Gene Regulation in the Context of EvoDevo

The Vertebrate Skeleton as a Case Study

Larousse, 1922

Paul Scherrer Institute

Sep 22th 2022

Patrick Tschopp

University of Basel

Endless forms most beautiful

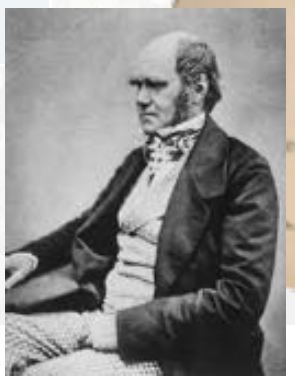
- Introduction
  - What is EvoDevo?
  - How are cell fate decisions controlled?
  - Gene regulation at single-cell resolution
- Two “vignettes” from the lab
  - The gene regulatory logic of skeletal progenitor specification
  - Patterning-relevant cell fate decisions in digit development

Endless forms most beautiful

"…from so simple a beginning endless forms most beautiful and most wonderful have been, and are being, evolved."

Charles Darwin

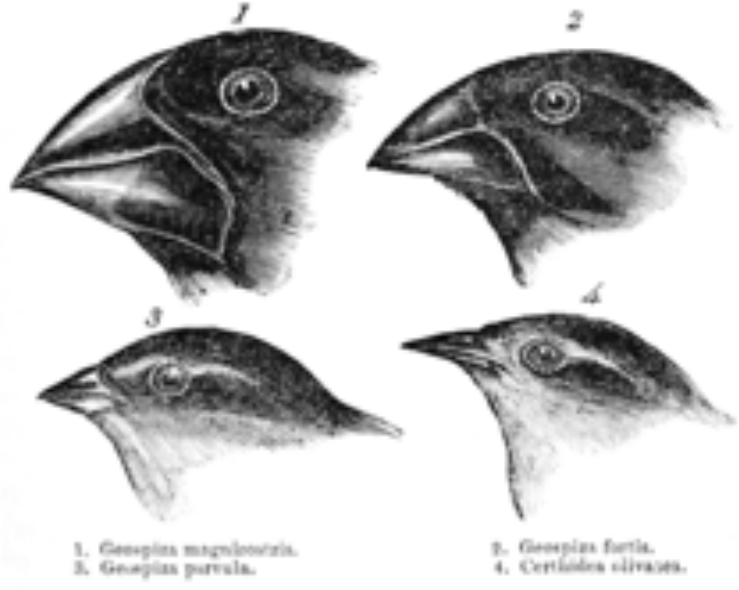
Alfred Russel Wallace



Animals are not fixed entities

artificial selection

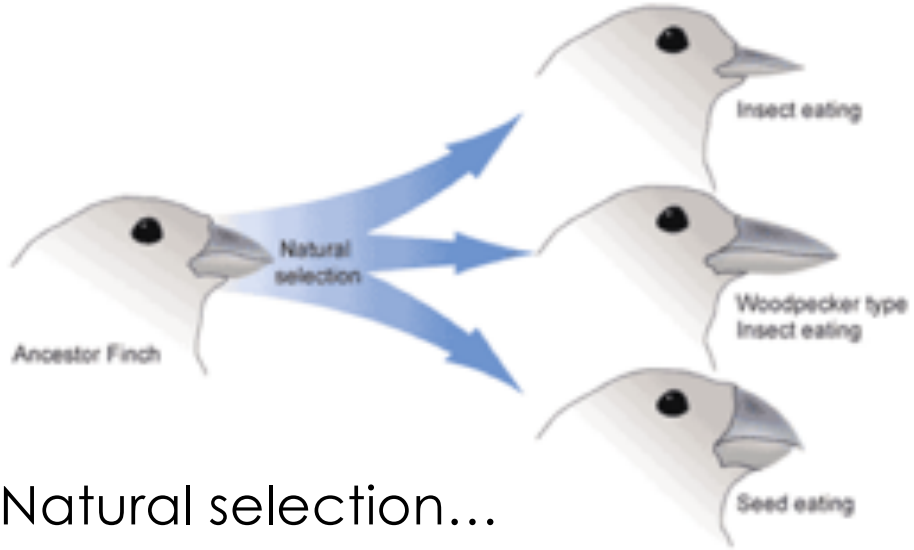
pigeon breeds



natural selection

Darwin finches

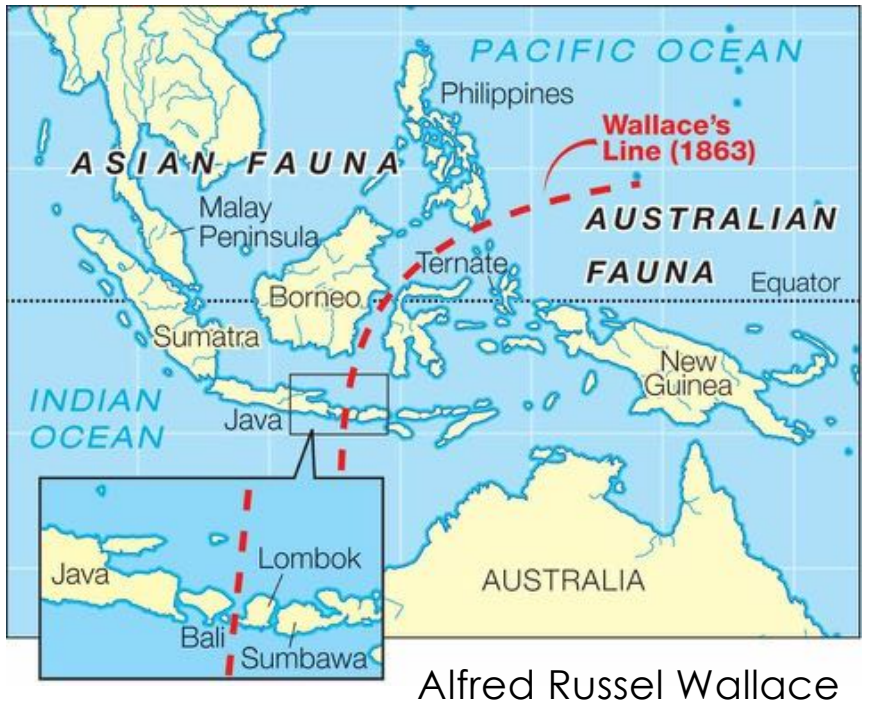
Change is heritable



Natural selection…

"descent with modification"
Charles Darwin

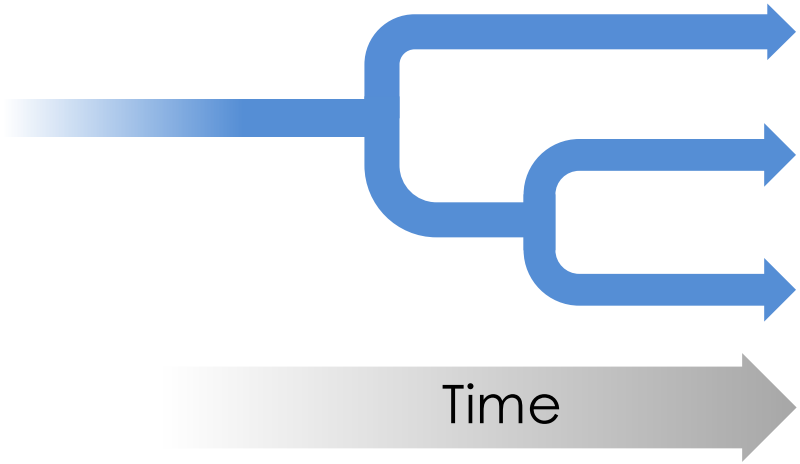
…and reproductive Isolation



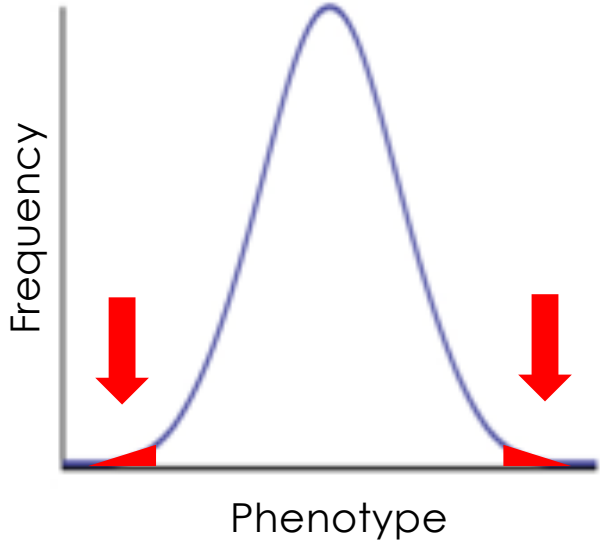
Alfred Russel Wallace

Diversity on two timescales

Evolution



Population/
Species



Individual

"translate" genetic diversity into phenotypic diversity

Development

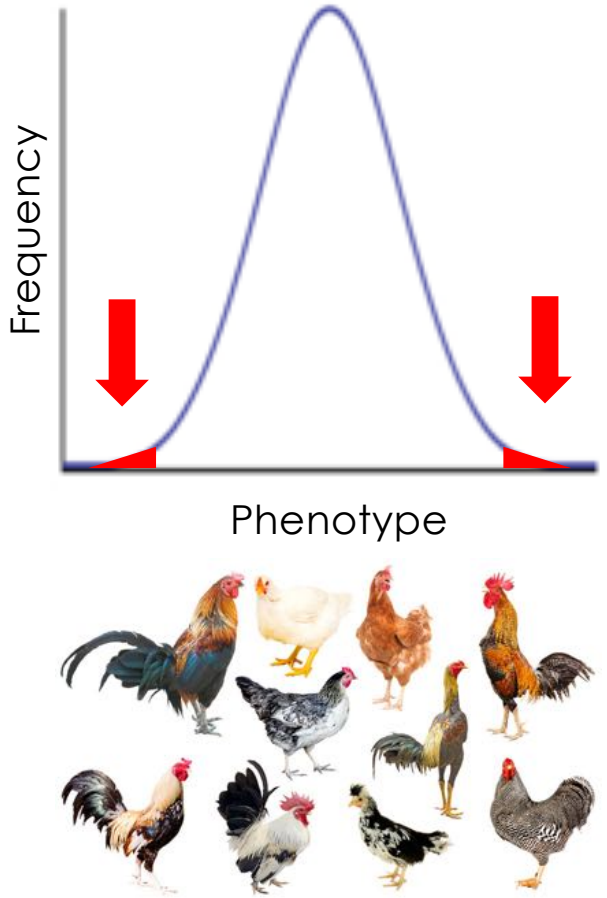
Diversity on two timescales

«EvoDevo» or
comparative DevBiol

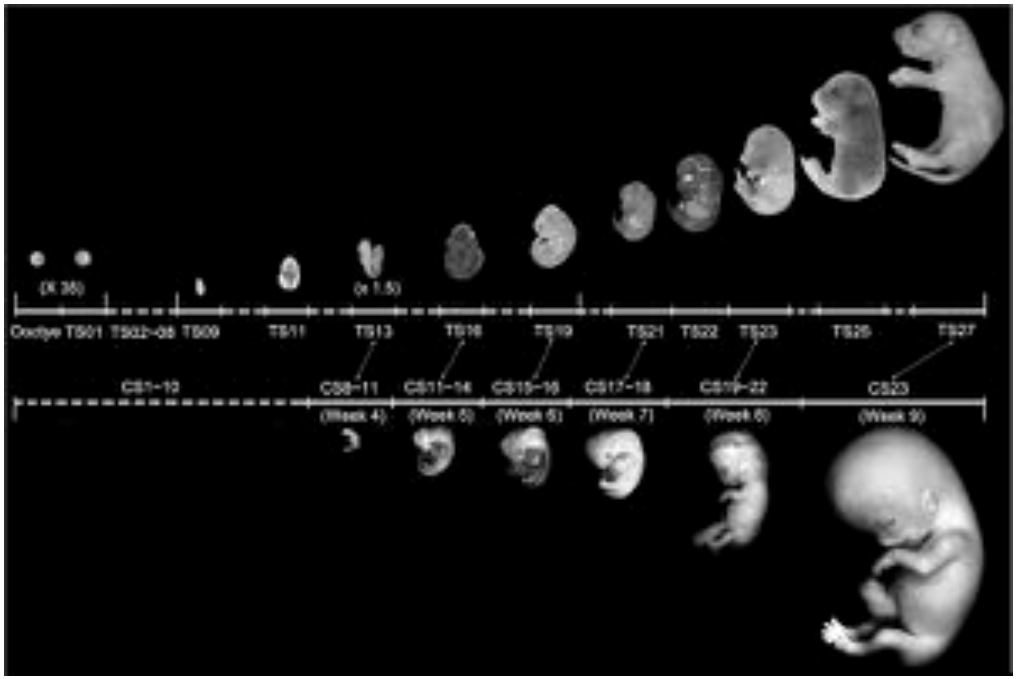
genetic and epigenetic factors?

[incl. gene expression, chromatin states, environmental variables, cell and tissue mechanics, etc...]

developmental constraint
versus plasticity?

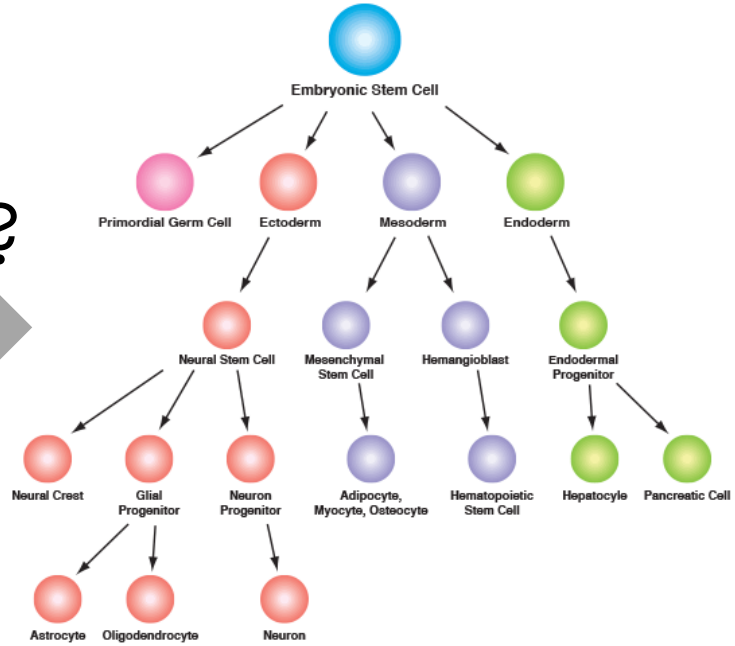


Development at cellular resolution



Morphological diversification
ACROSS species

???



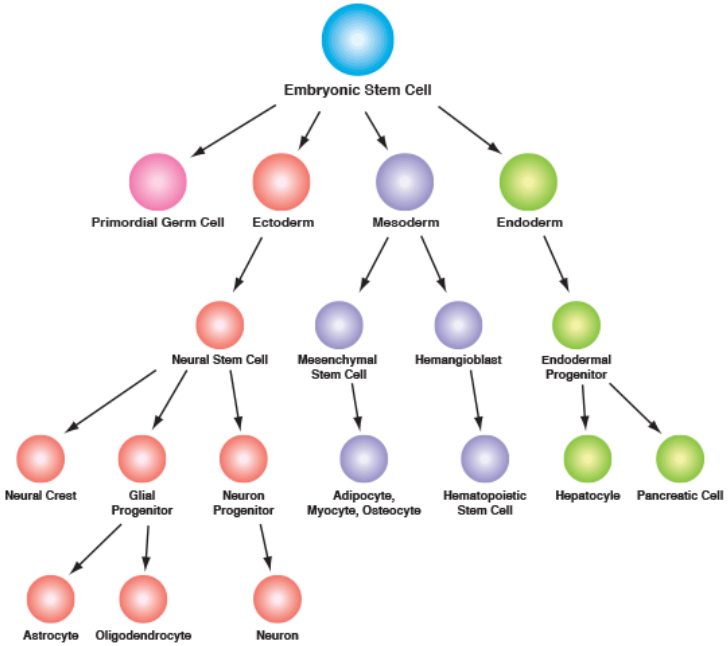
Cellular diversification
WITHIN species

Development at cellular resolution

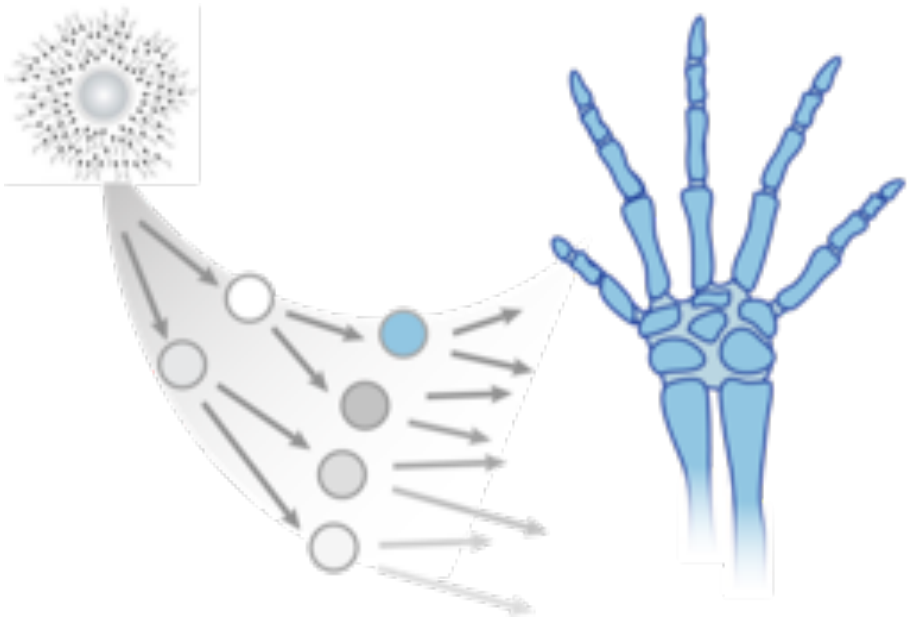
What controls cell fate decisions?

How can new cell types evolve?

How can these two processes impact morphological patterns?

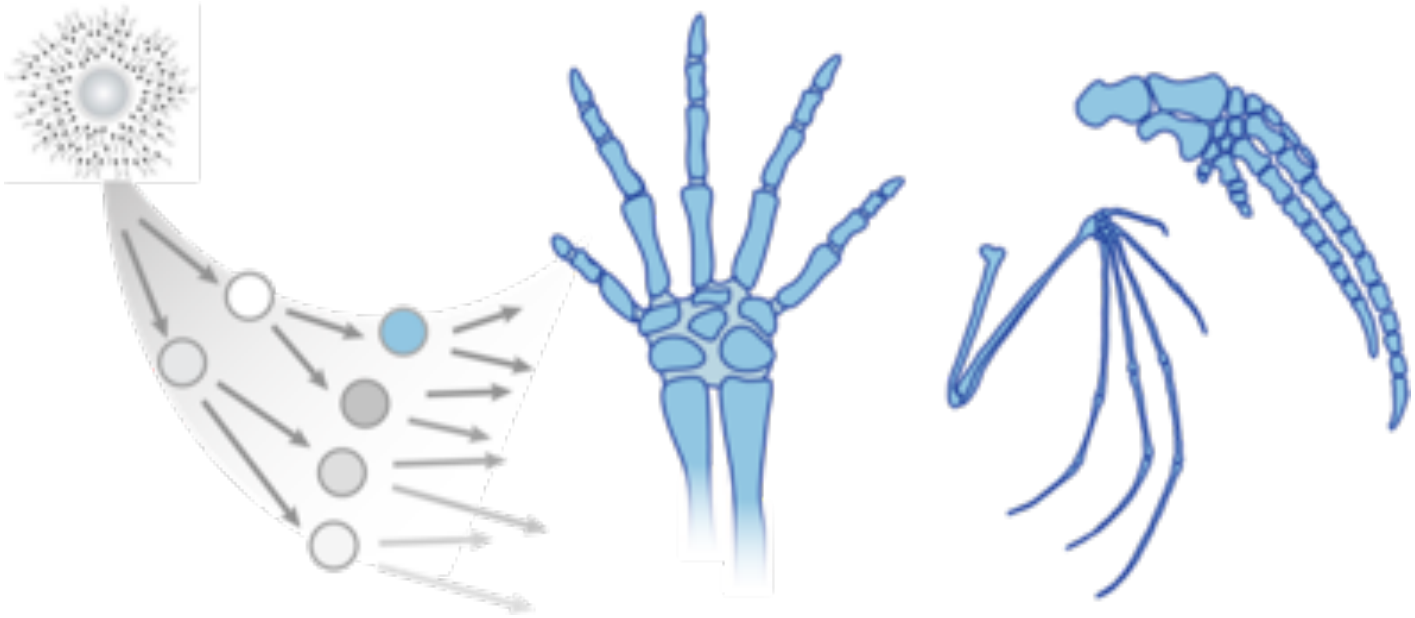


The vertebrate skeleton at cellular resolution



developmental
specification

The vertebrate skeleton at cellular resolution



developmental
specification

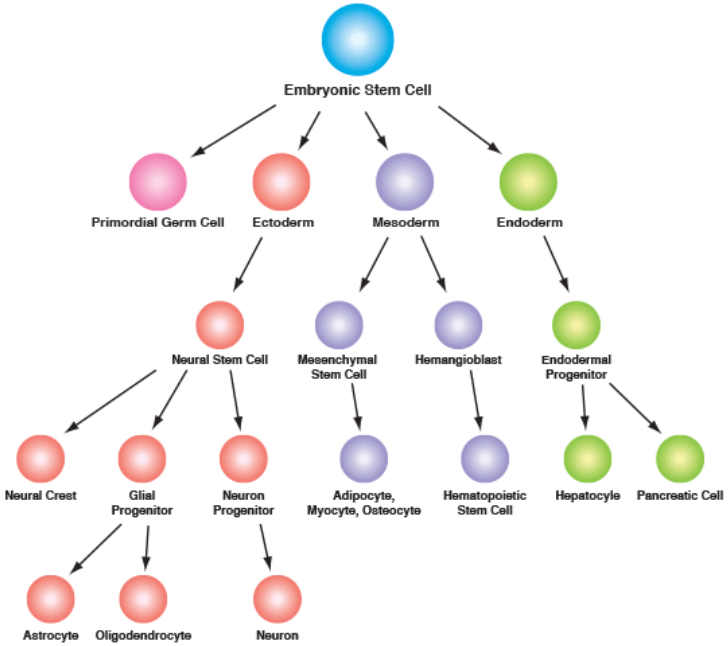
evolutionary
diversification

Development at cellular resolution

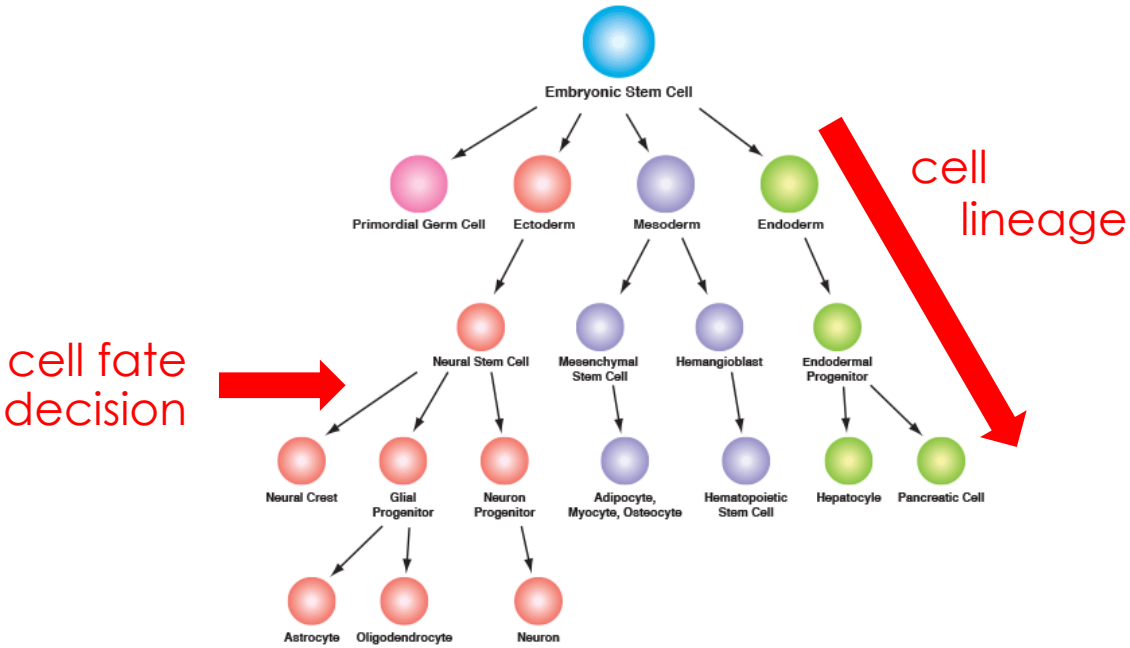
What controls cell fate decisions?

How can new cell types evolve?

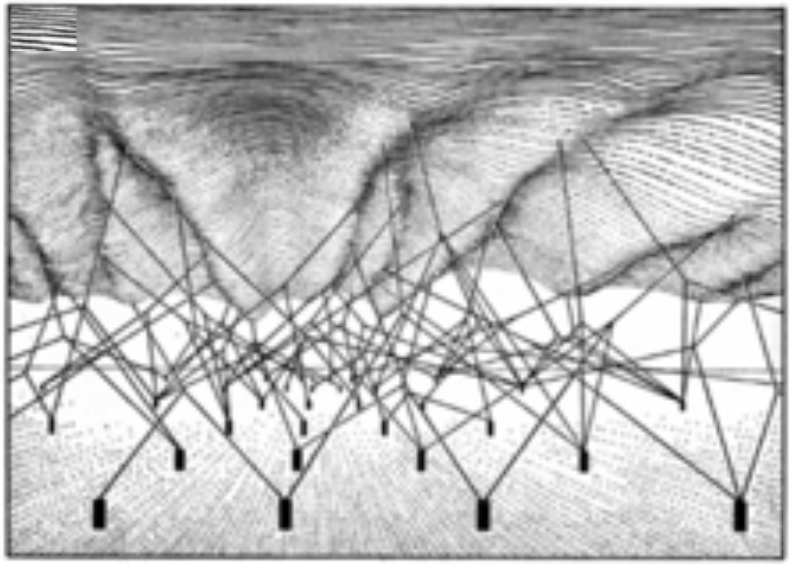
How do changes in these impact morphological patterns?



Control of cell fate decisions

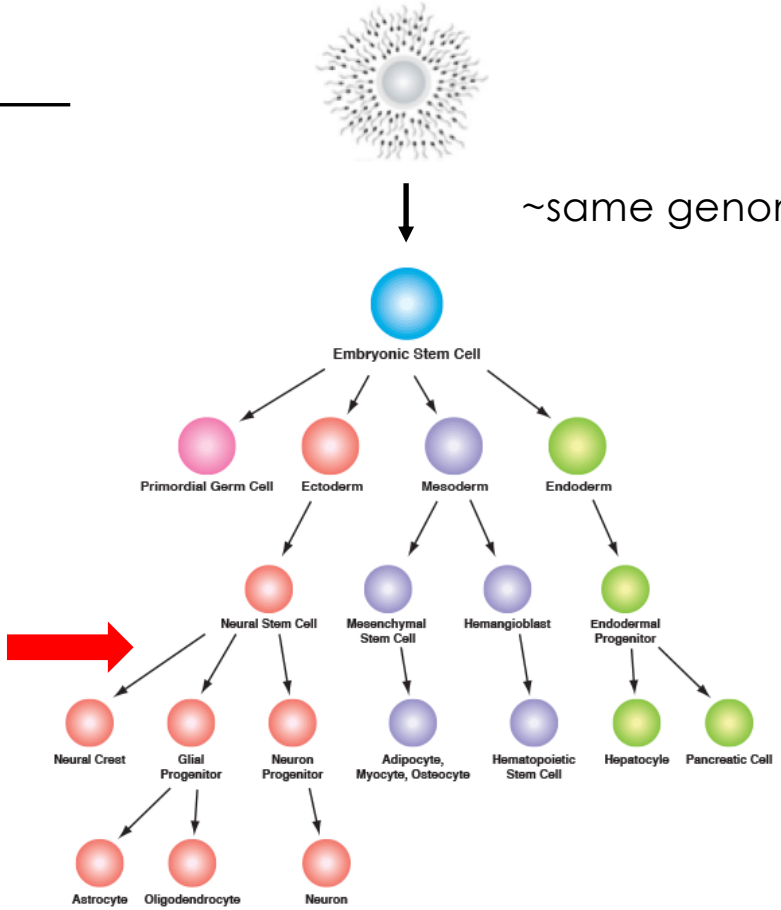


Control of cell fate decisions

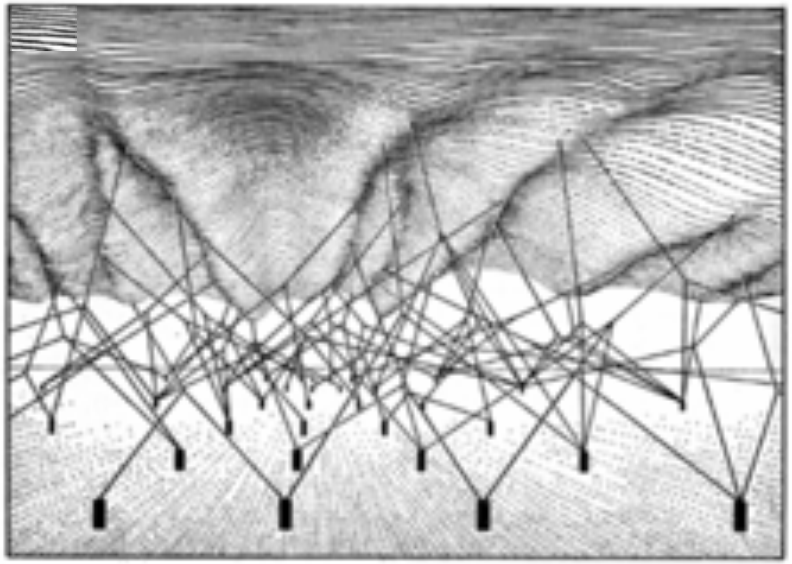


The "epigenetic landscape"
Conrad Waddington [1957]

cell fate decision



Control of cell fate decisions



The "epigenetic landscape"
Conrad Waddington [1957]

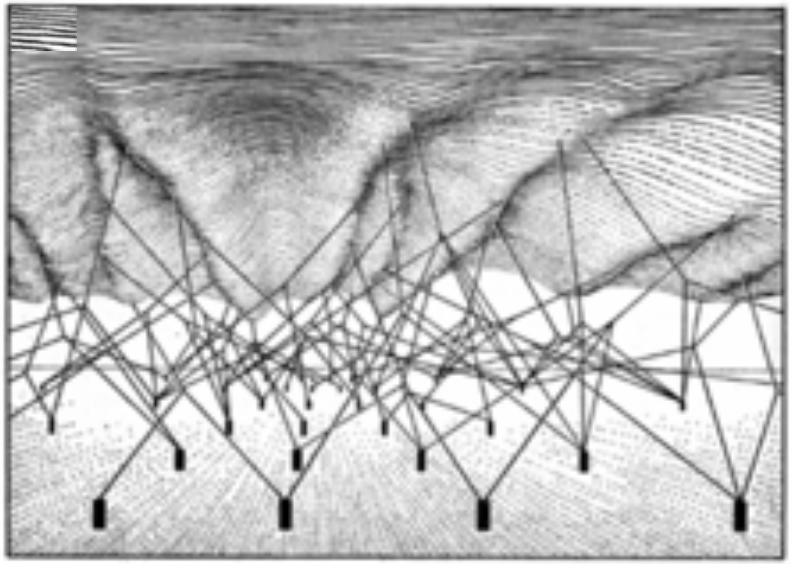
genome → ~ same for all cells [DNA]

transcriptome → cell-type specific [RNA]

proteome → cell-type specific [proteins]

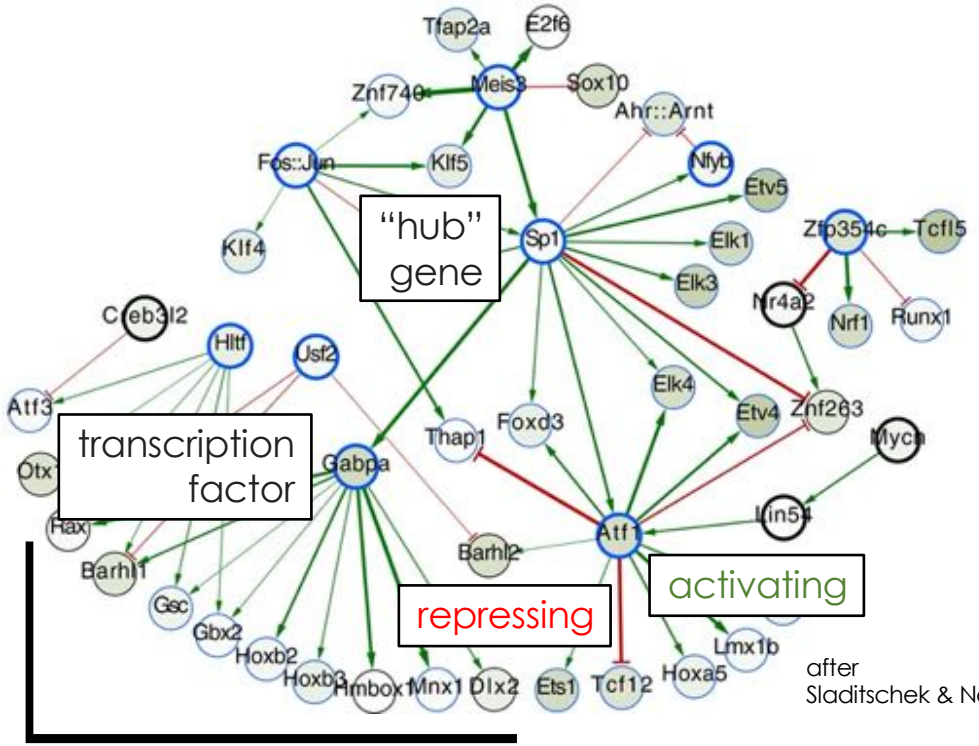
cistrome → cell-type specific [chromatin]

Control of cell fate decisions



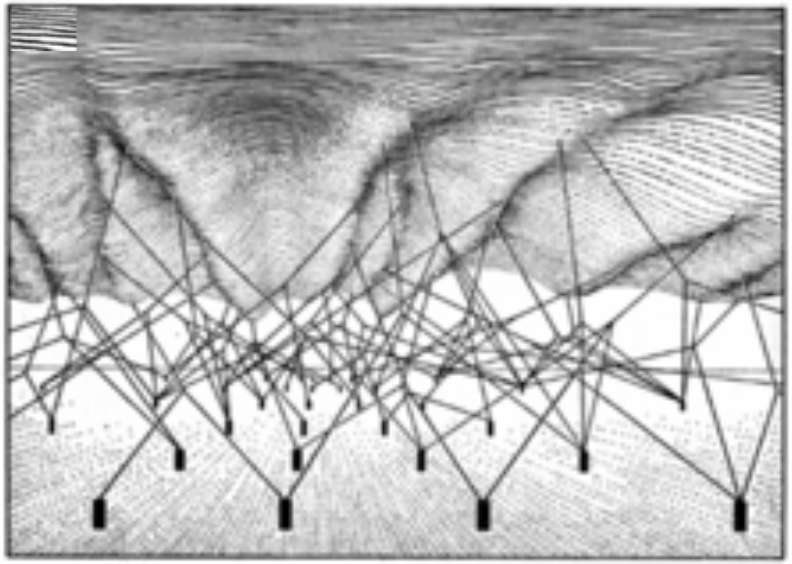
The "epigenetic landscape"
Conrad Waddington [1957]

Gene Regulatory Network [GRN]

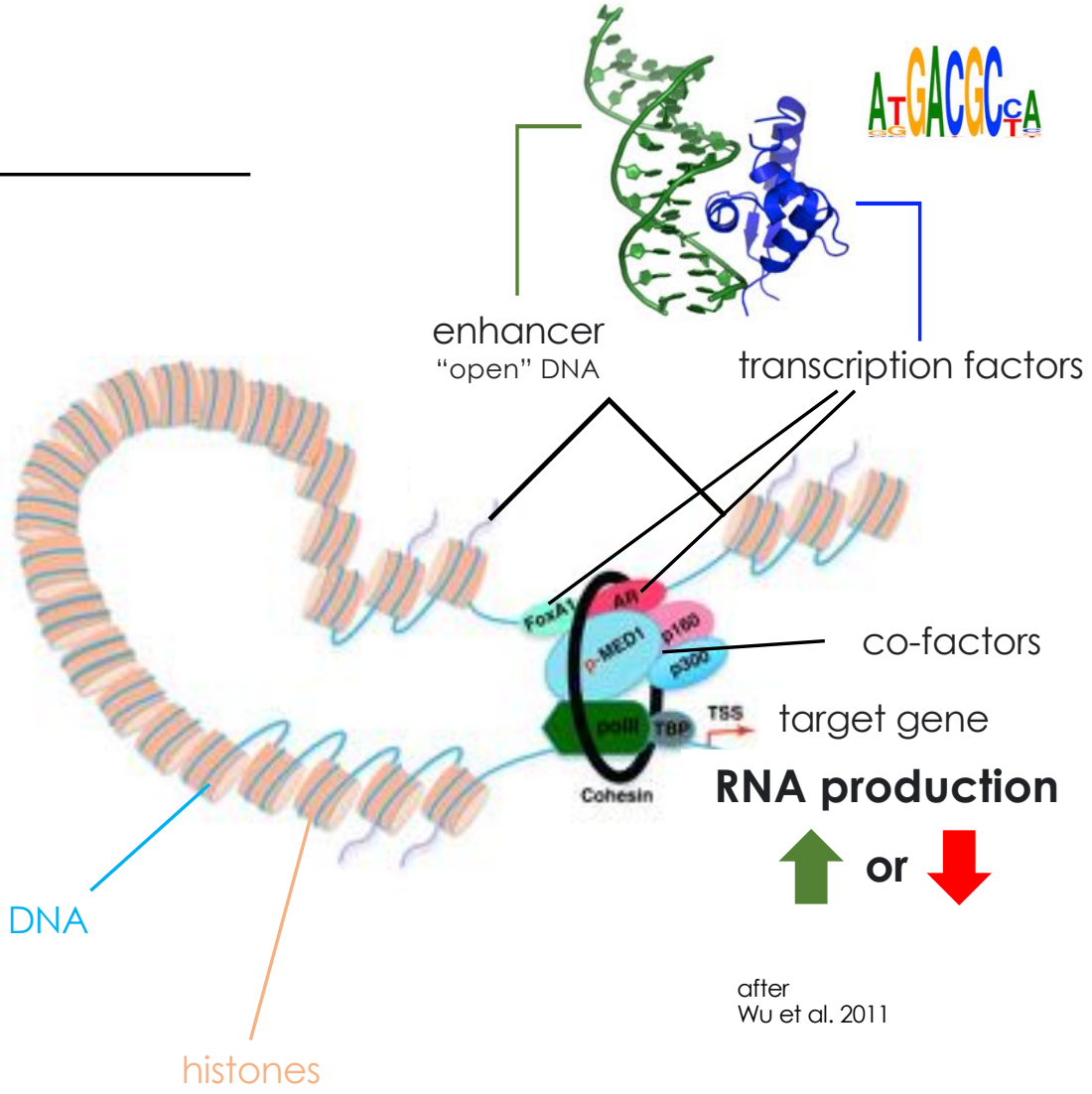


after
Sladitschek & Neveu 2019

Control of cell fate decisions

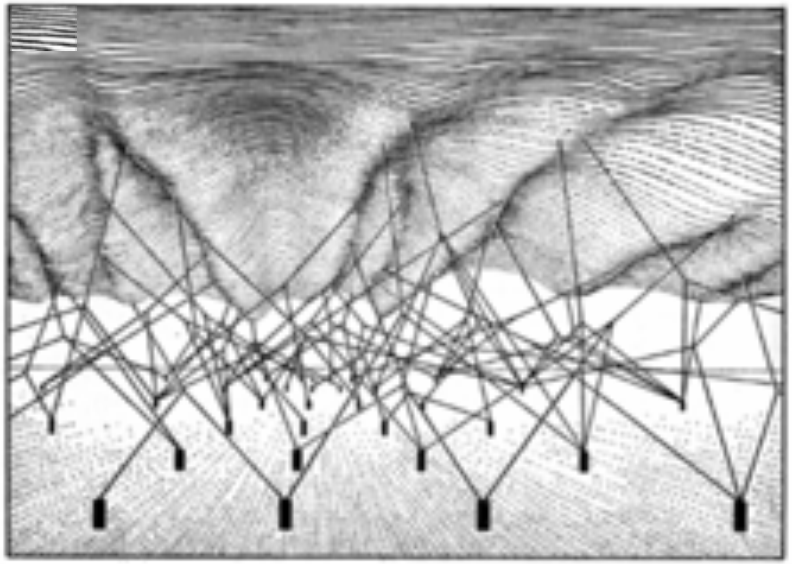


The "epigenetic landscape"
Conrad Waddington [1957]

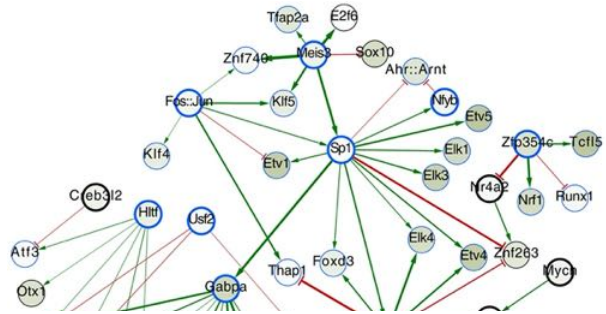


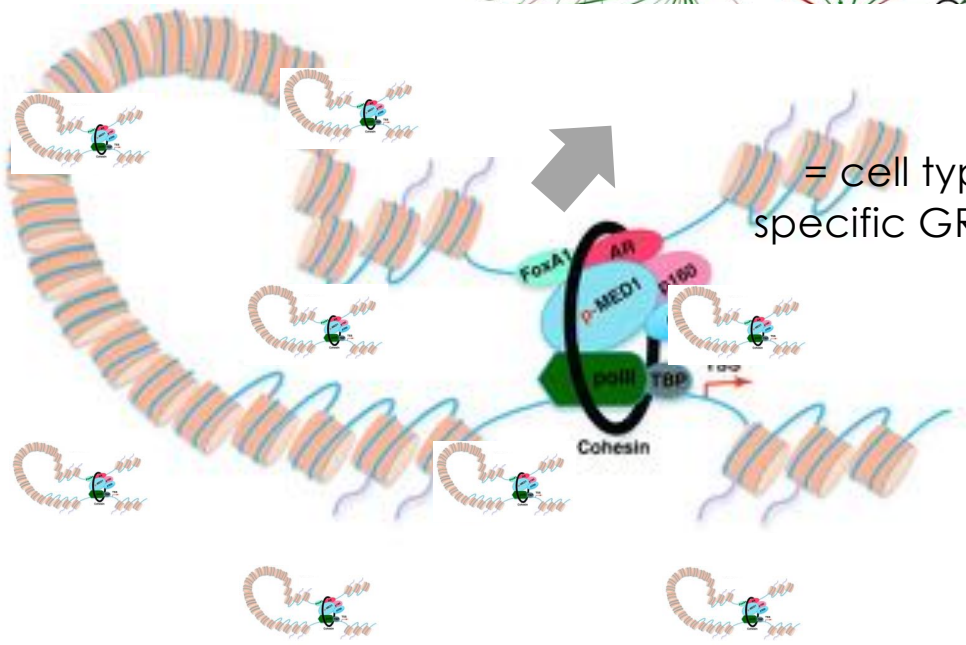
after
Wu et al. 2011

Control of cell fate decisions



The "epigenetic landscape"
Conrad Waddington [1957]

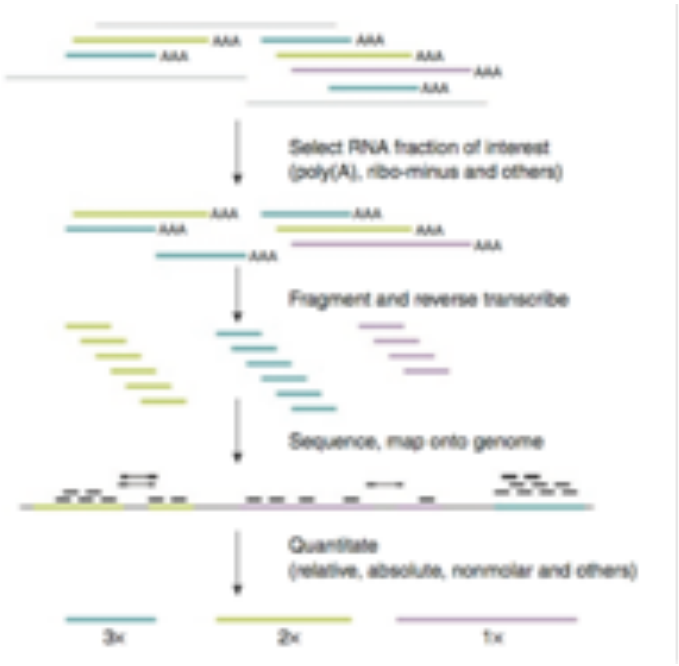


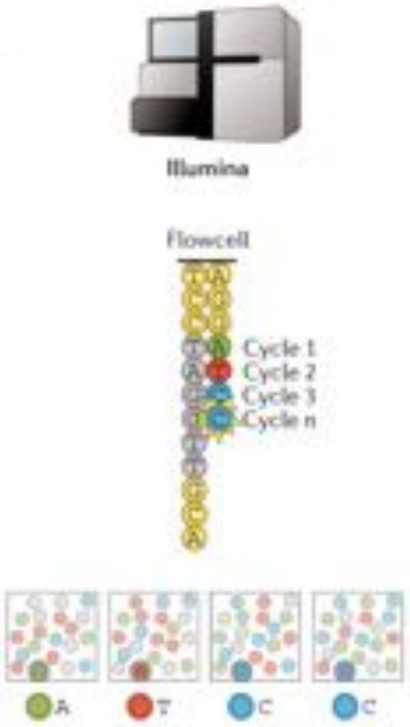


= cell type-specific GRNs

…and in different cell types

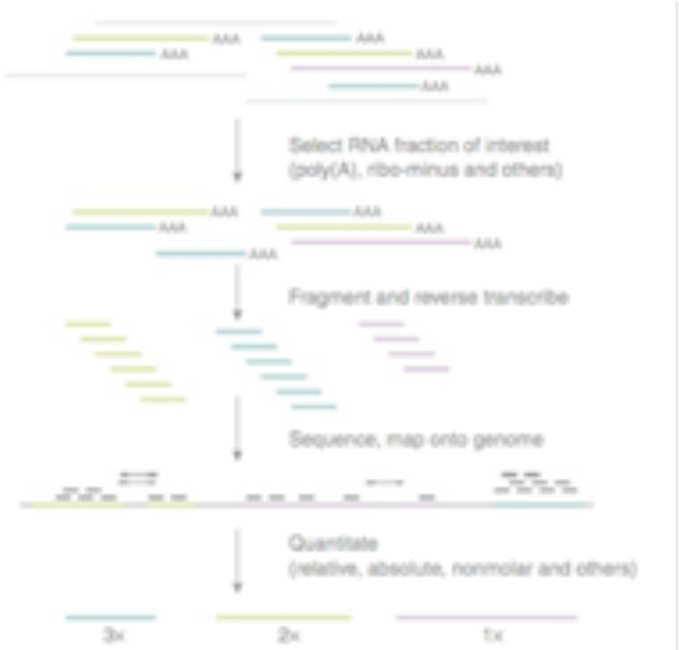
Measuring RNA…



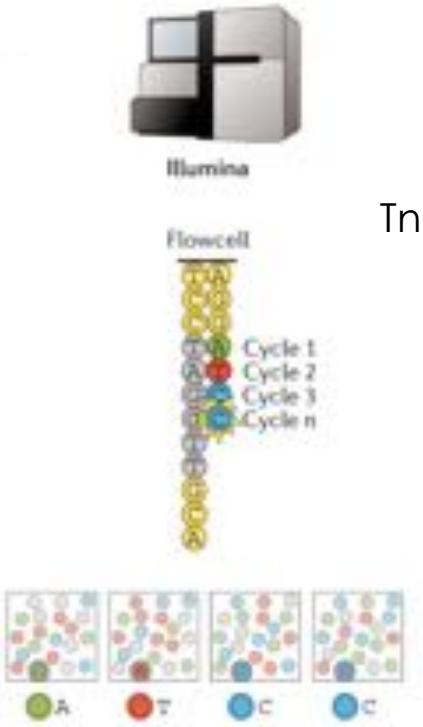


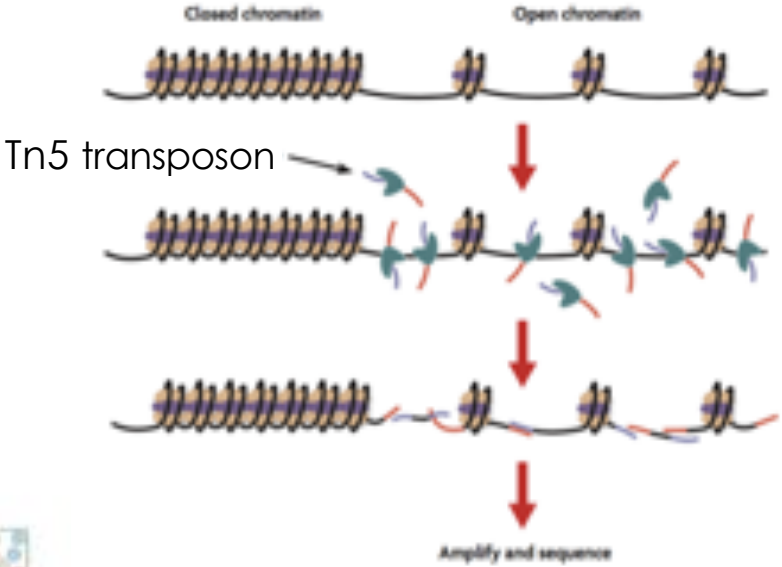
after
NYU GenCore
Nat Rev Genetics

Measuring RNA and DNA accessibility…



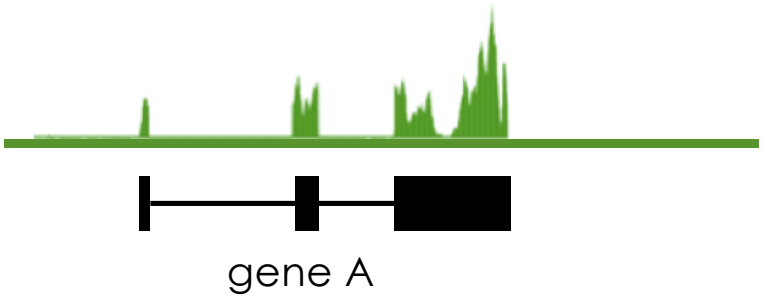
after
NYU GenCore
Nat Rev Genetics



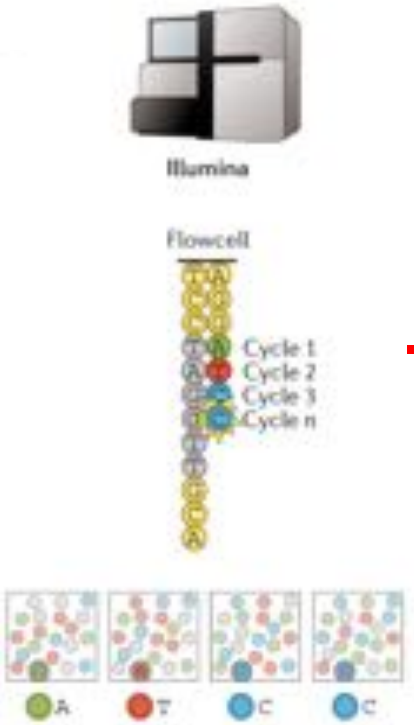


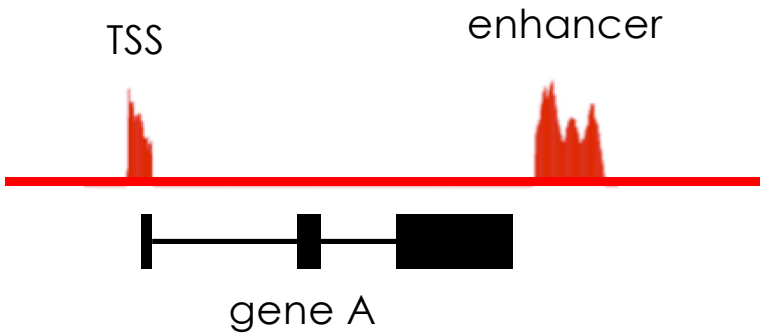
after
ActiveMotif

Measuring RNA and DNA accessibility…



RNA-seq

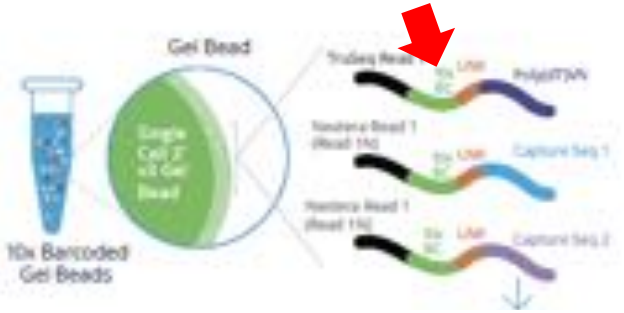


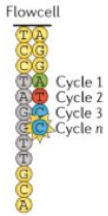


ATAC-seq

Measuring RNA and DNA accessibility with single cell resolution

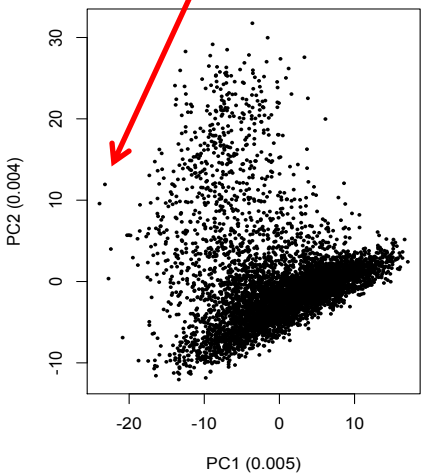
cellular DNA barcode

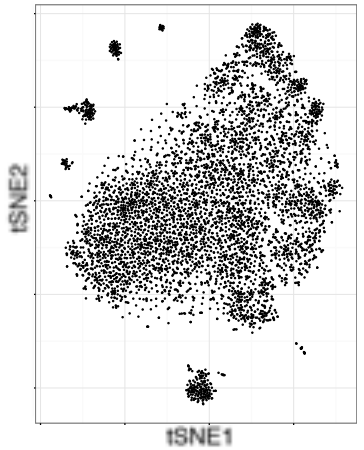




		cell 1	cell 2	cell 3	cell 4	cell 5	...	...	cell 5500	
gene 1	A2ML1_ENSGALG00000019254	0	0	0	0	0	...	...	0	0
gene 2	A4GALT_ENSGALG00000014128	0	0	0	0	0	...	...	0	0
gene 3	AAAS_ENSGALG00000013597	3	4	0	1	0	...	...	1	0
gene 4	AACS_ENSGALG00000002899	0	0	0	0	0	...	...	2	0
gene 5	AADAT_ENSGALG00000009655	1	0	1	0	0	...	...	0	0
...	...	...	...	...	...	...	...	...	...	...
...	...	...	...	...	...	...	...	...	...	...
gene 12999	ZYX_ENSGALG00000014688	0	0	1	0	1	...	...	4	3
gene 13000	ZZEF1_ENSGALG00000001546	1	0	0	0	0	...	...	0	0

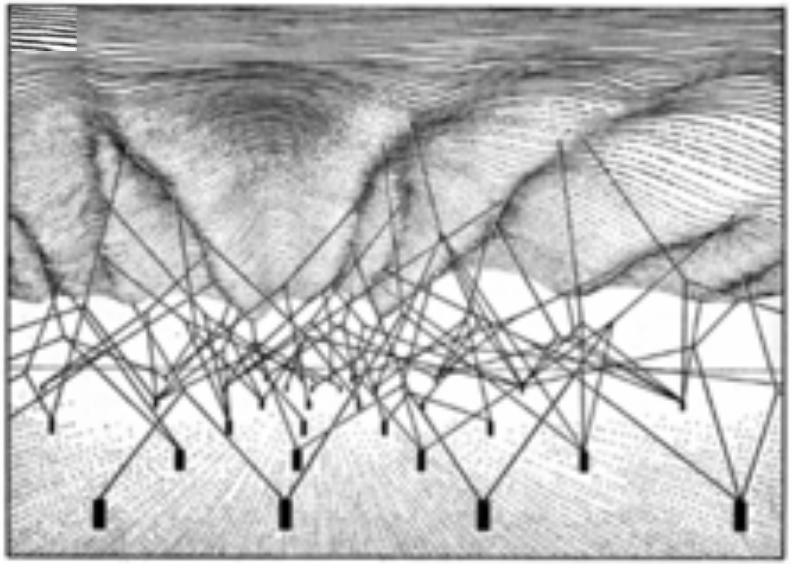
= 1 cell out of 5437 cells





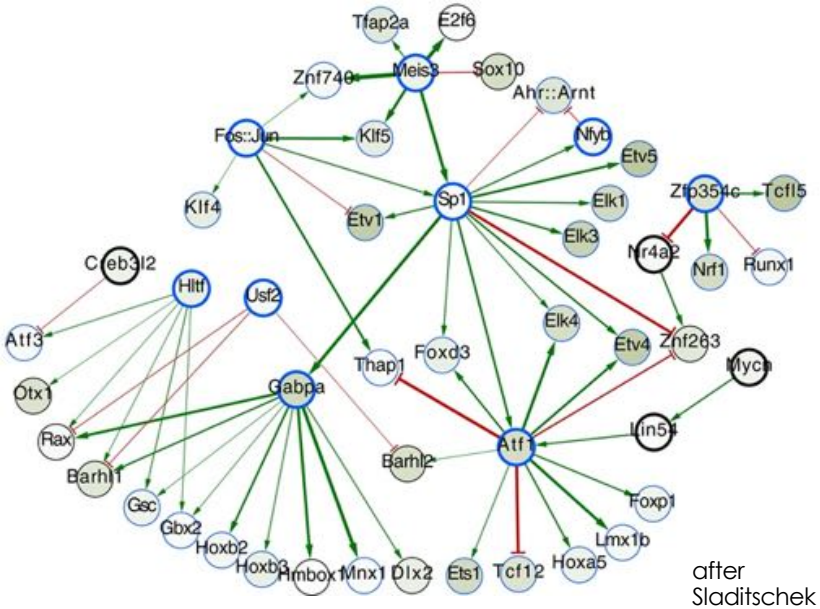
after
10x Genomics

Studying the control of cell fate decisions with single cell resolution



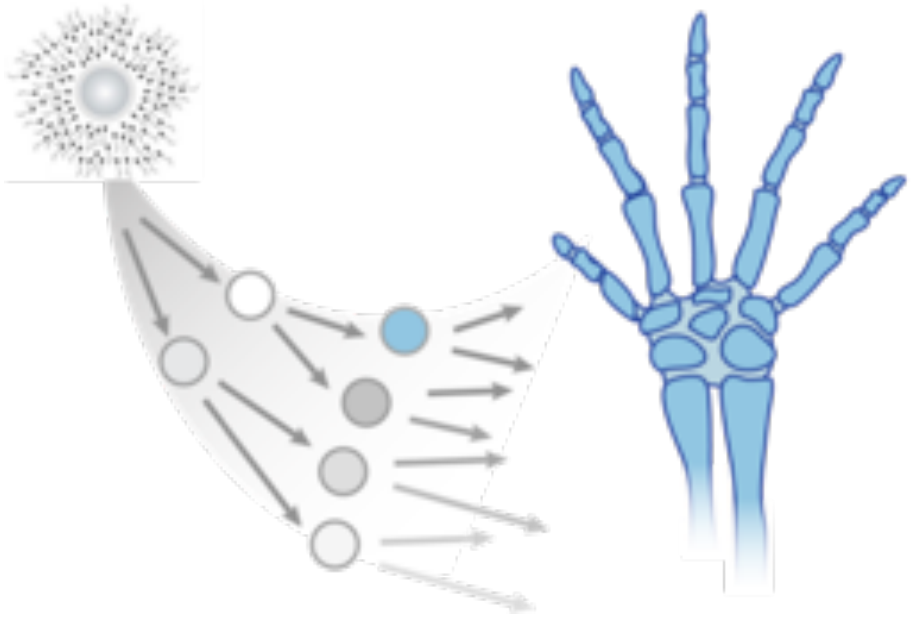
The "epigenetic landscape"
Conrad Waddington [1957]

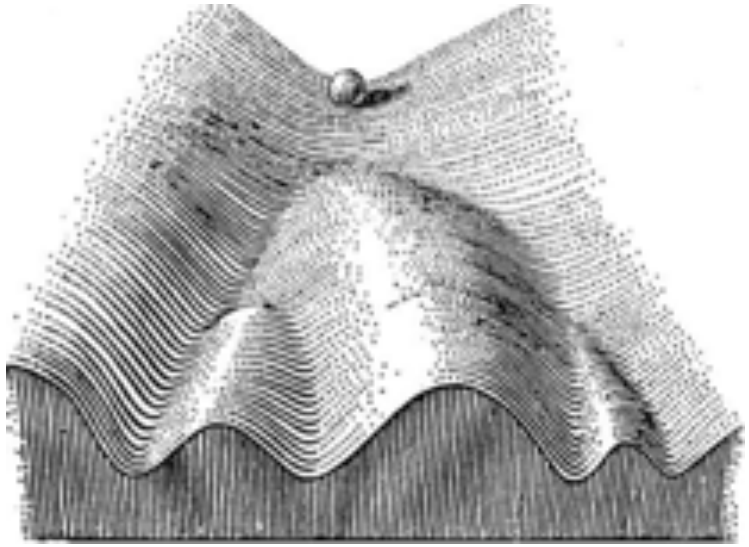
CELL TYPE-SPECIFIC
Gene Regulatory Networks [GRNs]



after
Sladitschek & Neveu 2019

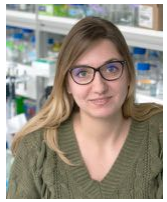
The gene regulatory logic of skeletal progenitor specification





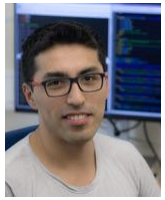
developmental
specification

Patterning-relevant cell fate decisions in digit development



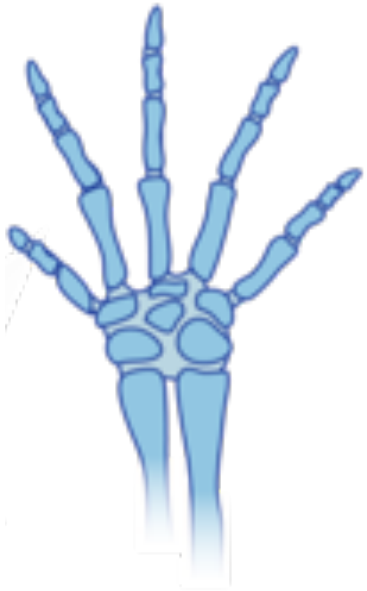
Emmanuelle Grall

Sabrina Fischer



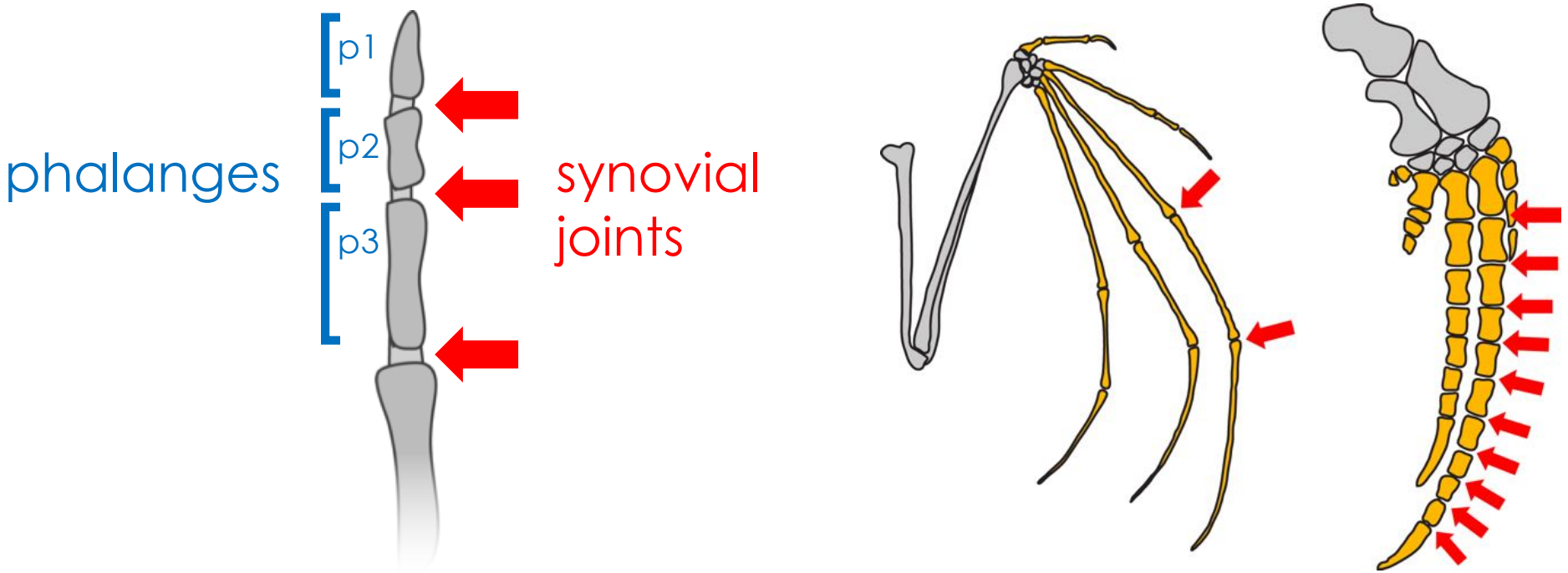
Christian Feregrino

Tom Hiscock
University of Aberdeen



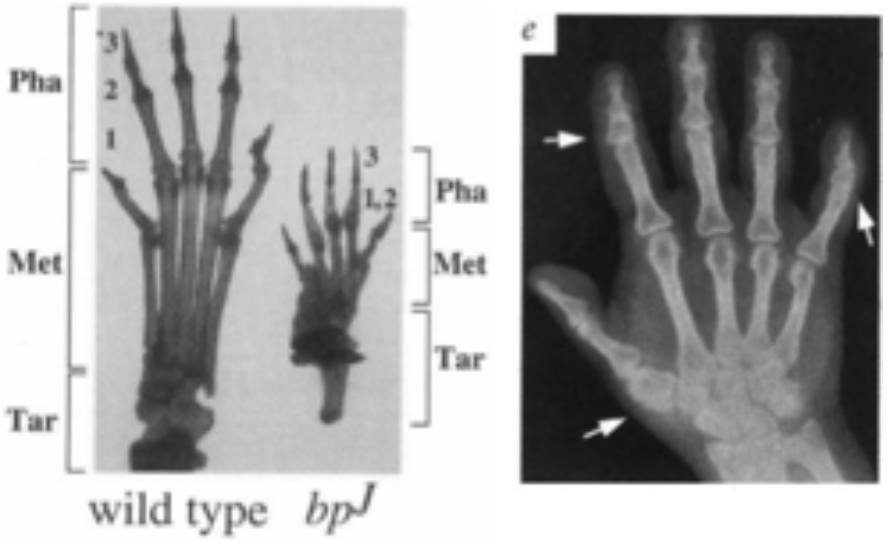
evolutionary
diversification

Tetrapod digit patterning

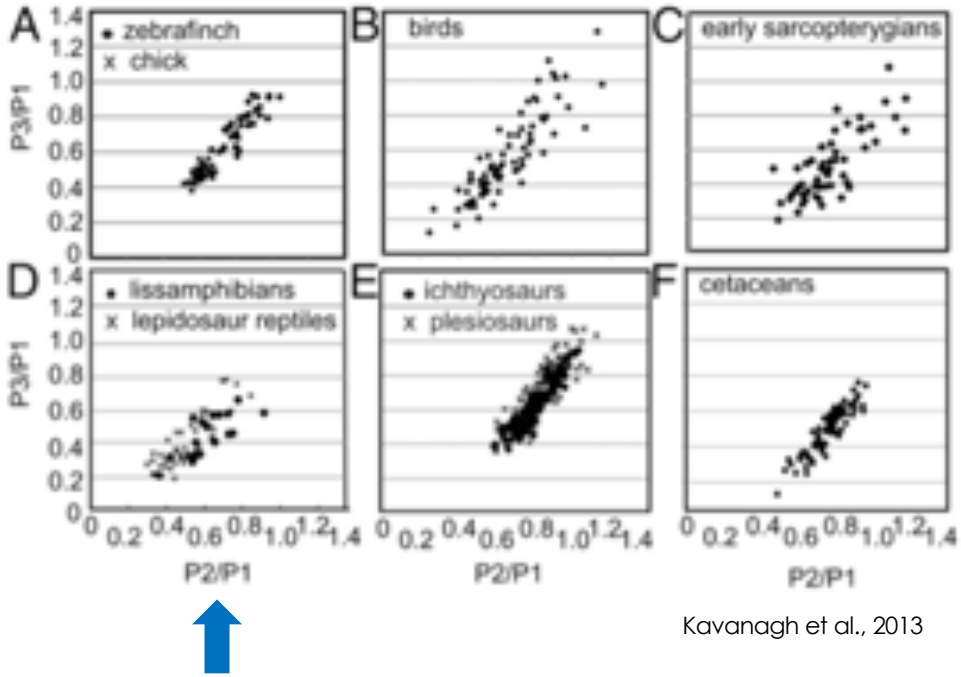


How are digit patterns specified and diversified ?

Tetrapod digit patterning



Storm et al., 1994,
Thomas et al., 1997

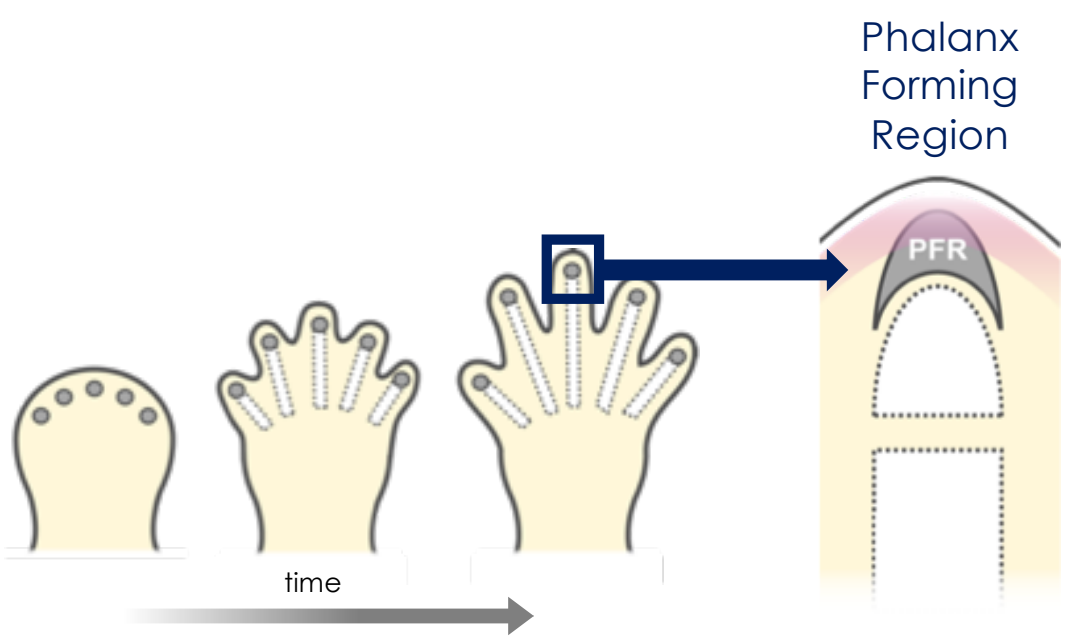


Kavanagh et al., 2013

role of
BMP/TGF-β signaling ?

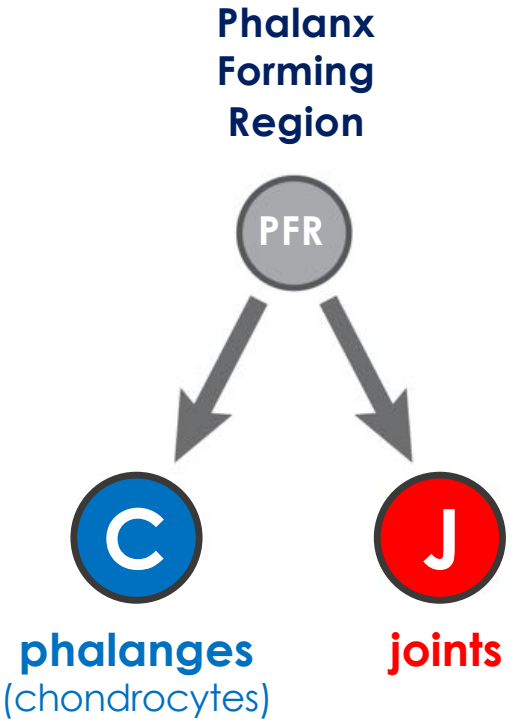
self-organizing
pattern ?

Tetrapod digit patterning



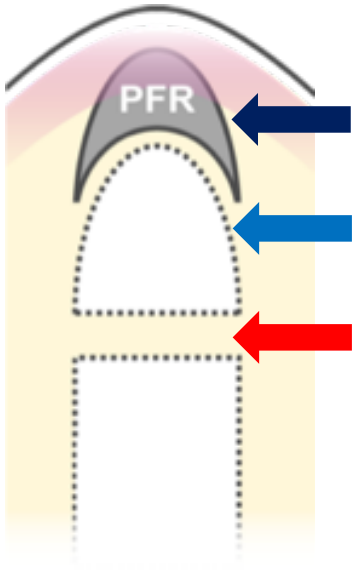
after Suzuki et al., 2008,
Hurle et al., 2008,
Hiscock et al., 2017

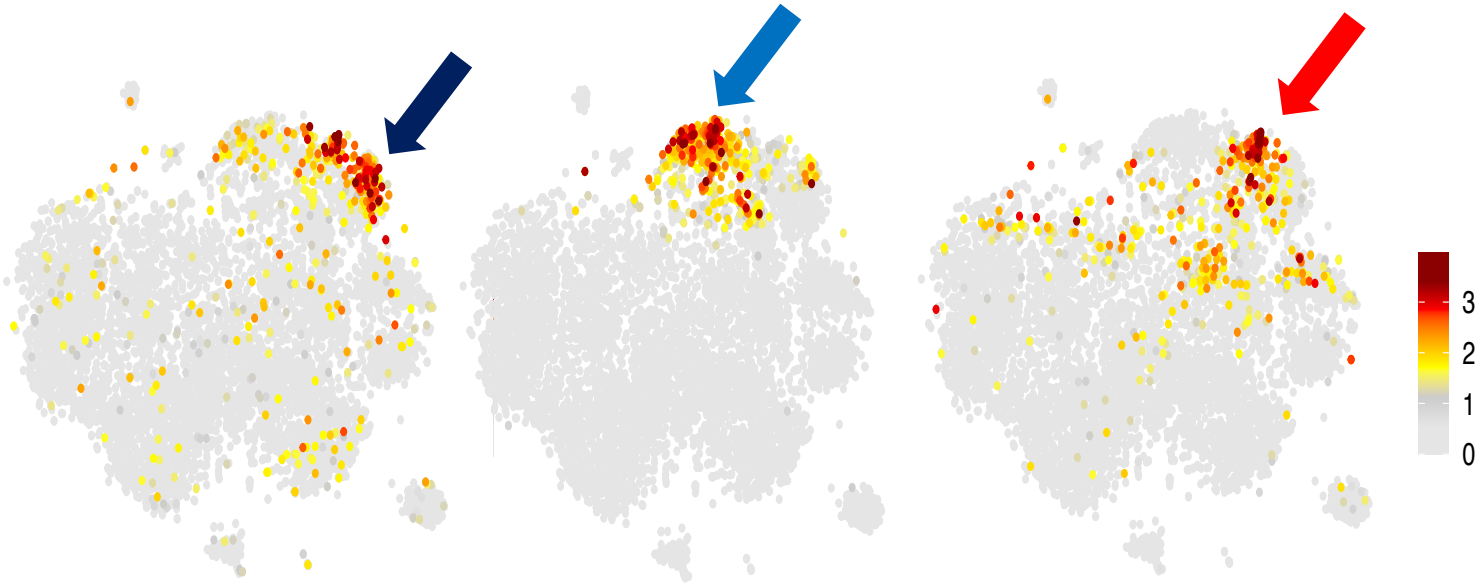
digit growth



…and cell fate decisions

Molecular dynamics at the Phalanx Forming Region



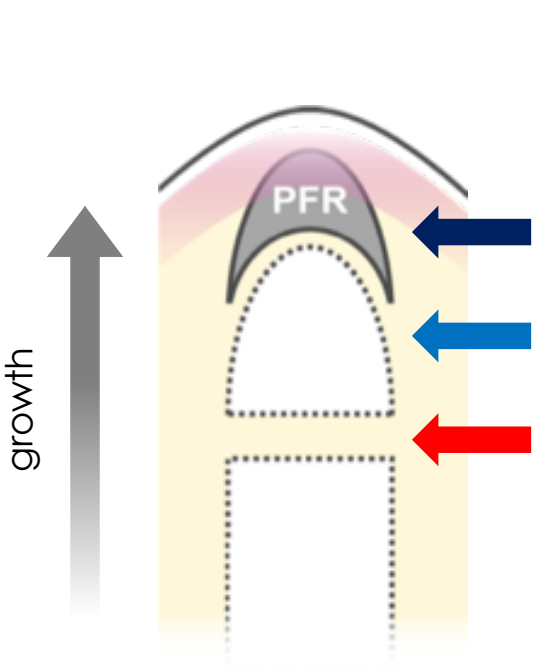


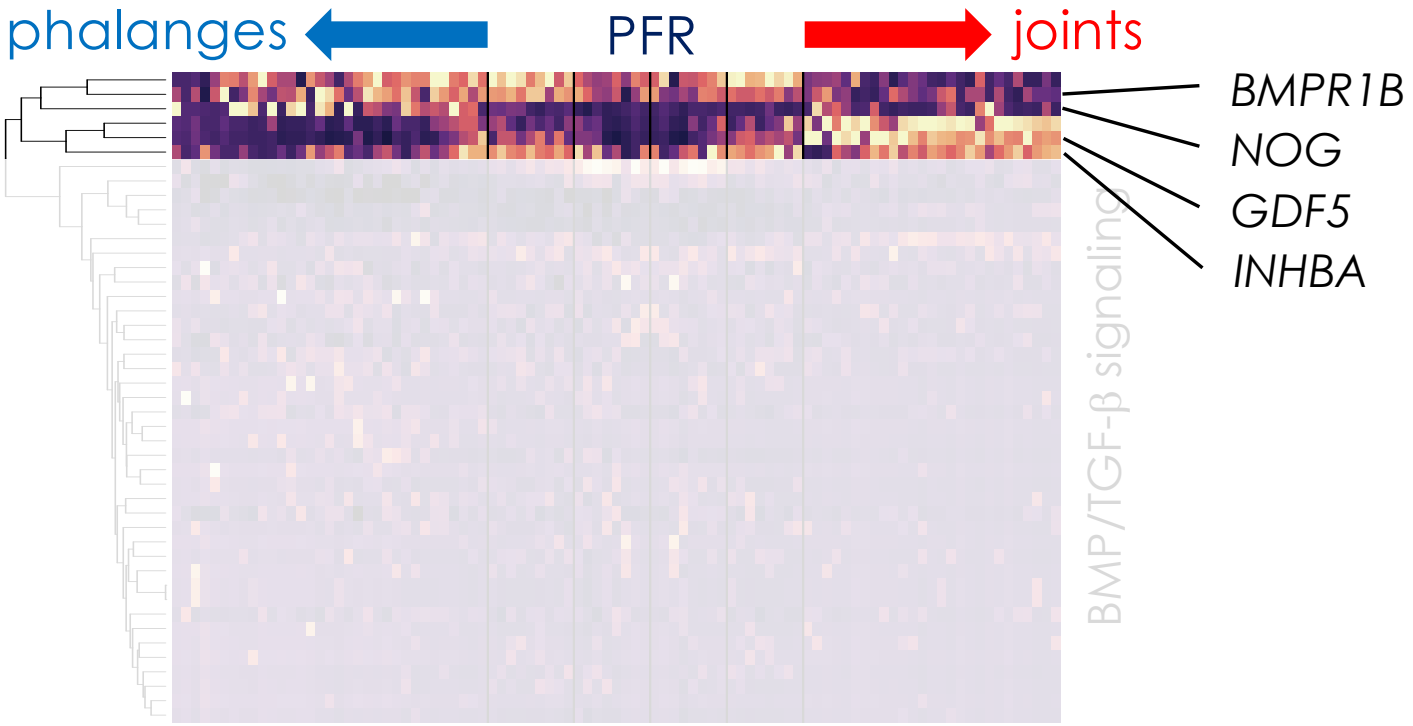
INHBA
~ PFR

COL9A1
~ phalanges

GDF5
~ joints

Molecular dynamics at the Phalanx Forming Region





space ~ time → ‘Pseudotime’ re-construction

Molecular dynamics at the Phalanx Forming Region

BMPR1B

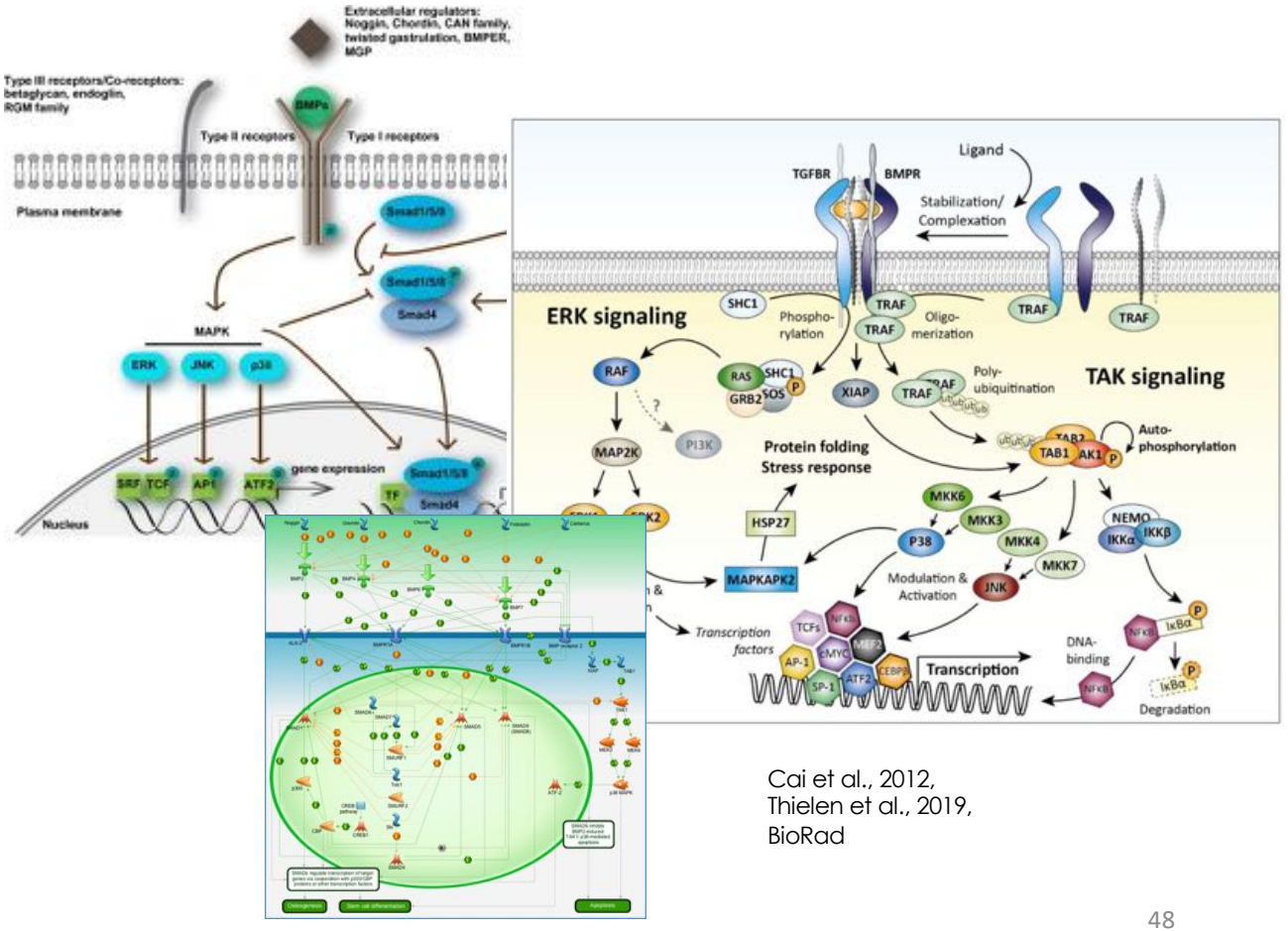
- *BMP* receptor

GDF5

- diffusible ligand

NOG

- diffusible competitor



Cai et al., 2012,
Thielen et al., 2019,
BioRad

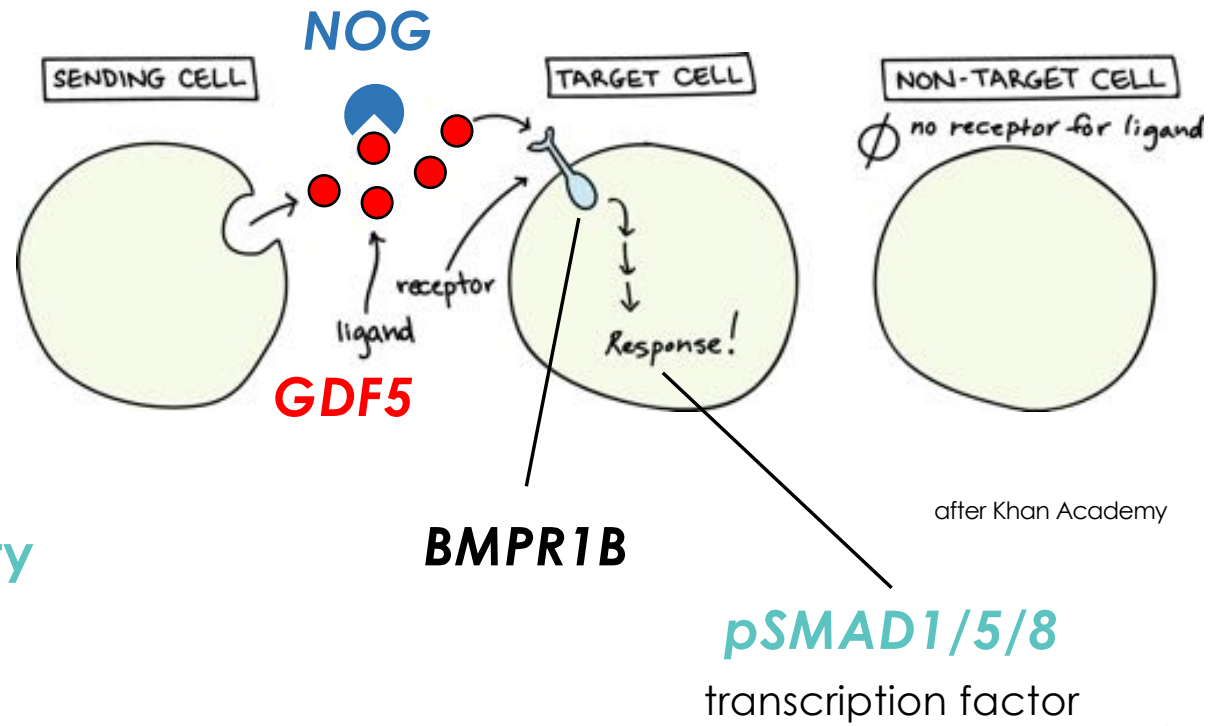
Molecular dynamics at the Phalanx Forming Region

BMPR1B
- *BMP* receptor

GDF5 **= *BMP* activator**
- diffusible ligand

NOG **= *BMP* inhibitor**
- diffusible competitor

pSMAD1/5/8 **~ *BMP* activity**



after Khan Academy

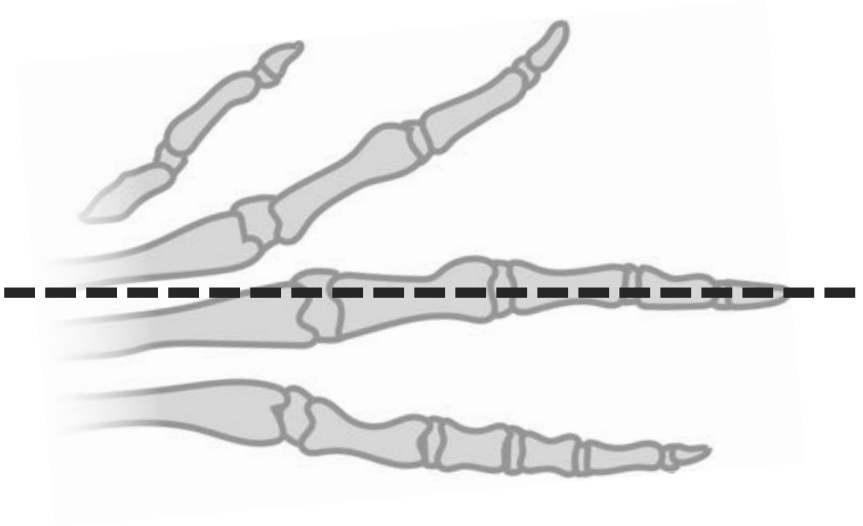
Molecular dynamics at the Phalanx Forming Region

BMPR1B
- *BMP* receptor

GDF5 **= *BMP* activator**
- diffusible ligand

NOG **= *BMP* inhibitor**
- diffusible competitor

pSMAD1/5/8 **~ *BMP* activity**



spatial and temporal dynamics *in vivo* ?

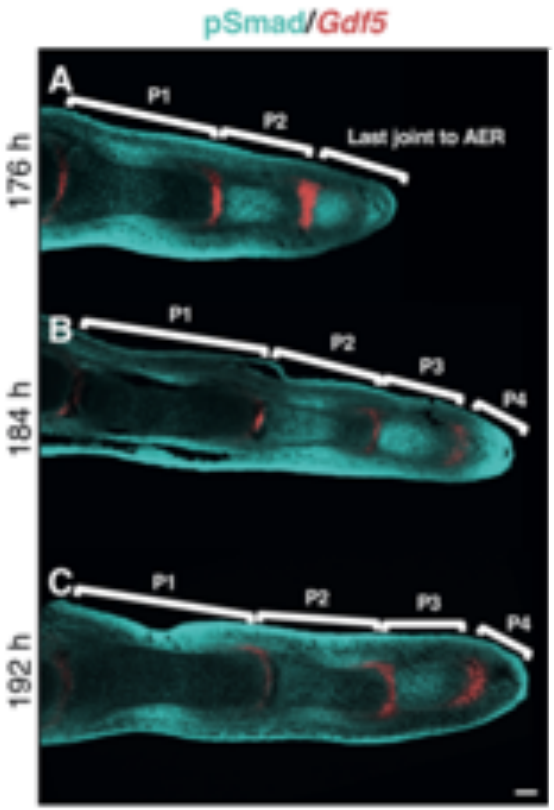
Molecular dynamics at the Phalanx Forming Region

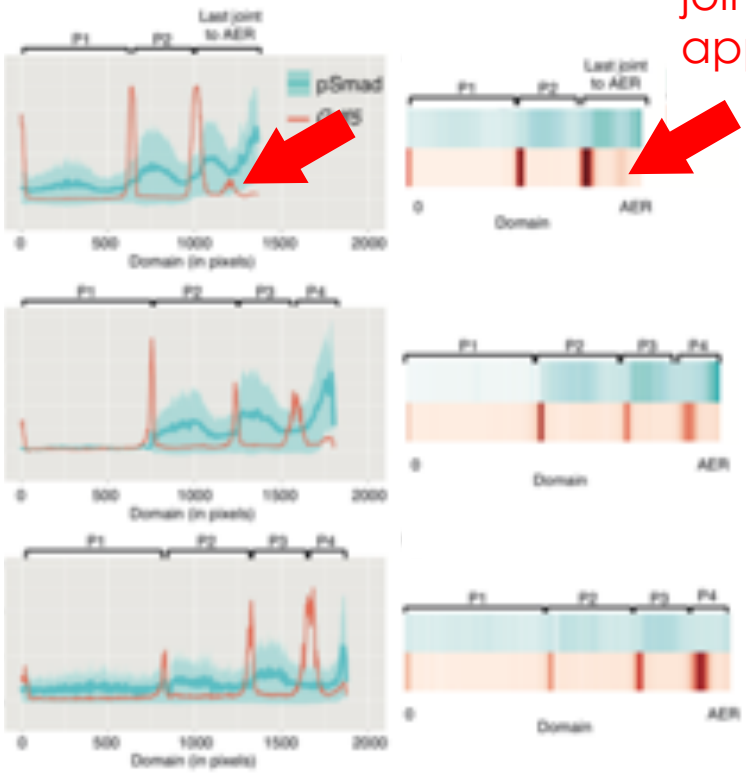
BMPR1B
BMP receptor

GDF5
***BMP* activator**

NOG
***BMP* inhibitor**

pSMAD1/5/8
~ *BMP* activity





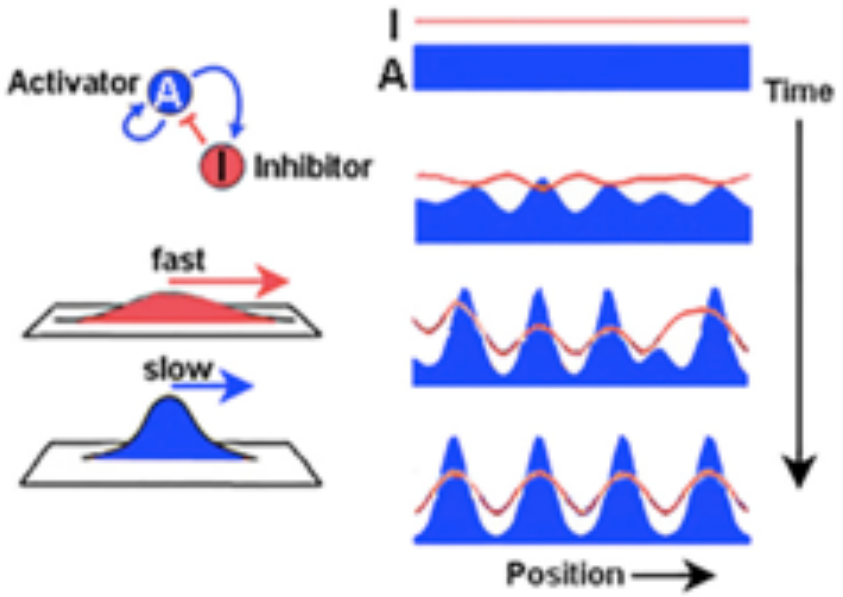
A Turing system to approximate digit patterning *in silico*

BMPR1B
BMP receptor

GDF5
***BMP* activator**

NOG
***BMP* inhibitor**

pSMAD1/5/8
~ *BMP* activity



after Hiscock & Meganson, 2015,
see Turing, 1952

see also e.g. Raspopovic et al. 2014,
Hiscock et al., 2017

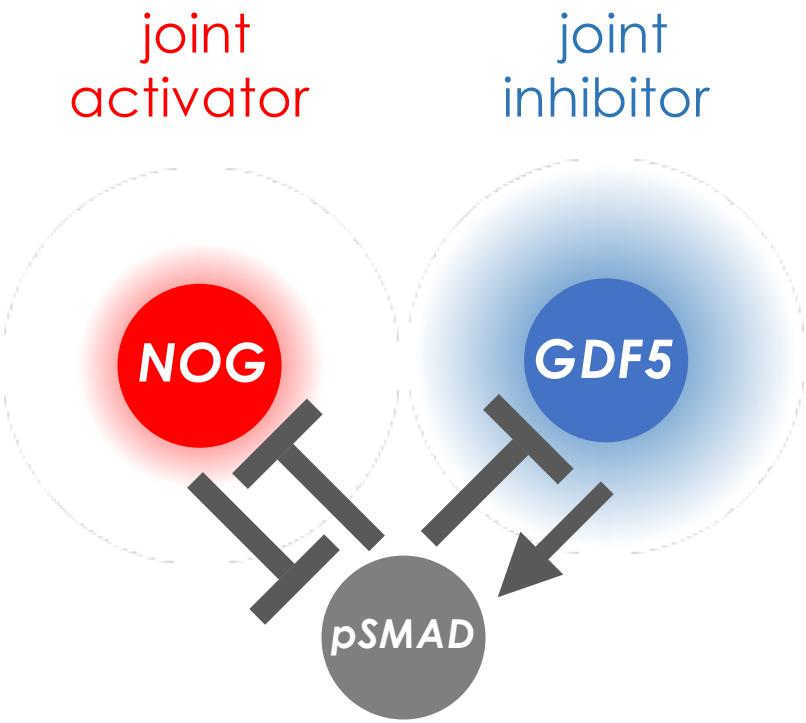
A Turing system to approximate digit patterning *in silico*

BMPR1B
BMP receptor

GDF5
***BMP* activator** ~ **Turing inhibitor**

NOG
***BMP* inhibitor** ~ **Turing activator**

pSMAD1/5/8
~ *BMP* activity ~ **represses joint fate**



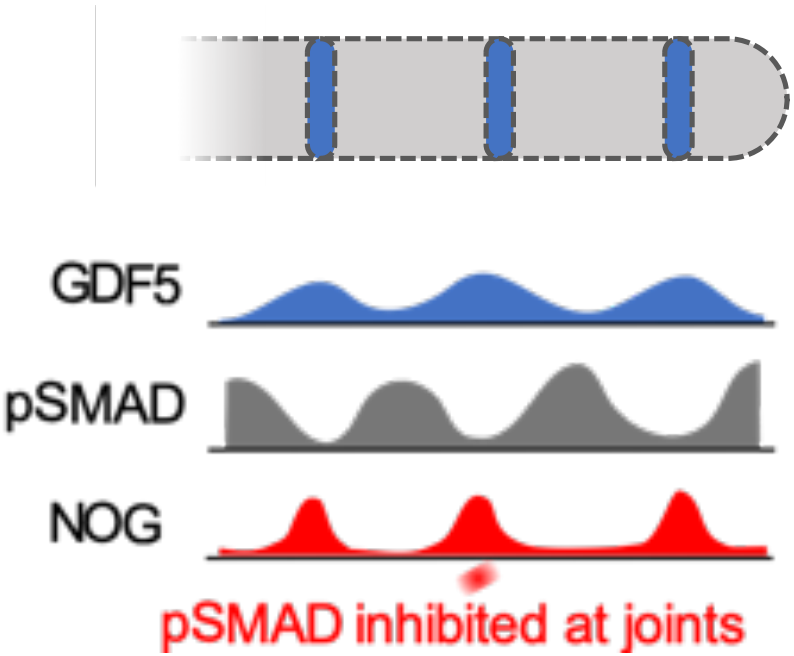
A Turing system to approximate digit patterning *in silico*

BMPR1B
BMP receptor

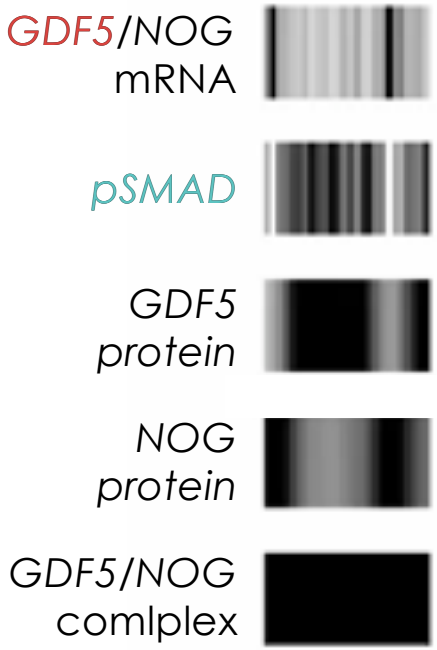
GDF5
BMP activator ~ **Turing inhibitor**

NOG
BMP inhibitor ~ **Turing activator**

pSMAD1/5/8
~ *BMP* activity ~ **represses joint fate**



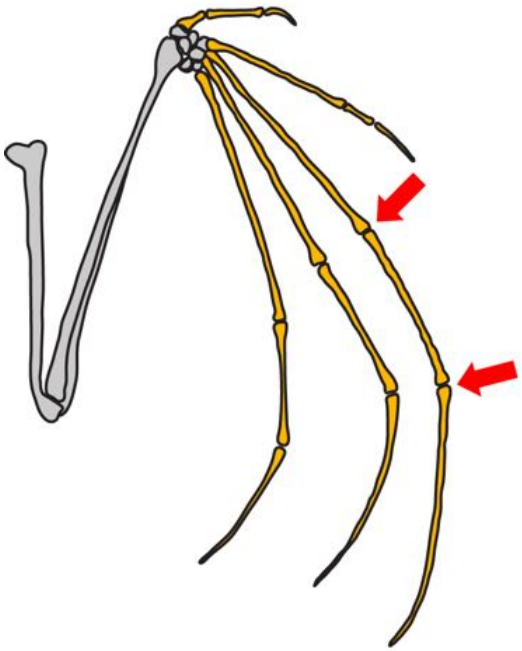
A Turing system to approximate digit patterning *in silico*



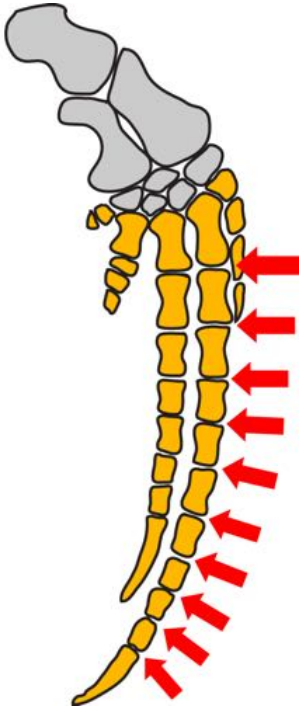
in silico

in vivo

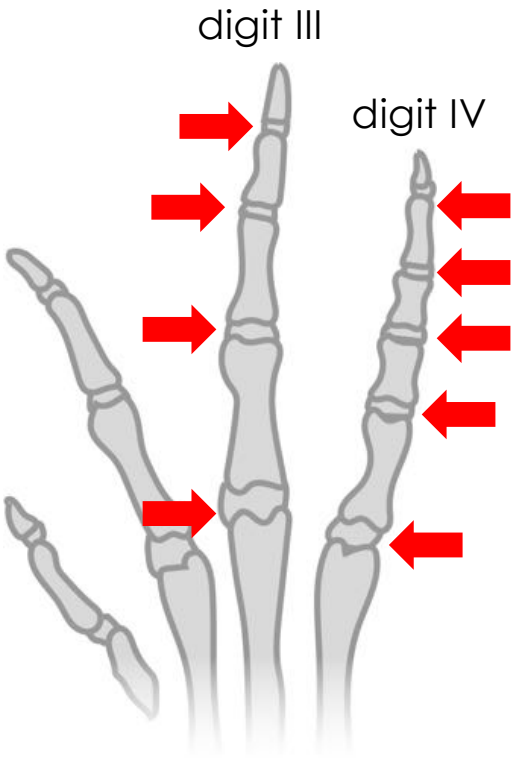
Tetrapod digit patterning diversity



bat

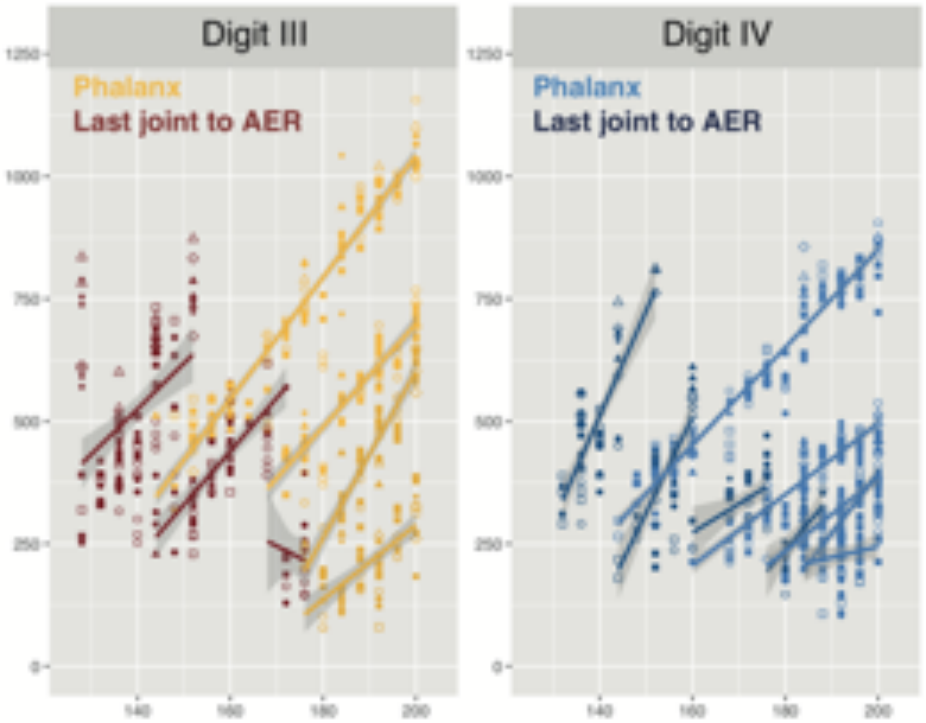


whale

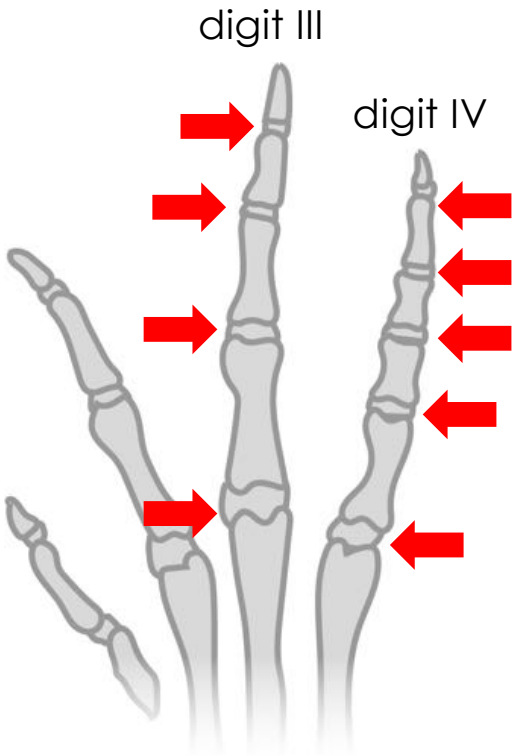


chicken

Tetrapod digit patterning diversity



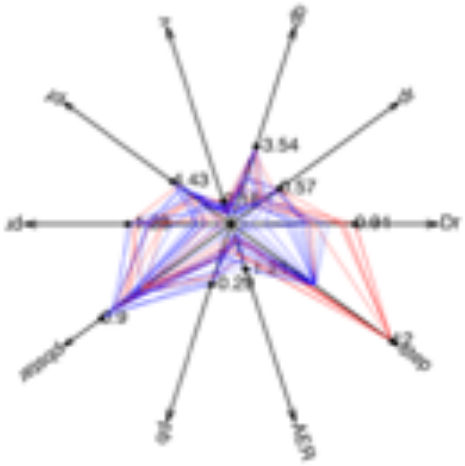
growth



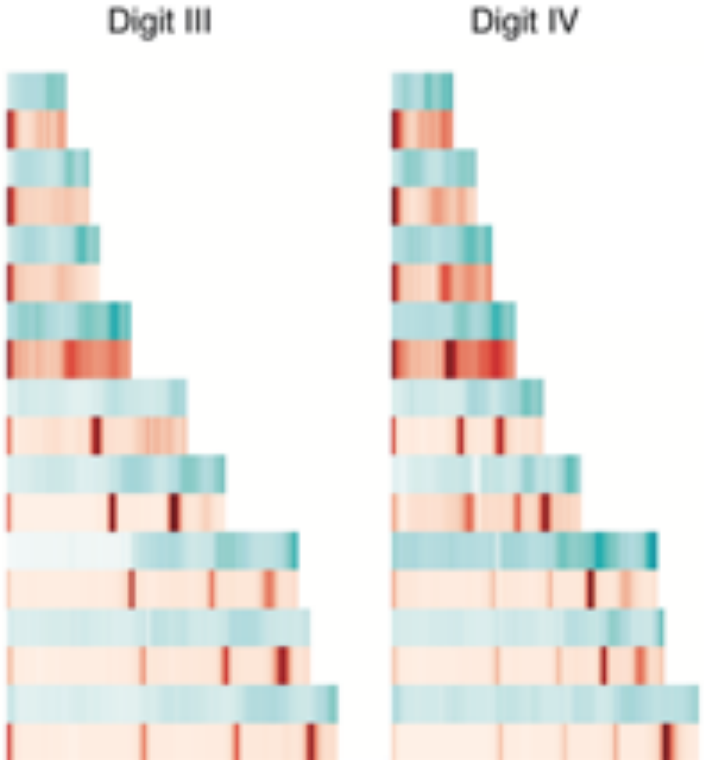
chicken

Tetrapod digit patterning diversity

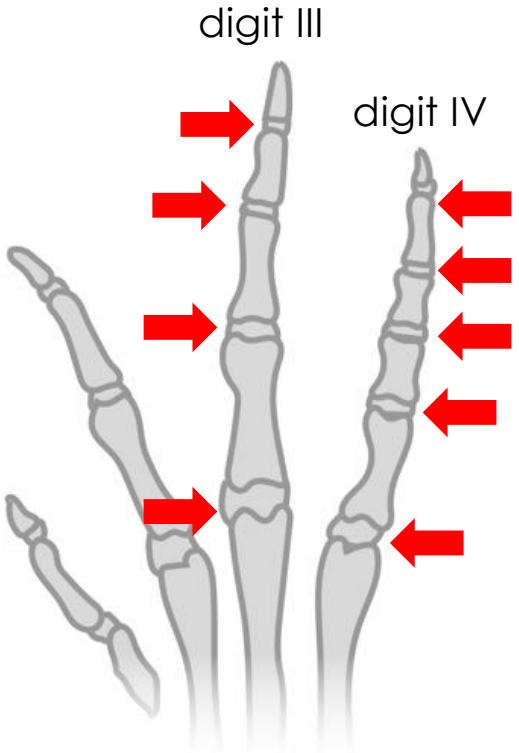
Outlook:
parameter screens



[see e.g. Barac, Iber]
digit III versus digit IV



signaling dynamics



chicken

Vertebrate skeletogenesis in development and evolution

- Why EvoDevo?
  - Mutation and selection *vs.* 'translation of diversity'
  - What is possible in development, what not?
- Development at cellular resolution
  - cell proliferation and fate specification ~ patterns
  - epigenetic factors control cell fate decisions
    [single cell genomics > TFs + enhancers > GRNs, cell signaling > modeling]
  - evolution of novel cell behaviors [and types]

developmental specification → novel morphologies

evolutionary diversification

Laboratory of Regulatory Evolution

Biank Berki
Aline de Courten
Ana di Pietro-Torres
Antoine Fages
Sabrina Fischer
Filomena Forte
Emmanuelle Grall
Maëva Luxey
Navaneeth Menon
Yasmin Picton
Fabio Sacher
Gabriela Stieger
Menghan Wang

Chloé Moreau
Christian Feregrino
Suvitha Subramaniam
Dominique Kolly

Collaborators

Tom Hiscock
University of Aberdeen
Diana Barac
Dagmar Iber
ETHZ
Daniel Ibrahim
MPI MolGen

@TschoppLab

Swiss 3R Competence Centre

Swiss National Science Foundation