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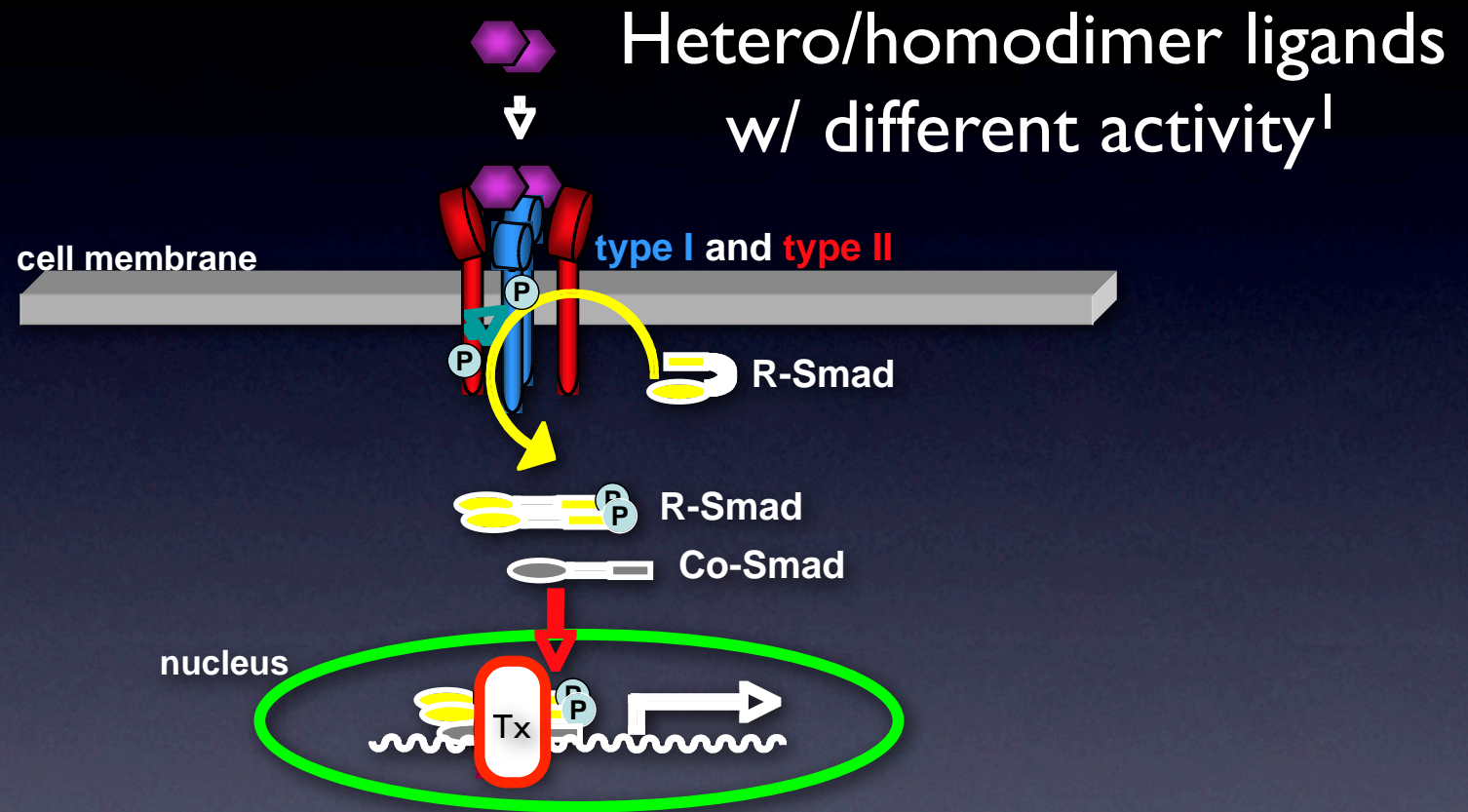
Dynamic simulation of Bone Morphogenetic patterning in a 3D model of the zebrafish embryo

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Conflict disclosure: none

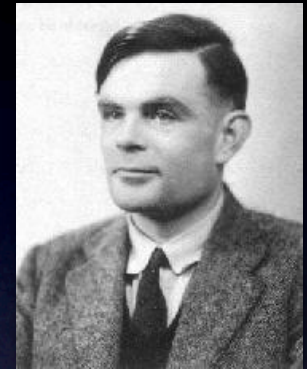
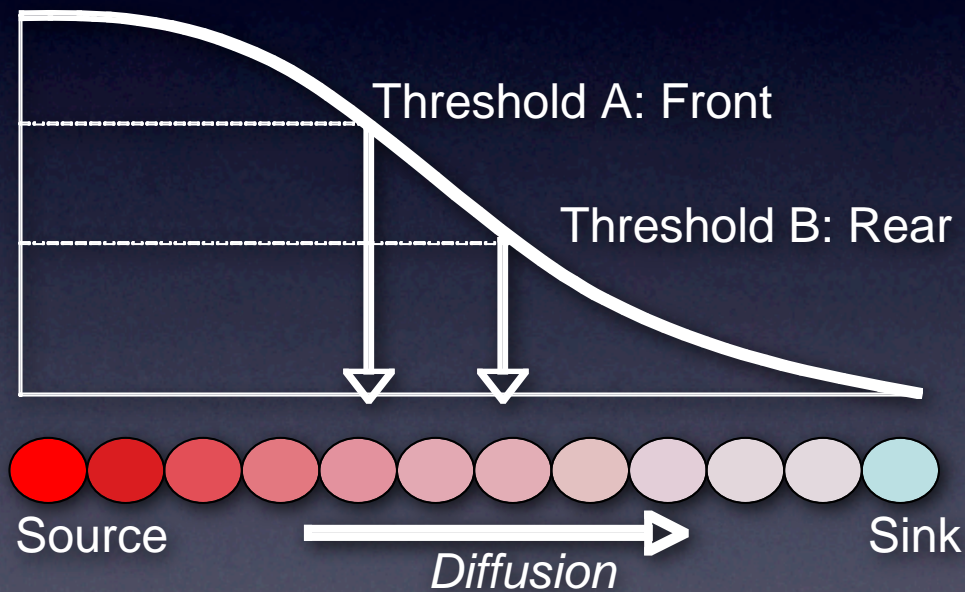
Canonical BMP pathway



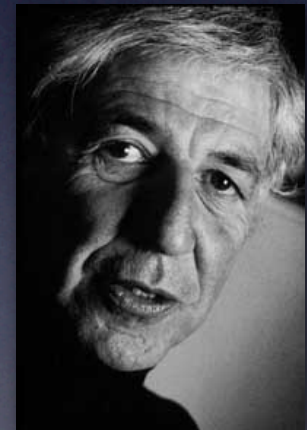
¹Shimmi, Umulis, Othmer & O'Connor, *Cell* (2005)

²For review see Umulis, et al. *Development* (2009)

Problems with the classical view of Morphogenesis

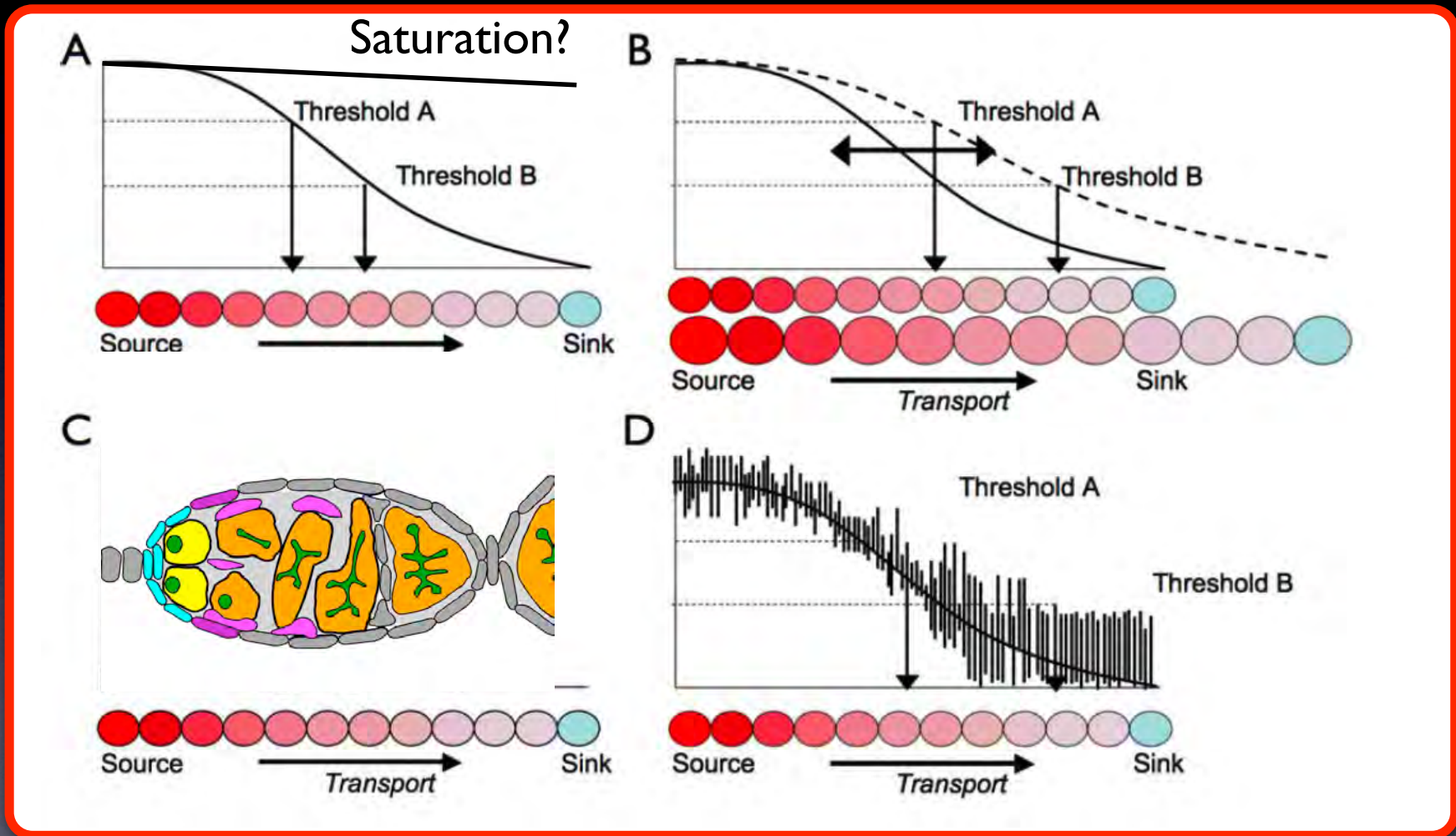


A.M. Turing



Lewis Wolpert

Problems?

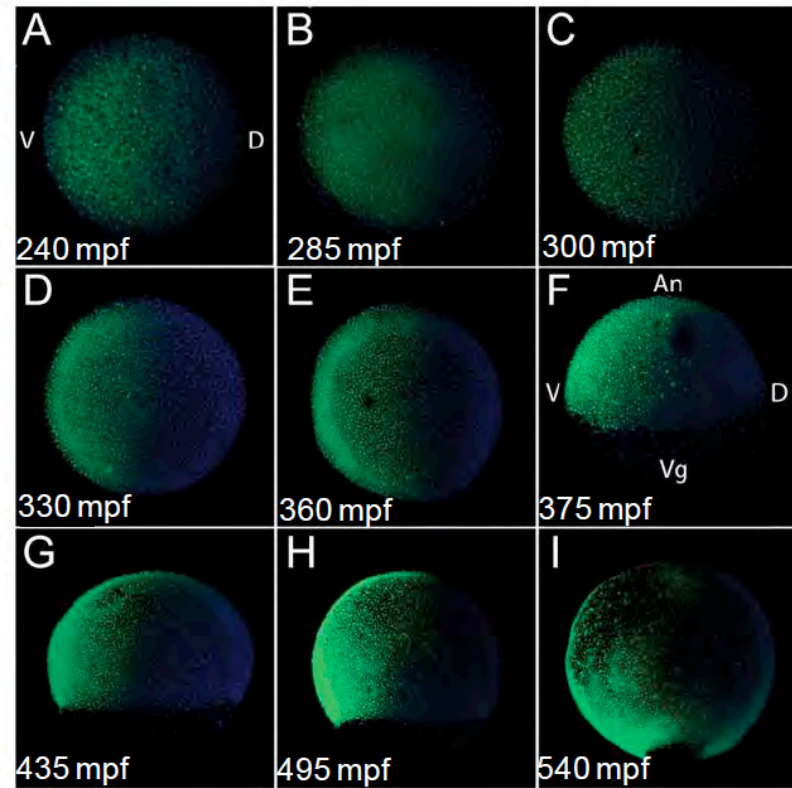
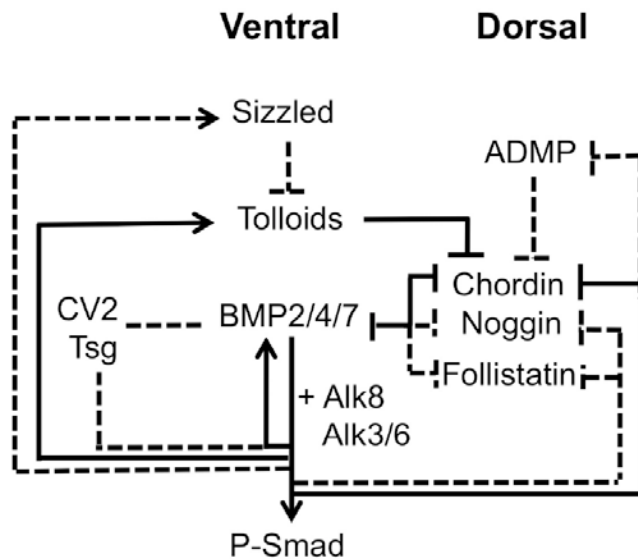
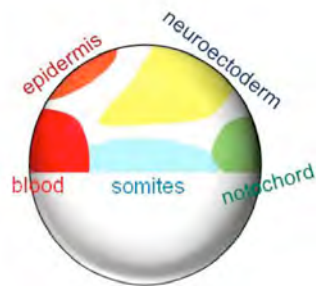


* Figure from Umulis, O'Connor, & Othmer. CTDB(2008)

Use of Comsol modeling in developmental biology

- Test alternative hypotheses
- Tackle inverse problem
- Measure biophysical properties
- Understand phenomena and behavior
- Estimate unknowns
- Translate expectations to new contexts
- Bridge genotype to phenotype

BMP regulation in zebrafish

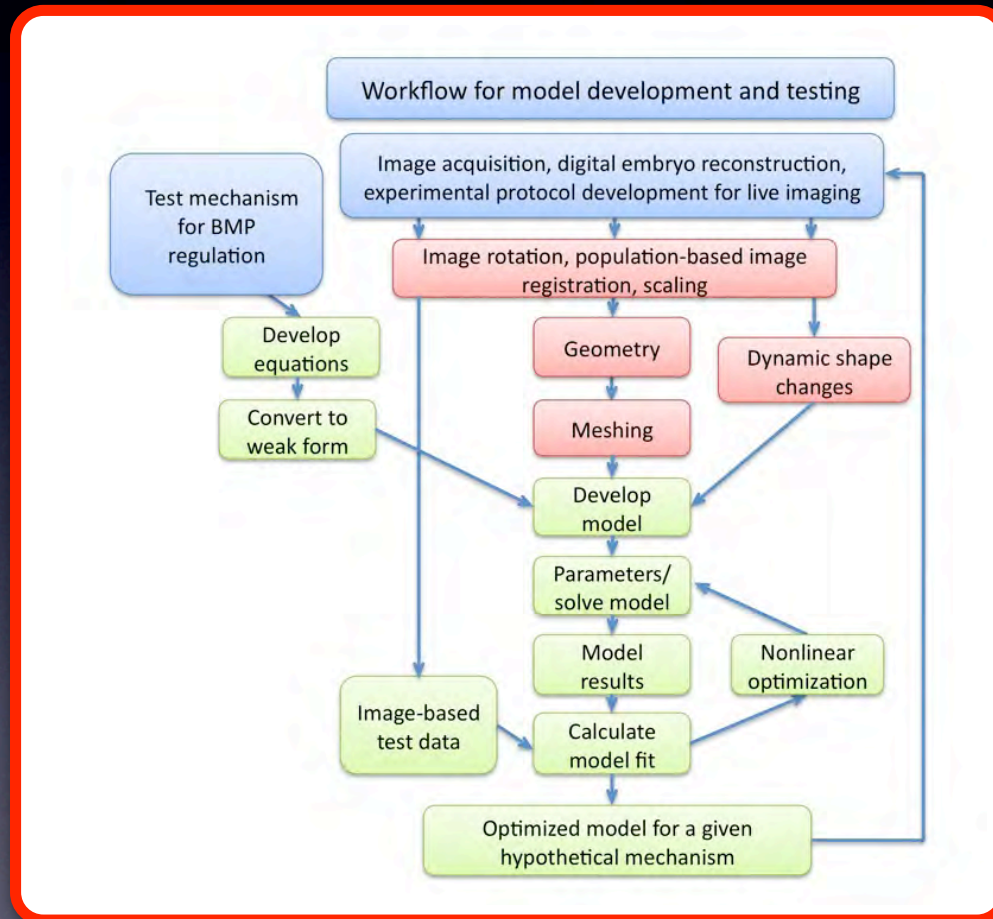


Using Comsol to reverse engineer zebrafish development

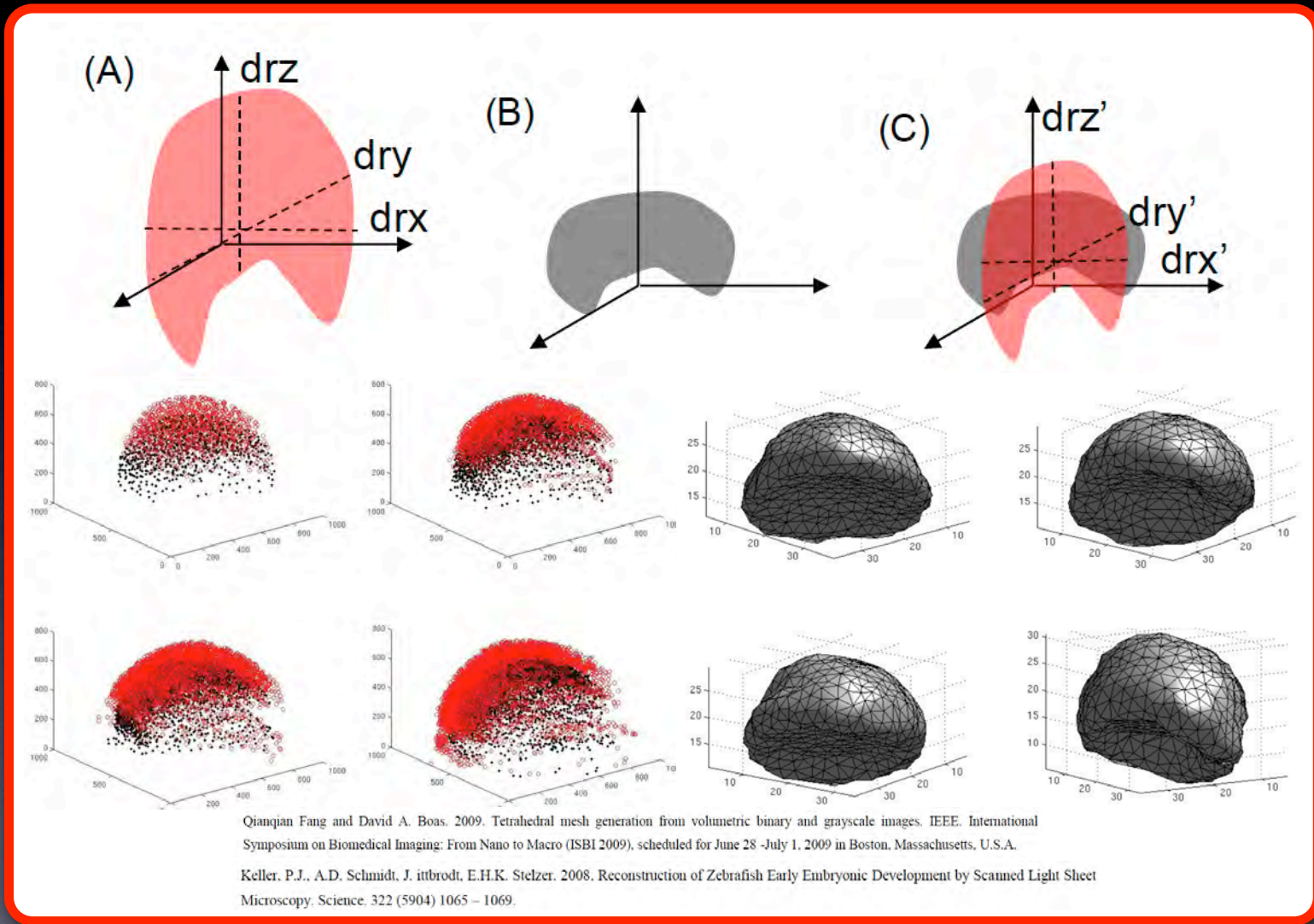
- >10 genes, >3 states each gene = 59,049 combinations at minimum

	Aero/Jet	Chemical	Cellular
Data	Quantitative	Quantitative	Semi/Qual
Theory	Mature	Mature	Early
Regime	Continuous	Continuous	+Stochastic
Environment	Dynamic	Steady-state	Dynamic
Sensing	$>10^3$ /sec	>10 /sec	up to days
Control strategies	Classical, model based, relatively well characterized		Challenging-sparse data
Tradeoffs	Reduced by design, \$\$\$		Inherent

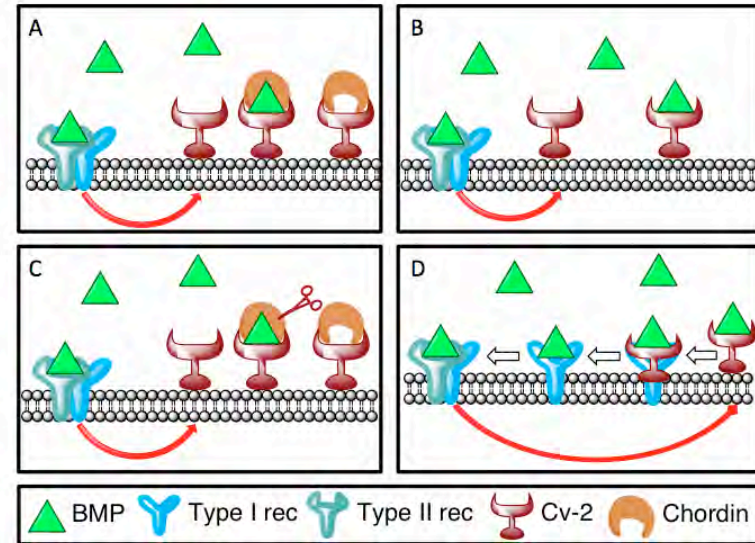
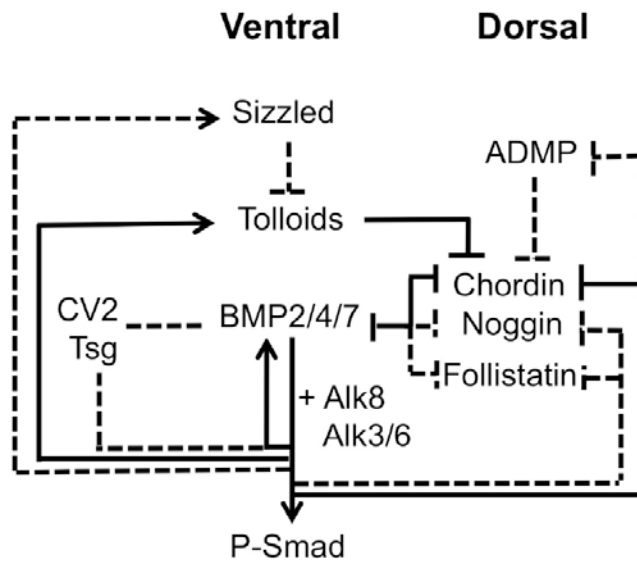
Discovery pipeline for modeling zebrafish embryonic patterning



Geometry development



Model development



$$\frac{\partial[L]}{\partial t} = D_L \nabla^2 [L] - k_{on}[L](R_0 - [LR]) + k_{off}[LR] - j_{on}[L][C] + j_{off}[LC] + V_L + K_{cat}[TLC]$$

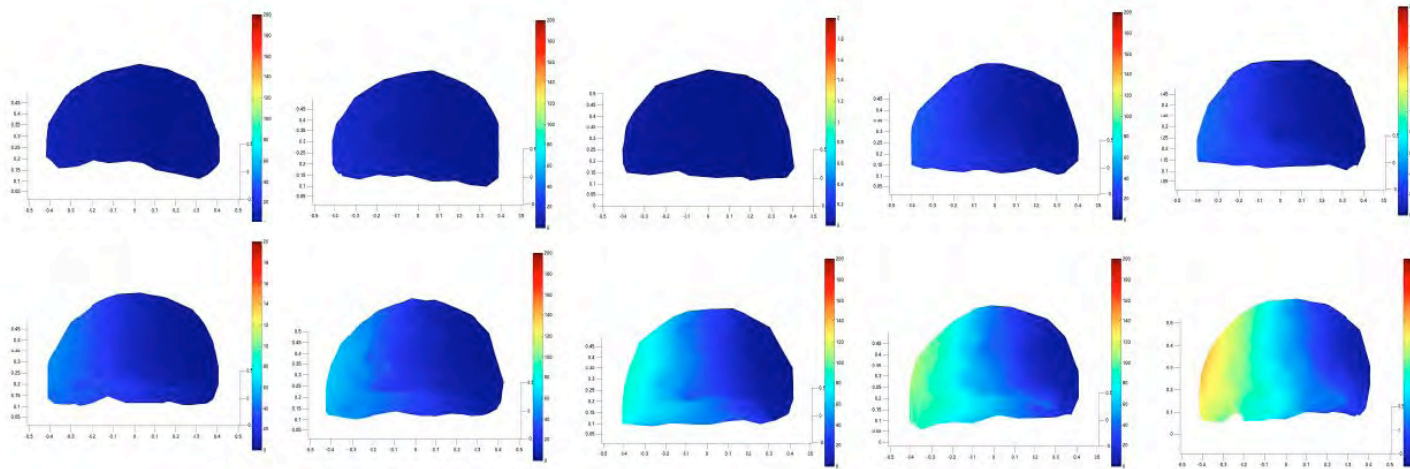
$$\frac{\partial[C]}{\partial t} = D_C \nabla^2 [C] - j_{on}[L][C] + j_{off}[LC] - p_{con}[T][C] + p_{coff}[TC] + V_C$$

$$V_C = \frac{V_{Cmax}}{1 + \gamma_c[LR]} + \begin{cases} V_{Corg} e^{-(b^*c)t} & \text{if } (x, y, z) \in Org \\ 0 & \text{if } (x, y, z) \notin Org \end{cases}$$

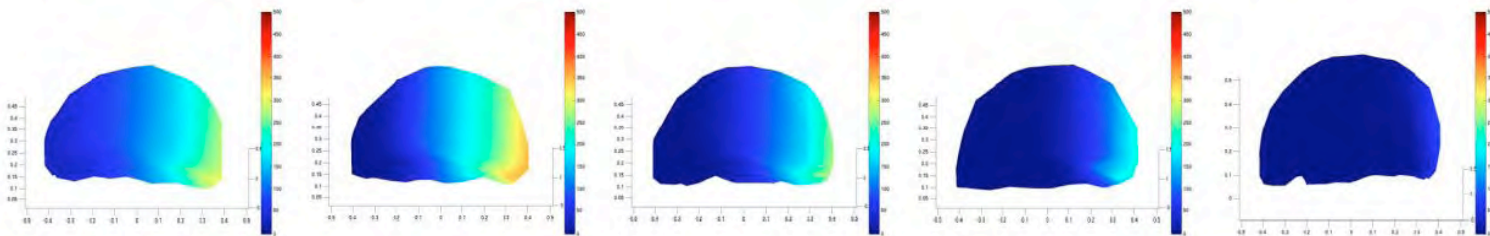
$$V_L = V_{Lmin} + \frac{V_{Lmax} - V_{Lmin}}{1 + \gamma_L/[LR]} + V_{Lmat} e^{-bt}$$

Model results

BMP-Alk8 (distributions of active signaling)

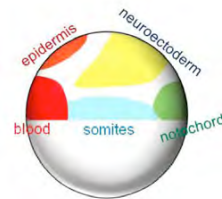
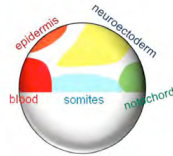
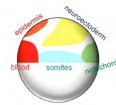


Chordin (distribution BMP inhibitor)



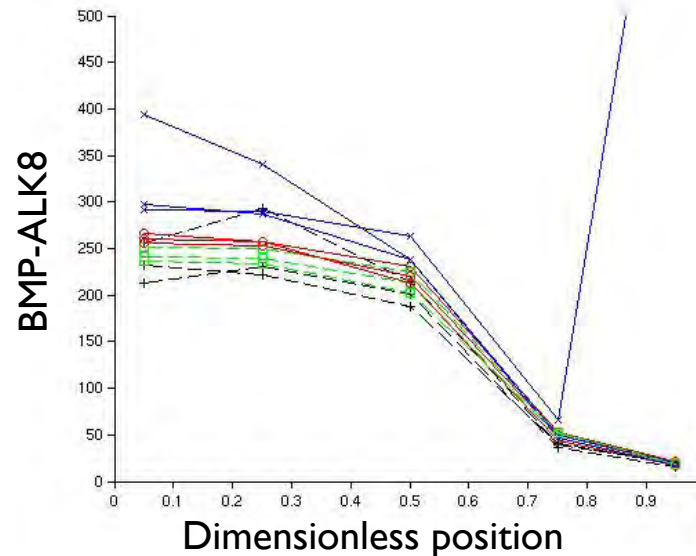
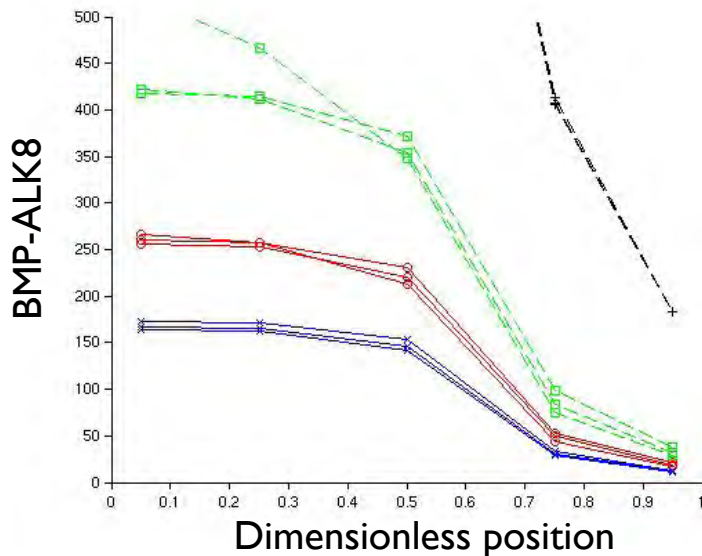
Model results

Model performance (scale-invariance)

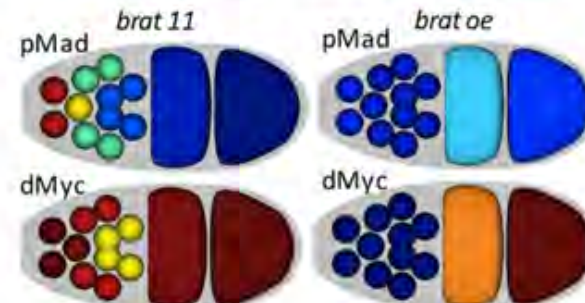
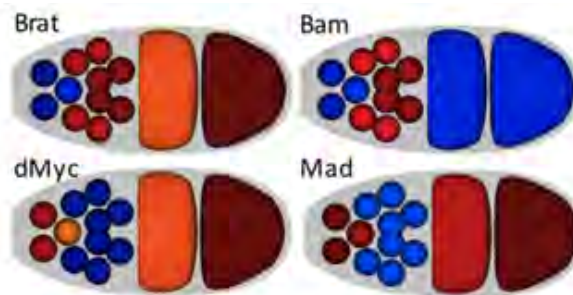
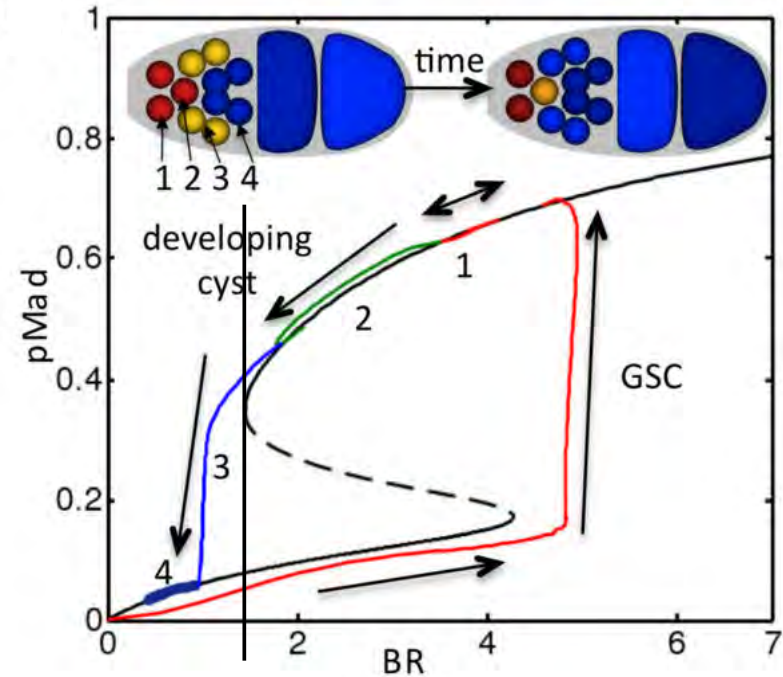
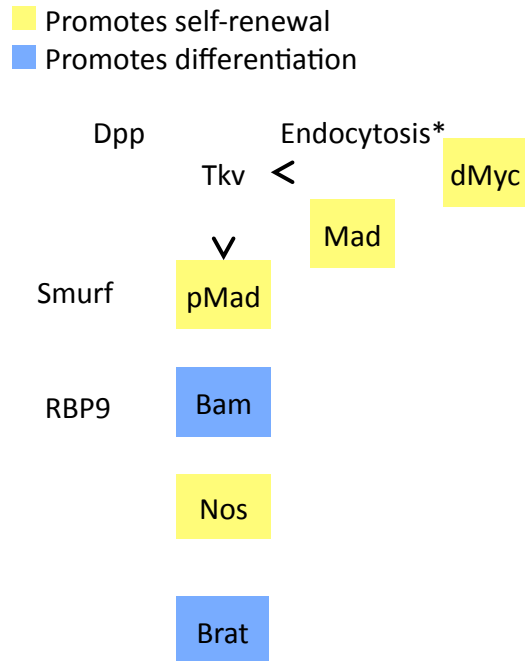


Chordin (Inhibitor secreted dorsally)

Tld (Chordin protease)

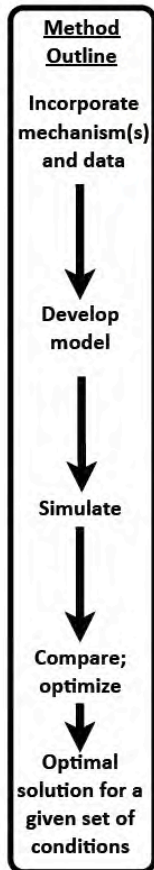


Other uses of Comsol in developmental biology: decipher stem cell regulation



Harris et al. Dev. Cell (2011)

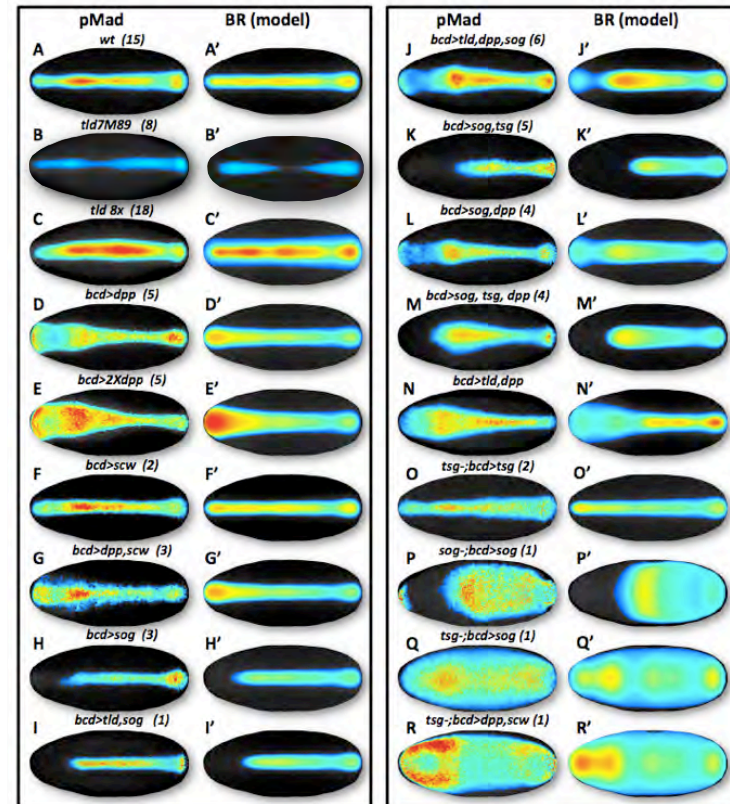
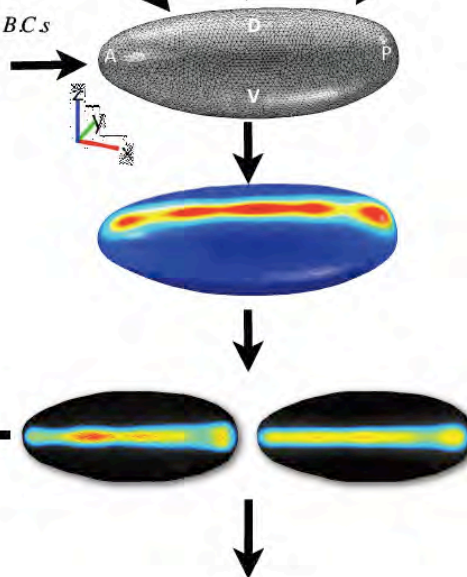
Other uses of Comsol in developmental biology: BMP pattern formation



tkv (*) *tld* (10) *sog* (10)

$$\frac{\partial c}{\partial t} = -\frac{\partial \phi}{\partial x} + R(c, p) + B.C.s$$

e.g. $\phi = -D \frac{\partial c}{\partial x}$

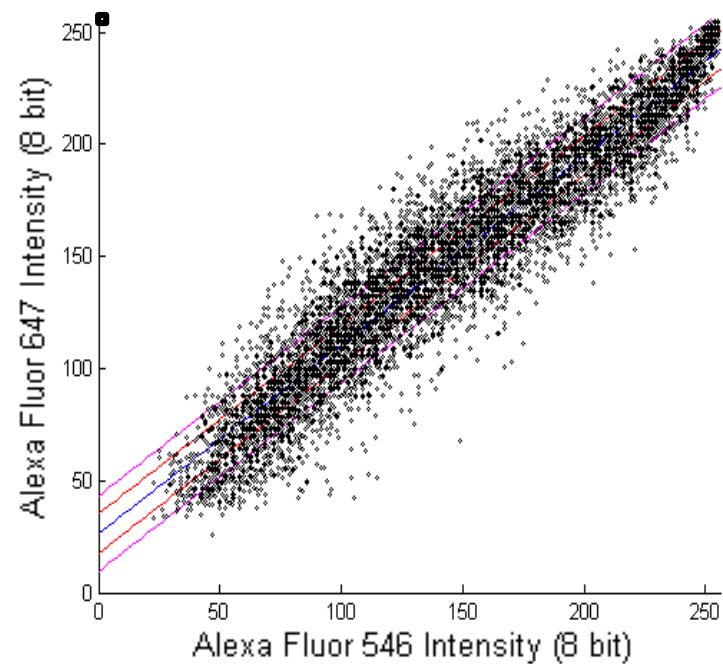
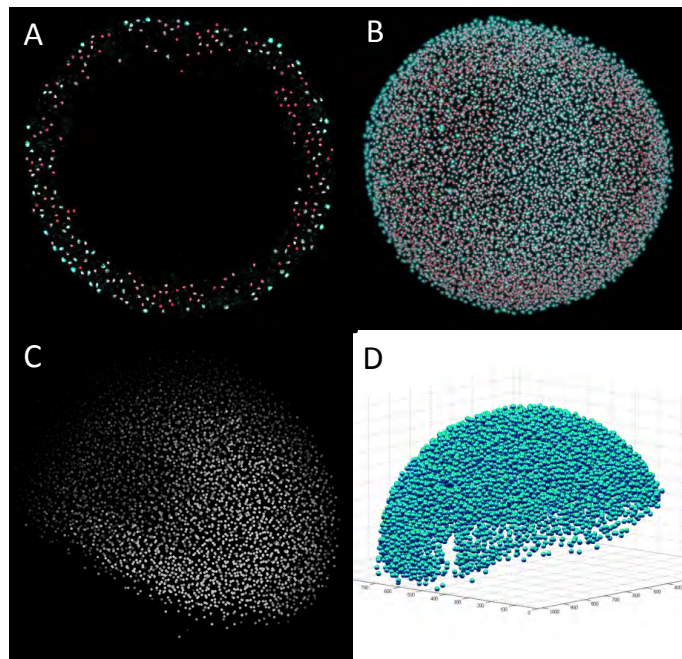


Umulis et al. Dev. Cell (2010)
Peluso et al. Dev. Cell (2011)

Concluding remarks

- Multidimensional data can be seamlessly integrated into mathematical models.
- Current zebrafish models are being used as a tool to drive discovery alongside experimental methods.
- BMP/Sizzled/Chordin/Tld network appears capable of providing automatic scale-invariance.

Future directions: Better integration



Joe Zinski
Mary Mullins, Ph.D.

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