

**AN INTRODUCTION TO
BIOMEDICAL ONTOLOGY 2
Sunday April 13, 2008**

Barry Smith

University at Buffalo

<http://ontology.buffalo.edu/smith>

Agenda · Day 2

An ontological introduction to biomedicine:
Defining organism, function and disease

The Gene Ontology (GO), the Foundational
Model of Anatomy (FMA) and the
Infectious Disease Ontology (IDO)

The OBO Foundry: A suite of biomedical
ontologies to support reasoning and data
integration

Applications of ontology outside biomedicine

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The OBO Foundry: A suite of biomedical ontologies to support reasoning and data integration

Applications of ontology outside biomedicine

Defining 'organism'

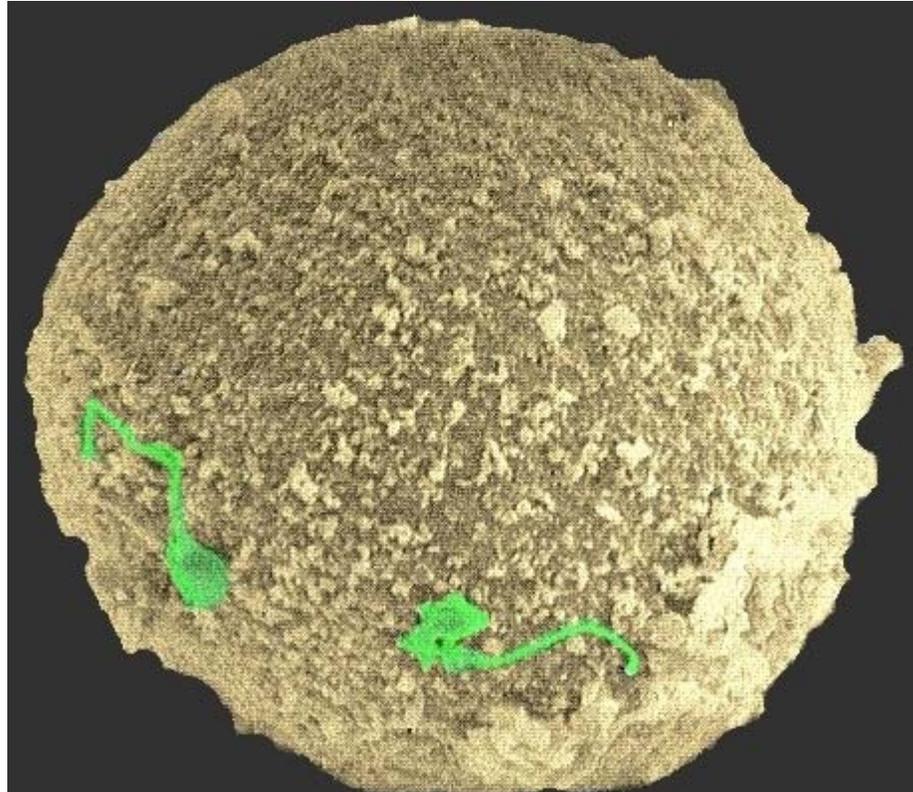
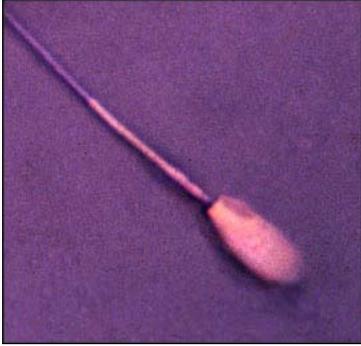
Organism =def. an independent
continuant, made of matter, which ...



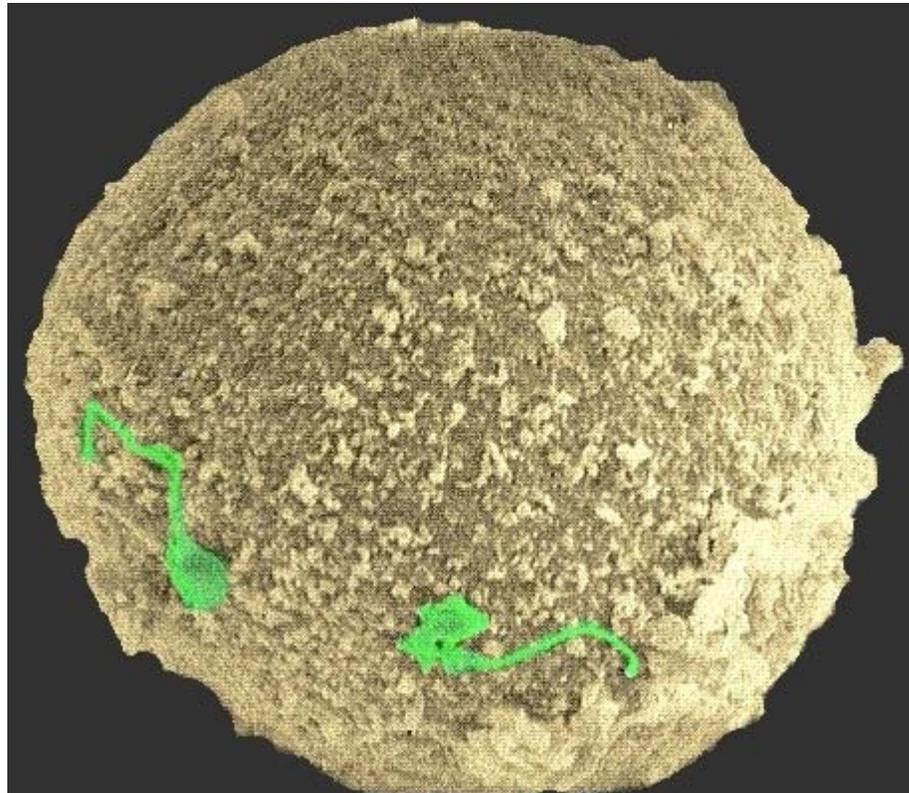
To fill in the gap, we consider the question: When does an organism begin to exist?



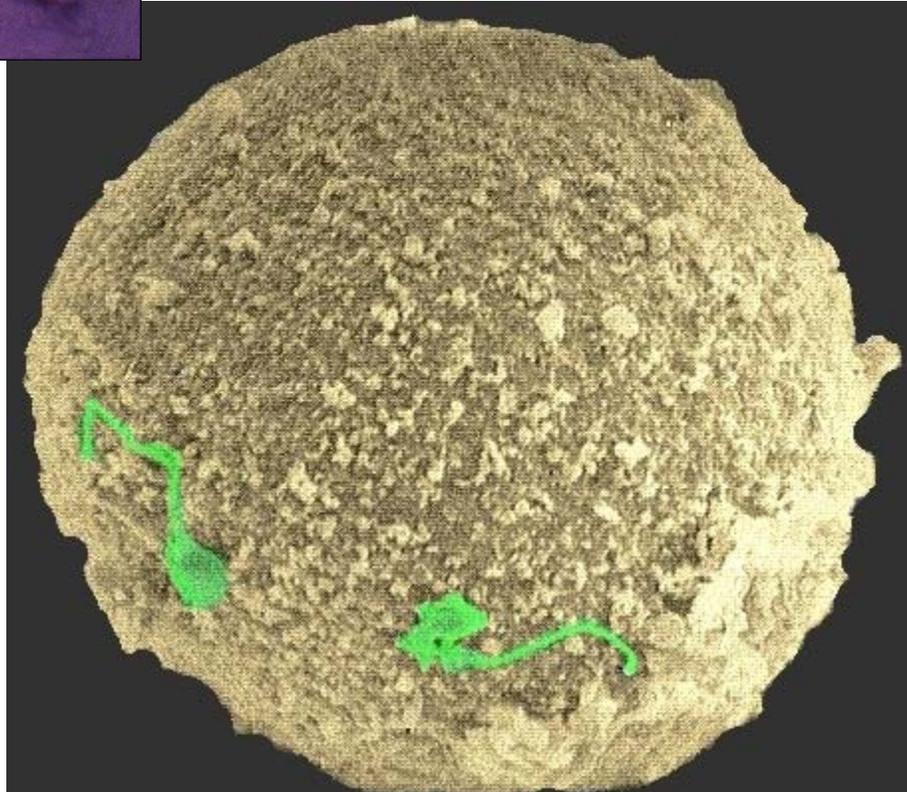
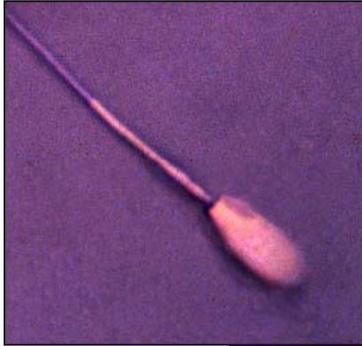
First there are two:

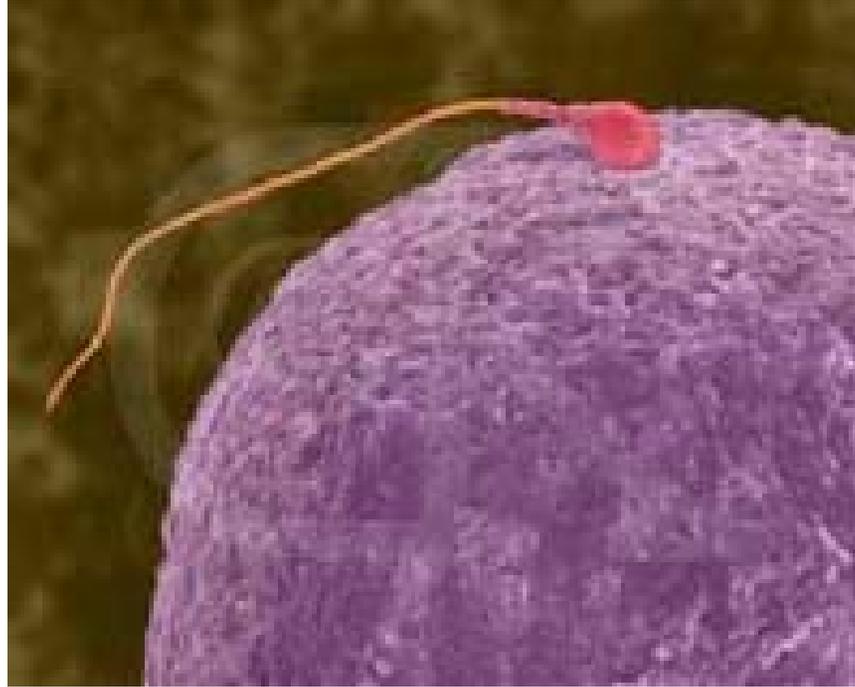


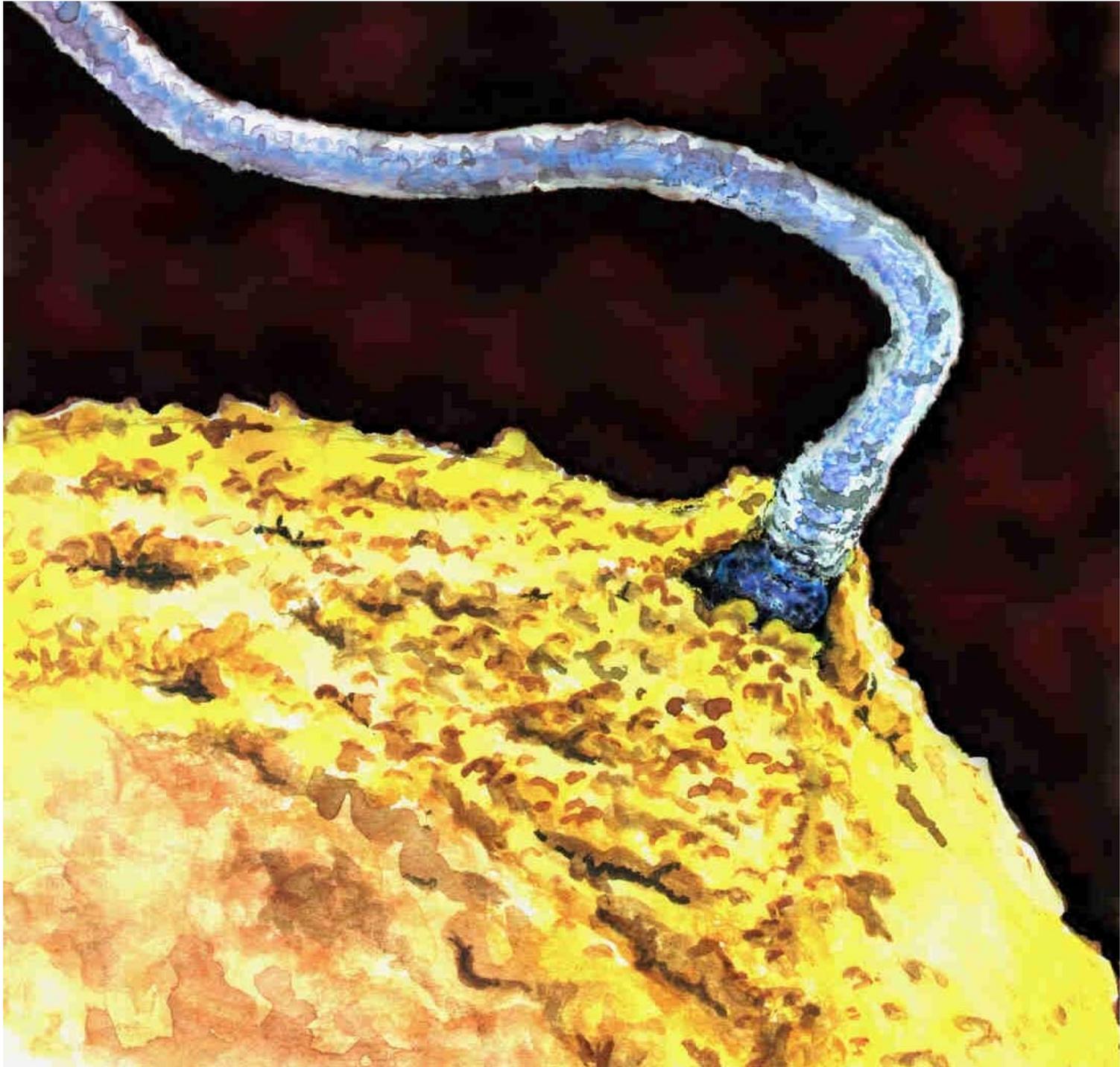
first there are two:



first there are two:





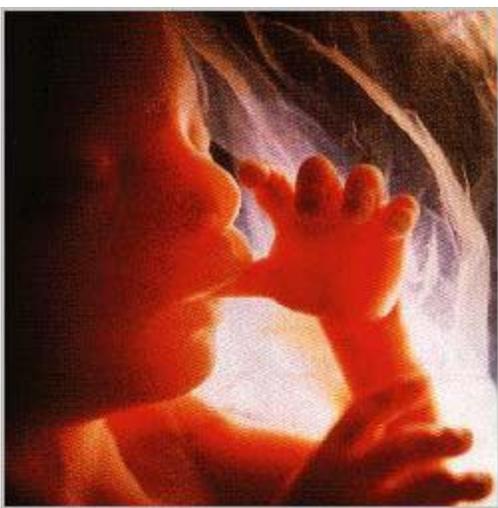






... and then there is one





This is an organism



This is not (yet) an organism



So where is the threshold?

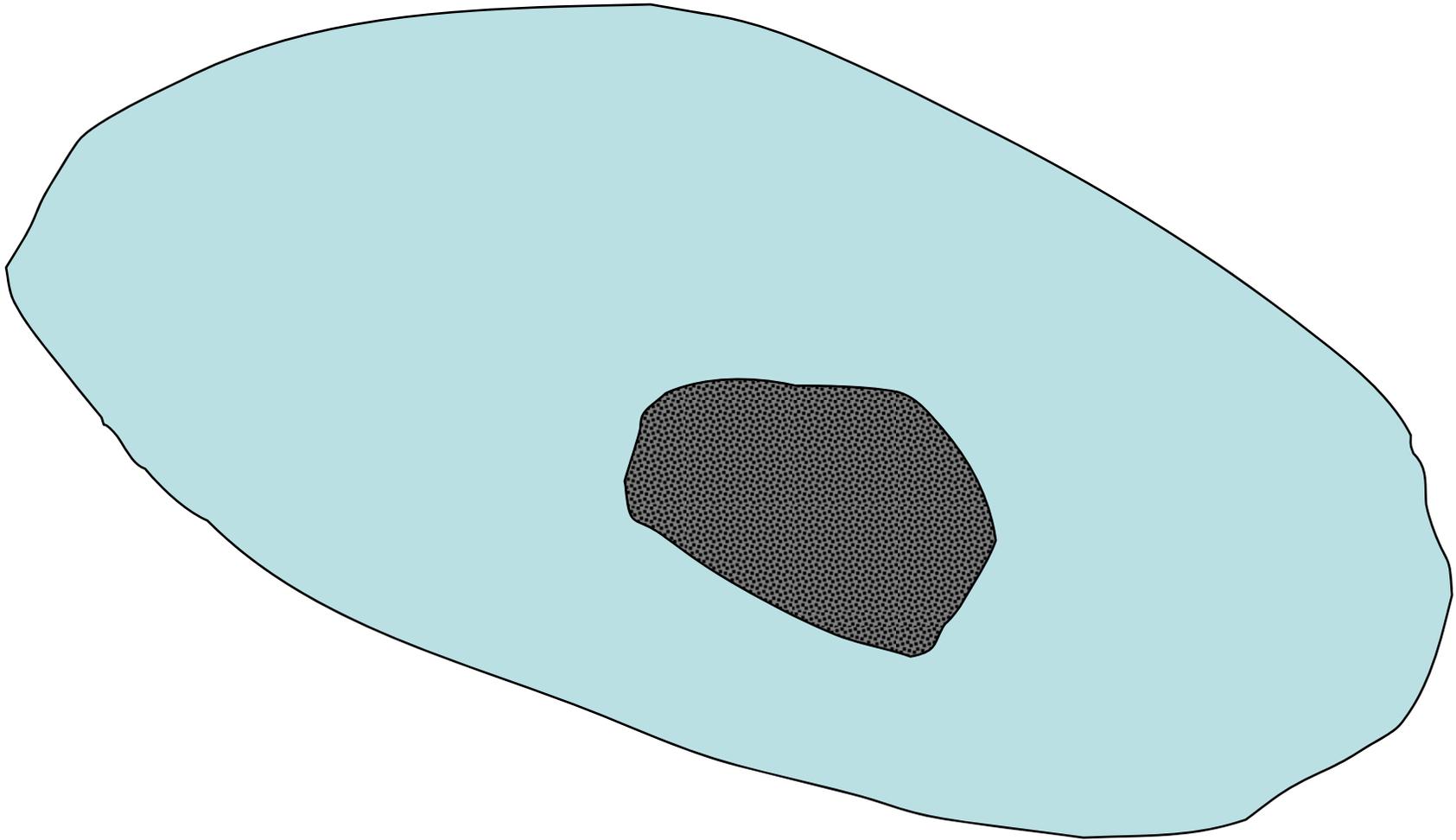
- a. zygote (single cell) (day 0)
- b. multi-cell (days 0-3)
- c. morula (day 3)
- d. early blastocyst (day 4)
- e. implantation (days 6-13)
- f. gastrulation (days 14-16)
- g. neurulation (from day 16)
- h. formation of the brain stem (days 40-43)
- i. end of first trimester (day 98)
- j. viability (around day 130)
- k. sentience (around day 140)
- l. quickening (around day 150)
- m. birth (day 266)
- n. the development of self-consciousness

Methodology for answering this question

Set forth criteria which an entity must satisfy to be an organism

And establish at which point in human development these criteria are first satisfied by an entity which can be transtemporally identical with the adult human being

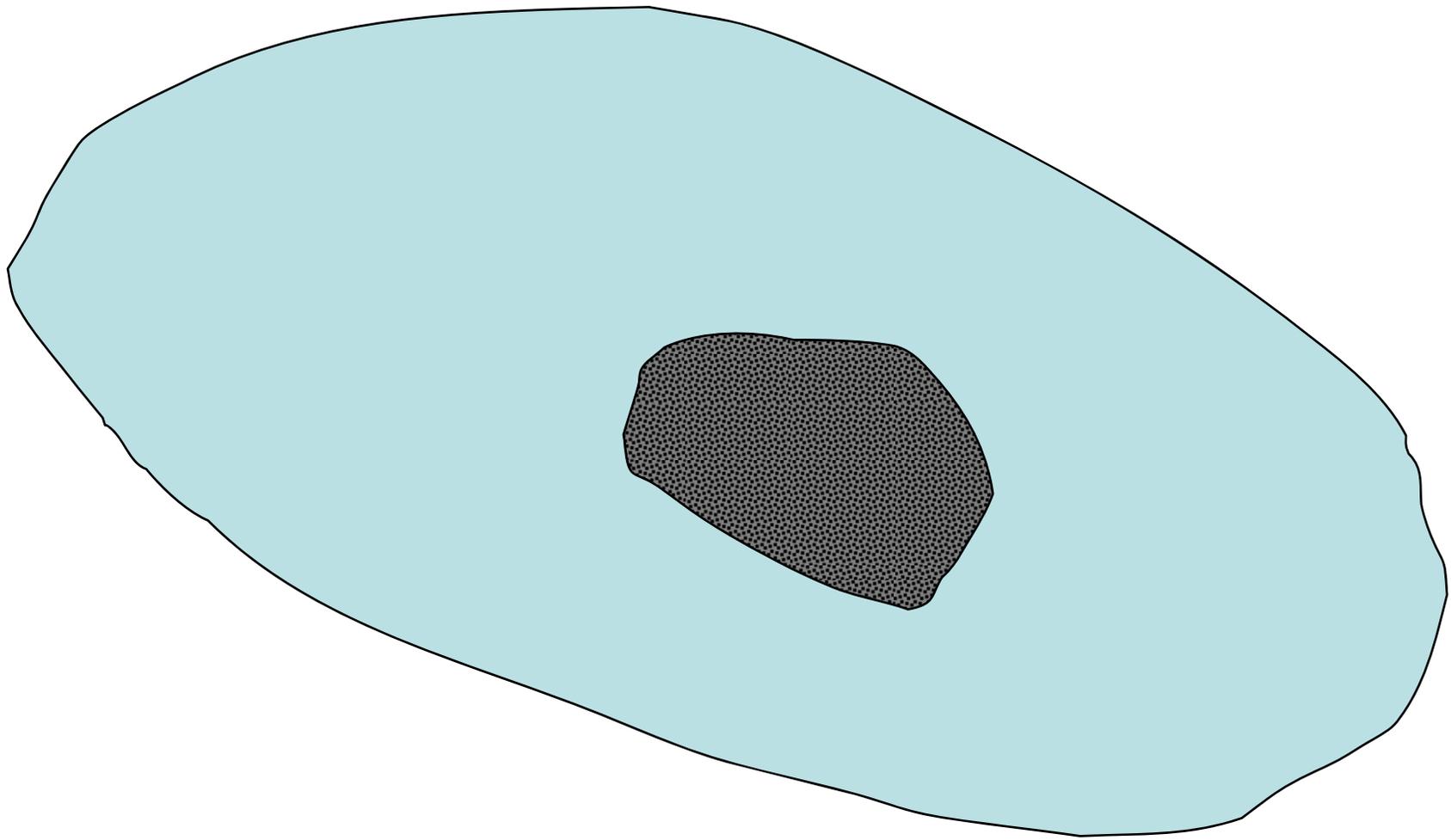
Is the zygote already an organism?



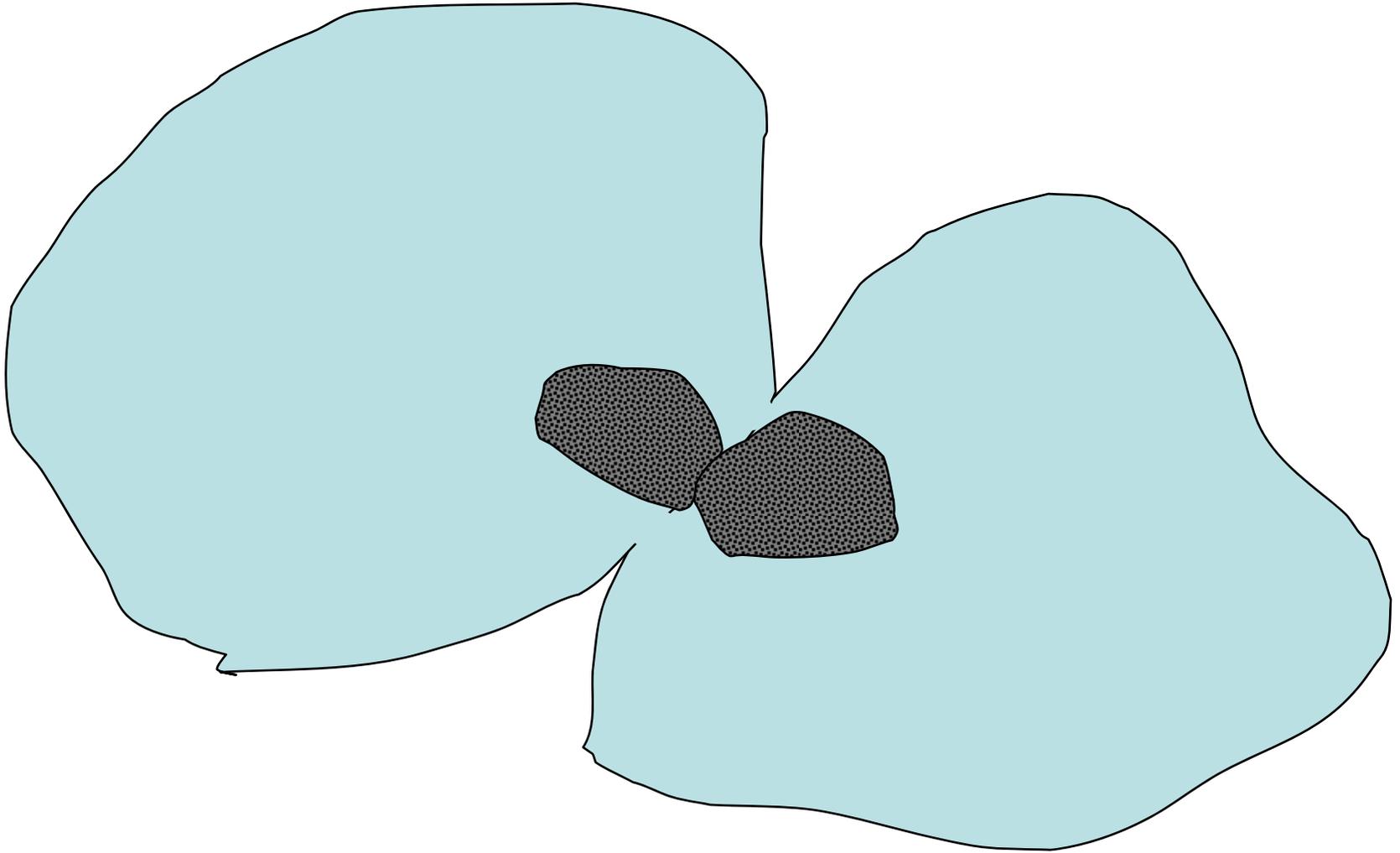
and is it the *same* organism as this?



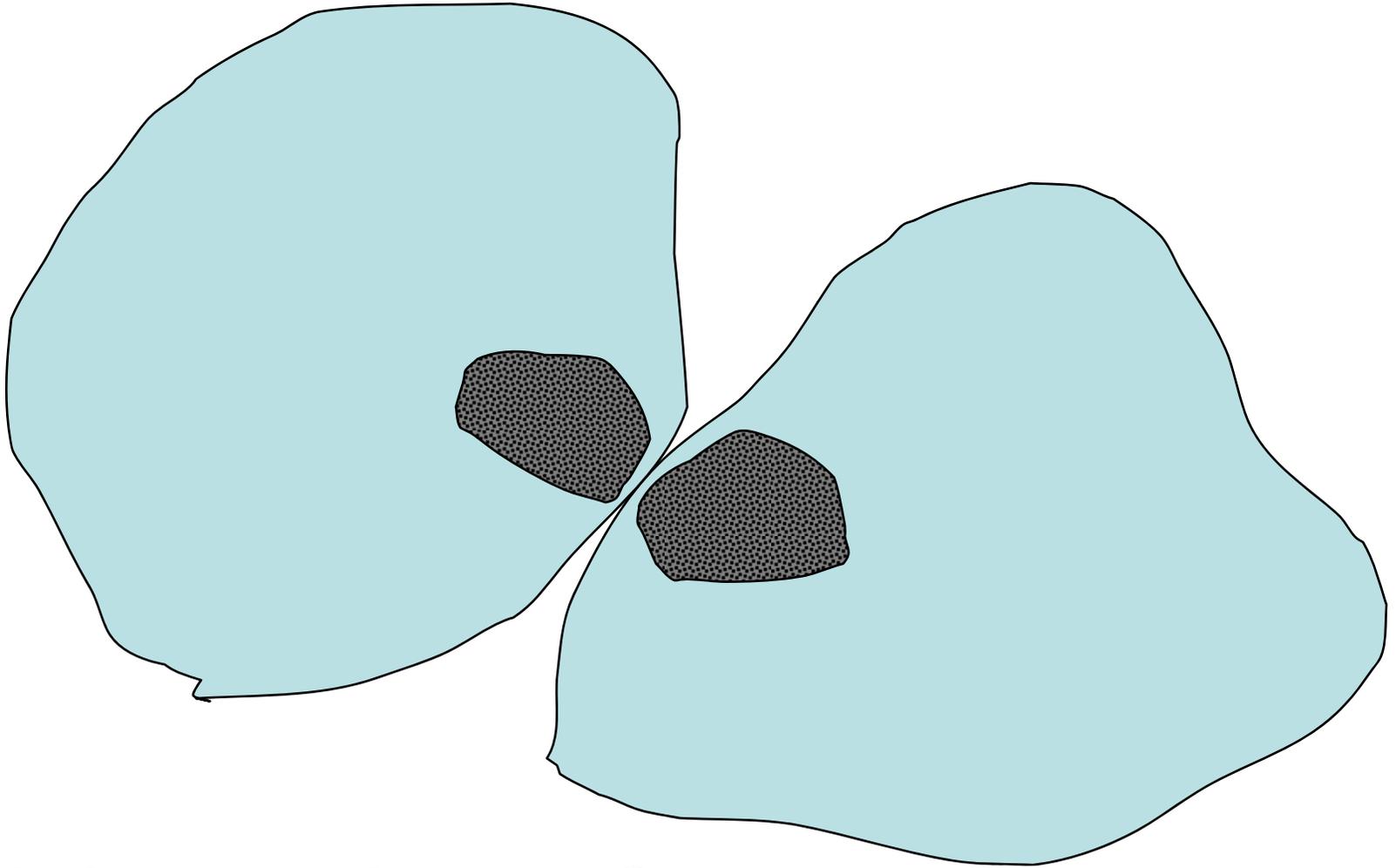
the problem is that this, almost immediately,



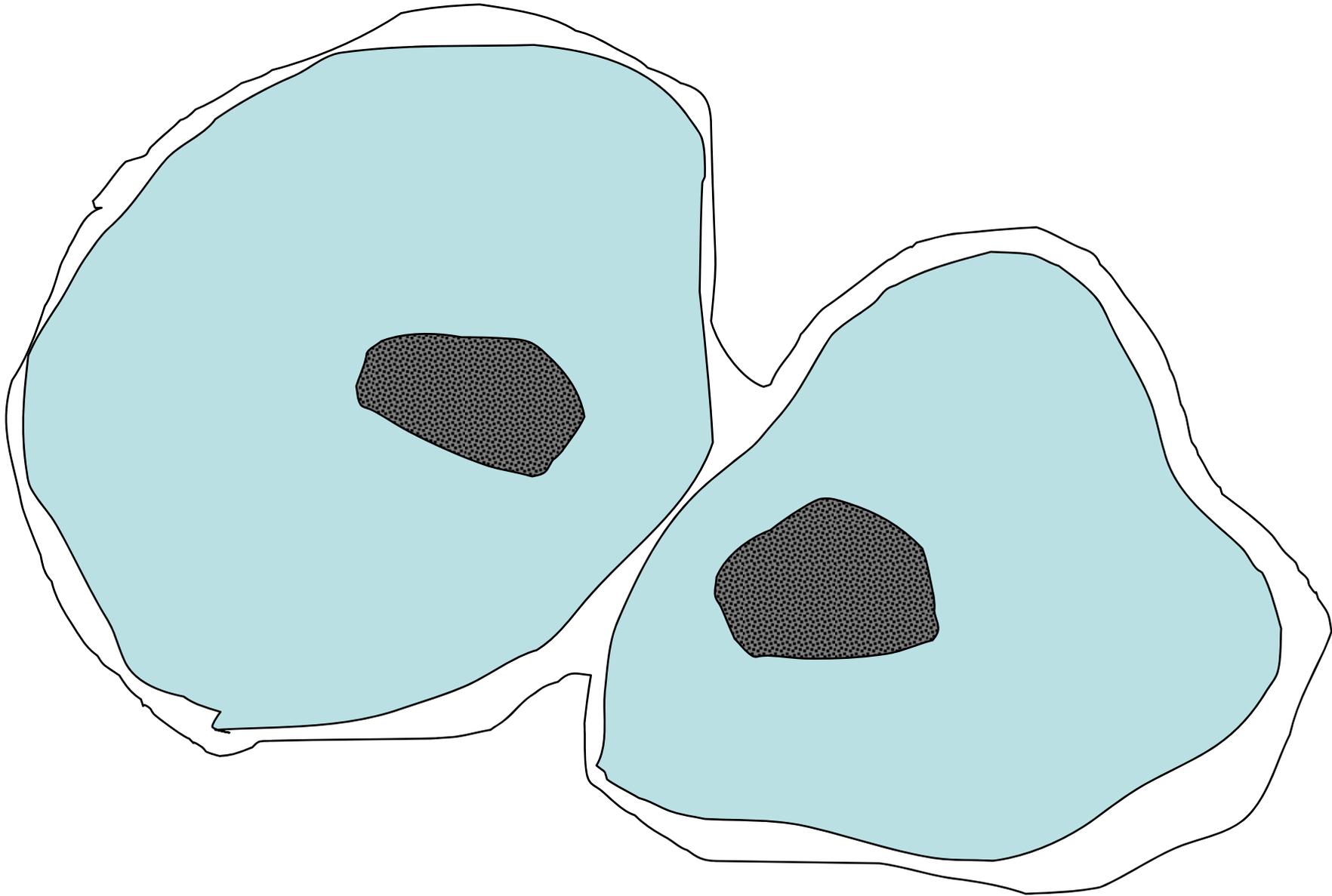
becomes this...



...and then cleavage



which one is me?

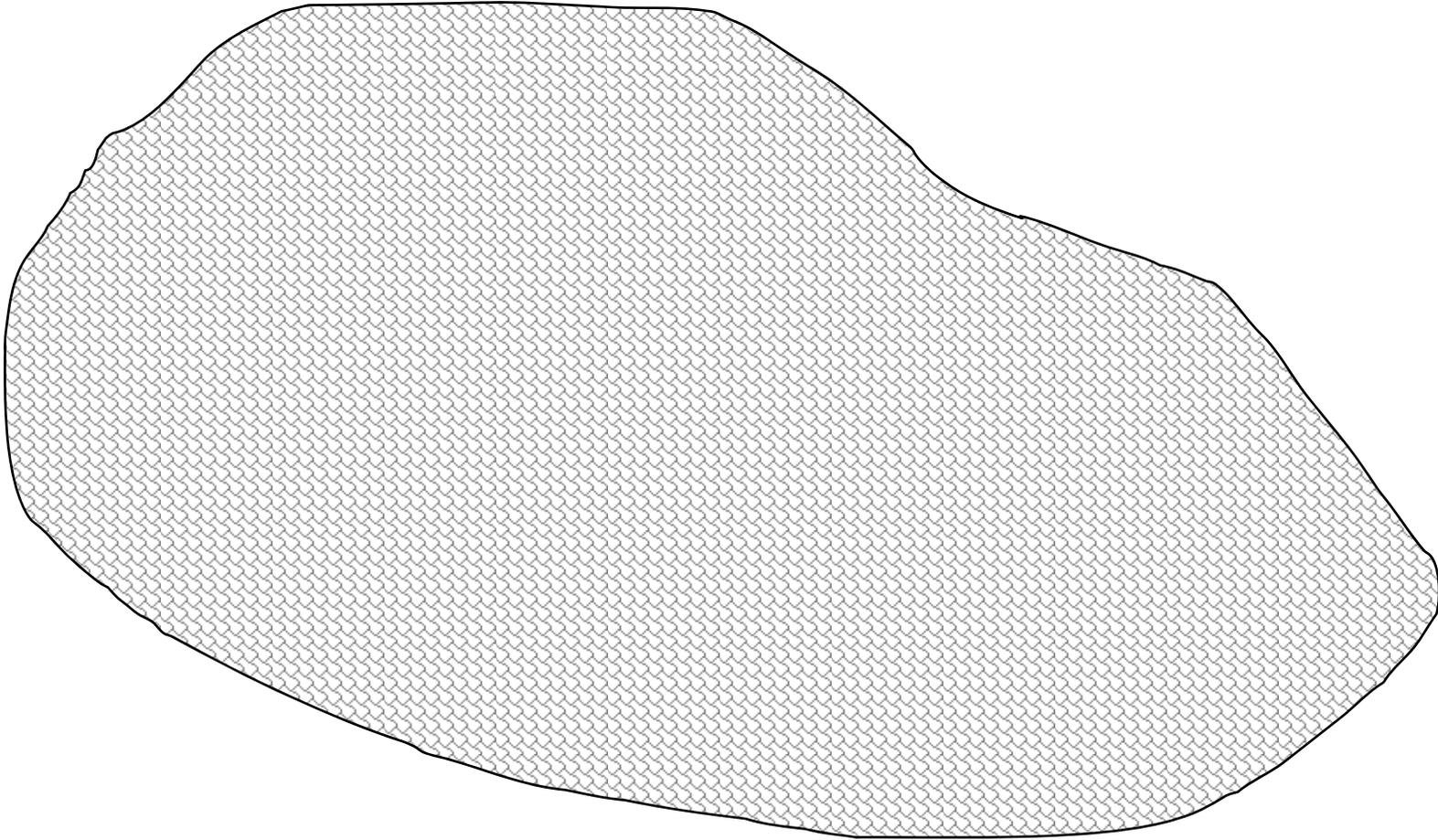


2 cells plus *zona pellucida*

is 1 of the cells at the 2-cell stage *me*?

these two cells of this new organism are cytoplasmically differentiated

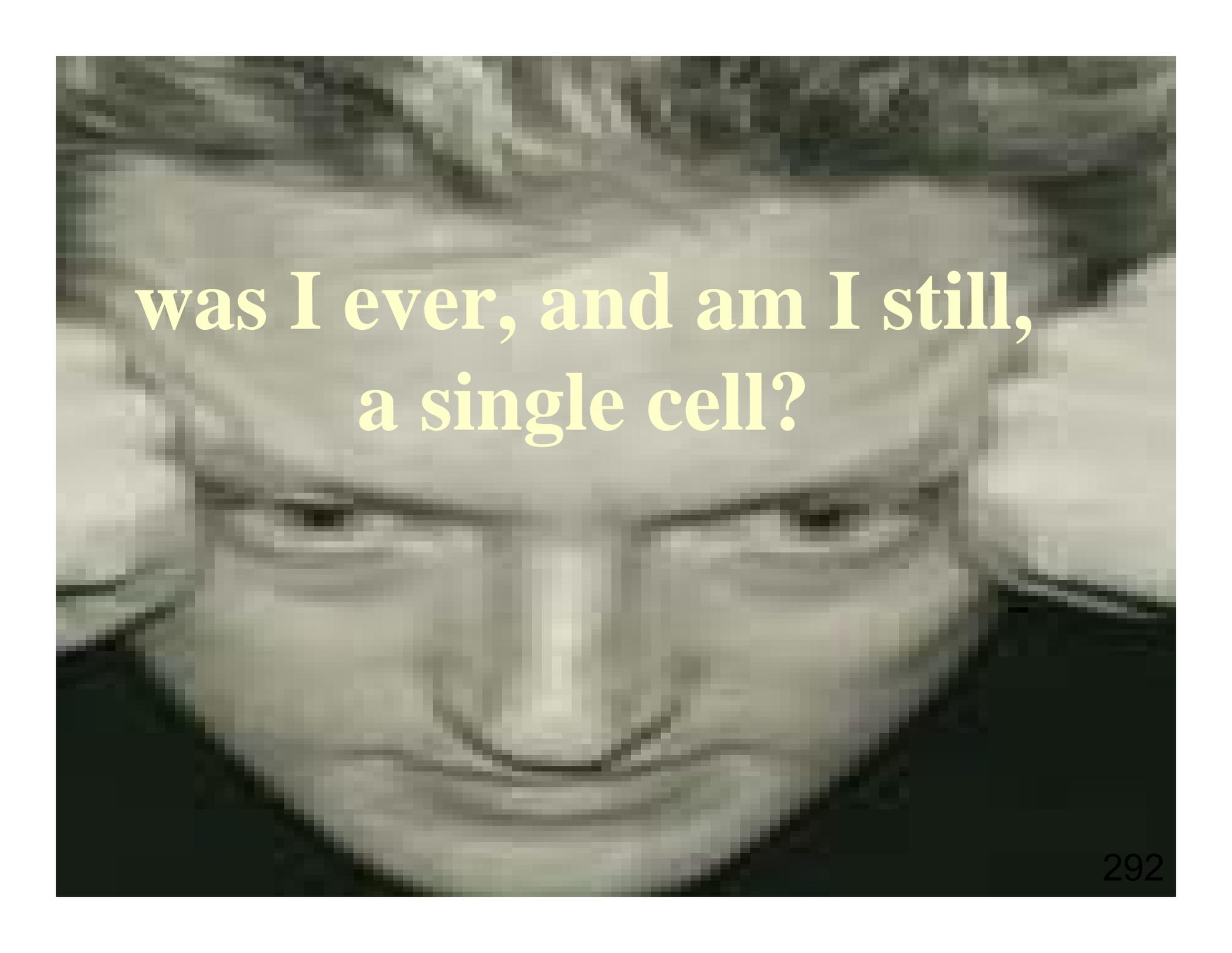
... but now, more cleavages, create a cell mass



which one of *these* cells is me?

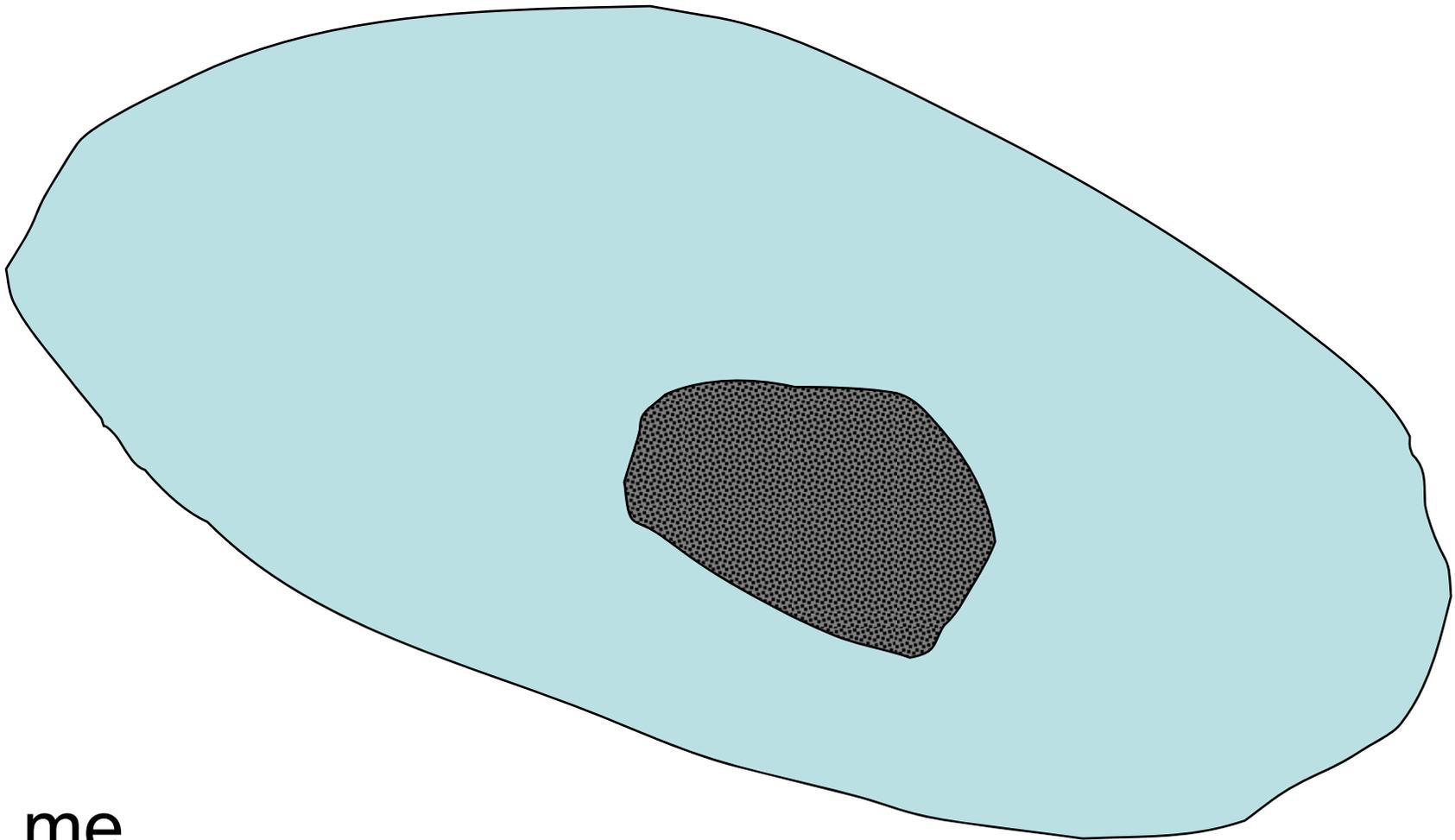
A grayscale micrograph of a cell, possibly a yeast cell, showing a central structure that could be a nucleus or a vacuole. The cell is roughly circular with some internal membrane structures visible.

and which one of the
cells *here* is me ?



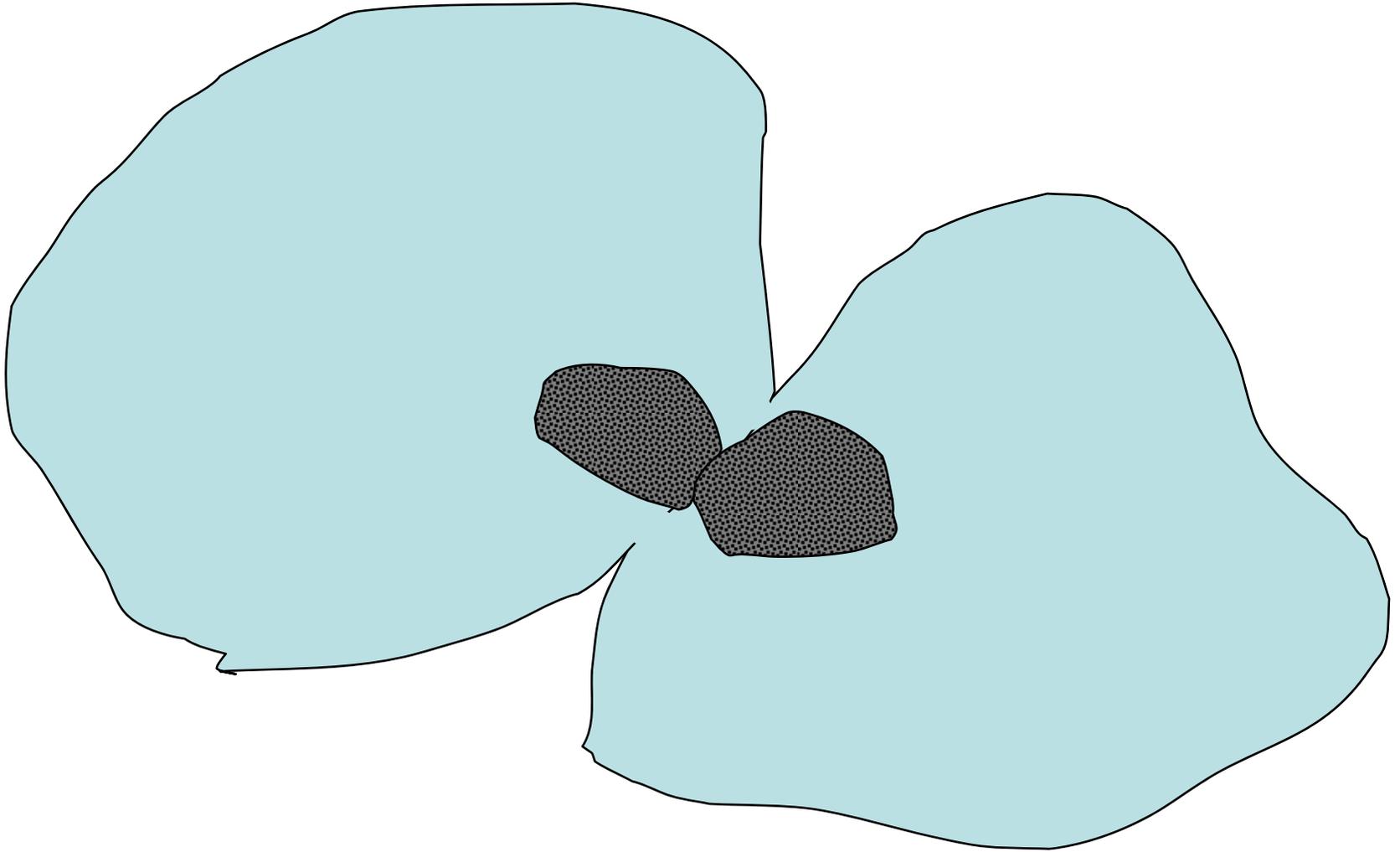
was I ever, and am I still,
a single cell?

An alternative story

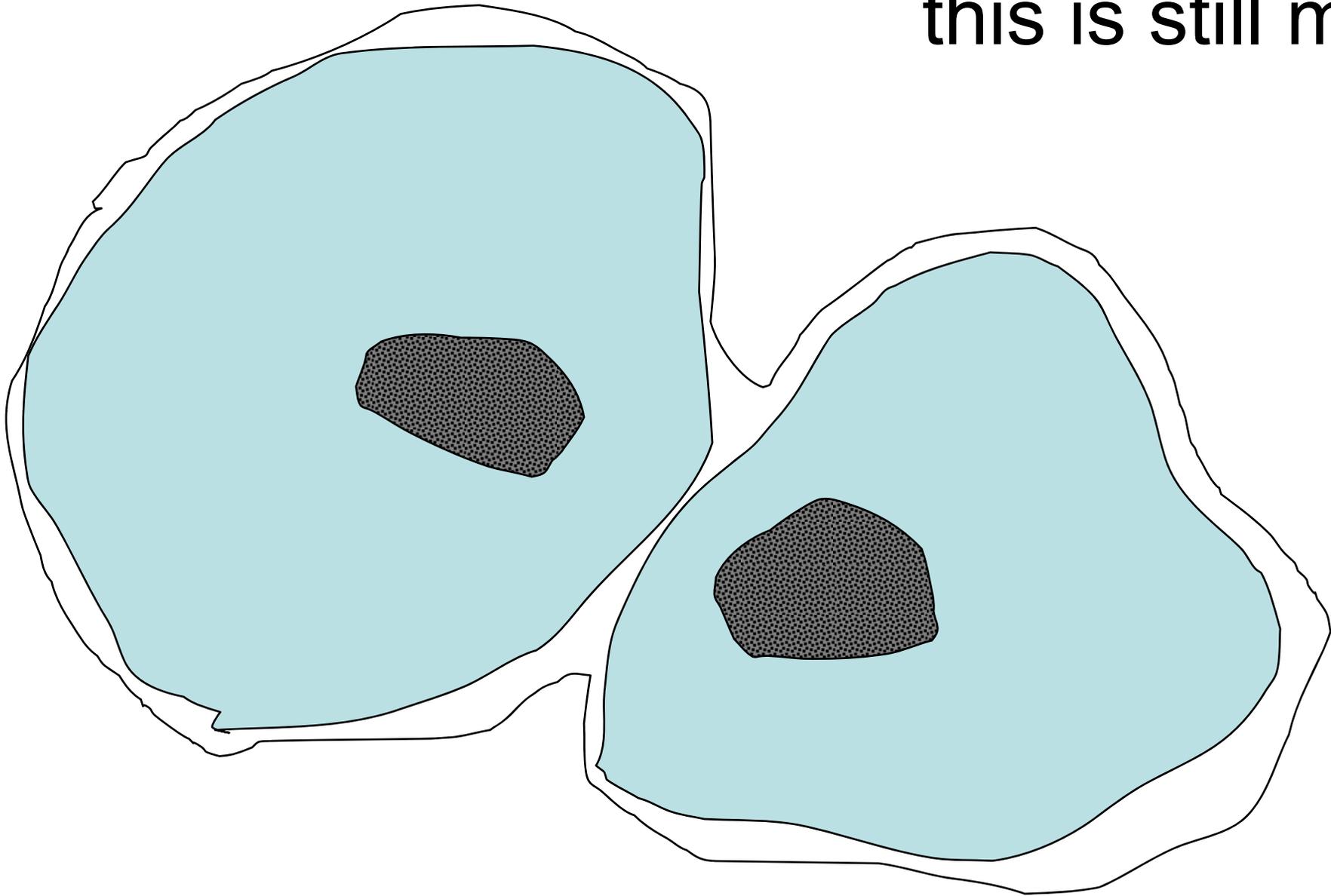


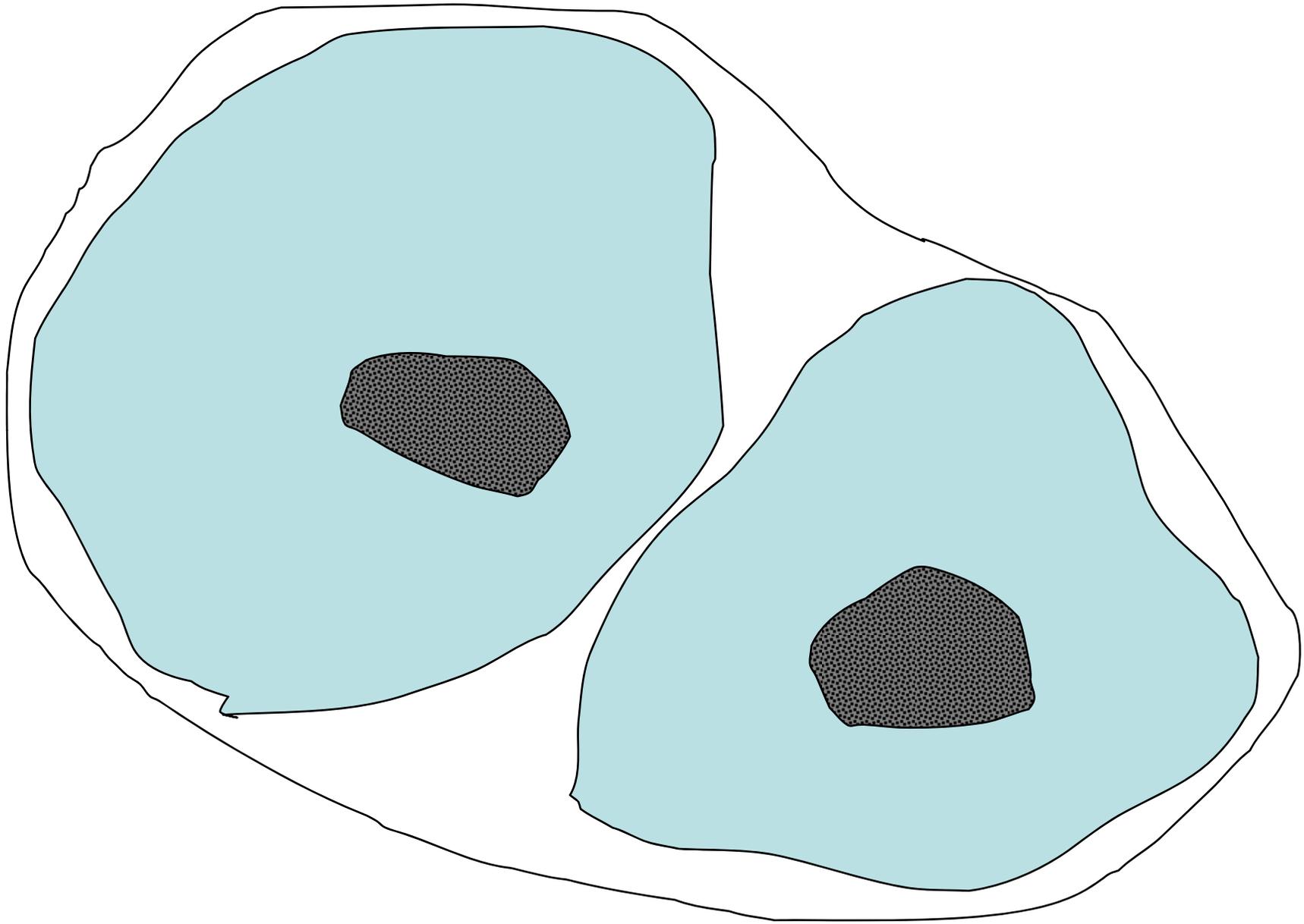
me

still me (all of it)



this is still me

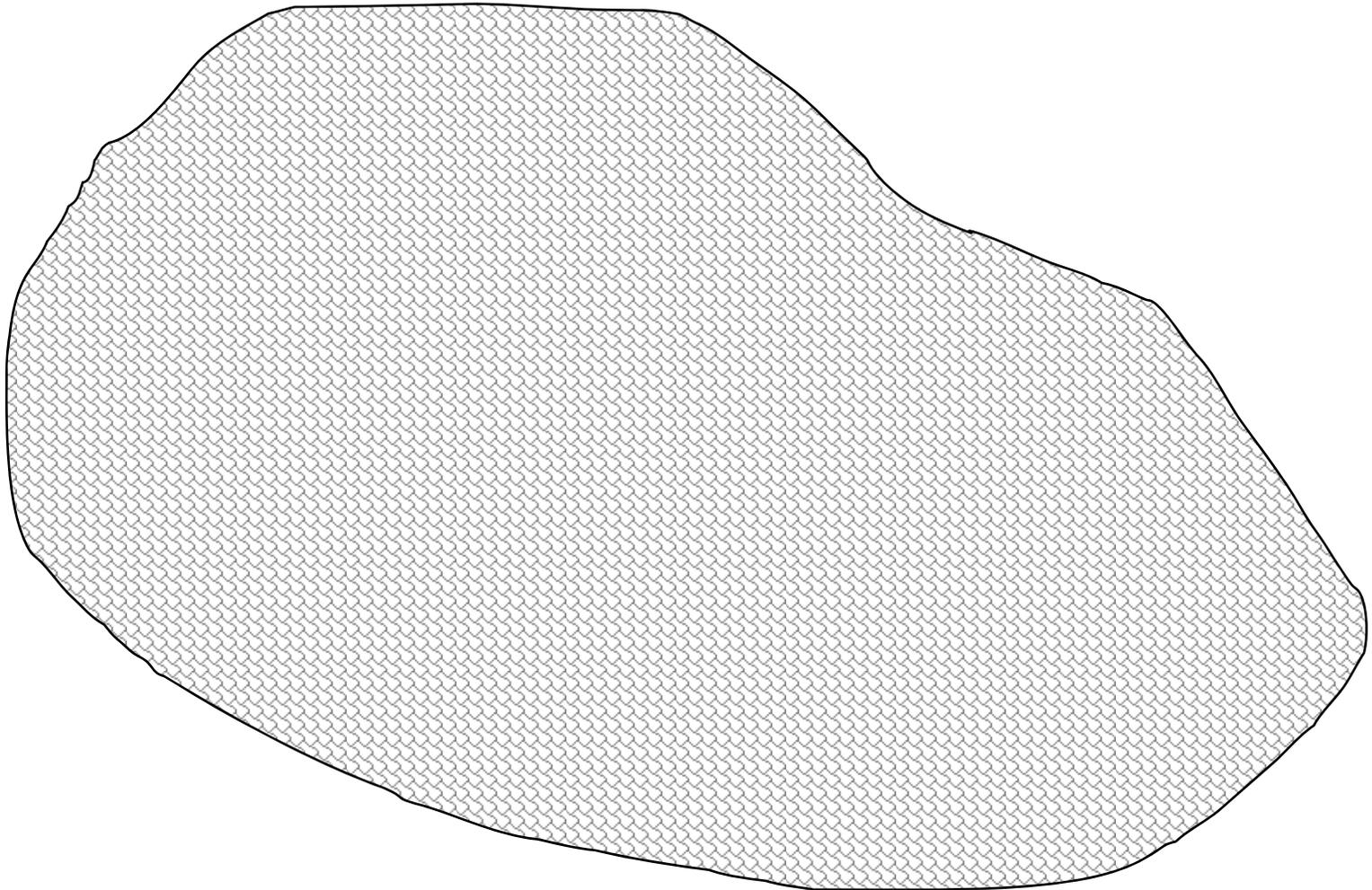




2 cells plus *zona pellucida*

This is still me:

I was once a whole blastula (60 cells)



Methodology for determining
which if these two accounts of
organism formation is correct

What are the criteria which an entity must
satisfy to be an organism?

First criterion

An organism must be an independent
continuant.

More specifically it must be what Aristotle
referred to under the term 'substance'

(= a maximally self-connected independent
continuant)

Conditions on Substance

1. Each substance is an entity which persists through time and remains numerically one and the same
2. Each substance is a bearer of change. (John is now warm, now cold)
3. Each substance is extended in space (The spatial parts of John are, for example, his arms and legs, his cells and molecules.)
4. Each substance possesses its own complete, connected external boundary
5. Each substance is connected in the sense that its parts are not separated from each other by spatial gaps. (Substances are thereby distinguished from heaps or aggregates of substances) (Exceptions: blood cells, immune system parts)
6. Each substance is an independent entity (Contrast: smiles, blushes)

Second criterion

An organism must be a relatively isolated causal system

Conditions on Relatively Isolated Systems

7. The external boundary of the entity is established via a physical covering (for example a membrane)
8. The events transpiring inside this covering divide between those with characteristic magnitudes (of temperature, etc.) inside a spectrum of allowed values and those outside
9. The covering serves as shield to protect the entity from damaging causal influences
10. The entity contains its own mechanisms for maintaining sequences of events falling within the spectrum of allowed values (mechanisms of self-repair)

These two criteria are to a degree independent

A block of ice is a substance, but it is not a relatively isolated causal system.

An orbiting space-ship, with its sophisticated mechanisms for self-repair, is both a substance and a causally isolated system.

Siamese twins may be one substance, but two causally isolated systems.

An amoeba is both a substance and a causally isolated system yet still *divisible*

Being a relatively isolated causal system is realized to different degrees by different entities.

Being a substance is realized always to the same degree: either wholly or not at all.

All substantial change is (practically) instantaneous.

Substantial change

two drops of water flow together and
become one

an ameoba splits and becomes two

‘Substance’ has to do with existence and structure. ‘Causal system’ has to do with function and functioning.

Being a relatively isolated causal system is often realized through modules organized hierarchically (nesting).

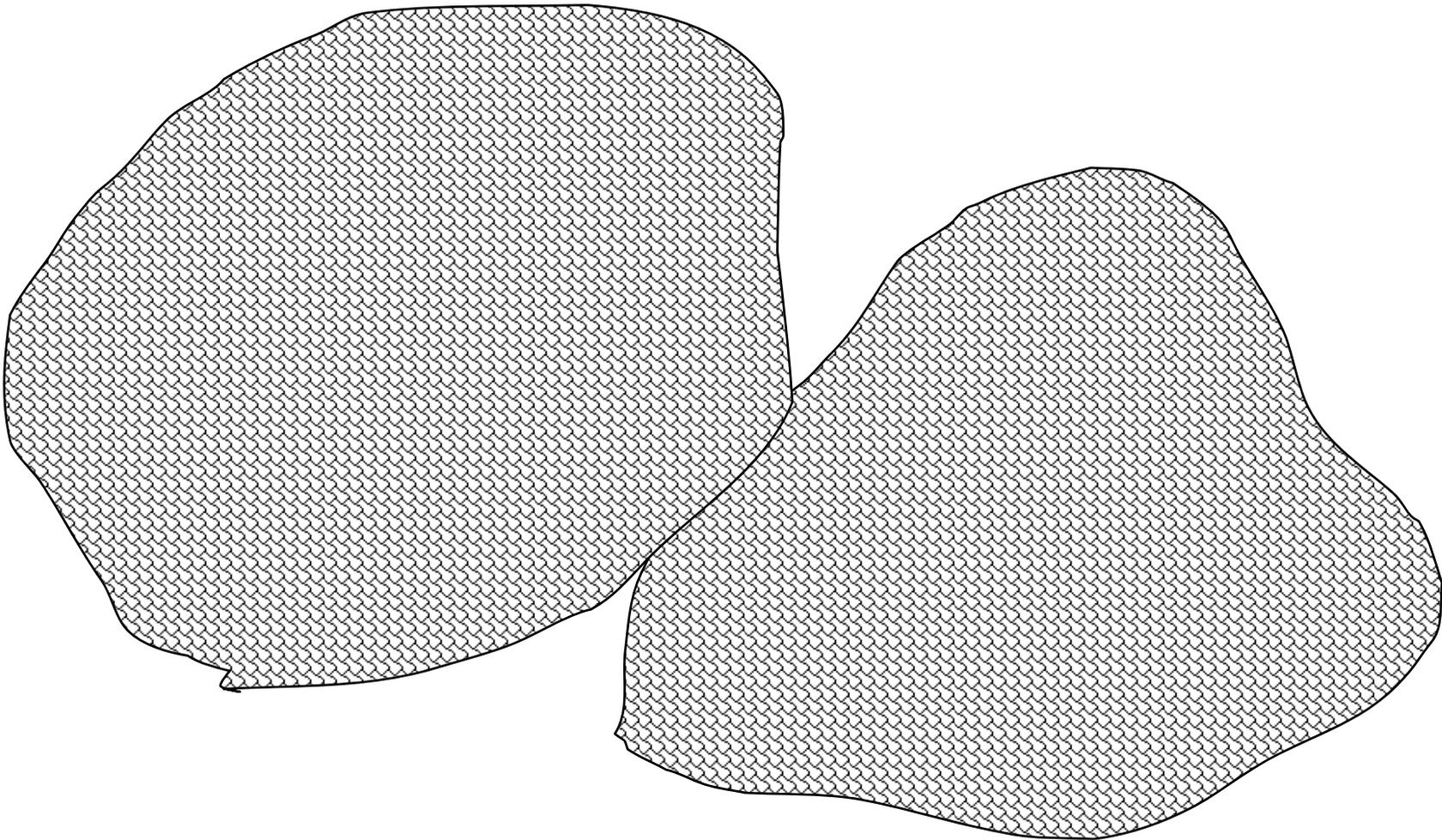
Thus functions, too, are often organized modularly.

Was I ever a blastula? (a whole blastula?)

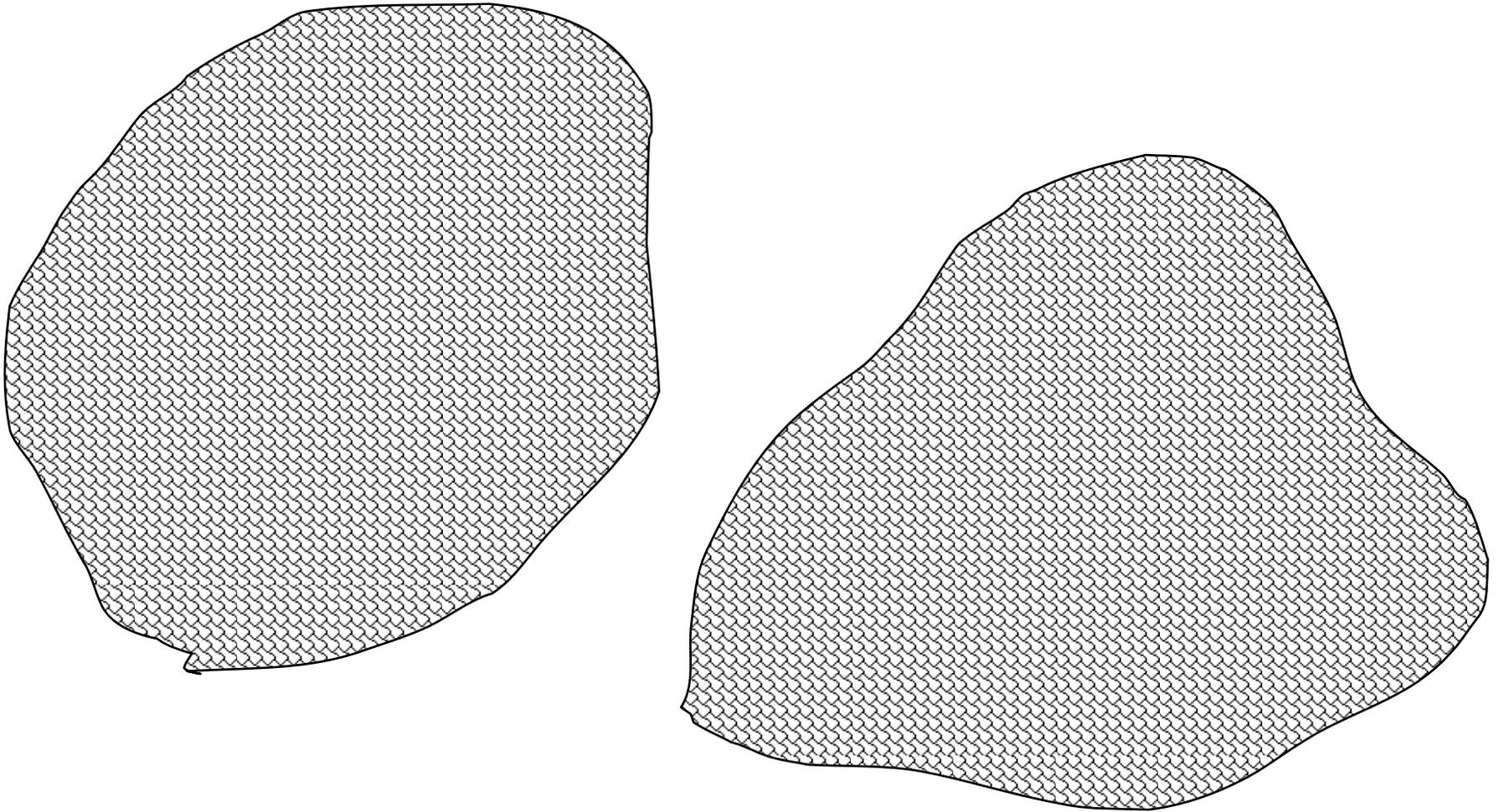
The blastula is **a single substance**: its cells together form a connected whole with a common physical boundary

But it lacks its own internal mechanisms in virtue of which its several parts would in case of disturbance work together as a whole to restore stability

If I was ever a blastula then I am such that it was once possible that *this* happened to me



blastulae are subject to division
(twinning)



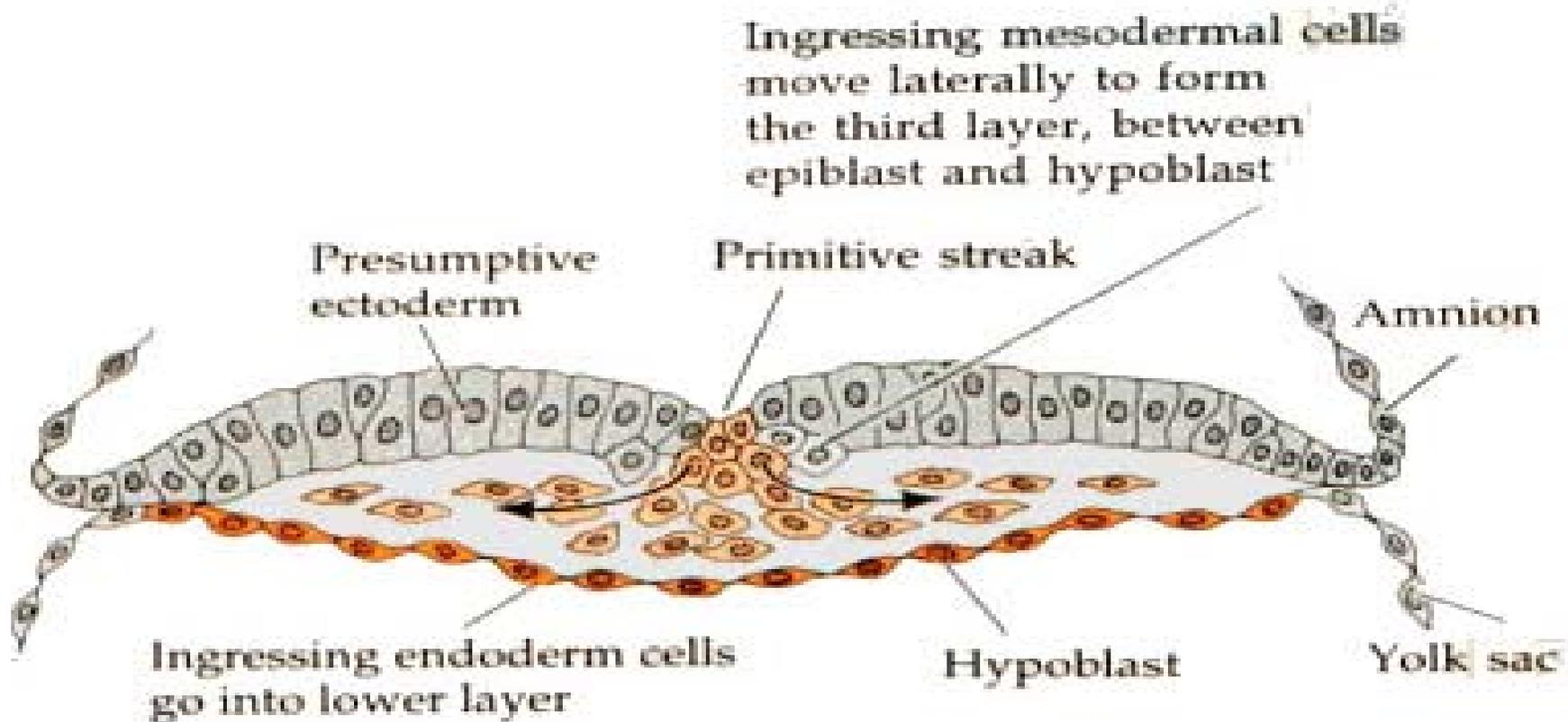
Gastrulation (Day 16)

Hypothesis: Gastrulation transforms the blastula from a putative cluster of cells into a single heterogeneous entity—a whole multicellular individual living being which has a body axis and bilateral symmetry and its own mechanisms to protect itself and to restore stability in face of disturbance.

Lewis Wolpert

“It is not birth, marriage or death, but gastrulation, which is truly the most important event in your life.”

Gastrulation



Gastrulation is analogous to the transformation of a mass of copper threads into a single integrated circuit

Neurulation (begins day 16)

transforms the gastrula by establishing the beginning of the central nervous system.

= a second nd massive migration of cells and topological folding and connecting and subsequent cell specialization yielding the neural tube

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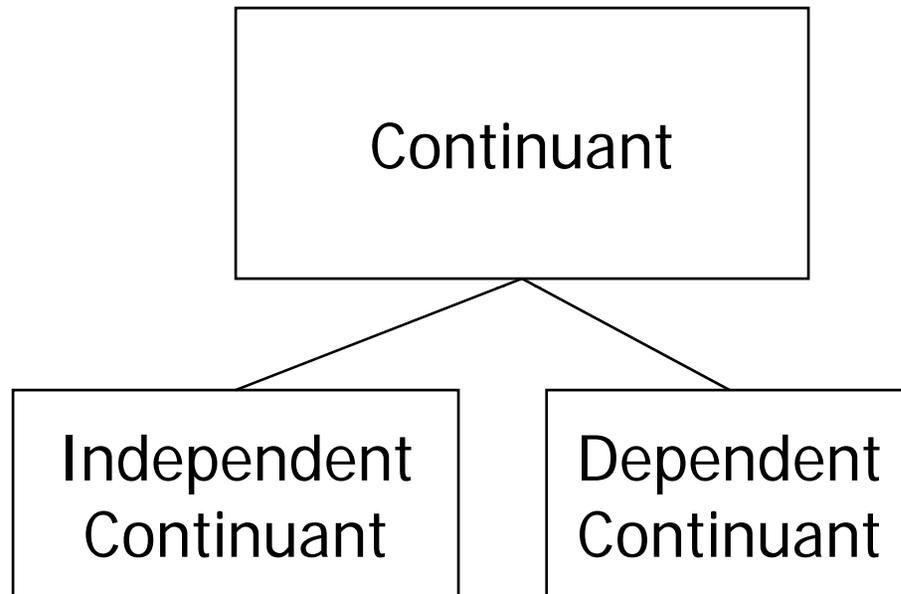
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- j. viability (around day 130)
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- l. quickening (around day 150)
- m. birth (day 266)
- n. the development of self-consciousness (some time after birth)

Further reading

Barry Smith and Berit Brogaard, “Sixteen Days”, *The Journal of Medicine and Philosophy*, 28 (2003), 45–78.

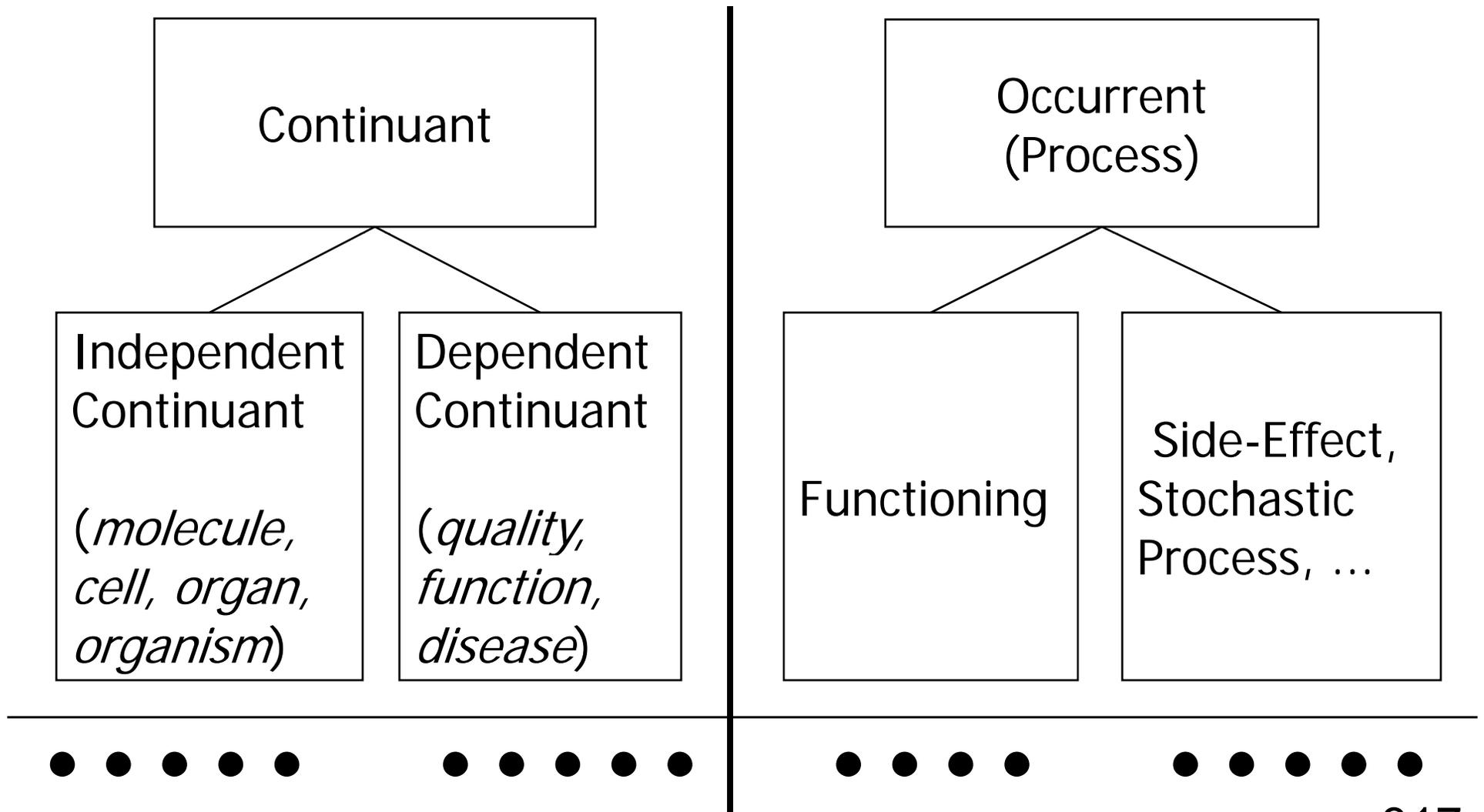
<http://ontology.buffalo.edu/smith/articles/embryontology.htm>

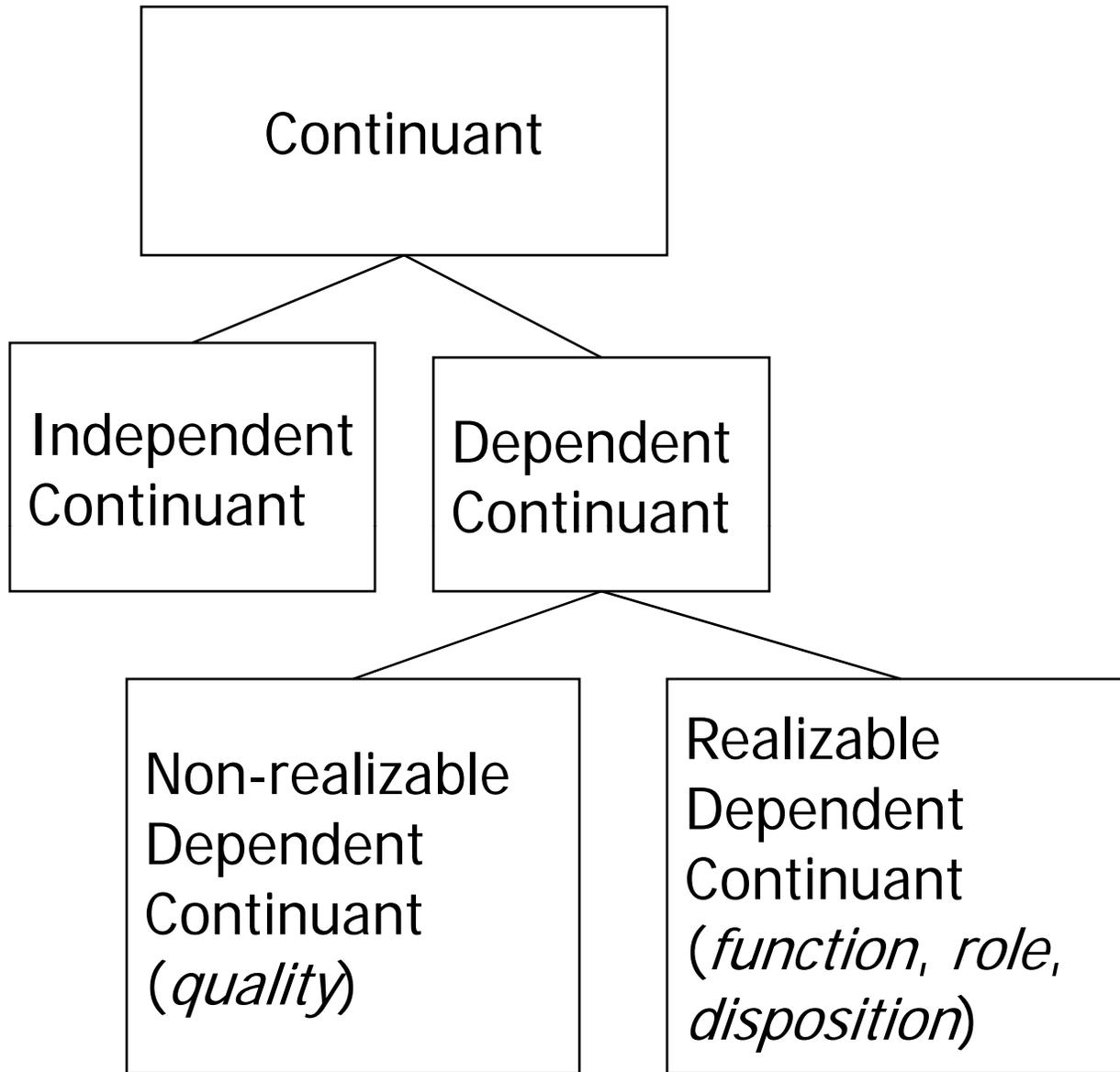
What is a function?



Occurrent
(always dependent
on one or more
independent
continuants
= participants)

BFO





the function of a screwdriver
the function of a heart

roughly: functions are beneficial
dispositions hard-wired into an entity

(a) by its maker

(b) by evolution

What is a disposition?

An object has a disposition to *M* when *C*
=def. it is physically structured in such a
way that it *Ms* when *C*.

e.g. An object has a disposition to shatter when
dropped

A disposition is a realizable dependent continuant

The process of shattering is the *realization* of the
disposition we call 'fragility'

The parts of the organism have functions

They are designed to ensure that the events transpiring inside the organism remain within the spectrum of allowed values and to respond when they move outside this spectrum of allowed values

What is a biological function?

First proposal: an entity x has a biological function if and only if x is part of an organism and has a disposition to act reliably in such a way as to contribute to the organism's survival

the function *is* this disposition

e.g. your heart is disposed to pump blood

Problem of aging and death

are there parts of the organism involved in bringing about or responding gracefully to aging processes?

is *this* their function?

Problem of reproductive organs

some organisms are such that the exercise of their reproductive organs brings death

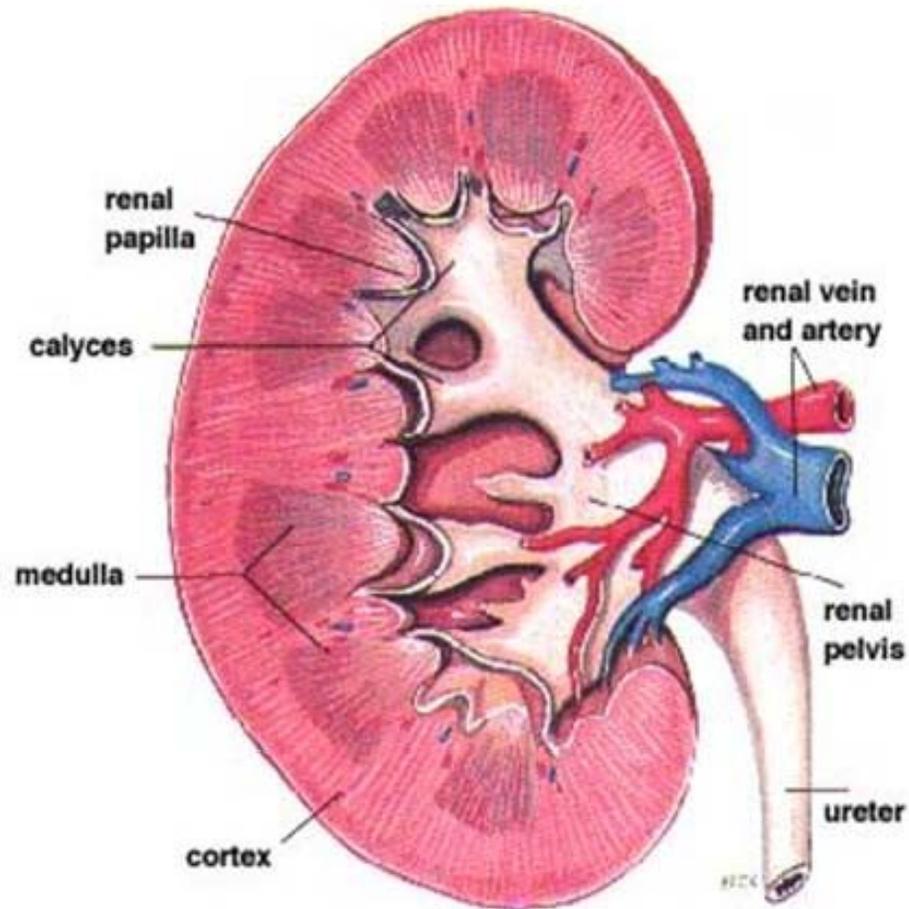
Perhaps: an entity has a biological function if and only if it is part of an organism and has a disposition to act reliably in such a way as to contribute to the **group's** survival?

seems too remote – think of my left upper molar

Functions are organized in modular hierarchies

The function of each functional part is: *to contribute to the functioning of the next larger whole*

We need to understand 'function' in relation to the immediate environing whole of the part in question. From this perspective the group seems structurally too far away

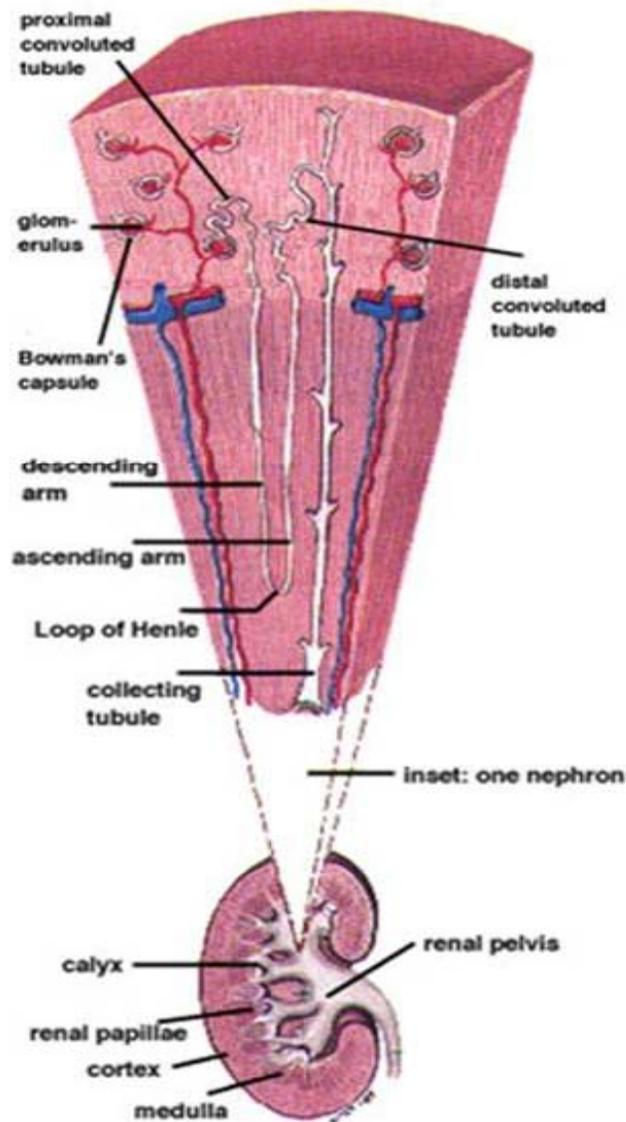


The function of the kidney is to purify blood

The *nephron* is the cardinal functional unit of the kidney

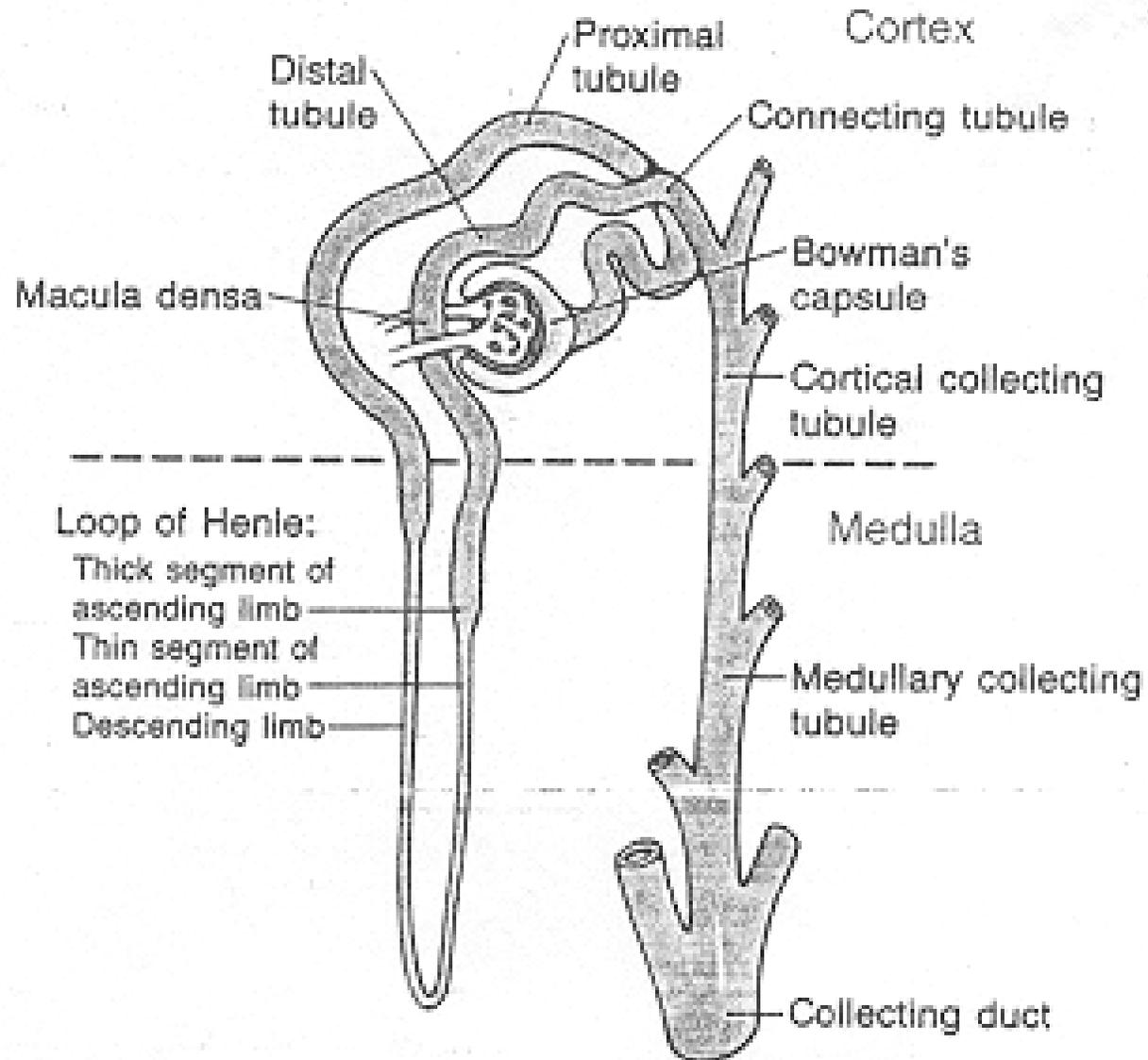
Functions

- to regulate the concentration of water and soluble substances like sodium salts in the blood
- to eliminate wastes from the body
- to regulate blood volume and pressure
- to control levels of electrolytes and metabolites
- to regulate blood pH



functional segments within the nephron

15 different cell types



... an entity has a biological function if and only if it is part of an organism and has a disposition to act *reliably* in such a way as to ...

Function is what gives rise to *normal* activity

Normality \neq statistical normality

That sperm exercise their function (to penetrate an ovum) is *rare*

That human adults have 32 teeth is *rare*

Functions and Malfunctionings

This is a screwdriver

This is a good screwdriver

This is a broken screwdriver

This is a heart

This is a healthy heart

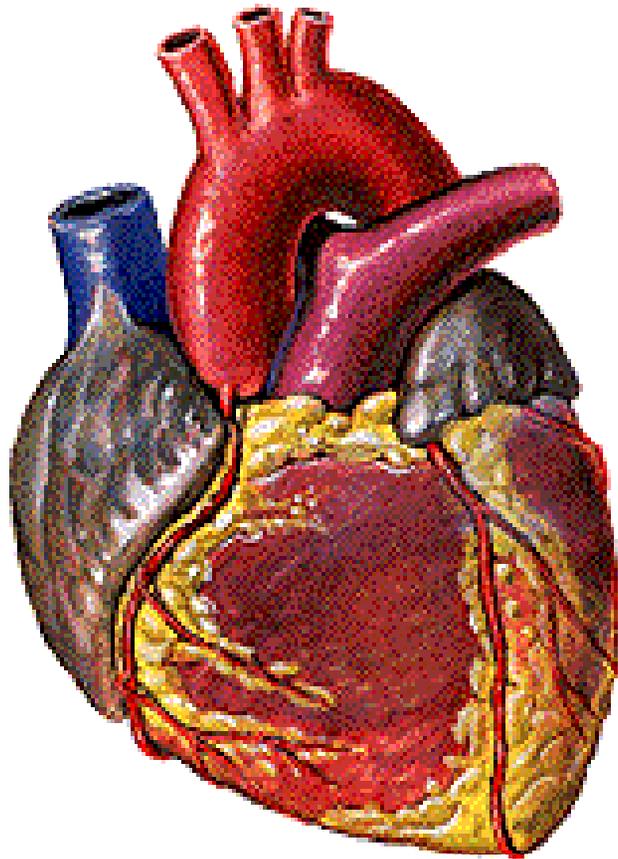
This is an unhealthy heart

Functions are associated with certain characteristic *process shapes*

Screwdriver: rotates and simultaneously moves forward simultaneously transferring torque from hand and arm to screw

Heart: performs a contracting movement inwards and an expanding movement outwards

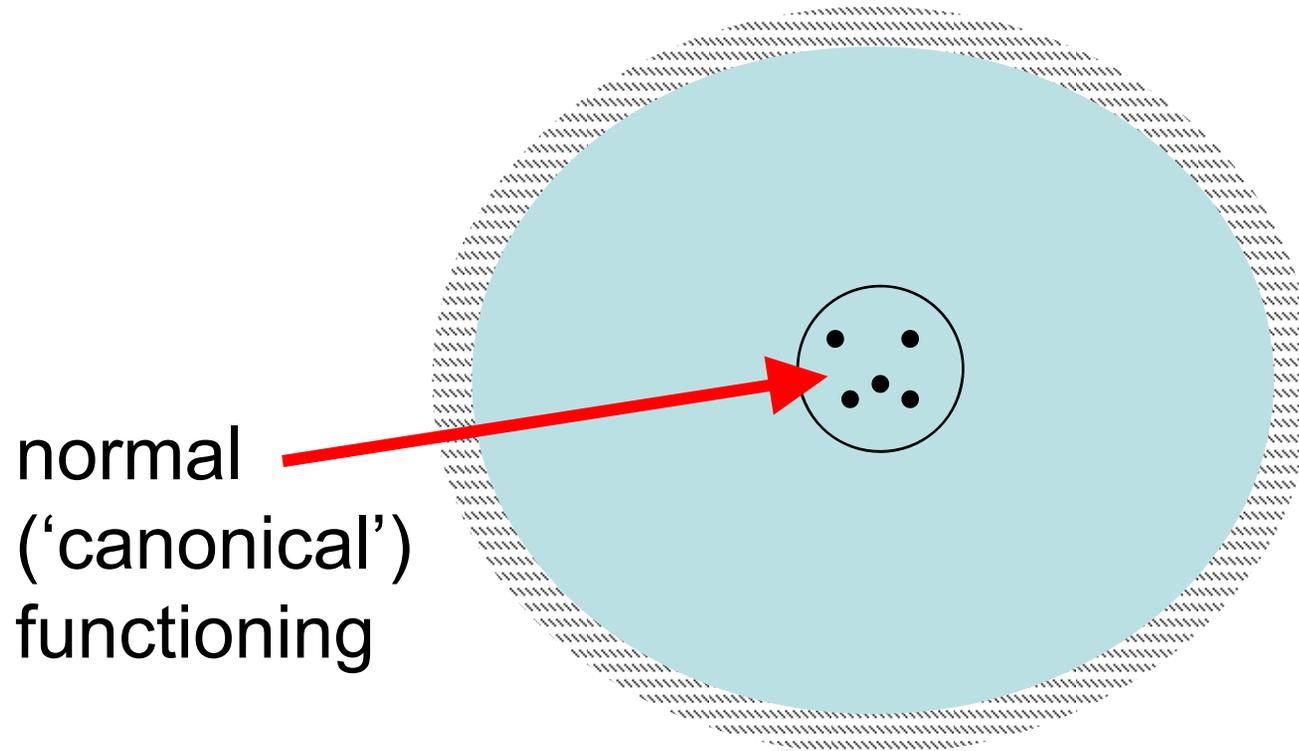
Functions and Prototypes



In its functioning, a heart creates a four-dimensional process shape.

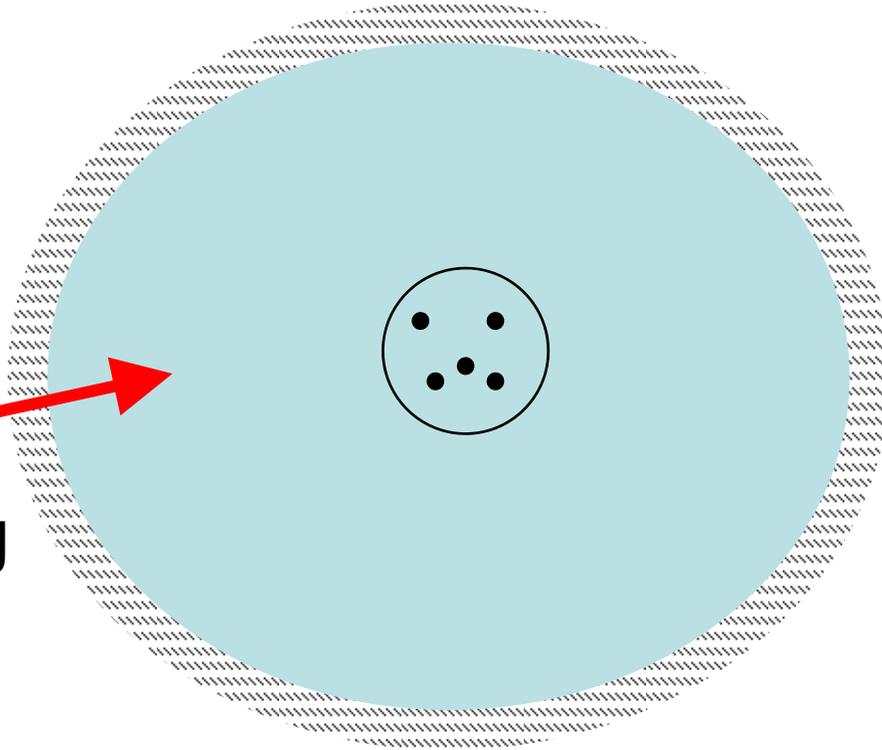
Good hearts create other process shapes than sick hearts do.

Prototypes

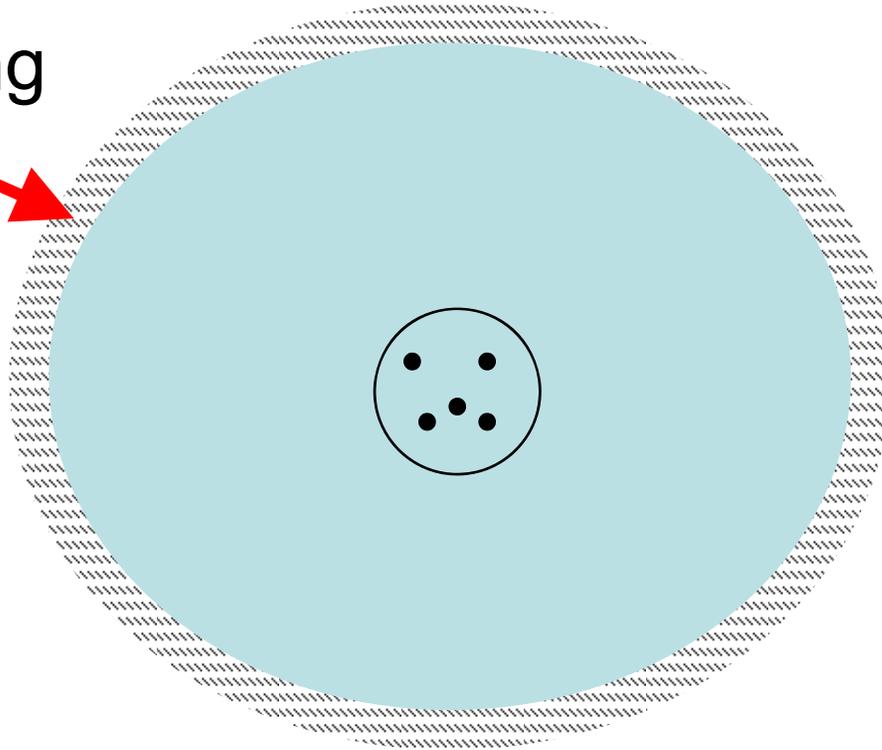


Map of process shapes

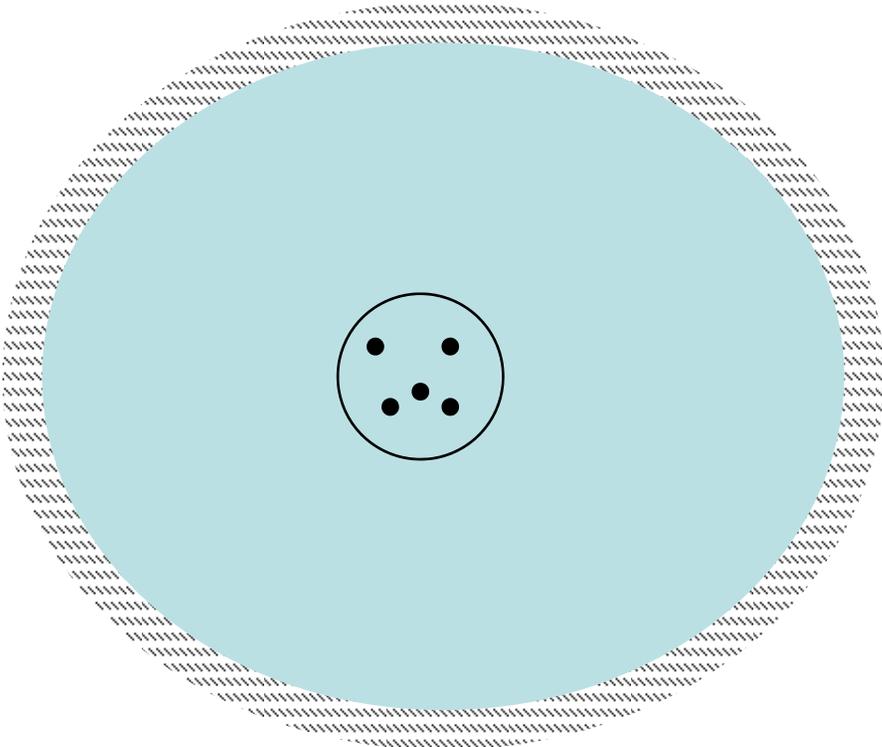
poor
functioning



malfunctioning



not
functioning
at all



Not functioning at all

leads to **death**, *modulo*

internal factors:

- plasticity

- redundancy (2 kidneys)

- criticality of the system involved

external factors:

- prosthesis (dialysis machines, oxygen tent)

- special environments

- assistance from other organisms

What is health?

Boorse: the state of an organism is theoretically healthy, i.e., free from disease, in so far as its mode of functioning conforms to the natural design of that kind of organism

What clinical medicine is for

to eliminate malfunctioning by fixing broken body parts

(or to prevent the appearance of malfunctioning by intervening, e.g. at the molecular level, before the breaks develop)

What, then, is function?

The Gene Ontology

represents only what is normal in the realm of (molecular) functioning

= what pertains to normal ('wild type') organisms (in all species)

The Gene Ontology is a canonical ontology

The GO is a canonical representation

“The Gene Ontology is a computational representation of the ways in which gene products normally function in the biological realm”

Nucl. Acids Res. 2006: 34.

The Foundational Model of Anatomy

a representation of canonical anatomy

a representation of universals, and relations between universals, deduced from the qualitative observations of the *normal* human body, the structure generated by the coordinated expression of the organism's own structural genes

Model organisms

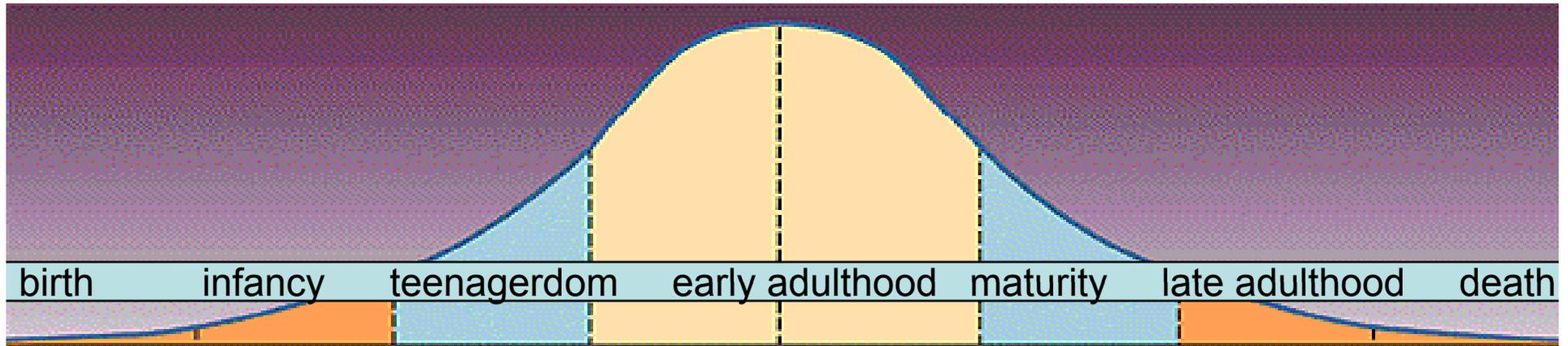
you can buy a mouse with the prototypical mouse *Bauplan* according to a precise genetical specification

A solution to the problem of defining function

For each type of organism there is not only a canonical *Bauplan*, but also a canonical life plan (canonical life *Gestalt*)

= the physiological counterpart of canonical anatomy

the canonical human life (plan)



For all animals the canonical life plan includes:

- canonical embryological development
- canonical growth
- canonical reproduction
- canonical aging
- canonical death

For humans

first, mewling and puking

then creeping like snail unwillingly to school

then sighing like furnace with woeful ballad made to
his mistress' eyebrow

then a soldier full of strange oaths

then justice in fair round belly

then the lean and slipper'd pantaloon

then second childishness and mere oblivion, sans
teeth, sans eyes, sans taste, sans everything.

As You Like It, II.vii.139-166

Family	Work	Money
Adoption Aging Birth Child care Death Disability Divorce Domestic Violence Driving Elder Care Empty Nesting Health Illness Kids Marriage Parenting Retirement Schooling Teenagers Travelling	Employment Injury Job Seeking Re-employment Small Business Self-employment Telecommuting Unemployment Volunteering Workplace Violence	Bankruptcy Budgeting Charitable Contributions College Credit Disasters Home Improvement Home Purchase Home Selling Insurance Investing IRS Audit Lawsuits Mortgage Property Renting Saving Taxes Trusts Wills

What does every human canonical life involve?

9 months of development

...

cycles of waking, sleeping; eating and not
eating; drinking and not drinking

...

death

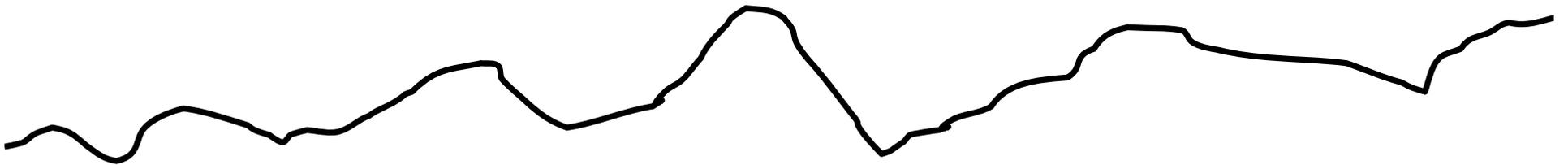
Iberall and McCulloch 20 action modes:

<u>Action Modes</u>	<u>% of time</u>
Sleeps	30
Eats	5
Drinks	1
Voids	1
Sexes	3
Works	25
Rests (no motor activity, indifferent internal sensory flux)	3
Talks	5
Attends (indifferent motor activity, involved sensory activity)	4
Motor practices (runs, walks, plays, etc.)	4
Angers	1
Escapes (negligible motor and sensory input)	1
"Anxioius-es"	2
"Euphorics"	2
Laughs	1
Aggresses	1
Fears, fights, flights	1
Interpersonally attends (body, verbal or sensory contact)	8
Enviess	1
Greeds	1

Total:

100% +/- 20% of time involvement

Water balance (from hour to hour)



Water balance (in the long run)

What does “function” mean?

Initial version:

an entity has a biological function if and only if it is part of an organism and has a disposition to act reliably in such a way as to contribute to the organism's survival

Improved version

an entity has a biological function if and only if it is part of an organism and has

a disposition to act reliably in such a way as to contribute to the organism's realization of the canonical life plan for an organism of that type

What is disease?

functions are, roughly, good dispositions relevant to the realization of the canonical life plan for an organism of the relevant type

diseases are (even more roughly) counterpart bad dispositions

