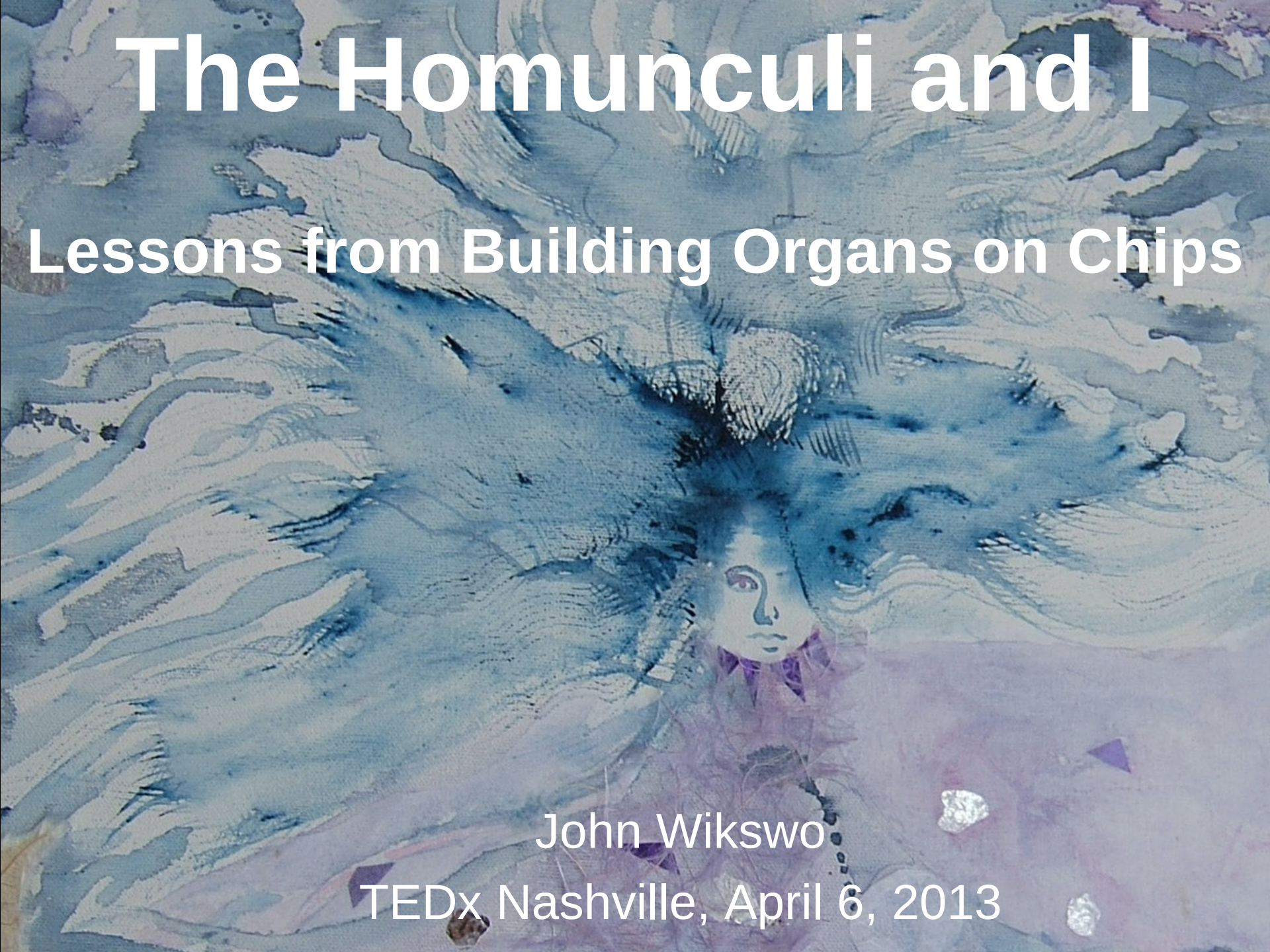


The Homunculi and I

Lessons from Building Organs on Chips

John Wikswo

TEDx Nashville, April 6, 2013

Abstract

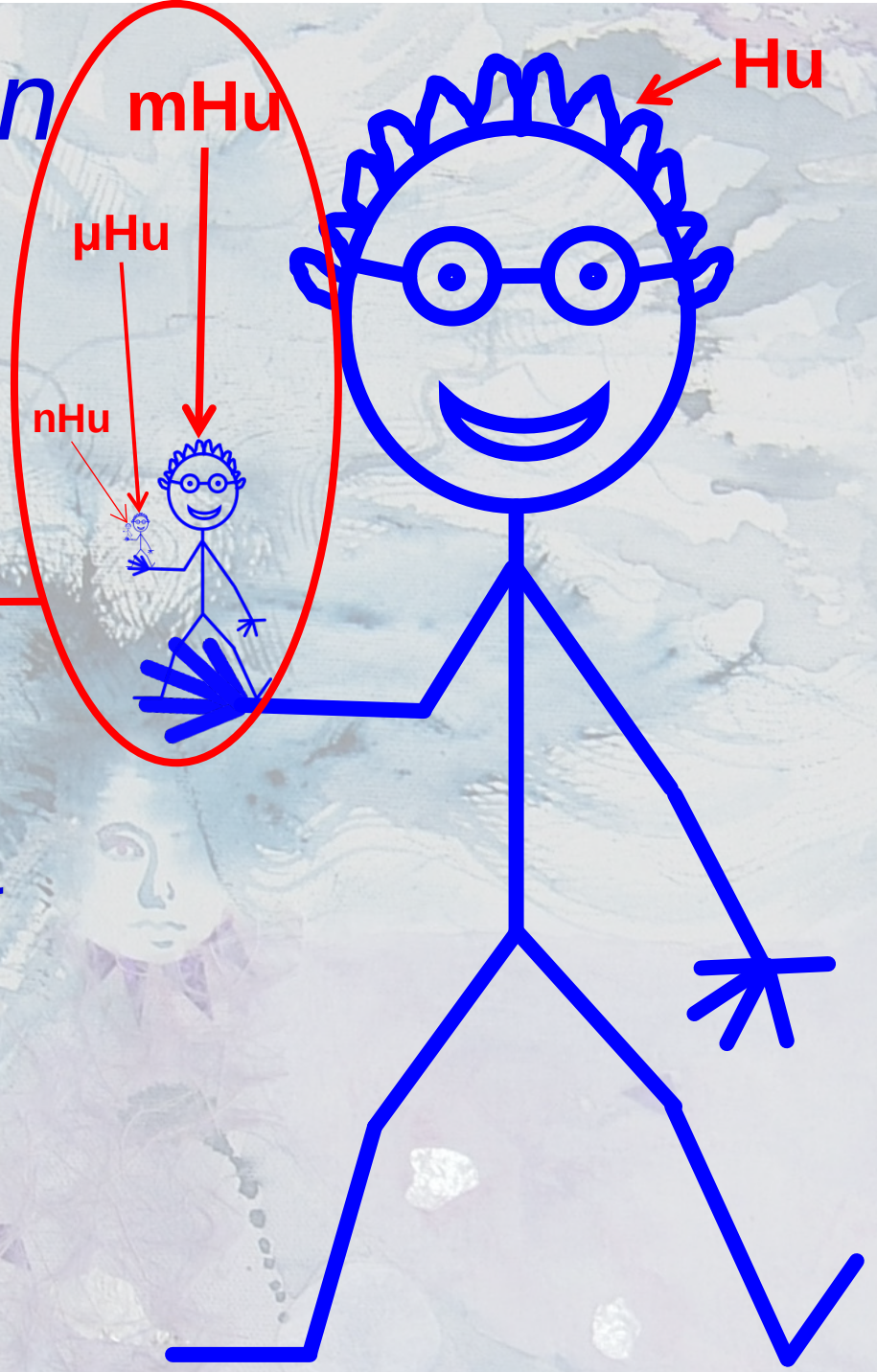
Why are we building two new species: *Homo chippus*, a milliHuman, and *Homo chippiens*, a microHuman? Microfabricated humans-on-a-chip! Why? Because it's fun and a REAL challenge. Using the tools of physics, chemistry, engineering, physiology and molecular biology, we are exploring the unfathomable complexity that affects our development and growth and individual responses to disease, drugs, and aging. Multidimensional phase space illustrates the variables that affect *H. chippus*, *H. chippiens* and the scientists doing the work.

Homunculus, *noun*

[hō-ˈmənŋ-kyə-ləs]

plural ho·mun·cu·li

A miniature representation of a human.



Why are we building homunculi?

- Human biology is complex
- Homunculi can simplify:
  - Drug development
  - Environmental toxicology
  - Physiology

Raise your hand if you or a friend have had an adverse drug reaction.

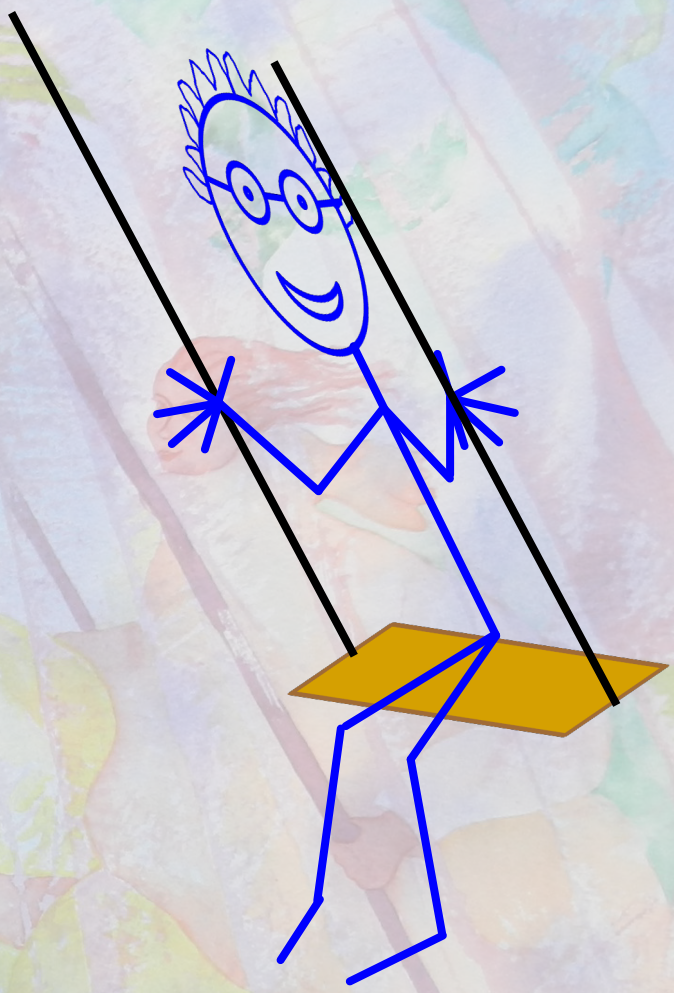
Do household cleaners, garden chemicals, fragrances, or air pollution bother you?


Multidimensional phase space illustrates the variables that affect homonculi and the physicians, scientists and engineers building them.

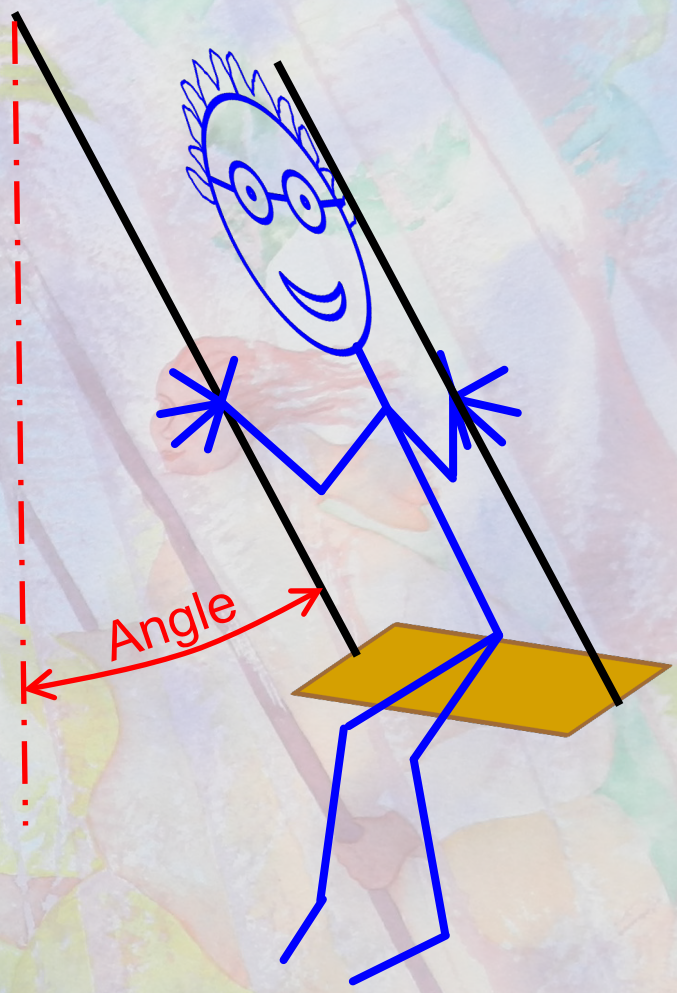
Phase space

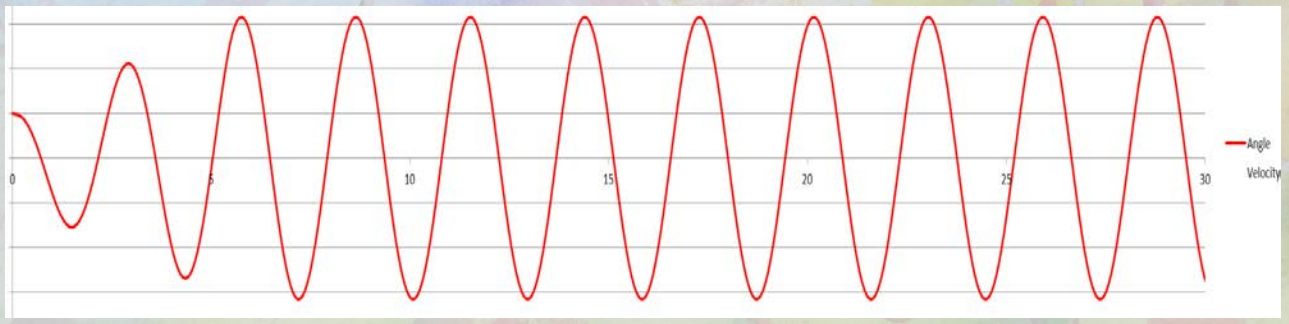
[fāz spās], noun

A geometrical space in which each possible state of a system is represented by a single point.



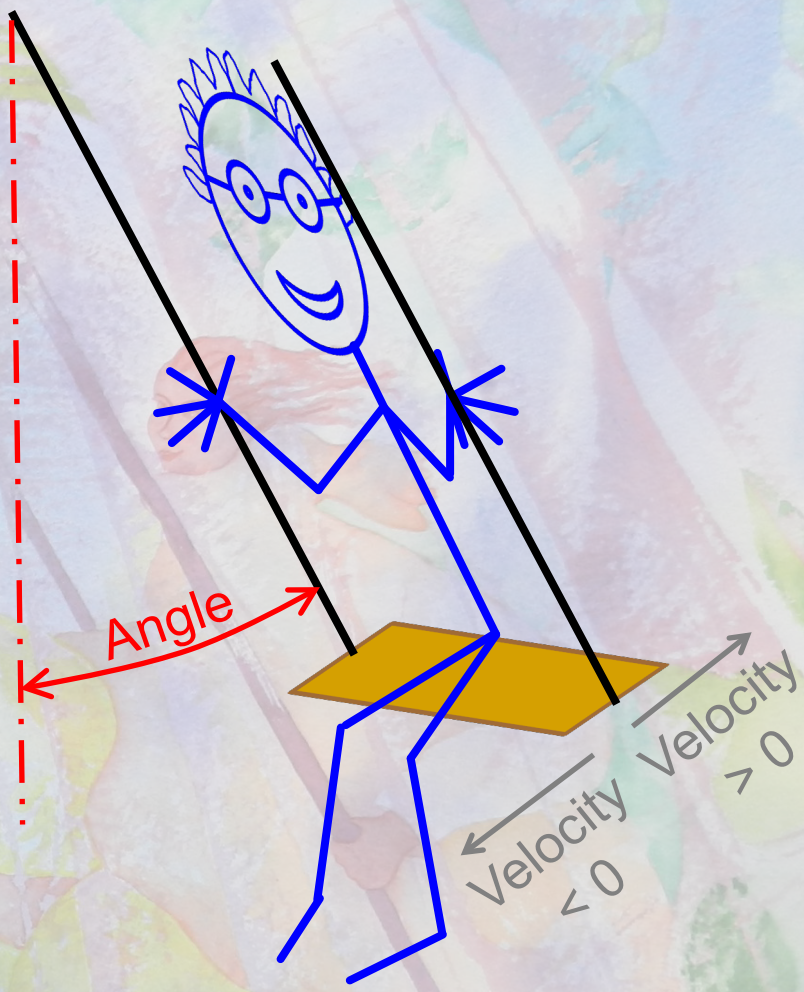
One axis in phase space can represent the range of one variable.

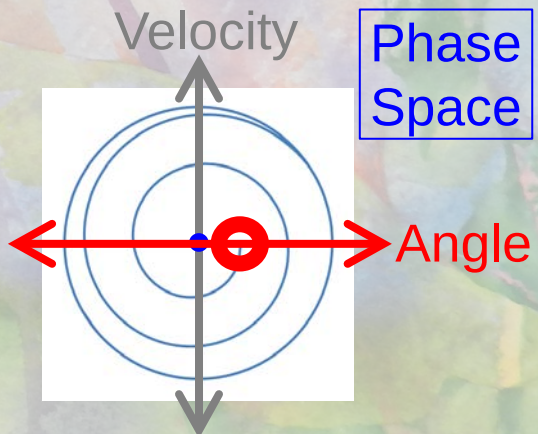




Phase Space

There are as many axes as variables.





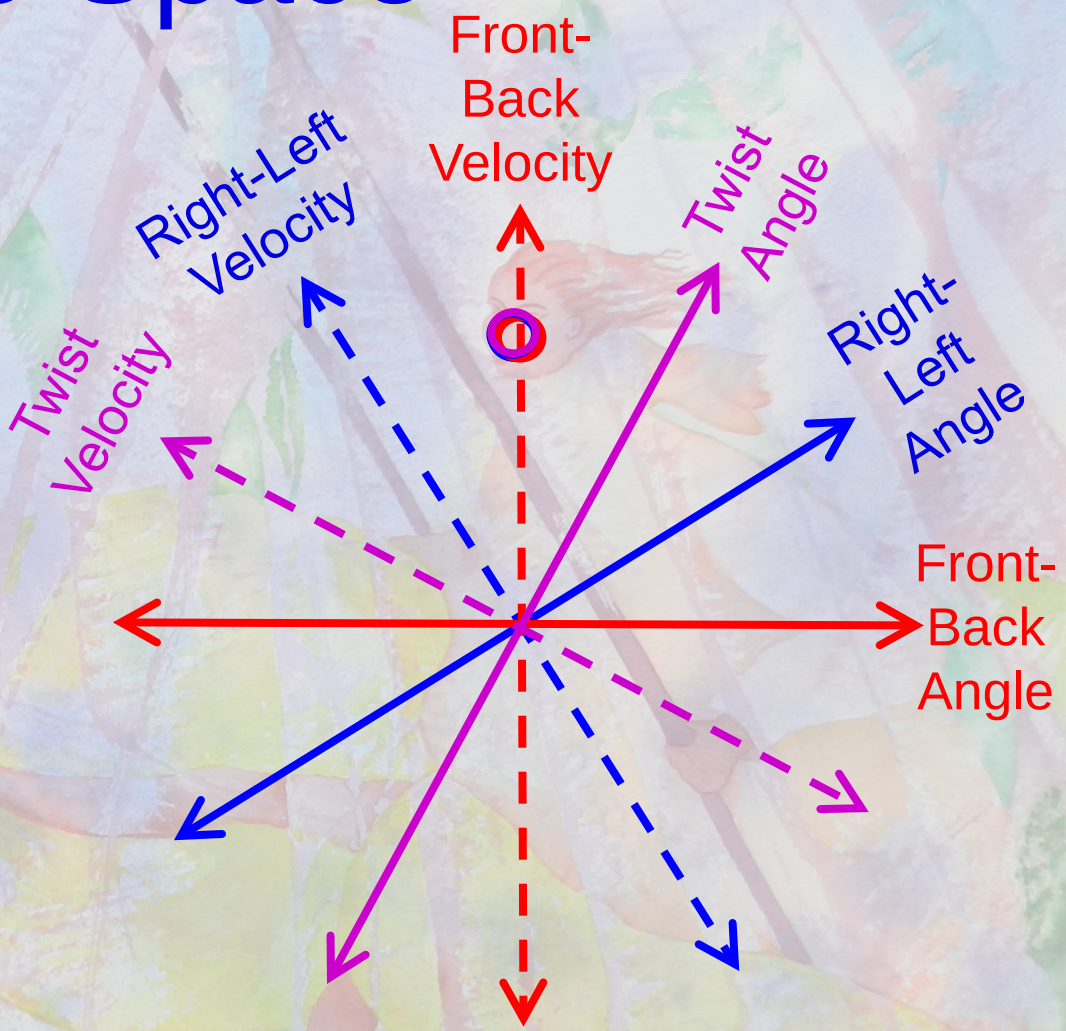
Swing Phase Space

Front and back

Left and Right

Orbit

Twist



Six-Dimensional Phase Space is fun!

You can do lots of things at one time!

Part of the problem is that human biology is COMPLEX.

Organs talk to each other, but we seldom hear what they are saying.

Organs, Organs, Organs

Cardiovascular

Heart
Blood
Blood vessels

Digestive

Salivary glands
Esophagus
Stomach
Liver
Gallbladder
Pancreas
Intestines

Excretory

Kidneys
Ureters
Bladder
Urethra

Immune

Leukocytes
Tonsils
Adenoids
Thymus
Spleen
Appendix

Reproductive

Ovaries
Fallopian tubes
Uterus
Vagina
Mammary glands
Testes
Vas deferens
Seminal vesicles
Prostate
Penis

Colon
Rectum
Anus

Endocrine

Hypothalamus
Pituitary gland
Pineal gland
Thyroid
Parathyroids
Adrenals

Integumentary

Skin
Hair
Nails

Muscular

Muscles
Golgi tendon organ

Nervous

Brain
Spinal cord
Nerves
Eyes

Respiratory

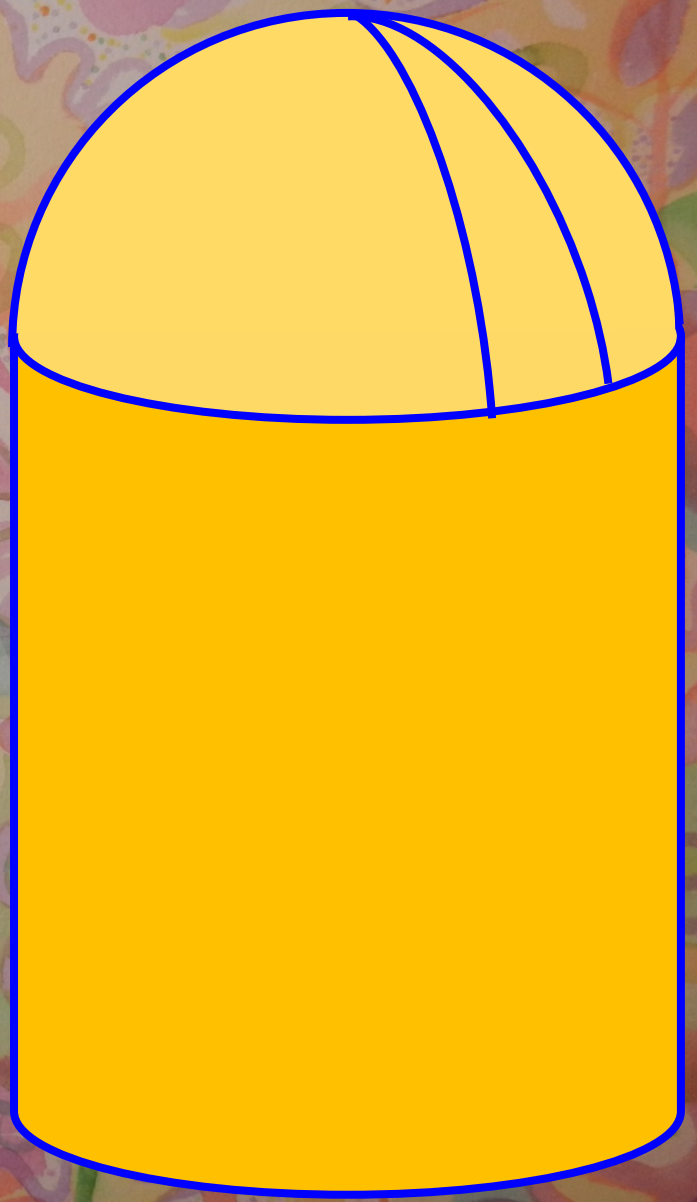
Pharynx
larynx
Trachea
Bronchi
Lungs
Diaphragm

Skeletal

Bones
Cartilage
Ligaments
Tendons

Silo -- A place to store stuff without mixing.

Silo Mentality -- Thinking without mixing.



Organ Silos


Thyroid
Pituitary
Adrenals
Brain
Lungs
Kidney
Heart
Liver
Eyes
Skin
Ears
Intestines
Gall Bladder
Pancreas
Spleen
Prostate
Uterus
Ovaries
Testis

How is a new drug tested?

Petri dishes

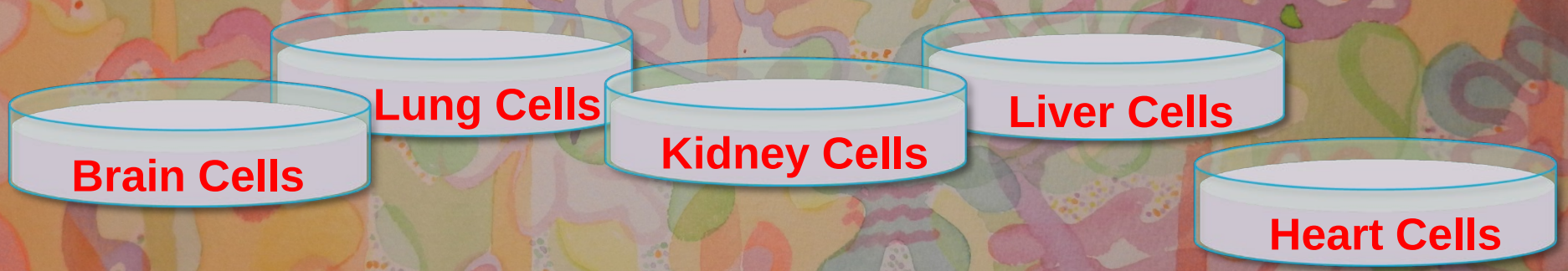
Mice

Humans

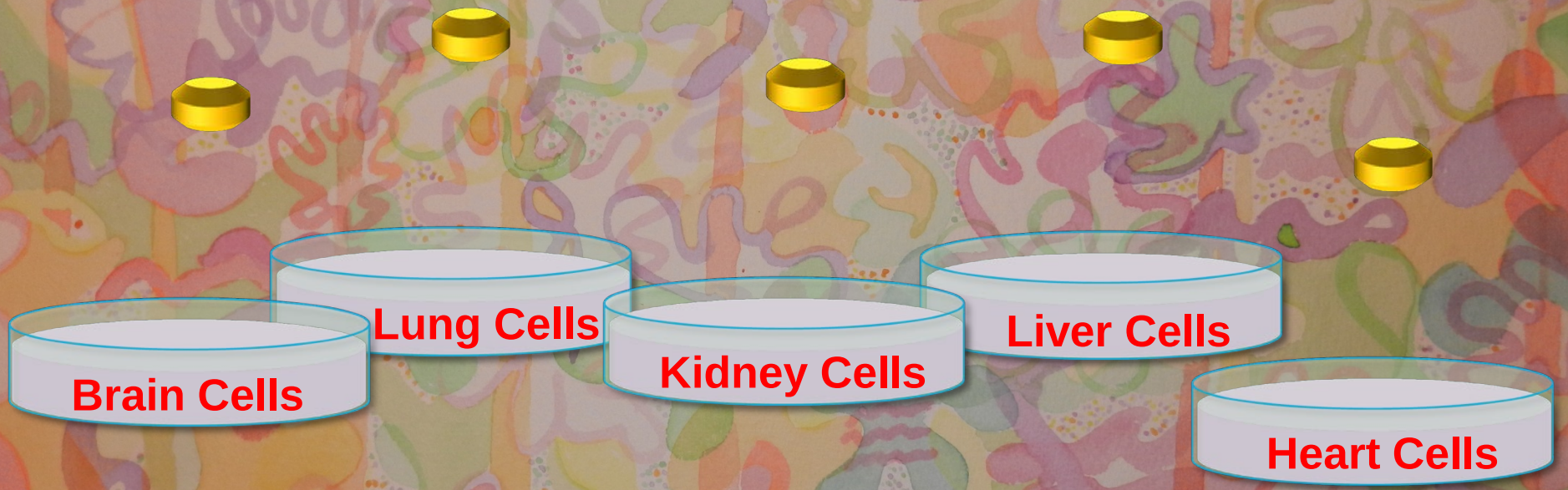
Organs from a Silo Mentality

Organs from a Silo Mentality

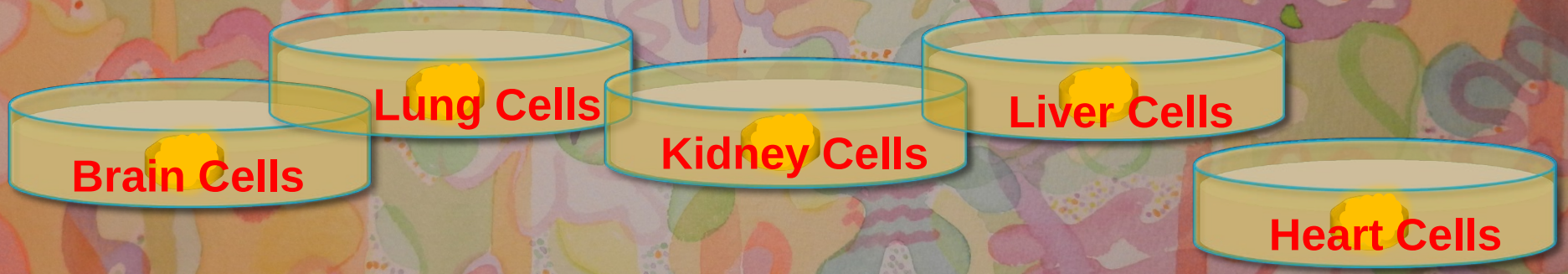
Organs from a Petri Dish Mentality



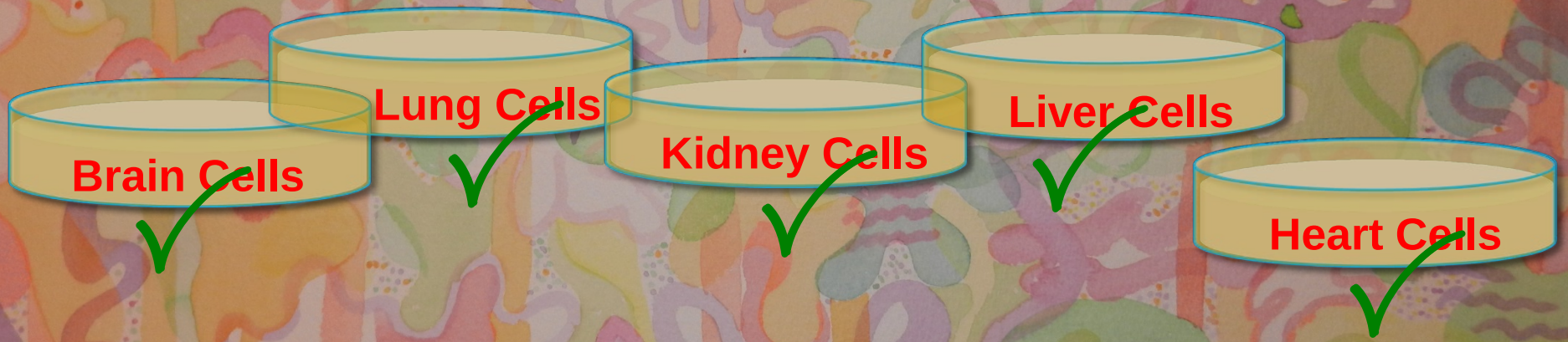
Testing drugs in Petri Dishes



Testing drugs in Petri Dishes



Testing drugs in Petri Dishes



How is a new drug tested?

Petri dishes

Mice ⇦

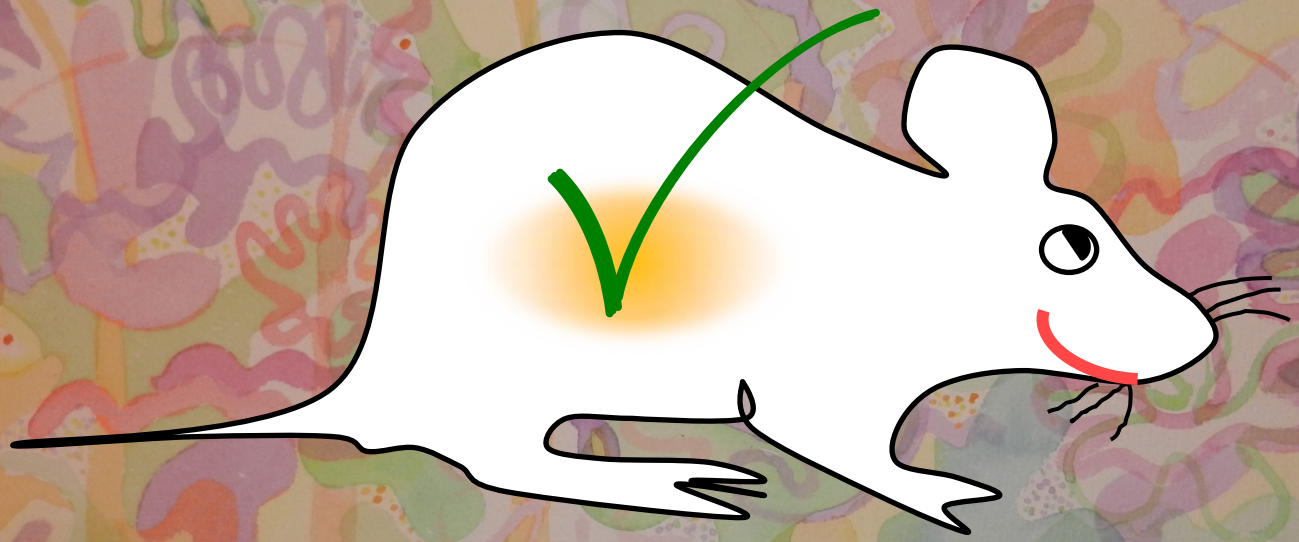
Humans

If each individual "organ" is OK, start testing that drug on mice.

Test drug in mice…

Test drug in mice…

Test drug in mice…



How is a new drug tested?

Petri dishes

Mice

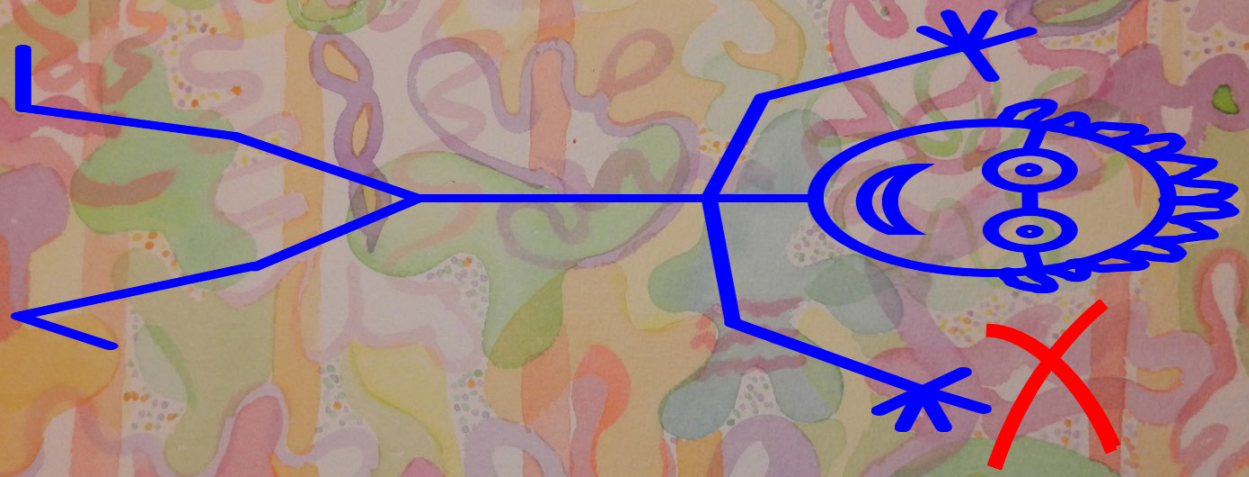
Humans 

If the mice are OK, then the drug is tested on humans.

Test drug in humans…

Test drug in humans…

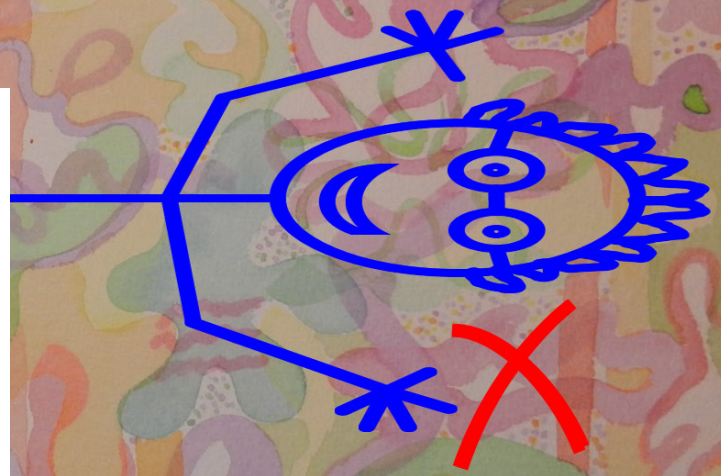
Test drug in humans…



Test drug in humans…

What went wrong?

- **Human genes ≠ mouse genes?**
- **Organ-organ interactions?**



How is a new drug tested?

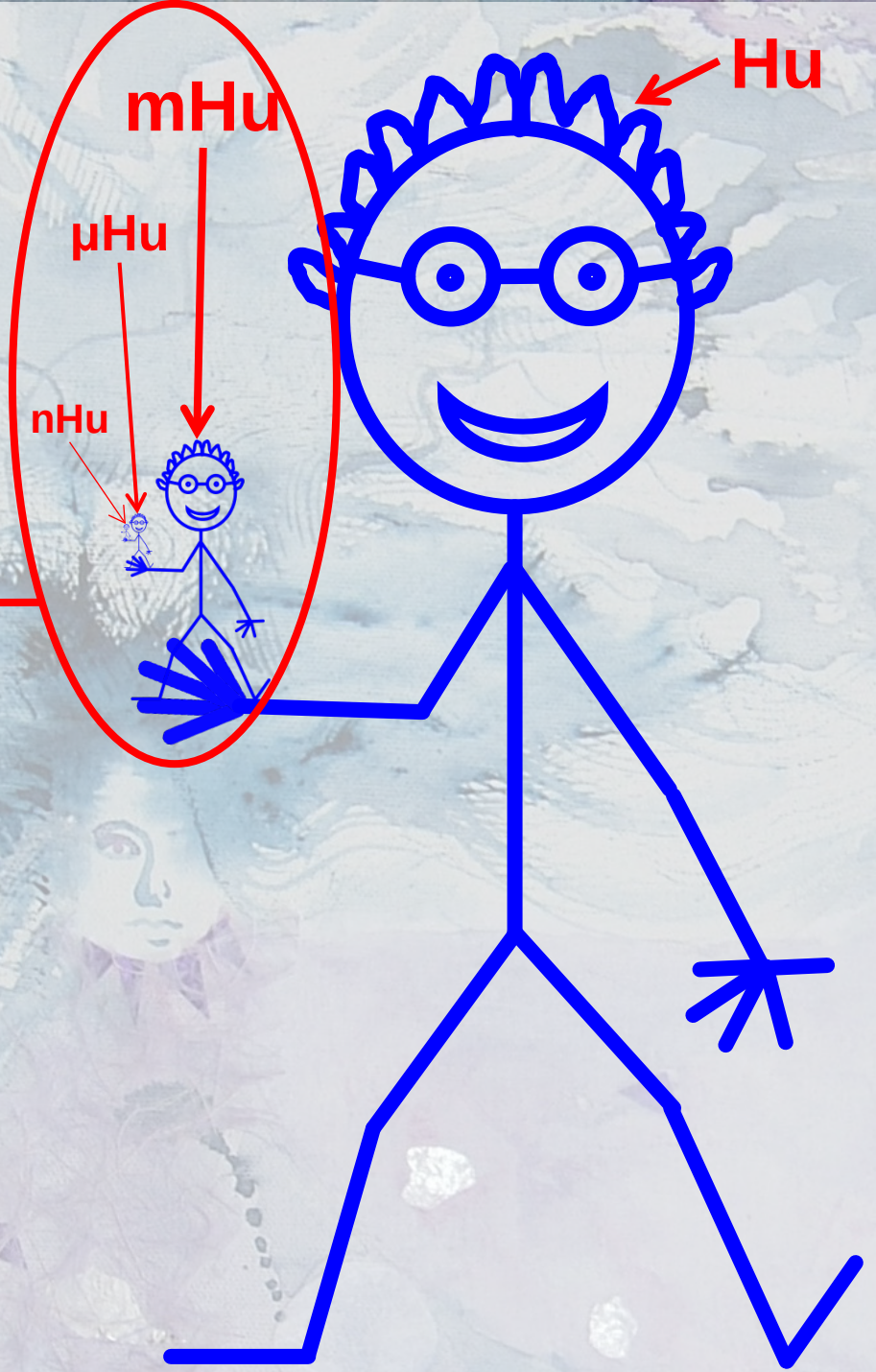
Petri dishes ✓

Mice ✓

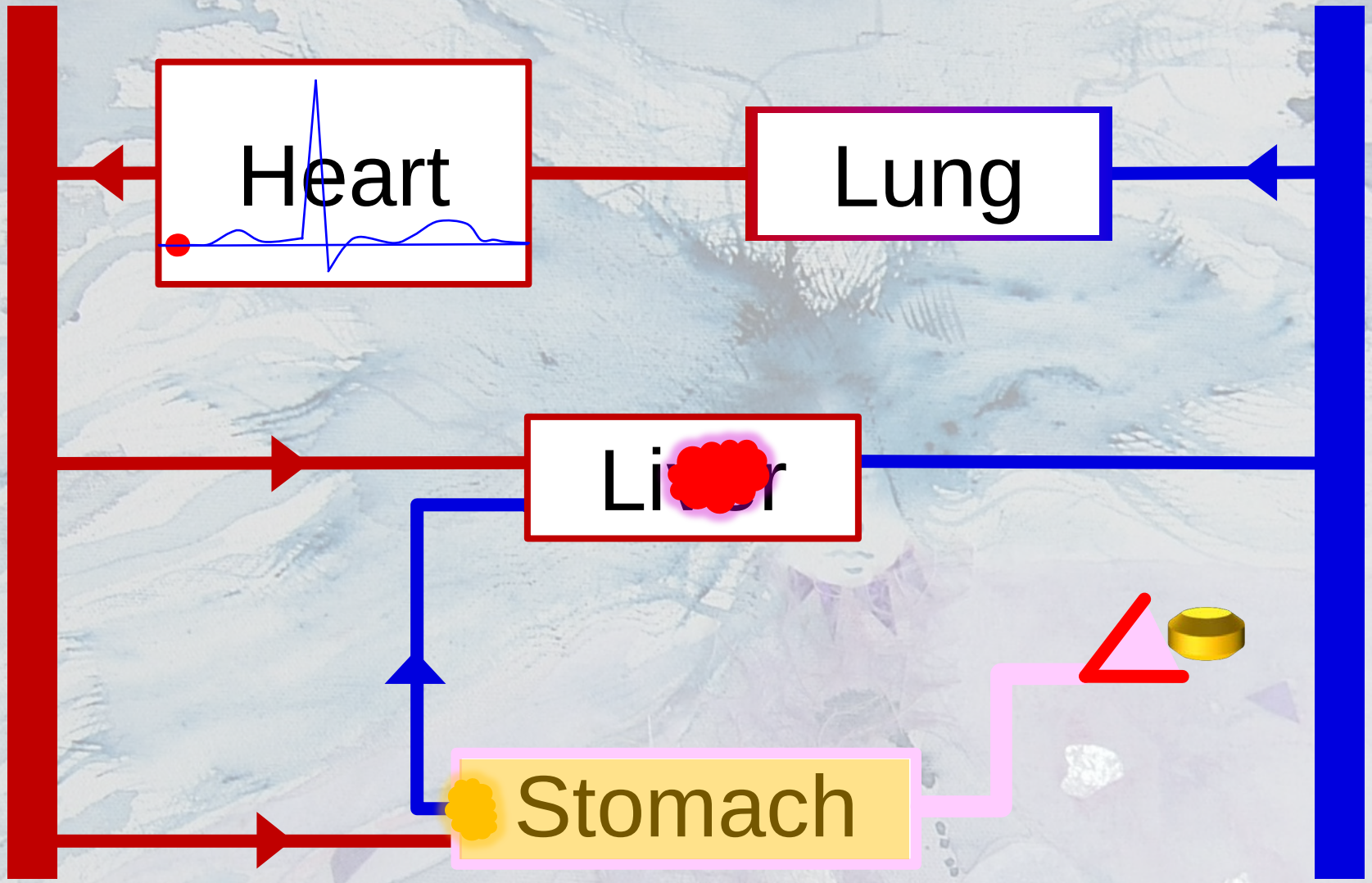
Homunculi ⇦

Humans ✗

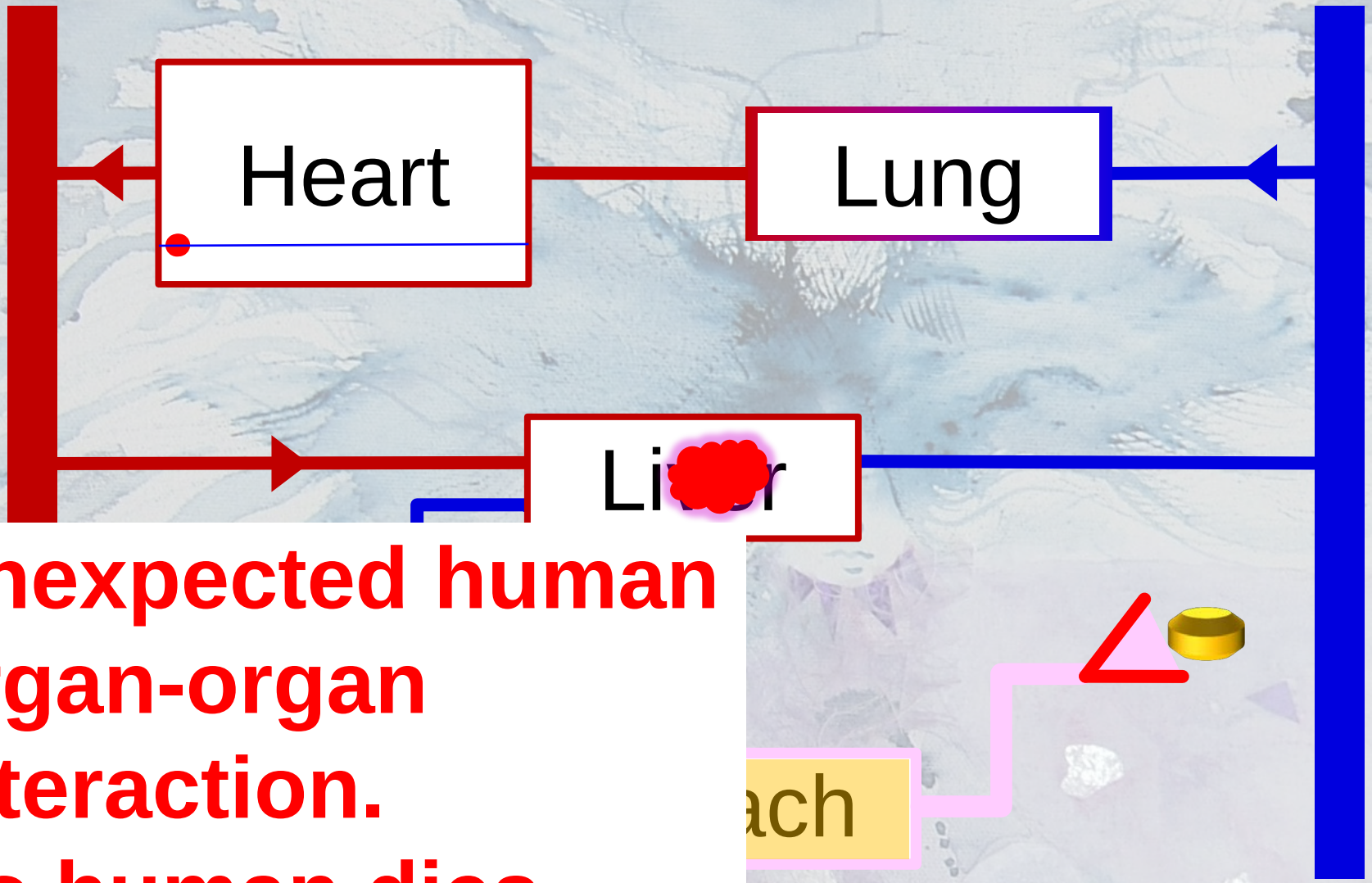
Our homunculi will be alive, built with human cells!



Test drugs in homunculi!



Test drugs in homunculi!



Unexpected human organ-organ interaction.

No human dies.

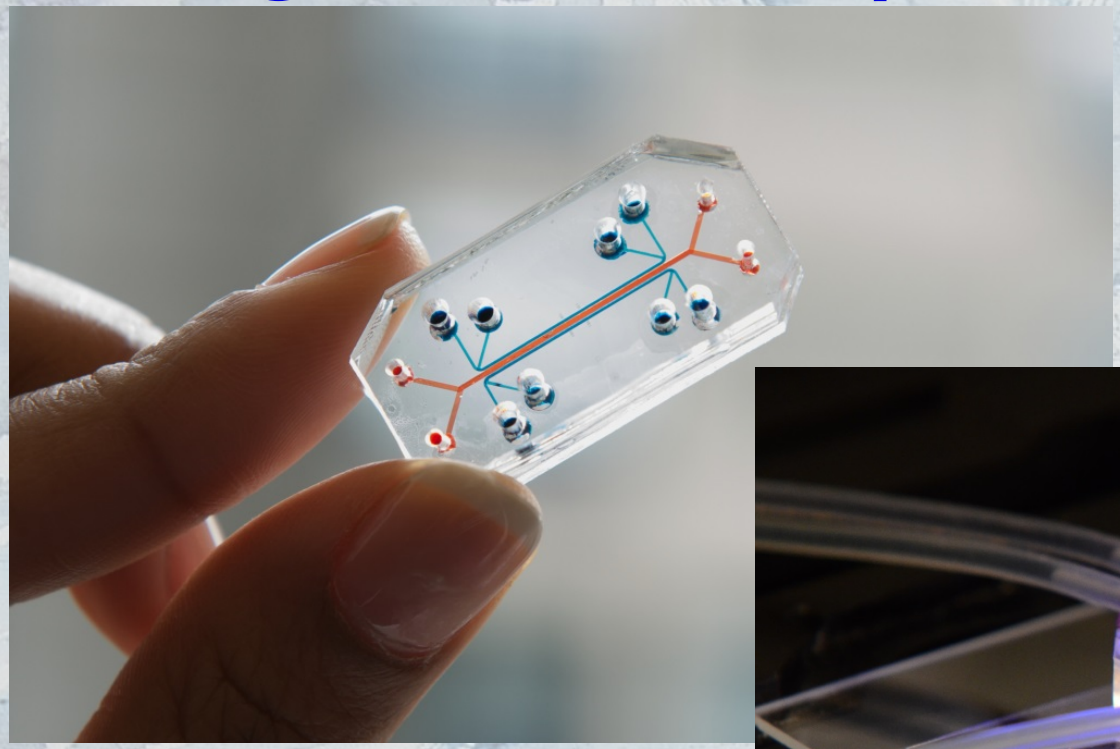
We've just seen why we are building homunculi

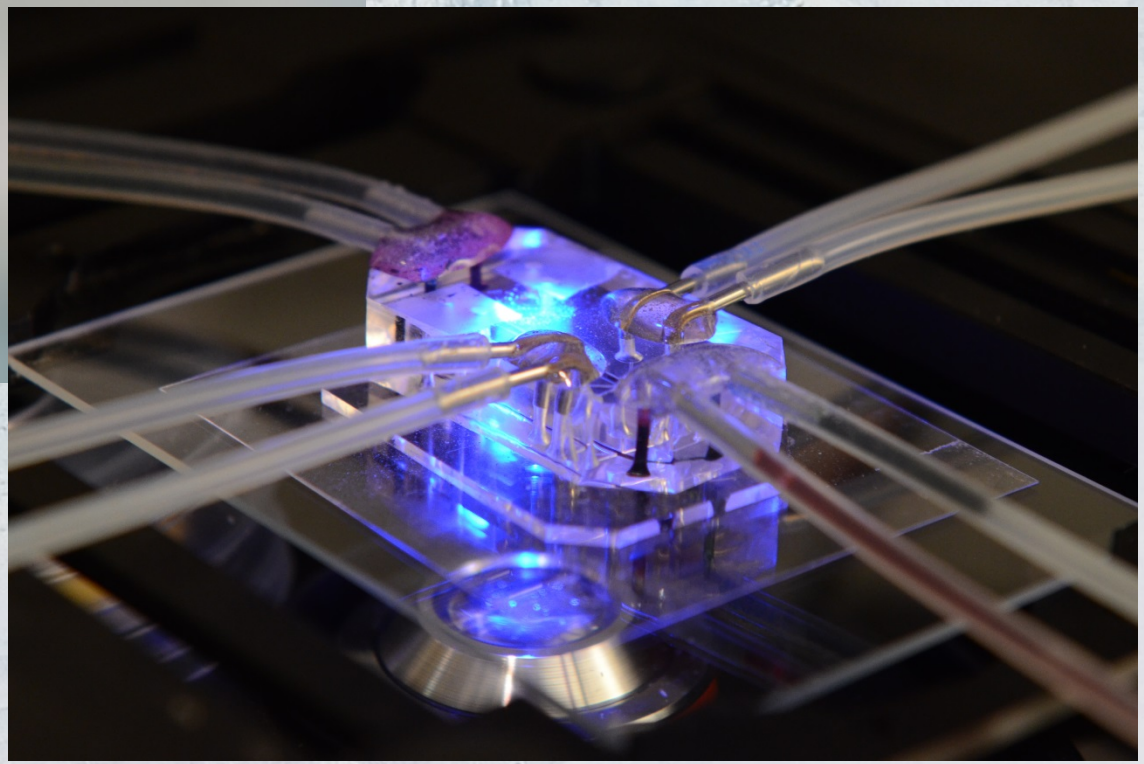
- Human biology is complex
- Homunculi can simplify:
  - Drug development
  - Environmental toxicology
  - Physiology

How do you build homunculi?

- Use human cells to make *microfluidic organ chips* that work like the real organs.
- Connect organs together.
- Do lots of things at the same time. (phase space)

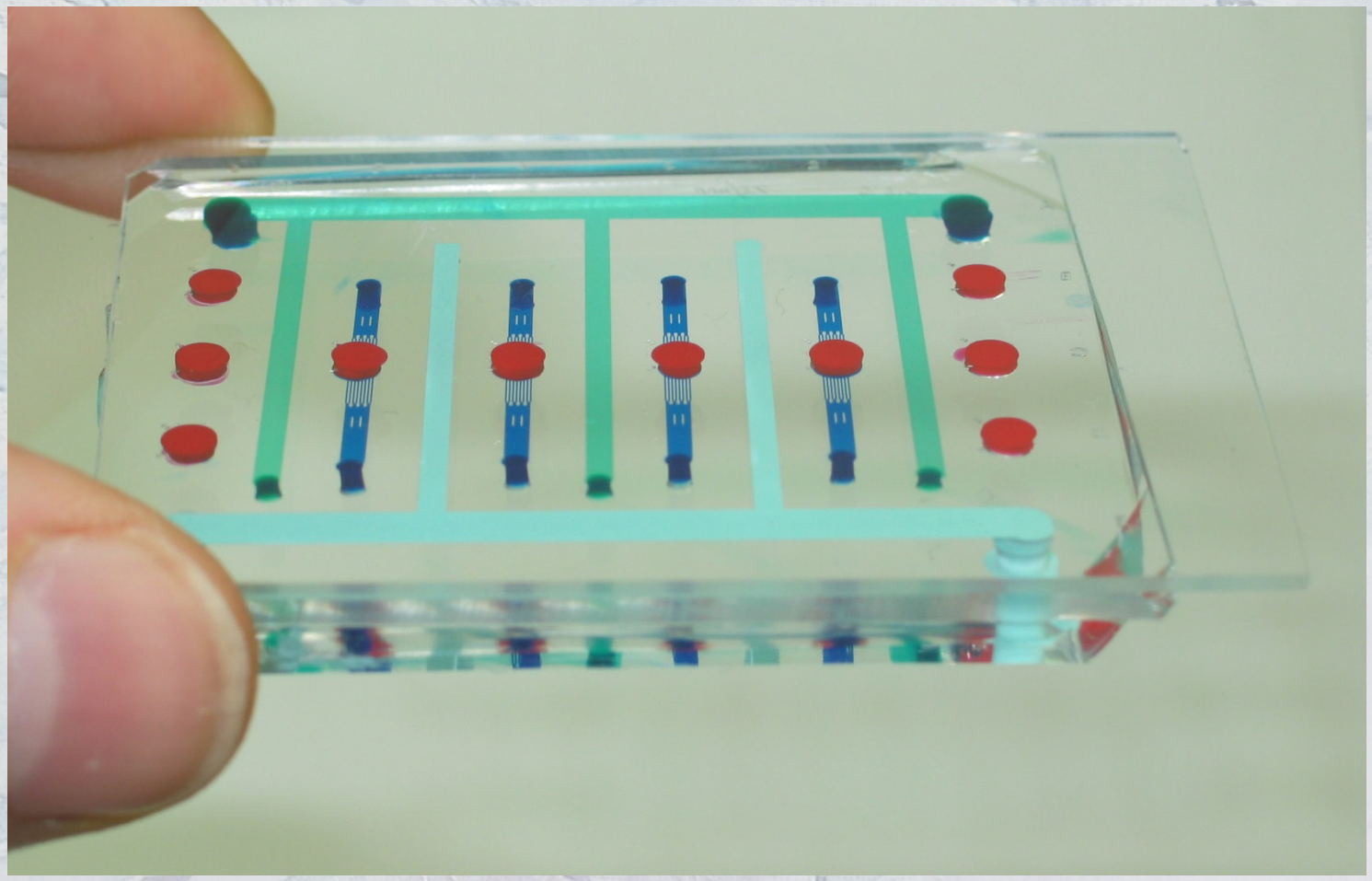
Lung on a chip





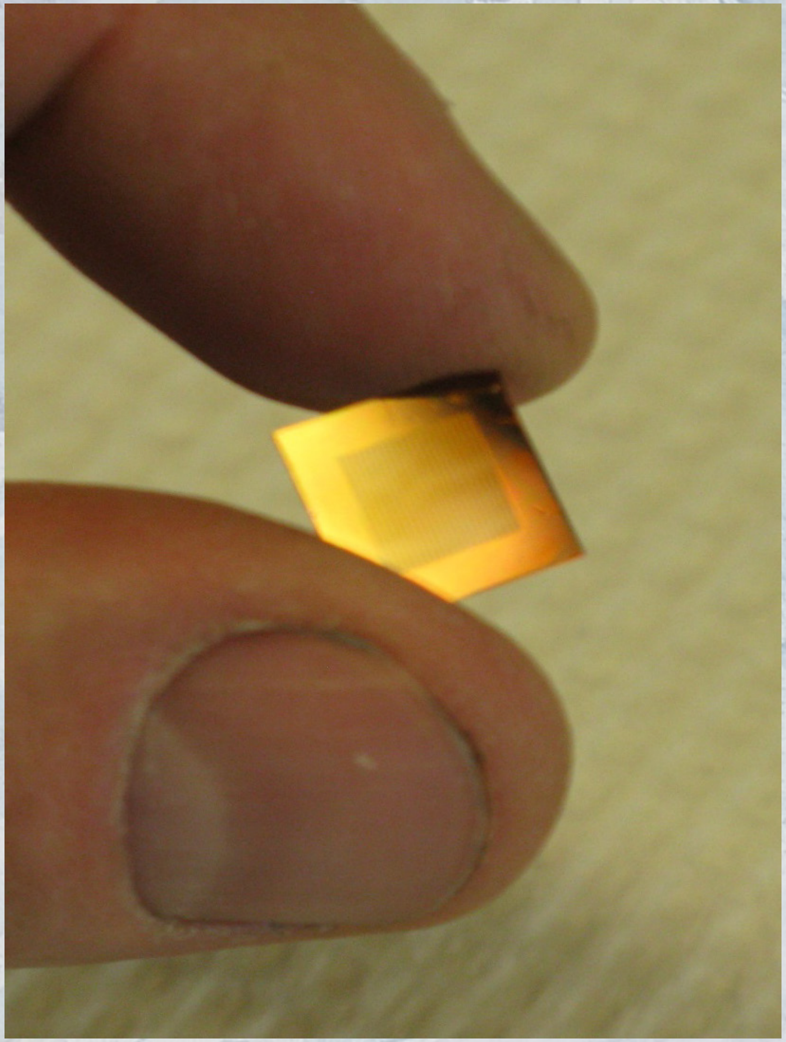
Don Ingber, Harvard

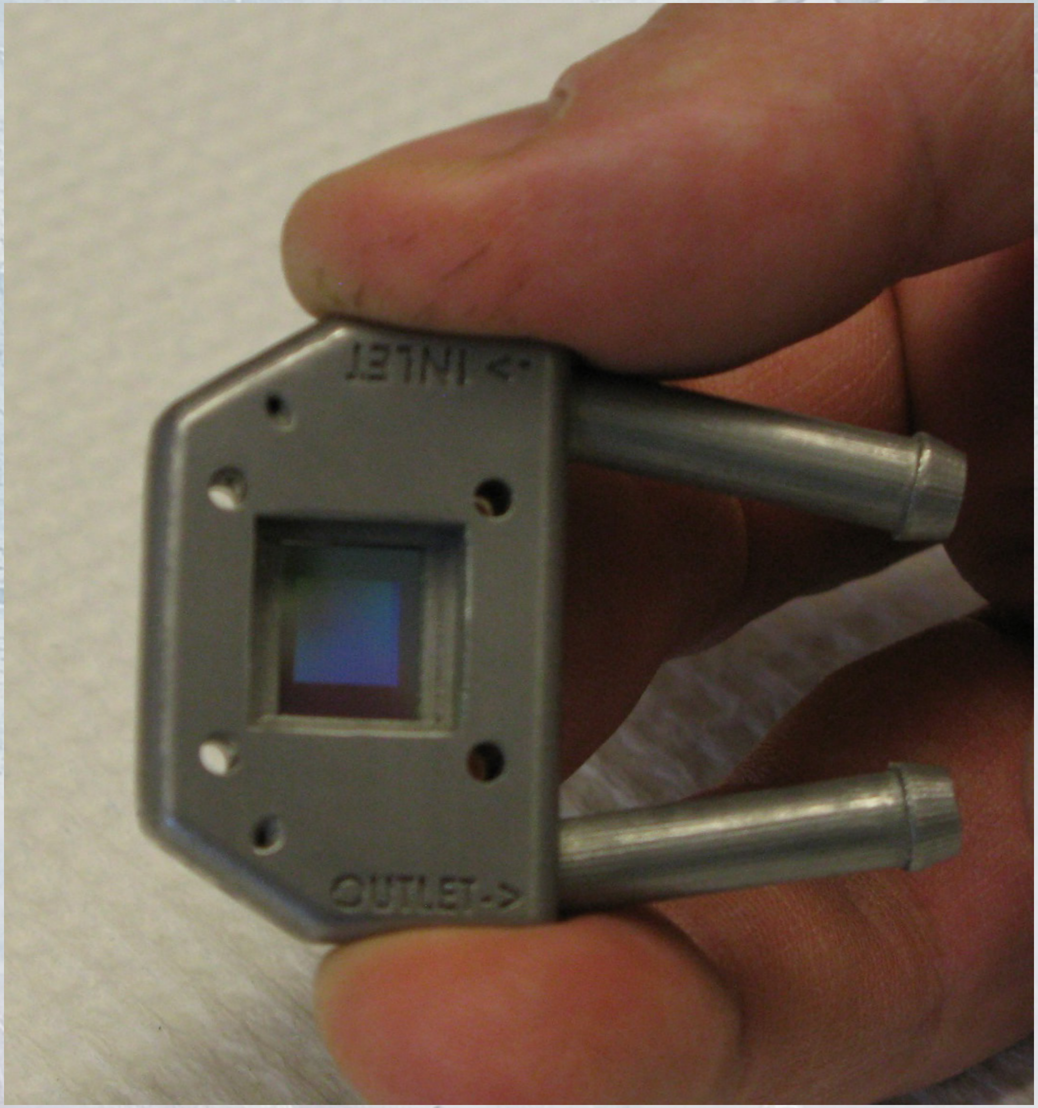
Mammary gland on a chip



Lisa McCawley and Dmitry Markov, Vanderbilt

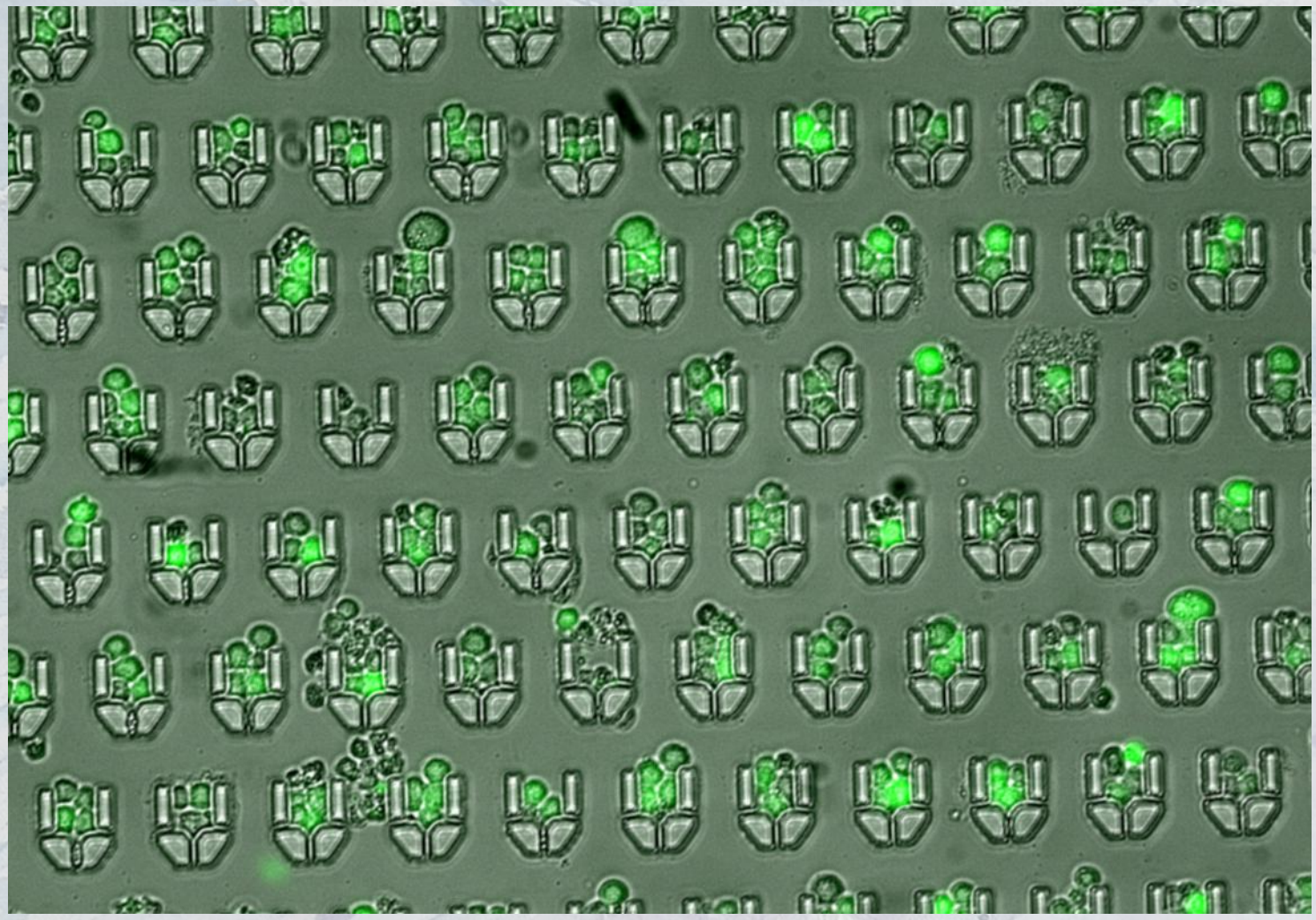
Kidney on a chip





Shuvo Roy, UCSF and Bill Fissell, Vanderbilt

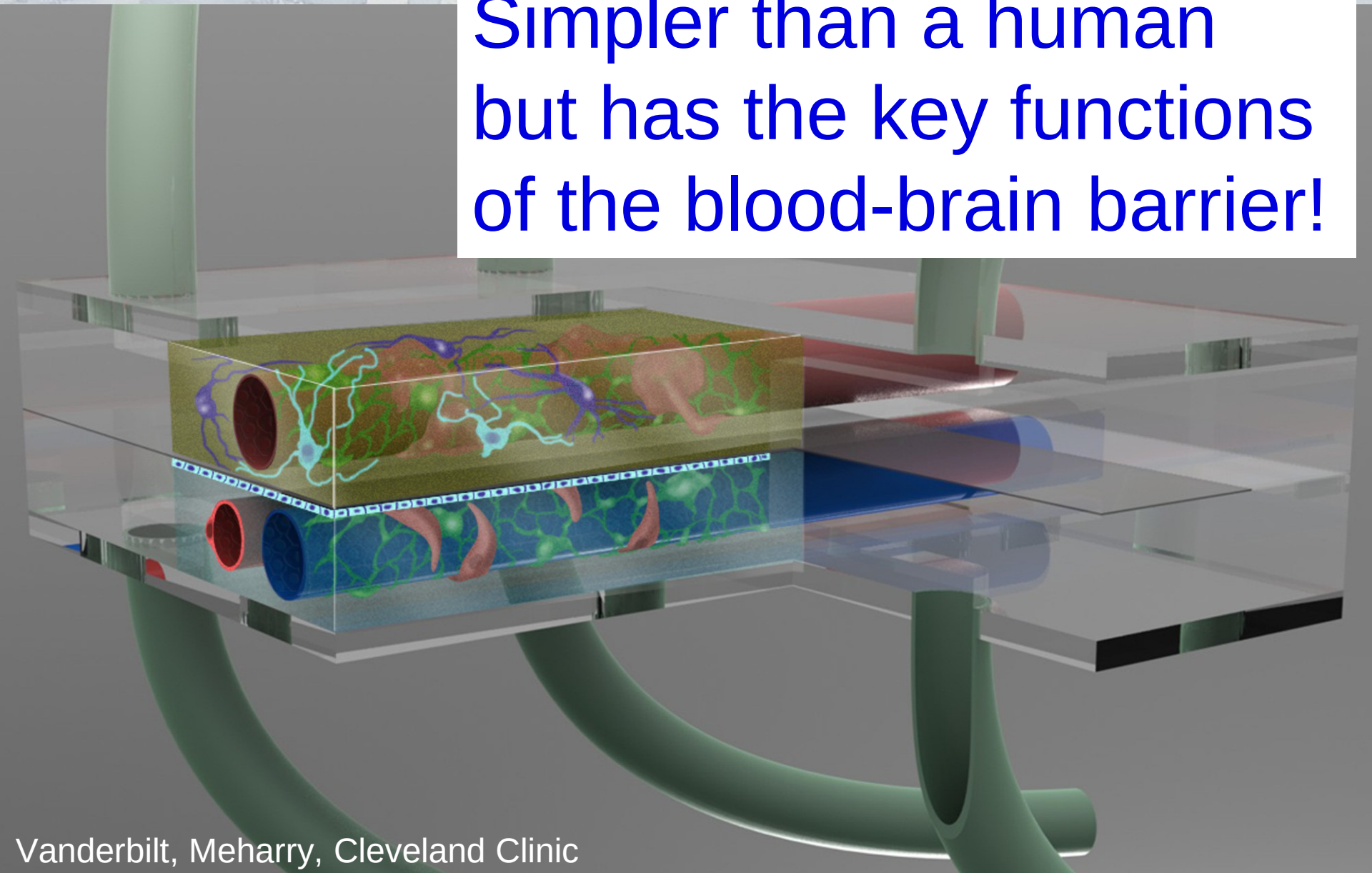
T cells in a lymph node on a chip



Kevin Seale, Jake Brady and Shannon Faley, Vanderbilt

Brain on a chip

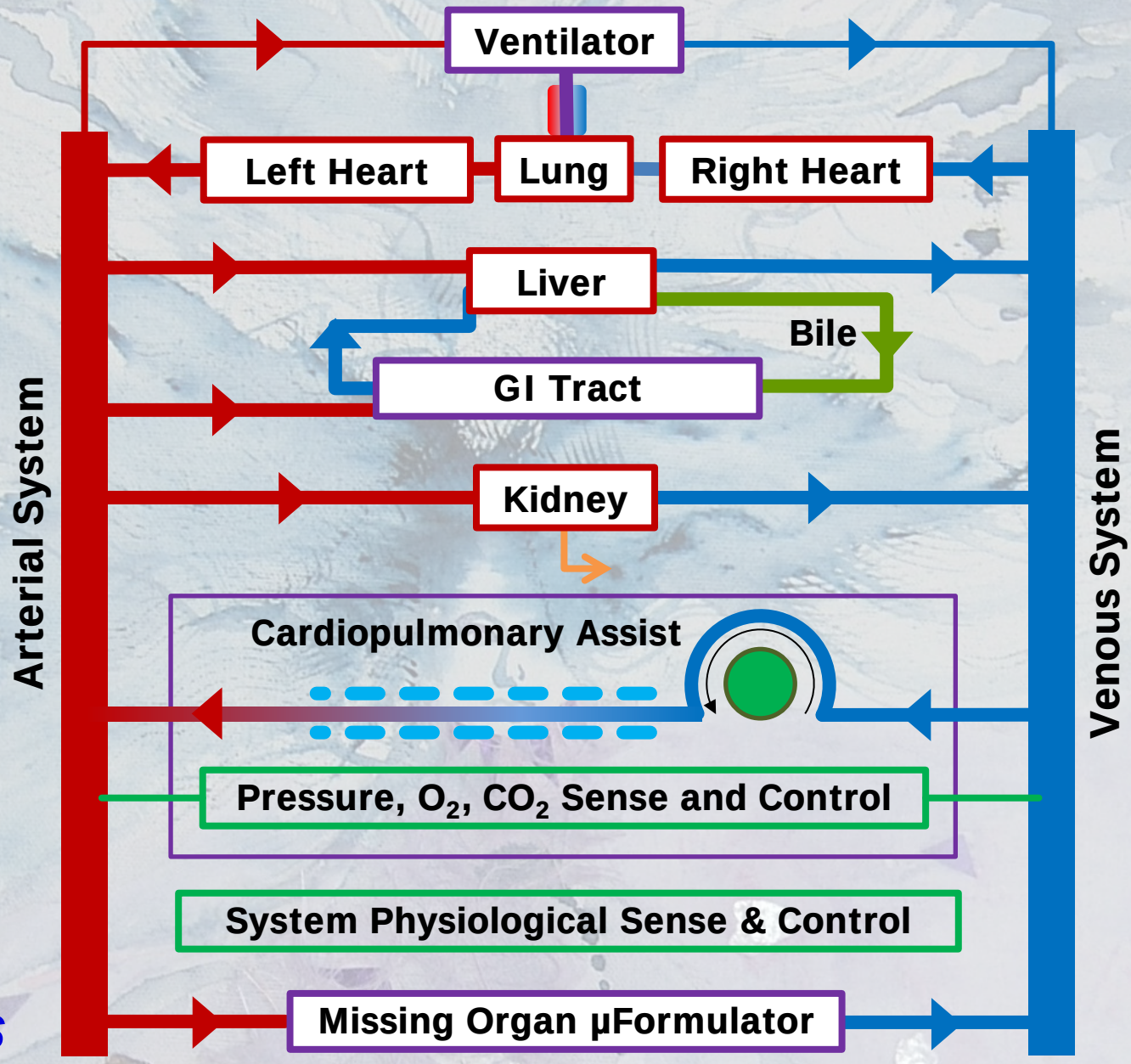
Simpler than a human but has the key functions of the blood-brain barrier!



Vanderbilt, Meharry, Cleveland Clinic

Advanced Tissue-engineered Human Ectypal Network Analyzer

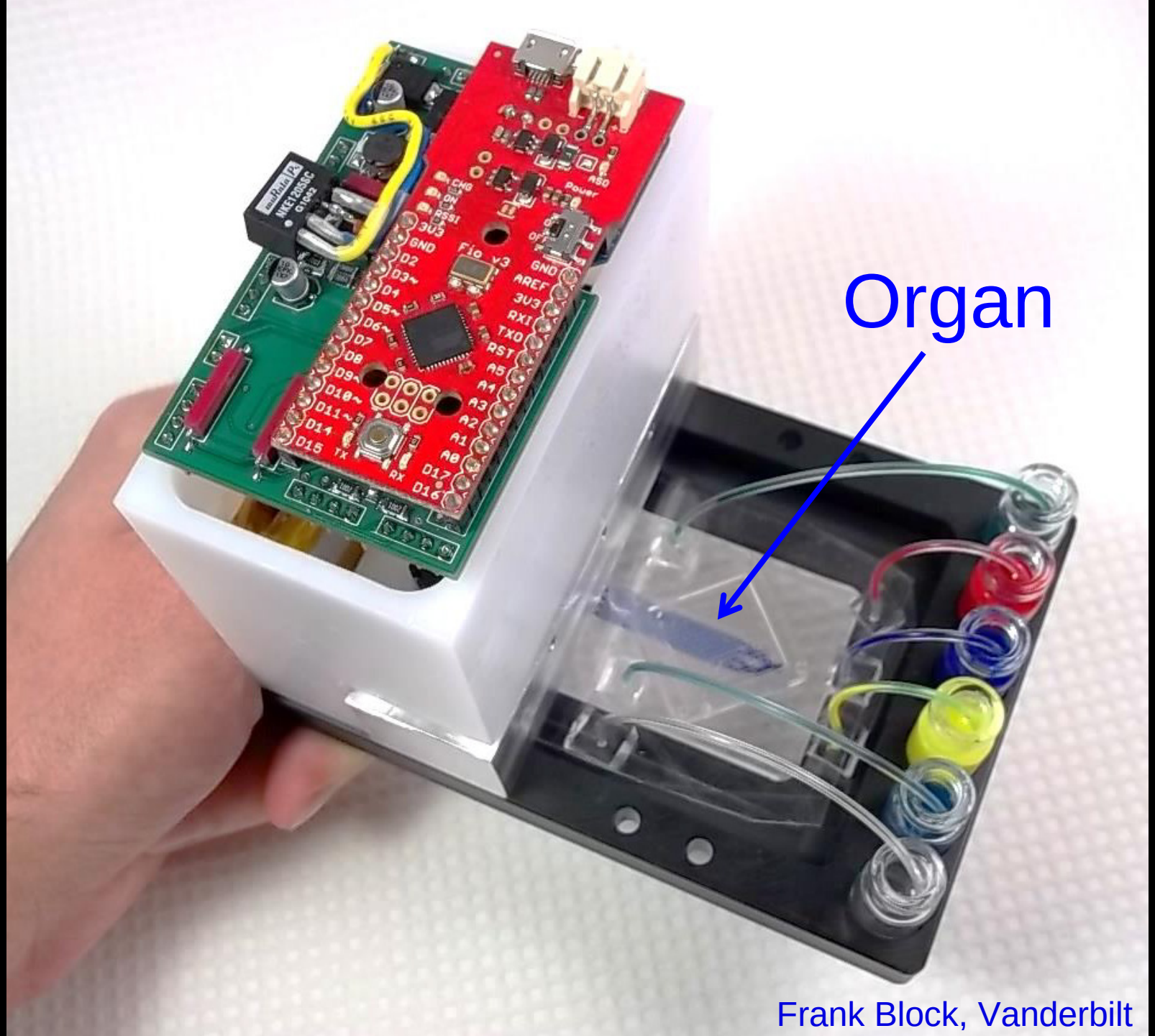
We call our chip Athena



milliHuman (mHu)

Homo chippus

Los Alamos National Laboratory, Vanderbilt, Harvard, Charité Hospital Berlin, UCSF, CFD Research Corporation



Frank Block, Vanderbilt

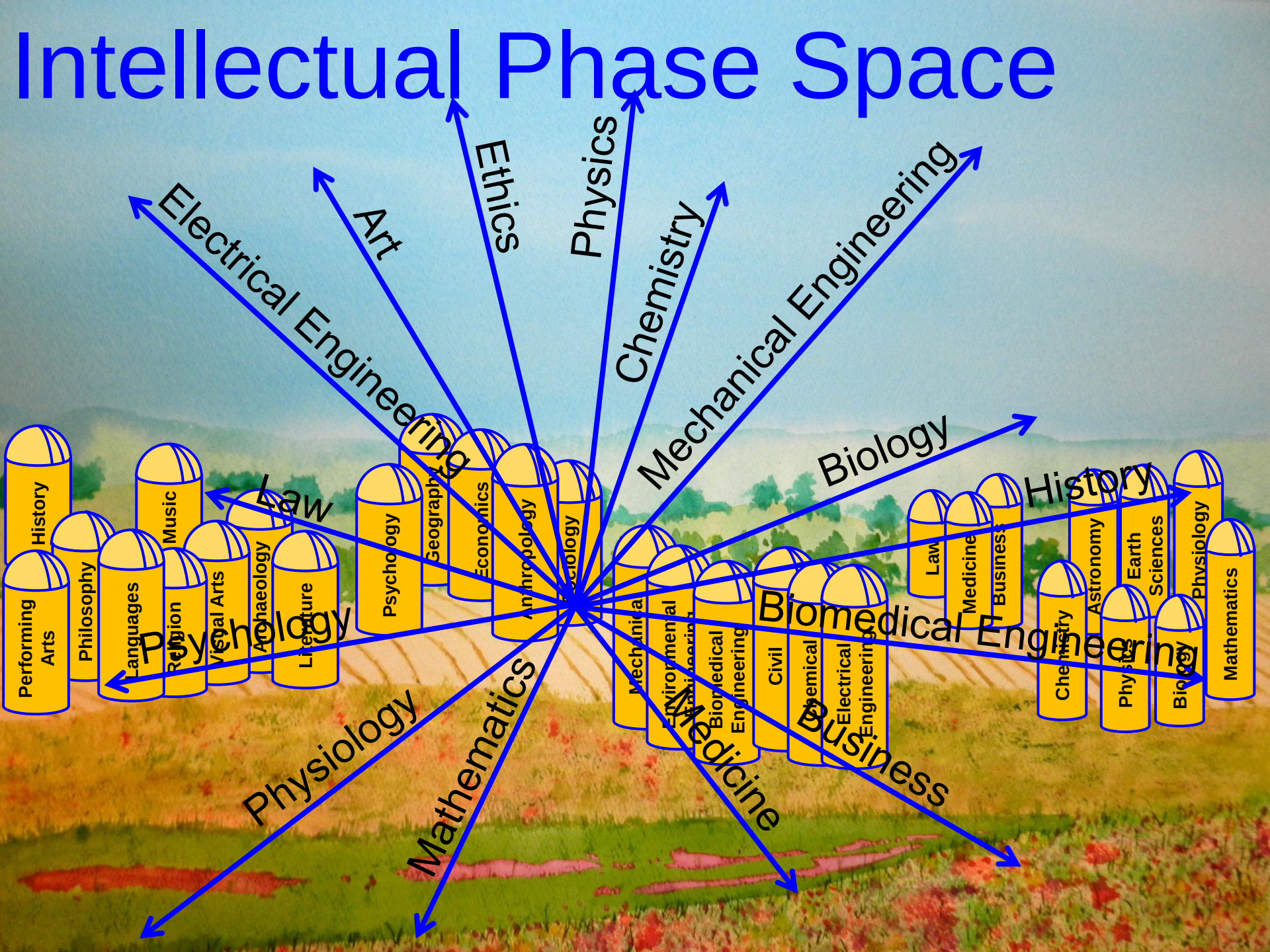
What kinds of people are building homunculi?

Fields of Knowledge

Silos of Knowledge

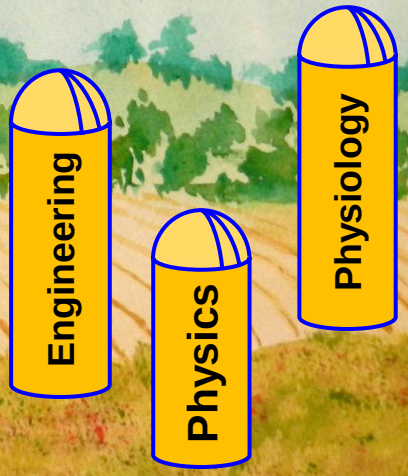
Athena needs a mix of disciplines

Intellectual Phase Space



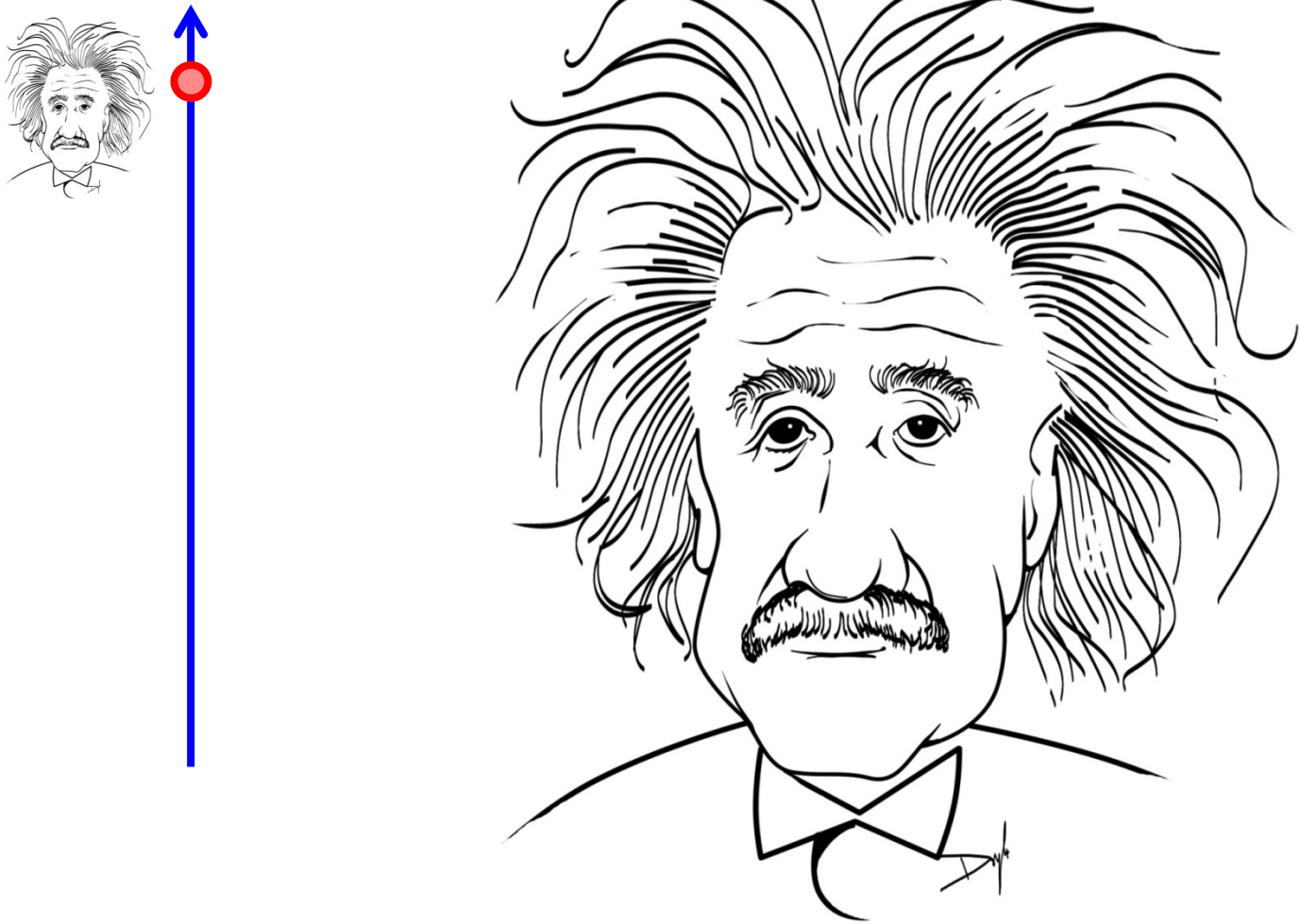
My Knowledge

You can be more than one thing at a time in phase space!



Intellectual Phase Space

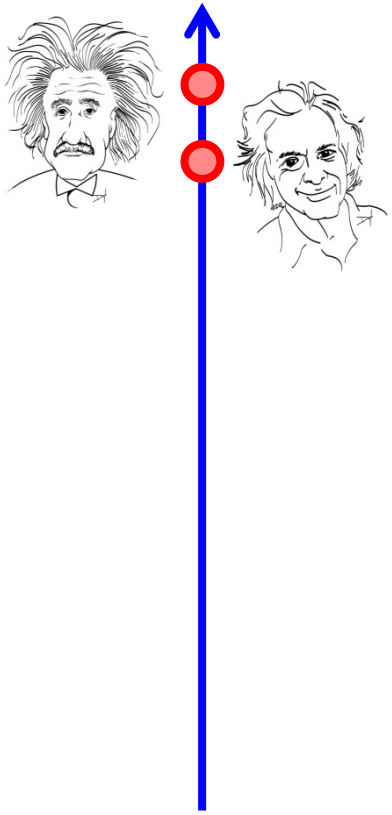
Physics



Albert Einstein
1879-1955

Intellectual Phase Space

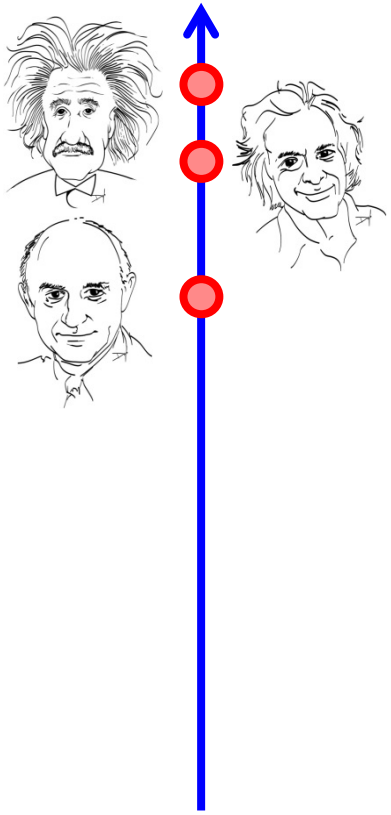
Physics



Richard Feynman
1918-1988

Intellectual Phase Space

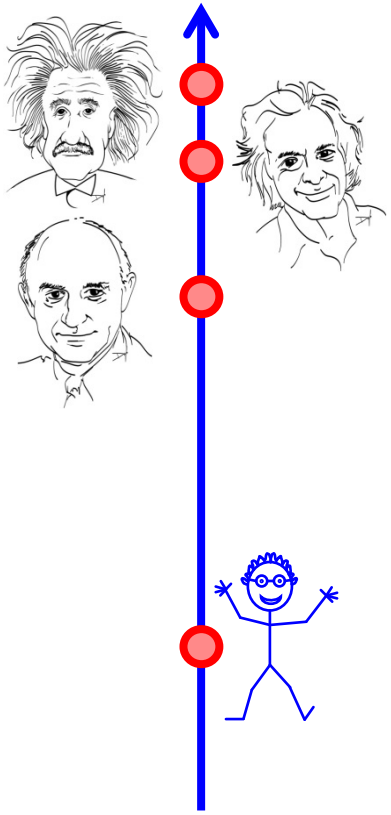
Physics



Enrico Fermi
1901-1954

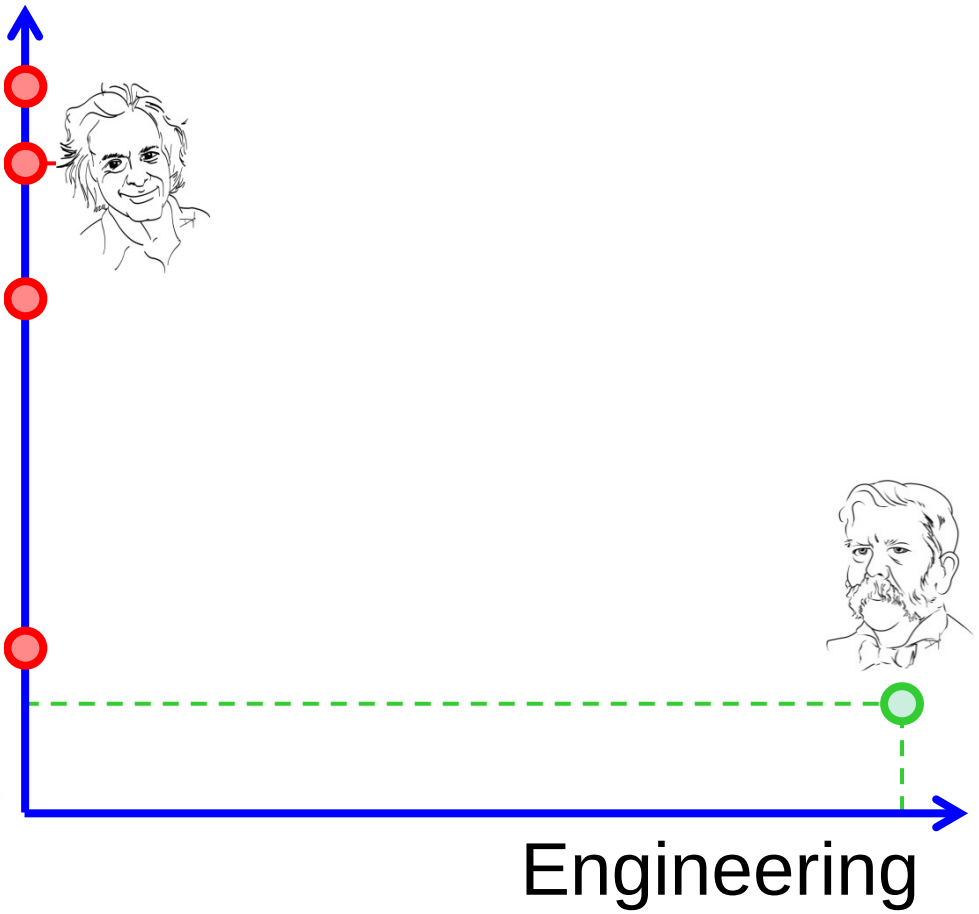
Intellectual Phase Space

Physics



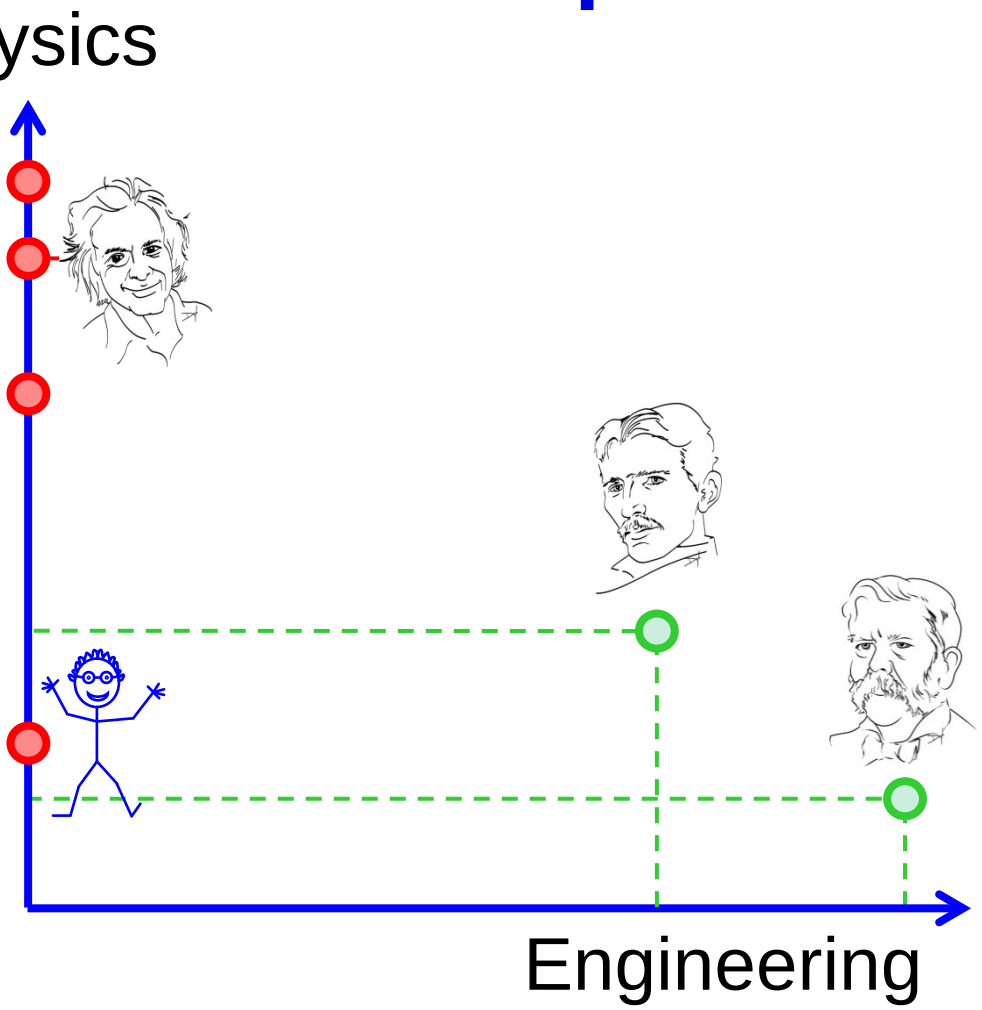
Intellectual Phase Space

George Westinghouse
1846-1914

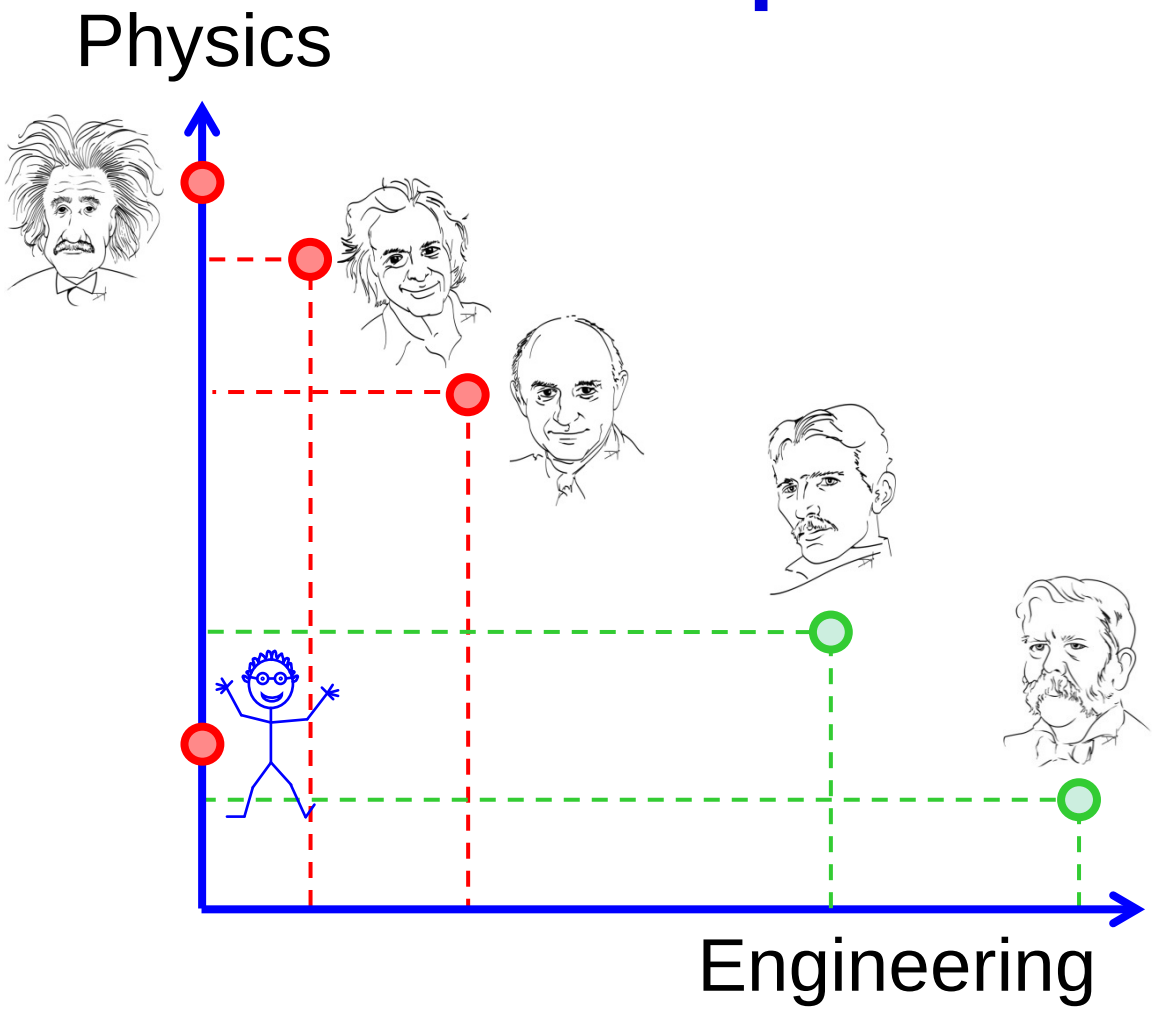


Intellectual Phase Space

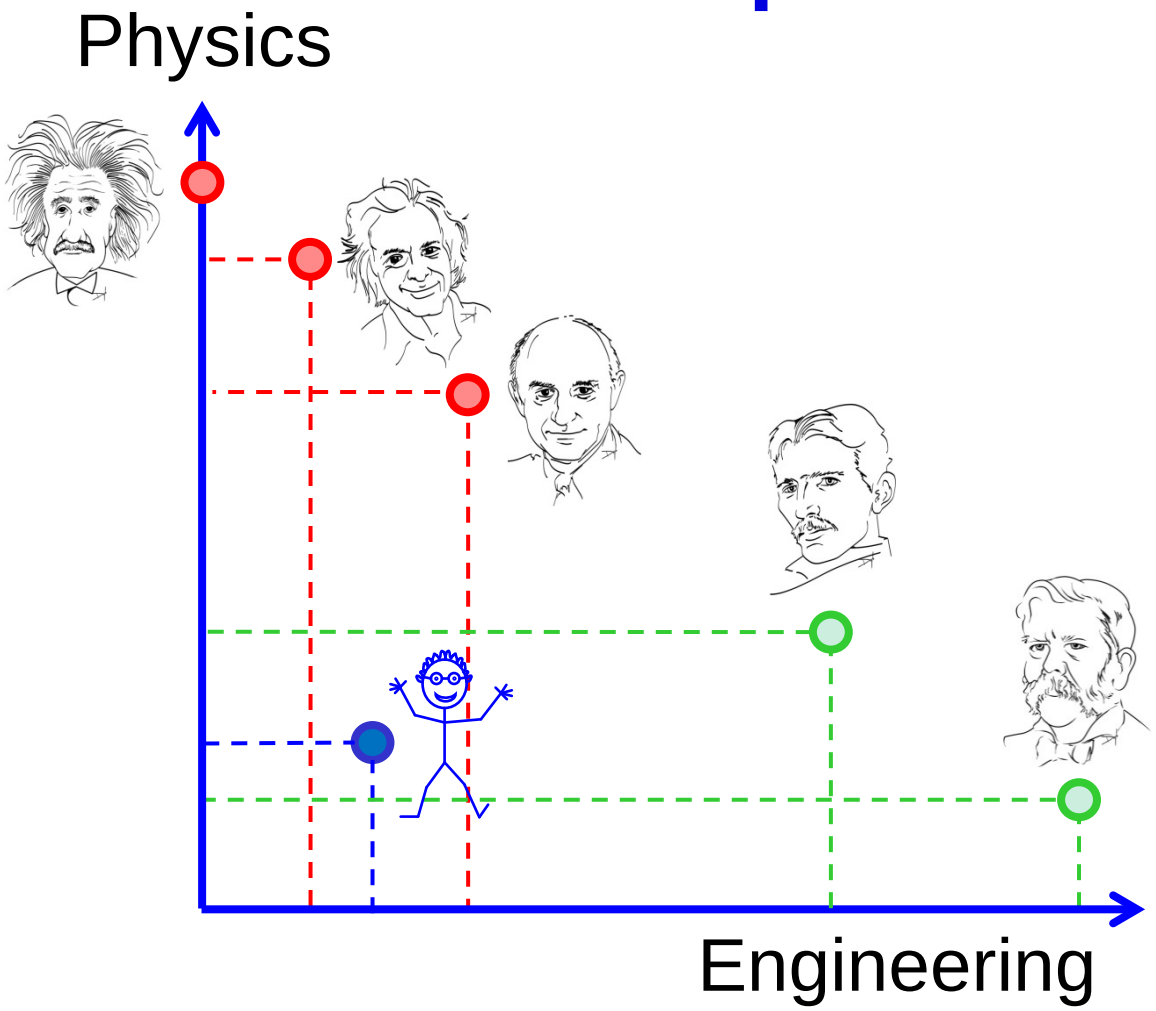
Nikola Tesla
1856-1943



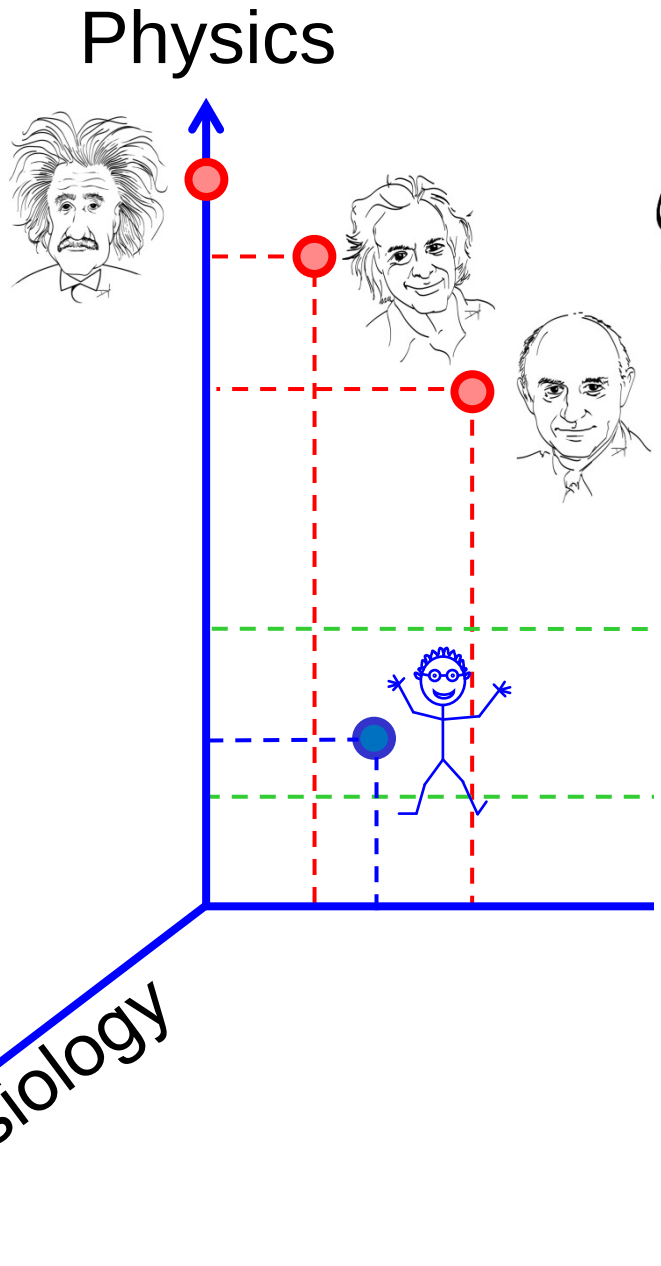
Intellectual Phase Space



Intellectual Phase Space

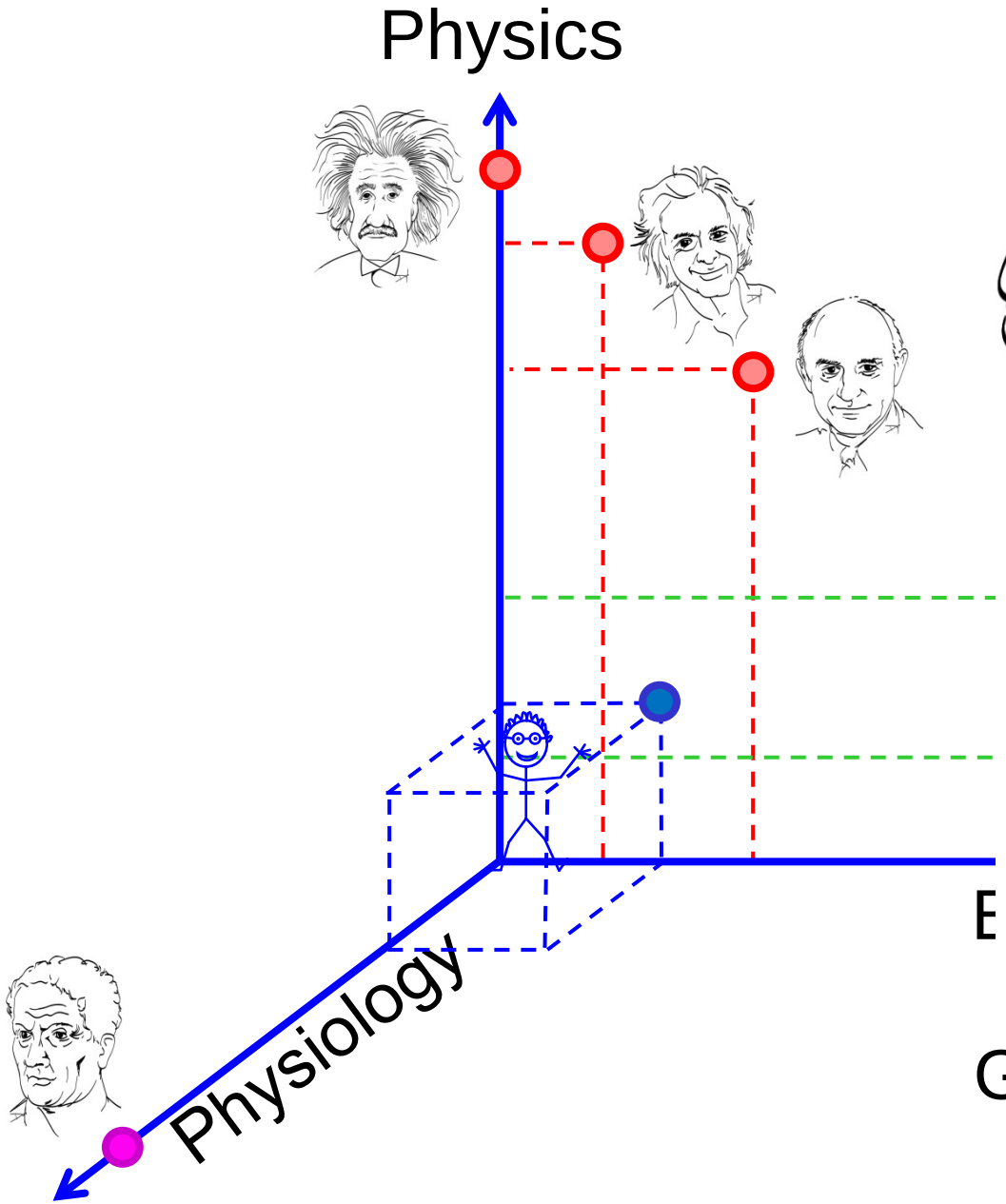


Intellectual Phase Space



Galen of Pergamon
AD 129-216

Intellectual Phase Space



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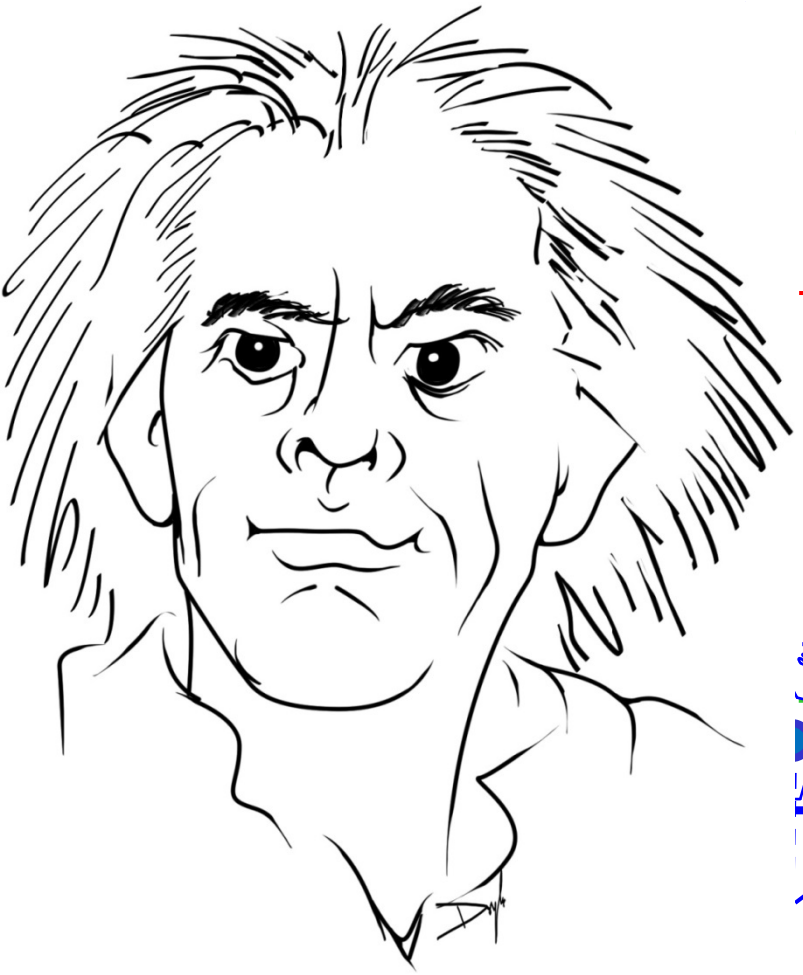
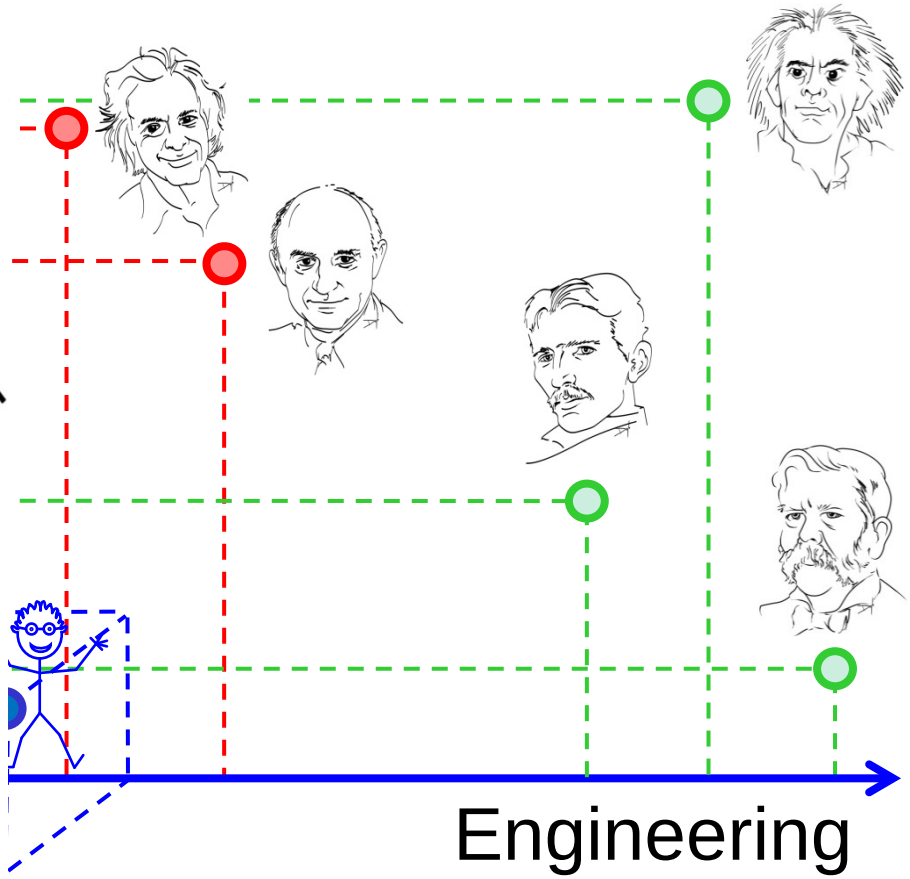
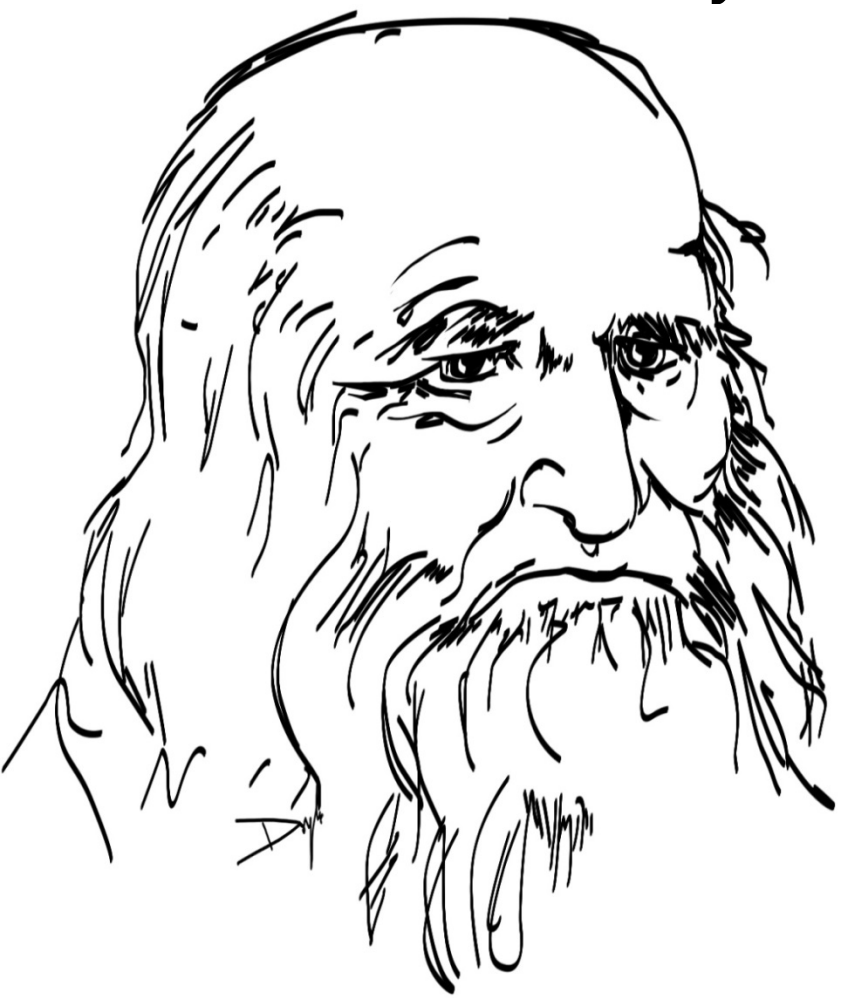
Intellectual Phase Space



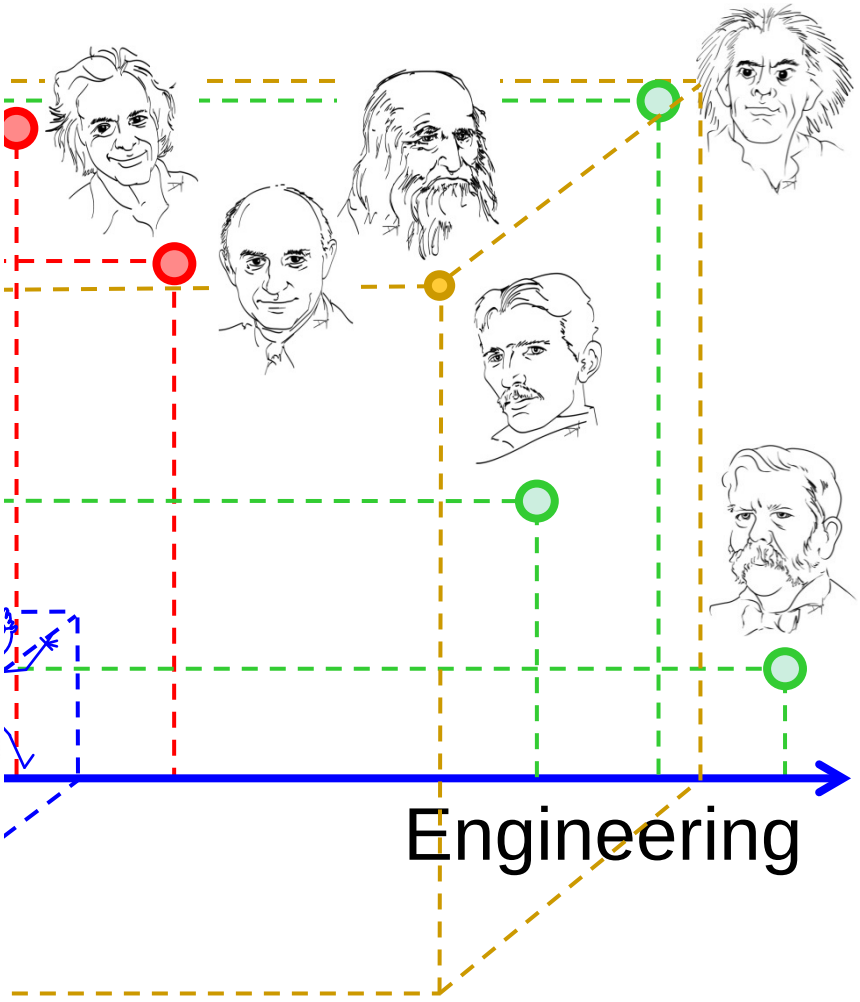
Emmett “Doc” Brown
1885-2015?



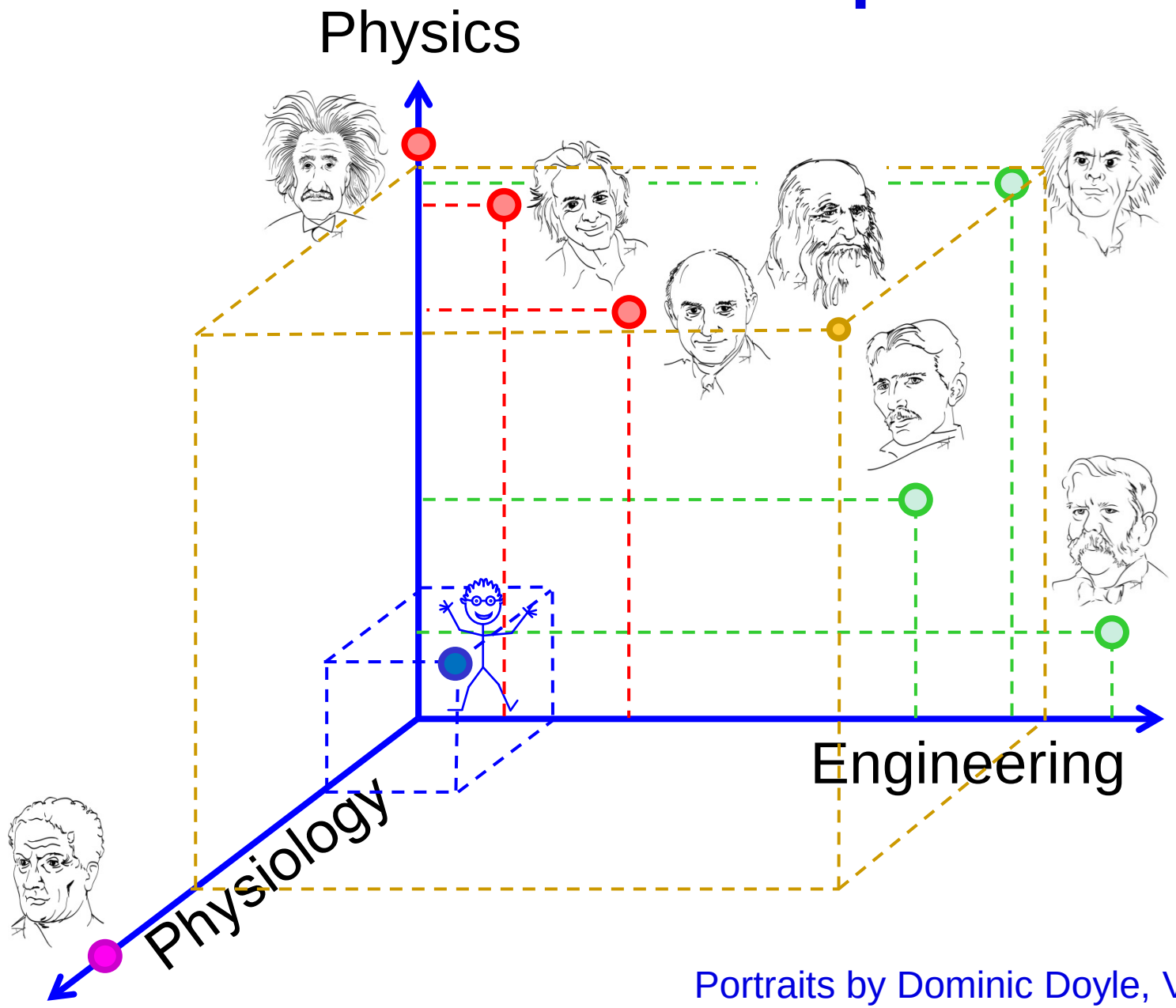
Intellectual Phase Space



Leonardo da Vinci
1452-1519

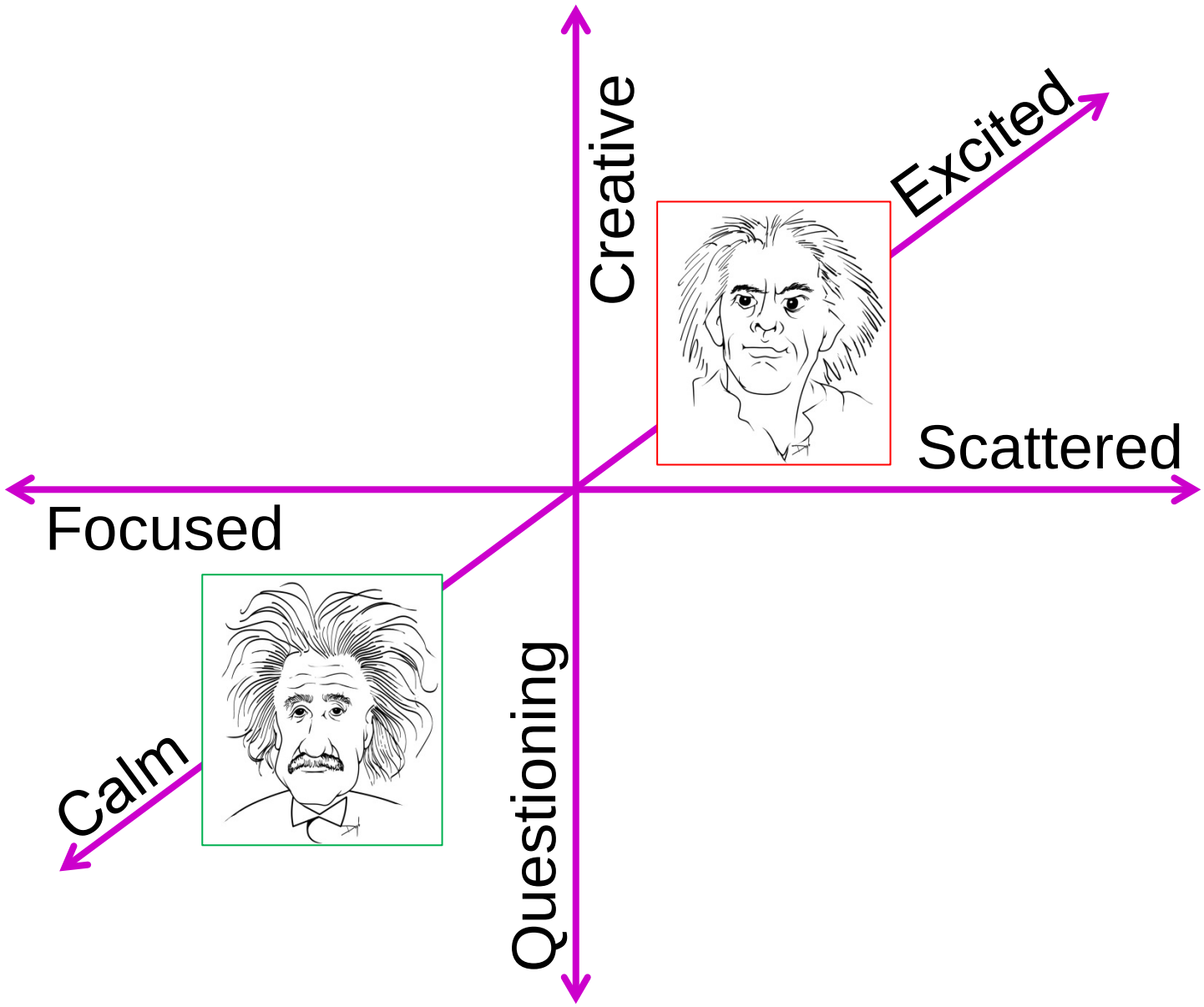


Intellectual Phase Space

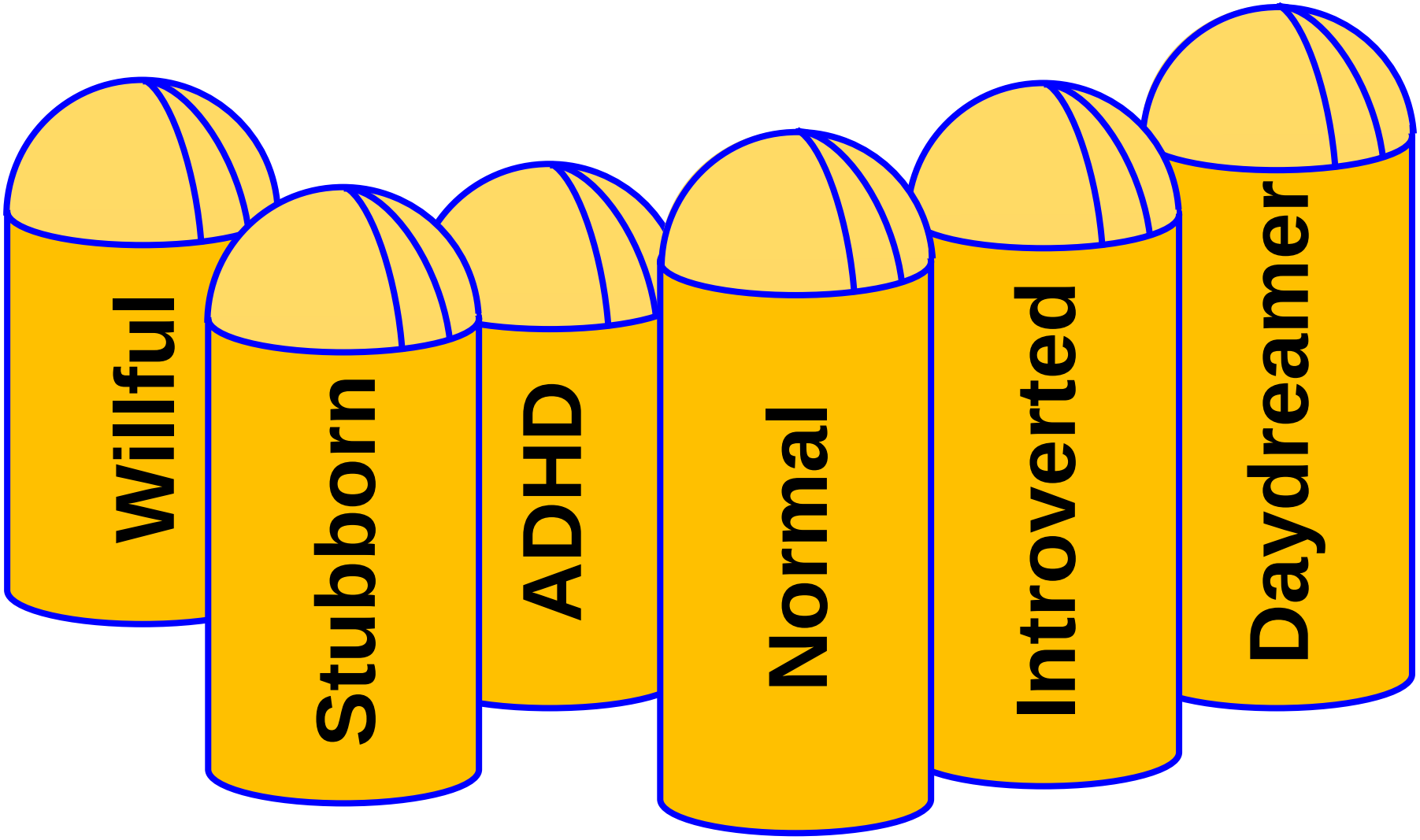


Portraits by Dominic Doyle, Vanderbilt

Behavioral Phase Space



Behavioral Silos



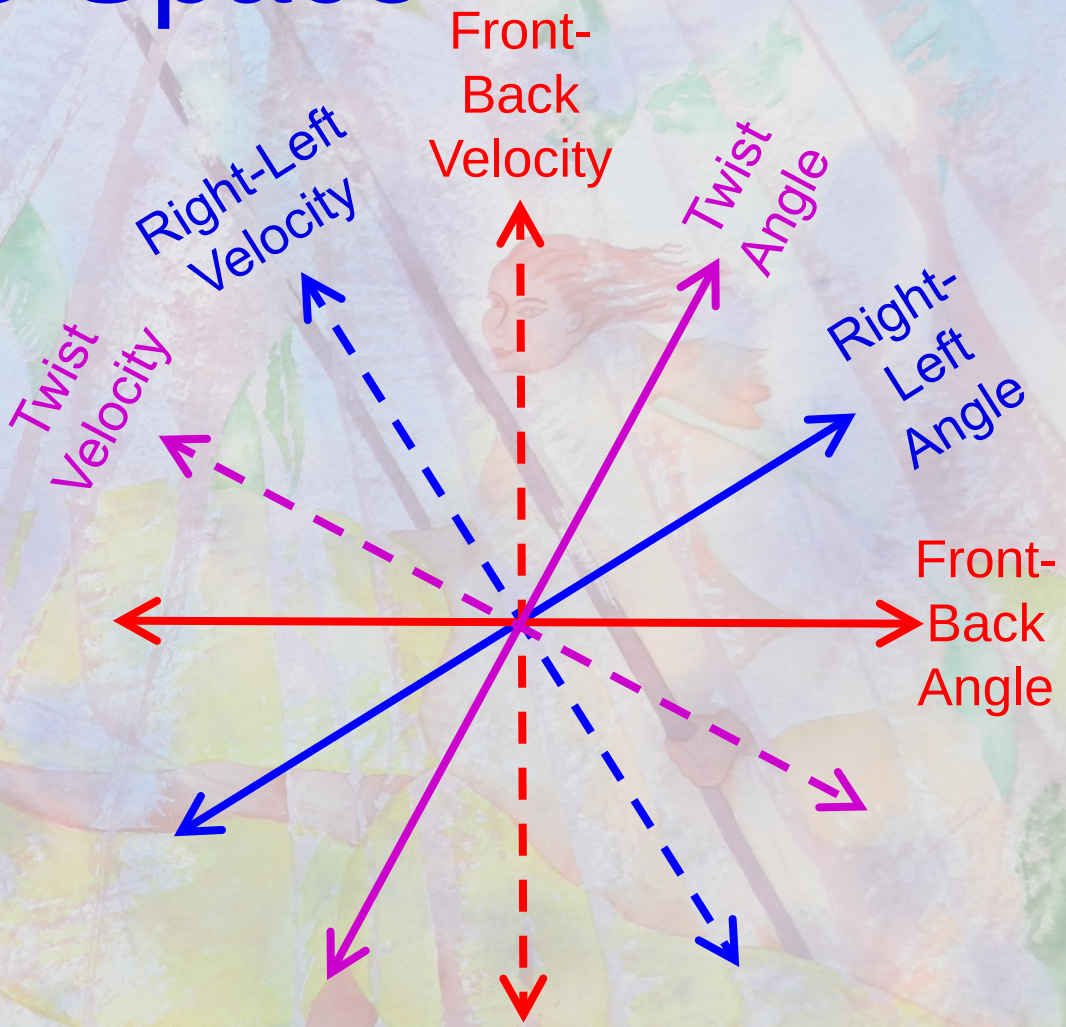
Swing Phase Space

Front and back

Left and Right

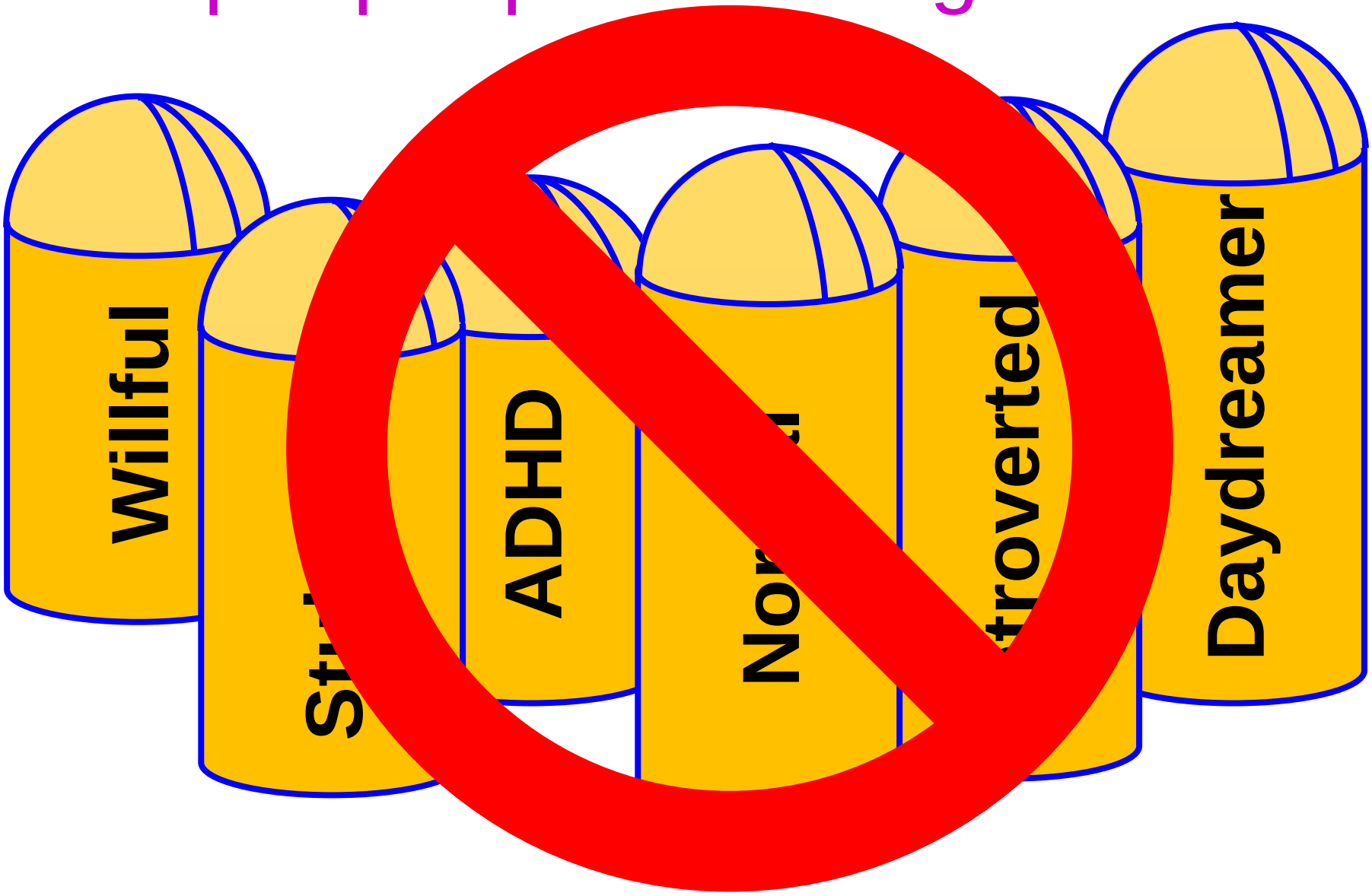
Orbit

Twist

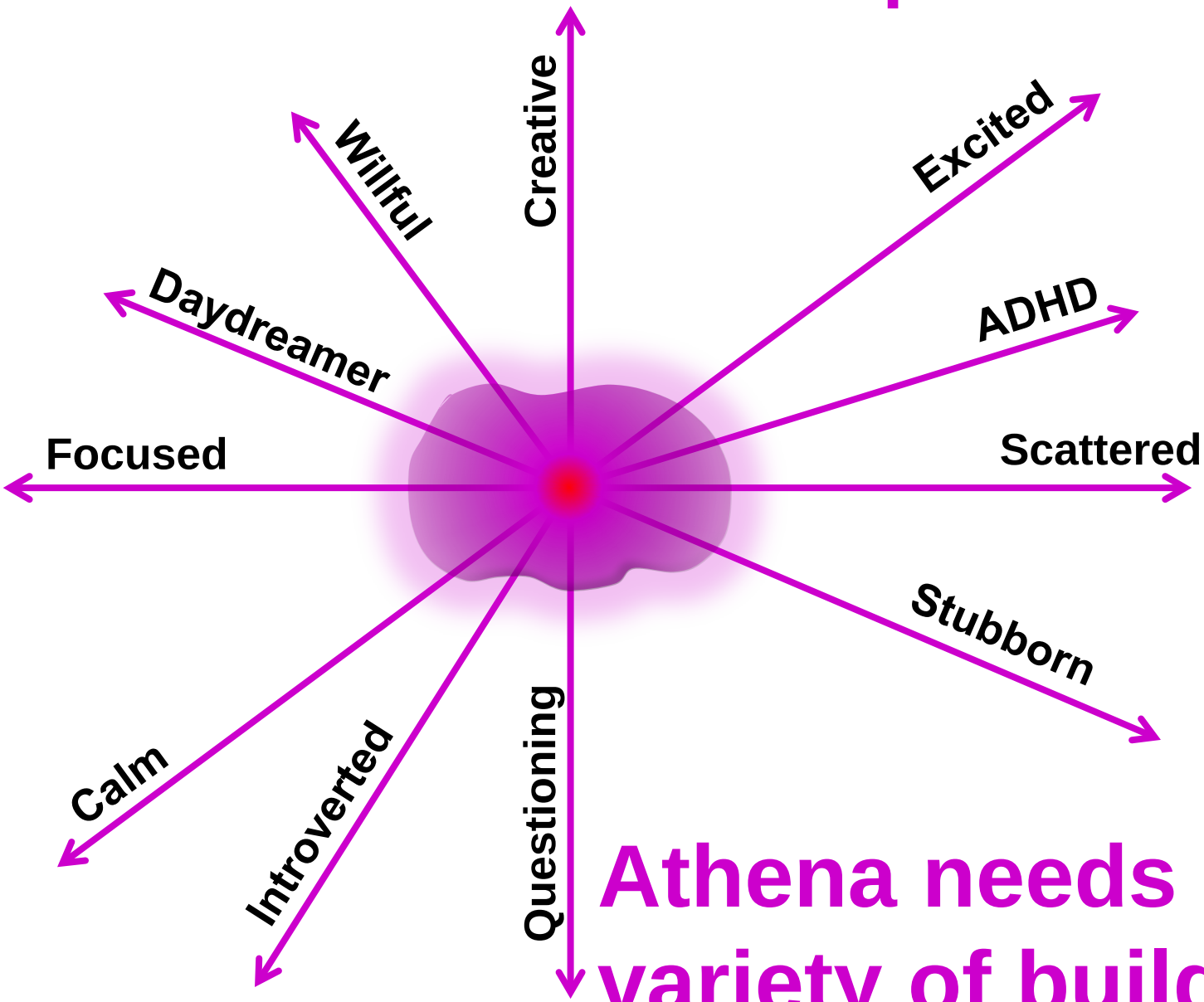


Six-Dimensional Phase Space is FUN, but often discouraged!

Don’t put people in a single silo!



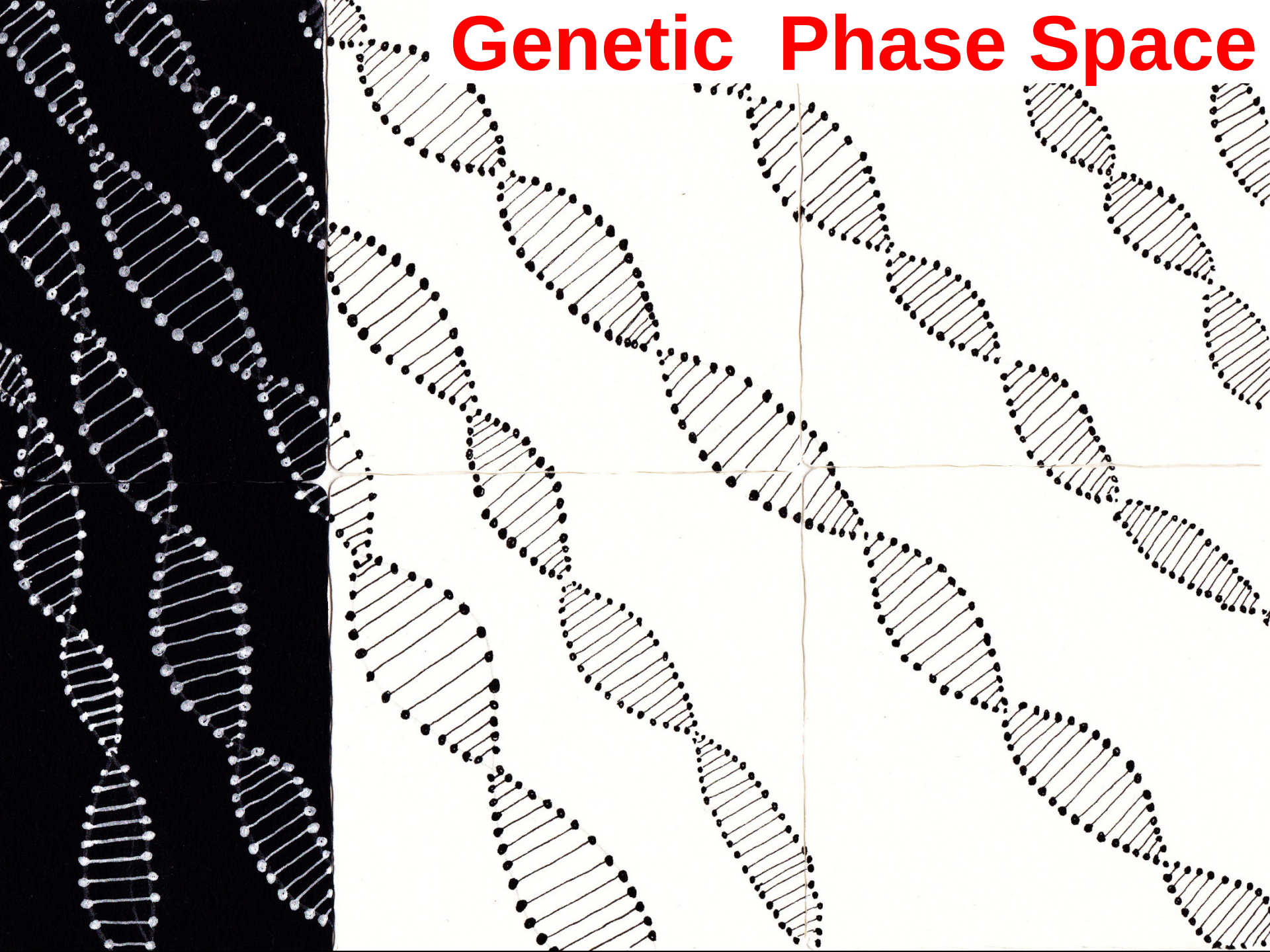
Behavioral Phase Space

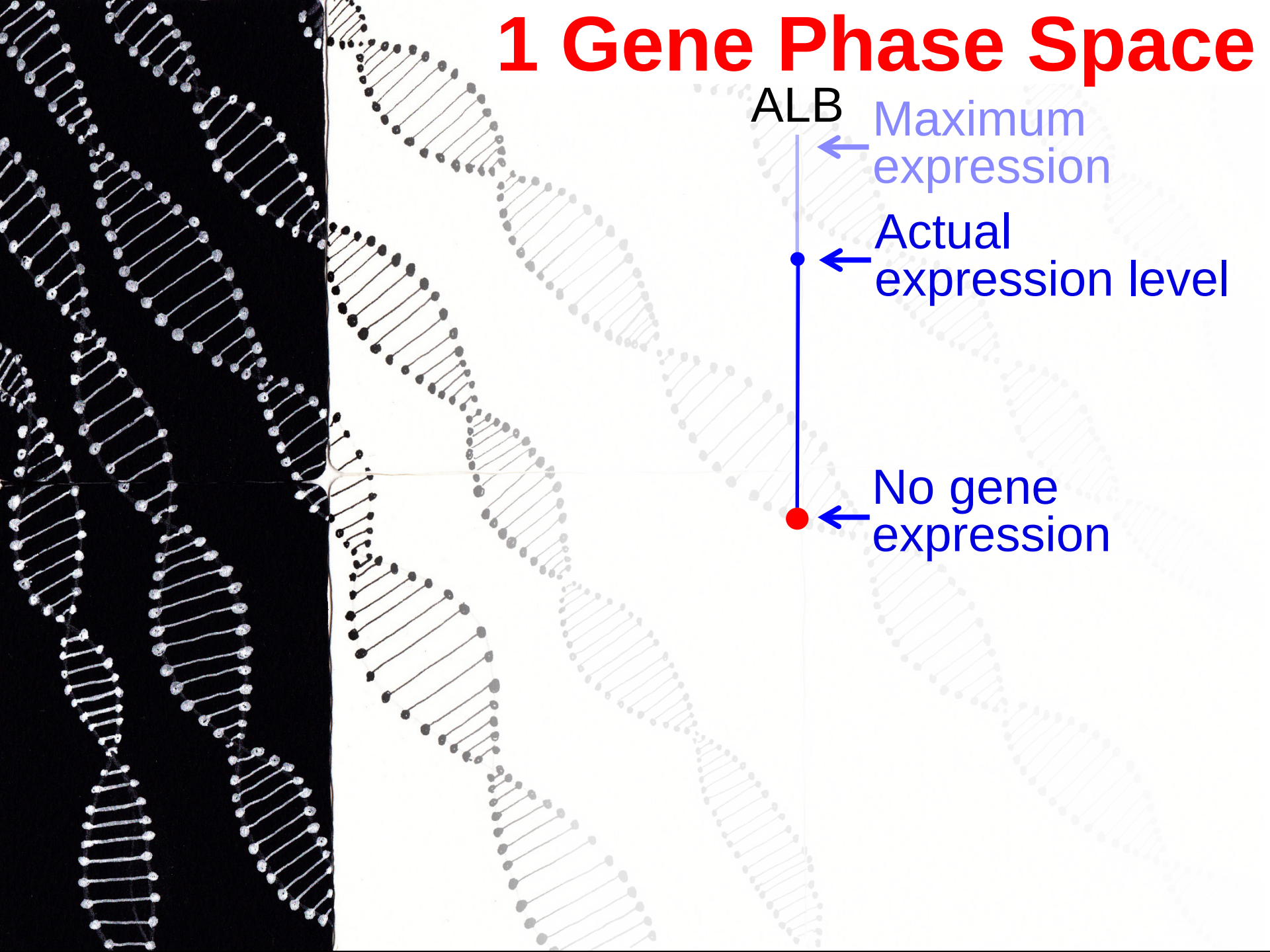


Athena needs a variety of builders!

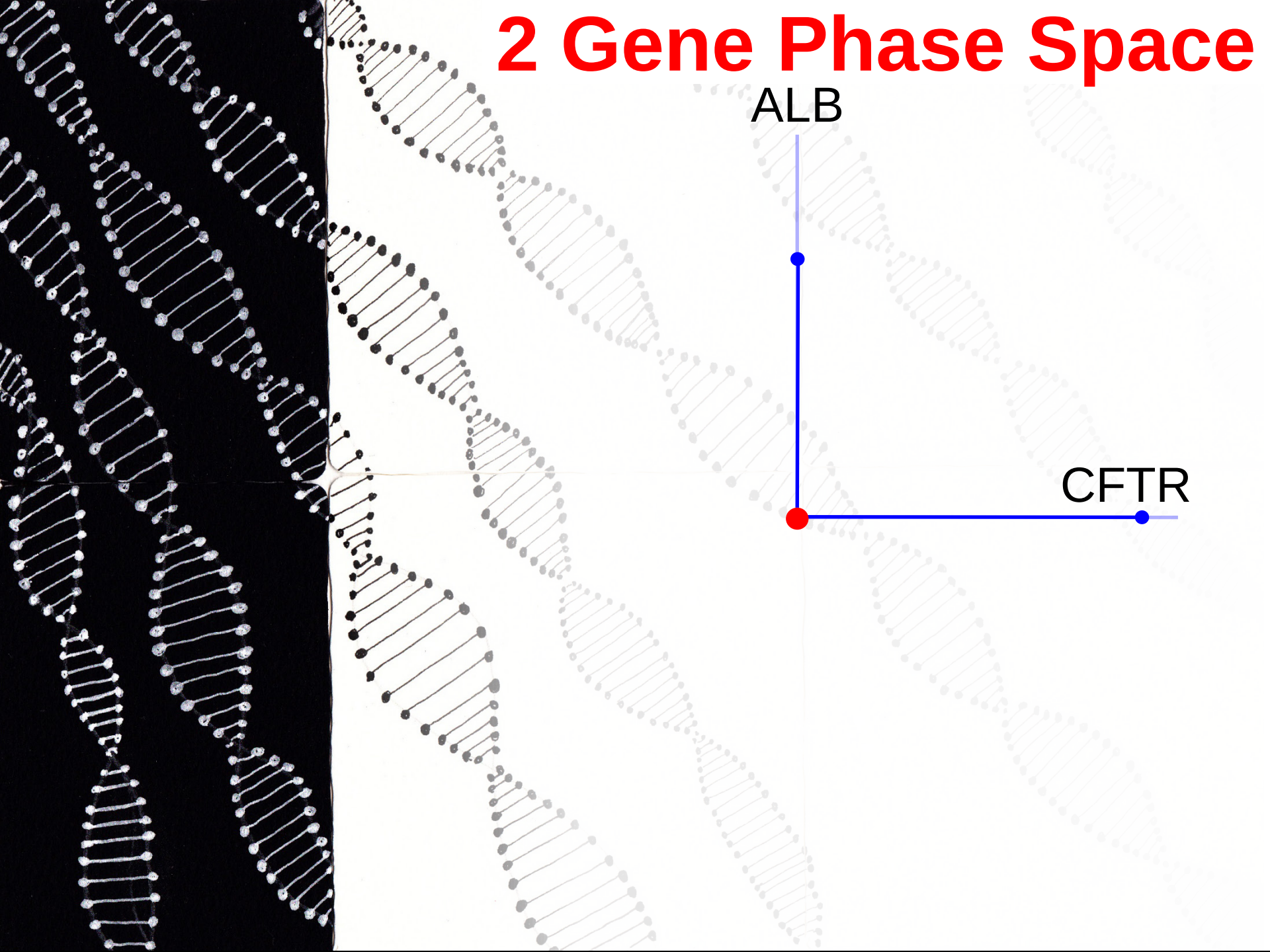
What are we learning?

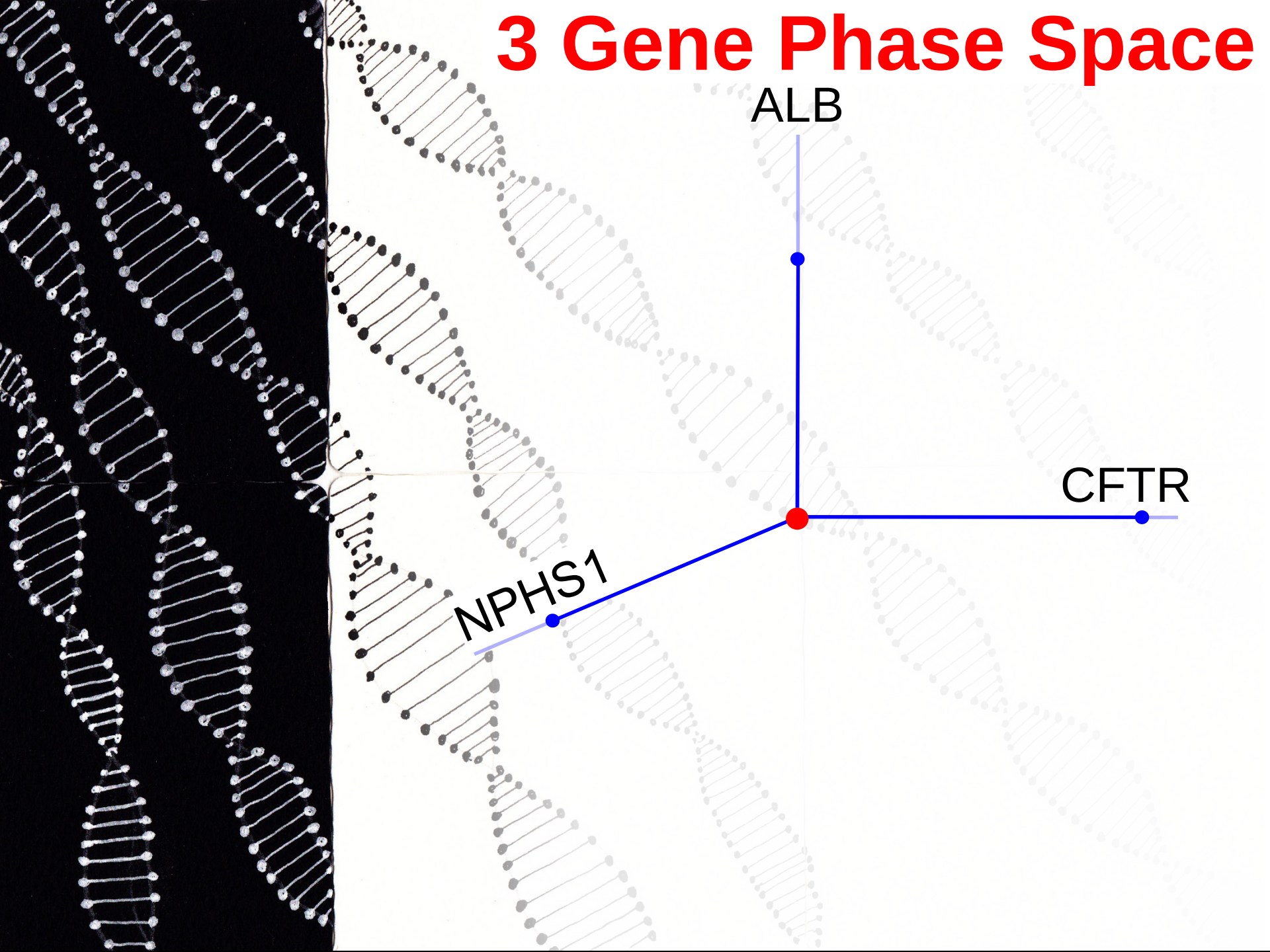
Genetic Phase Space



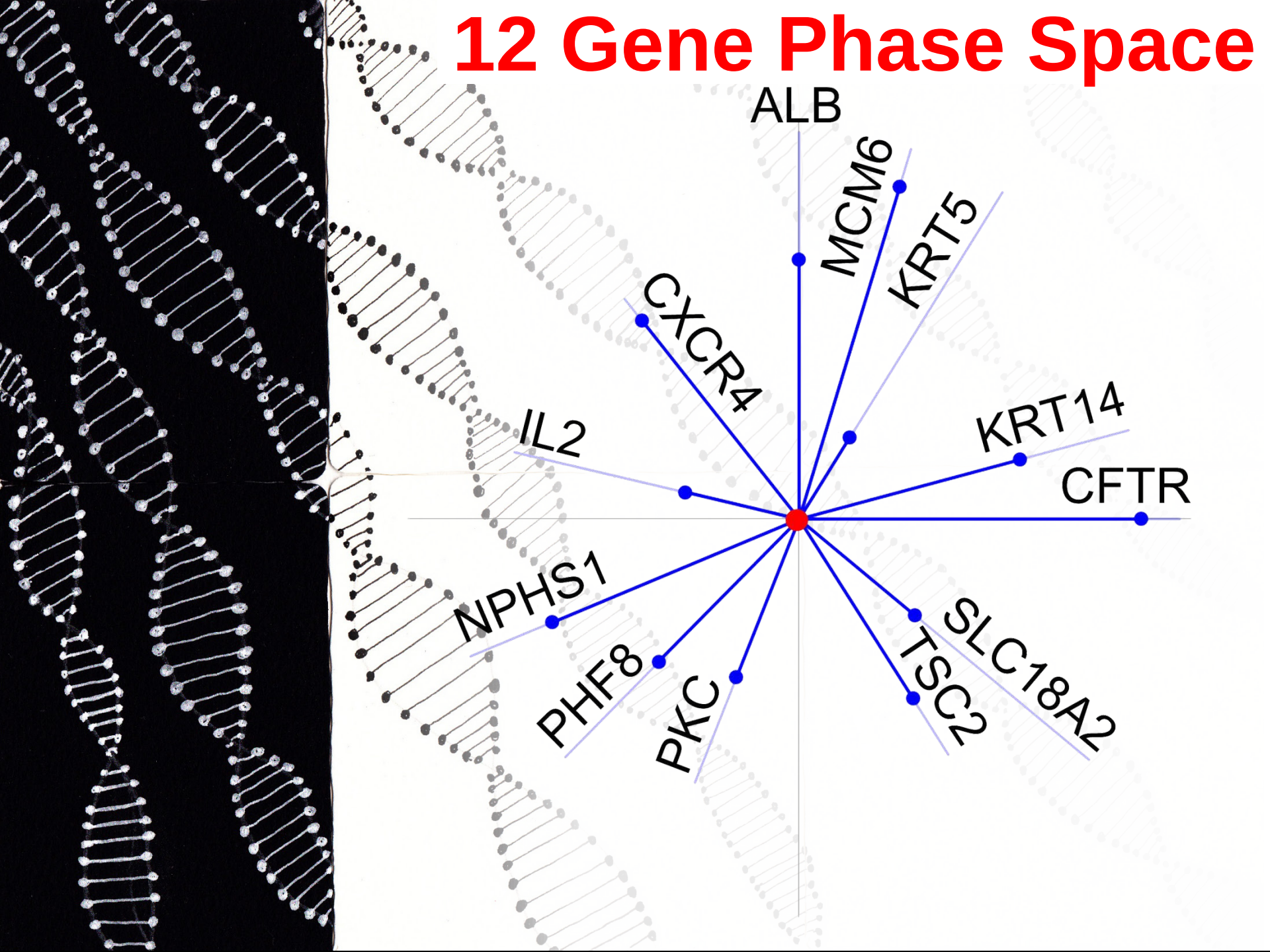

1 Gene Phase Space
ALB
Maximum expression
Actual expression level
No gene expression

2 Gene Phase Space

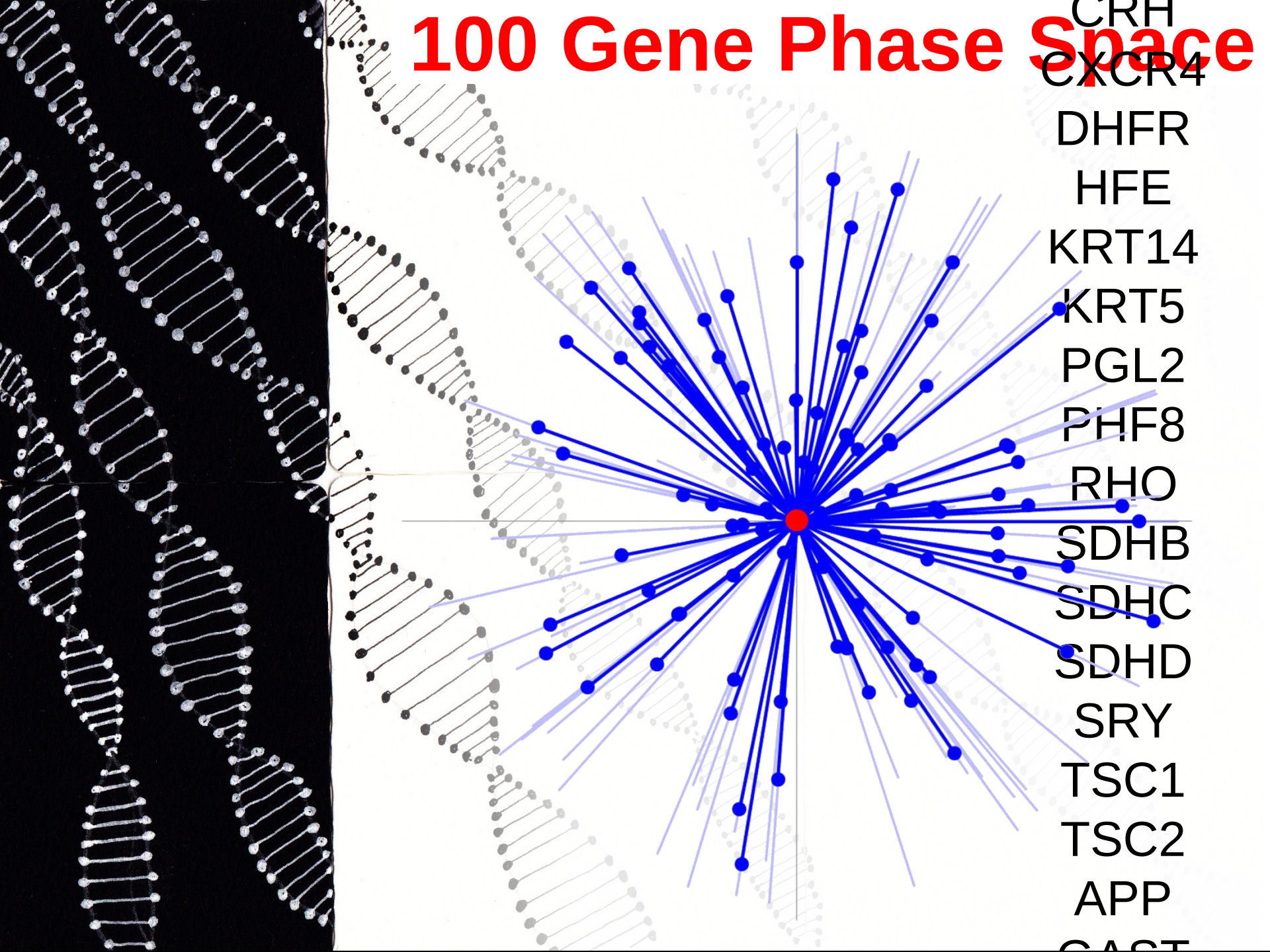



3 Gene Phase Space
ALB
CFTR
NPHS1

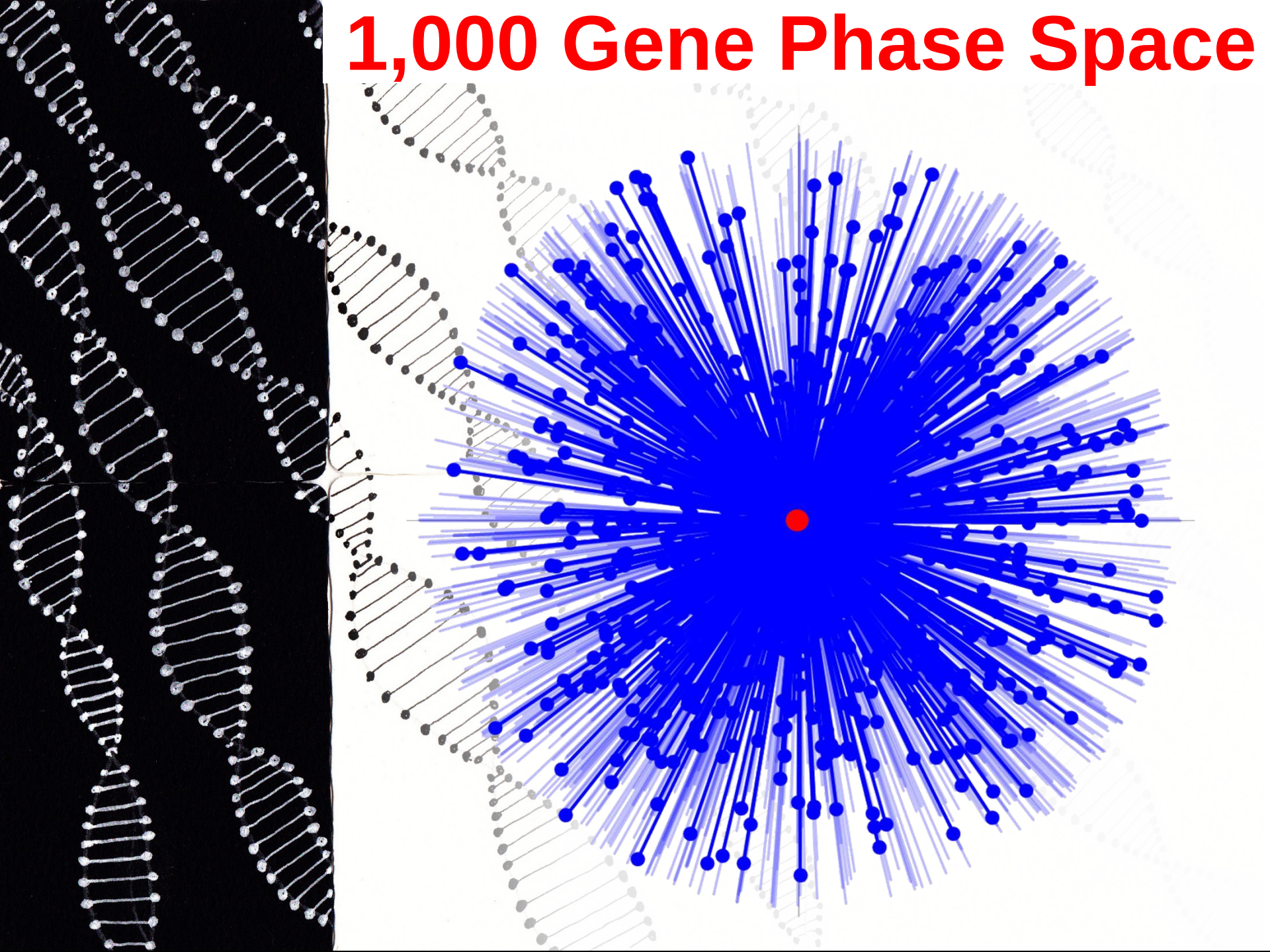
12 Gene Phase Space



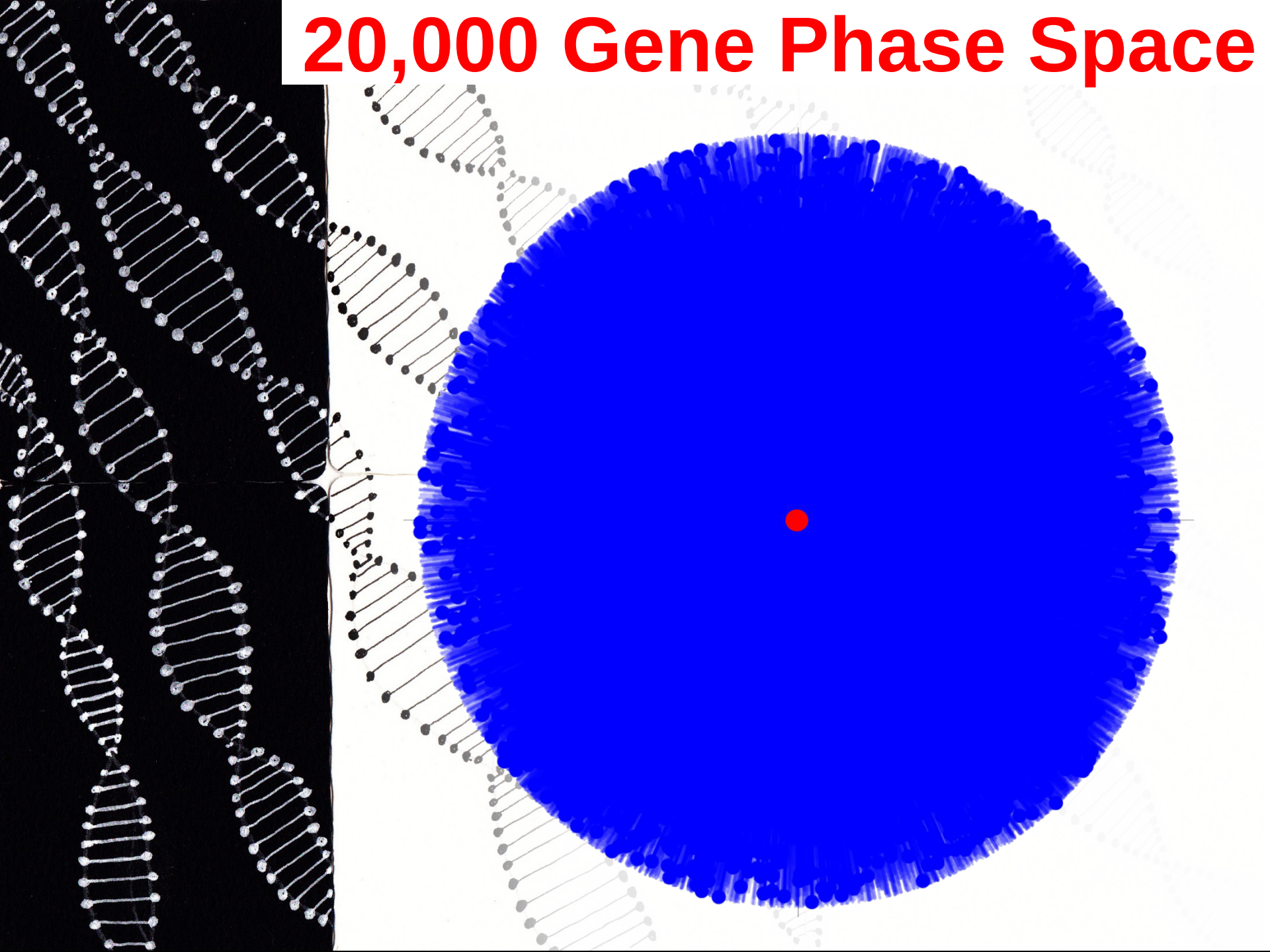
100 Gene Phase Space

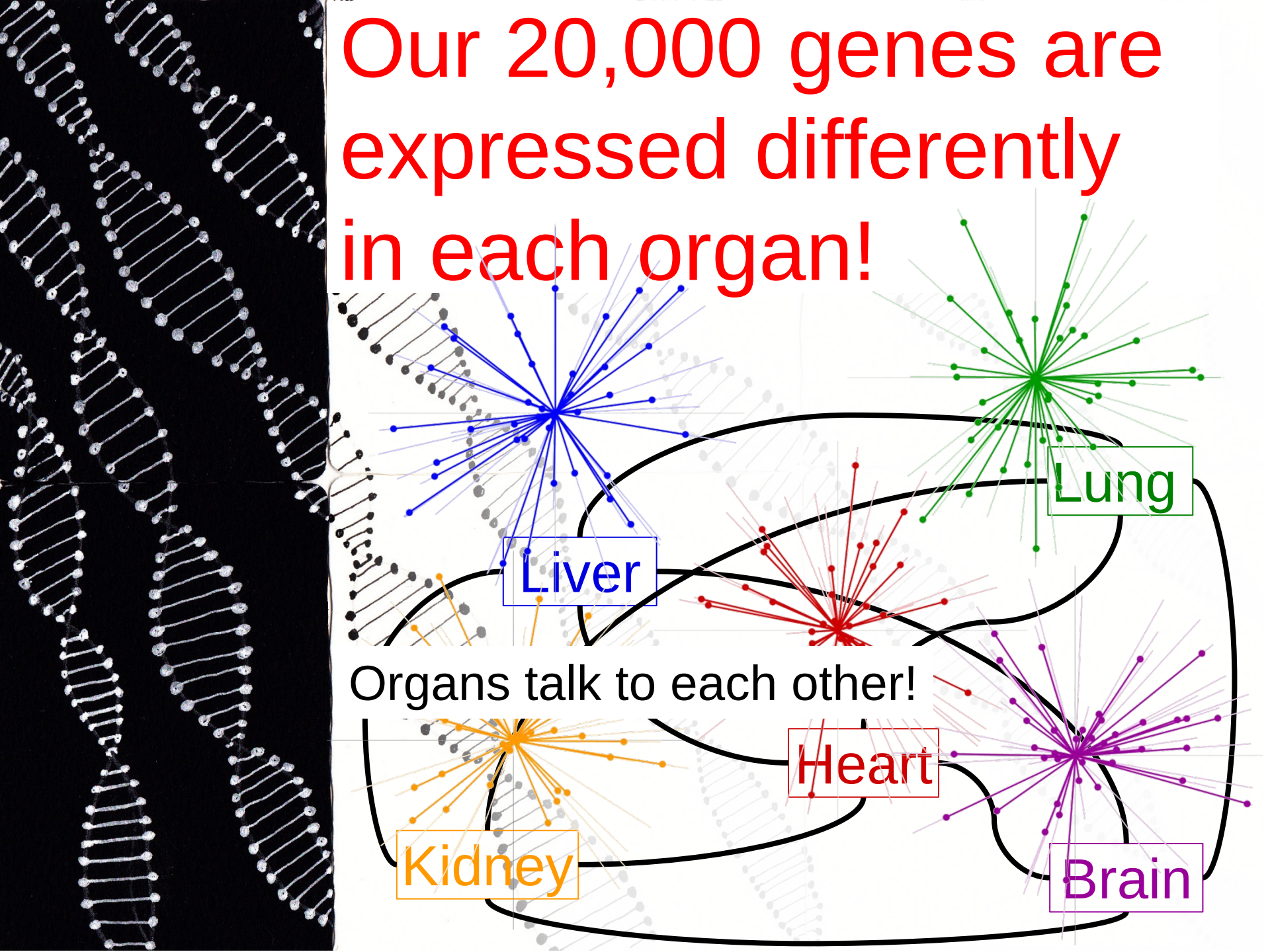


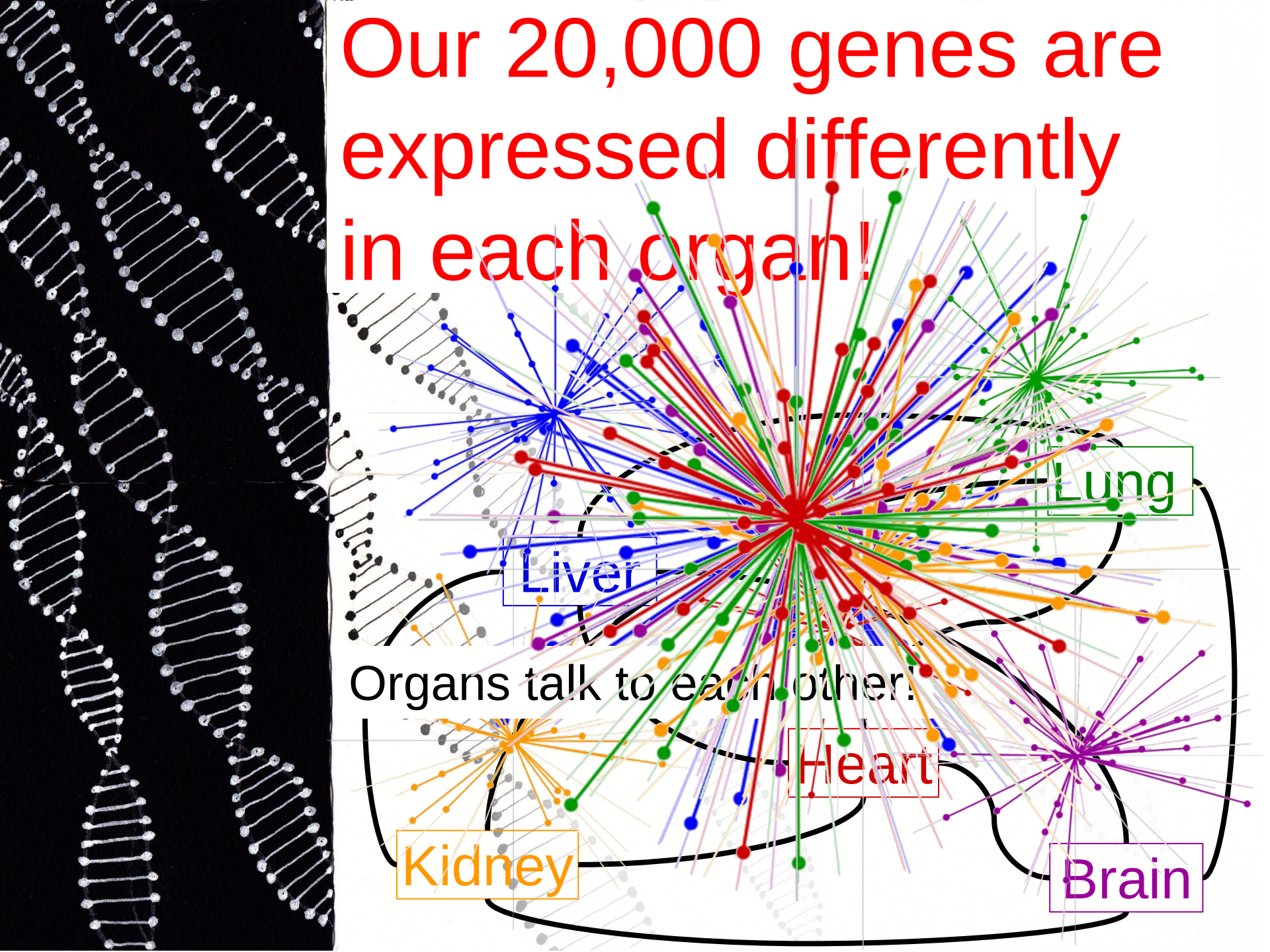
1,000 Gene Phase Space



20,000 Gene Phase Space




Our 20,000 genes are expressed differently in each organ!
Lung
Liver
Organs talk to each other!
Heart
Kidney
Brain


Our 20,000 genes are expressed differently in each organ!
Lung
Liver
Organs talk to each other!
Heart
Kidney
Brain


What does an organ
on a chip sound like?

Organ on a Chip V5.0

Frank Block, Vanderbilt