Abstract

The state equations of the 21st century allowed scientists to map the pattern of human protein-protein interactions in the last decade. Though this process so far is from complete, current datasets are being refined enough to conduct dynamic network analysis, to “turn on” the network and observe its behavior under given conditions and under certain noise perturbations. Since we are working with protein-protein interaction networks, the different starting conditions can be mapped to certain biomarker sets, and the outside perturbations correspond to the different drugs introduced to the system. Using the innovative, patent pending tool called Turbine [2,2], it becomes possible to infer sets of probable biomarkers and drug targets only from the topology and the dynamic equations of the observed network.

The Turbine network dynamics software

The core of the Turbine system is a very fast and versatile network simulator algorithm, which can simulate networks with millions of nodes in less than a minute, or small networks in a fraction of a second. Turbine is written in C++, with focus on speed, extendability and scalability. Any type of complex network can be simulated with Turbine with any algorithmically describable dynamic model. Moreover, any combination of external perturbations can be introduced at any stage of the simulation, with arbitrary waveforms. Memory usage only depends on the size of the network, not on the size of the input or output time functions. The program is highly optimized and supports CUDA and OpenMP for maximal utilization of computational resources. It has a plugin-based architecture and an embedded Python interpreter for extendability via C++ and Python. Turbine’s plugin architecture is based on a client-server model for scalability, and supports MPI for simulating extremely large networks using supercomputers. The image below shows the running times for simulating 1000 steps with the five-module model called “communicating attractors” [2] on a system having an Intel Core i7 920 CPU, 10 GB RAM and a GeForce GTX 660 GPU. The introduced advanced analysis type is patent pending.

3: Biomarker search

Another interesting biopharmaceutical use of Turbine is biomarker search. By comparing the possible steady states in select phenotypes or mutation sets, Turbine can find a set of biomarkers which, when compared to the reference “marking barcodes” described in the main text, can uniquely determine the underlying steady state, mutation set or other group out of the selected patient strata. By using the steady states observable in the healthy system and the 11 mutation sets to the right, it becomes possible to differentiate between healthy and cancerous states using 2 biomarkers (the activities shown in the table correspond to the healthy state), “differentiate among all 12 stratas with 7 biomarkers or differentiate among 116 of the 117 steady states using 14 markers. This information can thereafter be used for patient stratification and reclassification during clinical trials, or assessment of personalized treatment options.

Healthy vs cancerous

A) AKT + BAX or P38K, P21-

All strata

IKK, AMPK, TGF, PS3, PS3, UBC110, EVC, ETC-

All steady states

IKK, CCK, C, CCK-A, CDH2, UBC100, GSK, TGF, E2F, FOS(JUN), APC, MIZ-I, PS3, MDM2, ATM

More Information

The versatility of Turbine makes it possible to accommodate many other types of analyses involving networks such as simulating the predictable effects of a certain drug, analyzing treatment robustness, inference of missing elements or parameters of the analysed network based on experimental data, and much more. A demonstration version of the biomarker search and the intervention target design workflows of Turbine is available at http://dzzom.com/turbine-demo.

We are currently looking for business/collaboration opportunities. If you or your company would be interested in working with us to utilize the power of network dynamics in your project, please contact us at one of the following addresses:

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References


Checking the above results reveals that such interventions could easily kill healthy cells as well. Target sets which are predicted to be toxic for healthy cells are marked with red color in the table above. To make the designed targets more useful, we have introduced a verification step into the design process to make sure that healthy cells do not commit apoptosis while cancerous cells are still killed. The following table shows an alternative set of treatments which have been found not to induce apoptosis in healthy cells. The prevalence of RTK inhibitor perturbations agree with the wide adoption of RTK inhibitor drugs such as Axitinib (sorafenib), VEGFR or Vx-680 (sunitinib), EGFR. Based on the results, von Hippel-Landau inhibitors could prove to synergize well with RTK inhibitors. Such compounds (VHL inhibitors) are already actively investigated [7].

1: Steady-state analysis

In complex systems, only a very limited set of states can persist for a longer time. These are often referred to as steady states or attractors of the system. Knowledge of the identity of these states could be immensely helpful both for research and diagnostic purposes such as biomarker search, patient stratification or drug target identification, since unknown values of the network can be filled from values of the corresponding steady state. Turbine can identify most steady states, limit cycles and limit tori of networks even for continuous models, and estimate their size.

Attractors can have very different properties. We have explored the attractors of a human cancer signaling system [3] with regards to phenotypes and stability [4]. When modeling intracellular noise with different levels of additional pink noise, it appeared that the largest, apoptotic steady state was the only state resistant to noise [at typical intracellular noise levels [5], medium noise/Panel E in the figure below]. This gives additional merit to steady-state analysis, since we only need to identify the largest attractors of the system. The three types of steady states found in the system are shown on Panels A, B and C, while the transfer rates among these attractors are displayed in panels D, E and F, corresponding to 40%, 15% and 10% noise levels, respectively.

2: Identifying cancer-causing mutation sets

It is known [6] that genetic mutations change the attractor structure of the system. We have identified 11 mutation sets consisting of 1/4 stuck-on (On) or stuck-off (Off) mutations which change the attractor structure in a way that the largest attractor becomes proliferating, thus giving rise to cancer even when taking intracellular noise into account. These mutation sets, outlined in the table below, are used as the starting point for the next analysis steps.

3: Intervention target design

Turbine enables the identification of intervention targets by selecting an arbitrary start and target state. Turbine then calculates sets of proteins which when perturbed (drug response), the given starting state of the targeted cell is transferred to the given target state. We have tested the feasibility of this approach by selecting the largest attractor in all of the 11 mutation sets above, and calculating a transfer to the apoptotic state. We have disallowed trivial targets (downstream of, including cytokine c) and have also disallowed perturbing the mutated protein itself (since it is supposed to be malformed). We show a sample of the design process below (starting state, identified targets and the resulting state, in this order), as well as all the identities of the targets identified for the 11 corresponding mutation sets. Positive (+) signs correspond to activation of the given protein, while a negative (-) sign signifies inhibition. Proteins marked with yellow nodes are active, while black nodes are inactive in the figure.

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DYNAMIC ANALYSIS OF COMPLEX NETWORKS IN BIOMARKER DETECTION AND DRUG DESIGN

Introducing the Turbine advanced network dynamics software

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