this business-as-usual future largely bereft of birdsong and insect chirp.

Choosing to act now can make a difference to nature's plight. Most (61%) of the model combinations run by the authors indicated that implementing ambitious conservation actions led to a positive uptick in the biodiversity curve by 2050. Such conservation actions included: extending the global conservation network by establishing protected nature reserves; restoring degraded land; and basing future land-use decisions on comprehensive landscape-level conservation planning. This comprehensive conservation strategy avoids more than half (an average of 58%) of the biodiversity losses expected if nothing is done, but also leads to a hike in food prices.

When conservation actions were teamed with a range of equally ambitious food-system interventions, the prognosis for global biodiversity in the model was improved further. Including both supply- and demand-side measures, these approaches included boosting agricultural yields, having an increasingly globalized food trade, reducing food waste by half, and the global adoption of healthy diets by halving meat consumption. These combined measures of conservation and food-systems actions avoided more than two-thirds of future biodiversity losses, with the integrated action portfolio (combining all actions) avoiding an average of 90% of future biodiversity losses. Almost all models predicted a biodiversity about-face by mid-century. These food-system measures also avoided adverse outcomes for food affordability.

Leclère and colleagues' work complements the current global climate-change scenario framework (tools for future planning by governments and others, including scenarios called shared socio-economic pathways, which integrate future socio-economic projections with greenhouse-gas emissions), and represents the most comprehensive incorporation of biodiversity into this scenario framing[7] so far. However, a major limitation of the present study is that it does not consider the potential impact of climate change on biodiversity. This raises an internal inconsistency because, on the one hand, the baseline scenario considers land-use, social and economic changes under approximately 4 °C of global heating by 2100 (ref. 8), yet, on the other hand, it does not consider the profound effect of warming on plant and animal populations and the ecosystems they comprise[9]. Also absent from the models were other threats to biodiversity, including harvesting, hunting and invasive species[10]. Although Leclère and colleagues recognized these limitations and assigned them a high priority for future research, unfortunately for us all, omitting these key threats probably means that the authors' estimates of biodiversity's plight and the effectiveness of integrated global conservation and food-system action are overly optimistic. To truly bend the curve, Leclère and colleagues' integrated portfolio will need to be substantially expanded to address the full range of threats to biodiversity.

Although the models say that a better future is possible, is the combination of the multiple ambitious conservation and food-system interventions considered by Leclère *et al*. a realistic possibility? Achieving each one of the conservation and food-system actions would require a monumental coordinated effort from all nations. And even if the global community were to get its act together in prioritizing conservation and food-system transformation, would such efforts come in time and be enough to save our planet's natural legacy? We certainly hope so.

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1. Díaz, S. *et al*. *Science* **366**, eaax3100 (2019).
2. Leclère, D. *et al*. *Nature* **585**, 551–556 (2020).
3. Costanza, R. *et al*. *Glob. Environ. Change Hum. Policy Dimens*. **26**, 152–158 (2014).
4. Butchart, S. H. M. *et al*. *Science* **328**, 1164–1168 (2010).
5. Springmann, M. *et al*. *Nature* **562**, 519–525 (2018).
6. Montesino Pouzols, F. *et al*. *Nature* **516**, 383–386 (2014).
7. Kok, M. T. J. *et al*. *Biol. Conserv*. **221**, 137–150 (2018).
8. Leclère, D. *et al*. *Towards Pathways Bending the Curve of Terrestrial Biodiversity Trends Within the 21st Century* https://doi.org/10.22022/ESM/04-2018.15241 (Int. Inst. Appl. Syst. Analysis, 2018).
9. Warren, R., Price, J., Graham, E., Forstenhaeusler, N. & VanDerWal, J. *Science* **360**, 791–795 (2018).
10. Driscoll, D. A. *et al*. *Nature Ecol. Evol*. **2**, 775–781 (2018).

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Biotechnology

Yeast learns a sorceress's secret

José Montaño López & José L. Avalos

Yeast has been engineered to convert simple sugars and amino acids into drugs that inhibit a neurotransmitter molecule. The work marks a step towards making the production of these drugs more reliable and sustainable. **See p.614**

In Homer's *Odyssey*, the sorceress Circe slipped Odysseus' companions a poison to induce amnesia and hallucinations. Scientists have speculated[1] that Circe's concoction contained the plant jimsonweed (*Datura stramonium*), which is rich in drugs called tropane alkaloids that are used to treat asthma, influenza symptoms and pain, and that can induce hallucinogenic and other psychotropic effects. Tropane alkaloids, like most other plant natural products, are still typically extracted from natural sources, but this approach has many pitfalls. For instance, vulnerability to weather and market fluctuations can limit access for both patients and researchers, and extraction can be environmentally harmful[2,3]. In addition, plants typically contain very low levels of these active ingredients. On page 614, Srinivasan and Smolke[4] report an alternative way to make tropane alkaloids that could relieve these limitations – using engineered strains of the baker's yeast *Saccharomyces cerevisiae*.

Plants produce a variety of specialized compounds that help them to adapt and survive. Biosynthesis of these natural products often involves lengthy metabolic pathways that have complex dynamics and regulation. One of the major achievements in the field of metabolic engineering has been the development of microorganisms that can produce plant natural products[5–7]. However, the approach is far from routine because the enzymes involved in biosynthesis are often unknown, might be inactive in microbial hosts, and can be segregated across different plant subcellular compartments, cells or tissues.

Srinivasan and Smolke have overcome these challenges to produce a strain of *S. cerevisiae* that converts simple sugars and amino acids into two tropane alkaloids, hyoscyamine and scopolamine. These tropane alkaloids block the action of the neurotransmitter molecule acetylcholine[8]. They are used to treat nausea, gastrointestinal problems, excessive bodily secretions and neuromuscular disorders, including Parkinson's disease[9,10].

Srinivasan and Smolke genetically engineered their yeast strain to overexpress 26 genes from different kingdoms of life. Together, these genes encode several metabolic enzymes and transporter proteins. Key to the authors' achievement is the fact that they separated the enzymes and transporters into six subcellular locations – the cytosolic fluid, four organelles (the mitochondrion, peroxisome,vacuole and endoplasmic reticulum),

and the vacuolar membranes. Subcellular compartmentalization of enzymes can improve product biosynthesis by enabling proper enzymatic activity and isolating metabolic intermediates to reduce their toxicity and loss to competing pathways[11]. By restricting space, compartmentalization also increases local interactions between the enzymes and their targets. Such separation of enzymes is therefore akin to what happens in chemical factories, in which different synthesis steps are conducted in different reactors, and so each step can be separately optimized to maximize productivity.

The authors divide the biosynthetic pathway for hyoscyamine and scopolamine into five modules (Fig. 1), the first two of which they described in work published last year[12]. In module I, the glucose-derived amino acid glutamate is converted to another amino acid, arginine, in a series of reactions that occurs partly in the mitochondrion. Arginine is then converted to putrescine in the cytosol. In module II, putrescine is converted to tropine — the functional core that gives tropane alkaloids their name — through several cytosolic reactions, in addition to one catalysed in the peroxisome and another catalysed by an enzyme anchored to the membrane of the endoplasmic reticulum.

Module III occurs in parallel with modules I and II in the cytosol, and converts glucose and the amino acid phenylalanine into the molecule phenyllactic acid glucoside (PLA glucoside). For this module, the authors engineered their strain to express an enzyme called PLA UDP-glucosyltransferase, which is found in the deadly nightshade plant *Atropa belladonna* and catalyses the production of PLA glucoside.

The tropine produced in module II and the PLA glucoside from module III are imported into the vacuole. Next, in module V (which is counter-intuitively numbered last because all its elements constitute new discoveries), tropine and PLA glucoside are converted into the molecule littorine. Building module V involved two key steps. First, Srinivasan and Smolke engineered their strain to express a transporter protein from the tobacco plant *Nicotiana tabacum* that imports tropine into vacuoles. Second, they engineered the cells to express a variant of the *A. belladonna* enzyme littorine synthase (*Ab*LS). When expressed in yeast, *Ab*LS stalls in the trans-Golgi network (TGN; part of an organelle called the Golgi), and so cannot catalyse vacuolar littorine production. The authors therefore engineered *Ab*LS to become a transmembrane protein — these proteins are transported from the TGN to the vacuole by default. This *Ab*LS variant is able to catalyse littorine production in the vacuole.

The final step of the pathway, module IV, partly occurs in the membrane of the endoplasmic reticulum. In this module, littorine is converted to hyoscyamine and then to scopolamine. The final step in hyoscyamine production involves the enzyme hyoscyamine dehydrogenase (HDH), but the gene that encodes this enzyme was unknown. The authors analysed a data set of gene-expression profiles from *A. belladonna* to generate 12 candidate genes. They expressed each of these candidates in yeast strains to determine which had the desired enzymatic activity. They then compared the activity of the HDH-encoding gene from *A. belladonna* with equivalents from other plants, and finally selected the gene from Circe's jimsonweed as being optimal for hyoscyamine and scopolamine production.

Alongside these steps, Srinivasan and Smolke deleted enzymes native to *S. cerevisiae* that consume key intermediate metabolite molecules, and overexpressed others to increase the production of metabolites required by the biosynthetic pathway. Together, their work is a major achievement that demonstrates the potential of microbial platforms to enable cheaper, faster, more-reliable and more-sustainable means of producing pharmaceuticals. Their yeast strain produced only a few micrograms to milligrams of tropane alkaloids per litre of yeast culture — not yet sufficient to replace our current methods of production through plant extraction. Nonetheless, it is an essential milestone towards this goal.

To further increase production, it will be necessary to optimize each module of the pathway, as one would optimize each reaction in a chemical factory. This will involve increasing the rate of tropane-alkaloid biosynthesis by upregulating or downregulating native enzymes, boosting metabolite transport across subcellular compartments, and improving the activity of enzymes at metabolic bottlenecks (key steps in the pathway that impede faster biosynthesis).

Going forward, researchers should explore possible permutations of Srinivasan and Smolke's biosynthetic pathway. Perhaps variations in the pathway could lead to the discovery of new drugs that have improved efficacy and reduced side effects. We might even discover drugs to treat other ailments.

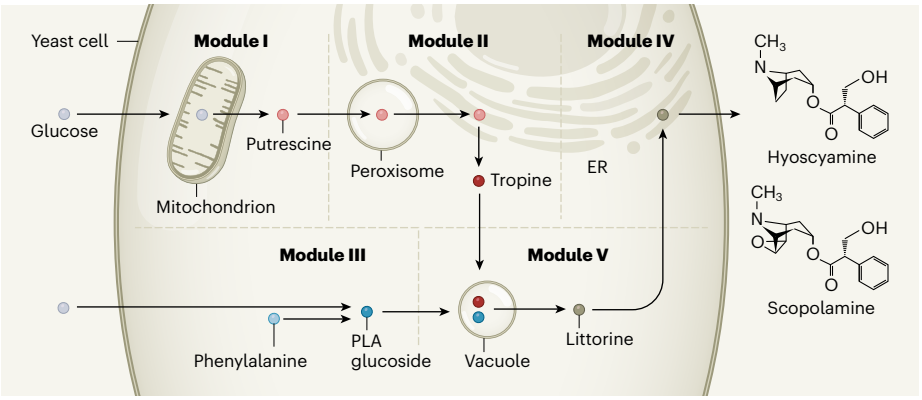

Figure 1 | Producing tropane-alkaloid molecules in yeast. Srinivasan and Smolke[4] engineered the yeast *Saccharomyces cerevisiae* to make the drugs hyoscyamine and scopolamine from glucose and amino acids. Their biosynthetic pathway is divided into five modules, and several reactions are restricted to membrane-bound organelles. In module I, glucose is converted to the molecule putrescine, by metabolic steps in the mitochondrion and cytosolic fluid. In module II, enzymatic reactions in the peroxisome and the membrane of the endoplasmic reticulum (ER) catalyse the conversion of putrescine to tropine. In module III (which occurs in parallel with modules I and II), glucose and the amino acid phenylalanine are converted to phenyllactic acid glucoside (PLA glucoside). In module V, tropine and PLA glucoside are transported into the vacuole and together converted to littorine. Finally, in module IV, part of which occurs in the ER membrane, littorine is converted to hyoscyamine, which is then converted to scopolamine.

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1. Kaplan, M. *Science Of The Magical: From the Holy Grail to Love Potions to Superpowers* (Simon & Schuster, 2015).
2. Cravens, A., Payne, J. & Smolke, C. D. *Nature Commun.* **10**, 2142 (2019).
3. Li, S., Li, Y. & Smolke, C. D. *Nature Chem.* **10**, 395–404 (2018).
4. Srinivasan, P. & Smolke, C. D. *Nature* **585**, 614–619 (2020).
5. Ro, D.-K. *et al. Nature* **440**, 940–943 (2006).
6. Ajikumar, P. K. *et al. Science* **330**, 70–74 (2010).
7. Brown, S., Clastre, M., Courdavault, V. & O'Connor, S. E. *Proc. Natl Acad. Sci. USA* **112**, 3205–3210 (2015).
8. Kohnen-Johannsen, K. L. & Kayser, O. *Molecules* **24**, 796 (2019).
9. Kukula-Koch, W. A. & Widelski, J. in *Pharmacognosy: Fundamentals, Applications and Strategy* (eds Badal, S. & Delgoda, R.) 163–198 (Elsevier, 2017).
10. Grynkiewicz, G. & Gadzikowska, M. *Pharmacol. Rep.* **60**, 439–463 (2008).
11. Hammer, S. K. & Avalos, J. L. *Nature Chem. Biol.* **13**, 823–832 (2017).
12. Srinivasan, P. & Smolke, C. D. *Nature Commun.* **10**, 3634 (2019).

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