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ELECANS—an integrated model development environment for multiscale cancer systems biology

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ABSTRACT

Motivation: Computational multiscale models help cancer biologists to study the spatiotemporal dynamics of complex biological systems and to reveal the underlying mechanism of emergent properties. **Results**: To facilitate the construction of such models, we have developed a next generation modelling platform for cancer systems biology, termed 'ELECANS' (electronic cancer system). It is equipped with a graphical user interface-based development environment for multiscale modelling along with a software development kit such that hierarchically complex biological systems can be conveniently modelled and simulated by using the graphical user interface/software development kit combination. Associated software accessories can also help users to perform post-processing of the simulation data for visualization and further analysis. In summary, ELECANS is a new modelling platform for cancer systems biology and provides a convenient and flexible modelling and simulation environment that is particularly useful for those without an intensive programming background.

Availability and implementation: ELECANS, its associated software accessories, demo examples, documentation and issues database are freely available at http://sbie.kaist.ac.kr/sub_0204.php

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Supplementary information: Supplementary data are available at *Bioinformatics* online.

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1 INTRODUCTION

The development and integration of complex multiscale biological models have been a great challenge in the area of cancer systems biology (Deisboeck *et al.*, 2011). However, the lack of a user-friendly and integrative software environment has made it difficult to develop such multiscale models and derive biological insights from them. This has been a problem particularly for experimental scientists and modellers who have a limited software development capability. Therefore, we have developed 'ELECANS' (electronic cancer system), a next generation modelling and simulation platform for cancer systems biology, to overcome such hurdles in multiscale modelling and simulation. ELECANS is equipped with a rich graphical user interface (GUI) studio coupled with a powerful software development kit (SDK). This GUI/SDK combination allows users to conveniently design the extra-cellular environment, cellular phenotypes and tissue models. Cell cycle and sub-cellular components can be modelled, executed and hot switched during simulations. The 2D and 3D discrete or hybrid simulation environments can also be constructed in ELECANS. Lattice types can be selected from predefined ones or customized via SDK. Simulation data can be exported to text or XML files, which can be visualized with ELECANS software accessories. Taken together, ELECANS helps advanced cancer research by providing a powerful and user-friendly modelling and simulation platform for cancer systems biology.

2 METHODS AND IMPLEMENTATION

Redundant n-tier architecture was used for the software design of ELECANS (Fig. 1A). The fully object-oriented Visual C# 4.0 with Microsoft .NET Framework 4.0 was used to implement the multi-agent system core of ELECANS and the front-end GUIs. OpenTK .NET (http://www.opentk.com), Steven Fortune's Voronoi (Fortune *et al.*, 1987) and Lundin's Mathparser (http://www.lundin.com/mathparser.aspx) libraries were used to implement 2D/3D visualization, off-lattice cell distribution and cell geometry vertex definition, respectively. ALGLIB (http://www.alglib.net) was used for matrix functions, and an in-house partial differential equation (PDE) solver was developed using the Alternating Directions Implicit (Chang *et al.*, 1991) method. This PDE solver does not support mesh partitioning for utilization with multi-core systems, but users can implement their own mesh-partitioning algorithms and concomitant PDE solvers using the ELECANS SDK for computational scalability.

The resulting software platform embeds a Studio with three editors: Agents Editor, Environment Editor and Simulation Editor (see Section 3 for details). The core engine object is shared and synchronized among these editors. The software was extensively tested by using black and white box testing approaches, and the issues list was made available online (Supplementary Table S1). Release notes and an updated bug database repository are also available for download (Supplementary Table S1). Simulation data can be visualized and analysed by the accompanying Matlab toolboxes or by user developed software (Supplementary Table S1).

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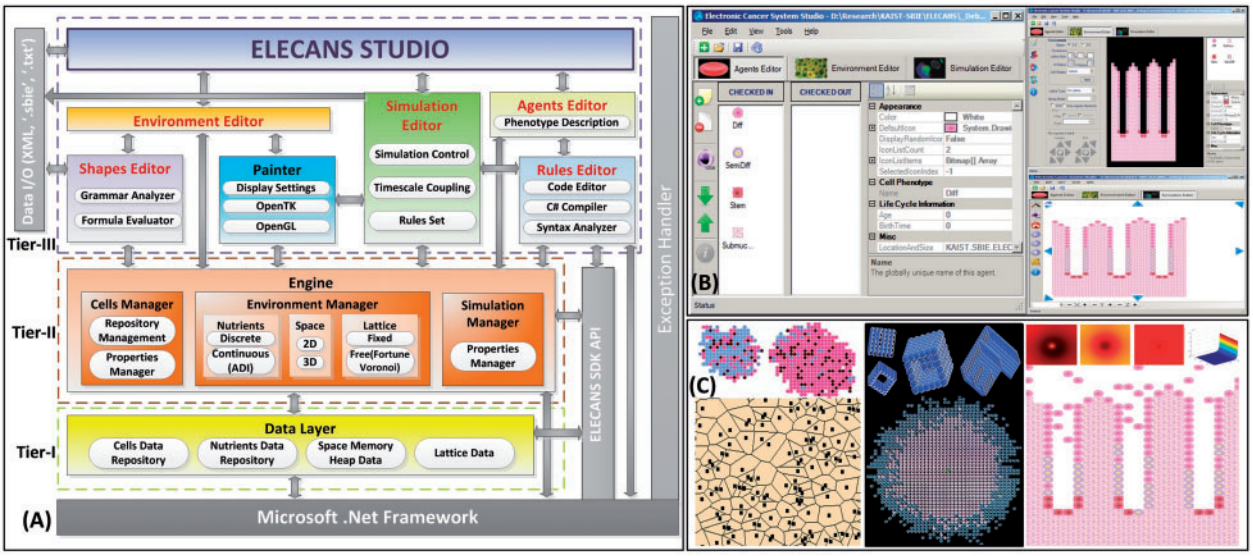

Fig. 1. ELECANS software design and simulation examples, (**A**) ELECANS architectural layout, (**B**) ELECANS Studio and Editors, (**C**) Illustration of various simulation scenarios and the cell environmental bio-molecular profiles that can be developed using ELECANS

3 KEY FEATURES OF ELECANS

ELECANS provides a modelling and simulation studio (Fig. 1B) with a user-friendly GUI (Supplementary Table S1) for cancer systems biology. The salient features and concepts of ELECANS are summarized below.

(1) **ELECANS SDK**—At the core of ELECANS platform, there is a multi-agent simulation engine for processing discretely defined cellular agents. To help construct finely detailed models, ELECANS accommodates user customization of its core 'Engine' via SDK application programming interface (API) ('Elecans_base.dll'). Modellers can selectively re-program ELECANS engine by writing wrapper classes over ELECANS SDK.

(2) **Rules Editors**—The ELECANS Rules Editor helps user to define two types of rules dynamic link libraries (DLLs): 'Cell Rules' and 'Simulation Rules'. Cell properties including cell cycle, signalling pathways and sub-cellular organelles can be programmed in cell rules DLLs. Simulation parameters and logic can be implemented as a separate simulation rules DLL. These rules DLLs are called during simulations where the cell rules DLLs can be hot switched seamlessly to exhibit cellular phenotypic evolution.

(3) **Tissue Geometry Editor**—ELECANS helps users to rapidly assemble tissue level models by creating cell assemblies and geometries in 'Cell Geometry Editor'. By defining mathematical equations, users can easily create template tissue shapes. Selected cells can then be placed at the coordinates defined by the equations. The template tissues can then be implanted in the environment, at the user-defined location.

(4) **Third Party .NET Bridges (C, Matlab, Python .NET and R)**—Numerous systems biology models have already been implemented in C, Matlab and Python. ELECANS can seamlessly access and execute these models via third party .NET DLL bridges. The DLL references to these third party models can be added into the Rules Editors. Simulation parameters can also be passed, and computed results can be returned (see Supplementary Table S5 for exemplars).

4 RESULTS AND CONCLUSION

ELECANS can be used to model diverse multi-scale biological phenomena. Figure 1C provides an illustration of several simulation examples developed and deployed in ELECANS. These include oncogenesis by mitochondrial incapacitation during the cell death process (Chaudhary *et al.*, 2011) (see Supplementary Data 'A' for model details and performance analysis), off-lattice cellular tissue development, various cell geometries assembled in ELECANS, hypoxic stress in epithelial tissue, visualization of a continuous description of environmental bio-molecules and a homeostatic cross-section of colon crypt (see Supplementary Table S3 for a step-by-step implementation). Several other examples were also provided (Supplementary Table S4) to highlight specific modelling capabilities and advantages of ELECANS. We also carried out comparative analysis between ELECANS and CompuCell3D (Izaguirre *et al.*, 2004) by assembling and simulating example models (see Supplementary Data 'B' for details). In conclusion, ELECANS provides a comprehensive model development environment for multi-scale cancer systems biology and offers a novel and powerful set of conveniently exercisable features, which empower the computational systems biologists as well as the experimental biologists.

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Conflict of Interest: none declared.

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