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Nanotechnology and Synthetic Biology: Implications and Opportunities for Alberta

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ALBERTA INSTITUTE OF AGROLOGISTS

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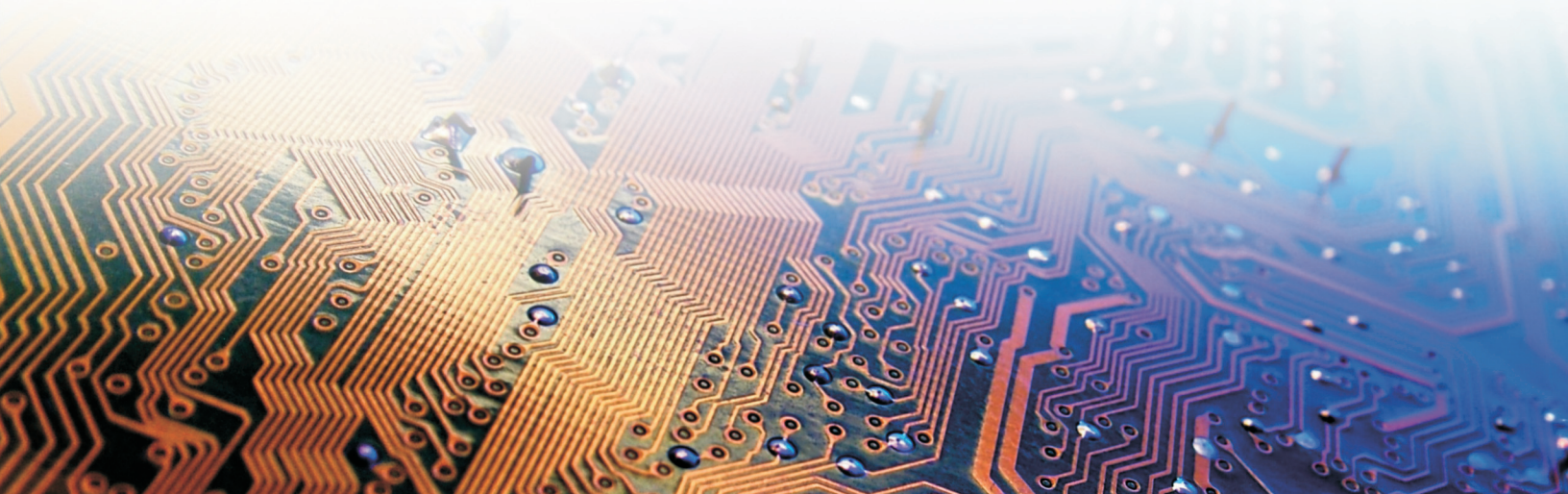

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Nanotechnology and Synthetic Biology: Implications and Opportunities for Alberta

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PREFACE

This document draws from recent work carried out by the Bio Economic Research Associates (Bio-Era) to explore which advances in enabling biotechnologies will affect the U.S. economy in coming years, with an eye to Alberta's unique environment. It is not a literature review, but a provocative opinion-editorial piece for further learning and discussion.

A familiarity with science is helpful but specialized knowledge of biology or chemistry is not required. The intention is increase awareness and perspective – to have the reader see the world around them in a different way after they finish. What won't be found here are definitive answers. These are young technologies that are evolving at a fantastic rate – never a good time for making accurate predictions, but a great time to decide to do some exploring.

We hope you enjoy this document and that you will share it with others.
Together, we will write Alberta's story.

Robert Carlson and Andrew Hessel
January, 2008

ABOUT THE AUTHORS

Dr. Carlson is a Principal at Biodesic, LLC, and a Senior Associate at Bio Economic Research Associates (bio-era). At the broadest level, he is interested in the future role of biology as a human technology. His writing on the growth dynamics if DNA technologies has resulted in the "Carlson Curve" being widely recognized as the biological equivalent of Moore's Law. Recent projects include a Department of Energy funded study on the economic impacts of Synthetic Biology and a finishing a book on synthetic biology. His current technical research focuses on developing new molecular assays for use as engineering tools and to quantify properties of single cells. An early application of the technology will be rapid, multiplexed cancer and disease diagnostics. From 2002 to 2007, Dr. Carlson was a Senior Scientist in the Department of Electrical Engineering at the University of Washington, and from 1997 to 2002, he was a Research Fellow at The Molecular Sciences Institute in Berkeley, CA. He earned a doctorate in Physics from Princeton University in 1997.

Andrew Hessel is a genomic scientist and consultant in DNA technologies. Working with leading academic and commercial groups, he has traveled the globe for more than 15 years in his exploration of new genome technologies. A major interest is synthetic biology, a science based on automated DNA synthesis that is transforming DNA into an easy-to-use programming language for biological systems. Andrew's work is empowering a new generation of young Canadian researchers to tackle big biology-related problems like sustainable fuel production, environmental cleanup, superbugs and cancer. He is a strong supporter of open source biology for accelerating innovation and as a counterbalance to proprietary, profit-driven biotechnology R&D. In 2008, Andrew will launch an Alberta-based open source biotechnology venture that aims to begin development of personalized, affordable medicines for breast cancer.

INTRODUCTION

Recent history has brought many revolutions. The industrial revolution brought mass production and inexpensive goods to the world; the green revolution led to massive increases in the world's agricultural output; and the digital revolution brought global change to communications and computing. Now we are on the cusp of what might be the most profound revolution yet – the biotech revolution. This will open the door to the widespread modification and manipulation of living organisms. This is virgin territory, as empty as the Alberta prairie was a hundred years ago, and it holds tremendous opportunities for those that are brave enough to venture into the unknown.

It's not as though we don't have some understanding of life on this planet. We've used animals and plants for thousands of years to fulfill our needs. Living things provide food, transportation, medicines, and raw materials for our homes and our clothing. We're experienced breeders, farmers, and fisherman. Over the centuries, we've amassed large catalogues of organisms, domesticated countless species, and literally changed the world by our efforts.

But we've only recently developed technology that permits direct control over life – tools that allow us to reach deep into living cells and tweak metabolism to our specific needs, to literally program what organisms are able to do with their biochemistry. We've had them for roughly for decades. This, of course, is genetic engineering, developed in the early 1970's.

Today, there's a new flavour of genetic engineering that is coming to the forefront. It's called synthetic biology and it will be explained detail in the sections that follow. It didn't exist until about a decade ago, and most people (including many scientists) still haven't heard of it. Despite this obscurity, it has still managed to grow into one of the most powerful new technologies of this century.

Nanotechnology, another field that is also not on most people's radar yet, has a fundamental role in this biotech revolution. Doing science requires tools – microscopes, scalpels, test tubes, and the like. Going into the heart of the cell and watching what is going on, or performing genetic surgery on DNA, requires hands and eyes that work at the molecular level. Nanotechnology provides these. But why limit ourselves to just two of each? Why not have thousands of eyes and hands, or millions, or even billions? That's why nanotechnology is making it possible for a lone scientist today to run more experiments in a single afternoon than his or her predecessor could have done in a lifetime. Parallelization and miniaturization is driving the pace of biological discovery off the chart.

All this is exciting, but why are these two technologies – synthetic biology and nanotechnology – so important for Alberta? The answer is quite simple: the province's fortunes are almost entirely derived from biomass – that is, plant and animal matter of some kind or another. Living things (including ourselves), and things that were once living, are

essential to our economy and to overall health and well-being of our communities, as is the greater environment that supports this life. We need to make wise and responsible choices about how to manage these resources. This requires being at the forefront of emerging biological technologies.

The impact of biological technologies cannot be understated. As they develop, they will allow us to better produce, utilize, refine, and transform the natural resources available in Alberta into things that people want and need, here and in other places around the world. They will increasingly impact human health, animal health, energy production, food production, and the manufacture of chemical compounds. And, in the not so distant future, biological technologies will require us to rethink things that we may have taken for granted, including the fundamental nature of what it means to be alive and even the inevitability of death.

Section 1 - GENETICS AS INFORMATION TECHNOLOGY

DNA as digital data

Despite being almost four decades old, genetic technologies still tend to intimidate most people. To a large degree, this is because the science is still so unfamiliar, far removed from our day to day life. It remains an elite science. Working with DNA code still requires a specialized degree and expensive, unfamiliar tools. Genetic engineering isn't something that we typically play around with at home for fun. Yet only thirty years ago, the same could've been said about computers. Keep this thought in mind as you read on.

What exactly is DNA? What is a gene? What is a genome?
Most people have come across these terms before but have only a rough idea of what they actually mean. Here, we'll try to provide some foundation. To do so, we will use something people are more familiar with – computers – by way of example.

If you are reading this document, you understand the English language and know that it consists of 26 characters and a few special symbols for punctuation, etc. This notation can be used to record, retrieve, and transmit any human idea that can be written down. Computers have a language as well, but instead of having 26 characters, they use only two, represented by the numbers 1 and 0. This language is digital, meaning that each character is discrete. It can be a 1 or a 0, but nothing else.

For a computer to process information – for example, the word "DNA" – the data must converted into digital code. The rules for converting text are provided by the American Standard Code for Information Interchange, or ASCII [1]. In this encoding format, seven 1's or 0's are required to encode a single letter. Doing this translation we get:
1000100 "D"
1001110 "N"
1000010 "A"

Of course, computers don't really store 1's and 0's on their hard drives or push them through their electronic processors. These characters are merely representations of electrons.

DNA is also a digital language, one that uses four letters, each representing one of the four different nucleotide molecules that are part of the DNA helix. These chemicals are depicted by the letters "A" (adenine), "T" (thymine), "G" (guanine), and "T" (thymine). In the DNA code, it takes three letters (a triplet) to encode an amino acid, the structural components of proteins. Since there are 20 amino acids, and an English letter that corresponds to each of them, we have a near-complete encoding scheme for writing English in DNA.

GAT "D" (aspartic acid)
AAT "N" (asparagine)
GCT "A" (alanine)

Thus "100010010011101000010" in the language of computing is equivalent to "GATAATGCT" in the language of biology.

DNA, then, is just a form of chemical data storage, roughly the same as information stored on a computer hard drive. To extend the comparison a bit more, a gene can be thought of as one of the programs on the disk, and all the information on the disk would be equivalent to a cell's genome. In general, DNA is software code for cells, and cells are biological hardware.

Hopefully, this explanation makes DNA, genes, and genomes a little more familiar to those that may not have previous experience with genetic science. What should be coming into clearer focus is that genetics is a language – in fact, it is a biological programming language – and anyone with even a basic understanding of computers is qualified to learn it.

Systems biology

For an electronic computer to function, it needs an operating system, like Windows XP, MacOS, or Linux. These are collections of programs that tell the computer how to do basic tasks, like how to keep track of where it writes information on the hard drive. Operating systems also manage how the computer deals with input signals (eg. from a keyboard) and, based on what instructions it receives, what output to generate (display on screen, print, etc.). A cell's genome has the same basic functionality.

What's the major difference, then, between a computer and a cell? It's replication. It may be easy to duplicate computer software, but computer hardware cannot reproduce by itself. It takes a computer manufacturing plant to churn out copies of other computers. We know how to make computer factories that can take raw materials from around the globe, like silicon and plastics and copper, to make new computers. But we are still struggling to learn how cells turn chemical building blocks in nature into new cells, and how the information contained in the genomes directs these many processes.

Biological science, including genetic science, thus has two major goals: the first is to reverse-engineer cells and genomes to understand how they work. This informs biologists about the operation of the cellular processor itself (metabolism) and how the genome directs these processes. Reverse engineering cells is tricky business, since we still don't have all the tools to dissect metabolism. However, we have developed the necessary technology – DNA sequencing – to read the all information contained in an entire genome. Collectively, the reverse engineering of biology is often called systems biology.

Through DNA sequencing and a growing arsenal of high resolution biological detection and analysis technologies, systems biology is rapidly expanding the knowledge of how cells function. But even for simple cells like bacteria, this is a challenging job. It's not unlike trying to comprehend one of Apple Computer's manufacturing plants by taking apart one of their laptops and studying each piece.

The second goal of genetic science is to write new genetic programs. This is forward engineering and in practice it's an easier task. Forward engineering is a bottom-up approach to understanding metabolism, where programs – small ones, at first – are written and executed, and the resulting cellular metabolism observed. Forward engineering is the foundation of genetic engineering.

Synthetic biology

Genetic engineering, then, is biological software development. Writing DNA-based programs for cells is still very difficult. The first reason is because, as mentioned earlier, we don't fully understand cellular metabolism. It's like trying to write software for a computer processor that we don't have the specifications for. If a software developer tried to do this today, most of their programs would not run properly.

The second reason why writing DNA code is hard is because, well, it's DNA. It's a chemical. Genetic engineering has, until very recently, been done by performing complex chemical reactions on the DNA molecule itself, editing the code with special enzymes that act as molecular scissors and glue, assembling letters and words as one might cobble together a ransom note. Obviously, having some type of word processor for DNA code would make the whole process a lot faster. In fact, this is the foundational improvement brought to genetic engineering by the new technology of synthetic biology.

There's nothing all that special about synthetic biology, really. What it does is make DNA code easier to play with, and that's about it. But the fundamental importance of DNA to life makes it a very powerful technology indeed. So powerful, in fact, that in the next few months, synthetic biologists are promising the first synthetic bacterial genome.

What is even more thought provoking is that, barring unforeseen interventions, the rapid evolution of synthetic biological technologies will make it increasingly easy for almost anyone to do the same thing. In our high schools, programming and booting up new life forms could very well become just another lab exercise alongside the dissection of frogs. By as early as 2010, there could be thousands of new species on Earth whose lineage will not be traced to some fossilized ancestor, but to a person. Perhaps to your son or daughter. Perhaps even to you.

Section 2 - ENABLING TECHNOLOGIES

Mastering any new language requires one to grasp reading, writing, and comprehension of that language. In the case of DNA, it's not as easy as picking up a textbook. The language of DNA, written in chemical letters, is as incomprehensible to us as trying to read the raw 1's and 0's that flow through the internet. Our fluency in DNA is dependent on technology-based tools, and our learning curve on advances in these technologies.

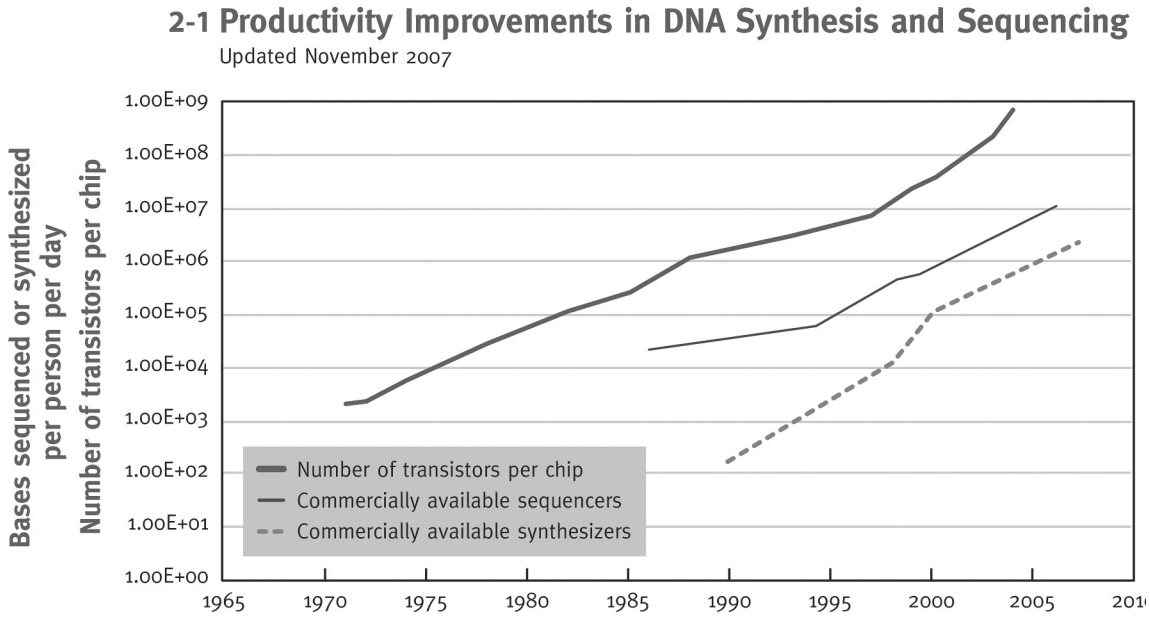

Figure 2-1. The amount of DNA that can be sequenced and synthesized by one person, running multiple commercially available instruments for one eight hour day, defined by the time required for pre-processing and sample handling on each instrument. For comparison, the number of transistors per Intel microprocessor is shown, representing Moore's Law.

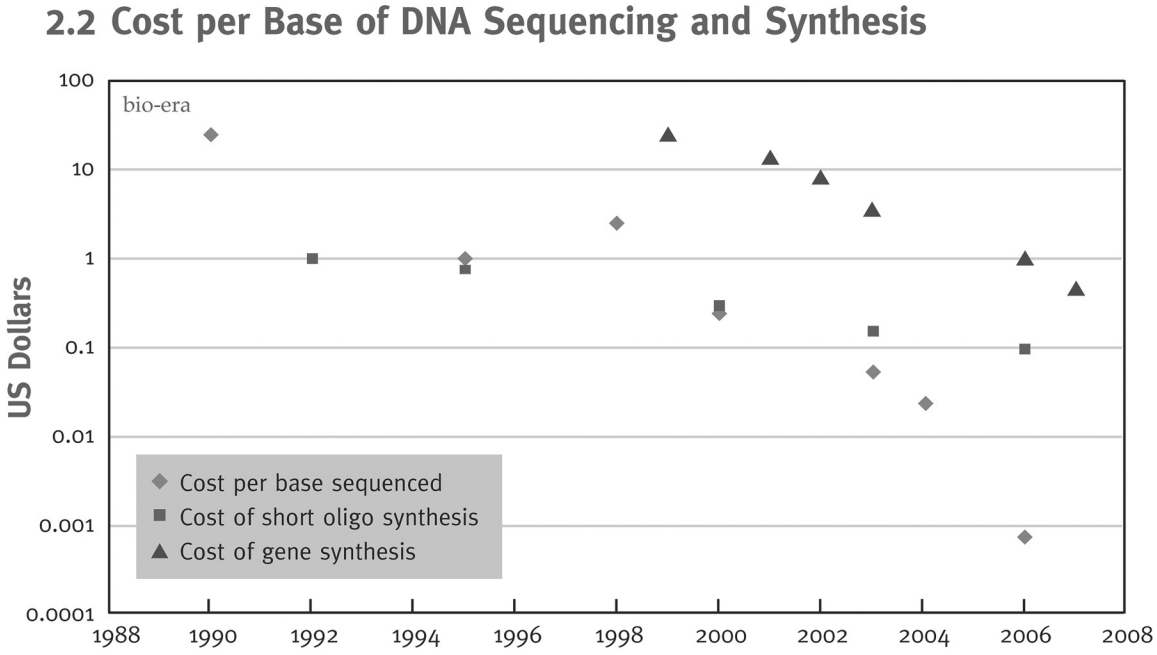

Figure 2-2. There have been dramatic cost improvements in synthesis and sequencing technologies achieved over the past twenty years. The continuation of these cost trends will be a major driver of genome sequencing and design capability in the years ahead.

DNA sequencing technology

DNA sequencing allows us to read genetic code. Fred Sanger developed the first sequencing technique in the late 1970's. It was tedious to perform and required toxic and/or radioactive chemicals. Although refinements were made throughout the 1980's, the basic technology remained virtually unchanged until the late 1990's, with the commercialization of capillary DNA sequencers. These units, the workhorses of the human genome project, provided better performance and were amenable to automation, significantly increasing outputs. This generation of equipment has recently been retired in favor of new nanotechnology-based "sequencing by synthesis" devices that deliver marked improvement in cost per base and speed, but still cost about $500,000 to purchase and $10,000 per sequencing reaction [2].

The next generation of machines to appear may still be expensive to buy, but will be very affordable to run. Fueling their development is the Archon X Prize, a $10M winner-take-all incentive award up for grabs to the first group able to sequence 100 humans in ten days at a cost of no more than $10,000 per genome [3]. Working prototypes that put the prize within reach are expected by 2012, with commercialization to follow by 1-2 years. As of January, 2008, six groups were registered in the competition. Somewhat disappointingly, no Canadian entries are in the running. Whatever group does win will collect some serious bragging rights. The first human genome, completed in 2000, cost roughly $3B to produce. Today, a full sequence can be ordered on demand, but the price remains high – about $300,000. [4].

Sequencing is a highly competitive business, but there is money to be made. The market for sequencing services exceeded $7 billion globally in 2006 and is expected to grow 10-15 percent through 2009 as DNA diagnostics in medicine and metagenomic (population genomics) and bio-prospecting (high value gene/organism searches) efforts continue to ramp up. These estimates may prove to be on the low side, however, as private genomic screening services such as 23andMe [5] and deCodeME [6], launched in late 2007, are opening up new consumer markets for DNA sequencing services and genetic analysis. Realistically, the need for DNA sequencing is not going to peak for decades.

DNA synthesis technologies

Technologies for writing DNA have lagged a few years behind technologies for reading – hardly surprising in the context of learning a new language. As with sequencing, the basic chemistry of DNA synthesis – the stepwise addition of phosphoramidite-modified nucleic acids – has remained almost unchanged for over two decades. The result of DNA synthesis is DNA biologically indistinguishable from natural DNA. However, although the chemistry is greater than 99% efficient per step, cumulative errors limit the size of the DNA that can be produced to short fragments (oligonucleotides, or simply oligos) of 100 bases or less.

Performance improvements have again come from nanotechnology, which has permitted parallelization and miniaturization of the synthesis reactions, allowing more bases to be made per dollar.

Chip-based technologies that allow synthetic DNA manufacture directly on glass slides are the current state of the art. They are based either on microelectromechanical (MEMS) chips developed by Texas Instruments that use micromirrors to drive light-directed DNA synthesis chemistries, or ink-jet deposition systems that can precisely meter out picolitre volumes of the chemical reagents at precise locations. Their use has reduced the cost per base of synthetic oligos by several orders of magnitude, but the fundamental chemistries are still the same. Chip-based DNA is now widely used in diagnostic applications in the form of microarrays. As the quality of this DNA has improved, groups have also begun using these oligos as the starting point for assembling longer DNA strands.

A thriving DNA synthesis industry has emerged over the last decade, with dozens of so-called DNA "foundries" appearing around the world. Productivity has increased something on the order of 700 fold over this period, a doubling every 12 months or so, while costs have dropped from about $30 per base in 1998 to about $0.50 today. In 2006, the market for DNA synthesis services reached nearly $1 billion. Most commercial groups offer oligosynthesis and gene synthesis via mail-order, outsourcing that is creating the possibility of entirely new biotechnology business models. However, the construction of longer sequences or full genomes is still very rare given the cost per base.

For the moment, the greatest technical challenge in DNA synthesis remains the assembly of oligos into longer sequences. While there is no theoretical limit to the size of the sequence that can be assembled using current technologies (the largest published is 582,970 bp), the low reliability of currently assembly techniques combined with the relatively expensive cost per base limits the number of groups that can afford to design longer sequences. Integrated chip-based oligo synthesis and assembly, such as that reported by Tian et al [7], promise megabase-sized fragments at a cost of about a penny per base.

Bioinformatics

Information technologies provide comprehension about the structure of the DNA language and inform researchers on how cellular hardware execute the programs. Of the three major enabling technologies, this is by far the most challenging to develop. It requires the cooperation of a large number of individuals and groups and the management of vast amounts of data. The scale of the challenge is roughly equivalent to the Google Earth project, except instead of integrating datasets about the planet surface, the goal would be to model the metabolic processes occurring within a cell.

Bioinformatics faces an uphill battle. Data management and analysis is already falling behind the ability to generate raw data from DNA sequencing farms. Furthermore, it is a highly

specialized field that has almost no commercial market other than a handful of pharmaceutical firms. Bioinformatic software development tends to be grant-supported. Moreover, the hardware requirements necessary to perform dynamic modeling simulations on millions of interacting molecules are daunting and, again, tend to be supported by research grants. Although the volume and complexity of biological data is growing exponentially, there are few opportunities to directly monetize the data in support of the necessary IT infrastructure – a losing game in the long run.

Compounding the problem is the fragmentation of life science data. Standardization was largely overlooked during the rapid expansion of systems biology, despite the larger trend in software development to create standards. As new biological measurement tools are developed that are faster and more reliable, it may be easier simply to create new datasets from scratch.

Meanwhile, synthetic biology is actually starting from scratch. It has also benefited in that two seminal thinkers in the field, Tom Knight and Drew Endy, were first trained engineers before they moved into biology. As such, they recognized from the outset the need for standardization and modularity if reliable genomic programs were to be developed. Furthermore, rather than doing genetic engineering in fulfillment of a singular research goal, where the objective is to generate data as quickly as possible to avoid being scooped by a competitor, they embarked on a fundamental effort to create a library of genetic modules with defined functions and "snap together" ends. In theory, these modules could be assembled in almost any combination, tuned or modified as isolated blocks of code, and reused at will. Inspired by Lego™ blocks, they called these their genetic modules BioBricks™.

BioBrick™ parts, they reasoned, should reduce the need to continually synthesize DNA from scratch and also permit the construction of more complex genetic circuits from precursor parts. In turn, these more complex circuits become parts themselves, which can then be assembled to create even more complex systems, and so on. But would these ideas actually work in practice?

Modular biological engineering

The power of innovation through combination of existing components is demonstrable in fields such as electronics, software, and more recently, combinatorial chemistry, where new innovations are typically built on a foundation of previous developments. In commercial software development, for example, new applications are often created from assembling pre-existing code modules into new configurations. Nature also uses this approach. Modularity is evident in the organizational structure of the genome and metabolic networks of E. coli and other organisms. In other words, life seems to prefer plug and play configurations of genome code that make it easy to swap out modules.

Not all metabolic engineers agree that a standards-based engineering approach is useful. There is certainly plenty of ammunition for cynicism. A metabolic circuit whose performance in a particular E. coli strain is well-characterized and predicable under defined environmental conditions may well produce unpredictable results if transferred to a related species or even a different E. coli strain, or even the same strain if the environmental conditions are altered. In addition, biological systems face the inherent instability resulting from mutation and genetic drift, forces that typically do not come into play in other engineered systems. (Airplanes, for example, do not evolve after they have been made.) Still, creating standardized gene modules would seem an obvious way to reduce unknown variables and increase the chance of success, particularly without full comprehension of underlying cellular processes.

Working with synthetic biology and modular BioBricks™ is sufficiently different from traditional genetic engineering approaches that biological education requires significant reform. To begin this process, Knight and Endy developed their own applied teaching program called the Intercollegiate Genetically Engineered Machines competition (iGEM), which launched in the summer of 2004 with 5 teams. In 2005, with the addition of a Toronto, Canada team to the competition, intercollegiate was revised to international.

iGEM allows widespread yet low-cost exploration of whether biological systems can be built with modular biology. Beyond this goal, the founders hoped to promote an open and transparent biological engineering community, in the spirit of the open source programming community. Each participating team is provided with parts and instructions to manipulate them or to make more of them. One of the few rules is that teams must share any new parts they create, plus any associated data on their project.

The iGEM program has grown exponentially. In the 2007 season, the competition attracted over 750 participants and led to the creation of 800 new BioBrick™ parts. Significantly, in just a few years, iGEM results have awakened many researchers to both the concept and value of standardized biology. There is growing evidence that both standard parts and the open biology strategy not only works, but also boosts innovation while increasing efficiencies [8]. Certainly, creativity appears to be enhanced. A sampling of the over fifty projects presented at MIT last November included a self-powered biosensor for toxins [9], a bacterial-based computer [10], and E. coli bacteria modified to be artificial blood cells [11].

The BioBricks Foundation (BBF) [12], a not-for-profit organization also founded by Endy, is now examining the larger issues pertaining to the technical and legal standards of modular biology.

Societal and economic shifts

Electronic computers had existed for over thirty years before they started to significantly reshape society. Their use was limited to academic groups, governments, and large corporations. As the cost of computing began to fall, they became individually affordable. People began to experiment and play with computers at home as a hobby. Small computer-based businesses were created. Courses were developed. The mainstreaming of computers quickly led to new markets, industries, and applications, many of which were not predictable in advance of their appearance. For example, the economic potential of internet search and social networking only became apparent after their deployment. It is not hyperbole to state these technologies changed the world.

Because of the falling costs of and growing capability of enabling technologies, genetic engineering is similarly poised to move into the mainstream. Predictably, we will see a trend towards smaller biotech companies operating this sector, with a broader range of applications under development. Some of these companies may operate as virtual entities, designing biotechnologies from cafes or from basement offices. We should expect to see a much more complex biological ecosystem in a few years than the one that exists today.

Focus on Alberta

- There's a sad story about how Alberta lost the early lead in DNA sequencing technology. The capillary DNA sequencing technology that enabled the human Genome Project was in fact prototyped and developed at the University of Alberta by Drs. Norm Dovichi and Jianzhong Zhang [13] in the late 1980's, far in advance of any competitors. It is a case study in lost opportunity. At the time of the development, the university was unwilling to patent the invention. Repeated attempts to access public sources of funding for Canadian research were met with failure, forcing Dovichi to seek foreign funds. Although Canadian industry eventually provided funding and licensed the IP from the University of Alberta, the lack of timely IP protection gave rise to a competing IP that weakened the value of the patents and the return to both the University and the inventors. A commercial success in the hands of Applied Biosystems, the technology licensee, the invention represented an overall loss for Canada in lost royalties, job creation, and loss of talented staff to the US. Shortly thereafter, Dr. Dovichi himself left Alberta to accept a position at the University of Washington, where he remains as an Endowed Professor of Analytical Chemistry.

- Alberta is expected to be a heavy user of sequencing technologies in basic research, health technologies, livestock management, environmental monitoring, and bioprospecting, particularly in relation to oilsands operations, where the identification of microbial processes could facilitate recovery of petroleum products, performing heavy crude upgrading, or reduce the environmental contamination that results. The province should consider making larger investments in prospecting, as such surveys can reveal new metabolic pathways with high commercial value.

No incentive prize has yet emerged to accelerate innovation in synthesis technologies. Incentives of this type identify to the sponsors technology leaders regardless of their geographical location, and facilitate early licencing and commercialization opportunities. Properly protected, a breakthrough in synthesis technology could very well lead to a major new biotech company within the province. Should Alberta consider sponsoring such a prize?

- Molecular archeology could one day become a prominent area of research for Alberta. Dinosaur Provincial Park is the source of some of the world's best-preserved dinosaur fossils. With advanced sequencing technologies, the full genome of these creatures can be recovered from only a few well-preserved cells.

- Dr. Mike Ellison, at the University of Alberta, is a leading authority on the computer modeling of the E. coli bacterium. In general, Alberta has considerable expertise in systems biology and bioinformatics.

- Alberta entered the iGEM competition in 2006 with a team from Calgary led by Dr. Christian Jacob, a professor of computer science. Teams from the University of Lethbridge and the University of Alberta joined in 2007, for a total of about 50 students and supervisors. Up to 100 students could be involved in 2008. Alberta Ingenuity provides a comprehensive support package for iGEM teams in the province.
Do you want to participate?

- Alberta universities have undergraduate courses in synthetic biology beginning in Fall 2008. In addition, the Digital Biology Network, a 'professional' version of the iGEM program that aims to seed applied projects and companies, launched in January, 2008.

- What might a next generation biotech startup look like? What might people decide to program with DNA when a million basepair construct costs $1000? Or a gigabase construct?

- Attracting researchers focused in synthetic biology could be a challenge for Alberta. Researchers experienced in this area are in high demand and are being offered attractive incentives by leading institutions. Cooperation will be required by institutions, funding/investment groups, and government to compete for top talent.

Section 3 - GENOME ENGINEERING APPLICATIONS

Advances in genomic technologies have the potential to affect virtually every major sector the Alberta economy. In addition to companies that may focus on developing enabling technologies, improvements in DNA sequencing and synthesis, together with high performance informatics, will permit a larger number of researchers and companies to engineer novel metabolic pathways for the production of energy, chemical, and pharmaceutical products.

From an economic standpoint, the choice of what applications to develop will be very important for those that choose to focus on metabolic designs. In general, application space that is novel (no competition), addresses large markets (potential revenues, mass market appeal), does not release GMOs or biologically modified compounds into the environment (low safety concerns), and is not a human therapeutic (low regulatory barriers) represent good choices for exploration.

A number of key industrial sectors have already been targeted by early adopters of these technologies. A selection is summarized below in Table 3-1.

Table 3-1. Application areas for biological engineering and design.

Industrial Sector	Bioprocess Advantages	Representative Companies
Chemicals - commodity or specialty, plastics, polymers, enzymes	Favorable reaction conditions/reduced energy use, reduced waste, biodegradability, cost	Dupont, Metabolix
Pharmaceuticals and Healthcare	Cost of discovery, manufacturing costs, synthetic sources, personalized medicine	Achemix, Amyris, Sembiosys, Geneart, Oncolytics Biotech
Vaccines	Speed, flexibility of development, ease of storage, rapid distribution	GeneArt
Energy, biomass to fuel. Biofuels, hydrogen	Reduced emissions and wastes, petroleum alternatives, enhanced recovery	BP, Armyris, LS9, Synthetic Genomics
Pulp and paper	Lignin removal, waste reduction, reduced chemical costs	Cargill
Agriculture	Yield improvement, drought resistance, output traits	Cargill, Monsanto, Performance Plants
Electronics	Precision materials deposition and assembly	HP, Agilent, Intel
Bioremediation	Toxic wastes in soil, air Wastewater disposal	Greenfuel

The chemical industry is one of the largest and most important sectors for the application of genome engineering. Industrial biotechnology is yielding new methods for producing chemicals with environmental or performance advantages, and is making significant inroads into the $1.8 trillion global chemicals sector. The range of possible end-products from industrial biotechnology ranges from inexpensive bulk chemicals such as ethanol to specialty chemicals that cost thousands per gram. Currently, the most economical applications are fine chemicals and pharmaceuticals, but an expanded range of products is expected in the coming years.

Driving this shift is interest in green chemistry, degradable materials, sustainability of resources, and waste minimization. Bioprocesses are attractive because of the reduced energy requirements for production, and the reduction or elimination of high pressures, temperatures, and corrosive conditions required for chemical synthesis. Additionally, the outputs may be more environmentally friendly than chemically-produced outputs, particularly in the case of biodegradable plastics. Biotechnology start-ups, agribusiness companies and large chemical conglomerates are participating in this transition. For example, DuPont has set a corporate goal of deriving 25% of its overall product sales from renewables by 2010. Virtually any chemical derived from carbon in petroleum, including widely used products such as lubricants, waxes, plastics, synthetic rubber and asphalt, can be produced from renewable plant resources.

Attracting wide attention right now is how genome engineering and design approaches are creating the possibility of clean, sustainable fuels while also addressing the issues of environmental pollution. This is explored in greater detail in Section 5.

Application development will soon extend to completely novel organisms. Once this is achieved, a new evolutionary selection process, one driven by human ideas about fitness rather than natural selection, will emerge. This memetic evolution could drive synthetic species development at a pace equivalent to 100 million years per calendar year. It could also produce radically different metabolic processes than could be selected for in the natural environment.

Focus on Alberta

- Alberta's prosperity in large part is derived from the oil and gas sector. The province's conventional oil industry accounts for thousands of jobs in exploration, production, transportation, refining, distribution, and marketing, and generated $3.7 billion in royalty payments between 2003 and 2006. Similarly, oil sands are also an important resource for Alberta, generating $4.3 billion in royalties between 2004 and 2007 [14]. Genome engineering has the potential to enhance this industry in the short term, and to replace it with sustainable energy options in the long term. Diverting even a small fraction of the resources these firms currently invest in conventional infrastructure could significantly accelerate life science research in the province.

Oil sands are the most expensive and polluting source of oil in large scale production, producing as much greenhouse gases in a day as a third of California's automobiles [15]. Freshwater is also consumed in substantial quantities, potentially threatening the health of the Athabasca river ecology. Some of this water ends up as liquid waste in highly toxic tailing ponds, a long-term liability for the oil sands industry. Biotechnologies are likely to play an essential role in environmental reclamation and remediation efforts.

• Tailing ponds may harbor organisms able to accelerate remediation processes [16]. Ocean metagenomic efforts have identified new species and genes in large quantity [17]. Similar techniques applied to tailing ponds could provide valuable insights into engineering organisms for cleanup purposes.

• Calgary-based Sembiosys Genetics hopes to enter the global pharmaceutical market. SemBioSys technology permits proteins to be expressed in plant-oil seed bodies, facilitating large scale manufacturing, storage, and processing of products. The company is leveraging this technology to address high-value market opportunities, including pharmaceuticals such as insulin, used in the treatment of diabetes, and Apo AI, a cardiovascular therapy, as well as vaccines and animal health products.

• University of Calgary professor Peter Facchini is using metabolic engineering to control plant secondary metabolite production. His research focuses on Papaver somniferum (opium poppy), which has the unique ability to synthesize morphine, codeine, and a variety of other alkaloids of pharmaceutical importance. The metabolic engineering of these pathways could create new value-added organisms worth billions, while potentially reducing illicit drug trafficking opportunities.

Section 4 - NANOTECHNOLOGY AND APPLICATIONS

Overview

Nanotechnology refers to applied sciences and technologies that involve the control of matter or the fabrication of devices on the nano-scale, typically between 1 and 100 nanometres (10-9 metres, nm), or roughly the atomic to molecular scale. For perspective, the diameter of a human hair is about 80,000 nm.

It is a young and rapidly growing area of research and an exact definition of the field nanotechnology can be elusive. Some nanotechnologists believe that measurement or visualization at atomic or molecular scale constitutes nanotechnology, while others maintain that demonstrating control and restructuring of matter at the nanoscale – for example, the atom-by-atom design and fabrication of structures – is a necessary element. In general, nanotechnology can be considered science and engineering performed on a molecular scale.

How matter functions and organizes on the nanoscale has yet to be completely understood. It is complicated by the fact that at this scale even well characterized elements such as gold, silver, and silicon can display very different physical properties because of quantum effects.

Beyond basic understanding of matter at this scale, a major challenge is determining how to actually assemble different types of nano-sized particles into more complex systems with useful functions. Other challenges include how to control these devices, and how to address issues of safety, persistence, and toxicity of nanoparticles in the environment.

Like synthetic biology, nanotechnology is considered a general purpose "platform" technology because of its potential impact on almost all industries and all areas of society. Nanomaterials and processes are expected to increasingly influence applications that include electronics and computing, biomedical and environmental sensors, and drug development. Dr. Mihail Roco of the U.S. National Nanotechnology Initiative has outlined four generations of nanotechnology development (Figure 4-1). Today, most nano-materials are passive materials in that they are designed to perform one task. Many consumer products have begun to incorporate passive nanoparticles into their formulations – sometimes delivering significant performance benefits, sometimes delivering only a new marketing buzzword. Such products include paints, waxes, antibacterial wound dressings, and air filters [18].

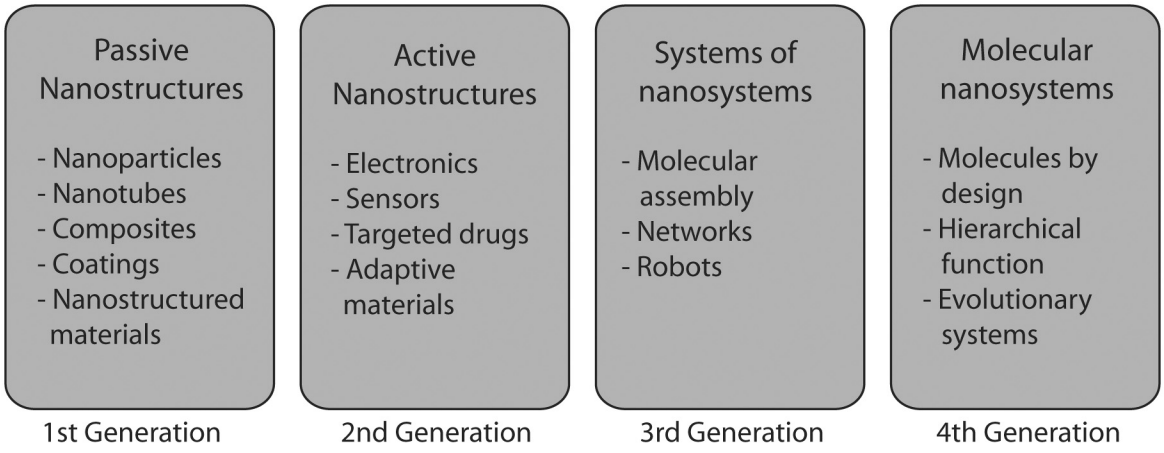

Figure 4-1. Expected evolution of nanostructured materials.

One area that is attracting wide attention is the use of nanomaterials in battery technology. New methods of manufacturing electrodes have increased efficiencies and shortened recharge times. A leader in this area is A123 Systems, based in Watertown, MA. The company is commercializing high capacity lithium ion battery packs that allow plug-in recharging for a number of automotive manufacturers..

The pharmaceutical industry has also explored applied nanotechnology. It has been estimated the industry sells over $1B of nano-particle drug formulations (which can have very different activities than the same drug prepared in conventional ways), particle-based drug delivery systems, or drug-coated devices like cardiac stents.

Second generation nanoproducts – the current state of the art – introduces the idea of active nanostructures that can perform multiple functions, for example, materials that can sense their environment and perform simple logic operations, such as determining whether to release a drug compound or not. Such products share some similarity with simple genetically engineered machines and electronic circuits. For example, carbon nanotubes were recently shown they could be tuned to receive FM radio signals [19]. The researchers claim the system could also be configured as a transmitter.

Third generation nanoproducts are expected to begin emerging around 2010 and could see the creation of complicated systems with hundreds or thousands of components and multiple functions, not unlike a bacterium or genetically engineered machine. Nanosystems of this type may be able to form networks and work cooperatively, potentially organizing into hierarchical systems with complexity on the order of cells. For the moment, this generation and beyond remain little more than speculative exercises.

Bio-Nanotechnology

One of the most fascinating areas of scientific convergence today is the intersection of nanotechnology and biology and this is where our discussion will focus. As noted earlier in this report, the advances in enabling technologies that are driving biological engineering mainly result from nanotechnology-based improvements to otherwise conventional chemistries and devices. Soon, these advances may be reciprocated.

The late Richard Smalley, a Nobel prizewinning chemist and discoverer of the "buckyball", made the distinction between "dry" (or engineered) nanotechnology and "wet" (bio-engineered) nanotechnology. Living systems already display the features of the fourth generation nanosystems. The engineering of atoms and molecules into complex systems (and also the reverse – the breaking down complex molecules in to components) may be difficult for nanotechnologists and chemists, but these are processes that living systems do naturally and routinely, with incredible specificity.

Further convergence of biotechnologies and nanotechnologies could see new innovations in both fields. In practice, these areas inform (if not inspire) the other. High resolution molecular sensing permits nondestructive cellular visualization in real time, leading to better understanding of how cells function. For example, nanoscale instrumentation has been central to the analysis of gene expression, while fluorescent semiconductor particles, or quantum dots, have become common reagents in molecular imaging applications. The data fuels understanding of the cell as a complex yet tractable (and programmable) biological machine.

Conversely, the enzymatic mechanisms and functional diversity observed in cellular metabolism provides clues to how life processes like self-assembly, self-repair, and catalytic reactions can be engineered into dry nanosystems and used in new applications. Such research could lead to nano-based DNA 'typewriters' able to precisely string together billions of DNA bases in minutes under computer-control.

Enthusiastic proponents of nanotechnology suggest that it may one day be possible to manufacture almost anything from simple chemical stocks – recall Star Trek's Captain Picard sitting in his ready room ordering a hot cup of Earl Grey tea. Conceptually, nanofactories of this type might evolve from today's 3-D printing technologies, where polymers are deposited layer by layer to manufacture physical prototypes of any shape, with size being limited by the physical dimensions of the printer. Nanofactories would in theory permit printing of complex, fully-functional devices – for example, a cell phone, or even another nanofactory. The idea is so compelling that it has been explored in dozens of science fiction novels in recent years, but practical, real-world devices are not expected any time soon.

What is not science fiction, however, is automated DNA synthesis – what Drew Endy calls a "matter compiler" for DNA synthesis. We can essentially create any DNA program we want, and use this to program any cell we want. Cells already display fourth generation nanostructure characteristics. Indirectly, then, DNA synthesis allows us to leapfrog directly to fourth generation "wet" nanosystems. Cells can't make cellphones (yet), but the outputs do encompass a wide range of economically important outputs. Through DNA, nanomanfacturing is alive and well.

Nano-toxicology

Nanotechnology may challenge conventional risk models used to assess environmental impact. The routes of exposure, biological uptake, tissue distribution and toxicology may be very different for nanoparticles and even for nanoparticle formulation of well-studied compounds [20]. Conflicting reports have been published and further study will be required. As with synthetic biology, a global and integrated approach to risk management will be necessary to ensure public safety without unnecessarily slowing development.

Focus on Alberta

- Edmonton is the home of the National Science and Engineering Research Council's National Institute for Nanotechnology (NINT). Founded in 2001 as a partnership between NRC, government, and the University of Alberta, the $120 state-of-the-art Institute was completed in 2006 and has some of the best laboratory facilities in the world. It secures Alberta's position at the center of this growing field and is on track to be one of the top five global nanotechnology centers by 2010. The facility is headed by Dr. Nils Petersen.

- U of A professor Steve Kuznicki researches nanotechnology-based "molecular sieves" that permit controlled separation of molecules at extremely high resolution, allowing for improved processing of oil sands and the possibility of new semiconductor materials. Dr. Kuznicki is also exploring nanoparticulate silver formulations with antimicrobial properties, now a common coating in materials like bandages and automotive interior panels.
- NINT research Hicham Fenniri develops studies self-organization of molecules into structures with predefined dimensions and physical properties. His group has also devised a technique for spectrographic barcoding with uses in high-throughput drug development, genomics, and diagnostic applications.

Section 5 -BIO-ECONOMICS

The size and shape of the bio-economy

The words "biotechnology" and "biotech" are often used in very limited and inconsistent ways. They may be used to describe only pharmaceutical products, or in another context only the industry surrounding genetically modified plants, while in yet another context a combination of biofuels, plastics, chemicals, and plant extracts. The total economic value of biotechnology is therefore difficult to assess, and it is challenging to disentangle the component of revenue due each to public and private firms. Further complicating the situation is that results from private companies are self-reported and there are no publicly available documents that can be used for independent verification. One estimate, based on data from 2004 (explicitly excluding agricultural, industrial, and environmental biotech firms), suggested approximately 85% of all "biotech" companies are private, accounting for a bit less than 50% of employment in the sector and 27% of revenues[21].

These numbers are explored in more detail below, but a rough summary is as follows: As of 2006, biotech drugs accounted for about US$ 65B in sales worldwide, with about 85% of that in the U.S. Genetically modified crops accounted for another US$ 6 B, with industrial applications (including fuels, chemicals, materials, reagents, and services) contributing another US$ 50-80B, depending on who is counting and how. Annual growth rates over the last decade appear to be 15-20% for medical and industrial applications, and 10% for agricultural applications. Revenues within the U.S. are estimated about US$125B, or approximately 1% of GDP, and growing at a rate of 15-20% annually. In comparison, total Alberta bioindustry revenues for 2006 were estimated to be approximately CDN $814M [22].

Health Care Biotech

The pharmaceutical industry amounts to about US$ 250B in sales annually in the U.S. and US$ 600 billion worldwide[23]. Estimated sales of biologics in the U.S. range between US$ 40 and $53B in sales in 2006, with a 20% annual growth rate over the preceeding five years [23, 24]. The rest of the pharmaceutical market - the small molecules - depends heavily on biological technologies during drug development and clinical trials. Including the sales of small molecules that were developed and tested using biotech tools would bring the total contribution of biotech to the U.S. economy to 3-4% of GDP.

The industry is changing. Approvals of new small molecule drugs have fallen by about 30% over the last decade despite a doubling in R&D spending[25]. Companies are also focusing on populations where drugs have a higher likelihood of being effective, an emerging branch of health care called "personalized medicine". This tailoring of treatment to the individual relies on the field of pharmacogenomics. Beyond this lies "theragnostics", denoting the fusion of therapeutics and diagnostics, integrating information from a diverse set of biomarkers (e.g., genomic, proteomic, metabolomic, etc.) [26]. The desire to tailor treatment and drug regimes to individuals helps to explain a recent trend in acquisitions.

Pharmaceutical companies are increasingly buying firms that provide diagnostic tools and services. Synthetic biology companies could prove even more attractive (or disruptive) to Pharma by offering the potential of therapeutics on demand.

Agricultural Biotech

The value of agricultural production in the US was about US$ 300B in 2006 [27]. The recent run-up in commodities prices pushes this rather higher. Genetically modified crops are still a relatively small fraction of total revenues, but GM acreage has been growing globally at just over 10% each year for the last decade. Brazil, Argentina, and Canada are similarly planting increasing amounts of GM crops.

While most existing GM crops are modified with a single gene altering a single trait, the next generation will contain multiple genes that confer more complex traits (known as "stacking"). The cost of developing these crops is expected to be so large that even the biggest agricultural biotech companies are partnering up to share risk and financial burdens. Synthetic technologies have yet to be widely applied in plant applications.

The complex interaction of consumers, interest groups, and regulators still pose significant risks, barriers, and challenges to companies developing GM crops. At the Agricultural Biotechnology Industry Conference (ABIC) held in Calgary in September of 2007, the lack of clear regulation was a common complaint. This suggests Alberta could attract increased agricultural biotechnology R&D investment merely by streamlining approval processes.

Animal health technologies are also expected to benefit from the rapid growth of biotechnologies and nanotechnologies. Biometrics, biomarkers, and rapid diagnostics will enhance tracking and certifications from farm to fork. Cloned animals were quickly approved for human consumption by the FDA [28]. Consumer acceptance, if not demand, of engineered specialty organisms and foodstuffs could grow, particularly for products actively sought by end users with verified health advantages.

Industrial Biotech

The size of this segment is the most problematic to assess, as portions of it might be attributed either to pharmaceutical biotech or to the chemicals industry. Thanks to the biofuels boom of the last few years, it is also growing rapidly. In general, the segment is attractive because the regulatory burden for non-pharmaceutical products is much lower. From laundry enzymes, to ice nucleating proteins used in snowmaking, to nutritional supplements, to bioplastics, to enzymes and organisms producing biofuels, the products of industrial biotech are becoming pervasive in the U.S. economy, and represent end applications for which Alberta biotechnology companies could potentially compete.

Microbial Synthesis of biofuels

Over the next five to ten years, fundamentally new biological technologies to produce biofuels will begin entering the market. Given the dependence of Alberta's current economy on petroleum production, it is crucial that research, development, and investment in this area be a majority priority for the province.

In the near term, microbes will be subject to modification to improve their existing fermentation pathways. For example, DuPont's improved butanol-producing bacteria could begin having an impact in the market within the next two years. Similarly, SunEthanol is focused on improving the yield from the so-called "Q Microbe", Clostridium phytofermentans[29], a naturally-occurring anaerobic microbe that converts cellulose to ethanol with a surprisingly high efficiency.

But a more significant change will soon follow, expanding biofuels beyond ethanol and butanol. The strategy of improving the biofuels production pathways in existing organisms will rapidly be supplanted by wholly synthetic organisms, engineered specifically for the direct conversion of feedstocks into transportation fuels similar to gasoline or diesel. It is here that the utility of rapid gene synthesis and standardized, composable parts will become increasingly significant to Alberta in the next few years. The application of these technologies to industrial biotechnology is already well past academic exploration and well into commercialization.

The economic landscape is already shifting to the benefit of regions not typically known for conventional oil reserves. In 2006, Amyris Biotechnologies received a US$ 20 million investment specifically for direct production in microbes of fuels and fuel precursors. The company recently received the first tranche of B Series financing to the tune of US$ 70 million[30], with additional funding expected in the round. Amyris is pursuing microbial production of a general aviation fuel comparable to Jet-A, which CEO John Melo suggests will compete with petroleum at prices as low as $45 a barrel[31] by 2011. Achieving this goal could immediately open up a 3.2 billion-gallon-per-year market – the U.S. Air Force is planning to replace at least half its petroleum-derived JP-8 with synthetic fuels by 2010.

Amyris is by no means alone in this effort. Another company, cryptically named LS9, has received significant investment for the microbial production of "Renewable Petroleum" and of hydrocarbon fuels[32]. The number of companies pursuing biofuel production via synthetic biology, or a similar approach, is growing rapidly. However, to date, Alberta has no companies slated to enter this space. This, despite the fact that biology offers the possibility of producing fuels at volume, without the substantial infrastructure costs that characterize the traditional petroleum industry, suggesting the province could face new and unfamiliar global competition in the coming decades. Assuming these companies are successful, it is worth Alberta considering the resulting impact on the liquid fuels market, and more generally, the effects on structure of the economy as a whole.

Butanol, for example, is likely to emerge in the near-term as an alternative to ethanol for both physical and economic reasons. Unlike ethanol, butanol has only a limited miscibility in water. At concentrations above about eight percent, butanol begins to phase-separate from water, with additional amounts collecting above the aqueous phase. While this concentration is toxic to naturally occurring Clostridium species, efforts to build an organism that can survive under these conditions are already underway. If successful, this organism would enable production by fermentation in which butanol is simply pumped or skimmed off the top of the tank in a continuous process. The resulting reduction in energy consumption would constitute an enormous cost improvement.

Costs will fall even further as production eventually moves from alcohols to hydrocarbon biofuels, similar to gasoline, that are completely immiscible in water. For example, if LS9 is successful, the fact that hydrocarbon fuels float on top of water will dramatically reduce finishing costs for fuel production. Distillation will no longer serve either as an economic advantage to those possessing such infrastructure or as a barrier to those hoping to enter the market. This could produce large shifts in the oil industry. Beer brewing presently occurs at scales from garages producing a hundred litres or less to commercial operations running fermenters that process thousands to millions of litres per year. Thus, once in possession of the relevant microbe, increasing production of a biofuel may well be feasible at many scales.

The materials used as feedstocks and where those materials come could become the more significant economic driver. Petroleum products are a primary feedstock of today's economy, both as a raw material for fabrication and for the energy they contain. Bio-production could provide fuel and materials from a very broad range of feedstocks, including waste available at the municipal level, including yard waste and sewage. The addition of photosynthetic pathways could also provide a solar boost to the recycling process. Conversion of municipal waste to liquid biofuels would provide a valuable and important commodity in areas of dense human population, exactly where it is needed most. Thus microbial production of biofuels could very well be the first recognizable implementation of distributed biological manufacturing[33]. In two decades, there is very real possibility of fueling up your car with biofuels produced within your own neighborhood, perhaps even your own home.

Looking further ahead, cars themselves might become a production unit for the fuels they consume. A paper published in the spring of 2007 demonstrated a synthetic pathway consisting of 13 enzymes that turns starch into hydrogen[34]. This suggests a future fueling infrastructure in which starch – a substance available at any grocery store – goes into the tank instead of gasoline, ethanol, or any other pre-processed fuel. The hypothetical fueling process is very simple; add starch, the enzymes chew on it, hydrogen gas bubbles out of the soup and is then used in a fuel cell to provide electric power for the car. This initial demonstration is a very long way from being a useful fuel source. But it is worth mentioning because the authors used 11 off-the-shelf enzymes (from spinach, rabbit, E. coli, and yeast) ordered from a commercial supplier (Sigma-Aldrich), and two they purified themselves

(from E. coli, and the archea P. furiosus). The fact that all these enzymes are un-modified means there is plenty of room for optimization, including a tailor-made microbe. In the latter case, the resulting car would become something of a cyborg, relying on living organisms to provide power to an inorganic shell.

Distributed biological manufacturing

While transportation fuels are an early target for commercialization of synthetic biology and metabolic engineering, it will eventually be possible to treat biomass or waste material as feedstocks for microbes producing more than just fuels. Dupont and Genencor have constructed an organism that turns starch into propanediol, which is then polymerized into a fiber called Sorona®, now successfully competing in the market against petroleum products. Production of Sorona® is approximately a factor of two more efficient than the industrial process it replaces, while consuming considerably less energy and resulting in lower greenhouse gas emissions[35]. The production pathway starts in microbes but requires a more traditional facility for polymerization. Sorona® enters a multibillion-dollar market at a substantial operating advantage, with only US$110 million initial investment in the finishing facility, and about US$ 10 million (estimated) to engineer the microbe. Sorona® likely represents only the tip of the iceberg. Predictably, many more economically important compounds will be "miniaturized" within biological systems, internalized within single-celled (and eventually, multi-celled) organisms.

There is substantial funding flowing to these efforts. To much fanfare, BP recently invested US$ 500 million in the Energy Biosciences Institute (EBI), a ten-year project to develop new biofuel technologies at UC Berkeley, University of Illinois at Urbana-Champaign, and Lawrence Berkeley Labs. A significant fraction of the funds pledged to the EBI are reportedly to be used for building new fuel production and processing pathways in modified organisms.

Closer to commercialization, Amyris Biotechnologies and Allylix are both working on the implementation of microbial synthesis of isoprenoids, a broad class of compounds with myriad industrial and healthcare uses. As a measure of the complexity of what is now possible, Amyris' production pathway for isoprenoids was assembled in yeast using ten genes from four organisms. As of spring 2007, the company and its academic collaborators had demonstrated a billion-fold improvement in yield in about six years. This foreshadows the potential for biological production as more capabilities are developed for synthetic biological systems.

Summary

This backdrop sets the context for today's increased reliance upon genetic modification of biological systems for the production of food, drugs, materials, and fuel. Amidst today's increasing worldwide fraction of GM crops, biofuels, and materials, we are clearly beginning to use biology in new ways.

The relative contribution of the different sectors to the total is worth considering. Until recently drugs dominated biotech revenues in the U.S., but now this contribution accounts for no more than half the total. This suggests that as biological technologies mature, becoming more useful and prevalent across different sectors of the economy, that industrial and agricultural applications will amount to a much larger share of total revenues. Synthetic biology and nanotechnologies could further drive development in non-drug sectors by reducing costs enough for existing companies to explore riskier applications or by seeding the market with a raft of niche start-up ventures.

Economic success is by no means guaranteed to any company or venture, nor will large investments by corporations and governments immediately transform our economy and society. The market, guided by the choices of policy makers, will be the ultimate test of any new biological technologies and products. Even in the context of exponentially improving productivity and exponentially falling cost, decades may pass before new technologies achieve significant market penetration. Certainly, it is by no means clear where the greatest competitive advantages will be found or what will prove to be the "killer" applications. But our history with information technology suggests that the technologies being developed will continue to accelerate, until one day we won't remember how we ever managed to live without them.

Focus on Alberta

- In December, 2007, Canada launched a $1.5 billion biofuels initiative that requires gasoline to contain an average of 5 percent renewable content by 2010 and requires diesel fuel and heating oil to have an average of 2 percent renewable content by 2012. To meet those requirements, Canada will need to more than quadruple its production of renewable fuels.

- Further investment will be necessary to keep pace with U.S. investments, where both government and venture funds have invested in synthetic biology start-ups. The stakes are high. The CEO of synthetic genomics, J. Craig Venter, has stated that a successful energy-producing organism could potentially be worth a trillion dollars [36].

- Alberta is rich in feedstocks for biological manufacturing that could make the province attractive as a bioproduction hub. Feedstocks include forest residuals, wood-processing waste, switchgrass, wheat, barley, canola, straw, chaff, and animal waste.

- The 2007 U of A iGEM team, known as the Butanerds, received national media attention for their work to make E. coli produce butanol – a bug that made Wired magazine's top 10 list of new organisms for 2007 [37]. The fact that a handful of undergraduate students with virtually no laboratory experience could, in a few months, keep pace with industrial leaders like BP underscores the disruptive potential of these technologies.

- The largest biorefinery in North America is under construction in Innisfail, Alberta, with a projected annual capacity of 300 million liters each of biodiesel and ethanol using canola as a feedstock [38].

Section 6 - RIDING THE WAVE: KEEPING ALBERTA ON THE CREST

Technology is accelerating. Few fields have blossomed as quickly as synthetic biology and nanotechnology have, but they are only getting started. With the majority of companies still pre-IPO and developing their initial product portfolios, the big rewards (and the big challenges) are still to come.

What can Alberta do to not fall behind this wave of development? Albertans take pride in being tough and capable people. Minus fifty temperatures, massive engineering projects, riding bulls, and dealing with a thousand head of cattle are everyday challenges here, and big challenges are usually tackled with swaggering confidence. But bio-nanotechnologies are unfamiliar territory, and which path to take is still unclear. Hopefully, this document provides some direction.

Because of a combination of factors that include a blistering economy, abundant feedstock, excellent universities and research groups, and a relatively small population, Alberta has an enviable opportunity to establish itself as a world-class bio-nanotechnology hub. Steps are already being taken towards this, but more needs to be done if Alberta is to be a serious contender in a field that already includes Berkeley and Beijing. Hubs are not created just by writing big cheques (although this certainly helps). They start from seeds - a powerful idea, a visionary person, a revolutionary innovation. Seeds grow when they find fertile soil, and when they are well tended.

If we want a crop of leaders and a thriving, knowledge-based bio-economy, we must recognize and attract the people keen to do this work to the province and give them the support they need to run at the head of the pack. Tough decisions will have to be made, and made faster than in the past, because the pace of the development is increasing globally. Even our economy pales beside China (expecting 8% annual growth between 2006 to 2010) and India (10 % annually). Competitors around the world have access to many of the same tools and raw materials as are present in Alberta. Alberta, however, has the advantage of a pre-positioning of talent, capital, and its own thriving economy.

What applications are going to be valuable? What company will become the Google of nanotechnology or synthetic biology? Can it be created in Alberta? Who are the experts we should trust to advise us on our policies? Where should we invest? What courses should our children take in school to have a lifelong, rewarding career in this area? There are more questions than answers right now, but one thing should be absolutely clear: like computing, these technologies are simply too compelling to ignore. They will grow and they will give rise to a completely new economic ecosystem. It's inevitable.

Those with high level perspectives - philosophers, politicians, CEOs, regulators and the like – will face difficult choices as they steer their organizations or communities into these waters. The potential risks of these technologies are real and substantial. How to best manage them

in the face of powerful drivers like better health, cheaper products, and cleaner technologies is a delicate balancing act that will take some practice. But for most of us, the pragmatic choices of daily life will prevail. We'll be consumers or users of these technologies, not producers. We'll decide to let them enter our lives if and only if we perceive value in them, just as we did with computers, cell phones, iPods, etc. that came along before these. Markets will decide.

Of the regions that will pursue these technologies, only a handful will enjoy the big economic rewards. Similarly, of the thousands of researchers and entrepreneurs that will devote their lives to realizing big ideas in these technologies, only a few will follow in the footsteps of Bill Gates or Sergey Brin. We must be realistic. But given the head start we have, if we decide we want to be in the race, there's no reason why we can't earn a podium finish.

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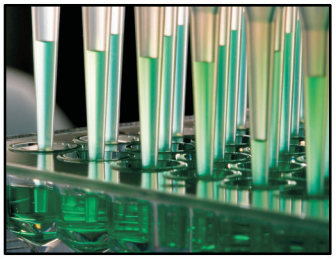

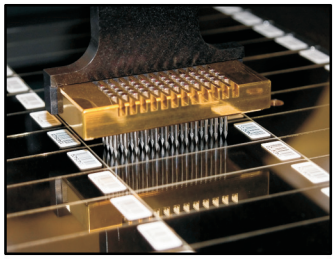
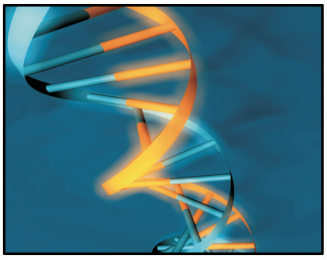

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