AN INTRODUCTION TO
BIOMEDICAL ONTOLOGY 2
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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
Agenda

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)

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


http://ontology.buffalo.edu/smith/articles/embryontology.htm
What is a function?

Continuant

Independent Continuant

Dependent Continuant

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

Continuant

Independent Continuant
(molecule, cell, organ, organism)

Dependent Continuant
(quality, function, disease)

Occurrent
(Process)

Functioning

Side-Effect, Stochastic Process, …
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

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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 ≠ 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

normal ('canonical') functioning
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
<table>
<thead>
<tr>
<th>Family</th>
<th>Work</th>
<th>Money</th>
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<tbody>
<tr>
<td>Adoption</td>
<td>Employment</td>
<td>Bankruptcy</td>
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<td>Aging</td>
<td>Injury</td>
<td>Budgeting</td>
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<td>Birth</td>
<td>Job Seeking</td>
<td>Charitable Contributions</td>
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<td>Child care</td>
<td>Re-employment</td>
<td>College</td>
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<td>Small Business</td>
<td>Credit</td>
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<td>Self-employment</td>
<td>Disasters</td>
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<td>Divorce</td>
<td>Telecommuting</td>
<td>Home Improvement</td>
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<td>Domestic Violence</td>
<td>Unemployment</td>
<td>Home Purchase</td>
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<td>Volunteering</td>
<td>Home Selling</td>
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<td>Workplace Violence</td>
<td>Insurance</td>
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<td>IRS Audit</td>
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<td>Lawsuits</td>
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<td>Kids</td>
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<td>Marriage</td>
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<td>Renting</td>
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<td>Retirement</td>
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<td>Saving</td>
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<td>Schooling</td>
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<td>Taxes</td>
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<tr>
<td>Teenagers</td>
<td></td>
<td>Trusts</td>
</tr>
<tr>
<td>Travelling</td>
<td></td>
<td>Wills</td>
</tr>
</tbody>
</table>
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:

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

_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