

Phase transitions in the nucleus of cells

Theories from physics & new experimental data are revealing the mechanisms that control structure and function of the human genome.

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(proudly Henrik's postdoc 1998-2001)

Coworkers: UniNA, MDC+MPI Berlin, UCSD, U.Texas, ...

Henrik physics (...*in my mind*)

Time translation invariant



Past century



Current century

(ChatGPT's correlation **95%**)

Henrik physics (...*in my mind*)

Time translation invariant



Past century

(ChatGPT's correlation **95%**)



Current century



Next century

(ChatGPT's ***prediction***)

Henrik physics (...in my mind)

Time translation invariant

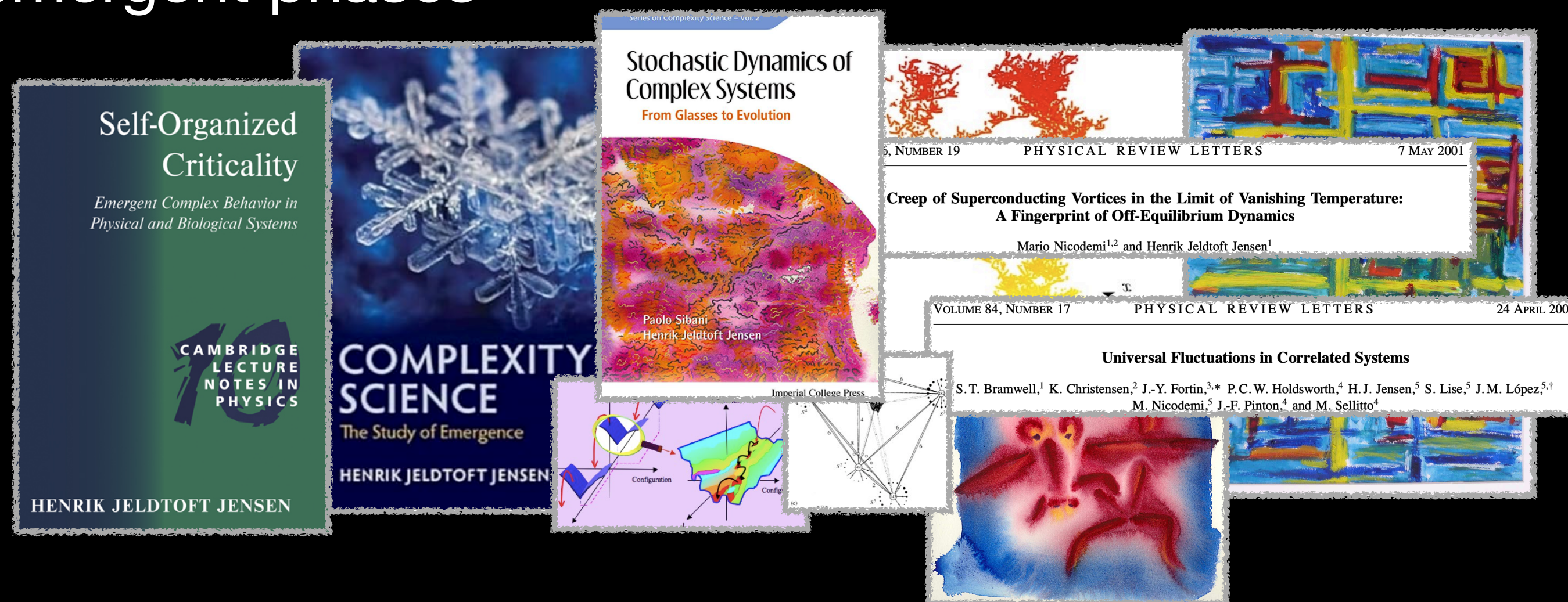


Past century



Current century

Many emergent phases



Henrik physics (...in my mind)

Time translation invariant

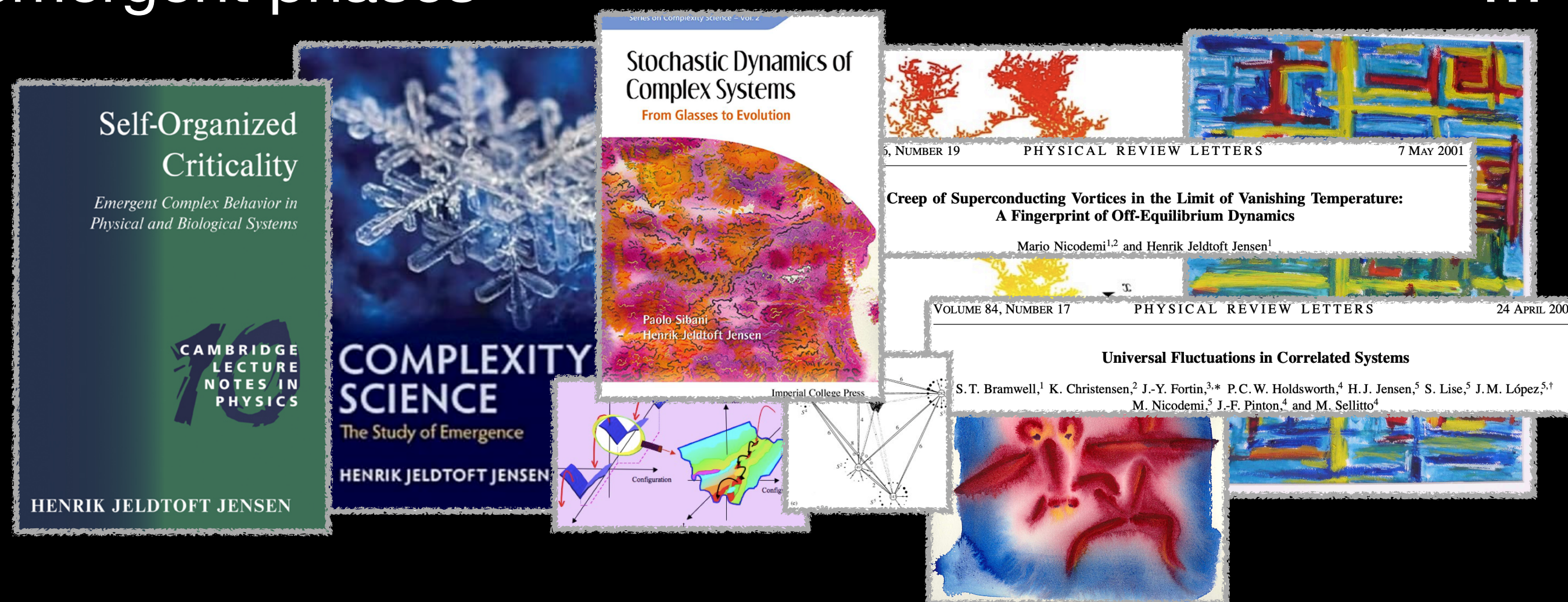


Past century



Current century

Many emergent phases



... and huge energy resources



Henrik physics (...in my mind)

Time translation invariant



Past century



Current century

... a state of wonder

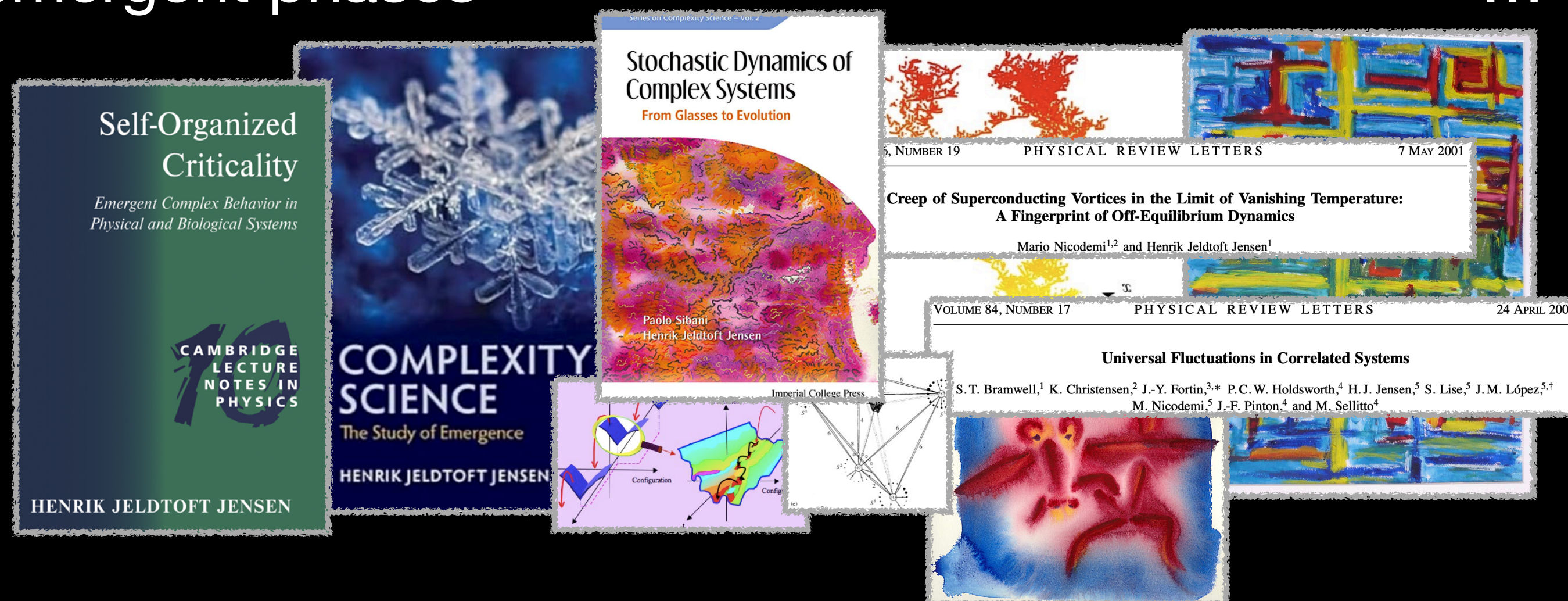
The purpose of art [& science] is rather the lifelong construction of a state of wonder.

G. Gould / Henrik's w.site

We shall explore, to arrive where we started and know the place for the first time.

T.S. Eliot / Henrik's w.site / where I am

Many emergent phases

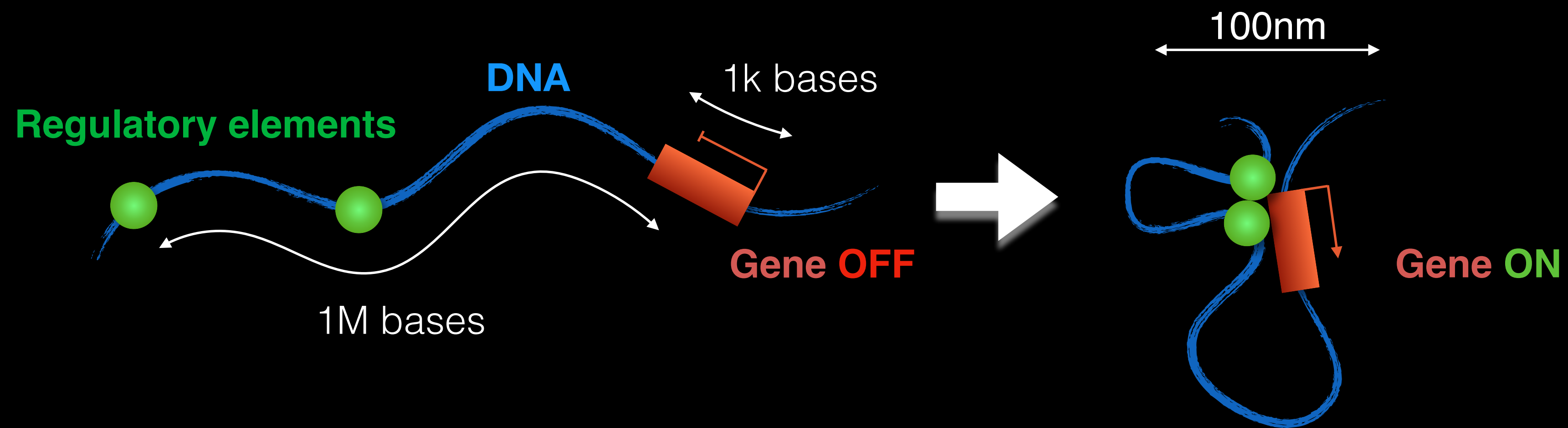


... and huge energy resources



Not just a linear sequence

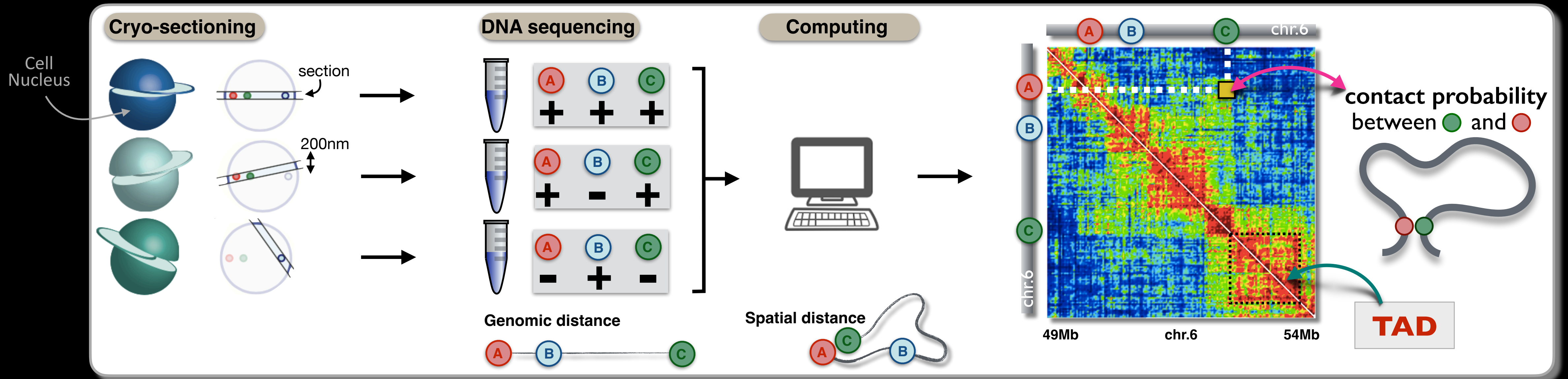
Non-coding DNA hides one of the keys to regulate our 20000 genes.



- 1) How to measure “who contacts whom”?
- 2) How does distal recognition occur?

Our GAM technology

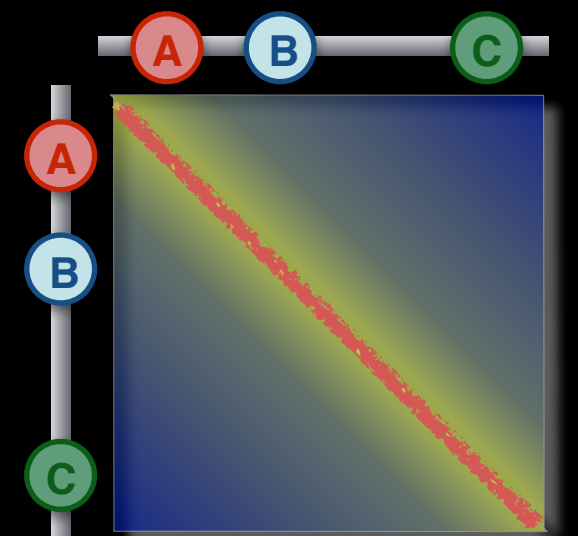
GAM identifies 3D contacts by sequencing DNA from nuclear sections: spatially closer sites more frequently fall into the same section, so are more frequently jointly sequenced.



GAM measures any combination of interactions (e.g., triplets, co-dependencies, etc.).

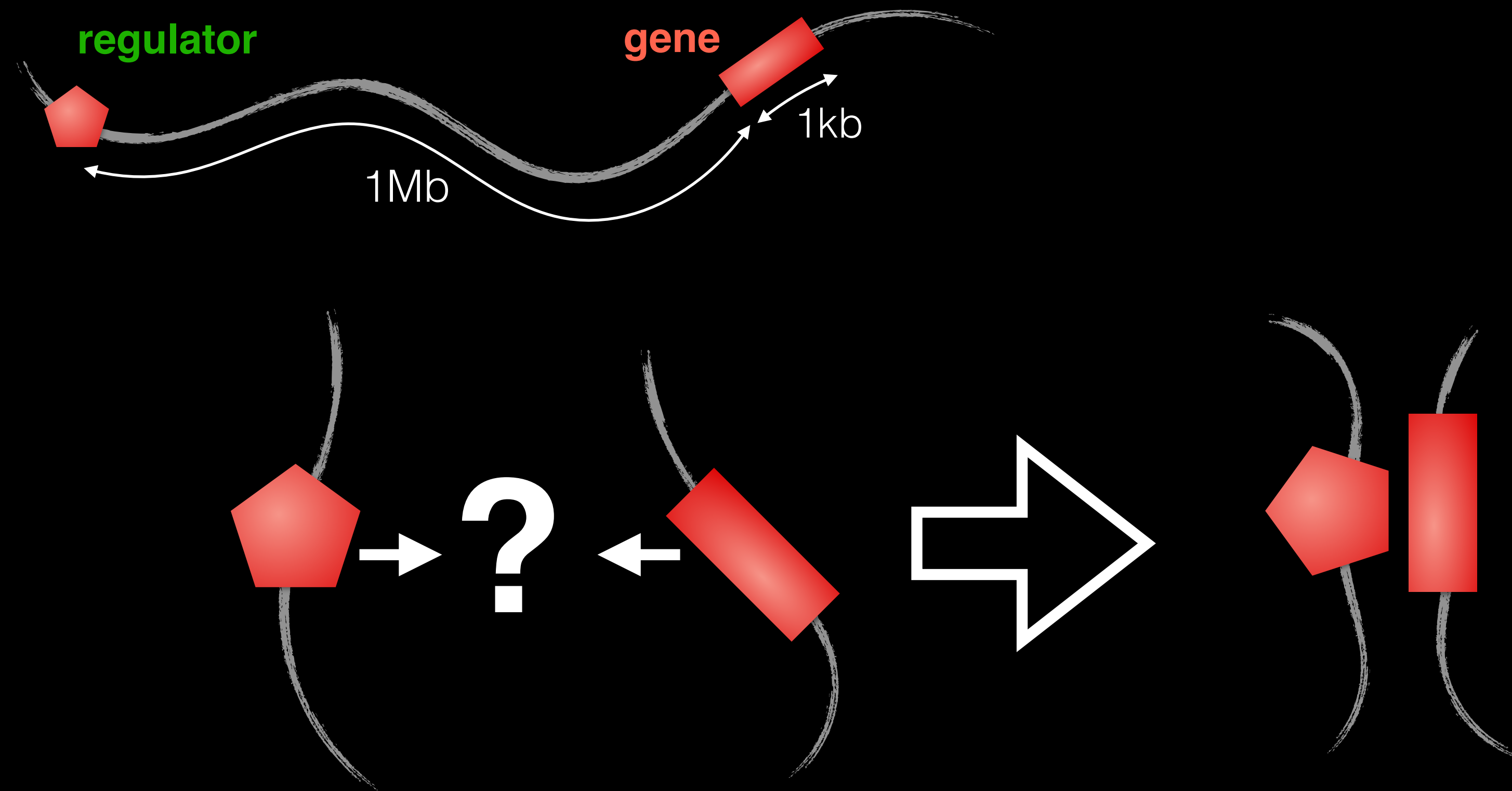
(Beagrie, Scialdone et al. *Nature* 2017, *Nature Meth.* 2023; Fiorillo et al. *Nature Meth.* 2021)

If DNA 3D structure were **random**:



Organisational mechanism

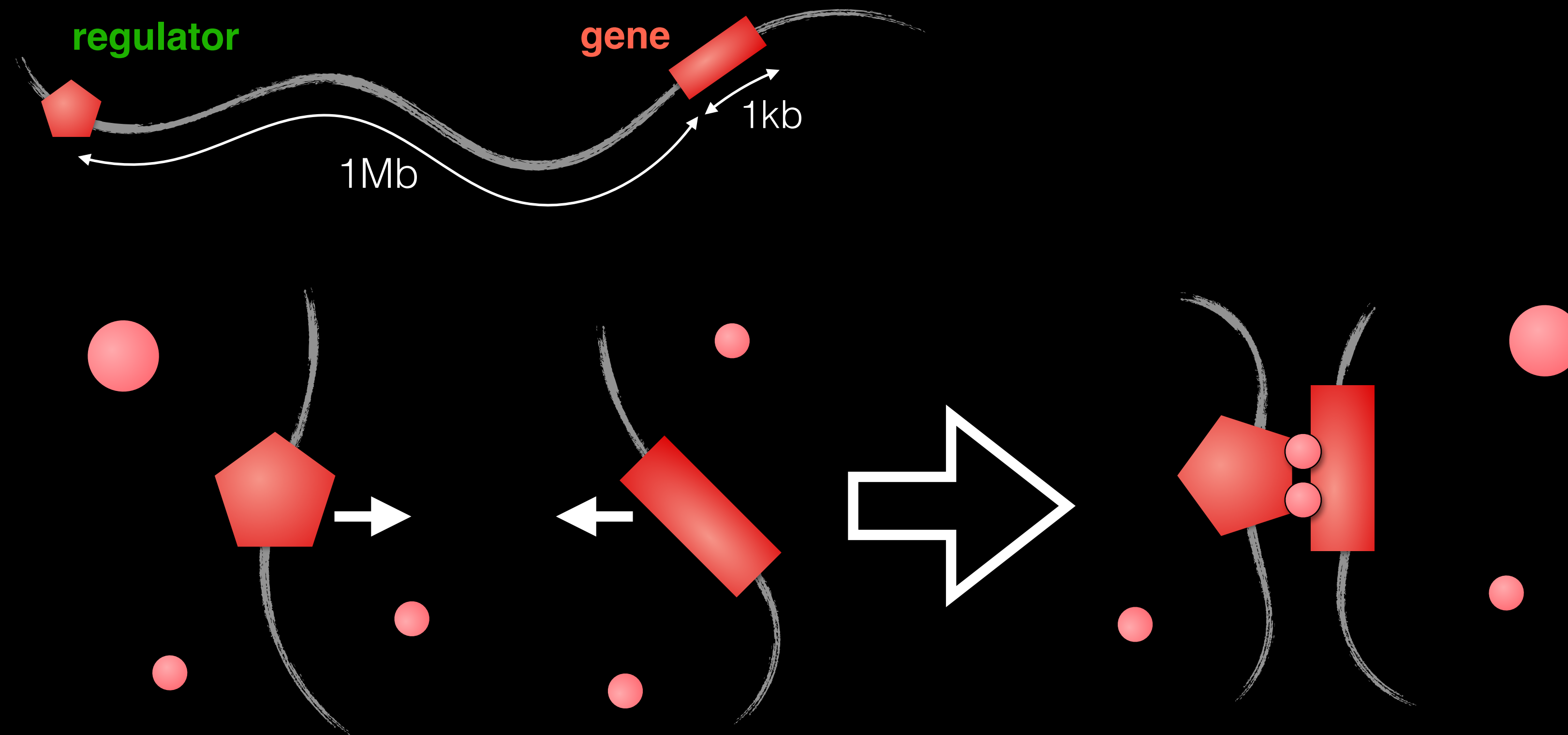
How can a gene and its distal regulator recognise each other?



What's the "force"?

Organisational mechanism

How can a gene and its distal regulator recognise each other?



... a “**particle**” produces the interaction.

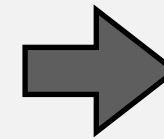
A stringent test of the theory

Use physics to predict the effects of mutations on 3D architecture and function of the genome.

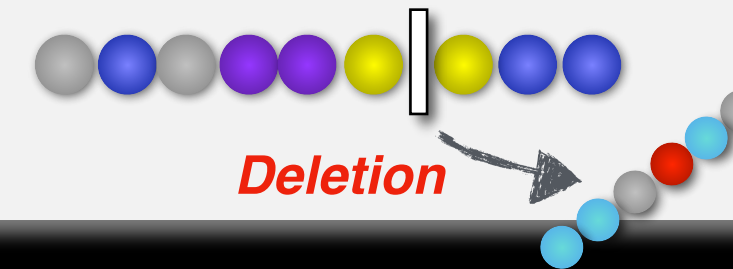
Our strategy:

1) take the WT polymer model

Polymer model



2) implement a **mutation** and derive how the model refolds

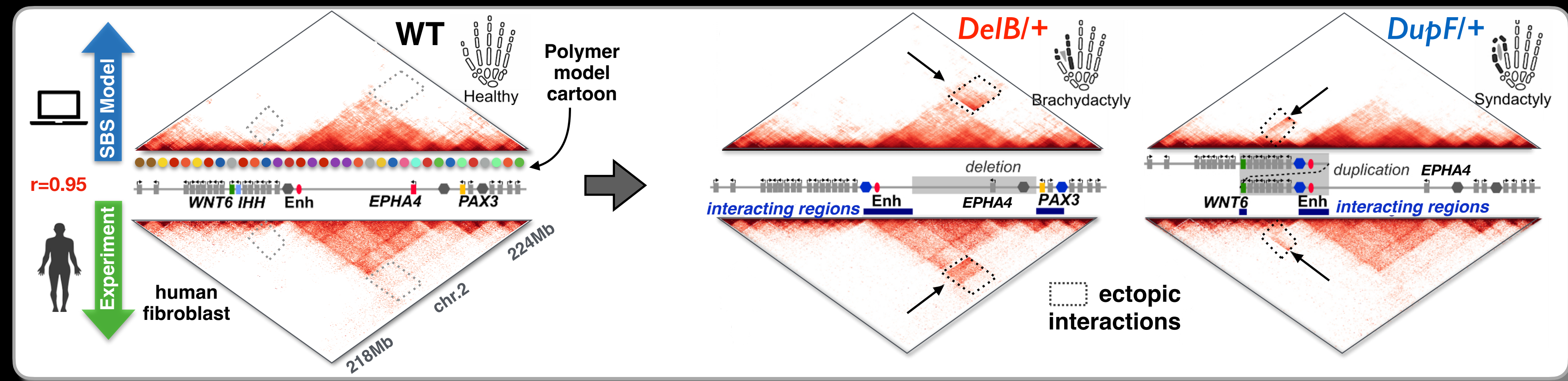


3) compare to experiments on the same mutation



No available fitting parameters!

Patterns form by polymer micro-phase separation.



Pax3, Wnt6 are upregulated in resp. *DelB/+*, *DupF/+* mice.

(Barbieri et al. *PNAS* 2012, *Nature SMB* 2017;
Bianco et al. *Nature Gen.* 2018; Ringel et al. *Cell* 2022;
Kragestein et al. *Nature Gen.* 2018)

Mutations rewire regulatory contacts and induce diseases.

Conclusions

... I am so happy to celebrate Henrik today! It's almost 30 years since my postdoc in his group. Thanks for your mentorship and all the wonderful memories.