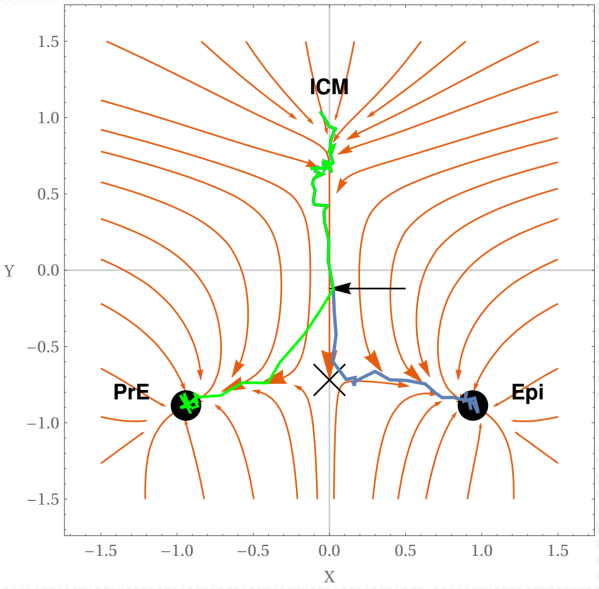
Geometric models of cell fate specification



Archishman Raju
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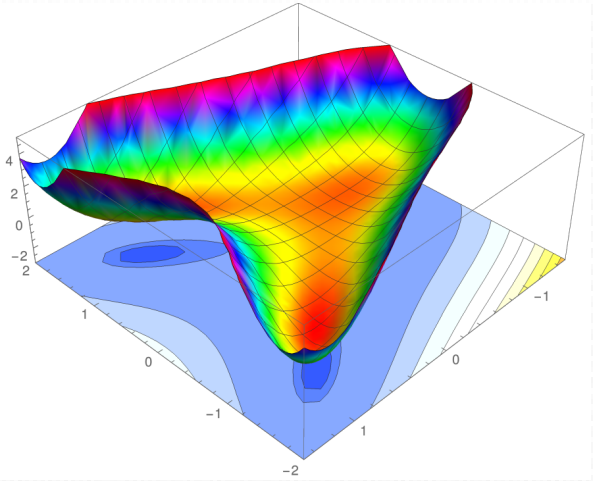
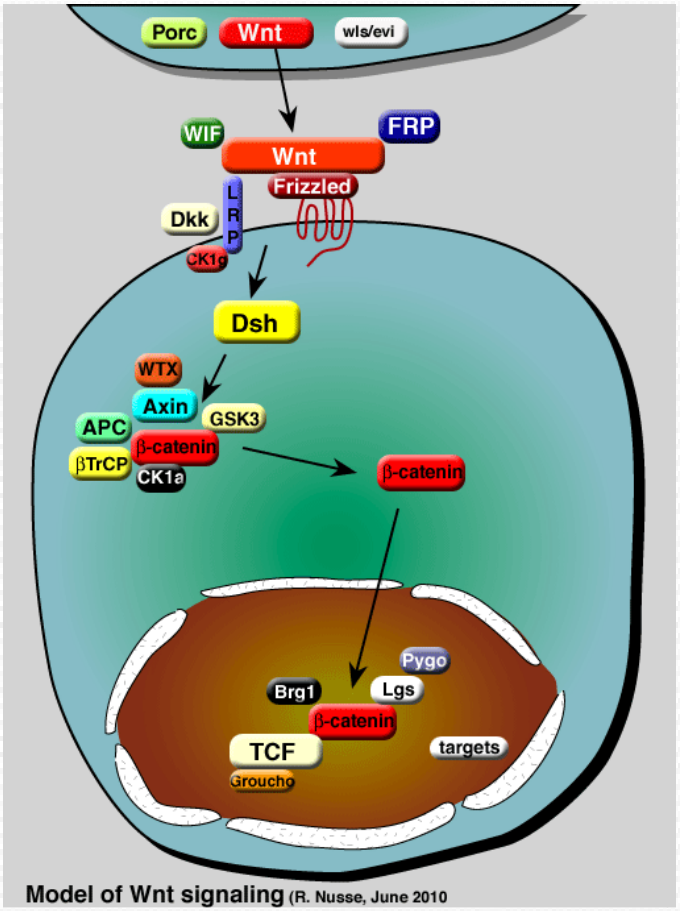
3 February 2023



With Eric Siggia (Rockefeller) and Kat Hadjantonakis (Sloan Kettering)

Cell Fate in Development

Cell Fate maps show a very ordered and robust pattern of development emerging from complicated signaling.

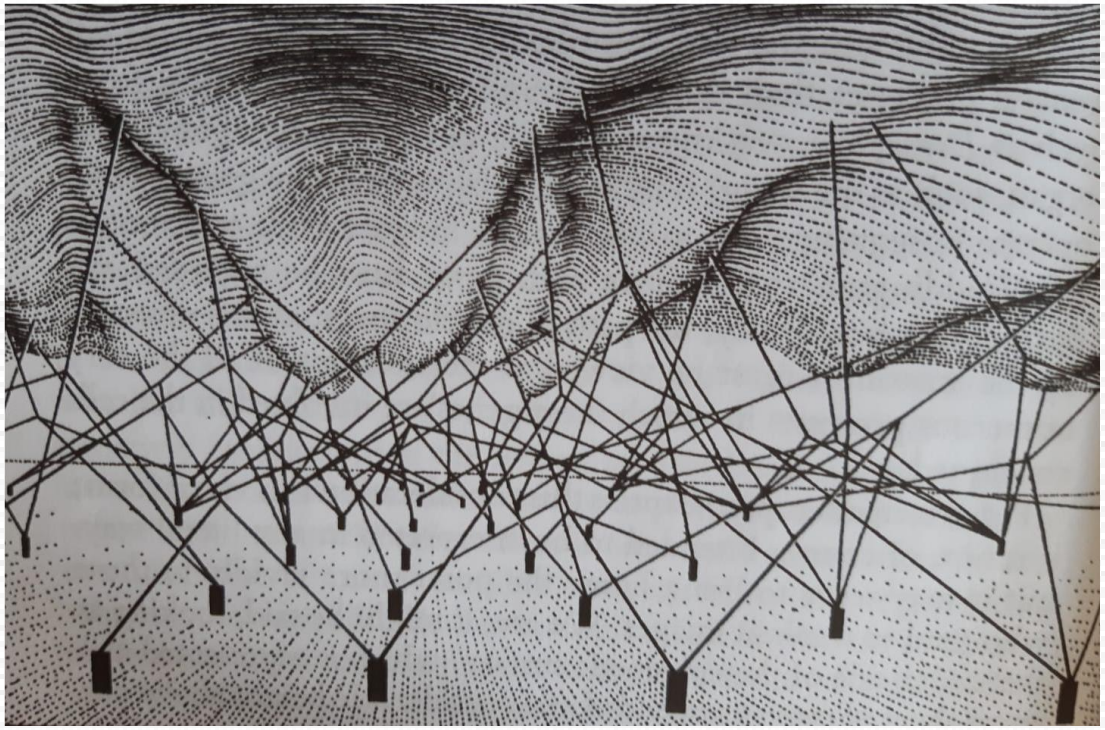


Wnt Signaling pathway components

Roel Nusse (2010)

Waddington approach to cell fate specification

- Waddington metaphor of a landscape is an early example of an "emergent" description.



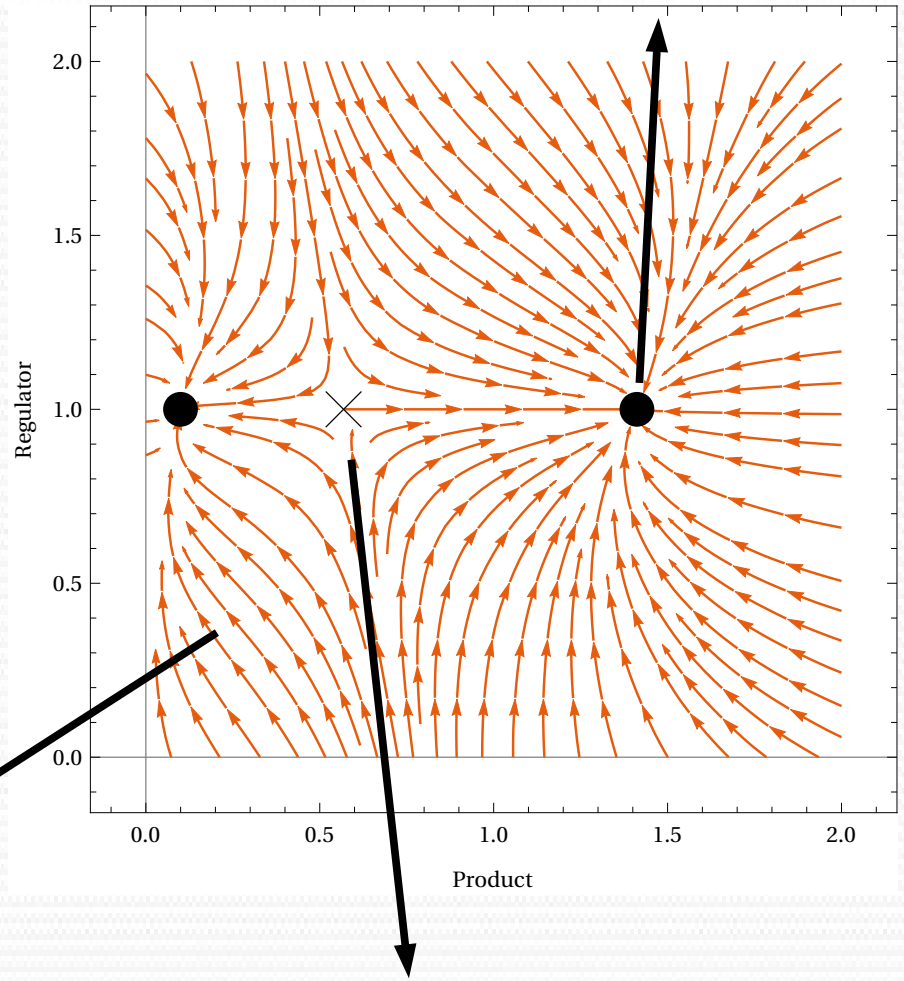
Waddington, The Strategy of Genes (1957)

Development as a Dynamical Systems

Gene production, decay and interactions (Chemistry)

$$\frac{dg_i}{dt} = f_i(g_1, g_2, \cdots g_n)$$

Change of gene activity with time.



Lewis, Slack and Wolpert (1977)
Slack (1991)

Morse Smale Systems

- Mathematically, Waddington landscapes are linked to Morse Smale Systems.
- Morse Smale system assume structural stability (small perturbations don't change the qualitative dynamics)

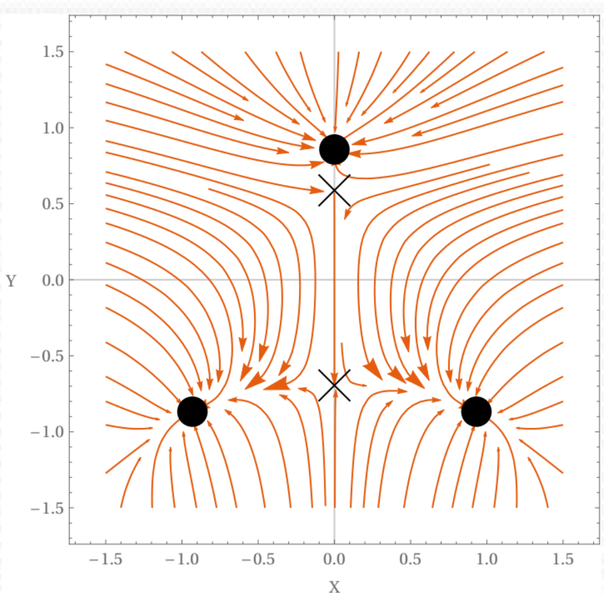
$$\dot{x_i} = v_i(x_k)$$

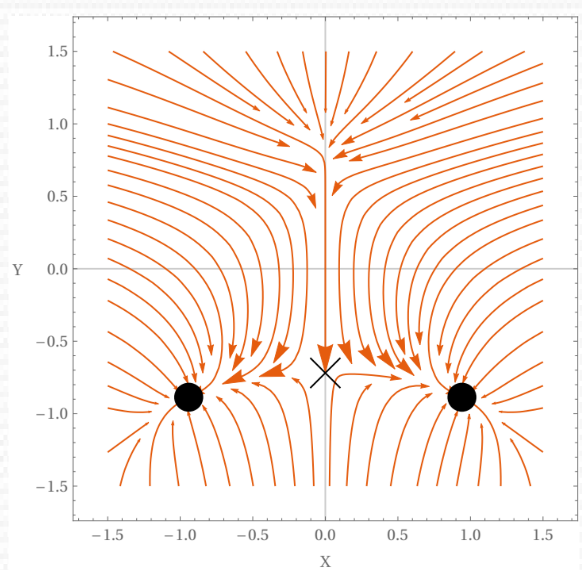
$$\dot{x_i} = -\sum_j g_{ij} \partial_j F$$

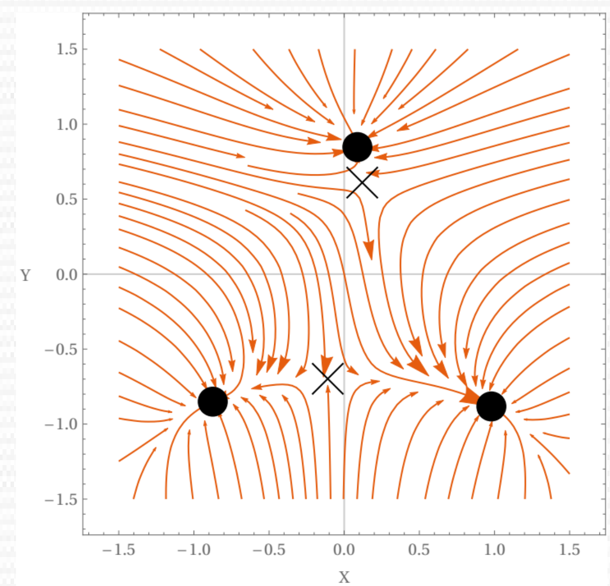
Rene Thom (1972)
Smale (1961)

Parameterize the Landscape

- You need to parameterize the landscape. Mathematics is agnostic to the parameter: could be decay rates, rate coefficients, concentration of a signaling molecule. Two bifurcations are *generic*: saddle-node and heteroclinic flip.

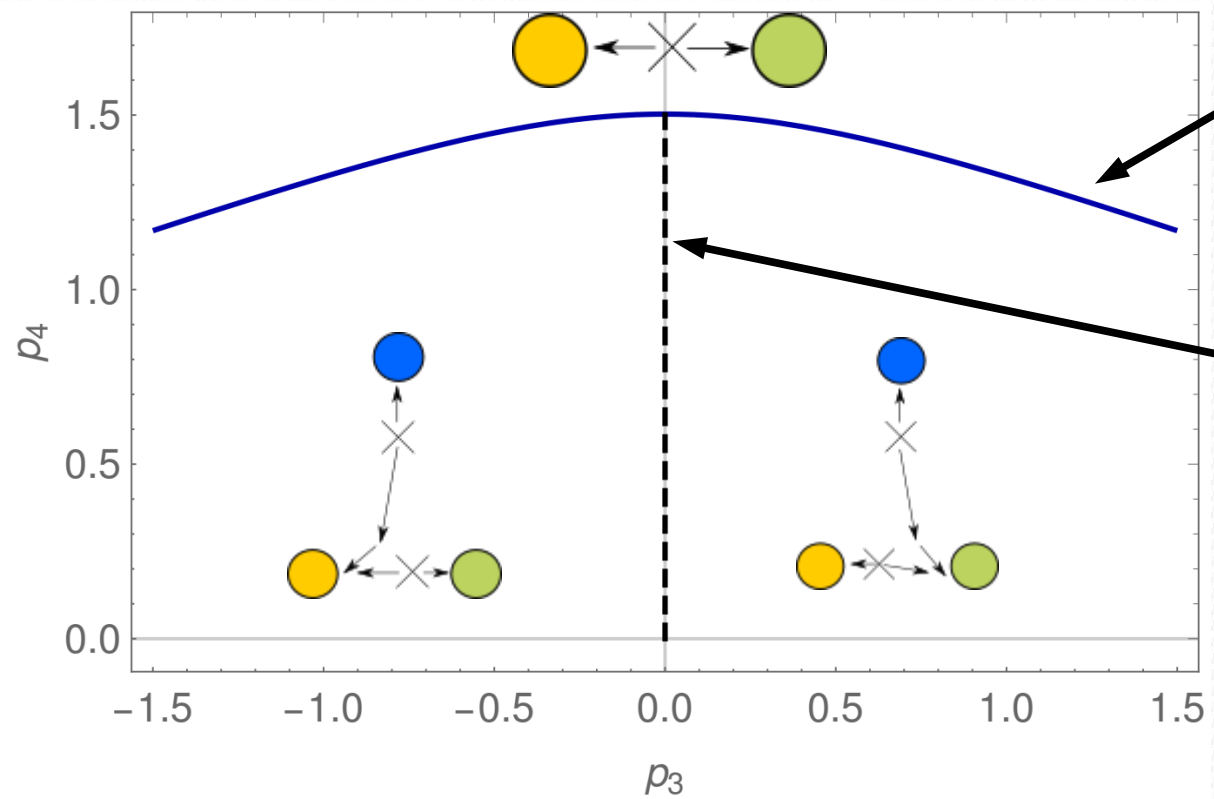






Bifurcation Theory (cont.)

In a two parameter space, there is a curve of bifurcations.



Saddle node

Heteroclinic Flip

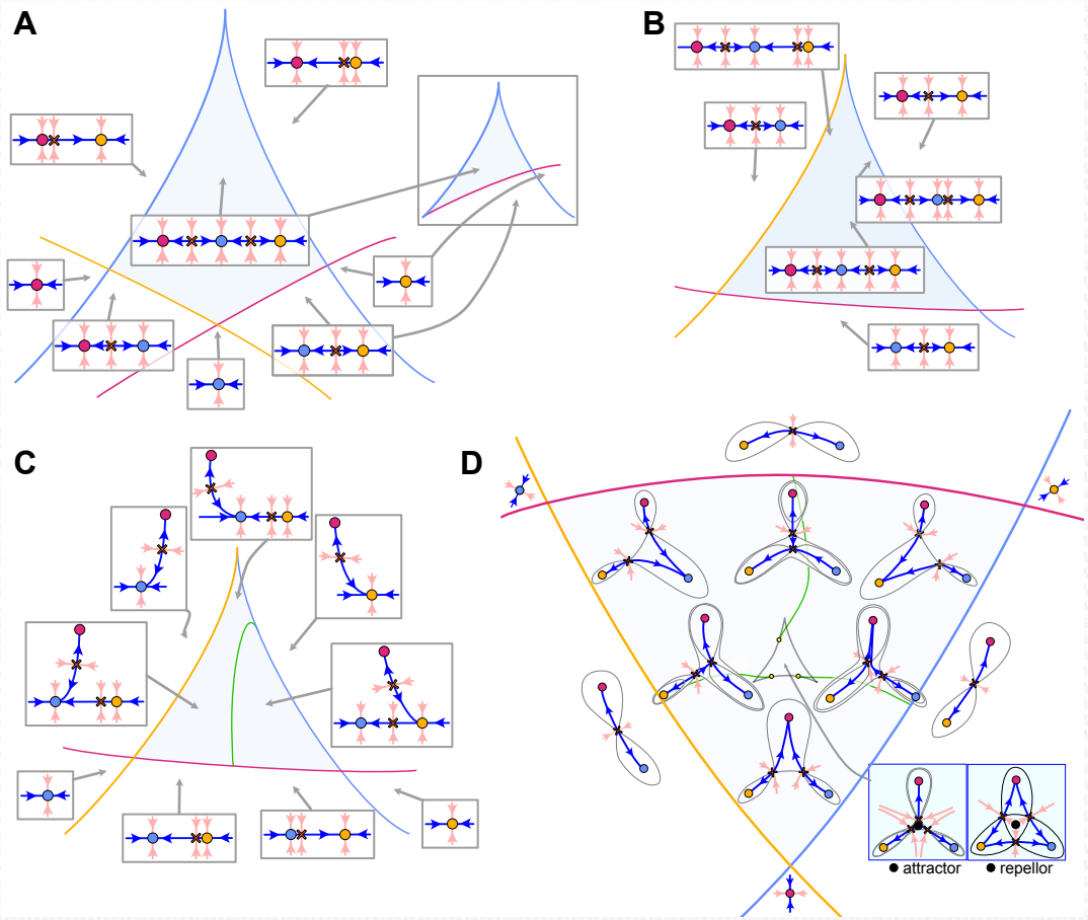
Minimal "phase" diagrams

Dual Cusp

Standard Cusp

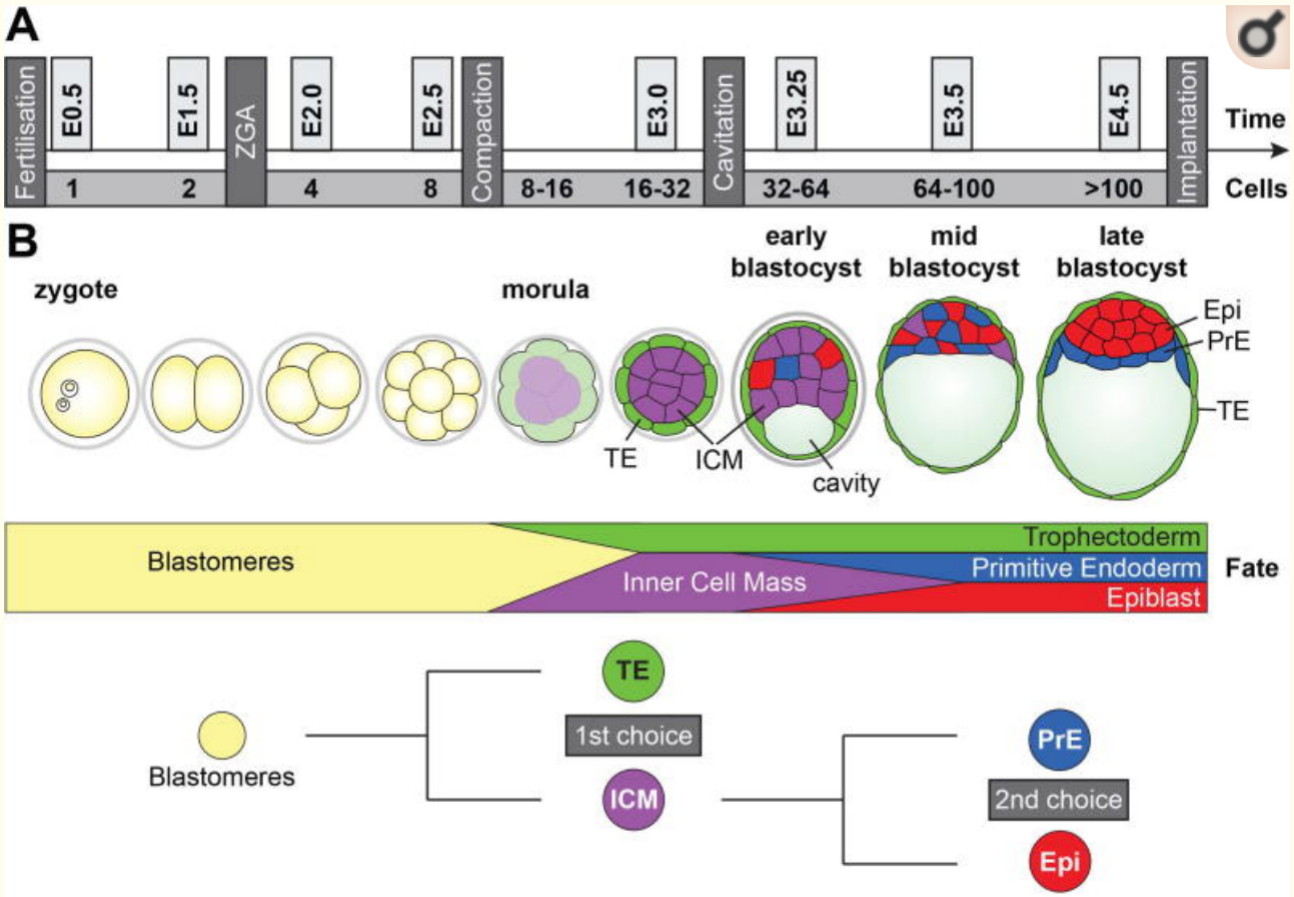
Standard Cusp with Flip

Elliptic Umbillic



D. Rand, A.Raju, M. Saez, F. Corson, E Siggia PNAS (2021)

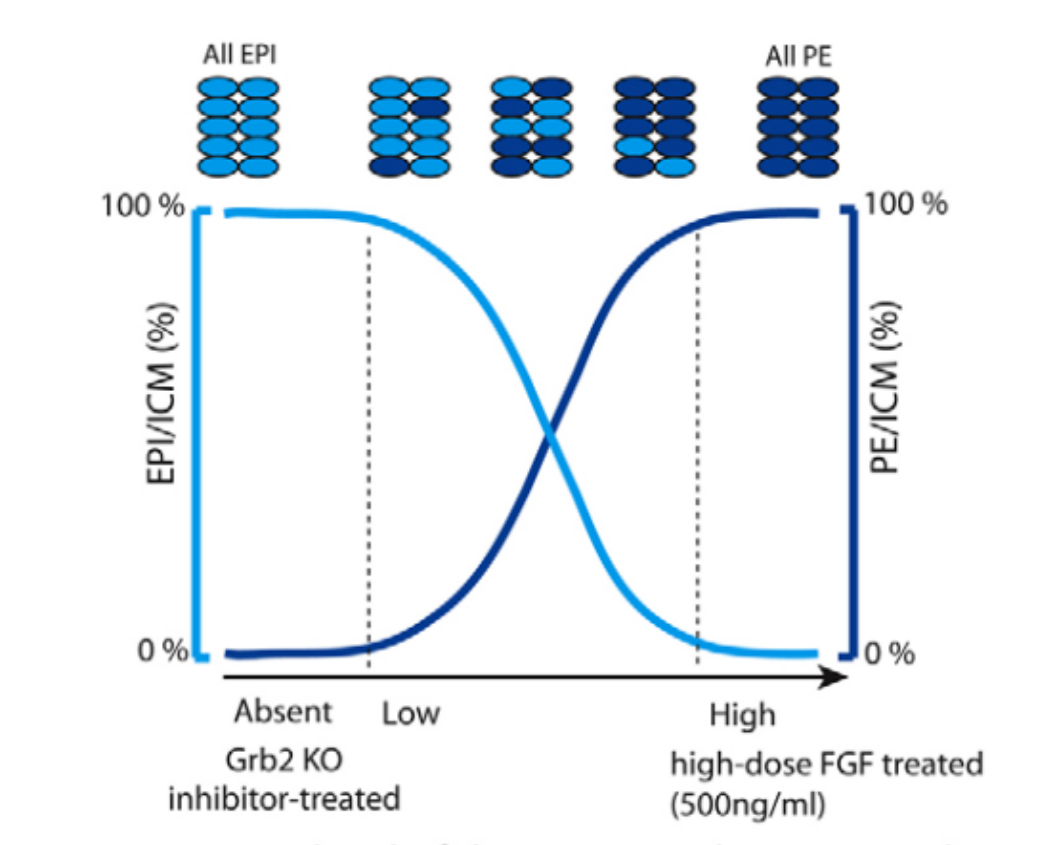
Mouse blastocyst development



Simon et al Wiley (2019)

FGF over-expression experiments

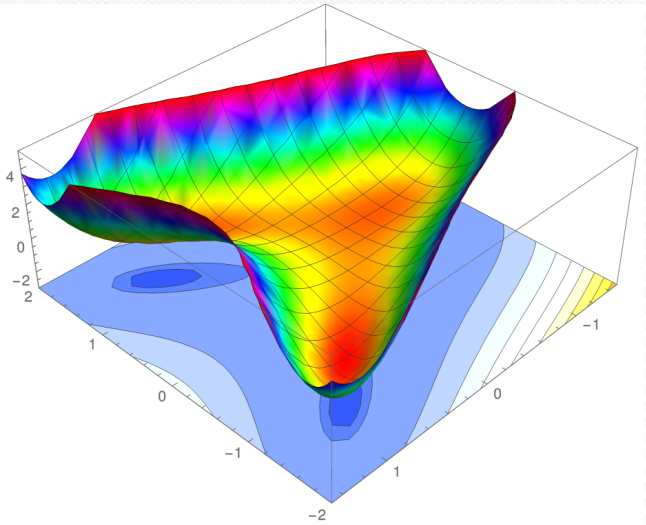
- Adding FGF leads to all PrE. Adding inhibitors or knocking out receptors leads to all Epi.

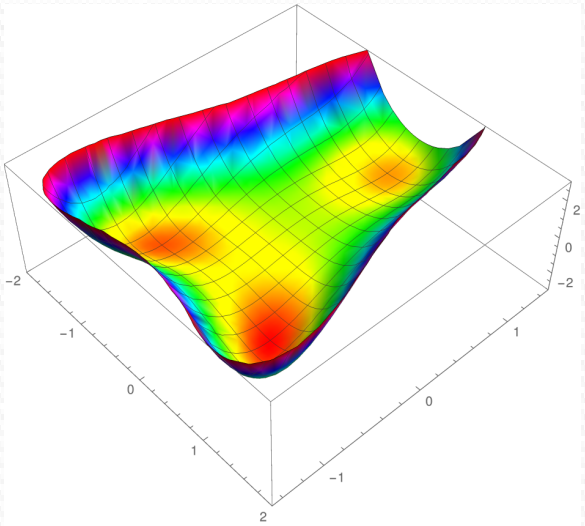


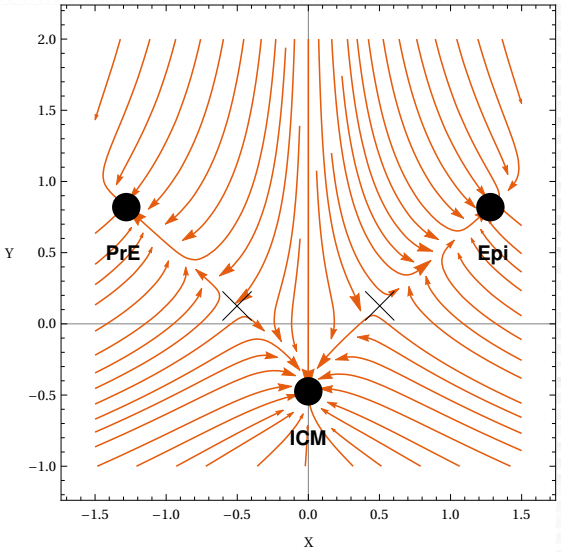
Yamanaka et al (2010)

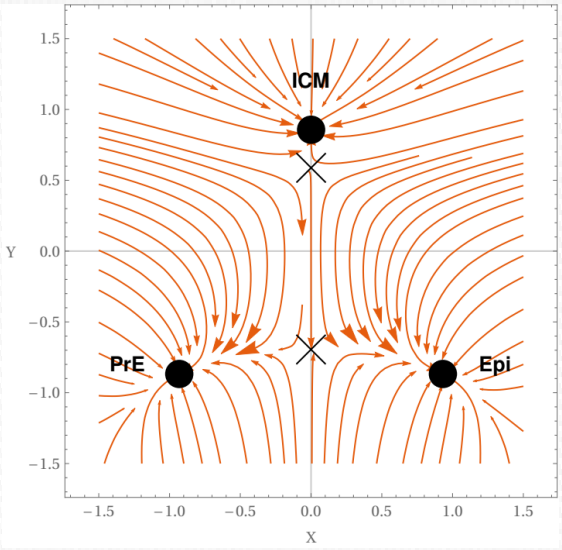
Geometric model

How are the three fates connected?



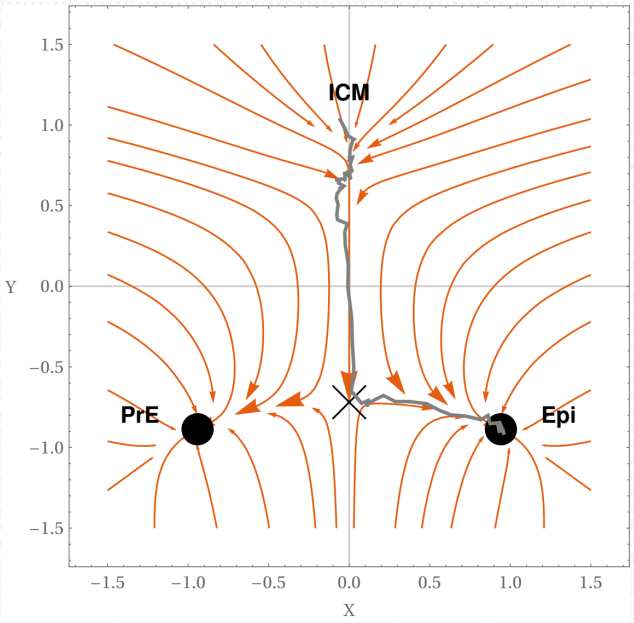




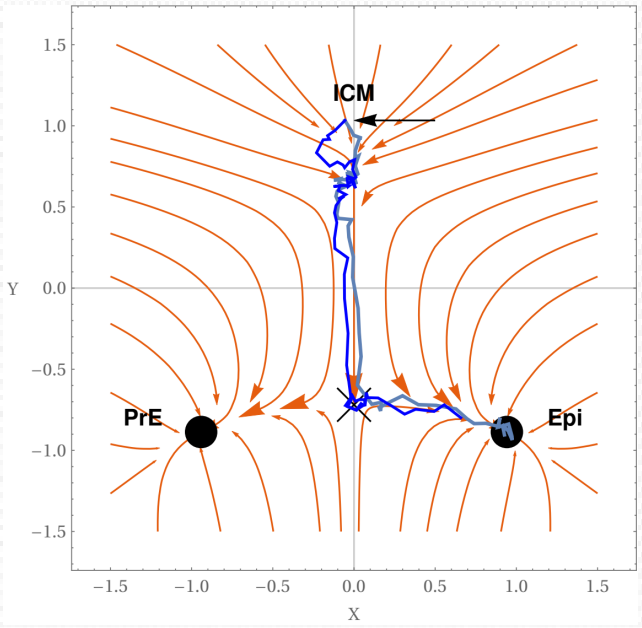


Time-dependent perturbations are informative

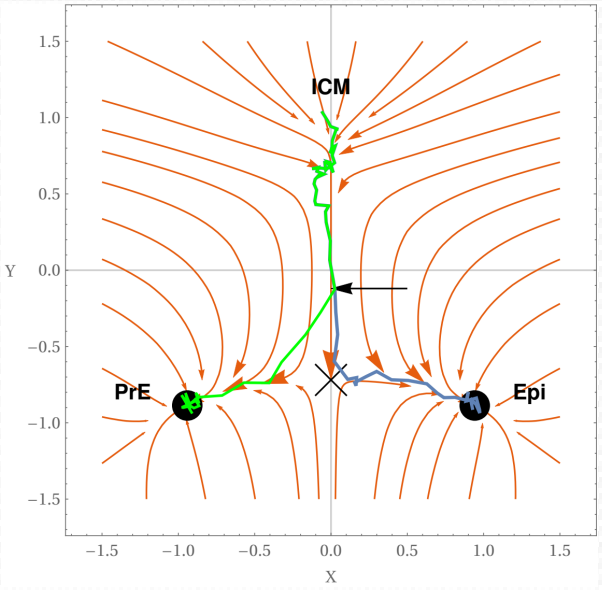
- Different parts of the trajectory have very different sensitivities to an Fgf perturbation.



"wild-type"



Early Fgf



Late Fgf

Conclusions

- Waddington's metaphor can be converted to a mathematical statement
- It is possible to classify models of cell fate specification in low dimensions into "normal forms" but this universality in dev. biology very different from physics!
- Potential models are a minimally parameterized way to fit data.