

Biotech Science Scan – Collected Speculations

1 Abstract

Early in 2004 I participated in a group convened by the [Royal Society of New Zealand](#) that was to produce a "biotechnology science scan" covering a 15 year span. This paper was my initial and belated contribution, arriving after the first discussions (and therefore benefitting from them). In it I outline a few concepts—which, as often occurs, tend to become statements of context—and some notes of caution. Then I give my thoughts on two kinds of biotech development: enablers and breakthroughs (*i.e.* evolutionary development of tools, and things that may shake all other predictions, respectively). The likely impact over the next 15 years is discussed. Anything that doesn't fit this scheme appears in an appendix.

The final report, *Biotechnologies To 2025*, was published by the Ministry of Research, Science & Technology (MoRST) early in 2005 and is [available from their website](#).

1.1 Proviso/disclaimer

I know and care a lot more about molecular biology (hence genetics, genomics, proteomics, biochemistry, etc.) than nanotechnology or IVF or aquaculture. The following is coloured by my prejudices and ignorance.

Also, there are 'rules for imagineers'¹:

1. Never imagine alone.
2. Involve thinkers from other disciplines.
3. Imagine along your vector of greed (great problems stimulate great imaginings).
4. Time-box (hard-deadline) your thinking.

I ignored all of these precepts to some degree.

¹

<http://www.computerworld.com/managementtopics/management/story/0,10801,82756,00.html>

2 The remit

(NB: This paper does not satisfy the following remit, as provided by the Royal Society and MoRST; however, the remit provided the context in which the paper was written.)

The intent was to identify some very newly emerging biotechnology tools or techniques; to highlight some very newly emerging areas of knowledge; to provide a global picture of where and what any investment in biotech-related science should be; to point out possible areas of application for these new tools/knowledge, to focus on global developments but also provide a sense of where New Zealand sits within this bigger picture; and to capture development not only in mainstream biotech science but also those involving convergence with other areas. Such forecasting can impact decisions regarding skills, regulation, markets and industry development, public communications and education, health sector etc.

We were specifically after science which will emerge/be significant in 10-20 years rather than existing science (in which there may be significant advances in the future), technologies or commercial outcomes. We were particularly keen to note those that are perhaps underfunded or underappreciated.

We used a "products via living systems" definition of biotechnology.

3 Relevant concepts and context

It seems to me easy to find possible divergences in *social* futurewatching (scenario: *what if we become a state of the Australian Union?* etc.) and call them real or throw them out. But almost every published paper in science suggests a possible future and needs closer analysis. It's a many-worlds problem! Nevertheless, to impose some sort of order I declare that the important bit about forks in the road ahead is that a scientific result might (i) destroy them or (ii) create them.

3.1 Sustainability and risk avoidance

The environmentalism trend was well-established in 1989 and continues to be credible. It is safe to say that it will still be around in 15 years time

This is a crucial trend and therefore should colour all predictions. With increasing education (however incomplete or plain wrong) comes a greater interest in risk and impact assessment, and greater risk averseness. This is an observable trend in many countries. Developing countries lag behind the G8 and associates here but the political activities of the rich

(particularly environmentalism, anti-globalization and security-related) ensure that 'sustainability' and environmental impact are high on all agendas. Whatever the potential developments of the next 15 years will be, they won't pass the public approval test if they aren't sustainable. The environmentalism trend was well-established in 1989 and continues to be credible. It is safe to say that it will still be around in 15 years time.

3.2 Food, water, climate

Whatever developments occur in biotechnology over the next 15 years, those that affect food and water supplies and security will have the highest profile (and, though this may not correlate) the greatest impacts. For example, we need to grow more food in the next 50 years than we did in the previous 5000, and we

need to do it on less land that we grew the food we consumed last century². Coupled with climate change, this points to where the big funding money and the governmental and public attention will be focussed in biological science. If biotechnology of one sort or another is detrimental to food or water supply or to the environment, it can, despite any other promises it may make, expect to be closed down. That's a generalization but one I think we should allow to affect our predictions.

3.3 *Being New Zealand*

There are two kinds of effect on New Zealand of a development in biotechnology:

1. Some bioscience developments will affect New Zealand because they will force us to adopt them or adapt to them in competition. An example might be improvements to agricultural processes (animal probiotics, Posilac-type hormones, productivity gains via GMOs, etc.)
2. We also have to futurewatch for bioscience development that affect New Zealand because they affect what everyone does. Examples are medical cloning, nanotech production methods.

New Zealand possesses a research advantage in its collaborative model of science but this is practical, near-term development. It's important not to focus on only that for a 15 year time-box. New Zealand will need a portfolio of research and funding to include blue skies stuff (not untargeted, just imaginative) that probably arises better in the research university/principal investigator scenario; what is the scope for far-reaching, high-risk research in a CRI with a significant percentage of its FRST funding tied up in a consortium with industry? Neither one model nor the other is best; having both is the way.

New Zealand's other point of distinction (which it would be nice to have as an advantage) is geographical – can we use this to, for example, be the source of luxury bioproducts to Asia (boutique bioactives?) while they are chomping krill and aquaculture products? Is there a benefit to our maritime position that applied bioscience can use?³ There has been talk of a time zone advantage, as possessed by India and accessed by Microsoft for 24hour programming and customer support.

If a biotechnology is sufficiently portable and importable, what other countries, for the lack of one or two aspects or conditions, are well-placed to be our competitors?

Part of any futurewatch activity has to include not only considerations of the New Zealand context but also an attempt to pin down what exactly is the character of any New Zealand advantage. If a biotechnology is sufficiently portable and importable, what other countries, for the lack of one or two aspects or conditions, are well-placed to be our competitors? For example, what would it take in terms of biotechnology, government, and social change and so on for Brazil to out-compete New Zealand's pastoral dairy industry? For China to direct its mighty land resources to compete with us?

The other aspect of being New Zealand that springs to mind is being a multicultural society. The effects on GMO legislation have been clear but predicting other effects on biotechnology development over the next 15 years is probably part of the remit of those doing social futurewatch.

² I heard this arresting statistic in a talk given by Professor Bob Goldberg (UCLA).

³ Any plan to advocate extended use of tidal and geothermal power being outside the scope of this paper, of course.

3.4 Platform technologies

Examples: cloning, viral vectors in functional genomics and gene therapy, use of protein-only heritable material, high-throughput epigenetic analysis ('epigenomics?'), chemical genetics, proteomics, transcript profiling, genetic marker acquisition (SNPs and co.), etc.

All will become massively parallel, high-throughput, cheaper and (for analytics) portable. Over the 15 year time-box I see them only as enabling other developments or as services rather than paradigm-busters⁴ (this doesn't mean they aren't impressive). We need to watch their development and use them appropriately as tools. Beyond that they may have greater importance but not just yet.

Some will fail to deliver; some of the biochemical and genetic analyses, such as the chemical genomics work, are based on certain assumptions about the level of complexity and parsimony we will find in nature and may yet be confounded by how messy and unplanned and complicated it really is down there in the dark ("From an engineering point of view [the human brain is] a fiasco" -- Bart Kosko).

3.5 Innovation is often imported⁵

The physicists or the mathematicians or the ecologists or the information technologists may well contribute the seed for the next great sea change in biology.

The management cliché is sometimes true: it's about achieving synergies. Input from other fields in the form of ideas, concepts, metaphors, alternative viewpoints, spin-offs, fruitful misunderstandings and so on are useful and affect how biotech will progress over the time-box we are considering. The physicists or the mathematicians or the ecologists or the information technologists may well contribute the

seed for the next great sea change in biology. It's exceedingly difficult to cover this in a futurewatch activity so I suppose it must just serve as a delimiter of our confidence intervals for prediction.

3.6 Diversity and choice

It's not that we will always supersede what we do today. Life, and even science, and even biotechnology, doesn't proceed like that. Another trend apparent in the last century or so of Western civilization that is spreading further is The Benefits of Choice. We won't lose our current biotechnologies but some may become minority sports (non-Sanger DNA sequencing, *Agrobacterium* transformation of soybean) or old-fashioned (manual DNA sequencing) or too trivial for comment (DNA sequencing!). The future doesn't look that different. This brings me to:

3.7 Two notes of caution

ONE: A small time-box

15 years isn't a long time. Consider these (admittedly cherry-picked):

⁴ This distinction is preserved in the rest of this document. I tend to think of emerging or promising biotechnologies as either enablers or paradigm-busters (yes this is a lousy taxonomy/terminology).

⁵ Where's the war? Innovation often proceeds along the vector of need (consider the technologies that came out of WWII or the Apollo program or, more trivially but still illustrative, the competition between computer manufacturers).

| Development | 1989 position | 2004 position |
|-------------------------------|--|--|
| Understanding gene expression | Venter's EST paper still 2 years away; microarrays and SAGE still 6 years away | Ubiquitous; trivial |
| DNA sequencing | Low throughput; automated sequencers only 3 years old | Staggering capability |
| Analyzing epigenetic effects | Primitive; some concepts in place; low-throughput techniques | About to be available in massively parallel assays; huge amount of research leading to many changes in understanding; shows much promise |
| Knowledge of whole genomes | Human genome project still in planning phase | 3 mammalian genomes complete; 100+ other genomes complete; 50+ programs ongoing |
| PCR | Technology 4 years old; use of thermostable polymerase 1 year old | Ubiquitous and trivial |
| Monocot plant transformation | First patents granted; first field tests ongoing | Many high-throughput functional genomics programs in monocots; still only a handful of products |
| Environmentalist politics | Possess credibility; gaining momentum | Still possess credibility; still gaining momentum |
| Cold fusion | In the headlines | In the dustbin |
| Cystic fibrosis | Gene sequence published | Still no therapies |

In other words, the developments over 15 years can often be characterized as enhancements or enablements, albeit spectacular ones. But some are best termed Colossal Disappointments: in 1989 there was a lot of confidence that cystic fibrosis would be dealt with pretty quickly and yet here we still are; cold fusion was briefly the biggest thing in town, and now? Futurewatching is speculative even when educated.

TWO: Revisionism

In some cases, what we think we know today will be superseded or corrected. A trivial example from genomics is the breakdown of the false equality "gene = function" (still rife in even peer-reviewed publications). Such changes are unpredictable today, and are where the future looks most different from the present.

4 Enhancements and enablements over 15 years

4.1 In 'genetic' modification⁶

In this category we will have made many enhancements and enablements in 15 years.

⁶ 'Genetic modification' is too limiting a term. This category covers the manipulation of living systems via functional molecules of all kinds, not just DNA.

- We will be better at stacking traits and building whole pathways, and we will be doing that in commodity organisms like crops and livestock.
- We will have eliminated the use of marker genes in field-released GMOs of all types except where functionally required.
- We will know a lot more (and apply it) about how structure leads to function in chromosomes, in RNAs, in proteins, in membranes. We will have tools to manipulate all these (most if not all high-throughput allowing massive knowledge discovery programs in companies and in public efforts).
- We will know many more (but not all) of the tricks the genome/nucleus/cell uses and we will be redeploying/hacking them all. These tricks will include but are not limited to
 - cunning post-translational modifications;
 - weird enhancers and genomic elements that affect function locally and globally;
 - ingeniously crafted regulatory elements and co-ordinated or deliberately disjointed networks thereof;
 - pre-programmed obsolescence or strict containment of genes, proteins, RNAs, functional molecules of other kinds including lipids;
 - overlaps, distortions, inter-gene ecological predation, and other tricks currently beyond our experimental expertise to find or employ.
- We'll also go wider in all our current technologies: we will be testing gene modifications and protein manipulations in combination for example not one gene knockout at a time but carefully chosen k-tuples.
- Use of new methods developed most probably in medical genetics e.g. new vehicles for delivery of functional molecules⁷.

For this kind of work to flourish it needs an environment that encourages brave science and allows innovators to benefit from it. These are all near-term applications and, while several (most?) won't lead to products in ten years they may be well on their way by 15. Such an environment would contain: thriving universities allowed to do research as well as research-and-development, sufficient but not onerous regulatory oversight, access to world-class facilities and knowledge.

4.2 In IT (where relevant to biotechnology)

The accumulation of vast repositories of biological information (genomes, protein profiles, transcript profiles, epigenetic profiles, and most importantly the associated literature) means that bioinformatics developments will be startling. (Comparative X-omics = a lot of what bioinformatics is, where X = gen or prot or whatever.) The tools (algorithms; interfaces; means of presenting data; integration across formats and across profile types) will improve; this will have some of the greatest impact (i.e. for example 'comparative genoproteomics'). The specificity and selectivity of tools will improve and be much broader/deeper than currently available. That is going to lead to changes in information sharing and available

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⁷ The Roslin Institute's recent report of the use of lentiviral vectors for improved efficiency in animal transgenics is a relevant example.

research goals (both amenable to legislative control). I predict that in the next 15 years there will be at least one major shock born out of purely desktop research. In the New Zealand context, this is a good thing: geography is less relevant when you don't need to be in the US to do it or be funded to do it.

The cross-compatibility of databases⁸ and the subsequent increase in data movement will facilitate all this. Small players like New Zealand will need to encourage open access and publicly funded work because we cannot do all this by ourselves. We'll need to make a contribution and for that we need farsighted funding in universities (and New Zealand's Crown Research Institutes?) that isn't required to lead to products.

For the internet, this has a couple of obvious enabling developments:

1. More data available. Whether this discourages or encourages data sharing will be a matter of luck and legislation.
2. More distributed effort (scientists, computing cycles, whatever) to bring to a particular problem

As flows of information increase still further, agility will be crucial to success. The ability to catch up and then overtake should be fostered. At the same time, this will be recognized and will discourage sharing. As appropriability becomes even easier than it already is and knowledge becomes the main currency, people hoard. New Zealand must produce (i.e. do original and far-sighted research in quantity and quality) if it is to be **allowed** to share.

4.3 In analysis tools and techniques

Over the next few years what might be called the 'array paradigm' will prosper. In other words, analytical tools in biotechnology will be applied in highly parallel, portable, surface-based motifs. What can be assayed slowly in specialist labs today (epigenetic status, DNA fingerprints, microstructural features, disease status, intestinal microflora, various pollutants and contaminants, species determination for biosecurity or medical diagnosis) will be analyzable in bulk, in situ and in real time.

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The main effect of this will be progress acceleration. More data will be collected and the bioinformaticians and biotechnologists will have more grist for their mills. The confidence levels of the users (which may include the public) may rise as a by-product of their ownership (e.g. testing for GE-free status), as may paranoia. The ability to test for something will often call for the deployment of the test whether this is a good or bad thing⁹. The ability to test so thoroughly and easily will have social effects beyond the scope of this paper.

⁸ See W3.org and the work in XML.

⁹ Three examples of the bad: DNA testing using markers that provide phenotypic information; the debate over health insurance for those with assayable inborn errors of metabolism; the public and social consequences of failures or successes of *in utero* testing.

5 Paradigm-busters and breakthroughs over the next 15 years

5.1 The longstanding challenges

There are lots of puzzles in biology but there are two big ones¹⁰ that have been around for longer than 15 years but which might fall in the next 15. They'll certainly be solved in the next 50. They are:

1. How does embryogenesis work in mammals?
2. How does the brain work?

Simplistically, they haven't been solved because we lack the tools to dissect (poor word choice!) the problems properly. Those tools are in development today. The knowledge derived from today's and tomorrow's genomics/epigenetics/mass transcript profiling/proteomics etc. will take us much closer in the 15 years. We may the following in that time:

- Non-destructive in vivo imaging of subcellular components
- Fine-grain neural imaging (magneto-electric status of individual neurons in living brains)
- Non-destructive sampling of subcellular components (or even functional molecules) from living samples
- Theoretical tools and concepts from model systems, and better understanding at the molecular level of the validity and shortcomings of those models.

5.2 Yet more complexity

The cell concept has been changing for years. Over the next 15 years we are going to understand just how complicated it really is. For years we thought it was a bag of stuff and for a quarter of a century we've been amending that opinion in favour of the cell being incredibly organized and dynamic, purposeful structure constantly rebuilding and retasking itself and its component parts, and controlled at dozens of levels. Consider the following: DNA sequence, DNA structure, ancillary chemical modification of DNA, DNA-associated RNAs or proteins, DNA editing, DNA repair, DNA interactions with RNA or proteins,

The cell is a multipurpose, self-repairing, micro-miniaturized engine for survival that bootstrapped itself into existence and spent 4 billion years taking out all the insurance options, backup plans and design decisions it could.

DNA interactions with DNA, RNA processing, RNA structure, RNA modification, RNA fidelity checkpoints, RNA targeting, interactions within and between RNAs, RNA degradation, RNA interactions with DNA or protein, protein production, protein structure, protein modification, protein targeting, protein degradation, protein-protein interactions, protein-nucleic acid interactions, lipid production, lipid structure, lipid targeting, lipid modification, lipid interactions with

other cellular components, organelle construction and maintenance, organelle replication and destruction, intra- and inter-organelle transport – every one of these processes and many others is either known or suspected to be a control

¹⁰ This list is from a pub conversation I was involved in with Dr Dave Hallahan. He won and this is his list; everyone else's suggestions were shown by him to be lacking in stature, immediacy, relevance, broadness of application or size of challenge in comparison.

point that has effects on cell behaviour. And over 15 years we are going to discover that every one of these processes and all the others are sometimes, rarely or always used as such. This doesn't take into account cell-to-cell interactions or cell-organ or cell-body interactions all the way up to pancreatic hormones causing mood disorders in brains. It's staggeringly complicated! When we thought the cell was a bag of stuff in which molecules floated around bumping fortuitously into each other we were very naïve: the cell is a multipurpose, self-repairing, micro-miniaturized engine for survival that bootstrapped itself into existence and spent 4 billion years taking out all the insurance options, backup plans and design decisions it could or would ever need in the face of constraints and situations which we as yet understand very, very poorly.¹¹

Fifteen years from now, we'll know better but we still won't know much (relatively speaking). Consider this an argument for what some call blue skies research: without sufficient funding for research that does not lead to a product within ten years, we won't know this stuff (or, more appropriately for New Zealand, we won't know this stuff before others do).

5.3 The end of biotechnology?

Could 15 years be enough to finish off biotechnology via marginalization, obsolescence or other means?

Nanotechnology promises much and has for twenty years. But true nanotech as envisaged back in 1986¹² isn't much closer. Nanotechnology as molecular-sized components arranged and designed to manufacture at those levels are still some way off. Molecular motors, optical switching and such are more likely to impact IT in the fifteen year time-box than directly affect biotechnology. True Drexler-esque nano-replicators would have profound impacts on all countries (e.g. rendering all of agriculture obsolete) but will remain part of science fiction for now.

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More realistically, 'poor' nanotechnology in the form of nanominiaturization to create products with micro- or nano-scale effects (including so-called smart materials) will be more prevalent in 15 years. Their effects on biotechnology are much smaller though.

Another way in which biotechnology could lose out is if it is rendered obsolete. Currently the creation of genetically modified plants and animals is a torturous scientific and regulatory process. Improvements in the science over the next decade or so will improve this but there remains that possibility that other technologies could supersede it if they can overcome other obstacles different to those faced by plant or animal transgenesis. For example, process upgrades to microbial biotechnology (using currently untapped archaeal or uncultivable diversity¹³, or with improved manipulation or fermentation of coliforms etc.) or increasing chemical synthetic expertise can sometimes produce a given product

¹¹ Analogy: In a crowd, even at a political rally, are the people at the front with the loudspeakers wholly and solely responsible for the crowd's behaviour and subsequent actions? Those speakers are the DNA, their loudspeakers are the messenger RNAs – at such a rally everything from the weather to the hairstyle of the tallest man in the crowd can have an effect.

¹² *Engines of Creation* by K.Eric Drexler is available at <http://www.foresight.org/EOC/index.html>

¹³ <http://arjournals.annualreviews.org/doi/abs/10.1146/annurev.micro.57.030502.090759>

more quickly. Some kinds of biotechnology are not agile thanks to their long lead-in times. This may be especially true for the production of biomaterials in commodity, where it could be socially or economically impossible to take over sufficient agricultural output to meet demand via plant transgenesis¹⁴. It may also apply where only micro-amounts are required (e.g. when a single source is sufficient for world demand). Advanced technology isn't always the answer¹⁵.

In a related way, biotechnology may fail due to overambition. Could it be that it is just too hard? A classic example: when nitrogen fixation was first fully characterized at the genetic and biochemical level, it was disappointing to discover that it was (and continues to be) unfeasible to transfer it to other plants such as cereals. That's because it requires a large number of genes (was it 20?), regulated in a co-ordinated fashion, and is so energetically demanding that biomass yields would drop to unacceptably low levels (down 20% or so, I seem to recall). We're better now at stacking and we're understanding more about regulation so the first two problems may have evaporated within 15 years but the third problem seems unassailable unless there is a Magic Yield Gene(!) that could offset it. Another possibility (yet to be proven) is in xenotransplantation: the scare stories in which pig hearts might-just-might lead to the creation of a new human virus. Some possible controlled-flight-into-terrain situations for currently-promising technologies:

- apomixis in crops may require complex chromosome disruptions or perturb so many other processes that it is incompatible with e.g. rice;
- efficient C4 photosynthesis may be proven impossible in C3 plants that haven't done it for millions of years or that have been developing specialized adaptations that confound its introduction;
- the specialization of stem cells into certain cell types, and the formation of fully-functioning human organs from same may not be technically feasible or even, in our time-box, comprehensible;
- the technologies needed to understand how the brain works may not be able to resolve the mechanisms;
- the reliable integration across literature and bioinformatic databases to create automated truth-finding algorithms for biology may be impossible in the real world;
- nanoreplicators as envisaged by Drexler may remain science fiction (Nobel prizewinner Raymond Smalley certainly believes them to be physically impossible¹⁶);
- any of the technologies currently in Moore's Law phase might hit the buffers (e.g. a physical law) and cease growth;

¹⁴ This is demonstrated by the oft-mentioned bioplastic research at Monsanto. The production of PHAs in agricultural crops is uneconomical due to the size of the industry producing the competing product: the scale and the economies of scale possessed by the petroleum-derived plastics industry have prevented the global deployment of 'phytopol'.

¹⁵ The classic example was tPA, where millions were invested in the biofermentation process while the drug was, for many patients, no more effective than aspirin. A non-example is Golden Rice which, despite Greenpeace's claims to the contrary, is a better solution to the problem than they have been keen to admit (do I detect a certain shiftiness and special pleading in their discussions of Golden Rice?). Golden Rice II, announced in *Nature* early in 2005, addresses their main concern (*Nature Biotechnology* 2005 doi: 10.1038/nbt1082).

¹⁶ <http://pubs.acs.org/cen/coverstory/8148/8148counterpoint.html>

- the dispersity of many heritable traits may be even more complicated than nitrogen fixation (apparently) is. Maybe it really required 200 genes to be subtly or grossly altered, along with certain select epigenetic and structural and chemico-electrical property changes, for significant, sustainable C4 photosynthesis and that is beyond our power
- climate change may come to a tipping point and all of a sudden we have problems that biotechnology in most forms is too slow to address
- lots, lots more.

A variety of Too Hard In 15 Years might be Too Expensive In 15 Years¹⁷. Many things that look promising today may simply be Too Hard within the 15 years. This is not cause for despair because in that time we should at least discover why. Perhaps sometimes the answer will be that they are Too Hard Forever. A physics example is faster-than-light travel; a biology example might be understanding the human brain (though I don't believe so). But none of this is a reason to develop policy or science research in different directions; you have to speculate to accumulate. Pessimism and naysaying are easy and always as far off the mark as optimism. Using 'it might fail' as a reason not to do biotechnology is not the way to better our existences¹⁸. I like the subtext of Shelley's Ozymandias: even the dreams of the great turn to dust in the end. Couple that with Clarke's First Law and I believe that nightmare visions about the limits of knowledge or of the difficulty of growing human hearts from cells in culture can turn to dust even quicker. It remains disappointing to some (me!) that we don't live in space stations here in the twenty-first century but we still have to give ourselves credit; there are long lists of quotes from people who thought there was nothing left to be discovered (then somebody else promptly came up with quantum physics or airplanes or desktop computers or spectrosopes or high-throughput sequencers or...).

Biotechnology's fate might be rejection; the public may wish to put the genie back in the lamp. The social changes accompanying [the risk-averseness trend](#) and [the environmental-awareness trend](#) could prevent the development of lots (all?) of biotechnology and nanotechnology.

The last way for biotechnology to be brought to a finish is if it were shown to be the cause of a catastrophe. Imagine if someone showed unequivocally (or, since it amounts to the same thing, with sufficient publicity!) that genome rearrangements in a GM plant had created a new virus or infective prion, or that nanotech grey goo had been created.

Governments and institutions (and individual scientists) are aware of this danger and understand its likelihood. Laws drafted to control perceived dangers (and bioterrorism)

Prediction: there will be prions found to occur naturally in plants.

will therefore impinge on what can be done in nano- and bio-technology, especially in near term with current technologies (and while attempting to develop better ones). There may be social and commercial consequences of this. For example, there is clearly a lot to be learned about protein-based inheritance¹⁹ and there will certainly be medical benefits to such research yet New Zealand's 'BSE-free' status, among other things, prevents some of our world-class researchers taking on CJD. The US government has also taken what some think of as a rather intrusive and overbearing interest in some aspects of biotechnology

¹⁷ Maybe apomictic rice works, but costs \$200 per kilo?

¹⁸ How many must starve before organic agriculture can feed the world?

¹⁹ Prediction: there will be prions found to occur naturally in plants. Not pathogenic ones. But there will be protein-only inheritance of traits going on. Both Darwin and Lamarck would be pleased.

research due to the potential for misuse. They, and many other governments, may move to legislate to avoid Guy Fawkes Scenarios²⁰.

5.4 The flowering of biotechnology

There are great opportunities offered by a number of new science discoveries. In futurewatching, 'great opportunity' red herrings are more common thanks to the constant refining of knowledge (see [Reversionism](#)) and the fact that almost every science paper (and certainly every patent) offers a different bright new future in the next 15 years. A selection is listed below:

- Certainly I think the 'array paradigm' stuff I discussed in the paper fits in here too. Many of the difficult, technically demanding assays available today or being developed will become ubiquitous, highly parallel and portable. I discussed some of the ramifications in that section and the thoughts about IT fit here too. There are a lot of exciting things being done on chips these days as people realise they can put more than just nucleic acids on there or that they can do more with nucleic acid chips that stick other nucleic acids on them. At a heavier level, the wider deployment of mass spectrometers, better electron microscopes and other such tech in many academic research environments as costs come down invites a lot more research to go all the way down to the molecular level (a good thing) and brings more inventive minds to the problems at hand (trivially, more mass specs means more and diverse kits and protocols means more questions get asked and answered). The possibilities for advancing knowledge are huge. And I think we all tend to work with a mindset that Knowledge Leads To Products. Perhaps that is worth questioning, but not in a science futurewatch.
- Electricity from bugs. In the next 50 years we can expect the fuel problem to become much more prominent (and many concerned parties are actively researching e.g. US DoE). This won't be because the oil runs out (not yet) but because of the issues discussed above (sustainability, pollution, and food-water-climate). It's interesting to consider whether biotechnology can provide answers here. As mentioned above, other industries may be more agile in this regard. But the generation of power from biological sources is still the biggest energy provider in the world (we just don't tap into it much, except as oil). Modifications to plants to produce power (either electrical energy –imagine that!–or chemical energy) should be entirely possible over the next decade and research should be encouraged.
- We will be inevitably surprised (and delighted) by the diversity of knowledge and opportunity offered by archaeal micro-organisms and by the 90+% of prokaryotes that still can't be grown and studied in culture
- Environmental changes and increasing public and governmental concern over food and water supply will mean all bio-based industries may need to adapt. Today's up-and-coming plant genetic modifications attempt to address some of these, with genes conferring tolerance traits for drought, salinity and temperature extremes. The responsibilities of agriculture as a major (*the* major?) user of land and water will become a focus of public concern and there is little doubt agriculture will be asked to do more on and with less. The effects of climate change may render many formerly

²⁰ A Guy Fawkes Scenario is one where it is very easy for anyone to create widespread damage. It's the reason for things like gun control, hazardous substances legislation, food inspectors and much else. In the current decade it has been shown that a viral genome can be easily synthesized and produced in a moderately well-equipped lab, and that weaponized anthrax can wreak havoc via the postal system – Guy Fawkes would have understood the possibilities.

productive regions or even countries agriculturally incompetent and biotechnology will be one of the few ways of either restoring competency or taking up the slack elsewhere. To this end, technologies such as the cloning of agricultural animals, the rapid production of quality plant seed via apomixis, and increases in photosynthetic efficiency via the activation/importation of C4 photosynthesis in ostensibly C3 plants are obvious routes to success that should be funded and well explored.

- Without an understanding of many other commodity industries, we can still presume that biological sources of their feedstocks will be useful. Certainly the paper industry rests entirely on biological productivity that can be improved or made more sustainable via biotechnological means. There must be others where biotechnology can provide gains and prove value.
- Lastly, the economy of scale available to the biologically-based industries might make some developments (or more correctly, products) feasible and economical. Agriculture is a huge industry and if turned towards land improvement, power generation, feedstock production or medicine manufacture it may be entirely capable of delivering the necessary quantities in a timely and cost-effective manner. Somebody is going to have to.

Specific nice-to-have's for the flowering of biotechnology:

- A working method for site-specific gene modification in non-model systems (e.g. the much-maligned chimeraplasty) would open up the GM field enormously
- Algorithms that make much more complicated cross-database, cross-profile comparisons much quicker (or new IT that has the same accelerating effect) would accelerate more or less everything in biotech research
- Reliable gene therapy in humans would have uncountable changes. And reversible gene therapy in humans would be startling and a little scary (compare plastic surgery and botox) .
- Undermining assumption. Confirmation of, for example, the heresy that obesity is due to a virus and the development of a therapy would create numerous shifts in society.
- Optimized economical methods to produce fuel substitutes from biomass e.g. ethanol (perhaps via a rapid cellulase produced via in vitro evolution) would alter geopolitical arrangements, lifestyles and agricultural practices enormously.
- Custom-built life (e.g. bacteria from component parts) would start another tree of life in the middle of ours.

Appendix –random other thoughts

Convergence

I'm ambivalent about the use of this term to describe so-called great leaps forward e.g. molecular biology being the convergence of chemistry and biology to form a new discipline. Sometimes I think just the name is new. Certainly, fusion/cross-fertilization/synergy of disciplines has always gone on. Today, I don't see disciplines as converging per se (were they diverging in the past, or running parallel?), but in a mass communication age they are interacting more and more. That's different to convergence because diversity is being maintained or (I'd argue) increased. The interaction gives birth to (sometimes temporary? on the timescale we're considering?) weird hybrids like molecular biology, bioinformatics, systems biology. I don't think that is 'melding'. So while I don't think it's anything qualitatively new under the sun, it probably deserves a mention as something quantitatively new (to, it should be said, a quite startling degree). This 'degree of startle' is hard to measure: one person's paradigm shift is another person's step change...and another person's "So what!?". Given all that, I think it's too early to call systems biology, for example, a 'discipline' (maybe 'approach' or 'field' or 'theory' or 'area' or 'philosophy' or--urgh!--'subdiscipline?') but molecular biology and bioinformatics have stood the test of time and I'll give them the label. I don't believe boundaries are breaking down; it's more that there is sufficient critical mass spanning some of the popular categories that they deserve to name themselves as 'systems biologists' or whatever.

Rife reductionism

I take the view that the holistic-versus-reductionist dichotomy has never been (a) what practising scientists actually do day in year out across the disciplines, or (b) something that happened particularly recently. We've been accusing the past of reductionism and patting ourselves on the back for taking a more holistic line ever since Capra wrote the first science book ever to thank John Lennon for being alive. However I think a fair bit of the historical analysis is just a labelling exercise occasionally informed by rose-tinted hindsight. We've always done both if we've been doing a good job.

Your mileage may vary.

Changing use of model systems in science

This could become a defunct approach. To quote Manfred Eigen: "A theory has only the alternatives of being wrong or right. A model has a third possibility: It may be right but irrelevant." While that is a bit sweeping, the use of models for knowledge discovery in genomics/RNomics/proteomics/gene therapy/etc. may be moribund. As technology develops, there is no need to do the work in mice or Arabidopsis or yeast when one is merely working up to cows or maize or *Streptomyces*; the tools for direct manipulation (and therefore knowledge discovery and product development) already or will soon exist.

There's interesting work on modelling the models in computers that touches on this. Why do a mouse experiment in the lab when you can do it virtually then proceed to human cells in culture that same afternoon?

Of course, we are going to continue to use models in medicine over the next 15 years. 15 years ago I was doing a miniproject in a lab on non-mammalian substitutes for the Ames test of carcinogenicity; Ames is still widely used and there are hardly any validated, credible animal-free tests for pharmaceuticals. Human cell culture will get better but won't become obsolete. Moreover, we'll also use former 'model' systems where appropriate e.g. for the production of certain heterologous proteins yeast is sufficient.

And we're going to need models to solve the Two Big Puzzles in Biology (embryogenesis and the brain). No question.

Science fiction

Aquaculture has always seemed to me very science fictional. It has been a background feature of a lot of science fiction books since the 70s and the biggest problems envisaged then was dealing with collection and processing and keeping out the hungry whales from eating all our plankton. The difficulties of ecology and disease aetiology in aquaculture farms weren't anticipated and I am not sufficiently abreast of the literature to make any comment. But in my mind, aquaculture belongs beside food pills and teleporters and taking the rocket to school.

The death or dearth of academic science

One comment in early discussions around the futurewatch was that "Peer review is falling apart; quality and professionalism are deteriorating; much more of science is in the hands of private enterprise and prevented from getting into the public domain"

I don't believe so. Certainly science is evolving. It is always the current generation that is reprimanded for being the one that is failing, that is selling short the hard work of previous generations. The golden age is never the current age. I don't believe this is true, and it isn't true in the small world of bioscience. How do you measure the lack of contemporary quality? (You need the perspective of decades.) Has our rate of innovation really dropped off? And what about the alleged deterioration of professionalism? I don't think such assertions should be made without supporting data. Then we could look at them, form hypotheses...do science!

Open access is an interesting development of late that is worth monitoring. It may have quite an impact on science and governmental policy about science. This is probably Information Futurewatch rather than Biotech Futurewatch though.

The percentage of scientists in the population may be flattening in the developed world but there are plenty of nascent minds out there that will contribute in the future. This goes back to the earlier point about the importance of food and water and the necessity for biotechnology to take on these problems: we have to feed and educate those minds to get their contributions.

I am concerned about what I see as a short-sightedness in high-science research these days. There is a lack of historical context that may or may not cause problems later on (it will certainly cause errors but these may have less impact in the fast-forward future). Plenty of published research seems to consider that nothing happened before 1996 (when journals started putting full text pdfs of research papers online) or before 1976 (the date of the earliest searchable full text patents on the US patent office database).