1723-1737 (2003)



Multiscale-modelling



Example 2

Hair & feathers morphogenesis



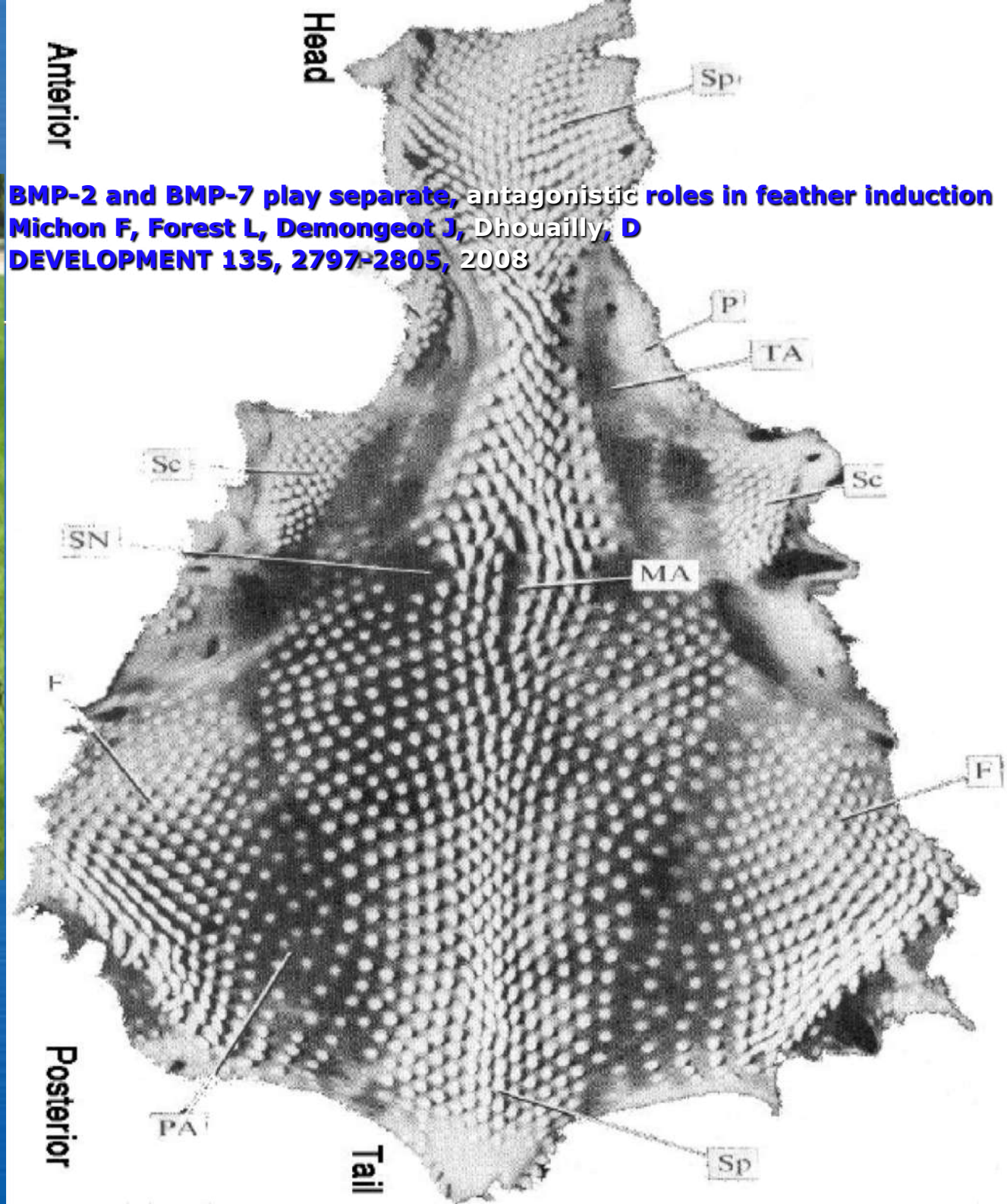
L. Forest

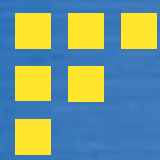
Rouen 22



Feather Primordia

10/07/2022





$v = \text{BMP-2}$

$u = \text{BMP-7}$

BMP-7

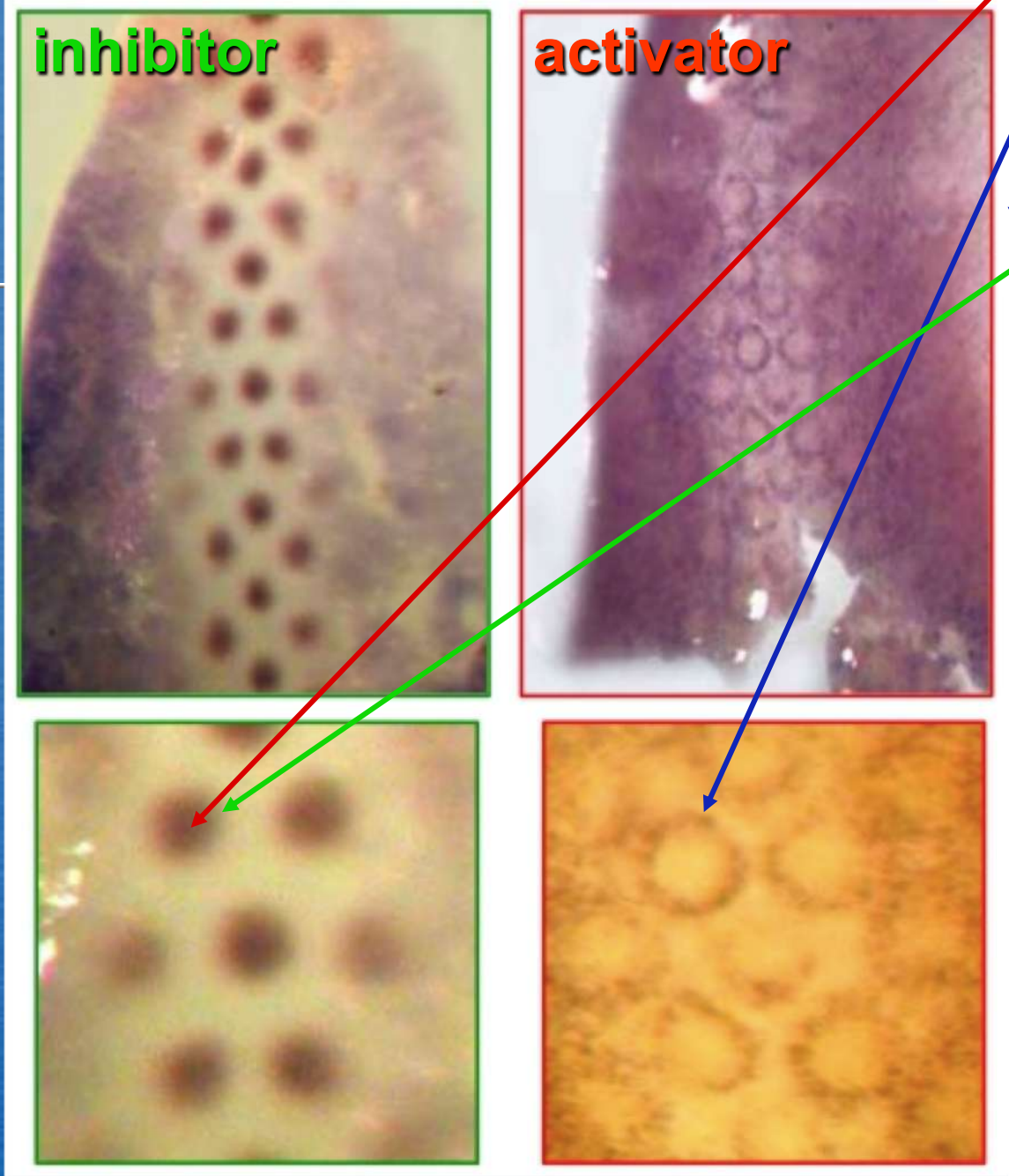
inhibitor

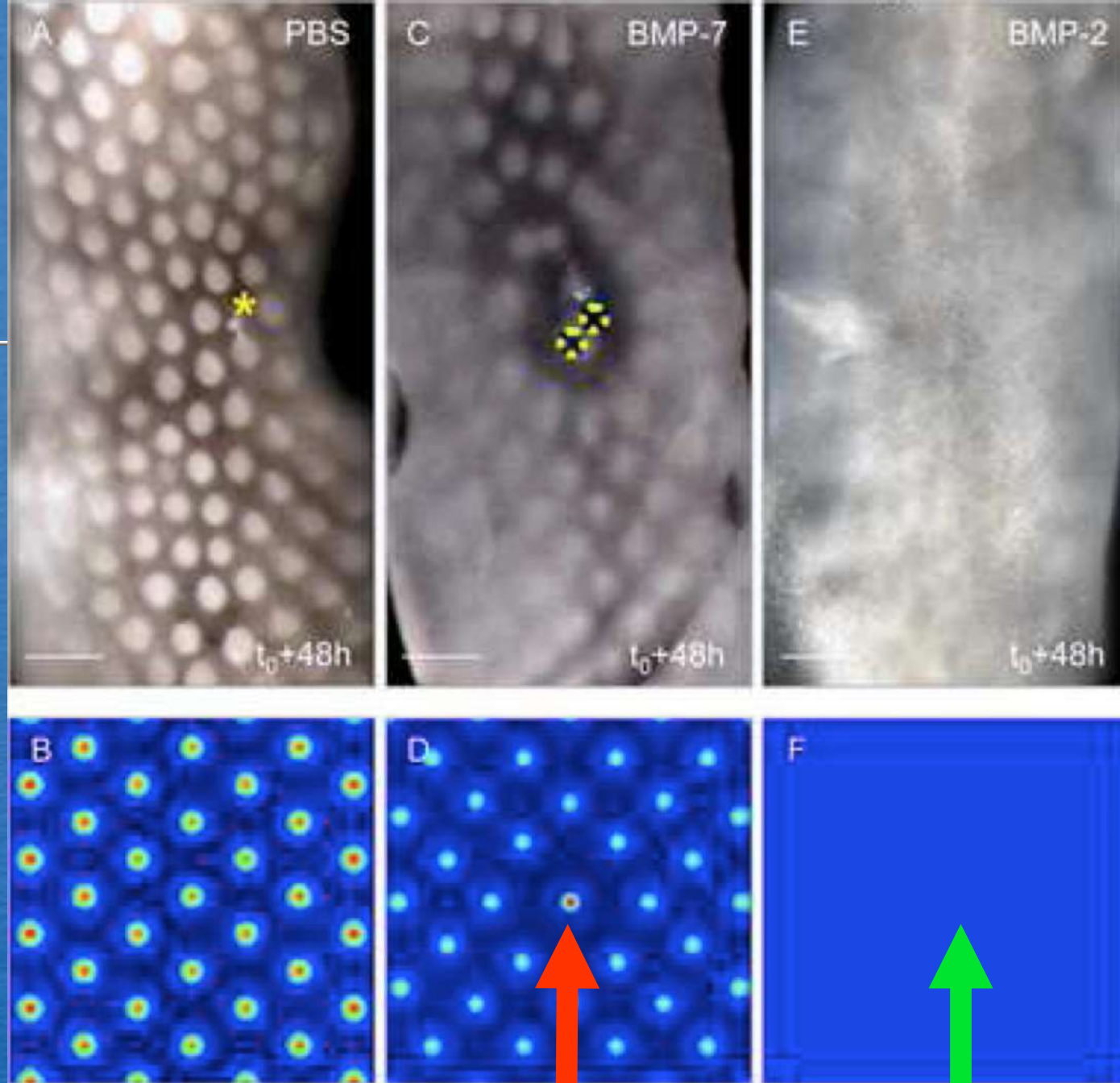
activator

Follistatine

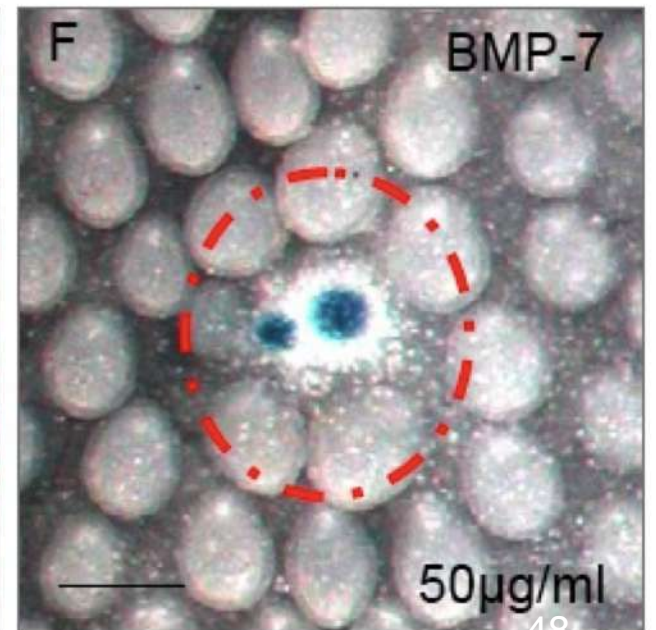
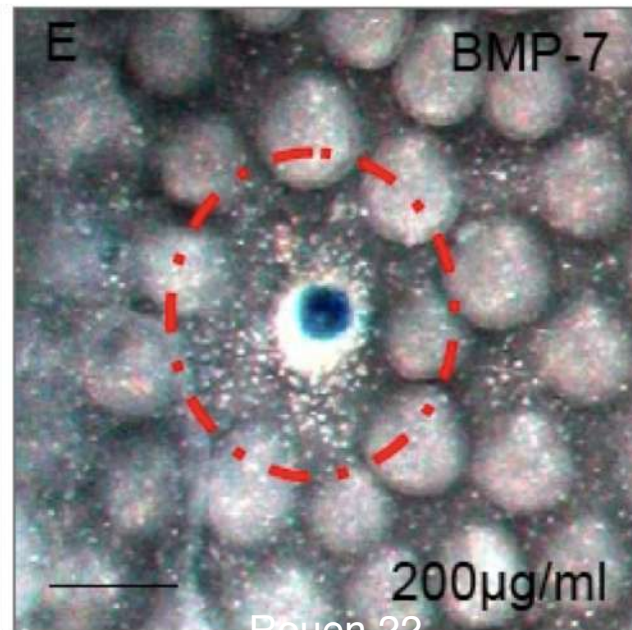
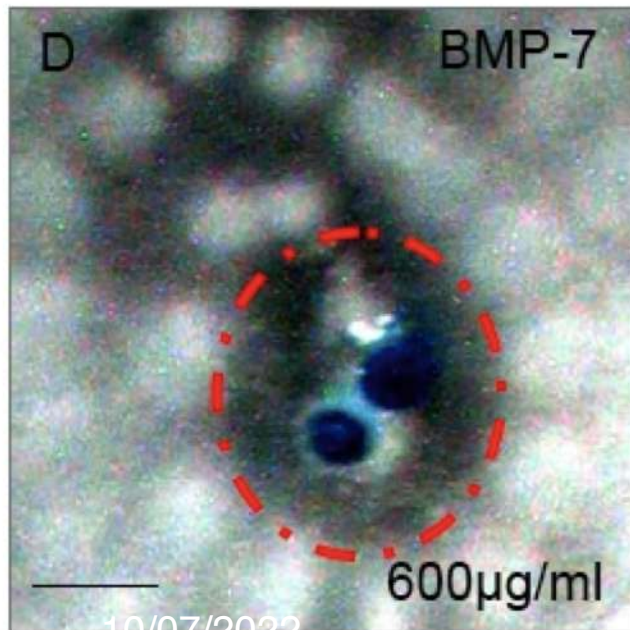
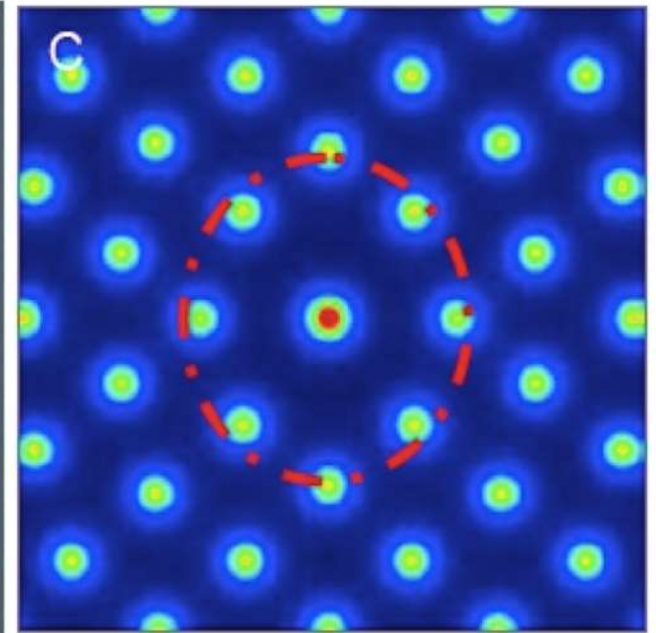
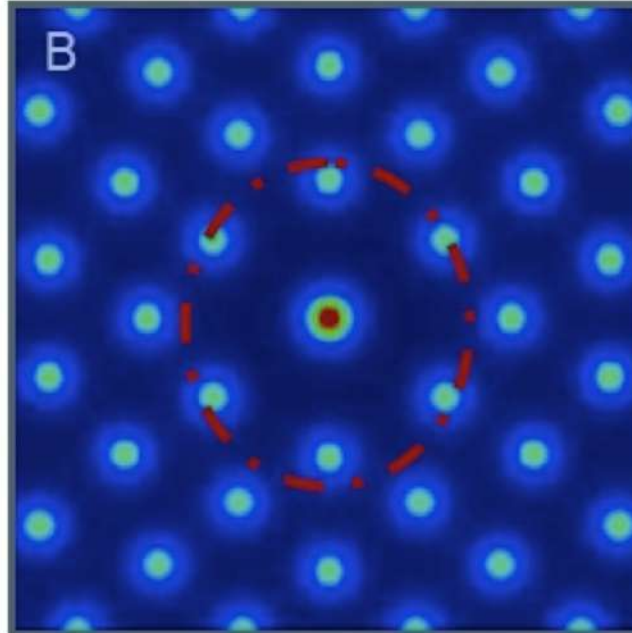
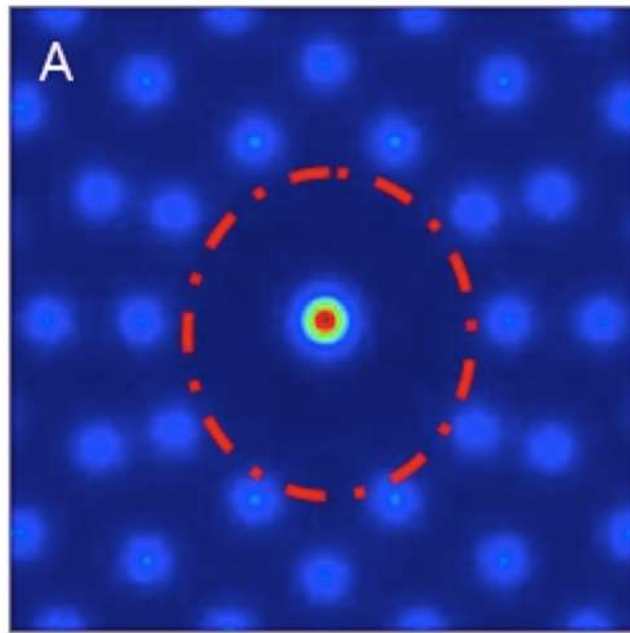
BMP-2

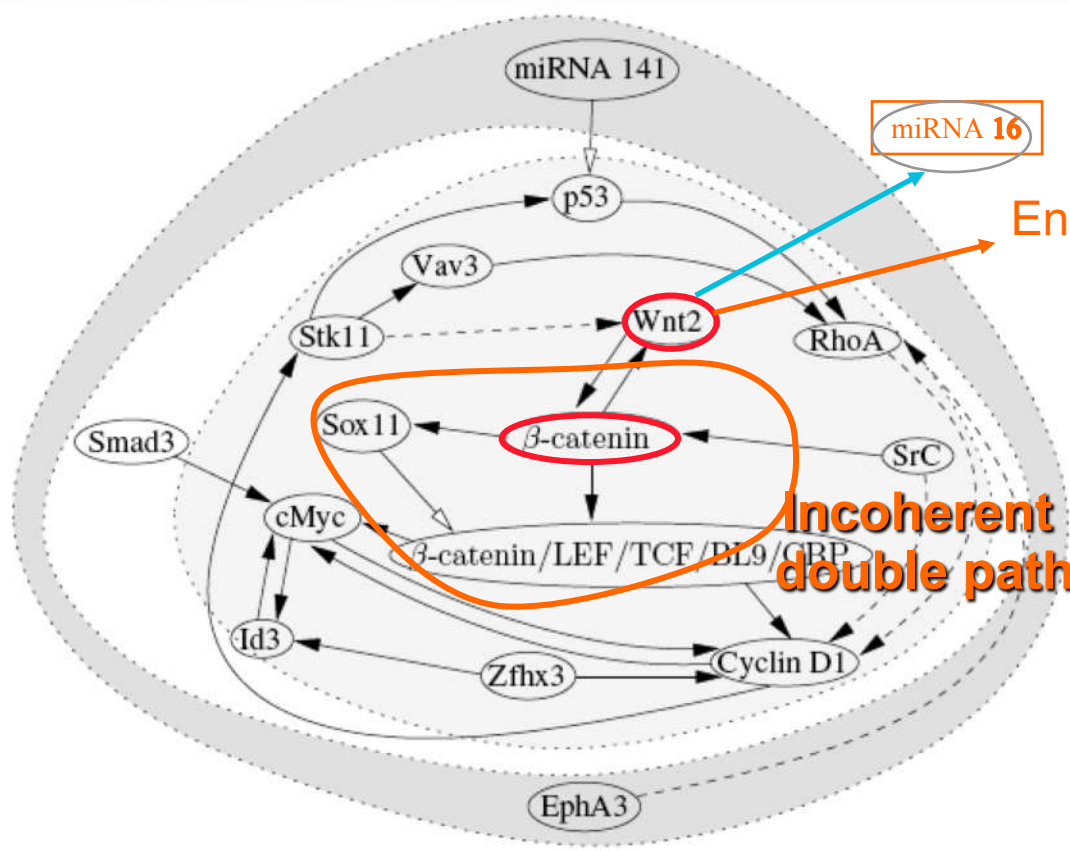
Lateral inhibition



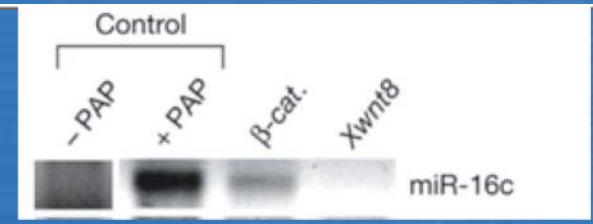


activator & **inhibitor**






Hair/Feather morphogenesis



S. Cadau

Nature	Sequential updating		Parallel updating		
	Attractor	ABRS	Attractor	ABRS	AD
Fixed point 1	000000000000000000	1.56%	000000000000000000	≈ 0.00%	0.75
Fixed point 2	0011111001101110	96.88%	0011111001101110	99.66%	4.14
Fixed point 3	0000010000001100	1.56%	0000010000001100	≈ 0.00%	0.5
Limit cycle 1	None	—	0011010001101100 0000111000001110	0.34%	2.45

miRNA 141, EphA3, p53, Vav3, Stk11, Wnt2, RhoA, Smad3, SrC, Id3, Cyclin D1, Zfhx3, Sox11, βcatenin, cMyc, βcatenin/LEF/TCF/BL9/CBP



$$\frac{\partial n_1}{\partial t} = \begin{cases} k_p n_1 (N - n_1) & \text{if } n_1 \leq QN \\ -k_d n_1 & \text{else} \end{cases}$$

Proliferating cells density

$$\frac{\partial n_2}{\partial t} = D_n \Delta n_2 - \nabla \cdot (\chi n_2 \nabla u) + f(n_1, t)$$

Migrant cells density

$$\frac{\partial u}{\partial t} = D_u \Delta u + \frac{c_1 n_2 (1 + c_2 u^2)}{(c_3 + u^2)(1 + v)} - k_u u$$

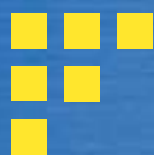
Chemo-attractant BMP-7 concentration

$$\frac{\partial v}{\partial t} = D_v \Delta v + c_4 n_2 u^2 - k_v v$$

$D_u < D_v$

Competitive inhibitor BMP-2 concentration

Zero Neumann boundary conditions



$$\frac{\partial u}{\partial t} = D_u \Delta u + f(u, v) - k_u u$$

$$\frac{\partial v}{\partial t} = D_v \Delta v + g(u, v) - k_v v$$

$$f(u, v) = \frac{c_1 n u^2}{(1 + v)}$$

$$g(u, v) = c_4 n u^2$$



- If $c_2, c_3 \gg 1$ and $v \ll 1$:

Amplitude controlling parameters

$$P = (k_u u^2 + k_v v^2) / 2$$

$$H = c_1 c_2 n_2 u^2 \text{Log}(1+v) - c_4 n_2 u^3 / 3$$

Frequency controlling parameters



Turing conditions

$$1) f_{0u} + g_{0v} < 0 \Rightarrow \frac{2c_1 k_v u_s}{k_v + c_2 u_s^2} - k_u - k_v < 0$$

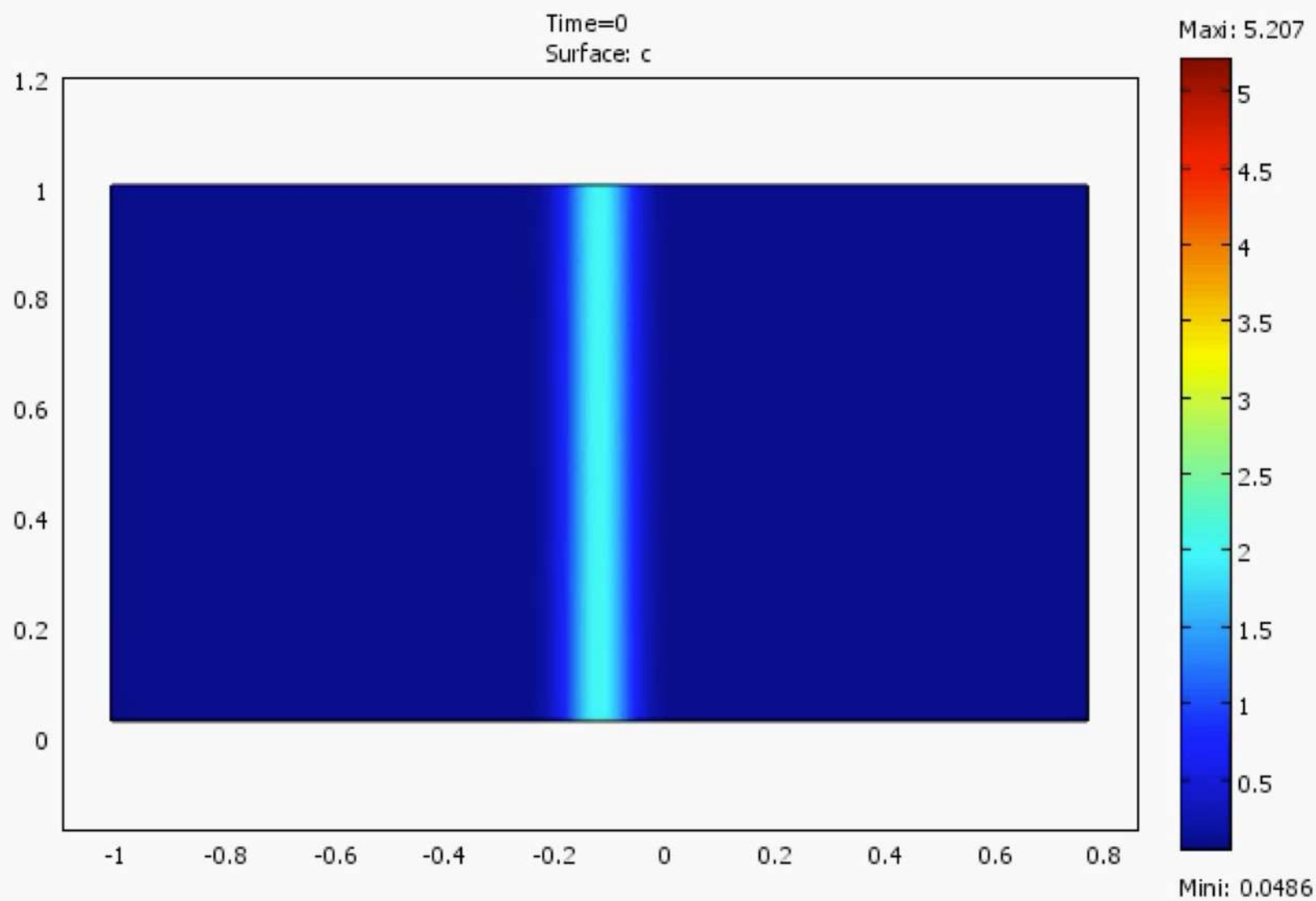
$$2) f_{0u}g_{0v} - f_{0v}g_{0u} > 0 \Rightarrow \frac{-2c_1 k_v^2 u_s}{k_v + c_2 u_s^2} + k_u k_v + \frac{2c_1 c_2 k_v^2 u_s^3}{(k_v + c_2 u_s^2)^2}$$

$$\Rightarrow k_u k_v - \frac{2c_1 k_v^3 u_s}{(k_v + c_2 u_s^2)^2} > 0$$

$$3) D_1 g_{0v} + D_2 f_{0u} > 0 \Rightarrow -D_u k_v - D_v k_u + \frac{2D_v c_1 k_v u_s}{k_v + c_2 u_s^2} < 0$$

$$4) (D_1 g_{0v} + D_2 f_{0u})^2 > 4D_u D_v (f_{0u} g_{0v} - f_{0v} g_{0u})$$

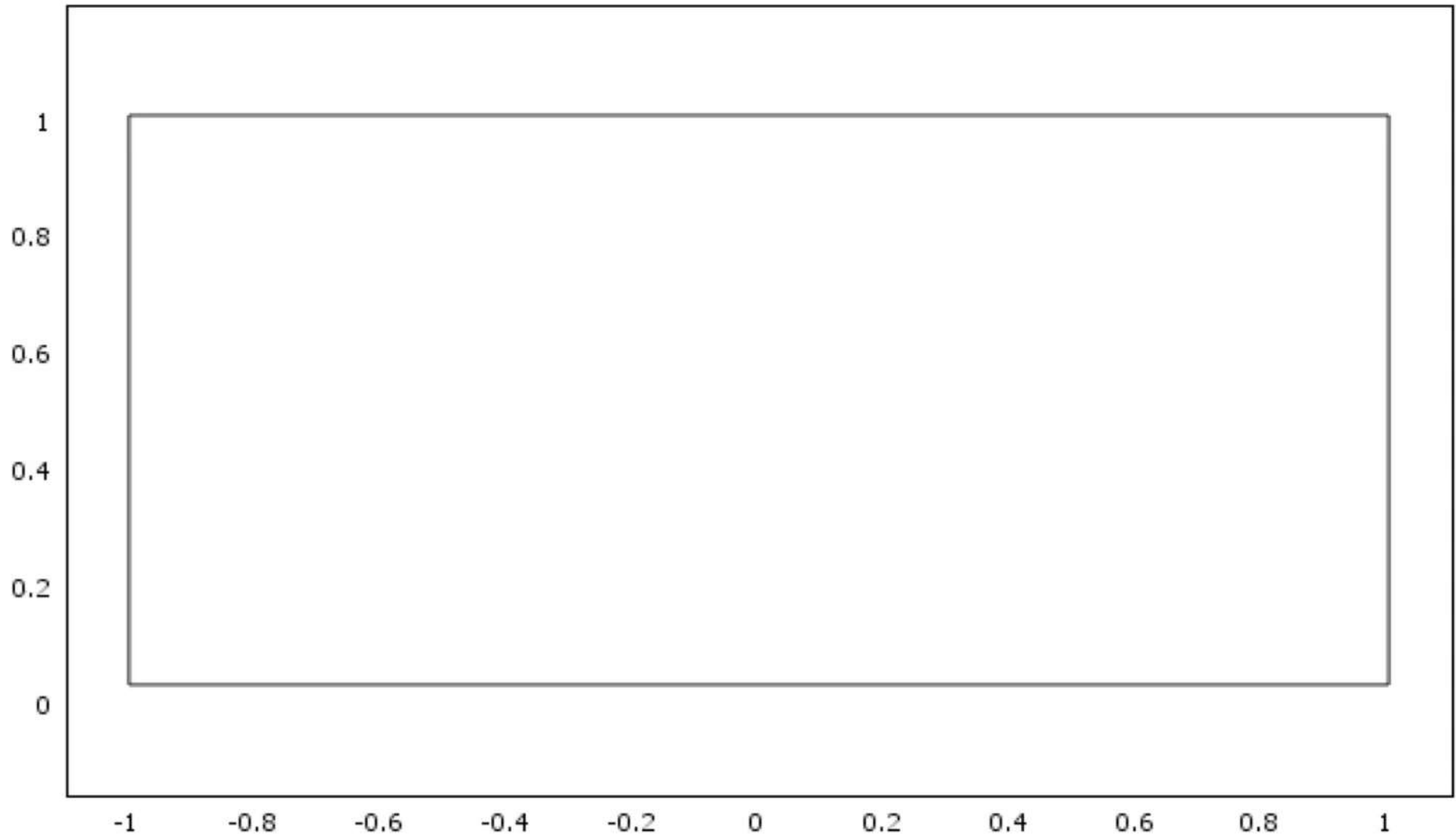
$$\Rightarrow \frac{2D_v c_1 k_v u_s}{k_v + c_2 u_s^2} - (D_u k_v + D_v k_u) > 4D_u D_v k_u k_v - \frac{8D_u D_v c_1 k_v^3 u_s}{(k_v + c_2 u_s^2)^2}$$



$$(\partial^2 u / \partial x^2) (\partial^2 u / \partial y^2) - (\partial^2 u / \partial x \partial y)^2 = 0$$

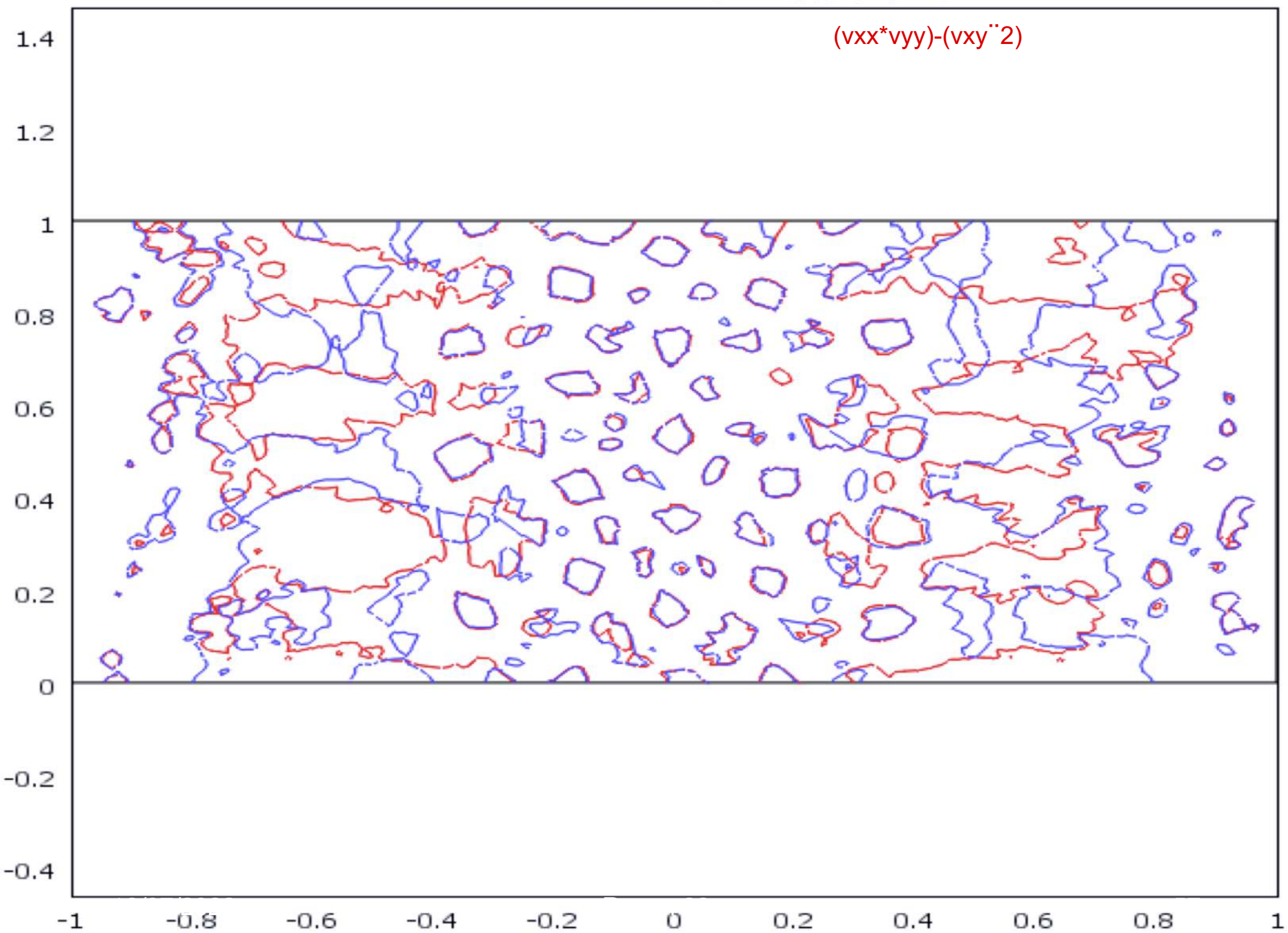
Time=0

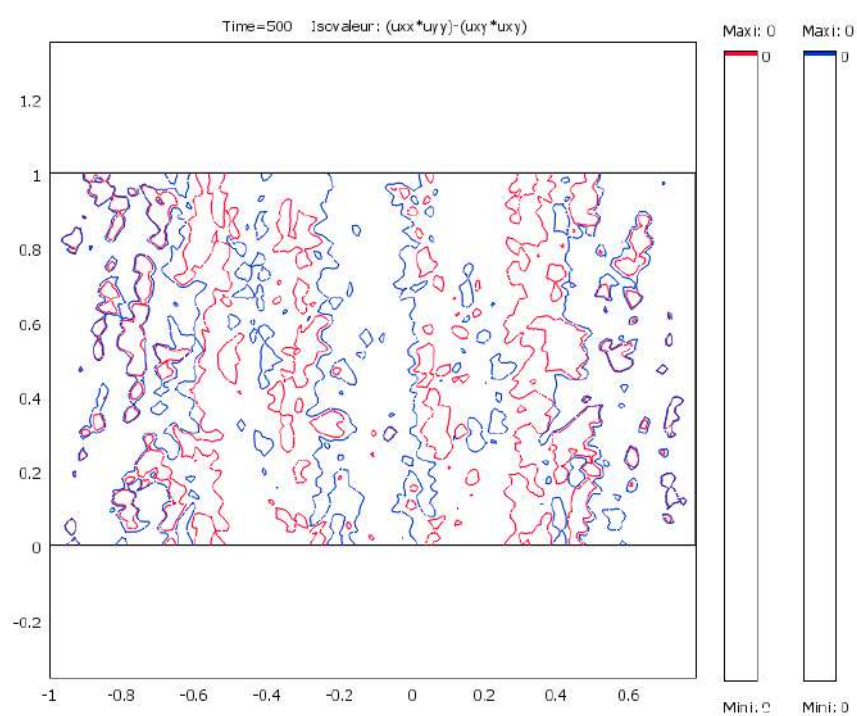
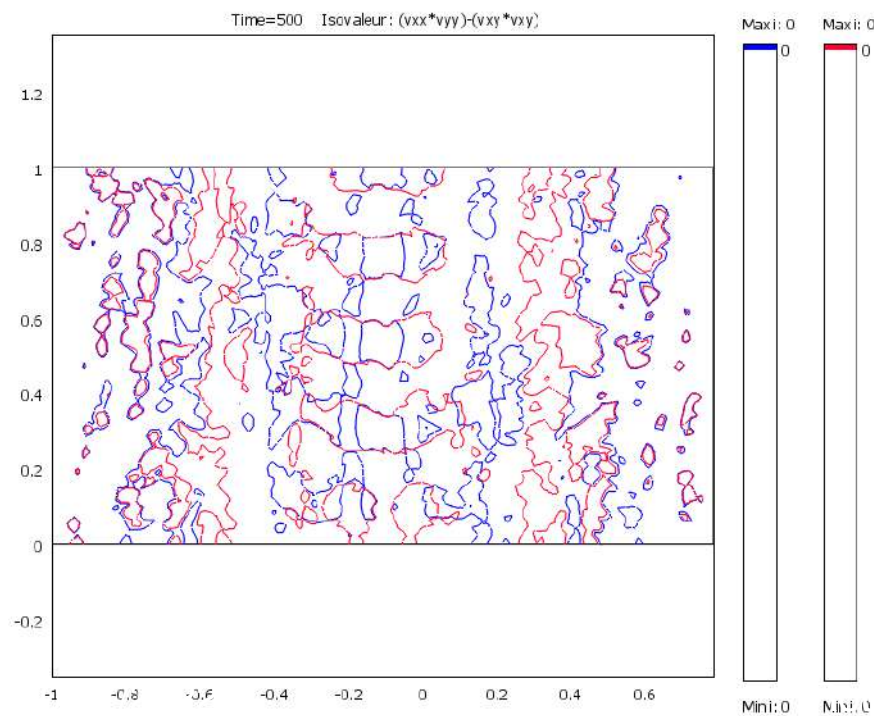
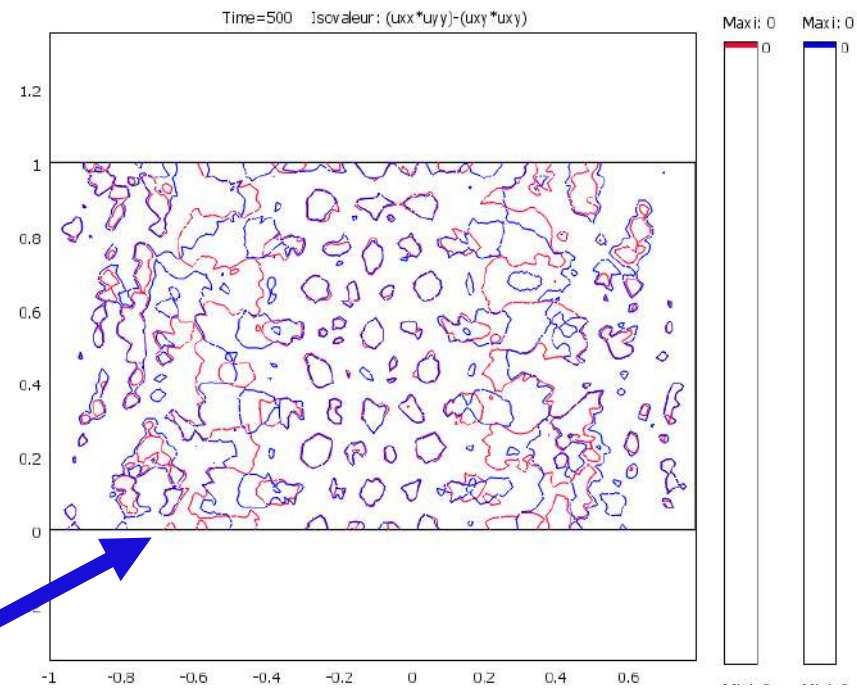
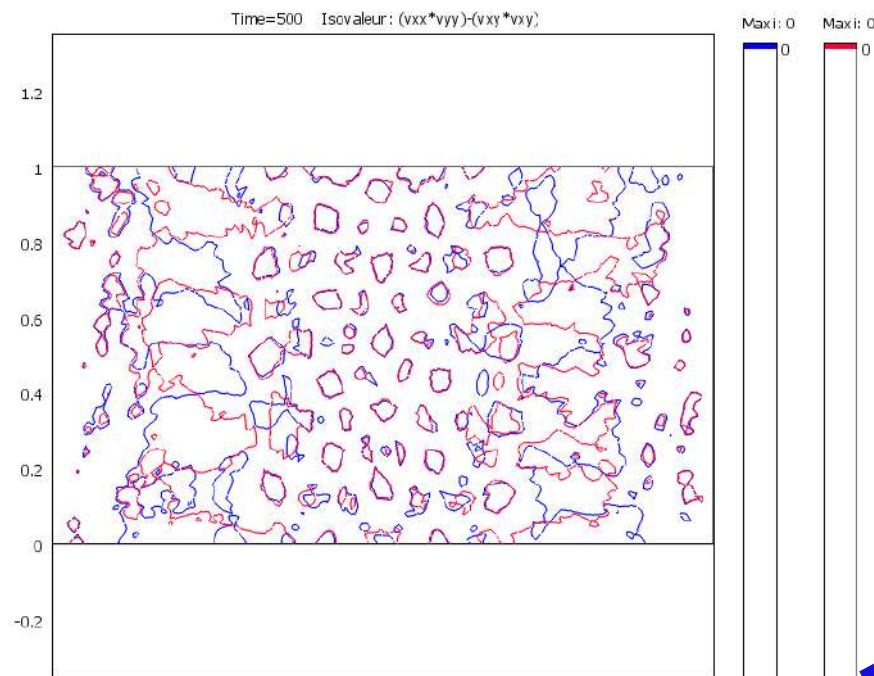
Isovaleur: (uxx*uyy)-(uxy*uxy)



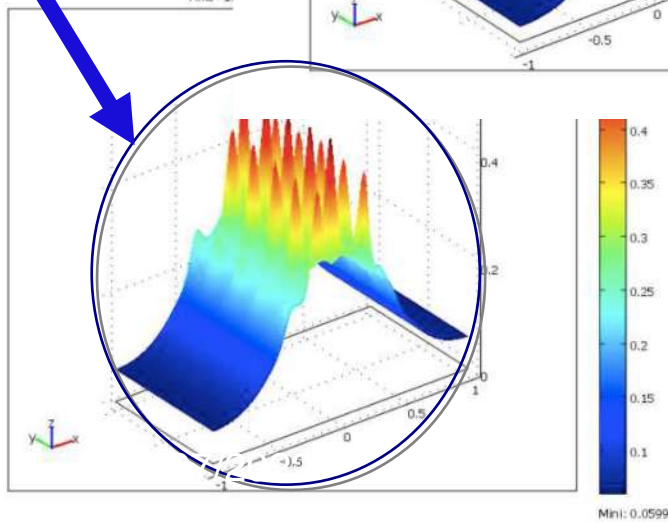
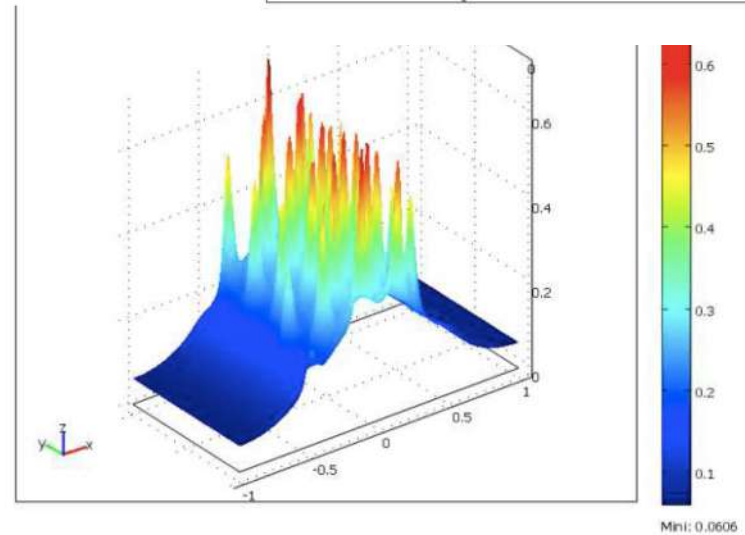
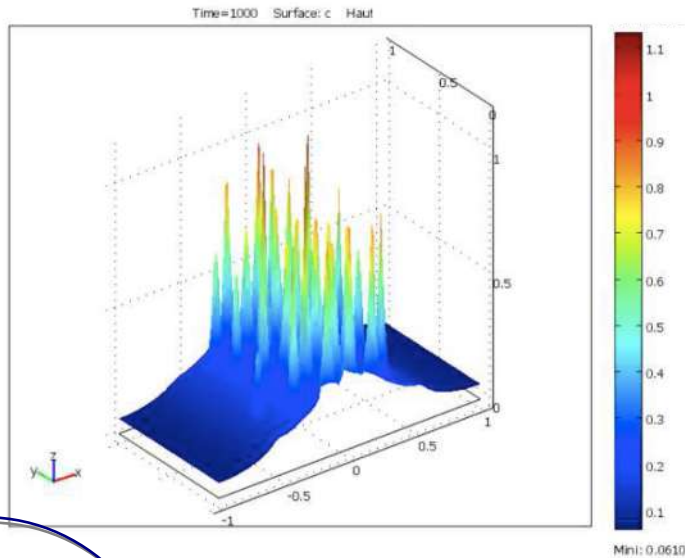
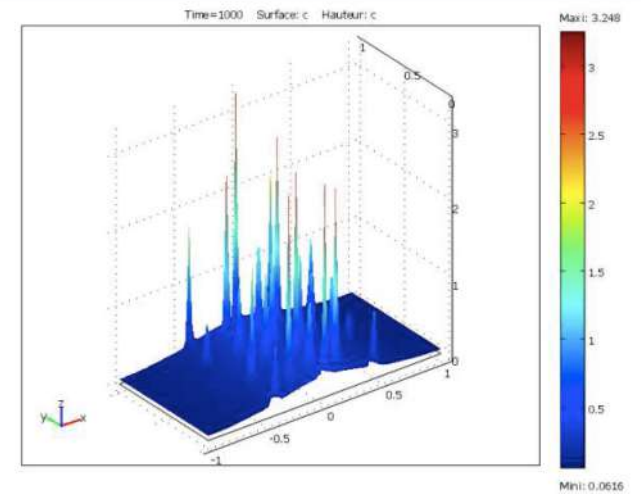
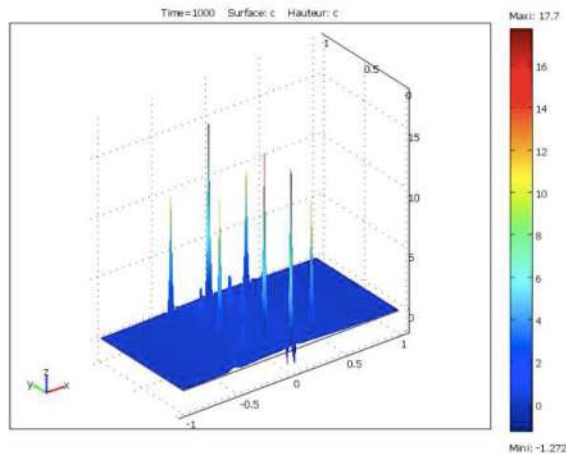
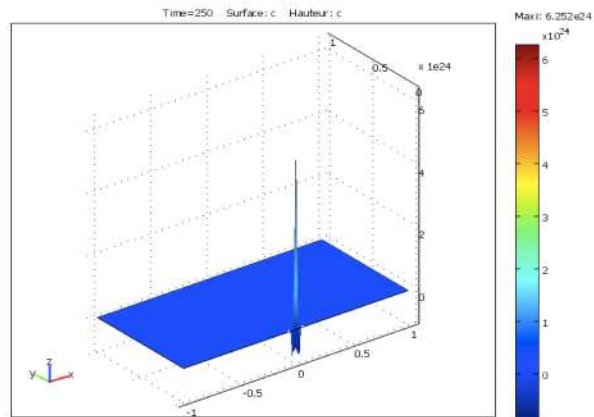
Time=500 Isovaieur: $(u_{xx} * u_{yy}) - (u_{xy}^2)$

$(v_{xx} * v_{yy}) - (v_{xy}^2)$



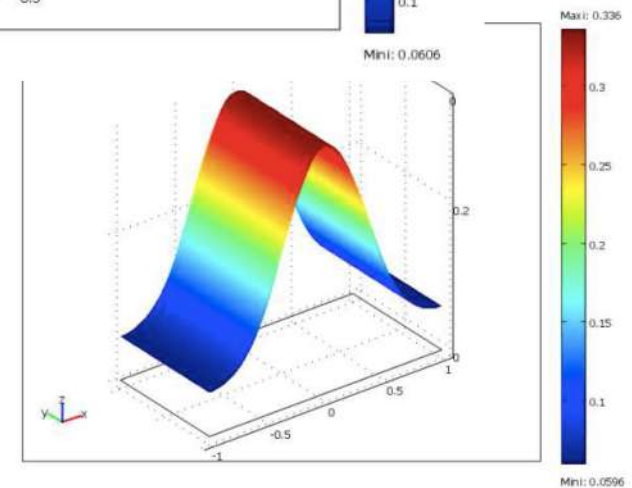


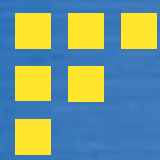
VISCOSITY RATIO



D_u/D_v from
0.01 to 0.07

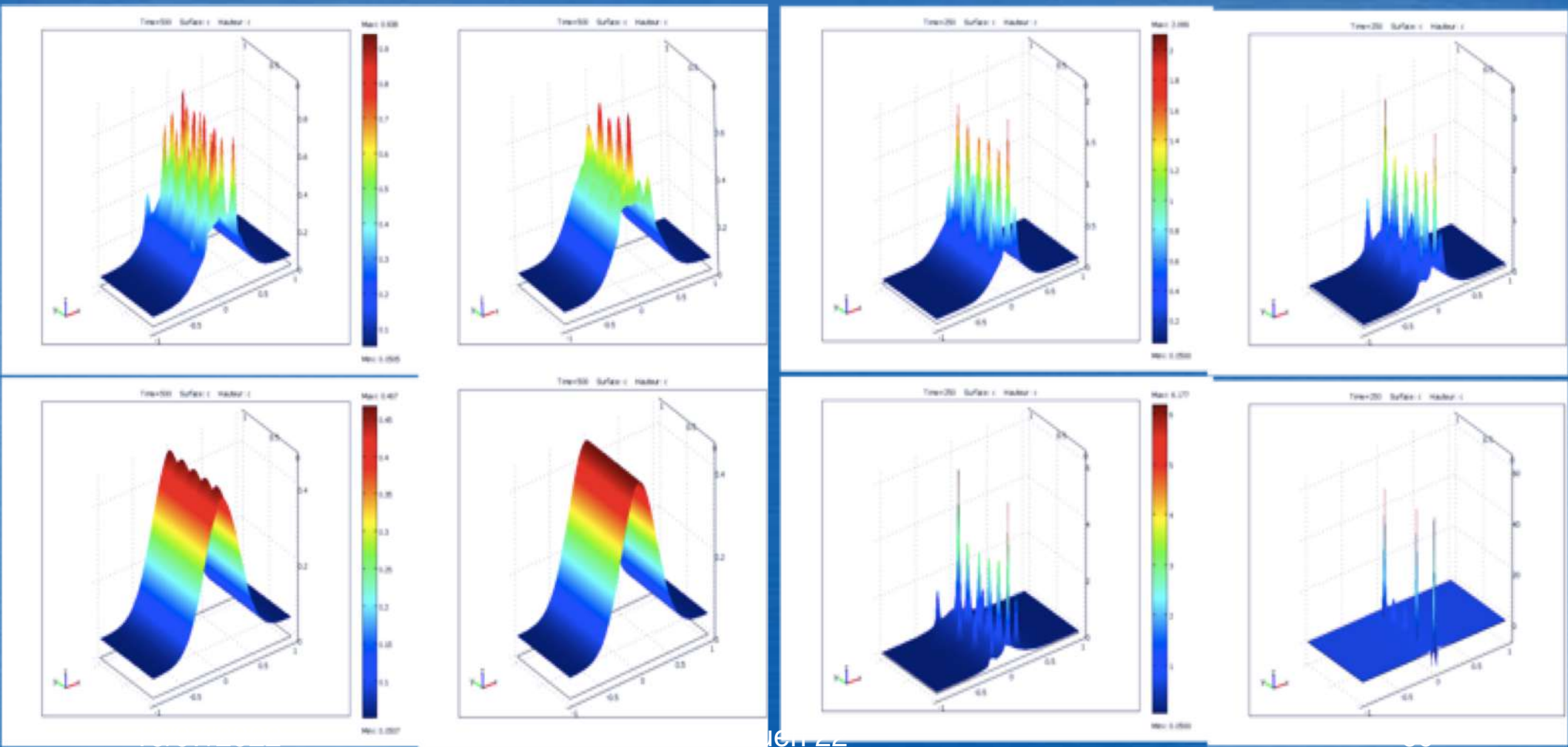
Rouen 22





On the left: diminishing k_v (from 35 to 0 with step of 5) causes the decrease of the feather number and amplitude.

On the right: diminishing c_2 (from 4500 to 1200 with step 1100) causes feather motifs disparition and diffusion wins over reaction



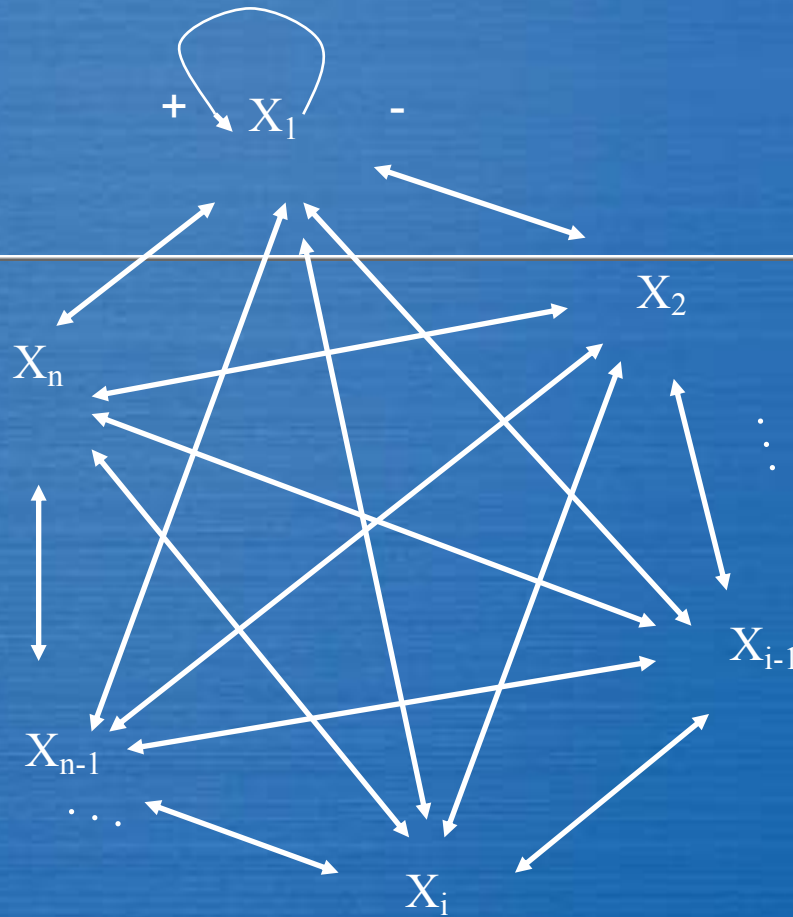
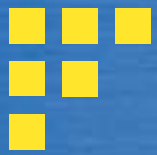


Example 3

N-switches

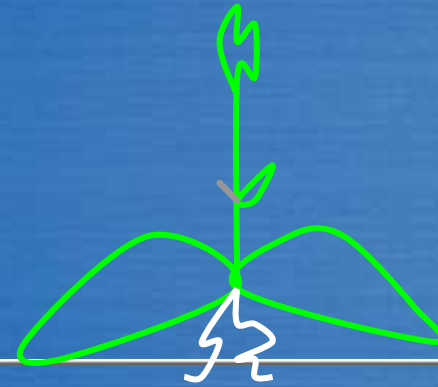


O. Cinquin

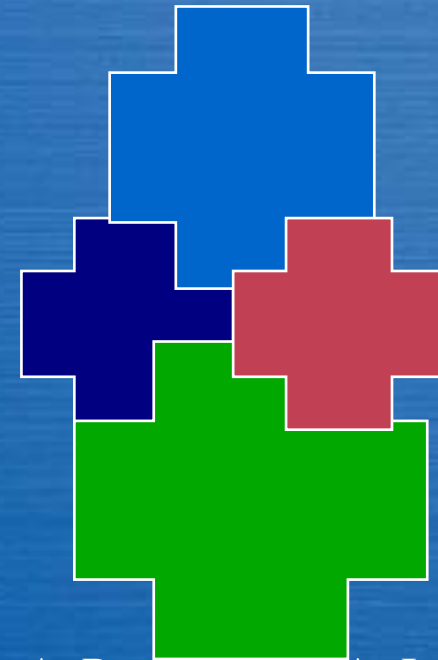


N-switch

any edge is negative, except
autocatalysis



M. Thellier, JD, J. Guespin,
C. Ripoll, V. Norris & R. Thomas.
Plant Biol., 10, 1055 (2004)



A. Prochiantz & A. Joliot
Nature Perspectives, 4, 814 (2003)

$$\frac{dx_1}{dt} = -x_1 + \frac{\sigma x_1^c}{1 + \sum_{i=1}^n x_i^c} + \alpha_1$$

...

$$\frac{dx_n}{dt} = -x_n + \frac{\sigma x_n^c}{1 + \sum_{i=1}^n x_i^c} + \alpha_n$$

$$y_i = (x_i)^{1/2}$$

$$P(y) = \sum_i y_i^2 / 4 - \text{Log}((1 + \sum_i y_i^{2c})^{\sigma/4c}) + \sum_i \alpha_i \text{Log}(y_i) / 2$$

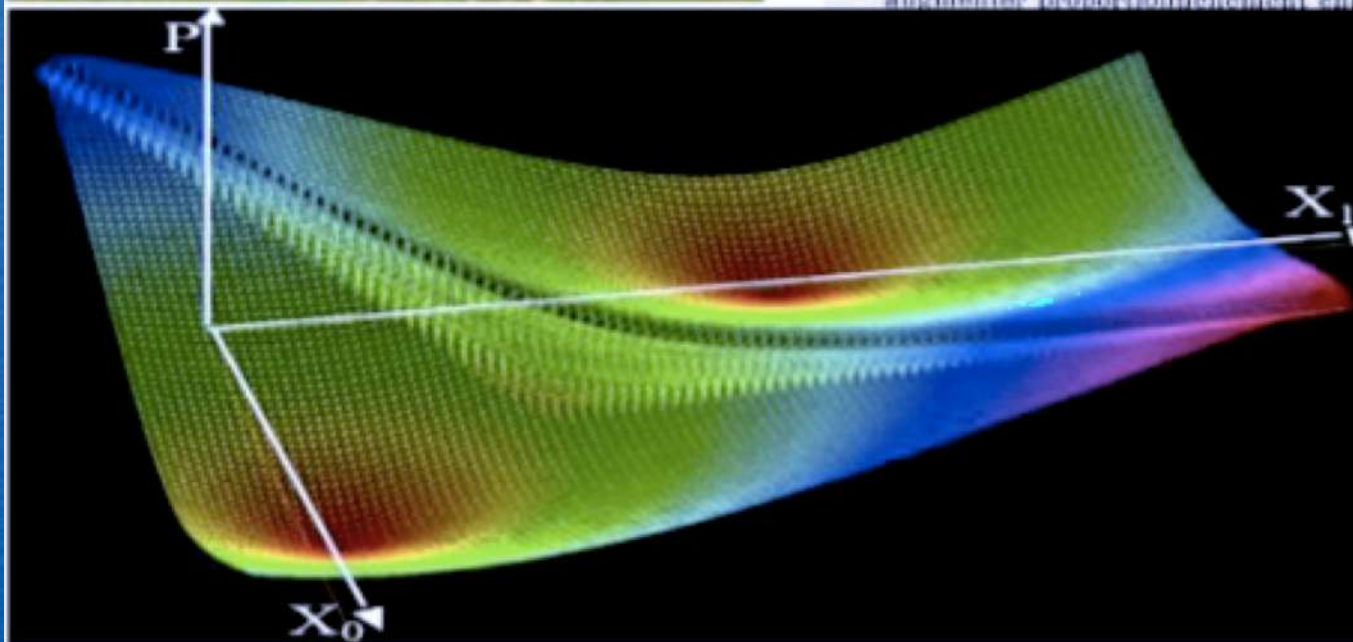
Potential system

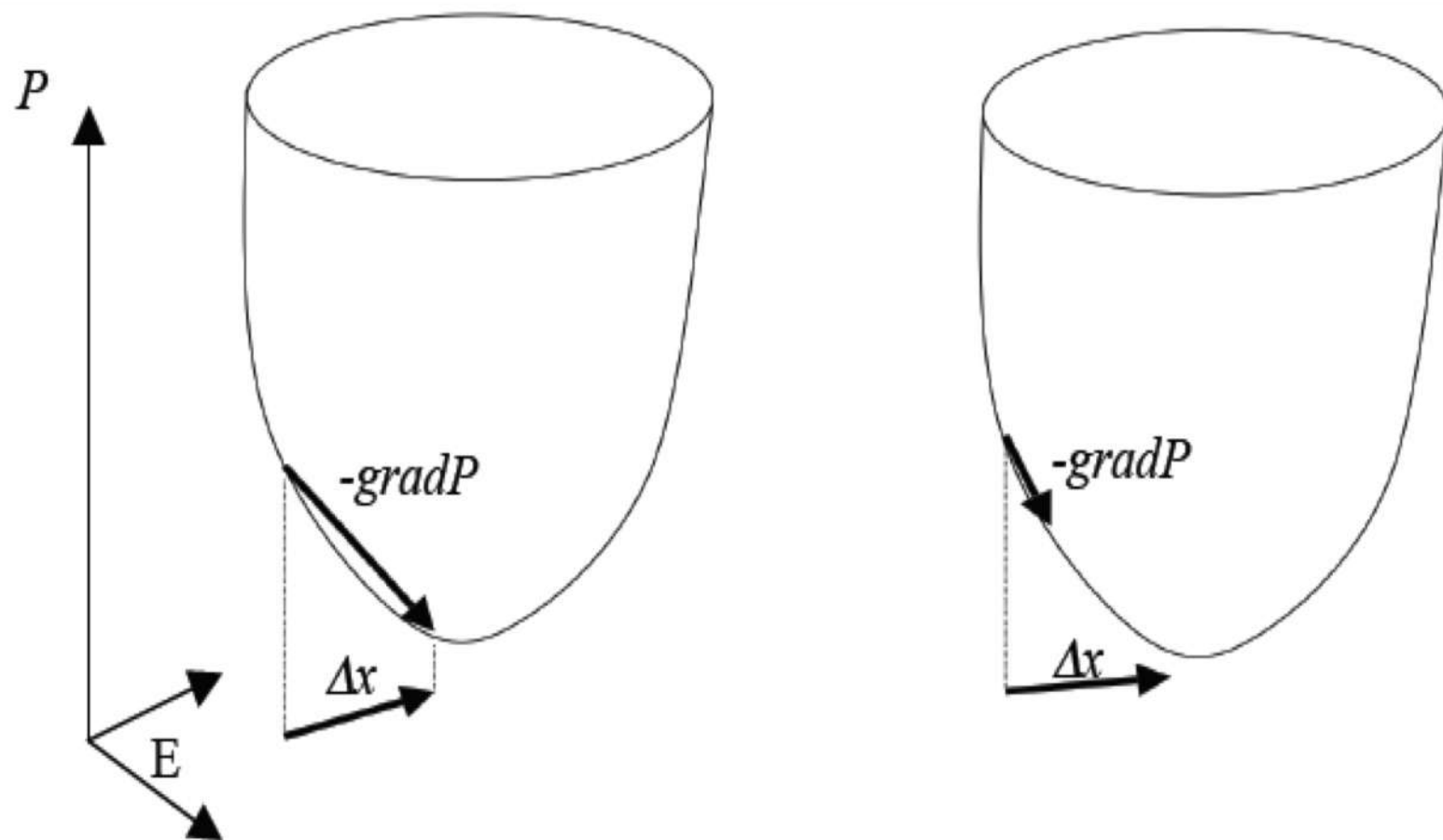


CHAPITRE III

DE LA NUTRITION ET DU DÉVELOPPEMENT

Le corps d'un animal est une espèce de moule intérieur, dans lequel la matière qui sert à son accroissement se modèle et s'assimile au total ; de manière que, sans qu'il arrive aucun changement à l'ordre et à la proportion des parties, il en résulte cependant une augmentation dans chaque partie prise séparément, et c'est cette augmentation de volume qu'on appelle développement, parce qu'on a cru en rendre raison en disant que l'animal étant formé en petit comme il l'est en grand, il n'était pas difficile de concevoir que ses parties se développaient à mesure qu'une matière accessoire venait augmenter proportionnellement chacune de ces parties (*).





Potential automaton with $\Delta x = -\text{grad}P$ (on the left) and automaton with a Lyapunov function decreasing on its trajectories (on the right).

This feature disappears with any addition of Hamiltonian term in the Hodge decomposition of the ODE



CHREODE

1952. C. H. Waddington. *The epigenetics of birds*



Genetic bifurcation

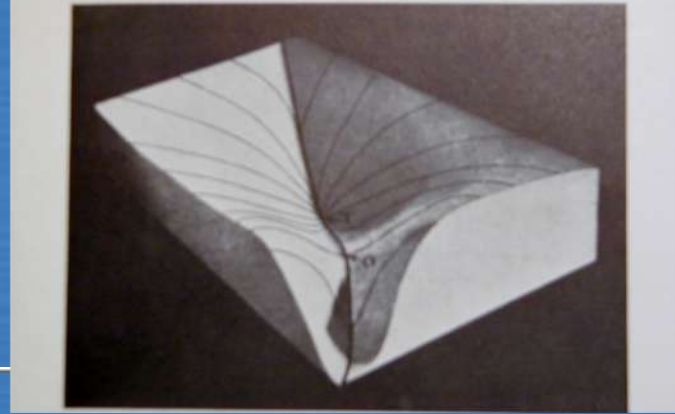
Epigenetic trajectory

GENE

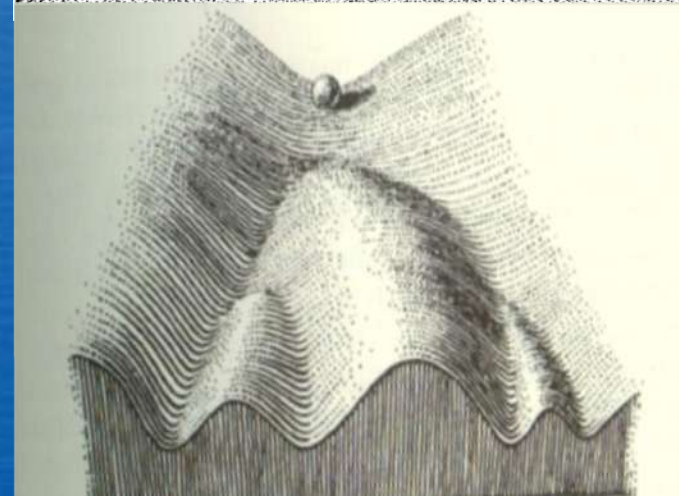
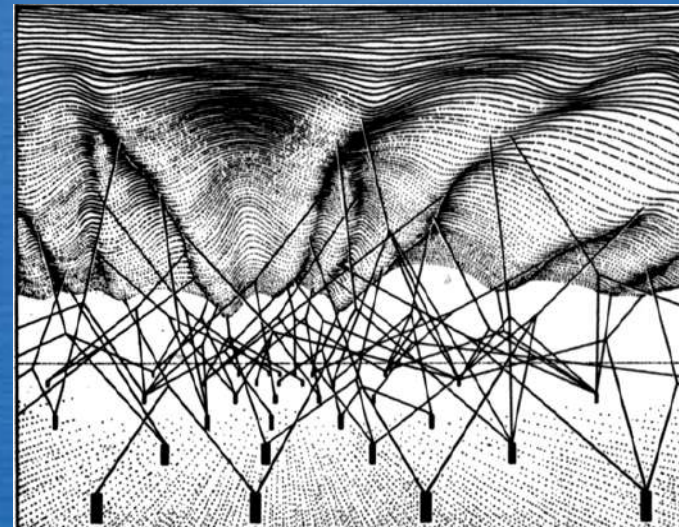


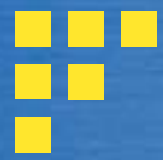
10/07/2022

Rouen 22



A. Lotka, in Needham J.
Order & Life, Yale Un. Press (1936)





Example 4

μ -tubules

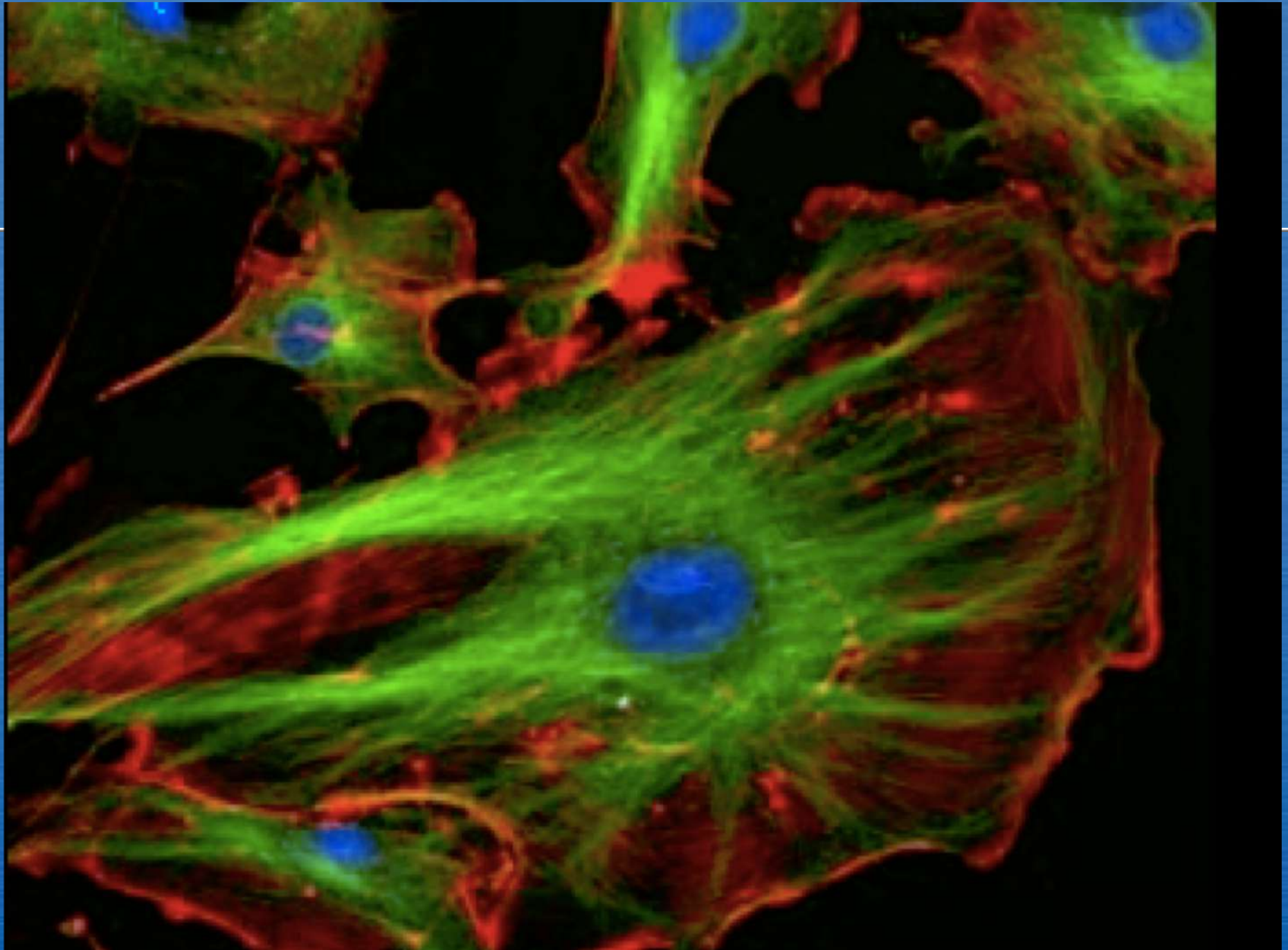


N. Glade

Rouen 22



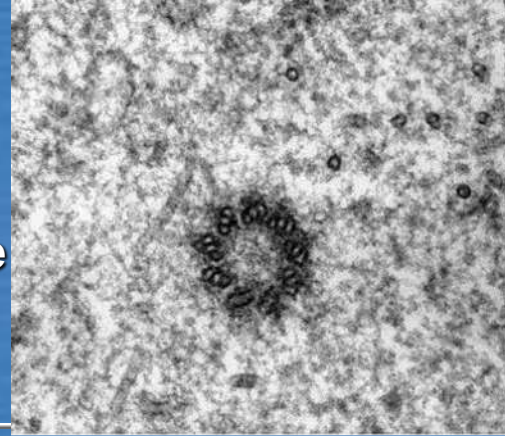






Aurora kinase C

Centrosome

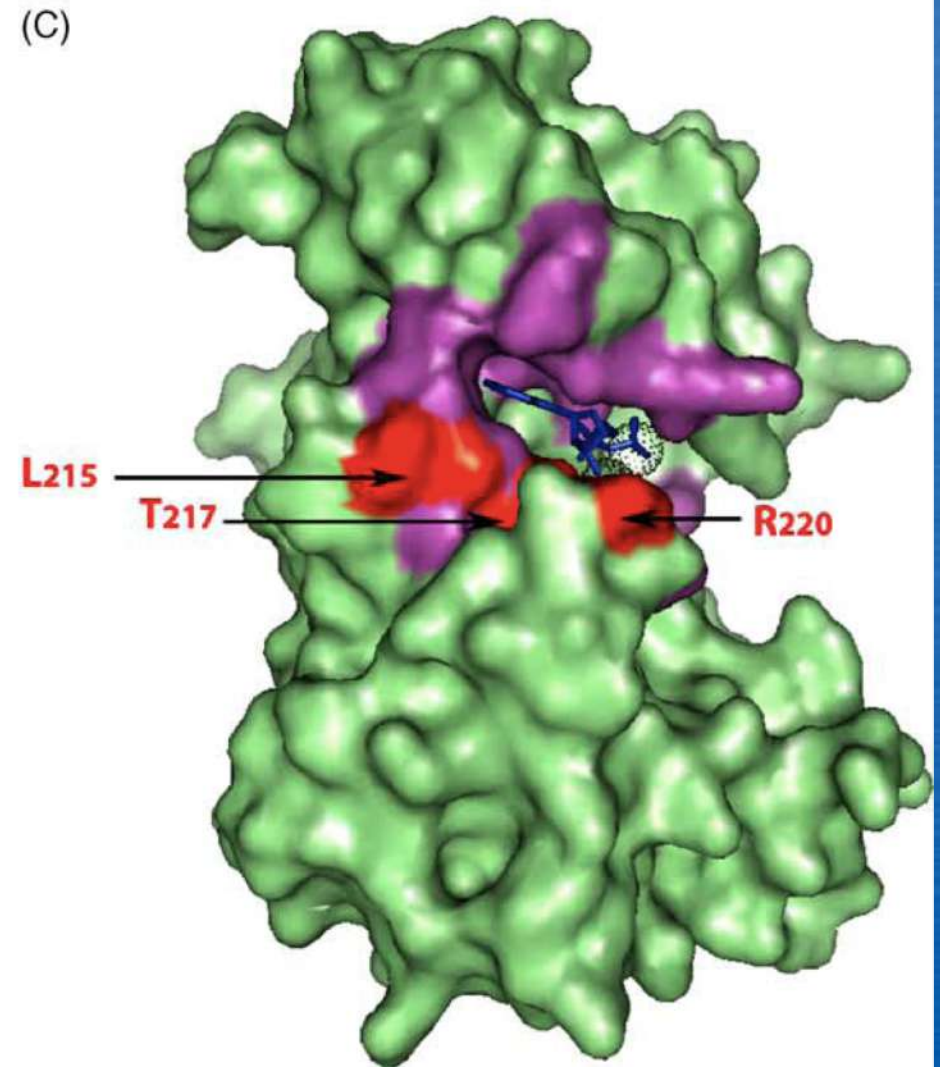
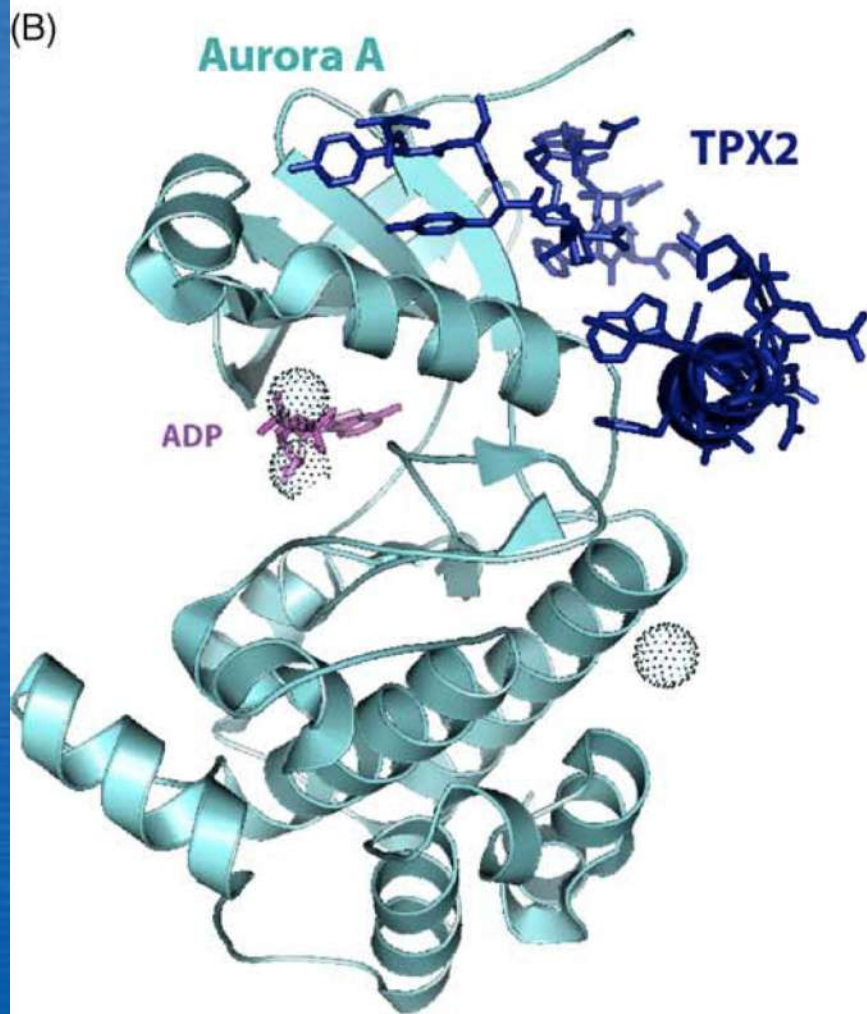


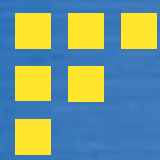
- Aurora A (aka Aurora 2) functions during prophase of mitosis and is required for correct function of the centrosomes (the microtubule organising centres in eukaryotic cells).
- Aurora B (aka Aurora 1) functions in the attachment of the mitotic spindle to the centromere.
- Aurora C (AURKC) works in germ-line cells and little is known about its function...

Homozygous mutation of AURKC yields large-headed polyploid spermatozoa and causes male infertility

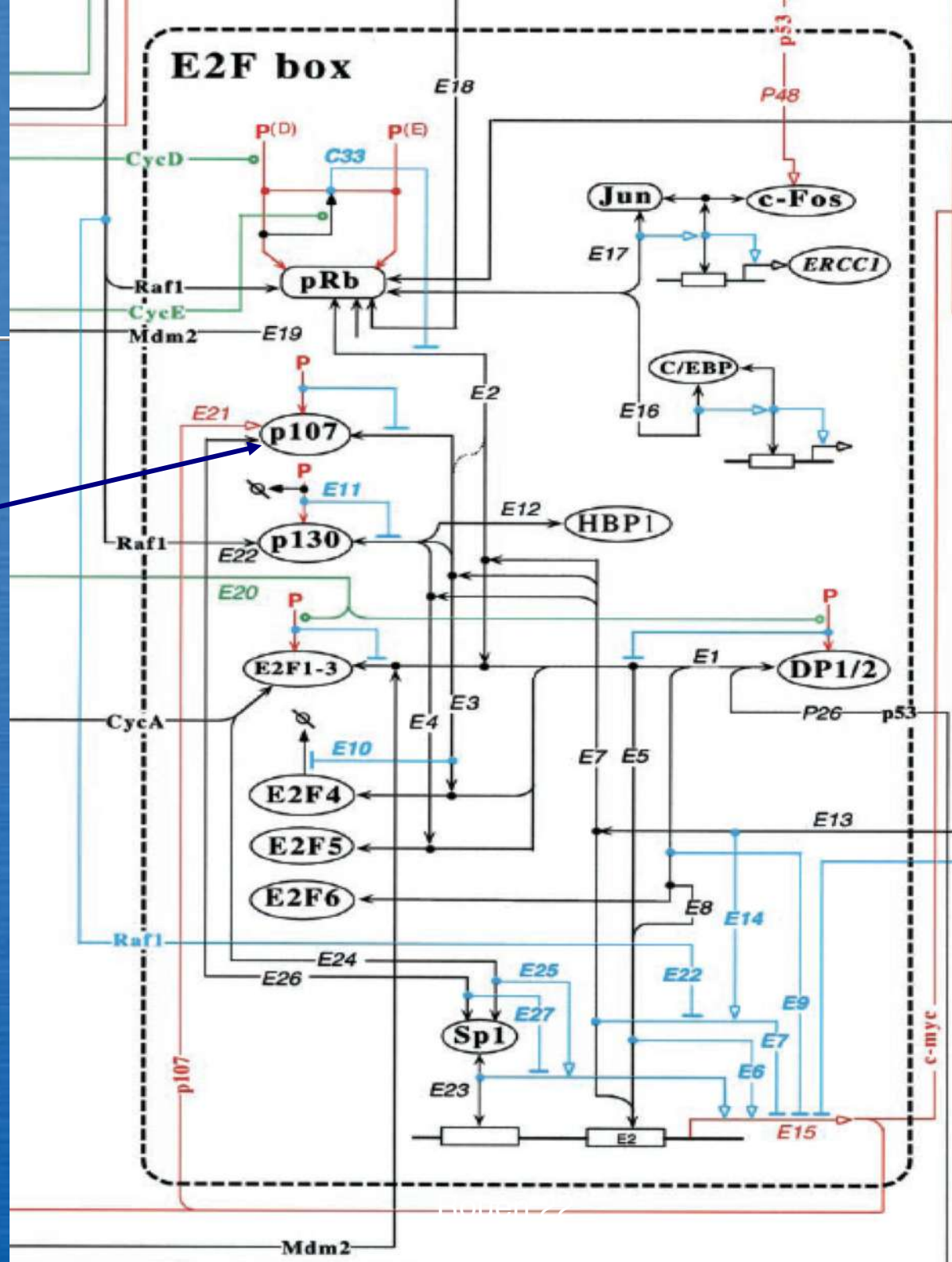
Aurora kinase

Aurora-A	SRL LKHNP SQR PMLREVLEHPWITANSSKPSNCQNKESASKQS	403
Aurora-B	SKLLRHNP SERLP LAQVSAHPWVRANSRRVLPPSALQSV----	274
Aurora-C	SRL LRYQPLERLP LAQILKHPWVQAHSRRVLPPCAQMAS----	306
	*:***:::* :* * :: ***: *: * :	

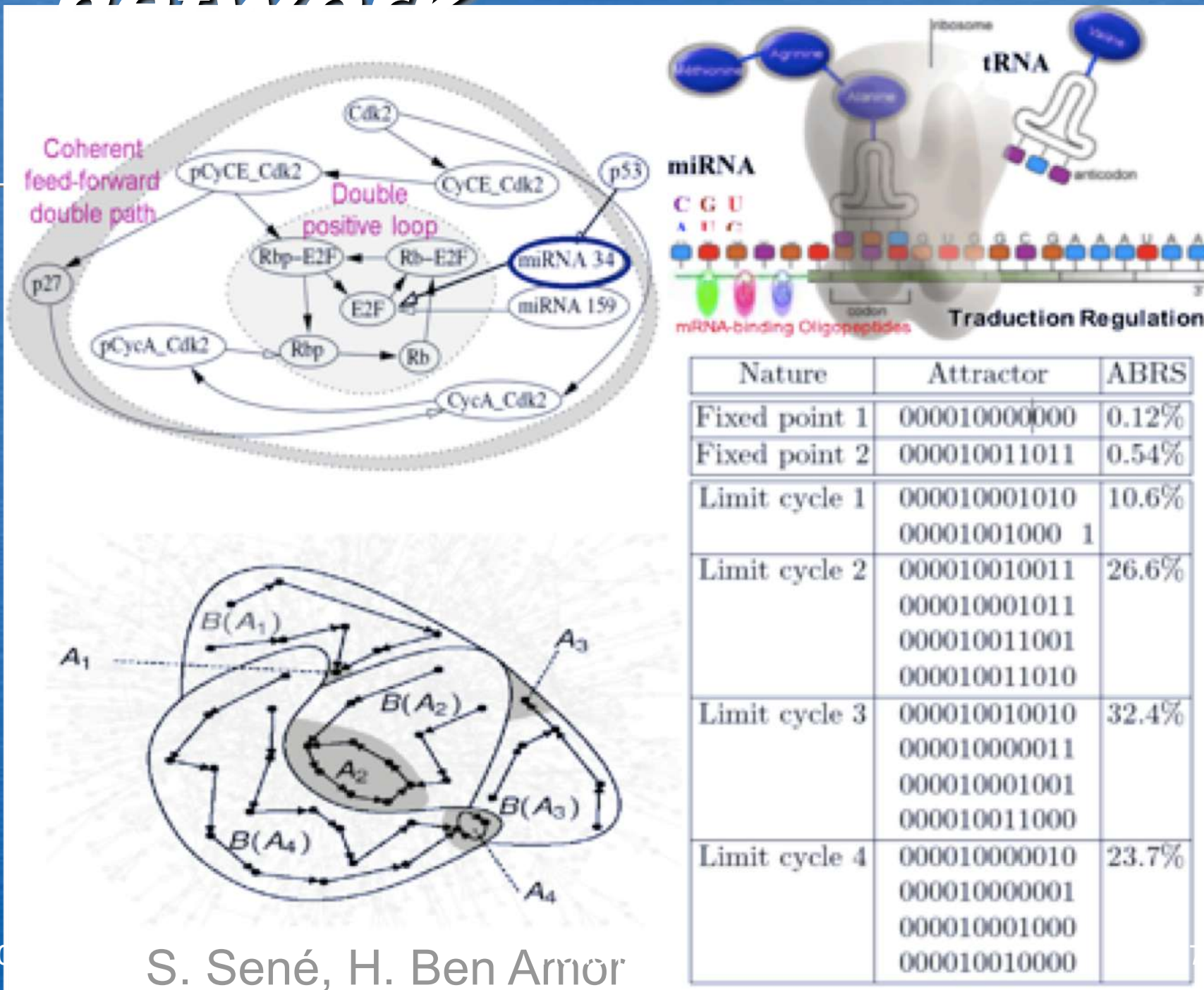




Aurora
kinase



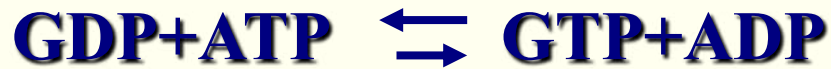
Cell-cycle control network



Simulation of μ -tubules polymerization



NDK



Diffusion-drift-reaction model

$$\frac{\partial M}{\partial t} = \eta_M \Delta M - \mu \cdot \nabla M + p(s)f(M, T, X) - p(s)g(M)$$

$$\frac{\partial T}{\partial t} = \eta_T \Delta T - p(s)f(M, T, X) + p(s)g(M)$$

$$\frac{\partial X}{\partial t} = \eta_X \Delta X - p(s)f(M, T, X) + p(s)g(M)$$

$$\frac{\partial M}{\partial \nu} = \frac{\partial T}{\partial \nu} \square \frac{\partial X}{\partial \nu} = 0$$

(Neumann boundary conditions),

where

$$f(M, T, X) = VT^k X^k M / ((K + T^k)(k + X^k)(J + M))$$

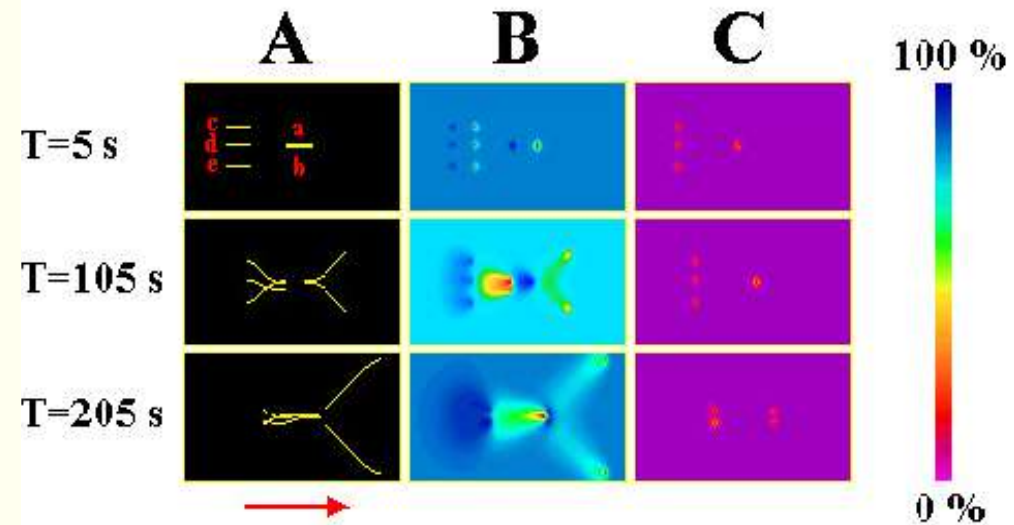
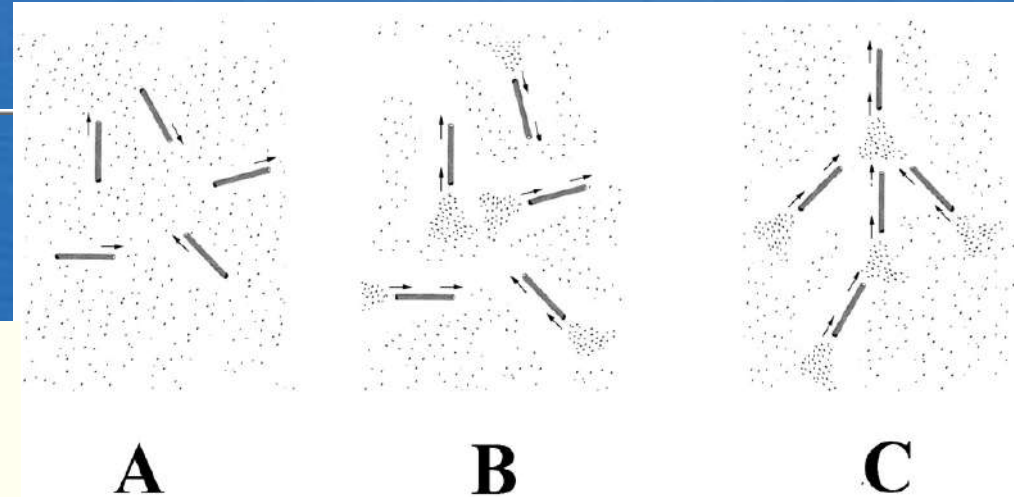
$$g(M) = WM / (J + M)$$

μ gravity vector

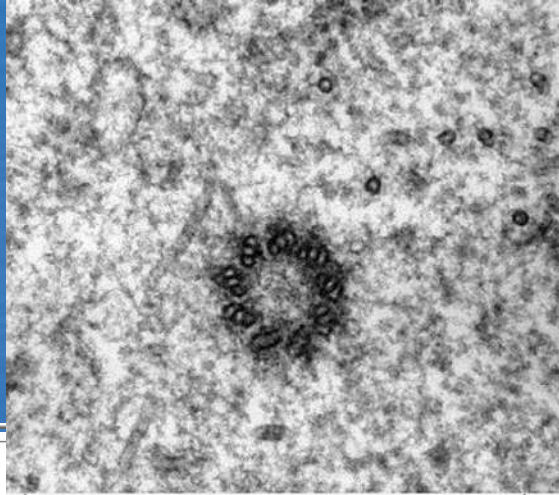
M μ -tubules of length $n-1$ or n concentration

T tubuline concentration

X GTP concentration

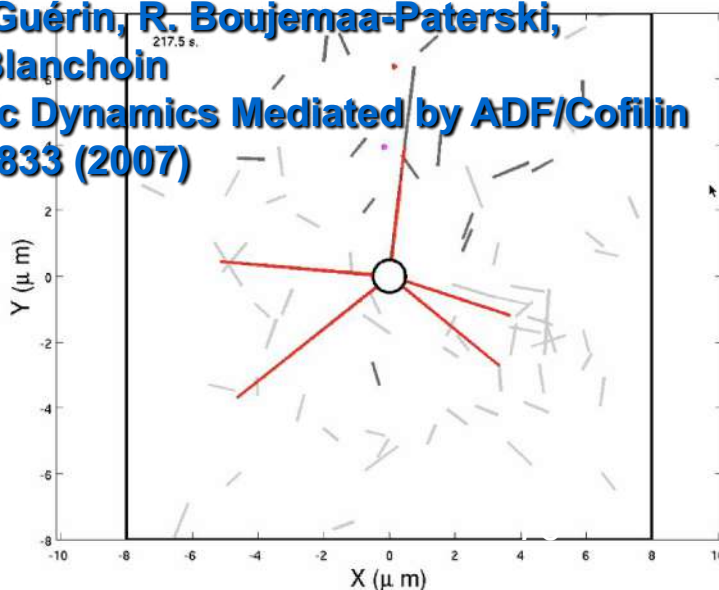
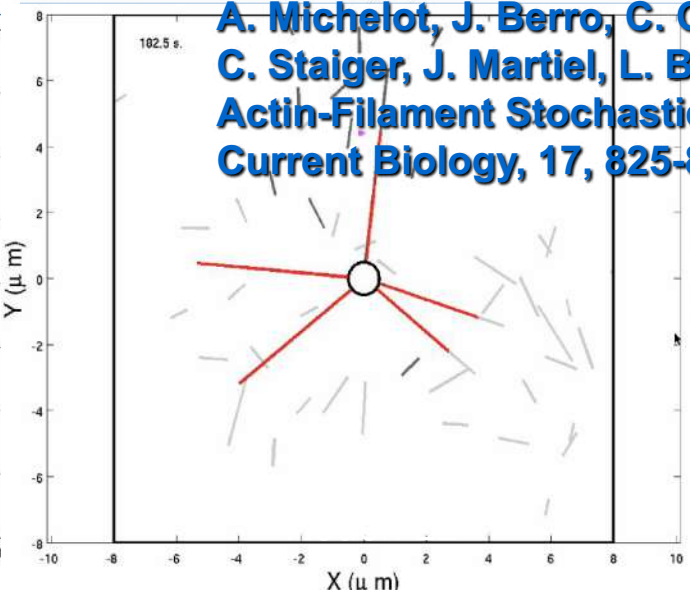
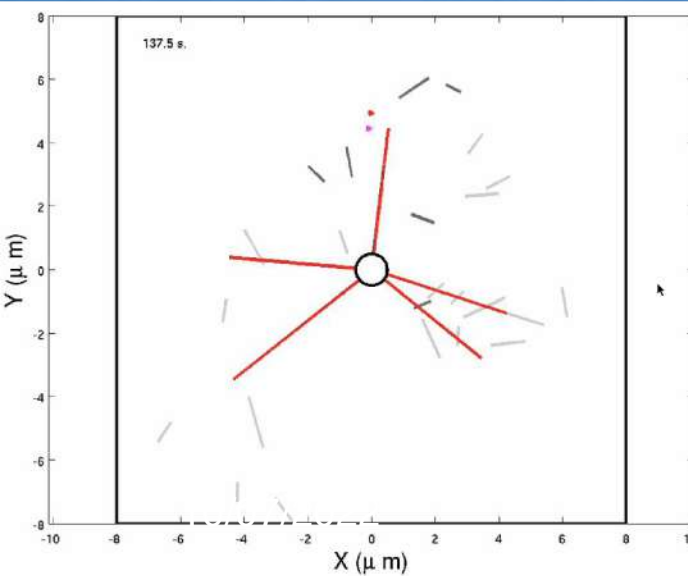
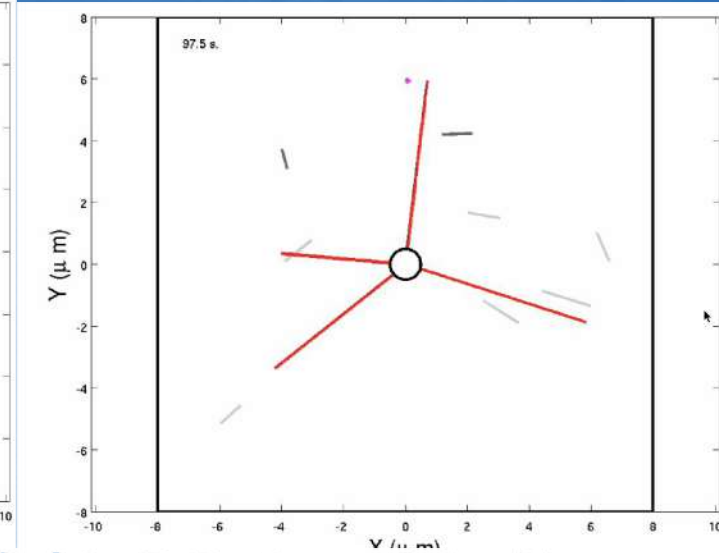
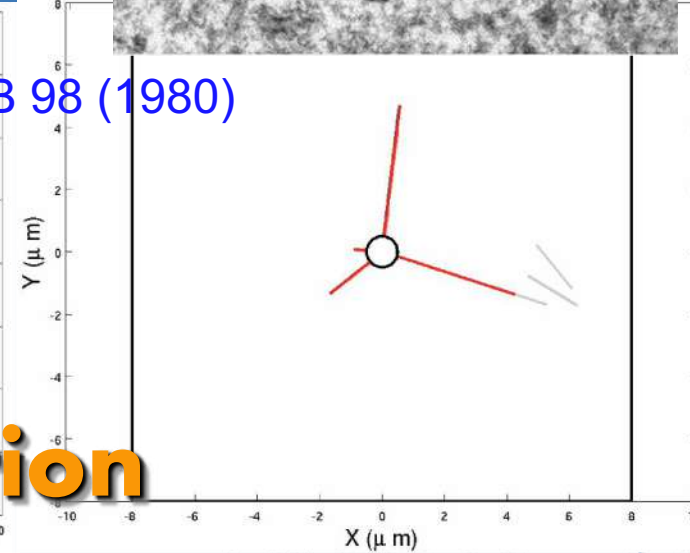
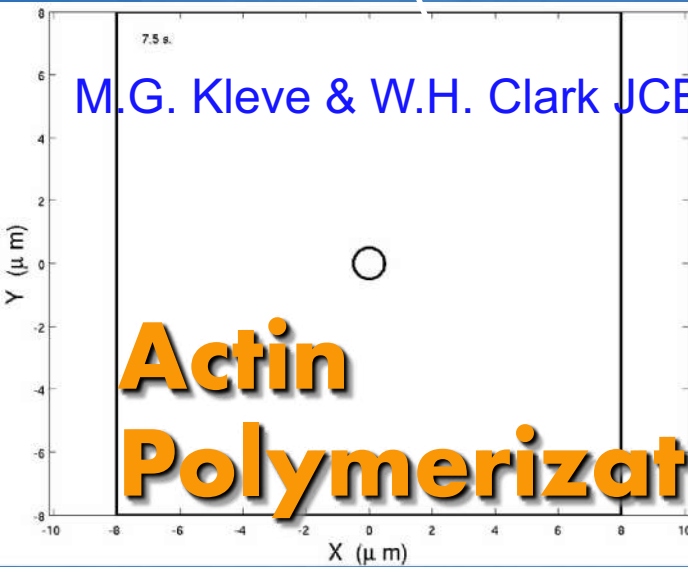


Centrosome

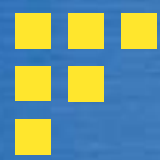


M.G. Kleve & W.H. Clark JCB 98 (1980)

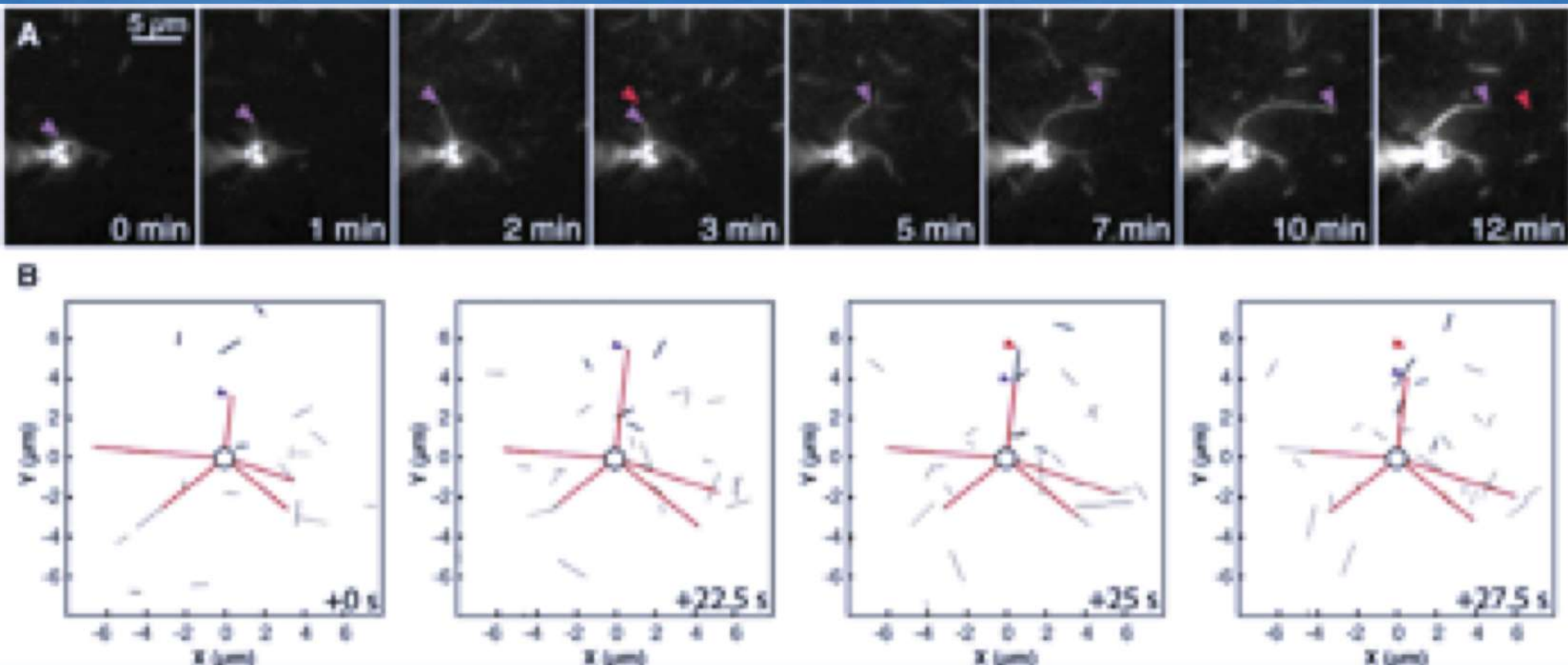
Actin Polymerization



A. Michelot, J. Berro, C. Guérin, R. Boujemaa-Paterski, C. Staiger, J. Martiel, L. Blanchoin
Actin-Filament Stochastic Dynamics Mediated by ADF/Cofilin
Current Biology, 17, 825-833 (2007)



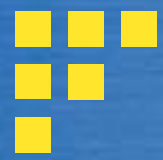
Actin Polymerization



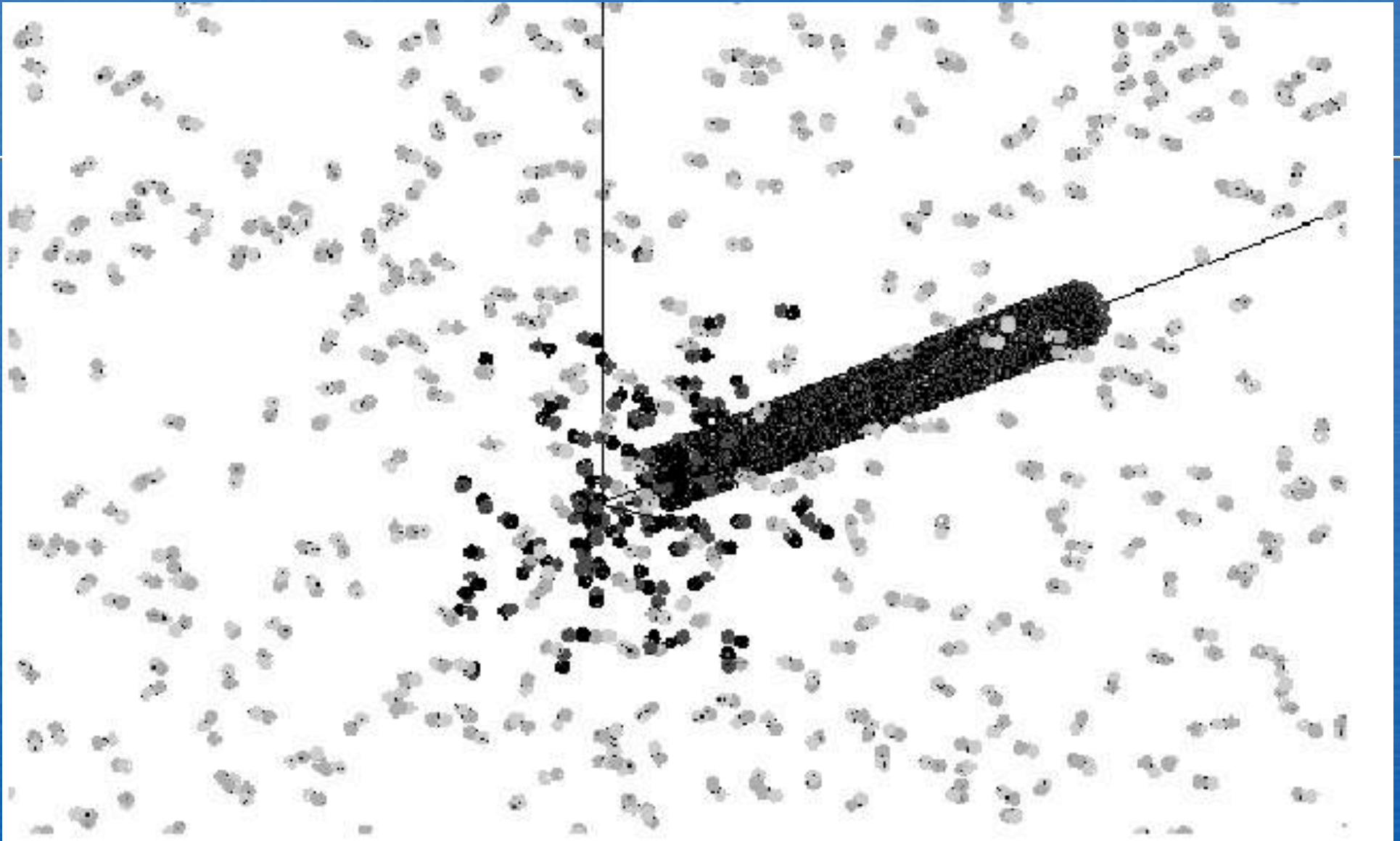
A. Michelot, J. Berro, C. Guérin, R. Boujemaa-Paterski, C.J. Staiger, J.L. Martiel & L. Blanchoin

Current Biology 17 (2007) & 20 (2010)

Rouen 22



Microtubules trail



N. Glade, Int. J. Unconventional Computing (2008)

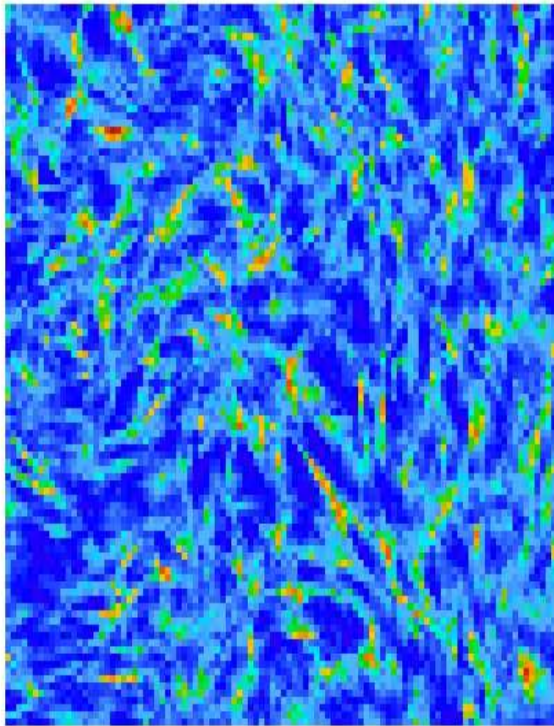


\oplus μ -tubules polymerization $(-)$

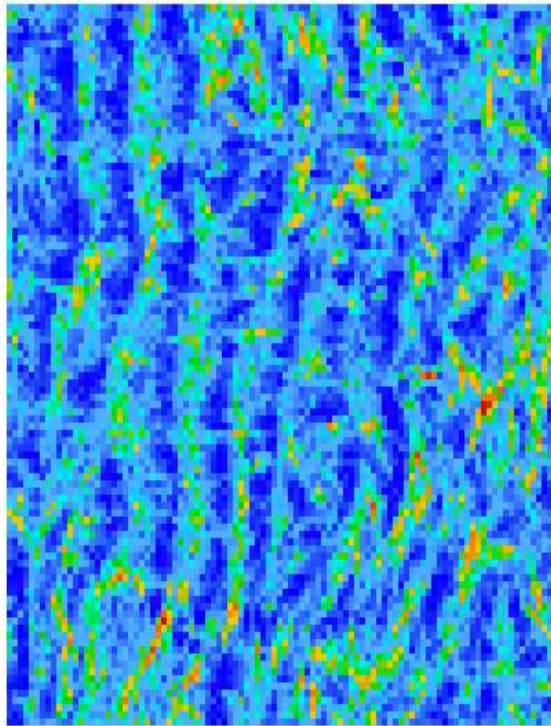


Simulated structures

40 μm



$\mu=0$



$\mu \nearrow$

40 μm





Conclusions

- Change of shape starts where the curvature is higher
- The bending propagates from the cells in the maximum-curvature area to the cells in the more planar area
- Vesslar morphogenesis
- Anatomico-functional approach of the ontogenesis = 5D anatomy
- Beyond a 5D surgery?



References

- **F. MICHON, L. FOREST, E. COLLOMB, J. DEMONGEOT & D. DHOUILLY**
BMP-2 and BMP-7 play antagonistic roles in feather induction.
Development, **135**, 2797-2805 (2008).
- **L. ABBAS, J. DEMONGEOT & N. GLADE**
Synchrony in Reaction-diffusion models of morphogenesis: applications to curvature-dependent proliferation and zero-diffusion front waves.
Phil. Trans. Royal Soc. A, **367**, 4829-4862 (2009).
- **J. DEMONGEOT, J. GAUDART, A. LONTOS, E. PROMAYON, J. MINTSA & M. RACHDI**
Least diffusion zones in morphogenesis and epidemiology.
Int. J. Bifurcation and Chaos, **22**, 1250028 (2012).
- **F. CARAGUEL, N. BESSONOV, J. DEMONGEOT, D. DHOUILLY & V. VOLPERT**
Wound healing modelling in Zebrafish.
Acta Biotheoretica, **64**, 343-358 (2016).
- **M. RACHDI, J. WAKU, H. HAZGUI & J. DEMONGEOT**
Entropy as robustness marker in genetic regulatory networks.
Entropy, **22**, 260 (2020).