

# 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](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.

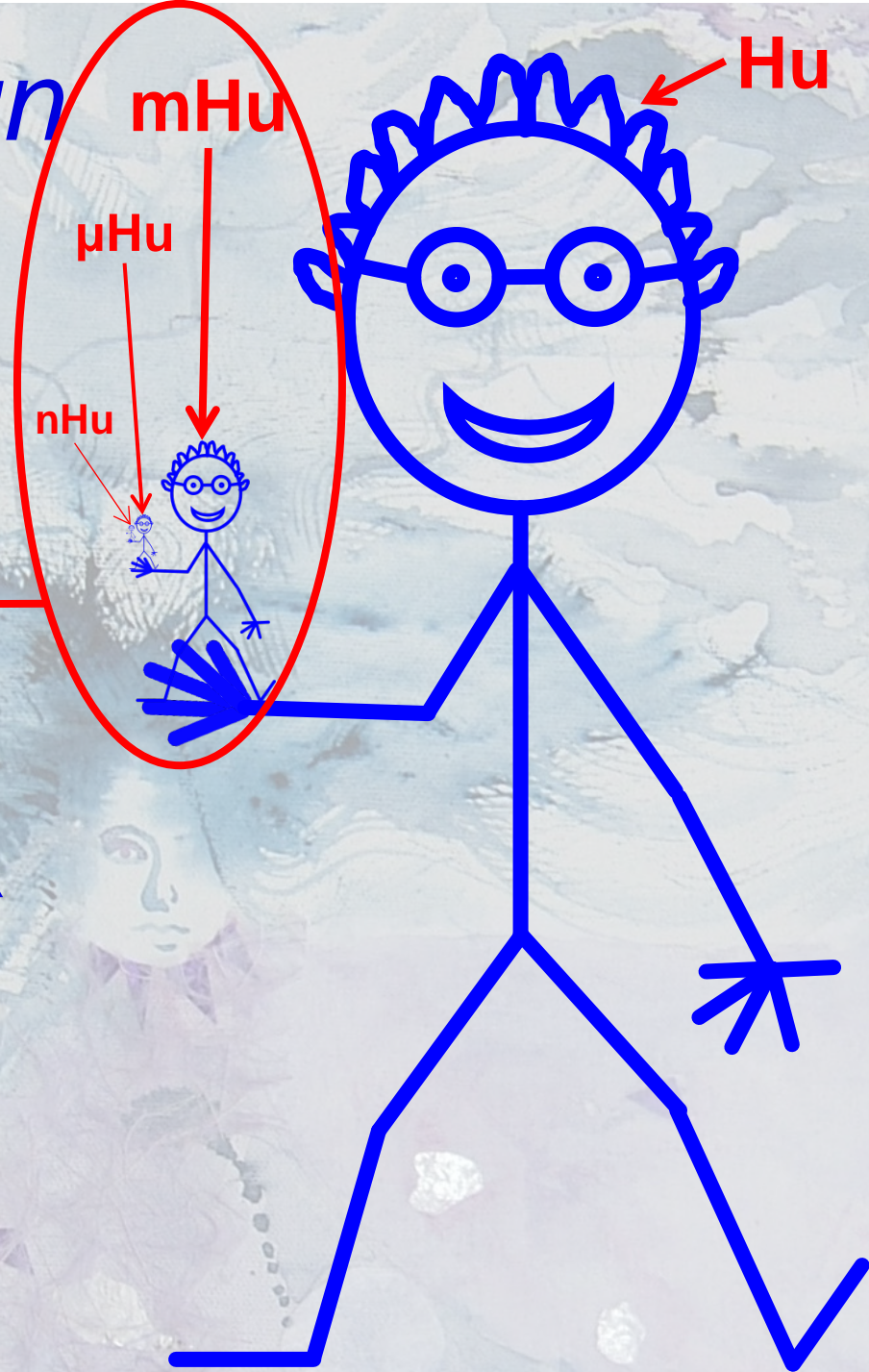


**Homunculus, *noun***

**[hō-'məŋ-kyə-ləs]**

***plural* ho·mun·cu·li**

**A miniature  
representation of a  
human.**

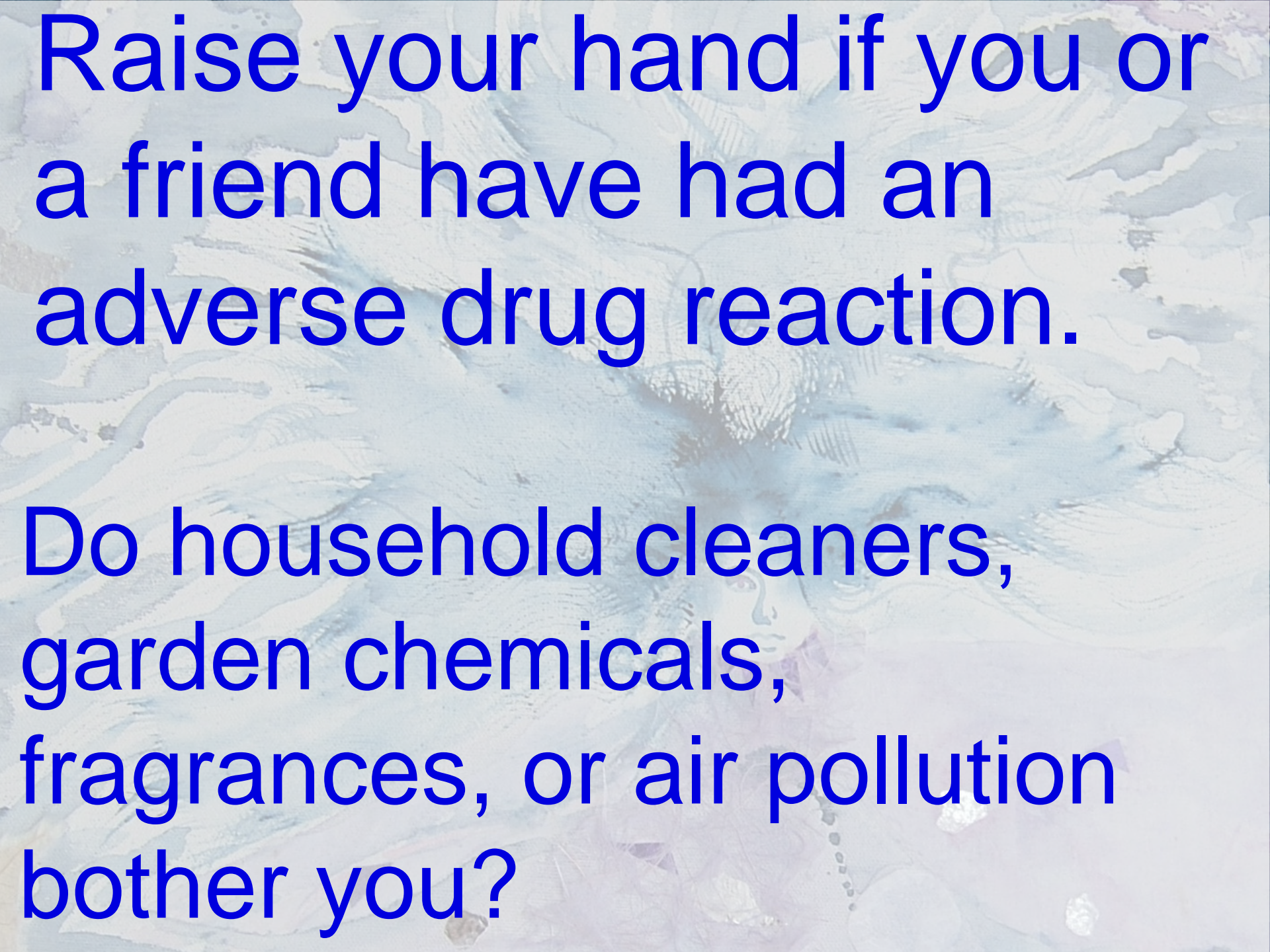




# Why are we building homunculi?

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

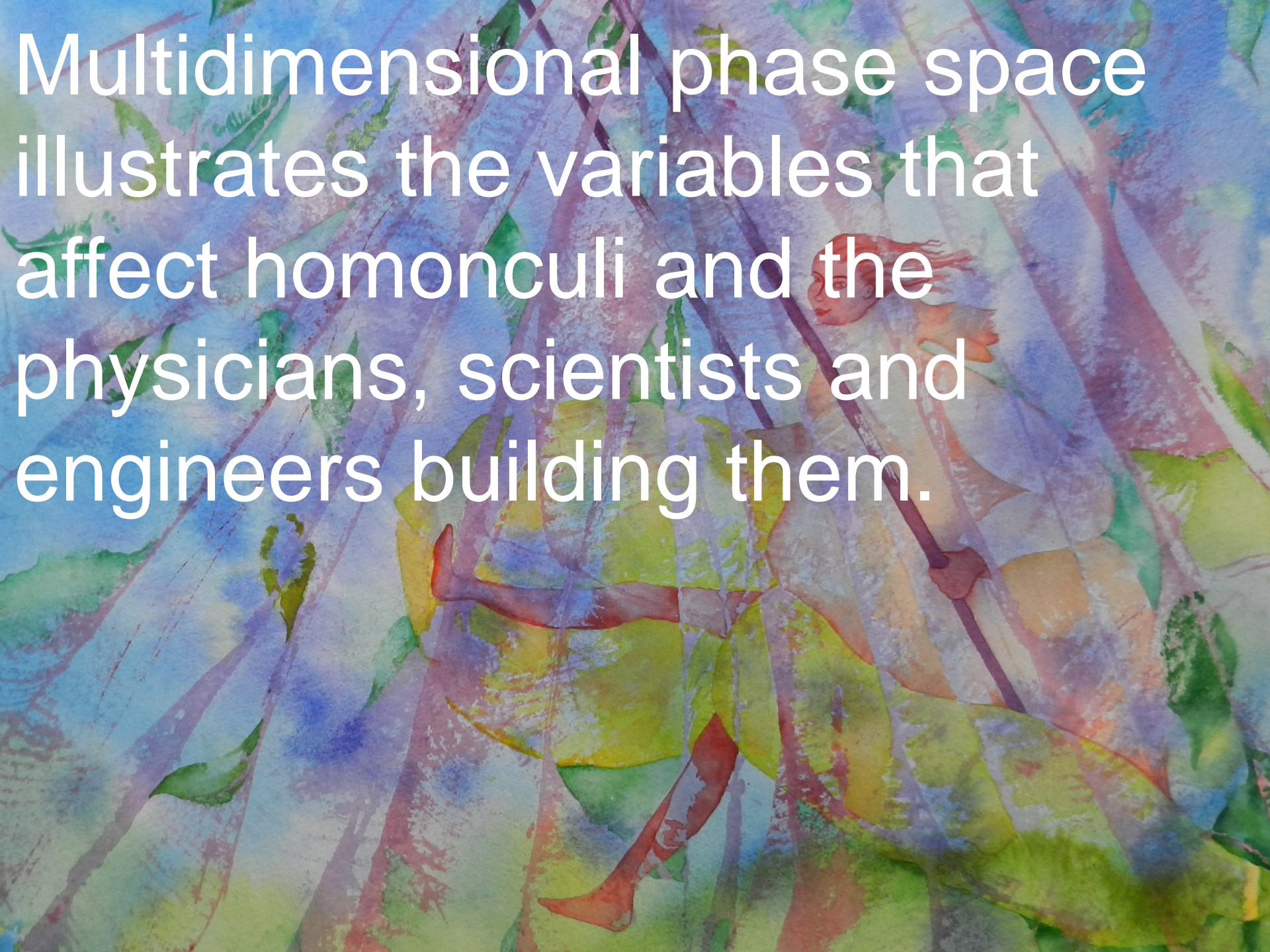




Raise your hand if you or  
a friend have had an  
adverse drug reaction.

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

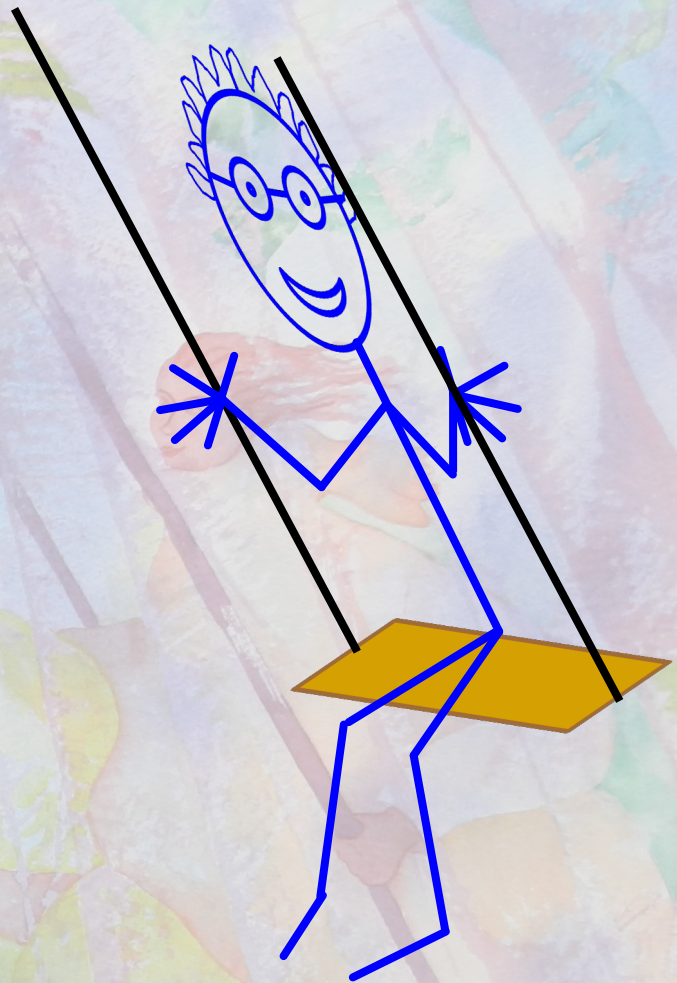


The background is an abstract watercolor painting. It features a woman's face in profile, looking towards the right, rendered in soft, blended colors. The overall palette is dominated by cool tones like blues and purples, with warm accents of yellow, green, and red. The brushstrokes are visible, creating a textured, layered effect.

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

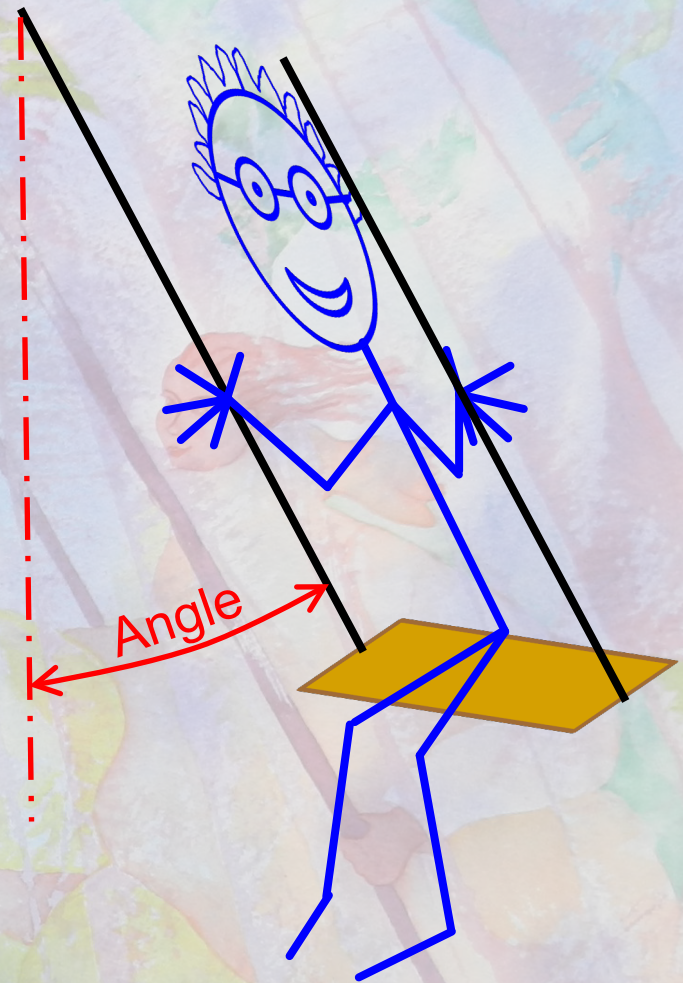


**Phase space**  
[fāz spās], noun  
A geometrical  
space in which  
each possible  
state of a system  
is represented by  
a single point.

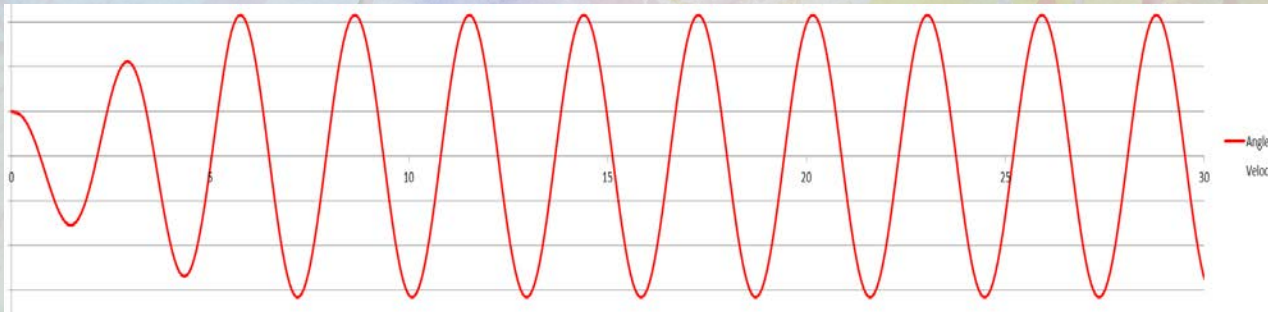




One axis in phase space can represent the range of one variable.

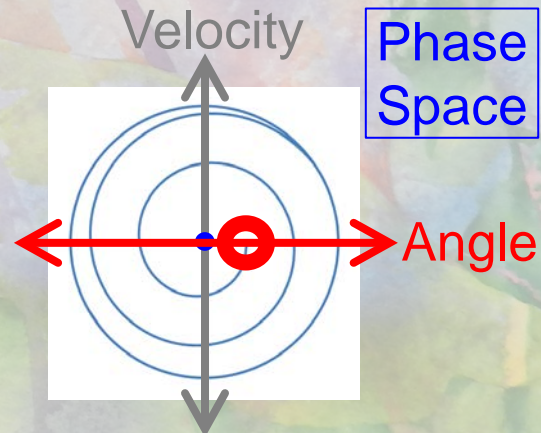
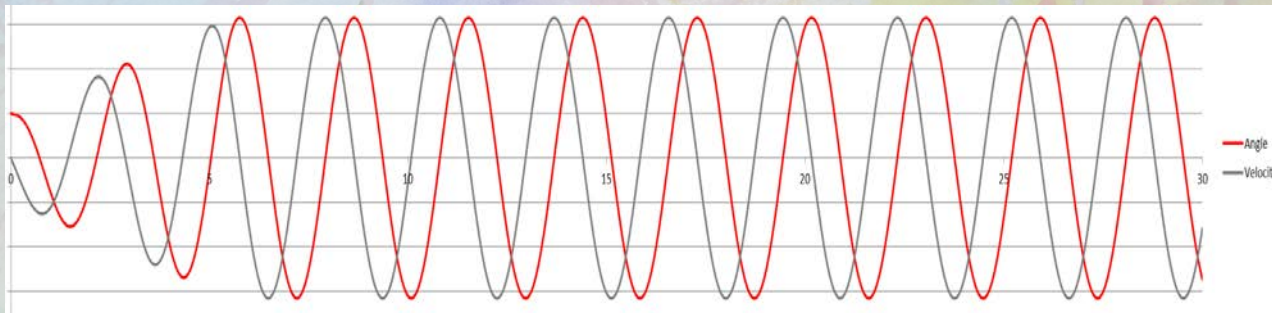
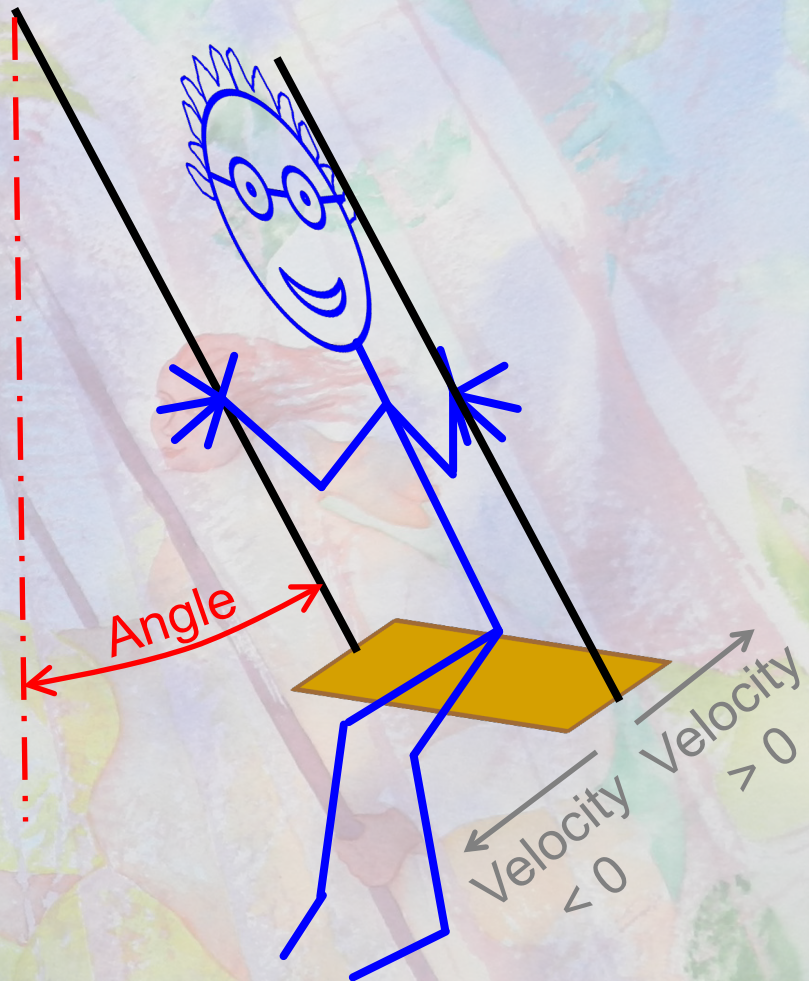


Phase Space





There are as many  
axes as variables.









# Swing Phase Space

Front  
and  
back



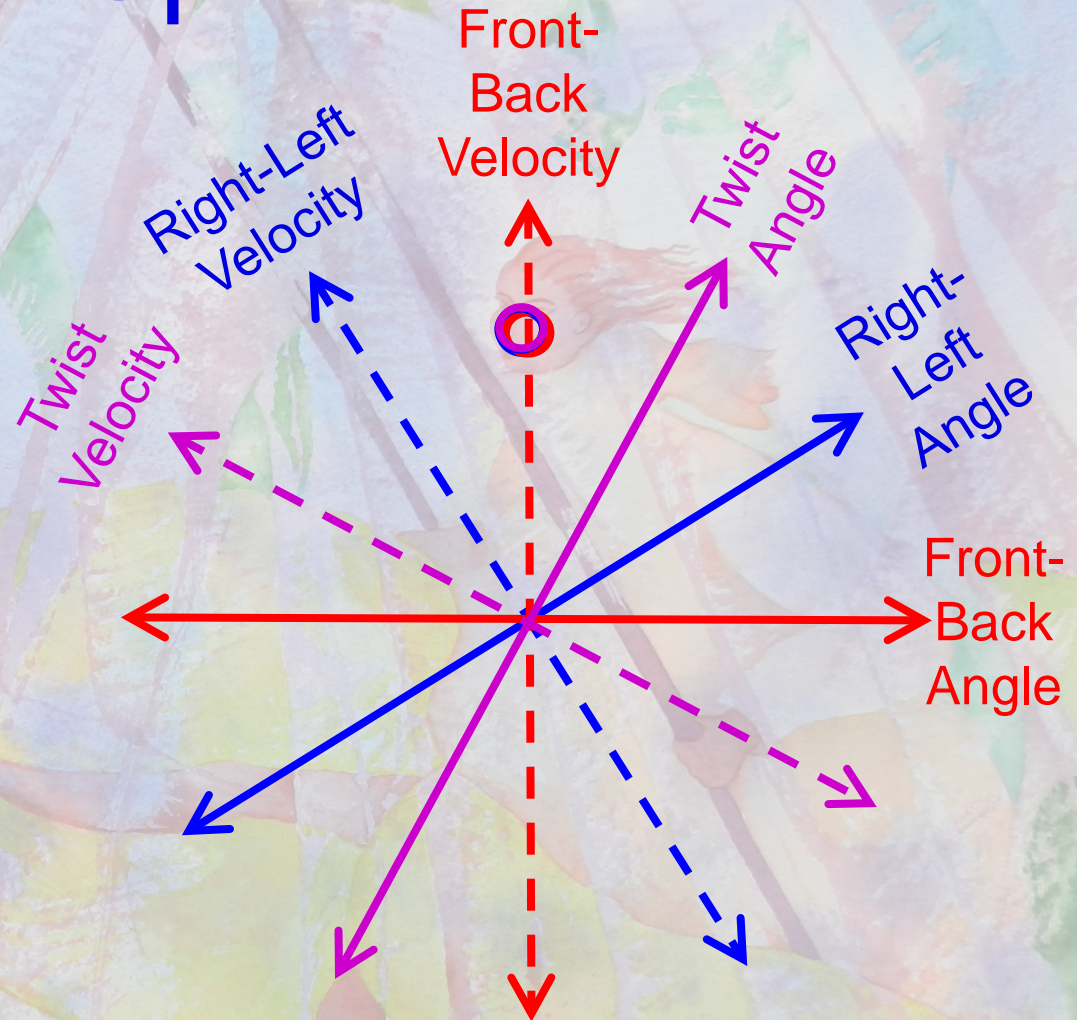
Left  
and  
Right



Orbit

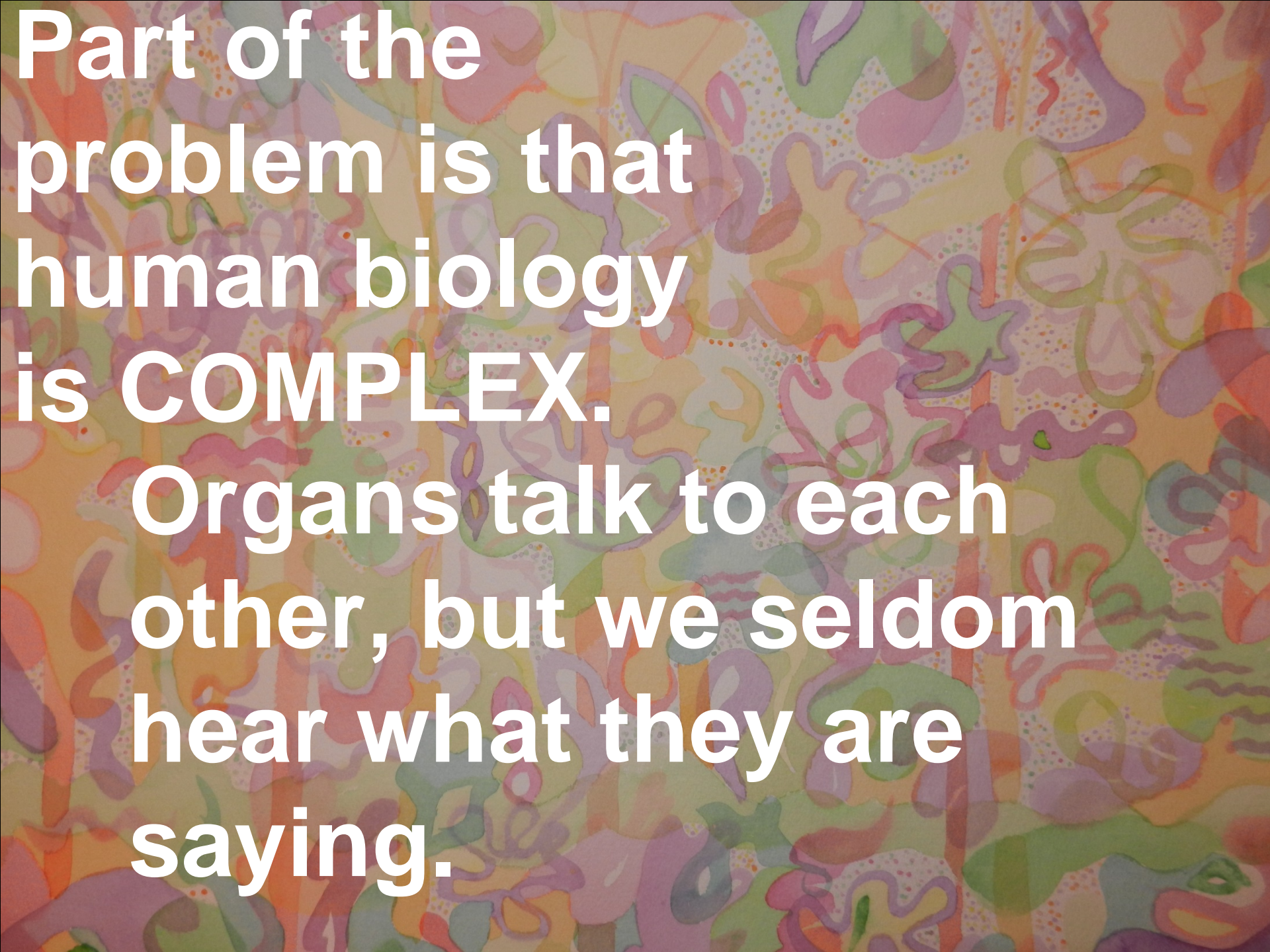


Twist



**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

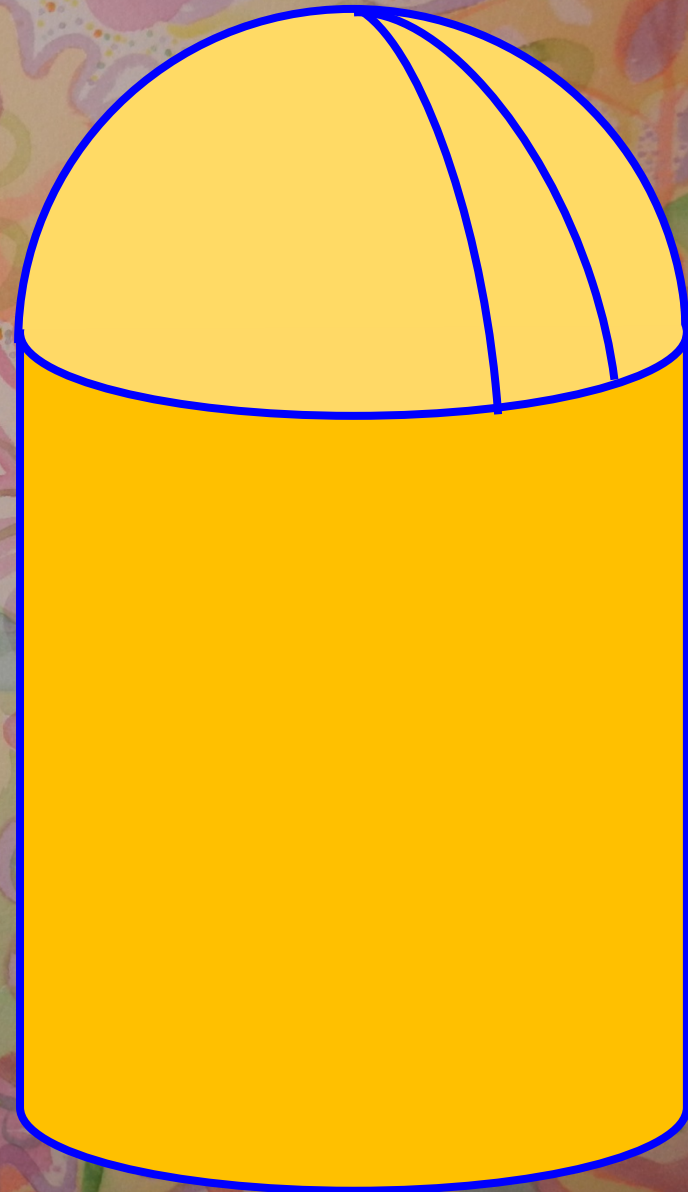
### Skeletal

Bones  
Cartilage  
Ligaments  
Tendons



**Silo** -- A place to  
store stuff without  
mixing.

**Silo Mentality** --  
Thinking without  
mixing.





# Organ Silos





# How is a new drug tested?

Petri dishes 

Mice

Humans



# Organs from a Silo Mentality



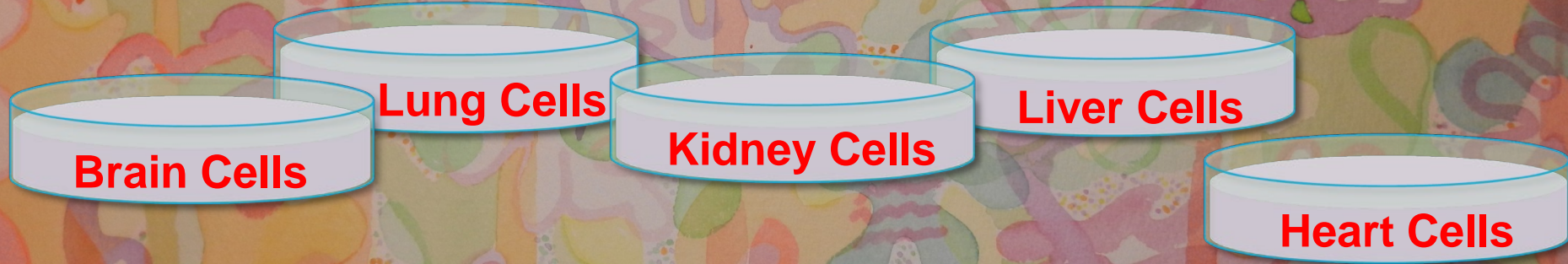


# Organs from a Silo Mentality



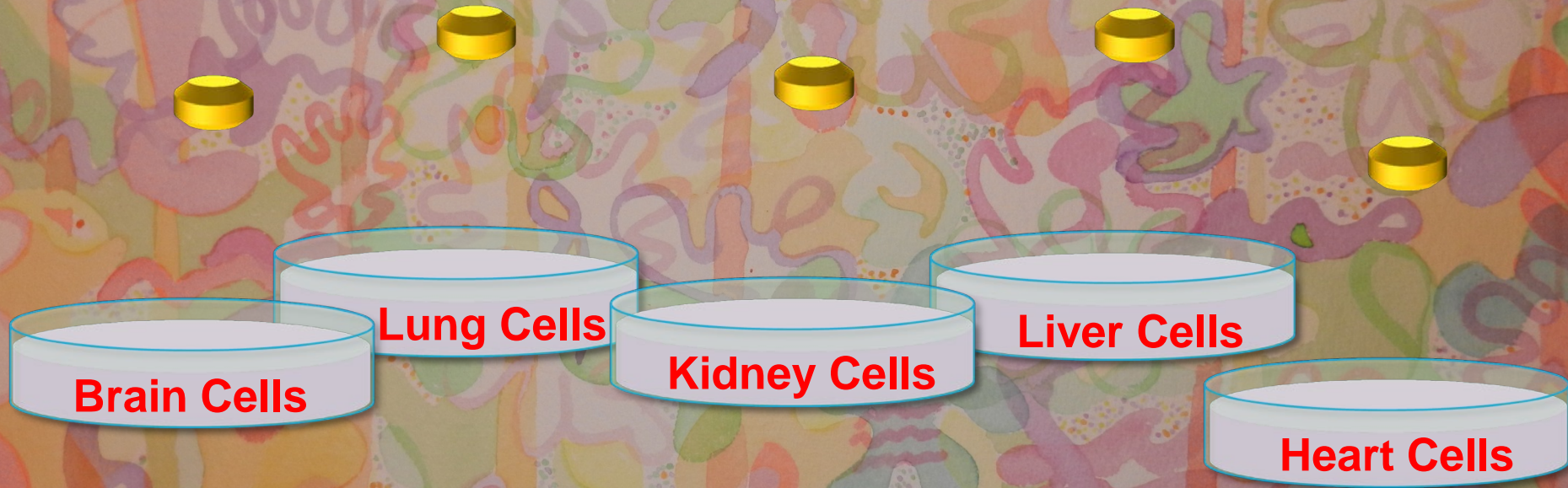


# Organs from a Petri Dish Mentality



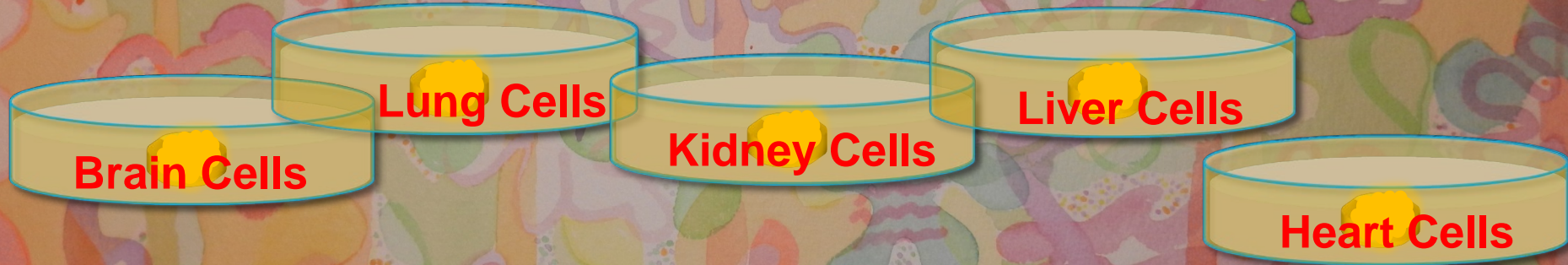


# Testing drugs in Petri Dishes



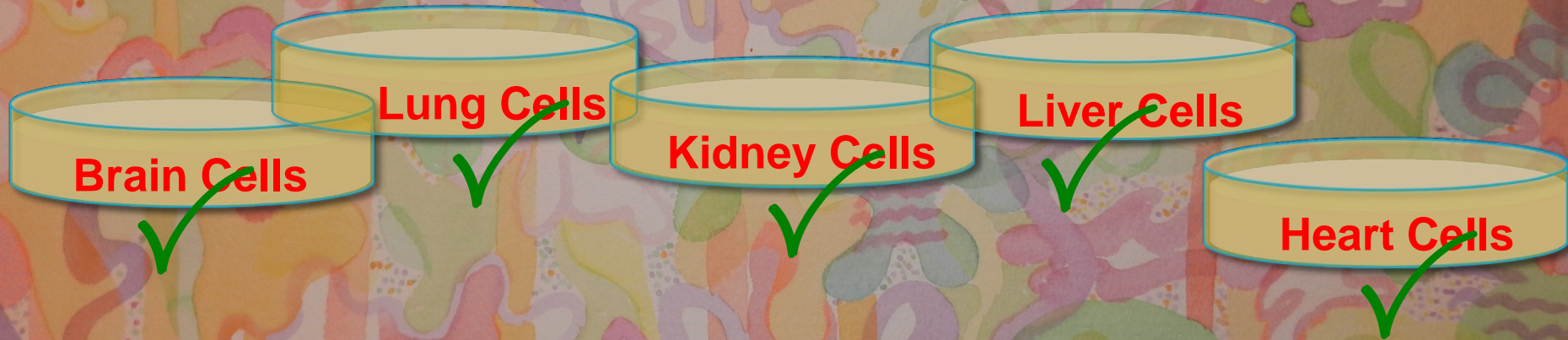


# Testing drugs in Petri Dishes





# 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...



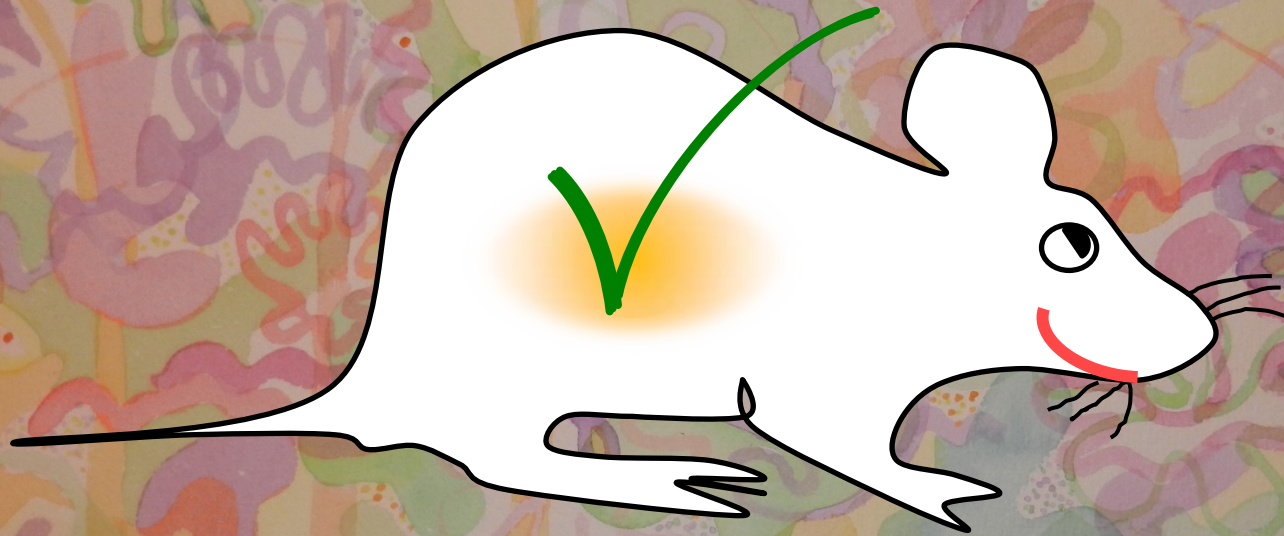


# Test drug in mice...





# Test drug in mice...





# How is a new drug tested?

Petri dishes

Mice

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

Humans ←



# Test drug in humans...



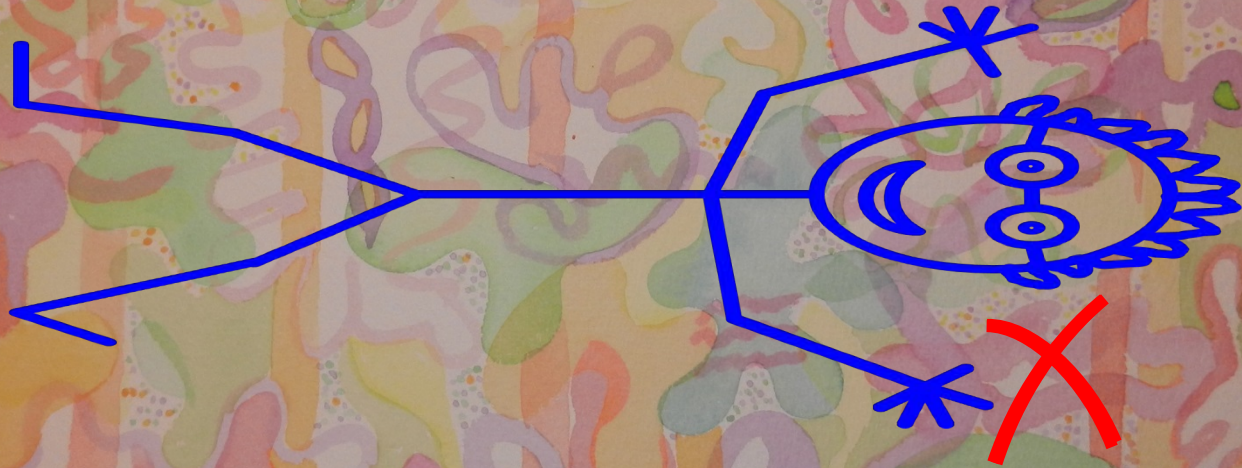


Test drug in humans...





# Test drug in humans...

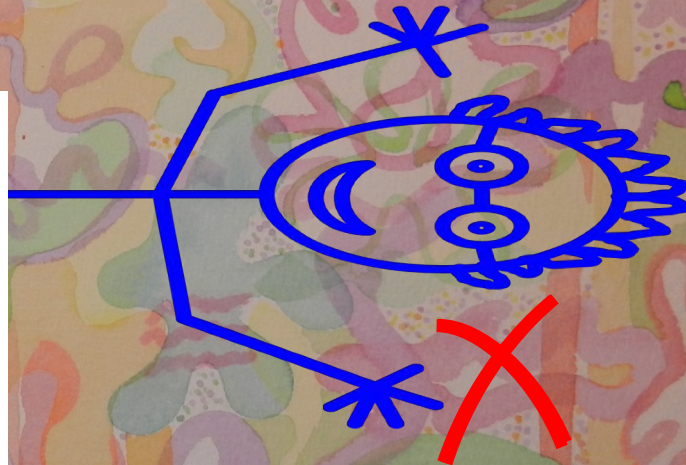




# Test drug in humans...

**What went wrong?**

- Human genes  $\neq$  mouse genes?
- Organ-organ interactions?





# How is a new drug tested?

Petri dishes ✓

Mice ✓

Homunculi ←

Humans ✗

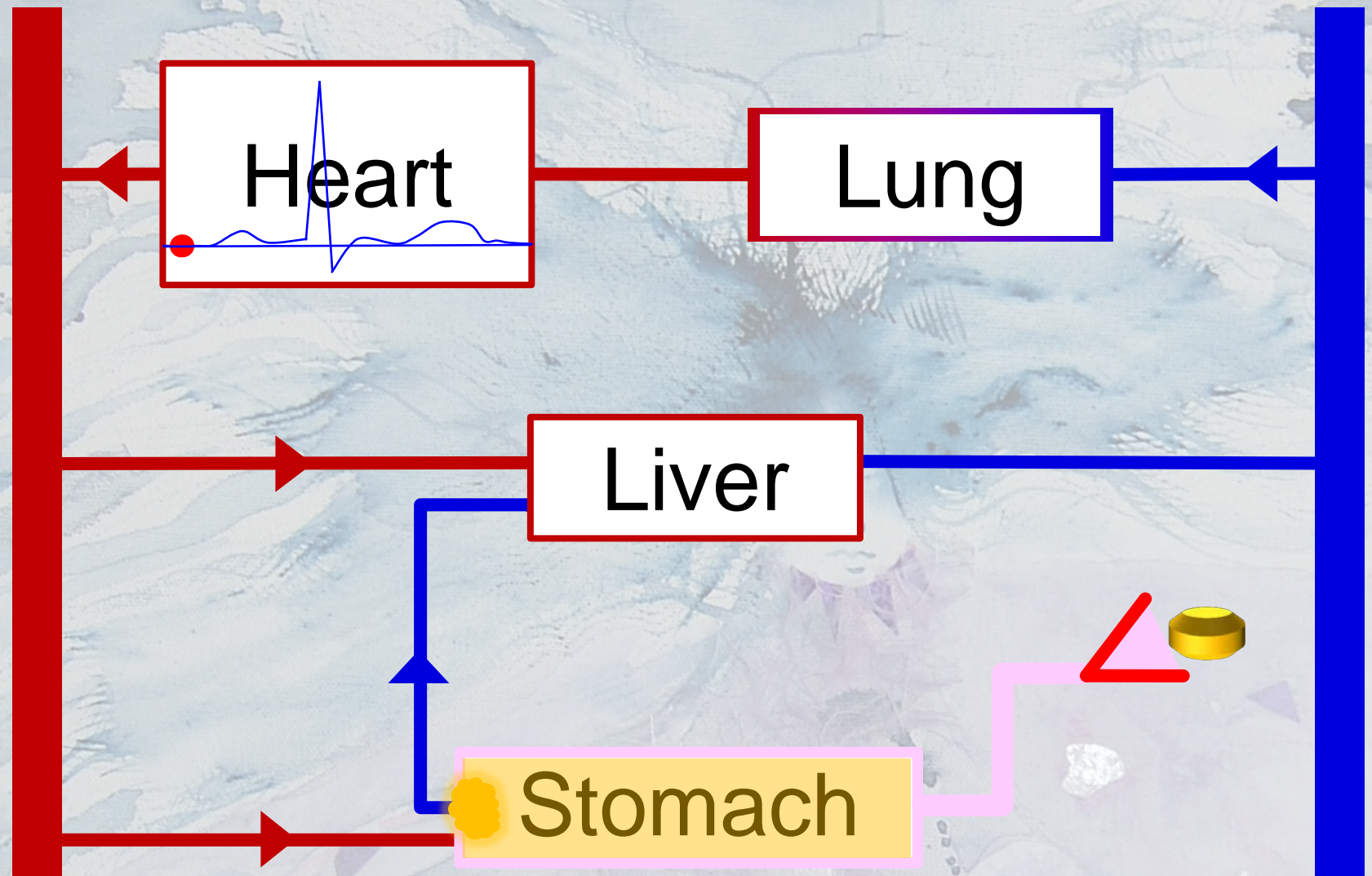


Our homunculi will  
be alive, built with  
human cells!



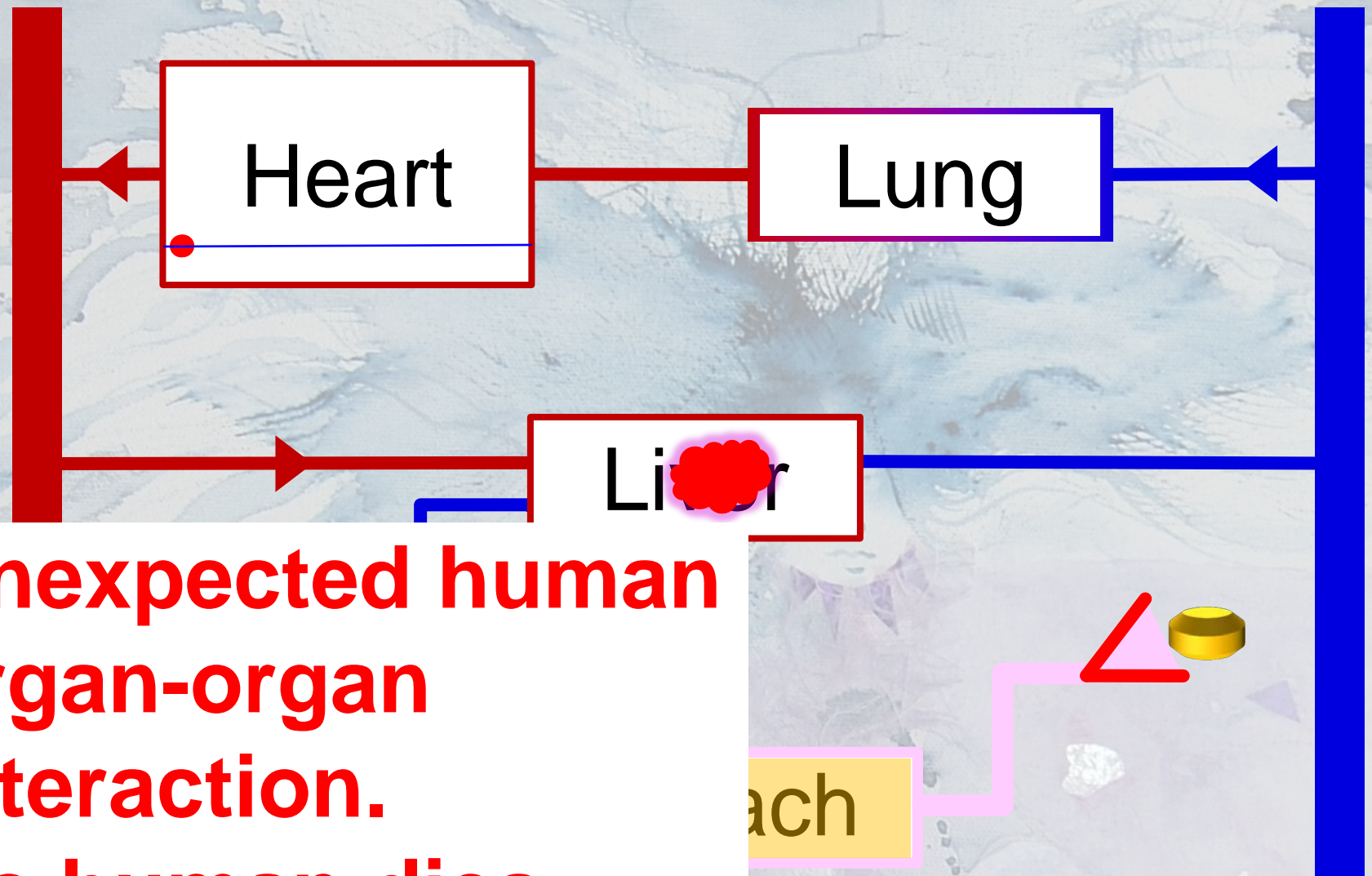


# Test drugs in homunculi!





# 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

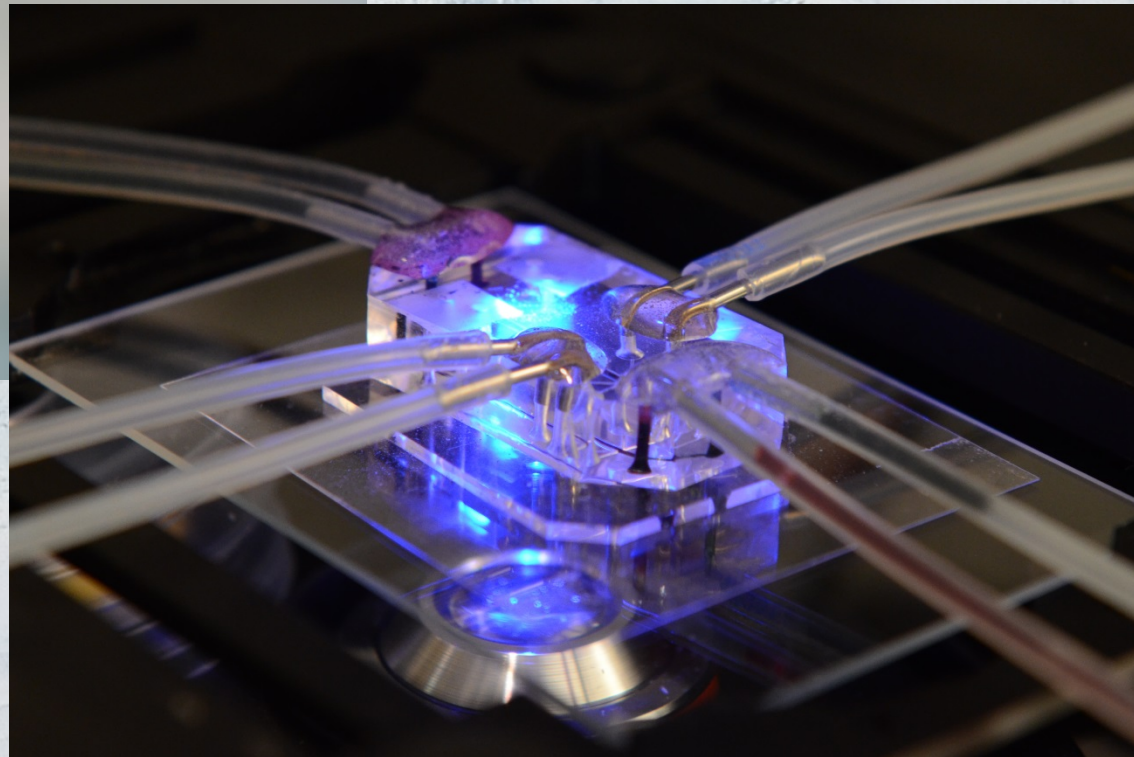
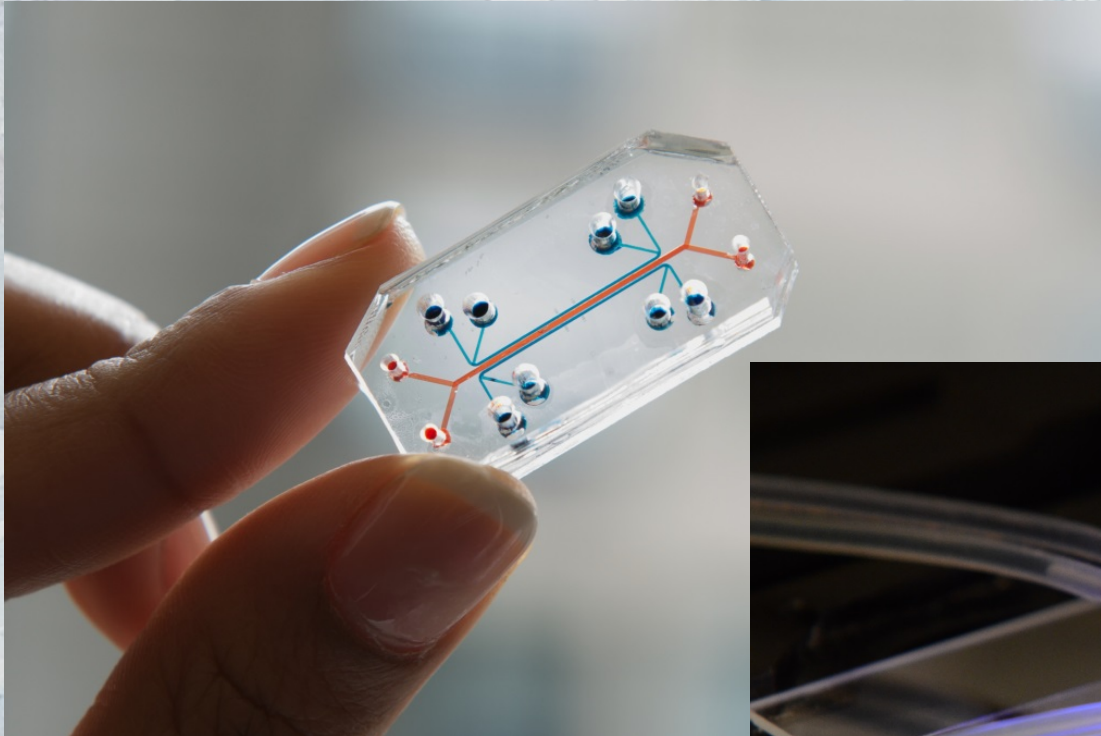


# How do you build homunculi?

- 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)

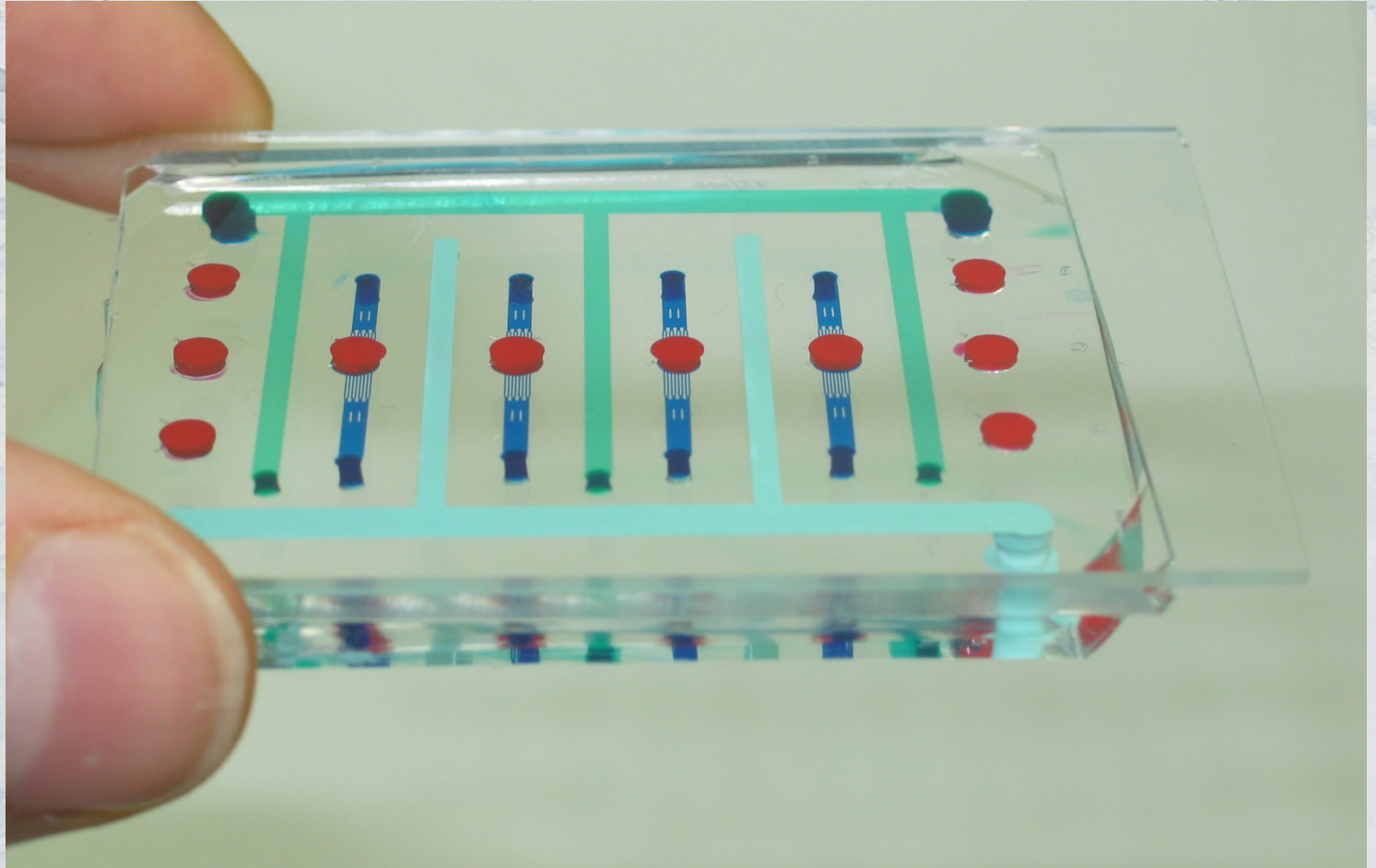


# Lung on a chip



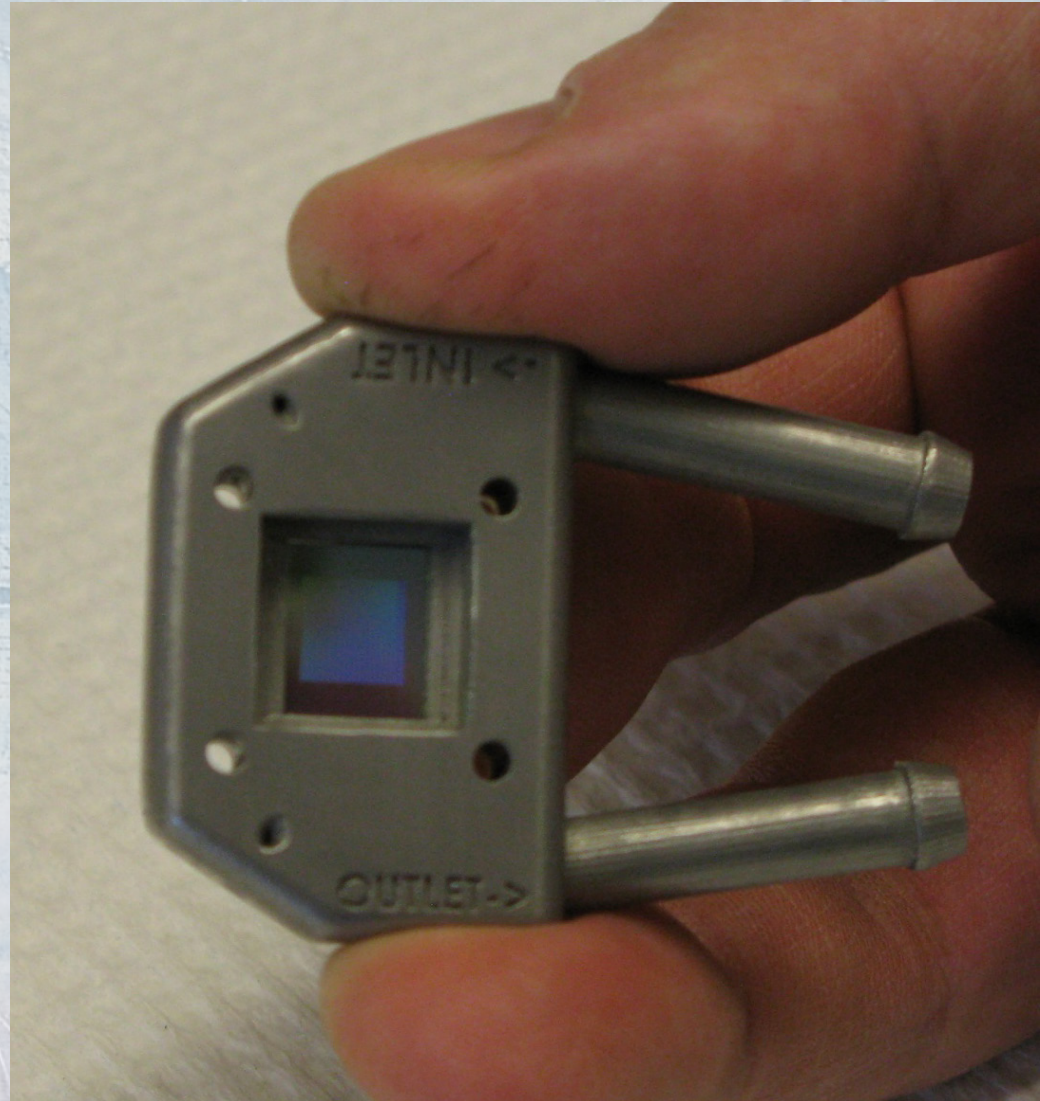
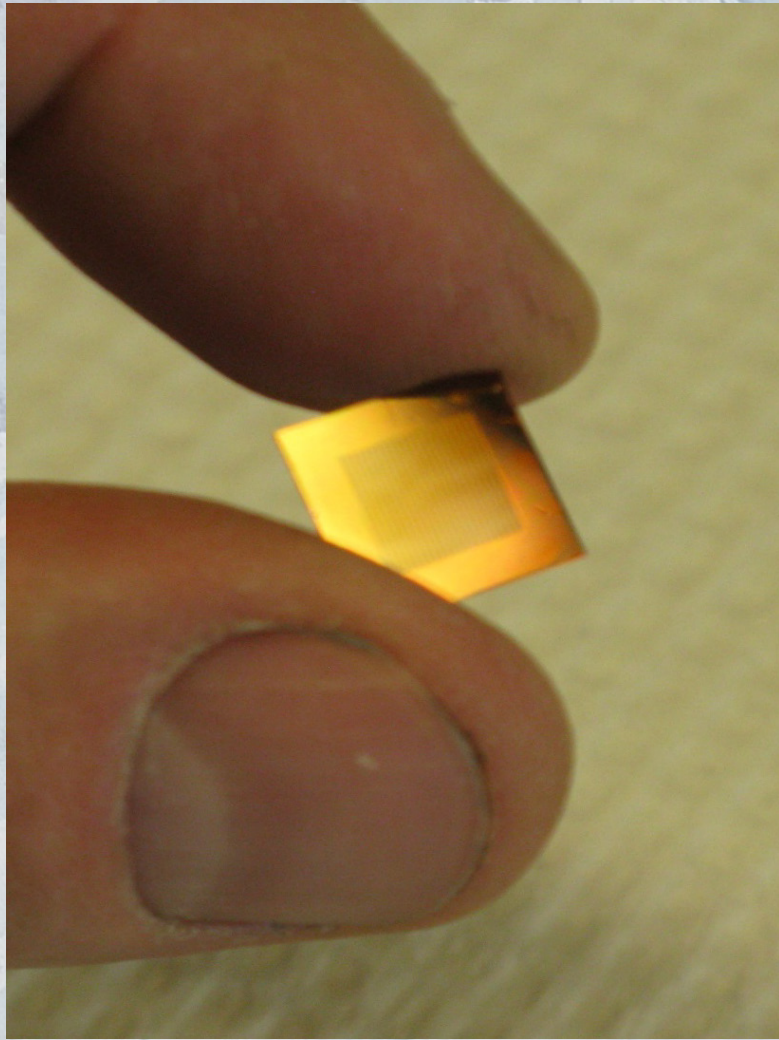


# Mammary gland on a chip





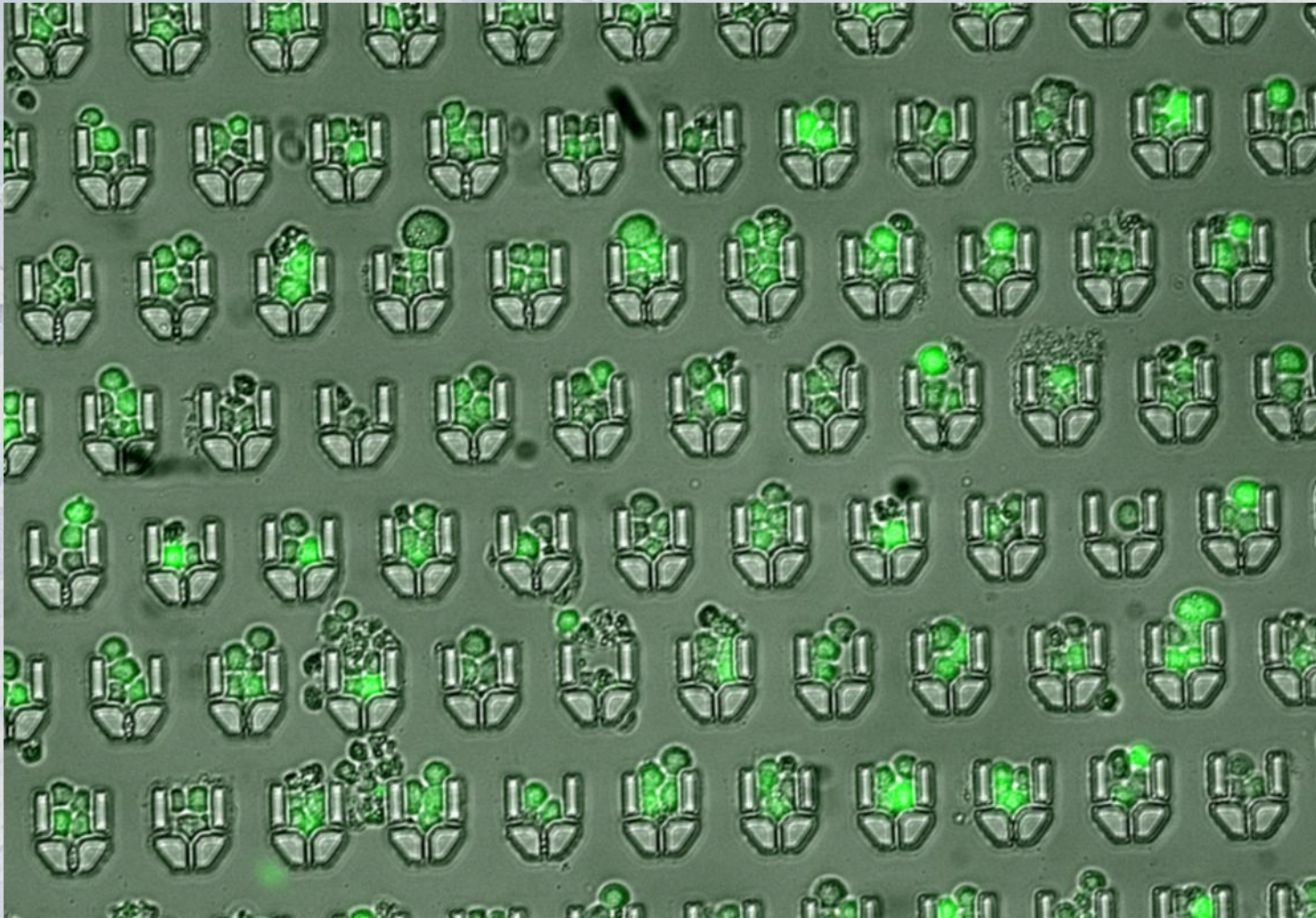
# Kidney on a chip



Shuvo Roy, UCSF and Bill Fissell, Vanderbilt



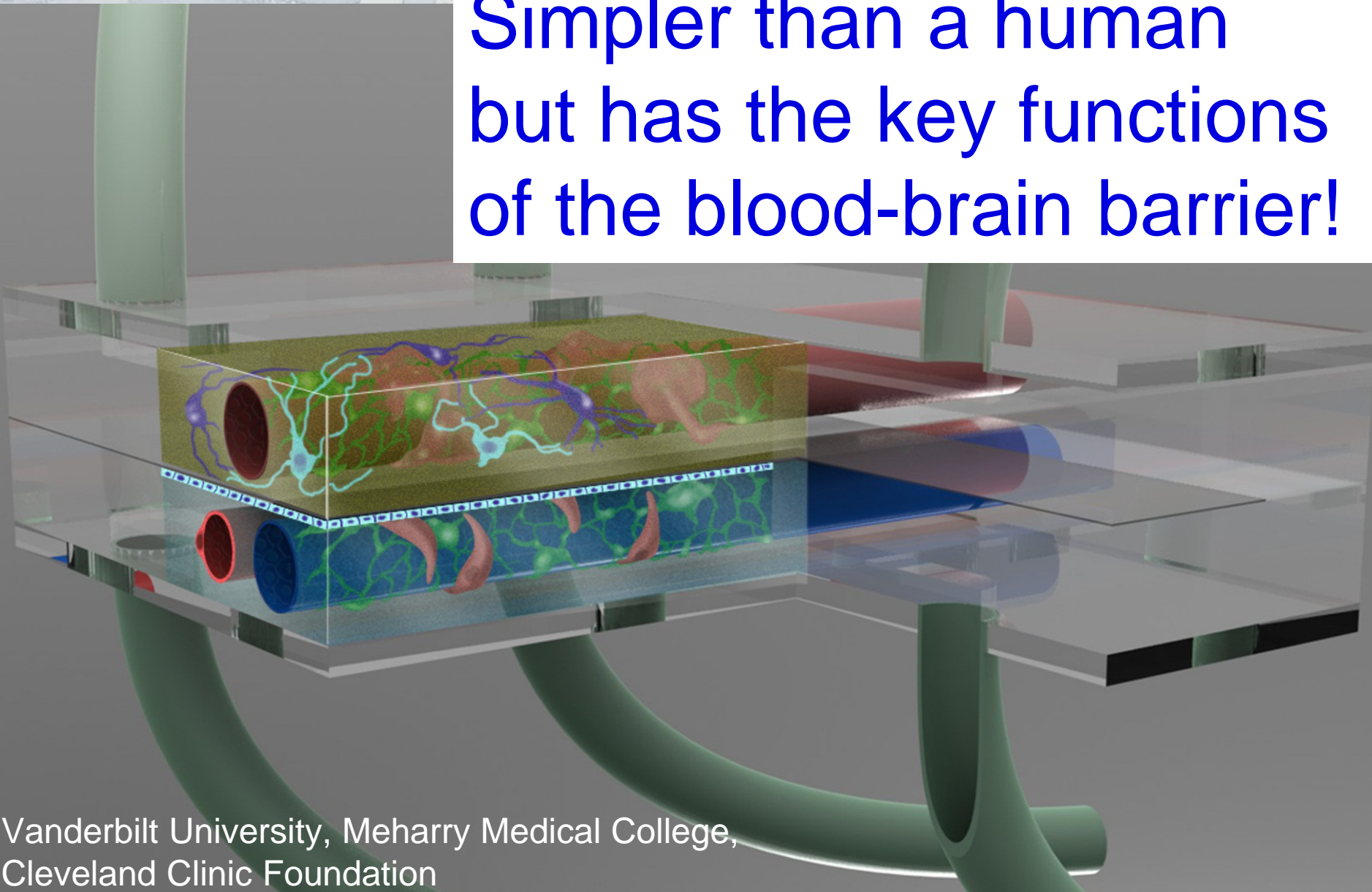
# T cells in a lymph node on a chip





# Brain on a chip

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



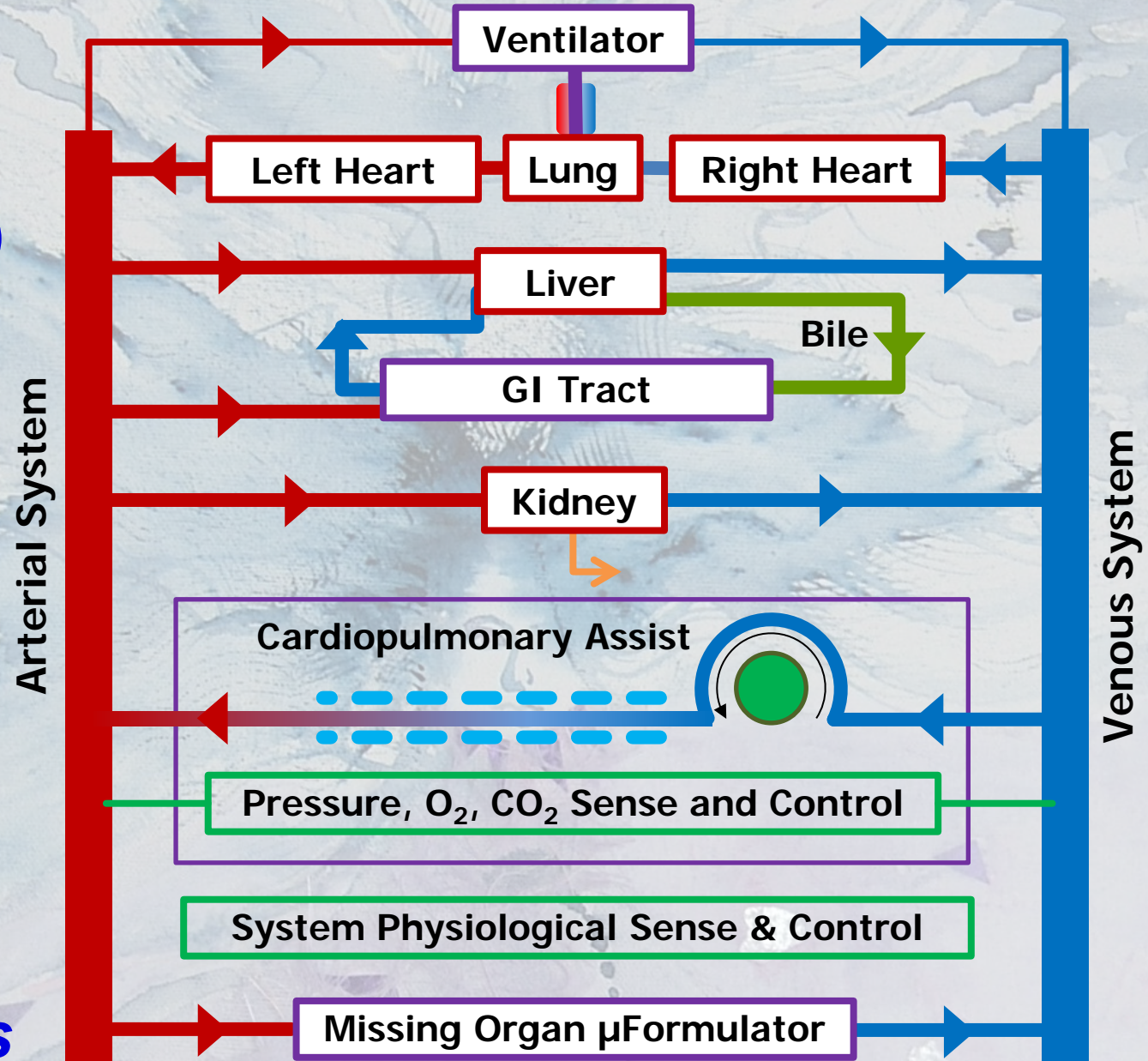


# Advanced Tissue-engineered Human Ectypal Network Aalyzer

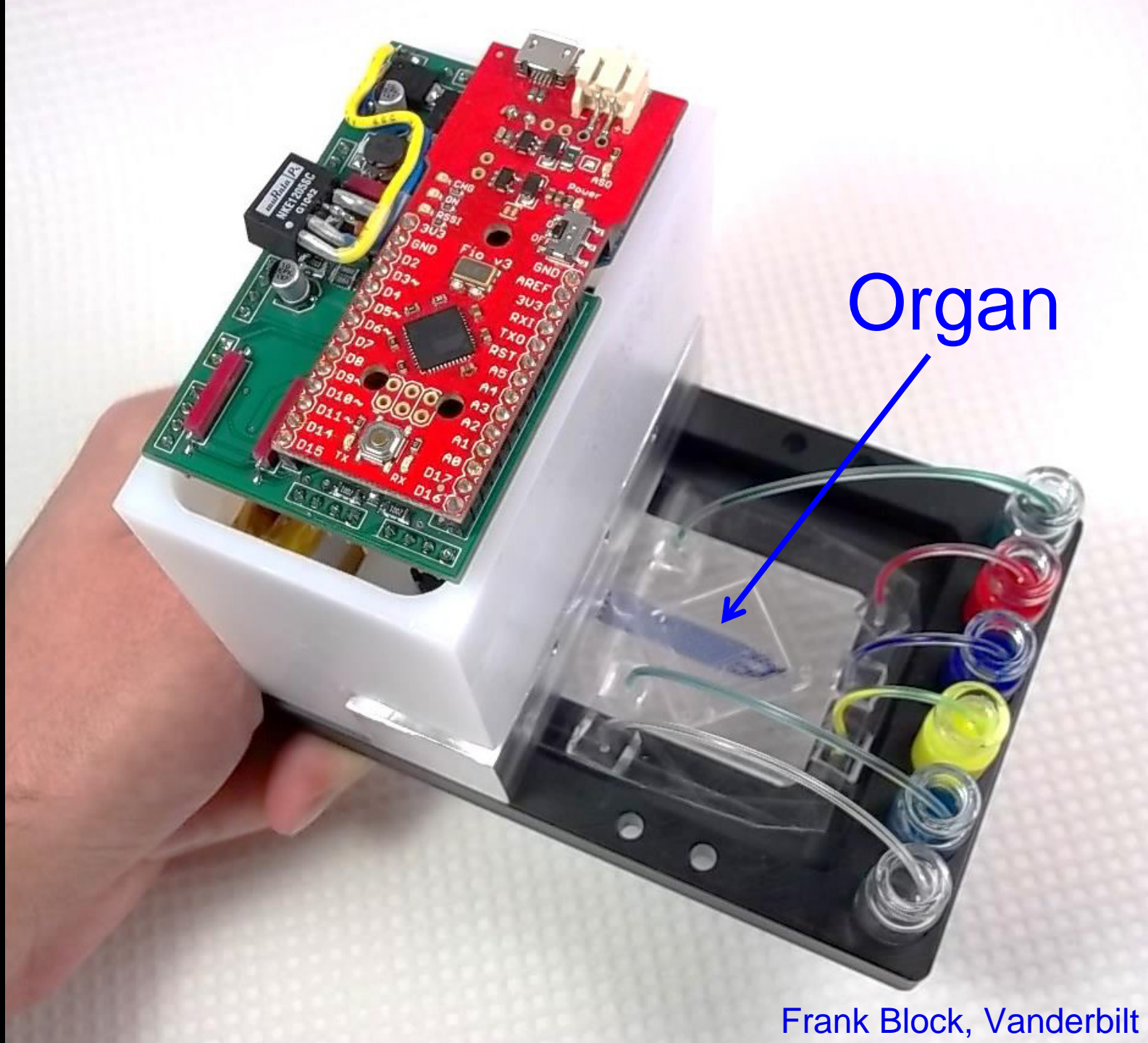
We call  
our chip  
Athena

milliHuman  
(mHu)

*Homo chippus*







Organ



The background is an abstract painting. It features a central, somewhat ethereal face with a pale complexion and dark, hollow eyes, looking directly forward. The face is surrounded by swirling, textured brushstrokes in shades of light blue, lavender, and white. Below the face, there are several geometric shapes, including triangles and circles, in muted colors like purple, pink, and grey. The overall composition is layered and dreamlike.

What kinds of people are  
building homunculi?



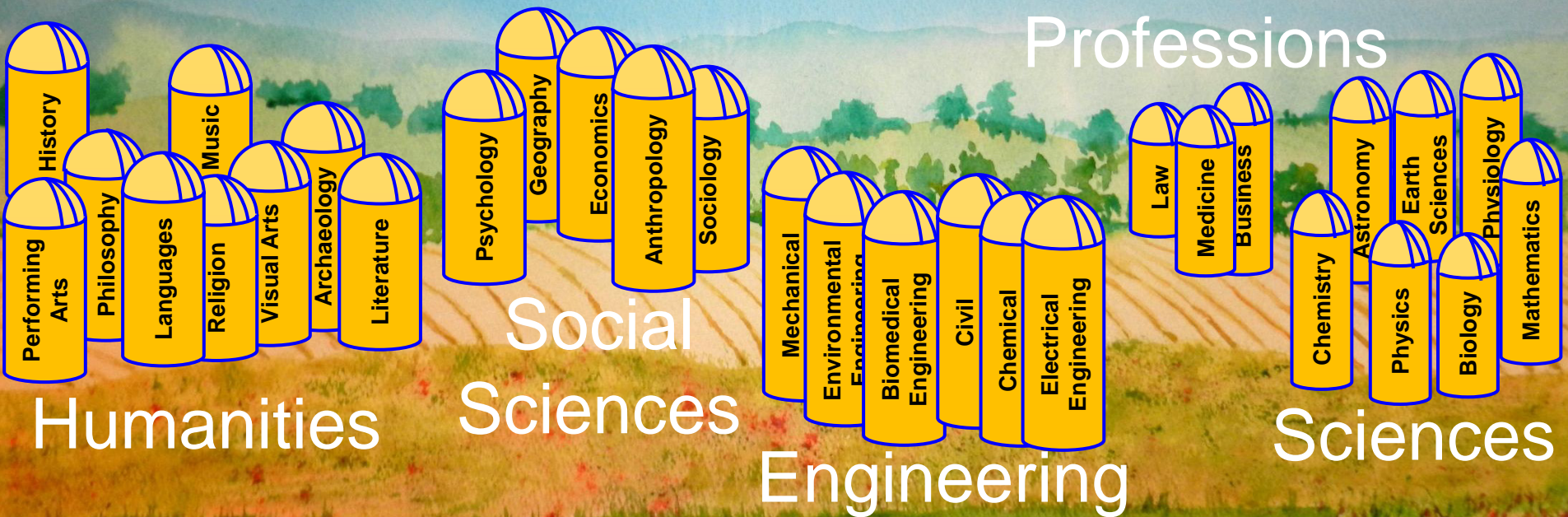
# Fields of Knowledge





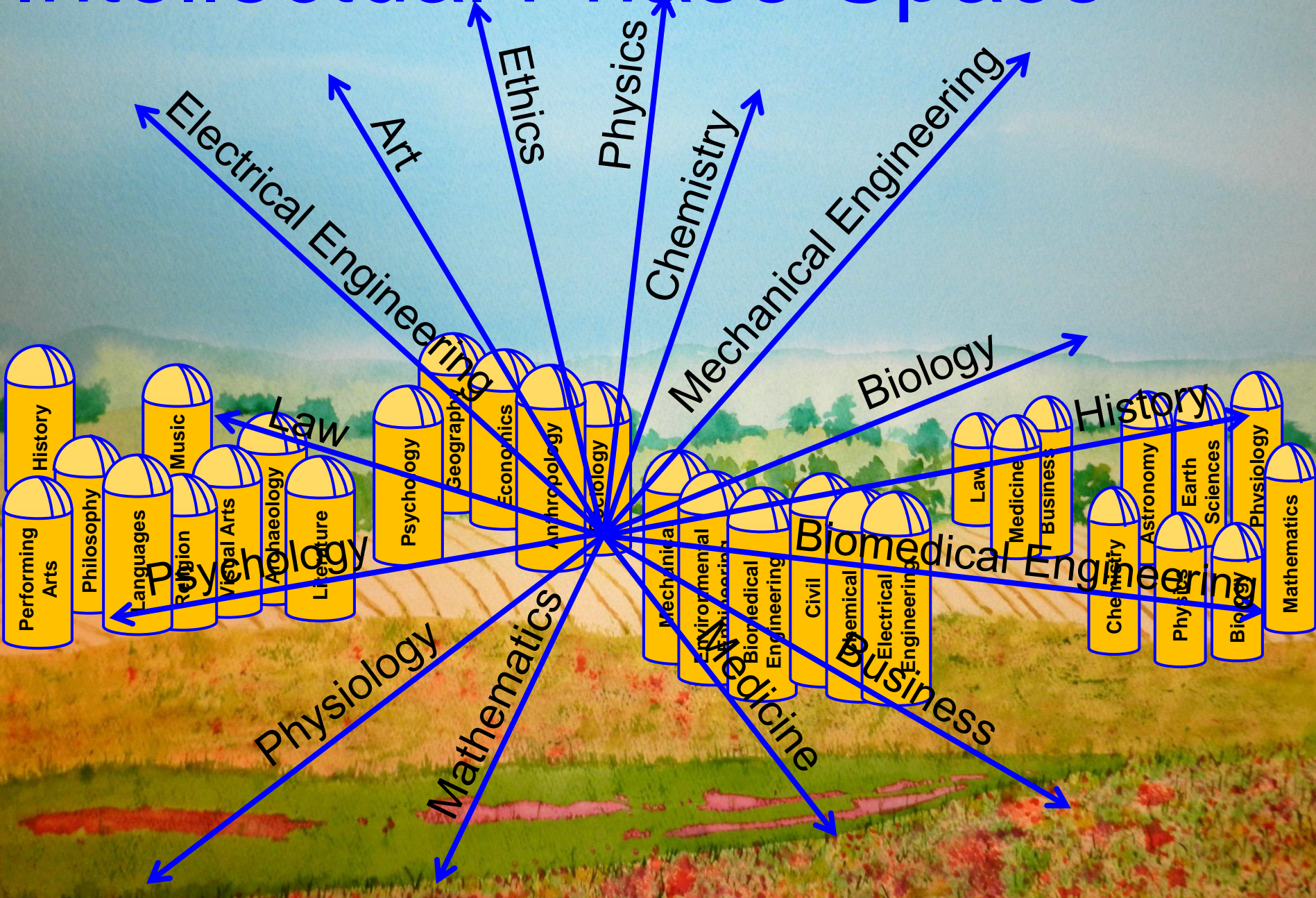
# Silos of Knowledge

Athena needs a mix of disciplines





# Intellectual Phase Space





# My Knowledge

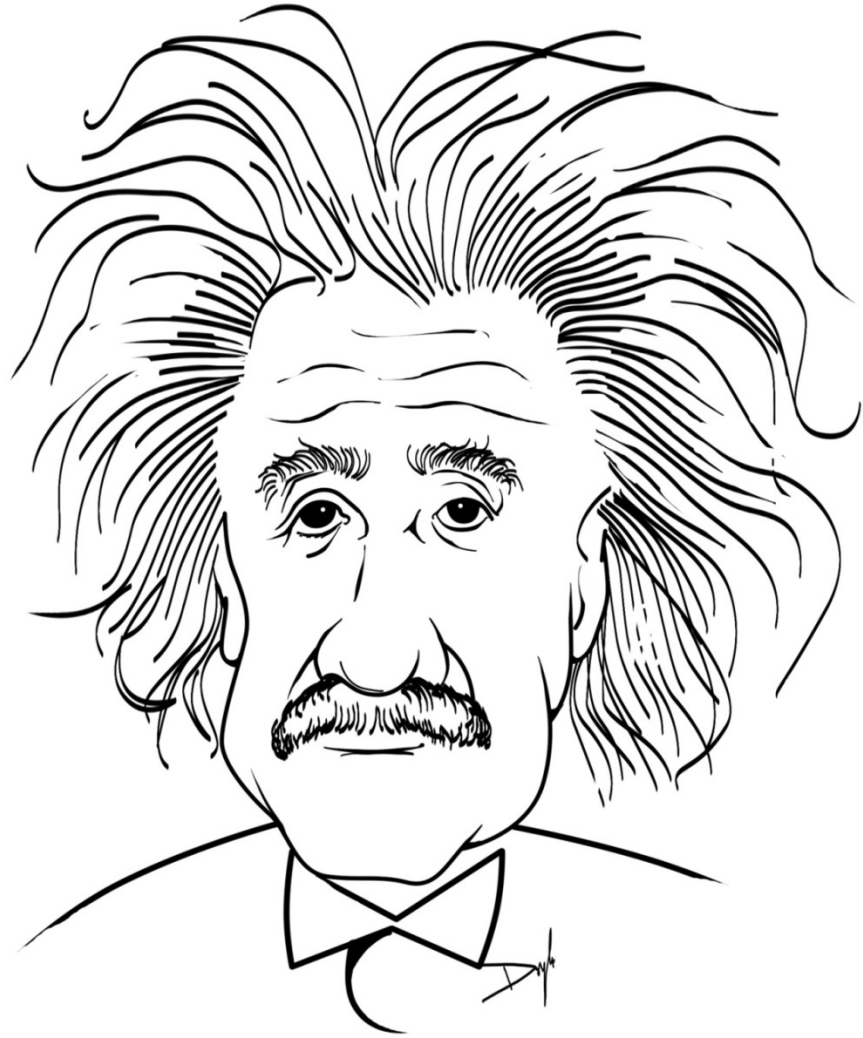
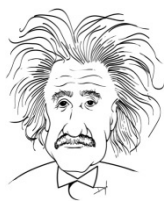
You can be more than one  
thing at a time in phase  
space!





# Intellectual Phase Space

Physics

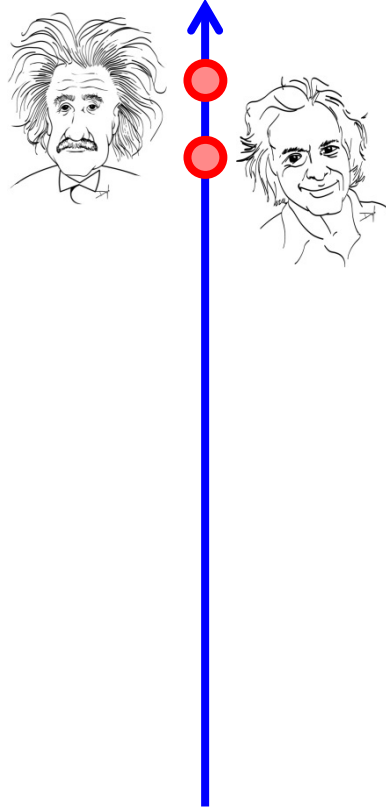


Albert Einstein  
1879-1955



# Intellectual Phase Space

Physics

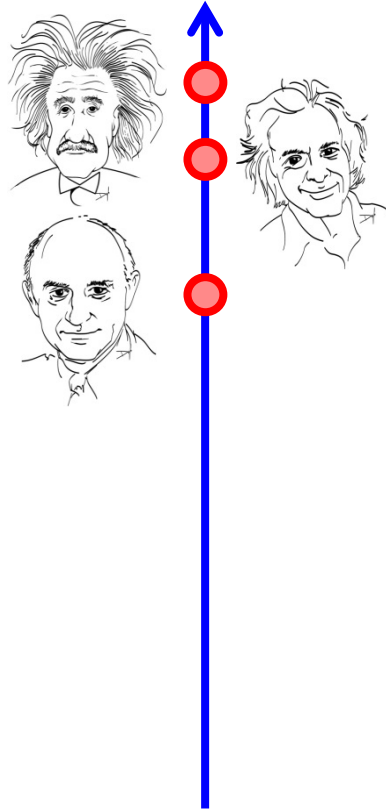


Richard Feynman  
1918-1988



# Intellectual Phase Space

Physics

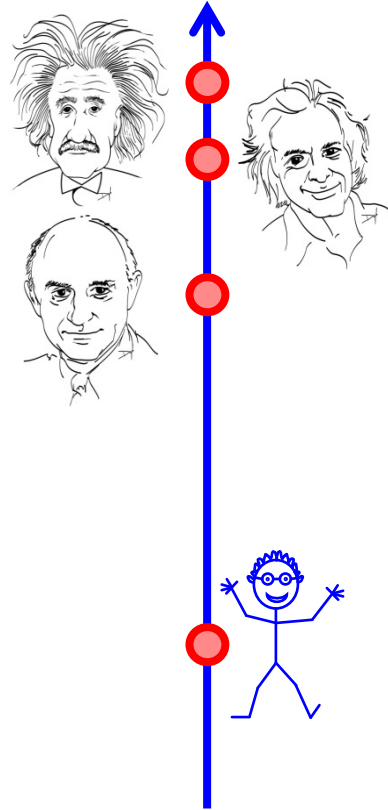


Enrico Fermi  
1901-1954



# Intellectual Phase Space

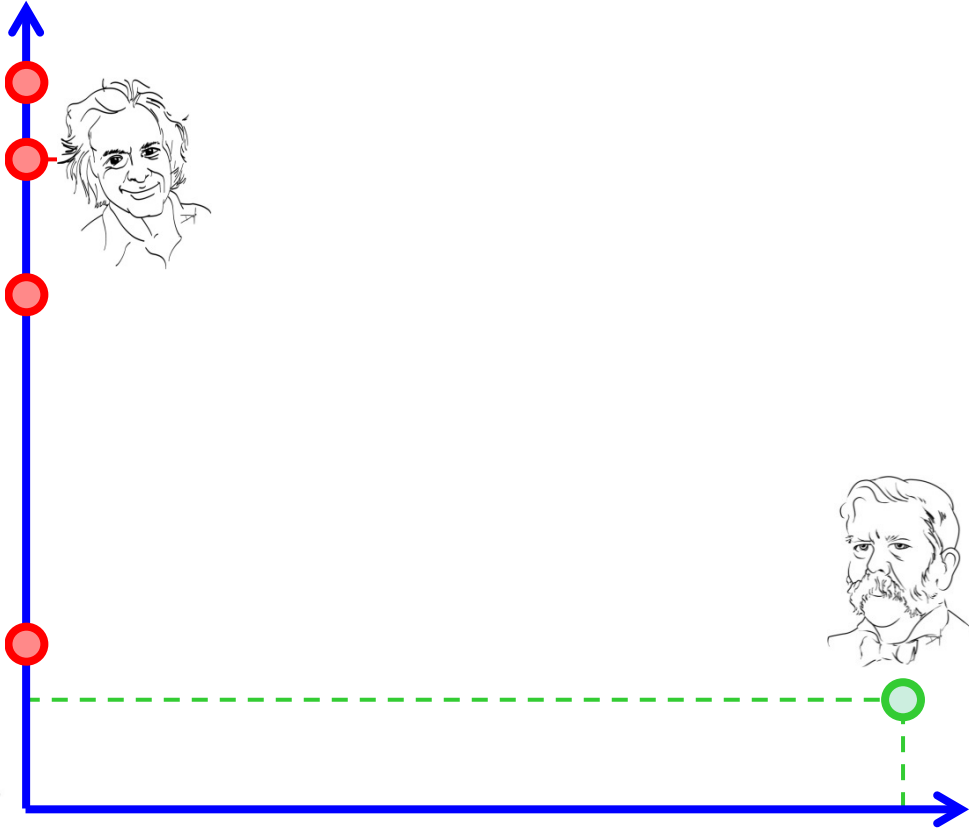
Physics





# Intellectual Phase Space

Physics



Engineering

George Westinghouse  
1846-1914

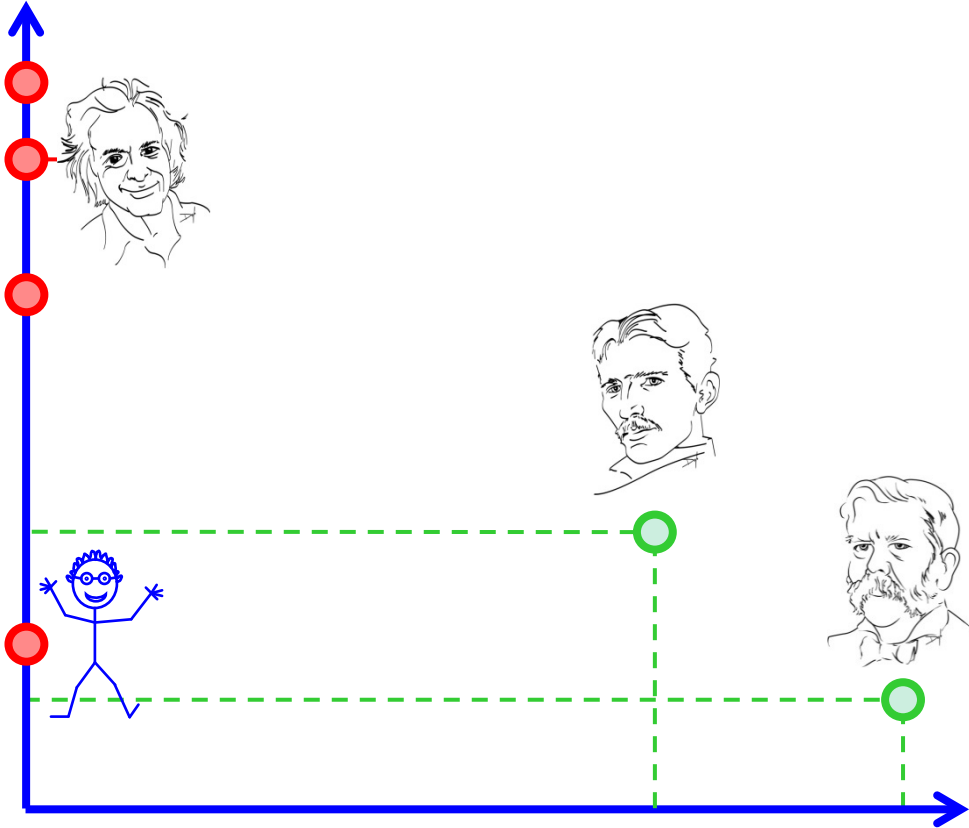


# Intellectual Phase Space



Nikola Tesla  
1856-1943

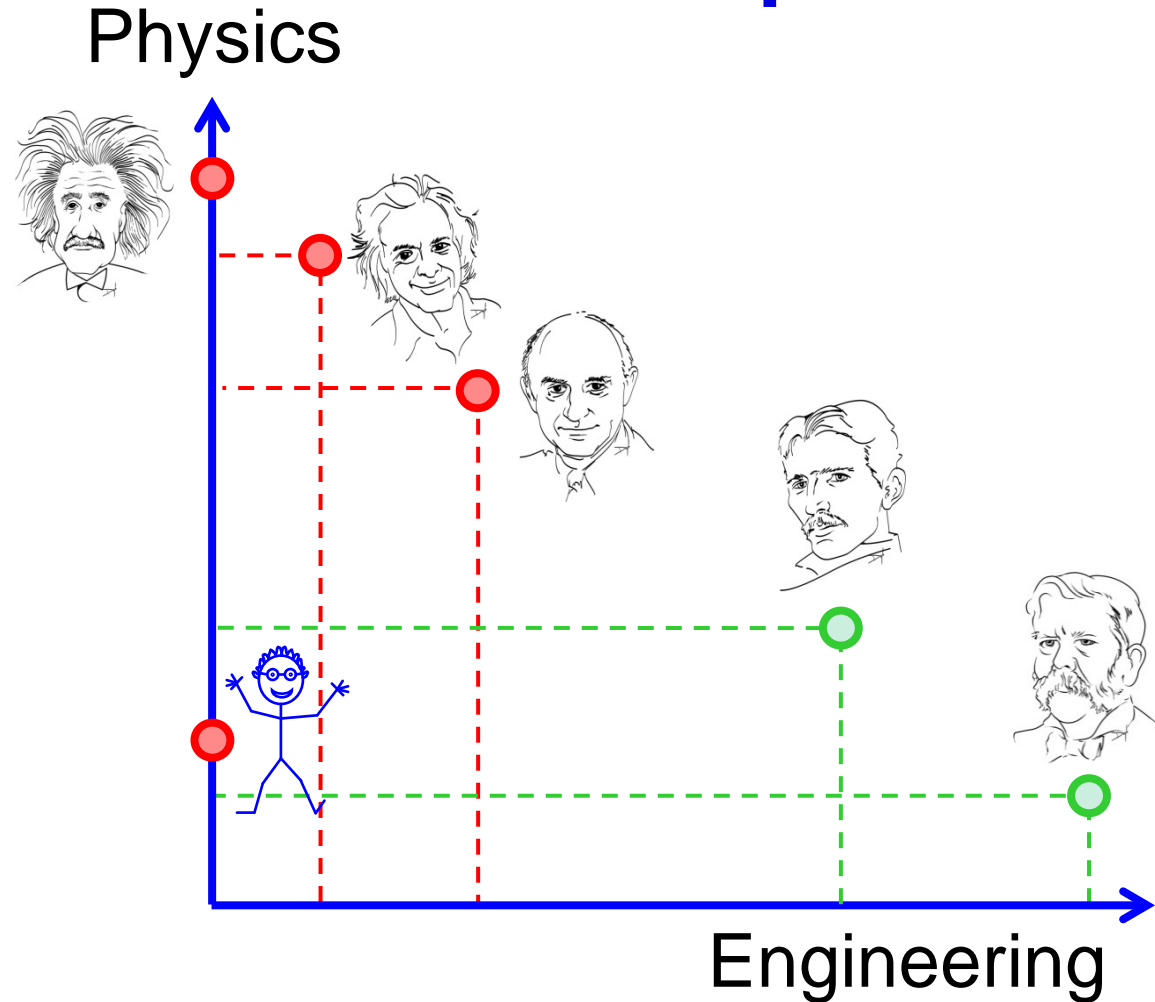
Physics



Engineering

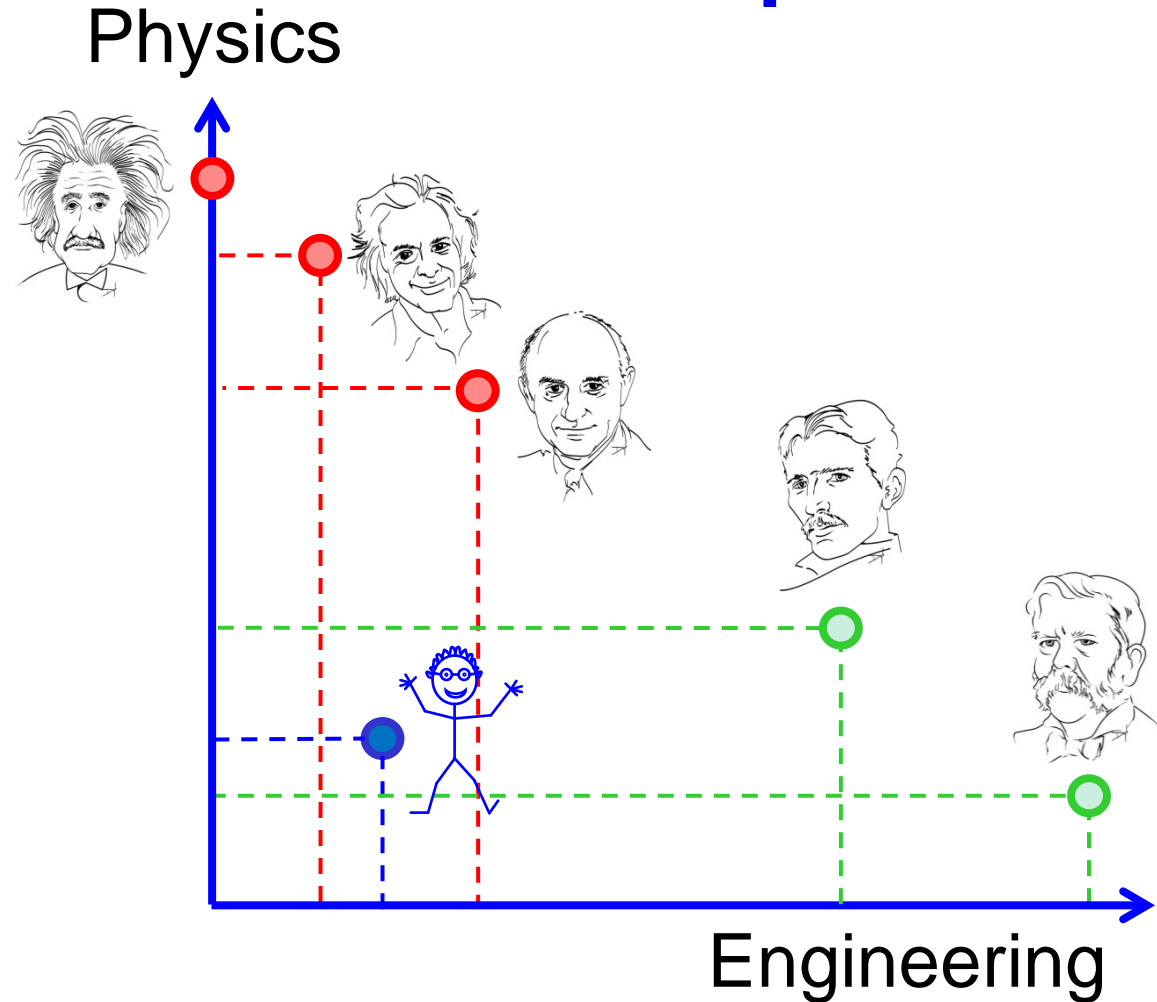


# Intellectual Phase Space



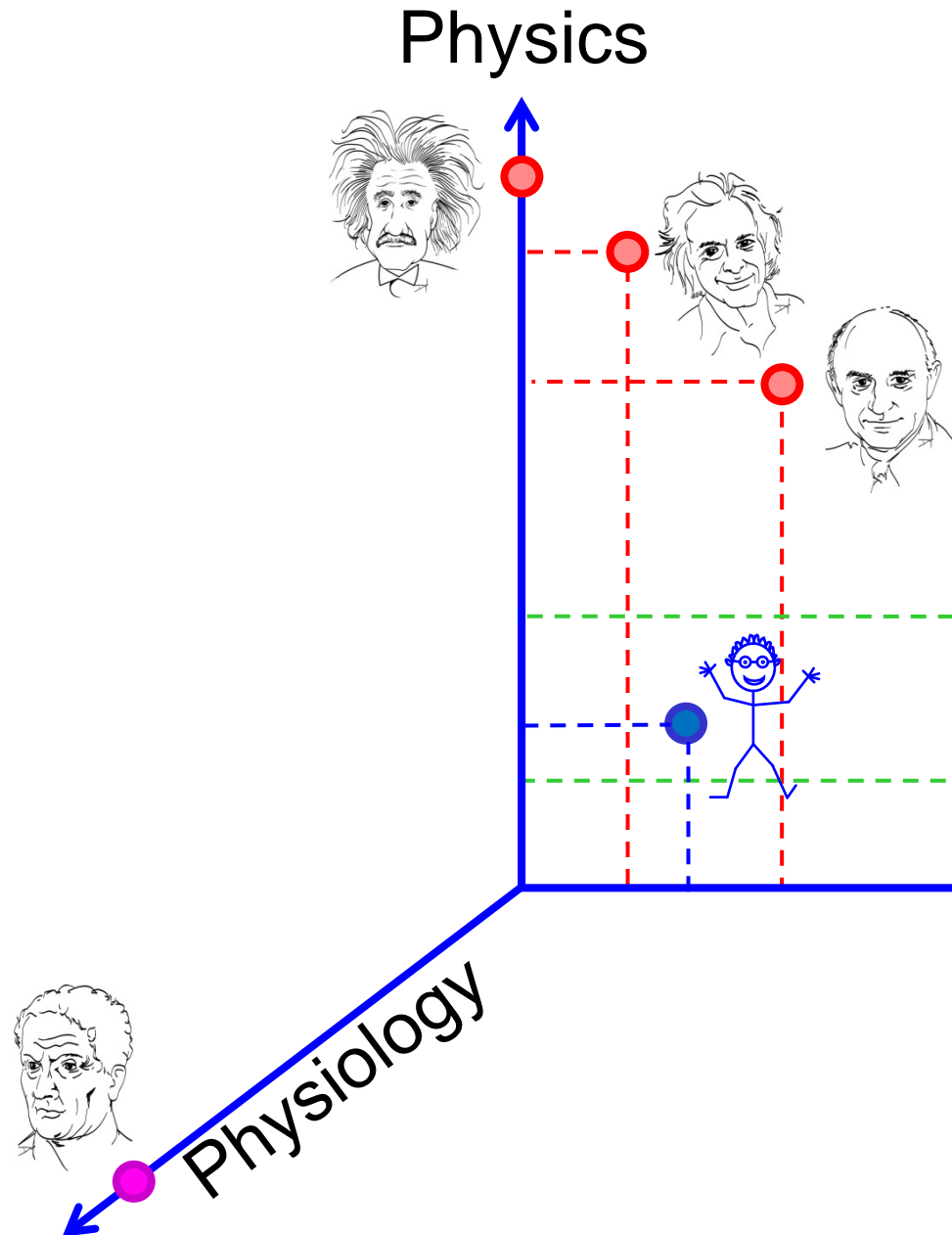


# Intellectual Phase Space





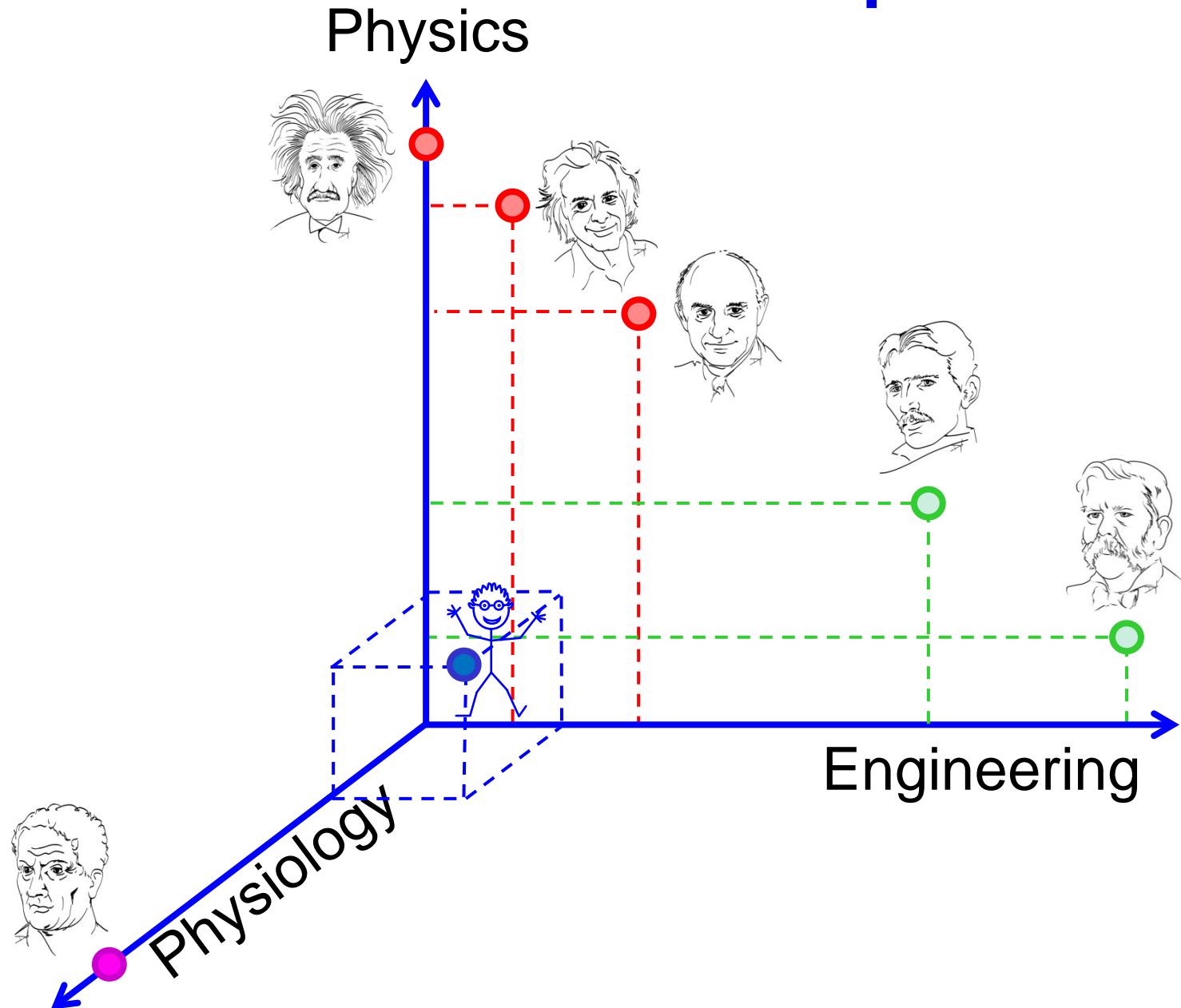
# Intellectual Phase



Galen of Pergamon  
AD 129-216



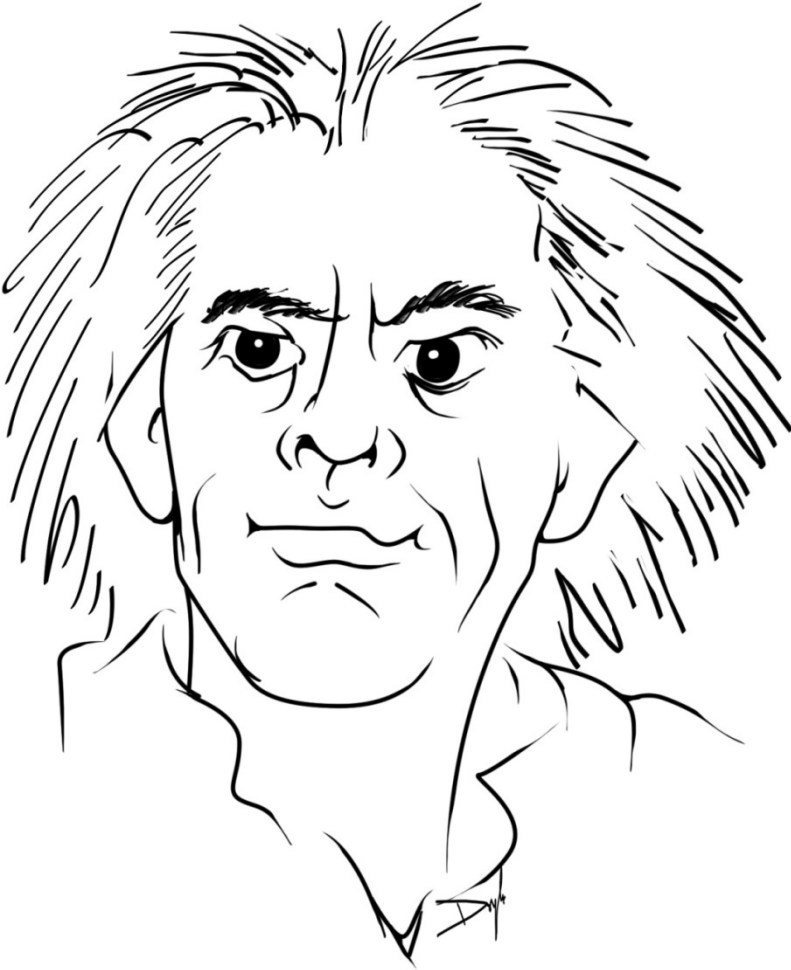
# Intellectual Phase Space



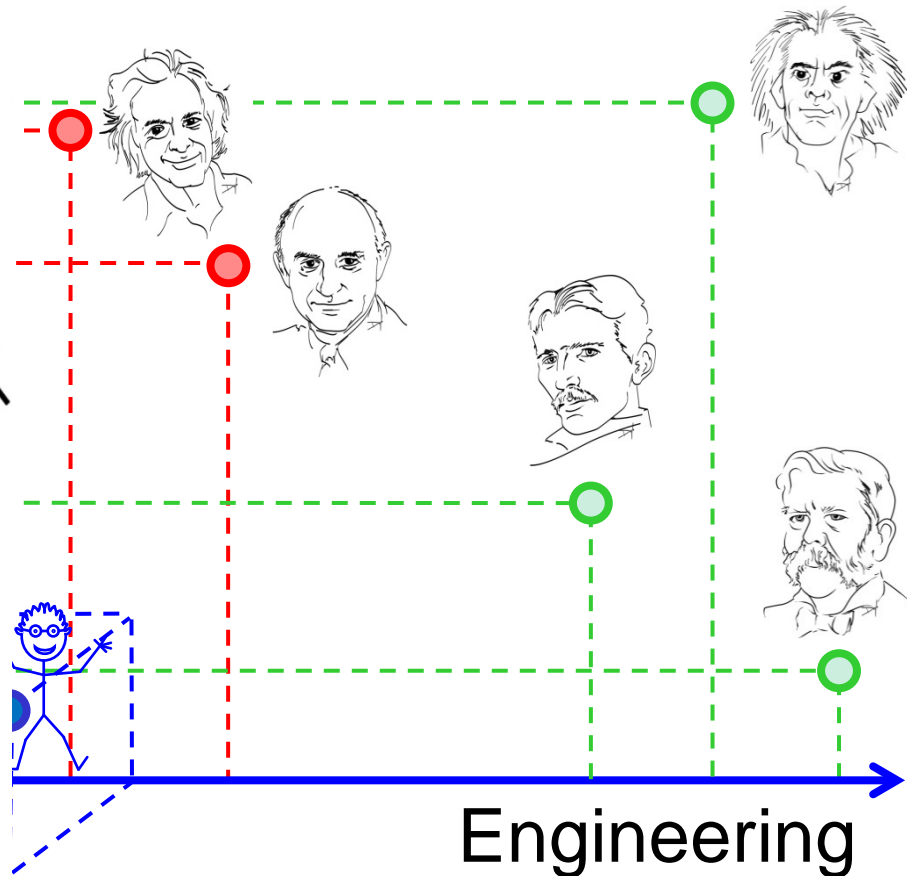


# Intellectual Phase Space

Physics



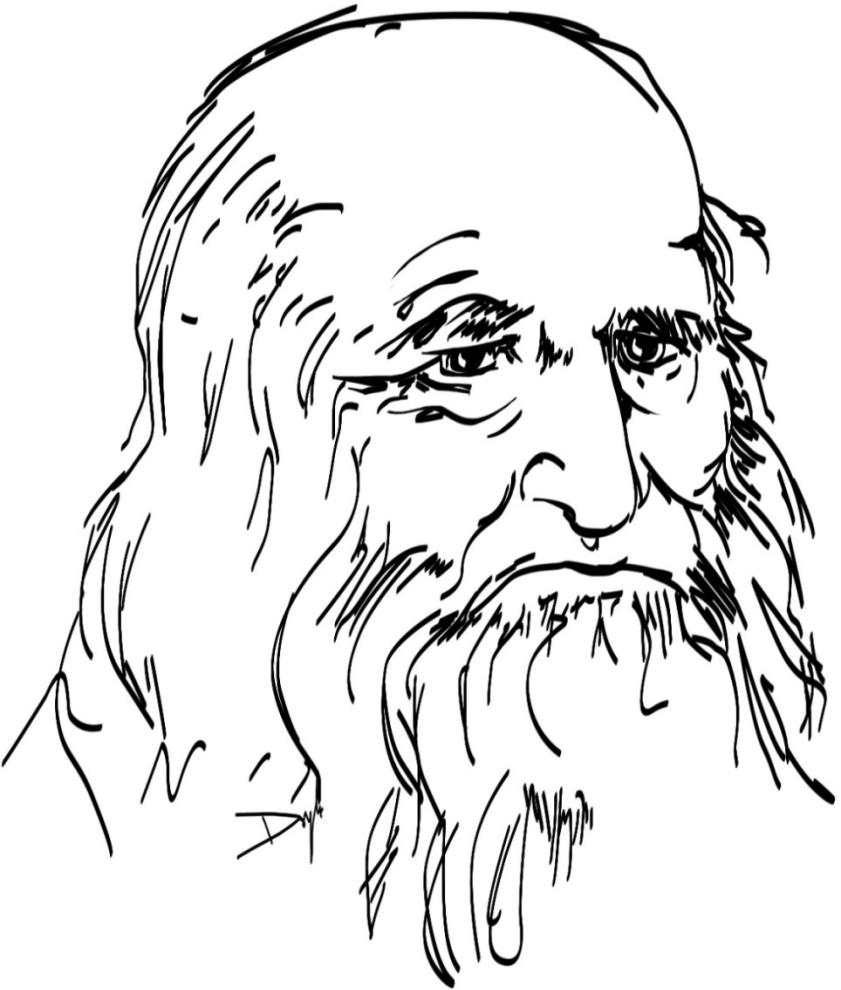
Emmett "Doc" Brown  
1885-2015?



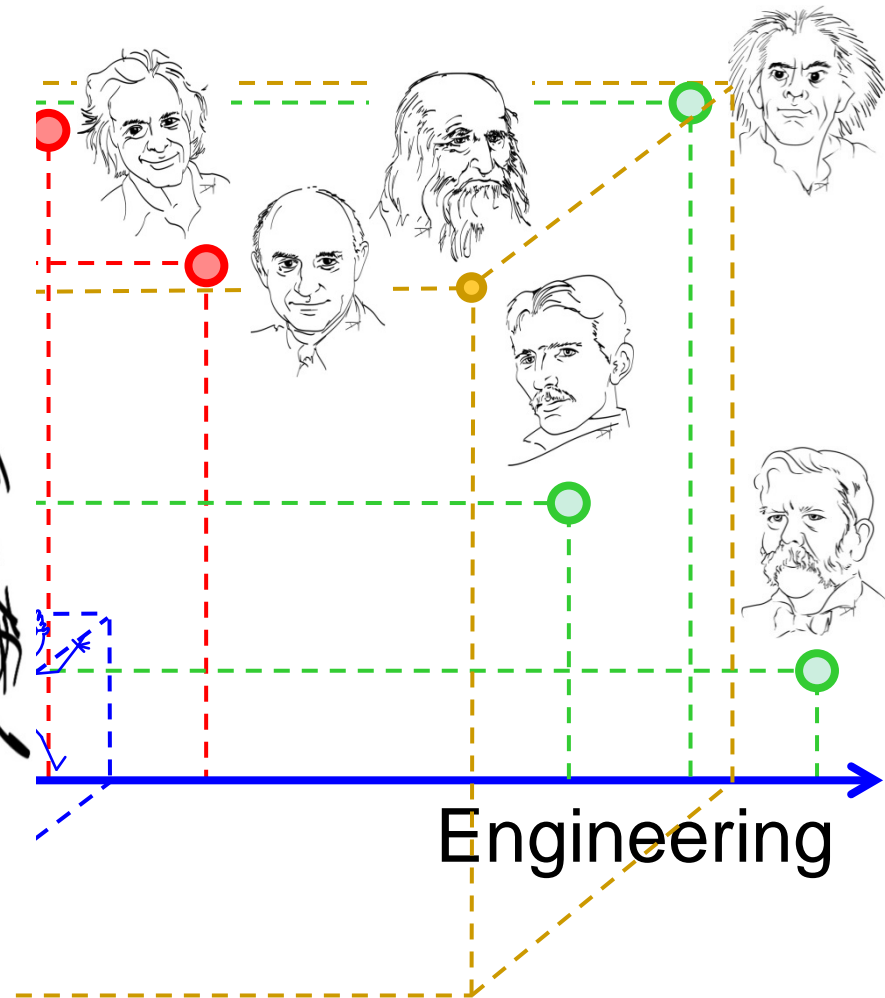


# Intellectual Phase Space

Physics

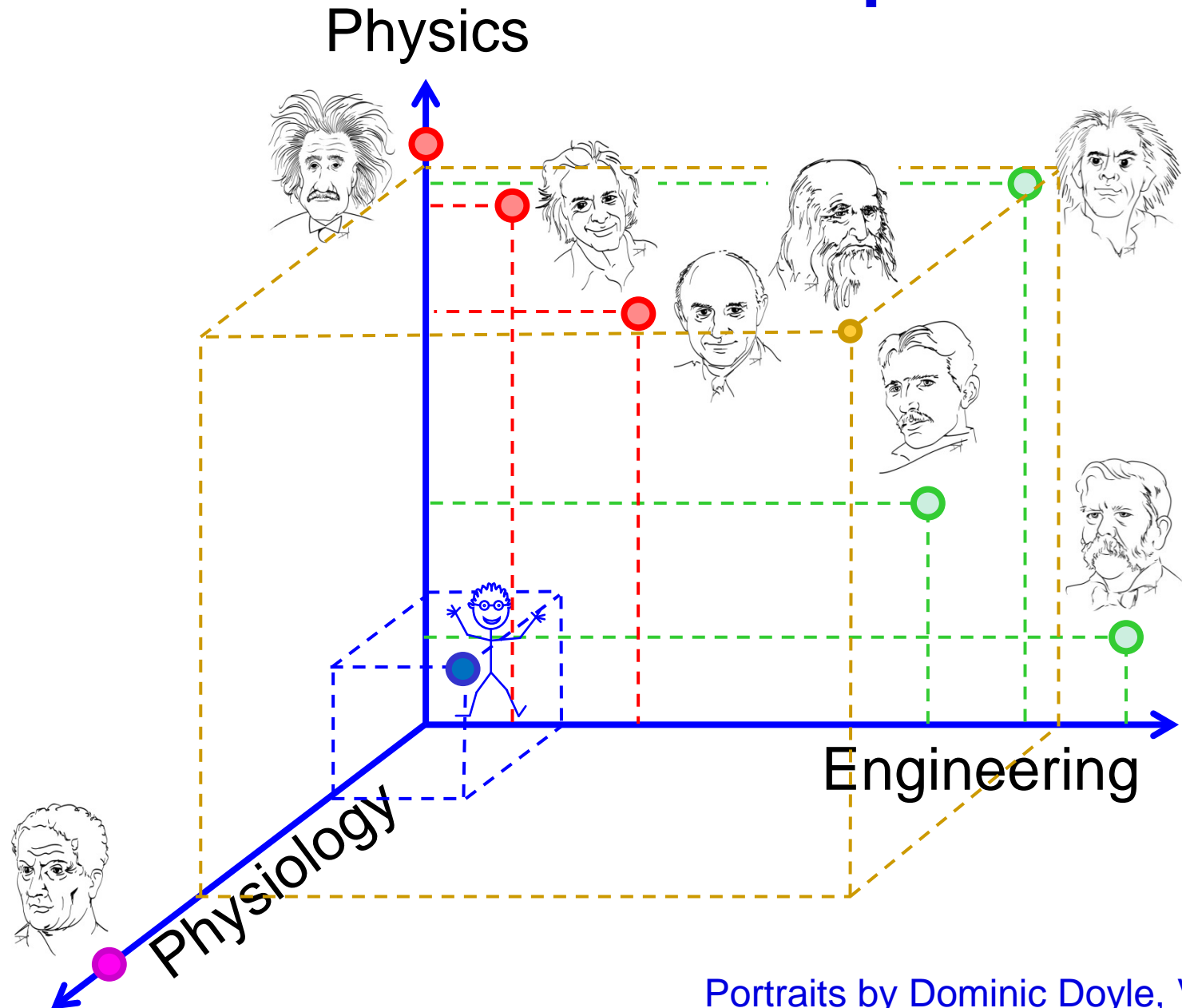


Leonardo da Vinci  
1452-1519





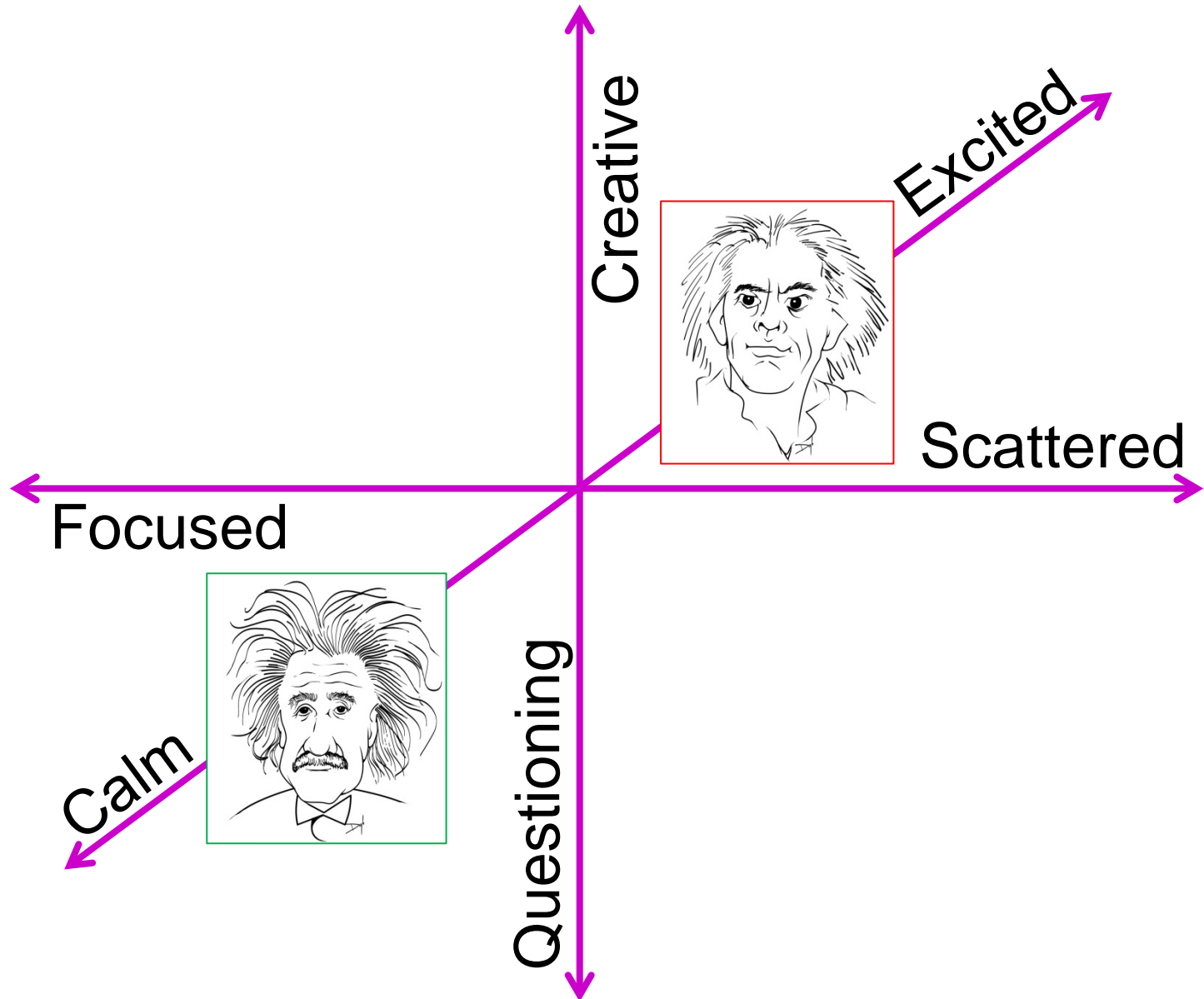
# Intellectual Phase Space



Portraits by Dominic Doyle, Vanderbilt

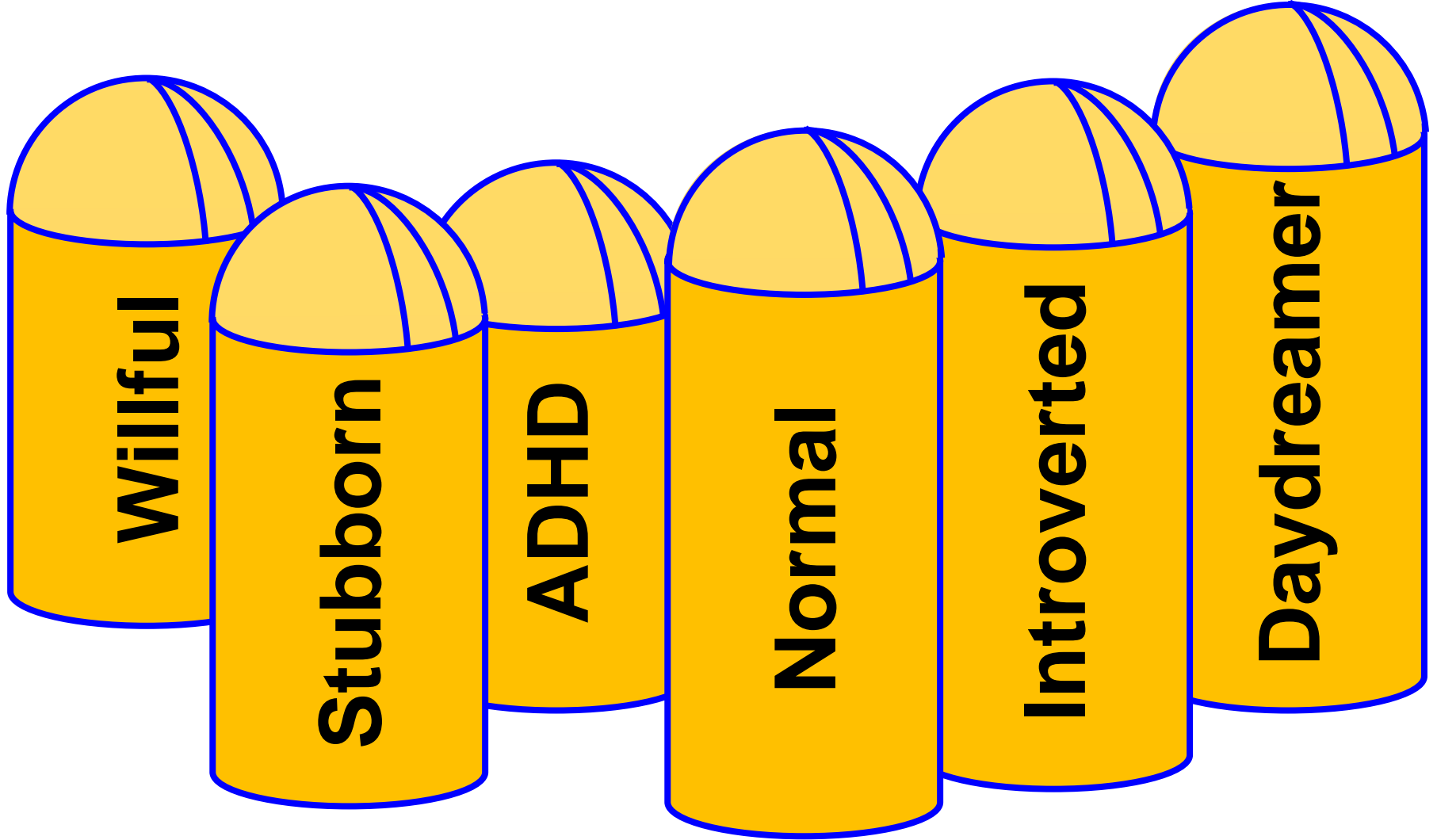


# Behavioral Phase Space





# Behavioral Silos





# Swing Phase Space

Front  
and  
back



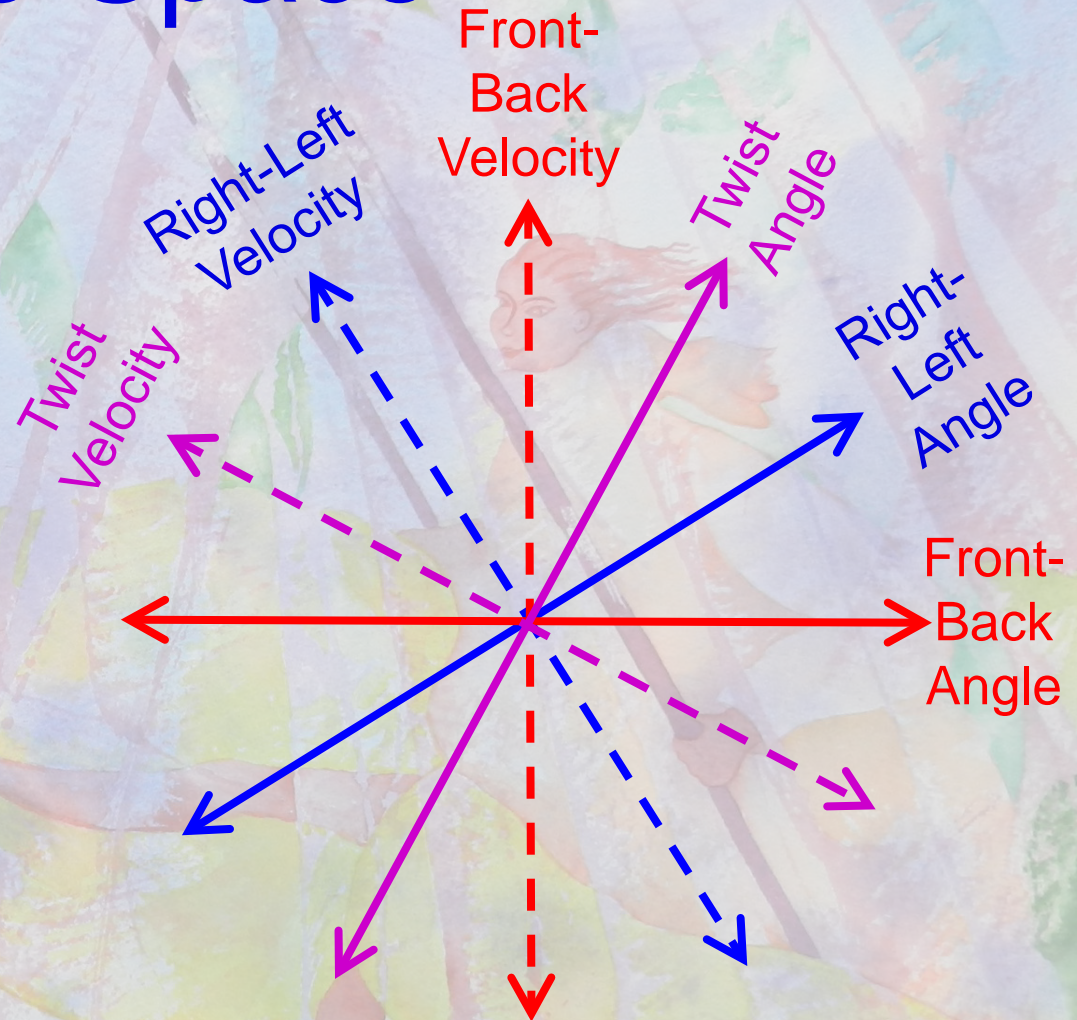
Left  
and  
Right



Orbit



Twist



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



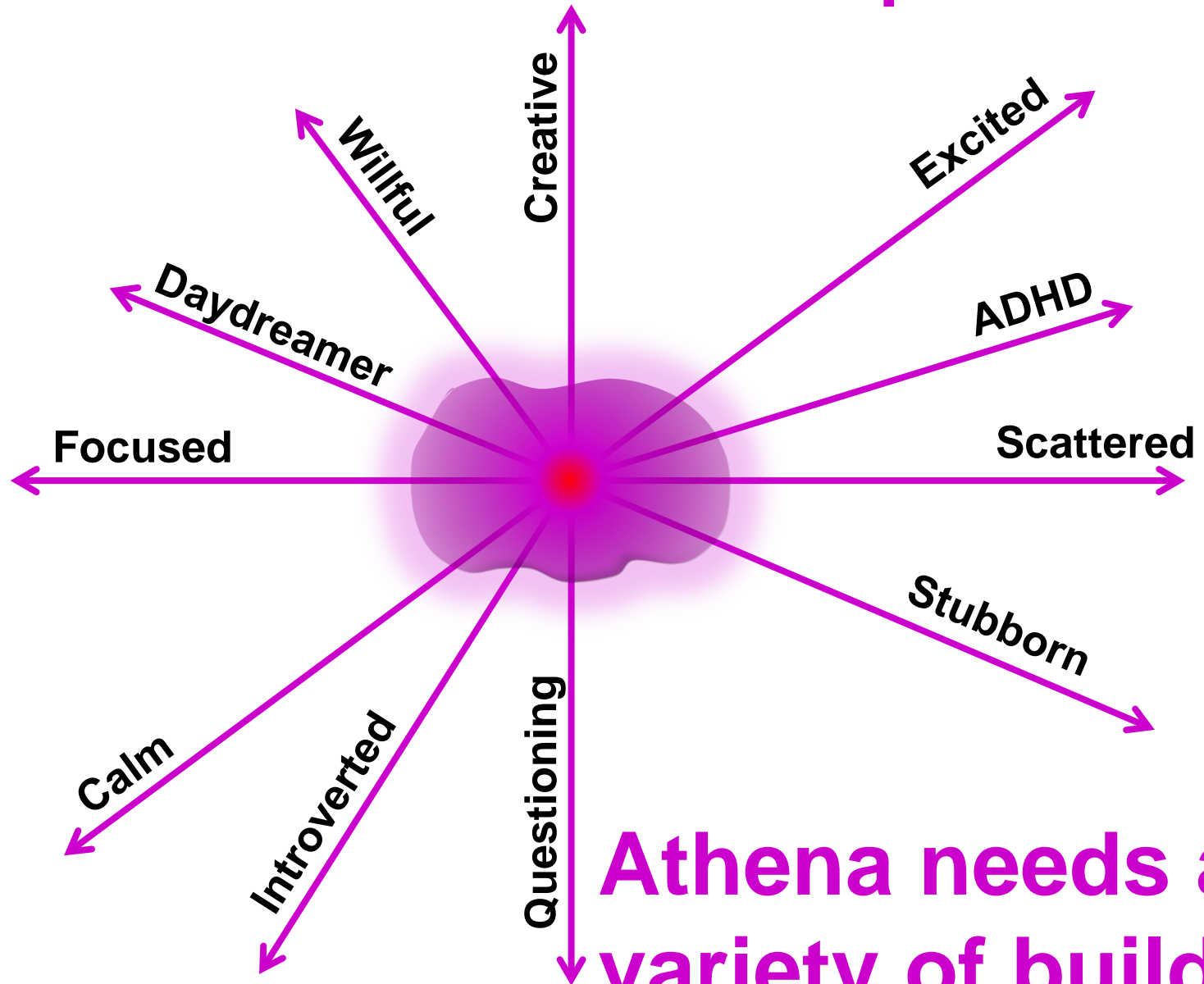
Don't put people in a single silo!



Daydreamer

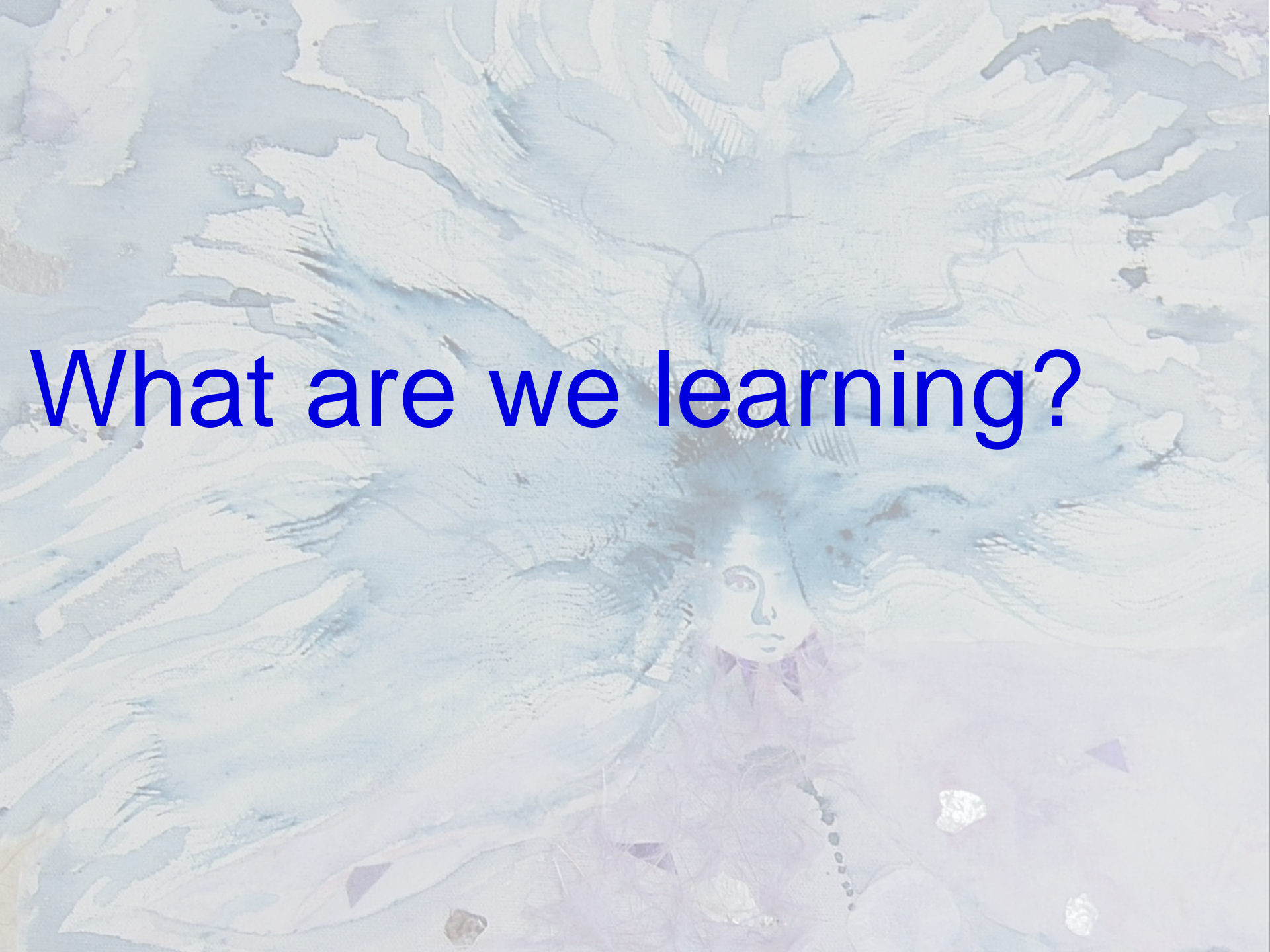


# Behavioral Phase Space



**Athena needs a  
variety of builders!**

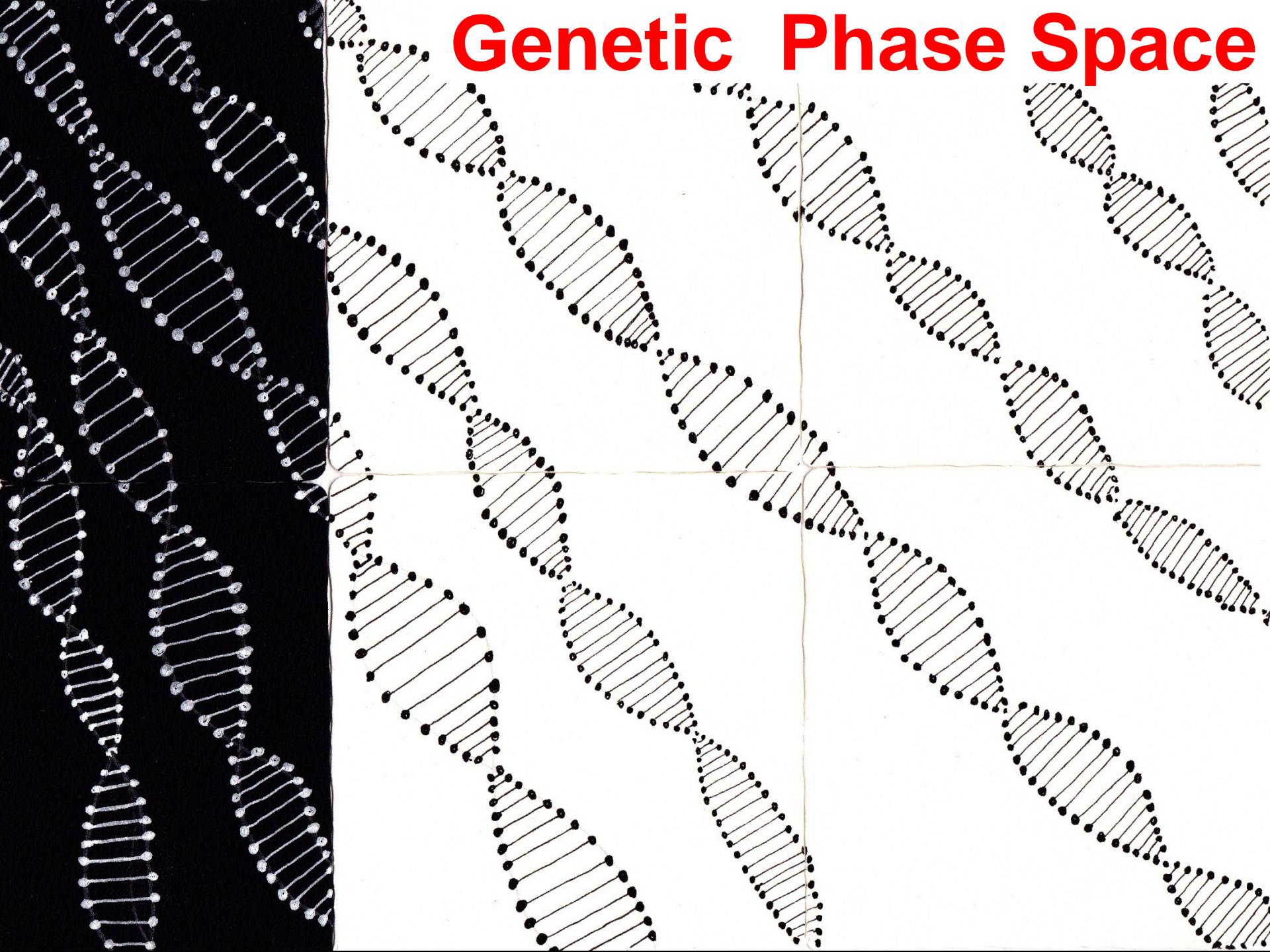




What are we learning?



# Genetic Phase Space





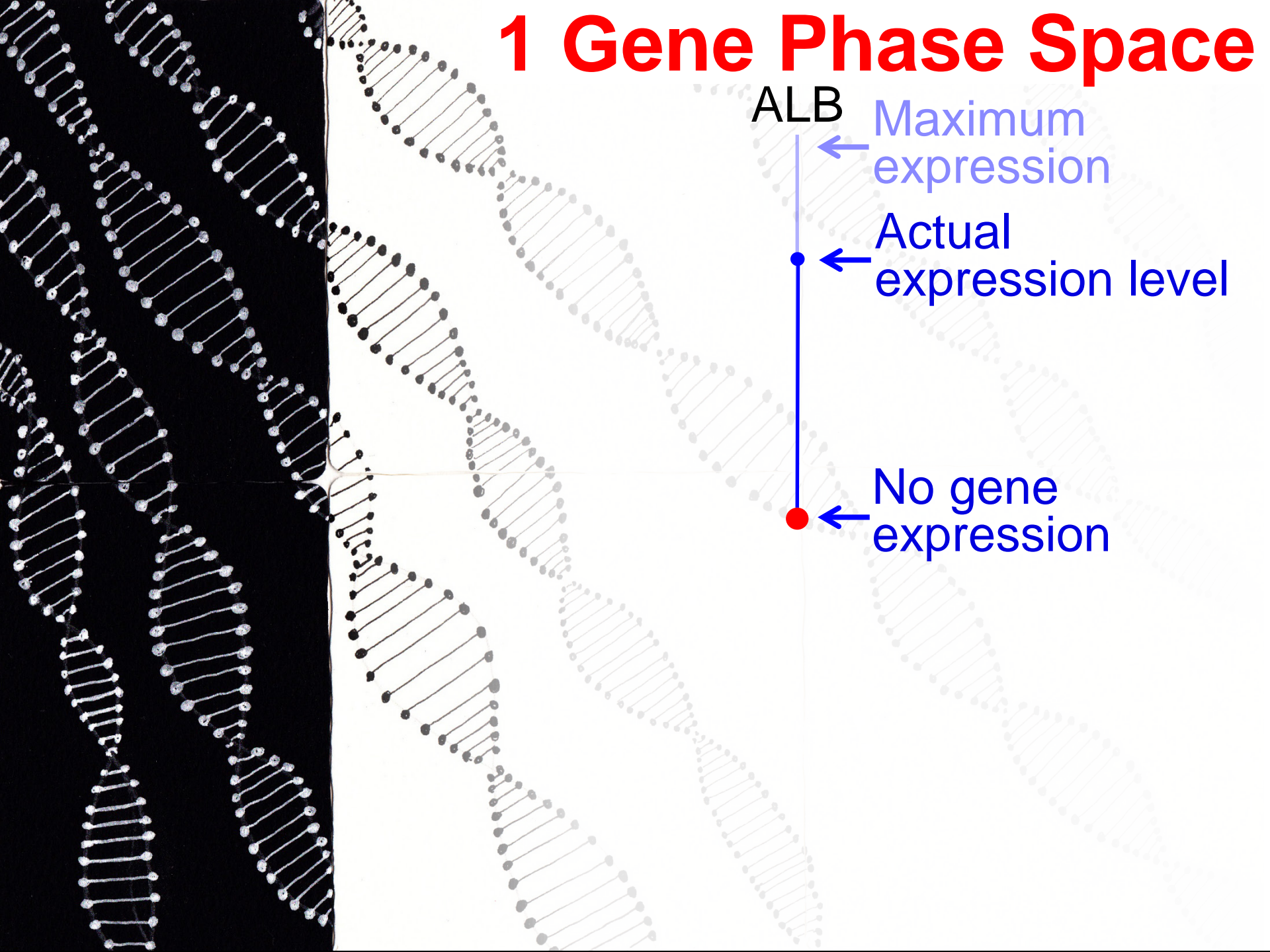
# 1 Gene Phase Space

ALB

Maximum  
expression

Actual  
expression level

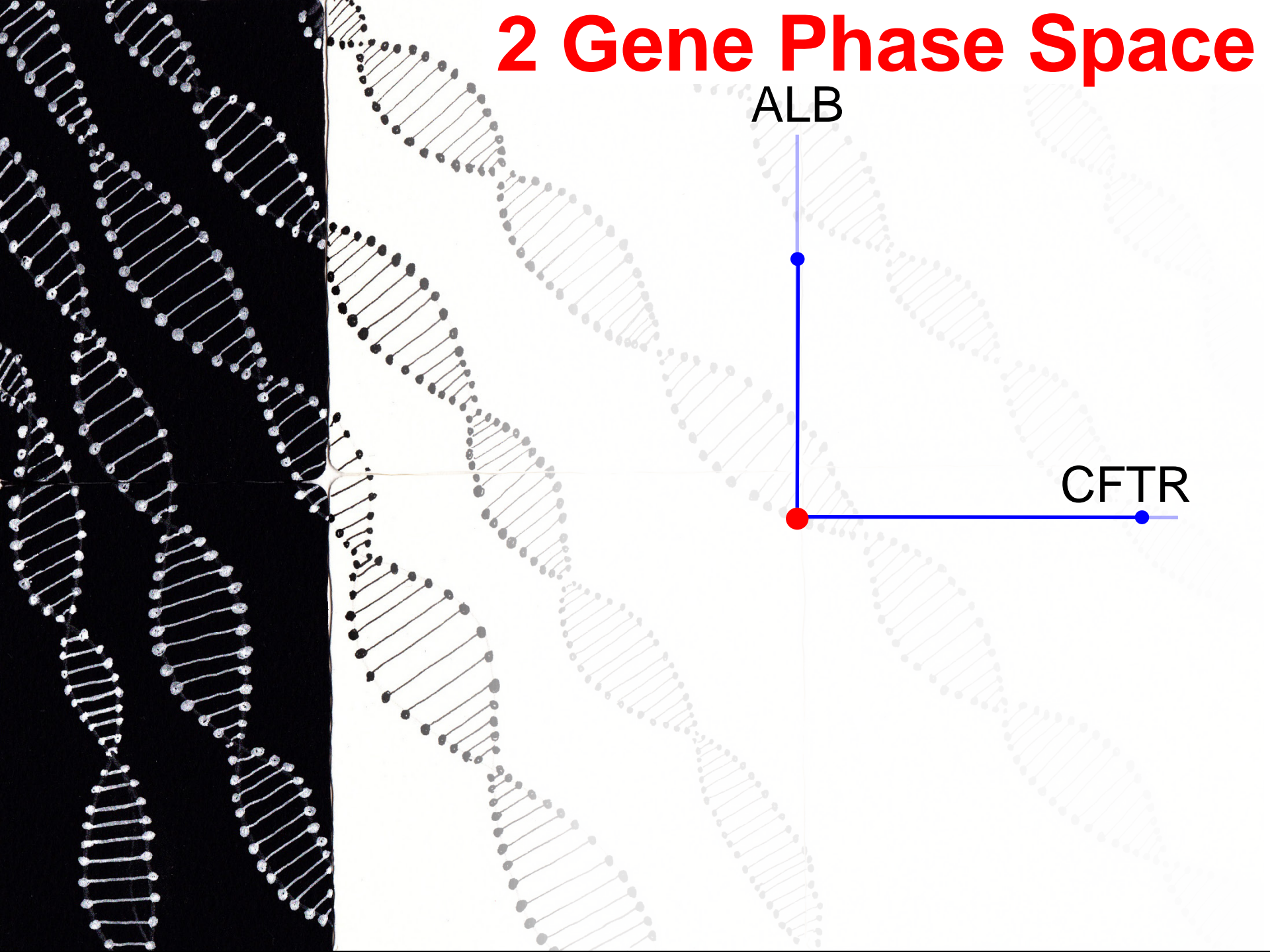
No gene  
expression



# 2 Gene Phase Space

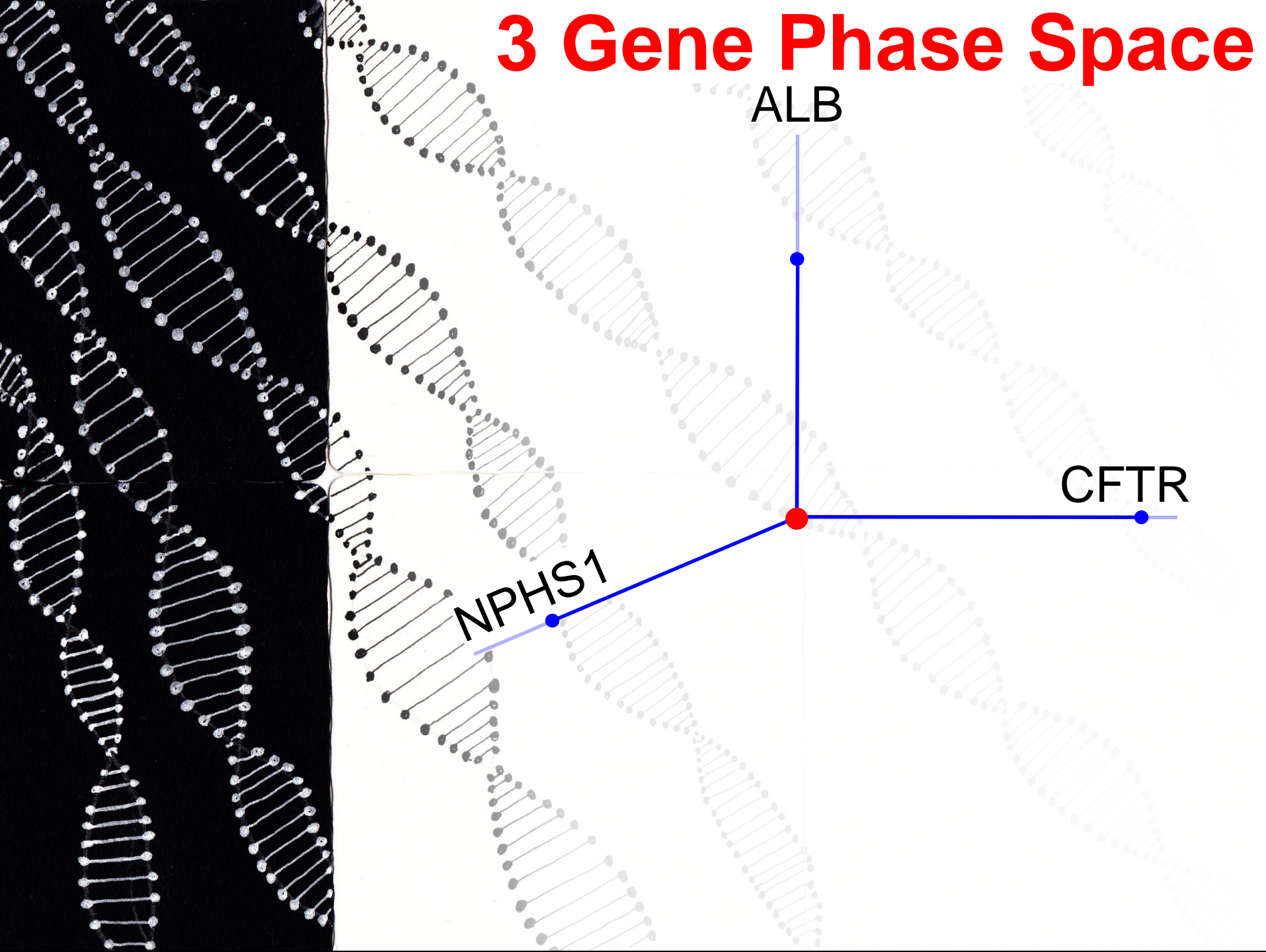
ALB

CFTR

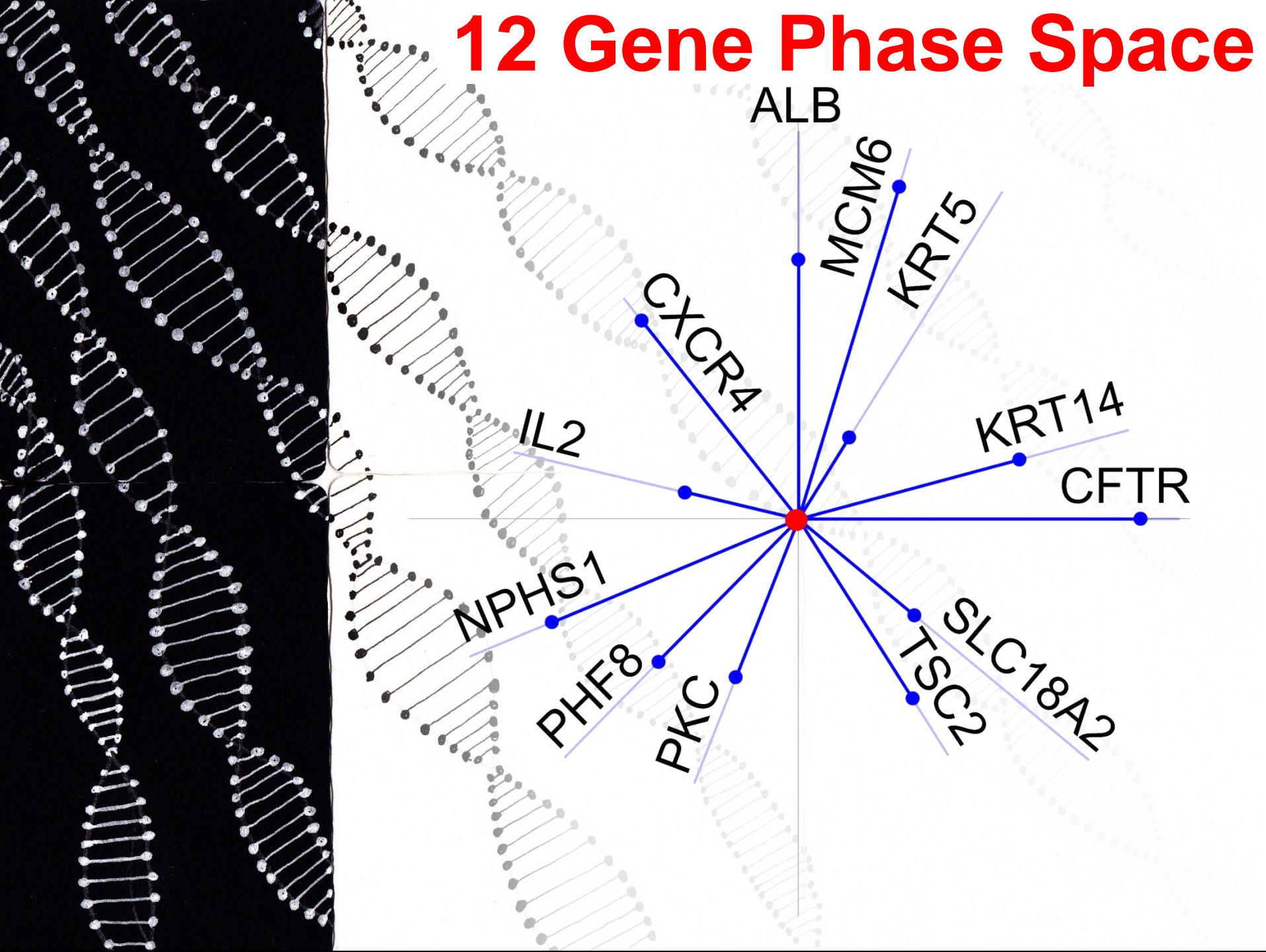




# 3 Gene Phase Space



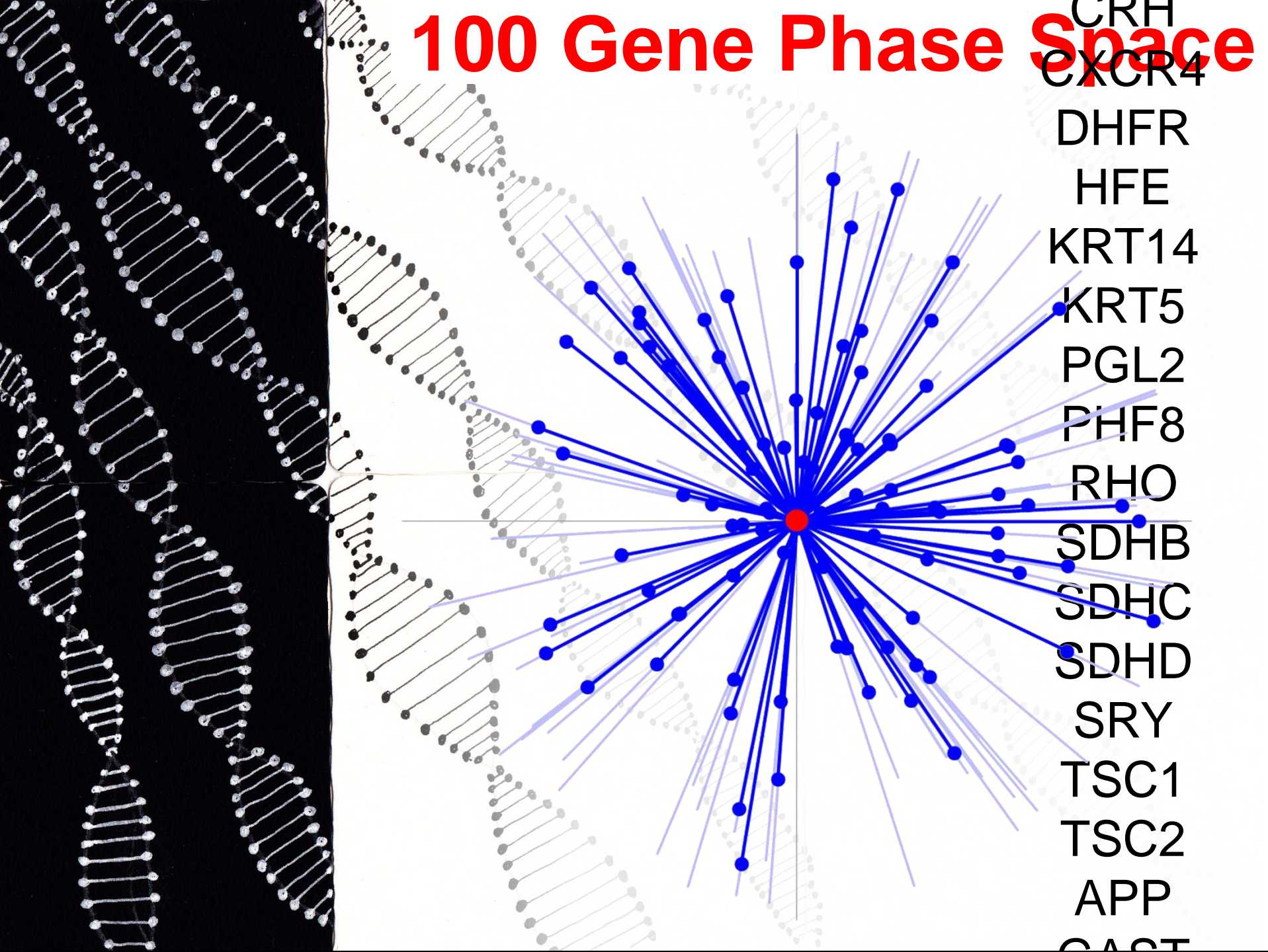
# 12 Gene Phase Space





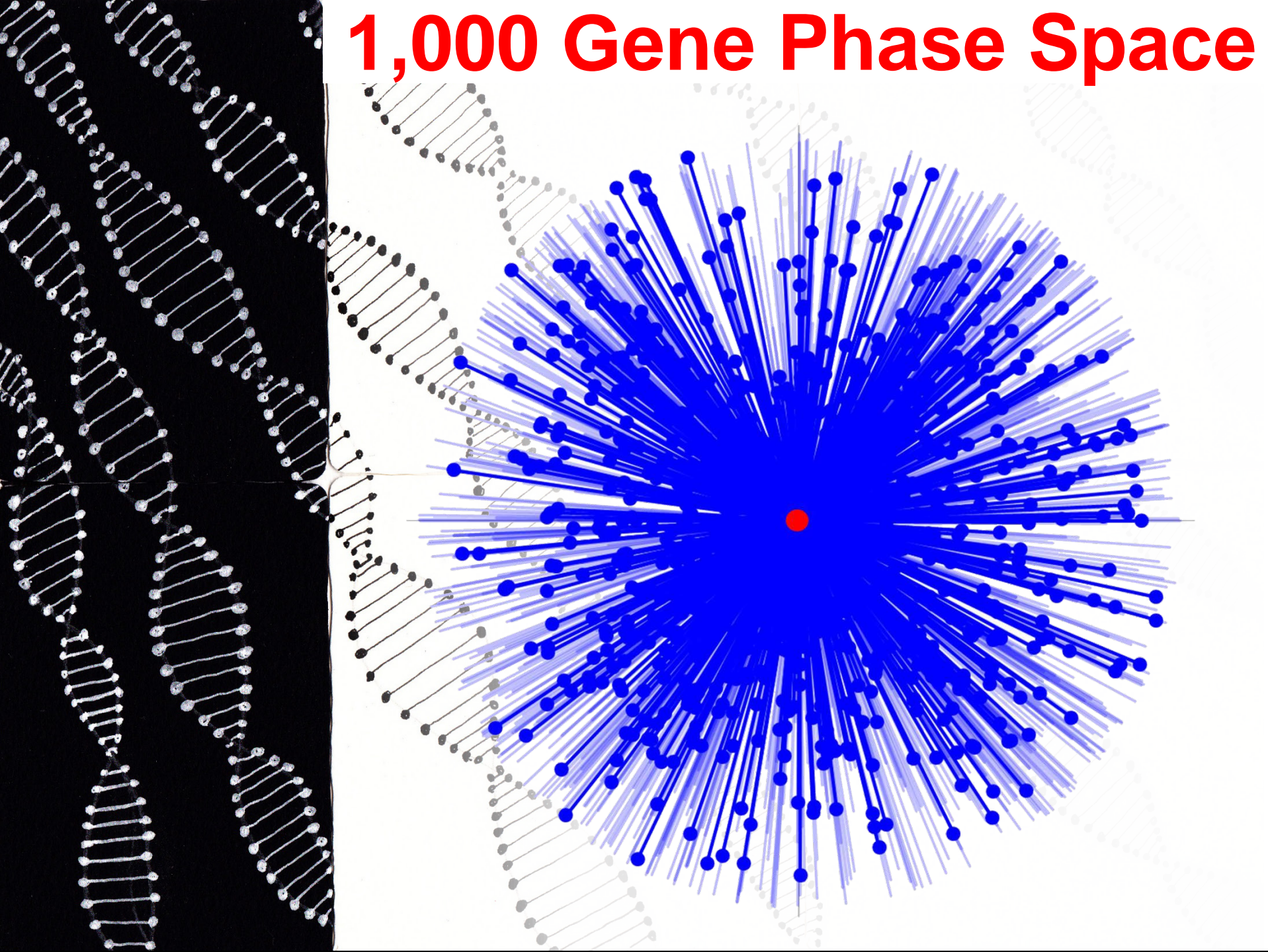
# 100 Gene Phase Space

CRH  
CXCR4  
DHFR  
HFE  
KRT14  
KRT5  
PGL2  
PHF8  
RHO  
SDHB  
SDHC  
SDHD  
SRY  
TSC1  
TSC2  
APP  
CAST



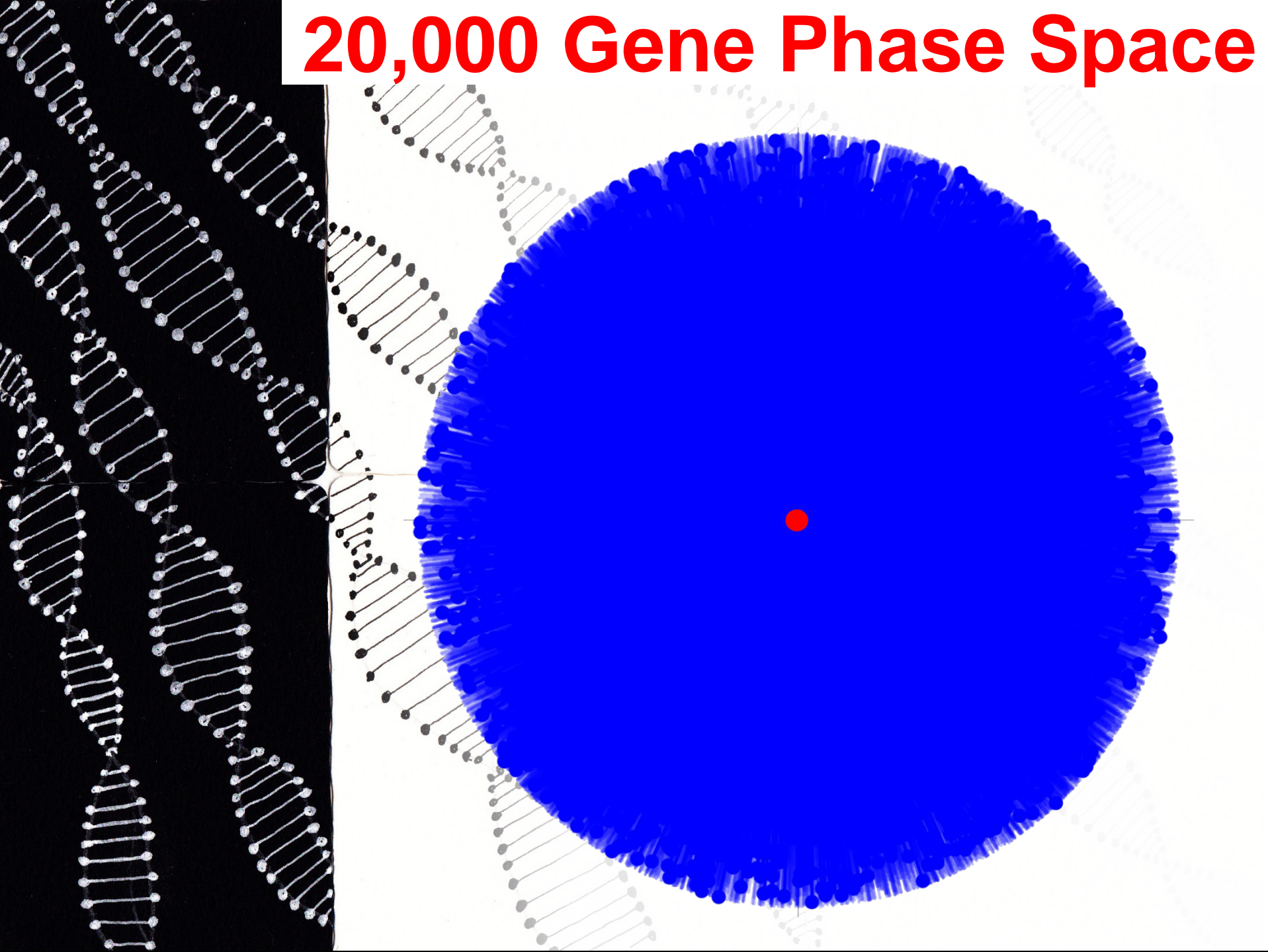


# 1,000 Gene Phase Space

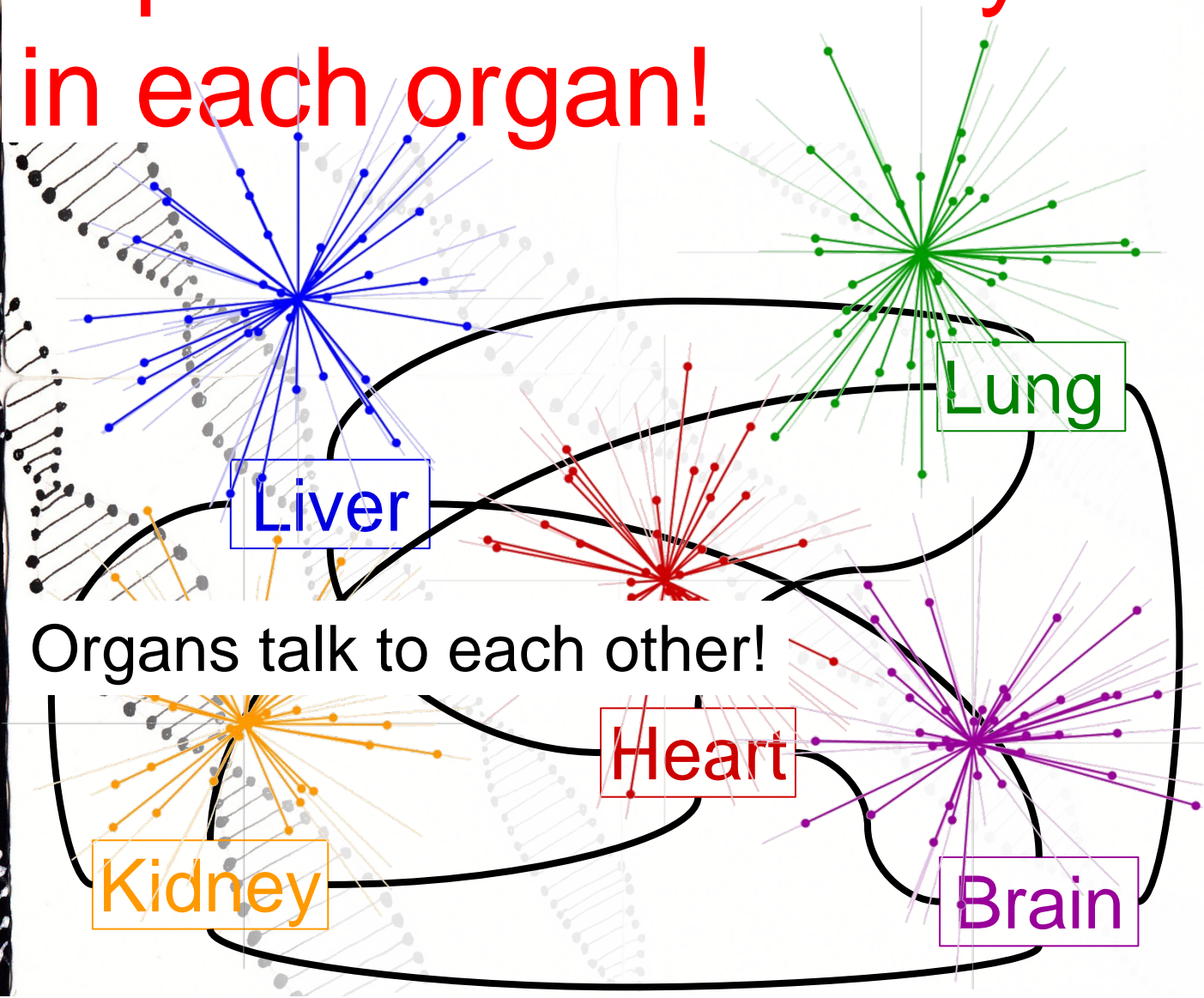




# 20,000 Gene Phase Space

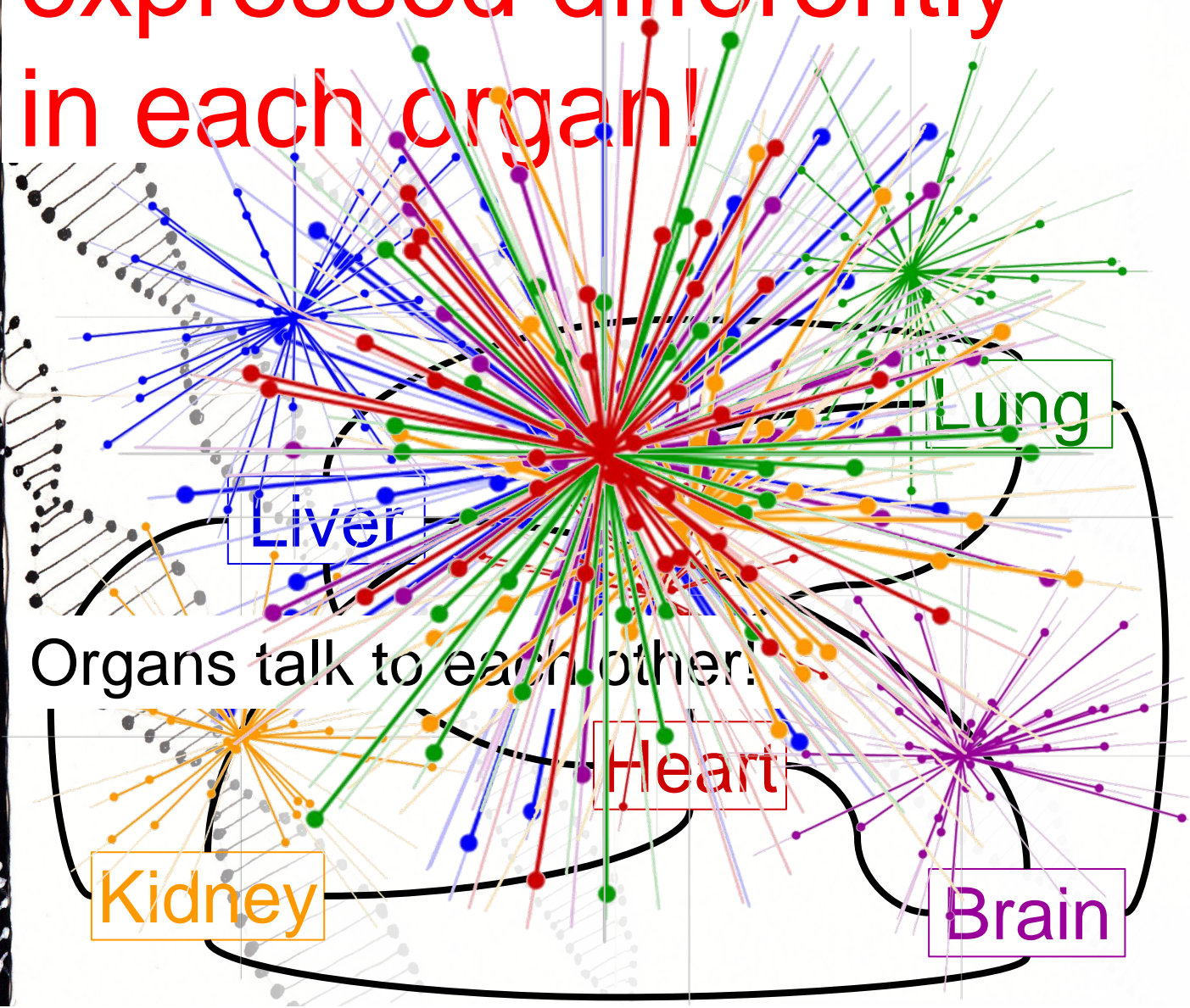


Our 20,000 genes are  
expressed differently  
in each organ!





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



Organs talk to each other!



What does an organ  
on a chip sound like?





# Organ on a Chip V5.0

