

## Alpha shock

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Any believable prediction will be wrong. Any correct prediction will be unbelievable. Either way, a futurist can't win. He is either dismissed or wrong ... Most people, particularly most smart people ... will err on the side of not being fantastical enough. Because absolutely no one wants to be dismissed. What's the point of making a prediction if no one is listening? So 99% of future predictions will fall short of the necessary unreasonableness for a correct prediction.

—Kevin Kelly, building on Arthur C. Clarke.

Sanjay shuffled bleary-eyed into the expansive kitchen. “Lordy,” he groaned. One-thirty in the afternoon. Well, New Year's Eve comes but once a year. Pouring himself some coffee, he sat at the table and took stock, his natural analytic bent slowly fighting to re-establish dominance. Through the floor to ceiling windows he looked out over a grey and gloomy London cityscape.

2037 was shaping up to be an important year for him. Although he was a widely respected academic, with a high Q-index, great SciDigg scores, three successful tenure renewals, and excellent student references, he knew that the game was changing. The world healthcare agency that was funding 80% of his lab was particularly interested in psychiatric illnesses. And he knew his chances of getting his biggest grant renewed next year were pretty poor if he didn't come up with something good. He was among the best known of the “crossover chemists”—academic drug-hunters—and he had been paid handsomely for his past successes. But the bar was being raised: while in the past his rewards had come from

finding leads, all the multi-national agencies (and the few remaining drug companies) were much more focused these days on clinical successes. Just coming up with cool new compounds didn't get you very far any more. At this very moment, in fact, he had seven half-written grant proposals on his desk, all due by the end of the month. Hard to believe how much more time-consuming it was lately to scrounge for grant money than when he had started his career a quarter-century earlier. Those were fat times, indeed! Now he knew that if he didn't keep up, even someone as well known as he was faced a real risk of losing his tenure at the end of his current 5-year contract.

At the New Year's party he had run into that nerdy simulator from the adaptive systems pharmacology department who had been arguing strongly that he knew how to treat a particular 11% subset of the gamma-type schizophrenics that had a very characteristic epigenetic pattern in the CA1b hippocampal subfield. It was simple, the kid said—just shut down the mitochondrial biogenesis program by 40 to 70% (depending on the severity of the heteroplasmic mutations and the haplogroup of each specific patient) while allosterically potentiating the  $\zeta_5$ GABA<sub>c</sub> receptor by three- to fourfold. “Just block these three targets”—the kid rattled them off—“and you'd normalize the pathways.” Sanjay only remembered this much because his voice recorders had logged the conversation and sent him a transcript. As memory slowly returned, Sanjay recalled being amused by the nerd, who was barely out of school and talked very fast, waving his arms wildly as he made his case with complete confidence. He had seen a lot of kids like that in his time. Usually they flamed out long before their first tenure decision.

Sanjay pulled up the auto-assistant. The windows automatically darkened and a set of icons appeared floating in front of his face. As always, it first updated him on his 37

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students scattered around the globe. The status panel was mostly green—no major problems—although, of course, the dozen UK-based students were listed as “on holiday.” Impossible to get the lazy buggers to work more than the contractual 80 hour per week minimum. The usual handful of problem students were glowing amber or red. He sighed. It was nice that universities had adopted a much more networked, virtual model in the 2020s, but occasionally he wondered whether the lack of direct contact hindered his ability to train people. The holographic projection systems and virtual lab assistants were fantastic—he couldn’t blame those. But it just seemed that there were always a few students who needed more personal attention and he couldn’t fly them from Japan or Brazil very often. He put all thoughts of his students aside and dismissed the status panel.

He issued a voice command and then gestured in the air. After a few seconds, brightly colored three-dimensional images of the relevant pathways appeared in front of him. Touching any node in the pathway brought up a brief synopsis of key literature findings around a specific target, as well as chemical structures of molecules that modulated the activity of each target. Requirements for electronic submission of chemical structures and data accompanying any journal submission had been instituted in 2021. Back in the 2010’s there had been a significant backlash due to the inability of researchers to reproduce scientific results from across all the disciplines, but computational papers were uniformly the worst. The resulting near-total breakdown (highlighted by several leading academics being fired for incompetence and outright fraud) finally brought about an emphasis on reproducibility and a new willingness among computational chemists and biologists to create a shared software infrastructure and develop software tools that could be easily enhanced and integrated. This level of collaboration led to the development of standard ontologies and to the first practical applications of the semantic web.

After a half-hour of fiddling, Sanjay was reasonably confident that he had found a three-drug combination that, while not perfect, had a reasonable enough profile to enable testing the nerd’s hypothesis. He was able to quickly link each of these compounds to suppliers around the world and found two in stock. Bots connected to five additional suppliers instantly submitted bids for the synthesis of the third compound. Sanjay reviewed their ratings on Amazon and chose a small company in the Greater Australian Confederation. Advances in microfluidics and flow chemistry had created a cottage industry for chemical synthesis. Like everyone in the drug discovery game, Sanjay worked through an extended network of collaborators and contractors whenever possible. His students around the world could take over whenever the vendors crapped out.

Having settled the synthesis issue, Sanjay thought it would be worthwhile to see what else he could learn about these pathways. A Google search found a group in Argentina that could run their virtual pharmacology assay on this mixture. He was in luck—he even knew the PI—they had done their post-docs in the same department. A quick video chat followed and Paolo offered to do it within a few days. Sanjay sipped his coffee in satisfaction. Off in the distance, near Big Ben, he saw the artificial fog rise from the Thames. “Keeps the tourists happy,” he chuckled.

On the afternoon of January 4th he got a vidgram from Paolo, who was quite excited. The results looked quite good—the mitochondrial pathway seemed highly relevant. Paolo added that this was consistent with some other recent results he’d just obtained. Sanjay toggled the telepresence feature on his iPhone (standard since IOS 27.2) and he and Paolo were instantly “together” examining a set of images from the virtual pharmacology study. As the images of the treatment group streamed by, Paolo touched one to bring up a hologram of the computer simulation of the action of these compounds on the brains of both humans and the three species of humanized primates. As Paolo rotated the image and focused on the hippocampus, Sanjay could see the model predicted the desired phenotypic effect based on the downregulation of the targeted pathways. The two then reviewed the range of probable outcomes in the standard behavioral models. Advances in pattern recognition and sensor technologies had largely reduced behavioral pharmacology to an objective set of scores, but Paolo still liked to review the video. By the end of the conversation Sanjay was convinced that the virtual model was quite robust and there was something here. Paolo cautioned that the model was not teaching anything about the specifics of the best ways to block the pathway, just that it played an important role in this subset of schizophrenics.

After thanking Paolo and signing off, Sanjay stared out the window of his office. This felt like a potential breakthrough. Even now, in an era when everyone was so proud of how efficient drug discovery had become, new insights into disease biology were precious—the bottleneck for all new therapy, same as had been true for his entire career. It wasn’t that some chemical design problems weren’t still a bit challenging, but the old fears of undruggable targets had long since disappeared, and he had learned to follow the biology wherever it led him. It was conceivable, he thought, that he might eventually want to put a combination of these three compounds into some test subjects. At least, he thought, this was a more enjoyable way to spend the afternoon than fixing the problem with his grad student in Malaysia. So he looked more closely at the properties of those three compounds, trying to anticipate how he could deliver them as a combo via nanobot. He set up a quick simulation, and while it was running, he had the

auto-assistant dig more deeply into the literature around the synthesis of these compounds.

The AA started by running a search against ScienceDigg. In the early 2020s, scientists had tired of the politics surrounding journal publication and simply begun blogging their results. The thousands of scientific blogs created a great deal of confusion and made it difficult to find the best science. In an attempt to identify the highest quality work, Science Magazine merged with Digg.com, to create a system that allowed scientists around the world to rate the work of their peers. A few assistant professors seeking tenure had initially tried to game the system by voting with bots, but the clever folks at Digg had dealt with that sort of thing before. By 2027 ScienceDigg had become so embedded that the Nordic Royal Academy used it to choose Nobel laureates. Like other scientific work, synthesis blog posts were annotated in a structure searchable format. (ScienceDigg simply ignored posts which were not properly annotated.) Thus it only took the AA a few seconds to identify a number of promising routes. These were instantly cross-referenced against available reagents and a request was posted to CollabNet. Sanjay was sure that he would get a quick response from both eager academics and privateers. He hoped that his collaborators would—as was usually but not always the case—simply want shared authorship rather than a slice of the IP.

Of course, the compounds were of little value if they couldn't be formulated. Sanjay was pressed for time, and nanobot development still took several weeks, so he had to go “old school.” Sanjay accessed World Crystallography Repository's (WCR) formulation suite and entered the 2D structures of his compounds. The system linked to the Amazon Hyper-Cloud and initiated a series of quantum chemical calculations to develop a custom force field for the solid phase simulations. Unfortunately the preliminary results were disappointing, even after more than 100 million combinations of excipients, particle sizes, focusing tails, and polymorphs had been analyzed in detail. He would run a more complete search overnight, but the chances were that the 10-min simulation was telling him what he needed to know: don't expect these exact compounds to be quite right.

But there was a more serious problem. He had pulled up Paolo's biosimulator module and noticed that the doses required to shut down those network nodes were high. He could get around the problem, perhaps, by a complete redesign into a single agent that selectively blocked those three enzymatic functions.

Sanjay switched to the WCR's Protein Analysis Tools, a suite of Open Source software tools developed over the past 5 years, and selected the comparison module. A voice command brought back the pathway map he had been looking at previously and color-coded the targets with

high-resolution NMR structures. Structures were only available for two of the three proteins so he had the system build a homology model for the third. Sanjay then tapped the three structures, and a superposition of the binding sites appeared in front of him with the common features flagged. The static structures appeared to superimpose nicely, but a few seconds of real-time molecular dynamics showed a loop movement that would be problematic on one of the three proteins.

Sanjay didn't see an obvious work-around; the sites were just too different. Low odds, and the compounds weren't straightforward to make—it could take more than a few months to answer the question. What about an old-fashioned approach—just design three separate new molecules and link them? That could work—but the doses were still high. It just smelled wrong. As he was reaching this conclusion, the AA chimed, and up popped summaries of quite a few patents and reports of competitive programs against two of the three targets. That's it, Sanjay thought; this is just not the way to go. He sipped his coffee.

It figured, he reflected. Clearly these weren't the best targets—anyone willing to do a little straightforward digging could have seen that—but these dorks in their fantasy worlds never had any common sense. But that was OK; it just made things a little more interesting. The biology was still sound. He could always start from the nodal network analysis that the nerd had done in the first place. Sanjay checked his contacts log—Dmitri Yuvenovich. He hadn't noticed the Russian accent, a fact he chalked up to beer and the loud Death Skaggai music at the party. He had the AA set up a videolink to Dmitri, whose visage, 3× life size, filled his picture window.

“Hi Sanjay,” Dmitri smiled in a superior kind of way. “—have you fully recovered from the party? I didn't expect to hear from you until next week.”

Sanjay kept his face impassive although he supposed that the neuromuscular analyzers in Dmitri's system would detect the faint surprise tinged with annoyance. Fighting back his desire to punch Dmitri's skinny face, he kept his voice level. “No, no, Dmitri,” Sanjay laughed. “I didn't drink as much as you think. I've been looking into the gamma-schiz networks,” he continued. “I'm not sure the three-target combo you mentioned is quite the best approach, but I love the concept of finding some way to adjust the signaling in these subsystems. I was wondering if I could look at your nodal network maps.” He paused to see how Dmitri would react. Normally junior faculty would jump at a request like this—a chance to grab a piece of his magic. But Dmitri merely nodded. “Sure, Sanjay. I've just sent it to you—you should have it coming up now.” Sanjay noted the incoming signal and accepted. A 4D roadmap, slowly rotating, filled the right side of the picture window. It was more complex than Sanjay had expected, with

embedded links to 17 different datasets used to validate the map. He realized with a shock that full genetic and epigenetic data from 43 million humans had been integrated to build the maps. Where would Dmitri have obtained all this information? While he was pondering this it dawned on him that Dmitri was speaking again. “Of course the three-target combo I mentioned was just to give you a sense for the broad strategy. That was my first idea, a month ago, but it didn’t hold up to scrutiny—I wouldn’t be surprised if you carried out much the same analysis that I did and rejected it for the same reasons. Of course you know more chemistry by far than I do, but my SimChem modules generally fill in for the holes in my experience.” He smiled again. “Mind if I drive?” Sanjay signaled his acceptance and the AA transferred control.

“In fact,” Dmitri continued, “I think the best tactic is to turn down the interaction of this transcription factor”—a protein popped out of one node on the map—“with that protein”—another protein materialized—“and this stretch of DNA.” A 3D model of the complex assembled in front of him, slowly rotating, with the most likely binding sites and points of intervention highlighted. “Of course, you only want to disrupt this interaction in the hippocampus, and only when D7 receptor functioning is high.” The relevant pathway maps showed the effects of the blockage on downstream signaling. “Oh, and naturally you also want to turn down oxphos in the mitochondria. So we need either a single molecule that can do both things, or a two-drug combo.” Sanjay was surprised at this level of detail. Who the hell *was* Dmitri?

It was then that Sanjay began to notice some of the details in view behind Dmitri. The room was enormous and from the view of London in the background, the kid lived in the most expensive part of the city. And it looked like a real wood floor. How could the nerd live so well on a junior faculty salary? At that moment, as if by cue, across the field of view a lovely young woman glided—tall and graceful. Dmitri noticed Sanjay’s eyes tracking the movement, and no doubt his neuromuscular analyzers registered the unspoken question. “No,” he smiled again, “it’s not my girlfriend; it’s a Lexus9000. Do you like her?” Sanjay was speechless. The Lexus9000 was the latest companion bot, one of the really expensive models with the high emotional intelligence. They were staggeringly expensive—at least *triple* Sanjay’s full professor salary and probably six times what Dmitri made. What the hell?

Dmitri gave him a few seconds to process this information before continuing. “Sanjay, I should tell you I’ve already patented all this information. I’d love to have you do the mopping up experiments...”—“you bastard!” Sanjay managed not to say—“...to refine the therapy. I could do it myself, but you’re better at the chemical details, and I’ve got a lot of other projects I need to work on

anyway. I’ll be glad to cut you in for 20% of any out-licensing revenues. But I’m the PI on the grants and I write up the results for my blog. Hope we can work together.” He flashed that superior smile again, then signed off without waiting for a response. The darkness was replaced by the only slightly less depressing grey of the London afternoon as the windows gradually regained their transparency.

For the second time in less than a minute Sanjay was speechless. He stared out at the skyline while he tried to collect his thoughts. He then launched a level three search on Dmitri, his fingers stabbing the commands into the air in front of his face. Two heartbeats later, up popped Dmitri’s face (Sanjay groaned inwardly) while a detailed bio scrolled down the screen. This was followed by a list of more than 100 patent applications, 17 of which, the AA noted, covered a range of psychiatric therapeutics and networks. A few seconds later, the financial analysis summary appeared, a flashing box catching his attention. Dmitri for the past 3 years had been a consultant for CerebraDyne. And based on the overlap of his publications and conferences with senior CerebraDyne officials, it was a safe bet that he had licensed all of the IP to them. Ah, that explains where all the money comes from.

Should he pursue this? Walk away? He was not used to playing second fiddle, but if this kid (Sanjay had subconsciously shifted away from “nerd”) was right, this could be an enormously valuable therapy. These were the few remaining hard-core schizophrenic patients. Healthcare agencies and private insurers—not to mention cops and politicians and school superintendents—would pay through the nose to fix these people. And getting a connection to CerebraDyne could be hugely valuable.

In the end, Sanjay’s competitive nature won out. There was no way that he was going to let Dmitri win. After all, Sanjay was a “drug hunter,” a species that had been rare for more than 100 years. He remembered that Paul, one of his students in the Republic of Texas, had developed a new algorithm for selectively enumerating all of the chemical reactions stored in the public BeilPubCAS repository. Sanjay accessed Paul’s Python code and deployed it onto the Amazon Hyper-Cloud. He then accessed the existing structures from the WCR and cross-referenced these against experimental data for available compounds and related targets. With the structures in hand, Sanjay ran the WCR’s AutoStere protocol to identify potential isosteric binding sites in the structures of interest. The virtual tethering protocol identified a site that might be able to restrict the loop movement and allow him to design a single agent to block both targets.

With the structures and custom function in hand, Sanjay was ready to initiate the docking study. But despite recent advances in the TIP32P\*\* water model, Sanjay still didn’t

completely trust the predicted protein-ligand binding energetics. Next, he transferred the experimental data into the Google Predictive Analytics engine and quickly designed a new empirical function to fit the experimental data. Now he launched the dynamic docking simulator, dropping the empirical function into the hopper. He always preferred to run his docking simulations using the slow protocols that incorporated solvated dynamics—“less haste less waste,” as his 107-year-old grandmother still liked to say as she carefully pruned her rose bushes. A progress bar appeared in front of him showing “ $10^{30}$  molecules remaining, 2,704 h 15 min to completion.” Sanjay quickly stopped the process and constrained the search to only those molecules that fell within the applicability domain of his empirical function. This reduced the search to  $10^{12}$  molecules and allowed the analysis to complete in a few minutes.

After a bit of visual inspection to confirm the results of his docking study, Sanjay moved on to the next step. He knew that slow binding kinetics could provide a means of lowering the dose for his compound. To check this, he ran a few seconds of real-time MD on each of the top 50,000 hits from the docking study. A quick scan of the results turned up 620 structures that appeared to have the required residence time. Sanjay submitted all these structures to PPKPDS, the Primate Pharmacokinetic and Pharmacodynamic Simulator, a project developed through a collaboration of industry, academia, and the World Drug Approval Agency. Of the compounds submitted, 52 appeared to have the necessary PK profile, including the ability to be actively transported into the brain. All but a few were predicted to be readily synthesizable. He felt satisfied that he could turn this problem over to his network of students.

There was one last step before he could stop for the day. Sanjay launched the automatic patent submission app, Patent Rationalizer, which recommended that he add a handful of other compounds (15 to be exact) to the 52 molecules on his short list, based on chemical changes compatible with various alternate routes of administration that could be desirable for certain patients. As usual, PatRat did a comprehensive search against the 279 million chemical patents stored in its database. The days when there was any ambiguity about whether one patent overlapped another were long gone, as were the days when patents covered zillions of completely irrelevant compounds. All of his 67 molecules were clean, and after answering a few questions about the details of how the claims should be structured, he hit the submit button. A few seconds later he received notification that the World Patent Clearinghouse had received the documents and were submitting them in the appropriate mix of formats and languages to the various patent offices around the globe.

By early March Sanjay thought he had the problem licked. The 27th molecule had excellent properties—reliable predictions of good brain uptake and low human dose; novelty;

the expected response against all the targeted biomarkers; limited off-target signaling. Admittedly, the mitochondrial gene response profile to elevated pH was not quite as sharp he would have liked, but for a first-in-class approach it was more than sufficient; patients would likely see the effects within a day or two. It was ready to go into the obligate trans-species experiments that were still required because up to 5% of the time the in vitro and computational models proved inaccurate, and the cowardly politicians feared repercussions if “someone got hurt.” The animal experiments, of course, did definitely hurt a lot of people, who suffered needlessly during the delay, but the gutless politicians’ didn’t care—their hands were clean. Of course, the fact that the humanized primates lived like kings, with active lifespans projected to be longer than a century, helped assuage everyone’s guilt over these experiments, but this remained the single most distasteful part of the job. Still, there was nothing that could be done about it if you wanted your drug approved anywhere in the world except the Nordic Alliance or California. Sanjay instructed the AA to program the flow reactor systems to crank out a few kilos over the weekend. By the middle of the following week all the necessary QA was complete, and the compound was shipped out to the Singapore humate colonies.

By the end of August the animal experiments and formulations work were completed, and S27 looked to be on track for human studies. But Sanjay, during the preceding months, had slowly come to realize that he was mostly going to be observing from the sidelines. The contract he had signed with CerebraDyne was explicit—they wanted him to hand over the molecule and stand back. His pride required him to ask about the clinical path for the molecule, and grudgingly the CerebraDyne people had shown him their plans. He had to admit that the clinical simulations were breathtakingly complex—they had simulated 14 million different strategies for running the trials—and if CerebraDyne could pull this off, they’d have all the data they needed for a provisional approval within 12 months. There really wasn’t anything for him to do. He had also come to appreciate the intensive role that Dmitri was playing, not just on this project, but also on quite a few others at CerebraDyne. Sanjay had poked a bit into these other projects, but Dmitri seemed uninterested in expanding their collaboration. Resigned, Sanjay went back to his old ideas for nano-delivery of combination medicines to damaged heart muscle and continued writing his grants.

It was a few months later at the faculty New Year’s Eve party that Sanjay again ran into Dmitri. Sanjay had actually been looking for him this time. He hadn’t been able to get any answers from the CerebraDyne flacks about how the clinical trials were going, and he hoped Dmitri could fill him in. Fortunately the band this year was more into the latest trend, a sort of acoustic punk metal infused with the obligatory cello and punctuated by the latest trendy

instrument, the neuro-kalimba. Whatever. It wasn't as likely to sterilize hamsters as Death Skaggai, and it was barely possible to actually hold a conversation. He pulled Dmitri away from his "date," which appeared to be one of the rumored prototype Lexus10Ks. Even the M6 spooks supposedly hadn't gotten their test model yet. She pouted slightly for effect but then turned away and cast a jaundiced eye over the room, looking for suitably interesting test subjects. Sanjay wondered what had happened to the 9,000 model but decided not to ask.

"Dmitri!" Sanjay shouted. The music wasn't *that* quiet. "What's happening to S27? When is CerebraDyne going to release the results? When should the drug get approved?"

Dmitri gave his maddening smile and beckoned to Sanjay. Come with me. They walked towards the faculty lounge, their footsteps echoing down the long, empty corridor. Glowing Festus greenery hung from all the light fixtures, casting wild shadows in all directions. They entered the lounge and Dmitri closed the door behind them, the music now dim in the distance. The high-ceilinged room, a loving *homage* to Darwin's study, was of course empty, the workstations and computer screens dark. Dmitri glanced around and said, "Better to talk outside. I don't think it's that cold, although there's a 59% chance of snow later." He led the way through the tall French doors out to the private patio that looked out over the University grounds.

He paused for a second. "Sanjay," he began, "technically I'm not supposed to be telling you this, but I think you deserve to know." He paused again, looking down the hill rather than at Sanjay. "CerebraDyne simultaneously ran gamma-schiz clinical trials on three different strategies this summer. They kept the whole thing under the table. Yours was the first; a second came from Bangalore, and the third came from Beijing. The CerebraDyne crew has been assisting me"—Sanjay blinked at this—"in the analysis of the results from all three trials. There's no question, the compound from Bangalore is the best. It's really quite amazing." Something close to animation came into his

robotic inflection. "They managed to do exactly what my simulations called for—they designed a nano-factory that only released the drug cargo when necessary, and with pinpoint control." Dmitri seemed almost aroused by the thought. "So they achieved more complete disease modification at lower doses. The cost of goods is higher but the pharmacoeconomics support their strategy." Dmitri smiled and went on. "The Chinese went for broke with a cellular strategy. I bet in a decade this will be the preferred approach, but for now they still have trouble optimizing delivery to the hippocampus. As a result, their control of symptoms was more sketchy and the nanobot images suggested less disease modification than either of the other strategies."

Sanjay regained his voice. "So what happens to my compound?"

Dmitri smiled. "Well, there's nothing wrong with it, but in light of the success of this new delivery paradigm, there is really no future for those kinds of molecules any more. CerebraDyne doesn't even want to retain the rights; it's yours for the taking. You might be able to sell it to one of the low-cost shops that peddle drugs to the poorest countries. Certainly you should still be able to publish the data and use that to help support your next grant application." Dmitri paused again, then tentatively put out a hand to the older man's shoulder. Sanjay shuddered involuntarily but didn't move. "If you need any help writing up the results for your blog, let me know." He glanced back into the faculty lounge and through the glass noticed a lithe form in the shadows. "Well, I think that's about it. See you, Sanjay." And with that, Dmitri went back inside, leaving Sanjay staring after him and his companion returning to the party, walking arm in arm. He was startled by the kiss of cold, wet snowflakes on his cheek.

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