Simulation of Mental Disorders: II. Computer Models, Purposes and Future Directions

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ABSTRACT

The complexity of the human brain and the difficulties in identifying and dissecting the biological, social and contextual underpinnings of mental functions confound the study of the etiology and pathophysiology of mental disorders. Simulating mental disorders in animal models or in computer programs may contribute to the understanding of such disorders. In the companion paper (30), we discussed selected concepts and pragmatics pertaining to mental illness simulation in general, and then focused on issues pertaining to animal models of mental disease. In this paper, we focus on selected aspects of the merits and limitations of the use of large scale computer simulation in investigating mental disorders. We argue that at the current state of knowledge, the biological-phenomenological gap in understanding mental disorders markedly limits the ability to generate high-fidelity computational models of mental illness. We conclude that similarly to the animal model approach, brain simulation focusing on limited realistic objectives, such as mimicking the emergence of selected distinct attributes of specific mental symptoms in a virtual brain or parts thereof, may serve as a useful tool in exploring mental disorders.

"The human quality of a human being is disregarded and neglected, for example, by those psychologists who adhere to either "the machine model" or "the rat model"… As for the first, I deem it to be a remarkable fact that man, as long as he regarded himself as a creature, interpreted his existence in the image of God, his creator; but as soon as he started considering himself as a creator, began to interpret his existence merely in the image of his own creation, the machine."
Viktor Frankl (1)

COMPUTER SIMULATION OF MENTAL DISORDERS

Computer models have a shorter history than animal models. Since computers are man-made machines, as opposed to living animals, the similarity between humans and computer programs run on general purpose machines or even on special purpose hardware seems far less intuitive with regard to most biological functions. Nevertheless, the "thinking" capacity of computers led Turing to suggest that "digital computers… can in fact mimic the actions of a human computer very closely" (2, p. 438).

In the twenty-first century computer-based simulation in life sciences is ubiquitous (3). It is being used in diverse biological fields and for various objectives including, but not limited to, the prediction of protein structure (4), estimating the pharmacological effect of chemical substances (5), mimicking pathological conditions (6, 7), providing physicians with practical tools to improve their procedural skills (8) and assist or perform medical decision-making (9).

There is a growing interest in applying computer simulation to expand our understanding of the etiology and pathophysiology of mental illness (10-19). The basic question is, shall we expect computers to be able to mimic the human brain, and specifically, in the context of the present discussion, simulate mental illness? And if so, is it expected to be genuinely useful?

TYPES OF COMPUTER SIMULATION OF MENTAL DISORDERS

For the purpose of discussion we distinguish three types of models in brain simulation: The phenotypic type of model, the biological type of model, and the heuristic type of model. These types of models differ from each other in their goal, methodology, and the capacity to simulate

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mental illness. The phenotypic type of model attempts to mimic clinical phenotypes, i.e., high-level manifestations of mental disorders; the biological type of model attempts to mimic psychiatric disorders via bottom-up simulation of low-level biological systems, i.e., molecular, synaptic and cellular, and their modeled dysfunction; and the heuristic type of model attempts to identify intermediate level explanations that connect low-level biological dysfunction to high-level psychiatric symptoms (Table 1). The main difference between these types of models relates to the fundamental question of how closely and in what sense one needs to mimic the target (i.e., in this case, the brain) in order to achieve a successful simulated object (20). This difference relates to the gap between the low-level biological functional architecture and its function as complex non-linear dynamic system with a high-level phenomenological output, i.e., overt behavior, emotion and thought.

Mental disorders are embedded in brain pathology, but, as noted above, at the same time are currently defined and categorized by the DSM (21) according to their phenotype manifestations. These disorders are entities that involve a wide spectrum of causes and expressions, ranging from largely obscure biological and environmental underpinnings to subjective experience and observable behavior. Each of the aforementioned types of models focuses on a different aspect of mental disorders, based on implicit or explicit, practical or theoretical assumptions that will be briefly explored below.

THE PHENOTYPIC TYPE OF MODELS

The phenotypic model of mental illness simulation focuses on mimicking the high-level phenotypical manifestation of the disorder. Turing's approach to brain simulation (2) is in line with this view. The "Turing test" suggests to replace the theoretical question whether computers can think with the operational question of whether a computer, under certain circumstances, can generate a human-like performance (in terms of answering to communicated questions) to the extent that a human judge will not be able to distinguish between the machine performance and the human performance. Hence if a human judge cannot tell whether the source of the answers is a computer or a human being, the computer is said to have passed the test.

The Turing test as a potential benchmark for the success of a computer simulation of mental disorders translates into the question whether the computer will be able to generate a spectrum of ongoing behaviors that will appear indistinguishable to an interrogating expert from those of a real person who suffers from a mental disorder. The focus on mental illness simulation is here hence the behavioral phenotype. Extending the simulation not only to a black

Table 1. *Computer Simulation of Mental Disorders: Three selected prototypes of computer simulation for the study of human mental disorders.*

	The Phenotypic Type of Model	The Biological Type of Model	The Heuristic Type of Model
Description	An attempt to mimic phenotypic, high-level manifestations of mental disorders.	An attempt to mimic psychiatric disorders via bottom-up simulation of low-level biological systems (i.e., molecular, synaptic and cellular).and their dysfunction.	An attempt to identify intermediate-level explanations that connect low-level biological dysfunction to high-level psychiatric symptoms.
Examples	A computer-based program that generates behavior indistinguishable from those of a real person suffering from a mental disorder ["Turing-style test, " (2)].	Large scale simulation that attempts to mimic cellular and circuit functions and connectivity in the brain (24).	A computational model that tries to explain the relationship between pathological brain connectivity and the characteristic signs and symptoms of schizophrenia (34).
Main Advantages	This model may accurately express behavioral manifestations of mental disorders. It can be used for educational purposes as a simulator for therapists in-training or family members of people who suffer from mental disorders.	May provide new information pertaining to the role of biological factors in the pathogenesis of mental disorders, and, in turn, contribute to the exploration of innovative pharmacological interventions.	This model may provide a representation of a specific biological system with the aim of testing the validity of a specific hypothesis pertaining to that system.
Main Limitations	The simulation might not be realistically linked to biological structures or the functioning of the brain. Thus, the phenotypical model will not provide new information pertaining to the role of biological factors in the pathogenesis of mental disorders, nor to the therapeutic effect of specific biological interventions.	It is questionable whether this model is capable of capturing the phenotypic dimension of mental illness, hence reliably simulate psychiatric symptoms.	One would not expect to be able to compare data drawn from the heuristic model and compare it, point for point, with data drawn from realistic biological instrumentation. A limited contribution to the finding of new pharmacological interventions.

box but also to a real-life-like system capable of somatic responses, the ideal phenotypic model should be capable not only to duplicate verbal-like characteristics of psychiatric disorders but also react "physiologically." For example, simulation of specific phobia disorder should include not only the verbal content expected from the phobic person, but also mimicry of the physiological fight-or-flight response (e.g., accelerated heart and respiratory rate, dilated pupils, etc.) upon confronting a fear-inducing object or situation. At its best, an artificial "body" may be hooked to the simulated brain in order to execute the phobic behavior. Yet even a computer-based virtual representation of the phobic behavior, in the absence of somatic reality, will no doubt be considered a major achievement.

It is of note that the phenotypic model does not intend to mimic the postulated native brain activity, so that, for example, the fight-or-flight response will be generated via a simulated neuronal sympathetic system. It is focused on reliably emulating the phenotypic manifestations of mental disorders, including thoughts, emotions and behaviors, as realistically as possible. Nevertheless, within the category of the phenotypic model, a range of subtypes could be suggested that differ from each other based on the degree in which a brain-like activity is represented. These range from artificial intelligence and machine learning systems that focus solely on the generation of psychiatric symptoms while being indifferent to the realistic biological mechanism in which these symptoms are generated in the brain, to a more biologically inspired cognitive architectures system that can generate useful functions in roughly brain-like ways, focusing on high-level architecture of the brain without necessarily simulating its low-level specifics.

A notable merit of the phenotypic approach, if successful, is that by being able to produce behavioral manifestations of mental disorders it may serve as a simulator for therapists in-training as well as for family members of those afflicted. As such, it may promote better understanding of these conditions and improve strategies of communication with those who suffer from these conditions.

Further, computer simulations of mental disorders may learn the characteristic emotional and verbal responses of a person who suffers from a certain mental disorder and serve as a simulator to study potential responses to various stimuli. It could even be possible to learn the basic relationship between symptoms and the underlying biological activity that correlates with or even generates these symptoms. Consider, for example, "Spaun" (Semantic Pointer Architecture Unified Network) (22), a neuronal model of the brain, in which a visual stimulus generates action (drawing) via a physically modeled arm; similarly, a phenotypic model of mental disorder may mimic the perception, cognitive analysis, and reaction processes involved in specific phobia disorder, such as cynophobia, i.e., fear of dogs. Namely, a stimulus of a dog may be presented to the cynophobia simulating system which will mimic the cognitive processing of the stimulus and the production of the cognitive, emotional and physiological responses to it. This simulation mode will capture a prominent characteristic of mental disorders in a quite realistic way: the interaction between the brain and the environment in the pathogenesis of psychiatric symptoms. It could also allow the investigation and demonstration of the process of systematic desensitization, a successful therapeutic intervention which is used in such cases. In addition, it may reassure patients that cognitive modification of automatic dysfunctional thoughts may reduce anxiety.

In spite of these potential merits, the phenotypic model is unlikely, in the foreseeable future, to display the same flexibility and creativity as the human brain. The phenotype of the simulated mental disorders will have to be linked to the real-life milieu, both intracorporeal and extracorporeal, of the brain. Thus, the phenotypic model will likely not provide new information pertaining to the role of some important biological and environmental factors in the pathogenesis of mental disorders, nor to the therapeutic effect of specific biological interventions that are based on intracorporeal interactions.

THE BIOLOGICAL TYPE OF MODELS

As opposed to the phenotypic model of mental illness simulation, the biological model is characterized by a bottom-up approach in which low-level brain activity and function is simulated via a detailed biologically based system that mimics the real cellular and connectivity characteristics of the brain (23). At its core, the biological model is embedded in the reductionist view according to which high-level mental phenomena (as well as mental deficiencies) emanate from a low-level biological activity. This type of approach is epitomized in Markram (24): "(Our) view of the brain would enable us to reclassify… diseases in biological terms rather than looking at them simply as sets of symptoms. The breadth of this perspective would allow us to move forward to develop a generation of treatments that selectively target the underlying abnormalities… we could program a certain mutation into the model and then observe how that mutation affects it at each step along the biological chain. If the resulting symptom, or constella-

tion of symptoms, matches what we see in real life, that virtual chain of events becomes a candidate for a disease mechanism, and we can even begin to look for potential therapeutic targets along it…"

The implicit theoretical framework that the proponents of the biological model hold is close to what philosophers of science would call "weak emergence" (25, 26). This conceptual framework implies that "the fundamental causal processes remain, ultimately, physical… at the microphysical level… different sorts of causal interactions may appear to dominate 'higher' levels of reality. But our inability to recognize in these emergent patterns new manifestations of the same fundamental processes is due primarily to currently limited state of our knowledge. For this reason weak emergence is sometimes called 'epistemological emergence,' in contrast to strong or 'ontological' emergence" (27, pp. 7-8).

Realistic brain simulation, if successful, may enable researchers, according to this approach, to conduct in silico experiments that will be difficult or even impossible to perform in vivo. However, other authors have raised doubts concerning the capacity of such simulation approach (e.g., HBP) to generate intelligent behavior like a human brain (3, 20). Among the various conceptual and practical concerns, the most urgent one in the context of mental illness relates to the questionable capacity of this approach to capture the phenotypical dimension of mental illness, or in other word, to reliably simulate psychiatric symptoms.

This is of concern for various reasons. Even if we assume, for the sake of discussion, that down the road of a large-scale simulation of the human brain we will ultimately encounter a realistic, faithfully simulated human brain, its applicability to the realm of mental illness would still be questionable since it is not clear how "along the biological chain" simulated genetic mutations become a "symptom, or constellation of symptoms" that match "what we see in real life." Should we indeed expect the emergence of the intermediate-level wiring of the brain in which biology becomes phenomenology and synapses evolve into thoughts and emotions? Consciousness-related psychiatric symptoms seem to be better explained by "strong" or "ontological" emergence (28). Thus, it is doubtful whether computer simulation is capable of modeling ontological emergence (29).

To simulate means to make an object look like or function as a target (30). We cannot simulate a hypothetical Dsmosaurus because we simply do not have a clue how a Dsmosaurus looks. In the same vein, we can wonder whether we might be able to mimic the "intermediate" level of the brain (functional neuronal circuits), which is probably responsible for the generation of mental symptoms, unless we have a solid understudying of this intermediate level in advance.

The assumption that the higher level activity of the human brain will emerge once the low-level layer of a brain is simulated, let alone that this will further understanding of the mechanisms involved, is embedded in the assumption that low levels do not only permit but also shape, causally inform, or instruct higher levels. An alternative view is that at least some high levels of organizational and functional complexity are in fact agnostic to the details of events within lower levels, and operate according to level-specific rules that do not emerge in an explanatory or causal manner from the lower level (3, 31, 32). This view hence implies that the assumptions that detailed identification of the events in the lower level will explain the higher level in toto, or, in the absence of such identification, a deux ex machina solution could be expected, are erroneous.

The present knowledge of biology in general and brain biology in particular does not allow the field to make a decisive informed selection between the aforementioned hypotheses, let alone in the context of the etiology and phenomenology of mental illness. Even with regard to the few conditions in which the genetic underpinning is understood, such as Fragile X syndrome (33), the precise pathophysiological mechanism that leads to the mental manifestation and the inter-level translation rules, of any, are as yet not understood. Thus, in our view, the road to revolutionary treatments resides in the discovery of the causal intermediate-level processes of mental disorders, rather than in attempting a detailed simulation of low-level biological processes.

But even if we take the stand that low levels completely inform the higher ones, in order to reach a "'holistic view of the brain' that 'would enable us to reclassify… diseases in biological terms rather than looking at them simply as sets of symptoms" (24), we need to proceed bottom-up level-by-level, including the intermediate levels in which low-level biology emerges into symptoms. However, at this point in time this process cannot be satisfactorily simulated because we do not have the proper level-specific benchmarks for a successful inter-level transformation, unless, again, we adapt deux ex machina as a legitimate argument in planning biological projects.

On top of it, even if we ever succeed in simulating the brain of a person who suffers from a mental illness, and even if the pathology is the patient's brain, it does not means that the brain of the patient is "schizophrenic" or "autistic" just because it "belongs" to the patient. We cannot meaningfully

address the quality of being "schizophrenic" to the brain, unless we can demonstrate decisively in what sense this specific brain is functionally different from a "normal" or "depressive" brain, i.e., in what sense this specific brain causes the specific symptoms of schizophrenia at a particular period of time. It is still to be determined how far the utility, in the sense of understanding, of a duplicated brain of a schizophrenic patient would be greater than the utility of the DNA of a schizophrenic patient. Unfortunately, the capacity to analyze the "low-level" genetic information of a schizophrenic patient has not led us thus far to a significant breakthrough with regard to the understanding of the pathophysiology and etiology of schizophrenia.

In sum, we highlight the fact that at least some versions of the biological type of models are based on the theoretical hypothesis that "high-level" phenomena will evolve directly by "low-level" brain simulation. Thus far, this hypothesis has not been supported by empirical findings. Therefore, at this point it seems that the simulation of the "intermediate level" requires a pre-knowledge concerning the causal link between the low-level biology and the high-level phenomena. The case of mental disorders genetics illustrates that a relatively detailed understanding of the low-level biology (i.e., the DNA of an individual patient) does not directly lead to the understanding of the high-level phenomenology (i.e., her signs and symptoms).

THE HEURISTIC TYPE OF MODELS

The third type of computer simulation, the heuristic type, creates a representation of a specific biological system with the aim of testing the validity of a specific hypothesis pertaining to that system. The heuristic type of models stands in between the phenotypic and the biological models. Its limited explanatory power is restricted to the intermediate-level that connects low-level biological dysfunction to high-level psychiatric symptoms. However, it differs from both the phenotypic and the biological models since it neither tries to realistically mimic symptoms nor biological structures, but rather to provide means for improved theoretical understanding of mental disorders. Thus, in this form of mental illness simulation one would not expect to be able to compare data drawn from the model point for point with data drawn from realistic biological entities.

Let us illustrate the heuristic model by referring to the work of Hoffman on schizophrenia (13, 34, 35). Several computational models have been developed to investigate the symptoms that are associated with schizophrenia (16). The diversity and complexity of the symptoms of schizophrenia have led to the notion that this disorder may not be understood as a localized brain pathology but rather as a dysfunctional state that result from reductions in connectivity between brain regions, possibly due to a mechanism of pathological excessive pruning during adolescent neurodevelopment (36). Hoffman and his colleagues (34) have tried to provide an answer to the question of how might a reduced brain connectivity produce characteristic signs and symptoms of schizophrenia. In other words, they were focusing on the intermediate level that connects low-level biology to high-level phenomenology.

They designed an attractor model network that simulated the function of 100 simplified entities representing neurons. After training, a pruning rule was imposed on the network which in turn led via "neural Darwinism" (37-39) to competitions among alternative neuronal projections for dendritic connections. They found that at high levels of pruning, the system began to demonstrate "pathology," including the production of a memory state that was different from any particular memory that was earlier stored in the network. The pathological pattern could be related to the positive symptoms of schizophrenia, such as intrusive thoughts and delusions. They have further shown that in their approach simulations of speech-perception networks can result in spontaneous output (i.e., output in the absence of input), and this was suggested to mimic another common positive symptom of schizophrenia: auditory hallucinations ("hearing voices"). This finding was interpreted as supporting the view that auditory hallucinations in schizophrenia arise from pathological activation of neurocircuitry involved with speech perception and not due to a pathological misidentification of ordinary inner speech.

Taking Hoffman's work (13, 34, 35) as an example of the heuristic model, it is evident that his neural networks do not characterize the underlying realistic etiology of schizophrenia. However, they provide useful theoretical insights pertaining to candidate causal links between pathologic neuro-developmental process and a constellation of "schizophrenic" symptoms. Beyond the proposed validity of the suggested findings to the pathogenesis of schizophrenia, Hoffman's approach demonstrates the potential use of neural network simulations in linking outward manifestations of neuropsychiatric disorders to underlying neurobiological processes. It seems that the main merit of heuristic models is their capacity to offer new (though simplified) theoretical concepts or metaphors that could promote and facilitate thinking about brain processes, and suggest directions for further scientific exploration. Nevertheless, limitations of

this approach relate to its predilection to simplicity over biological or phenotypical realism, which inherently reduces the usefulness and practical value of these models.

It is pertinent to mention a major limitation that applies to all the aforementioned three types of computational models: they are basically focused on the isolated brain at a particular point of time. However, environment-related life experiences have a critical role in shaping and maintaining our mental identity. These experiences dynamically alter our brain throughout life and are responsible for individual differences in the biology and functionality of our brain. Current types of computational simulations tend to lack the life-long dynamics that characterizes human behavior and certain dimensions of mental disorders. For example, the etiology of some mental disorders (e.g., PTSD) involves prior events in the history of the patient. In addition, the manifestation of several mental disorders (e.g., social phobia) requires a specific social context. Thus, computer simulation that focuses solely on an out-of-context brain, including brain in the absence of the interacting body, or is equipped with a relatively limited dynamic capacity, arguably misses key features of mental disorders. It is likely, however, that large scale computational models will in the future try to take into account such contextual temporal dynamics and its repercussions on the output of the simulation.

A POTENTIAL SCIENCE-CLINIC CONFLICT OF INTEREST

Discussion of mental illness simulation, whether in vivo in animal models or in silico in software running on a computer, must involve the question of the purpose(s) of mental illness simulation.

The long-term objective of mental illness simulation is to better understand the pathophysiological processes that cause mental disorders, and ultimately diagnose and treat these pathologies more effectively. However, it seems that mental illness simulation bifurcates into two main conceptual frameworks, stemming from two types of professional aspirations. Scientists and mental health providers may have different goals in mind based on their different professional agenda. The biological-phenomenological gap is not just a methodological or epistemic problem in the laboratory. It is also a gap between two different perspectives, or cultures, in approaching the problem of mental illness.

Many neuroscientists, mostly in the molecular and cellular sub-disciplines, are inclined to approach the problem of mental illness through the reductionist prism. For these practitioners of these highly successful and productive branches of neuroscience, the intuitive path which may lead to better understanding of mental illness moves bottom-up, from low- or medium-level biological underpinnings toward high-level mental symptoms. Many clinicians, on the other hand, for whom the starting point is the symptoms of the real patient, are inclined to approach mental illness through the high-level phenotypic prism.

Another difference relates to the focus of everyday work. While scientists' immediate and explicit objective is to expand the knowledge pertaining to mental illness, in the short run even irrespective (though mindful of) the expected therapeutic outcome of their intellectual effort, clinicians are mostly dedicated to ameliorate the symptoms and suffering of their patients, meaning here and now. These two cultural attitudes may intuitively lead to different orientations pertaining to the question of what would be the most urgent and valuable modality of mental illness simulation.

From the vantage point of many neuroscientists, brain simulation that is based on the vast available data in molecular and cellular neurobiology could seem advantageous since it is likely to advance knowledge faster and on more robust grounds, even though the therapeutic implications may end up being delayed. However, from the vantage point of the clinician, the main purpose of the mental illness simulation should be to find relief for the suffering of the sick. From this perspective the realistic nature of the simulation and its ability to coherently explain brain and behavior are less important as long as the simulation has the potential to yield practical outcome that can contribute to the well-being of the patients. Though this dichotomy is definitely a gross generalization, it is still valuable for appreciating how different professional audiences may perceive brain simulation differently in the context of mental disease.

In order to foster further thinking about the aforementioned postulated cultural divide let us address the differences between the two approaches by using a well-known analogy in psychology commonly ascribed to Freud (40). Mental disorders, so goes the analogy, are like icebergs. The top of the iceberg is equivalent to the phenotypic manifestation of mental illness, namely, mental symptoms. Underneath this tangible layer there are deeper layers. Freud suggested that the Id and the unconscious reside at the bulk of the iceberg; others prefer the biological approach according to which the foundations of the iceberg are genes, molecules and neurons, etc. In fact, we can observe only the tip of the iceberg (by accepting the subjective reports of patients) and fractions from its foundation (via scientific

investigation), but we lack a full view of the components that connect these strata to the top of the iceberg.

Regardless of the questions pertaining to the precise structure of the iceberg and the exact mechanism that led to its formation, it is clear that from the point of view of a sailing ship, the problematic components of the iceberg are its top and near-surface parts. It is the interaction between these parts of the iceberg and the environment that makes the iceberg hazardous to humans. If one can somehow deal with the risk posed by these parts, the iceberg ceases to be acutely dangerous. One may conclude that in order to prevent a collision with an iceberg there is no need to know in detail every hidden part of the iceberg but rather it may be good enough to know how to eliminate the above-water risk posed by the iceberg. As a result, the required depth of exploration of icebergs depends on the purpose of the exploration; for geologists any new piece of information pertaining to icebergs is a precious treasure, but for sea travelers, only those parts of icebergs that may become a hazard are of practical interest and relevance.

Similar to icebergs, mental disorders are expected to have deep foundations in the human brain. A sweeping search for the "best" mental illness simulation modality as such is in a way disoriented since the quality of the simulation depends on its purpose. For Turing, the phenotypic model would probably be satisfactory since it could mimic the phenomenologic manifestation of mental disorders very well. On the other hand, for the scientist who seeks thorough understanding of the pathophysiology, even the biologically based realistic type of model may not suffice.

From a clinical perspective, the "best" mental illness simulation modality would be the one that could most effectively and rapidly lead to a cure, or at least significantly ameliorate the suffering and dysfunction involved in mental illness, even in the absence of detailed knowledge concerning the detailed biological accuracy. The clinically oriented approach to mental illness simulation may require an intermediate route between the biological and the phenotypic type of models. Like in many other areas in medicine, technology could be very effective in providing a solution to human morbidity even without detailed understanding of the pathophysiological process, and vice versa, the pathophysiological process does not necessarily lead to an effective treatment, though it can be expected to facilitate the identification and development of such treatment. If the motivation for simulating mental illness is to find a treatment, the simulation approach should be tailored to best address the specific clinical challenge under investigation.

A NOTE ON FUTURE DIRECTIONS

Several issues concerning the future of simulation of mental illness are pertinent here.

a. The nature of mental illnesses and their complexity (and the current biological-phenomenological gap) may benefit from a multi-level approach that integrates multiple modes of simulation: a bottom-up "low-level" biologically oriented realistic mode and a top-down "high-level" symptom oriented phenotypic mode. Successful mental illness simulation could include two strata that correlate with the uppermost and bottommost layers of brain functioning. The realistic biological simulation may benefit from the methodologies of computational neuroscience while the phenotypic simulation may benefit from the use of artificial intelligence. One of the main merits of animal models of mental illness relates to the fact that they enable some degree of bidirectional manipulation of both the molecular and cellular level (e.g., via molecular genetics) and the phenomenological level (e.g., via controlled context). However, the phenomenological dimension of animal-based simulation suffers from low construct validity and face validity (30). One could hope that computational simulation of mental symptoms will mimic some aspects of human psychopathology more accurately. One of the expected outcomes of this simulation strategy would be the emergence of better understanding with regard to the intermediate-level brain activity in which the two subtypes of simulation are expected to interact.
b. In parallel to the suggested paradigm shift from "animal model" to "model animal" (see 30), the methodological and technological barriers involved in mimicking mental disorders may be tackled by focusing first on a single component of a specific mental disorder rather than trying to emulate a mental disorder in its full extent. Given that mental disorders consist of multiple signs and symptoms that are not necessarily or inherently interconnected to each other (as detailed above), it may be reasonable to compartmentalize or parcel out their simulation. For example, instead of trying to create a computer-based realistic simulation of schizophrenia it may be more realistic to simulate one component of schizophrenia, such as auditory hallucinations, by capturing both the phenomenology of the symptom and the presumed low-level biological components that are related to this symptom. This is clearly much less challenging than a simulation of an entire mental disorder. Since auditory hallucinations are not pathog-

nomonic with schizophrenia, their simulation may prove equally relevant to other mental disorders as well (e.g., psychotic depression, drugs intoxication, etc.). In fact, the relatively similar manifestation of auditory hallucinations in various mental disorders suggests that there is an independent brain-based neural basis for this symptom. Thus, it seems justified to apply the compartmentalized simulation approach in the study of auditory hallucination and, more broadly, in other dimensions of mental illness simulation as well.

In addition, it seems that certain mental disorders may be considered better candidates for computer simulation due to their relatively reduced-complexity phenomenology. For example, specific phobia is relatively limited to specific reactions to a specific set of inputs (e.g., seeing or hearing a dog). On the other hand, the pervasive nature of schizophrenia that is characterized by a constellation of symptoms (including constant misperception of various environmental stimuli, various pathological behaviors, cognitive deficiencies and dysfunctional social interaction), renders schizophrenia a much more challenging candidate for computational simulation than specific phobia. Flexibility is no doubt needed in adjusting the most appropriate simulation approach for each disorder, based on its unique nature and characteristics. Some disorders may require a more biologically oriented approach while others will be better understood by a more behaviorally-oriented approach.

c. It is not a given that success on the road to low-level biological brain simulation necessarily implies success on the road to mental disease simulation. A high-fidelity computational duplication of a specific brain area, including its structure and biological activity, may justifiably be considered an immense achievement in terms of brain simulation, but not necessarily in terms of mental illness simulation. The biological-phenomenological gap implies that mental disorders may not be easily reduced to low-level biological pathology.
d. Mental illness simulation can benefit from purpose-guidance. As explained above, different purposes may dictate different mode of simulation. A realistic low-level biologically based mental illness simulation is motivated by the (arguably too) simplified reductionist premise according to which all mental disorders are caused by lower-level pathology, such as "bad genes" or "bad connectivity." Even if one accepts this assumption, simulation of the whole brain, piece by piece, may not be required from a clinical perspective; innovative and effective treatments for mental disorders may be identified via a semi-realistic simulating system. This should not come as a surprise, as some attempts to currently develop treatments are conducted by drug screening engineering and screening irrespective of simulations of any type.
e. The effort to bridge the biological-phenomenological gap should be accompanied by a parallel effort to intertwine the biological and phenotypical orientations to mental illness simulation via the establishment of research teams combining scientists and clinicians (noting that both attributes may in fact sometimes merge in the same individual). Such conjoint effort may facilitate a stereoscopic view of mental illness and in turn may lead to mental illness simulations that will realistically capture both low-level and high-level brain function.
f. Last but not least, history indicates that unsound metaphysical assumptions may jeopardize scientific enterprises. The perception that humans are qualitatively superior to animals led to an ideological resistance in certain period to use animal models for human biology and, in turn, to stagnation in biological science. To use Viktor Frankl's phrase, quoted at the beginning of this article, the perception that man's existence is in the image of God has at times distanced humans from animals. However, the pendulum has long swung back. Frankl was concerned about the enthusiastic inclination of some scholars to adopt "the machine model" or "the rat model," which interpret human existence as a mere machine or animal. In the context of mental illness simulation, a rigid materialistic view that is unaware and uncritical to its limitations, could potentially prove a hindrance to scientific progress.

The hegemony of the biologically oriented reductionist approach, admittedly extremely successful and productive so far, in the scientific Zeitgeist may inadvertently lead investigators to believe that the road to effective psychiatric treatments passes through the biology of rodents or the computational simulation of "low-level" neural systems and functions. It is not unreasonable to suggest that there might be powerful stakeholders, such as pharmaceutical companies, interested in specifically fostering the biologically oriented reductionist approach. They might be inclined, for example, to bias investments toward rodent models and bottom-up computational models of mental illness. This approach to ameliorating human mental disorders may indeed prove of value, but one should keep in mind that it may come to dominate disproportionately the material and mantel resources devoted to attain practical therapeutics to the real-life, multi-faceted, human mental suffering. In the context of simulation, whatever type of model we pursue,

either the animal model type or the computational type, that approach should be considered as an element in the tool-box, not its replacement.

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