SignalStorm: A Java Game to Simulate Cancer Signaling Pathways

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SignalStorm is an original interactive game that simulates human cancer signaling networks. Players can learn about various signal receptors such as Receptor Tyrosine Kinase (RTK) and their corresponding intra-cellular signaling pathways.

The game supports simulation of 9 cancer signaling pathways including HedgeHog, Notch, Wnt, PI3K/AKT, GPCR, Ras, TGF-B, Jak/Stat and NF-kB.

The layout of the game is shown in Figure 1. The game is played in the cell panel, while a score panel on the right of the screen keeps track of level and grand scores, as well as more useful information about game play. A menu bar at the top provides various menu options, as well as buttons for **Play**, **Pause** and **Resume**.

The purpose of the game is to use four (4) supplied suppressor proteins to kill oncogenic signals (originating at receptors) before they reach nucleus and cause DNA Damage. Each kill is awarded two (2) points while a DNA damage by an oncogenic signal results in one (1) point loss. The game begins when user presses 'Play' button.

The four suppressors are controlled by 4 sets of four keys. The suppressor in lower right region is controlled by four arrow keys. The suppressor in upper right region is controlled by '7' (Left), '8' (Down), '9' (Up) and '0' (Right) keys. The suppressor in upper left region is controlled by '1' (Left), '2' (Down), '3' (Up) and '4' (Right) keys. The suppressor in lower left region is controlled by 'a' (Left), 's' (Down), 'w' (Up) and 'd' (Right) keys.

The game supports 6 different levels corresponding to increasing order of difficulty. Each level corresponds to number of pathways simulated for that level. For example at level 4, four pathways are simulated. Players can indicate their pathway preference by using the drop-down 'Signaling' menu. When selecting signaling pathways to simulate for a level, Player indicated preference is given priority. If player indicated pathway preference is less than the game level then other pathways are randomly picked.

The game can be paused any time by pressing the 'Pause' button and later resumed by pressing the 'Resume' button. The game level can be changed by using the slider. The game score can be saved by using the 'File' drop down menu and selecting Save or Save As. Players can also erase their bad scores by using 'Reset' drop down menu and either selecting 'Full' to reset scores for all level or 'Current' to reset score for current level.

The game level, level score and grand score along with mutated genes and associated cancers are displayed in score panel. Suppressors are shown in blue while flashing orange oval indicates oncogenic signal. Magenta is used for receptor proteins and Pink for nuclear protein for easy identification. Proteins in inactive pathways are shown in white.

The game can be terminated by selecting 'Exit' under 'File' drop-down menu.

Cancer Signaling

SignalStorm supports simulation of 9 cancer-signaling pathways:

HedgeHog Signaling: Binding of the Patched receptor by a Hedgehog ligand causes Patched to release Smoothened protein from inhibition. Smoothened then emits downstream signals that protect cytoplasmic Gli protein from cleavage. Intact Gli can then migrate to the nucleus and functions as transcription activator.

Notch Signaling: Upon binding one of its ligands, Notch is cleaved twice, liberating a cytoplasmic fragment that migrates to the nucleus and functions as part of a transcription factor complex.

Wnt Signaling: Acting through Frizzled receptors, Wnt suppresses the activity of GSK-3B, which otherwise would phosphorylate several key substrates including Beta-catenin and cyclin D1 tagging them for destruction. The spared Beta-catenin moves into the nucleus and activates transcription of key growth stimulating genes.

Jak/STAT Signaling: Receptors for cytokines form complexes with tyrosine kinase of the Jak class, which phosphorylate STATs (signal transducers and activators of transcription). The STATs form dimers, and migrate to the nucleus, where they function as transcription factors.

GPCR Signaling: Upon binding their extracellular ligands, G-protein-coupled receptors (GPCRs) activate cytoplasmic hetero-trimeric G proteins whose alpha subunit exchanges its GDP for GTP. The G-alpha subunit then dissociates from its two partners (G-beta + G-gamma) and proceeds to activate or inhibit a number of cytoplasmic enzymes having mitogenic or anti-mitogenic effects. The (G-beta + G-gamma) dimer activates its own effectors, including PI3K-gamma, PLC-beta, Src.

Ras Signaling: Three major downstream signaling cascades emanate from activated Ras via binding of its effector loop with downstream signaling partners - Raf kinase, PI3K, and RalGEF. Raf phosphorylates residues on MEK. The resulting activated MEK phosphorylates and activates Erk-1/2.

PI3K/Akt/mTOR Signaling: The phosphatidylinositol 3-kinase (PI3K) pathway depends on kinases phosphorylating a phospholipid and is important in suppressing apoptosis and in promoting the growth of cells.

NF-kB Signaling: The nuclear factor-kB signaling system depends on the formation of NF-kB homo- and hetero-dimers in the cytoplasm. The inhibitor of NF-kB (IkB) usually sequesters NF-kB in the cytoplasm but in response to signaling, is tagged for destruction by IkB kinase (IKK). This leaves NF-kB free to migrate into the nucleus, where it activates expression of at least 150 genes, some of which specify key anti-apoptotic proteins.

TGF-B Signaling: The TGF-beta signaling pathway involves the dispatch of cytoplasmic SMAD transcription factors into the nucleus, where they help activate a large contingent of genes. This pathway plays a major role in the pathogenesis of many carcinomas.

References

[1] Robert A Weinberg, “The Biology of Cancer”

Table 1 Screen Shot of SignalStorm