pharmacology and clinical safety can be minimized by installing appropriate counter measures. The costs and efforts involved as well as the disadvantages in positioning relative to stabilized competitor drugs, however, strongly suggest to us that such development routes should no longer be considered.

COMPETING INTERESTS STATEMENT
The authors declare competing financial interests: details accompany the full-text HTML version of the paper at http://www.nature.com/naturebiotechnology/.

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An economic and technical evaluation of microalgal biofuels

To the Editor:

In her News Feature "Biotech's green gold"[1], Emily Waltz details the 'hype' being propagated around emerging microalgal biofuel technologies, which often exceeds the physical and thermodynamic constraints that ultimately define their economic viability. Our calculations (**Supplementary Box 1**) counter such excessive claims[1,2] and demonstrate that 22 MJ m^{-2} d^{-1} solar radiation supports practical yield maxima of ~60 to 100 kl oil ha^{-1} y^{-1} (~6,600 to 10,800 gal ac^{-1} y^{-1}) and an absolute theoretical ceiling of ~94 to 155 kl oil ha^{-1} y^{-1}, assuming a maximum photosynthetic conversion efficiency of 10% (ref.3) (results summarized in **Table 1**). To evaluate claims and provide an accurate analysis of the potential of microalgal biofuel systems, we have conducted industrial feasibility studies and sensitivity analyses based on peer-reviewed data and industrial expertise. Given that microalgal biofuel research is still young and its development still in flux, we anticipate that the stringent assessment of the technology's economic potential presented below will assist R&D investment and policy development in the area going forward.

If sustainable and profitable processes can be developed, the potential benefits of these technologies for the common good appear compelling and include the production on nonarable land of biodiesel, methane, butanol, ethanol, aviation fuel and hydrogen, using waste or saline water, as well as CO_2 from industrial or atmospheric sources. We have examined industrial feasibility models of microalgal systems to identify the key economic drivers and provide an industrially relevant update on previous economic analyses[4,5]. Two of our models are described here as 'base case' (that is, integrating current technology) and 'projected case', which is considered achievable but has not yet been demonstrated at commercial scale. The 30-year internal rate of return (IRR; **Fig. 1** and **Supplementary Fig. 1**) and net present value (NPV; **Supplementary Fig. 2**) are used as a measure of the profitability of different production scenarios. IRR values of 15% and above are considered to indicate the potential for economic viability. Importantly, all subsidies including carbon credits have been deliberately excluded, as have financial optimization techniques, to provide a substantial financial contingency.

The base case is intended to represent an emerging scenario from the industry and involves the following assumptions: (i) production of microalgal biomass using 500 ha of microalgal production systems; (ii) the extraction of oil; (iii) the co-production and extraction of a high value product (HVP; e.g., β-carotene at 0.1% of biomass, \$600/kg); and (iv) the sale of the remaining biomass as feedstock (e.g., soymeal or fishmeal substitute). In contrast, the projected case is intended to represent the microalgal biofuel industry at maturity and no longer incorporates the co-production of HVPs. The base case is essentially a self-subsidizing, co-production model. Although it produces ~100 times more oil than HVP on a per tonnage basis, the revenue from HVPs is ~10 times that of oil due to their difference in value. In reality, deployment of this co-production approach will require the servicing of a diversity of HVP markets, as HVP markets are small and easily saturable. Consequently, a major consideration is that the technical developments required for the commercialization of individual HVPs can be as challenging as those required for biofuel production. Therefore, the existence of one or more suitable market-ready HVPs represents a central decision point for would-be biofuel producers. Improved microalgal productivity approaching the targets identified in the projected case will reduce the reliance on co-production (**Table 1**) as the industry matures.

All assumptions (variable settings) in this model are detailed in the **Supplementary Data** and are based on what are considered to be realistically achievable and published peer-reviewed values. The key findings of this model are summarized in **Figure 1** (also see **Supplementary Figs. 1** and **2**) as sensitivity analysis plots in which individual or multiple settings (e.g., biomass productivity and construction costs) are varied to evaluate their effect on the IRR. For example, as construction costs are reduced (**Fig. 1a**), the IRR increases. The appropriateness of using the IRR as a measure for profitability in this study is demonstrated in the **Supplementary Data** and **Supplementary Figure 2**. Detailed figures for NPV are also provided. This model deliberately does not discriminate between open pond and closed bioreactor systems, the pros and cons of which are hotly debated; instead, it compares construction costs versus yield (**Fig. 1e,f**) as this is the critical factor (that is, low cost/low yield and high cost/high yield reactors can theoretically be equally profitable).

We illustrate how key factors affect the IRR of both case studies (**Fig. 1**). These were (i) capital costs for construction of the ponds/reactors (**Fig. 1a**) and (ii) the biomass productivity (g m^{-2} day^{-1}) (**Fig. 1b**). In the base case, the third key factor was the role of HVPs (**Fig. 1c**), whereas in the projected case, the corresponding effect was oil price (**Fig. 1d**), but biomass oil content (see **Supplementary Fig. 1d**) was

Table 1 Practical and theoretical yield maxima for microalgal biomass and oil production[a]

Photosynthetic conversion efficiency (%)	Biomass energy (GJ ha^{-1} yr^{-1})	Biomass energy (MJ kg^{-1})	Oil (%)	Biomass prod. (g m^{-2} d^{-1})	Biomass yield (T ha^{-1} yr^{-1})	Oil yield (L ha^{-1} yr^{-1})	Residual biomass (T ha^{-1} yr^{-1})
2.1	1,677	22.98	25	20.0	73	19,837	55
6.4	5,101	27.95	50	50.0	183	99,390	92
6.5	5,220	22.98	25	62.2	227	61,400	170
6.5	5,220	27.95	50	51.2	187	100,943	93
8.0	6,424	22.98	25	76.7	280	75,570	210
8.0	6,424	27.95	50	63.0	230	124,237	115
10.0	8,030	22.98	25	95.9	350	94,462	262
10.0	8,030	27.95	50	78.6	287	155,297	143

[a]See **Supplementary Box 1** for full details on calculations and assumptions.

only a minor factor. In each case, HVPs or oil represent the dominant revenue streams at ~60% and ~50%, respectively. The diversification of products (HVPs, biomass and oil) in the base case has the potential to protect against oil price fluctuations and to subsidize oil prices.

Production area scales nonlinearly in our analysis (**Supplementary Fig. 1a**) with sizes <200 ha showing markedly reduced profitability. With small facility size, the profitability of a complete business model is quite low due to the high capital costs for establishment and low revenue stream. IRR rises rapidly with increased sizes but soon stabilizes. This biphasic trend reflects poorly scalable factors, such as harvesting/processing machinery and the staff complement. This indicates that economies of scale exist but only up to a point (~200 ha in our model). Total annual operating cost was also examined (**Supplementary Fig. 1e**) and reflects a resilience of the model to operating cost variations in comparison to other critical factors. We conclude that the minor contribution of each operating cost individually (e.g., nutrient, power or labor costs) would not culminate in major effects on IRR.

Figure 1e (base case) and **Figure 1f** (projected case) demonstrate that as technological developments simultaneously improve multiple key variables (e.g., bioreactor costs and net biomass productivity), even modest improvements synergize to generate substantial improvements in economic viability. This suggests considerable economic potential for microalgal biofuel technologies in the longer term. To rank the degree of influence of each of the factors on the base case (**Supplementary Fig. 2e**) and the projected case (**Supplementary Fig. 2f**), each factor was varied several-fold (e.g., 25%, 50%, 100%, 200%, 400% of the set value) as a function of NPV (15%), with the steepest NPV slopes representing the most influential variables within the target range.

Several other production models that met a profitability criterion of 15% IRR were also identified, confirming the flexibility of process development under current market conditions (**Supplementary Table 1**). Reduced reliance on HVP co-production is realistic at increasing productivities and commodity prices. Although companies pursuing such co-production strategies already exist, this need not be viewed as a linear progression from HVP- to oil-dominated business plans. Sustained initial investment into cost reduction and biomass productivity may provide an alternative route to successful stand-alone fuel systems.

From a policy and investment perspective, important conclusions can be drawn from our analysis. First, despite exaggerated claims, our economic analyses suggest that the ~400% increase in investment in microalgal biofuels observed during 2007–2008 (ref. 6; which has continued to increase in 2009) is sensible, given the potential to meet an IRR of 15% and the future potential to achieve higher returns as biotech and process improvements are made (**Fig. 1**). This raises the question of why economically viable microalgal biofuel production systems have not yet been demonstrated. In our view, this can be explained in two ways: first, existing pilot and demonstration plants (at <5 ha) are well below the size threshold for economic viability, and second, insufficient time has passed for the industry to evolve from recent capital injection (2006–2007) through to large-scale commercial production. Thus, the most appropriate and cost-effective mix of technologies are yet to be successfully integrated and optimized, and even realistic, viable enterprises are still in the commercial development phase.

It is important to note that several external factors are likely to increase both the need for, and the viability of, these

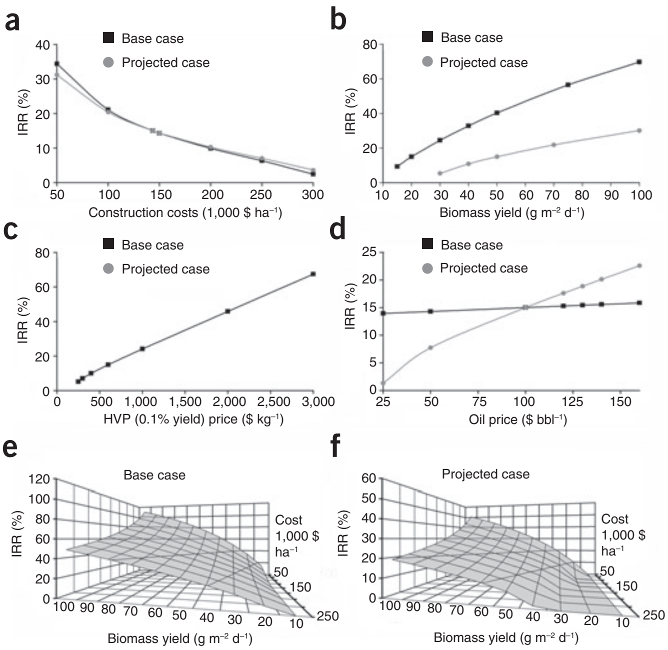

Figure 1 Sensitivity analysis. Using the parameters described in the text, an industrial feasibility study was constructed to model the effect of varying specific interconnected parameters on the internal rate of return (IRR). (**a**–**d**) The effect of these variables on the base case and projected case scenarios. (**e**,**f**) Potential gains from simultaneous advancement in the key factors of construction cost and biomass productivity.

systems. Examples include the possibility of a resurgence in oil price from $30/bbl recently (as of December 2008; http://tonto.eia.doe.gov/dnav/pet/hist/rwtcd.htm) back to and beyond the previous high of $147/bbl (July 2008) in the near future (modeled here as $100 per barrel in both cases), the introduction of more stringent CO_2 emissions targets and carbon trading schemes (potentially rising to ~$200 per ton CO_2 by 2050; refs. 7,8) and the increased demand for food and fuel by a population rising from 6.8 billion in 2009 to 9.4 billion in 2050 (refs. 9,10). All of these factors appear to be strong drivers for the economic viability of this technology. This analysis suggests that although microalgal biofuel systems remain in an early stage of development, they are now approaching profitability if the co-production systems in the base case, and/or the increased productivities in the projected case can be attained. A recent report by Huntley and Redalje[11] estimates that current technology could produce oil for $84/bbl (with no value attributed to the non-oil fraction), with reasonable advancements in technology reducing this cost to $50/bbl or less. This supports our conclusion that co-production is required in the short term and that at increased oil prices (that is, $100 in this model) an IRR of 15% could be obtained.

Considerable synergies also exist between microalgae biofuel production and a wide range of other industries, including human and animal food production, veterinary applications, agrochemicals, seed suppliers, biotech, water treatment, coal seam gas, material supplies and engineering, fuel refiners and distributors, bio-polymers, pharmaceutical and cosmetic industries, as well as coal-fired power stations (CO_2 capture) and transport industries, such as aviation. Sound opportunities therefore exist for the development of a rapidly expanding sustainable industry base whose productivity is independent of soil fertility and less dependent on water purity. Thus, these technologies can conceivably be scaled to supply a substantial fraction of oil demand without increasing pressure on water resources while potentially contributing to food production. Furthermore, as this study was conservatively modeled on published data, excluding subsidies (which are actually commonly used to develop other renewable energy sectors, for example, photovoltaics) and proprietary technologies, it follows that strategic partnerships and government policy decisions will play a large part in facilitating a coordinated scale-up and deployment of these technologies to contribute to future energy security.

Note: Supplementary information is available on the Nature Biotechnology website.

ACKNOWLEDGMENTS
The authors gratefully acknowledge the support of the Australian Research Council, IMBcom, and the economic advice of Liam Wagner.

COMPETING INTERESTS STATEMENT
The authors declare competing financial interests: details accompany the full-text HTML version of the paper at http://www.nature.com/naturebiotechnology/.

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Ontology engineering

To the Editor:

Gene Ontology (GO)[1] and similar biomedical ontologies are critical tools of today's genetic research. These ontologies are crafted through a painstaking process of manual editing, and their organization relies on the intuition of human curators. Here we describe a method that uses information theory to automatically organize the structure of GO and optimize the distribution of the information within it. We used this approach to analyze the evolution of GO, and we identified several areas where the information was suboptimally organized. We optimized the structure of GO and used it to analyze 10,117 gene expression signatures. The use of this new version changed the functional interpretations of 97.5% ($P < 10^{-3}$) of the signatures by, on average, 14.6%. As a result of this analysis, several changes will be introduced in the next releases of GO. We expect that these formal methods will become the standard to engineer biomedical ontologies.

Every year, over 400,000 new articles enter the biomedical literature[2], creating an unprecedented corpus of knowledge that is impossible to explore with traditional means of literature consultation. This situation motivated the development of biomedical ontologies, structured information repositories that organize biomedical findings into hierarchical structures and controlled vocabularies. GO is arguably the most successful example of a biomedical ontology. GO is a controlled vocabulary to describe gene and gene product attributes in any organism and includes 26,514 terms organized along three dimensions: molecular function, biological process and cellular component. GO has become even more intensively used with the introduction of high-throughput genomic platforms because of its ability to categorize large amounts of information using a controlled vocabulary to group objects and their relationships[1,3,4].

Today, GO and other biomedical ontologies are the result of a painstaking, costly and slow process of manual curation that requires reaching a consensus among many experts to implement a change. Furthermore, the topology of GO has become critically important because of the introduction of gene set enrichment methods. These methods have allowed investigators to characterize the results of a high-throughput experiment in terms of coherent, knowledge-defined sets of genes (e.g., pathways, functional classes or chromosomal locations) rather than in terms of anecdotal evidence about