

The Homunculi and I

Lessons from Building Organs on Chips

John Wikswo

TEDx Nashville, April 6, 2013

http://www.youtube.com/watch?v=aNF3TdUF_uw

Abstract

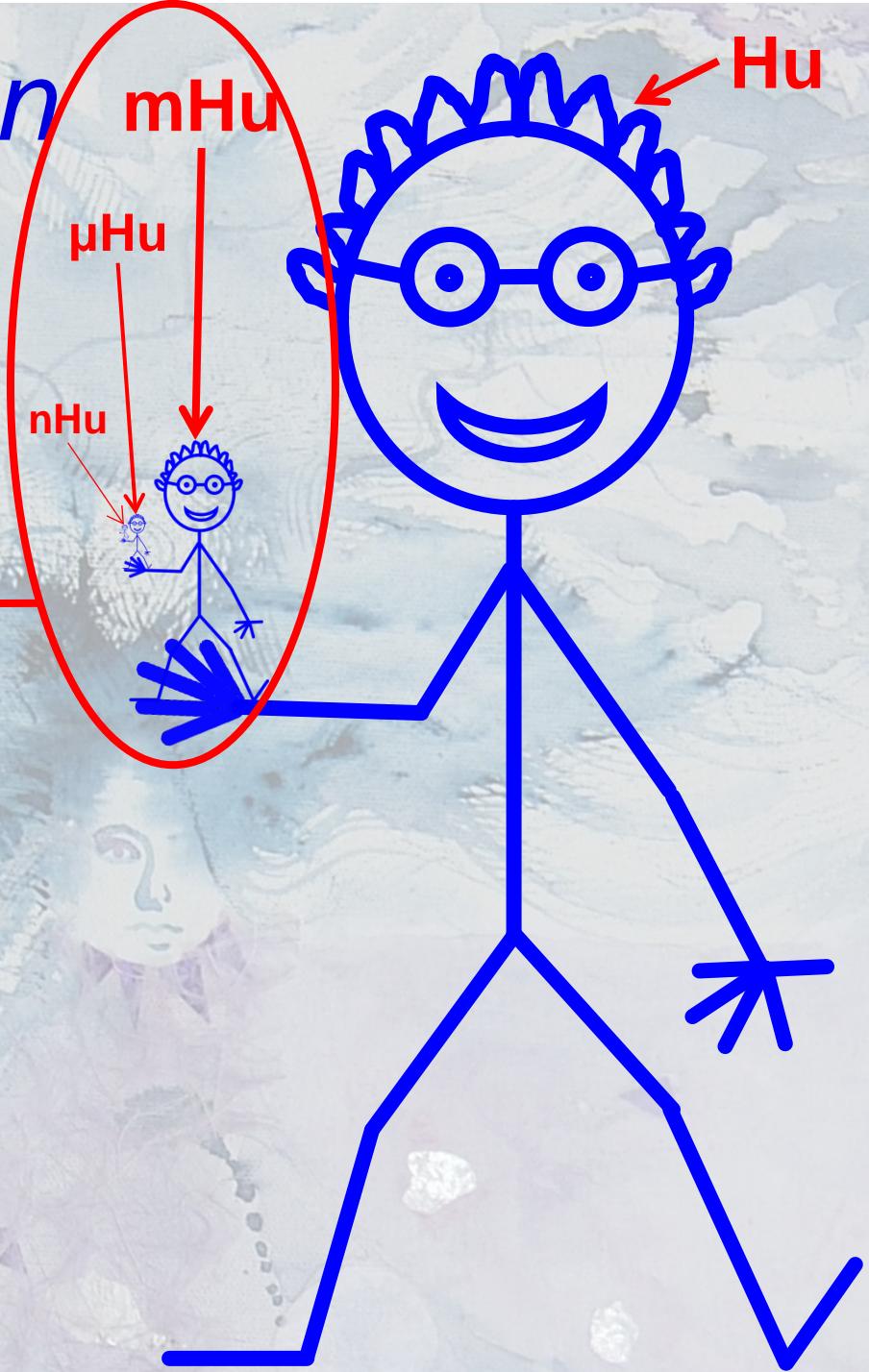
Why are we building two new species: *Homo chippus*, a milliHuman, and *Homo chippiens*, a microHuman? Microfabricated humans-on-a-chip! Why? Because it's fun and a REAL challenge. Using the tools of physics, chemistry, engineering, physiology and molecular biology, we are exploring the unfathomable 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- 'mən-kyə-ləs]

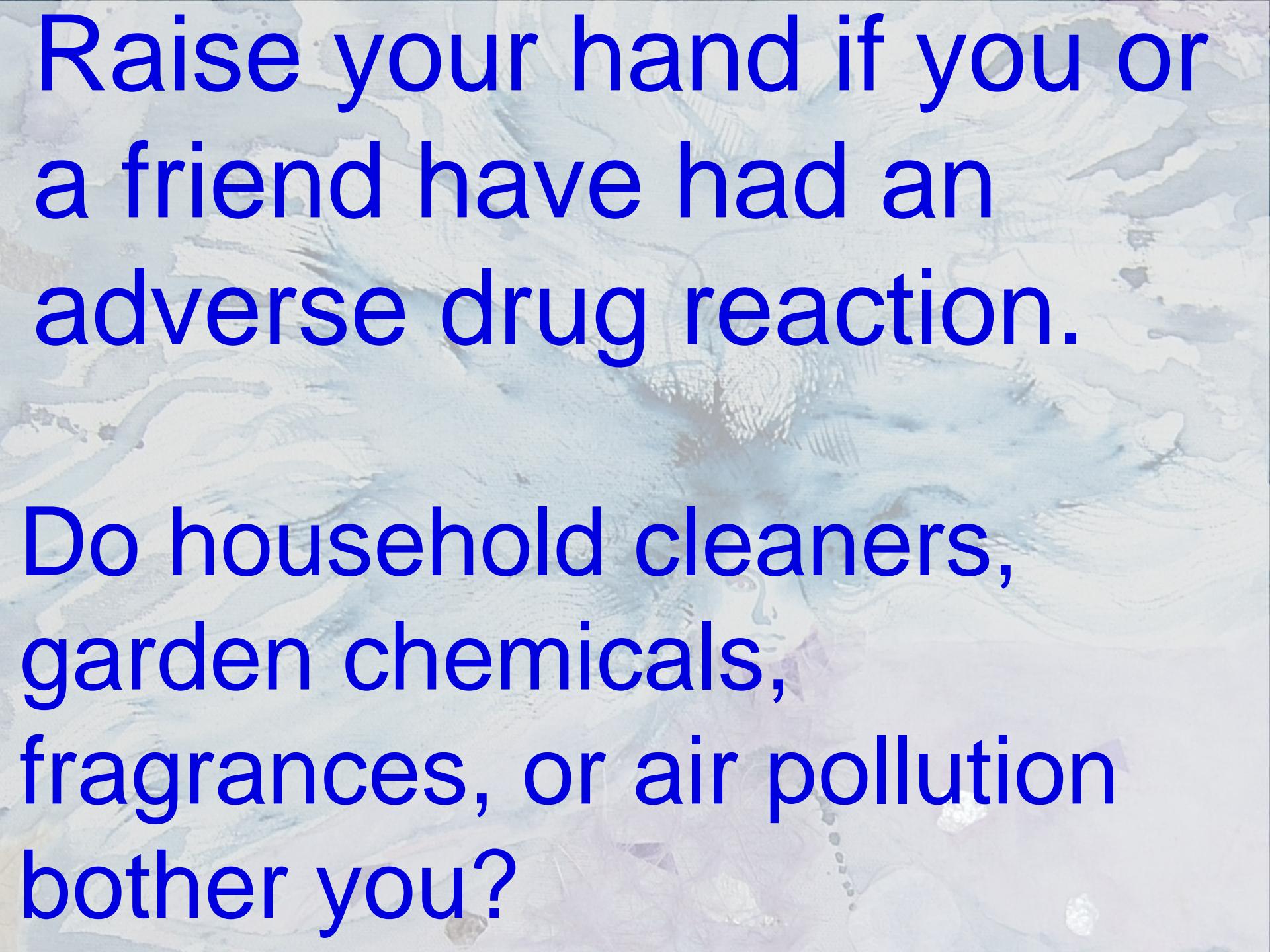
plural ho·muncu·li

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?

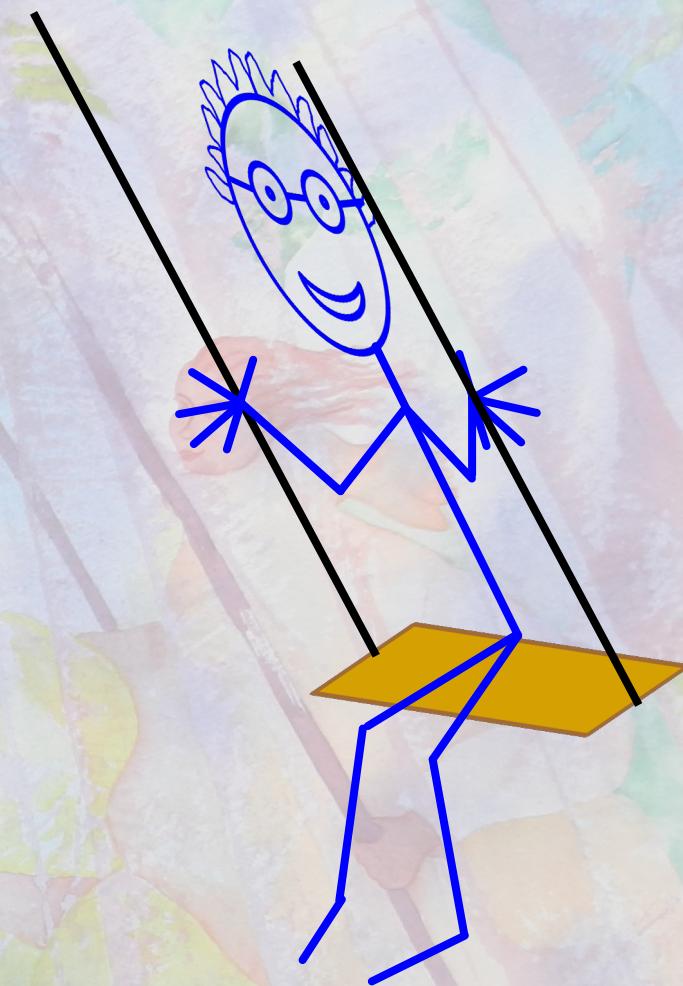


Multidimensional phase space
illustrates the variables that
affect homonculi and the
physicians, scientists and
engineers building them.

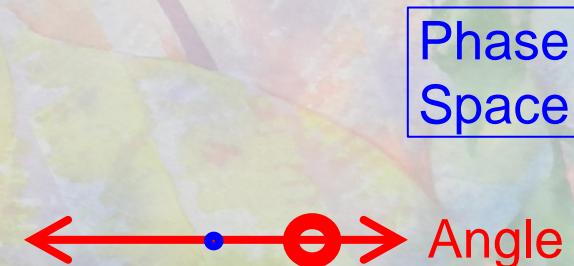
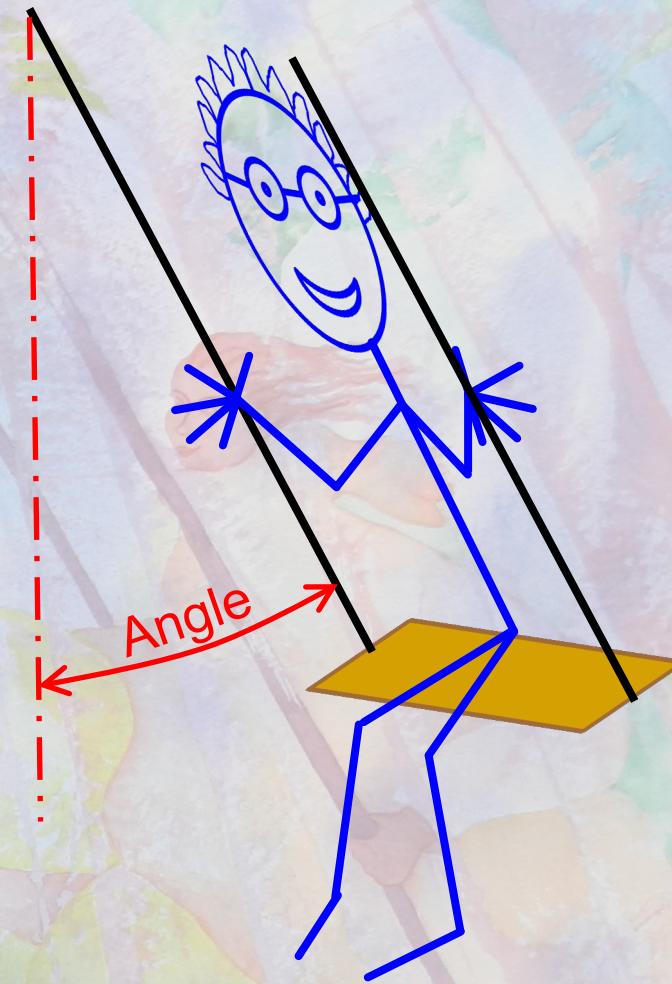
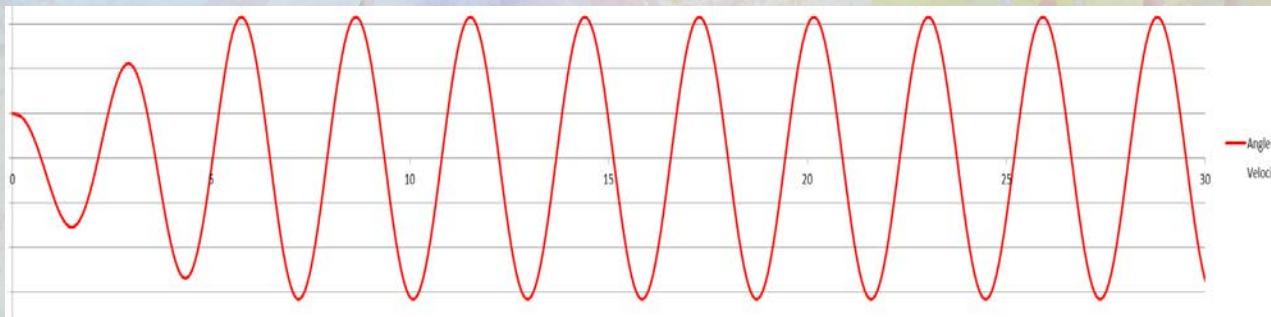
Phase space

[fāz spās], noun

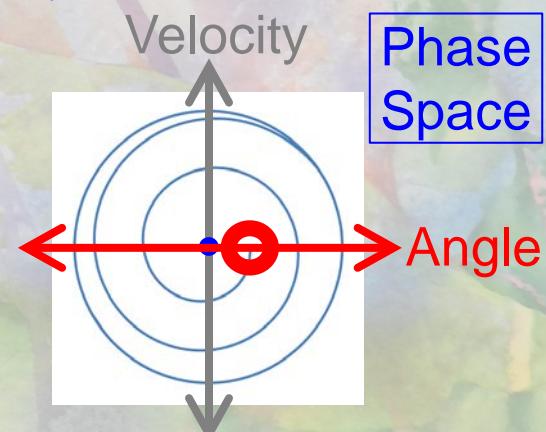
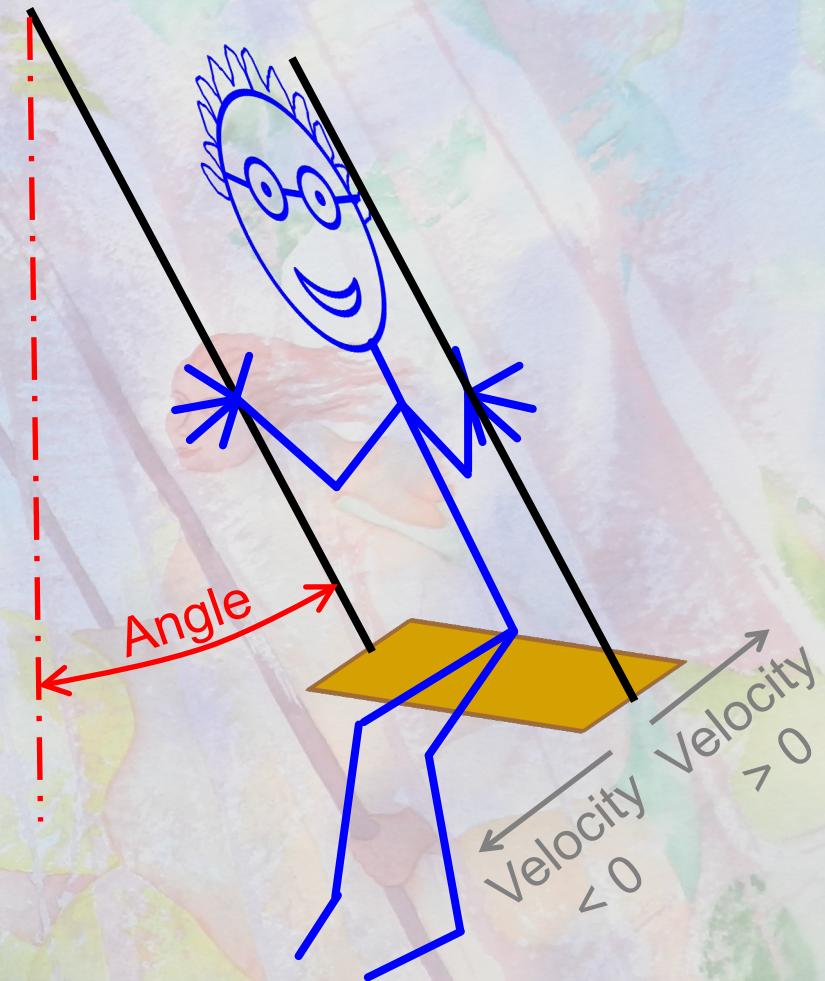
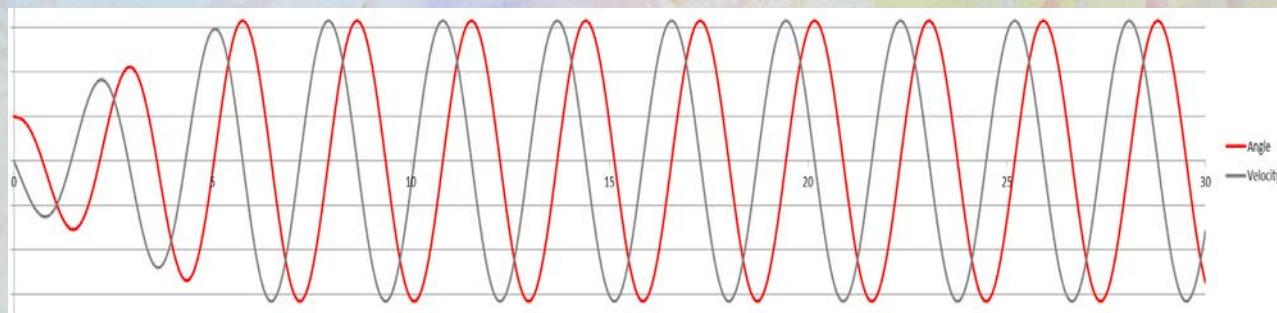
A geometrical space in which each possible state of a system is represented by a single point.



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



There are as many axes as variables.



Phase Space

Angle



Swing Phase Space

Front
and
back



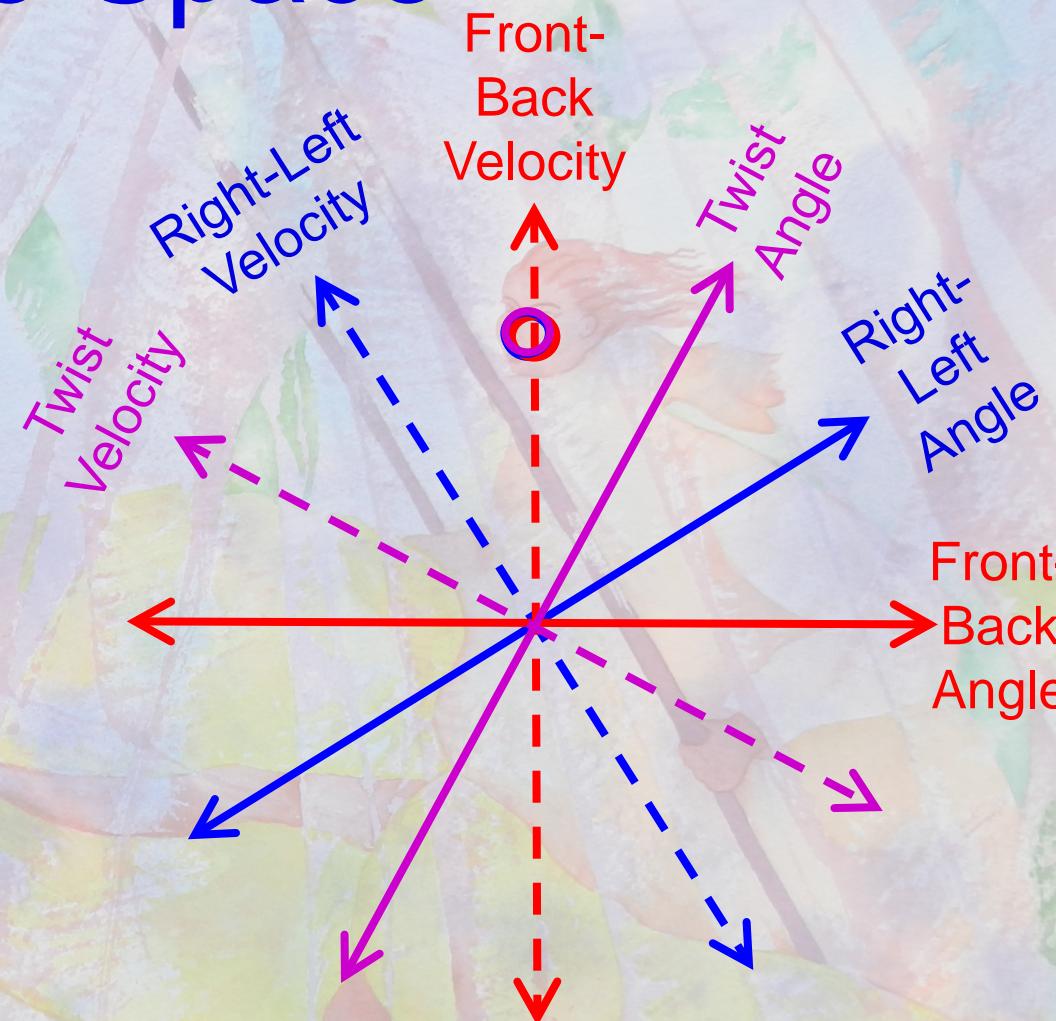
Left
and
Right



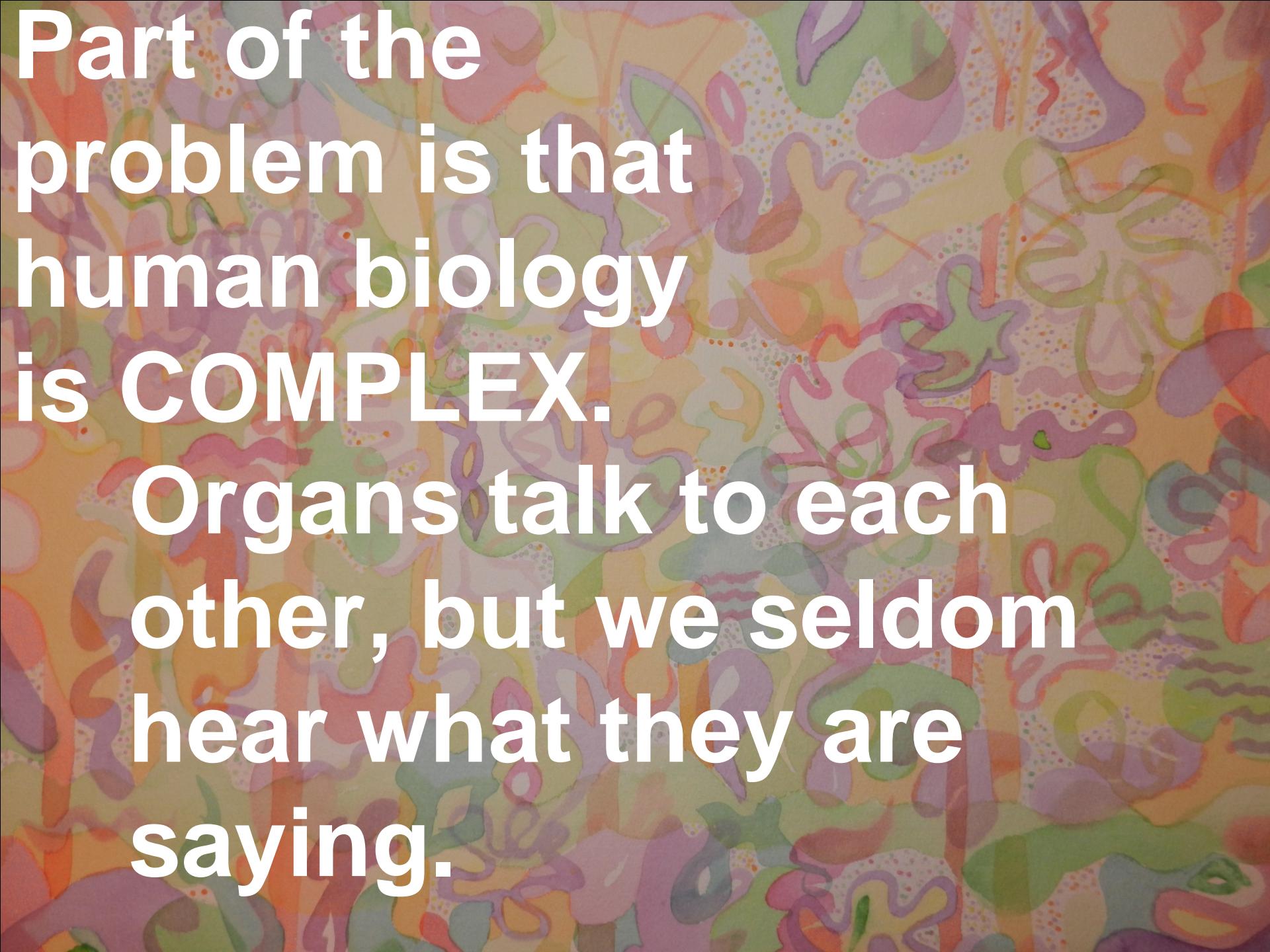
Orbit



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

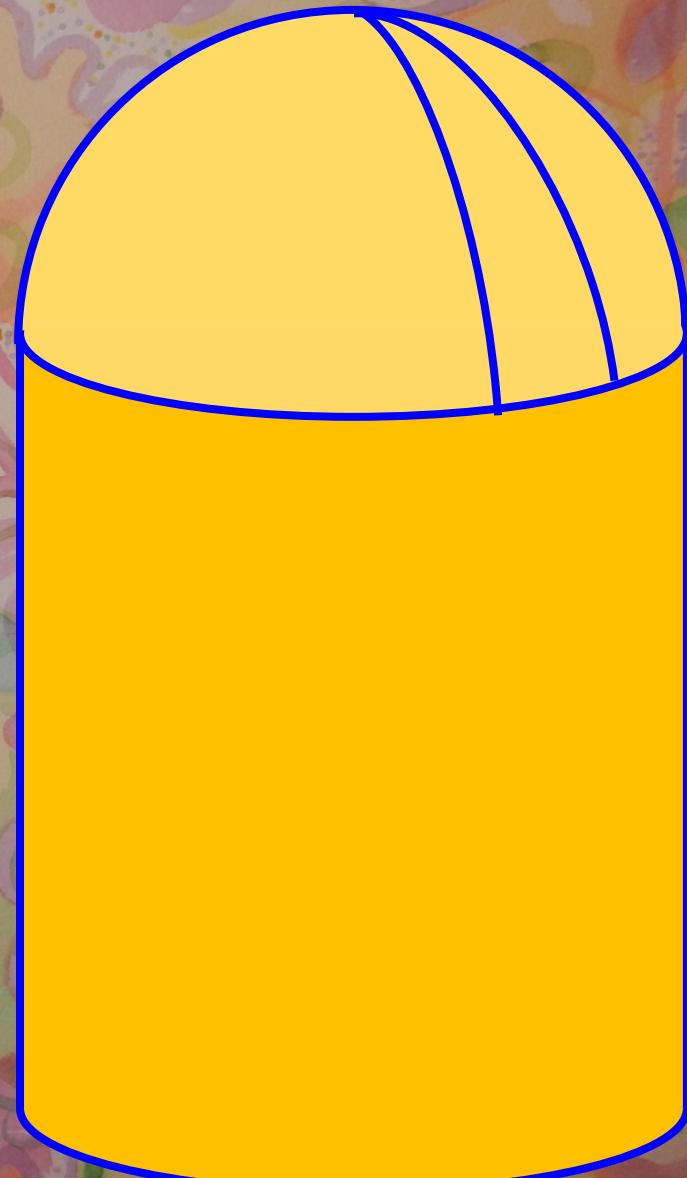
Cartilage

Ligaments

Tendons

Silo -- A place to store stuff without mixing.

Silo Mentality -- Thinking without mixing.



Organ Silos



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

M mentality

Brain Cells

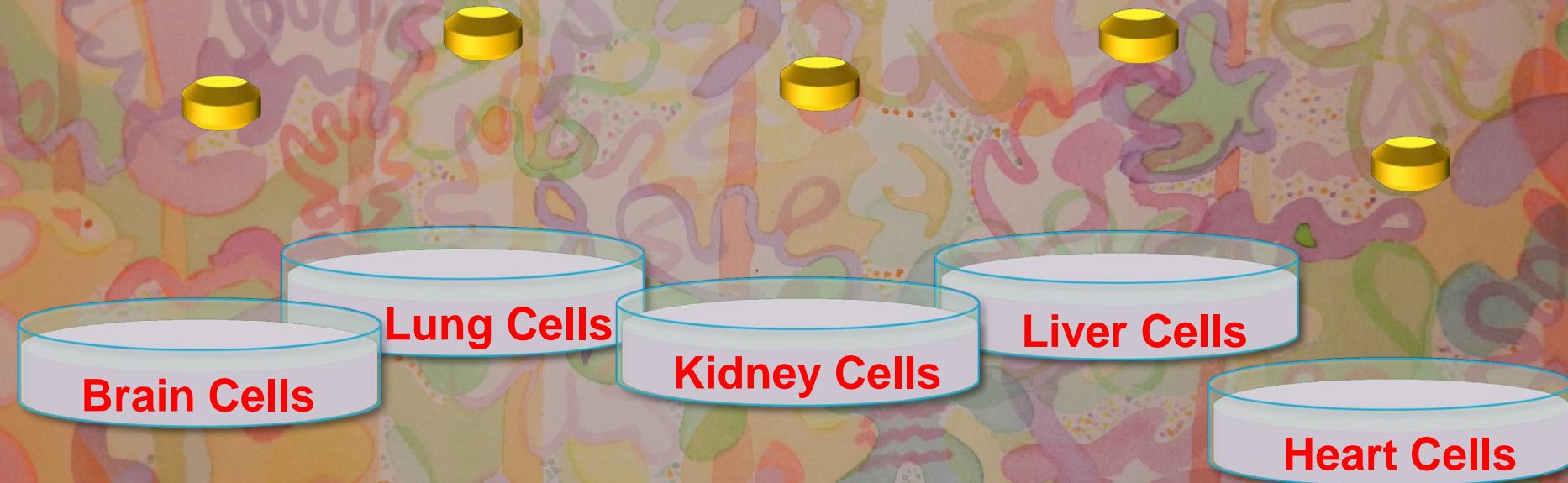
Lung Cells

Kidney Cells

Liver Cells

Heart Cells

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

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

Humans

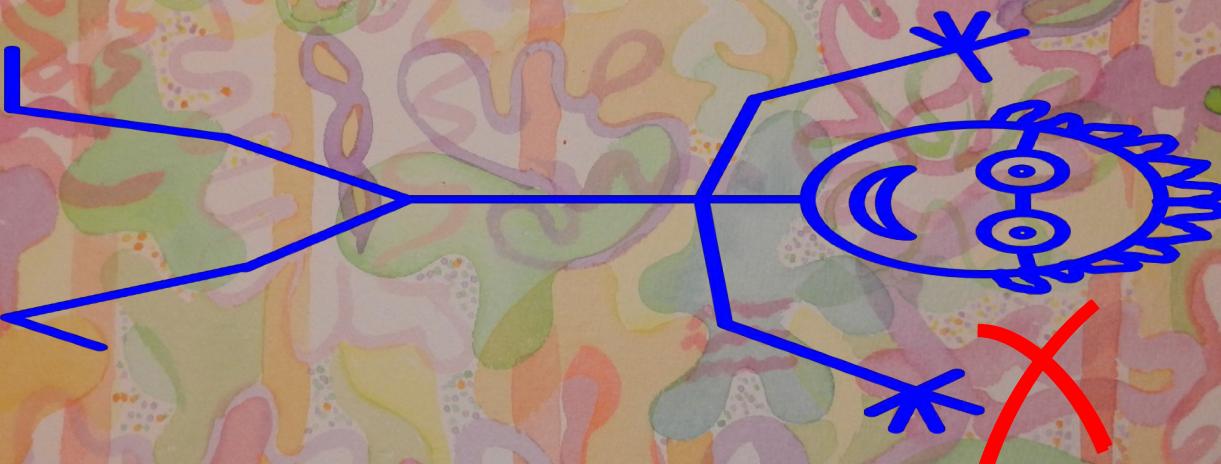
Test drug in humans...



Test drug in humans...



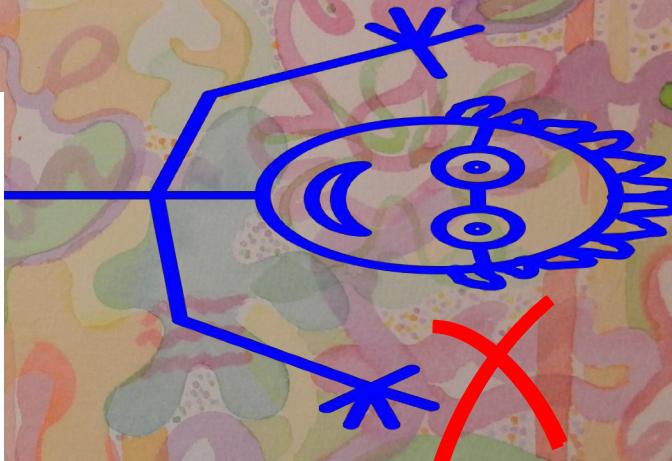
Test drug in humans...



Test drug in humans...

What went wrong?

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



How is a new drug tested?

Petri dishes

Mice

Homunculi

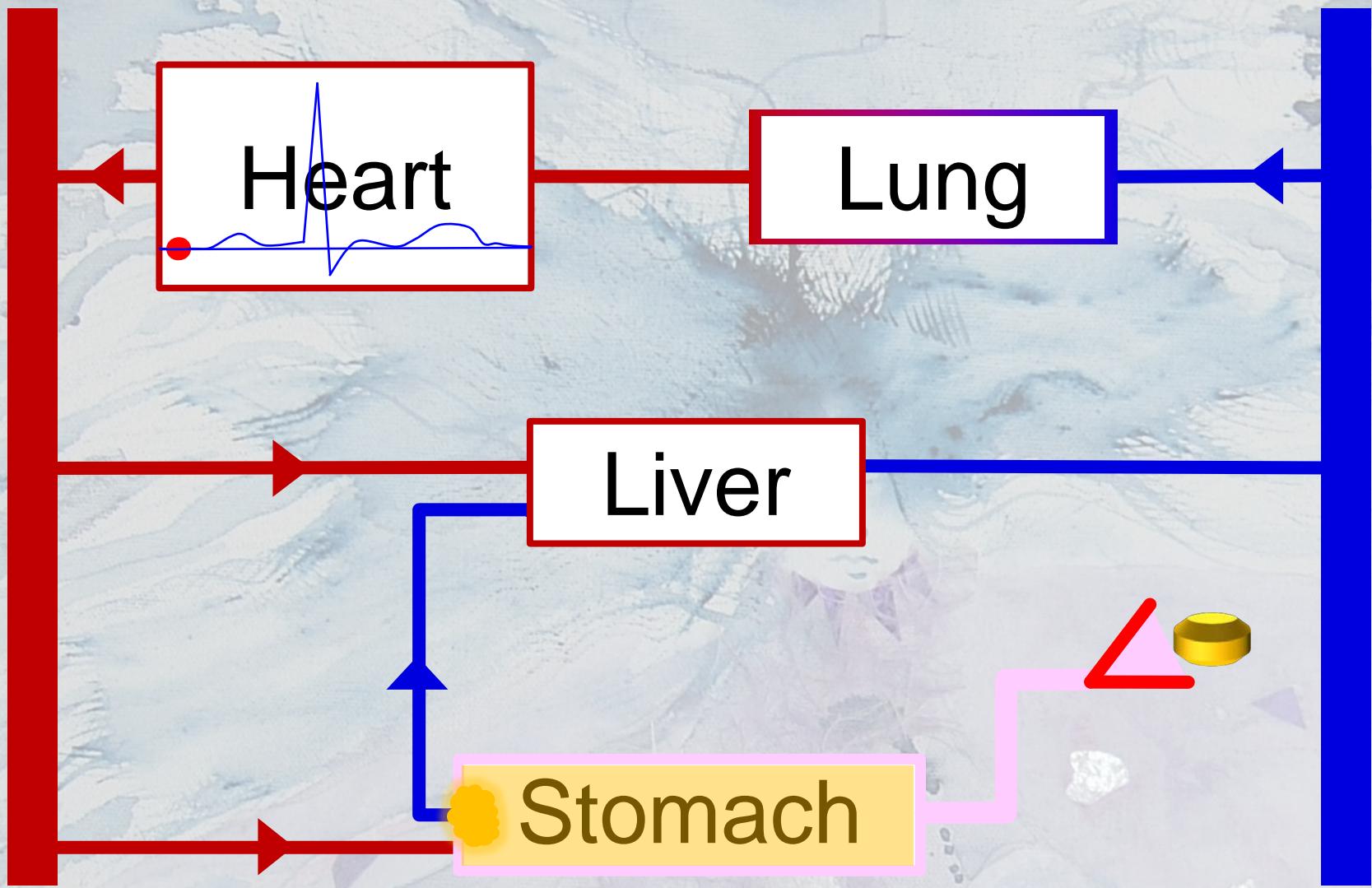
Humans



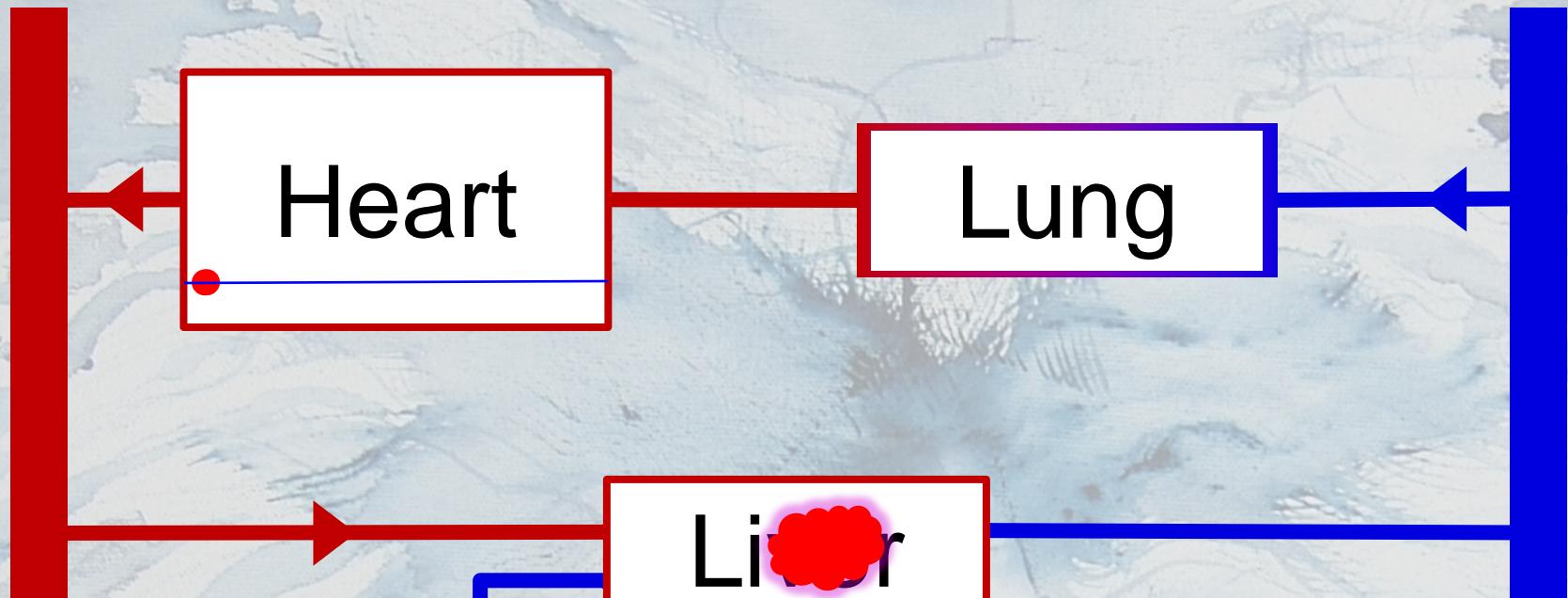
Our homunculi will
be alive, built with
human cells!



Test drugs in homunculi!



Test drugs in homunculi!



Unexpected human
organ-organ
interaction.
No human dies.



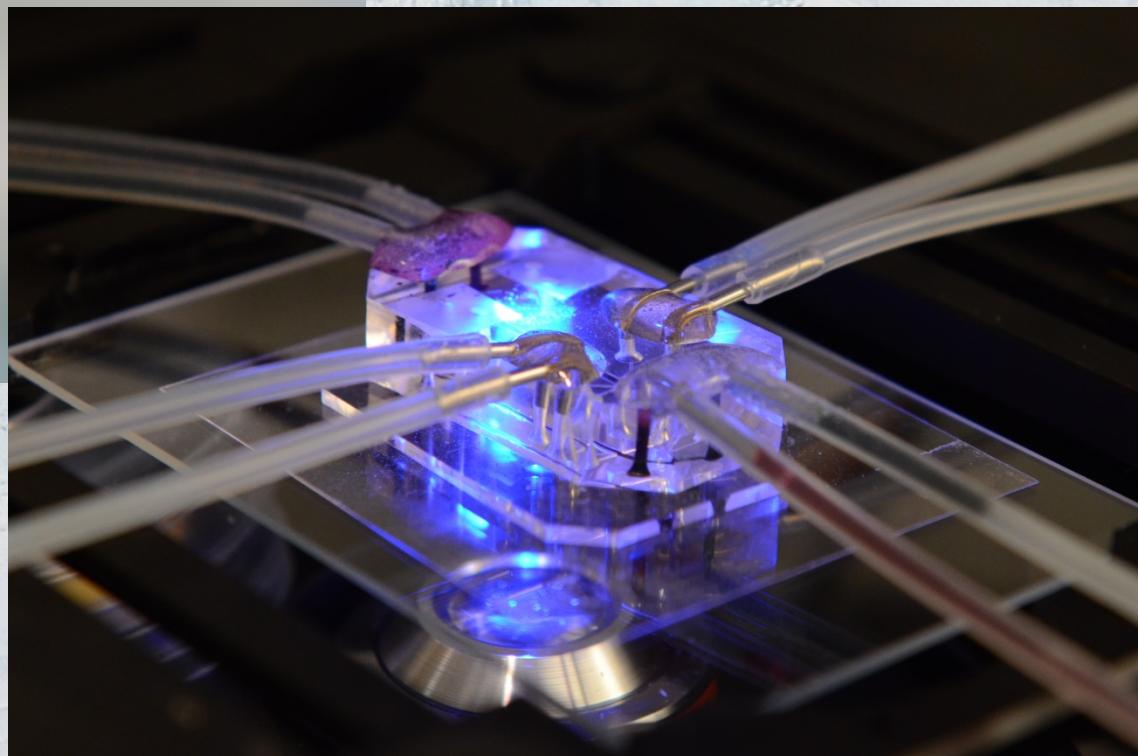
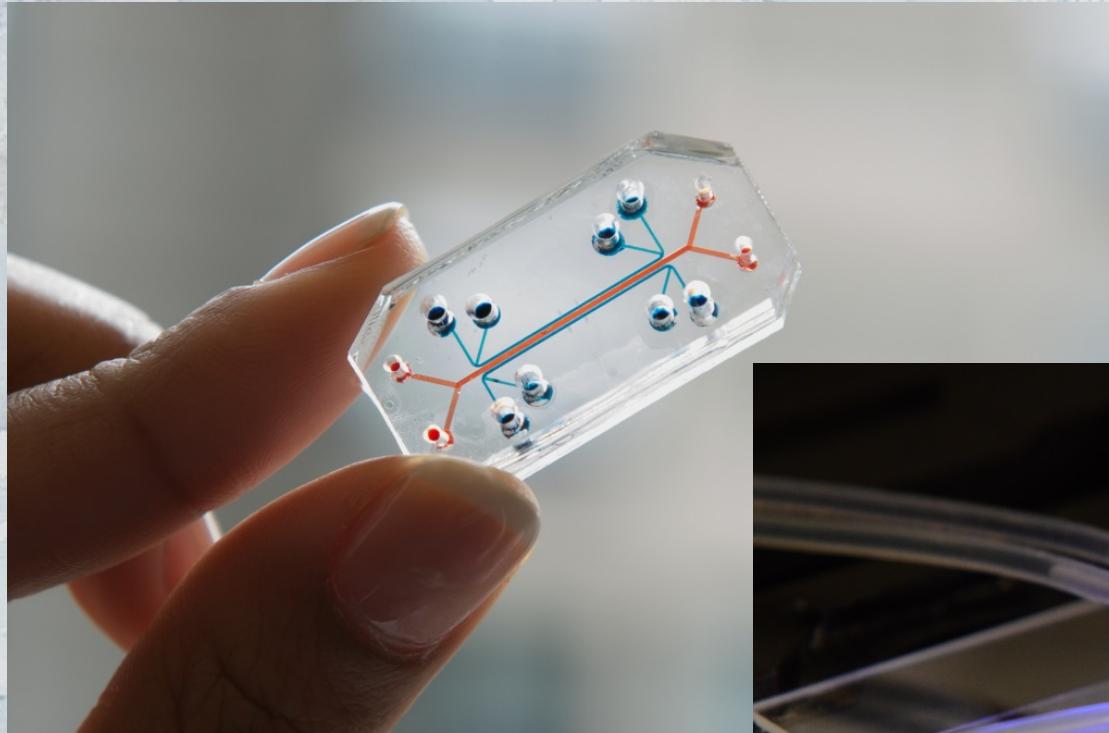
We've just seen why we are building homunculi

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

How do you build homunculi?

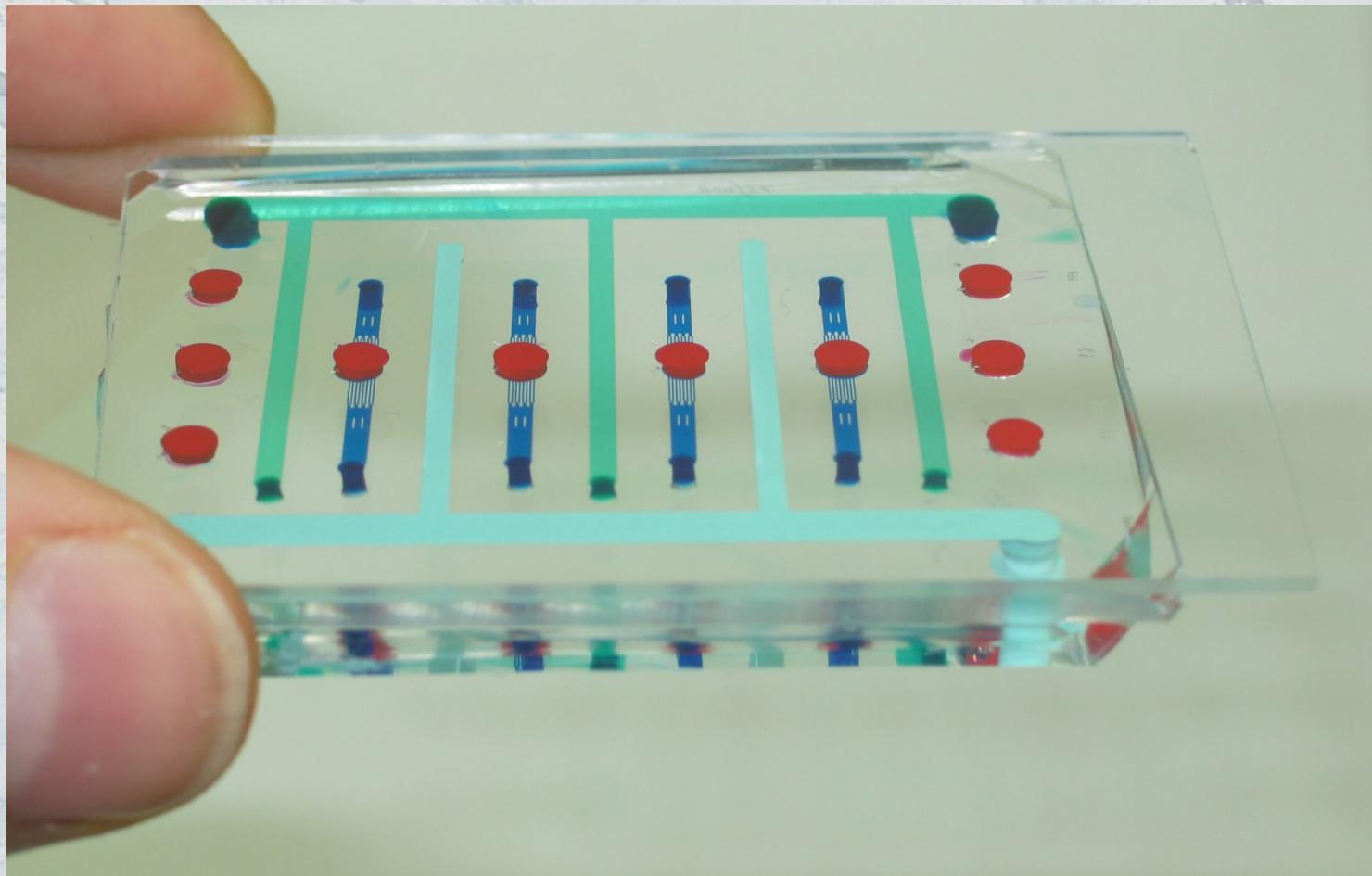
- Use human cells to make *microfluidic organ chips* that work like the real organs.
- Connect organs together.
- Do lots of things at the same time. (phase space)

Lung on a chip

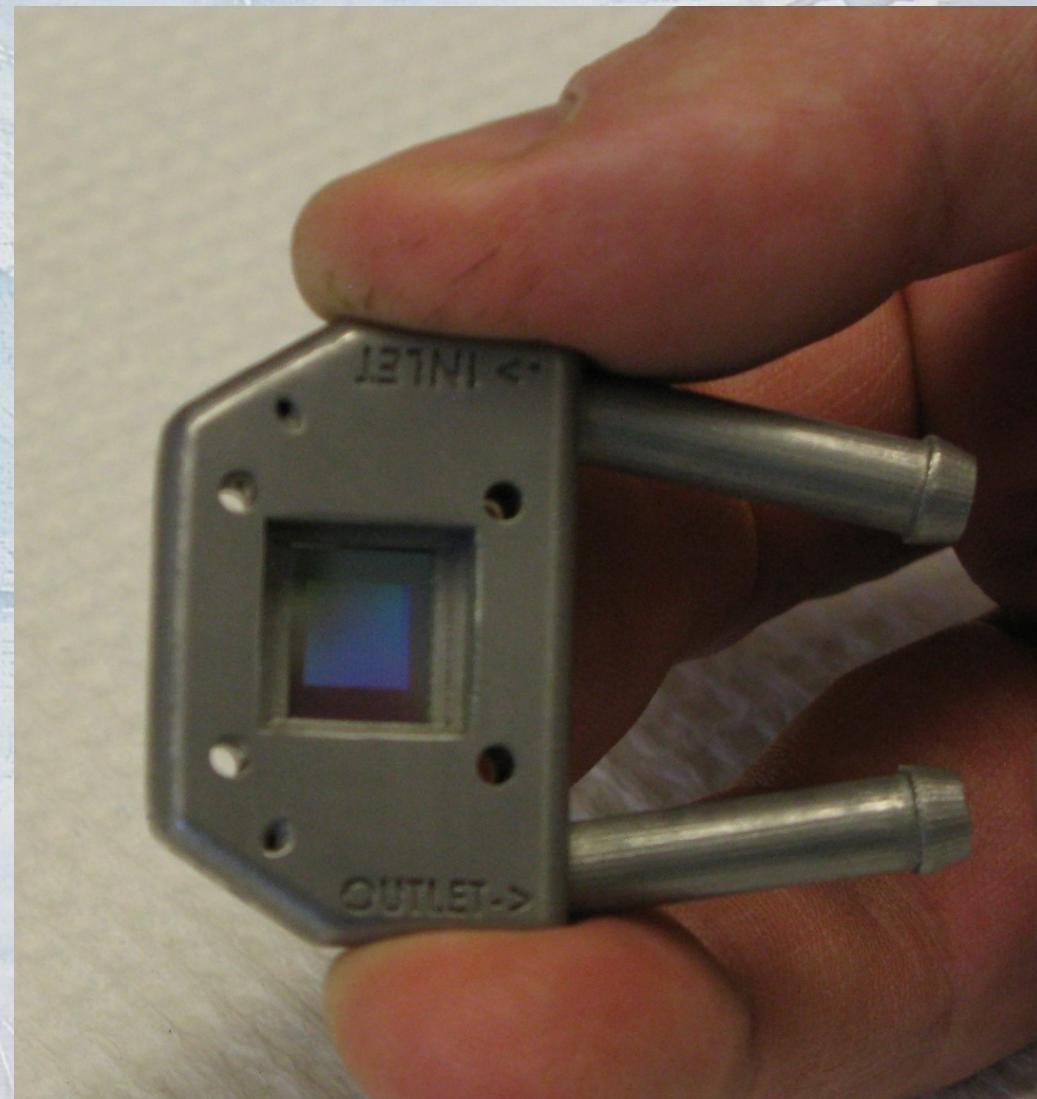
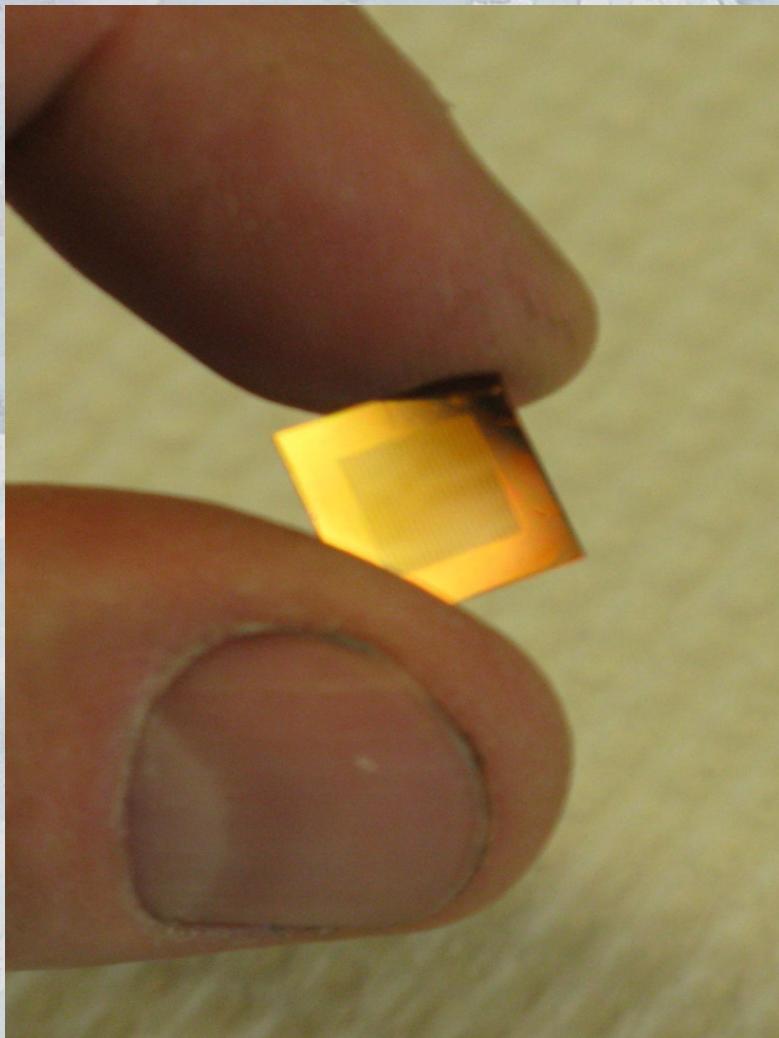


Don Ingber, Harvard

Mammary gland on a chip

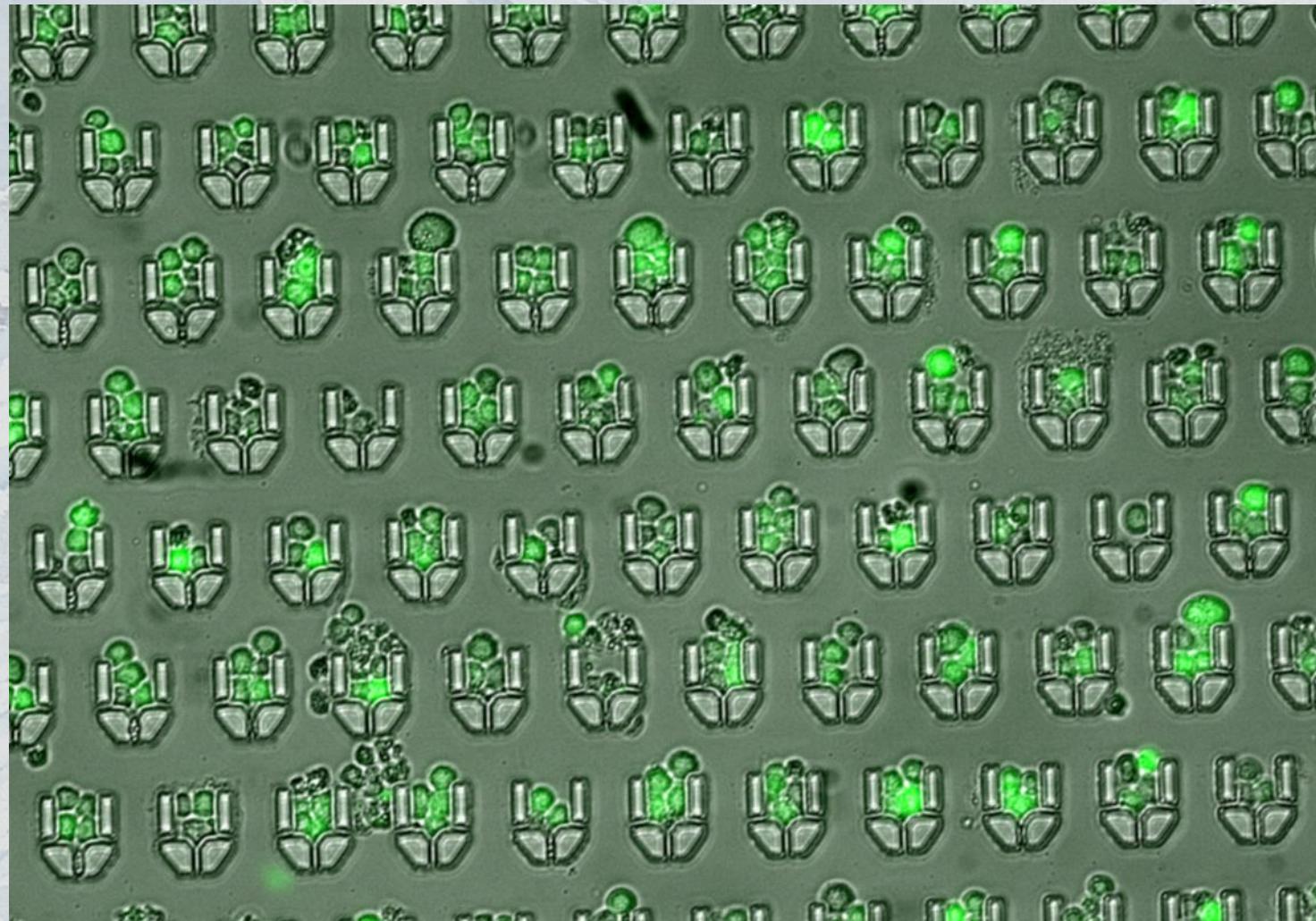


Kidney on a chip



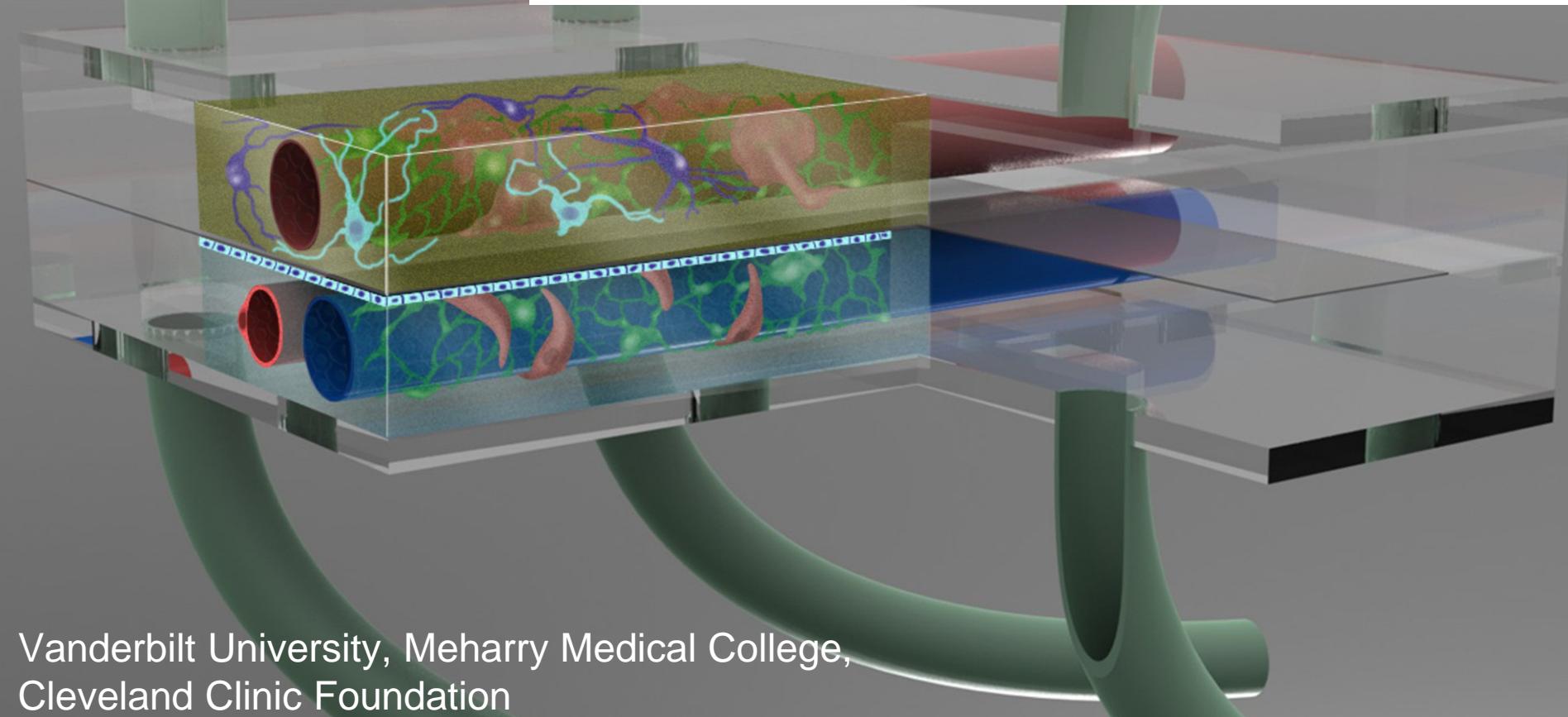
Shuvo Roy, UCSF and Bill Fissell, Vanderbilt

T cells in a lymph node on a chip



Brain on a chip

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

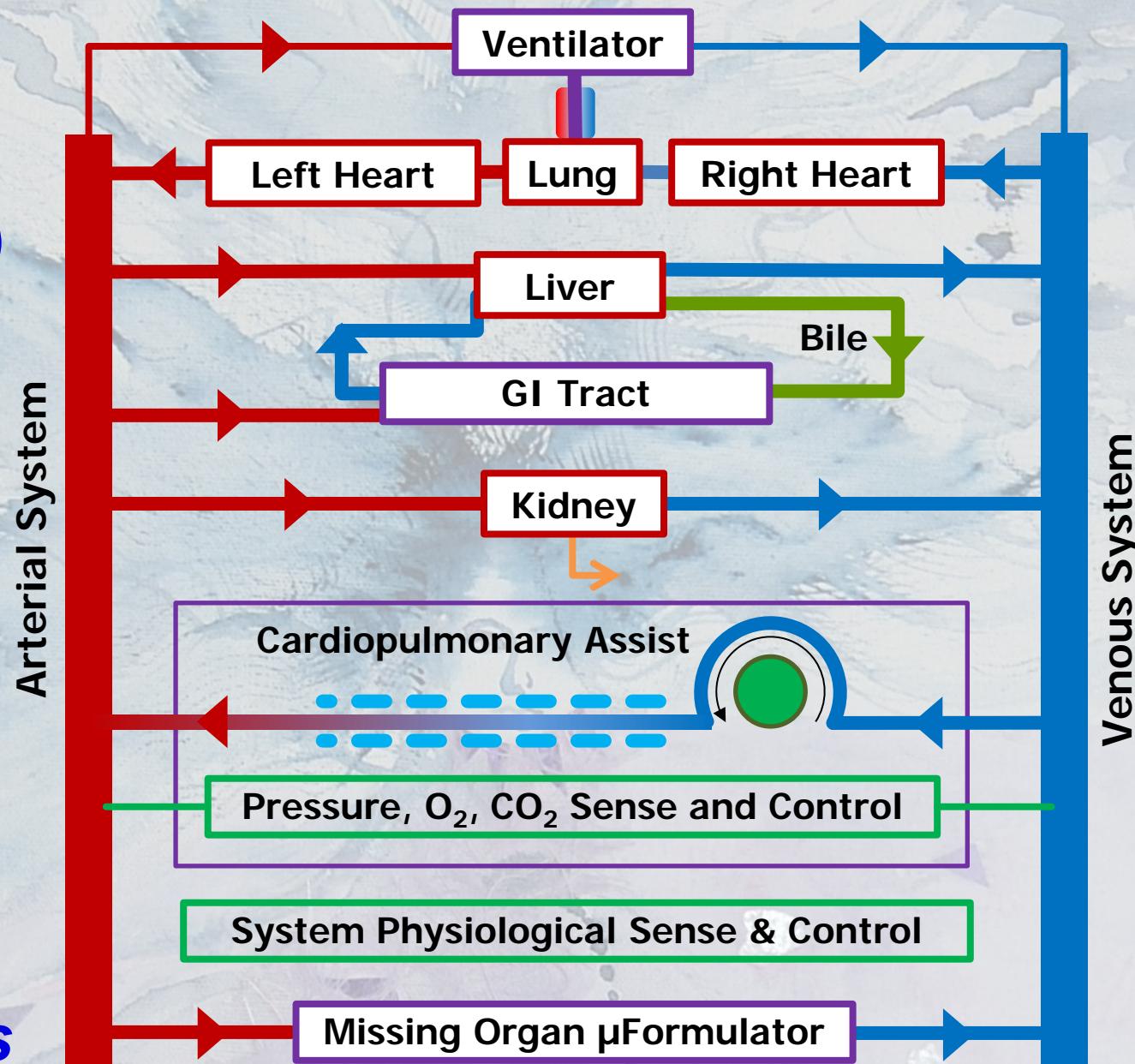


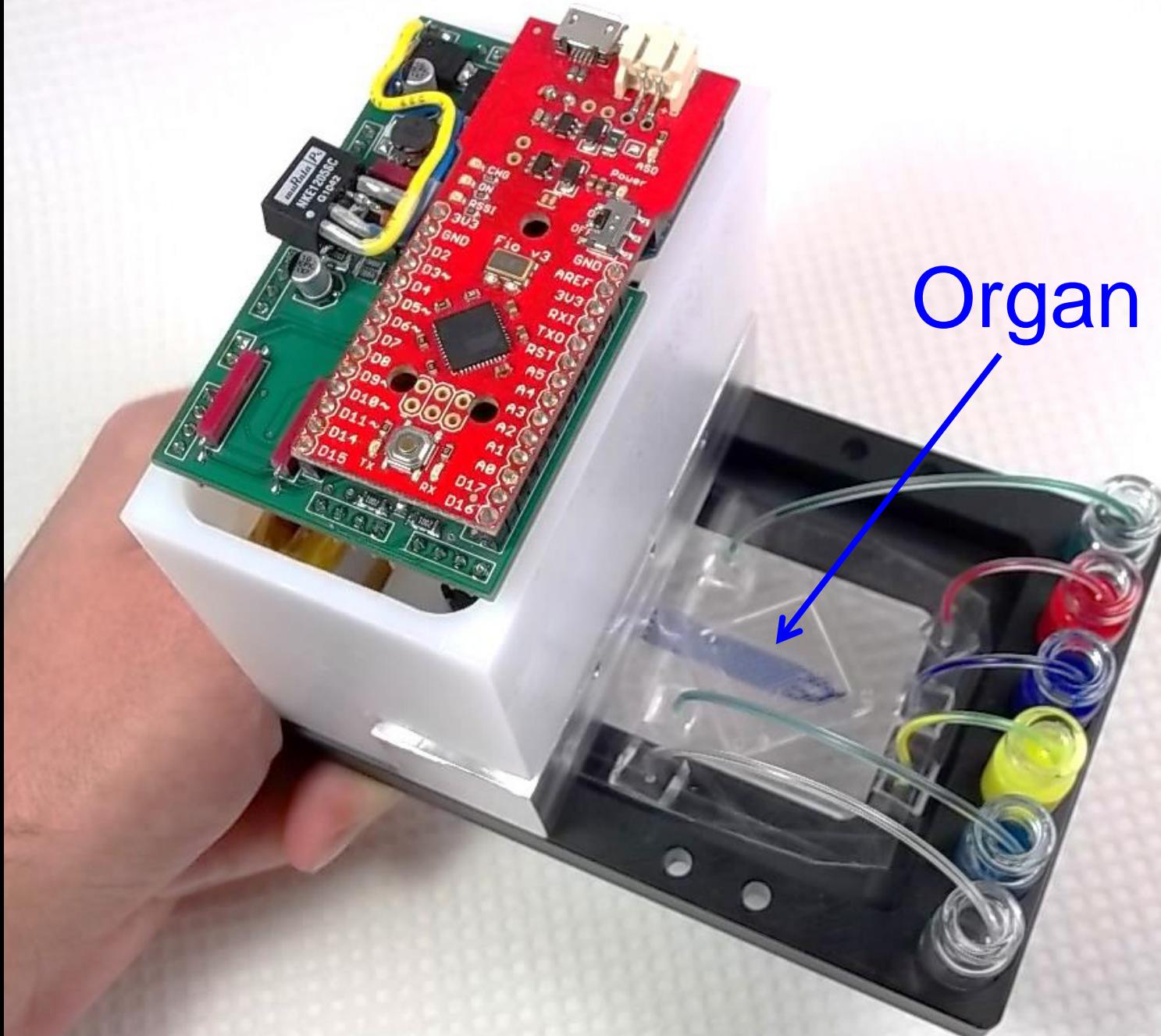
Advanced Tissue-engineered Human Ectypal Network Analyzer

We call
our chip
Athena

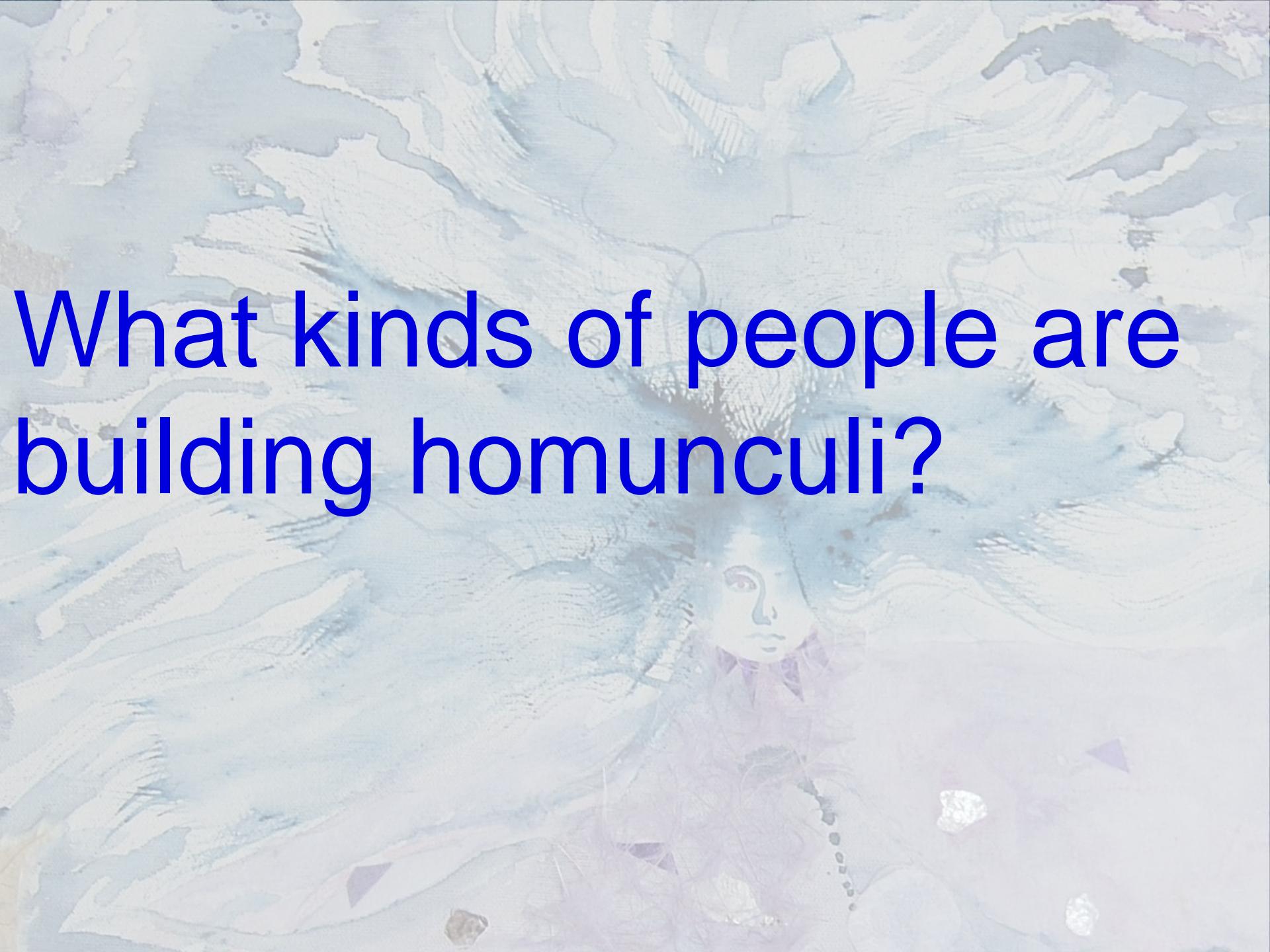
milliHuman
(mHu)

Homo chippus





Frank Block, Vanderbilt



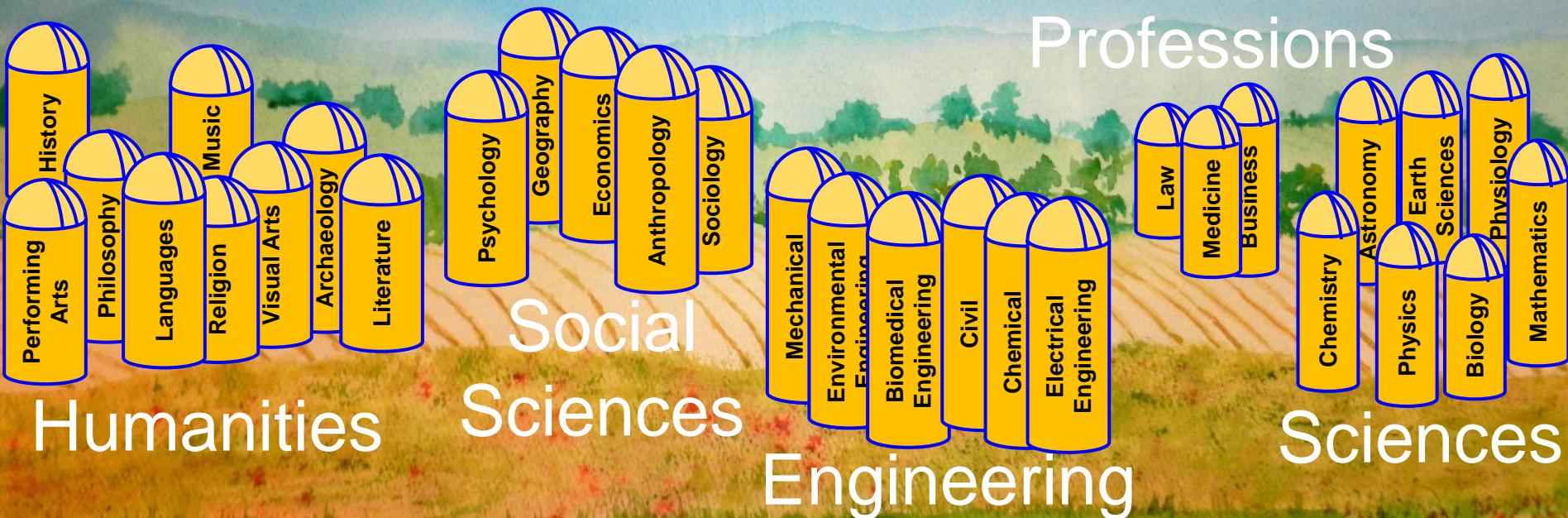
What kinds of people are building homunculi?

Fields of Knowledge

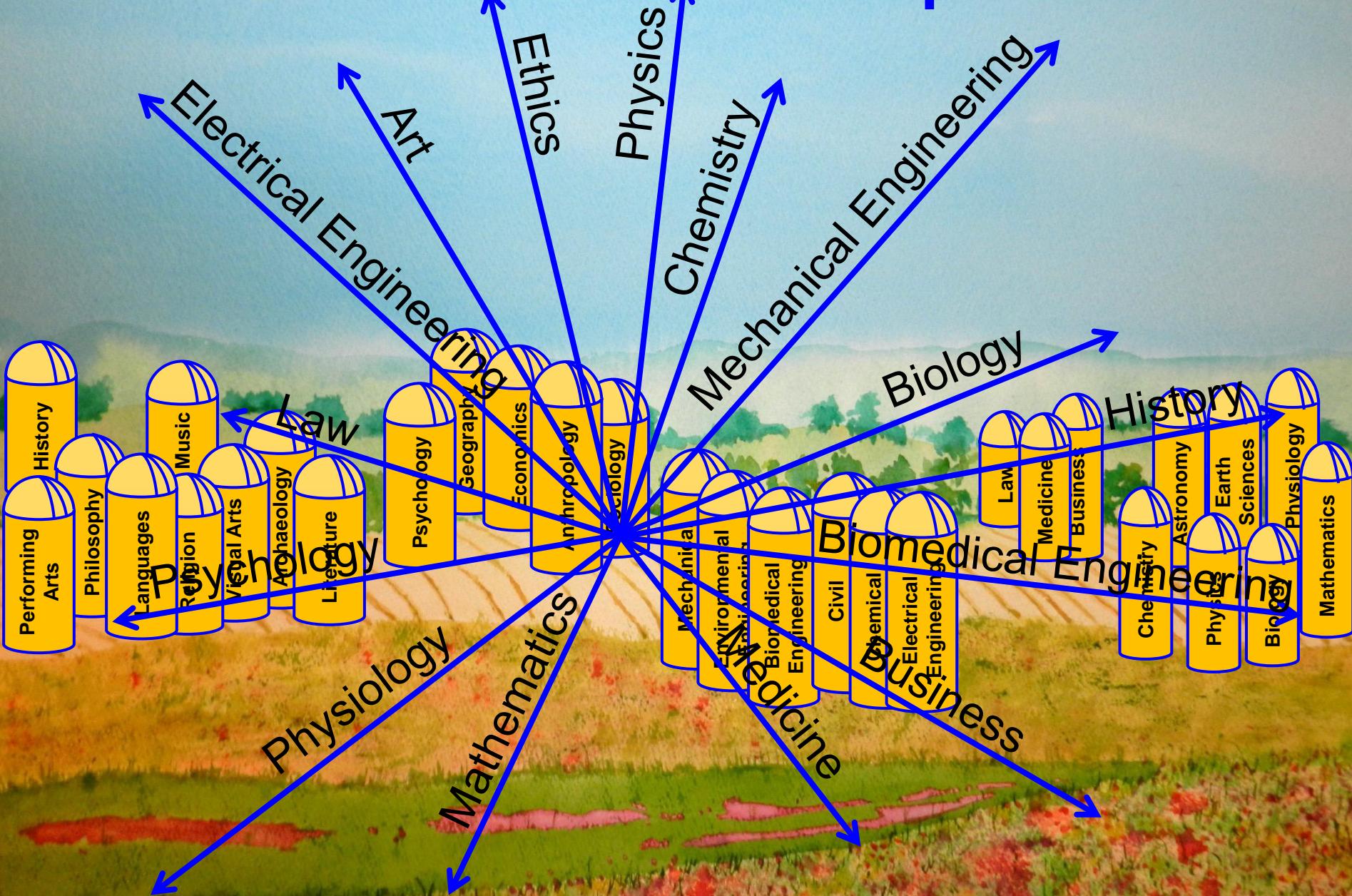


Silos of Knowledge

Athena needs a mix of disciplines

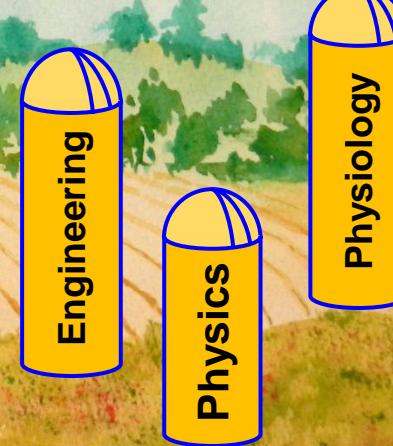


Intellectual Phase Space



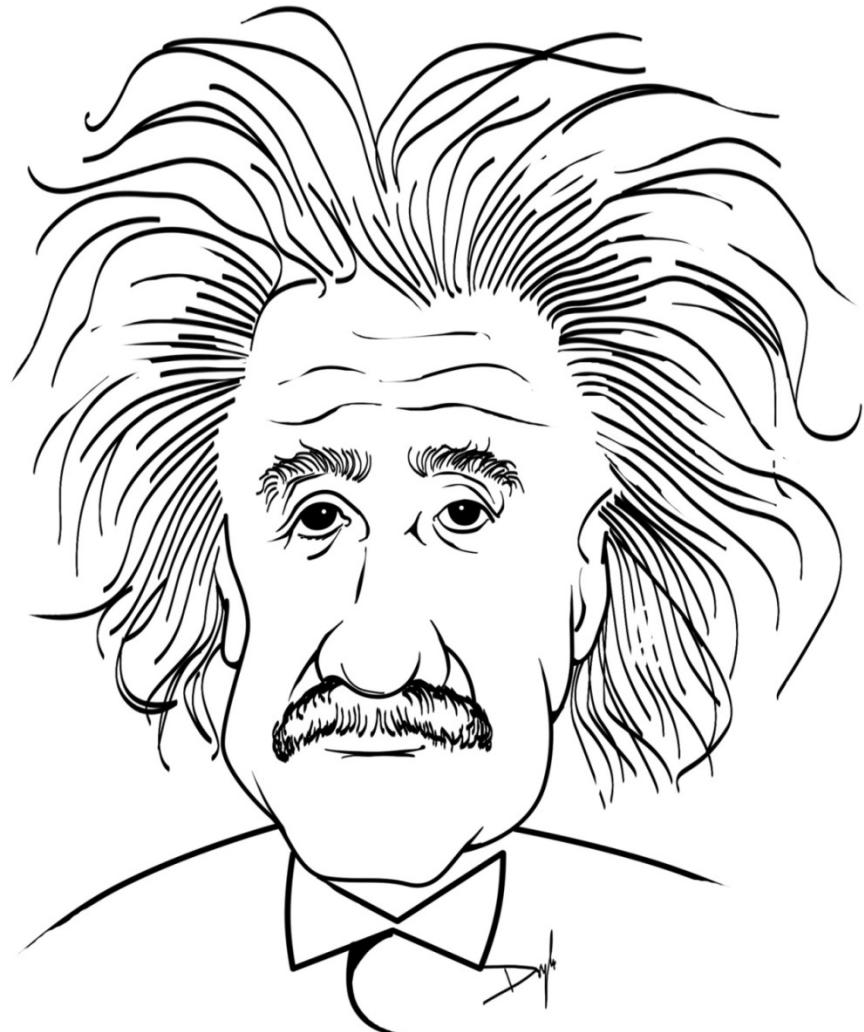
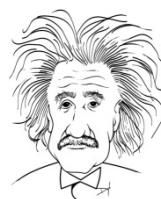
My Knowledge

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



Intellectual Phase Space

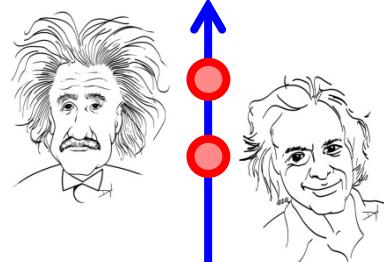
Physics



Albert Einstein
1879-1955

Intellectual Phase Space

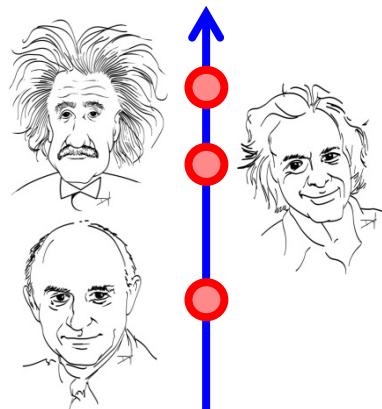
Physics



Richard Feynman
1918-1988

Intellectual Phase Space

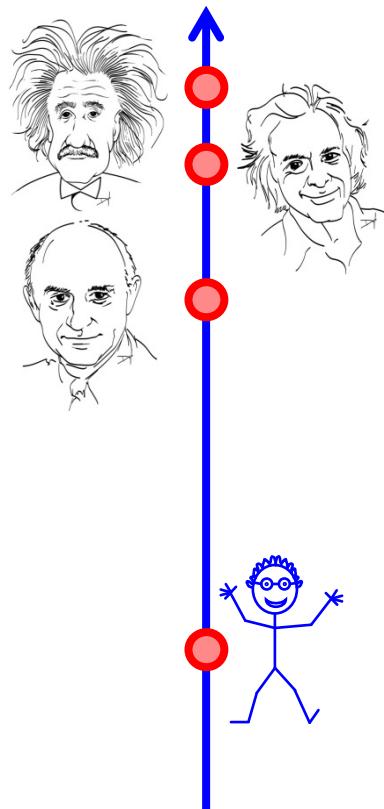
Physics



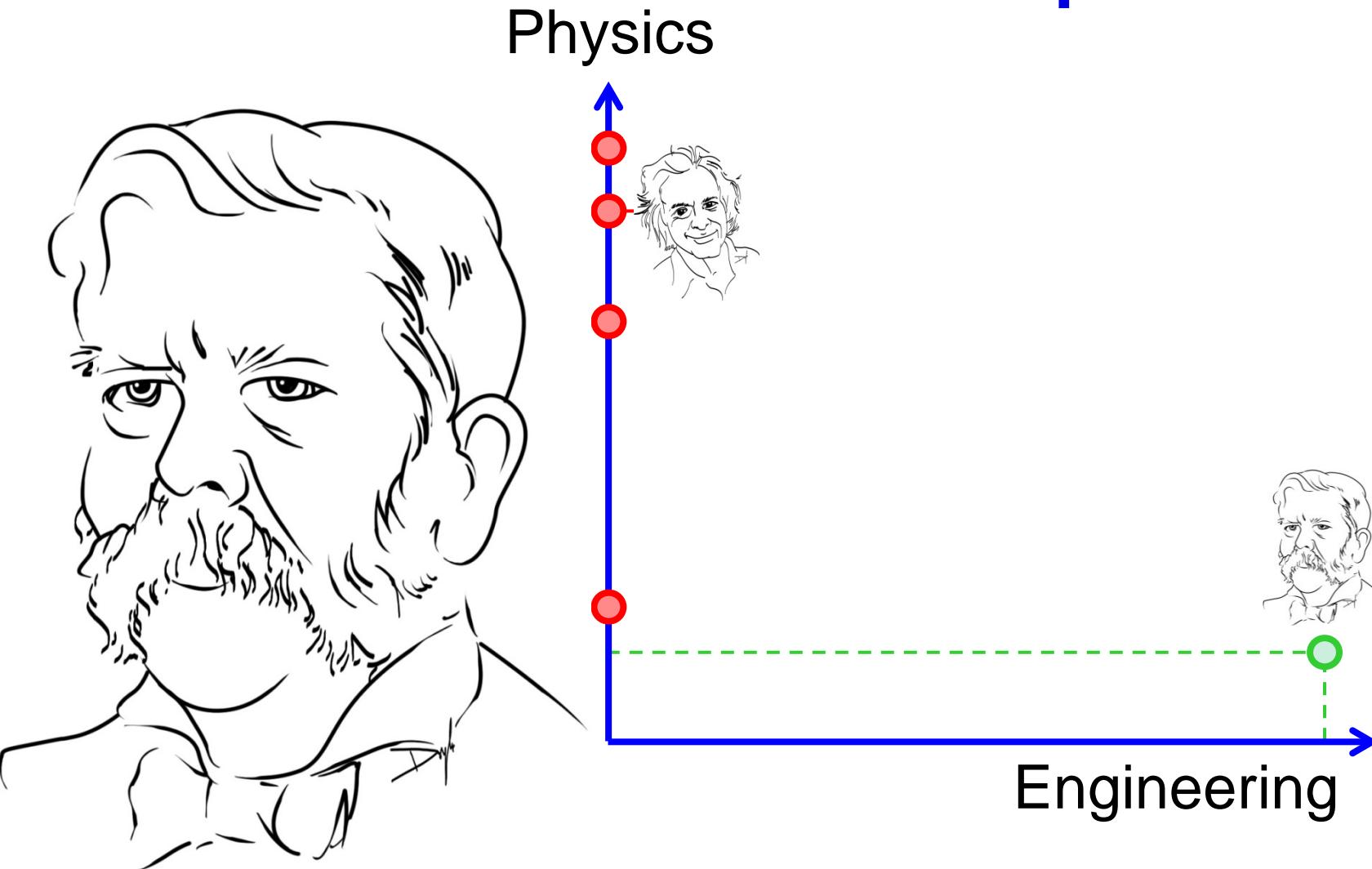
Enrico Fermi
1901-1954

Intellectual Phase Space

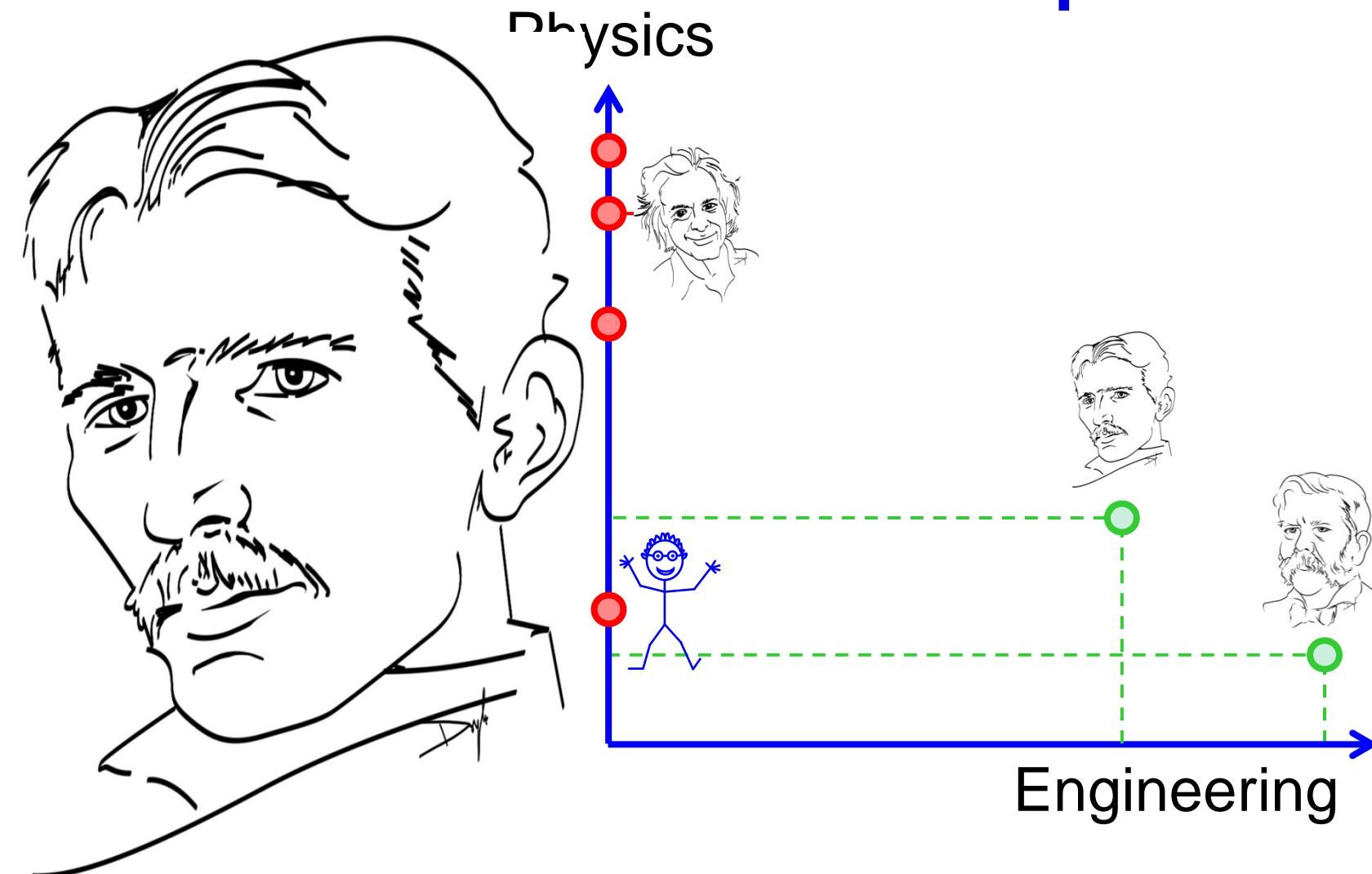
Physics



Intellectual Phase Space



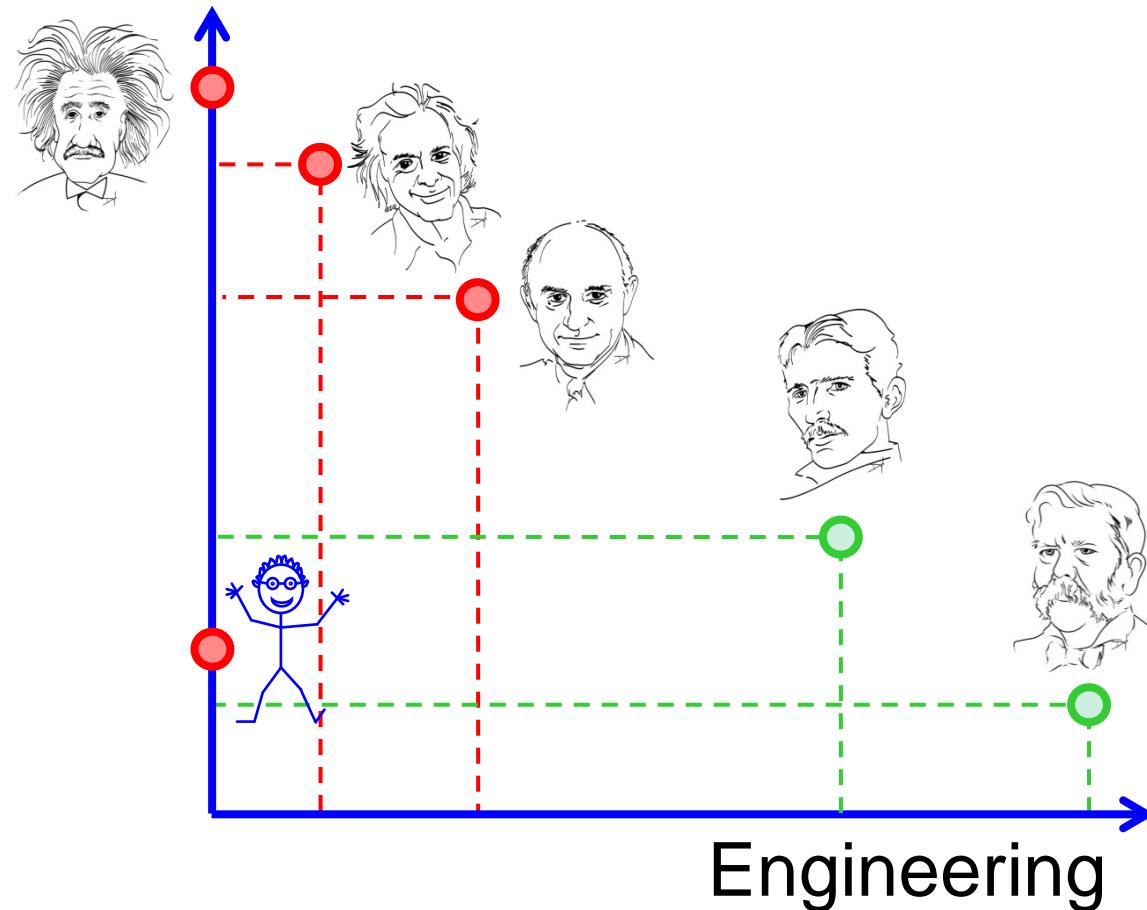
Intellectual Phase Space



Nikola Tesla
1856-1943

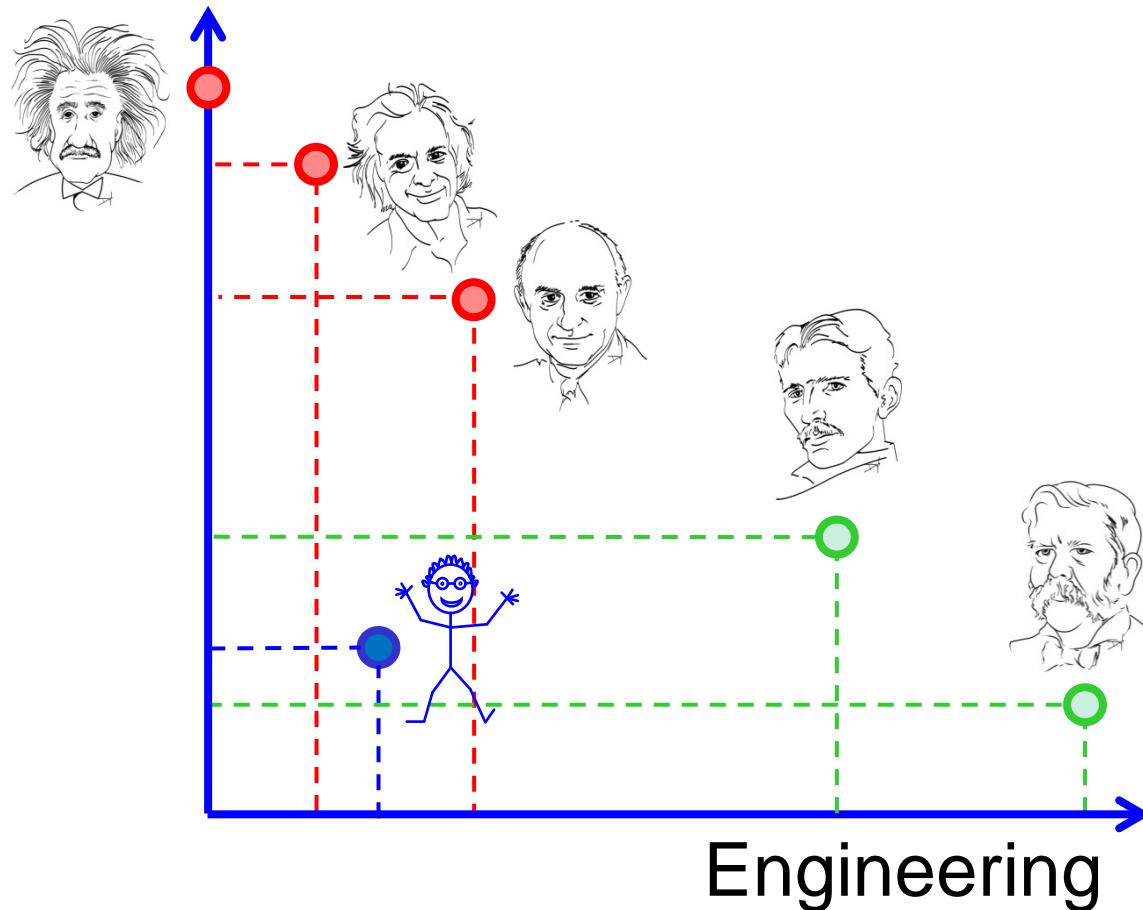
Intellectual Phase Space

Physics

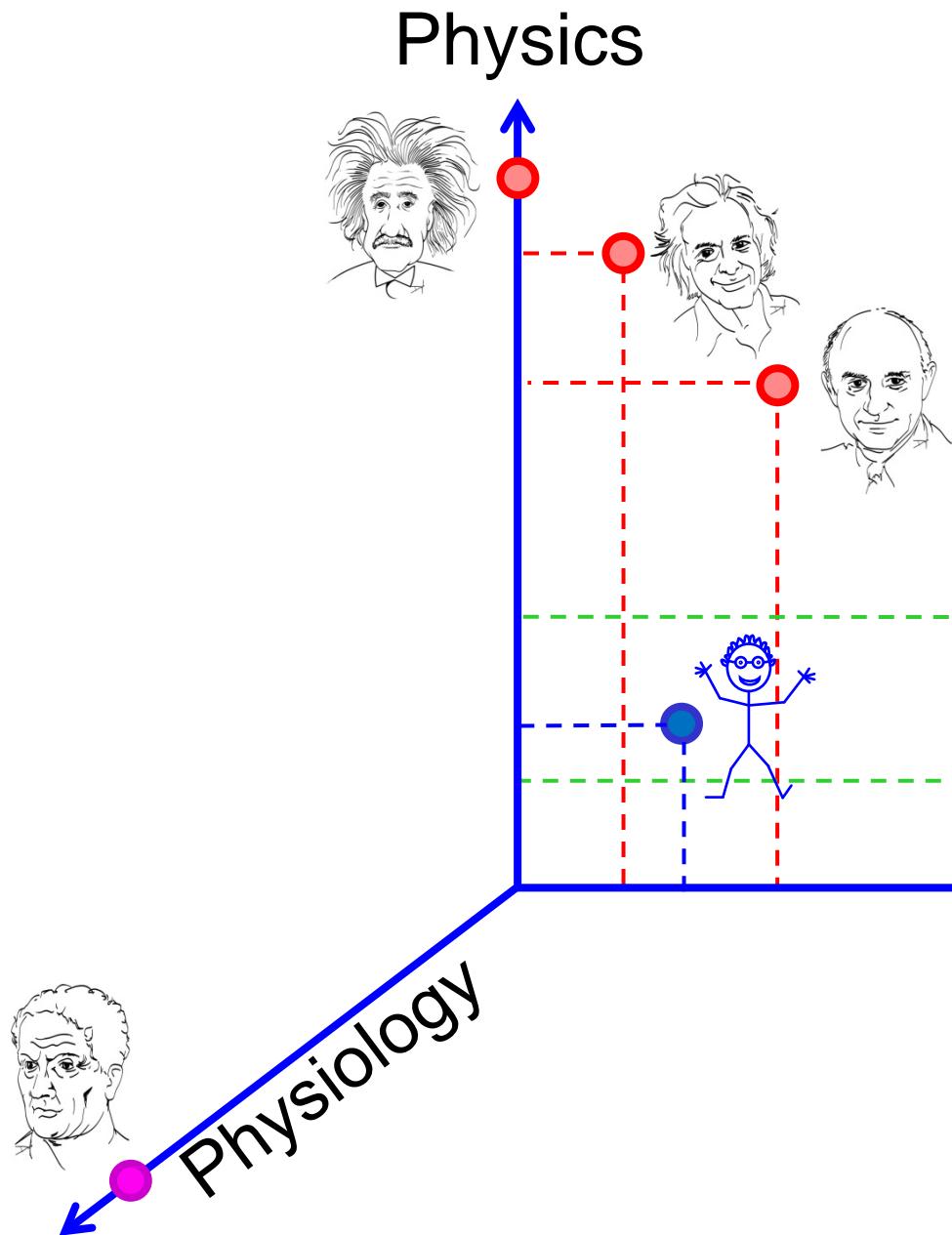


Intellectual Phase Space

Physics



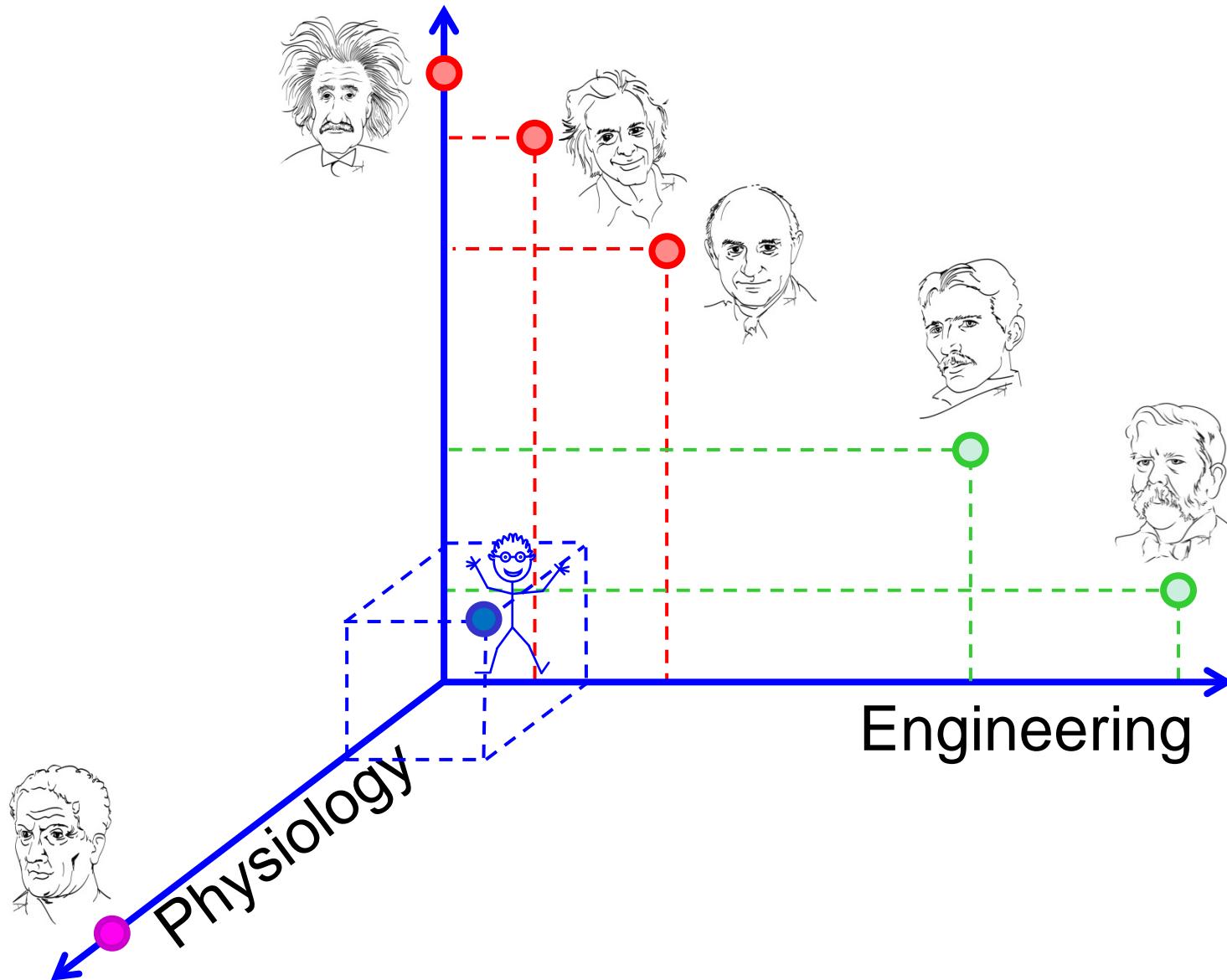
Intellectual Phase



Galen of Pergamon
AD 129-216

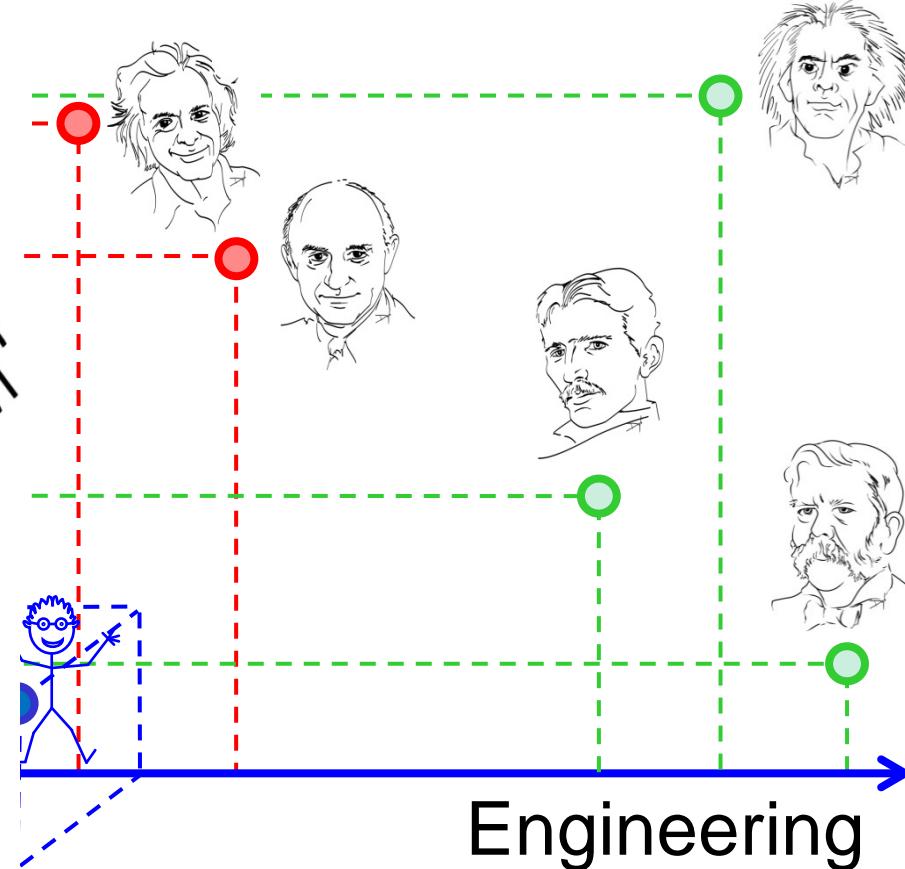
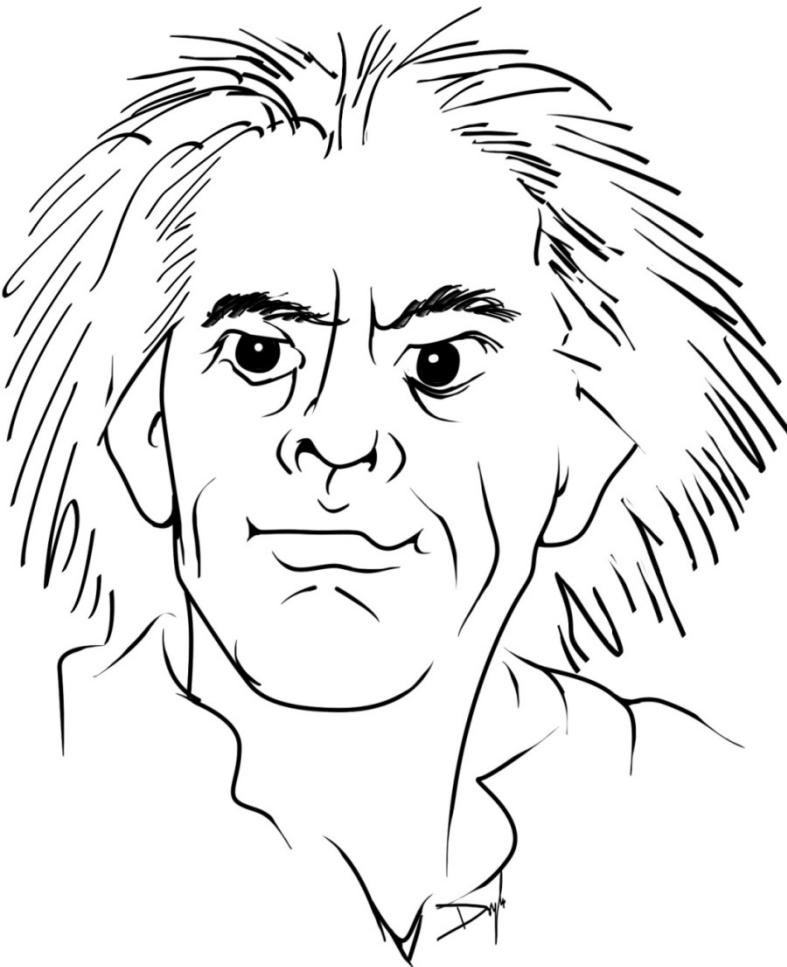
Intellectual Phase Space

Physics



Intellectual Phase Space

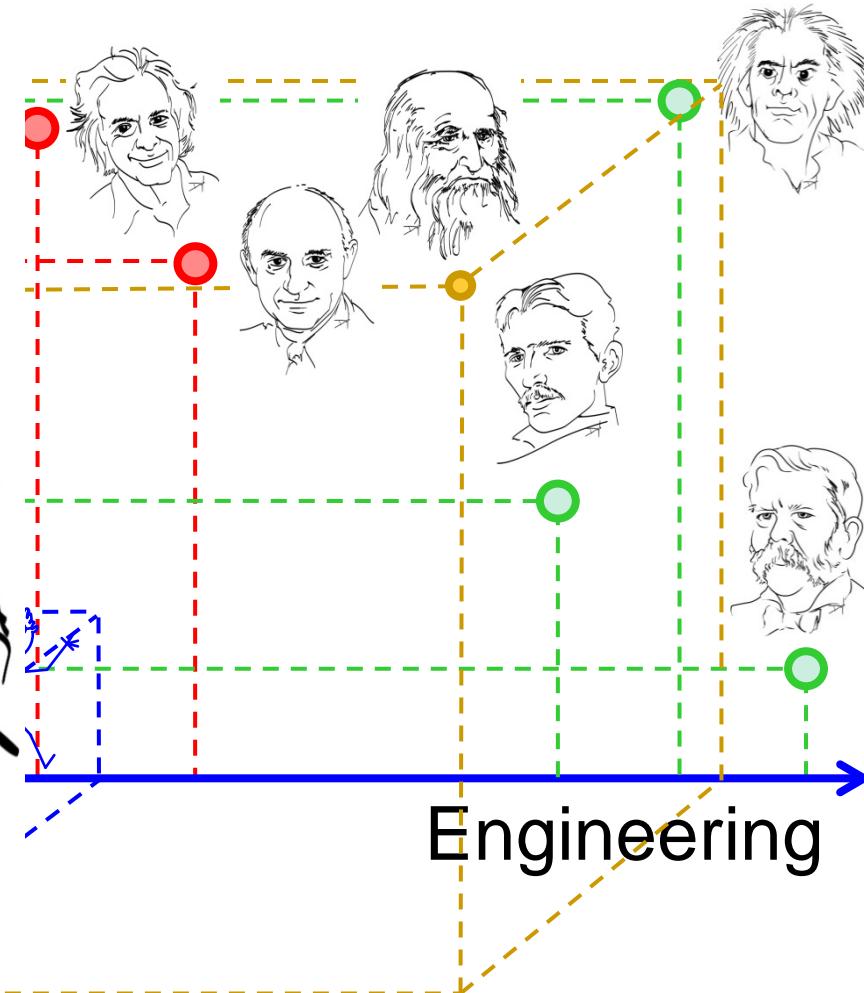
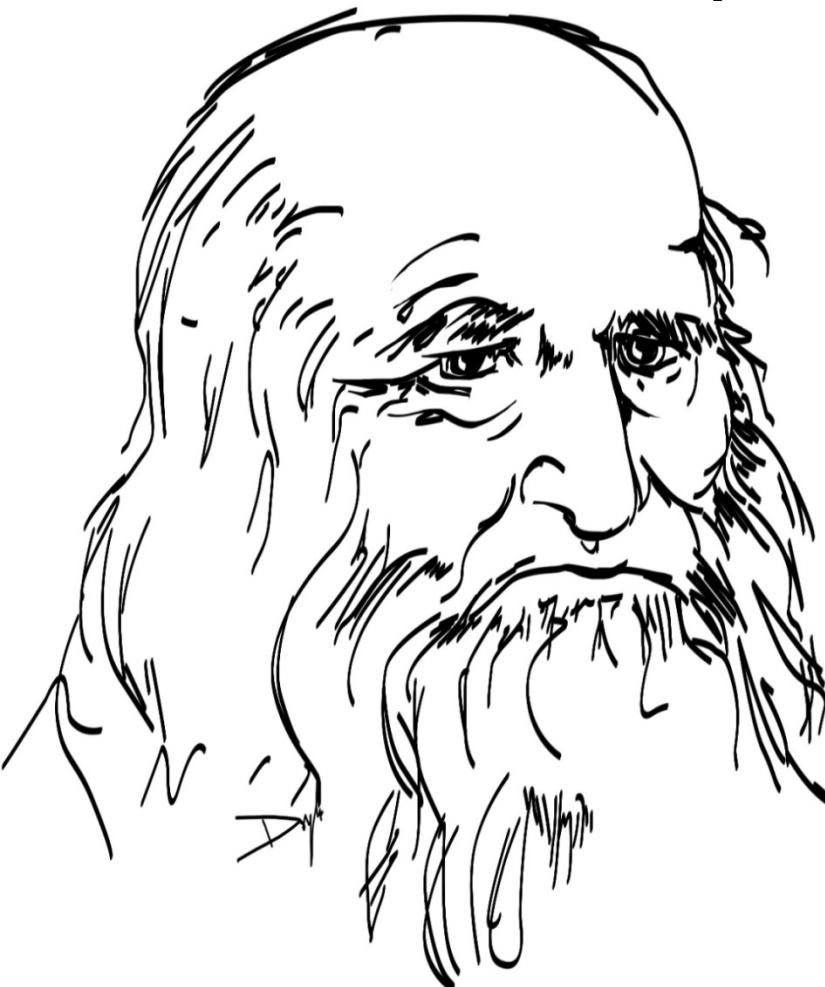
Physics



Emmett "Doc" Brown
1885-2015?

Intellectual Phase Space

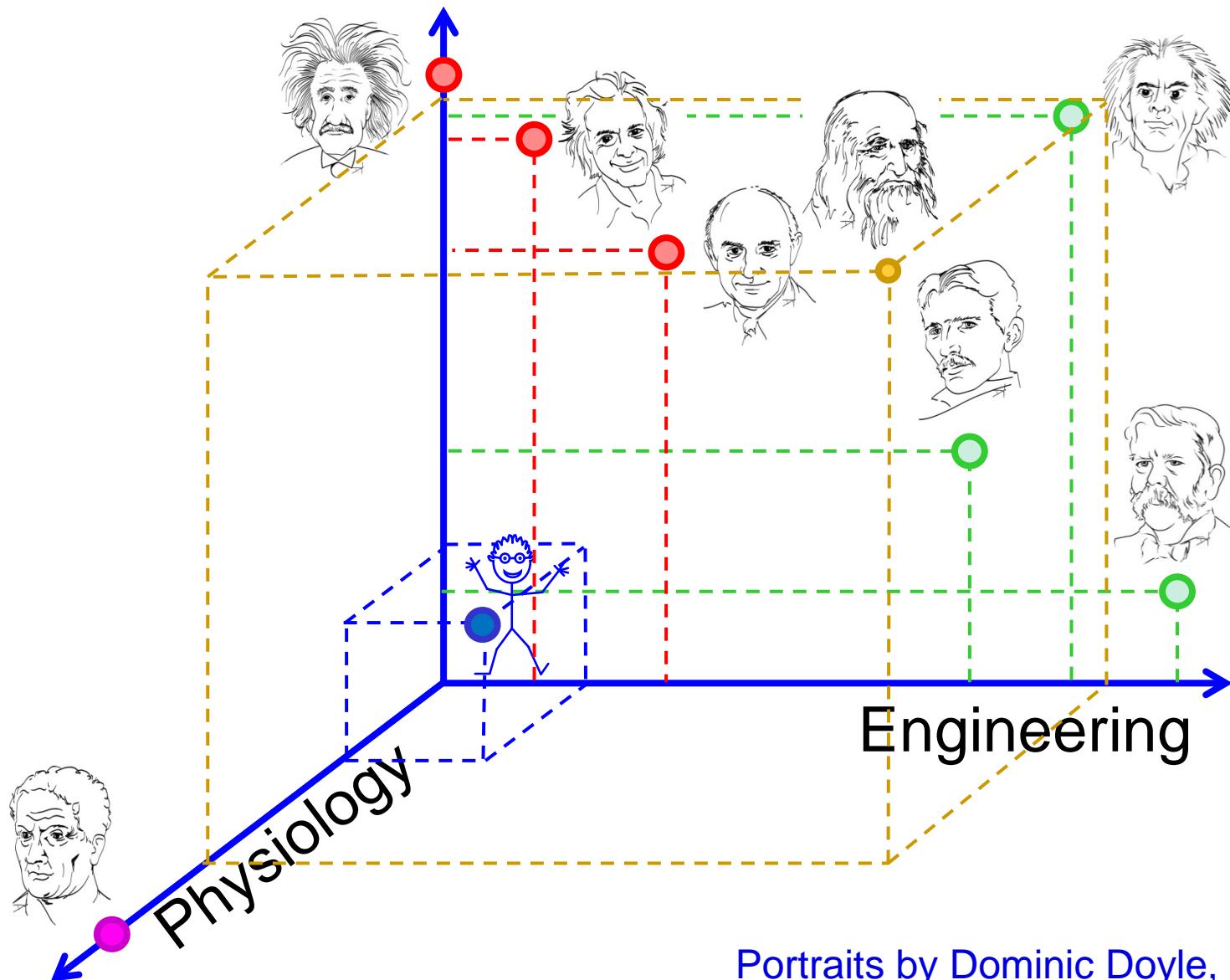
Physics



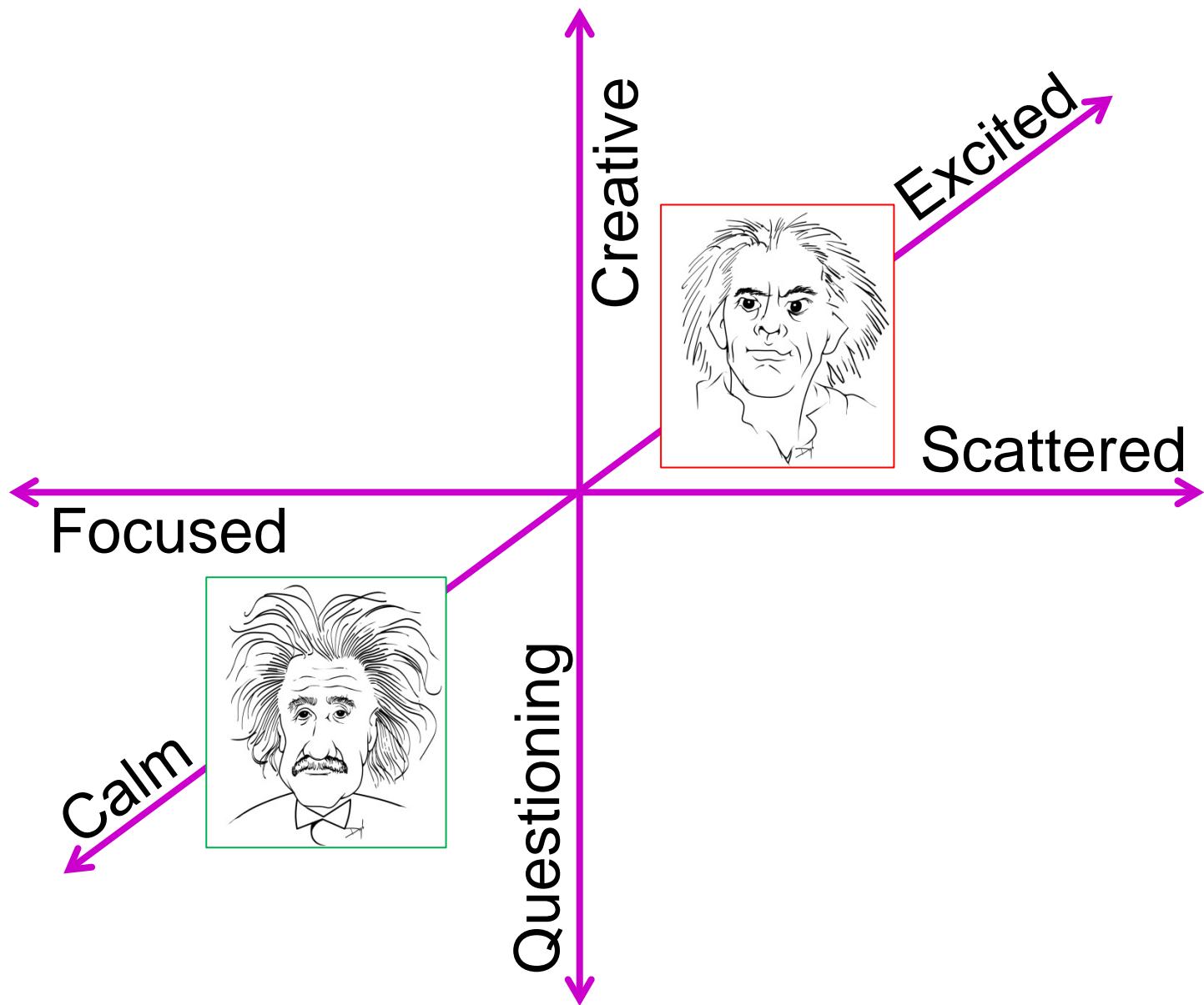
Leonardo da Vinci
1452-1519

Intellectual Phase Space

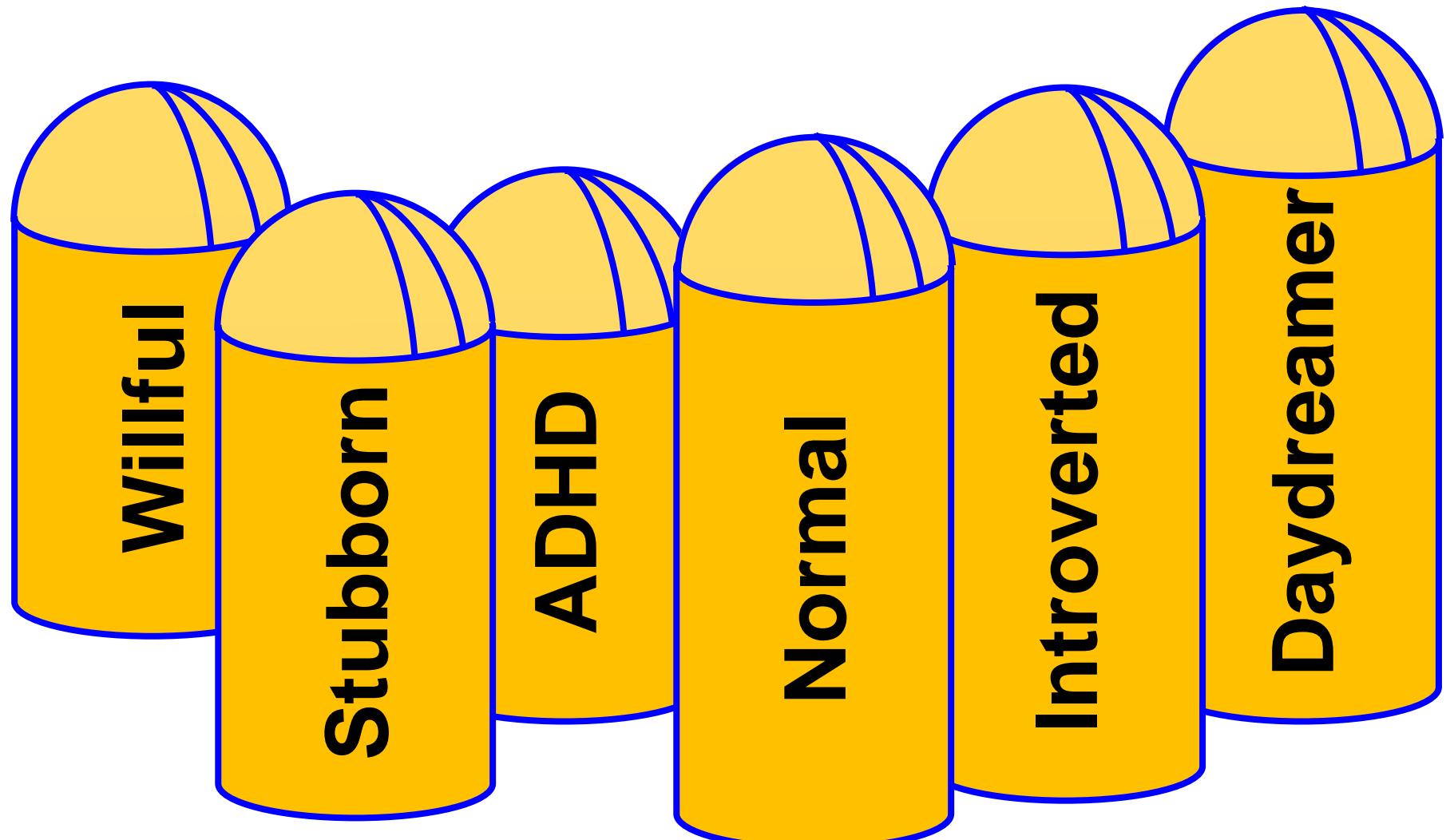
Physics



Behavioral Phase Space



Behavioral Silos



Swing Phase Space

Front
and
back



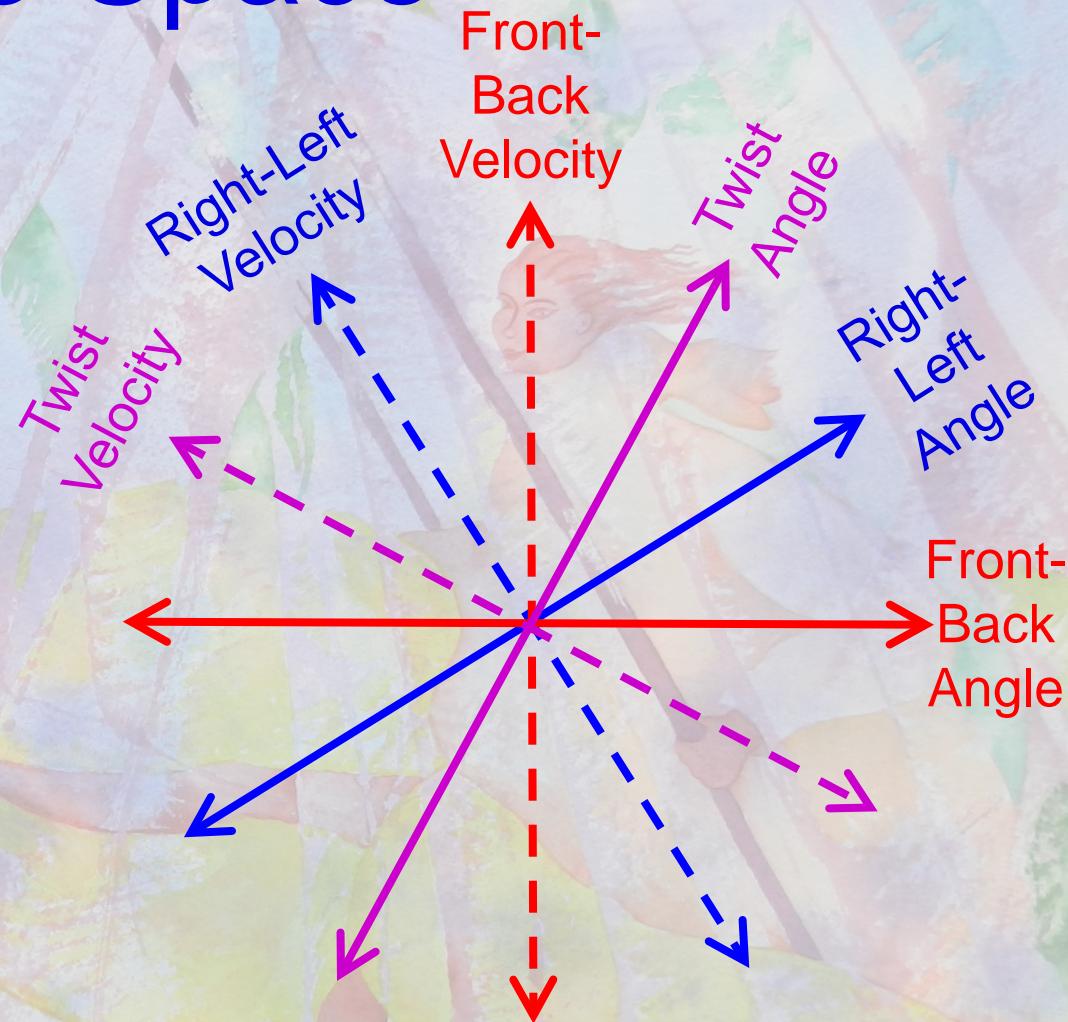
Left
and
Right



Orbit



Twist



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

Don't put people in a single silo!



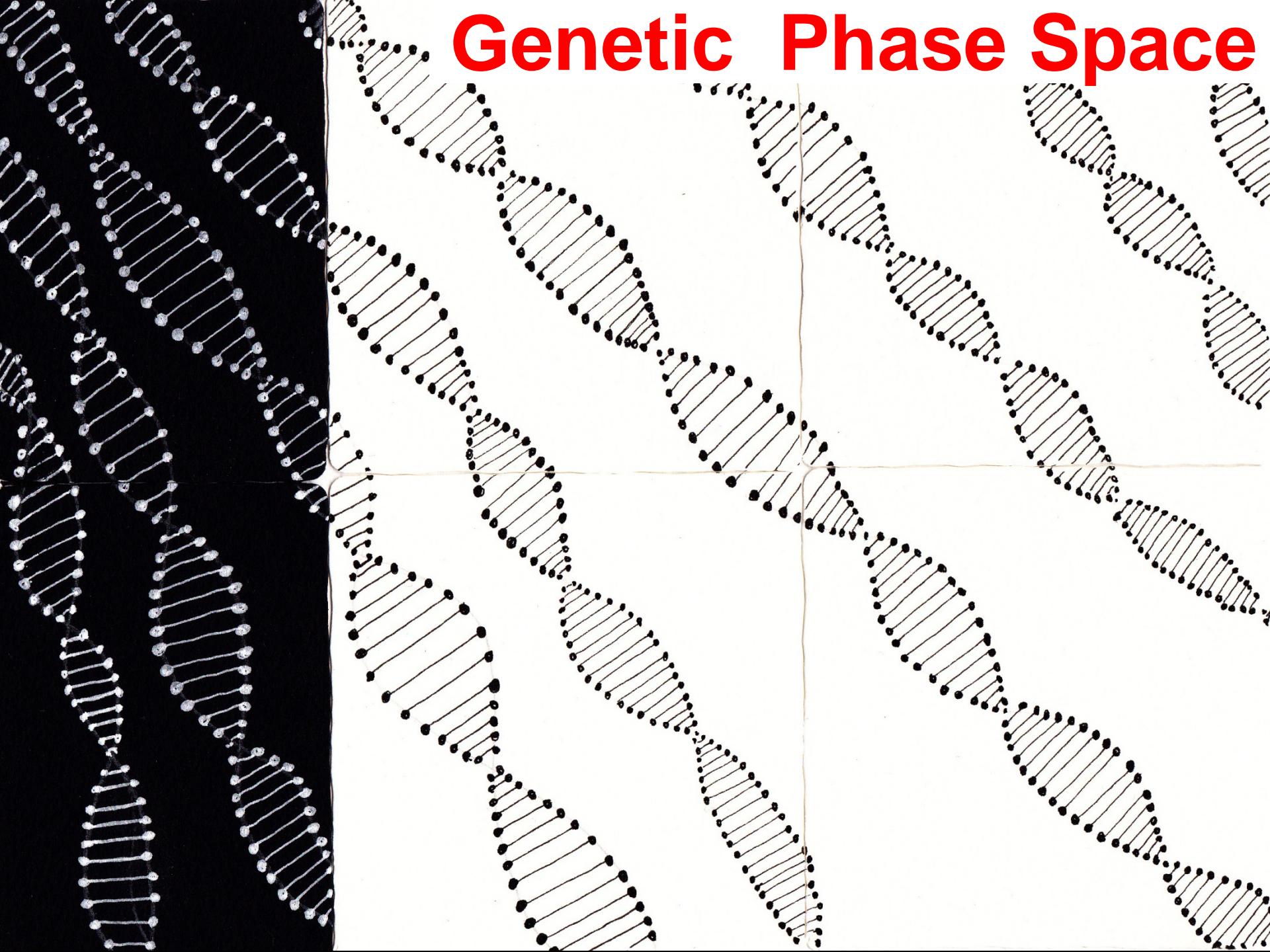
Behavioral Phase Space





What are we learning?

Genetic Phase Space



1 Gene Phase Space

ALB

Maximum
expression

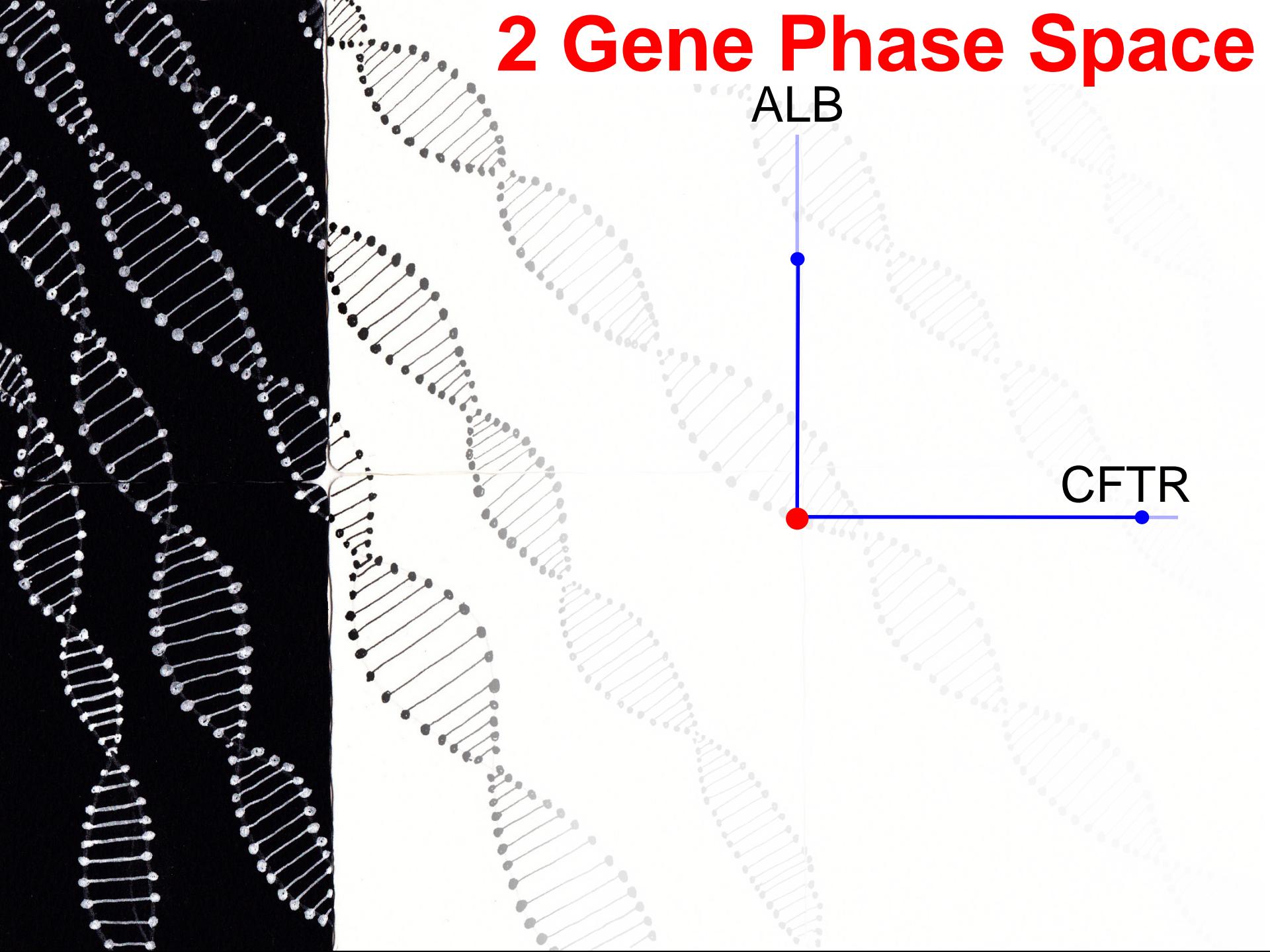
Actual
expression level

No gene
expression

2 Gene Phase Space

ALB

CFTR

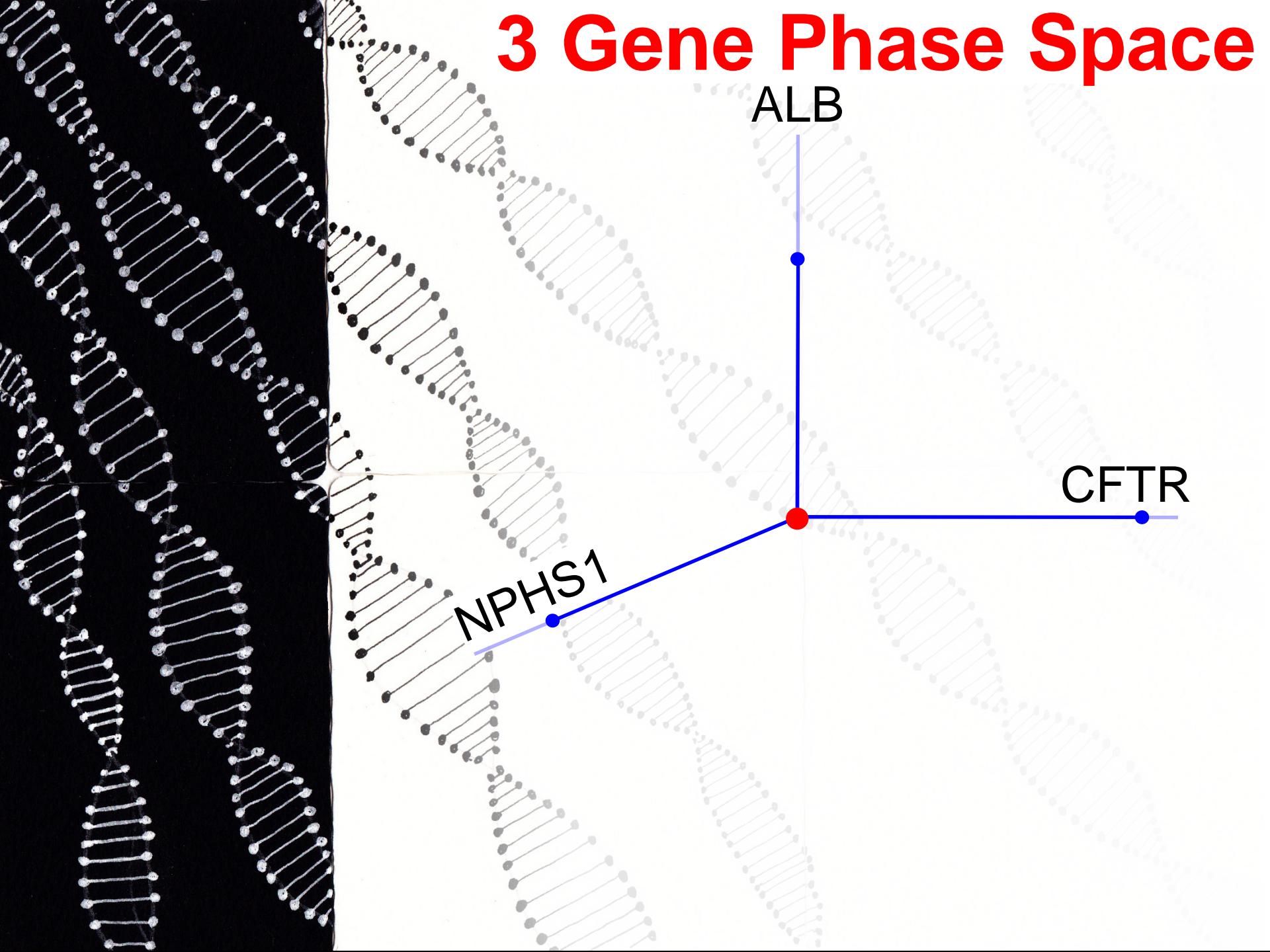


3 Gene Phase Space

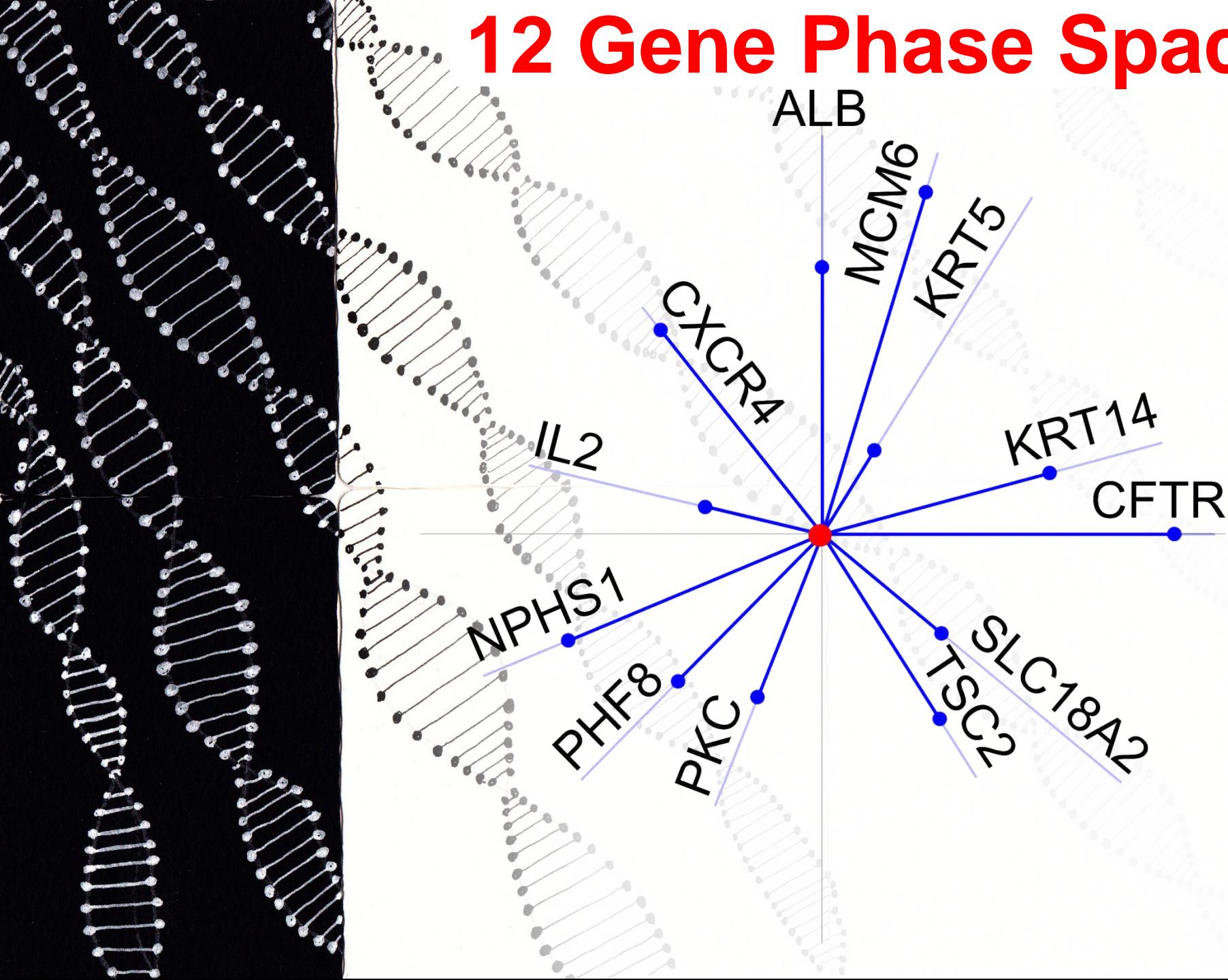
ALB

CFTR

NPHS1



12 Gene Phase Space



100 Gene Phase Space

CRH
CXCR4

DHFR

HFE

KRT14

KRT5

PGL2

PHF8

RHO

SDHB

SDHC

SDHD

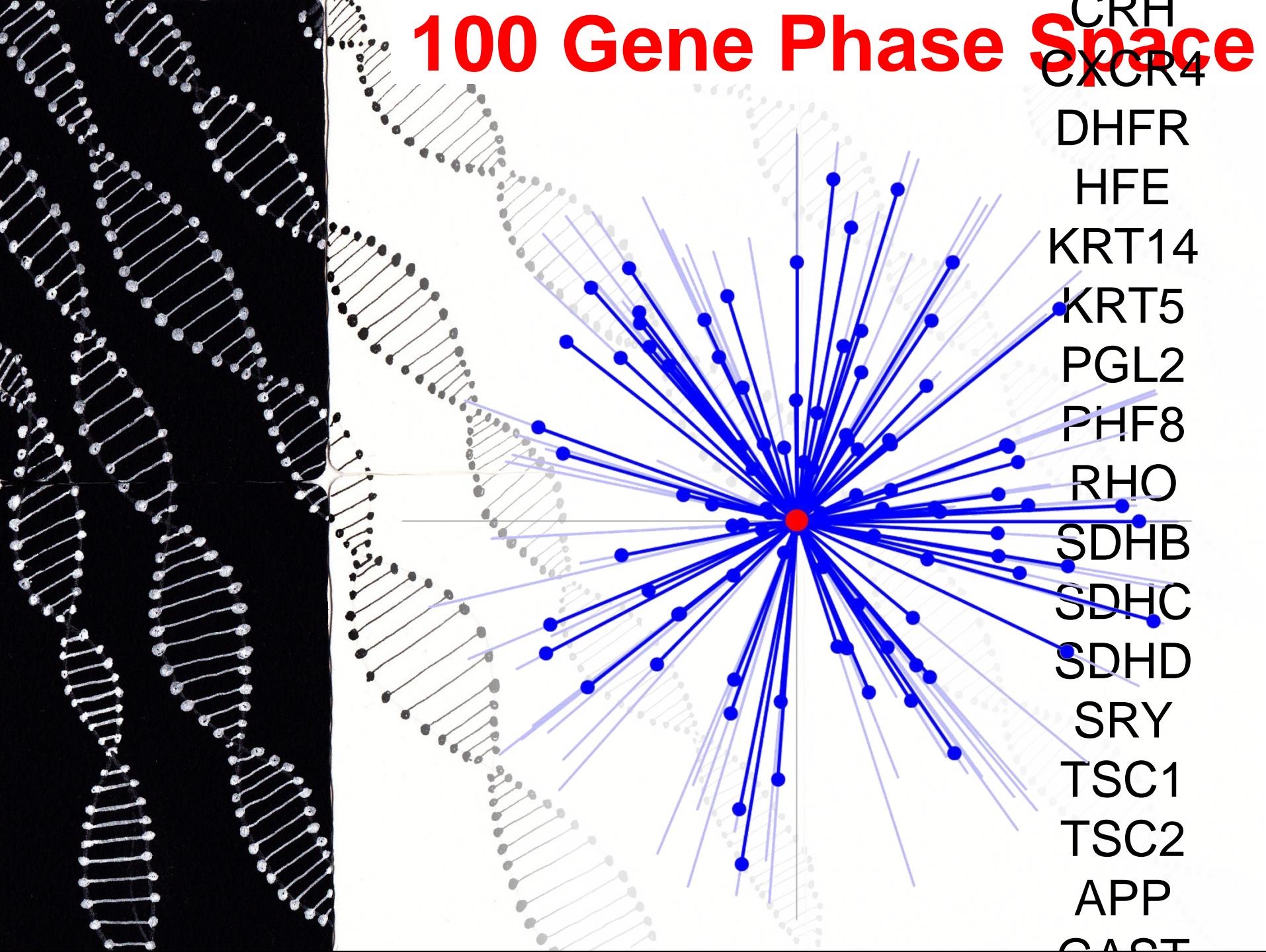
SRY

TSC1

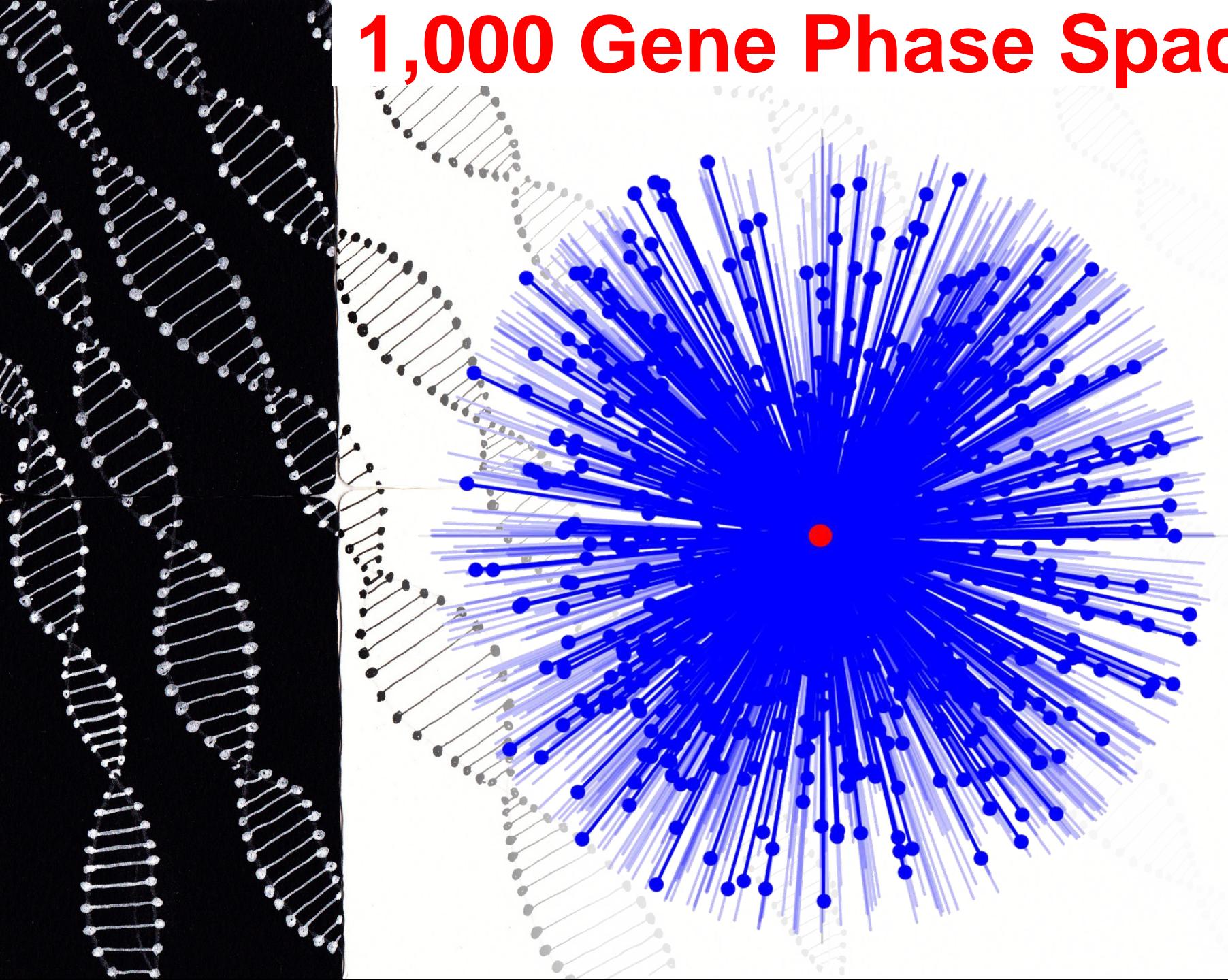
TSC2

APP

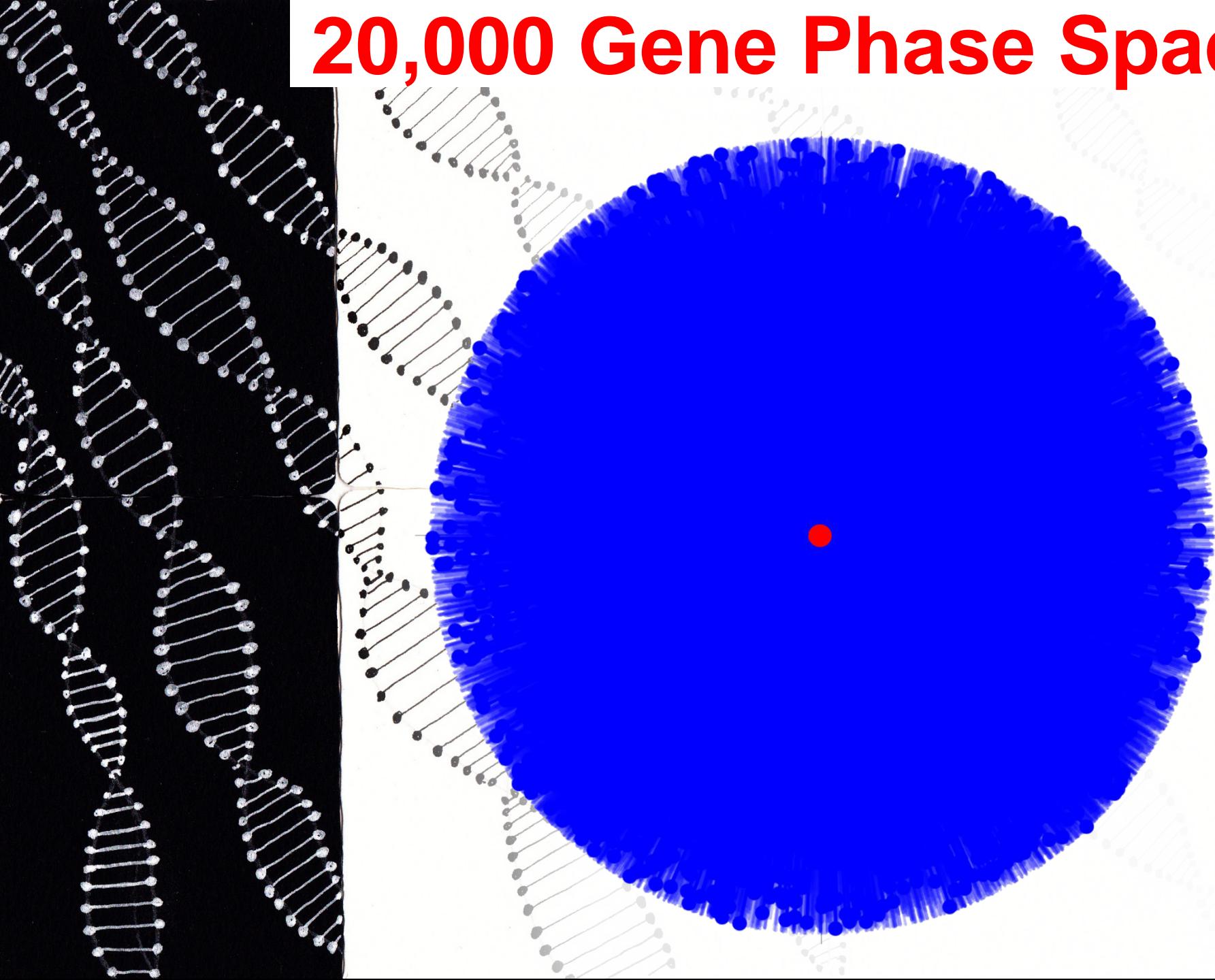
CACT

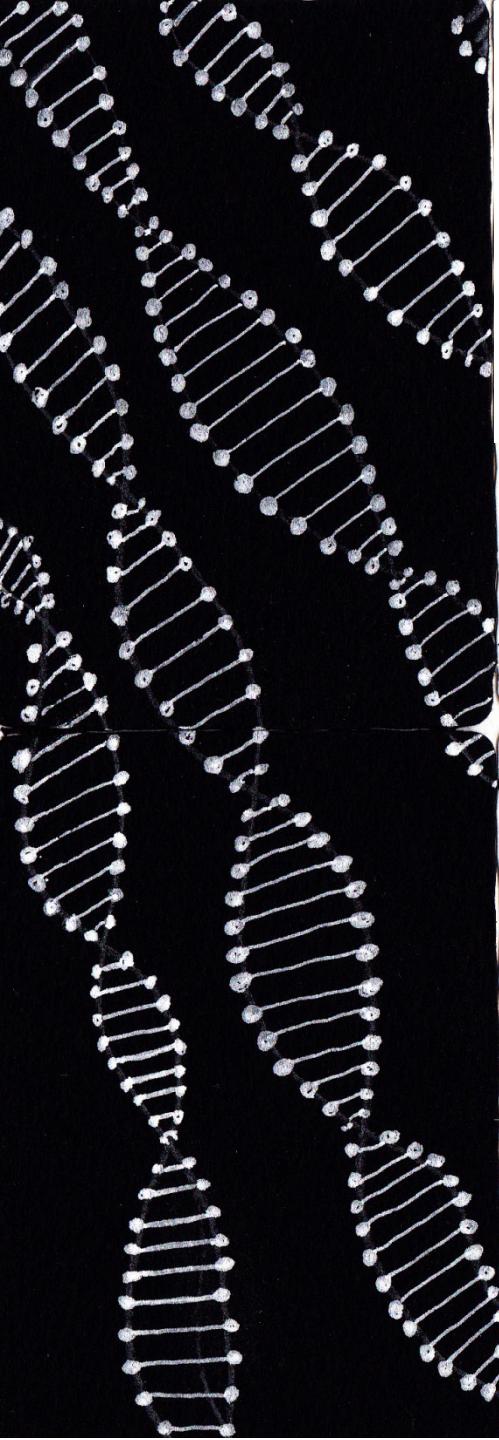


1,000 Gene Phase Space

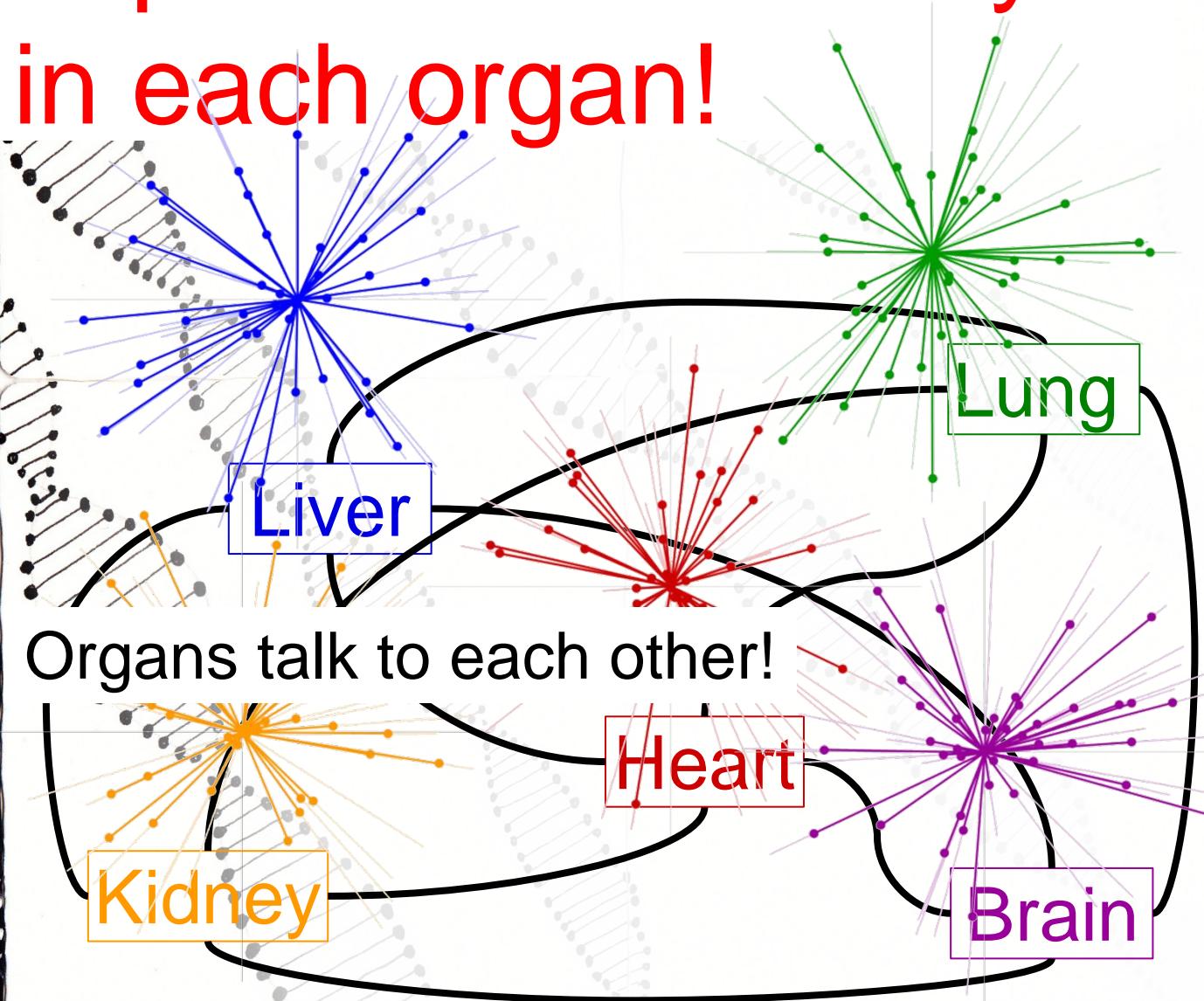


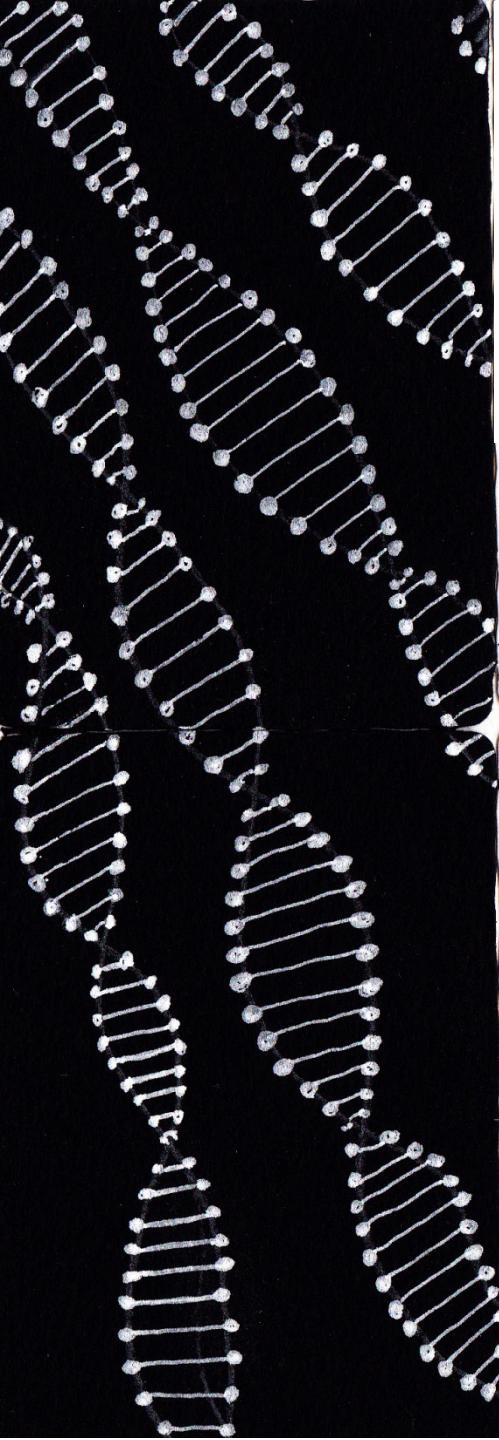
20,000 Gene Phase Space



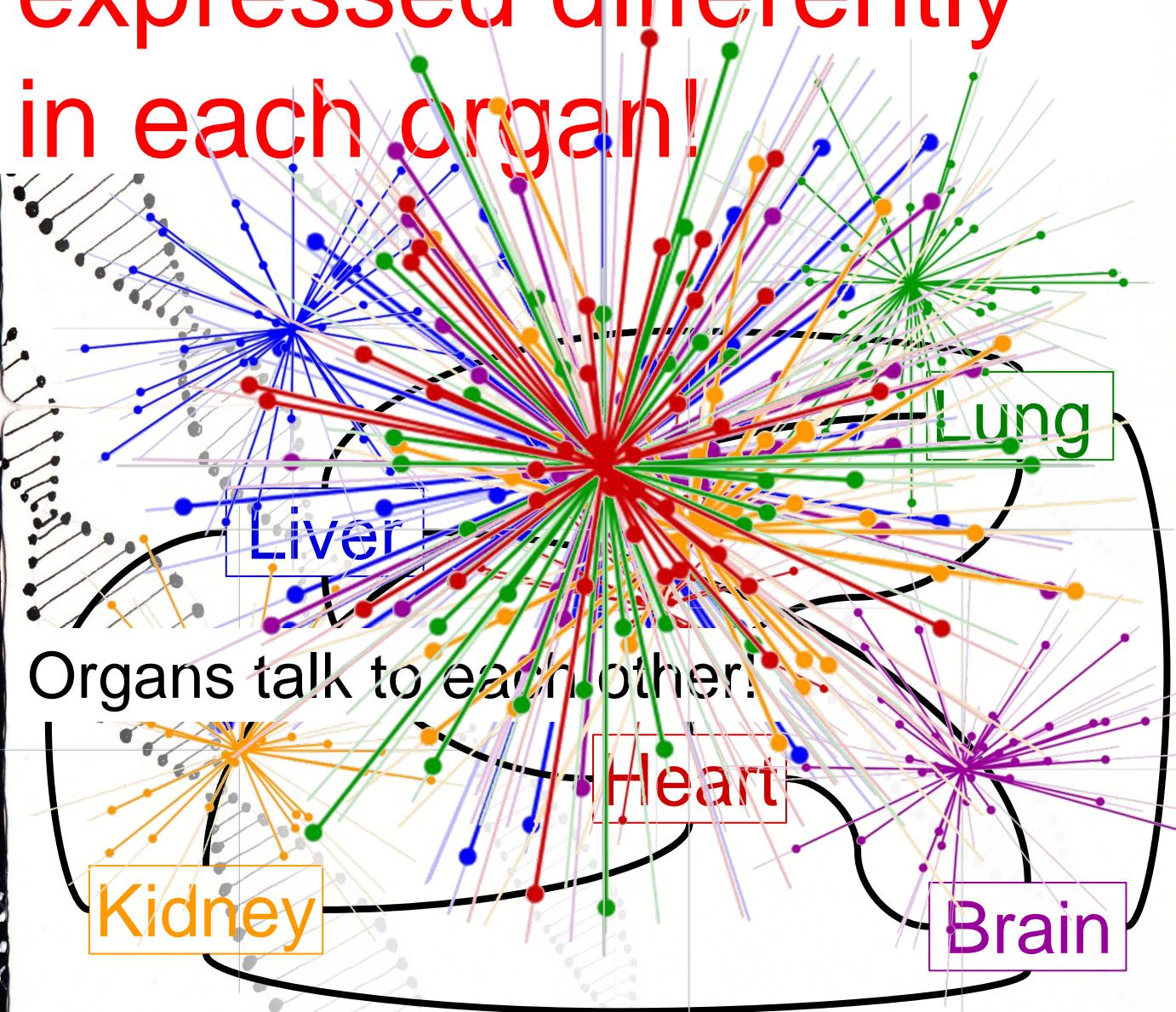


Our 20,000 genes are expressed differently in each organ!





Our 20,000 genes are expressed differently in each organ!



A high-magnification microscopic image of a tissue sample. The image shows a complex, three-dimensional structure of various tissue types. In the center, there is a distinct, rounded organoid-like structure with a purple-stained nucleus. The surrounding tissue is stained in shades of blue, purple, and pink, with visible blood vessels and cellular details.

What does an organ
on a chip sound like?

Organ on a Chip V5.0



Frank Block, Vanderbilt

