What is Life - Science Festival version. Comprehensive notes to accompany the slides.
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1) The illustration behind the title is a realistic scientific artists's impression, at the macro-molecular level, of a dividing cell. The artist is David Goodsell, and we will see more of his work later. Notice the cell membrane with its embedded proteins in blue and purple colours, the rope like strand of DNA being hauled through the narrowing division between cells, the ribosomes (large orange objects), reading (worm-like) RNA, translating it into new proteins. Real living cells are this packed with the complicated shapes of thousands of different proteins and other molecules. It seems chaotic, but life is extremely well organised engineering on this microscopic scale; and rather beautiful.

2) Indeed, at every scale you look, life is amazing and awe inspiring. It also poses a major challenge to scientific reductionism - the idea that every phenomenon, including our thoughts and feelings, can in principle be reduced to fundamental physics. Even the most humble bacterium seems to defy the laws of physics and this has led some physicists to claim that life indicates the need for new, as yet undiscovered laws of physics. Life remains a mystery, but it is one we are now feeling towards solving.

3) Of course no talk on the nature of life would be complete without Mr Spock, "It's life, Jim, but not as we know it", or more generally, as I have him saying "I am unable to define it, Captain". Developing a rigorous definition for life helps us understand it much better. What is it about life that is definitively different from non-life?

4) Most text books still try to define life using a list of properties, such as movement, growth and reproduction, etc. The problem with this is that many non-living things share those properties and some living things lack them. It also fails to pin down what life really is.

5) I am going to concentrate on these two because they are the most profound and discriminatory attributes (and we will see, the only definitive ones). Both indicate aspects of autonomy.

6) Autonomy is doing it for yourself, living by your own rules, being responsible for what you are and do and almost certainly involves making decisions and acting upon them.

7) To get to grips with autonomy we ask "why does a thing do what it does" - if the answer consists entirely of things beyond its control, then it is not autonomous. So we ask why is it cold inside the fridge? There are three kinds of answer: a) it is in its makeup to do that; b) it has control over that and c) it chose that from a set of options. Clearly with a fridge, a) is true by definition and b) indicates it possesses thermostatic self-control. Of course a fridge has no control over the way it was made, so is not at all constitutionally independent. But we have all heard of a self-made person, implying they are responsible for their own character.

8) Generalising, the three aspects of autonomy are a) *constitutional independence*, b) *cybernetic independence* and c) *cybernetic freedom* - the scope to choose from options

available to a self-controlling system. The question of autonomy is three-fold: to what extent did it make itself, to what extent does it decide for itself and how much scope for freedom of choice does it have.

9) I place these three aspects on a graph as axes of variation, emphasising that they are not all or nothing, each aspect is a gradation from no independence to total independence, on each axis. Actually, each axis can be quantified using a ratio, for example the degree of internal to external control.

10) So let us take self-control (cybernetic independence) first.

11) To compare an amoeba with a star in terms of homeostasis (internal control of conditions to maintain a healthy balance).

12) How is that achieved? In the star it is merely a natural balance between the imploding force of gravity and the exploding force of a perpetual nuclear explosion in the core. The star in no way manages this balance, it just happens. The amoeba is very different because it takes active control over its physiological balance (for example electrolyte balance), using a system entirely analogous to the thermostatic control of a fridge or central heating system. Detectors send information to a (cybernetic) control system which compares current levels with desired levels (the set-point) and sends an error correction signal to an actuator which takes appropriate action. This system of self-control, involving sensing, computation and deliberate action, is what we call *homeostasis*.

13) Clearly, the amoeba has it and the star does not. Stars are not alive.

14) Next let us focus on constitutional independence - the extent to which a thing is responsible for its own make-up.

15) Just to remind you - this is a comparison between a coral and a fire.

16) True self-making would mean being able to marshal all the material and organisational resources necessary to reproduce yourself. In the case of fire, there are just three components - fuel, oxygen and heat. What appear to be baby fires, born of the wider parent fire (here in the recent tragedy of Californian wild-fires) are started by the contribution of heat alone from the parent fire - they have the fuel and oxygen already provided. Two of the three needed components are externally provided. You may think that too trivial, so take the example of a computer virus, which replicates through a computer network as malware. At first glance, it is self-replicating, but that is because we are overlooking its total dependence on both the hardware and the software of the computers and their network for reproduction. By far the largest part of the necessary components are externally provided and this does not qualify as self-replication.

17) So I can cross off the fire and many other supposed examples of self-replication, but we know for sure that corals and indeed all living things do self-replicated.

18) To be fair, the computer virus was making an important step in the right direction, so let us ask if, in principle, an engineered system could be truly self-replicating. This was a hot topic during the second half of the 20th century.

19) A good place to start is this modern digitally controlled automatic milling machine, which is almost a universal fabricator of component parts. It could be programmed to make its own components. (CNC stands for computer numerical control).

20) The control system is critical and in particular its need to follow instructions given to it from an external source, e.g. computer encoded technical drawing (CAD).

21) That is, the CNC machine needs a design blueprint to follow, else it does not know what to do.

22) Therefore, if it is to replicate itself (autonomously) it must have its own internal copy of the designs of all its parts and how they are put together. This self-describing blueprint must be a part of the machine that is to replicate itself, so the blueprint has to be replicated as well. In other words, the blueprint must include the machine *including its blueprint*.

23) The blueprint must contain a copy of the blueprint, which must contain a copy of the blueprint …. add infinitum. This is termed an *infinite regress* and it defies logic.

24) The brilliant mathematician John Von Neumann worked out the solution to this conundrum. Essentially it cannot be done and the machine has to have a separate copy of its template (equivalent to blueprint). The meaning of separate is that it has to be purely information, not a physical part of the machine. That can be achieved if the blueprint is *encoded* in a way that isolates it from all the inner workings (does that idea remind you of anything?). (I show an implementation of the idea in a sort of computer code).

25) So here is how a machine could replicate itself, following Von Neumann's guide: first the machine reads its template to make a template-copier.

26) Then uses that template-copier to make a copy of its template.

27) Then using raw materials and reading its template, it fabricates and assembles a replica of itself.

28) Finally, it passes on the copy it made of the template to be used by the self-replica.

29) Of course, this process has been implemented in computer simulation - here is a nice example. It looks like a solid physical thing, but it is not. In fact all the coloured blocks here are pure information, represented by colour coded data - the whole thing is a computer simulation.

30) It is a purely cybernetic phenomenon - not physically embodied in matter. Doing that with embodied physical material is still too hard and nobody has even come close yet. That is important in comparison with life which does succeed, following Von Neumann's approach, using real physical material. Life is a physical embodiment of the Von Neumann self-replicator.

31) We already know how it manages that. The template is of course DNA - a recipe for life - and before splitting into two daughters, the mother copies her DNA using a copying machine that she has already made (out of bits of protein and RNA).

32) DNA is the recipe, the template and the blueprint … a gift passed from mother to daughter (chaps, note my comment on fathers).

33) Here we can see Von Neumann's idea as it is put into practice in every living cell. The South African Biochemist Jannie Hofmeyr worked this out, quite recently. He describes the process of self-making (the essence of replication) in terms of *material causes* (transforming material from one form to another by fabrication or assembly) and *efficient causes* (mostly catalysis in this case) - the doing of making. Start with nutrients, the raw material for a living cell. They can be fabricated into amino acids and nucleic acids - named chemicals that are the basic building blocks of proteins and RNA / DNA, respectively. These are assembled into specific polypeptides and nucleotide strings, which are then made into proteins and DNA or RNA by *folding* (tangling up in the right way). Now here is the really clever bit. To perform every one of the fabrication and assembly steps requires a component of the cell and that component is made by the fabrication and assembly process. For example making amino acids from nutrients requires metabolic enzymes, which are proteins made by fabricating amino acids. To make polypeptides the cell has to read instructions from RNA, which it does using *ribosomes* - little machines made from polypeptides and RNA. The RNA is made by other proteins acting on nucleic acids; proteins made by the ribosome that was made from the RNA that those proteins made.

In the end, you can see that everything makes everything else and following it round thinking in terms of cause and effect, every cause is caused by every other cause). This rather weird self-referential cycle is termed *closure to efficient causation*.

34) This idea turns out to be central to the difference between life and no-life. It is an extraordinary arrangement that we think only exists in living things and it is the most fundamental reason that life seems to defy physics (and even logic).

35) Being careful, we should understand that causes cannot really form a circle (if A causes B, then there must have been an A before B - chicken and egg). The answer is that the circle is really a spiral along the time-axis.

36) But this does have a profound logical consequence (to do with the chicken and egg paradox). It means that every living cell, every bacterium and every cell in your body and mine, the tree and the moss outside, all are great^n granddaughters of one particular great^n

grandmother cell. That cell, we call the last universal common ancestor (LUCA). Notice how the outer membrane, which continues to envelope the cell as long as it is alive, has never been broken, through all the billions of divisions leading from LUCA to a cell in your big toe. It has just kept stretching and budding into two parts, each containing a bit of the stuff (all those complicated molecules) that belonged to the mother. Of course we don't have any of the proteins or membrane of LUCA today - it has all worn out and been replaced many times over, like the proverbial favourite broom that had its head replaced three times and the handle replaced twice. But we are all - I mean all living things whatever the species - fragments of information from our LUCA, who likely was a primitive sort of bacterium.

37) Knowing this, and partly in search of the origins of life, scientists have made great efforts to synthesise a self-replicating cell: artificial life. So far we can make the membrane and rudimentary genetic material, but still need to use molecular machinery 'borrowed' from real life to make it work. So far, the closest to autonomously self-making cells are things like this - a *protocell* containing a relatively small RNA molecule that serves as both an enzyme for its own catalysis (RNA as the efficient cause of RNA) and the information template. RNA which can catalyse is called a *ribozyme* and the hunt is on for a ribosome that independently makes itself (a self-replicase). This has become 'the Holy Grail' of origin of life research.

38) Nobody has found it yet, but some are getting quite close. It is extremely remarkable that RNA can potentially catalyse its own fabrication and also provide the blueprint for the cell. Of course, artificial cells have been created in the lab, but these were made out of bits and pieces of real life, or synthesised direct copies. Here are two of the leading pioneers in the subject.

39) In summary, we can say that life is the only known system in the universe that can autonomously reproduce itself.

40) Because it follows the Von Neumann principle for self-replication, maintaining, reading and writing information in coded form, fabricating and assembling itself, it is computing using biochemistry as a substrate (as opposed to electrical charges in silicon-based semiconductor circuitry). Life is a process, not a thing. It is an algorithm that computes itself using biochemistry.

41) The essential components needed for that are all found in this very simple small bacterium (the most naturally stripped-down we have found). Notice the DNA strands, the ribosomes that translate the coded information into different proteins, such as the DNA binding proteins that help organise the flow and timing of information - all together implementing the algorithm. Notice also the membrane holding it all together and the embedded detectors and actuators that manage its internal chemistry: they will be the focus of the next part of the talk.

42) Recall that self-making (constitutional independence) is just one aspect of autonomy and the comparison between an amoeba and a star revealed that life also had cybernetic independence - the ability to actively control itself.

43) Living also means controlling yourself from within, determining what happens in defiance of the seemingly inevitable forces of cause and effect externally.

44) Biological autonomy includes deciding what to do and making it happen, independent of external processes and that appears as a violation of the basic notion of cause and effect. This is the second astonishing feature of life, which it shares with no other natural system.

45) Physical systems are supposed to follow simple laws, so they are predictable (excepting for randomness), hence if you throw a ball, its trajectory can be calculated: Newton's laws apply.

46) But as physicist Paul Davies points out, with consternation, if you throw a live bird in the air, there is no way to predict its trajectory. It seems to defy the laws of physics.

47) To understand why, note first that for every event, there is a prior cause. We label this event *e* at time *i* and attach it to its cause (the white arrow).

48) At any given time (*i*), there may be multiple events going on - labelled *e* - *f*, each with their prior cause.

49) The causes are earlier events - here they are…

50) Now labelled as occurring just before at time *i*-1 (notice one of these may be the cause of two or more later events).

51) We could, in principle, trace these chains of cause and effect all the way back to the 'big bang' - the primordial event at the beginning of the universe.

52) That's all very neat, but as soon as life enters into it, we see the appearance of events, seemingly without a prior cause. Events spontaneously appear directly from the living organism. This is termed *agent causation* and in standard physics it is not allowed.

53) Autonomy is causing this. The agent causation is in fact causation arising from within the organism, but where exactly and how?

54) Recall the closure to efficient causation - that circularity we saw in the processes of Hofmeyr's model of the living cell. It has a peculiar effect: it makes all the processes caught up in it into an organised whole that thereby gains *identity* so that its inside becomes distinct form outside.

55) In effect, those chains of cause and effect are formed into loops by closure to efficient causation.

56) Inside the loop it then becomes possible for a new cause to join the flow: the closed circularity makes that possible. Technically, it is because information is embodied within the loop and that information constrains the flow around the loop.

57) The source of this new cause is the set point for homeostatic (self)-control. It is *internalised* information with causal power, its cause is to determine the action (or not) of the actuator on the cell's surface, for example a controllable ion channel.

58) Cell boundaries keep all the parts of the organised whole together *inside* and anchor the sensors and actuators needed for a range of homeostatic control systems that maintain optimal conditions within the cell. We can now understand that they also form a causal boundary within which everything takes part in the loop; outwith the boundary lie the linear causal chains of familiar physics. The boundary causally isolates, leaving specialist detectors (transducers) to let the information through, whilst blocking the forces of causation. Outside are physical causes, inside are mere signals providing information about those causes.

59) The boundary of a cell is, at minimum, an amphiphilic oily bilayer. The sensory transducer physically changes when it detects what it is sensitive to and that change (often of its shape) triggers a biochemical response. What would have been physical cause followed by physical effect is now signal detection (perception) followed by response. The response signal can control an actuator, such as this G-protein coupled ion channel. The point is that the response is now determined, at least in part, by things within the cell.

60) Usually the detected signal is sent to biochemical control circuitry (computing in biochemical, rather than silicon-based components. The outcome of the computation determines the control signal sent to the actuator.

61) Computation is performed using proteins like this one, which acts as a logic-switch by changing shape at the functional end when it is stimulated by meeting a particular molecule on its (ligand binding) detection end.

62) Similarly, the set-point information is embodied in the details of the shape of particular molecules, sometimes singularly as in this case of a voltage-gated sodium channel, sometimes in complicated ways involving several interacting molecules.

63) This, then, is the foundation of the second major difference between life and non-life, that of cybernetic freedom, achieved by incorporating homeostasis. Note the major components, the set point, transducer, actuator and control computation and, of course, the boundary. These are only found in organisms (and now the tools we organisms make to extend our physical powers).

64) In summary, life is an algorithm that computes itself using biochemistry (hence reproduction), but also which controls itself, independently of physical chains of cause and effect, using homeostatic computational procedures on signals and responses within the

protective boundary. By transforming cause and effect into signal and response, it is able to exert its own will.

65) The will of life is very powerful, even on a planetary scale. Here is a comparison of Earth and Venus - sufficiently close and similar in planetary geology and relation to the sun that they ought not to be very different.

66) But the Earth is utterly different in physical and chemical conditions, mainly because life has dramatically transformed Earth’s atmosphere to be oxygen rich, removing almost all of the CO_2 greenhouse heat blanket, giving us a life-nurturing mean temperature of 15°C.

67) That manipulation is a sure sign of life - defying the laws of physics and taking control. Its ability to do that, to proliferate and change itself has led to the wonderful diversity and shear creative beauty we see in the world around us. Long may it continue!