Computational biology is poised to advance precision medicine with machine learing

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Today, scientists are attempting to model whole cells using computational biology, building virtual cells that capture the dynamics of living

In the post-genomic era, vast quantities of data describing the parts of living cells, both normally functioning and diseased, have been amassed. Understanding how cells behave has been the goal of reductionist science, and many of the principles are well understood.

In elucidating the details, complexity has been revealed to the degree that scientists have limited capacity to understand the systems underlying the biological networks. This is to say, cellular behavior is difficult to predict.

The growth of computational biology

In the 20th century, early adopters of limited computer resources did attempt to describe biology mathematically and were successful. Understanding nerve stimulation was modelled with equations and these findings initiated the idea that cells are dynamic in nature, changing both qualitatively and quantitatively with time [(1)].

Today, the cell is understood to be a network responsive to both internal and external stimuli such that it upregulates its specific function when needed and downregulates that activity when no longer of use.

A simple example would be the epithelial cells lining the intestine, responsive to the intake of nutrients during a meal by synthesizing protein transporters crucial to absorption. The steps for this activity require sensing by surface receptors, increase in the number of transporters on the cell surface, internalization, and release of the nutrients intracellularly.

While these appear to be linear events, other cellular components must coordinate the uptake, such as the cytoskeleton. Hence, a network ultimately describes the cell's behavior. (For further details of mathematical modeling in biology, please see [(2)].

Today, scientists are attempting to model whole cells, but it is early days, and vast amounts of the computer resources needed are not quite available.

But, in the interim, creating mathematical models of limited portions of the entire cellular network still provide useful predictions that can be validated experimentally. In doing so, benefits to human health await.

An example of a mathematical model

In an attempt to mathematically model cancer cells, normal function of certain subsystems, or pathways, has been undertaken, and these models demonstrated interesting systems properties not necessarily expected at the time.

For example, a critical regulator of the cell's response to DNA damage is a protein called p53, one of the most commonly mutated genes found across all cancers, was modeled. It can trigger a programmed cell death pathway if the damage is unrepairable. When normally functional p53 was examined, its protein levels oscillated, surprisingly [(3)].

Studies ensued to both understand which aspects of these oscillations were important for cell death (e.g., the amplitude or frequency of the oscillations) and for laboratory confirmation of the findings. This is just one of the many existing mathematical models that await advanced development that accounts for mutations altering function and, ultimately, the cancer phenotype.

An example of a pharmacodynamic model

Pharmacodynamic models describe the action of a drug of interest and its desired outcome in the network in which it will have an impact. In the case of cancer, the expected therapeutic consequence would be cell death due to intrinsic pathways.

In an important collaboration with the Frederick National Laboratory for Cancer Research and the ATOM Research Alliance, and BioSystems Strategies, LLC, important novel therapeutics were included in a model of the DNA damage response for further analysis that would pinpoint biomarkers that may improve the therapeutic outcome.

In this model, a generic inhibitor of PARP1, an initiator of the DNA damage response, was found to more effective when certain sensitivities were considered. Importantly, because the pharmacodynamic model, as all are, was evaluated over time, it was found that if the biomarker determining the sensitivity was considered, cell death would occur sooner.

Future studies confirming the computational result in the laboratory are essential, but the collaboration demonstrated a novel methodology to improve survival in cancer patients treated with PARP1 inhibitors.

What is machine learning and how can it help?

Machine learning is widely used to evaluate large datasets, and it's not uncommon now for a patient's tumor genome to be sequenced with an enumeration of the mutations.

At its essence, machine learning (ML) is the application of algorithms to vast datasets such as a sequenced genome to uncover patterns not discernable to human obervation. Thus, the "machine" is learning. For example, looking at a cohort of patients with ovarian cancer, genomic data analysis can identify mutations correlated with survival outcomes.

This analysis can be the first step to uncover critical molecular targets and biomarkers for drug discovery and development and, more so, if applied to the mathematical models described above.

It is important to note that ML has its limitations in that the patterns it defines sometimes are nonlinear in nature, meaning the features underlying the outcome of interest (e.g., improved survival) are not apparent. If static data such as genomic data are studied, the relevant biological mechanisms are difficult to discern.

Applying machine learning to mathematical models describing dynamic interactions, though, which offer vast amounts of data as well, has the advantage that the data reflects biological processes changing with time.

Once a model is formulated with the proteins, interactions, and parameters describing rates, it is simulated, and, for each component, changes over time are documented. It is this data that can now be evaluated by a ML algorithm to determine what component or components contribute(s) to a desired outcome, such as inhibition of cell growth or cell death in the case of a cancer patient.

Understanding biology like never before

Understanding these features will allow a closer look at biology than ever before and in the case of diseased state, opportunities for highly effective predictions for prognosis and cures.

Mathematical modeling combined with machine learning may be the wave of the future to tackle the challenge of basic biology and all its complexity, and it may also lead to the promise of precision medicine with safer therapeutics.

References

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