Imperial College London

Synthetic Biology Overview

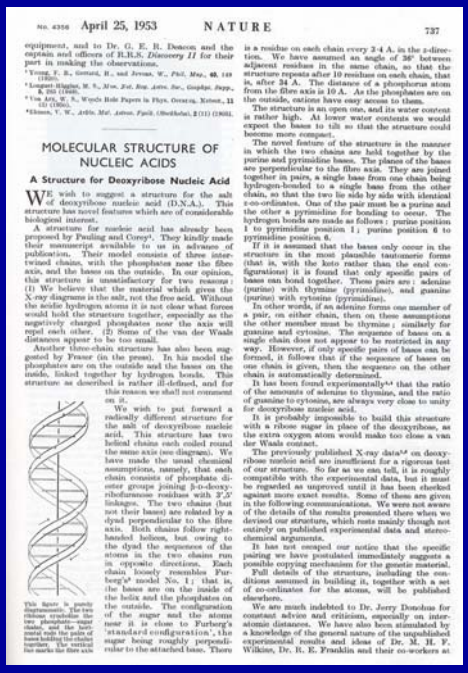
Foundation for Science and Technology 18th Nov 2009

Richard I Kitney

Chairman - The Imperial College Institute of Systems and Synthetic Biology

Co-Director of the EPSRC Centre for Synthetic Biology and Innovation

April 25th 1953



No. 4356 April 25, 1953 NATURE 737

equipment, and to Dr. G. E. R. Deacon and the captain and officers of R.R.S. *Discovery II* for their part in making the observations.

MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

WE wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

A structure for nucleic acid has already been proposed by Pauling and Corey[1]. They kindly made their manuscript available to us in advance of publication. Their model consists of three inter-twined chains, with the phosphates near the fibre axis, and the bases on the outside. In our opinion, this structure is unsatisfactory for two reasons: (1) We believe that the material which gives the X-ray diagrams is the salt, not the free acid. Without the acidic hydrogen atoms it is not clear what forces would hold the structure together, especially as the negatively charged phosphates near the axis will repel each other. (2) Some of the van der Waals distances appear to be too small.

Another three-chain structure has also been suggested by Fraser (in the press). In his model the phosphates are on the outside and the bases on the inside, linked together by hydrogen bonds. This structure as described is rather ill-defined, and for this reason we shall not comment on it.

We wish to put forward a radically different structure for the salt of deoxyribose nucleic acid. This structure has two helical chains each coiled round the same axis (see diagram). We have made the usual chemical assumptions, namely, that each chain consists of phosphate di-ester groups joining β-D-deoxyribofuranose residues with 3',5' linkages. The two chains (but not their bases) are related by a dyad perpendicular to the fibre axis. Both chains follow right-handed helices, but owing to the dyad the sequences of the atoms in the two chains run in opposite directions. Each chain loosely resembles Furberg's[2] model No. 1; that is, the bases are on the inside of the helix and the phosphates on the outside. The configuration of the sugar and the atoms near it is close to Furberg's 'standard configuration', the sugar being roughly perpendicular to the attached base. There is a residue on each chain every 3·4 A. in the z-direction. We have assumed an angle of 36° between adjacent residues in the same chain, so that the structure repeats after 10 residues on each chain, that is, after 34 A. The distance of a phosphorus atom from the fibre axis is 10 A. As the phosphates are on the outside, cations have easy access to them.

The structure is an open one, and its water content is rather high. At lower water contents we would expect the bases to tilt so that the structure could become more compact.

The novel feature of the structure is the manner in which the two chains are held together by the purine and pyrimidine bases. The planes of the bases are perpendicular to the fibre axis. They are joined together in pairs, a single base from one chain being hydrogen-bonded to a single base from the other chain, so that the two lie side by side with identical z-co-ordinates. One of the pair must be a purine and the other a pyrimidine for bonding to occur. The hydrogen bonds are made as follows: purine position 1 to pyrimidine position 1; purine position 6 to pyrimidine position 6.

If it is assumed that the bases only occur in the structure in the most plausible tautomeric forms (that is, with the keto rather than the enol configurations) it is found that only specific pairs of bases can bond together. These pairs are: adenine (purine) with thymine (pyrimidine), and guanine (purine) with cytosine (pyrimidine).

In other words, if an adenine forms one member of a pair, on either chain, then on these assumptions the other member must be thymine; similarly for guanine and cytosine. The sequence of bases on a single chain does not appear to be restricted in any way. However, if only specific pairs of bases can be formed, it follows that if the sequence of bases on one chain is given, then the sequence on the other chain is automatically determined.

It has been found experimentally[3,4] that the ratio of the amounts of adenine to thymine, and the ratio of guanine to cytosine, are always very close to unity for deoxyribose nucleic acid.

It is probably impossible to build this structure with a ribose sugar in place of the deoxyribose, as the extra oxygen atom would make too close a van der Waals contact.

The previously published X-ray data[5,6] on deoxyribose nucleic acid are insufficient for a rigorous test of our structure. So far as we can tell, it is roughly compatible with the experimental data, but it must be regarded as unproved until it has been checked against more exact results. Some of these are given in the following communications. We were not aware of the details of the results presented there when we devised our structure, which rests mainly though not entirely on published experimental data and stereochemical arguments.

It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.

Full details of the structure, including the conditions assumed in building it, together with a set of co-ordinates for the atoms, will be published elsewhere.

We are much indebted to Dr. Jerry Donohue for constant advice and criticism, especially on inter-atomic distances. We have also been stimulated by a knowledge of the general nature of the unpublished experimental results and ideas of Dr. M. H. F. Wilkins, Dr. R. E. Franklin and their co-workers at

We stand at the dawn of a new understanding of disease…

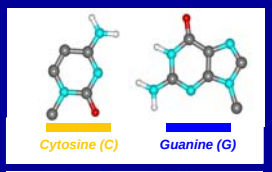
***Nature* 409, 860 - 921 (2001)**

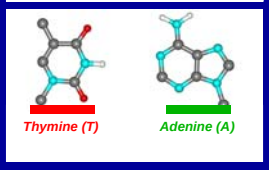
Initial sequencing and analysis of the human genome

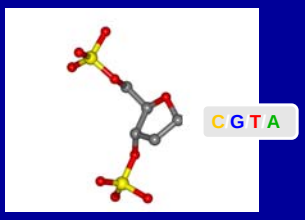
International Human Genome Sequencing Consortium

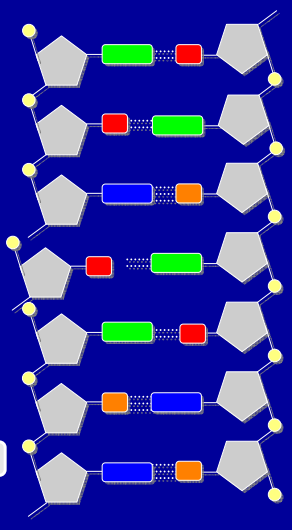
The human genome holds an extraordinary trove of information about human development, physiology, medicine and evolution. Here we report the results of an international collaboration to produce and make freely available a draft sequence of the human genome. We also present an initial analysis of the data, describing some of the insights that can be gleaned from the sequence.

DNA





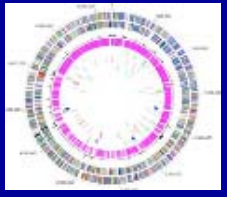




GCATGTAAGCA
GTTATAATGCG
TTATACGCTTA
GCGTTAGTTAT
AATGCGTGATA
CAGTTATAATG
CGATATACCAG
TTAGGATGCGT
TATACGCTGCA
GTTATAATGCG
GTCATAGTGCG
GCTATAATGCG

Reading the Genetic Code

- We can now read the genetic code which allows us to describe all the chemical parts that go into making a cell and organism
- This enables us to see how all of these components work together to form living organisms



Synthetic Biology

What is Synthetic Biology?

- Designing and making biological parts and systems that do not exist in the natural world using engineering principles

- Re-designing existing biological systems, again using engineering principles

- Or using engineering principles to build living organisms

Why now?

Why now?

- High speed DNA sequencing
- DNA synthesis
- Powerful computers
- Broadband networks
- The Internet
- The confluence of biology, engineering and physical science

What can be done with it?




Synthetic Biology

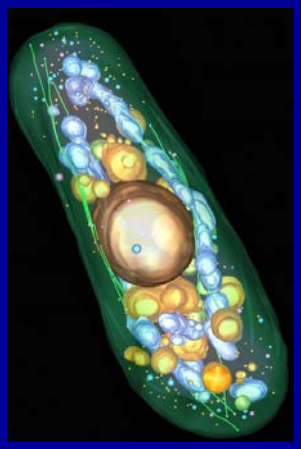
A Broad Church

- Bio nanotechnology
- Synthetic genomics
- Engineering

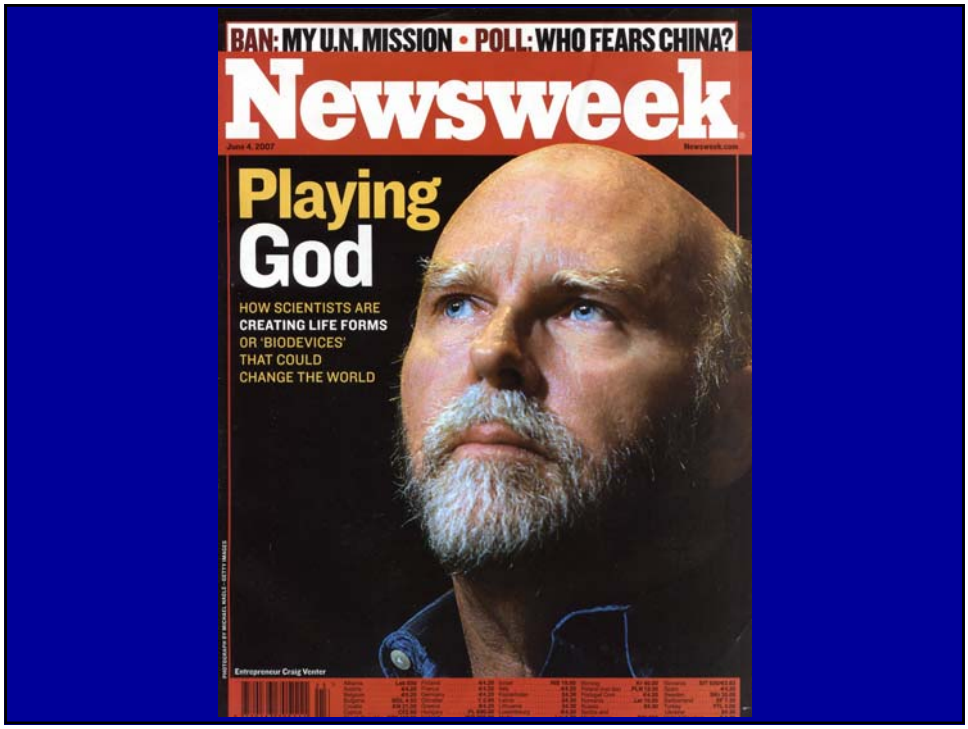
With Social Science and Ethics integrated part of the field

Four Approaches to Synthetic Biology

- Bottom Up
- Metabolic Engineering
- Chassis
- Parts, Devices and Systems



1. Bottom Up


BAN: MY U.N. MISSION • POLL: WHO FEARS CHINA?
Newsweek
Playing God
HOW SCIENTISTS ARE CREATING LIFE FORMS OR 'BIODEVICES' THAT COULD CHANGE THE WORLD
Entrepreneur Craig Venter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Science 29 February 2008:
Vol. 319. no. 5867, pp. 1215 - 1220
DOI: 10.1126/science.1151721
‹ Prev | Table of Contents | Next ›
RESEARCH ARTICLES
Complete Chemical Synthesis, Assembly, and Cloning of a Mycoplasma genitalium Genome
Daniel G. Gibson, Gwynedd A. Benders, Cynthia Andrews-Pfannkoch, Evgeniya A. Denisova, Holly Baden-Tillson, Jayshree Zaveri, Timothy B. Stockwell, Anushka Brownley, David W. Thomas, Mikkel A. Algire, Chuck Merryman, Lei Young, Vladimir N. Noskov, John I. Glass, J. Craig Venter, Clyde A. Hutchison, III, Hamilton O. Smith*
We have synthesized a 582,970–base pair Mycoplasma genitalium genome. This synthetic genome, named M. genitalium JCVI-1.0, contains all the genes of wild-type M. genitalium G37 except MG408, which was disrupted by an antibiotic marker to block pathogenicity and to allow for selection. To identify the genome as synthetic, we inserted "watermarks" at intergenic sites known to tolerate transposon insertions. Overlapping "cassettes" of 5 to 7 kilobases (kb), assembled from chemically synthesized oligonucleotides, were joined by in
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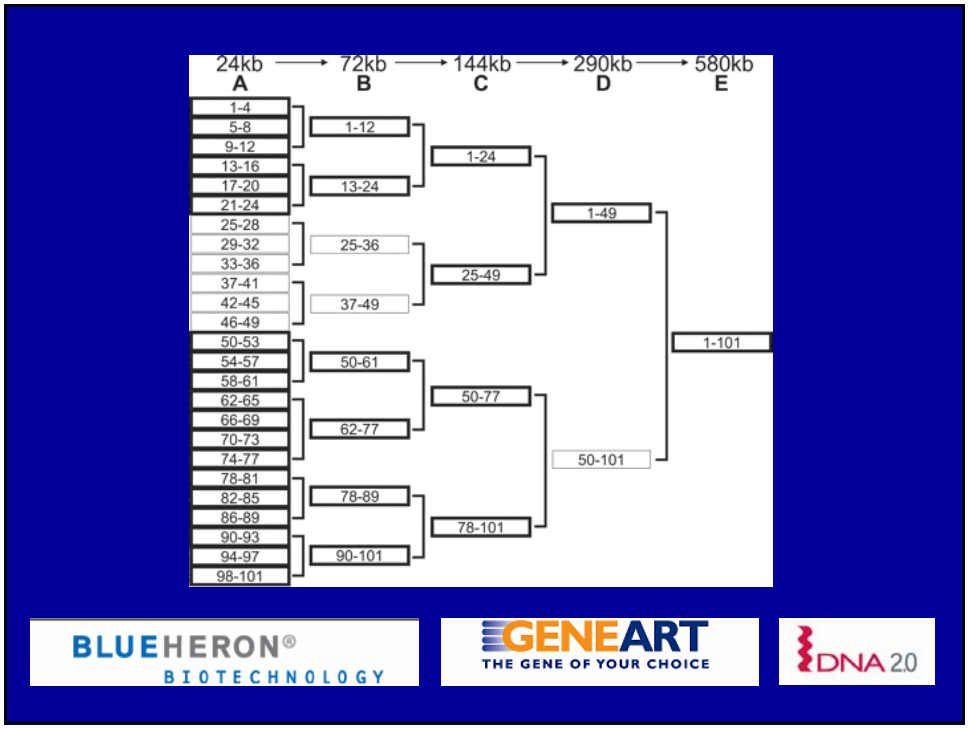


2. Metabolic Engineering

Malaria

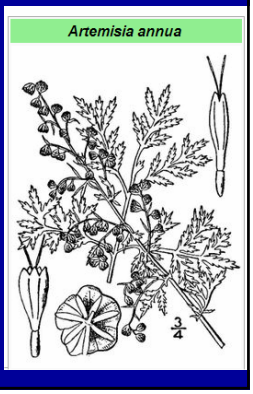
Artemisia

- Used by Chinese herbalists for more than 1000 years to treat Malaria
- 1972 - Tu Youyou discovered artemisinin in the leaves of the Artemisia Annua (annual wormwood)

Tu Youyou 屠呦呦 [sources / revisions]

Chief Research Fellow of the Institute of Chinese Traditional Medicines at the Chinese Academy of Traditional Chinese Medicine

Born: 1930



nature International weekly journal of science

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Letter

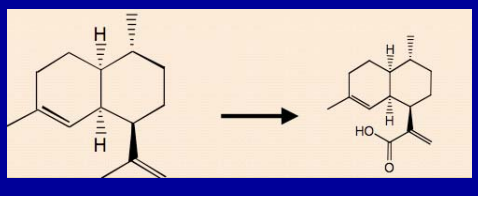
Nature **440**, 940-943 (13 April 2006) | doi:10.1038/nature04640; Received 22 December 2005; Accepted 9 February 2006

Production of the antimalarial drug precursor artemisinic acid in engineered yeast

Dae-Kyun Ro[1,7], Eric M. Paradise[2,7], Mario Ouellet[1], Karl J. Fisher[6], Karyn L. Newman[1], John M. Ndungu[3], Kimberly A. Ho[1], Rachel A. Eachus[1], Timothy S. Ham[4], James Kirby[2], Michelle C. Y. Chang[1], Sydnor T. Withers[2], Yoichiro Shiba[2], Richmond Sarpong[3] and Jay D. Keasling[1,2,4,5]

Making Complex Drugs

Anti-malarial drug Artemesinin



Amyris Biotechnologies

Institute for OneWorld Health

Making Biofuels

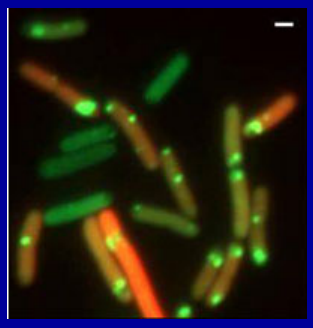
Engineering micro-organisms to make Bio-diesel

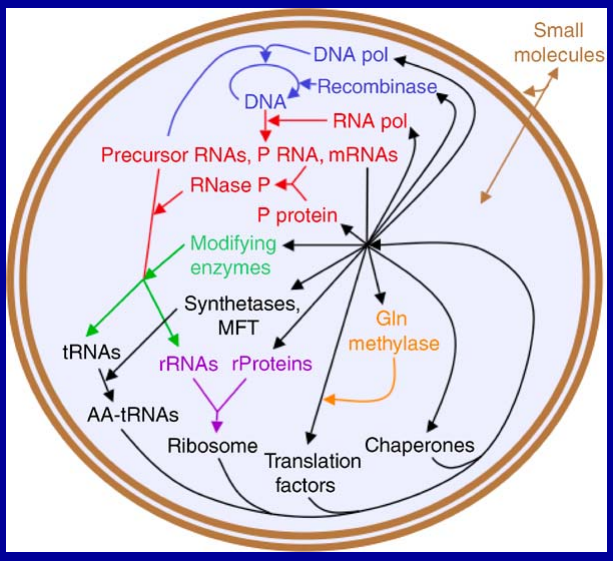
Using Green algae to convert CO_2 to Bio-diesel using sunlight

3. Chassis

Chassis

- Natural Chassis
  - E. Coli
  - B. Subtilis
  - Mycoplasma
  - Yeast
  - P. putida
- Minimal Cells
  - achieving control





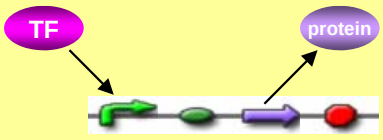
A minimal cell containing biological macromolecules and pathways proposed to be necessary and sufficient for replication from small molecule nutrients.

Forster and Church – Molecular Systems Biol (2006)

4. Parts, Devices and Systems

Engineering v Biology

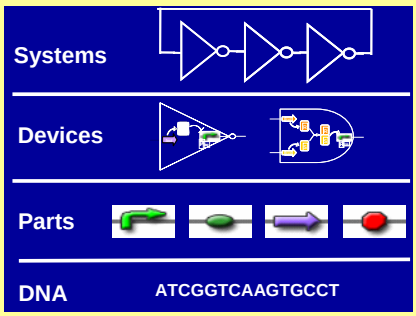
Modularity, Characterisation, Standardisation



Typical gene transcription module

- Ribosome binding site
- Protein coding sequence
- Terminator
- TF Transcription factor

A hierarchy for synthetic biology



Systematic Design

The basis of all engineering - parts, devices and systems

The Engineering Approach to Design

- Abstraction
- Decoupling
- Standardisation

The Engineering Approach to Design in Synthetic Biology

Engineering systems are built from a hierarchy

- Parts
- Devices
- Systems

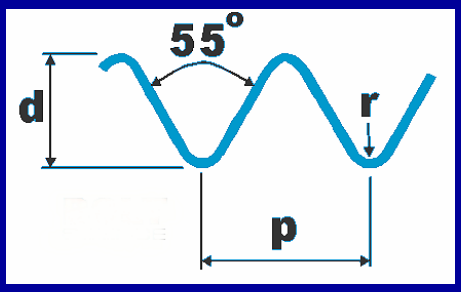
- At each level the characteristics of the Part, Device or System are well defined and reproducible
- In engineering the aim is to build a system on the basis of devices which comprise standard parts

Synthetic Biology: aims to build applications from Biobricks

- Parts – encode biological functions (ie often modified DNA)
- Devices – made from a collection of parts and encode human-defined functions (eg logic gates)
- Systems – perform tasks, eg counting

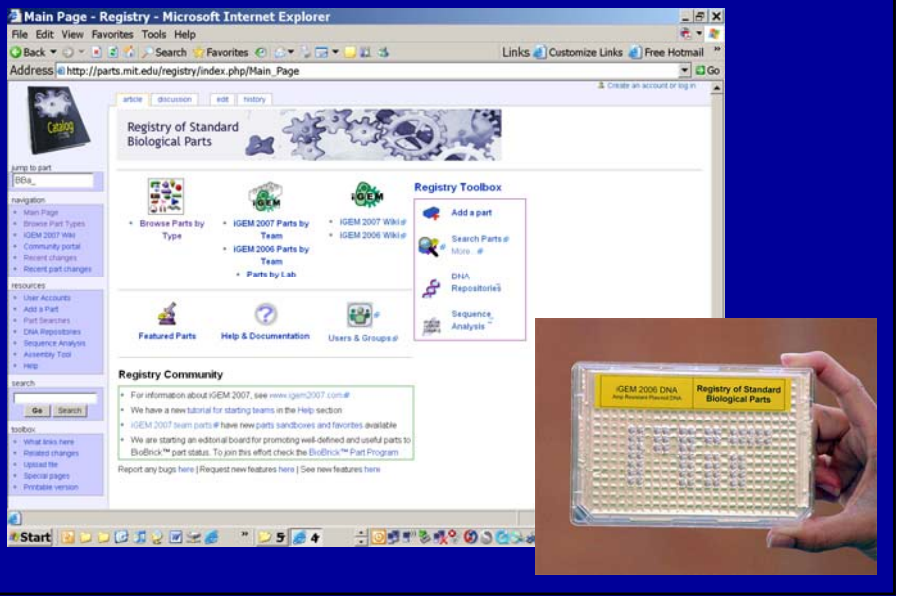
Standards

The Whitworth Thread

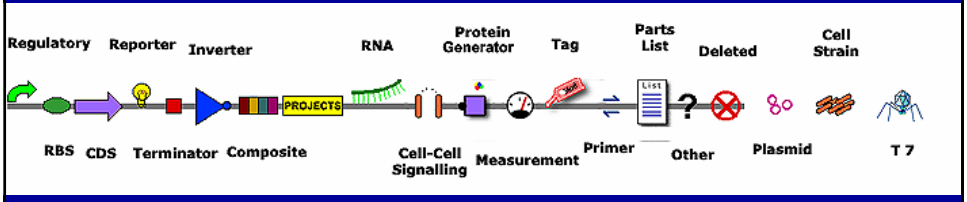


The first standard thread – Sir Joseph Whitworth 1841

The MIT Registry



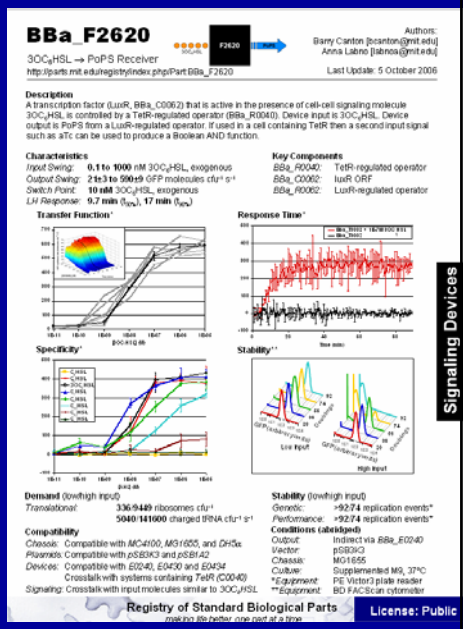
Examples of Parts



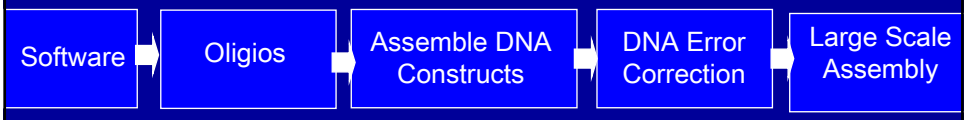
To see the catalogue of standard parts from the diagram above, hover over the part at the website below

http://parts2.mit.edu

Biobrick BBa_F2620



A Synthetic Biology Pipeline



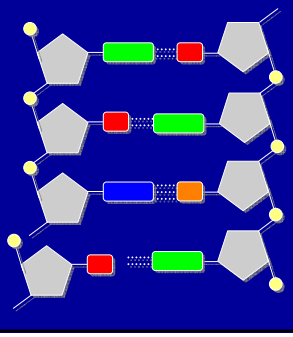
Data Devices Molecules

Making DNA to Order

Synthetic DNA can now be chemically made to order:

– type in the sequence GCGCTATCGCGG……

– get the DNA by mail order

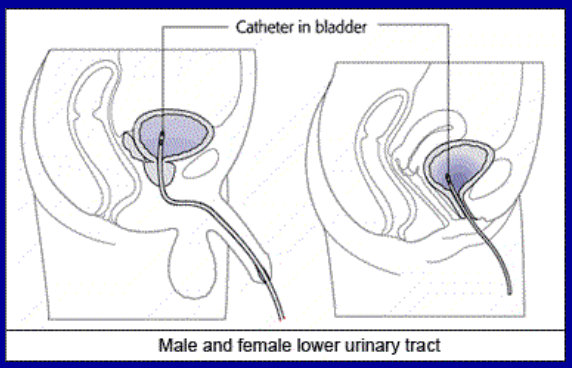


The Companies

Urinary Tract Infection (UTI)

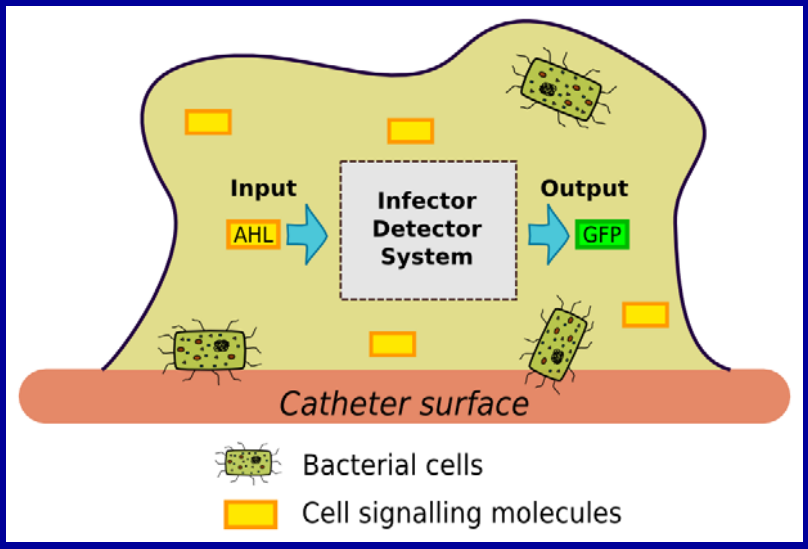
The Aim

To design a genetically engineered machine which detects the presence of biofilm infection on urinary catheters



Male and female lower urinary tract

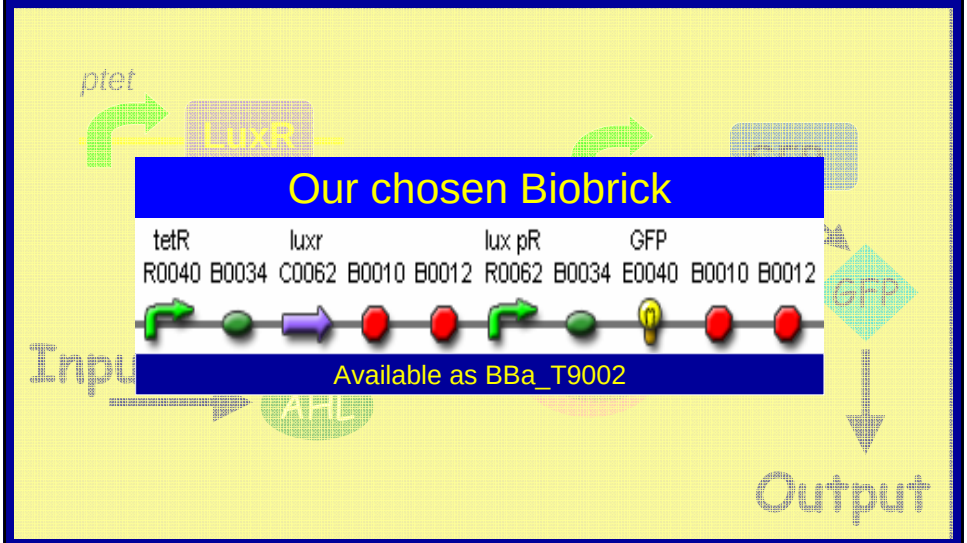
Our Detection Strategy

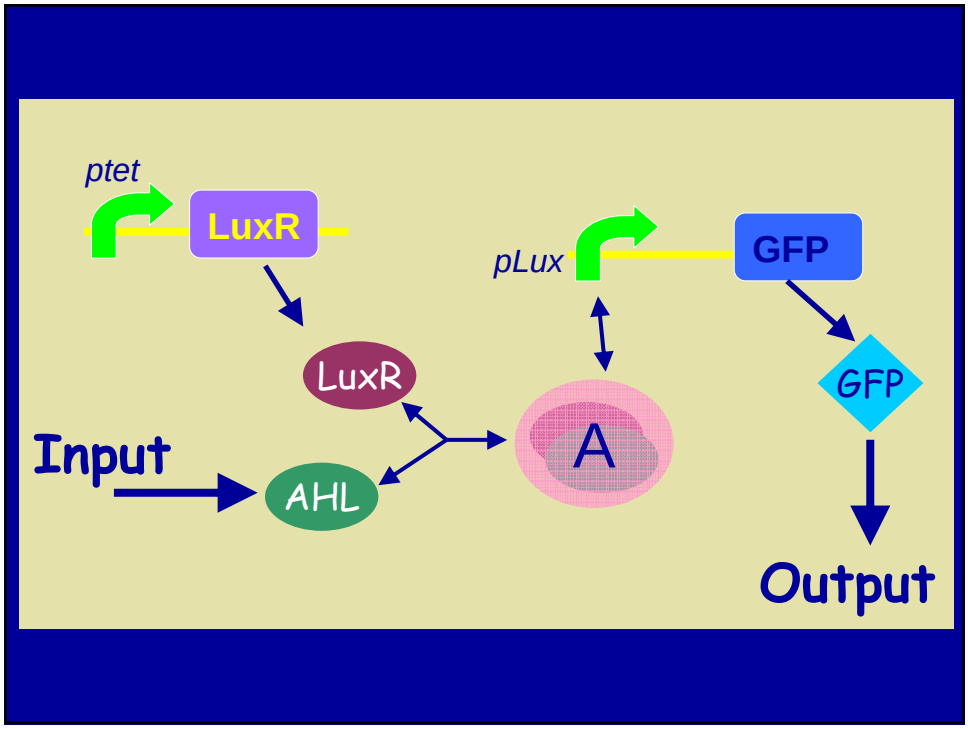


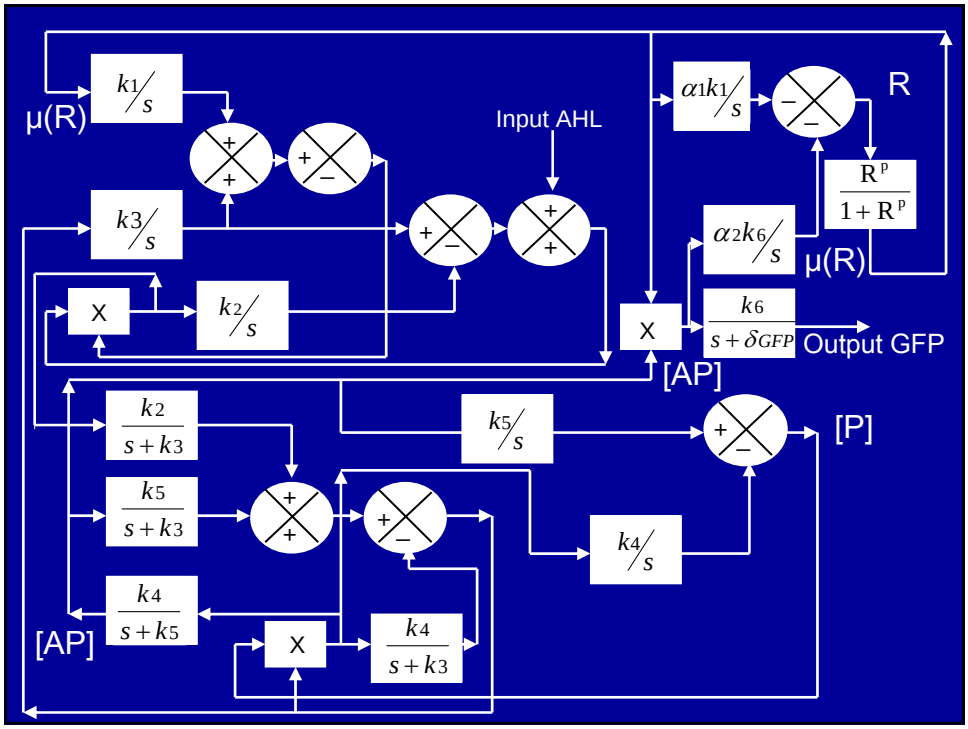
Urinary Tract Infection Detector – a three stage device

Detector	Amplifier	Indicator

The Biochemical Network – the basis of Infector Detector



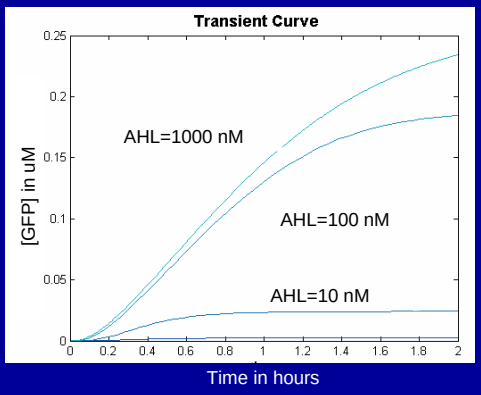

ptet
LuxR
pLux
GFP
LuxR
GFP
Input
AHL
A
Output


μ(R)
Input AHL
R
μ(R)
Output GFP
[AP]
[P]
[AP]

Typical Simulations

General Behaviour:

- Slow uptake
- Saturation after few hours (Resources exhausted)
- The higher the input (AHL) , the higher the output (GFP)

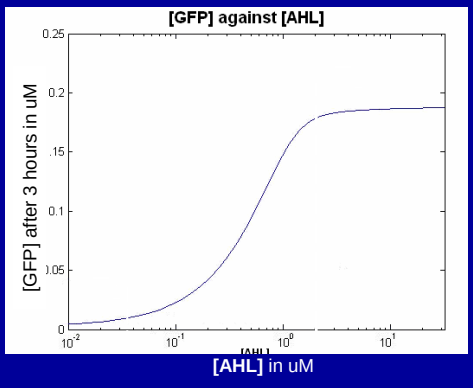


Transfer Function

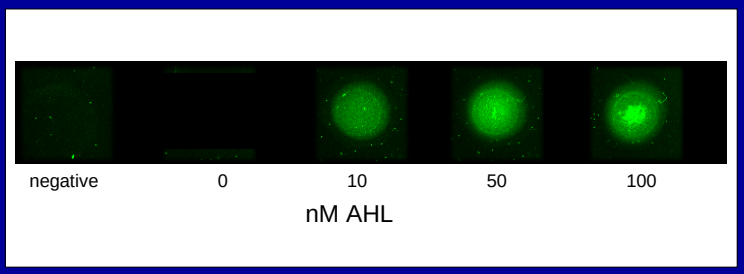
AHL → **Infector Detector** → **GFP**

GFP vs AHL

- Similar to F2620 in vivo
- Below T_1 : No detection
- Above T_2: Saturation

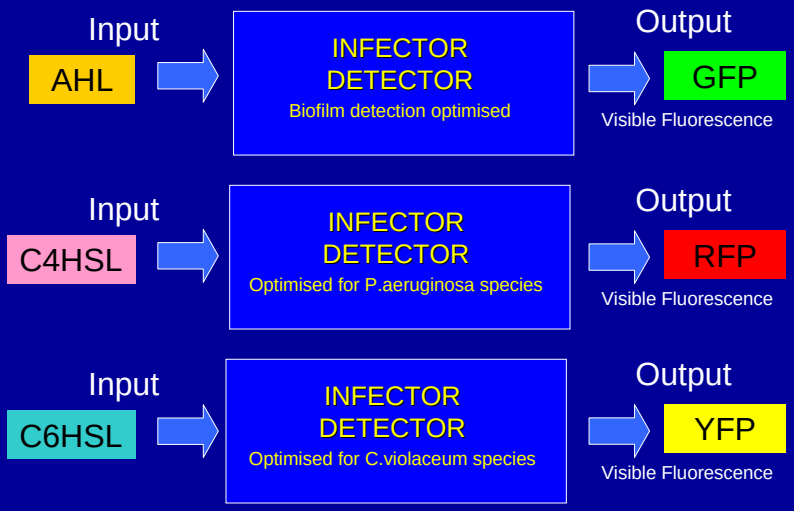


Testing Infector Detector on Agarose



Agarose drops with Infector Detector detecting different concentrations of AHL

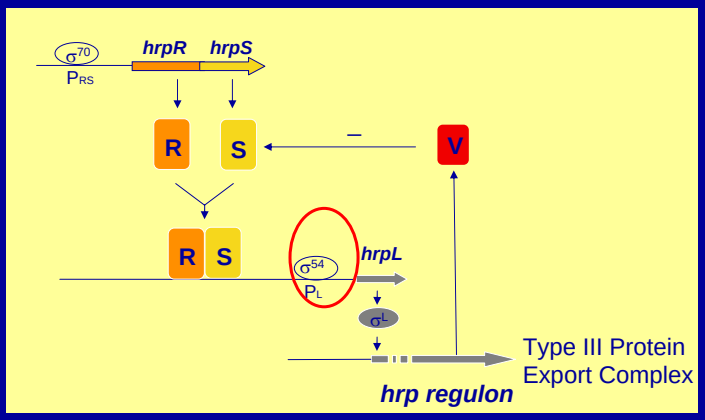
Ongoing Work: Customisation



Logic Gates

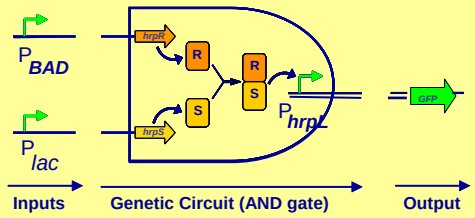
The hrp gene regulation system – a great system for modular biologically-based logical devices

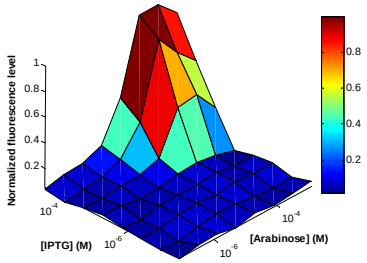
- *hrp* (hypersensitive response and pathogenicity)



***Pseudomonas syringae hrp* regulatory system**

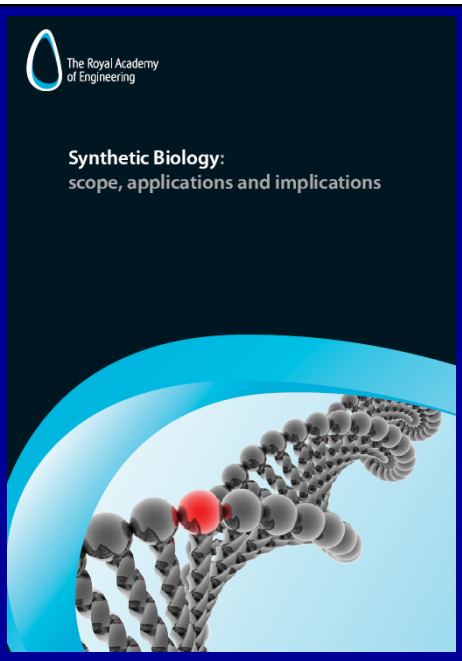
Characterising the Logical AND Gate





The full characterisation of the AND gate using GFP as reporter. The left chart shows the system output (normalised fluorescence level) versus various concentrations of the two input inducers – arabinose and IPTG (in E.Coli, MC4100, M9 supplemented MM with 0.01% glucose, 30˚C).

Strategy



http://www.raeng.org.uk/news/publications/list/reports/Synthetic_biology.pdf

The Research Councils

bbsrc

Engineering and Biological Systems Grants

Synthetic Biology Network Grants 2008 (with EPSRC)

EPSRC

Synthetic Biology was an area in the 2008 Science and Innovation Call - £8m investment at Imperial College to establish the EPSRC Centre for Synthetic Biology and Innovation

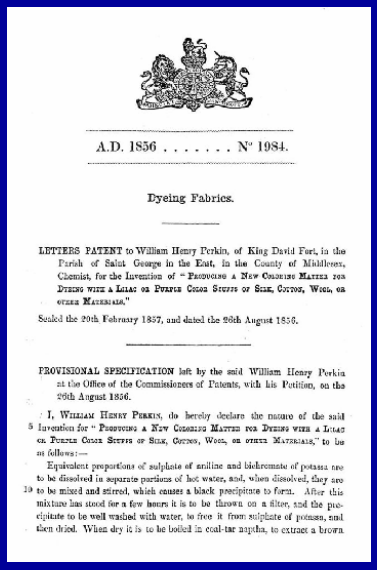
Response Mode Grants this year

wellcome trust

Currently thinking about the area, but now supporting UK teams in iGEM

There are strong parallels with Synthetic Chemistry in the 19th Century

Modern examples of natural dyes in the Mysore market in India



A.D. 1856 . . . . . N° 1984.

Dyeing Fabrics.

LETTERS PATENT to William Henry Perkin, of King David Fort, in the Parish of Saint George in the East, in the County of Middlesex, Chemist, for the Invention of "PRODUCING A NEW COLORING MATTER FOR DYEING WITH A LILAC OR PURPLE COLOR STUFFS OF SILK, COTTON, WOOL, OR OTHER MATERIALS."

Sealed the 29th February 1857, and dated the 26th August 1856.

PROVISIONAL SPECIFICATION left by the said William Henry Perkin at the Office of the Commissioners of Patents, with his Petition, on the 26th August 1856.

I, WILLIAM HENRY PERKIN, do hereby declare the nature of the said Invention for "PRODUCING A NEW COLORING MATTER FOR DYEING WITH A LILAC OR PURPLE COLOR STUFFS OF SILK, COTTON, WOOL, OR OTHER MATERIALS," to be as follows:—

Equivalent proportions of sulphate of aniline and bichromate of potassa are to be dissolved in separate portions of hot water, and, when dissolved, they are to be mixed and stirred, which causes a black precipitate to form. After this mixture has stood for a few hours it is to be thrown on a filter, and the precipitate to be well washed with water, to free it from sulphate of potassa, and then dried. When dry it is to be boiled in coal-tar naptha, to extract a brown

William Henry Perkin -1856, the production of synthetic quinine from benzene

Aspirin 1897

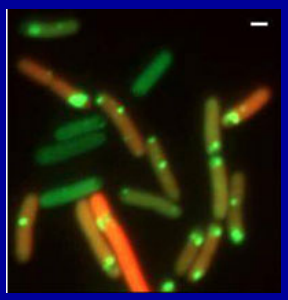
Chemist Felix Hoffmann, at Bayer in Germany

Synthetic Rubber

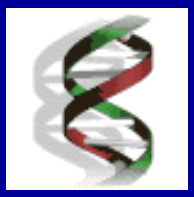
A New Industrial Revolution in the Making (?)

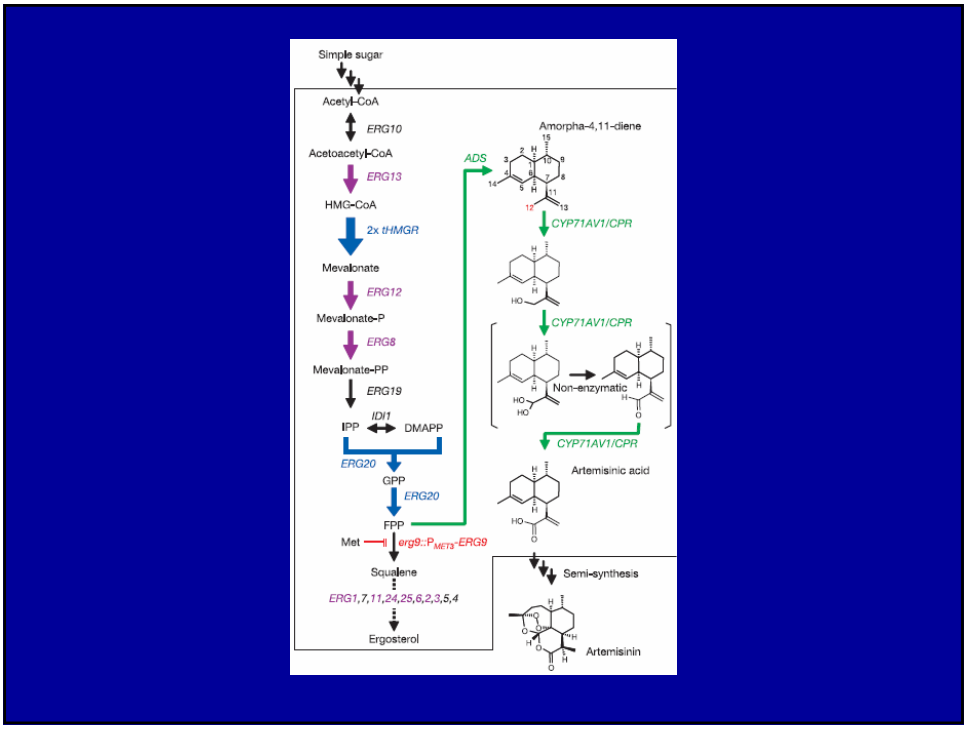
Synthetic Biology promises a shift comparable in importance to the ICT revolution with the power to revolutionise many sectors of the economy including:

- Biofuels
- Biomaterials
- Medicines
- Drugs
- Vaccines
- Biosensors
- Logical Devices – leading counters and, ultimately, control devices



The End




Simple sugar
Acetyl-CoA
ERG10
Acetoacetyl-CoA
ERG13
HMG-CoA
2x tHMGR
Mevalonate
ERG12
Mevalonate-P
ERG8
Mevalonate-PP
ERG19
IDI1
IPP
DMAPP
ERG20
GPP
ERG20
FPP
Met
erg9::P MET3 -ERG9
Squalene
ERG1,7,11,24,25,6,2,3,5,4
Ergosterol
ADS
Amorpha-4,11-diene
CYP71AV1/CPR
CYP71AV1/CPR
Non-enzymatic
CYP71AV1/CPR
Artemisinic acid
Semi-synthesis
Artemisinin